Chapter 13

Brominated Molecules From Marine Algae and Their Pharmacological Importance

Vinod K. Mandrekar*, Umesh B. Gawas† and Mahesh S. Majik‡,1

*Department of Chemistry, St. Xavier's College, Mapusa, India

†Department of Chemistry, Dnyanprassarak Mandal's College and Research Centre, Assagao, India

‡Department of Chemistry, Goa University, Taleigao-Plaetau, India

1Corresponding author: e-mail: majik@unigoa.ac.in

Chapter Outline

INTRODUCTION

Nature has always challenged humans in terms of chemodiversity and has always gifted humanity with a wide variety of flora and fauna which subsequently gave rise to biodiversity. Each plant or animal species existing in a natural habitat has a unique and complex biosystem which is difficult in most cases for humans to mimic. Plants and animals produce a wide variety of chemical compounds which not only help them in overall growth and development but also protect them against predators. These phytochemicals also assist them during the mating process [1]. These organic compounds are very

Studies in Natural Products Chemistry, Vol. 61. https://doi.org/10.1016/B978-0-444-64183-0.00013-0

important for mankind, as many of the isolated molecules are reported to exhibit antiviral [2], antimicrobial [3], antibacterial [4], antitumor [5], and antioxidant activities [6]. Metabolites isolated from marine sources are termed natural products and the ones which show bioactivity are referred to as bioactive natural products. It is considered that the next generation of drug discoveries will be driven by products from marine sources.

Marine algae form part of the human diet because of their high nutritional values—being comprised of minerals, vitamins, lipids, and proteins. Algae are found to be rich in biochemically active compounds and therefore can be used as herbal medicines for the treatment of gall stones, stomach ailments, eczema, cancer, renal disorders, scabies, psoriasis, asthma, arteriosclerosis, ulcers, and diseases related to the heart and lungs. Moreover, marine algae are useful in various industrial, pharmaceutical, and food applications like biofuels, fertilizers, plastics, prosthetics, pollution control, dentistry, antacids, etc. The metabolites produced by marine algae play an important role in chemical ecology.

For several decades, marine algae have been recognized as a rich resource of new and unusual organic molecules with diverse biological properties. The current need to develop new antifungal, anticancer, antibiotic, and antiviral drugs led to intense research into the discovery, isolation, and structural elucidation of potential medicinal agents from marine algae. In addition, many natural products have been found to be useful as biochemical tools for exploring cellular processes at the molecular level. A number of reviews of the chemistry and biology of halogenated molecules from marine sources have appeared in the literature [7–10]. However, until now, no reviews on isolation studies of brominated molecules from marine algae have been encountered in the literature. Considering the potential of brominated organic molecules isolated from marine algae as future therapeutic agents, we have attempted to provide a snapshot of the compounds reported from 2005 to 2017. We sincerely apologize that due to length restrictions placed on this chapter the content discussed herein excludes a few research papers.

CLASSIFICATION OF MARINE ALGAE

Macroalgae or seaweeds are among the most widely distributed marine plant species, occurring all over the world in all kind of habitats. These are usually found attached to rocks or hard substrata. Algae are defined as oxygenic photosensitizers other than embryophyte land plants [11]. Algae found in marine environments are very diverse with respect to their shape, size, and color. They are popularly known by their common name—seaweeds. Based on their color or the pigments they contain, seaweeds are classified into three major phyla: (1) Chlorophyta (green algae), (b) Rhodophyta (red algae), and (c) Ochrophyta (brown algae). Moreover, green and red algae are considered as plants (kingdom Plantae), whereas brown algae belong to the Chromista kingdom.

All marine green algae are classified in a common class called Ulvophyceae, a diverse group containing 1760 species distributed in the sea [12]. These algae have high capacity to absorb nutrients from seawater, which helps them to grow faster in the sea. Here the representative genera include *Caulerpa*, *Halimeda*, and *Ulva*. Another class is red algae. It is the most ancient species with colors ranging from pink to bright red, purple, and dark brown. Phycobilin pigment is responsible for the color of this type of algae. Some red algae appear green when chlorophyll dominates over phycobilin. At present, about 7100 red algal species have been recognized [13]. These red algae are usually found in various forms which include branched, plant-like, small bush, or tree. Representative genera include *Lithothamnion*, *Gelidium*, *Porphyra*, *Delesseria*, etc. The brown algae are represented by about 2098 species, currently classified in the class Phaeophyceae of the phylum Ochrophyta [14]. They occur in different shapes and sizes like green and red algae. Only a few of these brown algae grow as filamentous thin branched threads on rocks in the intertidal zones of the oceans and some, like kelp, can be found in quite deep water. The largest known algae are also a species of brown seaweeds which belong to the order Laminariales. Representative genera include *Ascophyllum*, *Cystoseira*, *Macrocystis*, and *Pylaiella*. Phytochemical studies were widely performed on brown algae followed by red algae. Initially, research was more focused on red algae but subsequently shifted to other species. Although green algae are widely distributed in the marine environment, they are studied to a lesser extent compared with brown and red algae. The diminutive occurrence of exciting biologically active phytochemicals could be the reason for fewer reports of isolation studies on green algae.

ECONOMIC IMPACT AND ECOLOGICAL IMPORTANCE

Nowadays, seaweeds are considered an economical resource for the supply of chemicals and food products. These algae have been used as food sources and also as traditional medicines due to their high nutritional and pharmaceutical values [15,16]. According to McHugh et al. [17] about 8 million tons of wet seaweed is annually harvested worldwide. Stranded seaweed worth about US$ 7.2 billion has been utilized as a fertilizer, raw material for production of industrially important phytochemicals, and as a source of phycocolloids (agar, alginate, and carrageenan) [18]. The greatest contribution is from brown algae followed by red algae and green algae, respectively. Asian countries are ranked first in terms of their consumption of seaweed [19]. In recent years, the Americans and Europeans have realized the importance of seaweed consumption and consequently it is set to rise in the coming years [20]. As a consequence, the significance of seaweeds as natural resources has increased further throughout the world. Detailed analysis of the biochemical constitution and phytochemical [21] content of marine algae has led to the identification of

fiber, minerals, antioxidants, vitamins, pigments, steroids, lectins, halogenated compounds, polyketides, polysaccharides, mycosporine-like amino acids, proteins, polyunsaturated fatty acids, and other lipids. Nutrient content was found to be variable. Within the same genus of seaweed there were great distinctions in nutritional constituents, depending on specific species and prevailing environmental conditions [22,23].

Chemical ecology helps with the understanding of the role of natural products and their correlations with the environment in which species live [24]. It is a well-established fact that marine macroalgae are important members of food chains in aquatic ecosystems. Marine algae have developed a complex array of biologically active secondary metabolites over many years, due to their stressful living conditions, such as extreme competition for space, light, nutrients, and pollution [25,26]. Small consumers, generally referred as mesoherbivores or mesograzers, strongly influence the composition and/or structure of marine communities. To protect themselves from such grazers marine algae are constantly developing chemical defense mechanisms [27,28]. The bioactive chemicals produced by marine algae control interactions between marine organisms and hence regulate their populations, structures, communities, and the ecosystem functions [29,30]. Recently, our group has reported the chemical defense mechanism of brown alga *Sargassum tenerrimum* against grazers, and observed that a bioactive sterol was responsible for its defense [31]. Many review articles have been published in the literature regarding the chemical ecology of marine algae [32,33]. However, only a few of them have highlighted the ecological importance of halogenated compounds from marine algae [34]. Direct antifeedant assays are widely used by researchers to understand the defensive effects of halogenated molecules in algae.

A few examples of brominated compounds used by algae for defensive effects are: A bromosesquiterpene, i.e., preintricatol, the chamigrene type of terpenes which exhibited antifeedant activity against *Schizaphis graminum* [35]; and brominated diterpenes (deoxyparguerol, 2-deacetoxydeoxyparguerol, parguerol triacetate) which displayed potent feeding-deterrent activity against young abalone *Haliotis discus ssp. hannai* [36]. Various bromophenols are also reported to possess antifeedant activity [37]. A few other bromophenols were reported to be toxic for some unicellular marine algae (*Skeletonema costatum* and *Olisthodiscus*) species [38]. In 2009, Lane et al. [39] demonstrated the importance of brominated metabolites (that act via a surface-mediated defense against pathogenic microbes) from red alga *Callophycus serratus*. They further proved that, the bromophycolides from algal extracts inhibited growth of *Lindra thalassiae* (a marine fungal pathogen). Lumbang et al. [40] demonstrated the ecological significance of three brominated sesquiterpenes, isolated from green seaweed *Neomeris annulata*, that were found to be highly effective feeding deterrents against herbivores at concentrations equal to or below natural concentrations.

Marine algae supply oxygen to the biosphere and provide food for fish, gastropods, echinoderms (sea urchins and starfish), and humans. At the same time, they are important sources of medicines and fertilizers. Because of their beneficial significance macroalgae are among the preferred and more commonly explored marine organisms for research. Marine algae play a vital role in controlling water pollution, as bioreactors to absorb CO_2 emissions from industrial gas effluents, and as biofilters in the purification of sewage water. Overall, only few research groups are working in the area of chemical ecology and there is a need for a multidisciplinary approach between chemists, biologist, and oceanographers to facilitate in-depth exploration of this field in the near future.

MEDICINAL IMPORTANCE

Throughout history humankind has used plants and their extracts for healing wounds and treating many diseases as part of the medicinal systems of Ayurveda, Siddha, and Unani. Marine algae have developed complex defense strategies due to their exposure to stressful and competitive environments. This has ultimately led to the creation of diverse chemical skeletons via various metabolic pathways. Therefore the biosynthesis of many primary as well as secondary metabolites is ongoing, many of which possess potent biological activity. In South Korea, nourishing mothers prefer to eat seaweed for the first month after delivery, as this food is supposed to provide rich nutrients for the mother as well as for her newborn [41]. The herpes simplex virus type-1 (prevalent pathogens belonging to the human herpes virus family) is responsible for causing genital herpes infections in humans. In China, brown alga *Undaria pinnatifida*, also known as wakame, is used as a traditional medicine for the inhibition of herpes reactivation and the amelioration of active infections [42]. Halogenation often grants interesting key features for generating bioactivity in phytochemicals from marine algae that are well known for their biochemical pathways for synthesizing halogenated metabolites. Most of the halogenated molecules show diverse biological properties such as antibacterial, antifungal, antiviral, antiinflammatory, antiproliferative, antifouling, antifeedant, cytotoxic, ichthyotoxic, and insecticidal activity [43]. Nowadays people are very concerned about their health and therefore prefer cholesterol-free diets. Interestingly, ingestion of wakane is reported to reduce cholesterol levels in animal models [44]. Fucoidans are long branched chains of sulfated sugars found particularly in brown algae, such as *Fucus vesiculosus*, *Undaria*, and *Laminaria* [45]. Fucoidans are known to possess biological activities, such as inhibition of leukocyte movement into tissues [46], modulation of metastasis [47], antilipidemic activity [48], and potent antiviral activity [49]. Seaweeds and their extracts were extensively investigated by researchers around the world in search of new anticancer agents. Several research groups have successfully isolated extracts from brown algae which are responsible for the

inhibition of carcinogen-induced breast cancers, lung metastases, and leukemia in xenograft models [50–52]. The detailed pharmacological properties of brominated molecules obtained from marine algae are discussed in the next section.

