PART I

Introduction to Algae and Their Importance

1

Biological Importance of Marine Algae

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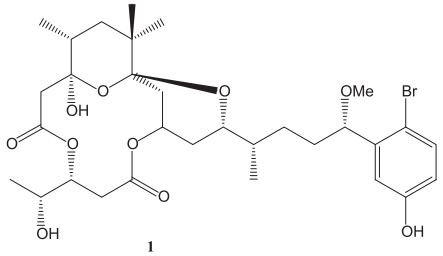
1.1 Introduction

Marine organisms are potentially productive sources of highly bioactive secondary metabolites that might represent useful leads in the development of new pharmaceutical agents (Iwamoto *et al*. 1998, 1999, 2001). During the last four decades, numerous novel compounds have been isolated from marine organisms and many of these substances have been demonstrated to possess interesting biological activities (Faulkner, 1984a,b, 1986, 1987, 1988, 1990, 1991, 1992, 1993, 1994, 1995, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002).

Algae are very simple, chlorophyll-containing organisms (Bold and Wynne, 1985) composed of one cell or grouped together in colonies or as organisms with many cells, sometimes collaborating together as simple tissues. They vary greatly in size – unicellular of 3–10 μm to giant kelps up to 70 m long and growing at up to 50 cm per day (Hillison, 1977). Algae are found everywhere on Earth: in the sea, rivers and lakes, on soil and walls, in animal and plants (as symbionts-partners collaborating together); in fact just about everywhere where there is a light to carry out photosynthesis.

Algae are a heterogeneous group of plants with a long fossil history. Two major types of algae can be identified: the macroalgae (seaweeds) occupy the littoral zone, which included green algae, brown algae, and red algae, and the microalgae are found in both benthic and littoral habitats and also throughout the ocean waters as phytoplankton (Garson, 1989). Phytoplankton comprise organisms such as diatoms (Bacillariophyta), dinoflagellates (Dinophyta), green and yellow-brown flagellates (Chlorophyta; Prasinophyta; Prymnesiophyta, Cryptophyta, Chrysophyta and Rhaphidiophyta) and blue-green algae (Cyanophyta). As photosynthetic organisms, this group plays a key role in the productivity of oceans and constitutes the basis of the marine food chain (Bold and Wynne, 1985; Hillison, 1977).

The true origins of compounds found in marine invertebrates have been a subject of discussion. They may vary from compound to another, but there are strong hints that dietary or symbiotic algae are one of the participants in the production of these metabolites. For example, as early as 1977, the blue-green algae, *Lyngbya majusula* was recognized as the source of aplysiatoxin **1** found in the sea hares *Aplysia* that feed on this alga (Mynderse *et al*., 1997). Similarly, a series of highly active antitumor compounds, dolastatin **2** and **3,** isolated from sea slugs are considered to be of blue-green algal origin (Shimizu, 2000). Also, eukaryotic algae and various dinoflagellate metabolites are found in shellfish and other invertebrates as toxins (Shimizu, 2000). Brevetoxins **4**, ciguatoxins **5**, and dinophysistoxins-1&2 and **6** and **7** are well known examples of paralytic shellfish toxins (Hall and Strichartz, 1990).



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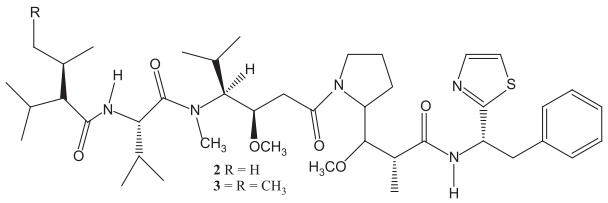
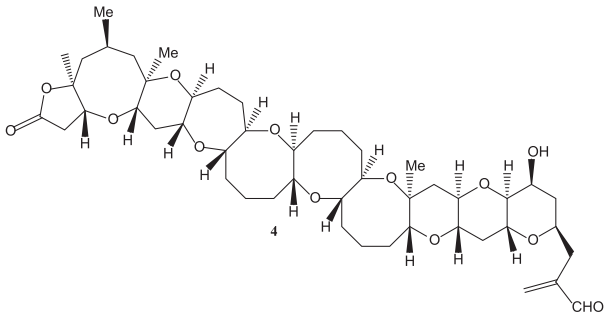
Handbook of Marine Macroalgae: Biotechnology and Applied Phycology, First Edition. Edited by Se-Kwon Kim.



2 R = H
3 = R = CH_3



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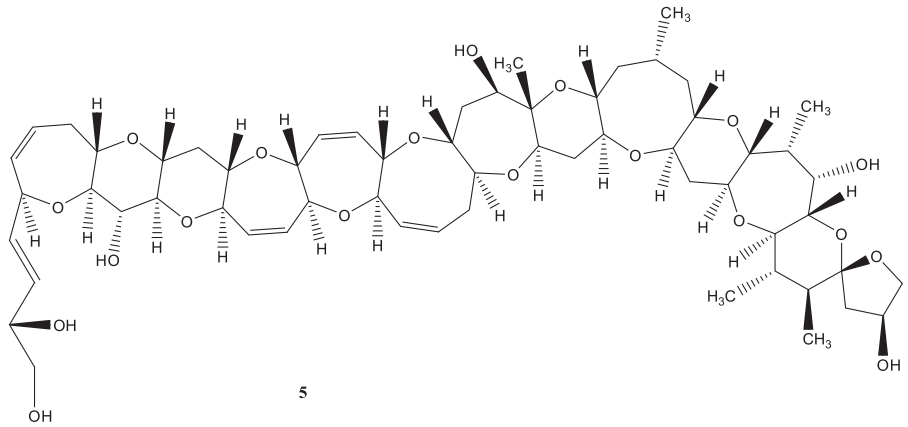
1.2 Interesting natural products and their biological activities from macroalgae (seaweeds)

Marine macroalgae or seaweeds have been used as foods especially in China and Japan and crude drugs for treatment of many diseases such as iodine deficiency (goiter, Basedow's disease and hyperthyroidism). Some seaweeds have also been used as a source of additional vitamins, treatment of various intestinal disorders, as vermifuges, and as hypocholesterolemic and hypoglycemic agents. Seaweeds have been employed as dressings, ointments and in gynecology (Trease and Evanes, 1996).

Macroalgae can be classified into three classes: green algae (Chlorophyta), brown algae (Phaeophyta) and red algae (Rhodophyta) (Garson, 1989).



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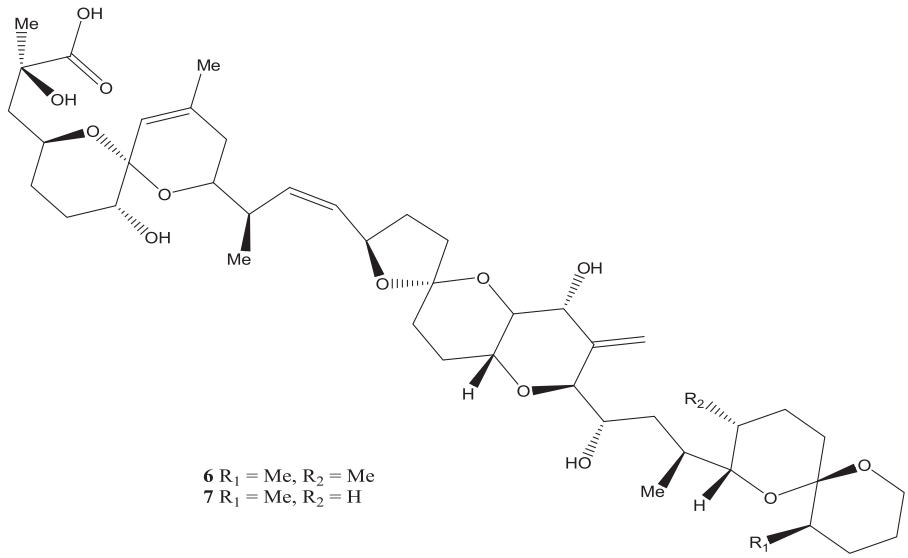


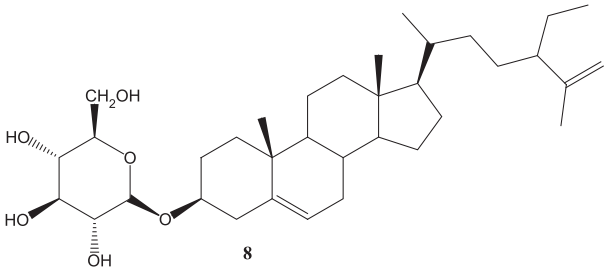
6 R_1 = Me, R_2 = Me
7 R_1 = Me, R_2 = H

1.2.1 Chlorophyta (green algae)

The characteristic green color of green algae is mainly due to the presence of chlorophyl *a* and *b* in the same proportion like higher plants (Bold and Wynne, 1985). There are few reports of novel secondary metabolites among the Chlorophyta than the other algal division; the following are the most important biologically active natural products isolated from these algae.

Anti-inflammatory substances

An anti-inflammatory, 3–0-β-D-glucopyranosylstigmasta-5,25-diene **8** have been isolated by Awad in 2000 (Awad, 2000) from the green alga *Ulva lactuca.*



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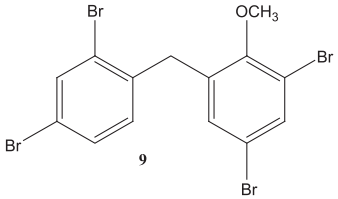
Habu is a deadly snake found in Okinawa where 200–300 people are bitten by the snake every year. A patient must be given immediate medical treatment with the serum prepared from a horse-developed antibody by injection of snake toxin. However, about 20% of the patients are allergic to the serum.

In order to develop an alternative drug, Okinawa Prefectural Institute of Public Health has been conducting screening strategies to find a compound with anti-inflammatory activity, which can be measured by the suppression of inflammation caused by the injection of toxin into a mouse limb. A diphenyl ether **9** isolated from an alga was found to be effective in this assay (Higa, 1989). The extract of the green alga *Cladophora fascicularis* was separated by different chromatographic methods to produce 2-(2′,4′ dibromophenoxy)-4,6-dibromoanisol (Kuniyoshi, Yamada and Higa, 1985), the first example of diphenyl ether from green algae. It was also active in inhibiting the growth of *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* (Kuniyoshi, Yamada and Higa, 1985).



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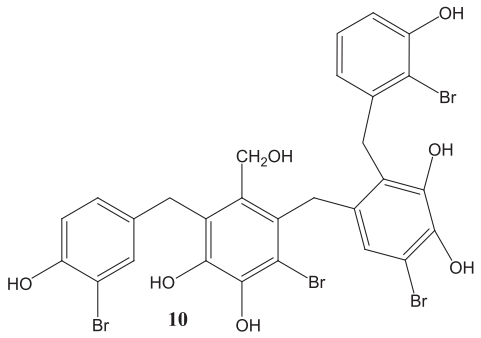
Cytotoxic and immunosuppressive activities

Bioassay-guided fractionation utilizing inhibitory activity against inosine -5′-monophosphate dehydrogenase inhibitor (IMPDH) leads to the isolation of a new brominated diphenylmethane derivative. Isorawsonol **10** was isolated from the tropical green alga *Arrainvilla rawsonii* by Chen and colleagues in 1994 (Chen *et al.*, 1994). The activity of IMPDH has been linked with cellular proliferation and inhibition of that enzyme has been demonstrated to have anticancer and immunosuppressive effects (Chen *et al.*, 1994).



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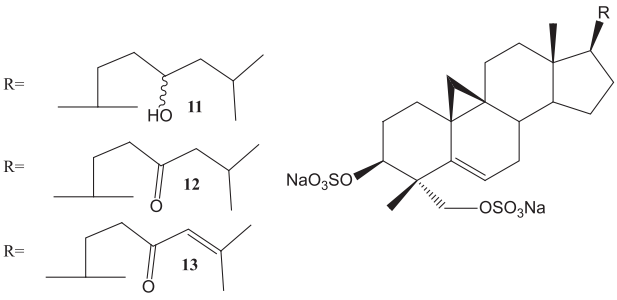
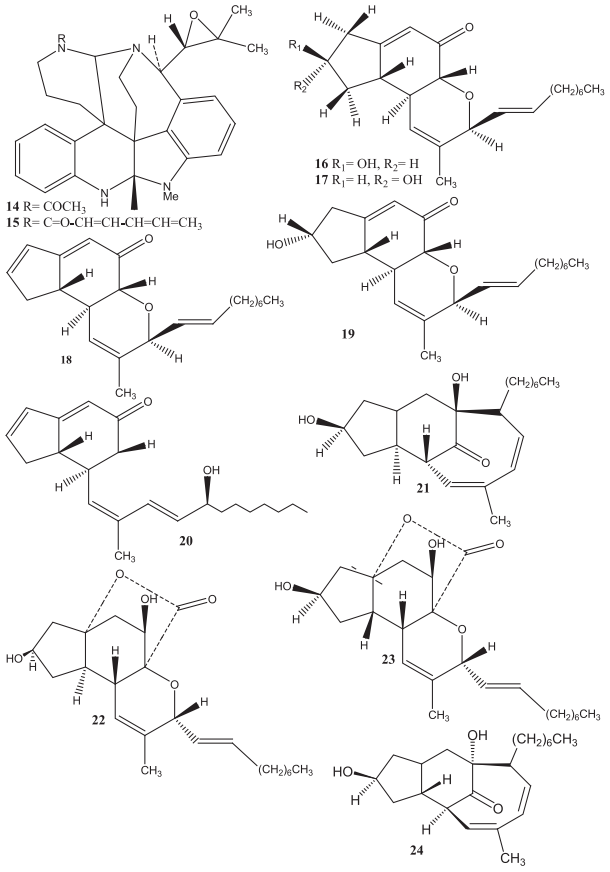
Bioactivity-directed fractionation of the extract of the green alga *Tydemania expeditionis* using the protein tyrosine kinase $pp60^{v\text{-}stc}$ led to the isolation of three new cycloartenol disulfates **11–13**; they showed modest inhibition of this enzyme (Govindan *et al.*, 1994).



Communesins A **14** and B **15**, exhibiting cytotoxic activity against cultured P-388 lymphocytic leukemia cells, were isolated from the mycelium of a strain of *Penicillium* species stuck on the marine alga *Enteromorpha intestinalis* (Numata *et al.*, 1993).

Penostatins A **16**, B **17**, C **18**, D **19** (Takahashi *et al.*, 1996) and E **20** (Iwamoto *et al.*, 1999) have been isolated from a strain of *Penicillium* species originally separated from the marine alga *Enteromorpha intestinalis* (L.) Link (Ulvaceae). The compounds A–C and E exhibited significant cytotoxicity against the cultured P388 cell line (Iwamoto *et al.*, 1999; Takahashi *et al.*, 1996). Penostatins F, G, H **21–23** and I **24**

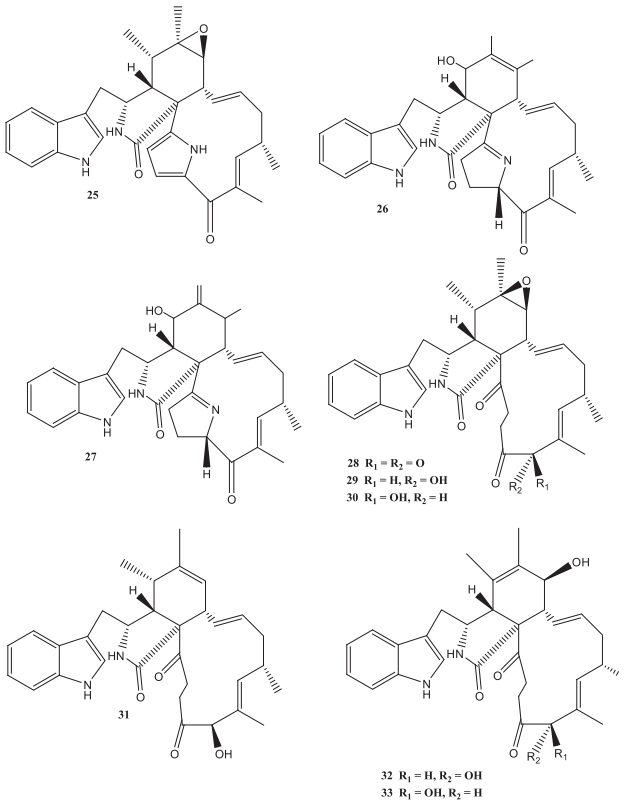
were isolated from a strain of *Penicillium* originally separated from the marine alga *Enteromorpha intestinalis* (L.) Link (Ulvaceae). All the compounds exhibit significant cytotoxicity against cultured P388 cells (Iwamoto *et al*., 1998).

