

# DECCAN PHARMA JOURNAL SERIES

ARMS Online Publications

[www.deccanpharmajournals.com](http://www.deccanpharmajournals.com)

(Review Article)

Received; accepted

## ANTIBIOTICS FROM MARINE ORGANISMS

Doshi Gaurav.M<sup>1</sup>, Aggarwal Gayatri.V<sup>1</sup>, Martis Elvis. A<sup>1</sup>, Shanbhag Pradnya Palekar<sup>1</sup>, Keyur shastri V<sup>1</sup>, Ojas Kumar Agrawal<sup>1</sup>, Vandana Panda S<sup>2</sup>

1. VES College of Pharmacy, Hashu Advani Memorial Complex, Collectors Colony, Chembur (East), Mumbai – 400074 India
2. Principal K. M. Kundnani College of Pharmacy, Plot no. 23, Jote Joy Bldg. Rambhau Salgaonkar Marg, CuffeParade, Colaba, Mumbai 400 005. India

### Keywords:

Marine, antibiotics, microorganisms, sponges, algae, molluscs, worms

For Correspondence:

**Gaurav M Doshi**

VES College of Pharmacy, Hashu Advani Memorial Complex, Collectors Colony, Chembur (East), Mumbai – 400074 India

E-mail:

[gaurav.pharmacology@gmail.com](mailto:gaurav.pharmacology@gmail.com)

### ABSTRACT

With the emergence of newer diseases, resistant forms of diseases and multi-drug resistant bacteria, it has become essential to develop novel antibiotics. Current antibiotics are those obtained from terrestrial life. The oceans represent virtually untapped resources from which novel antibiotics/compounds can be discovered. It is the marine world that will provide the pharmaceutical industry with the next generation of antibiotics.

Marine antibiotics are antibiotics obtained from marine organisms. Marine scientists have reported the discovery of various antibiotics from the following sources:

- From marine bacteria: aplasmomycin, himalomyces & pelagiomycins
- From sponges: Ara C, variabillin, strobilin, ircinin-1, aeroplysin, 3,5-dibromo-4-hydroxyphenylacetamide
- From coelenterates: asperidol, eunicin
- From mollusks: laurinterol, pachydietylol
- From tunicates: geranylhydroquinone, cystadytins
- From algae: cycloeuodesmol, aeroplysinin-1(+), prepacifenol, tetrabromoheptanone
- From worms: thelepin, 3,5-dibromo-4-hydroxybenzaldehyde
- From actinomycetes: marinomyces C & D

This indicates that the marine environment, representing approximately half of the global diversity is an enormous resource for marine organisms and this source needs to be explored for the next generation of antibiotics. The present article provides an overview of various antibiotics derived from marine sources.

## INTRODUCTION

Marine Drugs are the drugs obtained from marine plants, animals and microorganisms. About 70% of earth's surface is covered with water and it comprises 5,00,000 live species divided into 30 different phyla. The World Ocean has a coastline of about 3,12,000 km and a volume of  $137 \times 10^6 \text{ km}^3$  making it the largest ecosystem on earth.<sup>[1]</sup> (Thus, these statistics prove that there is a large source which still has not been utilized. It holds an outstanding potential for discovery and development of bioactive natural products. The ocean is packed with unique organisms. Most natural products from the sea are structurally novel and many may possess potent biological activities. The oceans have been recently described to be the "Medicine Chest of the New Millennium."<sup>[2]</sup> There is a gold rush amongst pharmaceutical and biotechnology companies to tap this newfound resource. Traditionally, many medicines have their origin from plants and animals that occur on land. However, most of the plants and animals on land have been discovered and many of the curative properties of the chemicals they contain have been found. The marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compounds with the potential for industrial development as pharmaceuticals, cosmetics, nutritional supplements, molecular probes, fine chemicals and agrochemicals.<sup>[3]</sup>

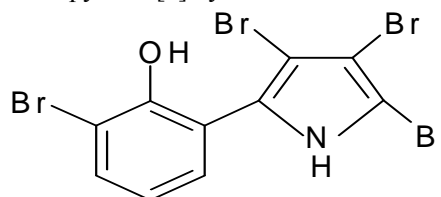
## NEED FOR MARINE DRUGS

The ocean is packed with unique organisms, which have compounds possessing different pharmacological activities. These compounds possess unique mechanism of action, are structurally novel and possess potent biological activities different from terrestrial organisms.<sup>[4]</sup> Approximately 25,000 compounds have been screened, about 30 of them are in clinical trials and 10 of them are commercially marketed.<sup>[5]</sup> Marine organisms have evolved biochemical and physiological mechanisms that include the production of

bioactive compounds for purposes such as reproduction, communication, protection against predation, infection and competition. Because of the physical and chemical conditions in the marine environment, almost every class of marine organism exhibits a variety of molecules with unique structural features. But beyond the chemical diversity, the sea also provides amazing biological diversity. Among 34 fundamental phyla of life, 17 occur on land whereas 32 occur in the sea.<sup>[6]</sup> From the fundamental point of view of biodiversity, the ocean is far more diverse as compared to the plants and animals found on land.

## ANTIBIOTICS FROM MICRO-ORGANISMS

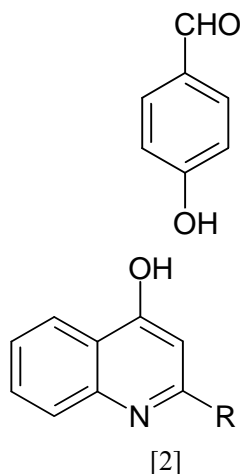
The first antibiotic substance from the marine bacteria to be isolated and identified was 2-(3', 5'-dibromo-2'-hydroxyphenyl)-3,4,5-tribromopyrrole [1] by Burkholder.<sup>[7]</sup>



[1]

The marine bacterium *Pseudomonas bromoutilis* was isolated by Burkholder from *Thalassia* (turtle grass) in Puerto Rico. The brominated antibiotic was shown to be highly active against Gram positive bacterial strains of *Staphylococcus aureus*, *Diplococcus pneumoniae*, and *Staphylococcus pyogenes*. The above organisms were inhibited at an antibiotic concentration of 0.0063 µg/ml in broth culture. However, the antibiotic failed to show a therapeutic value against *S. aureus* when administered simultaneously to mice.

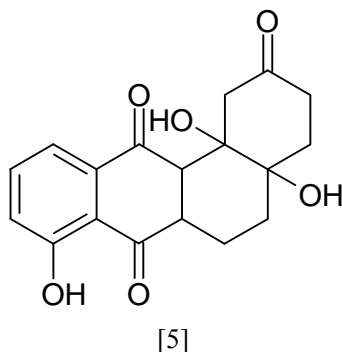
A yellow marine pseudomonad of the *Altermonas* species produces three antibiotic compounds 4-hydroxybenzaldehyde [2], 2n-pentyl-4-quinolinol [3] and 2n-heptyl-4-quinolinol [4]



[3] R= C<sub>5</sub>H<sub>11</sub> & [4] R= C<sub>7</sub>H<sub>15</sub>

2n-heptyl-4-quinolinol had previously been isolated from a terrestrial bacterium *Pseudomonas aeruginosa*. The two quinolinols [3] and [4] were active against *Staphylococcus aureus*, *Vibrio harveyi* and *Vibrio anguillarum* at 50ug/disc using disc assay technique.

An actinomycete *Chainia purpurogena* ss-228 later referred to as *Chainia* species was shown to produce an antibiotic which inhibited growth of Gram negative bacteria. On the basis of spectroscopic data the antibiotic ss-228 was shown to be a benz(a)anthracene derivative[5]



A new antibiotic, aplasmomycin, which inhibits growth of Gram-positive bacteria including mycobacteria in vitro, and plasmodia in vivo was obtained from ss-20 strain of *Streptomyces griseus* isolated from shallow sea sediment in Sagami Bay, Japan by Okami and his group. This antibiotic forms colorless needle-like crystals and has a molecular formula of C<sub>41</sub>H<sub>60</sub>O<sub>14</sub>Na. Based on its physical and chemical properties, aplasmomycin was

concluded to be a new antibiotic. The antibiotic was produced in selected media devised to relate to a marine environment.<sup>[8]</sup>

Michio Namikoshi (Tokyo University Of Fisheries), Andrey Dmitrenok (Suntory Institute for bio-organic research) isolated a marine bacterium *Ruegeria atlantica* (TUF-D) from a glass plate submerged in the coastal water. Three new chlorine containing compounds together with penicillic acid were obtained from a marine derived fungus *Aspergillus ostianus* strain TUF 01 F313 at Pohnpei having antibacterial activity against *R. atlantica*. The structure of these three new antibiotics were determined based on their spectral data as 8-chloro-9-hydroxy-8,9-deoxyasperlactone which inhibited *R. atlantica* at 5ug/disc with an inhibition zone of 12.7mm, 9-chloro-8-hydroxy-8,9-deoxyasperlactone and 9-chloro-8-hydroxy-8,9-deoxyaspyrone which inhibited *R. atlantica* at doses of 10.1mm and 10.5mm respectively.

*Alteromonas rubra* is an organism under current investigation in the University of Hawaii. [9] It contains an antibiotic molecule that is active against multi-drug resistant pathogenic bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*.<sup>[10, 11]</sup> This antibiotic can be extracted from the bacteria using a phosphate buffer, and can be purified with anion exchange. The molecule is larger than 30,000 Dalton. Future research will involve further structural elucidation.

Marine Biotechnology Institute, Shimizu Laboratories, Japan has found a new genus of marine bacterium *Pelagiobacter variabilis* which produced new phenazine antibiotics, pelagiomicins A, B and C.<sup>[12]</sup> The structure elucidation was done by spectroscopic data and chemical synthesis is being carried out. Pelagomicin A exhibits activity against Gram positive and Gram negative bacteria and anti-tumor activity in vitro and in vivo.

