Journal of Marine Bioscience and Biotechnology 2007, p. 209-223 Vol. 2, No. 4

Review

Bioactive Marine Natural Products in Drug Development

Se-Kwon Kim[1,2*], Y. Dominic Ravichandran[2,3], Moon-Moo Kim[4] and Won-Kyo Jung[5]

[1]Department of Chemistry, Pukyong National University, Busan 608-737, Korea
[2]Marine Bioprocess Research Center, Pukyong National University, Busan 608-737, Korea
[3]Department of Science and Humanities, Sri Krishna College of Engineering and Technology, Kuniamuthur, Coimbatore 641 008, India
[4]Department of Chemistry, Dong-Eui University, Busan 614-714, Korea
[5]Department of Marine Life Science, Chosun University, Gwangju 501-759, Korea

Abstract Nature is one of the most important sources of pharmacologically active compounds in the search for drugs against life threatening diseases. Even though plants and terrestrial microorganisms have played as an important source for the new drug candidates from nature, marine organisms such as tunicates, sponges, soft corals, sea horses, sea snakes, marine mollusks, seaweeds, nudibranches, sea slugs and marine microorganisms are increasingly attracting attention in recent years. Marine organisms also have the potential to develop into future drugs against important diseases, such as cancer, a range of bacterial and viral diseases, malaria, and inflammations. Even though the mechanism of action in the molecular level of most metabolites is still unclear, the mechanisms by which they interfere with the pathogenesis of a wide range of diseases have been reported. The knowledge of this is one of the key factors necessary to develop bioactive compounds into medicines. This is due to their structurally unique and pharmacologically active compounds. The potential pharmaceutical, medicinal and research applications of some of these compounds are discussed in hundreds of scientific papers, and are reviewed here.

Key words : Marine organisms, natural product, bioactivity, drug development.

Introduction

For ages natural products have been a strong source for novel drug products, or have been a model for a drug that has made it to market [22]. Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates [84]. Marine organisms have a shorter history of utilization in the treatment and/or prevention of human disease compared to the long standing historical medical uses of terrestrial plants. Spongothymidine from the Caribbean sponge (*Cryptotheca crypta*) were isolated in the early 1950s to be the first bioactive compounds from marine sources [22]. The importance of natural products in drug development has been discussed in recent reviews [5,52,62,84,85,90]. The significance of marine natural products on pharmacological activities like anti-inflammatory [113,118], anti-infective [6], antituberculosis [31], antimicrobial [76], antialzheimer's [76] and anticancer [40] has been reported earlier. The reasons for the interest of drug discovery from natural products in marine organism can be due to the diverse structures, intricate carbon skeletons that they produce. The need to develop products to fight diseases and infections commonly encountered triggers the search for new chemical entities.

The secondary metabolites of marine organisms have been studied extensively over the past three decades. Drug discovery research from marine organisms has gained acceleration and now evolved as an interdisciplinary research [14,40]. Much attention has been given to marine organisms in recent years due to their considerable biodiversity [51]. A number of structurally unique secondary metabolites have been isolated and

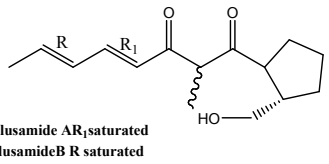
* Corresponding author
Phone: +82-51-620-6375, Fax: +82-51-628-8147
E-mail: sknkim@pknu.ac.kr

identified as drugs from marine organisms, while numerous other candidates are in clinical trials [12,82,83].