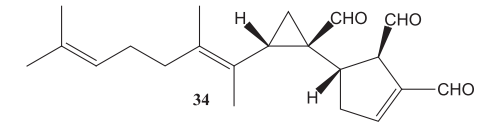


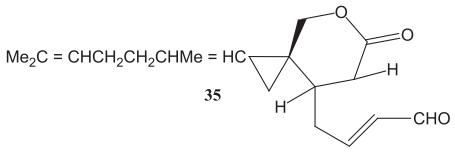
The novel compounds cytochalasins, penochalasins A–C **25–27** (Numata *et al*., 1996), D–H **28–32**, and chaetoglobosin O **33** (Iwamoto *et al*., 2001) were isolated from a strain of *Penicillium* species originally separated from the marine alga *Enteromorpha intestinalis*. All these compounds exhibited potent cytotoxic activity against cultured P388 cells.

Four new diterpenoid metabolites were isolated from several species of the green algae *Halimeda* (Udoteaceae). These new compounds show potent antimicrobial and cytotoxic properties in bioassays. Among these four compounds were halimediatrial **34** and halimedalactone **35** (Paul and Fenical, 1983). Halimedatrial **34** is a diterpene trialdehyde that was extracted from *Halmida lamouroux* (Chlorophyta, Udoteaceae) species. This compound was found to be toxic towards reef fishes, and significantly reduces feeding in herbivorous fishes (Paul and Fenical, 1983).

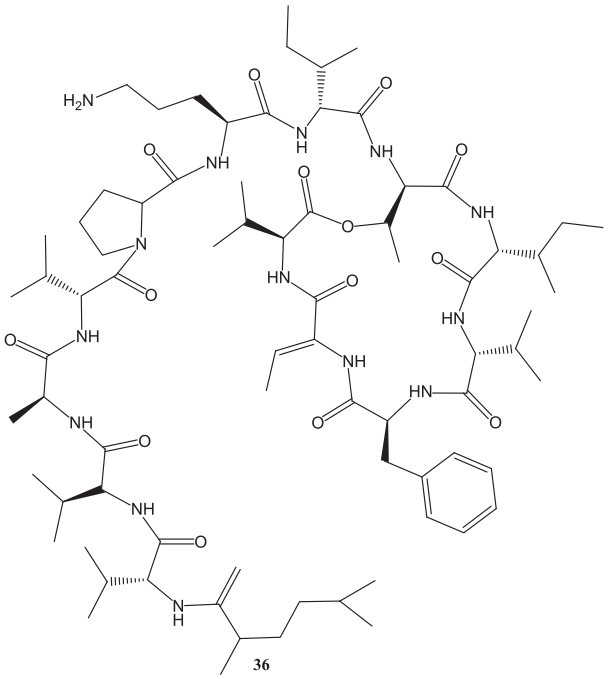
The cyclic depsipeptide kahalalide F **36** was originally isolated from both the mollusc *Elysia rufescenes* and from the dietary source, the green alga *Bryopsis* sp. (Hamann and Scheuer, 1993) was introduced into Phase I trials by Pharma Mar as a lead compound against prostate cancer.







The green alga *Bryopsis* sp. was the source of the cyclic depsipeptides kahalalide P **37** and Q **38**, with moderate inhibition of the HL-60 cell lines (Dmitrenok *et al*., 2006).



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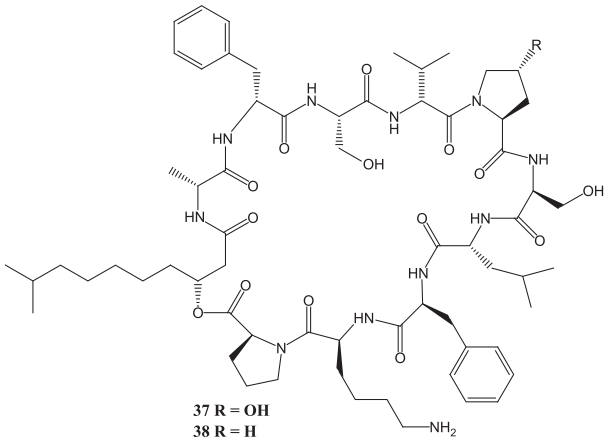
Antibacterial activity

Cycloeudesmol **39** is an antibiotic cyclopropane containing sesquiterpene; it was isolated from the marine alga *Chondria oppositiclada* Dawson (Fenical and Sims, 1974). Cycloeudesmol was found to be a potent antibiotic against *Staphylococcus aureus* and *Candida albicans.*

Lyengaroside A **40** was isolated from the green alga *Codium iyengarii* and displayed a moderate antibacterial activity (Ali *et al*., 2002).

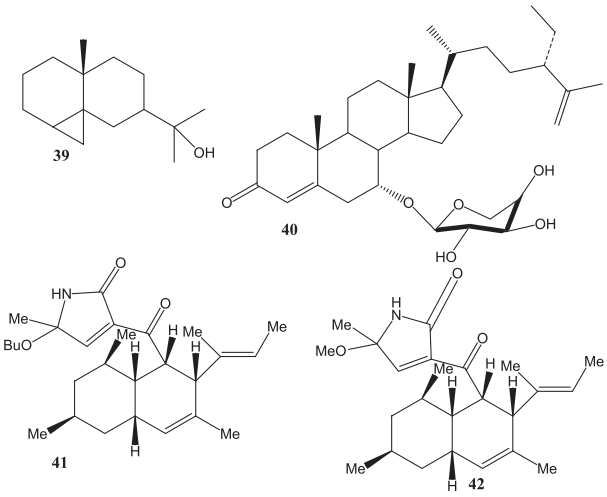
Green algae extract of *Caulerpa prolifera* exhibited moderate to significant activity against unidentified strains of marine bacteria (Smyrniotopoulos *et al*., 2003).



37 R = OH
38 R = H

Antiplasmodial activity

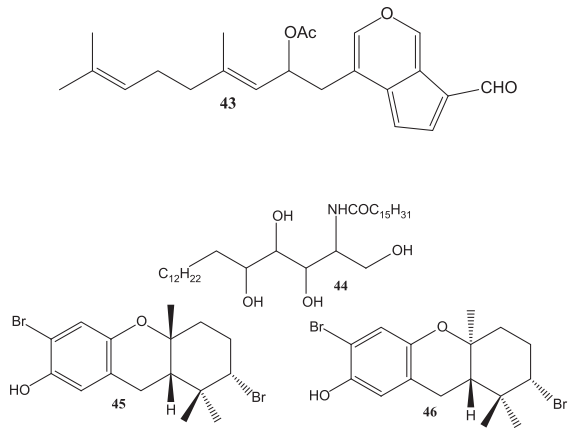
The endophytic and obligate marine fungus *Ascochyta salicorniae* was isolated from the green alga *Ulva* spp.. *Ascochyta salicorniae* was found to produce the unprecedented and structurally unusual tetrameric acid contiguous metabolites ascosalipyrrolidinones A **41** and B **42.** Ascosalipyrrolidinone A **41** has antiplasmodial activity toward *Plasmodium falciparum* strains Kl and NF-54, as well as showing antimicrobial activity and inhibiting tyrosine kinase p561ck (Osterhage *et al*., 2000).



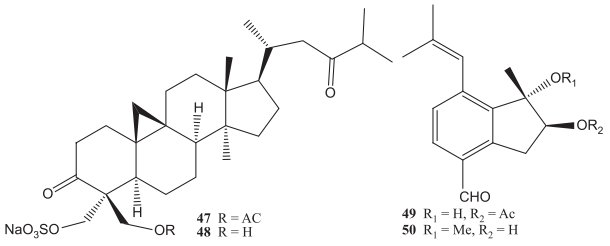
39 40 41 42

Antiviral activity

Halitunal **43** is a novel diterpene aldehyde possessing a unique cyclopentadieno [c] pyran ring system; it has been isolated from the marine alga *Halimeda tuna.* Halitunal shows antiviral against murine coronavirus A59 *in vitro* (Koehn *et al*., 1991).



43 44 45 46



In 1992 Garg and coworkers (Garg *et al*., 1992) isolated the antiviral derivative, sphingosine, *N*-palmitoyl-2-amino 1,3,4,5-tetyrahydroxyoctadecane **44**, which demonstrated antiviral activity and *in vivo* protection against Semliki forest virus (SFV). This compound was isolated from the Indian green alga *Ulva fasciata*.

Antimutagenic activity

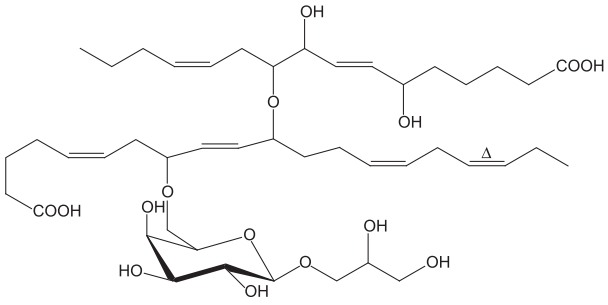
Two new compounds, cymobarbatol **45** and 4-isocymobarbatol **46** were isolated from the marine green alga *Cymopolia barbat*. Both compounds were found to be non-toxic over a broad concentration range against *Salmonella typhimurium* strains T-98 and T-100. Both compounds exhibited strong inhibition of the mutagenicity of 2-aminoanthracene and ethylmethanesulfonate towards, respectively, the T-98 strains plus a metabolic activator and T-100 (Wall *et al*., 1989).

Antifungal activity

Capisterones A **47** and B **48** are triterpene sulfate esters isolated from the green alga *Penicillus capitatus*. Both compounds exhibited potent antifungal activity against the marine algal pathogen *Lindra thallasiae* (Puglisi *et al*., 2004).

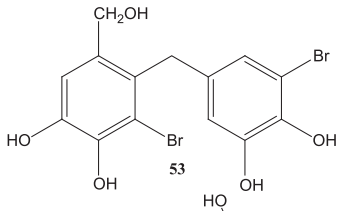
Two sesquiterpenes, caulerpals A **49** and B **50** were isolated from green alga *Caulerpa taxifolia* in addition to the known caulerpin (Aguilar-Santos, 1970); they were shown to be potent inhibitors of human protein tyrosine phosphatase 1 B (hPTP I B) (Mao, Guo and Shen, 2006). Capisterones A **47** and B **48**, originally isolated from *Penicillus capitatus* (Garg *et al*., 1992), were re-isolated and absolute stereochemistry assigned using electronic CD. In addition, the capisterones have been shown to significantly enhance fluconazole activity in *Saccharomyces cerevisiae* (Li *et al*., 2006).

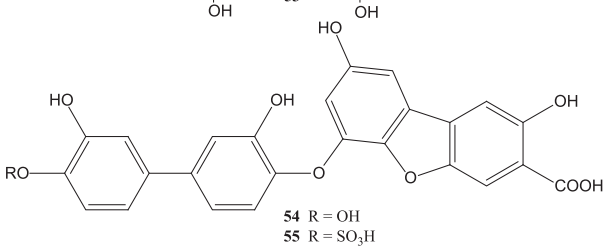
A new class of ether-linked glycoglycerolipids, nigricanosides A **51** and B **52** were isolated as methyl esters from the green alga *Avrainvillea nigrans*. Nigricanoside A dimethyl ester was found to be a potent antimitotic agent, acting by stimulating the polymerization of tubulin and inhibiting the proliferation of both MCF-7 and HCT-116 cells (Williams *et al*., 2007).



Protein tyrosine phosphate 1B inhibitors (PTP1B)

Hydroxyisoavrainvilleol **53** was originally isolated from the tropical green alga *Avrainvillea nigricans* (Colon *et al*., 1987) but has now been isolated from red alga *Polysiphonia urceolata* as a protein tyrosine phosphatase lB inhibitor (PTPlB) (Liu *et al*., 2008). A vanillic acid biphenyl derivative **54** and the sulfate adduct **55** were isolated from the Australian green alga *Cladophora socialis* as a protein tyrosine phosphatase 1B (PTPa1B) inhibitor (Feng *et al*., 2007).





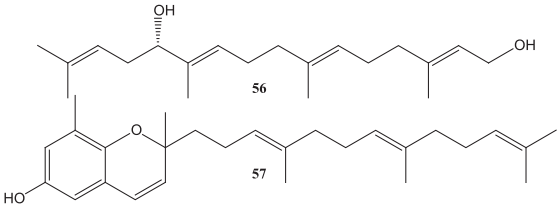
1.2.2 Phaeophyta (brown algae)

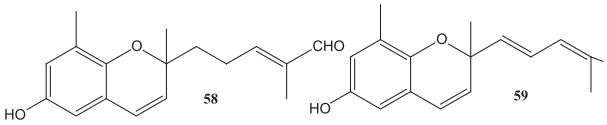
The brown color of these algae results from the dominance of the xanthophyll pigments and fucoxanthin; this masks the other pigments, chlorophyll *a* and *c*, β carotenes, and other xanthophylls (Bold and Wynne, 1985). Food reserves of brown algae are typically complex polysaccharides and higher alcohols. The principal carbohydrate reserve is laminaran. The cell walls are made of cellulose and alginic acid. Many bioactive metabolites have been isolated from brown algae with different pharmacological activities as shown below:

Cytotoxic and antitumor activity

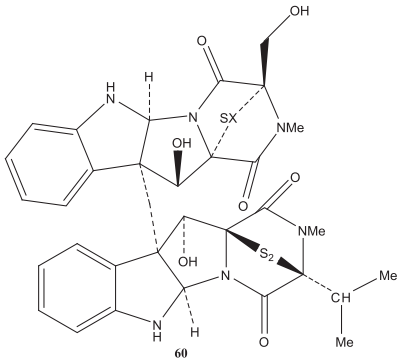
A linear cytotoxic diterpene bifurcadiol **56** was isolated from the brown alga *Bifurcaria bifurcata* by Guardia and colleagues in 1999 (Guardia *et al.*, 1999), which exhibits cytotoxicity against cultured human tumor cell lines (A549, SK-OV-3, SKL-2, XF 498, and HCT).

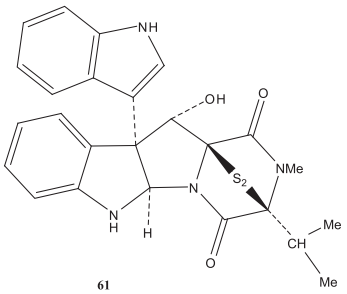
Meroterpenoids, sargol, sargol-I and sargol-II **57–59** were isolated from the brown alga *Sargassum tortile* and showed cytoxic activity (Numata *et al.*, 1991).