Loloatins A to D, a family of new cyclic decapeptide antibiotics have been isolated from laboratory cultures of a tropical marine

bacterium recovered from the Great Barrier Reef in Papua New Guinea.<sup>[13]</sup> Loloatins A, B exhibited in vitro antimicrobial activity against methicillin resistant *S. aureus* (MRSA), vancomycin resistant Enterococci and drug resistant *Streptococcus pneumoniae*.

Acebal C et al, isolated sesbanimide antibiotics which are cytotoxic compounds isolated from two marine agrobacterium strains - PH-103 which produces sesbanimide A and strain PH-A034C which produces sesbanimide C.<sup>[14]</sup>

Biabani, Laatsch et al from Germany isolated  $\delta$ - indomycinone, a new member of pluramycin class of antibiotics from a marine *Streptomyces* species.

Biabani, Laatsch, Helmke, Weyland et al also isolated 2-[Methyl-(3-phenylpropionyl) amino]-benzoic acid from a culture of *Streptomyces* species strain B7747. The esters of this anthranilamide had a Minimum Inhibitory Concentration (MIC) from 20-107ug/ml against *Chlorella vulgaris*, *Chlorella sorokiniana*, *Chlorella salina* and *Scenedesmus subspicatus*. However, they were inactive against *S. aureus*, *E. coli* and *Mucor miehei*.<sup>[15]</sup>

*Roseobacter gallaeciensis*, a member of the *Roseobacter* genus of marine bacteria often found on the surfaces of algae has been shown to produce a new antibiotic called tropodithetic acid. This compound shows strong inhibitory activity against marine bacteria and algae.<sup>[16]</sup>

Researchers from Scripps Institute Of Oceanography, University Of California isolated four anti-tumor antibiotics of a new structural class, the marinomycins A-D from a marine actinomycete of the recently discovered genus *Marinospora*. Marinomycins are unusual macrolides composed of dimeric 2-hydroxy-6-alkenylbenzoic acid lactones with conjugated tetraenepentahydroxy polyketide chains. Marinomycins A-D show significant antimicrobial activities against drug resistant bacterial pathogens and demonstrate impressive and selective cancer cell cytotoxicities against six of the eight

melanoma cell lines in the National Cancer Institute 60 cell line panel.<sup>[17]</sup>

Agrochelin, a new alkaloidal cytotoxic substance was produced by the fermentation of a marine agrobacterium of the *Agrobacter* species. Agrochelin and its acetyl derivative exhibited potent cytotoxic activity.<sup>[18]</sup>

Yoshikawa, Takadero et al of Shimizu Lab., Japan have isolated a novel antibiotic named Korormicin from the marine bacterium *Pseudoaltermonas* sp.F-420 from the surface of a macroalga *Halimeda*. Korormicin had specific inhibitory activity against marine Gram negative bacteria but was inactive against terrestrial microorganisms.<sup>[19]</sup>

One member of the *Streptomyces* genus *S. tenjimariensis* was isolated from mud samples in Sagami bay, Japan by Hotta et al. *S. tenjimariensis* is capable of producing a family of aminoglycoside antibiotics called istamycins which are effective against many Gram negative bacteria and Gram positive bacteria which are otherwise resistant to aminoglycosides. *S. tenjimariensis* has recently gained attention for its capacity to enhance production of istamycins when grown in presence of marine bacteria.<sup>[20]</sup>

Scientists from Indian Institute Of Chemical Biology, Calcutta have isolated an active antimicrobial compound from a microorganism which is a lipid and shows very strong activity against bacteria and fungi including several that are multiple drug resistant such as *S. aureus* (strain 23602), *E. coli* (strain DH50), *Aspergillus niger* (strain MTCC 1344). This microbe belonging to the *Actinobacterium* group of Gram positive bacteria was isolated from the marine environment of Sunderbans and is christened as *Actinobacterium* MS.<sup>[21]</sup>

Andrimid and moiramides A-C have been isolated from a marine bacterium *Pseudomonas fluorescens*. Andrimid and moiramides were found to exhibit potent in vitro inhibition of methicillin resistant *S. Aureus*. It was found that an acylsuccinimide fragment of andrimid is essential for its

antimicrobial activity. Recently it was shown that andrimid at the nanomolar level inhibits the acetyl CoA carboxylase of Gram negative bacteria.<sup>[22]</sup>

Three novel anticancer antibiotics designated as chandrananimycins A, B and C were isolated from the culture broth of a marine actinomycete of the *Actinomadura* species isolate M045 by Maskey et al of University of Gottingen, Germany.<sup>[23]</sup> Maskey also isolated and characterized new fridamycin type antibiotics from a marine *Streptomyces* isolate B6921. These are himalomycins A and B which are two new anthracycline antibiotics. Maskey's group also isolated resistomycin, resistoflavin, methyl ester of resistoflavin, tetracenomycin and 1-hydroxy-1-norresistomycin from the streptomycete B 8005.<sup>[24]</sup>

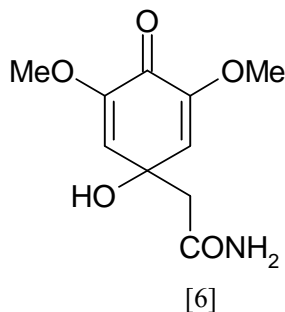
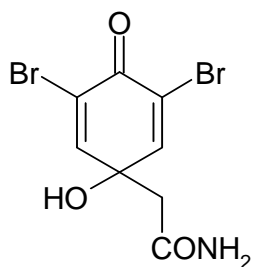
Inansetyo and Kamei, Saga University, Japan have discovered and characterized a phenolic anti-methicillin resistant *Staphylococcus aureus* (MRSA) substance from *Pseudoalteromonas phenolica*, a novel marine bacterium. MRSA causes a wide range of human diseases ranging from skin infections to pneumonia, endocarditis, meningitis, septicemia etc.<sup>[25]</sup> The isolated substance-3,3',5,5'-tetrabromo-2,2'-biphenyldiol also labelled MC21-A by these researchers demonstrates activity against Gram positive bacteria but is less active against *Streptococcus* species. This substance is not active against two Gram negative bacteria *P. aeruginosa* and *V. aglinoxyticus*. In this way it differs from the antibiotics produced by *Pseudoalteromonas luteoviolacea*, the *Pseudoalteromonas* species most closely related to *P. phenolica* sp 0-BC30. *P. luteoviolacea* produces pentabromopseudilin and violacein which are active against both Gram positive and Gram negative bacteria. MC21-A at 2µg/ml was able to kill MRSA ATCC-33591 completely, while vancomycin acted slowly even at eight times the MIC. It is postulated that MC21-A at the MIC rapidly permeabilizes bacterial cell membranes.<sup>[26]</sup>

5,10-dihydrophencomycin methyl ester, a new phenazine derivative and the known microbial metabolites (2-hydroxyphenyl)acetamide, menaquinone MK9 and phencomycin were isolated from an unidentified marine *Streptomyces* species. They showed weak antibiotic activity against *E. coli* and *B. subtilis*.<sup>[27]</sup>

Thiomarinols B, C, D, E, F and G, antimicrobial antibiotics produced by a new marine bacterium *Alteromonas rava* sp. Nov.SANK 73390 were isolated by Shiozawa and his group of researchers. The structure of thiomarinol, was deduced as a hybrid composed of a pseudomonic acid analogue and holothin by NMR spectral analysis and chemical degradation. Antimicrobial activity against Gram-positive and Gram-negative bacteria of thiomarinol was stronger than both of pseudomonic acids and pyrrothine antibiotics.<sup>[28-30]</sup>

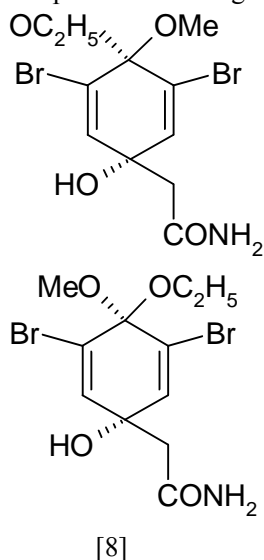
#### ANTIBIOTICS FROM SPONGES

In a broad survey of antimicrobial activity in the marine phyla, sponges have often shown the greatest percentage of active samples. However, the sponges are notoriously difficult to identify and thus many sponges having antimicrobial activity still remain unidentified. Sharma and Burkholder isolated a dienone[6] and the corresponding dimethoxy ketal[7] from methanolic extracts of *Verongia fistularis* and *Verongia cauliformis*. The ketal showed little antibiotic activity whereas the dienone was highly active.<sup>[31]</sup>



[7]

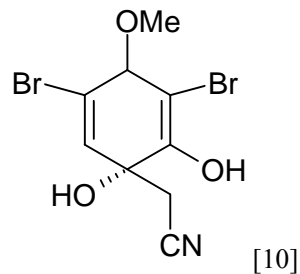
When an undescribed species of *Verongia* from the Gulf of California was extracted with ethanol, the major halogenated product was approximately 1:1 mixture of two diastereoisomer mixed ketals [8] and [9]. These compounds showed good antibiotic activity.



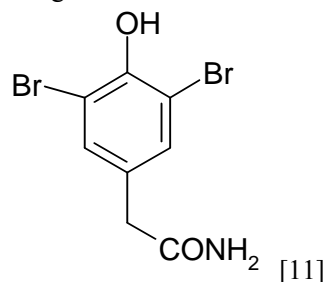
[9]

Two optical antipodes of Aerophysinin-1 [10] have been isolated from sponges. The dextro rotatory isomer (+) aerophysinin -1 was isolated from an acetone extract of *Verongia aerophoba*. The laevorotatory isomer (-) aerophysinin-1 was isolated from *Lanthella ardis*. Both enantiomers of aerophysinin -1

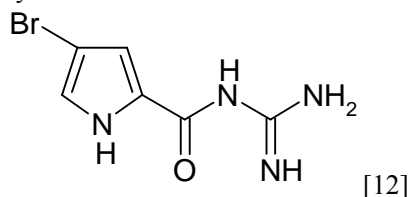
have approximately equal potency for inhibiting Gram negative and Gram positive bacteria.