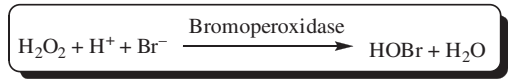
BROMINATED MOLECULES FROM ALGAE AND THEIR BIOLOGICAL ACTIVITIES

During the last few decades, oceanographers and biologists have also shown interest in researching marine algae in order to understand the ecological roles of the chemicals they produce [53]. Marine algae are unique in their defense mechanisms as they have to withstand stressful conditions during high/low tides and differences in exposure to sunlight when they remain submerged under water [3]. As a consequence, algae produce a variety of secondary metabolites to protect themselves from stressful environmental conditions. Many reviews have appeared in the literature deliberating on the biological and medicinal uses of marine algae. A vast number of compounds have been reported to date [54]. The presence of a bromine substituent in a natural product imparts a special biological importance to it [55]. In this chapter, we summarize bromine-containing natural products isolated from marine algae. The isolated molecules are categorized into three subclasses: (1) brominated terpenes, (2) phenolic and aromatic skeletons, and (3) miscellaneous brominated metabolites. Brominated terpenes and brominated phenols and aromatics contribute to the major share of chemicals reported from algae. Hence, we have discussed these two classes specifically. However, other important metabolites are placed together in the miscellaneous category, including diverse chemical families containing bromine substituents.

Mechanism for the Formation of Brominated Molecules in Algae

Brominated natural products from algae have been explored extensively for their structural characterization, ecological importance, and medicinal applications. It is well documented in the literature that vanadium haloperoxidase occurs abundantly in nature and is known to exist in large numbers of brown, red, and green algae [56]. Also, these enzymes are found in other marine phytoplankton like diatoms. Most of these seaweeds are known to contain vanadium bromo- and iodoperoxidase which helps in catalyzing the reaction of the substitution of bromine in organic molecules present as metabolites in marine algae [57]. One of the striking features of these enzymes is their stability under diverse environmental conditions. It is surprising to see their persistence in the environment even after death and decay of their host organism/algae [58]. The mechanism of introducing bromine into an organic molecule in marine algae occurs in two steps:

1. The first step involves the formation of HOBr by seaweeds using bromoperoxidases located at or near their surfaces. Most seaweeds contain vanadium bromo- or iodoperoxidase. The majority of halogenated compounds are formed by this enzymatic activity.



2. The second step involves the electrophilic attack or bromination of organic molecules (R-H) by HOBr.

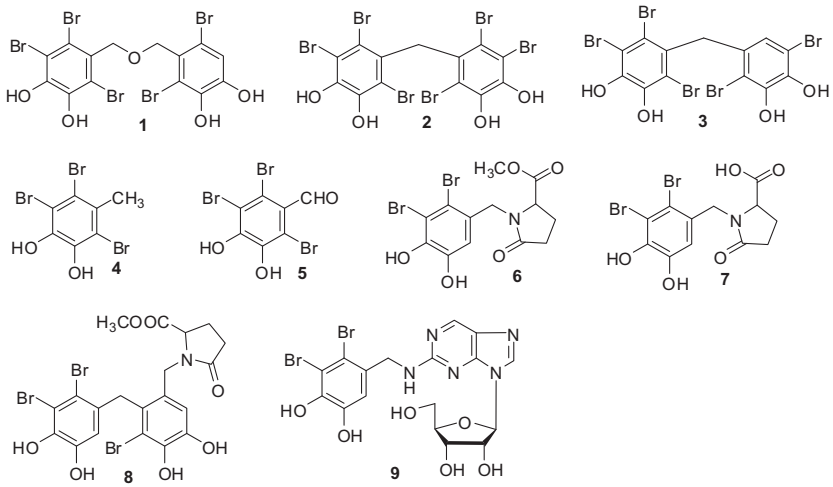
In 2001, Borchardt et al. [59] observed these phenomena in brown algae (*Laminaria digitata*, *Laminaria saccharina*, *Pelvetia canaliculata*). More recently in 2011, Sandy et al. [60] reported a similar process in another marine red alga *Delisea pulchra*. Wever et al. [61] reported another case study that supported HOBr biosynthesis by exposing alga *Ascophyllum nodosum*, in seawater, to direct sunlight and measuring HOBr generation. Hence, it can be concluded that the biosynthesis of brominated compounds by algae in the marine environment involves direct or indirect participation of vanadium haloperoxidases.

Brominated Phenolic and Aromatic Cores From Marine Algae

Aromatic rings with phenolic functionalities ranging from simple molecules to highly complex structures are widely found in many natural sources. It is interesting to note that the diverse phenolic skeletons in the marine world exist occasionally with halogen substituents. Red algae were extensively studied for chemical profiling and some were found to contain bromine substituted aromatic/phenolic cores as an important structural feature of their bioactivity. The presence of brominated compounds also protects algae from grazers.

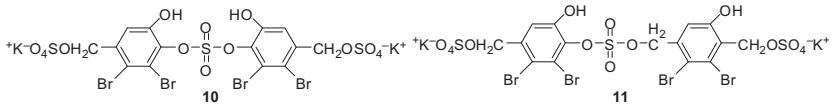
In 2005, Wang et al. [62] described the isolation and structural elucidation of three new bromophenols, i.e., 2,2′,3,6,6′-pentabromo-3′,4,4′,5-tetrahydroxydibenzyl ether (**1**), bis(2,3,6-tribromo-4,5-dihydroxyphenyl) methane (**2**), and 2,2′,3,5′,6-pentabromo-3′,4,4′,5-tetrahydroxydiphenylmethane (**3**), from red alga *Symphyocladia latiuscula* collected from the coast of Dalian, China. Similarly, two substituted bromophenols, i.e., 2,3,6-tribromo-4,5-dihydroxymethylbenzene (**4**) and 2,3,6-tribromo-4,5-dihydroxybenzaldehyde (**5**), were found from the same source—representing the first reported instance of their isolation. The aldose reductase (AR) inhibitory effects of isolated

compounds (**1**–**5**) were tested using the human muscle AR recombinant protein and were found to be better than the control, quercetin ($IC_{50} = 1.05\,\mu g/mL$), having IC_{50} values of 0.11, 0.40, 0.40, 1.15, 0.25 μg/mL for **1**–**5**, respectively.



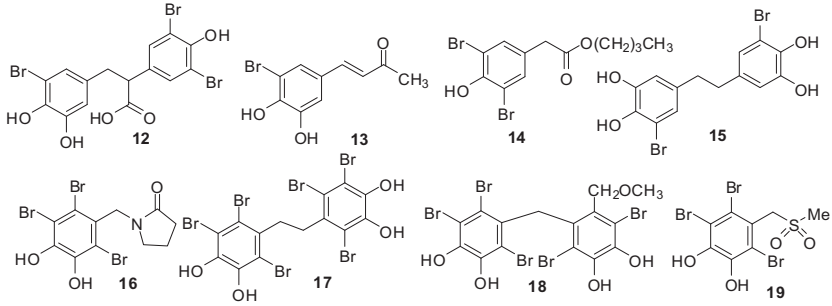
Further in 2005, Zhao et al. [63] reported other members of the bromophenol family containing pyroglutamic acid, its methyl esters (**6**–**8**), and deoxyguanosine (**9**) as substituents on a bromophenol ring from red alga *Rhodomela confervoides*. The isolated compounds were evaluated for their antimicrobial and anticancer activities [64]. However, these bromophenols were found to be inactive in both antimicrobial and anticancer assays.

Sulfated natural products are often reported from marine sources, however, very few sulfated secondary metabolites (other than polysaccharides) are known from marine red algae [65]. Two new sulfated bromophenols (**10** − **11**) were isolated by Carvalho et al. [66] from marine red alga *Osmundaria obtusiloba*. The applicability of a mild method of isolation and purification of sulfated compounds using Amberlite XAD-2 was the highlight of the work.



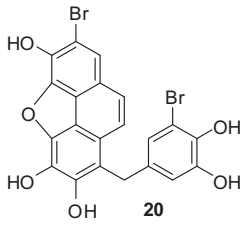
In 2007, Li et al. [6] reported isolation of three new naturally occurring bromophenols, i.e., 3-(3-bromo-4,5-dihydroxyphenyl)-2-(3,5-dibromo-4-hydroxyphenyl)propionic acid (**12**), (E)-4-(3-bromo-4,5-dihydroxyphenyl)-but-3-en-2-one (**13**), and (3,5-dibromo-4-hydroxyphenyl) acetic acid butyl ester (**14**), together with one known bromophenol, 1,2-bis(3-bromo-4,5-dihydroxyphenyl)ethane (**15**), from marine red alga *Polysiphonia urceolata*. The isolated compounds were tested for α,α-diphenyl-β-picrylhydrazyl

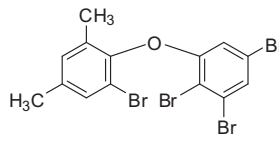
(DPPH) radical–scavenging activity and interestingly these compounds displayed significant activity with IC_{50} values ranging from 9.67 to 21.90 μm (83.84 μm for standard antioxidant butylated hydroxytoluene (BHT)).

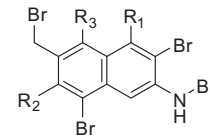


In 2007, Duan et al. [67] isolated four new members of bromophenols, i.e., 1-(2,3,6-tribromo-4,5-dihydroxybenzyl)-pyrrolidin-2-one (**16**), 1,2-bis(2,3,6-tribromo-4,5-dihydroxyphenyl) ethane (**17**), 6-(2,3,6-tribromo-4,5-dihydroxybenzyl)-2,5-dibromo-3,4-dihydroxybenzyl methyl ether (**18**), and 2,3,6-tribromo-4,5-dihydroxybenzyl methyl sulfone (**19**), from red alga *S. latiuscula*. These natural products (**16–19**) were evaluated for DPPH radical–scavenging activity and all were found to be potent, with IC_{50} values of 18.5, 10.2, 10.5, 24.0 μM, respectively (IC_{50} value of control BHT was 81.8 μM).

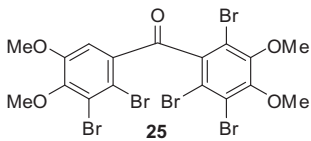
Li et al. [68] demonstrated the purification and structural elucidation of Urceolatin (**20**), a highly oxygenated bromophenol containing a benzykphenanthro [4,5-bcd] furan structural unit from red alga *P. urceolata*. They have also proposed a biogenetic pathway in which the intermolecular free-radical reactions [69] represented the key step, involving three molecules of 3-bromo-5-(hydroxymethyl)-benzene-1,2-diol to form Urceolatin. Compound **20** displayed significant DPPH radical–scavenging activity with an IC_{50} value of 7.9 μM compared with the positive control BHT with an IC_{50} value of 83.8 μM.