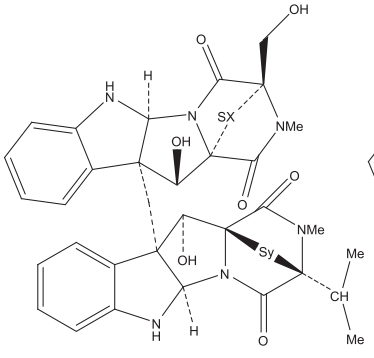




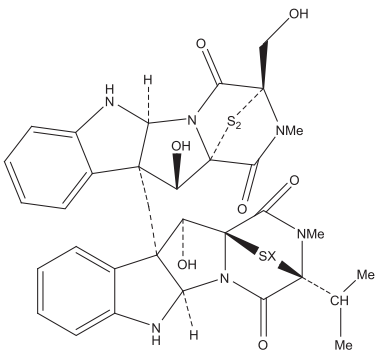
Leptosins A, B, C (I, X = 4,3,2 **60**), D, E and F (II, X = 2,3,4 **61**), belonging to a series of epipolythiodioxopiperazine derivatives, have been isolated from the mycelia of a strain of *Leptosphaeria* species attached to marine alga *Sargassum tortile*. All these compounds showed potent cytotoxicity against cultured P388 cells, except leptosins A and C, which exhibited significant antitumor activity against sarcoma 180 ascites (Takahashi *et al.*, 1994). Further investigation of the secondary metabolites of this fungus has led to the isolation of four additional cytotoxic compounds, named leptosins G, G1, G2 **62–64** and H **65** (Takahashi *et al.*, 1995a). Leptosins K, K1 **66–67** and K_2 **68** were also isolated and showed a potent cytotoxic activity against P388 cell line (Takahashi *et al.*, 1995b).







62 x = 4, Y = 3
63 X = 3, Y = 3
64 X = 2, Y = 3
65 X = 2, Y = 4



66 X = 2
67 X = 3
68 X = 4

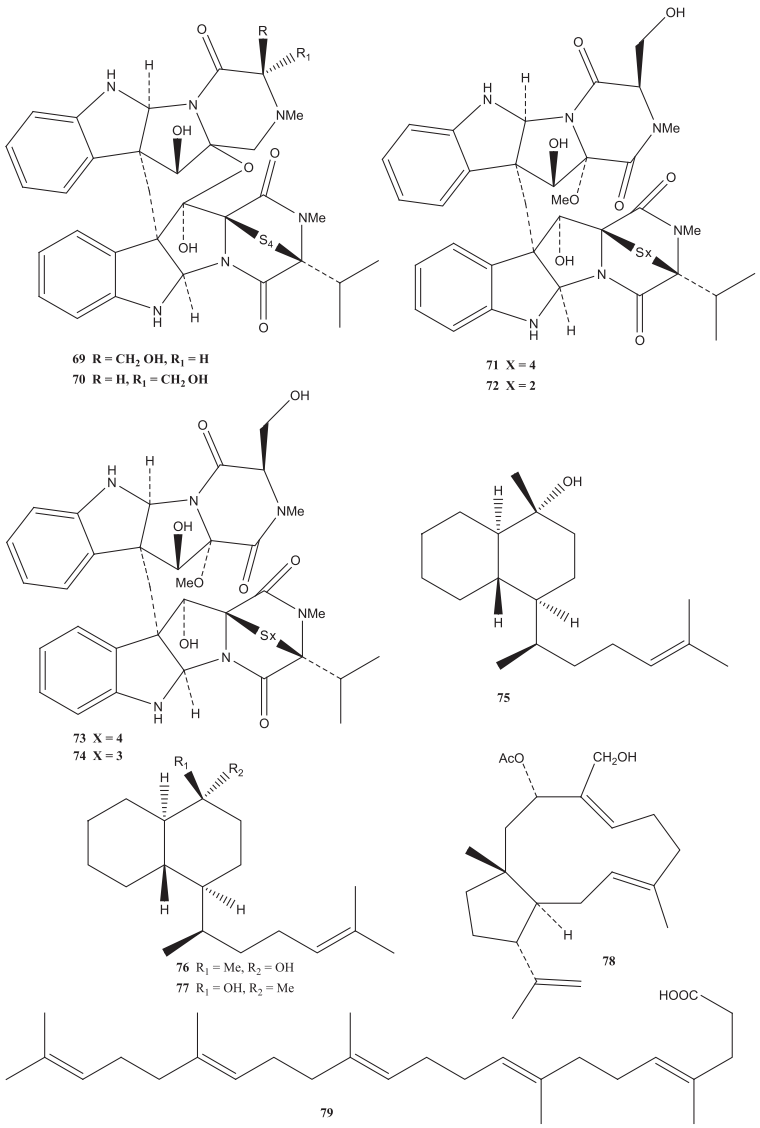
Leptosins I **69** and J **70** have been also isolated from the mycelia of a strain of *Leptosphaeria* species OUPS-4 attached to the marine alga *Sargassum tortile.* These compounds exhibited significant cytotoxic activity against cultured P388 cells (Takahashi *et al.*, 1994a,b).

Leptosins M, MI, N and N1 **71–74** that have been isolated from a strain of *Leptosphaeria* species were originally separated from the marine alga *Sargassum tortile.* All these compounds exhibited significant cytotoxicity against cultured P388 cells. In addition, leptosin M proved to exhibit significant cytotoxicity against human cancer cell lines, and to inhibit specifically two protein kinases, PTK and CaMKIII, and human topoisomerase II (Yamada *et al.*, 2002).

Three cytotoxic diterpenes dictyotins A, B and C **75–77** were isolated from the brown alga *Dictyota dichotoma* by Wu and coworkers in 1990 (Wu, Li and Li, 1990).

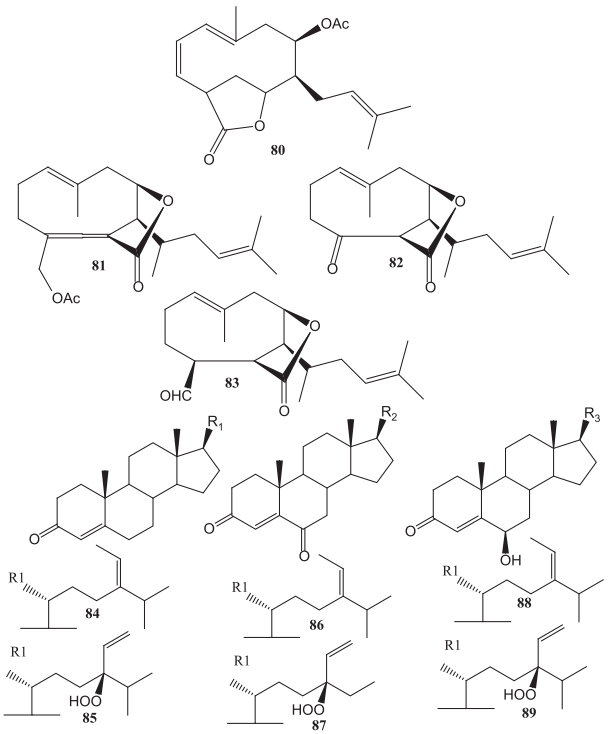
Dolabellane, a type of diterpene **78,** has been isolated from unidentified species of *Dictyota* and exhibits significant cytotoxicity. (Tringali, Prattellia and Nicols, 1984).

A cytotoxic compound named as turbinaric acid **79** was isolated from *Turbinaria ornate* (Asari, Kusumi and Kakisawa, 1989).



Four diterpenes with xenicane and norxenicane **80–83** have been isolated from another species of *Dityota dichotoma* from Okinawa Island. In addition, they showed antitumor activity.

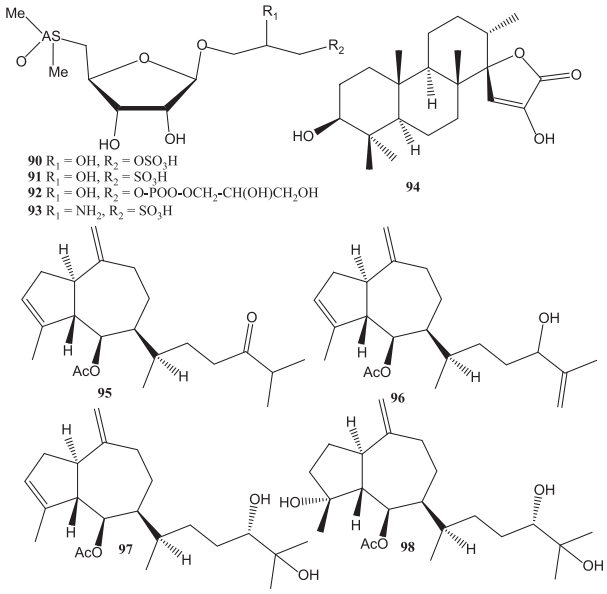
24-Ethylcholesta-4,24(28)-diene 3-one **84**, 24-ethylcholesta-4,28(29)-diene-3-one **85**, 24-ethylcholesta-4,24(28)-diene-3,6-dione **86**, 24β-hydroperoxy-24-ethylcholesta-4,28(29)-diene-3, 6-dione **87**, 60-hydroxy-24-ethylcholesta-4,24(28)-diene-3-one **88**, 24-hydroperoxy-6β-hydroxy-24-ethylcholesta-4,28(29)-diene-3-one **89** were isolated from the brown alga *Turbinaria conoides*. These oxygenated fucosterols exhibited cytotoxicity against various cancer cell lines (Sheu *et al*., 1999) including P-388, KB, A-549 and HT-29.



Four arsenic-containing ribofuranosides **90–93** together with inorganic arsenic have been isolated from the brown alga *Hizikia fusiforme*, which is eaten in Japan under the name hijiki (Edmonds, Morita and Shibata, 1987).

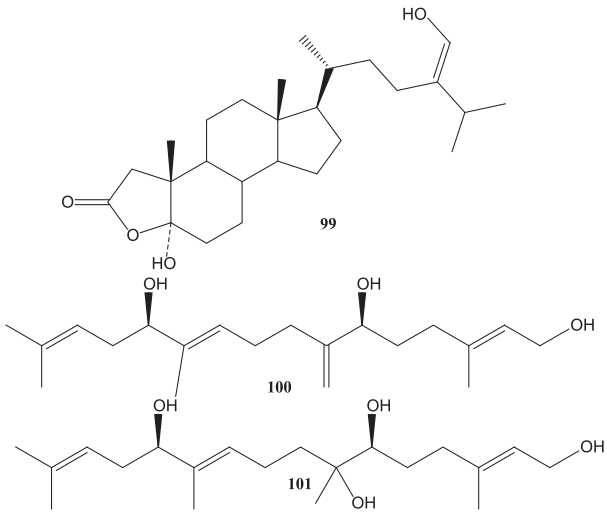
Stypolactone **94**, a diterpenoid of mixed biogenesis, has been isolated from the brown algae *Stypopodium zonale* and showed weak cytotoxic activity *in vitro* against the A-549 and H-116 cell lines (Dorta *et al*., 2002).

Four hydroazulene diterpenes, dictyone acetate **95**, dictyol F monoacetate **96**, isodictytiol monoacetate **97**, and cystoseirol monoacetate **98** were isolated from the brown alga *Cystoseira myrica* collected in the Gulf of Suez showed a moderate cytotoxicity against the murine cancer cell line KA3IT, but reduced cytotoxicity against normal NIH3T3 (Ayyad *et al*., 2003).

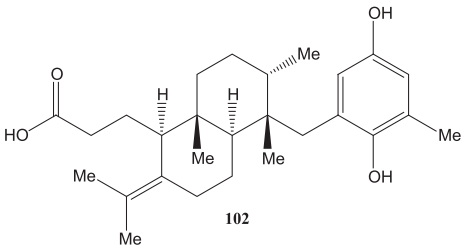


Sterols B **99** isolated from *Stypopodium carpophyllum* exhibited cytotoxic activity against several cultured cancer cell lines (Tang *et al*., 2002).

Two cytotoxic trihydroxylated diterpenes based on 12-hydroxygeranylgeraniol **100** and **101** were isolated from the brown alga *Bifurcaria bifurcate* (Gulioli *et al*., 2004).



The tropical brown alga *Stypopodium zonale* collected from the coast of Tenerife was the source of terpenoid C **102**; the methyl ester of C exhibited *in vitro* cytotoxic activity against HT-29, H-116 and A-549 (Dorta *et al*., 2002).



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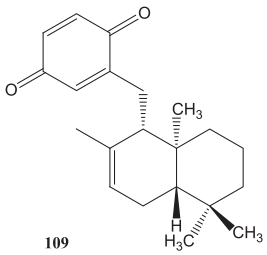

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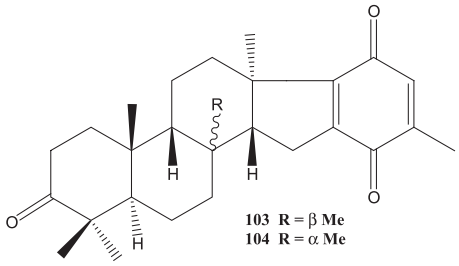
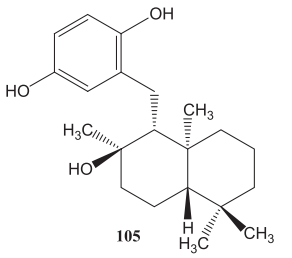
The brown alga *Taonia atomaria* was a source of meroditerpenes atomarianones A **103** and B **104,** cytotoxic agents against the NSCLC-N6 and A-549 cell lines (Abatis *et al*., 2005).



103 R = β Me
104 R = α Me

(±)-Yahazunol **105** (Ochi *et al*., 1979) and cyclozonarone **106** (Kurata, Tanguchi and Suzuki, 1996) were showed cytotoxic activity against several human tumor cell lines, while zonarol **107**, zonarone **108** and isozonarol **109** (Fenical *et al*., 1973) isolated from brown algae also displayed cytotoxicity against various human tumor cell lines (Laube, Beil and Seifert, 2005).



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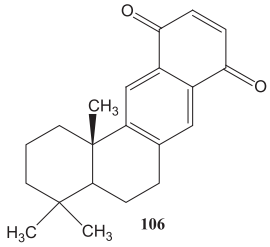

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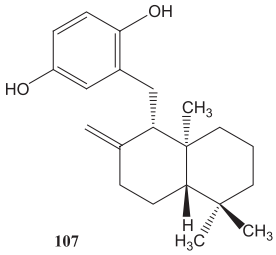

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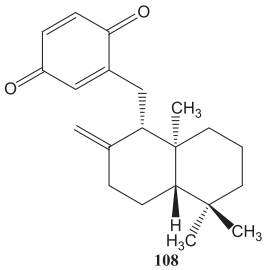


108

The brown alga *Perithalia capillaris* yielded new bisprenylated quinones **110**, **111**, both are inhibitors of superoxide production in human neutrophils *in vitro* and of proliferation of HL-60 cells (Blackman, Dragar and Wells, 1979).

Two diterpenes, 4,18-dihydroxydictyolactone **112** and 8α,11 dihydroxypachydictyol A **113**, were isolated from a *Dictyota* sp. (Jongaramruong and Kongkam, 2007). In bioassays, 4,18-dihydroxydictyolactone was strongly cytotoxic (NCI-H187) (Jongaramruong and Kongkam, 2007).

