Saudi Pharmaceutical Journal (2010) **18**, 1–25

King Saud University

Saudi Pharmaceutical Journal

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REVIEW ARTICLE

Biological importance of marine algae

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Available online 23 December 2009

KEYWORDS

Marine organisms;
Microalgae (blue green algae, dinophalgelate, and diatomes);
Macroalgae;
Biological importance

Abstract Marine organisms are potentially prolific sources of highly bioactive secondary metabolites that might represent useful leads in the development of new pharmaceutical agents. Algae can be classified into two main groups; first one is the microalgae, which includes blue green algae, dinoflagellates, bacillariophyta (diatoms)... etc., and second one is macroalgae (seaweeds) which includes green, brown and red algae. The microalgae phyla have been recognized to provide chemical and pharmacological novelty and diversity. Moreover, microalgae are considered as the actual producers of some highly bioactive compounds found in marine resources. Red algae are considered as the most important source of many biologically active metabolites in comparison to other algal classes. Seaweeds are used for great number of application by man. The principal use of seaweeds as a source of human food and as a source of gums (phycocollides). Phycocolloides like agar agar, alginic acid and carrageenan are primarily constituents of brown and red algal cell walls and are widely used in industry.

1. Introduction

Marine organisms are potentially prolific sources of highly bioactive secondary metabolites that might represent useful leads in the development of new pharmaceutical agents (Iwamoto et al., 1998; Iwamoto et al., 1999; Iwamoto et al., 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, 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 (microns) 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 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 micro algae are found in both bentheic and littoral habitats and also throughout the ocean waters as phytoplankton (Garson, 1989). Phytoplankton comprises organisms such as diatoms (bacillariophyta), dinoflagellates (dinophyta), green and yellow–brown flagellates

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doi:10.1016/j.jsps.2009.12.001

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(chlorophyta; prasino-phyta; prymnesiophyta, cryptophyta, chrysophyta and rhaphidiophyta) and blue–green algae (cyano-phyta). As photosynthetic organisms, this group plays a key role in the productivity of oceans and constitutes the basis of the marine food chain (Bold et al., 1985; Hillison, 1977).

1.1. Interesting natural products from microalgae and their biological activities

Recently, microalgae metabolites are attracting to enormous attention, and the topics have been discussed by a number of authors (Shimizu, 1996).

The microalgal phyla have been recognized to provide chemical and pharmacological novelty and diversity, moreover microalgae are considered as the actual producers of some highly bioactive compounds found in marine resources (Shimizu, 1996).

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 found in the sea hares *Aplysia* that feed on this alga (Mynderse et al., 1997). Similarly, a series of highly active antitumor compounds, dollastatins **1** and **2**, 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 3,** ciguatoxins and dinophysistoxins are we-ll known examples of paralytic shellfish toxins (Hall and Strichartz, 1990).

1.1.1. Cyanophyta (blue–green algae or cyanobacteria)

The blue–green algae (cyanobacteria) show many structural features in common with bacteria (Garson, 1989). However, they are classified with algae because they contain chlorophyll a and related compounds. All prokaryotes convert atmospheric nitrogen into ammonia which may explain why nitrogenous compounds occur frequently in blue–green algae. The cyanobacteria possess an interesting secondary metabolism producing many nitrogenous compounds and cyclic polyethers that have potent biological activities (Moore and Entzeroth, 1988).

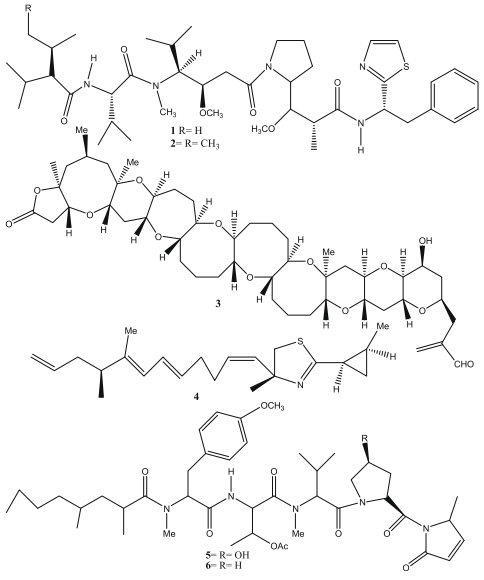
Morphologically, blue green algae appear in different shapes like filamentous, conical, unicellular, etc. Blue–green algae have very rich chemistry (Patters et al., 1994; Gerwick et al., 1994; Moore, 1996). The chemical diversity and novelty seen in blue–greens are comparable to those of Actino-mycetes which gave many important drugs. A single species of blue–greens produce many different chemotypes (*Lyngbya majuscula* is a good example). The variation in structures of the biologically isolated compounds from this filamentous algae is just incredible and most of them possess characteristic biological activity (Patters et al., 1994; Gerwick et al., 1994; Moore, 1996).

1.1.1.1. Anticancer and cytotoxic activities. Curacin A **4** isolated from the Curaso strain marine Cyanobacterium *Lyngbya majuscula* by Gerwick's group in 1994. It is an important lead compound for a new type of anticancer drugs. It is an antimitotic agent (IC_{50} values in three cell line ranging from 7 to 200 nm) that inhibits microtubule assembly and binding of cholchicine to tubulin (Gerwick et al., 1994).

Two linear cytotoxic pentapeptides; majusculamide D **5** and deoxymajusuculamide D **6** were isolated from a deep-water variety of the marine blue–green alga *Lyngby majuscula* by and Entzeroth in 1988.

A highly interesting bioactive compounds have been isolated from blue–green algae including alkaloids (e.g. lyngbyatoxin) **7**, polyketides (e.g. tolytoxin), cyclic peptide (e.g. microcystin), depsipeptide (e.g. majusculamide **8**) etc. Many of these compounds showed a versatile biological activity (Shimizu, 2000). Cryptophycin-l **9** from *Nostoc* species shows a fungicidal activity and rediscovered by Smith's group (Smith et al., 1994) as a microtubule depolymerizing agent. The compound and its analogues are very effective against solid tumors.

Lyngbyatoxin-A **7** identified in the blue green alga *Lyngbya majuscula*, the most thoroughly investigated from the biological point of view is responsible for a severe erythematous papulovesicular dermatitis (swimmer's itch) Cardelina et al., 1979 Lyngbyatoxin and shows cytotoxicity against P388 leukemia, but also act as a co-carcinogen. It has been suggested that this substance may play a role in human stomach cancer among the Hawaiians who consume large quantities of edible seaweed on which *Lyngbya majuscula* grows epiphytically (Moore, 1982).



1.1.1.2. Tumor-promoting activity. Dihydroteleocidin B **10**, which is a derivative of teleocidin B **11** from *Streptomyces*, showed potent tumor-promoting activity *in vivo* when painted on mouse skin. Although the chemical structure of **10** is entirely different from the phorbol esters, the tumor-promoting activity of **10** was comparable to that of 12-0-tetradecanoylphorbol 13-acetate (TPA) *in vivo*. Compounds **11**, from Streptomyces, lyngbyatoxin A **12** and debromoaplysaxitoxin **13** isolated from the marine blue–green alga *Lyngbya majuscula* induced ornithine decarboxylase activity when painted on mouse skin, their effects being similar to those of **10** and TPA. *13-cis*-Retinoic acid inhibited this ornithine decarboxylase induction when painted on the skin one hour before these natural products. Compounds **10**, **11** and **13** produced adhesion of human promyelocytic leukemia cells (HL-60) to the flasks and inhibited differentiation of Friend erthroleukemia cells induced by DMSO. The *in vitro* biological potencies of **11** and **12** were al-

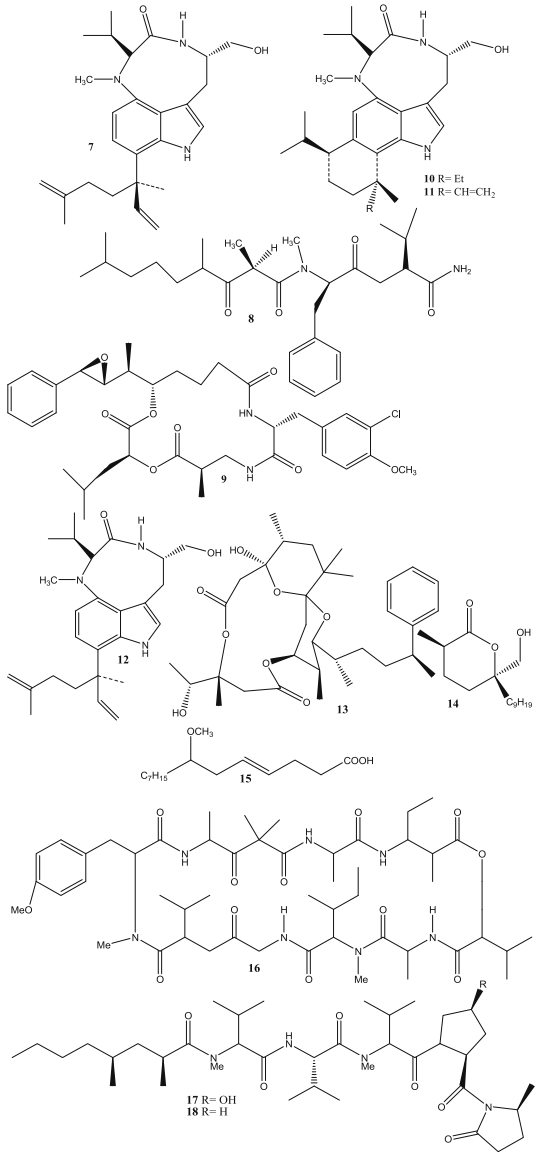
most as great as those of **10** and TPA, but that of debromoaplysiatoxin was much weaker (Fujiki et al., 1981).

1.1.1.3. Antibacterial activity. The γ-lactone malyngolide **14**, an antibiotic effective against *Mycobacterium smegmatis* and *Streptococcus pyogenes* was isolated from the dichloromethane extract of a shallow-water variety of the blue–green alga *Lyngbya majuscula* (Cardllina et al., 1979).

The major antimicrobial constituents of Puerto Rican specimens of the blue green *Lyngbya majuscula* are the elemental sulphur and (−)-(4*E*,7*S*)-7 methoxytetradec-4-enoic acid **15** (Faulkner, 1987).

1.1.1.4. Antifungal activity. Majuscuiamide C **16** is a cyclic depsipeptide from the deep-water variety of *Lyngby majuscula* that inhibit the fungal plant pathogens (Carter et al.,1984).

1.1.1.5. Immunosuppressive activity. The potent immunosuppressive lipoproteins, microcolins A **17** and B **18** have been isolated from a Venezuelan sample of the blue green algae *Lyngbya majuscula* by Koehn et al. (1992). The microcolins are potent inhibitor of the murine mixed lymphocyte response and murine P388 leukemia *in vitro* (Koehn et al., 1992).



1.1.2. Pyrrhophyta (Dinoflagellates)

Dinoflagellates are unicellular organisms that are best classified as primitive algae (Garson, 1989). Massive concentrations of these organisms appear on the surface of the ocean, causing high mortality of the fish by asphyxia. Also large concentration of this algae in the sea give the water a brown to red coloration because of their pigmentation (Trease and Evanes, 1996). Certain dinoflagellate species produce toxin which when consumed by filter feeders, such as shellfish, are concentrated in the flesh of the animals. Consumption of contaminated shellfish by man can result in severe health problems including death. The toxins are usually classified into paralytic shellfish poisons or diarrhetic shellfish poisons. Despite of the toxicity of some species of dinoflagelates, some other species produced unique compounds not separated from other phyla most of them showed a very potent biological activity. Dinoflagelates lies taxonomically between prokaryotics and eukaryotics and sometimes called mesokaryotes (Dodge, 1965). This unique situation makes the organism very interesting to secondary metabolite production (Dodge, 1965).

The structural types of dinoflagellate metabolites spread widely from heterocyclic compounds, polycyclic ethers, oxygenated polyketides and macrolides (Shimizu, 1993; Yasumoto and Maurata, 1993). Many dinoflagellate metabolites show very potent biological activity such as saxitoxin **19**, neosaxitoxin and gonyautoxins produced by *Alexandrium* and several other genera of dinoflagellates are highly selective sodium channel blockers (Hall and Strichartz, 1990). On the other hand, breve-toxins **3** produced by *Gymnodinium breve* are potent sodium channel activators. Another polycyclic ether, maitotoxin from *Gambierdiscus toxicus*, is a rare calcium channel activators (Yasumoto and Maurata, 1993).

