Natural 6-hydroxy-chromanols and -chromenols: structural diversity, biosynthetic pathways and health implications†

Marc Birringer, a, b Karsten Siems, a Alexander Maxones, a Jan Frank b, c and Stefan Lorkowski a, de

We present the first comprehensive and systematic review on the structurally diverse toco-chromanols and -chromenols found in photosynthetic organisms, including marine organisms, and as metabolic intermediates in animals. The focus of this work is on the structural diversity of chromanols and chromenols that result from various side chain modifications. We describe more than 230 structures that derive from a 6-hydroxy-chromanol- and 6-hydroxy-chromenol core, respectively, and comprise di-, sesqui-, mono- and hemiterpenes. We assort the compounds into a structure–activity relationship with special emphasis on anti-inflammatory and anti-carcinogenic activities of the congeners. This review covers the literature published from 1970 to 2017.

1. Introduction

In 1922, Bishop and Evans discovered α-tocopherol as an essential lipid-soluble factor that promotes the gestation of rat fetuses.1 Since then, numerous structurally related 6-hydroxy-chromanols and -chromenols have been discovered. Tocochromanols of the vitamin E class represent the most widely distributed and predominant chromanols in nature. However, only photosynthetic organisms, such as plants, algae, and cyanobacteria as well as fungi, corals, sponges and tunicates, are able to perform the biosynthetic steps leading to a chromanol ring system. However, mammals, including humans, rely on these resources (esp. plant oils), since vitamin E is essential for a wide range of higher organisms.2

The term vitamin E is traditionally used for the eight structurally related vitamers α, β, γ, δ-tocopherol, and α-, β-, γ-, δ-tocotrienol, with α-tocopherol being the compound with the highest vitamin activity.3

Tocochromanols belong to the family of prenylquinones that also include plastochochromanol-8, phylloquinones [vitamin K], and ubiquinones (coenzyme Q10). Due to its unique 6-hydroxy-chromanol structure, the vitamin E forms may act as antioxidants that prevent lipid peroxidation in cellular membranes and quench harmful reactive oxygen species (ROS) in plants and animals (including humans). The proton of the 6-hydroxy group can quench a reactive radical, in turn leading to a tocopheryl radical that, depending on the substitution pattern of the ring system, remains stable, with a half-life of several seconds, and can be subsequently recycled by vitamin C. The review does not aim to discuss the complex antioxidant and redox chemistry of tocopherols forming corresponding radicals, quinones, dimers or polymers. These issues have already been discussed in several excellent reviews.4,5 Further, biosynthesis, bioactivity and chemical properties of tocopherols and tocotrienols are summarized in several outstanding reviews,6 and will be discussed here only briefly. This work focuses on the structural diversity of chromanols due to side chain modifications and attempts to merge structural aspects with biological activity.

In general, 6-hydroxy-chromanols derive from the parent structure 2-methyl-3,4-dihydro-2H-chromen-6-ol (1) and 6-hydroxy-chromenols derive from 2-methyl-2H-chromen-6-ol (2) that comprise a class of bicyclic heterocycles formed by cyclisation of substituted 1,4-benzoquinones (Fig. 1).

Besides the methylation pattern (R1–R3) of the chromanol ring system, side chain modifications (at R4) show the highest structural variability. In particular tocotrienols are prone to (partial) reduction of the double bonds or oxidation of the methyl groups by cytochrome P450-dependent hydroxylases and oxidases, which ultimately results in the formation of oxidation products, such as alcohols, ketones, aldehydes, carboxylic

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra11819h

Cite this: RSC Adv., 2018, 8, 4803–4841

This journal is © The Royal Society of Chemistry 2018
acids, and truncations of the side chain. Furthermore, intramolecular cyclisation and/or rearrangements of the isoprene units can build up mono-, bi-, and tri-cyclic ring systems. These modifications are well known for compounds in marine organisms, especially in brown algae and sponges (see below), but have been found also in higher plant species. Along with side chain modifications, increased bioactivity is observed for many of these structures in vitro and in vivo.

The following chapters describe these compounds, sorted by the length of the carbon skeleton, following the order (mero)diterpenes, -sesquiterpenes, -monoterpenes and -hemiterpenes.

2. Methods

Chromanols and chromenols presented here were selected by a chemical substructure search of 1 and 2, respectively, within several databases. We received 307 matches from the Dictionary of Natural Products and 128 matches from the Dictionary of Marine Natural Products (both at Chemnet BASE). We included a PubMed substructure search and PubMed keyword searches for “toco(chromanol)**“, “toco(chromenol)**“ and “mero(di)terpenoid**“. Patents were searched by chemical names at the website of the European Patent Office. Finally, we performed a reference-related snowball sampling and deleted all doublets. All identified meroterpenoids were sorted by the length of their carbon skeleton and number of prenyl units, respectively. Numbering of the carbon skeleton of metabolites was conducted in analogy to IUPAC rules, however for better clearness, numbering of the carbon skeleton and number of prenyl units, respectively. These modifications are well known for compounds in marine organisms, especially in brown algae and sponges (see below), but have been found also in higher plant species. Along with side chain modifications, increased bioactivity is observed for many of these structures in vitro and in vivo.

The following chapters describe these compounds, sorted by the length of the carbon skeleton, following the order (mero)diterpenes, -sesquiterpenes, -monoterpenes and -hemiterpenes.

3. Meroditerpenes

3.1 Plants

In the last decades, hundreds of publications referring to tocopherols and tocotrienols have been published, covering chemical, physical and biological properties of vitamin E as well as analytical procedures to detect the vitamers from biological origin.

The main sources of the fat-soluble vitamin E are plant oils. To understand the structural variability of tocochromanols in plants and other photosynthetic organisms, a brief introduction into their biosynthesis is presented. The biosynthesis of tocochromanols was primarily investigated in the leaves of green plants, however all photosynthetic organisms as well as apicomplexa parasites such as Plasmodium falciparum* are capable of the necessary biosynthetic steps. The biosynthetic pathways of tocotrienols, tocomonoenols, tocopherols and plasto(chromanol)-8 are depicted in Fig. 2 and consist of five main steps. First, the transformation of 3-hydroxyphenylpyruvate (HPP) to homogentisic acid (HGA), which is catalyzed by hydroxyphenylpyruvate dioxygenase (HPPD). Second, the synthesis of the isoprenoid side chain that originates from the 1-deoxy-o-xylulose-5-phosphate (DOXP) pathway in plastids. Here, geranylgeraniol reductase (GG-reductase) determines the degree of side chain saturation that leads to dihydro-geranylgeraniol diphosphate (DHGG-DP), tetrahydro-geranylgeraniol diphosphate (THGG-DP) and phytol diphosphate, respectively. The reduction of the double bonds between C-3’–C-4’ and C-7’–C-8’ results in two R-configured stereogenic centers at C-4’ and C-8’ of the latter tocopherols (Fig. 3).

In addition, solanesyl diphosphate, containing nine isoprene units, is formed by solanesyl diphosphate synthase.* The above-mentioned diphosphates serve as substrates for transferases, which catalyze the alkylation of HGA, leading to benzoquinol derivatives, such as methyl-geranylgeraniol benzoquinol (MGGQ), methyl-tetrahydro-geranylgeraniol benzoquinol (MTHGGBQ), methyl-phytol benzoquinol (MPBQ), and methyl-solanesyl benzoquinol (MSBQ), respectively (step 3).

The methylation pattern of tocochromanols depends on the next steps (step 4 and 5) of the biosynthesis. â- and ß-tocochromanols are formed by immediate cyclization, followed by S-adenosyl methionine-dependent methylation of the chromanol ring, whereas γ-tocochromanols are build by methylation followed by cyclization. Finally, α-tocochromanols results from methylation of γ-tocochromanols. The cyclization of the prenylated quinones to chromanols by tocopherol cyclase occurs within plastoglobules. The latter biosynthetic step yields R-configuration at C-2 atom and thus seems to be unique for plant
According to the methylation pattern of the 6-hydroxychromanol ring system, tocopherols are divided into the most prominent vitamers \( \alpha \) (5,7,8-trimethyl)-tocopherol (3), \( \beta \) (5,8-dimethyl)-tocopherol (4), \( \gamma \) (7,8-dimethyl)-tocopherol (5) and \( \delta \) (8-methyl)-tocopherol (6), respectively (Fig. 3). The tocopherols are ubiquitously found in most plant oils, whereas tocotrienols occur only in non-photosynthetic organs of higher plants, mainly eudicots and monocots.\(^1\)\(^1\)\(^1\)

Alternative methylations of the chromanol ring lead to \( \gamma \)-tocopherol (5-methyltocol) (7), \( \beta \)-tocopherol (7-methyltocol) (8) and \( \xi \)-tocopherol (5,7-dimethyltocol) (9), which are found in trace amounts in rice bran.\(^1\)\(^3\) The latter congeners have not been described in recent literature and therefore their existence seems to be questionable and may have been the result of analytical artifacts.

In the past, all tocopherols and tocotrienols were studied in gestation-fetal resorption assays, with \( RRR-\alpha \)-tocopherol (3) being the most potent vitamer.\(^1\)\(^4\)

Although described in textbooks, primary literature on tocopherylesters at C-6 is scarce.\(^1\)\(^5\)\(^6\) Acylesters of saturated fatty acids (C12:0, C14:0, C16:0 and C18:0) and tocopherols were found in \textit{Nuphar luteum} and \textit{Nymphea alba}\(^1\)\(^5\) and in the pulp of yellow bell pepper (\textit{Capsicum annuum}).\(^1\)\(^6\) In the last decade, the occurrence, angiogenic and vasculogenic properties of \( \alpha \)-tocopheryl-phosphate were intensively studied by Azzi \textit{et al.}\(^1\)\(^7\)\(^1\)\(^8\) This molecule was found in food but only in low amounts.\(^1\)\(^8\)

Degradation pathways of tocopherols derive from the biochemical elimination between C-3 and C-4 of the chromanol ring and were first isolated as \( \alpha \)-, \( \beta \)- and \( \gamma \)-dehydrotocopherols (10, 11, 12) from wheat germ oil\(^1\)\(^9\) and from various \textit{Stemona} species, such as \textit{Korean Stemonae Radix} (Fig. 3) (\textit{Stemona tuberosa}).\(^2\)\(^0\)\(^2\)\(^1\) \( \gamma \)-Dehydrotocopherol shows proliferative effects on mouse NIH 3T3 fibroblasts and a potential use as wound healing agent has been suggested.\(^2\)\(^1\)

As mentioned above, \( \alpha \)-, \( \beta \)-, \( \gamma \)- and \( \delta \)-tocotrienols (14, 15, 16, 17) usually occur as trace vitamers, however, several plant tissues and oils accumulate higher amounts of tocotrienols. For example, \( \alpha \)-tocotrienol was found in barley (76 mg/100 g), \( \gamma \)- and \( \delta \)-tocotrienol in palm oil (36 mg and 8 mg/100 g, respectively). The distribution of tocotrienols in plant has been reviewed in detail elsewhere.\(^6\)\(^1\)\(^2\)\(^2\)
In contrast to tocopherols, tocotrienols exhibit higher bioactivity in vertebrates. Ashan et al. recently reviewed the bioactivity of tocotrienols, which may act as anti-cancer, anti-diabetic, anti-inflammatory, antioxidant, immune-stimulatory, cardio-, neuro-, hepato- and nephro-protective molecules.\(^2\)

Alternation in the methylation pattern has been also described for tocotrienols. Qureshi et al. found desmethyltocotrienol \((3,4\text{-dihydro}-2\text{-methyl}-2\text{-}(4,8,12\text{-trimethyltrideca-3',7',11'-tri-enyl})-2H\text{-}1\text{-benzopyran-6-ol}) (18)\) and didesmethyltocotrienol \((3,4\text{-dihydro-2-}(4,8,12\text{-trimethyltrideca-3',7',11'-tri-enyl})-2H\text{-}1\text{-benzopyran-6-ol}) (19)\) in rice bran\(^2\) (Fig. 3). Most interestingly, the latter compounds show cholesterol lowering activity in chicken, most likely by inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase, which catalyzes the rate-limiting step of the cholesterol biosynthesis pathway. The compounds reduced total serum cholesterol by 26% and 31% relative to a control diet and reduced LDL cholesterol by 41% and 48%, respectively. Similar to tocotrienols, both compounds suppress proliferation B16 melanoma cells\(^2\) (Table 3). Interestingly, oxidation of the aromatic methyl groups are rare in nature. Two unusual formyl-derivatives (at C-5 \((20)\) and C-7 \((21)\), respectively) of \(\delta\)-tocotrienol have been isolated in trace amounts from \textit{Garcinia virgata} (Fig. 4).\(^2\)

As a result of a partial reduction of the prenyl side chain by geranylgeraniol reductase during the synthesis of tocopherols, tocodienols and tocotrienols were found in several plant species (Fig. 4).\(^1\) \(\alpha\)-Tocodienol \((26)\) has recently been discovered as a trace compound (0.2% of the total vitamin E content) in palm oil.\(^3\) Nutritionally or physiologically effects of plastochromanol-8 in animals or humans have not been described so far. As a result of the non-enzymatic oxidation of plastochromanol-8 by singlet oxygen, hydroxy-plastochromanol

---

**Table 3**

| tocopherols | -R<sub>1</sub> | -R<sub>2</sub> | -R<sub>3</sub> |
|-------------|-------------|-------------|-------------|
| \(\alpha\) 3 | -CH<sub>3</sub> | -CH<sub>3</sub> | -CH<sub>3</sub> |
| \(\beta\) 4 | -CH<sub>3</sub> | -H | -CH<sub>3</sub> |
| \(\gamma\) 5 | -H | -CH<sub>3</sub> | -CH<sub>3</sub> |
| \(\delta\) 6 | -H | -H | -H |
| \(\varepsilon\) 7 | -CH<sub>3</sub> | -H | -H |
| \(\eta\) 8 | -H | -CH<sub>3</sub> | -H |
| \(\zeta\) 9 | -CH<sub>3</sub> | -CH<sub>3</sub> | -H |

| tocotrienols | -R<sub>1</sub> | -R<sub>2</sub> | -R<sub>3</sub> | -R<sub>4</sub> |
|-------------|-------------|-------------|-------------|-------------|
| \(\alpha\) 14 | -CH<sub>3</sub> | -CH<sub>3</sub> | -CH<sub>3</sub> | -CH<sub>3</sub> |
| \(\beta\) 15 | -CH<sub>3</sub> | -H | -CH<sub>3</sub> | -CH<sub>3</sub> |
| \(\gamma\) 16 | -H | -CH<sub>3</sub> | -CH<sub>3</sub> | -CH<sub>3</sub> |
| \(\delta\) 17 | -H | -H | -CH<sub>3</sub> | -CH<sub>3</sub> |
| desmethyl 18 | -H | -H | -H | -CH<sub>3</sub> |
| didesmethyl 19 | -H | -H | -H | -H |

---

**Fig. 3** Structures and substitution patterns of tocopherols (3 to 9), dehydrotocopherols (10 to 13) and tocotrienols (14 to 19).
(28) was identified in *Arabidopsis* leaves.\textsuperscript{33} Solanachromene (29) (plastochromenol-8) contains a double bond in the chromanol ring and was found in relatively high amounts (0.05\% of dry weight) in aged flue-cured tobacco leaves.\textsuperscript{35,36}

$\delta$-Garcinoic acid (30) ($E$-13'carboxy-$\delta$-tocotrienol, $\delta$-garcinoic acid), an oxidation product of $\delta$-tocotrienol, is probably the most investigated plant tocotrienol with side chain modification, so far (Fig. 5).\textsuperscript{37}$\delta$-Garcinoic acid was first isolated from *Clusia grandiflora* by Delle Monache \textit{et al.} and later by Teraschima \textit{et al.} from the African bitter nut *Garcinia kola* and was further characterized for its chemical and physiological properties.\textsuperscript{37,42} It has been detected in different amounts within the Clusiaceae family including *Tovomitospis psychotriifolia*, *Clusia obdeltifolia*, *Clusia burlemarxii*, *Clusia pernambucensis*, *Garcinia kola* and together with $\gamma$-garcinoic acid (31) in the bark of *Garcinia amplexicaulis*.$\textsuperscript{43,44}$ Recently, $\gamma$-garcinoic acid was isolated in small amounts from the Algerian conifer *Cedrus atlantica* (Pinaceae).\textsuperscript{45,46} A mixture of 2($Z$)-$\delta$-garcinoic acid and 2($E$)-$\delta$-garcinoic acid was isolated from the stem of *Clusia obdeltifolia*.\textsuperscript{46}

\textit{D}-Garcinoic acid exerts potent anti-inflammatory, anti-proliferatory and antibacterial properties (see corresponding sections). As a possible target for its anti-inflammatory action, microsomal prostaglandin $E_2$ synthase has been identified recently.\textsuperscript{44} The two natural ($\delta$- and $\gamma$-garcinoic acid) isomers as well as semi-synthesized $\beta$- and $\alpha$-garcinoic acid inhibited the enzyme with IC\textsubscript{50} values of 6.7, 2.0, 2.8 and 7.8 $\mu$M, respectively.

$\delta$-Garcinoic acid reduced the growth of C6 cells and RAW264.7 mouse macrophages with an EC\textsubscript{50} of 10 $\mu$M and 5 $\mu$M, respectively.\textsuperscript{37,38} As demonstrated by Maloney and Hecht, $\delta$-garcinoic acid inhibits DNA polymerase $\beta$ with an IC\textsubscript{50} of about 4 $\mu$M.\textsuperscript{47} Whether this inhibition is a useful approach to prevent growth of cancer cells needs to be elucidated.