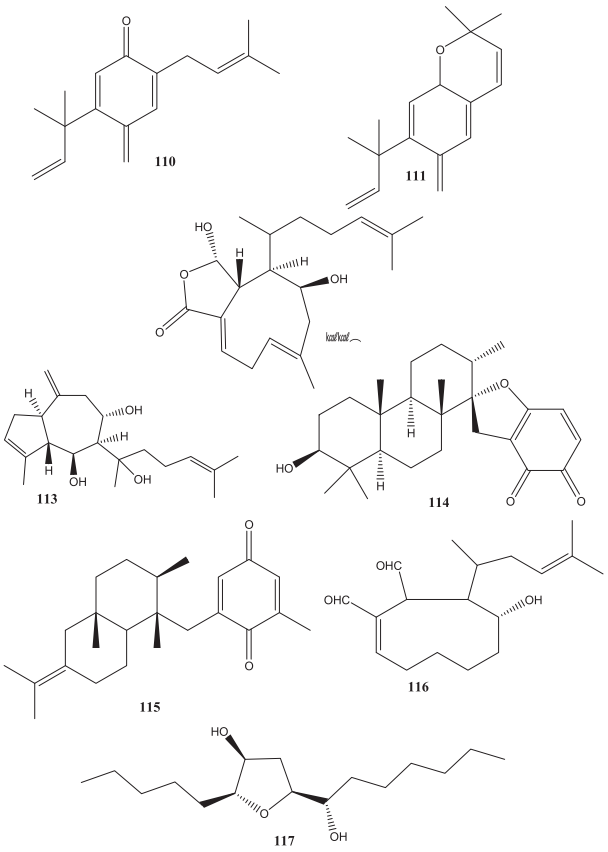
Ichthyotoxins and feeding-deterrent substances from brown algae

Stypoldione **114** was isolated from the brown alga *Stypopodium zonale*, which showed an ichthyotoxic effect. When fresh *S. zonala* is placed in an aquarium, water soon turns to a rust color and is rendered extremely toxic to the reef-dwelling herbivorous dam shellfish *Eupomocentrus leucostictus*. The fish immediately senses the toxins and attempts to jump out of the aquarium. This behavior is followed by erratic response to external stimuli, apparent difficulty in obtaining oxygen, loss of equilibrium, narcosis and eventually death. The toxic symptoms were then proved to be due to stypoldione isolated from *S. zonale* (Gerwick *et al*., 1979). Stypoquinonic acid **115** was isolated from the lipophilic extract of the same alga (Wessels, Konig and Wright, 1999) and showed inhibition of tyrosine kinase $p56^{lck}$ enzyme. Tyrosine kinase inhibitory activity was determined by enzyme-linked immunosorbent assay using a commercial test kit (Wessels, Konig and Wright, 1999).

The brown alga *Dictyota spinulosa* appeared not to be eaten by herbivores so that its constituents were examined by Tanaka and Higa in 1984 (Tanaka and Higa, 1984) and they isolated a new diterpene, hydroxydictyodial **116** as a major component among several other related compounds. Hydroxydictyodial has also been isolated from *Dictyota crenulata* (Kirkup and Moore, 1983).

Nematocidal activity

Chemical analysis of the brown alga *Notheia anomala* collected from the rock platforms along the southern coast of



Australia yielded *cis*-dihydroxytetrahydrofuran **117** derivatives. Tetrahydrofuran from *Notheia anomala* are reported for the first time as potent and selective inhibitors of the larval development of the parasitic nematodes *Haemonchus contortus* and *Trichostrongylus colubriformis* (Capon *et al*., 1998).

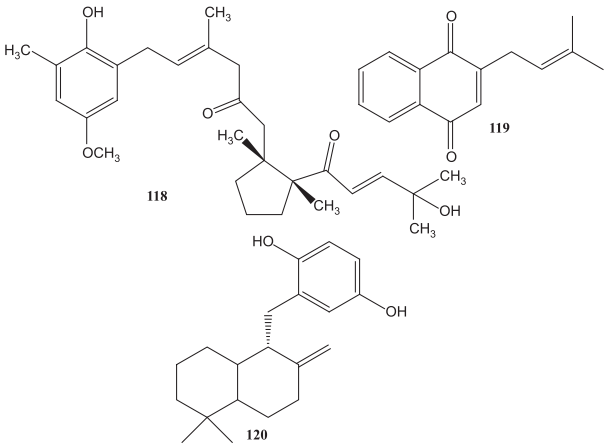
Antifungal activity

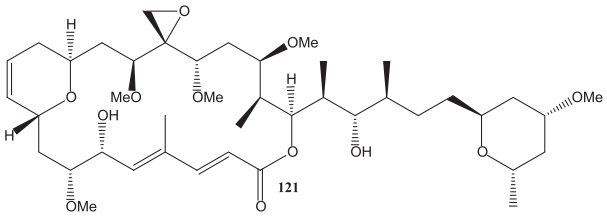
A meroditerpenoid has been isolated from the brown alga *Cystoseira tamariscifolia* and characterized as methoxybifurcarenone **118**. It possesses antifungal activity against three tomato pathogenic fungi and antibacterial activity against *Agrobacterium tumefaciens* and *Escherichia coli* (Bennamara *et al*., 1999).

A 1,4-napthaquinone derivative (deoxylapachol) **119**, from a New Zealand brown alga *Landsburgia quercifolia* was isolated by the bioactivity-directed isolation method. It showed activity against P388 leukemic cells (IC_{50} 0.6 μg/ml) and was also antifungal (Perry, Bluent and Munro, 1991).

An antifungal compound named as (+)-zonarol **120** was isolated from the brown alga *Dictyopteris zonaroides* by Fenical *et al*., (1973).

Lobophorolide **121** was isolated from the common brown alga *Lobophora variegata* and displayed a potent and highly specific activity against the marine filamentous fungi *Dendroyphiella salina* and *Lindra thalassiae* and a potent activity against *C. albicans* and was also antineoplastic (Kubanek *et al*., 2003).

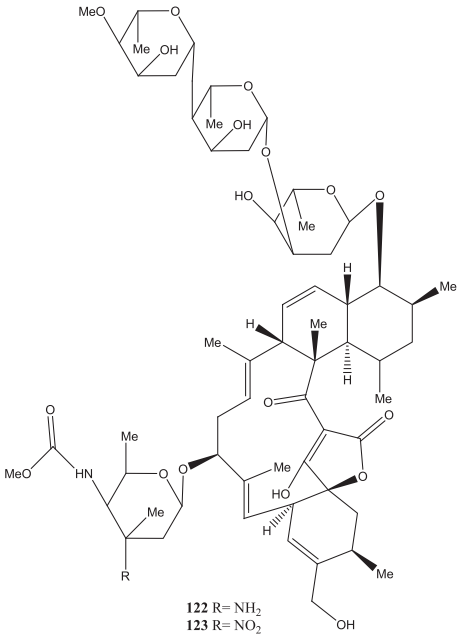




Anti-inflammatory activity

Two new anti-inflammatory macrolides, lopophorins A **122** and B **123** have been isolated from the fermented broths of a marine bacterium isolated from the surface of the Caribbean brown alga *Lobophora variegata* (Dictyotales). The new compounds are distantly related to antibiotics of the Kijanimicin class and are potent inhibitors of tropical

PMA-induced edema in the mouse ear assay when administered either topically or intraperitoneally (Jiang, Jensen and Fenical, 1999).



(*Z*)-Sargaquinone **124**, the more saturated analog **125**, and the known sargaquinone (Ishitsuka *et al*., 1979) were isolated from the brown alga *Taonia atomaria* and were anti-inflammatory agents by inhibition of leukotriene biosynthesis (Tziveleka *et al*., 2005).

Algicidal activity

A chlorine-containing perhydroazulene diterpene, dictyol J **126**, was isolated from the brown alga *Dictyota dichotoma* along with two known diterpenes, dictyolactone (Finer *et al*., 1979) and sanadaol (Ishitsuka, Kusumi and Kakisawa, 1982). All three metabolites were algicidal to the bloom-forming species *Heterosigma akashiwo* and *Karenia mikimotoi*. Dictyolactone also displayed a moderate activity against the dinoflagellate *Alexandrium catanella.*

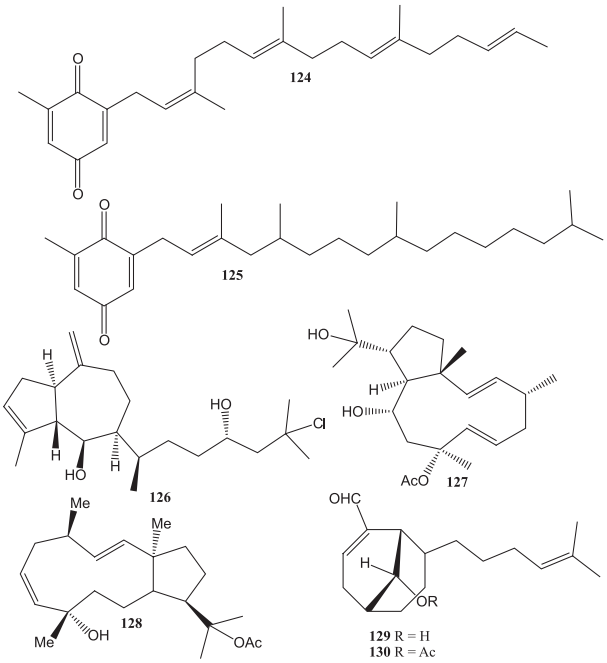
Hepatoprotective activity

Phloroglucinol (Cross, Bevan and Briggs, 1907) and phloroglucinol derivatives eckstolonol (Kang *et al*., 2003), eckol, phlorofucofuroeckol A (Fukuyama *et al*., 1990) and dieckol (Fukuyama *et al*., 1983) were isolated from the brown alga *Ecklonia stolonifera* as hepatoprotective agents (Kim *et al*., 2005).

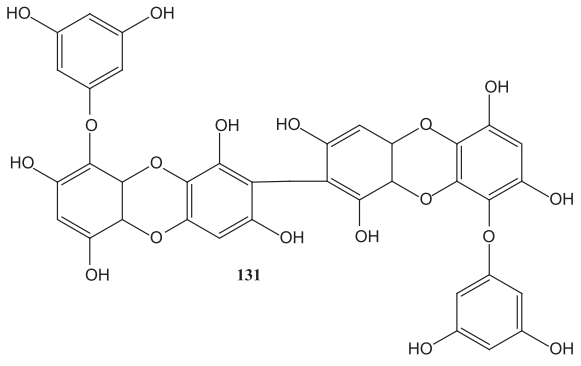
Antiviral activity

A new dollabelladiene derivative **127** and the previously isolated 10,18-diacetoxy-8-hydroxy 2,6-dollabeladiene **128** (Ireland and Faulkner, 1977) were characterized from the brown alga *Dictyota pfaffi* (Barbosa *et al*., 2004). Both compounds showed strong anti-human syncytial virus (HSV)-1 activity *in vitro* but little inhibition of human immunodeficiency virus (HIV)-1 reverse transcriptase.

The diterpenes (6*R*)-6-hydroxy dichototomo-3,14-diene-1,17-dial **129**, and the 6-acetate derivative **130**, from the brown alga *D. menstrualis* (Pereira *et al*., 2004) exhibited antiretroviral activity *in vitro*.



The phlorotannin derivatives 8,8′-bieckol **131** (Fukuyama *et al*., 1989) and 8,4′′-bieckol **132** from the brown alga *Ecklonia cava*, are inhibitors of HIV-1 reverse transcriptase (RT) and protease. Both compounds inhibited the RT more potently than the protease and the inhibitory activity of 8,8′-bieckol against HIV-I was comparable to that of a reference compound nevirapine.



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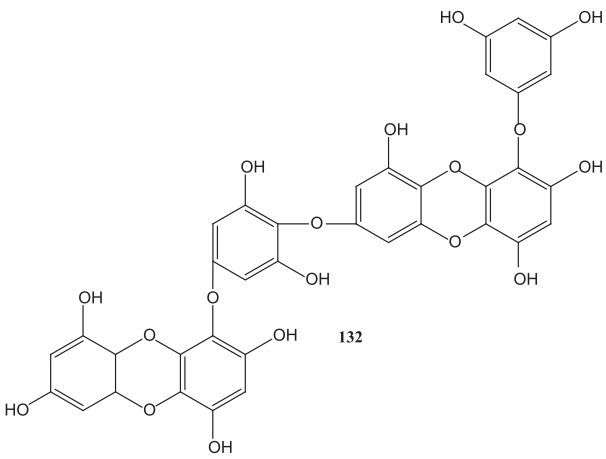
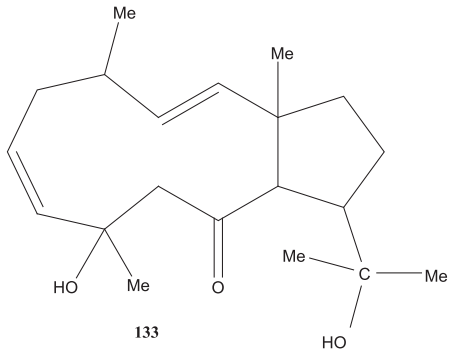


132

Protection against herbivorous animals

Dolabellane 1 **133**, originally isolated from the opisthobranch mollusk *Dolabella californica* (Ireland and Faulkner, 1977) has been characterized as the major secondary metabolite and active chemical defense against herbivores (sea urchins and fish) in the brown alga *Dictyota pfaffi* (Barbosa *et al*., 2003).

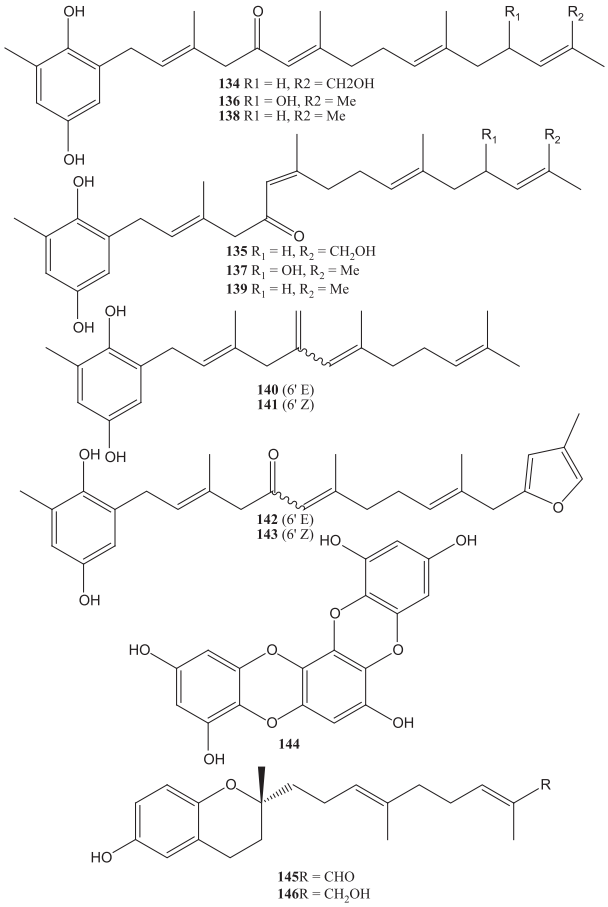


133

Free radical scavenger and antioxidant activities

Several prenyl toluquinones were isolated from the brown alga *Cystoseira crinita*. Compounds **134–141** exhibited potent radical-scavenging effects while **142** and **143** were less active (Fisch *et al*., 2003).

The brown alga *Ecklonia stolonifera* collected from South Korea yielded a new phlorotannin, eckstolonol **144**, which possessed a potent 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity (Kang *et al*., 2003).