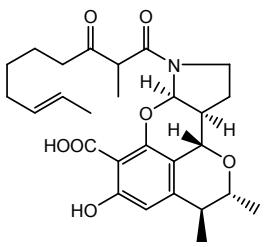
Marine natural products serve as an excellent resource for novel chemical entities. It is also observed that chemical compounds isolated from marine organisms have great potential as antimicrobials [91] or cytotoxic compounds [9]. Thousands of new compounds have been identified from marine organisms in the past three decades, giving researchers a good number of novel molecules from which they can find new leads [26]. Over 20 new drugs from natural source were launched on the market between 2000 and 2005, out of which 15 are from marine organism [22]. These approved compounds represent a very wide chemical diversity, together with several other natural products or their analogs that are undergoing clinical trials. These compounds also continue to demonstrate the importance of marine natural products in modern drug discovery. The purpose of this brief article was to review studies with bioactive marine natural products published during recent years and to classify them into major pharmacological categories. Only those articles reporting on the bioactivity and/or pharmacology of marine chemicals whose structures have been determined were included in the present review.

Antibacterial compounds

Scalusamides A – C, pyrrolidine alkaloids, originated from *Penicillium citrinum* separated from the gastrointestine of the parrot fish *Scalus ovifrons* (HedoCape, Okinawa). Scalusamide A showed antibacterial activity against *Micrococcus luteus* [114]. The same fungus also yielded the tetracyclic alkaloid, perinadine A, showing antibacterial against *M. luteus* and *Bacillus subtilis* [99].

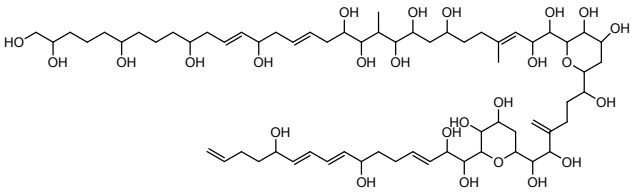


Scalusamide AR1saturated
ScalusamideB R saturated
Scalusamide C R,R1saturated



Perinadine A

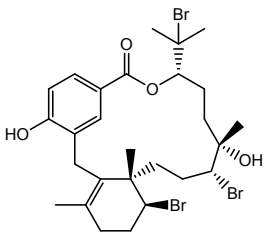
Luteophanol D, a antibacterial polyhydroxy compound, was obtained from an *Amphidinium* species, isolated from the marine acoel flatworm *seudaphanostoma luteocoloris* (Okinawa) [67].



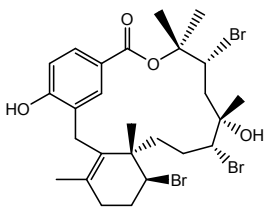
Luteophanol D

The polyketides (+)-epoxydon [24], gentisyl alcohol [101], 3-chlorogentisylalcohol [101] and methylhydroquinone [11] isolated from a marine-derived *Aspergillus* species were found as potent antibacterial agents against MRSA and multi-drug-resistant *Staphylococcus aureus* (MDRSA).

Callophycus serratus collected from several Fijian sites was the source of three antibacterial diterpene-benzoate compounds, bromophycolides A and B, and a non-halogenated compound [66].

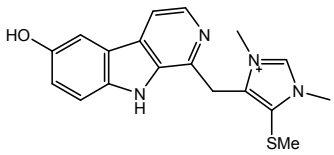


bromophycolides A



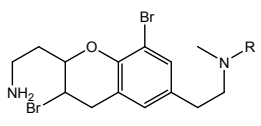
bromophycolides B

An Okinawan unidentified member of the Thorectidae family contained the antibacterial imidazoleb-carboline alkaloid gesashidine A [49].

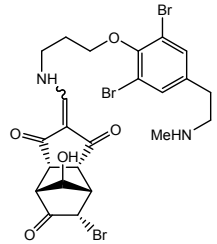


Gesashidine A

11-*N*-Methylmoloka'iamine, 11-*N*-cyano-11-methylmoloka'iamine and kuchinoenamine, all with antibacterial activity against the fish pathogen *Aeromonas hydrophila*, were obtained from a *Hexadella* species (Japan) [75].