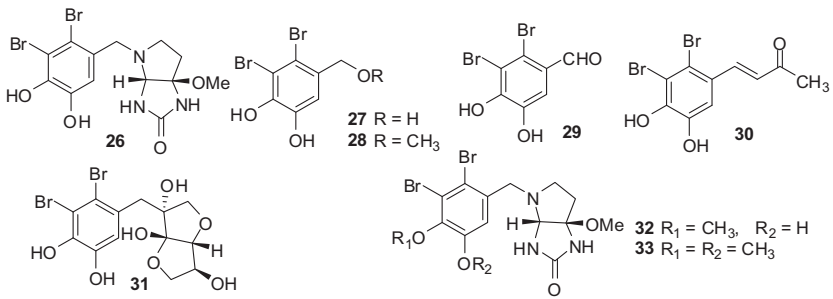




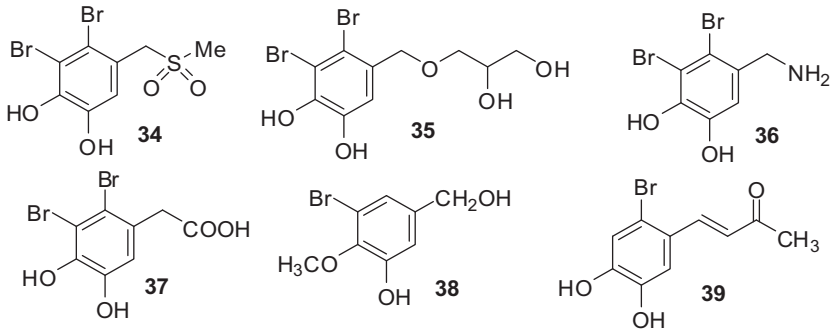
22 R_1 = Br, R_2 = H, R_3 = H
23 R_1 = H, R_2 = H, R_3 = Br
24 R_1 = H, R_2 = Br, R_3 = H



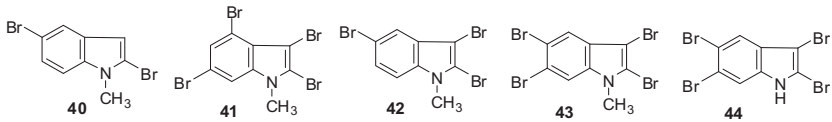
In 2010, Qin et al. [70] reported five novel highly brominated secondary metabolites from the extract of marine red alga *Laurencia similis*, i.e., a brominated diphenyl ether derivative **21**, three bromonaphthalene compounds (**22–24**), and a benzophenone derivative (**25**), characterized using various spectroscopic techniques. These compounds were tested against protein tyrosine phosphatase 1B (PTP1B) inhibitory activities. Compounds **21** and **25** showed strong inhibition with IC_{50} values of 2.97 and 2.66 μM, respectively, whereas compounds **22**, **23**, and **24** displayed moderate inhibitory activity on PTP1B with IC_{50} values of 102, 65.3, 69.8 μM, respectively. In 2009, Popplewell et al. [71] described the isolation of colensolide A, a novel nitrogenous bromophenol, along with bromophenol lanosol and four of its derivatives from marine red alga *Osmundaria colensoi*, found along the New Zealand coast. Compounds (**26–33**) were isolated from a methanolic extract of the alga using polymeric reversed-phase chromatography (PSDVB). These compounds were evaluated for their cytotoxic and antibacterial activity. Lanosol butenone (**30**) showed moderate activity against human leukemia cells with an IC_{50} value of 8.0 μM, whereas lanosol methyl ether (**28**), lanosol butenone (**30**), and rhodomelol (**31**) displayed moderate activity against the MC2155 strain of *Mycobacterium smegmatis* bacteria with IC_{50} values of 7.8, 26.2, and 28.1 μM, respectively.



In 2011, Li et al. [72] reported the structural elucidation and antioxidant activity of bromophenols (**34–39**) from marine red alga *R. confervoides*. Out of the 19 bromophenols, 6 were new and most of the isolated compounds displayed significant antioxidant activity against DPPH and ABTS radicals. These results indicate that consumption of marine algae could provide health benefits due to their antioxidant properties, provided that the compounds are not toxic. The novel compounds from this source include 3,4-dibromo-5-((methylsulfonyl) methyl)benzene-1,2-diol (**34**), 3,4-dibromo-5-((2,3-dihydroxypropoxy)methyl)-benzene-1,2-diol (**35**), 5-(aminomethyl)-3,4-dibromobenzene-1,2-diol (**36**), 2-(2,3-dibromo-4,5-dihydroxyphenyl)acetic acid (**37**), 2-methoxy-3-bromo-5-hydroxymethylphenol (**38**), and (E)-4-(2-bromo-4,5)dihydroxyphenyl) but-3-en-2-one (**39**).



Indole derivative: An indole alkaloid 2,5-dibromo-*N*-methylindole (**40**) was isolated from the organic extract of red alga *L. similis*, along with seven terpenoids. The structure was assigned based on detailed mass-spectrometry and 1-D and 2-D NMR spectroscopy [73]. In 2007, Ji et al. [74] reported the isolation of 2,3,4,6-tetrabromo-1-methyl-1H-indole (**41**), 2,3,5-tribromo-1-methylindole (**42**), and 2,3,5,6-tetrabromo-1-methylindole (**43**) from marine red alga *Laurencia decumbens*. All polybromoindoles were purified by column chromatography using silica gel, Sephadex LH-20, and finally with preparative TLC.



Later in 2015, Rahelivao et al. [75] reisolated other members of the brominated indoles (**41–43**) along with sesquiterpene debilone from alga *Laurencia complanata*. The column chromatographic separation gave two fractions: one containing mixtures of two compounds identified as the brominated indole alkaloids 2,3,5-tribromo-1-methylindole (**42**) and 2,3,5,6-tetrabromo-1-methylindole (**43**) with a 3:1 ratio as determined by GC–MS; the other fraction led to characterization of tetrabromoindole (**44**), whose biological activity against L-1210 tumor cells in a tissue culture was previously reported with an ID_{50} value of 3.6 μg/mL [76]. Compounds (**42**) and (**43**) displayed mild antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* in an agar diffusion test.

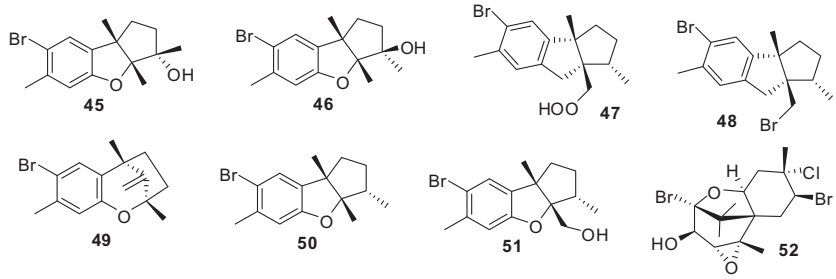
Brominated Terpenes From Marine Algae

In the last few years natural sources have been well known for producing a class of compounds belonging to the terpene family. An important feature of naturally occurring terpene oils is their volatile nature. Hence, this class of compound has become popular and plays an important role in the chemical

ecology of the environment. They serve as allelochemicals, pheromones, defensive agents against herbivores, signaling molecules, etc. Moreover, the terpenoid family is the dominant class of chemicals most commonly encountered in marine sources [77]. Natural marine terpenoids containing various substituents are known to display potent biological efficiency in a variety of assays, such as antiviral, antimalarial, antitubercular, etc.

Sesquiterpenoids

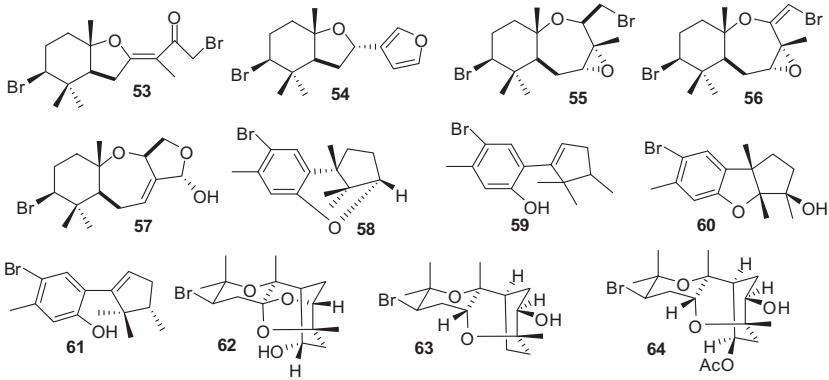
In 2005, Sun et al. [78] purified two new brominated sesquiterpenoids, i.e., 10-hydroxyepiaplysin (**45**) and 10-hydroxyaplysin (**46**), from the ethanolic extract of air dried red alga *Laurencia tristicha*. The structures were confirmed based on HSQC experiments. Isolated molecules were evaluated for cytotoxic activity against several human tumor cell lines such as HCT-8, Bel-7402, BGC-823, and A549, but showed mild activity with IC_{50} values greater than 10 μg/mL.



In 2005, Mao et al. [79] isolated two new brominated cuparene-derived sesquiterpenoids, i.e., laureperoxide (**47**) and 10-bromoisoaplysin (**48**), along with other known molecules from the organic extract of *Laurencia okamurai* Yamada. Compounds (**47**) and (**48**) were evaluated for antifungal activity and were found to be inactive against fungus *Cladosporium cucumerinum*. Later in 2005, Sun et al. [80] described the isolation of a series of sesquiterpenoids from red alga *L. tristicha*. Among the list of 14 isolated compounds the share of brominated sesquiterpenes includes 4-bromo-1, 10-epoxylaur-11-ene (**49**), aplysin (**50**), aplysinol (**51**), and johnstonol (**52**). All metabolites (**49–52**) were found to be moderately active with IC_{50} values greater than 10 μg/mL against several human cancer cell lines such as lung adenocarcinoma (A549), stomach cancer (BGC-823), hepatoma (Bel 7402), colon cancer (HCT-8), and HELA cell lines.

Furthermore, in 2005, Kuniyoshi et al. [81] described the chemical investigation of marine red alga *Laurencia luzonensis* collected from the reef at Kudaka Island, Okinawa. They succeeded in purification of five new sesquiterpenoids belonging to snyderane class of sesquiterpenoids, i.e., luzonenone (**53**), luzofuran (**54**), 3,4-epoxypalisadin B (**55**), 1,2-dehydro-3,4-epoxypalisadin

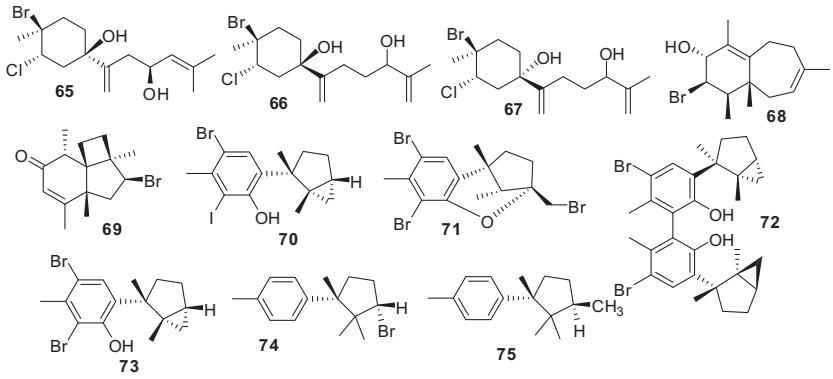
B (**56**), and 15-hydroxypalisadin A (**57**). Surprisingly, neither the biological activities nor the synthetic studies for these natural products (**53–57**) have been explored to date.