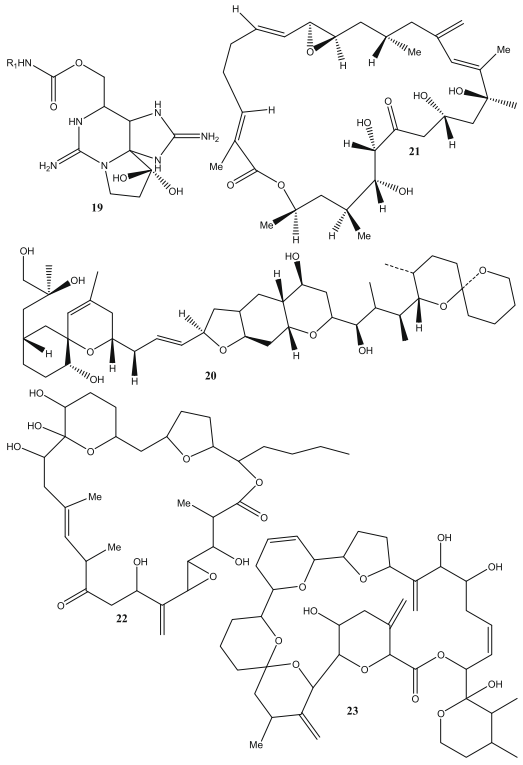
A number of compounds are known to act on the signal transduction system in the cell. Okadaic acid **20** and its derivatives found in *Prorocentrum* species and *Dinophysis* species are very potent inhibitors of serine/threonine-specific protein phosphatase and 2A (Fujiki and Suganuma, 1993).

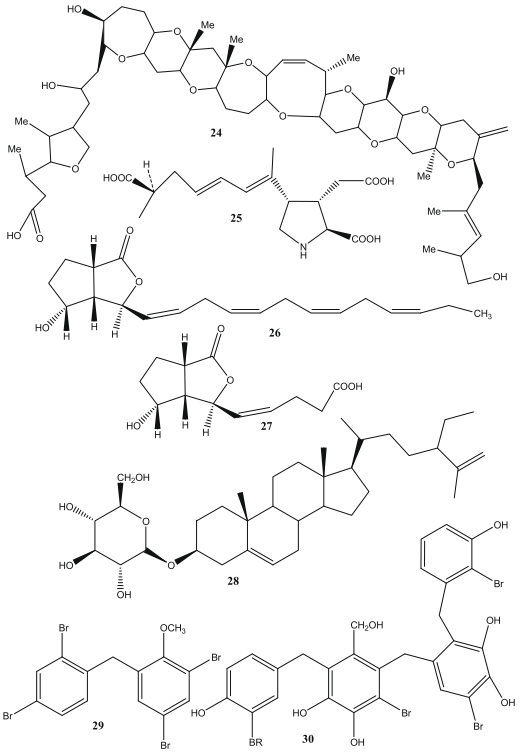
Kobayashi and Ishibashi (1993) reported that a symbiotic *Amphidinium* species from a flatworm contain a series of macrolides, amphidinolides most of them are very cytotoxic. They were also screened *Amphidinium* species From Caribbeans for antitumor agents, also isolated a series of compounds including amphidinolide B **21** reported by kobayashi's group (Kobayashi and Ishibashi, 1993). The structure of amphidinolide B isomers as strongly cytotoxic macrolides produced by a free-swimming dinoflagellate, *Amphidinum* sp. was reported by Bauer group (Bauer et al., 1994). One of the compound carbenolide I **22** was extremely cytotoxic and active *in vivo* (Bauer et al., 1995).

Many of dinoflagellate metabolites have strong antifungal activity. Goniodomin A **23** from *Goniodoma* (*Alexandrium*) sp. is a strong antifungal agent isolated by Murakami et al. (1988).

A potent antifungal agent (gambieric acid **24**) discovered by Yasumoto's group Yasumoto and Maurata (1993) in the culture medium of *Gambierdiscus toxicus*.

The above data proved that the probability of finding bioactive compounds from dinoflagellates is very high.





1.1.3. Bacillariophyceae (diatoms)

Bacillariophyceae is a versatile and abundant family, which is probably the most important in the primary production in the oceans. Diatoms are fast growing and more easy to culture on a large scale. Unlike dinoflagellates, very few secondary metabolites have been reported from the diatoms (Shimizu, 2000).

Domic acid **25** has been isolated from *Pseudo-nitzschia multiseries* and other species; it is a harmful glutamate agonist which causes amnesic shellfish poising (Wright et al., 1989). It also produced a new type of cyclic eicosanoid bacillariolides **26**, **27** (Wang and Shimizu, 1990; Wang et al., 1993). Bacillariolide I **26** has on inhibitory activity against phospholipase A2 (Shimizu, 1996).

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 hypocholesterolaemic 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).

1.2.1. Chlorophyta (green algae)

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

1.2.1.1. Antiinflammatory substances. An anti-inflammatory, 3-0-β-D-glucopyranosy-lstigmasta-5,25-diene **28** have been isolated by Awad in (2000) from the green alga *Ulva laetuea.*

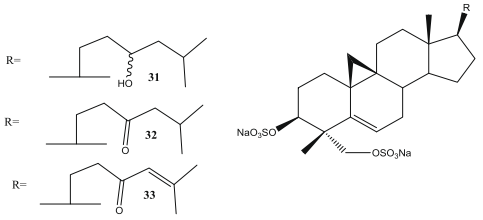
Habu is a deadly snake inhabit in Okinawa where 200–300 people are bitten by the snake every year. A patient must be given immediate medical treatment with the serum prepared from a horse-developed antibody by injection of snake toxin. However, about 20% of the patients are allergic to the serum.

In order to develop an alternative drug, Okinawa Prefectural Institute of Public Health has been conducting screening to find out a compound with antiinflammatory activity that can be measured by suppression of the inflammation caused by the injection of the toxin on a mouse limb. A diphenyl ether **29** 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 furnish 2-(2′,4′-dibromophenoxy)-4,6-dibromoanisol (Kuniyoshi et al., 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 et al., 1985).

1.2.1.2. Cytotoxic and immunosuppressive activities. Bioassy-guided fractionation utilizing the inhibitory activity against inosine-5′-monophos-phate dehydrogenase inhibitor (IMPDH)

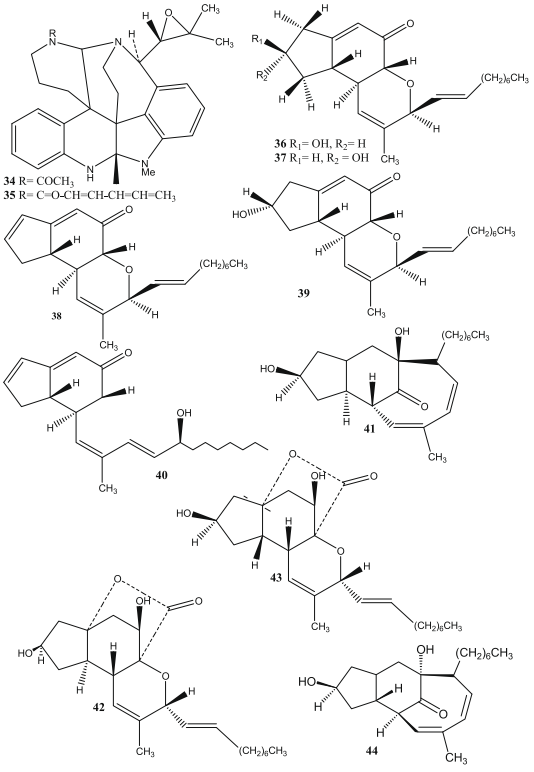
leads to isolation of new brominated diphenylmethane derivative. Isorawsonol **30** has been isolated from the tropical green alga *Arrainvilla rawsonii* by Chen et al. (1994). The activity of IMPDH has been linked with cellular proliferation and inhibition of that enzyme has been demonstrated to have anticancer and immunosuppressive effects (Chen et al., 1994).

Bioactivity-directed fractionation of the extract of the green alga *Tydemania expeditionis* using the protein tyrosine kinase $pp60^{v\text{-}stc}$ leads to the isolation of three new cycloartenol disulfates **31**–**33**; they showed modest inhibition of this enzyme (Govindan et al., 1994).



Communesins A **34** and B **35**, exhibiting cytotoxic activity against the cultured P-388 lymphocytic leukemia cells, were isolated from the mycelium of a strain of *Penicillium* species stuck on the marine alga *Enteromorpha intestinals* (Numata et al., 1993).

Penostatins A **36**, B **37**, C **38**, D **39** (Takahashi et al., 1996) and E **40** (Iwamoto et al., 1999) have been isolated from a strain of *Penicillium* species originally separated from the marine alga *Enteromorpha intestinalis* (Linne) Link (Ulvaceae). The compounds A–C and E exhibited a significant cytotoxicity against cultured P388 cell line (Iwamoto et al., 1999; Takahashi et al., 1996) Penostatins F,G,H **41**–**43** and I **44** were isolated from a strain of *Penicillum* originally separated from the marine alga *Enteromorpha intestinalis* (Linne) Link (Ulvaceae). All the compounds exhibit significant cytotoxicity against cultured P388 cells (Iwamoto et al., 1998).

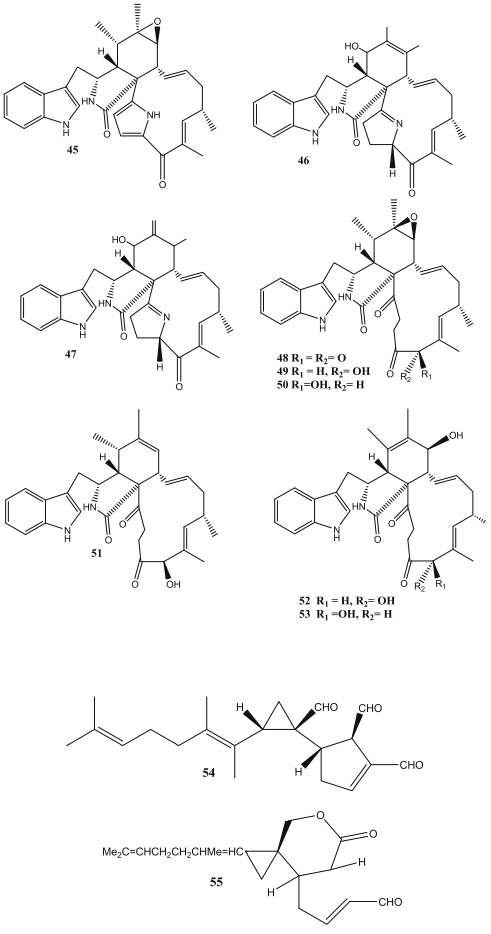


The novel compounds cytochalasans, penochalasins A B,C **45**–**47** (Numata et al., 1996), D–H **48**–**52** and chaetoglobosin O **53** (Iwamoto et al., 2001) were isolated from a strain of *Penicillium* species originally separated from the marine alga *Enteromorpha intestinalis*. All these compounds exhibited potent cytotoxic activity against cultured P388 cells.

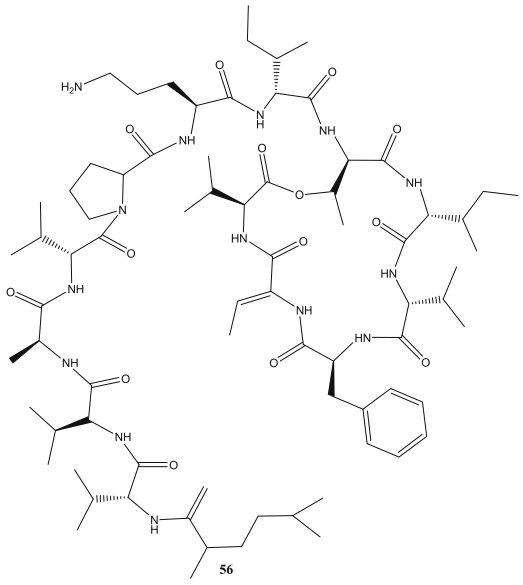
Halimedatrial **54** is a diterepene trialdhyde was separated from *Halmida lamouroux* (chlorophyta, Udoteaceae) species. This compound was found to be toxic towards reef fishes, significantly reduces feeding in herbivorous fishes and has cytotoxic and antimicrobial activities (Paul and Fenical, 1983).

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 4 compounds were halimediatrial **54** and halimedalactone **55** (Paul and Fenical, 1984).

The cyclic depsipeptide Kahalalide F **56** was originally isolated from both 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.



Green alga *Bryopsis* sp. was the source of the cyclic depsipeptides Kahalalides P **57** and Kahalalides Q **58** with moderate inhibition of the HL-60 cell lines (Dmitrenok et al., 2006).