As mentioned above, $\gamma$-garcinoic acid and $\delta$-($E$)-deoxy-amplexichromanol (32) (see below) were isolated together with a $\delta$-methoxy-$\delta$-garcinoic acid derivative (33) from *Cedrus atlantica* (Fig. 5).\textsuperscript{45} All compounds showed only moderate antibacterial activity against different bacterial strains (see Table 3).

As a by-product of the isolation of garcinoic acid, garcinal (34) ($\delta$-($E$)-garcinal), with a terminal aldehyde group, was found in the *G. kola* nut.\textsuperscript{44} So far, the bioactive properties of garcinal are unknown.

Another interesting group of side chain-modified compounds with large structural variability has been isolated from the bark of *Garcinia amplexicaulis*, an endemic shrub from New Caledonia. $\delta$- and $\gamma$-amplexichroman (35) and (36) are terminal-hydroxylated $\delta$- and $\gamma$-tocotrienols, respectively, carrying two hydroxy-groups at carbon-13' and -14' (Fig. 5).\textsuperscript{45} Both compounds inhibited capillary formation of VEGF-induced human primary endothelial cells at 25 nM concentration. Interestingly, only $\delta$-amplexichromanol decreased the adhesion of VEGF-induced human primary endothelial cells whereas $\gamma$-amplexichromanol had no significant effect, suggesting different modes of action. $\delta$-Dihydroxy-amplexichromanol (37) results from dihydroxylation of the double bond between C-7' and C-8'. Besides $\gamma$-($Z$)- and $\gamma$-($E$)-deoxy-amplexichromanol (38) as well as $\delta$-($Z$)- and $\delta$-($E$)-deoxy-amplexichromanol, two aldehydes, namely $\gamma$-($E$)-deoxy-amplexichromanol (39) (which is identical to $\gamma$-($E$)-garcinal) and $\delta$-($E$)-amplexichromanol (40) were isolated from *Garcinia amplexicaulis*.\textsuperscript{45,48} $\delta$-($E$)-Deoxy-amplexichromanol (32) has also been described in *Cedrus atlantica*.\textsuperscript{45} $\delta$-($Z$)-Deoxy-
amplexichromanol was earlier described by Teixeira et al. in *Clusia obdeltifolia*.

In addition, dimeric oxidation and condensation products of amplexichromanols have been characterized.

From the methanolic extract of leaves of *Litchi chinensis* (Sapindaceae), several δ-tocotrienol derivatives with side chain and chromanol modifications were isolated and investigated for their anti-cancerogenic potential. Litchtocotrienols A–G (41–47) are hydroxylated at C-11′ with R-configuration and E-F (45, 46) contain a ketone group at C-11′ (Fig. 6). An additional methoxy-group is introduced at position C-5 of the chromane ring for litchtocotrienols B, D, F and G, respectively. Position C-12′ is hydroxylated for A, B, G or methoxylated for C and D. Macrolitchtocotrienol A (48) derives from an intramolecular condensation between C-12′ and C-6 to form an ansa-chromane. The structural motive is similar to the smenochromene sesquiterpenes. Finally, cyclolitchtocotrienol A (49) with a cyclohexene ring within the side chain was isolated. The latter compound is a structural isomer of walsurol (50) with related biosynthesis (Fig. 7). Litchtocotrienols presumably derive from the precursor 11′-12′-epoxide that undergoes nucleophilic ring opening and further modifications. Litchtocotrienols A–G and macrolitchtocotrienol A showed moderate cytotoxicity in HepG2 liver cells and gastric epithelial cells (AGS), with IC₅₀ values ranging from 10–50 μM (Table 2).

All isolated compounds from *Garcinia amplexicaulis* and *Litchi chinensis* show high structural similarity to tocochromanols from *Saragassum* species (see section on Algae). In conclusion, *Garcinia amplexicaulis* and *Litchi chinensis* present the highest degree of structural variability among angiosperms.

Side chain-modified tocochromanols have been found in the fruits of the Amazonian Myristicaceae *Iryanthera juruensis* and *Iryanthera grandis* and in vegetal parts of the Mexican Asteraceae *Roldana barba-johannis*. *Iryanthera* leaves were used by the indigenous population to treat infected wounds and cuts, and the latex of the bark was used against infections. δ-Sargachromenol (51) was found in all the above-mentioned plants and was obtained in 0.4% and 0.8% yield (dry mass) from *Roldana* and *Iryanthera* species, respectively. δ-Sargachromenol is a δ-dehydrotocotrienol derivative with a carboxyl group located at C-15′ of the side chain and is thus a structurally related form of δ-garcinoic acid (30) (Fig. 5). Sargachromenol was named after the brown algae *Sargassum serratifolium*, from which it was first isolated by Kusumi et al. For a detailed description of the biological properties, please see the section on Algae.

Besides δ-sargachromenol, 7-methyl-sargachromenol (52) (γ-sargachromenol) was isolated from the fruits of *Iryanthera juruensis* by Silva et al.

To the best of our knowledge, besides cyclolitchtocotrienol A (49), walsurol (50) obtained from the bark of the Yunnan tree *Walsura yunnanensis* (Meliaceae) is the only meroditerpene in higher plants that forms a 6-membered ring structure within the side chain. Interestingly, walsurol was obtained as the main lipid constituent from powdered bark (0.08% yield). Here, the authors discussed a possible mechanism that leads to cyclization reactions in the side chain. Epoxidation of the

---

**Fig. 5** Structures and substitution patterns of garcinoic acids (30 to 33) and meroditerpenes (34 to -40) from *Garcinia amplexicaulis*.
Fig. 6  Structures and substitution patterns of litchtocotrienols (41 to 48) from Litchi chinensis, sargachromenols (51) and (52).

| Litchtocotrienol | -R₁ | -R₂ | -R₃ |
|------------------|-----|-----|-----|
| A 41             | -H  | -OH | -OH (R) |
| B 42             | -OCH₃ | -OH | -OH (R) |
| C 43             | -H  | -OCH₃ | -OH (R) |
| D 44             | -OCH₃ | -OCH₃ | -OH (R) |
| E 45             | -H  | -H  | =O   |
| F 46             | -OCH₃ | -H  | =O   |
| G 47             | -OCH₃ | -OH  | =O   |

Fig. 7  Scheme of an acid-catalyzed cyclization cascade including final cyclization of the chromane ring according to Etse et al.61 Examples are cyclolitchtocotrienol (49) and walsurol (50).
terminal double bonds in isoprenoid structures are well

described for squalene and also for tococtrienols.56,57 Nucleo-
philic ring-opening results in a 11',12'-diol structure that has

also been described for algae.58–60 Etse et al. proposed an acid-
catalyzed rearrangement that leads to a variety of cyclic struc-
tures formed from the diol. Elimination of water and ring

closure between carbon 7’ and 12’ forms endo- (e.g. (49)) and

exo-double bonds (e.g. (50)), respectively (Fig. 7).61 The meta-

bolic pathway described here also applies to the formation of

chromarols (see section on sponges).

3.2 Fungi

Although mushrooms and fungi produce a large number and

variety of meroterpenoids,62,63 our database search found only

scarce information on long-chain or cyclic 6-hydroxy-

chromanols or -chromenes. The occurrence of α-, β-, γ-, and

δ-tocopherols has been summarized in a review by Ferreira

et al.64 Interestingly, no tococtrienols have been found in fungi so

far. Several meroterpenoid structures were described with a 5-

hydroxy-chromene ring, which originated from orsellinic acid

as the aromatic precursor.65

3.3 Marine organisms

Since 1960, more than 20 000 distinct chemical compounds

discovered from marine organisms.65 Of these, algae and

sponges form two third of all natural marine products found

from 1965 to 2007.66 Marine natural products [MNP] with iso-

prenoi structures account for almost 60% of all natural prod-

ucts found in marine organisms.67 Several excellent reviews

have summarized meroterpene structures from marine fungi,68

invertebrates,69 and algae.70,71 Tocopherols are well known to

be produced by algae as well as marine invertebrates and

microorganisms.69,72 Most interestingly, δ-tocotrienol (17) is

widely distributed (especially in algae and sponges) and appears

as the lead structure of most of the diverse compounds
described in this review. Among them, sargachromanols, sar-

gachromenols, cystoseira metabolites, chromarols, epi-
taoniols, smenochromes and strongylrophorines constitute

the largest and best studied groups. Anti-bacterial, anti-viral,

anti-inflammatory and cytotoxic properties were attributed to

these compounds, making them potential lead structures for

drug development.73

3.3.1 Brown algae (Phaeophyceae). Brown algae (Phaeo-

phyceae) consist of around 2000 species of which the family of

Sargassaceae, Dictyophycidae and Fuceaceae produce most of

the meroterpenes described here.74

There is increasing interest in and knowledge about the

isolation, and structural elucidation of meroterpenes and

their quinone precursors from brown algae. Recently, Culioli

and colleagues described the analytical procedure for the

extraction, chromatographic isolation and structural determi-

nation by sophisticated one- and two-dimensional nuclear

magnetic resonance spectroscopic methods.74

As mentioned above, sargachromanols and sargachrome-
nols show the highest structural diversity among all mer-

oditerpenes. They derive from the common precursor

geranylgeranyltoluquinol and subsequently from δ-tocotrienol

and δ-dehydro-tocotrienol, respectively. δ-Tocotrienol-11’-12’-

epoxide (53) was one of the first sargachromanols discovered in

brown algae by Kato et al. in 1975.39 The activation of the
terminal double bond leads to hydroxyl-, oxo-, and cyclic
derivatives, respectively. However, the sequence of the chemical

reactions leading to cyclic derivatives remains elusive (see also

Fig. 7). Observational studies showed that an extract of

Sargassum tortile induced the settling of swimming larvae of the

hydrozoa Coryne uchidai, thus obviously acting as an intercel-
lular signaling molecule.75 The epoxide was found by

bioactivity-guided fractionation of the lipid extract.

In 2005, Jang et al. isolated a series of sargachromanols (A to

P) (54–69) from Sargassum silicuastrum and characterized them

by extensive two-dimensional nuclear magnetic resonance

experiments.76 Later, Lee et al. isolated the structures Q to S (70–

72) from the same species.77 Since sargachromanols A, B and S

are sesquiterpenes, they are described here in the correspond-

ing section.

Sargachromanol C (56) contains a 9'-hydroxy group with R-

configuration in the δ-tocotrienol side chain. The two diols,
sargachromanols D (57) and E (58) possess hydroxyl groups at C-

9’ and C-10’ and are diastereomers of each other. Sargachroma-
nol F (59) has a methoxy group at C-9’ and a hydroxyl group with

R-configuration at C-10’. Sargachromanols G to J (60–63) share

similar side chain modifications consisting of a C-9’ carboxyln

and a C-10’ hydroxyl group. They differ in the numerator and type of

saturation of the double bonds between C-7’ and C-8’ (I, J) (62,

63) and between C-11’ and C-12’ (H, J) (61, 63), respectively, and

a double bond shift from C-7’ to C-6’ (H) (61). Sargachromanol K

(64) is an isomer of sargachromanol G, where the carboxyl and

hydroxyl groups are shifted to C-10’ and C-9’, respectively.

Two-dimensional nuclear magnetic resonance experiments revealed

that sargachromanols L to P underwent carbon skeleton rearr-

rangements of the terminal prenyl group. Thus, the C-8’–C-9’

bond is rearranged to C-8’–C-10’. Sargachromanol L (65) contains

a hydroxyl group at C-9’, whereas sargachromanols M (66) and N

(67) are structural cis/trans-isomers containing an aldehyde
group at C-9’. In addition, the double bond from C-7’ migrated to

C-8’–C-10’. Further oxidation of sargachromanol L leads to

sargachromanol O (68), which bears a carboxyl group at C-9’ and

is thus a structural isomer of δ-garincioic acid (30) (Fig. 8). The

highest isolation yield was obtained for sargachromanols G (60)

and I (62) (0.062 and 0.04%, respectively).76

The formation of an αβ-unsaturated cyclopentenone within

the side chain leads to sargachromanol P (69). Sargachromanols

Q (70) and R (71) share high structural similarity to sargach-

romanols D and E, respectively, but bear an additional tert-

hydroxyl group at the saturated C-4’ (Fig. 9).77

Sargachromanols D, F, H and L are strong Na+/K+-ATPase ion

pump inhibitors, with IC_{50} values of 3.6, 6.0, 4.6 and 7.0 μM,

respectively.78 The study revealed that the hydroxyl groups at C-

9’ and/or C-10’ are important for this inhibitory activity.

Bioassay-guided fractionation of Sargassum silicuastrum

extracts revealed anti-inflammatory action of sargachromanol

D.79 The compound reduced lipopolysaccharide (LPS)-induced

production of nitric oxide and prostaglandin (PG) E_{2} in
murine RAW 264.7 macrophages and inhibited the expression of the pro-inflammatory enzymes inducible nitric oxide synthetase (iNOS) and COX-2. In addition, the production of the pro-inflammatory cytokines TNF-α, interleukin-1β (IL-1β) and IL-6 was reduced by sargachromanol D. Recently, sargachromanol D was suggested as an anti-hypertensive agent, since it showed dual antagonistic activity towards an L-type Ca²⁺-channel and endothelin A/B2 receptor (Table 3). The use of sargachromanols is protected by several patents.

*Sargassum siliquastrum* was also used as a natural source of sargachromanol E and G for bioactivity studies. Both compounds inhibited the expression of pro-inflammatory cytokines in LPS-stimulated murine RAW 264.7 macrophages. In addition, sargachromanol E induced apoptosis via caspase-3 activation in promyelocytic HL-60 leukemia cells and inhibited ultraviolet A-induced ageing of human dermal fibroblasts. Sargachromanol G showed anti-osteoclastogenic effects on the expression of IL-1β-induced osteoclastogenic
factors in the human osteoblast cell line MG-63 and suppressed the activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) in receptor activator of NF-κB ligand (RANKL)-induced RAW264.7 cells.\textsuperscript{85,86}

Besides sargachromanol I and K, another two sargachromanols, (2R)-9’-9’-oxo-δ-tocotrienol (73) and (2R)-7’-8’-dihydro-9’-oxo-δ-tocotronil (74) were isolated from \textit{Sargassum micracanthum}, however, in very low yield (Fig. 9).\textsuperscript{89}

Seo \textit{et al.} isolated a racemic mixture of thunbergol A (75) from \textit{Sargassum thunbergii} (order Dictyotales). The compound features a 3-hydroxyhydrobenzopyran structure with a 15’-carboxy group and thus presumably arises from sargachromanol (Fig. 9).\textsuperscript{90}

Cyclic sargachromanols are widely distributed in brown algae. Taondiol (76) (Fig. 10) was the first cyclic side chain-derivative of tocotrienol that was isolated in 0.05% yield from \textit{Taonia atomaria} (order Dictyotales).\textsuperscript{91} The authors proposed an enzyme-initiated synchronous cyclization cascade of the prenylated 1,4-hydroquinone leading to the tetracyclic ring system. We and others propose an alternative cyclization mechanism starting from 1,4-hydroquinone-14-15-epoxide (77), analogous to lanosterol synthesis\textsuperscript{92,93} (Fig. 10). The protonation of 77 via an epoxide-hydrolase enzyme would increase the susceptibility of intramolecular attacks of the C-2-C-3 and C-6-C-7 double bonds. The stereochemistry of the possible isomers of taondiol at C-2 and C-3 and C-6 and C-7 has been a matter of debate. Recently, Areche \textit{et al.} assigned the stereochemistry of isoeptaonadiol (78) isolated from \textit{Stypopodium flabelliforme} to the formerly described isohtaondiol.\textsuperscript{94} By now, the structures of taondiol, isoeptaonadiol, epitaondiol (79) and 2β,3α-epitaondiol (80) (Fig. 10) have been unambiguously assigned.\textsuperscript{94-96}

Eptaonadiol (79) was isolated from \textit{Stypopodium zonale} and \textit{Stypopodium flabelliforme} (both species are members of the order Dictyotales) and its bioactivity was intensively studied.\textsuperscript{93,95-100} The polycyclic compound shows ichthyotoxic, anti-herpes and anti-human metapneumovirus (HMPV) activity and acts as an anti-inflammatory agent \textit{in vitro} and \textit{in vivo} (see Tables 1–3).\textsuperscript{98,99,103} Further, epitaondiol inhibited cell proliferation of human colon adenocarcinoma (Caco-2), human neuroblastoma (SH-SY5Y), rat basophilic leukemia (RBL-2H3) cells, and murine macrophages (RAW.267), but not of non-cancer Chinese hamster fibroblasts (V79) (Table 2).\textsuperscript{100} 2β,3α-Eptaonadiol (80) exhibited moderate neurotoxicity towards mouse neuro-2a cells with LC\textsubscript{50} values of 2 μM.\textsuperscript{92} Eptaonadiol was effective in the prevention of HCl-ethanol-induced gastric lesions in mice at an ED\textsubscript{50} value of 40 mg kg\textsuperscript{-1} bodyweight.\textsuperscript{101,102} Anti-insecticide activity was found against \textit{Spodoptera frugiperda}.\textsuperscript{96} Finally, the compound induced the settlement of the mussel \textit{Perna perna}.\textsuperscript{98}

A series of cyclic meroditerpenes was isolated from different \textit{Cystoseira} species collected along the Mediterranean and contiguous Atlantic coasts.\textsuperscript{104} According to AlgaeBase,\textsuperscript{105} more than 289 species (and infraspecific) names were found, of which 42 have been marked as currently accepted taxonomically.