Phytochemical studies of the organic extract of marine red alga *Laurencia microcladia* found it to contain two brominated cuparene squiterpenoids (**58**) and (**59**) [82]. The isolated metabolites were evaluated for cytotoxicity studies. Compound (**58**) showed moderate activity with IC_{50} values of 196.9 μM against NSCLC-N6 and 242.8 μM against A549 cancer cell lines. Compound (**59**) displayed significant activity with IC_{50} values of 73.4 μM (NSCLC-N6) and 52.4 lM (A549). They proposed compound (**59**) as an artifact or rearranged product of compound (**58**), but were unable to prove the hypothesis based on experimental work. Phytochemical studies of Chinese red alga *L. okamurai* resulted in the isolation of 3β-hydroxyaplysin (**60**) and laurokamurene A (**61**), along with other known natural products [83]. Compounds (**60**) and (**61**) were found to be inactive for antifungal activity against *C. cucumerinum*, although many *Laurencia* sesquiterpenes are reported to possess antibacterial and antifungal properties [84]. In 2006, Carvalho et al. [85] reported the purification of three novel brominated oxacyclic classes of basabolene-type sesquiterpenoids, i.e., aldingenin B, C, and D (**62–64**), from the organic extract of red alga *Laurencia aldingensis*. The structures were proposed based on extensive NMR studies. Furthermore, in 2012 Crimmins et al. [86] synthesized the proposed structure on aldingenin B (**62**). However, it did not match with the characterization data of the isolated natural product. They have suggested that the structure was misinterpreted and needs to be reassigned.

Three new halogenated β-bisabolene sesquiterpenoids (**65–67**) were isolated from marine red alga *Laurencia scoparia* [87]. Extensive NMR and mass spectrometric analysis were used for the structural analysis of all three molecules. The structure of compound (**65**) was confirmed by single-crystal

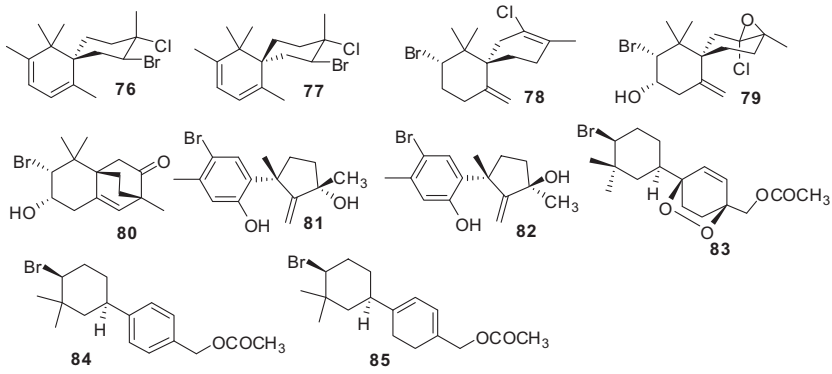
X-ray crystallographic analysis. Moreover, the authors could not determine the absolute configuration at C-10 in compounds (**66–67**) due to an inadequate number of metabolites from the natural source. Compound (**65**) was found to possess moderate antiparasitic activity, with an in vitro EC_{50} value of 0.11 mM against *Nippostrongylus brasiliensis*, whereas compounds (**66**) and (**67**) were inactive.



Kladi et al. [88] described the isolation and structural characterization of two new brominated sesquiterpenes (**68–69**) from marine red alga *Laurencia obtusa*. The alga was collected from the coastal rocks of the Aegean Sea. The isolated metabolites were tested for cytotoxicity against five human tumor cell lines, i.e., K562, MCF7, PC3, HeLa, A431, and CHO (Chinese hamster ovary). Compound (**68**) showed consistent cytotoxicity with IC_{50} values of 28.2–80.2 μM, whereas compound (**69**) displayed moderate activity with IC_{50} values ranging from 111.3 to >300 μM. Furthermore, the phytochemical studies by Kladi et al. [89] on marine red alga *L. microcladia*, collected from Chios Island in the North Aegean Sea, led to the isolation of several known and unknown terpenoids. A few new brominated sesquiterpenoids (**70–71**, **73–75**) and dimeric bromosesquiterpenoid (**72**) were isolated from the organic extract of the alga. The compounds were purified by vacuum column chromatography and normal phase HPLC methods. Metabolites (**70–75**) were evaluated for their cytotoxicity against HT29, MCF7, PC3, HeLa, and A431 cell lines. All metabolites were found to possess significant toxicity among which compounds (**70**) and (**73**) displayed relatively higher cytotoxicity against tested human cell lines with IC_{50} values of 75.2 (PC3) and 78.4 (HT29), respectively.

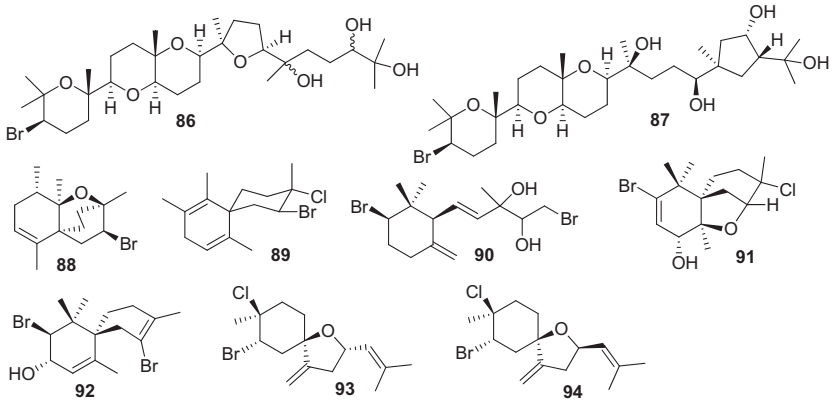
In 2007, Ji et al. [90] isolated two novel diasterioisomers of brominated sesquiterpenoids (**76–77**) and other known natural products from the chloroform extract of marine red alga *L. okamurai* Yamada. Diastereomers (**76** and **77**) were

inseparable by column chromatography and preparative thin layer chromatographic techniques. The structures were assigned based on the well-resolved duplicate peaks in NMR spectra. The structures were further confirmed with the aid of 2-D NMR, HMQC, HMBC, and COSY experiments.



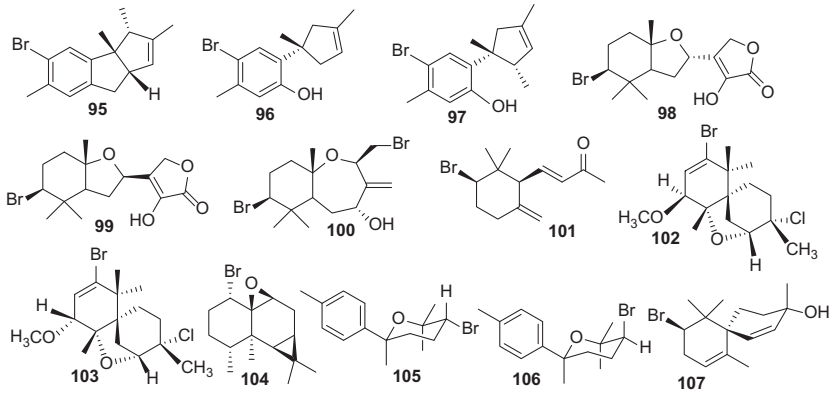
Furthermore, in 2007, they described the isolation of 10 compounds which included 3 brominated sesquiterpenoids, i.e., 9-deoxyelatol (**78**) and two synthetically known sesquiterpenes (**79**) and (**80**), from marine red alga *Laurencia mariannensis* [91]. Interestingly, compounds (**79**) and (**80**) were previously reported (in 1982) as intermediates in a biomimetic construction of rhodolaureol and rhodolauradiol [92]. Compound (**78**) showed weak antibacterial activity against *S. aureus* and *E. coli*, as well as weak antifungal activity against *C. albicans* and *Aspergillus niger*. In 2008, they reported isolation of laurane-derived brominated sesquiterpenes, i.e., 4-bromolaur-11-en-1,10α-diol (**81**) and 4-bromolaur-11-en-1,10β-diol (**82**), from marine red alga *L. tristicha*, along with other phytochemicals [93]. Vairappan et al. [94] reported isolation of three halogenated sesquiterpenes, i.e., acetylmajapolene A (**83**), acetylmajapolene B (**84**), and tiomanene (**85**), from Malaysian *Laurencia* species collected from Pulau Tioman. Acetylmajapolene A (**83**) showed moderate activity while tiomanene (**85**) was found to display weak antibacterial properties. Acetylmajapolene B (**84**) was inactive against marine bacteria *Chromobacterium violaceum*, *Proteus mirabilis*, *Proteus vulgaris*, and *Erwinia* sp. (*Vibrio parahaemolyticus* and *Vibrio alginolyticus*) [94]

Two new highly oxygenated bromosesquiterpinoids, i.e., laurenmariannol (**86**) and (21α)-21-hydroxythyrsiferol (**87**), were isolated from the organic extract of marine red alga *L. mariannensis* [95]. Compounds (**86**) and (**87**) were found to exhibit good cytotoxicity toward the P-388 tumor cell line with IC_{50} values of 0.6 and 6.6 μM, respectively, versus the positive control VP-16 (etoposide, with an IC_{50} value of 0.30 μM).



Furthermore, in 2009, they reported two more brominated sesquiterpenoids, i.e., 2-bromospironippol (**88**) and laurencomposidiene (**89**), from the organic extract of red alga *Laurencia composita* [96]. They demonstrated the ecological significance of the isolated molecules as new reference compounds useful in distinguishing two species of marine algae collected from different locations, i.e., *L. composita* and *L. okamurai*. Su et al. [97] reported a dibrominated sesquiterpene (**90**) from the organic extract of marine red alga *L. similis*. The presence of two bromine atoms in the molecule was concluded from the cluster of peaks at 399/401/403(1:2:1) $[M\text{-}H_2O+Na]^+$ in ESI-MS. The molecule was found inactive toward the human liver adenocarcinoma (BEL7402) cell line with an IC_{50} value greater than 10 μg/mL. Furthermore, *Laurencia saitoi*, a marine red alga from the coast of China was found to contain four new brominated sesquiterpenoids, i.e., 10-bromo-3-chloro-2,7-epoxychamigra-9-en-8α-ol (**91**), 2,10β-dibromochamigra-2,7-dien-9α-ol (**92**), (9S)-2-bromo-3-chloro-6,9-epoxybisabola-7(14),10-diene (**93**), and (9R)-2-bromo-3-chloro-6,9-epoxybisabola-7 (14),10-diene (**94**) [98].