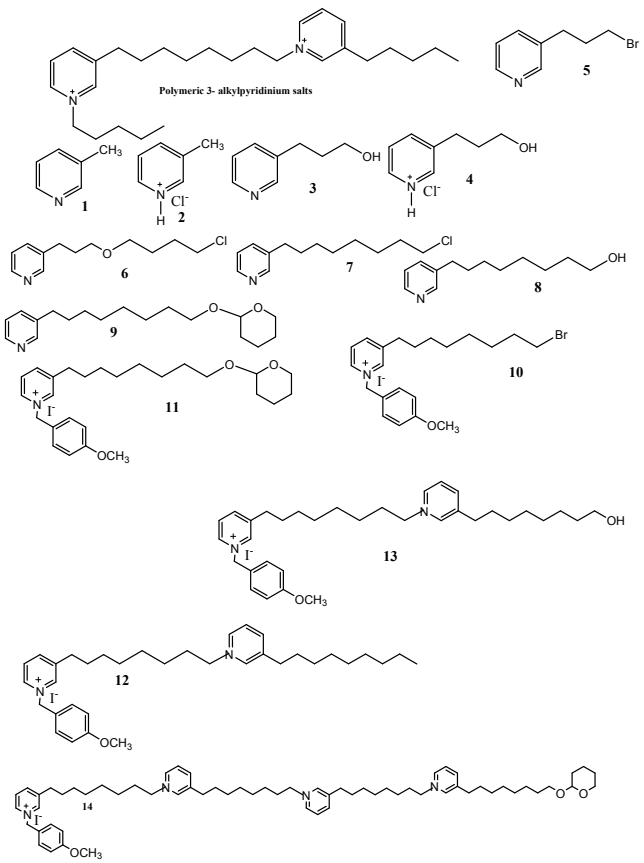


R=H :11- methylmoloka'iamine
R=CN :11-N-cyano-11- methylmoloka'iamine



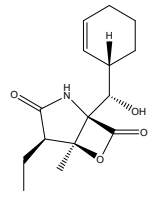
Kuchinoenamine

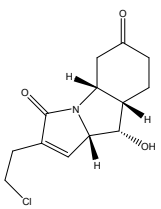
Water-soluble polymeric 3- alkylpyridinium salts and 14 related synthetic analogues showed considerable antibacterial activity against marine biofilm bacteria and may represent good candidates as natural biocides for marine technology applications [19].



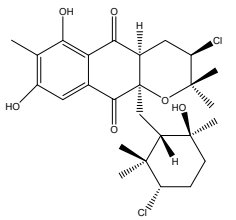
Anticancer compounds

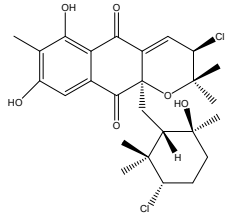
Salinosporamide A [34] that had been isolated from the actinomycete *Salinispora tropica*, contained several related metabolites, salinosporamides B and C [116] and the unprecedented chlorinated macrolides sporolides A and B [8]. Even though salinosporamides A and B inhibited human colon carcinoma HCT-116 cells, salinosporamide A was found to be the most potent. Salinosporamide A also exhibited extreme potency against several non-small cell lung, CNS and breast cancer cell lines at the NCI [116].

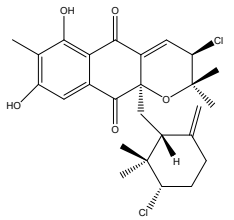

Salinosporamide B

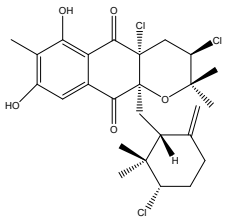

SalinosporamideC

Three chlorinated dihydroquinones have also been isolated from a new genus of actinomycete from deep water sediment of La Jolla, California. Two known analogues were also isolated [35,36]. These Compounds were cytotoxic to human colon carcinoma HCT-116 cells and displayed significant activity against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VREF) [106].