It was suggested that the following cyclic diterpenes origin from a common biosynthetic precursor, namely bifurcarenone (81) (Fig. 11). Among them, mediterraneols C (82), D (83), and E (84) have been isolated as their trimethoxy-derivatives from \textit{Cystoseira mediterranea} in high yield (0.11, 0.14 and 2.0% from dry weight algae, respectively).\textsuperscript{106,107} Mediterraneols C and D are stereoisomers at C-4’ and compromise a bridged cyclooctane structure with two dienol moieties. Mediterraneol E (84) is a tricyclic oxygen-bridged diterpene with antineoplastic activity.\textsuperscript{107} So far, the biosynthesis of mediterraneols is largely unknown.\textsuperscript{106,108} Mediterraneanes have been found to inhibit the mobility of sea urchin sperm and the mitotic cell division (ED\textsubscript{50} values of 2 μg ml\textsuperscript{-1}) of fertilized urchin eggs.\textsuperscript{106}

Recently, cystophloroketal E (85), a meroditerpene with a 2,7-dioxabicyclo[3.2.1]octane core was isolated from \textit{Cystoseira tamariscifolia}.\textsuperscript{109} The authors assumed that ketal formation was preceded by a Michael addition of phloroglucinol onto the unsaturated carbonyl of 4-methoxy-bifurcarenone. The compound showed anti-bacterial, anti-microalgal and anti-invertebrate activity (Table 3).

Another group of complex bicyclic compounds was isolated from \textit{Cystoseira stricta}, \textit{Cystoseira mediterranea} and \textit{Cystoseira tamariscifolia}. Cystoseirols A (86), B (87) and C (88)
| Compounds | Test system | Effective concentrations | References |
|-----------|-------------|--------------------------|------------|
| **Meroditerpenes** | | | |
| α-Tocopherol (3) | IL-1β-stimulated A549 cells | 8% nitric oxide inhibition at 10 μM | 279 |
| | | 25% iNOS inhibition at 10 μM | |
| | | IC50 PGE2 inhibition: >50 μM (A549 cells) | |
| γ-Tocopherol (5) | IL-1β-stimulated A549 cells | IC50 PGE2 inhibition: 7.5 μM (RAW264.7) | 279 |
| | | IC50 5-LOX inhibition: >50 μM | 245,257 |
| δ-Tocopherol (6) | IL-1β-stimulated A549 cells | IC50 COX-2 (A549 cells) inhibition: >50 μM | 257 |
| | | IC50 5-LOX inhibition: >50 μM | |
| | | IC50 PGE2 inhibition: 3 μM (A549 cells) | |
| α-Tocotrienol (14) | LPS-induced RAW 264.7 cells | 5% NO inhibition at 33 μM | 280 |
| δ-Tocotrienol (17) | | 31% NO inhibition at 26 μM | |
| γ-Tocotrienol (16) | | 19% NO inhibition at 30 μM | |
| 13′-carboxy-α-tocopherol (205) (α-13′-COOH) | IL-1β-stimulated A549 cells | IC50 PGE2 inhibition: 1 μM (A549 cells) | 245 |
| | | Total inhibition at 2.7 μM | 255 |
| | LPS-induced RAW 264.7 cells | IC50 NO production: 0.2-0.5 μM | |
| 13′-carboxy-δ-tocopherol (229) (δ-13′-COOH) | Inhibition of COX-1 and COX-2 | IC50 COX-1 [bovine] inhibition: 5.0 μM | 245 |
| | | IC50 COX-2 [human] inhibition: 4.0 μM | 245 |
| | | IC50 COX-2 (A549 cells) inhibition: 4.0 μM | 257 |
| 13′-Hydroxy-α-tocopherol (204) (α-13′-OH) | LPS-induced RAW 264.7 cells | IC50 NO production: 0.2 | 241,256 |
| | | 53-60% iNOS inhibition at 10 μM | |
| | | 54% PGE2 inhibition at 10 μM | |
| | | 44-69% NO inhibition at 10 μM | |
| 13′-Hydroxy-δ-tocopherol (231) (δ-13′-OH) | LPS-induced RAW 264.7 cells | IC50 NO production: 1.0 μM | 260 |
| δ-Garcinoic acid (30) | Inhibition of COX-2 and 5-LOX | IC50 NO production: 1.0 μM | |
| | | IC50 NO production: 1.0 μM | |
| α-, β-, γ-, δ-Garcinoic acid (209, 232, 231, 230) | Inhibition of PGE2-synthase (PGES-1) | IC50 7.8 (α-), 2.8 (β-), 2.0 (γ-), 6.7 (δ-) garcinoic acid | 44 |
| δ-Sargachromenol (51) | TPA-induced mouse ear edema | IC50 edema reduction: 0.36 mg per ear | 53 |
| | | 98% COX-1 inhibition at 100 ppm | 52 |
| | | 84% COX-2 inhibition at 100 ppm | |
| | LPS-induced RAW 264.7 and BV-2 cells | IC50 NO production: 82 μM (RAW264.7) | 129 |
| | | IC50 PGE2 inhibition: 30.2 μM (RAW264.7) | |
| | | IC50 NO production: 1.3-2.7 μM (BV-2) | 134,261 |
| | | IC50 NO production: 40 μM (RAW264.7) | 79 |
| | | IC50 PGE2 inhibition: 15 μM (RAW264.7) | |
| Sargachromanol D (57) | LPS-induced RAW 264.7 cells | IC50 NO production: 16.3 μM | 83 |
| Sargachromanol E (58) | LPS-induced RAW 264.7 cells | IC50 NO production: Ca. 15 μM | 84 |
| Sargachromanol G (60) | LPS-induced RAW264.7 cells | IC50 NO production: 0.6(A), 4.0(B), 0.7(C), 1.1 μM(D) | 154 |
| Chromarols (A-D) (113-116) cyclic | Inhibitors of 12- and 15-LOX | 12-hLO IC50: all >100 μM | |
| Epitaondiol (79) cyclic | TPA-induced mouse ear edema | IC50 edema reduction: 20.7 μg per ear | 99 |
| | | IC50 myeloperoxidase activity: 17.8 μg per ear | |
| | | IC50 (TXB2) generation: 3.8 μM | 99 |
| | | IC50 (LTB4) generation: 30.1 μM | |
| **Merosesquiterpenes** | | | |
| Capillobenzoppyranol (172) cyclic | LPS-induced RAW 264.7 cells | 36.7% NO inhibition at 10 μM | 202 |
| 9′-Carboxy-δ-tocopherol (206) (δ-9′-COOH) | Inhibition of COX-1, -2 | IC50 COX-1 [bovine] inhibition: >20 μM | 245 |
| | | IC50 COX-2 [human] inhibition: >20 μM | |
| | | IC50 COX-2 (A549 cells) inhibition: 6.0 μM | |
possess a oxabicyclo[5:4:1]dodecane ring that results from a single methyl group displacement, supplementary bridges and ring fissions. Cystoseiraiole A (86) inhibited plant tumor formation in a crown-gall potato bioassay (73% at 10 μM). Amico et al. isolated cystoketal chromosome (89) from the Sicilian brown alga Cystoseira balearica. Structural elucidation revealed a tricyclic ring system within the side chain and an epimeric mixture at C-2 (Fig. 11). Thus, the authors proposed cystoketal chromosome to be an artefact of the extraction process. Later, demethoxy cystoketal chromosome (90) was isolated from Mediterranean Cystoseira amentacea and recently from Cystoseira tamariscifolia. Demethoxy cystoketal chromosome showed cytotoxic activity with high selectivity towards HepG2 cells (IC₅₀ = 14.77 μg ml⁻¹). A screening of 55 Cystoseira species found several bicyclic meroterpenes, namely 14-methoxymethylchromone (91), amentolchromane and cystoseirone, respectively. The latter two compounds were unstable and were therefore isolated as their acetate derivatives. Interestingly, isolated amentolchromane acetate (92) could be transferred to cystoseirone acetate (93) by chemical oxidation with meta-chloroperoxybenzoic acid in methylenechloride. Again, it was suggested that amentols and cystoseirone have a common biosynthetic precursor, bifurcarenone (81) bearing the typical cis orientation for the bridgehead methyls.

Finally, bifurcarenone chromosome (94), the cyclization product of 81, was found in Cystoseira baccata, and Sargassum muticum, from which it was isolated as epimeric mixture at C-2 (Fig. 11). The mixture showed anti-leishmanial activity at IC₅₀ values of 44.9 μM and decreased the intracellular infection index (IC₅₀ value of 25.0 μM). Sargaole (95) or dehydro-δ-tocotrienol is the potential biosynthetic precursor for most of the chromenos found in brown algae. It was originally isolated from Sargassum tortile collected at the Japanese Tanabe Bay. A lipid extract of the algae exhibited high cytotoxic activity and was used as a skin-lightening agent. Fractionation of the extract resulted in the isolation of sargaole (95), sargadiols-1 (96) and -II (97), and sargatriol (98) (Fig. 12). All compounds were moderately cytotoxic towards murine P-388 leukemia cells with ED₅₀ values of 52, 34, 41 and 42 μM, respectively (Table 2). Sargadiols (96) and (97) bear a hydroxyl group at C-6’ and C-8’, respectively, and sargatriol has two hydroxyl groups at C-5’ and C-6’. All compounds were suggested to be artefacts of the isolation since epimers at C-2 were found in all cases. In addition, heating of the corresponding 1,4-hydroquinones in organic solvents led to the epimeric chromenes described in this paragraph.

Two chromenos were isolated as minor compounds from Desmarestia menziesii collected from the Antarctic King George Island, one bearing a hydroxy group at C-13’ (99) and the other a carboxy group at C-13’ (100). The latter is a structural isomer of δ-sargachromenol (51) (see below) and shares structural similarity with garcinoic acid (30). Again, no optical activity was found for the two chromenos suggesting an epimeric center at C-2. However, the authors suggested a non-enzymatic ring closure within the living algae since no corresponding 1,4-benzoquinone was found as a potential precursor. A C-15’-aldehyde-bearing chromenol (101) with anti-leishmanial activity was found as minor compound in the...
| Compound | Isolated from | Cell line/organism | Effective concentration | Reference |
|----------|---------------|--------------------|-------------------------|-----------|
| **Meroditerpenes** | | | | |
| α-Tocopherol (3) | Plant oils | HepG2 cells, MDA-MB-231, MCF7 cells | >100 μM | 39 |
| γ-Tocopherol (5) | Plant oils | Jurkat, HBTII, MCF7, MCF7-C3 cells | Not achieved | 281 |
| δ-Tocopherol (6) | Plant oils | Jurkat, HBTII, MCF7, MCF7-C3 cells | >50 μM | 267 |
| α-Tocotrienol (14) | Palm oil | MDA-MB-435, MCF7, B16 cells | IC50: 210 μM, 14 μM, 110 μM | 25,273 |
| | | MDA-MB-231, MCF7 cells | IC50: 24 μM, 26 μM | 281 |
| | | Jurkat, HBTII, MCF7, MCF7-C3 cells | ~50%, 35%, 30%, 35% at 50 μM | 267 |
| δ-Tocotrienol (17) | | | | |
| Sargachromanol E (Crassumtocopherol B (Crassumtocopherol A (134)) | Plant oils | SKBR3 cells, BT474 cells | IC50: 11 μM, 15.6 μM | 281 |
| | | | IC50: 4.1 μM, 4.4 μM | 275 |
| | | | | |
| Sargax (95) | *Sypodium flabeliorme* | Human epithelial gastric cells | IC50: 12 μM | 103 |
| | | Human fibroblasts | | |
| Desmethyltocotrienol (18) (P25-tocotrienol) | Rice bran | P338 leukemia cells | EC50: 52 μM | 120 |
| | | | IC50 > 1 μM | 24 |
| Didemethyltocotrienol (19) (P26-tocotrienol) | | | | |
| 13'-Carboxy-δ-tocopherol (229) | Semisynthetic from *Garcinia kola, human metabolites* | Glioma C6 cells | n.d. | 38 |
| | | HepG2 cells | EC50: 6.3 μM (δ-13-COOH) | 39 |
| | | THP-1 macrophages | EC50: 11.1 μM (δ-13-COOH) | 277 |
| | | HCT-116 cells | EC50: 8.9 μM (δ-13-COOH) | 257 |
| | | HT-29 | EC50: 8.9 μM (δ-13-COOH) | 257 |
| 13'-Hydroxy-α-tocopherol (204) | | | | |
| | | HepG2 cells | EC50 > 100 μM | 39 |
| | | THP-1 macrophages | EC50 > 100 μM | 277 |
| 13'-Carboxy-α-tocopherol (205) | | | | |
| | | HepG2 cells | EC50: 13.5 μM (α-13-COOH) | 39 |
| | | THP-1 macrophages | EC50: 7.4 μM (α-13-COOH) | 277 |
| δ-Garcinoic acid (30) | *Garcinia kola* | Glioma C6 cells | EC50: 10 μM | 38 |
| | | RAW264.7 macrophages | EC50: 5.5 μM | 255 |
| | | HCT-116 cells | EC50: 16 μM (δ-garcinoic acid) | 257 |
| | | HT-29 | EC50: 17 μM (δ-garcinoic acid) | 257 |
| | | | Inhibition of DNA polymerase β | | 47 |
| δ-Sargachromenol (51) | *Sargassum sagamiamum* | Caspase-3 induced apoptosis in HaCaT cells | IC50: 4 μM | EC50: 11.8 μM | 126 |
| Fallachromenoic acid (105) | *Sargassum falax* | P338 leukemia cells | IC50 > 27–29 μM | 133 |
| | | | Effective at 25 nM and 2.5 μM | 43 |
| δ-Amplexichromanol (35) | *Garcinia amplexicalis* | Antiangiogenicity in VEGF-induced HUVECs | | |
| | | | | |
| γ-Amplexichromanol (36) | | | | |
| | | | | |
| Lichhtocotrien A-G (41–47) | *Litchi chinensis* | HepG2 cells | IC50: 11.1 (A), 14.2 (B), 22.7 (C), 10.7 (E), 12.3 (F), 34.1 (G) μM | 49 |
| | | | IC50: 10.9 (A), 32 (B), 24.2 (C), 26.8 (D), 27.4 (E), 49.2 (G) μM | |
| | | | | |
| Crassumtocopherol A (134) | *Lobophytum crissum* | P338 leukemia cells | IC50: 6.7 μM | 169 |
| | | | IC50: 5.2 μM | |
| Crassumtocopherol B (135) | | | | |
| Sargachromanol E (58) | *Sargassum siliquastrum* | Cytotoxicity in HT-29 cells | IC50: 7.5 μM | 82 |
| | | | Caspase-3 induced apoptosis in promyelocytic HL-60 leukemia cells | | |
| | | | | |
| Sargatriol (98) | *Sargassum tortile* | P-338 leukemia cells | EC50: 42 μM | 118 |
| Sargadiol-I (96) | | | EC50: 34 μM | 120 |
| Sargadiol-II (97) | | | EC50: 41 μM | |
| Sargadiol I (96) | | | | |
| Epitaondiol (79) *cyclic* | *Sypodium flabeliorme* | Human epithelial gastric cells | IC50: 29 μM | 103 |
| | | Human fibroblasts | IC50: 19 μM | |
| | | RAW 264.7 | IC50: 12.7 μM | 100 |
| | | | | |
| Isoepitaondiol (78) *cyclic* | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
Table 2  (Contd.)

| Compound                                      | Isolated from              | Cell line/organism                  | Effective concentration | Reference |
|------------------------------------------------|----------------------------|-------------------------------------|-------------------------|-----------|
| Macrolithecotrienol A (48) cyclic              | *Litchi chinensis*         | HepG2 cells                         | IC₅₀: 16.5 μM           | 49        |
| Cystosierol A (86) cyclic                      | *Cystoseira mediterranea*  | Crown-gall potato bioassay          | 73% tumor inhibition at 10⁻² M | 110      |
| Demethoxy cystoketal chromane (89) cyclic      | *Cystoseira amentacea*     | Cytotoxicity in HepG2 cells         | IC₅₀: 35 μM             | 113      |
| Strongylophorine 2 (117) cyclic                | *Cystoseira tamariscifolia*| Cytotoxicity in HeLa cells          | IC₅₀: >100 μM           | 163      |
| Strongylophorine 3 (118)                       | *Petrosia corticata*       |                                     |                         |           |
| Strongylophorine 4 (119)                       |                            |                                     |                         |           |
| Strongylophorine 22 (128)                      |                            |                                     |                         |           |
| Strongylophorine 23 (129)                      |                            |                                     |                         |           |
| Strongylophorine 24 (130)                      |                            |                                     |                         |           |
| *All cyclic*                                   |                            |                                     |                         |           |
| Merosesquiterpenes                             |                            |                                     |                         |           |
| Riccardiphenol C (146) cyclic                  | *Riccardia crassa*         | P338 leukemia cells                 | IC₅₀: > 80 μM           | 177      |
| Aureol (155) cyclic                            | *Smenospongia aurea*       | A549, HT-29, EL-4                    | IC₅₀: 13.6 μM           | 189      |
| Panicein A2 (160) cyclic                       | *Reniera mucosa*           | P388, A549, MEL20, HT29             | EC₅₀: 14.8 μM           | 195      |
| Panicein F2 (161) cyclic                       |                            |                                     | EC₅₀: 14.2 μM           |           |
| Monoterpenes                                   |                            |                                     |                         |           |
| Cordiachromene A (173)                         | *Aplidium antilense*       | Human carcinoma KB                  | EC₅₀: 14.3 μM           | 212      |
|                                               |                            | Murine leukaemic P388                | EC₅₀: 20.5 μM           |           |
|                                               |                            | Lymphoblastic leukemia CEM-WT cells  | IC₅₀: 30 μM             | 213      |
| Didehydroconicol (185)                         | *Aplidium aff. densum*     | Lymphoblastic leukemia CEM-WT cells  | IC₅₀: > 10 μM           | 213      |
| Epiconicol (184)                               |                            |                                     | IC₅₀: 60 mM             | 218      |
| Didehydroconicol (185)                         | *Aplidium aff. densum*     | Sea urchin eggs of *P. luidus* and *S. granularis* | IC₅₀: >25 μM and 9.8 μM | 220      |
| Epiconicol (184)                               |                            |                                     | IC₅₀: >11.3 μM and >25 μM |           |
| Chaetopyranin (188)                            | *Chaetomium globosum*      | HMEC, SMMC-7721, A549               | IC₅₀: 49 μM, 90 μM, 124 μM | 220      |
| 2-CEHC (208)                                   |                            |                                     | Growth inhibition at 50 μM | 282      |
| γ-CEHC (233)                                   |                            |                                     | 42% (γ), 83% (γ)       |           |
|                                               |                            |                                     | 34% (γ), 58% (γ)       |           |
|                                               |                            |                                     | 9% (β), 19% (γ)       |           |
| Sargasal-I (176)                               | *Sargassum tortile*        | P-338 leukemia cells                 | EC₅₀: 20.3 μM           | 118      |
| Sargasal-II (177)                              |                            |                                     | EC₅₀: 21 μM             | 120      |
| Hemiterpenes                                   |                            |                                     |                         |           |
| Mollugin (189)                                 | *Rubica cordifolia*        | MCF-7/adriamycin                     | IC₅₀ of doxorubicin decreased from 60 to 7.5 μg ml⁻¹ at 10 μM mollugin | 226      |

Abbreviation: human gastric adenocarcinoma cells (AGS), human microvascular endothelial cells (HMEC), hepatocellular carcinoma cells (SMMC-7721), human lung epithelial cells (A549), human hepatocellular carcinoma cells (HepG2), B16 melanoma cells, vascular endothelial growth factor (VEGF), human umbilical vein endothelial cells (HUVEC). *Estimated from original publication. † For better comparison μg ml⁻¹ were converted to μM.