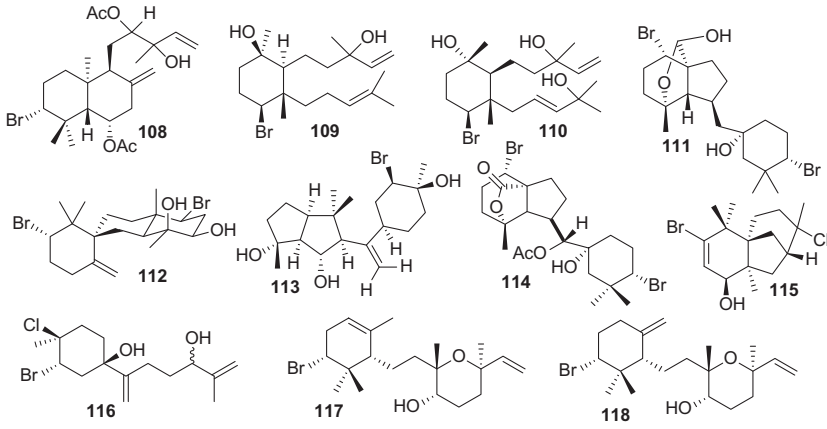
Phytochemical studies of the Australian marine alga *Laurencia filiformis* gave two new sesquiterpenoids, i.e., cycloisoallolaurinterol (**95**) and isoallolaurinterol (**96**), along with other known terpenoids [99]. Chemical constituent profiling of the extract and the interconversion of the secondary metabolites were studied using both an on-flow and stop-flow HPLC–NMR technique. They proposed that both compounds (**95**) and (**96**) are formed as artifacts from allolaurinterol (**97**). In 2009, Su et al. [100] reported the isolation of four new sesquiterpenes, i.e., 2-hydroxyluzofuranone (**98**), 2-hydroxyluzofuranone B (**99**), 4-hydroxypalisadin C (**100**), and 2-bromo-g-ionone (**101**), from marine red alga *L. saitoi*. However, there are no reports on the biological activity of these molecules.



Two brominated C_{16} chamigrenes, i.e., cycloelatanene A (**102**) and B (**103**), were isolated from the Australian marine alga *Laurencia elata*, along with other known terpenoids [101]. They used different spectroscopic methods for structure elucidation of the isolated pure compounds. Relative configurations were assigned using selective 1-D NOE NMR analysis, however, the absolute configurations of the molecules were not known. The crystalline sponge method was subsequently used by Lee et al. [102] to assign the absolute configuration of the molecules (**102 − 103**). This newly developed X-ray technique involves absorption of the oily compounds on the crystalline porous complexes that have ordered cavities. The compounds show mild antitumor activity. In 2010, Li et al. [73] isolated a new brominated sesquiterpenoid (**104**) along with several known terpenoids and indole derivatives from marine red alga *L. similis*, collected from Malaysian Borneo. In 2012, Liang et al. [103] isolated three new sesquiterpenoids (**105–107**), two bisabolanes (**105–106**), and one chamigrane derivative (**107**) from *L. okamurai*, in addition to a number of diverse secondary metabolites. Compounds (**105–107**) show moderate or weak activity against brine shrimp *Artemia salina*.

Diterpenoids

In 2005, Suzuki et al. [104] reported isolation studies of a novel brominated diterpene (**108**) along with other known terpenoids from unknown red algae species found along the coast of Japan. Another new diterpene named luzudiol (**109**), possessing a new carbon skeleton, was isolated along with five new sesquiterpenes from red alga *L. luzonensis*. In 2007, Ji et al. [74] isolated two new natural products (**110 − 111**) from an organic extract of marine red alga *L. decumbens*. Its spectral characterization upon interpretation revealed two brominated diterpines, i.e., laurendecumtriol (**110**) and 11-*O*-deacetylpinnaterpene C (**111**).

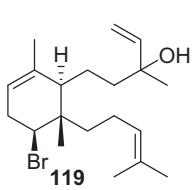


A new diterpene, 10-hydroxykahukuene B (**112**), was isolated along with other phytochemicals from marine red alga *L. mariannensis*. Compound (**112**) displayed weak antibacterial activity against *S. aureus* and *E. coli*, with a zone inhibition diameter of 6.5 mm [91]. In 2009, Chatter et al. [105] described the isolation of a new tricyclic brominated diterpenoid, neorogioltriol (**113**), from the organic extract of marine red alga *Laurencia glandulifera*. The species was collected from the island of Kefalonia in western Greece. The isolated compound (**113**) displayed antiinflammatory activity and was found to inhibit NF-κB transactivation and TNFα release at concentrations below 62.5 μM.

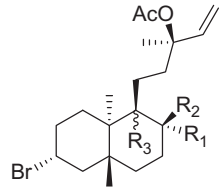
A new brominated diterpene, 10-acetoxyangasiol (**114**), was isolated from an unknown Malaysian red alga species of genus *Laurencia*, collected from the coastal waters of Borneo [106]. The compound was obtained by purification of organic extract with column chromatography and HPLC. The structure and stereochemistry was assigned based on HR-ESI-TOFMS, NMR, COSY, HSQC, and NOESY. Compound (**114**) showed a minimum inhibitory concentration value of 100 μM against *Vibrio cholerae*. In 2010, Ji et al. [107] reported two novel brominated terpenoids (**115**) and (**116**) isolated from marine red alga *Laurencia composita*. The stereochemistry and structure of both the compounds were confirmed by mass and NMR spectroscopic analysis. Kladi et al. [108] isolated two brominated diterpenoids, i.e., glandulaurencianols A (**117**) and B (**118**), from red alga *L. glandulifera*. Compound (**117**) was previously isolated from the mollusk *Aplysia punctate*, indicating that mollusks feed on these red algae.

A brominated diterpene (**119**), sphaerodactylomelol, belonging to the dactylomelane family, along with several known organic compounds, were obtained from red alga *Sphaerococcus coronopifolius* harvested from the Portuguese coast [109]. Compound (**119**) was cytotoxic toward human cancer cell lines of hepatocellular carcinoma (IC_{50} value of 720 μM), induced

inhibition of cell proliferation (IC_{50} value of 280 μM), and displayed moderate antibacterial activity toward *S. aureus* (IC_{50} value of 96.3 μM).



119

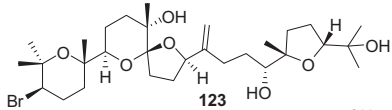


120 R_1 = OH, R_2 = Me, R_3 = H
121 R_1 = Me, R_2 = OH, R_3 = H
122 R_1 = H, R_2 = Me, R_3 = OH

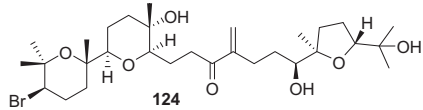
Dziwornu et al. [110] in their recent report revealed three new brominated labdane class diterpenes (**120 − 122**) isolated from the organic extract of marine red alga *Laurencia alfredensis*. The compounds were tested for antiproliferative activity against MDA-MB-231 triple negative breast carcinoma and HeLa human cervical carcinoma. Compound (**121**) exhibited the best antiproliferative activity against the tested cancer cell lines (IC_{50} value of 9.3 μM against breast carcinoma).

Triterpenes

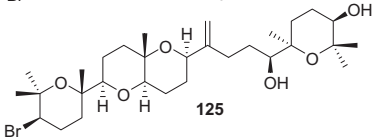
In 2010, Cen Pacheco et al. [111] reported the purification of two new squalene-derived triterpene polyethers, i.e., spirodehydrovenustriol (**123**) and 14-keto-dehydrothyrsiferol (**124**), from the organic extract of marine alga *Laurencia viridis*. Compound (**123**) did not show any cytotoxic effects against Hs578T and T47D breast cancer cell lines below a concentration of 10 μg/mL. Furthermore, in 2011, they reported two new brominated polyether triterpenes, namely, iubol (**125**) and 22-hydroxy-15(28)-dehydrovenustatriol (**126**), along with other secondary metabolites from marine red alga *L. viridis* [112]. Compounds (**125**) and (**126**) showed the highest cytotoxicity, with IC_{50} values the range of 2.0–3.5 μM, against human tumor cell lines. The compounds were also found to be active against the CADO-ES1 human Ewing's sarcoma cell line.



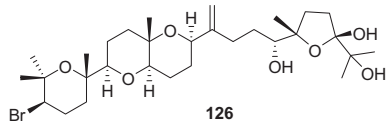
123



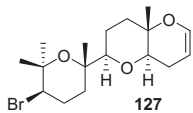
124



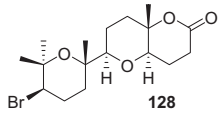
125



126



127

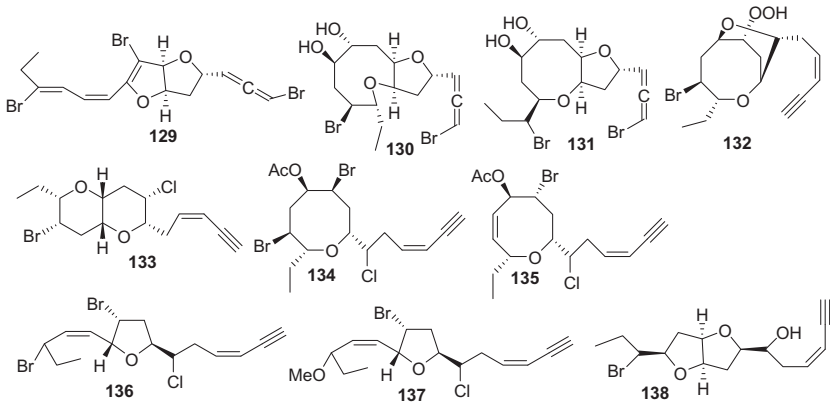


128

Two new C_{17} terpenoids, i.e., adejen A (**127**) and adejen B (**128**), were isolated during the phytochemical content study of marine red alga *L. viridis*, along with two novel triterpenoids [111]. The spectral data of the new compounds revealed structural similarity to the spectra of the known compound thyresenol A. Furthermore, the exact structures and stereochemistry were assigned based on NMR, MS, COSY, ROESY, and other experiments.

C_{15}-acetogenins

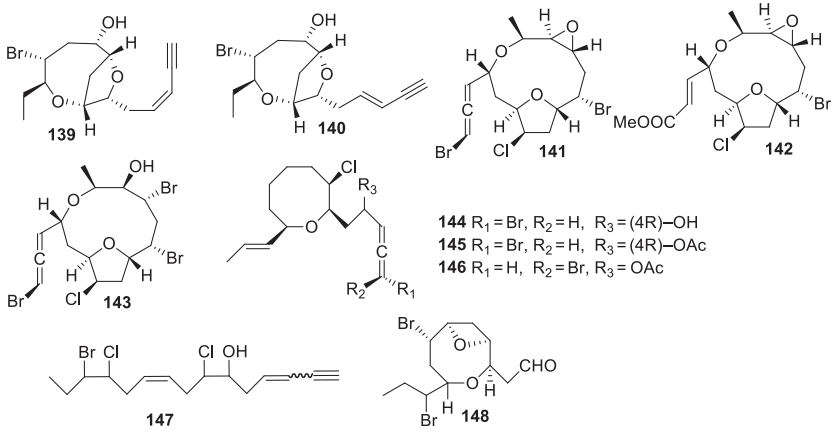
In 2007, Ji et al. [91] successfully isolated a new C_{15}-acetogenin named, laurenmariallene (**129**), from marine red alga *L. mariannensis*. It was evaluated for its antibacterial activity against *S. aureus* and *E. coli* and antifungal activity against *C. albicans* and *A. niger*. Compound (**129**) showed minimal antibacterial activity against *E. coli* with a zone inhibition diameter of 7.0 mm and was found inactive against fungi.