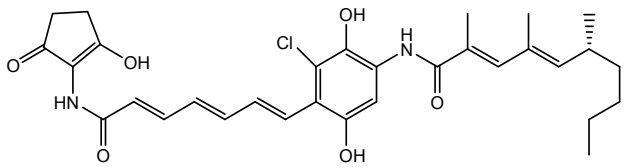

chlorinated dihydroquinone 1

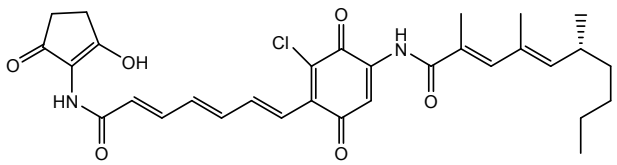

chlorinated dihydroquinone 2


chlorinated dihydroquinone 3

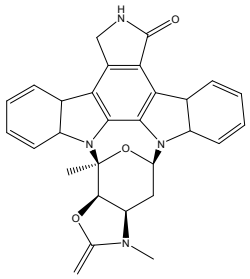

chlorinated dihydroquinone 4

Streptomyces species obtained from sediment of Jiaozhou Bay, China, yielded the chlorine containing manumycin derivatives, chinikomycins A and B and both displayed antitumour activity against a number of human cancer cell lines [68].


Chinikomycins A

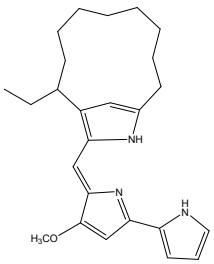

Chinikomycins B

An inhibitor for the proliferation of a variety of murine and human cancer cell lines staurosporine analogue ZHD-0501, was isolated from the *Actinomadura* species in sea sediment (Jiaozhou Bay, China) [43].



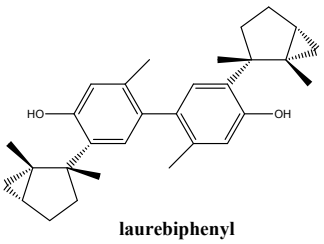
ZHD-0501

The known microbial pigment metacycloprodigiosin [115] was isolated from the actinomycete *Saccharopolyspora* sp. associated with the sponge *Mycale plumose* of Qingdao coast, China and displayed significant cytotoxicity against five human cancer cell lines [69].



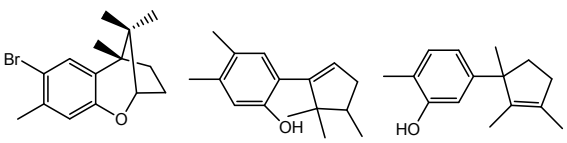
metacycloprodigiosin

A dimeric sesquiterpene laurebiphenyl, previously reported from *Laurencia nidifica* [102], was isolated and exhibited moderate cytotoxicity against several human cancer cell lines [111].



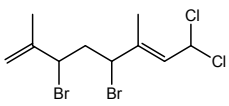
laurebiphenyl

The sesquiterpenes, cuparene isolated from *L. microcladia* of Chios Island, North Aegean Sea, were cytotoxic against the NSCLC-N6 and A- 549 cancer cell lines [5].

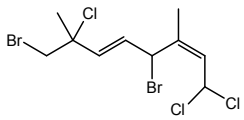


cuparene sesquiterpenes

Plocaralides B and C, isolated from a *Plocamium* species [45,109] and *Aplysia californica* [50], displayed moderate activity against the human oesophageal cancer cell line WHCO1 [60].