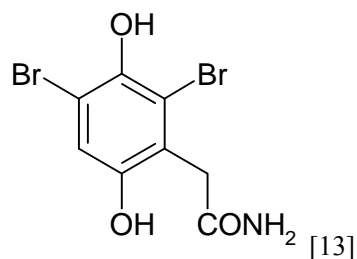
Stempien and his research team isolated 3,5-dibromo-4-hydroxyphenyl acetate [11] from *Verongia archeri*. They showed that it inhibited the growth of *E. coli*. [32]



Stempien also reported that a compound 4-bromopyrrole -2-carbonylguanidine [12] obtained from a Caribbean sponge of the *Agelas* sp. showed remarkable antimicrobial activity. [33]

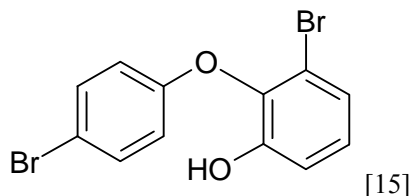
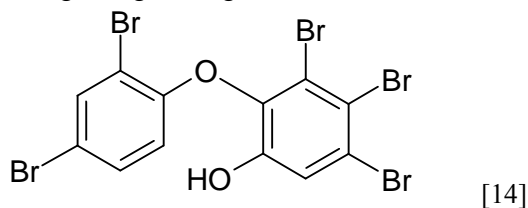


A brominated hydroquinone [13] was isolated from *Verongia aurea*. The hydroquinone which was identified by X-ray analysis inhibited the growth of *B. subtilis*, *E. coli* and *P. atroventum*.

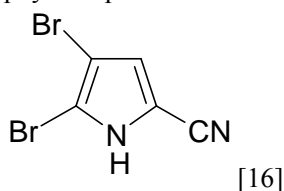


Two closely related antimicrobial agents 2-(2',4'-dibromophenoxy)-3,4,5-

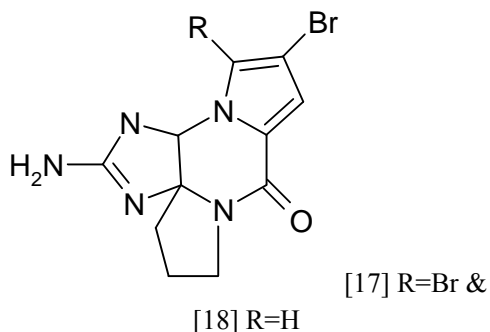
tribromophenol[14] and 2-(4'-bromophenoxy)-3-bromophenol [15] were isolated from *Dysidea herbacea* an Indonesian sponge, which showed activity against *B.subtilis* but not against gram negative bacteria.



Minale and co-workers have reported isolation of 4,5-dibromo - 2- cyanopyrrole[16]. This compound was found to be active against *Streptococcus*, *Diplococcus*, *Candida albicans* and *Trichophyton* species.<sup>[34]</sup>

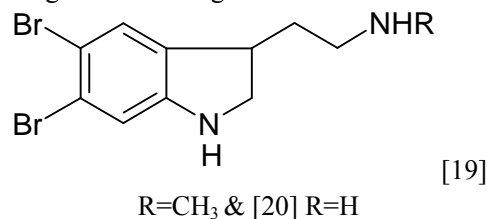


Assmann and his group of researchers isolated 4,5-dibromophakelin[17] and 4-bromophakelin[18] from *Phakellia flabellate*. These compounds were reported to exhibit a strong antibacterial action against *E. coli* and *B. subtilis*.<sup>[35]</sup>

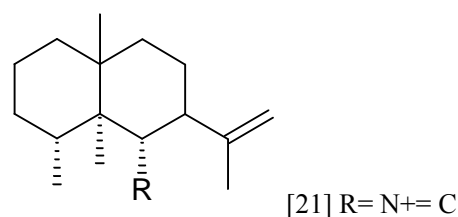


Two indole derivatives viz. 3-(2-methylaminoethyl)-5,6 dibromoindole[19] and 3-(2-aminoethyl)-5,6-dibromoindole[20] were isolated from *Polyfibrospongia maynardii*. Both these compounds inhibited Gram

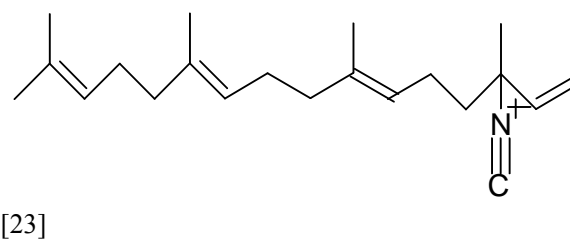
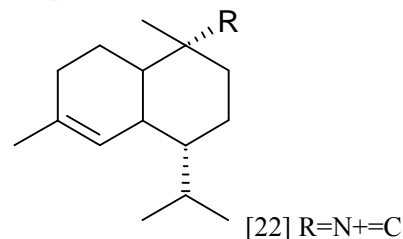
negative and Gram positive bacteria at 25-250ug/ml in in vitro assay but failed to provide protection against bacterial infection during in vivo testing.



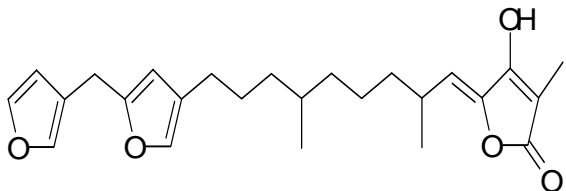
Marine sponges of the order *Halichondra* often contain terpenoid isonitriles, some of which have been reported to inhibit bacterial growth.<sup>[36]</sup> Minale isolated Acanthellin-1 [21], one such isonitrile from *Acanthella acuta* and found a Minimum Inhibitory Concentration of 12ug/ml against *Mycobacterium* sp. from this isonitrile.



Burreson and his group have shown that the antimicrobial activity of *Halichondria* species was due to the isolated mixture of two isonitriles. The two isonitriles were an amorphane derivative [22] and a linear diterpene[23].<sup>[37]</sup>

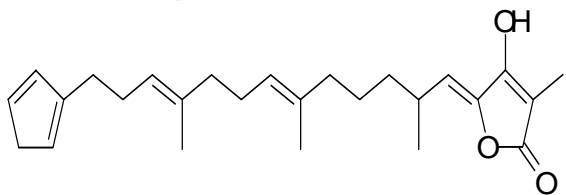


Linear sesterterpenes containing a tetronic acid moiety have quite a pronounced antimicrobial activity. *Ircinia oros* was found to contain a stereoisomeric mixture of two sesterterpenes Ircinin-1 and Ircinin-2 [24], which inhibited *Diplococcus* species and *S. aureus*.

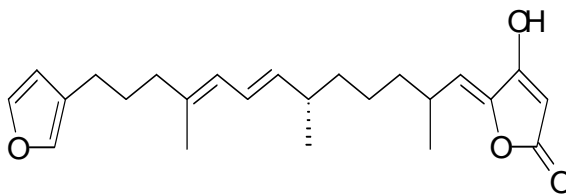


[24]

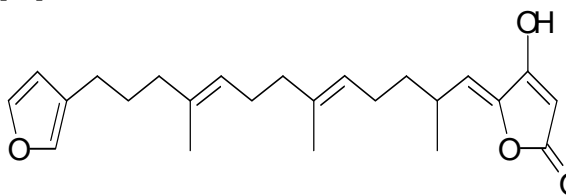
Sesterterpene tetronic acids have also been reported from *Ircinia variabilis*, *Ircinia fasciculata*, I and *Ircinia strobilina*. The structures of the compounds isolated from these sponges were determined and named as variabilin[25], fasciculatin[26] and strobilin[27] respectively.



[25]



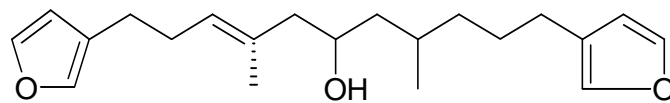
[26]



[27]

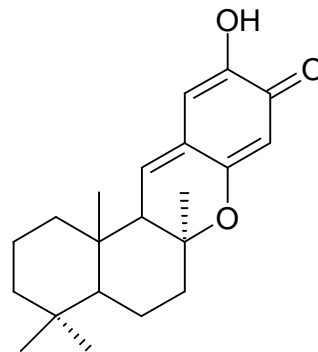
Nitenin a C21 metabolite of *Spongia nitens* has been reported to possess antimicrobial activity against *Mycobacterium* species. Furospogin-1 [28] has been isolated as a major metabolite from *Spongia officinalis*, *Hippospongia communis* and 5 Australian *Spongia* species. Furospogin has been reported to show activity at 0.5 ug/ml against

*Diplococcus* sp. and 1ug/ml against *Streptococcus* sp.<sup>[38]</sup>



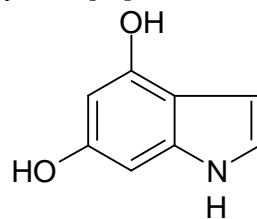
[28]

B.N. Ravi and his research group isolated an antimicrobial compound chondrosione [29] from a bright yellow sponge of the *Chondrosia* sp. Some quantitative data for in vitro antimicrobial activity was obtained and this compound exhibited good activity.<sup>[39]</sup>

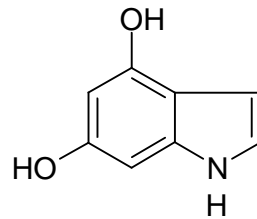


[29]

In 1966, Stempien et al reported strong antibiotic activity from a sponge of the *Agelas* species. It was found that the activity was due to the metabolites which were either 4,6-dihydroxyindole[30] or 6,7-dihydroxyindole[31].