Furthermore, in 2007, they reported four new C_{15}-acetogenins, i.e., laurendecumallene A (**130**), laurendecumallene B (**131**), laurendecumenyne A (**132**), and laurendecumenyne B (**133**), which were isolated from the organic extract of marine red alga *L. decumbens* [113]. None of these C_{15}-acetogenins displayed any significant cytotoxicity toward tumor cell line A549. Two new brominated C_{15}-acetogenins (**134–135**) were isolated along with other acetogenins from the organic extract of marine red alga *L. glandulifera*, collected from the island of Crete in Greece [114]. Compounds (**134–135**) did not show any antistaphylococcal activity against drug resistant *S. aureus* at a concentration of 128 μM. In 2009, Kladi et al. [115] reported the isolation of two new brominated C_{15}-acetogenins (**136–137**), having a rare tetrahydrofuran moiety, from an organic extract of *L. glandulifera*. Compounds (**136–137**) did not show any significant cytotoxicity toward tested human tumor cell lines. Halogenated C_{15}-acetogenins and sesquiterpenoids are

known to occur as secondary metabolites in various species of marine red algae. A new C_{15}-acetogenin, namely, laurenidificin (**138**), was purified from the ethyl acetate fraction of the crude extract of *Laurencia nidifica* [116].

Two new brominated cyclic ether acetogenins (**139–140**) and four new acetogenins were isolated from a marine red alga from an unknown source collected in the Philippines. The brominated cyclic ethers were *cis–trans* isomers, and were named laurefurenynes E (**139**) and F (**140**) [117]. Compound (**139**) showed very weak cytotoxic activity against a solid tumor murine colon 38 cell line, while compound (**140**) was found to be moderately cytotoxic against human tumor cell line leukemia L1210 and human normal cells CFU-GM.



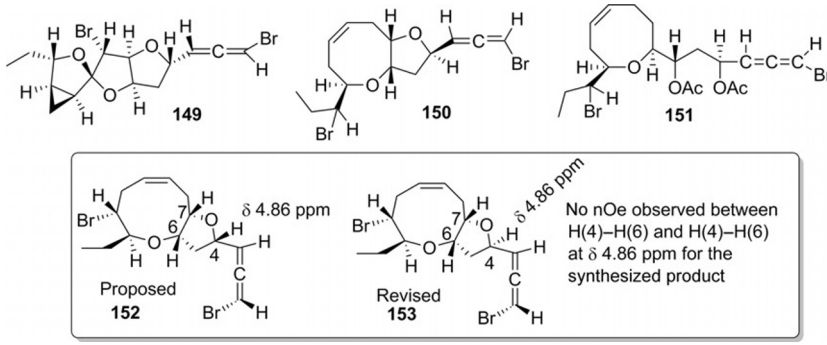
In 2011, other members of halogenated C_{15}-acetogenins (**141–147**) were isolated from marine red alga *Laurencia marilzae*. All the compounds were evaluated for their cytotoxicity toward human tumor cell lines and were found to be inactive [118]. Liang et al. [103] isolated a new acetogenin, okamuragenin (**148**), along with several sesquiterpenoids from marine red alga *L. okamurai*.

Miscellaneous Brominated Compounds From Marine Algae

Marine algae are known to produce a variety of brominated compounds. In addition to brominated aromatic or terpene molecules described in the sections entitled "Brominated Phenolic and Aromatic Cores from Marine Algae," "Brominated Terpenes from Marine Algae," and "C_{15}-acetogenins," many other diverse groups of chemicals are found in marine algae. In 2013, Wang and coauthors [119] wrote an excellent review on the topic entitled "Halogenated Organic Molecules of Rhodomelaceae Origin: Chemistry and Biology," covering a survey of 697 different secondary metabolites isolated

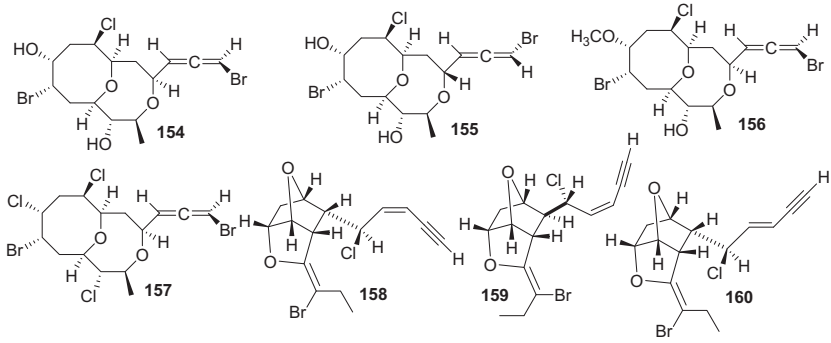
from species belonging to the family Rhodomelaceae. In this section, we have attempted to present various brominated molecules from different chemical families isolated from marine algae.

In 2005, Suzuki and coworkers [104] described the purification and structural elucidation of a new brominated allene (**149**) from the extract of an unknown red alga belonging to the *Laurencia* species, collected from Japanese waters. They successfully characterized this new compound belonging to a C_{15}-acetogenin family and named it chinzallene. Lyakhova et al. [120] reported two new brominated allenes, i.e., nipponallene (**150**) and neonipponallene (**151**), isolated from red alga *Laurencia nipponica*, collected from Russian shores. The structure and absolute stereochemistry of the molecules were determined using NMR spectroscopy, modified Mosher's method, chemical transformations, along with biogenetic understanding. To determine the absolute stereochemistry of nipponallene (**150**), i.e., either 4R,6S,7S,12R or 4S,6R,7R,12S, its hydrogenation over Adams catalyst was carried out to give a known product (laurallene analogue) which was previously studied and comprehends (4R,6S,7S,12R) absolute stereochemistry [121]. This was further confirmed using Mosher's method [122].



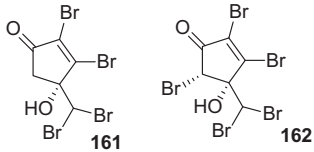
In 2002, Suzuki et al. [123] isolated (+)-itomanallene A (**152**) from marine red alga *Laurencia intricate*, collected from Itoman, Japan. However, the relative stereochemistry of the bromoallene unit and the bicyclic skeleton was not properly determined, hence, two possible structures were proposed for the molecule. The exact structure was confirmed by Jeong et al. [124] using the asymmetric total synthesis of itomanallene A (**153**). The ^{1}H NMR spectrum of synthesized compound (**153**) differs from that of natural itomanallene A (**152**), however, it has the same specific optical rotation value. Careful observation using NMR spectroscopy indicated that the chemical shift values of the C-4 protons were significantly different in both molecules. Furthermore, NOE experiments revealed the presence of α, α′-*trans*-tetrahydrofuran connectivity at C-4 and C-6 protons rather than *cis* connectivity which was proposed in the original isolation report.

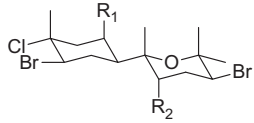
Gutiérrez-Cepeda et al. [125] described the isolation, structural elucidation, and biogenetic pathway of four new brominated allenes, i.e., marilzabicycloallenes A–D (**154–157**), from red alga *L. marilzae* collected from the Canary Islands. The nonterpenoid compounds contained a [5.5.1]bicyclotridecane ring system in their structure. Compounds (**154**) and (**155**) were tested for antiproliferative activity against six human tumor cell lines, i.e., A2780 (ovarian), HBL-100 (breast), HeLa (cervix), SW1573 (nonsmall-cell lung), T-47D (breast), and WiDr (colon), at a concentration of 10 μg/mL. However, no significant activity was observed.



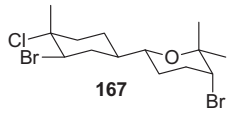
In 2011, Ayyad et al. [126] reported three new brominated C_{15}-acetogenins, i.e., (12Z)-*cis*-maneonene-D (**158**), (12E)-*cis*-maneonene-E (**159**), and (12Z)-*trans*-maneonene-C (**160**), isolated from the organic extract of red alga *L. obtusa*. These metabolites were evaluated for their apoptosis-inducing or inhibiting effect with IC_{50} values of the tested compounds being 23 μM for (**158**), 15 μM for (**159**), and 0.9 μM for the positive control dexamethasone. The isolated compounds (**158–160**) from the red alga were responsible for the regulation of programmed death in the initiation and propagation of inflammatory responses.

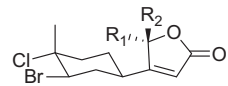
In 2014, Greff et al. [127] described the isolation and ecological importance of two brominated cyclopentenones derivatives, i.e., mahorone (**161**) and 5-bromomahorone (**162**), from the organic extract of red alga *Asparagopsis taxiformis*, collected from Mayotte in the Indian Ocean. The natural 2,3-dibromocyclopentenone derivatives (**161–162**) were the first of their class isolated from the source. Both compounds were evaluated for antibacterial activity against various strains such as *Acinetobacter baumannii*, *E. coli*, *Pseudomonas aeruginosa*, and *S. aureus*. Mahorone (**161**) and (**162**) showed mild antibacterial activity against the human pathogen *A. baumannii* with MIC_{80} values of 8 and 16 μg/mL, respectively.





163 R_1 = OAc, R_2 = OH
164 R_1 = OH, R_2 = OAc
165 R_1 = OAc, R_2 = OAc
166 R_1 = OAc, R_2 = H





168 R_1 = Me, R_2 = OMe
169 R_1 = OMe, R_2 = Me

Lhullier et al. [128] reported seven new halogenated secondary metabolites from red alga *Laurencia catarinensis*. In addition, six other known compounds were isolated from the same source. Isolated metabolites (**163**–**169**) were tested for cytotoxic activity against three human tumor cell lines, i.e., HT29, MCF7, and A431. Compound (**163**) was found to exhibit significant activity with IC_{50} values lower than 20 μM versus the positive control miltefosine (48.6 μM). Other metabolites (**164**–**169**) displayed either weak or no activity.

CONCLUSIONS

The marine environment possesses a variety of algae that is a good source for the discovery of chemicals with high therapeutic values. It has been observed that red algae has been widely explored in the literature for metabolite profiling and contains preferentially brominated compounds as a major class of metabolites. Most of the brominated compounds compiled in this chapter have been assessed for selective biological activity studies in which antimicrobial activity was tested on most occasions. The scarcity of these compounds in natural sources could be one reason for their limited prospects in terms of their thorough biological evaluation. Brominated phenols or diphenylethers have been evaluated for antibacterial studies in which lanosol methyl ester (**28)** showed the highest activity against *M. smegmatis* bacteria. Moreover, lanosol butanone (**30)** showed good cytotoxicity against human leukemia cells and urceolatin (**20)** exhibited the highest antioxidant activity. The brominated terpenes reported in this chapter have been tested preferentially for anticancer activity against different cell lines. The chemical structures covered in this chapter will definitely interest budding researchers and perhaps trigger the formulation of new ideas for either exploring molecules for therapeutic applications or for synthetic chemistry applications, in order to meet the increasing demand for chemicals from natural sources.

ACKNOWLEDGMENT

The author M.S.M. is thankful to UGC-BSR (New Delhi, India, project No.F.30-102/2015/BSR) for providing a start-up grant and research funding. V.K.M. would like to thank UGC (project No.F.47-1186/14/WRO) for providing research funding. U.B.G. would like to acknowledge the Research Centre of Dnyanprassarak Mandal's College (project No.DNY/CC/2014-15/03/1198) for their financial support.