134 R1 = H, R2 = CH2OH
136 R1 = OH, R2 = Me
138 R1 = H, R2 = Me

135 R_1 = H, R_2 = CH_2OH
137 R_1 = OH, R_2 = Me
139 R_1 = H, R_2 = Me

140 (6′ E)
141 (6′ Z)

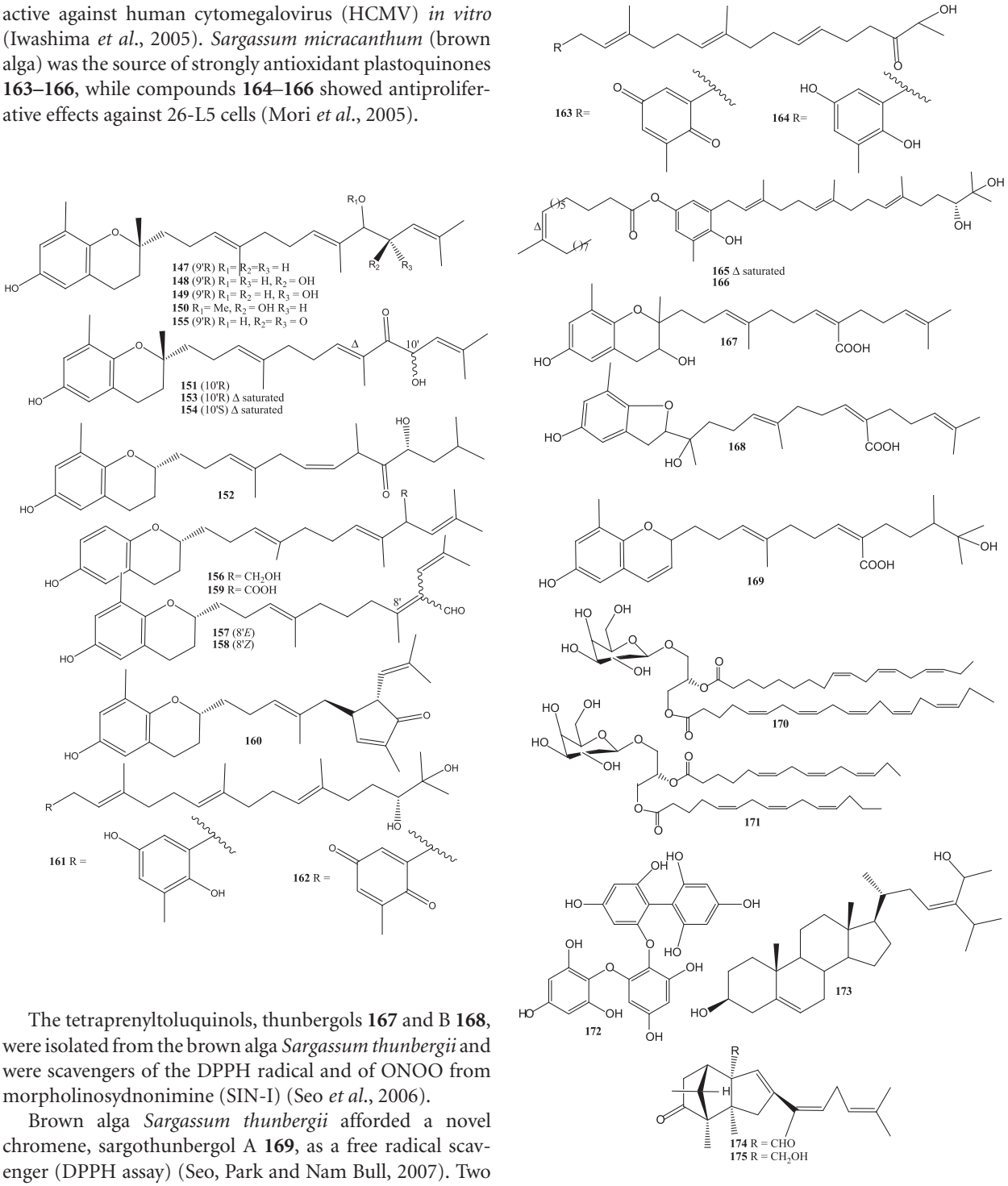
142 (6′ E)
143 (6′ Z)

144

145R = CHO
146R = CH_2OH

The sargachromanols A–P (compounds **145–160**, meroterpenoids of the chromene class, were isolated from the brown alga *Sargassum siliquastrum*. All the isolated compounds exhibited significant activity in the DPPH assay while compounds **151** and **159** were also inhibitors of butyl choline esterase (Jang *et al*., 2005). The known plastiquinones (**161** and **162**) were isolated from the brown alga *S. micracanthum*. Compound **161** displayed significant antioxidant activity, while in contrast **162** was potently

active against human cytomegalovirus (HCMV) *in vitro* (Iwashima *et al*., 2005). *Sargassum micracanthum* (brown alga) was the source of strongly antioxidant plastoquinones **163–166**, while compounds **164–166** showed antiproliferative effects against 26-L5 cells (Mori *et al*., 2005).



The tetraprenyltoluquinols, thunbergols **167** and B **168**, were isolated from the brown alga *Sargassum thunbergii* and were scavengers of the DPPH radical and of ONOO from morpholinosydnonimine (SIN-I) (Seo *et al*., 2006).

Brown alga *Sargassum thunbergii* afforded a novel chromene, sargothunbergol A **169**, as a free radical scavenger (DPPH assay) (Seo, Park and Nam Bull, 2007). Two monogalactosyl diacylglycerols **170** and **171** were isolated from *S. thunbergii* (Kim *et al*., 2007). Fucodiphlorethol G **172**, a tetrameric phlorotannin, was isolated from *Ecklonia cava*, and was a strong radical scavenger (DPPH assay) (Ham *et al*., 2007).

The known compounds taondiol (Gonzalez, Darias and Martin, 1971) isoepitaondiol (Rovirosa *et al*., 1992) stypodiol, (Gerwick and Fenical, 1981), stypoldione (Gerwick *et al*., 1979) and sargaol (Numata *et al*., 1992), isolated

from the brown alga *Taonia atomaria* exhibited free radical-scavenging activity (DPPH and chemiluminescence tests) (Nahas *et al*., 2007).

Antidiabetic activity

*In viv*o testing of fucosterol, which was isolated from the brown alga *Pelvetia siliquosa*, demonstrated that it is the main antidiabetic principle from *Pelvetia siliquosa* (Lee *et al*., 2004).

Antihypertensive activity

Some known phlorotannins isolated from the brown alga *Ecklonia stolonifera*, namely eckol (Fukuyama *et al*., 1983), phlorofucofuroeckol A (Fukuyama *et al*., 1990) and dieckol (Fukuyama *et al*., 1983) were shown to have marked inhibitory activity against angiotensin-converting enzyme (ACE) (Jung *et al*., 2006).

Morphological abnormality in a plant pathogen

Stypopodium carpophyllum from South China Sea was the source of two new bioactive sterols A **173** and B **99.** These sterols induced morphological abnormality in the plant pathogenic fungus *Pyricularia oryzae* (Tang *et al*., 2002a).

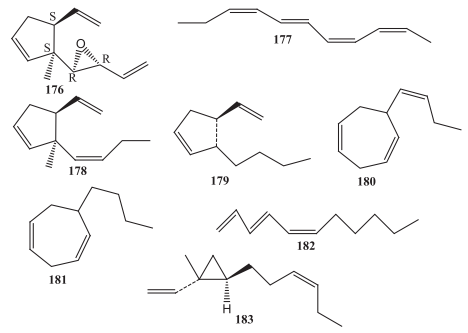
Antifeedent activity

Two diterpenoids with a novel skeleton, diterpenoids A **174** and B **175**, were isolated from the brown alga *Dilophus okamurae* and displayed antifeedent activity against young abalone (Suzuki, Yamada and Kurata, 2002). 10,18-diacetoxy-8-hydroxy 2,6-dollabeladiene **128** (Ireland and Faulkner, 1977) was the antifeedent compound of brown alga *D. pfaffi* against the sea urchin *Lytechinus variegatus* and generalist fishes (Barbosa *et al*., 2004).

Gamete-releasing, gamete-attracting and sperm-attractants pheromone from brown algae

Most algae form some sort of spore, which is a cell that is often motile and serves to reproduce the organism. Algae also have sex, often a very simple kind of sex where the algae themselves act as gametes, but sometimes very complicated with egg and sperm-like cells.

(+)-Caudoxirene **176** is a new gamete-releasing and gamete-attracting pheromone isolated from brown alga *Perithalia cudata* (Muller *et al*., 1988). Giffordene **177** is another gamete-attractant of brown algae *Giffordia* (*Hinksia mitchellae*) (Boland *et al*., 1987) The female gametes of *Chorda tomentosa* secrete a mixture of multifidene **178**, 3-butyl 4-vinylcyclopentene **179**, ectocarpene **180** and (–)-dictyopterene C **181** that trigger an explosive discharge of spermatozide from ripe antheridia prior to chemotaxis (Maier *et al*., 1984). Two sperm-attractants of *Cystophora siliquosa* and *Hormosira hanksii* were identified as cystophorene **182** and hormosirene **183** (Muller *et al*., 1985).



1.2.3 Rhodophyta (red algae)

The red color of these algae results from the dominance of the pigments phycoerythrin and phycocyanin; these mask the other pigments, chlorophyll *a* (no chlorophyll *b*), *β*-carotene, and a number of unique xanthophylls (Bold and Wynne, 1985). The walls are made of cellulose, agars and carrageenans. Several red algae are eaten; amongst these is dulse (*Palmaria palmata*) and carrageen moss (*Chondrus crispus* and *Mastocarpus stellatus*). However, "Nori" popularized by the Japanese is the single most valuable marine crop grown by aquaculture with a value in excess of 1 US billion $.

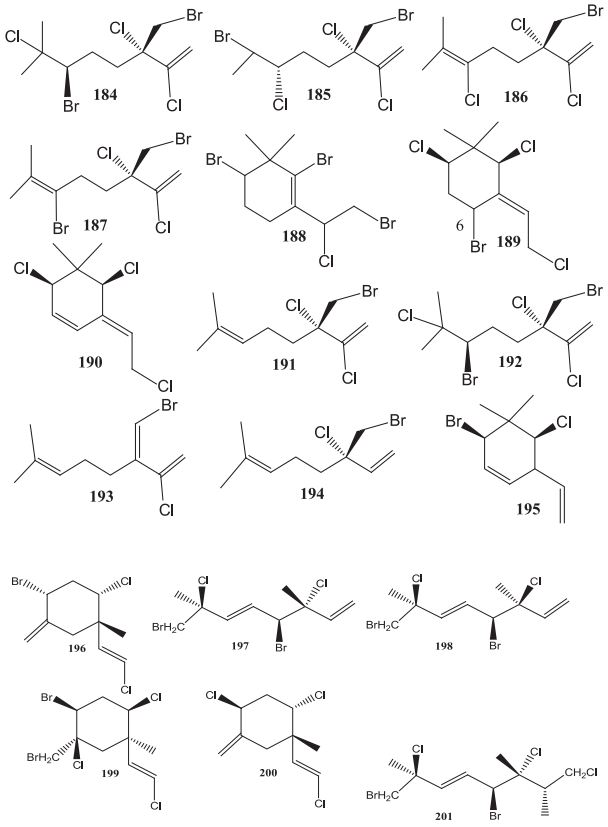
The red algae *Kappaphycus* and *Betaphycus* are now the most important sources of carrageenan, a commonly used ingredient in food, particularly yogurt, chocolate milk, and prepared puddings. *Gracilaria*, *Gelidium*, *Pterocladia*, and other red algae are used in manufacture of the all-important agar, used widely as a growth medium for microorganisms and biotechnological applications.

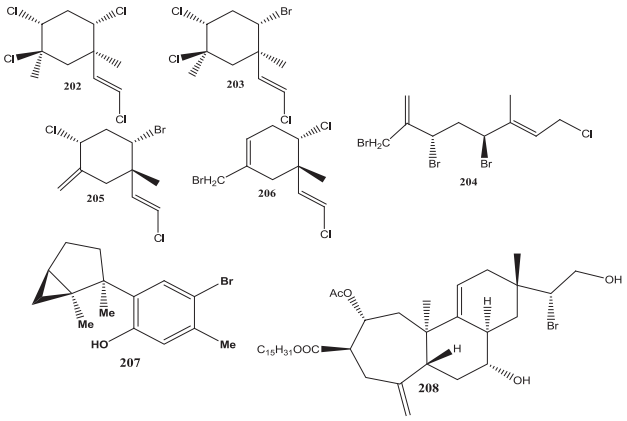
There are about 8000 species of red algae, most of which are marine. These are found in the intertidal and subtidal zones to depths of up to 40, or occasionally, 250 m. Red algae are considered as the most important source of many biologically active metabolites in comparison to the other algal class.

Cytotoxic activity

Halmon **184** is a polyhalogenated monoterpene isolated from the red alga *Portieria hornemanii* and is considered as a novel *in vitro* antitumor agent by the National Cancer Institute (NCl). The NCI Decision Network Committee selected halmon as a preclinical drug for development

(Fuller *et al*., 1992, 1994). Ten halogenated monoterpenes **185–194**, related to the novel antitumor compound halomon **184** or to the carbocyclic analog (Fuller *et al*., 1992), have been isolated from different geographic collections of the red alga. These compounds were comparatively evaluated alongside compounds **184** and **190** in the US National Cancer Institute's *in vitro* human cancer cell line screening panel. The results provide insights into structure/activity relationships in this series as follows. Compounds **184–187** exhibited similar cytotoxicity to that reported earlier for **184** (Fuller *et al*., 1992). These results suggested that halogen at C_7 was not essential to the activity. In contrast, compound **191** was relatively weakly cytotoxic and the minimally differential activity showed no significant correlation to that of **184**, indicating that a halogen at C_6 was essential for the characteristic activity of **184–187**. The halogen at C_2 was required for halomone-like activity. Carbocyclic compounds such as **188** and **195** were considerably less cytotoxic than **204–207.** Compound **189** was more comparable to the overall (panel-averaged) potency to halomon. However, there was little differential response of the cell lines, and consequently no significant correlation to the profile of **184**.



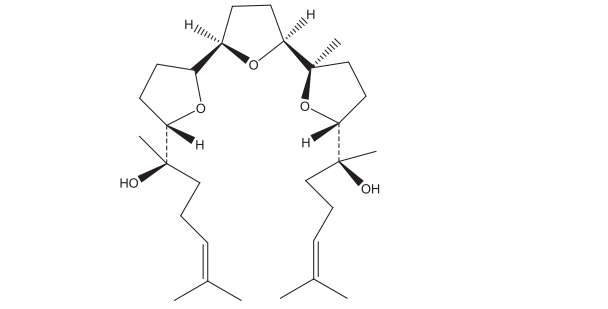


The polyhalogenated monoterpene content of six samples of the tropical marine red alga *Plocamium hamatum* **196–206**, collected from the southern, central and northern regions of the Great Barrier Reef, Australia was assessed. The biological activities of compounds **197–203** and **206** were assessed and indicated that compounds **199** and **201** have moderate cytotoxic activity. (Koing, Wright and Linden, 1999).

The invention of laurinterol (LOEL) **207**, which was isolated from *Laurencia okamurai* is considered as invention for the prevention and inhibition of melanoma (Moon-Moo, Sang-Hoon and Se-Kwon, 2009) LOEL can effectively inhibit the growth of melanoma cells by inducing apoptosis therein without adverse effect as in synthetic medicines. Thus, LOEL exhibited a dose-dependent inhibitory effect on the growth of melanoma cells as it was observed that cells are treated with LOEL at 10 μg/ml and the growth of melanoma cells by was inhibited 50%. Addition of 1 μg/ml of LEOL exerted 30% inhibition on the growth of melanoma cells in the presence of fetal bovine serum (FBS) (Moon-Moo, Sang-Hoon and Se-Kwon, 2009).

2-Acetoxy-15-bromo-6,17-dihydroxy3-palmitoyl-neoparguera-4(19), 9(11)-diene **208**, a novel secoparguerane skeleton has been isolated from the red alga *Laurencia obtuse* from Okinawa and showed a cytotoxic activity (Cortes *et al*., 1990).