[30]



[31]

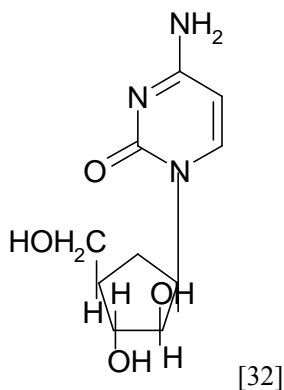
The Caribbean sponge *Agelas Conifera* was found to produce a variety of bromopyrrole alkaloids of which oroidin and sceptrin were screened by the disc diffusion assay for antibacterial activity against *E. coli* and *B.*



*subtilis*, for antifungal activity against the yeast *Saccharomyces cerevisiae*, against the opportunistic human pathogenic fungi *Absidia corymbifera* and *Absidia ramase*, against the phytopathogenic fungi *Botrytis cinerea*, *Cladosporium cucumerinum*, *Fusarium oxysporum*, *P. expansum*, *R. oryzae* and *Trichoderma horzianum*, the ubiquitous fungi *A. niger* and *Mucor pusillus*. The compounds were strongly active against bacteria and against all yeast and against only one fungus *T. horzianum*.

Several chemical studies of the *Agelas* sp. have been published reporting the presence of sceptrin, oxysceptrin, monobromosceptrin, ageilferin and glycosphingolipids. Pharmacological properties of these and similar compounds include antiviral, antihistaminic and antimuscarinic activities. Sceptrin isolated from the related species *Agelas mauritiana* was found to disrupt cell membranes of both prokaryotic and eukaryotic cells.

Ara-C[32] is 1- $\alpha$ -D-arabinofuranosylcytosine or cytosine arabinoside. It was obtained as a synthetic compound based on knowledge of naturally occurring moieties viz. spongiosine and spongouridine present in Caribbean sponges. Ara-C is used in treatment of acute myelogenous leukemia and human acute leukemia for therapeutic purposes. It is active against Erlich carcinoma, sarcoma-180 and L-210 leukemia in mice.<sup>[40]</sup>



Macquarie University, Australia researchers led by Dr. Peter Karuso have isolated a chemical AR5 from a sponge at Bondi. It

exhibits very strong toxicity against the bacteria *E. coli*, *S. aureus* and *P. aeruginosa* which indicates its potential antibiotic activity. This research is in progress.

Novel thiopeptide antibiotics YM-266183 and YM-266184 were found in the culture broth of *Bacillus cereus* QNO3223 which was isolated from the marine sponge *Halichondria japonica*. These antibiotics exhibited potent antibacterial activities against Staphylococci and Enterococci including multiple drug resistant strains whereas they were inactive against Gram negative bacteria. This work was done by Nagai, Kamigiri et al of Institute of Drug Discovery Research, Japan.<sup>[41]</sup>

*Dendrilla membranosa* is among the few Antarctic sponges known to produce terpenes. Most potent biological activity is associated with alkaloids from *D. membranosa* such as a yellow isoquinolone pigment which has antibiotic activity and picolinic acid which has tube foot retraction activity.<sup>[42]</sup> Discorhabdin C, from the sponge *Latrunculia apicalis*<sup>[43]</sup> (Yang et al., 1995) and the pigment from the sponge *Dendrilla membranosa*, proved to be the most active antimicrobial compounds. Researchers at the Mc Murdo Sound benthos station have shown that select sponge metabolites<sup>[43]</sup> (Yang et al., 1995) and associated bacteria can inhibit water-column and sponge-derived microorganisms<sup>[44]</sup> (Thornton, 1995). The bright red sponge *Kirkpatrickia variolosa* produces the unusual variolin alkaloids such as variolin A, B and its analogue, deoxyvariolin B which was shown to have cyclin-dependent kinase inhibitor activity.<sup>[45]</sup>

*Suberites* sp. is a common Mcmurdo Sound Benthos sponge that has a muted yellow colour. Suberitenones A and B originally discovered from King George Island were isolated from the Mcmurdo collection of sponges. Suberitenones were active in both the tube foot retraction assay and the antibiotic assay.<sup>[46]</sup> (Amser et al., 2001).

Dr. Alejandro Mayer discovered that the marine chemical menzamine A extracted from

a marine sponge of the *Haliclona* sp. inhibits mediator formation in microglia isolated from newborn rats without killing healthy cells.<sup>[47]</sup>

Researchers from University of Queensland, Australia discovered *Salinospora* strains of actinobacteria which produce compounds of the Rifamycin class including Rifamycin B and Rifamycin SV.<sup>[48]</sup>

Sponge metabolites that have exhibited significant anti-HIV activity using various biochemical assays designed for chemotherapeutic strategies are avarol, avarone, ilimaquinone and several phloroglunicols.<sup>[49]</sup> (Maurer et al., 2003).

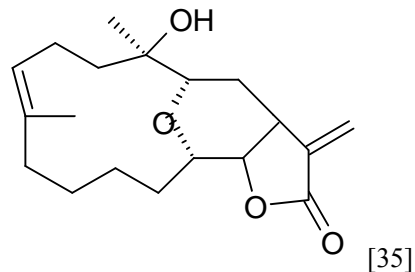
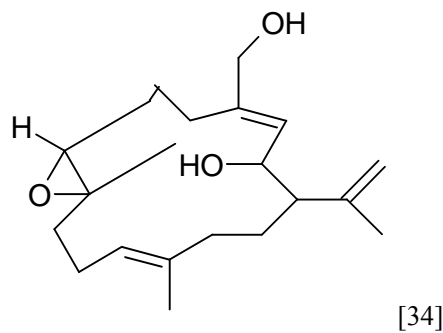
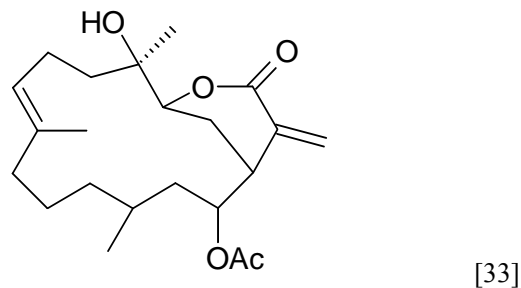
#### ANTIBIOTICS FROM COELENTERATES

The coelenterates are a group of invertebrates which include hydroids, sea anemones jelly fish, soft corals, stony corals, gorgonians and sea pens. The majority of marine natural product research has been concerned with Caribbean gorgonians and Indo-Pacific soft corals. Gorgonians:-

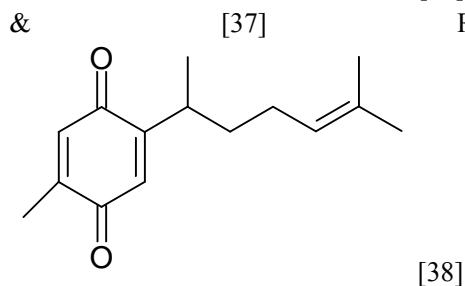
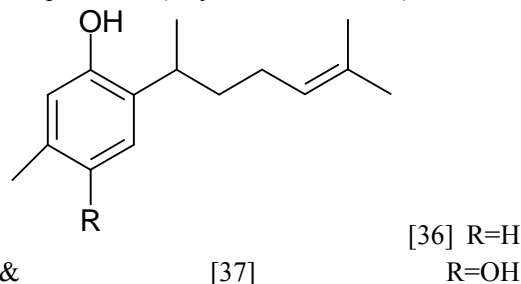
The gorgonians have yielded a series of diterpenoid d-methyl lactones which were described as mildly antibiotic.<sup>[50]</sup>

Crassin acetate [33] which may be isolated from *Pseudoplexauva porosa*, *P. flagellosa* and *P. wagnaari* was active against *Entamoeba histolytica* at 20ug/ml.<sup>[51]</sup>

Asperdiol[34] isolated from *Eunicea asperula* and *E. toumeforti* showed anticancer activity against *Klebsiella* (24ug/ml), *Pseudomonas* (6ug/ml) and LE (6ug/ml) cell lines in vitro. Eunicin [35] isolated from *E. mammosa* was reported to inhibit the growth of *S. aureus* and *C. fesi*.

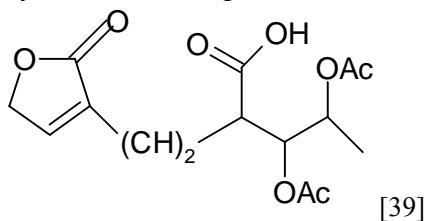


The sesquiterpene fraction of *Pseudopterogorgia rigida* contained a phenol [36], a hydroquinone [37] and a quinone[38], all of which showed mild antibiotic activity. The phenol inhibited the growth of *S. aureus* at 7ug/disc and was the most active compound.<sup>[52]</sup> (Haydelba et al., 2000).



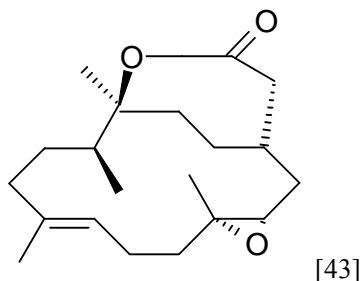
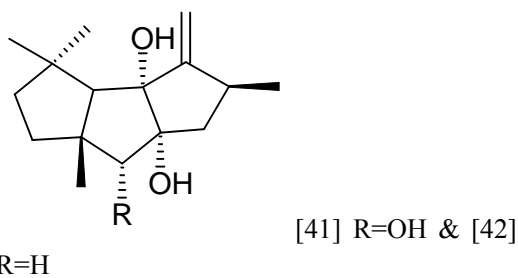
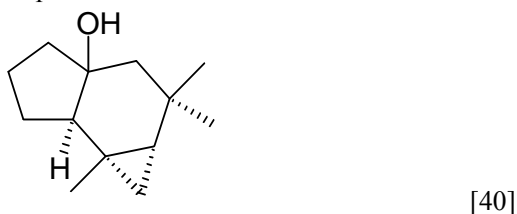
[38]

The gorgonian *Pterogorgia guadalupensis* contains a lactone [39] which exhibited mild antibiotic activity against *S. aureus* and *Mycobacterium smegmatis*.