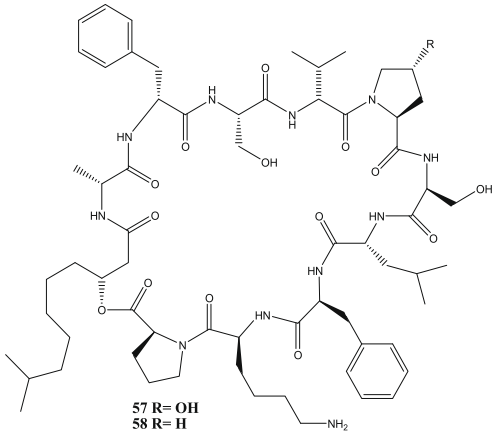


56

1.2.1.3. Antibacterial activity. Cycloeudesmol **59** is an antibiotic cycloproane containing sesquiterpene; it was isolated from the marine alga *Chondria oppositiclada* Dawson (Fenical and Sims, 1974). Cycloeudesmol was found to be potent antibiotic against *Staphylococcus aureus* and *Candida albicans*.

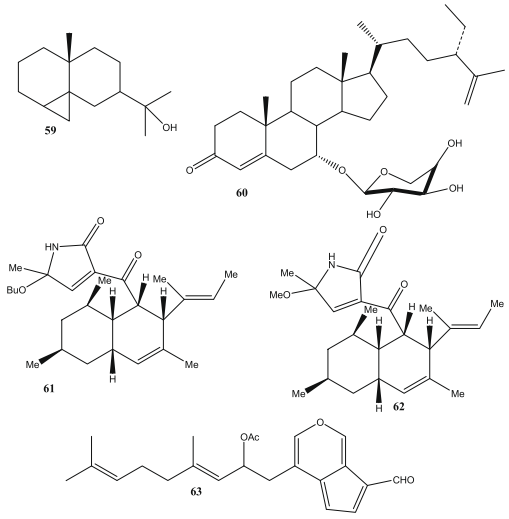
Lyengaroside A **60** was isolated from the green alga *Codium iyengarii* and displayed a moderate antibacterial activity (Ali et al., 2002).

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



57 R= OH
58 R= H

1.2.1.4. Antiplasmodial activity. From the green alga *Ulva* species, the endophytic and obligate marine fungus *Ascochyta salicorniae* was isolated. *Ascochyta salicorniae* was found to produce the unprecedented and structurally unusual tetramiric acid contiguous metabolites ascosalipyrrolidinones A **61** and B **62**. Ascosalipyrrolidinones A **61** has antiplasmodial activity toward *Plasmodium falciarum* strains Kl and NF 54, as well as showing antimicrobial activity and inhibiting tyrosine kinase p561ck (Osterhage et al., 2000).



59 60 61 62 63

1.2.1.5. Antiviral activity. Halitunal **63**, 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).

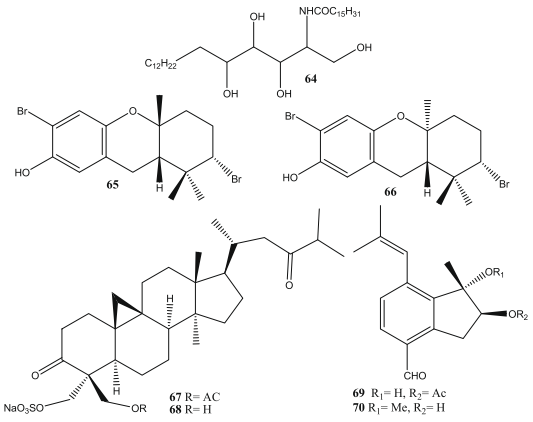
In 1992 Garg et al. (1992) isolated the antiviral derivative, sphingosin, *N*-palmitoyl-2-amino 1,3,4,5-tetyrahydroxyoctadecane **64** which demonstrated antiviral activity *in vivo* protection against Semeliki forest virus (SFV). This compound was isolated from Indian green alga *Ulva fasciata*.

1.2.1.6. Antimutagenic activity. Two new compounds, cymobarbatol **65** and 4-isocymobarbatol **66** were isolated from the marine green alga *Cymopolia barbat*. Both compounds were found to be nontoxic over a broad concentration range against *Salmonella tybimurium* strains T-98 and T-lOO. Both compounds exhibited strong inhibition of the mutagenicity of 2-aminoanthracene and ethylmethanesulphonate towards the T-98 strains plus a metabolic activator and T-100 (Wall et al., 1989).

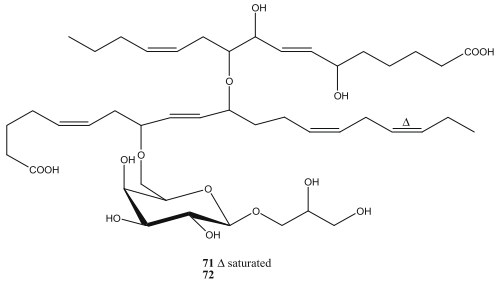
1.2.1.7. Anti fungal activity. Capisterones A **67** and B **68** are triterpene sulphate esters isolated from green alga *Panicillus capitatus*. Both compounds exhibited potent antifungal activity against the marine algal pathogen *Lindra thallasiae* (Puglisi et al., 2004).

Two sesquiterpenes, caulerpals A **69** and B **70** were isolated from green alga *Caulerpa taxifolia* in addition to the known caulerpin (Aguilar-Santos, 1970); they were shown to be potent inhibitor of human protein tyrosine phosphatase 1 B (hPTP I B) Mao et al., 2006. Capisterones A and B, 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).

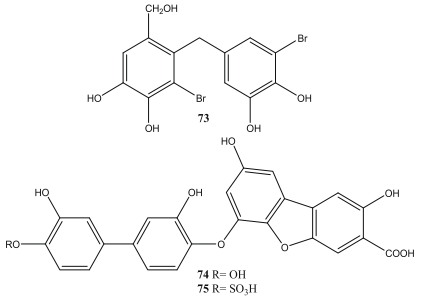


A new class of ether-linked glycoglycerolipids, nigricanosides A **71** and B **72** were isolated as methyl esters from the green alga *Avrainvillea nigrans*. Nigricanoside A dimethyl ester was found to be a potent antimitotic agent, acting by stimulating the polymerisation of tubulin and inhibiting the proliferation of both MCF-7 and HCT-116 cells (Williams et al., 2007).



1.2.1.8. Protein tyrosine phosphate 1B inhibitors (PTP1B). Hydroxyisoavrainvilleol **73** was originally isolated from the tropical green alga *Avrainvillea nigrican* (Colon et al., 1987) but has now been isolated from red alga *Polysiphonia urceolata* as a protein tyrosine phosphatase 1B inhibitor (PTP1B) Liu et al., 2008.

A vanillic acid biphenyl derivative **74** and the sulfate adduct **75** were isolated from the Australian green alga *Cladophora socialis* as a protein tyrosine phosphatase 1B (PTPa1B) inhibitors Feng et al., 2007.

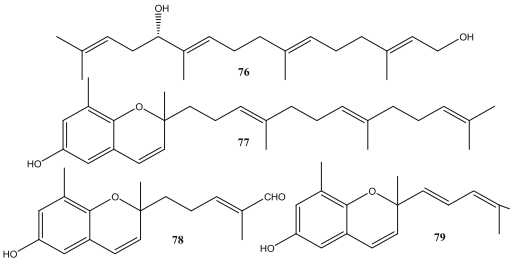


1.2.2. Phaeophyta (brown algae)

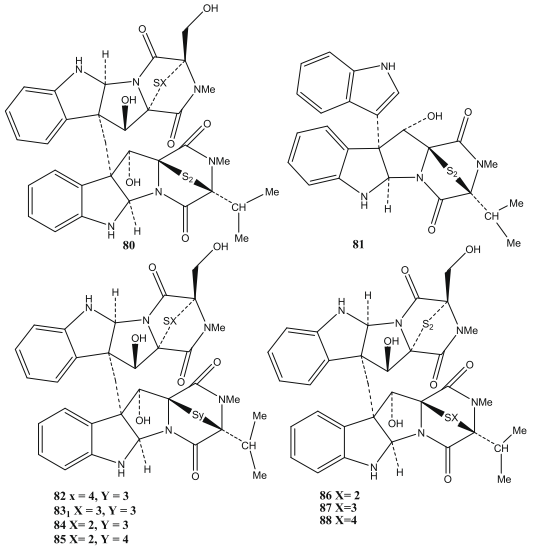
The brown colour of these algae results from the dominace of the xanthophyll pigments and fucoxanthin; this masks the other pigments, chloro-phyll *a* and *c*, *β*-carotenes and other xanthophylls (Bold et al., 1985). Food reserves of brown algae are typically complex polysaccharides and higher alcohols. The principal carbohydrate reserve is laminarin. 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.

1.2.2.1. Cytotoxic and antitumor activity. A linear cytotoxic diterpene bifurcadiol **76** was isolated from the brown alga *Bifurcaria bifurcata* by Guardia et al. (1999) which exhibit cytotoxicity against cultured human tumor cell lines (A-549, SK-OV-3, SKL-2, XF 498 and HCT).

Meroterpenoids, Sargol, Sargol-I and sargol-ll **77**–**79** were isolated from the brown alga *sargassum tortile* and showed a cytoxic activity (Numata et al., 1991).



Leptosins A, B, C (I, X = 4, 3, 2 **80**), D, E and F (II, X = 2, 3, 4 **81**), belonging to a series of epipolythiodioxopiperazine derivatives, have been isolated from the mycelium of a strain of *Leptsphaeria* species attached to marine alga *Sargassum tortile*. All these compounds showed potent cytotoxicity against cultured P388 cells except leptosins A and C exhibited significant antitumor activity against Sarcoma 180 ascites (Takahashi et al., 1994a). Further investigation of the secondary metabolites of this fungus has led to the isolation of four additional cytotoxic compounds, named leptosins G, G1, G2 **82**–**84** and H **85** (Takahashi et al., 1995a). Leptosins K, K1 **86**–**87** and K_2 **88** were also isolated and showed a potent cytotoxic activity against P388 cell line (Takahashi et al., 1995b).



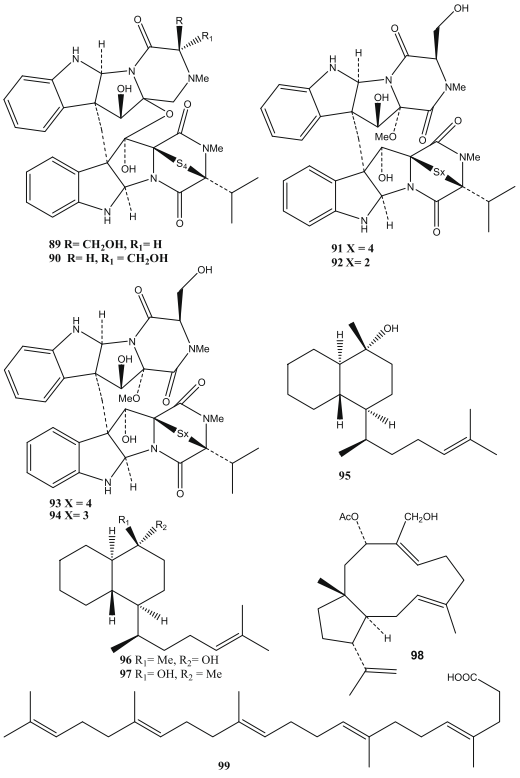
Leptosins I **89** and J **90** have been also isolated from the mycelium of a strain of *Leptosphaeria* species OUPS-4 attached to the marine alga *Sargassum tortile*. These compounds exhibited significant cytotoxic activity against cultured P388 cells (Takahashi et al., 1994b).

Leptosins M, MI, N and N1 **91**–**94** that have been isolated from a strain of *Leptsphaeria* 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 **95**–**97** were isolated from brown alga *Dictyota dichotoma* by Wu et al. (1990).

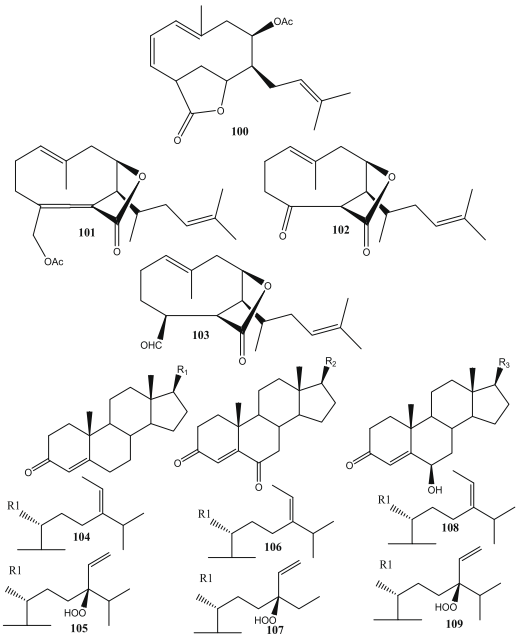
Dolabellane type of diterpene **98** have been isolated from unidentified species of *Dictyota* exhibit significant cytotoxicity (Tringali et al., 1984).