Southern Australian brown alga *Sargassum paradoxax* and the Japanese algae *Sargassum yamadae.*

δ-Sargachromenol is one the most investigated meroditerpenoid obtained from marine organisms. As mentioned above, its unique structure resembles a δ-chromenol ring system with an unsaturated side chain containing a carbonyl group at C-15. δ-Sargachromenol is widely distributed in *Sargassum* species such as *Sargassum sagamianum,* *Sargassum serratifolium,* *Sargassum micracanthum,* *Sargassum horneri,* *Sargassum macrocarpum,* and *Sargassum fallax.* The latter species contains δ-sargachromenol as high as 0.13% of the dry weight. It has also been isolated from *Myagropsis myagroides* (Sargassaceae), from the tunicate *Botryllus tuberatus* and other algae. Kusumi *et al.* claimed 51 to be an artefact that is produced from sargauquinic acid during the clean-up procedure. Although there is an asymmetric carbon center at C-2, the authors found no optical rotation. Literature data on the stereochemistry of sargachromenol are inconsistent. δ-Sargachromenol isolated from plant species showed optical
rotation with an $[\alpha]_D$ of $+5^\circ$, whereas $\delta$-sargachromenol isolated from *Sargassum fallax* showed an $[\alpha]_D$ of $-23.7^\circ$. Choi *et al.* isolated a racemic mixture from *Botryllus tuberatus* and separated $\delta$-sargachromenol stereoisomers by chiral HPLC coupled with circular dichroism spectroscopy. They determined the absolute configuration for $R$-sargachromenol with an $[\alpha]_D$ of $-68^\circ$ and $S$-sargachromenol with an $[\alpha]_D$ of $+88^\circ$. It is yet not clear whether sargachromenol should be considered as an artefact of the work-up procedure or as a natural product.

Sargachromenol received attention in drug research since it has inhibitory activity against enzymes related to Alzheimer’s disease, strong anti-inflammatory activity and anti-hyperproliferative properties in skin cells (Tables 1–3). Several patents are pending on the use of sargachromenol as drug candidate.

Choi *et al.* found acetylcholinesterase- and butyrylcholinesterase-inhibitory activity with IC$_{50}$ values of 32.7 and 7.3 $\mu$M, respectively. Recently, Seong *et al.* repeated the enzyme assays and determined slightly higher IC$_{50}$ values (97.3 and 9.4 $\mu$M, respectively) for these enzymes. In addition, the authors found that 51 is a non-peptidic, noncompetitive inhibitor of $\beta$-site amyloid precursor protein-cleaving enzyme 1 (BACE1) with an IC$_{50}$ value of 7.0 $\mu$M and a $K_i$ value of 2.9 $\mu$M. Molecular docking experiments revealed that sargachromenol interacts with the allosteric side of BACE1. In line with these results, sargachromenol promotes neurite outgrowth and survival of rat PC12D pheochromocytoma cells via activating phosphatidylinositol-3 kinase. Based on its lipid-solubility and low molecular weight (<500 Dalton), sargachromenol should be able to cross the blood brain barrier, making $\delta$-sargachromenol an interesting drug candidate for treating Alzheimer’s disease and other neurodegenerative diseases.

Similar to $\delta$-garcinoic acid, sargachromenol is a potent anti-inflammatory compound that prevented TPA-induced ear edema in mice with an IC$_{50}$ value of 0.36 mg per ear. In addition, $\delta$-sargachromenol inhibits lipoxygenase (LOX) (76% at 100 ppm) and cyclooxygenase (COX)-1 and -2 (98% and 84% at 100 ppm; Table 1). Sargachromenol inhibited LPS-induced inflammation markers in murine RAW 264.7 macrophages. Production of PGE$_2$ and nitric oxide was inhibited (IC$_{50}$ values of 30.2 and 82 $\mu$M, respectively) accompanied by a reduced protein expression of iNOS and COX-2. Kim *et al.* reported the inhibition of nitric oxide formation in LPS-stimulated murine microglial BV-2 cells with an EC$_{50}$ value of 1.14 $\mu$g ml$^{-1}$ (2.7 $\mu$M). These effects are accompanied by a suppression of the

---

**Fig. 11** Structures of mediterraneols (82 to 84), cystophloroketal E (85), cystoseirols (86 to 88), chromanes (90 to 92), (94) and cystoseirone (93) from *Cystoseira* species. Bifurcarenone (81) as the common biosynthetic precursor is depicted in the center of the figure.
Table 3: Miscellaneous biological activities of chromanols and chromenols\textsuperscript{a}

| Compound                        | Activity                               | Species                          | Effective concentration                      | reference |
|---------------------------------|----------------------------------------|----------------------------------|---------------------------------------------|-----------|
| Meroditerpenes                  |                                        |                                  |                                             |           |
| \(\gamma\)-Dehydrotocopherol (12) | Proliferation, wound healing           | Chicken                          | Reduction of total cholesterol (mmol L\(^{-1}\)) vs. control diet: 26% and 31% | 21        |
| Desmethyltocotrienol (18)       | Hypocholesteremic activity             | Chicken                          | Reduction of LDL cholesterol (mmol L\(^{-1}\)) vs. control diet: 41% and 48% | 24        |
| (\(P_{23}\)-tocotrienol)        |                                        |                                  |                                             |           |
| Didemethyltocotrienol (19)      |                                        |                                  |                                             |           |
| (\(P_{33}\)-tocotrienol)        |                                        |                                  |                                             |           |
| \(\delta\)-Garcinoic acid (30)  |                                        |                                  |                                             |           |
| Sargoliol (95)                  | Gastroprotective against HCl/ethanol-induced gastric lesions | In vitro                        | IC\(_{50}\): 3.6 \(\mu\)M, 6.0 \(\mu\)M, 4.6 \(\mu\)M, 7.0 \(\mu\)M | 78        |
| Taonidiol (76)                  |                                        |                                  |                                             |           |
| Sargachromanol D, F, H, L (57, 59, 61, 65) | Ion pump inhibitor Na\(^+\),K\(^+\)-ATPase | In vitro                        | IC\(_{50}\): 1.6 \(\mu\)M | 152       |
| Epitaonidiol (79)               | Anti-viral                             | HSV-1                            | EC\(_{50}\): 1.34 M                        | 98        |
| Strongylophorine 3 (118)        | Insecticidal activity                  | Spodoptera littoralis            | IC\(_{50}\): 60 ppm                        | 157       |
| Bifurcarenone chromane (94)     | Photoprotection                        | Human fibroblasts                | IC\(_{50}\): 5–20 \(\mu\)g ml\(^{-1}\)     | 116       |
| Bifurcarenone chromene (107)    | Anti-macroalgal                        | Sargassum muticum                | IC\(_{50}\): 2.5 \(\mu\)g ml\(^{-1}\)     | 143       |
| Sargadiol-I (96)                | Anthelmintic                           | Nippostrongylus brasiliensis     | EC\(_{50}\): 307 \(\mu\)g ml\(^{-1}\)     | 123       |
| 11',12'-dihydroxy-3,4-dehydro-\(\delta\)-tocotrienol (102) | Inhibition of bone resorption         | Osteoclast-like cells (OCLs)     | IC\(_{50}\): ~8 \(\mu\)M\(^{6}\)         | 59        |
| 11',12'-dihydroxy-3,4-dehydro-\(\delta\)-tocotrienol (102) | Ion pump inhibitor Na\(^+\),K\(^+\)-ATPase | Heterosigma akashiwo             | Mean mortality after 4h at 1 \(\mu\)g ml\(^{-1}\): 78% | 182       |
| Sarcocromenol sulfate A (110)   |                                        | Chattonella antiqua               |                                             |           |
|                                |                                        | Heterocapsa                      |                                             |           |
|                                |                                        | circularisquama                  |                                             |           |
| Merosesquiterpenes              |                                        |                                  |                                             |           |
| Chromazonarol (154)             | Algicidal activity                     | Chattonella antiqua              |                                             | 78%       |
|                                |                                        | Heterocapsa                      |                                             | 42%       |
|                                |                                        | circularisquama                  |                                             | 93%       |
| Monoterpenes                    |                                        |                                  |                                             |           |
| Cordiachromene A (173)          | Anti-bacterial                         | Staphylococcus aureus            | 2–64 \(\mu\)g ml\(^{-1}\)                 | 212       |
|                                |                                        | Streptococcus faecalis           | 1–64 \(\mu\)g ml\(^{-1}\)                 | 213       |
|                                |                                        | Escherichia coli                 | MIC > 2 mmol                              |           |
|                                |                                        | Micrococcus luteus               | MIC > 0.51 mmol                           | 213       |
|                                |                                        | Escherichia coli, Micrococcus luteus | MIC > 2 mmol, MIC > 0.51 mmol          | 213       |
|                                |                                        | Cossackievirus                   | 6.8 \(\mu\)M                              |           |
|                                |                                        | Osteoelast-like cells (OCLs)     | IC\(_{50}\): 1.6 \(\mu\)M\(^{6}\)        | 59        |
|                                |                                        | Mean mortality after 4h at 1 \(\mu\)g ml\(^{-1}\): 78% | 182       |
|                                |                                        |                                               |                                             |           |
| Hemiterpenes                    |                                        |                                  |                                             |           |
| Precocere 2 (194)               | Anti juvenile hormone                  | Induction of precocious metamorphosis in milkweed bug | 0.7 \(\mu\)g cm\(^{-2}\) 90% precocious adults | 230       |
| Daedalin A (199)                | Inhibition of melanin synthesis        | Tyrosinase inhibition            | IC\(_{50}\): 194 \(\mu\)M                  | 234       |

\textsuperscript{a} Abbreviations: herpes simplex virus 1 and 2 (HSV-1 and -2), minimum concentration that inhibits (MIC) bacterial growth, 2-aminoanthracene (2AN), ethyl methanesulfonate (EMS). \textsuperscript{b} Estimated from original publication.
release of TNF-α, IL-1β, and IL-6.134 Several markers of vascular inflammation were also decreased in primary endothelial cells by δ-sargachromenol, namely TNF-α induced ICAM-1 and VCAM-1 expression, adhesion of monocytes to HUVEC and decreased production of monocyte chemoattractant protein-1 and matrix metalloproteinase-9 (MMP-9).128 Both epimers of sargachromenol bind to human farnesoid X receptor and inhibit its transactivation (IC50 values of 9.0 μM (R-epimer) and 17.0 μM (S-epimer), respectively). It is known that farnesoid X receptor agonists decrease plasma triacylglycerides and increase HDL cholesterol by regulating the expression of apolipoprotein C-I and C-IV.135 Summarizing the evidence (also from plant species), δ-sargachromenol (51) clearly is a candidate for an anti-atherogenic drug.

Sargachromenol has also been suggested as a drug for skin health, since it induced apoptosis in hyperproliferative human keratinocyte HaCaT cells and suppressed MMP-1, -2 and -9.126,130 Finally, insecticidal activity was found against the larvae of Spodoptera frugiperda with a LD50 value of 2.94 mg l−1.136

Iwashima et al. synthesized a dihydroxylation product of sargachromenol from the corresponding plastoquinone precursor that had been isolated from Sargassum micracanthum.58 To the best of our knowledge, 11′,12′-dihydroxy-sargachromenol (102) (Fig. 13) has never been isolated as a natural product from algae before. However, the compound has been investigated for its anti-viral activity against human cytomegalovirus,156,157 its anti-ulcer activity in ethanol-induced gastric lesions in rats,158 and inhibitory activity in osteoclastogenesis (bone resorption), thus suggesting that this compound is an interesting pharmacological lead structure.59

Multiple biosynthetic oxidation steps lead to a highly oxidized chromane (103), which was found in Halidrys siliquosa (Sargassaceae) from the French Atlantic coast.159 Two keto groups at positions C-2′ and C-10′ and a hydroxyl group at C-9′ with R-configuration could be assigned by two-dimensional NMR spectroscopy.

Natural derivatives of δ-sargachromenol 52 have been isolated from different algae species. Besides δ-sargachromenol, sargohanthen B (104), a sargachromenol with two additional hydroxy groups at C-11′ and C-12′, was isolated as a minor compound from Sargassum thunbergii, collected from the shore of the Korean Youngdo Island.66,140 Fallachromenoic acid (105) from the Australian alga Sargassum fallax is an interesting variation as it bears a chlorine atom at C-11′ and a terminal double bond (Fig. 13).133,141 Fallachromenoic acid was isolated in 0.06% yield (dry mass) and exhibited moderate anti-tumor activity in the murine leukemia P388 cell assay (IC50 value of 29 μM).

Along with the sargachromanols described by Jang et al.,76 mojabanchromanol (106) has been isolated from Sargassum siliquastrum,142 showing a rearranged carbon skeleton at C-3′ of the side chain.

Only two chromenols with cyclic side chain modifications were found in the literature. A 3,4-unsaturated analogue of bifurcarenone chromane (107) was identified in Cystoseira amentacea collected from the French Riviera and an unsaturated analogue of compound 107 from Cystoseira baccata.143

3.3.2 Phytoplankton (green algae, cyanobacteria, phytoflagellates). Green algae, cyanobacteria, phytoflagellates and other microalgae are members of the phytoplankton that produces α-tocopherol, which is essential for higher marine organisms. In addition, spirulina (Arthrospira platensis) is nowadays used in human nutrition as a food supplement. A screening of microalgae for α-tocopherol content reported various amounts starting from 58.2 μg g−1 (dry weight) for Isochrysis galbana up to 669 μg g−1 (dry weight) for Chlorella stigmatophora.144 The amount of α-tocopherol in spirulina varied between 5 and 14 μg g−1 dried spirulina.145 As a subject of culture conditions, the phytoflagellate Euglena gracilis Z produces high amounts of α-tocopherol and -tocotrienol (7 mg g−1 and 2.6 mg g−1 dry weight, respectively).146

As reported by Yamamoto et al., cold water fish contains a substantial amount of marine-derived tocopherol (25) (MDT),
an \( \alpha \)-tocomonoenol with a terminal double bond between C-12' and C-13' (Fig. 14). Since tocochromanols are only synthesized by photoactive organisms, the authors suggested a dietary source for MDT in fish. In fact, phytoplankton contains up to 21% (of total tocopherol) MDT. Also Antarctic krill (\textit{Euphausia superba}) contains up to 8% (of total tocopherols) MDT. The biosynthesis of \ref{25} is largely unknown; however, the authors suggested that the terminal double bond is introduced by side chain desaturation of \( \alpha \)-tocopherol, similar to that of fatty acids.

Recently, an unusual \( \alpha \)-tocopheroid, \( \alpha \)-tocoxylenoxy (\ref{108}), containing a 3,5-dimethylphenoxyl moiety was isolated from the seaweed \textit{Caulerpa racemosa}, taxonomically also belonging to the green algae (\textit{Chlorophyta}).