Two new cyclic ethers consisting of squalene carbon skeleton, teurilene **209** and thyrsiferyl 23-acetate **210**, have been isolated from the red alga *Laurencia obtuse* (Suzuki *et al*., 1985). Thysiferyl 23-acetate **210** (bromo ether) showed remarkable cytotoxic property (ED_{so} of 0.3 μg/ml) against P388 *in vitro* cell line



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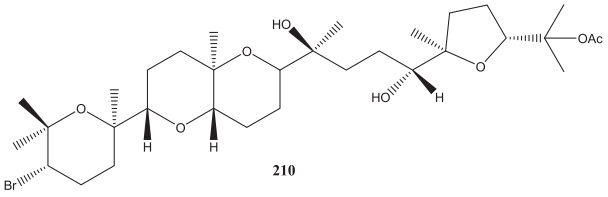
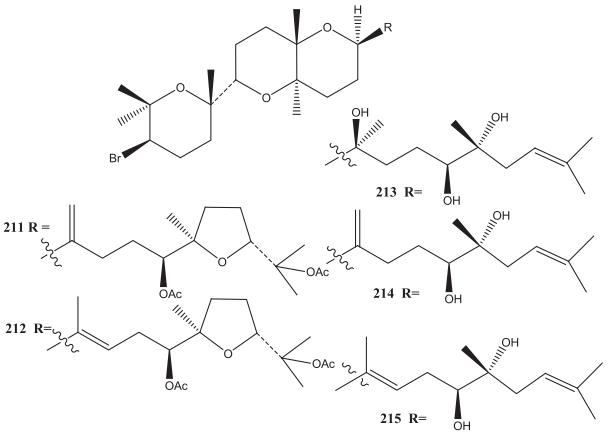


210

Five new cytotoxic triterpenes: triterpenoids 28-anhydrothyrsiferyl diacetate [15,28-didehydro-15-deoxythyrsiferyl] diacetate **211**, l5-anhydrothyrsiferyl diacetate [15,16-didehydro-l5-deoxy-thyrisferyl] diacetate **212**, magireol-A **213**, magireol B **214** and magireol C **215** were isolated from Japanese red alga *Laurencia obtuse* (Suzuki *et al*., 1987).

Several cyclic monoterpenes **217–225** have been isolated from the Japanese red alga *Desmia hornemanni*, and some chemical modification has been done on these compounds to find the most active one for cytotoxic activity (Higa, 1985). Compound **216** exhibited relatively high activity against P388, A549 lung carcinoma, and HCT-8 human colon adenocarcinoma.



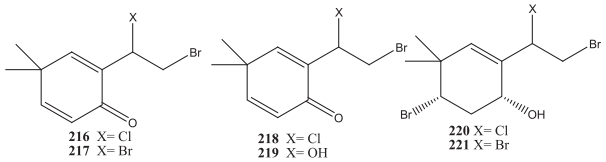
211 R =

212 R=

213 R=

214 R=

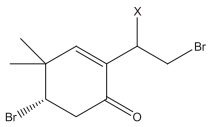
215 R=



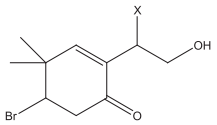
216 X= Cl
217 X= Br

218 X= Cl
219 X= OH

220 X= Cl
221 X= Br



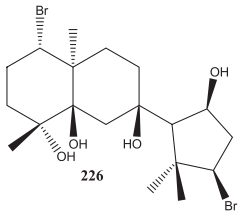
222 X= Cl
223 X= Br



224 X= Cl
225 X= Br

Okianwa red alga *Laurencia yonaguniensi* was the source of neoirietetraol **226**, a brominated diterpene based on the rare neoirieane skeleton; it was toxic to brine shrimp and was also active against marine bacteria *Alcaligenes aquamarinus* and *E. coli* (Takahashi *et al*., 2002).

Furoplocamioid C **227**, perfuroplocamioid **228**, pirene **229** and tetrachlorinated cyclohexane **230** from the red alga *Plocumium carttilagineum* (Argandona *et al*., 2002) exhibited selective cytotoxicity against human tumor cell lines with pirene showing a specific and irreversible effect on SW480 cells (de Ines *et al*., 2004).



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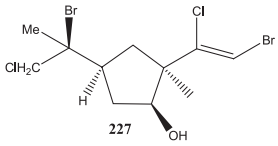

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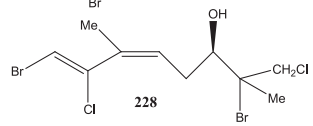

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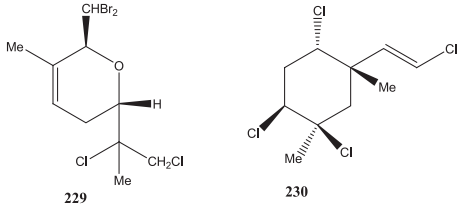

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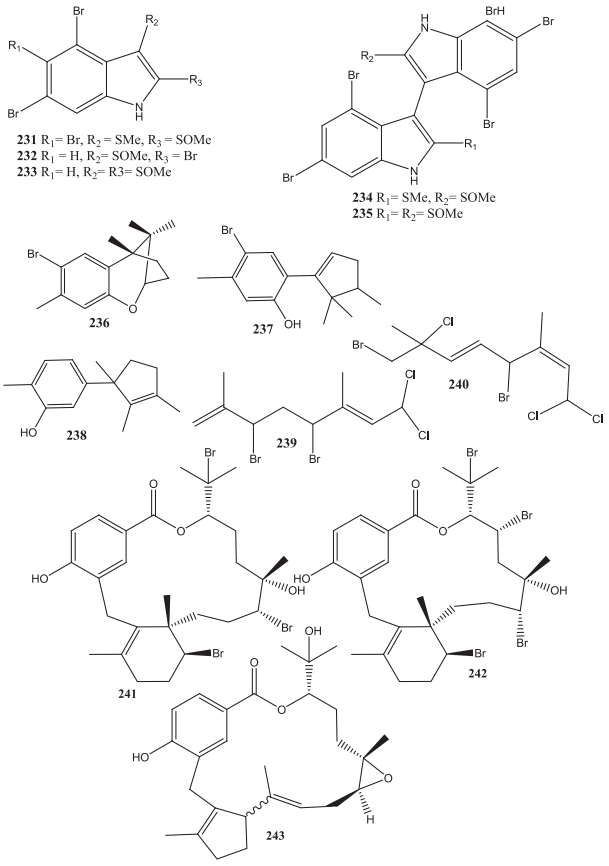
Five sulfur-containing polybromoindoles **231–235** were isolated from the red alga *Laurenda brongniartii*, of which **234** and **235** were active against P388 cells and **234** against HT-29 cells (El Gamal, Wang and Duh, 2005). The cuparene

sesquiterpenes **236–238**, isolated from the red alga *L. microcladia* were cytotoxic against the NSCLC-N6 and A549 cancer cell lines. (Kladia *et al*., 2005).

Plocaralides B **239** and C **240** isolated from *Plocamium* species (Steierle, Wing and Sims, 1979; Higgs, Vanderah and Faulkner, 1977) and *Aplysia californica* (Ireland, 1976) displayed moderate activity against the human esophageal cancer cell line WHCOI (Knott *et al*., 2005).

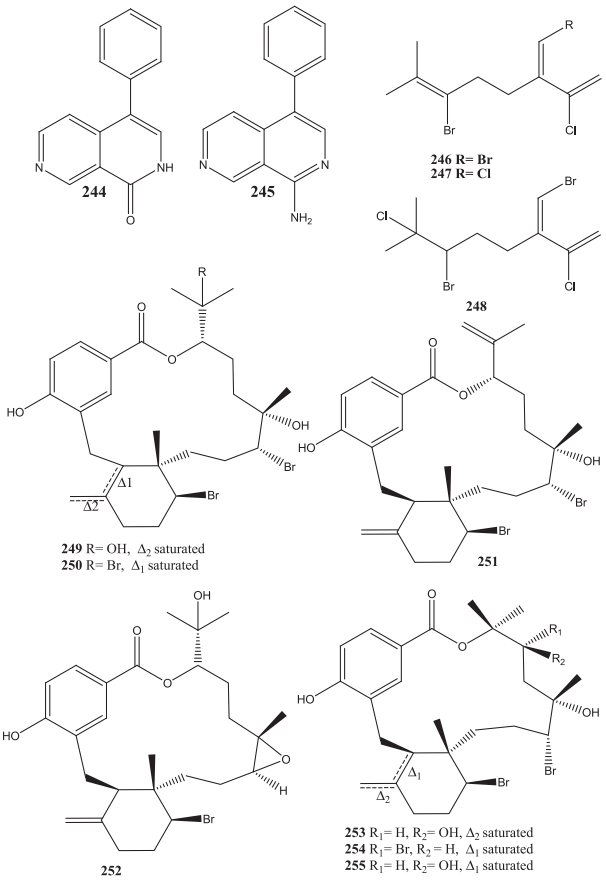
The red alga *Callophycus serratus* was the source of three antibacterial and antifungal diterpene-benzoate compounds, bromophycolides A **241** and B **242**, and a non-halogenated compound **243**. Bromophycolide A **241** was cytotoxic against several human tumor cell lines by specific induction of apoptosis (Kubanek *et al*., 2005).



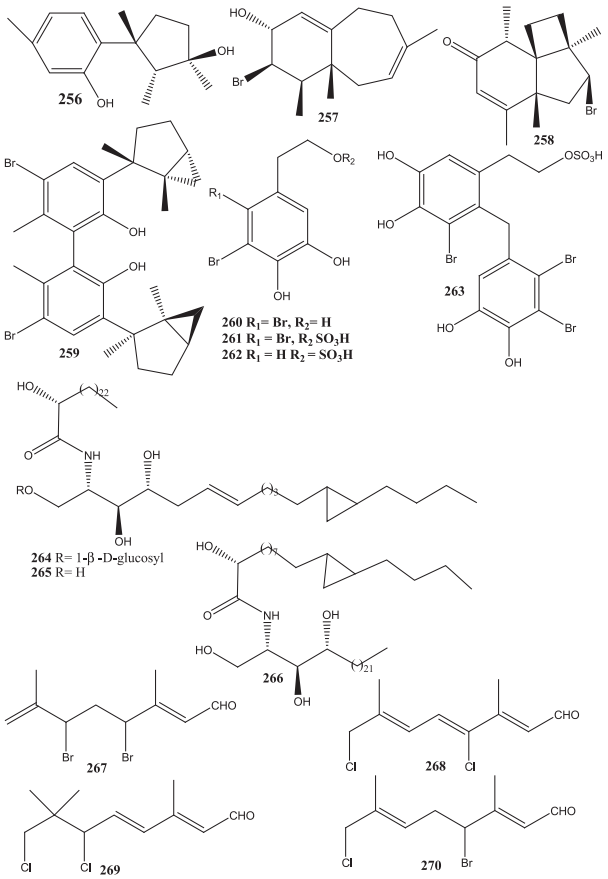
The alkaloids 2,7-naphthyridine lophocladines A **244** and B **245** were isolated from the red alga *Lophocladia* sp. Lophocladine A displayed affinity to *N*-methyl-D-aspartate (NMDA) receptors and was also a *δ*-opioid receptor antagonist, while lophocladine B **245** was moderately active against NCI-H460 human lung tumor and MDA-MB-435 breast cancer cell lines and shown to be an inhibitor of microtubules (Gross *et al*., 2006).

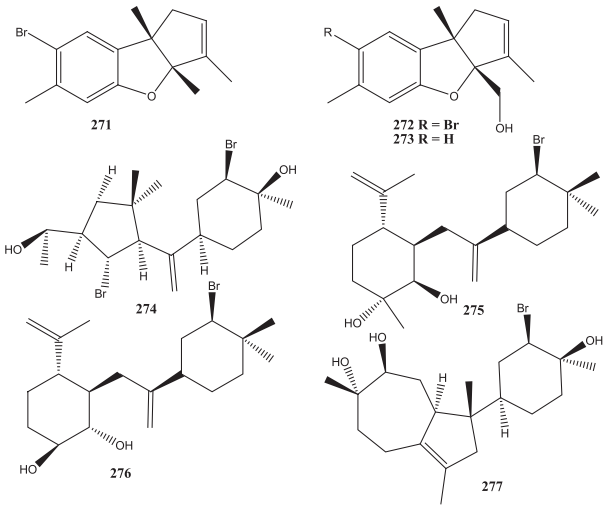
Three halogenated monoterpenes **246–248** were isolated from the red alga *Portiera hornemannii* along with the known compound halomon (Fuller *et al*., 1992). Both halomon **184** and **248** were moderate inhibitors of DNA methyl transferase-1 (Andrianasolo *et al*., 2006).

Bromophycolides C-I **249–255** are diterpene-benzoate macrolides isolated from the red alga *Callophycus serratus* with modest activity against a range of human tumor cell lines. (Kubanek *et al*., 2006).



The red alga *Laurencia obtusa* was a source of sesquiterpenes 3,7-dihydroxydihydrolaurene **256**, perforenol B **257** and **258**, while *L. microcladia* yielded a dimeric sesquiterpene **259**. Compounds **256–258** were tested against five human tumor cell lines and the Chinese hamster ovary (CHO) cell line. Perforenol B **257** exhibited strong activity while sesquiterpenes **256** and **258** exhibited weak activity. The sesquiterpene **259** was moderately cytotoxic against NSCLC-N6 and A549 lung cancer cell lines (Kladi *et al*., 2006). The red alga *Rhodomela confervoides* was the source of four bromophenols **260–263.** They exhibited moderate cytotoxicity against several human cancer cell lines (Ma *et al*., 2006).





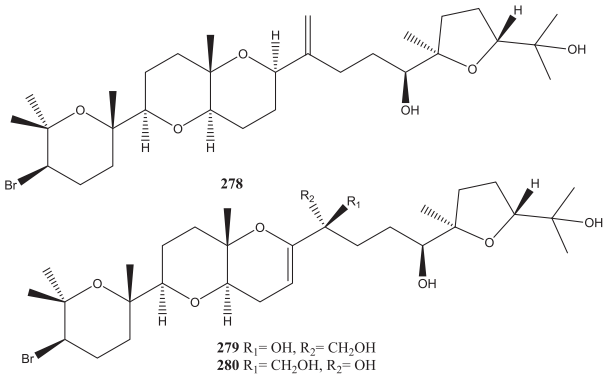
The red alga *Gracilaria asiatica* was the source of three cyclopropyl derivatives, the cerebroside gracilarioside **264** and the ceramides gracilamides A **265** and B **266**, which were mildly cytotoxic to the human A375-S2 melanoma cell line (Sun *et al*., 2006).

Four somewhat air-unstable halogenated monoterpene aldehydes **267–270** were characterized from the red alga *Plocamium corallorhiza*, of which **287** was significantly cytotoxic against an esophageal cell line.(Mann *et al*., 2007).

Three sesquiterpenes, aplysin-9-ene **271**, epiaplysinol **272** and debromoepiaplysinol **273,** were isolated from the red alga *Laurencia tristicha*. Debromoepiaplysinol **273** displayed selective cytotoxicity to the HeLa cell line (Sun *et al*., 2007).

Diterpenes neorogioldiol B **274** and prevezol B **275** isolated from the red alga *Laurencia obtusa* displayed significant cytotoxicity against the human tumour cell lines MCF7, PC3, HeLa, A431, and K562, while prevezol C **276** exhibited significant cytotoxicity against HeLa and A431 cell lines. Prevezol D **277** was moderately active against all cell lines (IIopoulou *et al*., 2003).