A cytotoxic compound named as turbinaric acid **99** was isolated from *Turbinaria ornate* (Asari et al., 1989).



Four diterpene with xenicane and norxenicane **100**–**103** have been isolated from another species of *Dityota dichotoma* from Okinawa Island. In addition, showed antitumor activity.

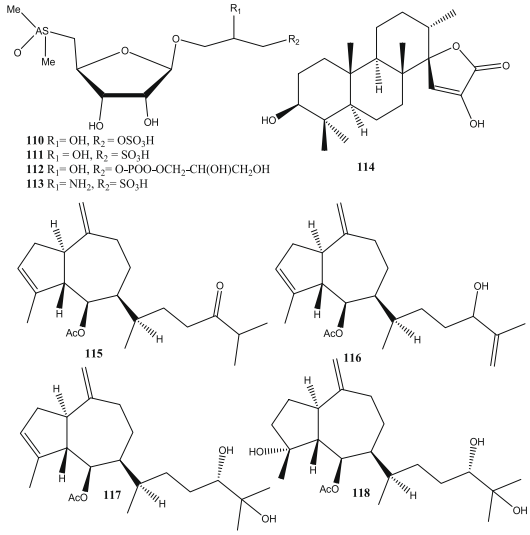
24-Ethyl cholesta-4,24(28)-diene 3-one **104**, 24-ethylcholesta-4,28(29)-diene-3-one **105**, 24-ethylcholesta-4,24(2 8)-diene-3,6-di one **106**, 24-β-hydroperoxy-24-ethylcho lesta-4,28 (29)-diene-3, 6-dione **107**, 6-hydroxy-24-ethylcholesta-4,24(28)-diene-3-one **108**, 24-hydroperoxy-6-β-hydroxy-24-ethylcholesta-4,28(29)-diene-3-one. **109** 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 cell lines.



Four arsenic-containing ribofuranosides **110**–**113** together with inorganic arsenic have been isolated from the brown alga *Hizikia fusiforme* which is eaten in Japan under the name hijiki (Edmonds et al., 1987).

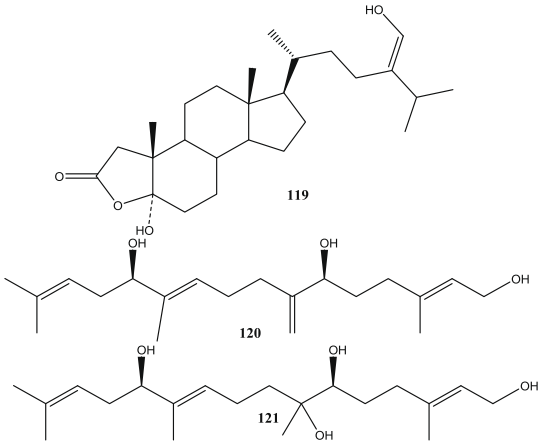
Stypolactone **114**, a diterpenoid of mixed biogenesis has been isolated from the brown algae *Stypopdium zonale* and showed weak cytotoxic activity *in vitro* against the A-549 and H-116 cell lines (Dorta et al., 2002a).

Four hydroazulene diterpenes, dictyone acetate **115**, dictyol F monoacetate **116**, isodictytriol monoacetate **117** and cystoseirol monoacetate **118** were isolated from the brown alga *Cystoseira myrica* collected in the Gulf of Suez canal showed a moderate cytotoxicity against the murine cancer cell line KA3IT, but reduced cytotoxicity against normal NIH3T3 (Ayyad et al., 2003).

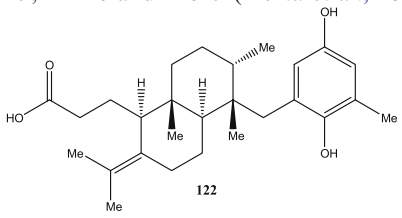


Sterols B **119** isolated from *Stypopdium carpophyllum* exhibited cytotoxic activity against several cultured cancer cell lines (Tang et al., 2002a).

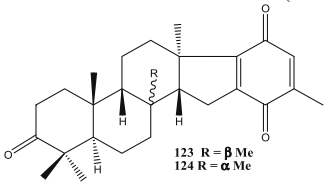
Two cytotoxic trihydroxylated diterpenes based on 12-hydroxygeranylgeraniol **120**–**121** were isolated from brown alga *Bifurcaria bifurcate* (Gulioli et al., 2004).



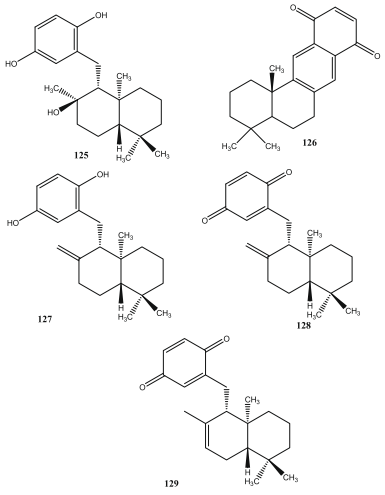
The tropical brown alga *Styolpopdium zonale* collected from the coast of Tenerife was the source of terpenoid C **122**; the methyl ester of C exhibited *in vitro* cytotoxic activity against HT-29, H-116 and A-549 (Dorta et al., 2002b).



The brown alga *Taonia atomaria* was a source of meroditerpenes atomarianones A **123** and B **124,** the cytotoxic agents against the NSCLC-N6 and A-549 cell lines (Abatis et al., 2005).



(+)-Yahazunol **125** (Ochi et al., 1979) and cyckozonarone **126** (Kurata et al., 1996) were showed cytotoxic activity against several human tumor cell lines, while zonarol **127**, zonarone **128** and isozonarol **129** (Fenical et al., 1973) isolated from brown alga also displayed cytotoxicity against various human tumour cell lines (Laube et al., 2005).



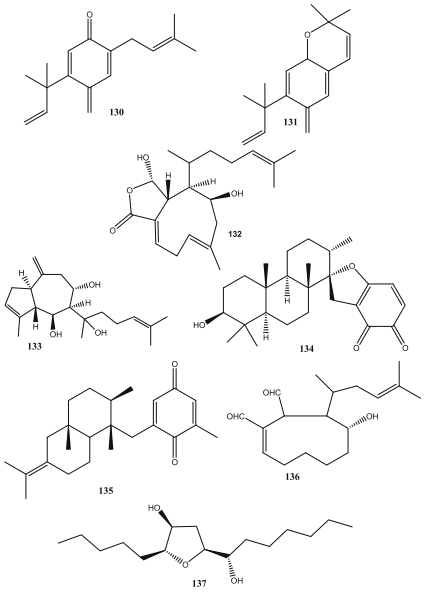
Brown alga *Perithalia capillaris* yielded new bis-prenylated quinones **130**, **131**, both are inhibitors of superoxide production in human neutrophils *in vitro* and of proliferation of HL-60 cells (Blackman et al., 1979).

Two diterpenes, 4,18-dihydroxydictyolactone **132** and 8α,11 dihydroxypachydictyol A **133**, were isolated from a *Dictyota* sp. (Jongaramru, 2007). In bioassays, 4,18-dihydroxydictyolactone was strongly cytotoxic (NCI-H187) (Jongaramru, 2007).

1.2.2.2. Ichthyotoxins and feeding-deterrent substances from brown alga. Stypoldione **134** was isolated from the brown alga *Stypodium zonale* which showed an ichthyotoxins effect. When fresh *S. zonala* is placed in an aquarium, water soon turns to a rust colour and rendered extremely toxic to the reef-dwelling herbivorous dam selfish *Eupomcentrus 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, apparently 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 **135** was isolated from the lipophilic extract of the same alga (Wessels et al., 1999) and showed inhibition of tyrosine kinase $p56^{lck}$ enzyme. Tyrosine kinase inhibitory activity was determined by ELISA using a commercial test kit (Wessels et al., 1999).

Brown alga *Dictyota spinulosa* appeared not to be eaten by herbivores so that its constituent was examined by Tanaka and Higa (1984) and they isolated a new diterepene, hydroxydictyodial **136** as a major component among several other related compounds. Hydroxydictyodial has also been isolated from *Dictyota crenulata* (Kirkup and Moore, 1983).

1.2.2.3. Nematocidal activity. Chemical analysis of the brown alga *Notheia anomala* collected from the rock platforms along the southern coast of Australia yielded *cis* dihydroxyte-trahydrofuran **137** derivatives. Tetrahydrofuran from *Notheia anomala* are reported for the first time as potent and selective inhibitor of the larval developments of parasitic nematodes *Haemonchus contortus* and *Trichostrongylus colubriformis* (Capon et al., 1998).

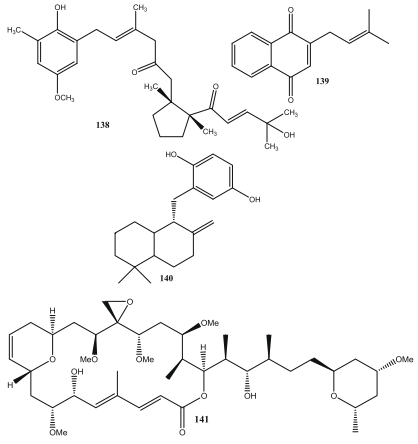


1.2.2.4. Antifungal activity. A meroditerpenoid has been isolated from the brown alga *Cystoseira tamariscifolia* and characterized as methoxybifurcarenone **138.** It possesses antifungal activity against three tomato pathogenic fungi and antibacterial activity against *Agrobacterium tumefaciens* and *Escherichia coli* (Bennamara et al., 1999).

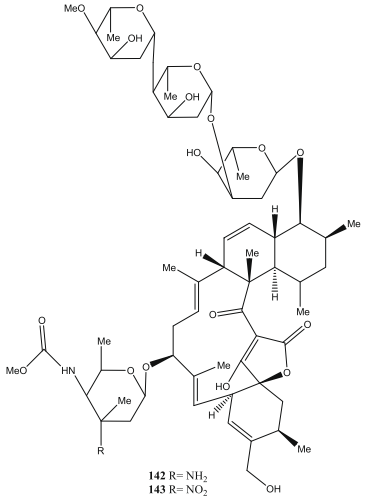
A 1,4-napthaquinone derivative (deoxy lapachol) **139**, from a New Zealand brown alga *Landsburgia quercifolia* was isolated by the bioactivity-directed isolation method. It showed activity against P388 leukemic cells (IC_{50} 0.6 μg/ml) and was also antifungal (Perry et al., 1991).

An antifungal compound named as (+)-zonarol **140** was isolated from the brown alga *Dictyopteris zonaroides* by Fenical et al. (1973).

Lobophorolide **141** was isolated from the common brown alga *Lobophora variegate* and displayed a potent and highly specific activity against the marine filamentous fungi *Dendryophiella salina* and *Lindra thalassiae* and a potent activity against *C. albicans* and antineoplastic (Kubanek et al., 2003).



1.2.2.5. Antiinflammatory activity. Two new antiinflammtory macrolides, lopophorins A **142** and B **143** 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 Kijanimicin class and are potent inhibitors of tropical PMA-induced edema in the mouse ear assay when administered either topically or IP (Jiang et al., 1999).



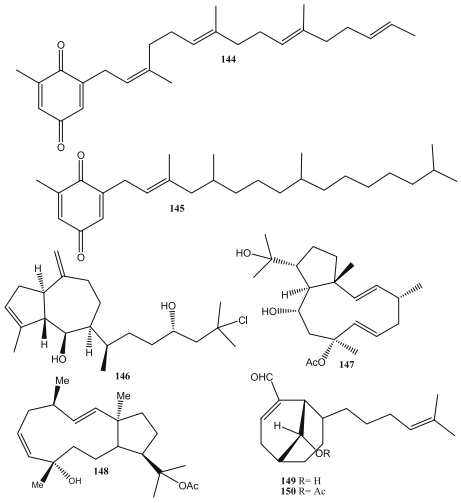
(*Z*)-Sargaquinone **144**, the more saturated analogue **145**, and the known sargaquinone (Ishitsuka et al., 1979) were isolated from the brown alga *Taonia atomaria* and were anti-inflammatory agents by inhibition of leukotriene biosynthesis (Tziveleka et al., 2005).

1.2.2.6. Algicidal activity. A chlorine-containing perhydroazulene diterpene, dictyol J **146**, was isolated from the brown alga *Dictyota dichotoma* along with two known diterpenes, dictyolactone (Finer et al., 1979) and sanadaol (Ishitsuka et al., 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 catenella*.