### 3.3.3 Invertebrates (sponges, Ascidiae, soft corals)
Sponges or \textit{Porifera} comprise a group of more than 9000 species. In the last decades, sponges have attracted scientists to investigate the diversity of natural products and their properties. From a chemotaxonomic point of view, it is worth to note that some of the structures found in sponges that contain a chromene core lacking the typical methylation pattern. These sarcochromenols and the group of strongylophorines possess the highest structural variability in the organisms presented in this review.
A hypothetic biosynthetic precursor of the chromene structure was found in the Western Australian sponge *Fasciospongia* species (order of Dictyoceratida, family of Thorectidae).\(^{153}\) Fascioquinol F (109) is a demethylated 3,4-dehydro-tocotrienol that might undergo cyclization to form complex ring systems in analogy to taondiols (see the section on Brown algae). The structure is similar to sargal (95), but lacks the methyl group at C-8 (Fig. 14). Fascioquinol F revealed moderate antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (IC\(_{50}\) values of 13 and 30 mM, respectively).

Sarcochromenols A (110), B (111) and C (112) are a group of long-chain tocopherenols with five, six and seven isoprene units, respectively (Fig. 14). They were isolated from the Pacific Ocean sponge *Sarcotragus spinulosus* (Schmidt) (family of Thorectidae) and showed Na\(^+\)/K\(^-\)-ATPase inhibitory activity similar to that of the sargachromanols D, F, H and L (IC\(_{50}\) value for sarcochromenol A of 1.6 mM).\(^{78,152}\) The compounds have also been isolated from the Indian sponge *Ircinia fasciculate* (Spargillidae).\(^{153}\) In addition, an un-sulfated form of sarcaol A was isolated in 0.1% yield.

A screening for selective human 15-LOX inhibitors from an extract of the Papua New Guinean sponge *Psammocinia* (order of Dictyoceratida, family of Irciniidae) revealed chromarols A to D (113 to 116; Fig. 15). The IC\(_{50}\) values for chromarols A to D were 0.6, 4.0, 0.7 and 1.1 mM, respectively. The authors found high selectivity since the IC\(_{50}\) values for 12-LOX were above 100 mM. The biosynthesis of the cyclohexene ring system in the side chain of chromarols presumably derives from an acid-catalyzed cyclization.

Several sponges produce a group of eight polycyclic strongylophorines that resemble taondiol structural motives (Fig. 16). They contain a demethylated aromatic ring and modifications at the methyl groups at C-13' and/or C-15'. They were discovered by Braekman et al. because of their ichthyotoxic activity.\(^{155}\) The biosynthesis follows that of taondiol and is an enzyme-catalyzed cyclization cascade (see Fig. 10). Strongylophorines 2 (117), 3 (118), 4 (119), and 5 (120) were isolated from *Strongylophora durissima* from Maricabiin Island, Philippines,\(^{156}\) and a different, as yet undescribed *Strongylophora* species from Ilocos Sur, Philippines.\(^{157}\) These molecules contain a cyclic lactone, a carboxy, an aldehyde or a hydroxy group moiety at C-13', respectively. Strongylophorine 3, bearing a terminal carboxy group, was isolated with 0.1% yield (dry weight).\(^{156}\) Furthermore, the known strongylophorines 3, 9 (121) and 11 (122) were isolated from a Taiwanese species of *Strongylophora durissima*. The 6-methoxy (121) and 6-acetyl (122) derivatives are structurally related to strongylophorine 2, which contains a cyclic lactone moiety.\(^{158}\) Liu et al. isolated the strongylophorines 15 (268) and 16 (265) (124), respectively, from the Okinawan sponge *Strongylophora strongylata* as epimers at the hemiacetal carbon.\(^{159}\) Biosynthetic O-methylation and O-ethylation gave the acetals 26-O-methoxystrongylophorine 16 (125) and 26-O-ethoxystrongylophorine 16 (126), respectively.\(^{160,161}\) Noda et al. found a mixture of strongylophorines 15 and 16 to be strong inhibitors of the proteasome with IC\(_{50}\) values of 3.6 mM.\(^{162}\) The same study compared the proteasome-inhibitory activity of structurally related strongylophorines and found the following order: hemiacetal > acetal > carboxy > lactone > no modification.

On their search for inhibitors of protein tyrosine phosphatase 1B, an enzyme that plays a crucial role in the regulation of insulin and leptin signalling, Lee et al. found inhibitory activity for 125, 117, 118, 123, and strongylophorine 17 (127) with IC\(_{50}\) values of 8.5, 24.4, 9.0, 11.9, and 14.8 mM, respectively.\(^{163}\) Strongylophorines 2 and 3 also inhibited hypoxia-inducible factor-1-dependent luciferase expression in engineered U251-HRE glioma cells with IC\(_{50}\) values of 8 and 13 mM.\(^{162}\) Strongylophorines 22 (128), 23 (129), 24 (130), and 17 (127) were isolated from the Okinawan sponge *Petrosia corticata* and displayed moderate cytotoxic activity against human cervical carcinoma epithelial (HeLa) cells (Table 2).\(^{164}\) All strongylophorines exhibited ichthyotoxic, insecticidal, anti-bacterial, fungicidal, and cytotoxic properties. Strongylophorine 22 and fascioquinol D are epimers at C-2 and were isolated from *Fasciospongia sp.*\(^{165}\) The latter compounds displayed anti-microbial activity against *Staphylococcus aureus* and *Bacillus subtilis* with IC\(_{50}\) values of 25 and 2.3 mM (for strongylophorine 22) and 7.8 and 2.8 mM (for fascioquinol D), respectively.

---

**Fig. 15** Structures of chromarols (113 to 116) from *Psammocinia* species.
Recently, Yu et al. presented the first semi-synthesis of strongylophorine 2 starting from isocupressic acid.\textsuperscript{164}

### 3.3.4 Ascidiaea/tunicates.

Ascidians, tunicates or sea squirts belong to a group of more than 3000 species, most of them not investigated in terms of bioactive metabolites. In a recent review, Palanisamy et al. described almost 600 chemical structures found in tunicates.\textsuperscript{165} Here, we describe meroditerpenes, such as an epimeric mixture of R- and S-sargachromenol and two epimeric chromenes called tuberatolide B and 2'-epi-tuberatolide B (131), obtained from the tunicate Botryllus tuberatus.\textsuperscript{135} Tuberatolide B contains a γ-lactone moiety within the side chain that presumably derives from a C-15'-carboxy, C-6'-hydroxy-precursor (Fig. 17). Both tuberatolides were strong farnesoid X receptor agonists with IC\textsubscript{50} values of 1.5 and 2.5 μM, respectively.\textsuperscript{135}

### 3.3.5 Soft corals.

Soft corals (Alcyonacea) belong to the class of Anthozoa and compromise approximately 800 species living mostly in warm seawater. In recent years, the number of new metabolites discovered from soft corals was estimated to represent 22% of the total new marine natural products.\textsuperscript{166} Many metabolites showed anti-tumor, anti-viral, anti-fouling and anti-inflammatory activities (reviewed in (ref. 167)).

Bowden et al. isolated tocotrichromenol (132), an isomer of sargaol (95), and its dihydro derivative (133) from an unknown Australian Nephthea species.\textsuperscript{168} The precursor quinone was also isolated, but did not convert into the chromenol under the work-up conditions; however, no optical activity was found at C-2.

Two α-tocopherol derivatives with three hydroxyl groups at C-8', C-11', and C-12', respectively, were isolated from Lobophytum
crissum (Fig. 17). Crassumtochopherol A (134) (R=H) and B (135) (R=acetyl) showed moderate cytotoxicity against murine P-388 leukemia cells with IC<sub>50</sub> values of 6.7 and 5.2 μM, respectively. Compound 135 also showed cytotoxicity against the human colon adenoma cell line HT-29 with an IC<sub>50</sub> value of 7.5 μM.

4. Merosesquiterpenes

4.1 Plants

The biosynthesis of chroma(e)nols with sesqui-, mono- and hemiterpene moieties within the plant kingdom is only poorly understood. These molecules most likely derive from homogentisate condensed with farnesyl-, geranyl- and isoprenylphosphates, respectively.

Oligandrol (136), a sesquiterpenechromane with an unsaturated side chain, was isolated together with methoxy-oligandrol (137) from the bark of the Australian tree Beilschmiedia oligandra (Lauraceae),<sup>178</sup> and from the leaves of the genus Pseudowaria indochninensis Merr, an Annonaceae variety from the Yunnan province in China (Fig. 18).<sup>171</sup> Cytotoxic assessment revealed no activity against promyelocytic HL-60 leukemia cells and human SMMC-7721 hepatocarcinoma cells.<sup>171</sup>

The methoxy-derivative of dehydrooligandrol (138) was obtained from the root of Beilschmiedia erythrophyloia<sup>272</sup> and the free dehydrooligandrol (139) from the leaves of Seseli farreynii (Umbelliferae). However, the latter was suggested to be an artefact from the work-up procedure.<sup>272</sup> Zhao et al. isolated a dehydrooligandrol with a terminal (Z)-carboxy and a 13’-hydroxy group, respectively, which the authors named pseudindochin (140).<sup>171</sup>

Polycerasoidol (141), an oligandrol derivative with a terminal (Z)-carboxy-group and its 6-methoxy-derivative polycerasoidin (142) were found in the stem bark of the Papua New Guinean <i>Polyalthia cerasoides</i>.<sup>174</sup> Later, the methyl ester of polycerasoidin (143) and the E-isomer of polycerasoidol, termed isopolycerasoidol (144), were identified in the same species.<sup>175</sup>

Polycerasoidol was isolated at 0.13% yield (dry weight). Polyalthidin (145), a structural isomer of polycerasoidin with a double bond shift from C-7’–C-8’ to C-6’–C-7’ was isolated from <i>P. cerasoides</i> at a yield of 0.09% (Fig. 18).<sup>176</sup> Polycerasoidol, polycerasoidol and polyalthidin were found to be inhibitors of the mitochondrial electron transfer chain that block NADPH oxidase activity with IC<sub>50</sub> values of 37, 11 and 4.4 μM, respectively.<sup>176</sup>

Riccardiphenol C (146), a sesquiterpene from the New Zealand liverwort <i>Riccardia crassa</i>, is an example of a chromanol that undergoes intramolecular cyclization to form a condensed ring system. Purification of the crude extract yielded riccardiphenol C in 4 mg g<sup>–1</sup> of dry liverwort (Fig. 18). The compound showed cytotoxicity against African green monkey BSC-1 kidney cells and inhibited the growth of <i>Bacillus subtilis</i>.<sup>177</sup>

4.2 Fungi

A sesquiterpene chromene (147) with a truncated tocochromene-like structure was isolated from <i>Chroogomphus rutulus</i>.<sup>178</sup> The mushroom is also known as brown simecap and lives ectomycorrhizally with <i>Pinus</i> species. The compound shows R-configuration at the chiral center C-2 (Fig. 19).

Polycyclic sesquiterpenes were isolated from the fruiting bodies of the tropical rot fungus <i>Ganoderma cochlear</i>.<sup>179</sup> Ganocin A to C (148–150) possess a spiro[4,5]decane ring, and ganocin D (151) has an eight-membered ring system. As a biosynthetic key step, the authors suggest a Diels–Alder reaction of fornicin C to build up the polycycles. In the same fungus, Dou et al. found cochlearol B (152) with an unusual 4/5/6/6/6 polycyclic ring system (Fig. 19). The compound is a strong inhibitor of the TGF-β/Smad signaling pathway.<sup>180</sup>

4.3 Marine organisms

4.3.1 Brown algae. Jang et al. described a series of meroderpenes, the sargachromanols (A to P), from <i>Sargassum siliquastrum</i>. Sargachromanols A, B and S possess a sesquiterpene skeleton with a terminal aldehyde- (sargachromanol A) (54), alcohol- (sargachromanol B) (55) or carboxy-function (sargachromanol S) (72), respectively.<sup>76–78</sup> All compounds were assigned R-configuration at C-2 (Fig. 20).

Dictyochromenol (153) and its cyclization product chromazonarol (154) were both isolated from the Japanese brown alga <i>Dicyopteris undulata</i>.<sup>181–183</sup> Dictyochromenol is comprised of a demethylated chromanol ring which is attached to an unsaturated sesquiterpene moiety. A chemical synthesis route of dictyochromenol was described by Aoki et al..<sup>184,185</sup> Kurata et al. suggested an acid-catalyzed cyclization of farnesyl hydroquinone towards zonarol (1,4-hydroquinone) followed by a second acid-catalyzed formation of the epimeric center at C-2 of chromazonarol (Fig. 20).<sup>186</sup> Chromazonarol showed algicidal activity towards <i>Heterosigma</i> and <i>Chattonella</i> species.<sup>182</sup>
4.3.2 Sponges. A structural isomer of chromazonarol, aureol (155), and its 5-chloro-derivative (156) were isolated from the Caribbean sponge *Smenospongia aurea*.\(^{187,188}\) It has been suggested that aureol results from a rearrangement of the drimane skeleton of chromazonarol. Aureol showed moderate cytotoxic activity against several cell lines, such as human adenocarcinomic A549 alveolar basal epithelial cells, human colon adenocarcinoma HT-29 cells, and murine EL4 lymphoma cells with IC\(_{50}\) values of 13.6, 14.9 and 31.5 μM, respectively.\(^{189}\) In 2002, Nakamura *et al.* presented a chemical synthesis of aureol.\(^{190}\) Besides aureol, 2-epichromazonarol was isolated (2.2% dry weight) from *Smenospongia aurea*.\(^{187}\) Recently, a structurally related meroterpenoid, puupehenol (157), with potent antimicrobial properties was isolated from the Hawaiian sponge.
Dactylospongia sp. (Fig. 20). The authors suggested that the well-known puupehenone may be a work-up artefact of the natural precursor puupehenol.

Two epimeric sesquiterpene chromenols, named cyclorenierin A and B (158), were found in Haliclona sp., an Indo-Pacific sponge from Vanuatu.

The biosynthesis of the cyclohexenone ring system seems to follow that of walsurol (Fig. 6). Panicein B2 (159) bears a chromene ring and an aromatic ring system in the side chain (Fig. 21). It was first isolated by Cimino et al. from Haliclona panacea and later from the Mediterranean sponge Reniera fulva.192 Panicein B2 was also found in Reniera mucosa along with panicein A2 (160) and F2 (161).193,194 It has been suggested that the aromatic group of the side chain is formed from cyclorenierin A/B by a 1,2-methyl migration and subsequent oxidation.193 All paniceins show racemic carbon centers at C-2 suggesting that these compounds may be artefacts from the work-up procedure.

Faulkner et al. isolated a series of unusual ansa chromene macrocycles from Smenospongia sp., a sponge from the Seychelles.196 Smenochromes A to D (162-165) were isolated with 0.26% yield (dry weight) for A and 0.037% for B, C and D, respectively (Fig. 22). The compounds showed no optical activity and thus occurred as racemic mixtures. The structurally related likonides A (166) and B (167) were isolated from the Kenyan sponge Haytella sp. with 0.06 and 0.04% yield.197 The biosynthesis of ansa chromenes presumably starts from a farnesylated hydroquinone followed by alkylation at C-5 of the activated hydroquinone ring or alternatively by O-alkylation of the terminal double bond.197

4.3.3 Asciidae/tunicates. Longithorol E (168) was isolated as a minor metabolite from the Australian ascidian Aplidium longithorax (Fig. 22).198

4.3.4 Molluscs. There is emerging interest in the metabolites of marine nudibranchs. Since these animals completely lost their protective shell, the production or accumulation of toxins from their prey is used as defense systems.199 Two oligandrol-like structures (169) and (170) were isolated from Cratena peregrine, and a chromenol (171) with a C-6 ketone moiety was found in the frilled nudibranch Leminda millecra that is only found in South Africa (Fig. 23).

4.3.5 Soft corals. Although sesquiterpenes are widely distributed in soft corals, we only found sparse information on sesquiterpene chromanes and chromenes, respectively.200 Capillobenzopyranol (172) was isolated from the Australian soft coral Sinularia capillosa and showed moderate cytotoxicity against P-388 cells (ED50 values of 12.7 µM).202 Its quinone precursor has been isolated from Sinularia lochmodes.203 The compound with a terminal furanyl moiety showed in vitro anti-inflammatory activity against LPS-activation in murine RAW 264.7 macrophages. Protein expression of iNOS was inhibited by 36.7% at 10 µM concentration of 172 (Table 1), however expression of COX-2 was not affected.
5. Monoterpenes

Monoterpenes from plant origin have been used since ancient times to treat certain diseases, such as inflammation or cancer. De Sousa and colleagues summarized the anti-cancer and anti-inflammatory activities of monoterpenes in an outstanding recent review.\textsuperscript{204} The monoterpene cordiachromene A (173) was isolated from the heartwood of the tropical American tree Cordia alliodora (Boraginaceae) by Manners \textit{et al.}\textsuperscript{205} The authors proposed geranyl benzoquinol as the biogenic precursor of the compound. Interestingly, the woods of \textit{Cordia alliodora} are recognized for their durability in marine uses. Cordiachromene A was also

5.1 Plants

The monoterpene cordiachromene A (173) was isolated from the heartwood of the tropical American tree \textit{Cordia alliodora} (Boraginaceae) by Manners \textit{et al.}\textsuperscript{205} The authors proposed geranyl benzoquinol as the biogenic precursor of the compound. Interestingly, the woods of \textit{Cordia alliodora} are recognized for their durability in marine uses. Cordiachromene A was also
isolated from the extract of different tunicates and was further tested for its bioactivity (see section on Tunicates (5.2)).

As part of the investigation of *Garcinia amplexicaulis* (see section on Diterpenes), a short-chain chromane (175) with a truncated C-9 carbon skeleton was found (Fig. 24).