#### SOFT CORALS:-

The chemistry and biological activity of soft corals has been reviewed by Tursch and his group. Africanol[40] from *Lemnalia africana*, capnellenes[41],[42] from *Capnella imbricata* and sinularioidide [43] from *Sinularia flexibilis* have shown to inhibit the growth of unicellular algae *Chaetoceros septentrionalis*, *Asterionella japonica*, *Thaalisioscira excentricus*, *Procentrum micans* and *Amphidinium carterae*.<sup>[53]</sup>

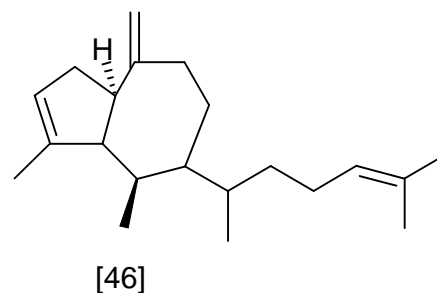
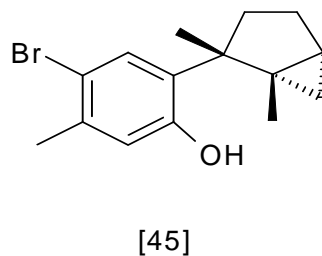


#### ANTIBIOTICS FROM MOLLUSCS

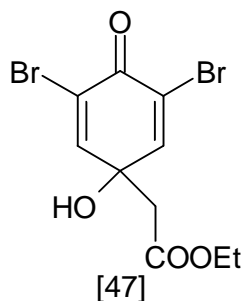
The marine natural products chemistry of molluscs has been directed almost exclusively towards the opisthobranch molluscs such as

sea hares and nudibranchs.<sup>[54]</sup> Their chemical constituents are predominantly dietary in origin. The chemical constituents of the California sea hare *Aplysia californica* are derived from red algae such as *Plocamium* and *Laurencia* species which form a major portion of the sea hare's diet. Extract of the digestive gland of *A. californica* inhibited the growth of marine and terrestrial bacteria due to the presence of laurinterol[45]. This work was carried out by Stallard and Faulkner of California.

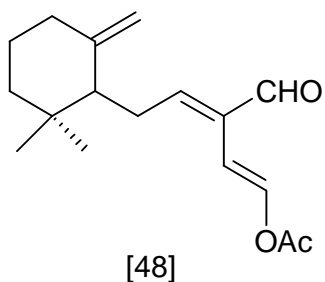
Another California sea hare *Aplysia vaccaria* was shown to yield the mild antibiotic diterpenoid pachydietylol A [46] by Faulkner and Vanderah. It appears that *A. vaccaria* concentrates this diterpenoid by grazing on the brown alga *Pachydietyon coriaceum* or on various related *Dictyota* species known to contain pachydietylol A.



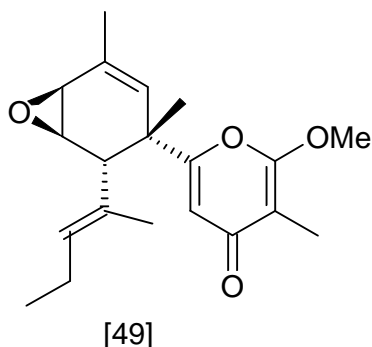
The opisthobranch mollusc *Tylodina fungina* lives exclusively on sponges of the genus *Verongia*. Ethanolic extracts of *T. fungina* contained a dienone ester[47] which inhibited the growth of *S. aureus* and *E. coli*.



When irritated, the opstibranch molluscs *Onchidella binneyi* secreted a white mucus containing an antibiotic substance. This antimicrobial compound was identified to be onchidal [48] which inhibited the growth of *S. aureus*.

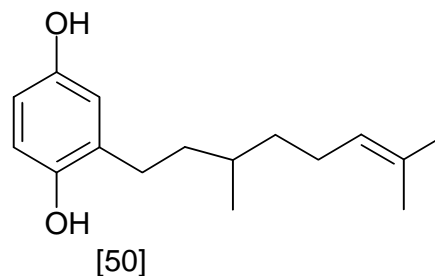


The saccoglossan *Tridachiella diomedea* was found to contain two closely related compounds one of which showed good antibiotic activity against *Vibrio anguillarum*, the structure of which is given below.



#### ANTIBIOTICS FROM TUNICATES

Fenical found that a tunicate of the genus *Aplidium* contained large quantities of geranyl hydroquinone [50]. It has been subsequently found to inhibit the growth of *S. aureus* and *Candida albicans*.<sup>[55]</sup>



Dr. D.J. Faulkner (University of California, San Diego) has reported isolation of 6-bromotryptamine from a Californian tunicate *Didemnum candidum*.<sup>[56]</sup> Similarly, scientists from Japan have isolated cystadytins with cytotoxic activity from the marine tunicate *Cystodytes dellechiaiei*. The tunicates *Eudistoma olivaceum* and *Riterella sigllinoides* have also been known to give eudistomins which are potent inhibitors of Gram positive bacteria.<sup>[57]</sup>

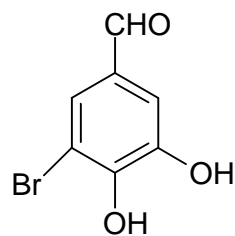
Robert Lehrer (UCLA, USA) and Steve Taylor (Amylin Pharmaceuticals, USA) elucidated the structures of antimicrobial peptides from the tunicates (sea squirts) *Styela clava*, *Styela plicata* and *Ciona intestinalis*. Plicatamide, a small peptide isolated from the blood cells of *S. plicata* is composed of only eight amino acids making it one of the smallest antimicrobial peptides found to date. Plicatamide was observed to have excellent activity against methicillin resistant *Staphylococcus aureus* and appeared to kill this important human pathogen in an unusual manner. *S. clava*, a solitary tunicate yielded the peptides- clavanins A,B,C,D. These peptides contain 23 amino acid residues, are histidine rich and are C-terminally aminated. Clavanin A displayed antimicrobial activity against *E. coli*, *Listeria monocytogens* and *C. albicans* with a vigor related to pH. There is an additional member in this family called clavaspurin. Unlike clavanins A-D, clavaspurin had potent cytotoxic and also unfortunately hemolytic activity. Clavaspurin, as a non-specific killer in the immune system is not a promising drug candidate.

Two antimicrobial peptides from the ascidian *C. intestinalis* were isolated, characterized and designated as cionarin H and cionarin I. These peptides have many characteristics in common with large molecular weight polypeptides and proteins isolated from ascidian blood cells including ferreascidin, the *Ascidia* and *Mogula* blood cell polypeptides and morulin Pm isolated from the sea squirt *Phallusia mammillata*. This work was an important milestone according to Taylor, because these unusual peptides might be used as a template for a more stable peptide antibiotic. The fact that these compounds are gene-coded opens the possibility of engineering drugs with desirable traits, using the genes in tunicates as a starting point.<sup>[58]</sup>

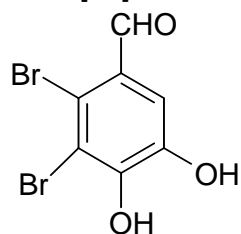
#### ANTIBIOTICS FROM ALGAE

The isolation and identification of antibiotics from algae has proceeded more rapidly than similar studies on invertebrates. Most, if not all, species of *Polysiphonia* (red algae) contain brominated phenols which are responsible for antibacterial activity.

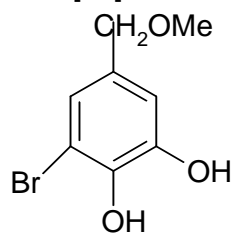
In 1955, Saito and Anto described the isolation of 5-bromo-3,4-dihydroxybenzaldehyde [51] from *Polysiphonia morrowii*. In 1966, Katsui isolated 2,3-dibromo-4,5-dihydroxybenzaldehyde [52] and 2,3-dibromo-4,5-dihydroxy-1'-methoxytoluene [53] from *Rhodomela larix*.



[51]

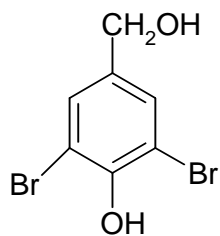


[52]

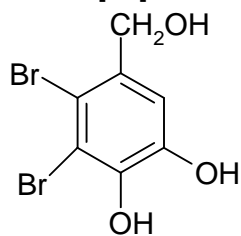


[53]

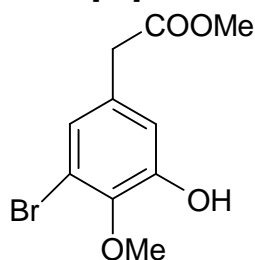
Craigie and Greunig identified 3,5-dibromo-4-hydroxybenzylalcohol [54] in both *Odonthalia dentata* and *Rhodomela confervoides*. Kurata et al have extracted and identified 2,3-dibromo-4,5-dihydroxybenzyl alcohol [55] from the red alga *Rhodomela confervoides*. Examination of the red alga *Halopytis incurvus* resulted in isolation of methyl-3,5-dibromo-4-methoxyphenylacetate [56] and methyl-3,5-dibromo-2',4-dimethoxycinnamate [57].



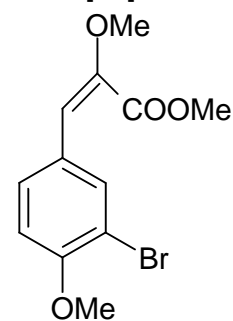
[54]



[55]



[56]



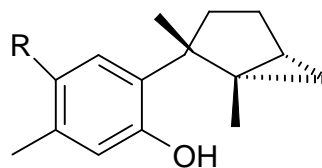
[57]

The antibacterial activities of all these compounds against *B. subtilis*, *E. coli*, *Sarcina pelagia*, *Sarratia marinoruba* and *Vibrio phytoplankton* have been reported and found to be potent.