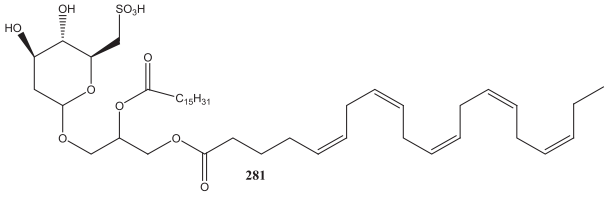
Two new polyether squalene derivatives, thyresenol A and B **279**, **280** have been isolated from *Laurencia viridis* together with the previously isolated dehydrothyrsiferol **278** (Norte *et al*., 1997, Pec *et al*., 2003). All these compounds showed a potent cytotoxic activity against P388 cell lines The marine polyether triterpenoid dehydrothyrsiferol **278**, originally isolated from the red alga *Laurencia pinnatifida* was shown to induce apoptosis in estrogen-dependent and -independent breast cancer cells (Norte *et al*., 1997, Pec *et al*., 2003).



Antiviral activity

Sulquinovosyldiacylglycerol, KM043 **281**, a new sulfolipid KM043, which belongs to the 6-sulf-α-D-quinovopyranosyl-(l→3′)-1′,2′-diacylglycerol (SQDG) class of compounds has been isolated from the marine red alga *Gigartina tenella* (Ohata *et al*., 1998) as a potent inhibitor of eukaryotic DNA and HIV-l reverse transcriptase type 1. The inhibition was dose dependent, and complete (more than 90%) inhibition of DNA polymerase α (pol.α),

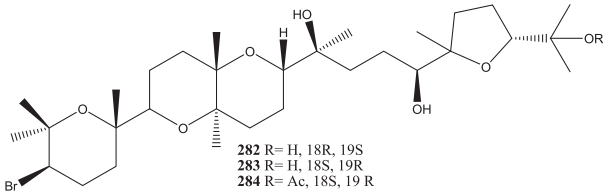
DNA polymerase β (pol.β) and HIV-reverse transcriptase type 1 (HIV-RT) was observed at concentrations 5, 10 and 30 μM, respectively.



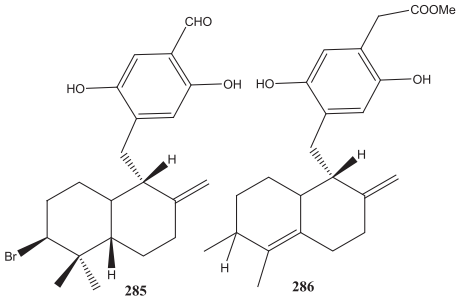
2,3,6-Tribromo4,5-dihydroxybenzyl methyl ether (Park *et al*., 1999) isolated from the red alga *Symphyocladia latiuscula* was active against wild type HSV-l, as well as APr HSV-I and TK-HSV-l and significantly delayed the appearance of lesions in infected mice without toxicity (Park *et al*., 2005).

The invasive species *Caulerpa racemosa* was the source of the known compound sulfoquinovosyldiacylglycerol, previously isolated from a terrestrial plant (Amarquaye *et al*., 1994) and from the marine brown alga *Ishige okamurai* (Tang *et al*., 2002b), and displayed selective antiviral activity against Herpes simplex virus 2 (HSV-2) (Wang *et al*., 2007).

Venustatriol **282**, thyrsiferol **283** and thyrsiferyl 23-acetate **284** were isolated from the red alga *Laurencia venusta* and all displayed significant antiviral activity against vesicular stomatitis virus (VSV) and HSV-l (Sakemi *et al*., 1986).

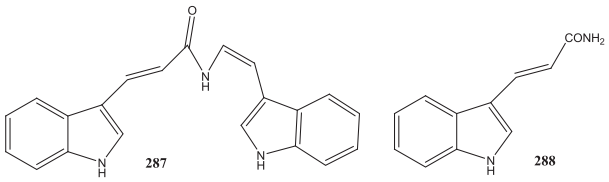


During a survey of marine organisms for anti-HIV RT activities, two new sesquiterpene hydroquinones, peyssonol A **285** and B **286** have been isolated from the active anti-HIV RT extracts of the Red Sea alga *Peyssonnelia* spp. (Talpir *et al*., 1994).



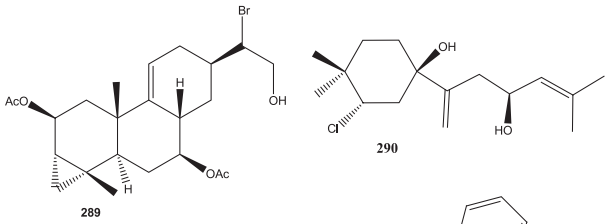
Anthelmintic activity

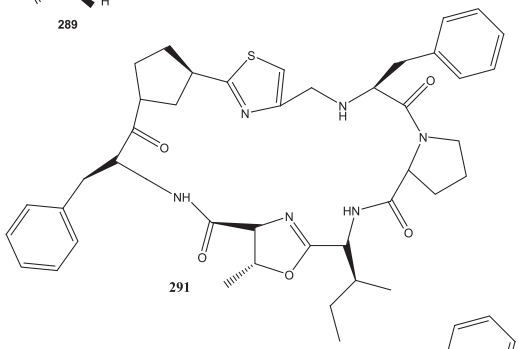
Chondriamide C **307**, a new bis(indole) amide and 3-indolacrylamide **308** have been isolated from the red alga *Chondria atropurpurea* and showed anthelmintic activity against *Nippostrongylus brasiliensis* (Davyt *et al*., 1998).

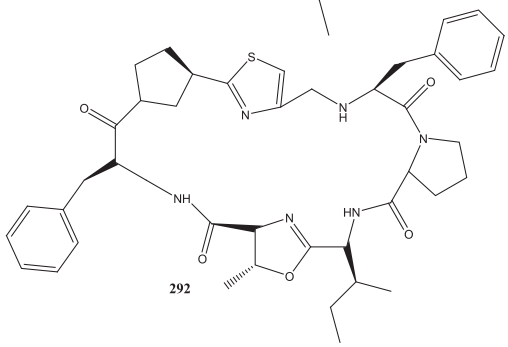


Brominated diterpenes of the parguerene and isoparguerene series were isolated from the red alga *Jania rubens* including the novel deoxyparguerol-7-acetate **309**. All the isolated diterpenes had anthelmintic activity (Awad, 2004).

The red alga *Laurencia scoparia* was a source of halogenated β-bisabolene sesquiterpenes **310** (Awad, 2004; Davyt *et al*., 2006). It showed weak *in vitro* anthelmintic activity against *Nippostrongylus brasiliensis* (Davyt *et al*., 2006).



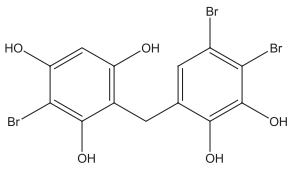




Anti-inflammatory activity

Chemical investigation of the marine red alga *Ceratodictyon spongiosum* containing the symbiotic sponge *Sigmadocia symbiotica* collected from Indonesia, afforded two isomers of a new bioactive thiazole-containing cyclic heptapeptide: *cis*,*cis*-ceratospongamide **291** and *trans*,*trans*-ceratospongamide **292** (Tan *et al*., 2000). Isolation of these peptides was assisted by bioassay-guided fractionation using a brine shrimp toxicity assay. *trans*,*trans*-ceratospongamide exhibits potent inhibition to sPLA2 expression in a cell-based model for anti-inflammation (ED_{50} 32 nM), whereas the *cis*,*cis* isomer is inactive. *trans*,*trans*-Ceratospongamide was also shown to inhibit the expression of a human-sPLA2 (secreted phospholipase A2) promotor-based reporter by 90%. The degree of anti-inflammatory activity of compounds **291** and **292** was measured as the inhibition of secreted phospholipase A2 by hepatocellular carcinoma cells stimulated with 1L-1β. The *trans*,*trans* form is a potent inhibitor of sPLA2 expression with ED_{50} 32 μM. Both compounds showed only moderate potency in the brine shrimp toxicity assay.

The anti-inflammatory bromophenolic metabolites named vidalols A **293** and B **294** were isolated from the Caribbean red alga *Vidalia obtusaloba* that acts through the inhibition of phospholipase enzyme (Wiemer, Idler and Fenical, 1991). The new compounds were discovered as part of an organized effort to isolate new naturally occurring anti-inflammatory agents with a focus upon those that may function through inhibition of phospholipase A2.



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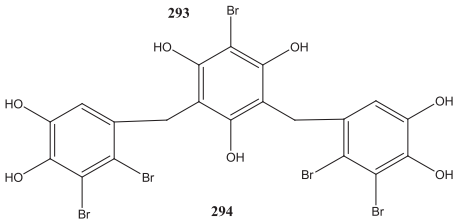
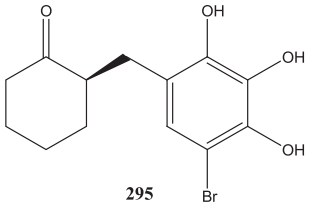


294

Free radical scavenger activity

(2R)-2-(2,3,6-tribromo-4,5-dihydroxybenzyl) cyclohexanone **295** was isolated from the red alga *Symphyocladia latiussula*, which has a free radical scavenger activity. The antioxidant activity was expressed and calculated in terms of IC_{50} [μg/ml or μM required to inhibit l,1-diphenyl-2-picrylhydrazyl radical, (DPPH), formation by 50%] (Choi *et al*., 2000).



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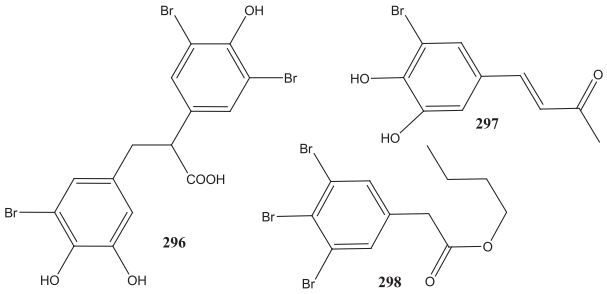
Three bromophenols **296**–**298** and the previously reported 1,2-bis(3-bromo-4,5-dihydroxyphenyl ethane (Kurata, Amiya and Nakano, 1976) were isolated from the red alga *Polysiphonia urceolat*a All compounds were potent DPPH radical scavengers (Li *et al*., 2007).

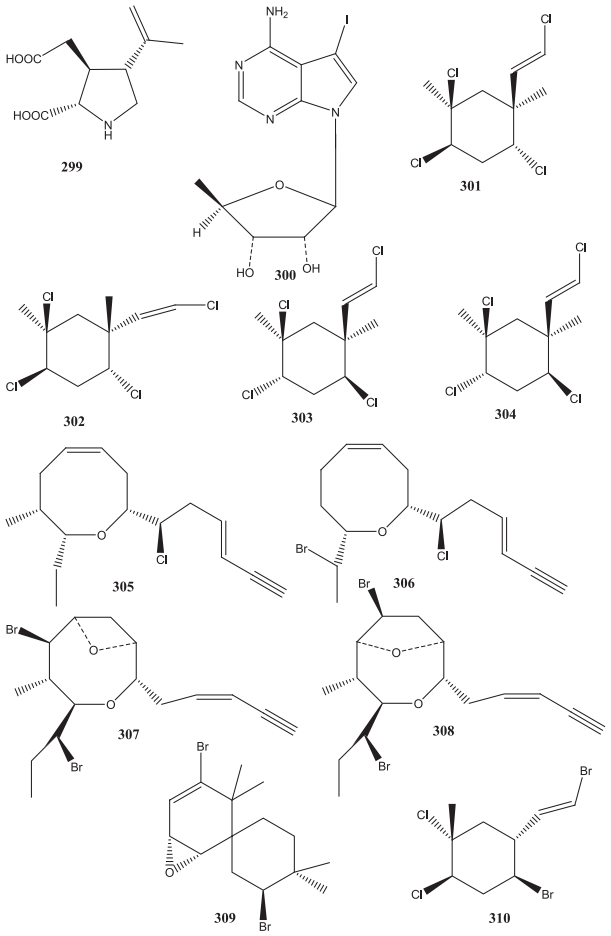


296 **297** **298**

Five known bromophenols, bis (2,3,6-tribromo-4,5-dihydroxyphenyl) methane (Wang *et al*., 2005), bis (2,3,6-tribromo-4,5-dihydroxybenzyl) ether (Kurata and Amiya, 1980), 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (Kim *et al*., 2002), 2,3,6-tribromo-4,5-dihydroxymethylbenzene (Li *et al*., 2007) and 2,3,6-tribromo-4,5-dihydroxybenzaldehyde (Kurata and Amiya, 1980) were co-isolated and were also potent free radical scavengers (Duan, Li and Wang, 2007).

Neurophysiological activity

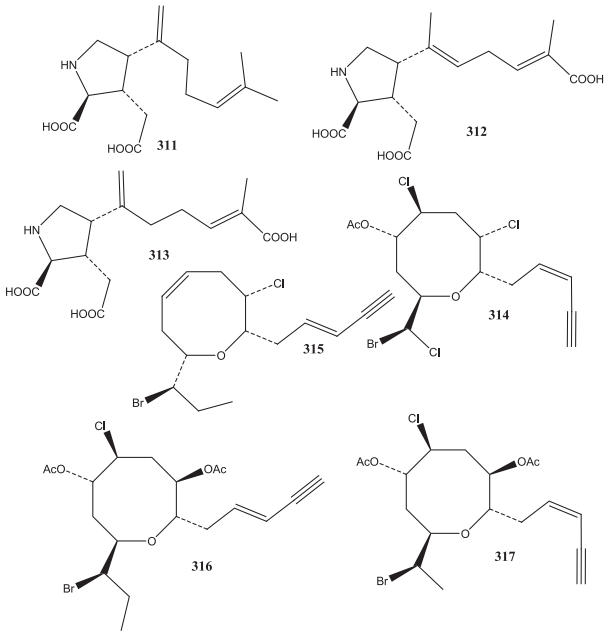
The amino acid (α-alkokainic acid **299** isolated from the red alga *Digenea simplex* showed a potent neurophysiological activity in mammals (Biscoe *et al*., 1975; Ferkany and Coyle, 1983). 5-Iodo-5′-deoxy-tubercidin **300** was isolated from the red alga *Hypnea valendiae*, which causes pronounced relaxation of muscles and hypothermia in mice and it blocks polysynaptic and monosynaptic reflexes. This compound is one of the most interesting algal metabolites which were discovered by using a bioassay-directed isolation procedure (Kazlauskas *et al*., 1983).

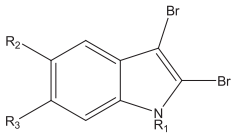


Insecticidal activity

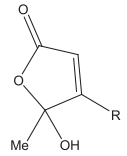
The insecticidal and acaricidal polyhalogenated monoterpenes **301**–**304** have been isolated from Chilean specimens of the red alga *Plocamium cartilagineum.* The insecticidal activity of these compounds proved to be effective against the Aster leafhopper (San-Martin, Negrete and Rovirosa, 1991). Laurepinacine **305** and isolaurepinnacin **306** are acetylinic sesquiterpene ethers isolated from the red alga *Laurancia pinnata* that demonstrated insecticidal activity (Fukuzawa and Masamune, 1981). (*Z*)-Laureatin **307**, (*Z*)-isolaureatin **308** and deoxyprepacifenol **309** are other related compounds from the red alga *Laurencia nipponica* Yamada. They show strong insecticidal activity against the mosquito larvae *Culex pipens pallens* (Watanabe, Umeda and Miyakado, 1989; El Sayed *et al*., 1997). Telfairine **310** is another related monoterepene reported from the red alga *Plocamium telfairia,* with strong insecticidal activity against the mosquito larva *Culex pipens pallens* (Watanabe *et al*., 1988).