5.2 Marine organisms

5.2.1 Brown algae. Next to the large number of di- and sesqui-terpenes, only a few monoterpenes have been described in the literature. Numata *et al.* isolated side chain truncated aldehydes and named them sargasal-I (176) and sargasal-II (177), respectively (Fig. 24).71,120

**5.2.2 Green algae.** Cymopochromenol (178) was the first halogenated metabolite found in green algae. The 7-bromochromene was isolated from the Bermudan *Cymopolia barbata* as an optically inactive oil with 0.17% yield and also from Canary Island species with a yield of 0.02% dry weight.181,206 Later, Dorta *et al.* isolated two further chromenes, namely 3'- (179) and 4'-hydroxy-cymopochromenol (180), from the same source.207 Interestingly, both compounds showed optical activity with R-configuration at C-2. Two cyclic chromenes with two bromo atoms were isolated from *Cymopolia barbata* found in Puerto Rico.208 Cymobarbatol (181) and its epimer isocymobarbatol (182) showed anti-mutagenic activity. Debromo-isocymobarbatol (183) was isolated from *Cymopolia babata* (yield 0.2%, dry weight) collected at the Florida Keys and exhibited anti-feedant activity.209

**5.2.3 Ascidiacea/tunicates.** Targatt *et al.* first reported the occurrence of cordiachromene A (173) in the marine ascidian *Aplidium constellatum* found around the Georgian coast.210 Later, cordiachromene A was isolated from *Aplidium antillense* from Guadeloupe, *Aplidium aff. densum* from Masirah Island (Oman), Japanese *Aplidium multiplicatum* and *Aplidium conicum*, respectively.211–215 Cordiachromene A showed anti-inflammatory activity *in vitro* and *in vivo*.211,214,216 The compound reduced carrageenan-induced rat paw edema with an IC₅₀ of 18.9 μM and inhibited PGI₂ synthesis in arachidonic acid-stimulated peritoneal rat macrophages (IC₅₀ value of 8.2 μM).211,216 Sato *et al.* isolated cordiachromene A and 7-methoxy-cordiachromene A (174) from Japanese *Aplidium multiplicatum*...
and observed strong inhibitory activity against 15-LOX with IC\textsubscript{50} values of 0.82 \(\mu\text{M}\) and 1.9 \(\mu\text{M}\), respectively.\textsuperscript{218}

Cordiachromene A showed anti-bacterial activity against methicillin resistant \textit{Staphylococcus aureus} and \textit{Streptococcus faecalis},\textsuperscript{219} but weak activity against \textit{Micrococcus luteus} (the minimum inhibitory concentration was 0.51 mmol L\textsuperscript{-1}).\textsuperscript{219} Cytotoxic activity was found against a panel of cancer cell lines, such as murine leukemia P388 cells, human adenocarcinomic A549 alveolar basal epithelial cells, human colon adenocarcinoma HT-29 cells, and African green monkey CV-1 kidney fibroblasts, and drug-sensitive human leukemic lymphoblasts (IC\textsubscript{50} value of 30 \(\mu\text{M}\)).\textsuperscript{219,217}

So far, three cyclization products of cordiachromene A were found; conical (184), a mixture of C-3, C-4 epimers called epiconicol, and didehydroconicol (185) with a condensed aromatic ring system (Fig. 24).\textsuperscript{213,215,217,218} All compounds showed cytotoxic and weak anti-bacterial activity.

Two optically active cordiachromenes were isolated from the Australian tunicae \textit{Aptidium solidum}, one with an additional 2’–3’ double bond (186), the other with a saturated side chain and a 2’-ketone group (187; Fig. 25).\textsuperscript{219}

5.2.4 Marine algal-derived endophytic fungi. Chaetopyranin (188) with a C-7 skeleton was isolated from the marine red algal-derived endophytic fungus \textit{Chaetomium globosum} (Fig. 25).\textsuperscript{228} Biosynthetically, it may be generated from a meromonoepitropane and loss of two methyl groups or – more likely – from a derivative of flavoglucin, which is quite common in different fungi strains. The fungus was derived from the red alga \textit{Polysiphonia urceolata}. Chaetopyranin was cytotoxic against human microvascular endothelial cells, hepatocellular carcinoma cells (SMMC-7721) and human lung epithelial cells (A549) with IC\textsubscript{50} values of 15.4, 28.5 and 39.1 \(\mu\text{M}\), respectively.

6. Hemiterpenes

6.1 Plants

The following hemiterpenes exhibit interesting biological and pharmacological activities, among them mollugin (189) (methyl 2,2-dimethyl-6-hydroxy-2H-naphtho[1,2-b]pyran-5-carboxylat) from the Chinese medicinal plant \textit{Rubia cordifolia}. Biogenetically, mollugin was formed by a cyclisation of a prenylated naphthoquinone and is not related to the biosynthetic pathway of tocopherols (Fig. 2). Mollugin has been first reported by Schildknecht \textit{et al.} as a pigment from the rhizomes of \textit{Galium mollugo} and was further investigated for pharmacological effects, such as anti-platelet aggregation activity and anti-viral activity against hepatitis B virus.\textsuperscript{222} Mollugin has been shown to induce apoptosis in different types of cancer cells. It exhibited IC\textsubscript{50} values of 12.3 \(\mu\text{M}\), 23 \(\mu\text{M}\) and 60.2 \(\mu\text{M}\) on human colon cancer cells (Col2),\textsuperscript{221} human Jurkat T-cells\textsuperscript{224} and murine NIH 3T3-L1 preadipocytes,\textsuperscript{225} respectively. In the presence of 10 \(\mu\text{M}\) mollugin, a human multidrug-resistant breast cancer cell line (MCF-7/adr) was more susceptible to doxorubicin (IC\textsubscript{50} decreased from 60 to 7.5 \(\mu\text{g ml}^{-1}\)).\textsuperscript{226} Several patents describe the use of mollugin for different applications (Fig. 26).\textsuperscript{227}

Several low molecular weight chromenes, such as pterochromenes L1 (190), L2 (191) and L4 (192), were isolated from Taiwanese \textit{Pteris linginpinna}. 6-Hydroxyeupatoriochromene B (193) was obtained from \textit{Ageratina riparia} (Asteraceae) and finally, one of the first insect anti-juvenile hormones, precocene 2 (194) (6,7-dimethoxy-2,2-dimethylchromene) was found in \textit{Ageratum houstonianum} (Asteraceae).\textsuperscript{228} Lapacheno (195), a naphthaleine derivative, was isolated from the heartwoods \textit{Paratecoma peroba} and \textit{Tabebuia chrysantha} and \textit{Tabebuia heptaphylla}.\textsuperscript{211,212} 3-Hydroxy (196) and 3-,4-dihydroxy-chromanes (197) were isolated from a trunkwood extract of \textit{Tabebuia heptaphylla}.\textsuperscript{222}

Zhuang \textit{et al.} isolated illihenryipyranol A (198) from roots of \textit{Illicium henryi} in minor amounts.\textsuperscript{233}

6.2 Fungi

Deadalin A (199), also called quercinol, was independently discovered by Morimura \textit{et al.} and Gebhardt \textit{et al.} from the mycelial culture broth of \textit{Daedalea dickinsii} and \textit{Daedalea quercina}, respectively.\textsuperscript{234,235}

Later, 5-methoxy-deadalin A (200), 6-methoxy-deadalin A (201), and 9-deoxy-deadalin A (202) were isolated from \textit{Daedalea dickinsii} by Morimura and colleagues (Fig. 27).\textsuperscript{228} Deadalin A has been shown to have anti-tyrosinase activity (IC\textsubscript{50} of 194 \(\mu\text{M}\)) from the Chinese medicinal plant \textit{Rubia cordifolia}. Biogenetically, mollugin was formed by a cyclisation of a prenylated naphthoquinone and is not related to the biosynthetic pathway of tocopherols (Fig. 2). Mollugin has been first reported by Schildknecht \textit{et al.} as a pigment from the rhizomes of \textit{Galium mollugo} and was further investigated for pharmacological effects, such as anti-platelet aggregation activity and anti-viral activity against hepatitis B virus.\textsuperscript{222} Mollugin has been shown to induce apoptosis in different types of cancer cells. It exhibited IC\textsubscript{50} values of 12.3 \(\mu\text{M}\), 23 \(\mu\text{M}\) and 60.2 \(\mu\text{M}\) on human colon cancer cells (Col2),\textsuperscript{221} human Jurkat T-cells\textsuperscript{224} and murine NIH 3T3-L1 preadipocytes,\textsuperscript{225} respectively. In the presence of 10 \(\mu\text{M}\) mollugin, a human multidrug-resistant breast cancer cell line (MCF-7/adr) was more susceptible to doxorubicin (IC\textsubscript{50} decreased from 60 to 7.5 \(\mu\text{g ml}^{-1}\)).\textsuperscript{226} Several patents describe the use of mollugin for different applications (Fig. 26).\textsuperscript{227}

Several low molecular weight chromenes, such as pterochromenes L1 (190), L2 (191) and L4 (192), were isolated from Taiwanese \textit{Pteris linginpinna}. 6-Hydroxyeupatoriochromene B (193) was obtained from \textit{Ageratina riparia} (Asteraceae) and finally, one of the first insect anti-juvenile hormones, precocene 2 (194) (6,7-dimethoxy-2,2-dimethylchromene) was found in \textit{Ageratum houstonianum} (Asteraceae).\textsuperscript{228} Lapacheno (195), a naphthaleine derivative, was isolated from the heartwoods \textit{Paratecoma peroba} and \textit{Tabebuia chrysantha} and \textit{Tabebuia heptaphylla}.\textsuperscript{211,212} 3-Hydroxy (196) and 3-,4-dihydroxy-chromanes (197) were isolated from a trunkwood extract of \textit{Tabebuia heptaphylla}.\textsuperscript{222}

Zhuang \textit{et al.} isolated illihenryipyranol A (198) from roots of \textit{Illicium henryi} in minor amounts.\textsuperscript{233}

Fig. 25 Structures of monoterpenes (186 to 188) from tunicates and algal derived endophytic fungi.
regulatory and signaling molecules. Studies on vitamin E metabolism were summarized in several outstanding reviews;\textsuperscript{17,238,239} we therefore describe here only briefly the formation and activities of these metabolites.

The hepatic metabolism of tocopherols follows the classical activation of branched chain hydrocarbons by cytochrome P\textsubscript{450} enzymes (most likely CYP4F2) within the endoplasmic reticulum.\textsuperscript{240} ω-Hydroxylation of \(\alpha\)-tocopherol forms \(\alpha\)-13'-hydroxytocopherol (189) (13'-OH) with subsequent oxidation to \(\alpha\)-13'-carboxy-tocopherol (190) (13'-COOH) by aldehyde dehydrogenase (Fig. 28). Both metabolites were detected in human plasma and show anti-inflammatory and cytotoxic activity in \textit{in vitro} and \textit{in vivo} systems (see corresponding Section 8 and 9).\textsuperscript{241,242}

Further degradation of the long-chain metabolites (LCM) occurs like that of methyl branched-chain fatty acids by β-oxidation, subsequently cutting out 2- and 3-carbon units, respectively. The β-oxidation takes place in the peroxisomes and results in 11'-COOH and 9'-COOH LCM.\textsuperscript{240} Mustacich et al. suggested that further degradation occurs within the mitochondrial matrix where intermediate-chain metabolites (7'-COOH and 5'-COOH) and short-chain metabolites 3'-COOH (or carboxy-ethyl-hydroxy-chromanol (CEHC)) were detected.\textsuperscript{240} CEHCs were the first metabolites identified in human and animal (rats and mice) studies, since they are secreted in urine.\textsuperscript{243} 5-9'-COOH (191), \(\alpha\)-5'-COOH (also known as \(\alpha\)-carboxy-methylbutyl-hydroxy-chromanol, \(\alpha\)-CMBHC; 192), and \(\alpha\)-3'-COOH (\(\alpha\)-CEHC; 193) were investigated for their anti-inflammatory properties \textit{in vitro}.\textsuperscript{244,245} Interestingly, the degradation of tocotrienols results in the formation of CEHC, suggesting a similar degradation mechanism as seen for
tocopherols. Indeed, analogous catabolic steps were found for tocotrienol in vitro and in vivo\(^2_{42,246}\) (Fig. 28). Initial \(\omega\)-hydroxylation followed by five cycles of \(\beta\)-oxidation follows in principle that of tocopherols; however, the double bonds between C-4'-C-5', C-7'-C-8' and C-11'-C-12' undergo a saturation step, which is catalyzed by 2,4-dienoyl-CoA reductase and 3,2-enoyl-CoA isomerase (Fig. 28). The following metabolites of tocotrienol were identified by in vitro experiments in hepatic adenoma HepG2 cells and in mice feces, respectively:\(^2_{42,246}\) 13'-carboxy-trienols (\(\alpha\)-, \(\gamma\)-, \(\delta\)-tocotrienol-13'-COOH; \(209, 31, 30\)) which are identical with the naturally occurring garcinoic acids, e.g. \(\alpha\)-, \(\gamma\)-, and \(\delta\)-garcinoic acid, carboxy-dimethyl-decadienyl-hydroxy-chromanol (\(\alpha\), \(\gamma\), \(\delta\)-CDMD(en)2HC or \(\alpha\), \(\gamma\), \(\delta\)-CDMD(en)2HC; \(210, 211, 212\)), carboxy-dimethyl-octenyl-hydroxy-chromanol (\(\alpha\), \(\gamma\), \(\delta\)-CDMOenHC or \(\alpha\), \(\gamma\), \(\delta\)-CDMOenHC; \(213, 214, 215\)), as well as carboxy-dimethyl-octenyl-hydroxy-chromanols (\(\alpha\), \(\gamma\), \(\delta\)-CDMOenHC or \(\alpha\), \(\gamma\), \(\delta\)-CDMOenHC; \(216, 217, 218\)), carboxy-methyl-hexenyl-hydroxy-chromanol (\(\alpha\), \(\gamma\), \(\delta\)-CMHenHC or \(\alpha\), \(\gamma\), \(\delta\)-CMHenHC; \(219, 220, 221\)), and carboxy-methyl-butadienyl-hydroxy-chromanol (\(\alpha\), \(\gamma\), \(\delta\)-CMBenHC or \(\alpha\), \(\gamma\), \(\delta\)-en-5'-COOH (\(222, 223, 224\)). Tocotrienols are metabolized with a higher rate than \(\alpha\)-tocopherol; thus, depending on dietary tocotrienol intake, the plasma concentrations exceed that of \(\alpha\)-tocopherol metabolites. Except for the 13'-carboxy-trienols (see next section), biological properties of tocotrienol metabolites are largely unknown.

All tocopherol and tocotrienol metabolites can occur in free form or as phase II conjugates, such as sulfates or glucuronides.\(^2_{42,247}\)

Bardowell et al. investigated the role of the murine Cyp4f14 gene, an orthologue of the human CYP4F2 gene, in vitamin E metabolism in Cyp4f14-knockout mice and found two new metabolites, namely 12'-hydroxy-tocopherol (12'-OH: \(\gamma\) and \(\delta\)-12'-OH, (\(225\) and \(226\))) and 11'-hydroxy-tocopherol (11'-OH: \(\gamma\) and \(\delta\)-11'-OH, (\(227\) and \(228\))) in fecal pellets of mice fed a diet rich in \(\gamma\)-tocopherol.\(^2_{48,54}\) The metabolites derive from \(\omega\)-1 and \(\omega\)-2-hydroxylation and were excreted via bile into feces of mice and humans.
8. Anti-inflammatory activity of tocochromanols and -chromenols

Many diseases, including atherosclerosis, diabetes or even cancer, are related to inflammatory processes. A decreased grade of inflammation could lead to a reduced risk for these diseases. In the past, human clinical trials with α-tocopherol as an anti-inflammatory agent revealed contradictory results.27,217,250,251 We here like to broaden the view to structurally related chromanols and chromenols and compare their anti-inflammatory in vitro activity.

The anti-inflammatory activities of tocopherols and tocotrienols from the human diet are well known and are compiled in Table 1.219,245,252 In general, the chromanols with saturated and unsaturated side chains showed good to moderate inhibitory activity depending on the anti-inflammatory marker measured and the in vitro system used.253,254 For example, Jiang et al. investigated the inhibition of COX-2 catalyzed PGE2 synthesis in IL-1β-stimulated human lung epithelial A549 cells of a series of tocopherols and tocotrienols, respectively.245 The inhibitory activities reached from IC50 > 50 μM for α-tocopherol to IC50 = 1–3 μM for δ-tocopherol and γ-tocotrienol.

The LCM of tocopherols and tocotrienols with a terminal C-13′-carboxy and -hydroxyl group, respectively, were found in nanomolar concentration in human plasma and intensively studied as anti-inflammatory agents. The research on the LCM was promoted by the facile semi-syntheses from garcinonic acid that can be efficiently isolated from Garcinia kola.28,29

α-13′-Carboxy-tocopherol (205) (α-13′-COOH) inhibited the expression of iNOS by 100% at 5 μM and the formation of nitric oxide by 100% at 2.7 μM, respectively.255,256 A recent investigation on the anti-inflammatory activity of α-13′-COOH showed strong inhibition of recombinant 5-LOX and only moderate inhibition of COX-1, leukotriene (LT) C4 synthase, PGES-1 and epoxide hydrolase.245 Human recombinant COX-2 was not inhibited by α-13′-COOH at low concentrations.