Red algae of the genus *Laurencia* contain sesquiterpene phenols and brominated phenols as their antibiotic metabolites. Laurinterol [45] and debromolaurinterol [58] were first isolated from *Laurencia intermedia* and have subsequently been isolated from *L. nipponica*, *L. okamurai*, *L. pacifica* and *L. johnstonii*.

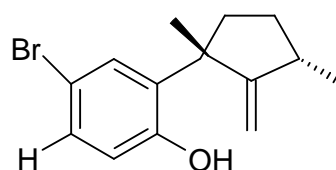
Both inhibit *S. aureus*, *M. smegmatis* and *C. albicans*. Laurinterol is more active than debromolaurinterol against *S. aureus* and *M. smegmatis* but neither inhibit *E. coli* or *Salmonella choleraesius*.<sup>[59]</sup>

Isolaurinterol [59] was found in *L. intermedia*. 7-hydroxy-laurene [60] was found to be the major antimicrobial metabolite of *L. subopposita*, while 10-bromo-7-hydroxy-laurene [61] was found to be the constituent *L. filliformis* and a minor metabolite of *L. subopposita*.<sup>[60]</sup>

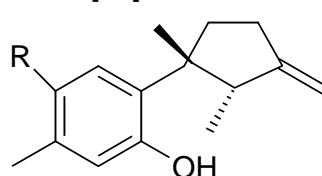


[45] R= Br

[58] R= H



[59]

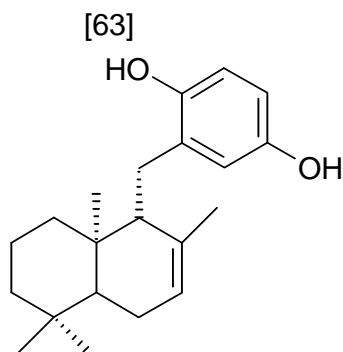
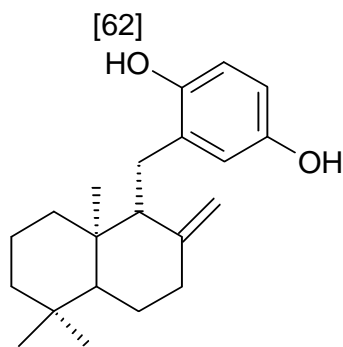
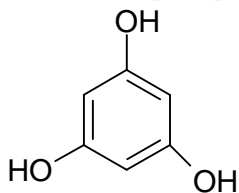


[60] R= H

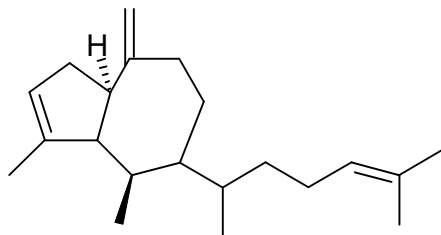
[61] R =Br

Many brown algae which are shown to inhibit bacterial growth contain polyphenolic compounds. Brown algae have been studied by Craigie in Canada and Glombitza in Germany. The polyphenol found was phloroglucinol [62]. Two fungitoxic hydroquinones zonarol [63] and isozonarol [64] were isolated from brown alga *Dictyopteris zonaroides*.<sup>[61]</sup> Both compounds inhibited the growth of *Phytophthora cinnamoni*, *Rhizoctonia solani*,

Sclerotinia sclerotiorum and Sclerotium rolffii which are all plant pathogenic fungi.

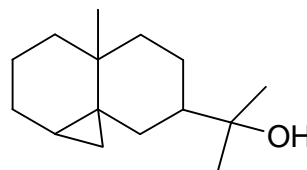


[64]  
Pachydictol A [46] isolated from the brown alga Pachydicton coriaceum was found to have mild antibiotic activity against *S. aureus*.



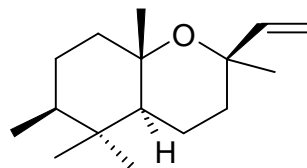
[46]  
The sesquiterpene cycloeudesmol [65] was isolated from *Chondria oppositoclada*. Cycloeudesmol inhibited the growth of *S. aureus* (10-50 ug/ml), *Mycobacterium*

*smegmatis* (10-50ug/ml) and *Candida albicans* (10-50 ug/ml)<sup>[62]</sup>

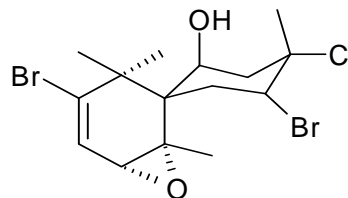


[65]

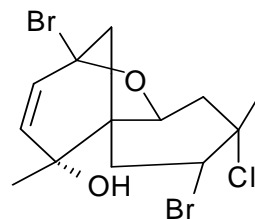
3 B - Bromo-8-epicaparrapi oxide [66] obtained from *Laurencia obtusa* was mildly active against *S. aureus*. Prepacifenol [67], a metabolite of *L. filiformis* and the precursor of Pacifenol [68] found in *L. pacifica* inhibited the growth of *S. aureus* (10-100 ug/ml) and *M. smegmatis*.



[66]

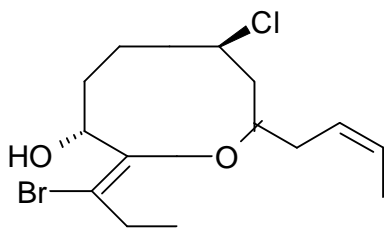


[67]



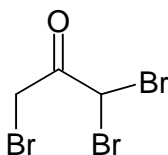
[68]

Chondriol [69] exhibited antiviral and mild antibacterial activity against *S. aureus* and *M. smegmatis*. Chondriol was isolated from a red alga originally identified as *Chondria oppositoclada* but later known as *Laurencia yamada*.<sup>[58]</sup>

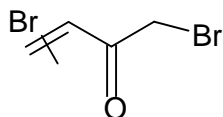


[69]

Fenical obtained seven polyhalogenated acetones and four polyhalogenated 3-buten-2-ones from chloroform extract of *Asparagopsis taxiformis* with 1,1,3-tribromoacetone [70] and tribromo-3-buten-2-one [71] as the major constituents.

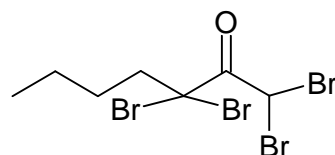


[70]

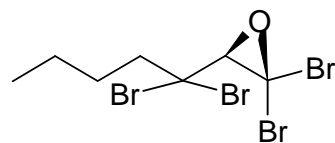


[71]

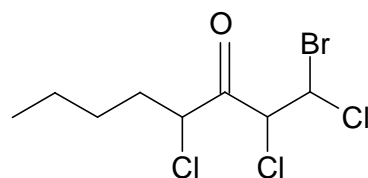
The major metabolite of *Bonnemaisonia hamifera* was shown to be 1,1,3,3-tetrabromo-2-heptanone [72] which inhibited the growth of *B. subtilis* and showed low activity against *S. cervisiae* and *P. atroventum*. The major metabolite of *Bonnemaisonia nooktana* was found to be the epoxide [73]. *Bonnemaisonia asparagoides*, *Delisia fimbriata* and *Ptilonia australasica* were all shown to contain polyhalogenated 1-octen-3-ones. The major constituent of *B. asparagoides* was E-1-bromo-1,3,4-trichloro-1-octen-3-one [74] which showed potent activity against *S. aureus*.



[72]

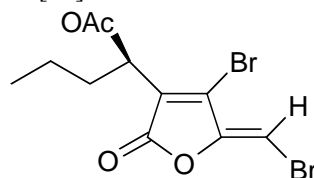


[73]

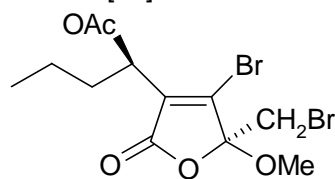


[74]

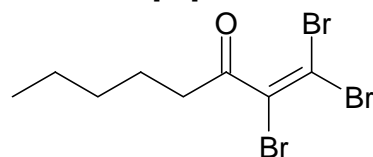
Two groups have reported that the antibiotic activity of *Delisia fimbriata* could be traced to a mixture of lactones called fimbrolides. The structures are given as [75] and [76]. *Delisia fimbriata* contains 1,1,2-tribromo-1-octen-3-one [77] which shows antifungal activity.



[75]



[76]

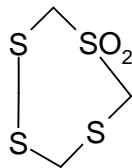


[77]

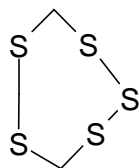
Acrylic acid was detected in *Phaeocystis pouchetti* which is an organism responsible for



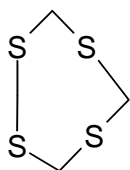
phytoplankton bloom in Antarctica. Transfer through marine food chain to the Antarctic penguin was shown to be the cause of the antibacterial activity in the GIT of the penguin.<sup>[58]</sup> The sulphur content of a number of marine algae was determined, but only one brown alga *Chordaria flagelliformis* contained a significant quantity of sulphur.



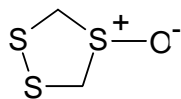
[78]



[79]



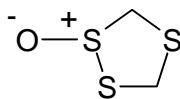
[80]



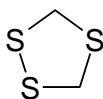
[81]

The major sulphur containing constituent of *C. californica* was the sulphone [78] which was also an effective antimicrobial agent. This sulphone inhibited the growth of *Vibrio anguillarum*, *Proteus mirabilis*, *Salmonella typhimurium* and *E. coli* at 10ug/ml.