The new insecticidal amino acids, namely isodomic acid A **311**, isodomic acid B **312** and isodomic acid C **313**, were isolated from the red alga *Chondria arnata.* They show significant insecticidal activity when they are injected subcutaneously into the abdomen of American cockroach (Maeda *et al*., 1986). *Laurencia obtusa*, collected from off Symi Island in the Greece, Aegean Sea was the source of C_{15} acetogenins 13-epilaurencienyne (3*Z*) **314**, 13-epinnatifidenyne (3*E*) **315** and two diacetoxypentadec-3-en-1-yne derivatives (**316**, **317**). Compounds **314** and **315** exhibited strong toxicity against ants with considerable knockdown effect from the first day, while compounds **315** and **316** exhibited gradual toxicity that was escalated at the fourth day with >70% mortality (IIopulou *et al*., 2002).

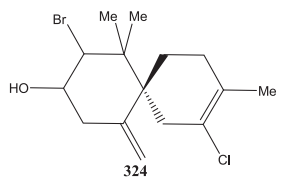




318 R_1= CH_3, R_2= H, R_3 = Br
319 R_1= CH_3, R_2= Br, R_3= H
320 R_1= H, R_2=R_3= Br
321 R_1= CH_3, R_2= R_3= Br



322 R= Br
323 R= Cl



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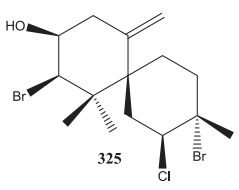


325

Antimicrobial activity

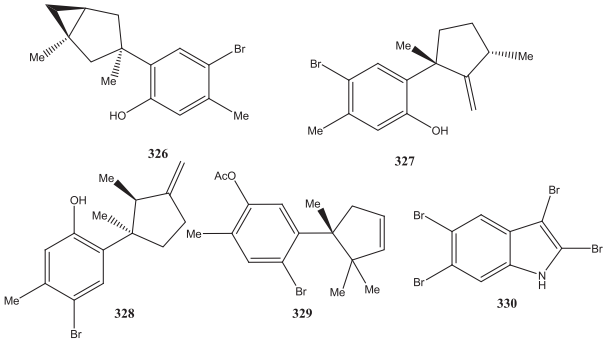
The antimicrobial activity of the red alga *Laurencia brongniarti* against *Bacillus subtilis* (a Gram-positive bacterium) and *Saccharomyces cerevisiae* (yeast) has been traced to the four polybrominated indoles **318–321** (Carter *et al*., 1978).

From the air-dried red alga *Beckerella subcostatum,* bromobeckerelide **322** epimer (the major fraction) and chlorobeckerelide **323** epimers (the minor fraction) were isolated. In laboratory tests, both compounds showed activity against *Bacillus subtilis* (Ohta, 1977).

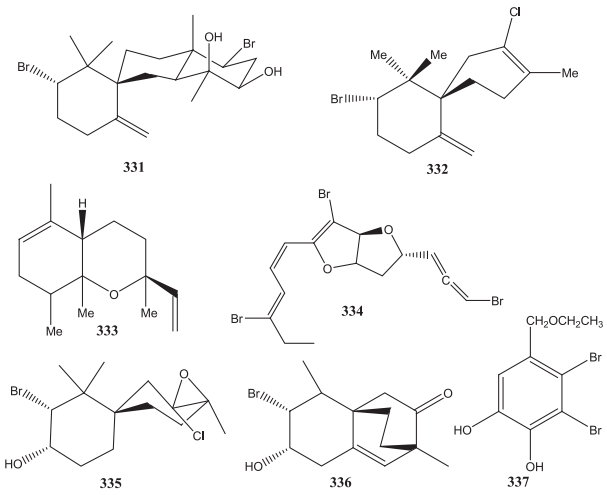
From the MeOH extract of' *Marginisporum aberrans*, showing antimicrobial activity against *Bacillus subtilis*, *P*-hydroxybenzaldhyde, dichloroacetamide, and 3,5-dinitriguaiacol were obtained. All these compounds showed activity against *Bacillus subtilis* (Ohta and Takagi, 1977).

Elatol **324**, a halogenated sesquiterpene alcohol from the red alga *L. elata* (Sims, Lin and Wing, 1974), inhibited six species of human pathogenic bacteria with significant antibacterial activities against *Staphylococcus epidermidis*, *Klebsiella pneumonia* and *Salmonella* sp. (Vairappan, 2003). Iso-obtusol **325** from the red alga *L. obtusa* (Gonzalez *et al*., 1976, 1979) exhibited antibacterial activity against four bacterial species with significant activity against *K. pneumonia* and *Salmonella* sp.

Halogenated metabolites from the red alga *Laurencia* species were tested for antibacterial activity against 22 strains of human pathogenic bacteria, including seven strains of antibiotic-resistant bacteria. Laurinterol **326** (Irie *et al*., 1966), isolaurinterol **327** (Irie *et al*., 1970), *allo*-laurinterol **328** (Kazlauskas *et al*., 1976), cupalaurenol **329** (Ichiba and Higa, 1986) and 2,3,5,6- tetrabromoindol **330** (Carter *et al*., 1978) displayed a wide spectrum of antibacterial activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant *Enterococcus faecalis* and *E. faecium.* Laurinterol and *allo*-laurinterol were particularly effective (Vairappan *et al*., 2004).

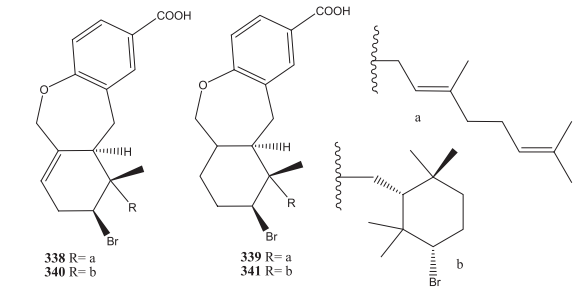


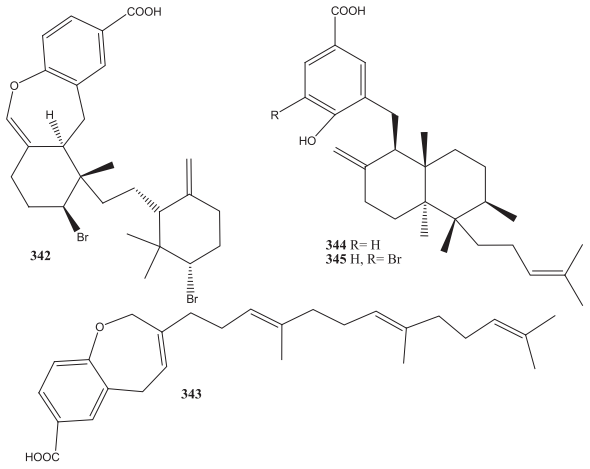
The red alga *Laurencia mariannensis* afforded a number of new metabolites: the brominated diterpene, 10-hydroxykahukuene B **331**, two sesquiterpenes, 9-deoxyelatol **332** and isodactyloxene A **333**, one brominated C15-acetogenin, laurenmariallene **334**, and two new naturally occurring halogenated sesquiterpenes **335** and **336** that were obtained previously as intermediates in a biomimetic synthetic study of rhodolaureol and rhodolauradiol (Gonzalez *et al*., 1982). Both 10-hydroxykahukuene B **331** and laurenmariallene **334** had modest antibacterial activity.



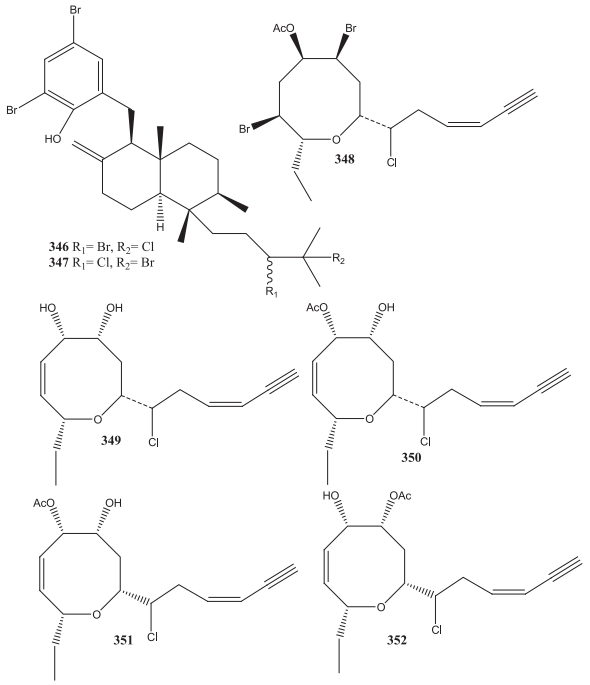
Lanosol enol ether **357**, originally isolated from the brown alga *Fucus vesiculosus* has been shown to be an antibacterial and antifungal component of the brown alga *Osmundaria serrata* (Barreto and Meyer, 2006).

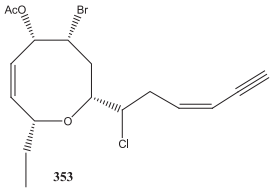
Eight novel diterpenebenzoic acids, callophycoic acids A–H **338–345**, and two halogenated diterpene-phenols, callophycols A **346** and B **347**, were isolated from red alga *Callophycus serratus*, some of which displayed moderate antibacterial, antimalarial, antitumor, and antifungal activity (Lane *et al*., 2007).





Five new C_{15} eight-membered cyclic ethers (**348, 350–353**) (Kladi *et al*., 2008) with a characteristic terminal *cis*-ene-yne moiety in addition to the previously reported acetylenic chlorodiol **349** (Blunt *et al*., 1981) were isolated from the red alga *Laurencia glandulifera*. All these metabolites were tested for their antistaphylococcal activity and the minimum inhibitory concentration (MICs) of **349–352** were in the range of 8–256 μg/ml.

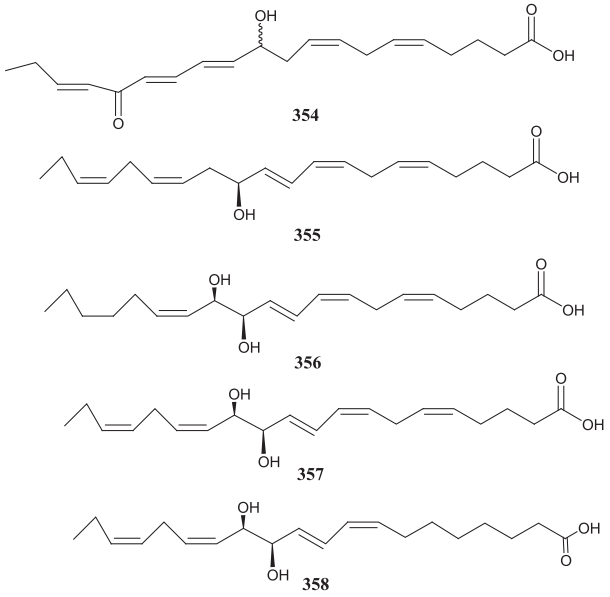




Lipooxygenase inhibitor

The eicosanoids are biologically active arachidonic acid derivatives frequently found in marine organisms. Ptilodene **354** (new fatty acid) is an eicosanoid from the red alga *Ptilotafilicina* sp. that showed inhibitory activity to human 5- lipooxygenase, dog kidney Na^+/K^+-ATPase and the growth of several pathogenic Gram-positive and -negative bacteria (Lopez and Gerwick, 1988). Another eicosanoid derivative, which is a potent inhibitor of platelet aggregation, is 12-(*S*)-hydroxyeicosapentaenoic acid **355** isolated from the red alga *Murrayella periclados* (Bernari *et al*., 1994).

Three biologically active eicosanoids, (12*R*,13*R*)-dihydroxy-eicosa-5(*Z*),8(*Z*),10(*E*), 14(*Z*)tetraenoic acid **356**, (12*R*,13*R*)-dihydroxyeicosa-5(*Z*),8(*Z*), 10(*E*),14(*Z*),17(*Z*)-pentaenoic acid **357** and (10*R*,11*R*)-dihydroxyoctadeca-6(*Z*),8(*E*),12(*Z*)-trienoic acid **358** were isolated from the red alga *Farlowia mollis* (Solem, Jiang and Gerwick, 1989).



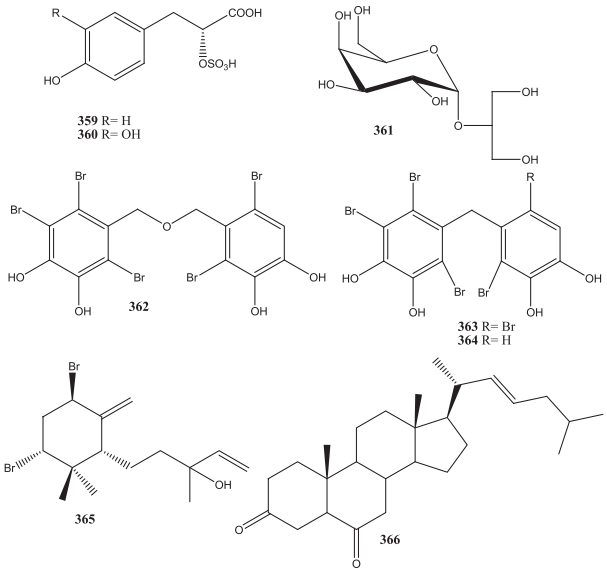
Antifeedent activity

Two phenylpropanoic acid derivatives, tichocarpols A **359** and B **360** were isolated from the red alga *Tichocarpus crinitus*. These two compounds along with floridoside **361** (Roh *et al*., 1994) which is also isolated from the alga, exhibited

antifeedant activity against the sea urchin *Strongylocentrotus intermedius* (Ishii *et al*., 2004).

Aldose reductase inhibitor activity

The new bromophenols **362–364** and two bromophenols known previously only as synthetic compounds (Diers *et al*., 2004; Nishizawa and Satoh, 1975; Lightowler and Ry1ance, 1964) isolated from the red alga *Symphyocladia latiuseula* have significant aldose reductase inhibitors (Wang *et al*., 2005).



Antimalarial activity

Snyderol sesquiterpene **365** derivative isolated from the red alga *Laurencia obtusa* was active against D6 and W2 clones of the malarial parasite *Plasmodium falciparum* (Topeu *et al*., 2003).

Anti-elastase activity against porcine pancreas elastase

3,6-Diketo steroid **366** was isolated from the red alga *Hypnea musciformis* collected on the Atlantic coast of Morocco exhibited anti-elastase activity against porcine pancreas elastase (Gosavi *et al*., 1995).

Inhbition of isocitrate lyase enzyme

A number of bromophenols isolated from the red alga *Odonthalia corymbifera* exhibited potent inhibitory activity against isocitrate lyase, an important enzyme in the rice fungal pathogen, *Magnaporthe grisea.*

The compounds 3,5-dibromo-4-hydroxyphenylethylamine (Diers *et al*., 2004) 2,20,3,30-tetrabromo-4,40,5,50-tetrahydroxydiphenylmethane (Craigie and Gruenig, 1967), 2,3-dibromo-4,5-dihydroxybenzyl alcohol (Hodgkin, Craigie, and McInnes, 1966), 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (Katsui *et al*., 1967), 2,20,3-tribromo-30,4,40,5-tetrahydroxy-60-hydroxymethyldiphenylmethane (Kurata and Amiya, 1977) and 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol also protected rice plants from infection by *Magnaporthe grisea* (Lee *et al*., 2007). This was the first report of 3,5-dibromo-4-hydroxyphenylethylamine as a natural product (Lee *et al*., 2007).

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