The δ-tocopherol metabolite δ-13′-carboxy-tocopherol (229) (δ-13′-COOH) showed a slightly reduced activity, and inhibited iNOS protein synthesis by 56% at 5 μM and nitric oxide formation by 79% at 5 μM, respectively, in LPS-activated murine RAW264.7 macrophages. δ-13′-COOH further inhibited the LPS-induced upregulation of COX-2 expression in the same cells with IC50 values of 4-5 μM.245,257 5-LOX activity was inhibited in the range from 0.5–2.0 μM, depending on the assay used.251

The 13′-Hydroxy-tocopherols of α, and δ-tocopherol (α-13′-OH (204) and δ-13′-OH (231)) are synthetically available and have been therefore intensively studied. α-13′-OH reduced COX-2 expression (49%) and PGE2 synthesis (54%) and both alcohols inhibited iNOS expression by 53–60% at 10 μM in LPS-induced murine RAW264.7 macrophages.245,258 Both alcohols can be biochemically converted by mammalian cells to the corresponding acids, thus making it difficult to distinguish between the activity of 13′-OH and 13′-COOH (unpublished results).

As described in the section on human metabolism, the metabolic truncation of the LCM leads to several medium- and short-chain metabolites, such as 9′-carboxy-tocopherols (9′-COOH), CMBHC and CEHC, respectively. In general, the anti-inflammatory activities of the medium- and short-chain metabolites seem to decrease with the decreasing lengths of the side chains, resulting in higher IC50 values (Table 1).245

In summary, although the number of in vitro studies is still limited and different markers of inflammation cannot be compared directly, we roughly estimate the anti-inflammatory activity of tocopherols, tocotrienols and their metabolites as follows: α-tocopherol < non-α-tocopherol ~ tocotrienols ≪ 13′-OH ~ 13′-COOH ≫ 9′-COOH > CMBHC ~ CEHC. However, it must be kept in mind that the molecular modes of action of these molecules seem to be quite different. It is obvious that the impact of the metabolites depends on individual metabolism rates (pharmacokinetics) of the tocochromanols from the diet. Grebenstein et al. proposed that the affinity of vitamers towards the α-tocopherol transfer protein (α-TTP) may predict their degradation by cytochrome P450 enzymes.28 α-TTP has the strongest affinity for α-tocopherol with Kd of 25 nM and much higher Kd values for the other vitamin E forms, depending on their methylation pattern and side chain saturation.239,259 Accordingly, the catabolism of non-α-tocopherol vitamers into the corresponding LCM may occur much faster than that of α-tocopherol, thus generating more anti-inflammatory metabolites. As a result, α-tocopherol per se is less active than all other vitamers following the order: δ-tocopherol ~ γ-tocotrienol > γ-tocopherol ≫ α-tocopherol.239

δ-Garcinonic acid (30) is the main constituent of several Garcinia species, which are known for their anti-inflammatory properties in African ethnomedicine.27 δ-Garcinonic acid was reported to inhibit COX-2 (IC50 = 10 μM) and, even stronger, 5-LOX with IC50 ranging from 0.04 to 1.0 μM.257 δ-Garcinonic acid downregulated the LPS-induced expression of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1β, COX-2 and iNOS in macrophages and reduced production of nitric oxide (IC50 value of 1 μM).255,260 A direct comparison of several carboxy-tocotrienols (tocotrienol-13′-COOH metabolites) from plant origin as inhibitors of microsomal PGE2 synthase-1 revealed the following order of activity: γ-garcinonic acid (31) > β-garcinonic acid (232) > δ-garcinonic acid (30) > α-garcinonic acid (209); however the methylation pattern had only moderate impact.24

Structurally related forms of δ-garcinonic acid, such as δ-sargachromenol (51) with a 15′-COOH group and a chromene ring system, showed only moderate inhibitory activity on in LPS-stimulated production nitric oxide and PGE2 in murine RAW 264.7 macrophages (IC50 values of 82 μM and 30.2 μM, respectively);239 however, much higher activity was observed in BV-2 microglial cells (IC50 value for inhibition of nitric oxide production of 1.3–2.7 μM).234,235

As described above, 13′-OH metabolites have a similar anti-inflammatory potential than the corresponding 13′-COOH. Thus, natural products such as sargachromenol D (57), E (58) and G (60), respectively, with hydroxyl-groups at C-9′ and C-10′ are interesting intermediates. They all showed moderate inhibitory activity on nitric oxide production in LPS-stimulated murine RAW 264.7 cells (IC50 values of 15–40 μM).79,81,84

Cyclic meroterpenes such as epitaenodiol (79) and the chromanols A to D (113 to 116) exhibited anti-inflammatory activity in vitro and in vivo (Table 1).99,104 The four chromanols A to D

This journal is © The Royal Society of Chemistry 2018

RSC Adv., 2018, 8, 4803–4841 | 4831
inhibited 15-LOX with IC$_{50}$ = 0.6(113), 4.0(114), 0.7(115) and 1.1 µM (116), respectively, but not 12-LOX. Epitaondiol was effective in a TPA-induced mouse ear edema study (IC$_{50}$ = 20.7 µg per ear) and inhibited eicosanoid synthesis with an IC$_{50}$ of 3.8 µM for thromboxane B$_2$ (TXB$_2$) and an IC$_{50}$ of 30.1 µM for LTB$_4$.

The cyclic sesquiterpenes capillobenzopryanol (172) only moderately inhibited nitric oxide production in LPS-stimulated macrophages by 37% at 10 µM. The monoterpenic cordiacromene A (173) inhibited soybean 15-LOX with an IC$_{50}$ of 0.82 µM and lipid peroxidation with an IC$_{50}$ of 2 µM.

Only moderate anti-inflammatory activity was observed for the hemiterpene quercinol (199), whereas it inhibited COX-2 expression with an IC$_{50}$ of 0.63 µM.

In Fig. 29 we postulate the structural motives that are essential for the anti-inflammatory activity based on the structures and properties discussed above. The most effective compounds described are the diterpenes 13'-COOH, 13'-OH, garcinoic acid and δ-sargachromenol, respectively, with strong potential as anti-inflammatory drug candidates. A recent SAR study revealed that the effects of human LCM depend on the presence of the chromanol ring and modifications in the side chain and less on the substitution pattern at the aromatic ring. This study is in line with the observation of Silva et al. with δ-sargachromenol (51) and its precursor 1,4-benzoquinone sargauqonic acid; the latter had less inhibitory activity towards LOX- and COX-enzymes.

In addition to the natural compounds described above, the anti-inflammatory and anti-diabetic drug troglitazone exhibits a 6-hydroxy-chromane ring system. Troglitazone was used a PPAR-γ receptor agonist but was withdrawn from the market since it caused hepatotoxicity. Obviously, anti-inflammatory activity is enhanced by the occurrence of a 6-hydroxy-chromane and -chromene moiety, respectively.

In conclusion, meroditerpenoids with a functional group (COOH, OH) at the side chain have much higher anti-inflammatory activity than the parent chromanols and chromenols, respectively.

9. Anti-proliferative and cytotoxic activity of chromanols and chromenols

Dietary tocopherols and tocotrienols have been extensively investigated for their cancer-preventive potential in several human intervention trials (reviewed in, but widely failed to prove beneficial effects. However, in vitro studies with tocopherols and tocotrienols in cell cultures and in vivo studies have shown pronounced anti-neoplastic and anti-carcinogenic effects.

The susceptibility of the cell lines tested for anti-carcinogenic activity varied tremendously and makes thus it difficult to compare the compounds discussed in this section. For example, HepG2 liver cells exhibit greater resistance to drugs and toxins compared to other cells lines, since they actively express phase I and II enzymes. As a result, higher IC$_{50}$ values are expected for drug resistant cell lines, such as HepG2.

Structure–activity relationship studies revealed that chemical modifications at C-6 of the aromatic ring (ethers or esters) magnified the cytotoxic potential of vitamin E compounds. In general, drug candidates that were ‘redox-silent’ at C-6, such as tocopherol-succinate, showed promising results in animal studies. Although most of the redox-silent compounds were chemically synthesized, distinct structure–activity relationships have been derived from these experiments. The studies revealed the importance of three major domains of the chromanols tested: first, the functional domain (I) that needs to be ‘redox silent’ to exert the cytotoxic properties. Second, the signaling domain (II) modified by the methylation pattern of the chromanol ring system. Third, the hydrophobic domain (III) that is mostly covered by saturated and unsaturated side chains. Reviewing the structural features of the molecules presented here, we further specify the domains that are relevant for cytotoxicity.

Tocopherols seem to have low or moderate anti-cancer activity in the different cell model systems. α-Tocopherol (3) in particular is well-tolerated by adenoma and cancer cells in supra-physiological concentrations (above 100 µM) (see Table 2). γ-Tocopherol (5) at 25 µM, however, had anti-proliferative activity on colon carcinoma (CaCo-2), androgen-sensitive (LNCaP) and androgen-resistant (PC-3) prostate, lung adenocarcinoma (A549), and osteosarcoma (SaOs-2) cells, but did not induce apoptosis in these cell lines. Accordingly, we postulate the following order of activity for tocopherols: γ-tocopherol (5) > δ-tocopherol (6) > α-tocopherol (3).

Tocotrienols showed anti-proliferative and pro-apoptotic effects in vitro and in vivo and are in general more potent in the prevention of cancer than tocopherols. Several molecular targets were identified for γ- and δ-tocotrienol (16) and (17) (γ- and δ-tocotrienol), respectively (summarized by). Induction of mitochondrial apoptosis, demonstrated by activation of caspase-3 and -9, along with modulation of apoptogenic genes such as Bcl-2, Bcl-xl and Bax, respectively, has been observed for most of the tocotrienols tested.

α-Tocotrienol (14) showed low to moderate pro-apoptotic activity against different breast cancer (MDA-MB-435, MDA-MB-231, and MCF7) and melanoma (B16) cells, respectively (Table 2). In contrast, γ- (16) and δ-tocotrienol (17) induced apoptosis at low micromolar concentrations in most of the cell lines tested. Sargaoil (95) (3,4-dehydrosso3-tocotrienol), has been tested with moderate activity in human gastric epithelial cells, human fibroblasts and murine...
lymphocytic leukemia P388 cells.\textsuperscript{103,120} Interestingly, fascioquinol F (109) [3,4-dehydro-desmethyl-tocotrienol] showed no inhibitory activity against human gastric adenoma (AGS) and human neuroblastoma (SH-SY5Y) cells, respectively.\textsuperscript{135} In contrast, desmethyl- and didesmethyl-tocotrienol (18) and (19) strongly induced apoptosis in B16 melanoma cells (IC\textsubscript{50} values of about 1 \textmu M).\textsuperscript{24,25} In conclusion, the activity order is determined by the methylation pattern of the chromanol ring: desmethyl-tocotrienol (18) \textless didesmethyl-tocotrienol (19) \textless \gamma- tocotrienol (16) \textless \delta-tocotrienol (17) \textless 3,4-dehydro-\delta-tocotrienol (95) \textless \alpha-tocotrienol (14).

Only recently, tocopherol- and tocotrienol-metabolites were investigated for their anti-carcinogenic activity. \textsuperscript{13} 13'-Carboxylic acids, including garcinoic acid, induced apoptosis in the lower esophageal squamous carcinoma (ESCC) cells\textsuperscript{136} (Table 2).\textsuperscript{38,257,277} The natural product and tocotrienol metabolite garcinoic acid (30) showed similar activities.\textsuperscript{136} Sargachromanol (51) and fallachromenoic acid (105) were both active in the lower micromolar range.\textsuperscript{126,131} Thus, the shift of the carboxylic group at C-15' does not affect the pro-apoptotic activity.

The introduction of hydroxyl group(s) within the side chain is associated with pro-apoptotic effects. Crassamotocopherols A (134) and B (135) (C-8’–C-11’–C-12’-triols) showed strong inhibitory activity towards murine P338 leukemia and human colon adenocarcinoma HT-29 cells (IC\textsubscript{50} values of 5.2–7.5 \textmu M).\textsuperscript{139} Somewhat lower activities were found for diols such as \delta- and \gamma-amplexichromanols (35) and (36) (C-13’–C-14’-diols), litchtocotrienol A (41) (C-11’–C-12’-diol), and sargachromanol E (58) (C-9’–C-10’-diol) (Table 2).\textsuperscript{41,49,82} Sargatriol (98) (C-5’–C-6’-diol), as well as sargadiol-I (96) (C-6’–OH) and -II (97) (C-8’–OH) are weak inhibitors in P338 leukemia cells with IC\textsubscript{50} values between 30 and 40 \textmu M.\textsuperscript{116,122} All compounds with mono-hydroxy-substituted side chains showed low to no cytotoxic activity. Based on the hydroxylation pattern of the side chain, we estimate the following activity order: C-8’–C-11’–C-12’-triol \textless C-13’–C-14’-diol \textless C-11’–C-12’-diol \textless C-9’–C-10’-diol \textless C-8’–OH \textless C-5’–C-6’-diol \textless C-6’–OH \gg C-13’–OH.

Cyclizations of the tocotrienol side chain lead to epitaenodiols, stronglyphorines and bifurcarenecarboxylic acids. All compounds tested showed moderate to weak anticancerogenic activities (Table 2).

Unfortunately, only few data exist for the anti-cancer activities of sesquiterpenes. Paniceins A2 (160) and F2 (161) both inhibited growth of P330, lung adenocarcinoma A549 cells, uveal melanoma MEL20 cells, and colon adenocarcinoma HT-29 cells with IC\textsubscript{50} values of around 15 \textmu M (ref. 195) and riccardiphenol C (146) was not active.\textsuperscript{177}

Monoterpenes and hemiterpenes both demonstrated medium to low inhibitory activity towards cancer cells (Table 2).

In conclusion, meroterpenoids exhibited the strongest inhibitory activity towards cancer cells among all meroterpenoids described, especially when a carboxy or more than one hydroxyl group is present at the terminal end of the side chain (Fig. 30).

### 10. Discussion

This review describes more than 230 6-hydroxy-chromanols and -chromenols, respectively that were found in terrestrial and marine organisms. Fig. 31a highlights the distribution of meroterpenes within different phyla. Marine organisms, led by brown algae (Phaeophyceae), cover two thirds of the molecules presented in this review, followed by plants and fungi. Interestingly, sponges (Porifera) produce 18% of the natural products presented here, mainly cyclic di- and sesqui-terpenes.

Meroterpenes represent almost two thirds of all compounds discussed and are divided into 63% with linear and 37% with cyclic side chains, respectively (Fig. 31b). The occurrence of sesquiterpenes was dominant in sponges, whereas hemiterpenes were only found in plants and fungi.

During the course of this compilation, the question arose whether or not the stereo-controlled cyclization of toluquinols to a chromane or chromene ring with R-configuration at C-2 occurs exclusively in terrestrial species. The evidence for this process in plants is well documented and the isolation of several cyclases substantiates the biosynthetic step. Marine-derived meroterpenes were often isolated as mixtures of stereoisomers at C-2 and several authors debated the isolation of chrom(e)nols as artefacts of the work-up procedures or as non-enzymatic reaction products within the organism. In addition, the monocyclic 1,4-benzoquinone precursors were isolated in most cases with high yields, whereas toluquinols in plant species occur only in trace amounts and were rarely described. From the 49 diterpenes isolated from plants, 46 (94%) were described with R-configuration. A statistical analysis of chromanols and chromenols from marine species revealed that 73% of chromanols were isolated as R-enantiomers, whereas only 26% of all chromenols show optical activity with R-configuration. In conclusion, we postulate that marine organisms most likely produce chromanols via enzyme-catalyzed cyclization, whereas chromenols may mostly originate from non-enzymatically cyclization or as an artefact during sample work-up.

![Fig. 30 General structural motives important for the anti-cancer activities of meroterpenoids.](image-url)
The structural variability of the compounds described in this review is remarkable. Side chain modifications by oxidation and/or cyclization occur widely, especially in marine organisms. Cytochrome P₄₅₀ enzymes are most likely responsible for the initial oxidation to epoxy-, hydroxy- and carboxy-derivatives, respectively, although the corresponding enzymes were studied only in animal vitamin E metabolism and are not fully understood yet.²⁴⁸,²⁴⁹

Cyclization of the prenylated side-chain occurs via different pathways. The first pathway begins with an acid-catalyzed cyclization cascade between C-2–C-7, C-6–C-11 and C-10–C-15 of the sesquiterpenes and diterpene backbone, respectively, that leads to di- or tricyclic 1,4-hydroquinones. This is followed by a second acid-catalyzed formation of the chromane ring as described by Kurata et al. (Fig. 20).²⁴⁸ Several examples for this cyclization, such as chromazoranol (154) or strongylophorines (117–130), are described above.

The second cyclization pathway occurs via an epoxidation of the terminal double bond, followed by an acid-catalyzed cyclization cascade with a final cyclization of the chromane ring, as first described by Etse et al.²⁵¹,²⁵²,²⁵³ (see also Fig. 7 and 10). It remains unclear, if these mechanisms occur simultaneously or sequentially. Walsurol (50), cyclolitchtocotrienol A (49) or the taondiols (76–80) are examples of the second pathway.

A third cyclization pathway occurs via the formation of the 1,4-hydroquinone precursor bifurcarenone (81) by an acid-catalyzed anti-Markovnikoff cyclization between C-7 and C-11.²⁷⁸ Subsequent cyclization reactions lead to cystoketal chromane (89), mediterraneols (82–84) and cystoseirols (86, 87).