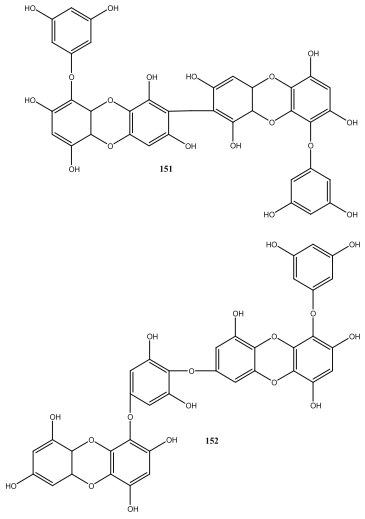
1.2.2.7. Hepatoprotective activity. Phloroglucinol (Cross et al., 1907) and phloroglucinol derivatives eckstolonol, (Kang et al., 2003) eckol, phlorofucofuroeckol A (Fukuyama et al., 1990) and dieckol (Fukuyama et al., 1983) were isolated from the brown alga *Ecklonia stolonifera* as hepatoprotective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

1.2.2.8. Antiviral activity. A new dollabelladiene derivative **147** and the previously isolated 10,18-diacetoxy – 8-hydroxy 2,6-dollabeladiene **148** (Ireland and Faulknar, 1977) were characterized from the brown alga *Dictyota pfaffi* (Barbosa et al., 2004). Both compounds showed strong anti-HSV-1 activity in vitro but little inhibition of HIV-1 reverse transcriptase.

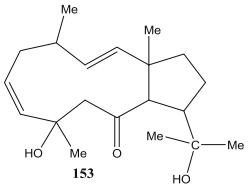
The diterpenes (6*R*)-6-hydroxy dichototomo 3,14-diene-1,17-dial **149**, and the 6-acetate derivative **150**, from the brown alga *D. menstrualis* (Pereira et al., 2004) exhibited antiretroviral activity *in vitro*.



The phlorotannin derivatives 8,8′-bieckol **151** (Fukuyama et al., 1989) and 8,4″-bieckol **152** 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.

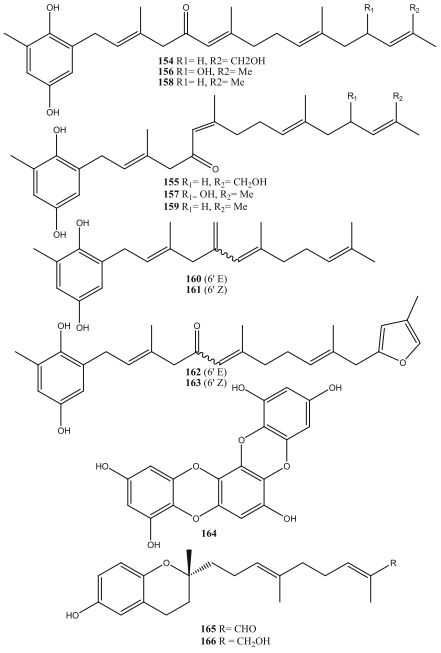


1.2.2.9. Protection against herbivous animals. Dolabellane 1 **153**, originally isolated from the opistobranch mollusc *Dolabella californica* (Ireland and Faulknar, 1977) has been characterized as the major secondary metabolite and active chemical defence against herbivores (sea urchins and fish) in the brown alga *Dictyota pfaffi* (Barbosa et al., 2003).

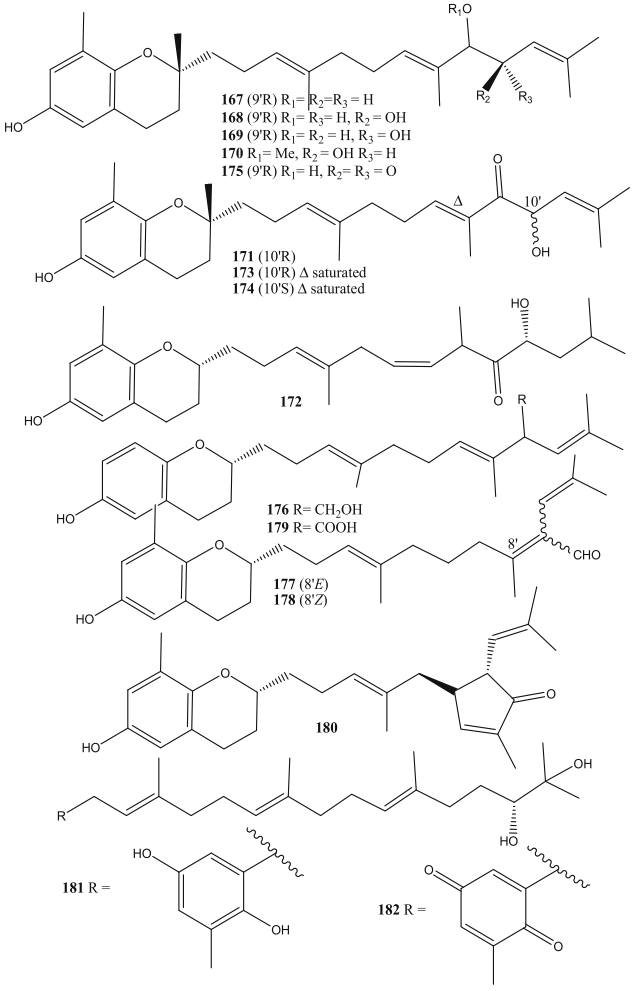


1.2.2.10. Free radical scavenger and antioxidant activities. Several prenyl toluquinones were isolated from the brown alga *Cystoseira crinita*. Compounds **154–161** exhibited potent radical-scavenging effects while **162** and **163** were less active (Fisch et al., 2003).

The Brown alga *Ecklonia stolonifera* collected from S. Korea yielded a new phlorotannin, eckstolonol **164** which possessed a potent DEPP radical-scavenging activity (Kang et al., 2003).

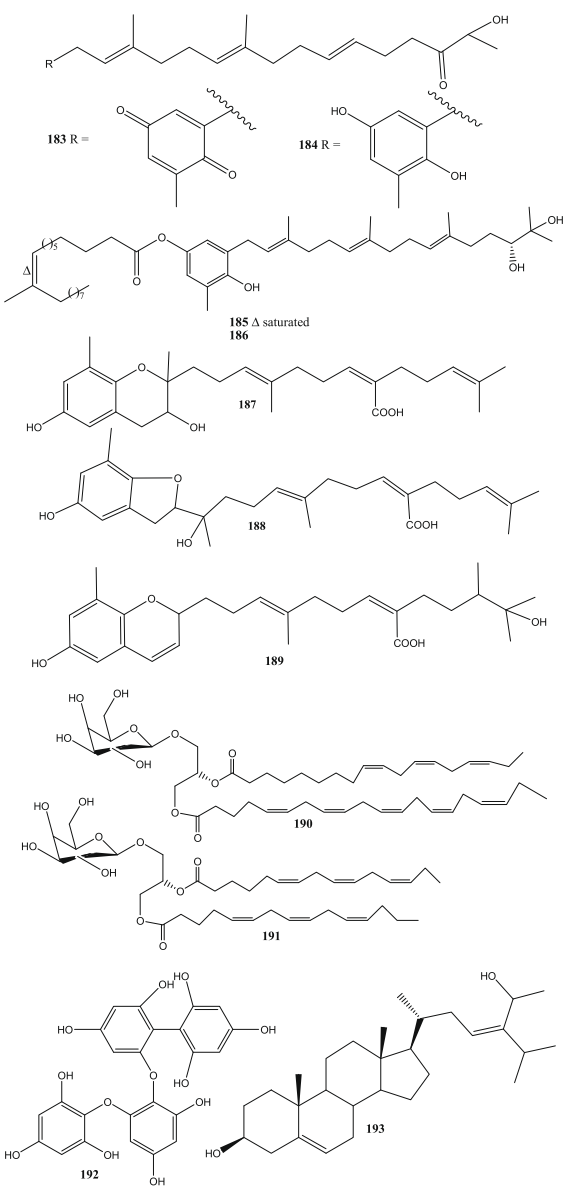


The sargachromanols A–P (compounds **165–180**, meroterpenoids of the chromene class, were isolated from the brown alga *Sargassum siliquastrum*. All the isolated compounds exhibited significant activity in the DPPH assay while compounds **171** and **179** were also inhibitors of butyl choline esterase (Jang et al., 2005). The known plastiquinones (**181 and 182**) were isolated from brown alga *S. micracanthum*. Compound **181** displayed significant antioxidant activity while in contrast, **182** was potentely active against human cytomegalo virus (HCMV) *in vitro* (Iwashima et al., 2005). *S. micracanthum (brown alga)* was the source of strongly antioxidant plastoquinones **183–186**, while compounds **184–186** showed antiproliferative effects against 26-L5 cells (Mori et al., 2005).



The tetraprenyltoluquinols, thunbergols **187** and B **188**, were isolated from the brown alga *Sargassum thunbergii* and were scavengers of the DPPH radical and of ONOO from morpholino-sydnonimine (SIN-I) (Seo et al., 2006).

Brown alga *Sargassum thunbergii* afforded a novel chromene, sargothunbergol A **189**, as a free radical scavenger (DPPH assay) (Seo et al., 2007). Two monogalactosyl diacylglycerols **190** and **191** were isolated from *S. thunbergii* (Kim et al., 2007). Fucodiphlorethol G **192**, a tetrameric phlorotannin, was isolated from *Ecklonia cava*, and was a strong radical scavenger (DPPH assay) (Ham et al., 2007).



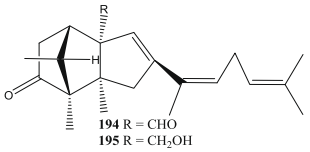
The known compounds taondiol (Gonzalez et al., 1971) isoepitaondiol (Rovirosa et al., 1992) stypodiol, (Gerwick and Fenical, 1981), stypoldione (Gerwick et al., 1979) and sargaol (Numata et al., 1992), isolated from brown alga *Taonia atomaria* exhibited free radical-scavenging activity (DPPH and chemiluminescence tests) (Nahas et al., 2007).

1.2.2.11. Anti-diabetic activity. *In vivo* testing fucosterol which was isolated from the brown alga *Pelvetia siliquosa* demonstrated that it is the main antidiabetic priciciple from *Pelvetia siliquosa* (Lee et al., 2004).

1.2.2.12. 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).

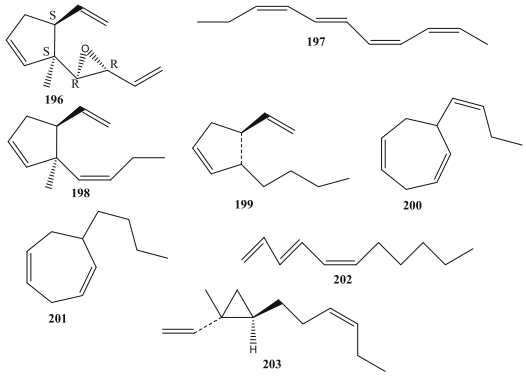
1.2.2.13. Morphological abnormality in the plant pathogen. *Stypopdium carpophyllum* from South China Sea was the source of two new bioactive sterols A **193** and B **119.** These sterols induced morphological abnormality in the plant pathogenic fungus *Pyricularia oryzae* (Tang et al., 2002a).

1.2.2.14. Antifeedent activity. Two diterpenoids with a novel skeleton, dictyterepenoids A **194** and B **195** were isolated from the brown algae *Dilophus okamurae* displayed antifeedent activity against young abalone (Suzuki et al., 2002). 10,18-diacetoxy-8-hydroxy 2,6-dollabeladiene **148** (Ireland and Faulknar, 1977) was the antifeedent compound of brown alga *D. pfaffi* against the sea urchin *Lytechinus variegates* and generalist fishes (Barbosa et al., 2004).



1.2.2.15. Gamete-releasing, gamete-attracting and sperm-attractants pheromone from brown algae. Most of 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 **196** is a new gamete-releasing and gamete-attracting pheromone isolated from brown alga *Perithalia cudata* (Muller et al., 1988). Giffordene **197** is another gamete-attractant of brown algae *Giffordia* (Hink sia mitchellae) (Boland et al., 1987) The female gametes *of Chorda tomentosa* secrete a mixture of multifidene **198**, 3-butyl 4-vinylcyc!opentene **199**, ectocarpene **200** and (−)-dictyopterene C **201** that triggers and explosive discharges of spermatozide from ripe antheridia prior to chemotaxis (Maier et al., 1984). Two sperm-attractants of *Cystophora siiiquosa* and *Hormosira hanksii* were identified as cystophorene **202** and hormosirene **203** (Muller et al., 1985).