Lenthionine [79] and 1,2,4,6 – tetrathiepane [80] have also been found to be present in marine algae. These compounds have previously been found in the mushroom *Lenthinus endodes*. Two related sulphoxides [81] and [82] which could be synthesized from 1,2,4-trithilane [83] were also found to be mildly antibiotic.



[82]

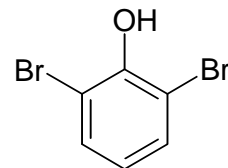


[83]

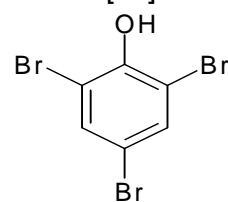
#### ANTIBIOTICS FROM WORMS

There are relatively few reports of chemical constituents of worms, but of these few studies all report the isolation of brominated phenols. Brominated phenols are best considered as antiseptic compounds but their use in internal

medicine is restricted as their antifungal and antibacterial properties are coupled with toxicity. Ashworth and Cormier isolated 2,6-dibromophenol [84] from the Hemichordate *Balanoglossus biminiensis*.<sup>[59]</sup> Both 2,6 – dibromophenol and 2,4,6 –tribromophenol [85] were subsequently isolated from a mud dwelling tube worm *Phoronopsis viridis*.

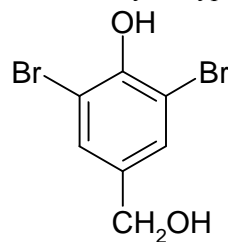


[84]

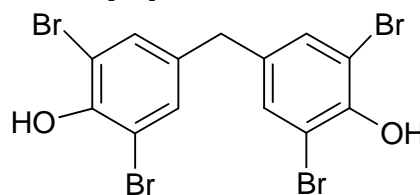


[85]

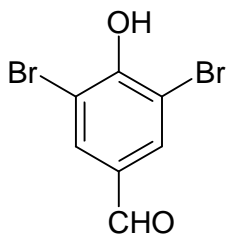
The marine anelide *Thelepus setosus* was shown to contain 3,5-dibromo-4-hydroxybenzylalcohol [86] and bis-(3,5-dibromo-4-hydroxyphenyl) methane [87]



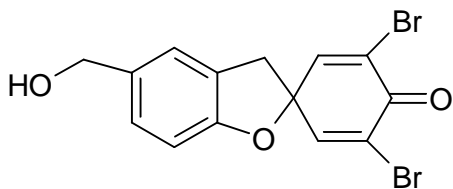
[86]



[87]

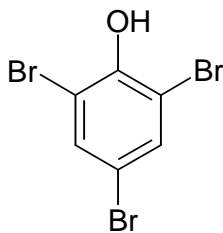


[88]

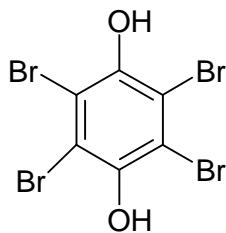


[89]

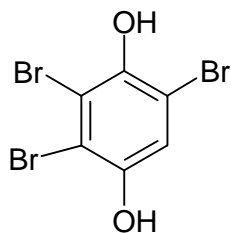
All are brominated phenols except thelepin [89] which resembles griseofulvin in both structure and antifungal activity (Fusetani et al., 1998). Higa and Scheuer have isolated 2,4,6 tribromophenol [90] from the Hemichordate *Phycodera flava laysanica*, together with tetrabromohydroquinone [91] and tribromohydroquinone [92]. Work on determination of their antibiotic activity is in progress.<sup>[60]</sup>



[90]



[91]



[92]

Newer compounds could be isolated from the following classes of worms: - Annelida (segmented worms), Sipunculida (peanut worms), Platyhelminthes (flat worms),

Nemertinea (ribbon worms), Enteropneusta (acorn worms).

### LIMITATIONS

A serious problem with regard to drug development and sustainable production that occurs with marine sponges, tunicates and other chemically interesting invertebrates lies in the limited amounts of biomass of most marine invertebrates available from wild stocks. Thus, most pharmacologically active marine natural products can only be isolated in minute yields (Rouhi, 1995). Total synthesis of pharmacologically active natural products has been successfully established but is in many cases economically not feasible due to the complexity of the molecular structures and the low yields.<sup>[61]</sup>

Many pharmacologically interesting marine natural products such as ecteinascidin 743 (ET-743) from the tunicate *Ecteinascidia turbinata*, the halichondrins from the *Lissodendoryx* sponges or the bryostatins from the bryozoan *Bugula neritina*, all of which are presently under clinical evaluation or candidates for clinical trials can be isolated only in minute yields.<sup>[62]</sup>

For example, in order to obtain approximately 1 g of the promising anti-cancer agent ET-743, close to 1 metric tonne (wet weight) of *E. turbinata* has to be collected and extracted. Based on these extremely low yields, clinical trials with patients are already a formidable challenge not to speak of the supply problem that will have to be met once a compound makes it to the market as a drug.<sup>[63]</sup> (Proksch et al., 2003).

The useful drugs in these organisms rarely constitute more than a fraction of 1% by weight and typically several kilogram of dried material are required for further extraction. Also, seasonal dependence of bioactivity has been noted in several instances. The potency of drugs depends on source material as well as locale, season, depth and species.<sup>[64]</sup>

### CONCLUSION

The oceans continue to provide new opportunities for the discovery of marine-

derived medicines. Increased sophistication in the tools available to explore the deep seas has expanded the habitats that can be sampled and has greatly improved the opportunities for discovery of new species and the chemical compounds they produce. Recent advances in biosynthetic pathway discoveries from these symbiotic bacteria herald a new era in which biosynthetic genes will be cloned rapidly to provide promising molecules from marine invertebrates.

Marine organisms, in relatively shallow waters near the shores, can be collected by scuba diving. This is being practiced in nearly every coastal country whether rich or poor. The more developed among them are now in the process of expanding their undersea programmes and use submersibles to collect marine plants and animals.<sup>[65]</sup>

Many interesting marine natural products with promising pharmacological properties are being developed and will continue to play an important role in studying biochemical events and unraveling their role in cell regulation.

There needs to be extensive collaborations between chemists and pharmacologists so that these sources meet their full potential and become good candidates for laboratory culture. The future promises heterologous expression of important marine natural products through manageable microbial fermentation.<sup>[66]</sup>

#### REFERENCES:

- 1) Surajit Das, P.S. Lyla, S. Ajmal Khan Marine Microbial Diversity And Ecology, Current Science, 2006 90 :1325-1332.
- 2) Ellis, R. 2001 Aquagenesis. The origin and evolution of life in the sea; Viking Eds.: New York,
- 3) Kerr, R. G.; Kerr, S. S. 1999 : Marine natural products as therapeutic agents. 9 : 1207-1222.
- 4) Newman, D. J.; Cragg, G. M.; Snader, K. M 2000: . The influence of natural products upon drug discovery. Nat. Prod. Rep. 17 : 215-234.
- 5) Sharma C ,OhjaSK, 2005 : Recent Status Of Drugs obtained from marine sources, Pharma times 37: 24-28.
- 6) Argulis, L., Schwartz, K. Five Kingdoms, an illustrated guide to the phyla of life on Earth, 16-17.
- 7) Burkholder B R , Pfister R M , Leity F M , 1966 Applied Microbiology 14 : 646.
- 8) Okami Y, Okazaki T, Kitahara T, Umezawa H. 1976. Studies on marine microorganisms. V. A new antibiotic, aplasmomycin, produced by a streptomycete isolated from shallow sea mud. : J Antibiot (Tokyo) 29(10): 1019-25.
- 9) Baumann, P., Gauthier, M, Baumann L , 1972, : Genus *Alteromonas rubra* , J Syst Bacteriol 48:247-256.
- 10) Gauthier MJ. 1976a. *Alteromonas rubra* sp. Nov., a New Marine Antibiotic-Producing Bacterium. International Journal of Systematic Bacteriology. 26(4):459-466.
- 11) Gauthier MJ. 1976b. Modification of bacterial respiration by a polyanionic antibiotic produced by a marine *Alteromonas*. Antimicrob. Agents Chemother. 9:361-366.
- 12) Imamura N, Nishijima M, Takadera T, Adachi K , Sakai M, San 1997 : New anticancer antibiotics pelagiomicins produced by marine bacterium *Pelagiobacter variabilis* Journal Of Antibiotics, 45 : 769-783.
- 13) Missing References
- 14) Acebal C, Alcazar R, Canedo LM, Calle F, Rodriguez P, Fernandez R, Puentes JL. 1998. Two marine *Agrobacterium* producers of sesbanimide antibiotics. J Antibiot 51(1):64-67.
- 15) Biabani M, Flaatsch H.; Helmke , Weyland H 1997.  $\delta$ -Indomycinone : A new member of pluramycin class of antibiotics isolated from marine *Streptomyces* sp, Journal of antibiotics 50 : 874-877.
- 16) Brinkhoff T , Bach G , Heidorn T , Liang L, Holler U, König G , Wright A . 1997 : Two New Sesterterpene Tetrone Acids from the Marine Sponge *Ircinia oros* J. Nat. Prod 60 :832 -835.
- 17) Kwon HC, Kauffman CA, Jensen PR, Fenical W- 2006 : Marinomycins A-D, antitumor antibiotics of a new structure class from a marine actinomycete of the