Only three meroterpenes with a cyclic side chain have been described in plants, namely walsurol (50), cyclolitchtocotrienol A (49) (Fig. 7) and riccardiphenol C (146) (Fig. 19).

With some exceptions, all higher plants produce side chain-saturated tocopherols with the typical methylation pattern α-, β-, γ-, and δ-, respectively. Next, several algae have the ability to produce tocopherols, although in low yields. 8-Methyl- or desmethyl-tocotrienol moieties were found in most of the structures described from marine organisms. Only three tocopherol-derivatives with a full methylation pattern (α-) were identified in marine organisms, namely marine-derived tocopherol (25) from phytoplankton, α-tocoxylxenoxy (108) from the green alga *Caulerpa racemosa* and chrassumtocopherol from the soft coral *Lobophytum crissum*.

The primary biological function of the side chain modifications remains unclear. On the one hand, cytotoxicity, algicidal and anti-macroalgal activity was found for several metabolites. On the other hand, the settling of sea urchins and perna eggs was induced by several compounds. Thus, side chain-modified metabolites are presumably used as chemical protectants or as signalling molecules for intercellular communication or both.

Recent advances in the research on human vitamin E metabolites led us to a comprehensive search for chromanol- and chromenol-structures with anti-inflammatory and cytotoxic properties (see Tables 1 and 2). The number of structurally related compounds exceeded our expectations. We therefore merged the available information on over 30 compounds and identified structural motives that correspond to high anti-inflammatory activities (Table 1). Most of the compounds described here affected arachidonic acid metabolism and also the synthesis of pro-inflammatory cytokines. Inhibition of COX-1 and COX-2 expression, respectively, reduced prostaglandin metabolite formation and inhibition of 5- and/or 12-LOX blocked leukotriene synthesis. Further studies will have to reveal if meroterpenoids have the potential to be developed into anti-inflammatory drug candidates.

Cytotoxicity data of approximately 50 compounds were collected (Table 2). Like the anti-inflammatory activities of meroterpenoids, diterpenes showed the strongest activity, led by side chain-modified chromanols. Anti-proliferative and cytotoxic properties were modulated by the presence of hydroxyl and carboxy groups. Activation of caspases-3 and -9, respectively, suggested that most of these compounds induce a mitochondrial death pathway.

Rangasany et al. evaluated the drug-likeness of several natural products isolated from algae and found δ-sargachromenol (51) and epitaondiol (79) as good fits to Lipinski’s ‘Rule
of Five’. This rule estimates the potential of a drug candidate based on physio-chemical properties, such as molecular weight, number of hydrogen bond acceptors and donors, and distribution coefficient (log P).\textsuperscript{21,44} We screened a series of compounds described in this review (ESI Table 1\textsuperscript{t}) and found many with good predicted oral bioavailability, based on these calculations which were conducted \textit{via} Molinspiration WebME editor version 1.16 (http://www.molinspiration.com).

We and others tested several vitamin E metabolites for their biological activity \textit{in vitro} and \textit{in vivo} and found them to have anti-bacterial, anti-viral, anti-inflammatory and cytotoxic properties (Tables 1 to 3). In general, any modification of the prenyl side chain increased their biological activity.

In this review, we thoroughly described the class of 6-hydroxy-chromanols and -chromenols within living nature and summarize their biological properties, in particular their anti-inflammatory and anti-carcinogenic potential. Based on the presented evidence, we conclude that the presence of a hydroxyl or carboxy group in the side chain enhances the anti-inflammatory activity of natural chromanols and chromenols. With respect to anti-proliferative and anti-cancer activities, we conclude that, among all meroterpenoids described, meroterpenoids have the strongest inhibitory activity towards cancer cells, in particular when, again, bearing a carboxy or more than one hydroxyl group at the terminal end of the side chain. We therefore propose that the presence of a terminal hydroxyl or carboxy group in the side chain of the long-chain vitamin E metabolites warrants further investigation and might help us to unravel the as yet unknown essential biological function(s) and modes of action of vitamin E in animals.

Conflicts of interest
There are no conflicts to declare.

Acknowledgements
We acknowledge support by the Open Access Publishing Fund of Hochschule Fulda – University of Applied Sciences. The work of Marc Birringer is supported by grants from the Internal Research Support of Hochschule Fulda – University of Applied Sciences. The work of Stefan Lorkowski is supported by grants from the Federal Ministry of Education and Research (01EA1411A), the Deutsche Forschungsgemeinschaft (DFG; RTG 1715), the German Ministry of Economics and Technology (AiF 16642 BR) \textit{via} AiF (the German Federation of Industrial Research Associations) and FEI (the Research Association of the German Food Industry), and by the Free State of Thuringia and the European Social Fund (2016 FGR 0045).

References
1 H. M. Evans and K. S. Bishop, Science, 1922, \textbf{56}, 650–651.
2 R. Brigelius-Flohe and M. G. Traber, \textit{FASEB J.}, 1999, \textbf{13}, 1145–1155.
3 H. M. Evans, O. H. Emerson and G. A. Emerson, \textit{J. Biol. Chem.}, 1936, \textbf{113}, 319–332.
4 D. C. Liebler, J. A. Burr, L. Philips and A. J. Ham, \textit{Anal. Biochem.}, 1996, \textbf{236}, 27–34.
5 L. Gille, T. Rosenau, A. V. Kozlow and W. Gregor, \textit{Biochem. Pharmacol.}, 2008, \textbf{76}, 289–302.
6 H. Y. Peh, W. S. D. Tan, W. Liao and W. S. F. Wong, \textit{Pharmacol. Ther.}, 2016, \textbf{162}, 152–169.
7 European Patent Office, https://www.epo.org/.
8 R. A. C. Sussmann, W. L. Fotoran, E. A. Kimura and A. M. Katzin, \textit{Parasites Vectors}, 2017, \textbf{10}, 461.
9 (a) A. Block, R. Fristedt, S. Rogers, J. Kumar, B. Barnes, J. Barnes, C. G. Elowsky, Y. Wamboldt, S. A. Mackenzie, K. Redding, S. S. Merchant and G. J. Basset, \textit{J. Biol. Chem.}, 2013, \textbf{288}, 27594–27606; (b) Y. Yan, Y. Liu, H. Zhang, Y. Du, X. Liu and Z. Zhang, \textit{Molecules}, 2017, \textbf{22}, pii: E510.
10 (a) L. Spicher and F. Kessler, \textit{Curr. Opin. Plant Biol.}, 2015, \textbf{25}, 123–129; (b) J. Falk and S. Munné-Bosch, \textit{J. Exp. Bot.}, 2010, \textbf{61}, 1549–1566; (c) P. Dörmann, \textit{Planta}, 2007, \textbf{225}, 269–276; (d) R. Szymańska and J. Kruk, \textit{Plant Physiol. Biochem.}, 2018, \textbf{122}, 1–9.
11 J. Kruk, A. Pisarski and R. Szymańska, \textit{J. Plant Physiol.}, 2011, \textbf{168}, 2021–2027.
12 G. Horvath, L. Wessjohann, J. Bigirimana, M. Jansen, Y. Guizez, R. Caubergs and N. Horemans, \textit{Phytochemistry}, 2006, \textbf{67}, 1185–1195.
13 (a) J. Green, D. McHale, S. Marcinkiewicz, P. Mamalis and P. R. Watt, \textit{J. Chem. Soc.}, 1959, 3362–3373; (b) J. Green and S. Marcinkiewicz, \textit{Nature}, 1956, \textbf{177}, 86–87.
14 (a) J. Bunyan, D. McHale, J. Green and S. Marcinkiewicz, \textit{Br. J. Nutr.}, 1961, \textbf{15}, 253–257; (b) J. Bunyan, \textit{Nature}, 1961, \textbf{181}, 1237.
15 G. Klink, A. Buchs and F. O. Gülacar, \textit{Phytochemistry}, 1994, \textbf{36}, 813–814.
16 S. Krauš, S. Hammann and W. Vetter, \textit{J. Agric. Food Chem.}, 2016, \textbf{64}, 6306–6311.
17 F. Galli, A. Azzi, M. Birringer, J. M. Cook-Mills, M. Eggersdorfer, J. Frank, G. Cruciani, S. Lorkowski and N. K. Özer, \textit{Free Radical Biol. Med.}, 2017, \textbf{102}, 16–36.
18 J.-M. Zingg, M. Meydani and A. Azzi, \textit{BioFactors}, 2012, \textbf{38}, 24–33.
19 W. Müller-Mulot, G. Rohrer, G. Oesterhelt, K. Schmidt, L. Allemann and R. Maurer, \textit{Fette, Seifen, Anstrichm.}, 1983, \textbf{85}, 66–71.
20 B. Brem, C. Seger, T. Pacher, M. Hartl, F. Hadacek, O. Hofer, S. Vajrodaya and H. Greger, \textit{Phytochemistry}, 2004, \textbf{65}, 2719–2729.
21 Y.-S. Kil, J. Park, A.-R. Han, H. A. Woo and E.-K. Seo, \textit{Molecules}, 2015, \textbf{20}, 5965–5974.
22 F. Shahidi and A. C. de Camargo, \textit{Int. J. Mol. Sci.}, 2016, \textbf{17}, 1745–1774.
23 H. Ashan, A. Ahad, J. Iqbal and W. A. Siddiqui, \textit{Nutr. Metab.}, 2014, \textbf{52}, 1–22.
24 A. A. Qureshi, H. Mo, L. Packer and D. M. Peterson, \textit{J. Agric. Food Chem.}, 2000, \textbf{48}, 3130–3140.
25 L. He, H. Mo, S. Hadissusilo, A. A. Qureshi and C. E. Elson, \textit{J. Nutr.}, 1997, \textbf{127}, 668–674.
250 H. Bruunsgaard, H. E. Poulsen, B. K. Pedersen, K. Nyyssonen, J. Kaikkonen and J. T. Salonen, *J. Nutr.*, 2003, 133, 1170–1173.

251 S. Devaraj, R. Tang, B. Adams-Huet, A. Harris, T. Seenivasan, J. A. de Lemos and I. Jialal, *Am. J. Clin. Nutr.*, 2007, 86, 1392–1398.

252 E. J. Goetzl, *Nature*, 1980, **288**, 183–185.

253 Z. Jiang, X. Yin and Q. Jiang, *J. Immunol.*, 2011, **186**, 1173–1179.

254 A. Koeberle, personal communication.

255 M. Wallert, L. Schmölz, A. Koeberle, V. Krauth, M. Glei, F. Galli, O. Merz, W. Birringer and S. Lorkowski, *Mol. Nutr. Food Res.*, 2015, **59**, 1524–1534.

256 L. Schmölz, M. Wallert, N. Rozzino, A. Cignarella, F. Galli, M. Glei, O. Merz, A. Koeberle, M. Birringer and S. Lorkowski, *Mol. Nutr. Food Res.*, 2017, **61**(12), DOI: 10.1002/mnfr.201700562.

257 Y. Jang, N.-Y. Park, A. L. Rostgaard-Hansen, J. Huang and Q. Jiang, *Free Radical Biol. Med.*, 2016, **95**, 190–199.

258 N. Grebenstein, M. Schumacher, L. Graeve and J. Frank, *Mol. Nutr. Food Res.*, 2014, **58**, 1052–1060.

259 C. Panagakbo, S. Morley, M. Hernandez, P. Cassolato, H. Gordon, R. Parsons, D. Manor and J. Atkinson, *Biochemistry*, 2003, **42**, 6467–6474.

260 M. Wallert, personal communication.

261 S.-J. Oh, E.-J. Youn, M.-S. Kwon, B. Lee, T. Utsuki, C.-W. Oh and H.-R. Kim, *J. Med. Food*, 2016, **19**, 1023–1031.

262 (a) A. Aljada, R. Garg, H. Ghanim, P. Mohanty, W. Hamouda, E. Assian and P. Dandona, *J. Clin. Endocrinol. Metab.*, 2001, **86**, 3250–3256; (b) V. A. Dixit and P. V. Bharatam, *Chem. Res. Toxicol.*, 2011, **24**, 1113–1122; (c) K. Kassahun, P. G. Pearson, W. Tang, I. McIntosh, K. Leung, C. Elmore, D. Dean, R. Wang, G. Doss and T. A. Baillie, *Chem. Res. Toxicol.*, 2001, **14**, 62–70; (d) C. Funk, C. Ponelle, G. Scheuermann and M. Pantze, *Mol. Pharmacol.*, 2001, **59**, 627–635.

263 A. K. Smolarek and N. Suh, *Nutrients*, 2011, **3**, 962–986.

264 (a) E. A. Klein, I. M. Thompson, C. M. Tangen, J. J. Crowley, M. S. Lucia, P. J. Goodman, L. M. Miniasian, L. G. Ford, H. L. Parnes, J. M. Gazzano, D. D. Karp, M. M. Lieber, P. J. Walther, L. Klotz, J. K. Parsons, J. L. Chin, A. K. Darke, S. M. Lippman, G. E. Goodman, F. L. Meyskens and L. H. Baker, *JAMA, J. Am. Med. Assoc.*, 2011, **306**, 1549–1556; (b) C. S. Yang, N. Suh and A.-N. T. Kong, *Cancer Prev. Res.*, 2012, **5**, 701–705; (c) E. R. Miller, R. Pastor-Barriuso, D. Dalal, R. A. Riemersma, L. J. Apple and E. Guallar, *Ann. Intern. Med.*, 2005, **142**, 37–46; (d) D. Q. Pham and R. Plakogiannis, *Ann. Pharmacother.*, 2005, **39**, 1870–1878.

265 J. Ju, S. C. Picinich, Z. Yang, Y. Zhao, N. Suh, A.-N. Kong and C. S. Yang, *Carcinogenesis*, 2010, **31**, 533–542.

266 J. Neuzil, M. Tomasetti, Y. Zhao, L.-F. Dong, M. Birringer, X.-F. Wang, P. Low, K. Wu, B. A. Salvatore and S. J. Ralph, *Mol. Pharmacol.*, 2007, **71**, 1185–1199.

267 M. Birringer, J. H. EyTina, B. A. Salvatore and J. Neuzil, *Br. J. Cancer*, 2003, **88**, 1948–1955.

268 (a) L.-F. Dong, G. Grant, H. Massa, R. Zobalova, E. Akporiaye and J. Neuzil, *Int. J. Cancer*, 2012, **131**, 1052–1058; (b) L.-F. Dong, R. Freeman, J. Liu, R. Zobalova, A. Marin-Hernandez, M. Stantic, J. Rohlana, K. Valis, S. Rodriguez-Enriquez, B. Butcher, J. Goodwin, U. T. Brunk, P. K. Witting, R. Moreno-Sanchez, I. E. Scheffler, S. J. Ralph and J. Neuzil, *Clin. Cancer Res.*, 2009, **15**, 1593–1600.

269 S. E. Campbell, W. L. Stone, S. Lee, S. Whaley, H. Yang, M. Qui, P. Goforth, D. Sherman, D. McHaffie and K. Krishnan, *BMC Cancer*, 2006, **6**, 13.

270 (a) R. Gysin, A. Azzi and T. Visarius, *FASEB J.*, 2002, **16**, 1952–1954; (b) Q. Jiang, J. Wong and B. N. Ames, *Ann. N. Y. Acad. Sci.*, 2004, **1031**, 399–400.

271 (a) P. W. Sylvester, M. R. Ald, A. Malaviya, P. Parajuli, S. Ananthula, R. V. Tiwari and N. M. Ayoub, *BioFactors*, 2014, **40**, 49–58; (b) W. Xu, Y. Mi, P. He, S. He and L. Niu, *Molecules*, 2017, **22**, pii: E1299.

272 M. M. Kanchi, M. K. Shanmugam, G. Rane, G. Sethi and A. P. Kumar, *Drug Discovery Today*, 2012, **17**, 1765–1781.

273 N. Guthrie, A. Gapor, A. F. Chambers and K. K. Carroll, *J. Nutr.*, 1997, **127**, 5445–5448S.

274 N. Guthrie, A. Gapor, A. F. Chambers and K. K. Carroll, *Asia Pac. J. Clin. Nutr.*, 1997, **6**, 41–45.

275 O. A. Alawin, R. A. Ahmed, B. A. Ibrahim, K. P. Briski and P. W. Sylvester, *J. Nutr. Biochem.*, 2016, **27**, 266–277.

276 K. Nesaretnam, R. Stephen, R. Dils and P. Darbre, *Lipids*, 1998, **33**, 461–469.

277 M. Wallert, S. Mosig, K. Rennert, H. Funke, M. Ristow, R. M. Pellegrino, G. Cruciani, F. Galli, S. Lorkowski and M. Birringer, *Free Radical Biol. Med.*, 2014, **68**, 43–51.

278 H. H. Sun, N. M. Ferrara, O. J. McConnell and W. Fenical, *Tetrahedron Lett.*, 1980, **21**, 3123–3126.

279 Q. Jiang, I. Elson-Schwab, C. Courtemanche and B. N. Ames, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 11494–11499.

280 M.-L. Yam, S. R. Abdul Hafid, H.-M. Cheng and K. Nesaretnam, *Lipids*, 2009, **44**, 787–797.

281 R. Loganathan, K. R. Selvaduray, K. Nesaretnam and A. K. Radhakrishnan, *Cell Proliferation*, 2013, **46**, 203–213.

282 F. Galli, A. M. Stabile, M. Betti, C. Conte, A. Pistilli, M. Rende, A. Floridi and A. Azzi, *Arch. Biochem. Biophys.*, 2004, **423**, 97–102.