1.2.3. Rhodophyta (red algae)

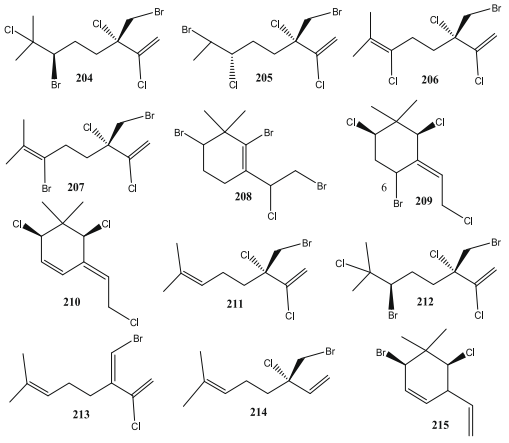
The red colour of these algae results from the dominace of the pigments phycoerythrin and phycothcyanin; this mask the other pigments, chlorophyll *a* (no chlorophyll *b*), *β*-carotene and a number of unique xanthophylls (Bold et al., 1985). The walls are made of cellulose, agars and carrgeenans. Several red algae are eaten, amongst these is dulse (*Palmaria palmate*)

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 1US 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 of marine source. These are found in the intertidal and in subtidal 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.

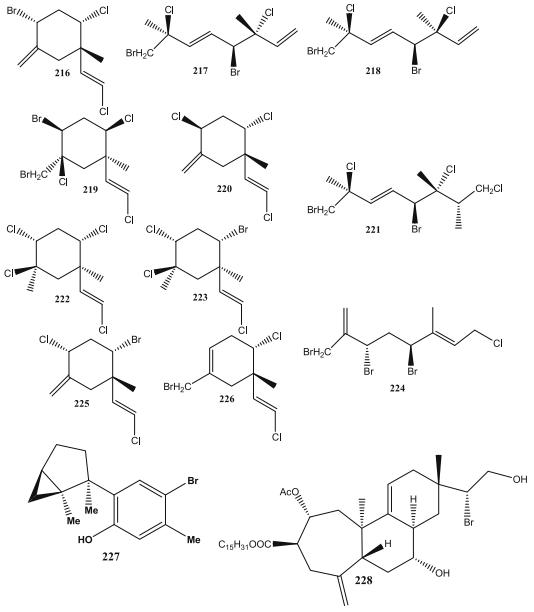
1.2.3.1. Cytotoxic activity. Halmon **204** is a polyhalogenated monoterpene isolated from the red alga *Portieria hornemanii* is considered as a novel *in vitro* antitumor agent by National Cancer institute (NCl). The NCI Decision Network Committee selected halmon as a pre-clinical drug for development (Fuller et al., 1992, 1994). Ten halogenated monoterpenes **205**–**214** related to the novel antitumor compound halomon **204** 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 **204** and **210** in the US National Cancer Institute's *in vitro* human cancer cell line screening panel. The results insights into structure/activity relationships in this series as follows: Compounds **204**–**207** exhibited similar cytotoxicity to that reported earlier for **204** (Fuller et al., 1992). These results suggested that halogen at C_7 was not essential to the activity. In contrast, compound **211** was relatively weekly cytotoxic and the minimally differential activity showed no significant correlation to that of **204**, indicating that a halogen at C_6 was essential for the characteristic activity of **204**–**207**. halogen at C_2 was required for halomone like activity. Carbocyclic compounds like **208** and **215** were considerably less cytotoxic than **204**–**207.** Compound **209** 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 **204**.



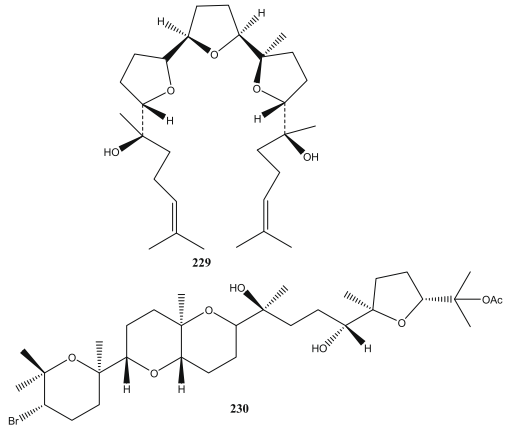
The polyhalogenated monoterpene content of six samples of the tropical marine red alga *Plocamium hamatum*, **216**–**226** collected from the southern, central and northern regions of The Great barrier Reef, Australia was assessed. The Biological activities of compounds **217**–**223** and **226** were assessed and indicated that compounds **219** and **221** have moderate Cytotoxic activity (Koing et al., 1999).

The invention of Laurinterol (LOEL) **227** which was isolated from *Laurencia okamurai* is considered as invention for the prevention and inhibition of melanoma (Moon-Moo et al., 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 et al., 2009).

2-Acetoxy-15-bromo-6,17-dihydroxy3-palmitoyl-neoparguera-4(19), 9(11)-diene **228**, a novel seco-parguerane skeletone have 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 **229** and thyrsiferyl 23-acetate **230**, have been isolated from the red alga *Laurencia obtuse* (Suzuki et al., 1985). Thysiferyl 23-acetate **230** (bromo ether) showed remarkabaly cytotoxic property (ED_{so} of 0.3 μg/ml) against P388 *in vitro* cell line.

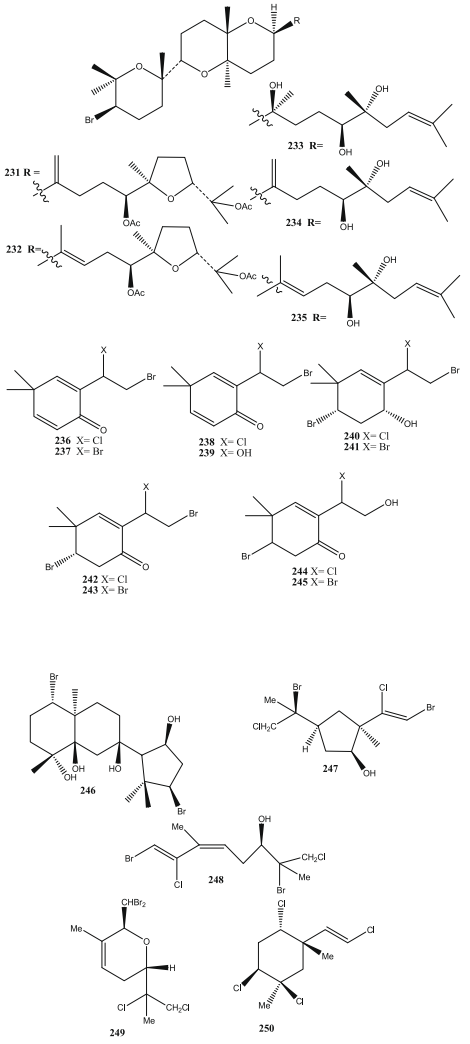


Five new cytotoxic triterpenes: triterpenoids 28-anhydrothyrsiferyl diacetate [15,28-didehydro-15-deoxythyrsiferyl] diacetate **231**, l5-anhy-drothyrsiferyl diacetate [15,16-didehydro-l5-deoxy-thyrisferyl] diacetate **232**, magireol-A **233**, magireol B **234** and magireol C **235** were isolated from Japanese red alga *Laurencia obtuse* (Suzuki et al., 1987).

Several cyclic monoterpenes **237**–**245** have been isolated from the Japanese red alga *Desmia hornemanni*, and some chemical modification have been done on these compounds to get the most active one for cytotoxic activity (Higa, 1985). Compound **236** exhibited relatively high activity against P388, A-549 lung carcinoma, and HCT-8 human colon adenocarcinoma.

Okianwa red alga *Laurencia yonaguniensi* was the source of neoirietetraol **246** a brominated diterpene based on the rare neoirieane skeleton was toxic to brine shrimp and was also active against marine bacteria *Alcaligenes aquamarinus* and *E. coli* (Takahashi et al., 2002).

Furoplocamioid C **247**, perfuroplocamioid **248**, pirene **249** and tetrachlorinated cyclohexane **250** from the red alga *Plocumium carttilagineum* (Argandona et al., 2002) exhibited selective cytotoxicity against human tumour cell lines with pirene showing a specific and irreversible effect on SW480 cells (de Ines et al., 2004).

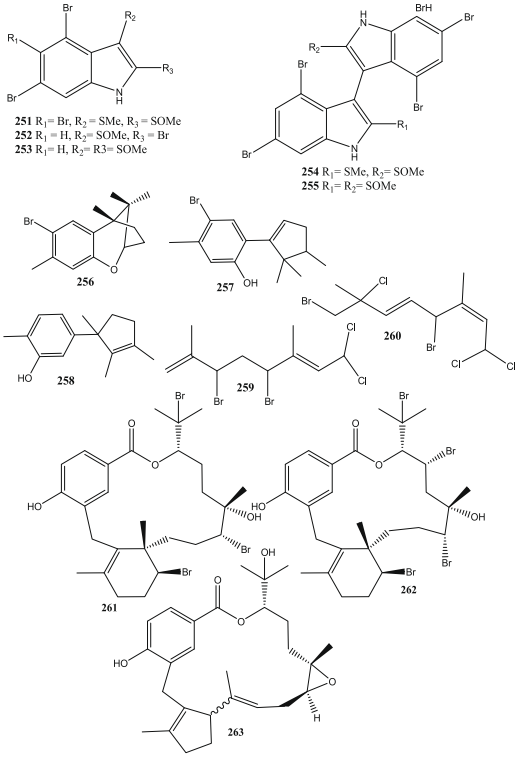


Five sulfur-containing polybromoindoles **251–255** were isolated from the red alga *Laurenda brongniartii*, of which **254** and **255** were active against P388 cells and **254** against HT-29 cells (El Gamal et al., 2005). The cuparene sesquiterpenes **256–258**, isolated from red alga *L. microcladia* were cytotoxic against the NSCLC-N6 and A-549 cancer cell lines (Kladia et al., 2005).

Plocaralides B **259** and C **260** isolated from *Ploeamium* species (Steierle et al., 1979; Higgs et al., 1977) and *Aplysia ealiforniea* (Ireland et al., 1976) displayed moderate activity against the human oesophageal cancer cell line WHCOI (Knott et al., 2005).

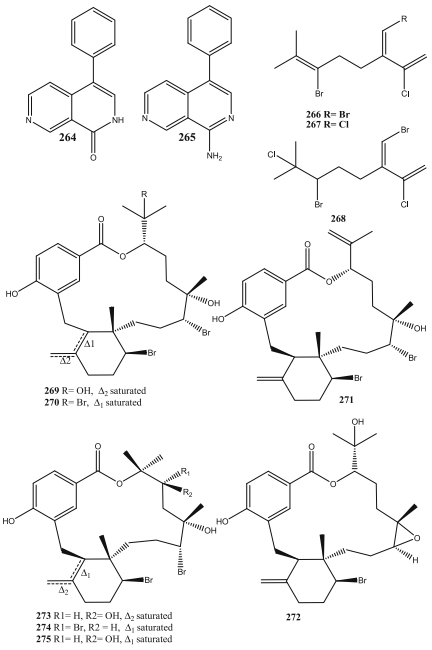
Red alga *Callophyeus serratus* was the source of three antibacterial and antifungal diterpene-benzoate compounds, bromophycolides A **261** and B **262**, and a non-halogenated compound **263**. Bromophycolide A **261** was cytotoxic against several human tumour cell lines by specific induction of apoptosis (Kubanek et al., 2005).

The alkaloids 2,7 naphthyridine lophocladines A **264** and B **265** 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 **265** was moderately active against NCI-H460 human lung tumour and MDA-MB-435 breast cancer cell lines and shown to be an inhibitor of microtubules (Gross et al., 2006).

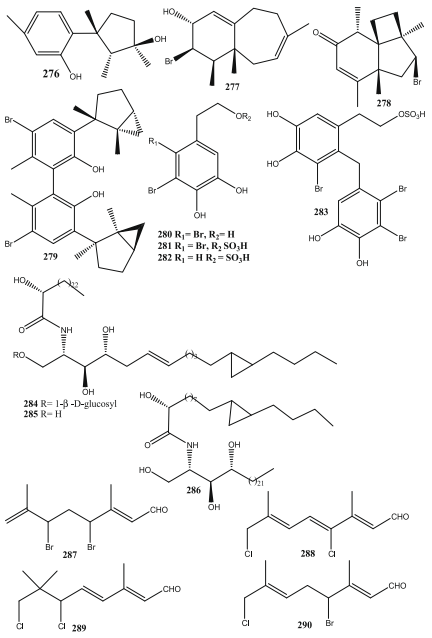


Three halogenated monoterpenes **266–268** were isolated from the red alga *Portiera hornemannii* along with the known compound halomon (Fuller et al., 1992). Both halomon **204** and **268** were moderate inhibitors of DNA methyl transferase-1 (Andrianasolo et al., 2006).

Bromophycolides C-I **269–275** 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 obtuse* was a source of sesquiterpenes 3,7-dihydroxydihydrolaurene **276**, perforenol B **277** and **278**, while *L. microcladia* yielded a dimeric sesquiterpene **279**. Compounds **276–278** were tested against five human tumour cell lines and the Chinese hamster ovary (CHO) cell line. Perforenol B **277** exhibited strong activity while sesquiterpenes **276** and **278** exhibited weak activity. The sesquiterpene **279** was moderately cytotoxic against NSCLC-N6 and A-549 lung cancer cell lines (Kladi et al., 2006). The red alga *Rhodomela confervoides* was the source of four bromophenols **280–283.** They exhibited moderate cytotoxicity against several human cancer cell lines (Ma et al., 2006).