ABBREVIATIONS

AR	Aldose Reductase
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
BHT	Butylated hydroxytoluene
COSY	Correlation Spectroscopy
DPPH	2,2-diphenyl-1-picrylhydrazyl.
E. coli	Escherichia coli
ESI-MS	Electrospray ionization mass spectrometry
GCMS	Gas chromatography–mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High-performance liquid chromatography
IC50	Inhibition Concentration
IC50	infectious dose 50
L.	Laurencia
μg	Microgram
mL	Milli Litre.
S. aureus	Staphylococcus aureus
NMR	Nuclear Magnetic Resonance Spectroscopy
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
PTP1B	protein-tyrosine phosphatase 1B
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
TLC	Thin Layer Chromatography
A549	adenocarcinomic human alveolar basal epithelial cells
Bel-7402	Human Hepatocellular Carcinoma Cell Line
BGC-823	human gastric cancer cell line
HCT-8	human colon carcinoma cell lines
K562	chronic myelogenous leukemia
MCF-7	Michigan Cancer Foundation-7
PC3	human prostate cancer cell line
A431	human epidermoid carcinoma line
CHO cell lines	Chinese hamster ovary cells
HT29	human colon adenocarcinoma cell line
MDA-MB-231	Metastasis Breast adenocarcinoma
A2780	human ovarian cancer cells
WiDr	colon adenocarcinoma cell line
HBL-100	breast cancer cell line

REFERENCES

[1] V. Jormalainen, T. Ramsay, Oikos 118 (2009) 713–722.
[2] J.B. Lee, A. Takeshita, K. Hayashi, T. Hayashi, Carbohydr. Polym. 86 (2011) 995–999.
[3] C.S. Vairappan, S.P. Anangdan, K.L. Tan, S. Matsunaga, J. Appl. Phycol. 22 (2010) 305–311.

[4] G.M. Nylund, F. Persson, M. Lindegarth, G. Cervin, M. Hermansson, H. Pavia, FEMS Microbiol. Ecol. 71 (2010) 84–93.
[5] A.A. Matloub, N.E. Awad, Planta Med. 75 (2009) PE27.
[6] K. Li, X.M. Li, N.Y. Ji, B.G. Wang, Bioorg. Med. Chem. 15 (2007) 6627–6631.
[7] F.L. Bideau, M. Kousara, L. Chen, L. Wei, F. Dumas, Chem. Rev. 117 (2017) 6110–6159.
[8] C. Paul, G. Pohnert, Nat. Prod. Rep. 28 (2011) 186–195.
[9] M.T. Cabrita, C. Vale, A.P. Rauter, Mar. Drugs 8 (2010) 2301–2317.
[10] J.W. Blunt, B.R. Copp, W.-P. Hu, M.H.G. Munro, P.T. Northcote, M.R. Prinsep, Nat. Prod. Rep. 24 (2007) 31–86.
[11] T. Cavalier-Smith, in: J. Brodie, J. Lewis (Eds.), Unravelling the Algae: The Past, Present and Future of Algal Systematics, CRC Press, Boca Raton, London and New York, 2007, pp. 21–55.
[12] L.A. Lewis, R.M. McCourt, Am. J. Bot. 91 (2004) 1535–1556.
[13] M.A. Maggs, H. Verbruggen, C. De, in: J. Brodie, J. Lewis (Eds.), Unravelling the Algae: The Past, Present and Future of Algal Systematics, CRC Press, Boca Raton, London and New York, 2007, pp. 103–121.
[14] B. De Reviers, F. Rousseau, S.G.A. Draisma, in: J. Brodie, J. Lewis (Eds.), Unravelling the Algae: The Past, Present and Future of Algal Systematics, CRC Press, Boca Raton, London and New York, 2007, pp. 267–284.
[15] V. Besada, J.M. Andrade, F. Schultze, J.J. González, J. Mar. Syst. 75 (2009) 303–315.
[16] J. Ortiz, N. Romero, P. Robert, J. Araya, J. Lopez-Hernández, C. Bozzo, C. Navarrete, A. Osorio, A. Rios, Food Chem. 99 (2006) 98–104.
[17] D.J. McHugh, FAO Fish. Tech. Pap. 441 (2003) 105.
[18] A. Peña-Rodríguez, T.P. Mawhinney, D. Ricque-Marie, L.E. Cruz-Suárez, Food Chem. 129 (2011) 491–498.
[19] E. Marinho-Soriano, P.C. Fonseca, M.A.A. Carneiro, W.S.C. Moreira, Bioresour. Technol. 97 (2006) 2402–2406.
[20] C. Rebours, E. Marinho-Soriano, J.A. Zertuche-González, L. Hayashi, J.A. Vásquez, P. Kradolfer, G. Soriano, R. Ugarte, M.H. Abreu, I. Bay-Larsen, G. Hovelsrud, R. Rødven, D. Robledo, J. Appl. Phycol. 26 (2014) 1939–1951.
[21] M.N. de Oliveira, A.L.P. Freitas, A.F.U. Carvalho, T.M.T. Sarnpaio, D.F. Farias, D.I.A. Teixeira, S.T. Gouveia, J.G. Pereira, M.M.D.C. de Sena, Food Chem. 115 (2009) 254–259.
[22] S. Mabeau, J. Fleurence, Tr. Food Sci. Tech. 4 (1993) 103–107.
[23] S. Marsham, G.W. Scott, M.I. Tobin, Food Chem. 100 (2007) 1331–1336.
[24] N.A. Paul, R. de Nys, P.D. Steinberg, Mar. Ecol. Prog. Ser. 323 (2006) 1–9.
[25] E.A. Norse, Global Marine Biological Diversity: A Strategy for Building Decision Into Decision Making, Island Press, Washington DC, USA, 1993, p. 383.
[26] V.J. Paul, K.E. Arthur, R. Ritson-Williams, C. Ross, K. Sharp, Biol. Bull. 213 (2007) 226–251.
[27] C.D. Amsler, K. Iken, J.B. McClintock, B.J. Baker, Bot. Mar. 52 (2009) 535–545.
[28] M.E. Hay, W. Fenical, Oceanography 9 (1996) 10–19.
[29] R.C. Bolser, M.E. Hay, Ecology 77 (1996) 2269–2286.
[30] M.E. Hay, Ann. Rev. Mar. Sci. 1 (2009) 193–212.
[31] M.S. Majik, H. Adel, D. Shirodkar, S. Tilvi, J. Furtado, RSC Adv. 5 (2015) 51008–51011.
[32] C.D. Amsler, in: C.D. Amsler (Ed.), Algal Chemical Ecology, Springer, Berlin, Heidelberg, Germany, 2008, pp. 297–309.
[33] K.L. Poulson, R.D. Sieg, J. Kubanek, Nat. Prod. Rep. 26 (2009) 729–745.

[34] A.G. González, J.D. Martín, C. Pérez, M.A. Ramírez, Tetrahedron Lett. 17 (1976) 137–138.
[35] V.M. Dembitsky, G.A. Tolstikov, Chem. Sustain. Dev. 12 (2004) 1–12.
[36] K. Kurata, K. Taniguchi, Y. Agatsuma, M. Suzuki, Phytochemistry 47 (1998) 363–369.
[37] S. Toshiyuki, M. Taiko, M. Hideo, T. Reiji, K. Shigeo, Am. J. Plant Sci. 5 (2014) 387–392.
[38] J. McLachlan, J.S. Craigie, J. Phycol. 2 (1966) 133–135.
[39] A.L. Lane, L. Nyadong, A.S. Galhena, T.L. Shearerb, E.P. Stout, R.M. Parry, M. Kwasnik, M.D. Wang, M.E. Hay, F.M. Fernandez, J. Kubanek, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 7314–7319.
[40] W.A. Lumbang, V.J. Paul, J. Exp, J. Exp. Mar. Biol. Ecol. 201 (1996) 185–195.
[41] S. Moon, J. Kim, Int. J. Food Sci. Nutr. 50 (1999) 165–171.
[42] H.J. Field, J. Clin. Virol. 21 (2001) 261–269.
[43] J.W. Blunt, B.R. Copp, W.P. Hu, M.H.G. Munro, P.T. Northcote, M.R. Prinsep, Nat. Prod. Rep. 26 (2009) 170–244.
[44] N. Iritani, J. Nogi, Atherosclerosis 15 (1972) 87–92.
[45] J.G. Koo, K.S. Jo, J.R. Do, S.J. Woo, J. Korean Fish Soc. 28 (1995) 227–236.
[46] L.S. Ritter, J.G. Copeland, P.F. McDonagh, Ann. Thorac. Surg. 66 (1998) 2063–2071.
[47] D.R. Coombe, C.R. Parish, I.A. Ramshaw, J.M. Snowden, Int. J. Cancer 39 (1987) 82–88.
[48] H. Mori, H. Kamei, E. Nishide, K. Nisizawa, in: H.A. Hoppe, T. Levring (Eds.), Marine Algae in Pharmaceutical Science, vol. 2, Walter de Gruyter, New York and Berlin, 1982, pp. 109–121.
[49] D.J. Schaeffer, V.S. Krylov, Ecotoxicol. Environ. Saf. 45 (2000) 208–227.
[50] H. Funahashi, T. Imai, T. Mase, M. Sekita, K. Yokoi, H. Hayashi, A. Shibata, T. Hayashi, M. Nishikawa, N. Suda, et al., Jpn. J. Cancer Res. 95 (2001) 483–487.
[51] H. Ohigashi, Y. Sakai, K. Yamaguchi, I. Umezaki, K. Koshimizu, Biosci. Biotechnol. Biochem. 56 (1992) 994–995.
[52] J. Teas, M.L. Harbison, R.S. Gelman, Cancer Res. 44 (1984) 2758–2761.
[53] M.A. Vallim, V.L. Teixeira, R.C. Pereira, Braz. J. Oceanogr. 55 (2007) 223–229.
[54] Y. Shimizu, in: N. Fusetani (Ed.), Drugs From the Sea, Karger, Basel, 2000, pp. 30–45.
[55] G.W. Gribble, Mar. Drugs 13 (2015) 4044–4136.
[56] S. La Barre, P. Potin, C. Leblanc, L. Delage, Mar. Drugs 8 (2010) 988–1010 (and references cited therein).
[57] R. Wever, M.A. van der Horst, Dalton Trans. 42 (2013) 11778–11786.
[58] M. Almeida, S. Filipe, M. Humanes, M.F. Maia, R. Melo, N. Severino, J.A.L. da Silva, J.J.R.F. da Silva, R. Wever, Phytochemistry 57 (2001) 633–642.
[59] S.A. Borchardt, E.J. Allain, J.J. Michels, G.W. Stearns, R.F. Kelly, W.F. McCoy, Appl. Environ. Microbiol. 67 (2001) 3174–3179.
[60] M. Sandy, J.N. Carter-Franklin, J.D. Martiny, A. Butler, Chem. Commun. 47 (2011) 12086–12088.
[61] R. Wever, M.G.M. Tromp, J.W.P.M. van Schijndel, E. Vollenbroek, in: R.D. Oremland (Ed.), Biogeochemistry of Global Change, Chapman and Hall, New York, 1993, pp. 811–824.
[62] W. Wang, Y. Okada, H. Shi, Y. Wang, T. Okuyama, J. Nat. Prod. 68 (2005) 620–622.
[63] J. Zhao, M. Ma, S. Wang, S. Li, P. Cao, Y. Yang, Y. Lu, J. Shi, N. Xu, X. Fan, L. He, J. Nat. Prod. 68 (2005) 691–694.
[64] J. Carmichael, W.G. DeGraff, A.F. Gazdar, J.D. Minna, J.B. Mitchell, Cancer Res. 47 (1987) 936–942.
[65] J.M. Kornprobst, C. Sallenave, G. Barnathan, Comp. Biochem. Physiol. B 199 (1998) 1–51.
[66] L. Retz de Carvalho, S.M.P.d.B. Guimaraes, N.F. Roque, Rev. Bras. Bot. 29 (2006) 453–459.