- recently discovered genus *marinispora* J. Am. Chem. Soc., 1281: 622–1632.
- 18) Acebal C, Canedo L M, Fernandez Puentes J L P, Baz P, Romero. 1999: Agrochelin, a new cytotoxic antibiotic from a marine *Agrobacterium* taxonomy, fermentation, isolation, physico-chemical properties and biological activity, *Journal of antibiotics* 52: 983-987
- 19) Yoshikawa K, Takadera T, Adachi K, Nishijima M, Sano H- Korormicin, 1997 : a novel antibiotic specifically active against marine gram-negative bacteria, produced by a marine bacterium 50 : 949-953
- 20) John Stroncek 2007: Relationship Between Gene Expression and Cell metabolism in the marine Bacterium *Streptomyces tenjimariensis*, *JYI*, 16.
- 21) Saha M, Ghosh D, Garai D, Jaisankar P, Sarkar K K, Dutta P. K, Das S, Jha T, Mukherjee J 2005 : Studies on the production and purification of an antimicrobial compound and taxonomy of the producer isolated from the marine environment of the sundarbans *Applied microbiology and biotechnology* 66 : 497-505.
- 22) Needham J, Kelly M. T, Ishige M, Andersen R. J Andrimid 1994 : moiramides A-C, metabolites produced in culture by a marine isolate of the bacterium *Pseudomonas fluorescens* : structure elucidation and biosynthesis, *Journal of organic chemistry*, 59: 2058-2063.
- 23) Maskey RP, LiF Qin S, Fiebig HH, Laatsch H 2003: Chandranimycins A approximately C : production of novel anticancer antibiotics from a marine *Actinomadura* sp. Isolate MO48 by variation of medium composition and growth conditions *Journal of Antibiotics*.
- 24) Maskey RP, Helmke E, Laatsch H 2003: Himalomycin A and B: isolation and structure elucidation of new fridamycin type antibiotics from a marine streptomyces isolate *Journal of Antibiotics*.
- 25) Isansetyo A, Kamei Y. 2003: *Pseudoalteromonas phenolica* sp.nov. a novel marine bacterium that produces phenolic anti-methicillin resistant *Staphylococcus aureus* substances, *Int J Syst Evol Microbiol* 53: 583-588.
- 26) Isnansetyo A, Kamei Y .2003:MC21-A, a bactericidal antibiotic produced by a new marine bacterium, *Pseudoalteromonas phenolica* sp. nov. O-BC30(T), against methicillin-resistant *Staphylococcus aureus* *Antimicrobial Agents Chemotherapy* 47: 480-488.
- 27) Pusecker K, Laatsch H, Helmke E, Weyland H.1997 : Dihydrophencomycin methyl ester, a new phenazine derivative from a marine Streptomyce. *Journal Of Antibiotics* 50:479-483.
- 28) Shiozawa H, Kagasaki T, Torikata A, Tanaka N, Fujimoto K., Hata T, Furukawa Y, : *J Antibiot (Tokyo)*. 1995 Aug;48(8):907-9.
- 29) Shiozawa H, Shimada A, Takahashi S. *Journal of antibiotics (J. antibiot.)* 1997;50(5): 449-452.
- 30) Shiozawa H, Kagasaki T, Kinoshita T, Haruyama H, Domon H, Utsui Y, et al., Thiomarinol, a new hybrid antimicrobial antibiotic produced by a marine bacterium. Fermentation, isolation, structure, and antimicrobial activity. *J Antibiot (Tokyo)*. 1993 Dec;46(12):1834-42
- 31) Sharma G M, Burkholder, 1967 : *Tetrahedron Lett.* 4147-4150.
- 32) Chib JS, Stempien MF Jr, Mierzwa RA, Ruggieri GD, Nigrelli RF. 1978 : Physiologically active substances from marine sponges V: Isolation of physiologically active compounds from the sponge *Verongia archeri* *J Pharm Sci.*, 67:264-5.
- 33) Stempien M F, Chib JS, Nigrelli RF, Mierzwa RA in *Proceedings, Food Drugs from the sea conference Marine technology Society Washington* 105, 1973.
- 34) Minale L, Fattorusso J, Sodano G, 1987: Antimicrobial activities of marine sponges from the Mediterranean Sea, *Marine Biology*, 94.

- 35) Assmann M, Kock M. 2002: Monobromoisophakellin, a new bromopyrrole alkaloid from the Caribbean sponge *Agelas* sp., 57:153-156.
- 36) Bergmann, W., Feeney, R. 1951: Contribution to the study of marine sponges. The nucleosides of sponges., *J. Org. Chem.* 16: 981-987.
- 37) Hart, J. B.; Lill, R. E.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G 2000: The halichondrins: Chemistry, biology, supply and delivery. In *Drugs from the sea* 134-153.
- 38) Anderson AP, Beveridge AA, Capon R. 1994: Pharmacological properties of the natural marine product furospongins, *Clin Exp Pharmacol Physiol.* 21: 945-953.
- 39) Ravi B N , 1976 , PhD Thesis University Of Hawaii.
- 40) Jimeno J , Faircloth G , Fernández JM, Faro S, Scheuer P , Rinehart K 2004: New Marine Derived Anticancer Therapeutics – A Journey from the Sea to Clinical Trials, *Mar. Drugs* 2: 14-29.
- 41) Nagai K, Kamigiri K , Arao N, Suzumura K, Kawano Y , Yamaoka M, Zhang H., Proksch P , RuAngelie , Ebel E, Ebel R 2003 : *Drugs from the Sea - Opportunities and Obstacles* *Mar. Drugs* 1: 5-17.
- 42) Baker, B.J., R.W. Kopitzke, W.Y. Yoshida and J.B. McClintock. 1995. Chemical and ecological studies of the antarctic sponge *Dendrilla membranosa*. *J. Nat. Prod.* 58, 1459-1462.
- 43) Ankisetty S, Amsler CD, McClintock JB, Baker BJ 2004: Further membranolid diterpenes from the antarctic sponge *dendrilla membranosa* , *J Nat Prod.* 67:1172-1174.
- 44) Mayer A. 2000 Neuroinflammation, Finding A Marine Natural Product That Targets Microglia In Brain.
- 45) Kim K T , Hewavitharana A, Shaw N, John 2006 : A Discovery Of a New Source of Rifamycin Antibiotics in Marine Sponge Actinobacteria by Phylogenetic Distribution Fuerst School Of Molecular and Microbial Sciences, *Appl Environ Microbiol.*
- 46) Cimino, G.; De Rosa S.; De Stefano S 1984: Antiviral agents from a gorgonian *Eunicella cavolini*; one previously found in the sponge *Cryptotehya crypta*. *Experientia* 40:339-340..
- 47) Weinheimer AJ, Matson JA 1975: Crassin acetate, the principal antineoplastic agent in four gorgonians of the *Pseudoplexaura* genus.. *Lloydia.* 38: 378-82.
- 48) Kaisin M, Braekman JC , Daloze D , Tursch B 1985 Novel acetoxy capnellenes from the alcyonacean *Capnella imbricata*. *Tetrahedron* 41 :1067-1072.
- 49) Yamada, K, Okija, M., Kigoshi, H.; Suenaga, K 2000 : Cytotoxic Substances from Opisthobranch Molluscs: In *Drugs From The Sea*; Fusetani, N., Ed.; Karger AG: Basel, 59-73.
- 50) Fahy E, Potts B, Faulkner D J, Smith 1991: 6-bromotryptamine derivatives from the Gulf Of Californian tunicate *Didemnum candidum* *J Nat Products* 54 :564-569.
- 51) Hay M, Fenical W, Gustafson K 2000: Chemical Defense Against Diverse Coral-Reef Herbivores *Ecology*: 68 : 1581–1591.
- 52) Hudson J B , Abramozskwi N, Rinehart 1988 : The photoactive antimicrobial properties of eudistomins from the caribbean tunicate *Eudistoma olivaceum* photochemistry and photobiology, *Photochem. Photobiol.* 47 : 377-381.
- 53) Robert I Lehrer 2004 : Novel, Post – Translationally modified Peptide Antibiotics from solitary tunicates.
- 54) Irie T, Suzuki M, Kurosawa, E, Masamune T, 1966: Laurinterol and Debromolaurinterol, Constituents from *Laurencia intermedia*. *Tetrahedron Lett.* 1837-1840.
- 55) Irie T, Suzuki M., Kurosawa E, Masamune T 1970 : Laurinterol, Debromolaurinterol and Isolaurinterol, Constituents of *Laurencia intermedia* Yamada. *Tetrahedron* 26 :3271-3277.
- 56) Fenical W, Sims JJ, Squatrito D, Wing RM, Radlick P 1973 Zonarol and isozonarol, fungitoxic hydroquinones from the brown

seaweed *Dictyopteris zonarioides.*, J Org Chem. 29 :2383-2386.

57) Sims, J Mark S. Donnell, John V, Leary, Lacy G Antimicrobial Agents from Marine Algae Chemother. 1975 7: 320–321

58) Caccamese, S, Compagnini, A., Toscano R.M, 1986 : Pacifenol from the Mediterranean red alga *Laurencia majuscula.*, J-Nat-Prod. 49 : 173-174.

59) Virtue P, Nichols P D, Nicol S, Mcminn A, Sikes E L 1993 : The lipid composition of *Euphausia superba* Dana in relation to the nutritional value of *Phaeocystis pouchetii* (Hariot) Lagerheim Antarctic science 5: 169-177.

60) Raymond B. Ashworth, Milton J. Cormier 1967: Isolation of 2,6-Dibromophenol from the Marine Hemichordate, Science, 155 : 1558 – 1559

61) Higa, T., Scheuer, P.J 1975: Constituents of the hemichordate

*Ptychodera flava laysanica.* Marine Natural Products Chemistry 35-43.

62) Kerr, R. G. 2000 : Biosynthesis of bioactive marine natural products. In Studies in Natural Products Chemistry. Elsevier 21: 293–328.

63) Mutter, R.; Wills, M. 2003: Chemistry and clinical biology of the bryostatins. Bioorg. Med. Chem. 8:1841-1860.

64) Dean M , Gevose P 1998 : Marine Pharmacognosy; Action of marine biotoxins at the cellular level, 1-35.

65) De Vries, D. J.; Beart, P. M. 1995 : Fishing for Drugs from the Sea: Status and Strategies, TiPS 16 :275-279.

66) Halvorson, H. O. 1998 : Aquaculture, Marine Sciences and Oceanography: A Confluence Connection. New Engl. J. Higher Ed. Econ. 13: 28-42.