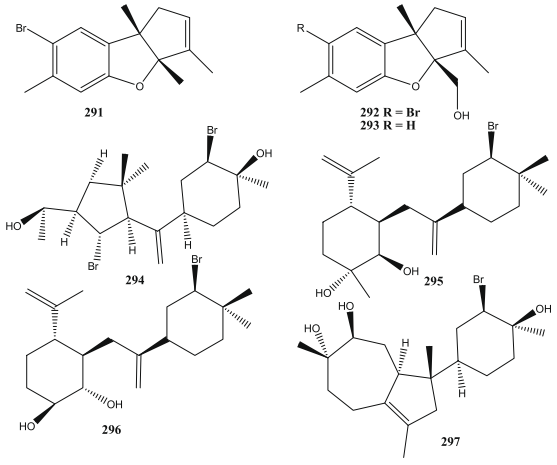


The red alga *Gracilaria asiatica* was the source of three cyclopropyl derivatives, the cerebroside gracilarioside **284** and the ceramides gracilamides A **285** and B **286** which were mildly cytotoxic to the human A375-S2 melanoma cell line (Sun et al., 2006).

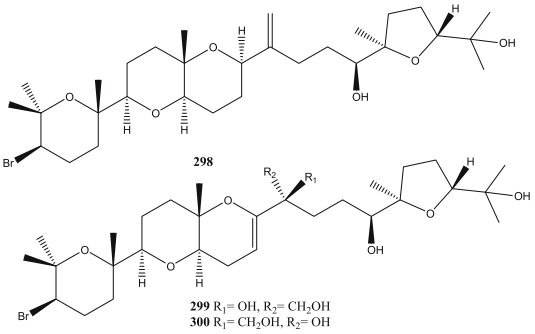
Four somewhat air-unstable halogenated monoterpene aldehydes **287–290** were characterised from red alga *Plocamium corallorhiza* of which **287** was significantly cytotoxic against an esophageal cell line (Mann et al., 2007).

Three sesquiterpenes, aplysin-9-ene **291**, epiaplysinol **292** and debromoepiaplysinol **293**, were isolated from red alga *Laurencia tristicha*. Debromo-epiaplysinol **293** displayed selective cytotoxicity to the HeLa cell line (Sun et al., 2007).

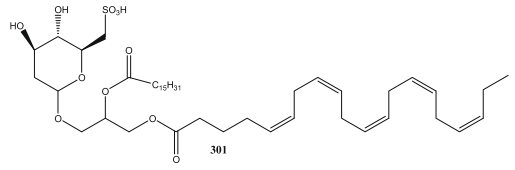
Diterpenes neorogioldiol B **294** and prevezol B **295** isolated from the red alga *Laurencia obtusa* displayed significant cytotoxicity against the human tumour cell lines MCF-7, PC3, HeLa, A431 and K562, while prevezol C **296** exhibited significant cytotoxicity against HeLa and A431 cell lines. Prevezol D **297** was moderately active against all cell lines (IIopoulou et al., 2003).



Two new polyether squalene derivatives, thyresenol A and B **299**, **300** have been isolated from *Laurencia viridis* together with the previously isolated dehydrothyrsiferol. **298** (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 **298**, originally isolated from the red alga *Laurencia pinnatifida* was shown to induce apoptosis in esterogen-dependent and independent breast cancer cells (Norte et al., 1997; Pec et al., 2003).



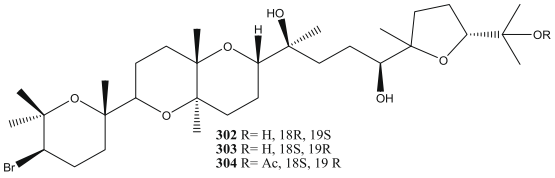
1.2.3.2. Antiviral activity. Sulquinovosyldiacylglycerol, KM043 **301**, a new sulfolipid KM043, which belongs to the 6-sulf-μ-D-quinovopyranosyl-(l → 3′)-1′,2′-diacylgly-cerol (SQDG) class of compounds has been isolated from the marine red algae *Gigartina tenella* (Ohata et al., 1998) as a potent inhibitor of eukaryotic DNA and HIV-l reverse transcriptase type 1. The inhibition was dose-dependent, and complete (more than 90%) inhibition of DNA polymerase μ (pol. μ), DNA polymerase μ (pol. μ) and HIV-reverse transcriptase type 1 (HIV-RT) was observed at concentrations 5, 10 and 30 μM, respectively.



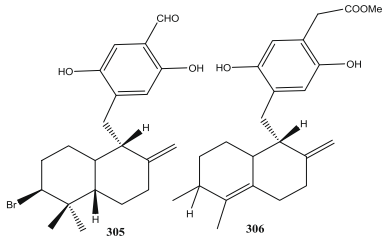
2,3,6-Tribromo 4,5-dihydroxybenzyl methyl ether (Park et al., 1999) isolated from the red alga *Symphyocladia latiuscula* was active against wild type HSV-l, as well as APr HSV-I and TK-HSV-l and significantly delayed the appearance of lesions in infected mice without toxicity (Park et al., 2005).

The invasive species *Caulerpa racemosa* was the source of know 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.

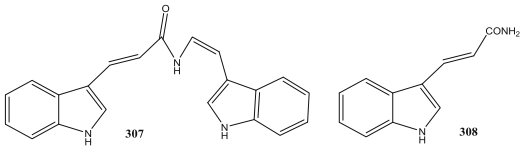
Venustatriol **302**, thyrsiferol **303** and thyrsiferyl 23-acetate **304** were isolated from the red alga *Laurencia venusta* and all displayed significant antiviral activity against *Vesicular stomatitis* virus (VSV) and *Herps simplex* virus type 1 (HSV-l) Sakemi et al., 1986.



During a survey of marine organisms for anti HIV RTs activities (reverse transcriptases of human immunodeficiency virus), two new sesquiterpene hydroquinone, peyssonol A **305** and B **306** have been isolated from the active anti HIV RTs extracts Red Sea alga *Peyssonnelia* species (Talpir et al., 1994).

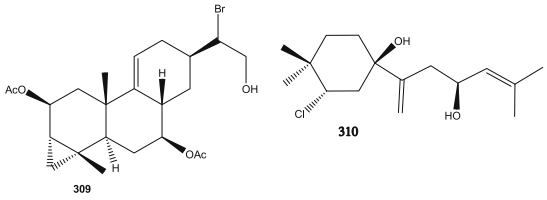


1.2.3.3. Anthelmintic activity. Chondriamide C **307**, a new bis (indole) amide and 3-indolacrylamide **308** have been isolated from the red algae *Chondria atropurpurea* and showed anthelmintic activity against *Nippostrongylus brasiliensis* (Davyt et al., 1998).



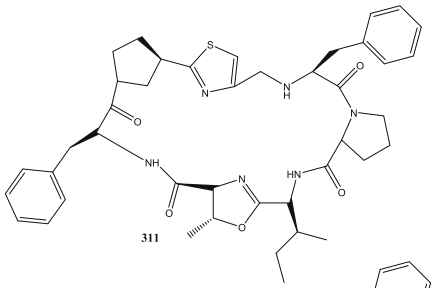
Brominated diterpenes of the parguerene and isoparguerene series were isolated from the red alga *Jania rubens* including the novel deoxyparguerol-7-acetate **309.** All the isolated diterpenes had anthelmintic activity (Awad, 2004).

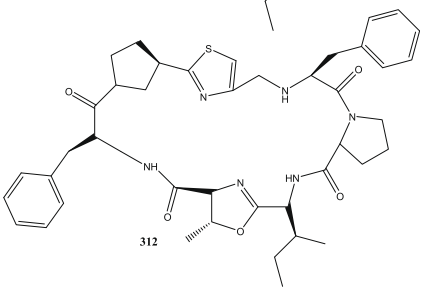
The red alga *Laurencia scoparia* was a source of halogenated β-bisabolene sesquiterpenes **310** (Awad, 2004; Davyt et al., 2006). It showed weak *in vitro* anthelmintic activity against *Nippostrongylus brasiliensis* (Davyt et al., 2006).

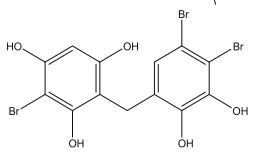


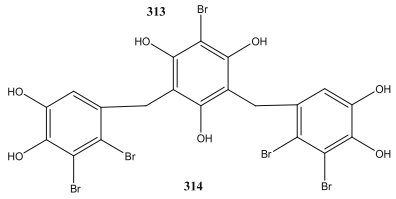
1.2.3.4. Antiinflammatory activity. Chemical investigation of the marine red alga *Ceratodictyon spongiosum* containing the symbiotic sponge *Sigmadocia symbiotica* collected from Indonesia, afforded two isomers of a new bioactive thiazole-containing cyclic heptapeptide: *cis, cis*-Ceratospongamide **311** and *trans, trans*-ceratospongamide **312** (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 antiinflammation (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 **311** and **312** was measured as the inhibition of secreted phospholipase A2 by hepatocellular carcinoma cells stimulated with 1L-1β. The *tans, trans* form is a potent inhibitor of sPLA2 expression with ED_{so} 32 μM. Both compounds showed only moderate potency in the brine shrimp toxicity assay.

The anti-inflammatory bromophenolic metabolites named vidalols A **313** and B **314** were isolated from the Caribbean red alga *Vidalia obtusaloba* that acts through the inhibition of phospholipase enzyme (Wiemer et al., 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 which may function through inhibition of phosolipase A2.

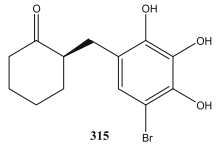




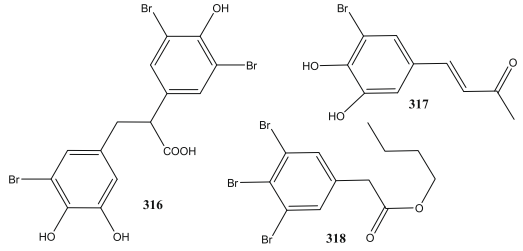




1.2.3.5. Free radical scavenger activity. (2R)-2-(2,3,6-tribromo – 4,5-dihydroxybenzyl) cyclohexanone **315** was isolated from the red alga *Symphyocladia latiussula* whish has a free radical scavenger activity. The Antioxidant activity was expressed in terms of IC_{50} [μg/ml or μM required to inhibit l,1-dipheny l-2-picrylhydrazyl radical, (DPPH), formation by 50%] and calculated (Choi et al., 2000).

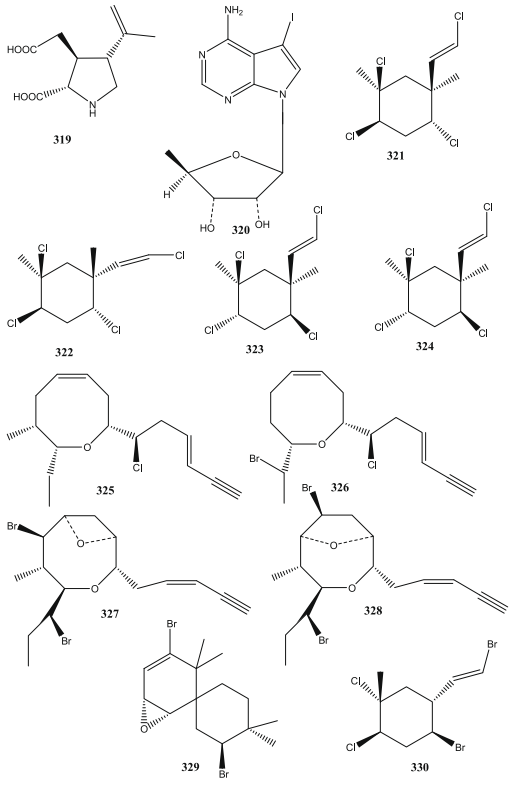


Three bromophenols **316**–**318** and the previously reported 1,2-bis (3-bromo-4,5-dihydroxyphenyl ethane (Kurata et al., 1976) were isolated from the red alga *Polysiphonia urceolata*. All compounds were potent DPPH radical scavengers (Li et al., 2007).



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 et al., 2007).

1.2.3.6. Neurophysiological activity. The amino acid (α-alkokainic acid **319** 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 **320** 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 is discovered by using a bioassay-directed isolation procedure (Kazlauskas et al., 1983).