[67] X.J. Duan, X.M. Li, B.G. Wang, J. Nat. Prod. 70 (2007) 1210–1213.
[68] K. Li, X.M. Li, N.Y. Ji, J.B. Gloer, B.G. Wang, Org. Lett. 10 (2008) 1429–1432.
[69] Q.W. Liu, C.H. Tan, T. Zhang, S.J. Zhang, L.J. Han, X. Fan, D.Y. Zhu, J. Asian Nat. Prod. Res. 8 (2006) 379–383.
[70] J. Qin, H. Su, Y. Zhang, J. Gao, L. Zhu, X. Wu, H. Pan, X. Li, Bioorg. Med. Chem. Lett. 20 (2010) 7152–7154.
[71] W.L. Popplewell, P.T. Northcote, Tetrahedron Lett. 50 (2009) 6814–6817.
[72] K. Li, X.M. Li, J.B. Gloer, B.G. Wang, J. Agric. Food Chem. 59 (2011) 9916–9921.
[73] C.S. Li, X.M. Li, C.M. Cui, B.G. Wang, Z. Naturforsch. 65b (2010) 87–89.
[74] N.Y. Ji, X.M. Li, C.M. Cui, B.G. Wang, Helv. Chim. Acta 90 (2007) 1731–1736.
[75] M.P. Rahelivao, M. Gruner, H. Andriamanantoanina, B. Andriamihaja, I. Bauer, H.J. Knölker, Mar. Drugs 13 (2015) 4197–4216.
[76] G.T. Carter, K.L. Rinehart Jr., L.H. Li, S.L. Kuentzel, J.L. Connor, Tetrahedron Lett. 19 (1978) 4479–4482.
[77] M.J. Abad, L.M. Bedoya, P. Bermejo, in: A. Mendez Vilas (Ed.), Marine Compounds and Their Antimicrobial Activities, Formatex publisher, 2011, pp. 1272–1280.
[78] J. Sun, L.J. Han, D.Y. Shi, X. Fan, S.J. Wang, S. Li, Y.C. Yang, J.G. Shi, Chin. Chem. Lett. 16 (2005) 1611–1614.
[79] S.C. Mao, Y.W. Guo, Helv. Chim. Acta 88 (2005) 1034–1039.
[80] J. Sun, D. Shi, M. Ma, S. Li, S. Wang, L. Han, Y. Yang, X. Fan, J. Shi, L. He, J. Nat. Prod. 68 (2005) 915–919.
[81] M. Kuniyoshi, P.G. Wahome, T. Miono, T. Hashimoto, M. Yokoyama, K.L. Shrestha, T. Higa, J. Nat. Prod. 68 (2005) 1314–1317.
[82] M. Kladi, C. Vagias, G. Furnari, D. Moreau, C. Roussakis, V. Roussis, Tetrahedron Lett. 46 (2005) 5723–5726.
[83] S.C. Mao, Y.W. Guo, J. Nat. Prod. 69 (2006) 1209–1211.
[84] D. Davyt, R. Fernandez, L. Suescun, A.W. Mombru, J. Saldaña, L. Dominguez, J. Coll, M.T. Fujii, E. Manta, J. Nat. Prod. 64 (2001) 1552–1555.
[85] L.R. de Carvalho, M.T. Fujii, N.F. Roque, J.H.G. Lago, Phytochemistry 67 (2006) 1331–1335.
[86] M.T. Crimmins, C.O. Hughes, Org. Lett. 14 (2012) 2168–2171.
[87] D. Davyt, R. Fernandez, L. Suescun, A.W. Mombrú, J. Saldaña, L. Dominguez, J. Coll, M.T. Fujii, E. Manta, J. Nat. Prod. 69 (2006) 1113–1116.
[88] M. Kladi, H. Xenaki, C. Vagias, P. Papazafiri, V. Roussis, Tetrahedron 62 (2006) 182–189.
[89] M. Kladi, C. Vagies, P. Papazafiri, G. Furnari, D. Serio, V. Roussis, Tetrahedron 63 (2007) 7606–7611.
[90] N.Y. Ji, X.M. Li, Y. Zhang, B.G. Wang, Biochem. Syst. Ecol. 35 (2007) 627–630.
[91] N.Y. Ji, X.M. Li, K. Li, L.P. Ding, J.B. Gloer, B.G. Wang, J. Nat. Prod. 70 (2007) 1901–1905.
[92] A.G. González, J.D. Martín, V.S. Martín, M. Norte, R. Pérez, Tetrahedron Lett. 23 (1982) 2395–2398.
[93] N.Y. Ji, X.M. Li, L.P. Ding, B.G. Wang, Nat. Prod. Res. 22 (2008) 715–718.
[94] C. Vairappan, M. Suzuki, T. Ishii, T. Okino, T. Abe, M. Masuda, Phytochemistry 69 (2008) 2490–2494.
[95] N.Y. Ji, X.M. Li, H. Xie, J. Ding, K. Li, L.P. Ding, B.G. Wang, Helv. Chim. Acta 91 (2008) 1940–1946.
[96] N.Y. Ji, X.M. Li, K. Li, J.B. Gloer, B.G. Wang, Biochem. Syst. Ecol. 36 (2008) 938–941.

[97] H. Su, D.Y. Shi, J. Li, S.J. Guo, L.L. Li, Z.H. Yuan, X.B. Zhu, Molecules 14 (2009) 1889–1897.
[98] N.Y. Ji, X.M. Li, K. Li, B.G. Wang, Helv. Chim. Acta 92 (2009) 1873–1879.
[99] D.A. Dias, J.M. White, S. Urban, Nat. Prod. Commun. 4 (2009) 157–172.
[100] H. Su, Z.H. Yuan, J. Li, S.J. Guo, L.P. Deng, L.J. Han, X.B. Zhu, D.Y. Shi, Helv. Chim. Acta 92 (2009) 1291–1297.
[101] D.A. Dias, S. Urban, Phytochemistry 72 (2011) 2081–2089.
[102] S. Lee, M. Hoshino, M. Fujita, S. Urban, Chem. Sci. 8 (2017) 1547–1550.
[103] Y. Liang, X.M. Li, C.M. Cui, C.S. Li, H. Sun, B.G. Wang, Mar. Drugs 10 (2012) 2817–2825.
[104] M. Suzuki, T. Kawamoto, C.S. Vairappan, T. Ishii, T. Abe, M. Masuda, Phytochemistry 66 (2005) 2787–2793.
[105] R. Chatter, M. Kladi, S. Tarhouni, R. Maatoug, R. Kharrat, C. Vagias, V. Roussis, Phytochem. Lett. 2 (2009) 25–28.
[106] C.S. Vairappan, T. Ishii, T.K. Lee, M. Suzuki, Z. Zhaoqi, Mar. Drugs 8 (2010) 1743–1749.
[107] N.Y. Ji, X.M. Li, B.G. Wang, Helv. Chim. Acta 93 (2010) 2281–2286.
[108] M. Kladi, D. Ntountaniotis, M. Zervou, C. Vagias, E. Ioannou, V. Roussis Tetrahedron, Tetrahedron Lett. 55 (2014) 2835–2837.
[109] D. Rodrigues, C. Alves, A. Horta, S. Pinteus, J. Silva, G. Culioli, O.P. Thomas, R. Pedrosa, Mar. Drugs 13 (2015) 713–726.
[110] G.A. Dziwornu, M.R. Caira, J.A.D.L. Mare, A.L. Edkins, J.J. Bolton, D.R. Beukes, S.N. Sunassee, Molecules 22 (2017) 513.
[111] F. Cen-Pacheco, L. Nordstrom, M.L. Souto, M.N. Martin, J.J. Fernández, A.H. Daranas, Mar. Drugs 8 (2010) 1178–1188.
[112] F. Cen-Pacheco, J.A. Villa-Pulgarin, F. Mollinedo, M. Norte, M.N. Martin, J.J. Fernández, A.H. Daranas, Mar. Drugs 9 (2011) 2220–2235.
[113] N.Y. Ji, X.M. Li, K. Li, B.G. Wang, J. Nat. Prod. 70 (2007) 1499–1502.
[114] M. Kladi, C. Vagias, M. Stavri, M.M. Rahman, S. Gibbons, V. Roussis, Phytochem. Lett. 1 (2008) 31–36.
[115] M. Kladi, C. Vagias, P. Papazafiri, S. Brogi, A. Tafi, V. Roussis, J. Nat. Prod. 72 (2009) 190–193.
[116] X. Liu, X.M. Li, C.S. Li, N.Y. Ji, B.G. Wang, Chin. Chem. Lett. 21 (2010) 1213–1215.
[117] W. Abdel-Mageed, R. Ebel, F. Valeriote, M. Jaspars, Tetrahedron 66 (2010) 2855–2862.
[118] A. Gutiérrez-Cepeda, J.J. Fernández, L.V. Gil, M. López-Rodríguez, M. Norte, M.L. Souto, J. Nat. Prod. 74 (2011) 441–448.
[119] B.G. Wang, J.B. Gloer, N.Y. Ji, J.C. Zhao, Chem. Rev. 113 (2013) 3632–3685.
[120] E.G. Lyakhova, A.I. Kalinovsky, A.S. Dmitrenok, S.A. Kolesnikova, S.N. Fedorov, V.E. Vaskovsky, V.A. Stonik, Tetrahedron Lett. 47 (2006) 6549–6552.
[121] T. Saitoh, T. Suzuki, M. Sugimoto, H. Hagiwara, T. Hoshi, Tetrahedron Lett. 44 (2003) 3175–3178.
[122] J.A. Dale, H.S. Mosher, J. Am. Chem. Soc. 95 (1973) 512–519.
[123] M. Suzuki, Y. Takahashi, Y. Mitome, T. Itoh, T. Abe, M. Masuda, Phytochemistry 60 (2002) 861–867.
[124] A.W. Jeong, M.J. Kim, H. Kim, S. Kim, D. Kim, K.J. Shin, Angew. Chem. Int. Ed. 49 (2010) 752–756.
[125] A. Gutiérrez-Cepeda, J.J. Fernández, M. Norte, M.L. Souto, Org. Lett. 13 (2011) 2690–2693.

[126] S.E. Nasr Ayyad, K.O. Al-Footy, W.M. Alarif, T.R. Sobahi, S.A. Bassaif, M.S. Makki, A.M. Asiri, A.Y. Al Halawani, A.F. Badria, F.A. Al-raheem Badria, Chem. Pharm. Bull. 59 (2011) 1294–1298.

[127] S. Greff, M. Zubia, G. Genta-Jouve, L. Massi, T. Perez, O.P. Thomas, J. Nat. Prod. 77 (2014) 1150–1155.

[128] C. Lhullier, M. Falkenberg, E. Ioannou, A. Quesada, P. Papazafiri, P.A. Horta, E.P. Schenkel, C. Vagias, V. Roussis, J. Nat. Prod. 73 (2010) 27–32.