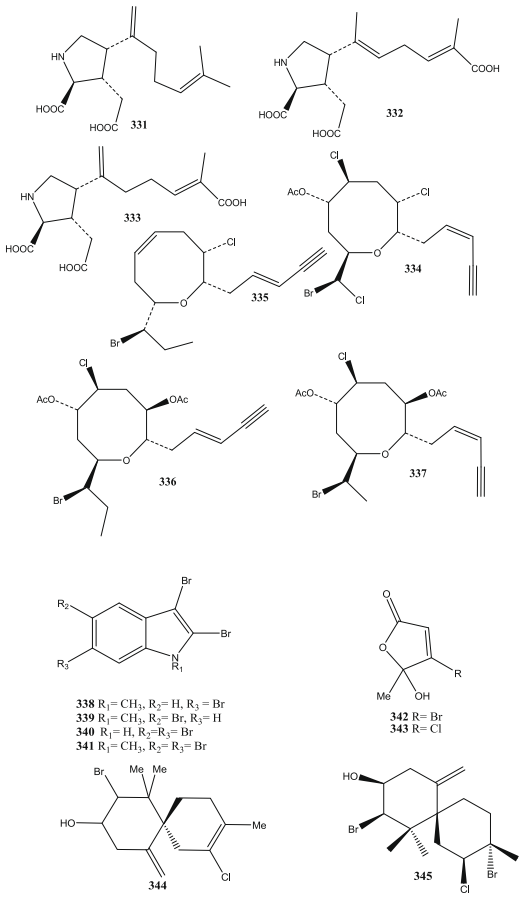


1.2.3.7. Insecticidal activity. The insecticidal and acaricidal polyhalogenated monoterpenes **321**–**324** have been isolated from Chilean specimens of the red alga *Plocamium cartilagineum*. The insecticidal activity of these compounds proved to be effective against the Aster leafhopper (San-Martin et al., 1991). Laurepinacine **325** and isolaurepinnacin **326** are acetylinic sesquiterpene ethers isolated from the red alga *Laurancia pinnata* that demonstrated isecticidal activity (Fukuzawa and Masamune, 1981). (*Z*)-Laureatin **327**, (*Z*)-isolaureatin **328** and deoxyprepacifenol **329** are other related compounds from the red alga *Laurencia nipponica* Yamada. They show strong isecticidal activity against the mosquito larvae *Culex pipens pallens* (Watanabe et al., 1989; El Sayed et al., 1997). Telfairine **330** is another related monoterepene reported from the red alga *Plocamium telfairia*, with strong insecticidal activity against the mosquito larvae *Culex pipens pal/ens* (Watanabe et al., 1988).

The new insecticidal amino acids namely, isodomic acid A **331**, isodomic acid B **332** and isodomic acid C **333** were

isolated from the red alga *Chondria arnata*. They show significant insecticidal activity when they are injected subcutanously into the abdomen of American cockroach (Maeda et al., 1986).

Laurencia obtuse, collected from off Symi Island in the Greece, Aegean Sea was the source of C_{15} acetogenins 13-epilaurencienyne (3*Z*) **334**, 13-epinnatifidenyne (3*E*) **335** and two diaceto-xypentadec-3-en-1-yne derivatives (**336**–**337**). Compounds **334** and **335** exhibited strong toxicity against ants with considerable knockdown effect from the first day, while compounds **335** and **336** exhibited gradual toxicity that was escalated at the fourth day with >70% mortality (IIopulou et al., 2002).



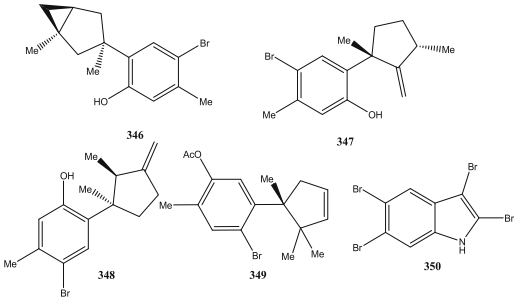
1.2.3.8. Antimicrobial activity. The antimicrobial activity of the red alga *Laurencia brongniarti* against *Bacillus subtilis* (a gram positive bacteria) and *Saccharomyces cerevisiae* (yeast) has been traced to the four polybrominated indoles **338–341** (Carter et al., 1978).

From the air dried red alga *Beckerella subcostatum*, bromobeckerelide **342** epimer (the major fraction) and chlorobeckerelide **343** epimers (the minor fraction) were isolated. In lab tests, both compounds showed activity against *Bacillus subtilis* (Ohta, 1977).

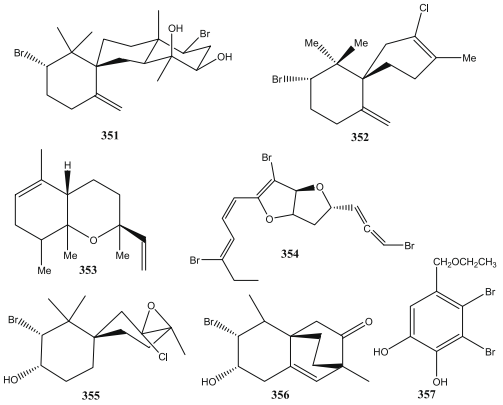
From the MeOH extract of *Marginisporum aberrans*, showing antimicrobial activity against *Bacillus subtilis, P*-hydroxybenzaldhyde, dichloro-acetamide, and 3,5-dinitriguaiacol were obtained. All these compounds showed activity against *Bacillus subtilis* (Ohta and Takagi, 1977).

Elatol **344**, a halogenated sesquiterepene alcohol from the red alga *L. elata* (Sims, 1974) inhibited six species of human pathogenic bacteria with significant antibacterial activities against *Staphylococcus epidermis*, *Klebsiella pneumonia* and *Salmonella* sp. (Vairappan, 2003). Iso-obtusol **345** 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 **346** (Irie et al., 1966), isolaurinterol **347** (Irie et al., 1970), *allo*-laurinterol **348** (Kazlauskas et al., 1976), cupalaurenol **349** (Ichiba and Higa, 1986) and 2,3,5,6-tetrbromoindol **350** (Carter et al., 1978) displayed a wide spectrum of antibacterial activity against gram positive bacteria including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococus pneumonia* 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 **351**, two sesquiterpenes, 9-deoxyelatol **352** and isoda-ctyloxene A **353**, one brominated C15-acetogenin, laurenmariallene **354**, and two new naturally occurring halogenated sesquiterpenes **355** and **356** that were obtained previously as intermediates in a biomimetic synthetic study of rhodolaureol and rhodolauradiol (Gonzalez et al., 1982). Both 10-hydroxykahukuene B **351** and laurenmariallene **354** had modest antibacterial activity.

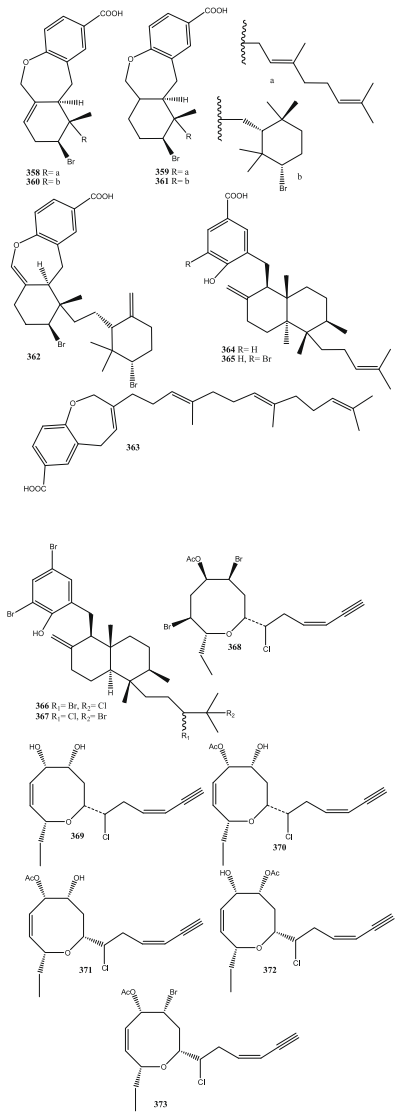


Lanosol enol ether **357**, originally isolated from the brown alga *Fucus vesiculosus* has been shown to be an antibacterial and antifungal component of the brown alga *Osmundaria serrata* (Barreto and Meyer, 2006).

Eight novel diterpenebenzoic acids, callophycoic acids A–H **358–365**, and two halogenated diterpene-phenols, callophycols A **366** and B **367**, were isolated from red alga *Callophycus serratus* some of which displayed moderate antibacterial, antimalarial, antitumour and antifungal activity (Lane et al., 2007).

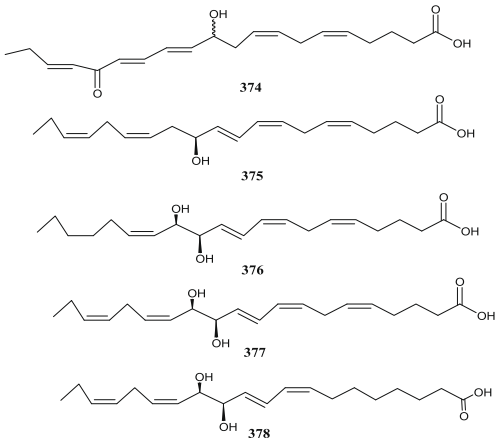
Five new C_{15} eight-membered cyclic ethers (**368, 370–373**) (Kladi et al., 2008) with a characteristic terminal *cis* eneyne

moiety in addition to the previously reported acetylenic chloro diol **369** (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 **369**–**372** were in the range of 8–256 μg/ml.



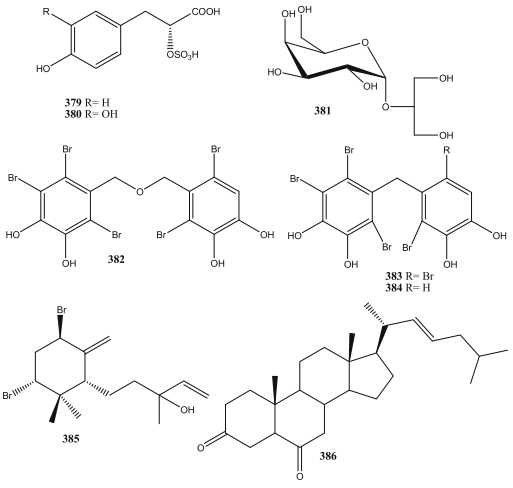
1.2.3.9. Lipooxygenase inhibitor. The eicosanoids are biologically active arachidonic acid derivatives frequently found in marine organisms. Ptilodene **374** (new fatty acid) is an eicosanoid from the red alga *Ptilotafilicina* sp. that showed inhibitory activity to human 5-lipooxygenase, dog kidney Na^+/K^+ ATPase and the growth of several pathogenic gram positive and negative bacteria (Lopez and Gerwick, 1988). Another eicosanoid derivatives which is a potent inhibitor of platelet aggregation is 12-(*S*)-hydroxyeicosapentaenoic acid **375** isolated from the red alga *Murrayella periclados* (Bernari and Gerwick, 1994).

Three biologically active eicosanoids, (12*R*, 13*R*)-dihydroxy-eicsa-5(*Z*),8(*Z*),10(*E*), 14(*Z*) tetraeonic acid **376**, (12*R*,13*R*)-dihydroxy eicosa-5(*Z*),8(*Z*), 10(*E*),14(*Z*),17(*Z*)-pentaenoic acid **377** and (10*R*,11*R*)-dihydroxyoctadeca-6(*Z*), 8(*E*), 12(*Z*) trienoic acid **378** were isolated from the red alga *Farlowia mollis* (Solem et al., 1989).



1.2.3.10. Antifeedent activity. Two phenylpropanoic acid derivatives, tichocarpols A **379** and B **380** were isolated from the red alga *Tichocarpus crinitus*. These two compounds along with floridoside **381** (Roh et al., 1994) which is also isolated from the alga, exhibited antifeedant activity against the sea urchin *Strongylocentrotus intermedius* (Ishii et al., 2004).

1.2.3.11. Aldose reductase inhibitors activity. The new bromophenols **382–384** 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).



1.2.3.12. Antimalarial activity. Snyderol sesquiterpene **385** 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).

1.2.3.13. Anti-elastase activity against porcine pancreas elastase (PEE). 3,6-Diketo steroid **386** was isolated from the red alga *Hypnea musciformis* collected on the Atlantic Coast of Morocco exhibited anti-elastase activity against porcine pancreas elastase (PEE) (Gosavi et al., 1995).

1.2.3.14. 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-hydroxyphe-nylethylamine (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 et al., 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-methoxyme-thylpyrocatechol also protected rice plants from infection by *Magnaporthe grisea* (Lee et al., 2007). This was the first report of 3,5-dibromo-4-hydroxyphenyle-thylamine as a natural product (Lee et al., 2007).

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