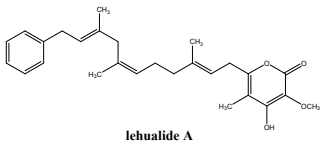


Plocaralide B

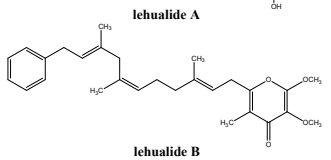


Plocaralide C

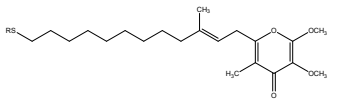
Four branched chain polyketide-derived metabolites, lehualides A – D, were isolated from a *Plakortis* species of Hawaii. These compounds and were cytotoxic to cancer cell lines [100].



lehualide A

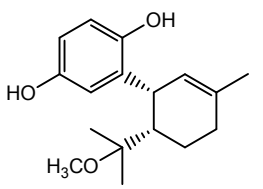


lehualide B

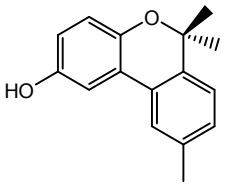


R = Ac, lehualide C
R = H, lehualide D

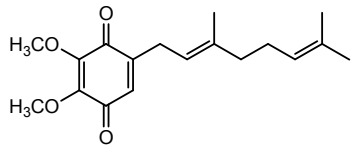
Aplidium affdensum (Oman) was the source of the meroterpenes methoxyconidiol and didehydroconicol [105], while the ubiquinone derivatives glabruquinones A and B were reported from *Aplidium glabrum* (Far East) [103]. Glabruquinones A was found to exhibit *in vitro* cancer preventive activity in a tumour cell transformation



methoxyconidiol



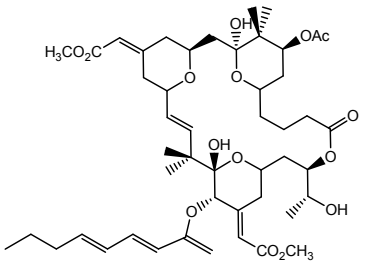
didehydroconicol



2'E, glabruquinone A
2'Z, glabruquinone B

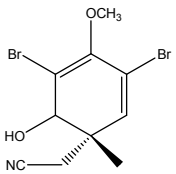
Bryozoans are sessile animals with a life style very similar to that of corals but, owing to their unique body plan, they constitute a phylum of their own. One particular bryozoan, *Bugula neritina,* has been the source of

a family of protein kinase C (PKC) inhibitors called bryostatins currently in clinical trials for cancer. Bryostatin-1 has been granted Orphan Drug status by the FDA and has been designated an Orphan Medicinal Product in Europe for oesophageal cancer in combination with paclitaxel [23,41].



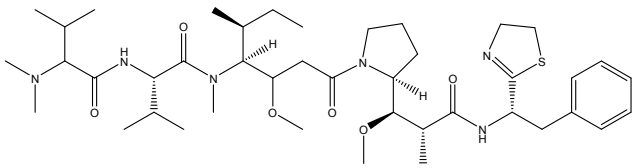
bryostatin 1

Several protein tyrosine kinase inhibitors have also been isolated from marine organisms. A brominated tyrosine metabolite aeroplysinin-1, from the sponge *Verongia aerophoba,* has been found to inhibit purified epidermal growth factor (EGF) receptor protein tyrosine kinase activity, to block EGF-stimulated proliferation of cancer cell lines, to induce their apoptosis at high nanomolar concentrations and to suppress angiogenesis *in vivo* [46,65,98].



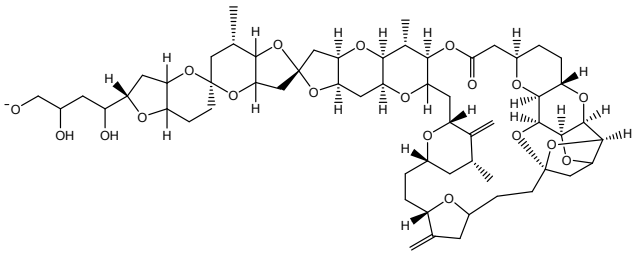
Aeroplysinin-1

Dolastatin is a marine natural peptide containing unique amino acids with microtubule-inhibitory and apoptotic effect. Dolastatin 10 has entered phase II clinical trial and cemadotin, discodermolide and the hemiasterlin analogue HTI286 have so far reached clinical development.



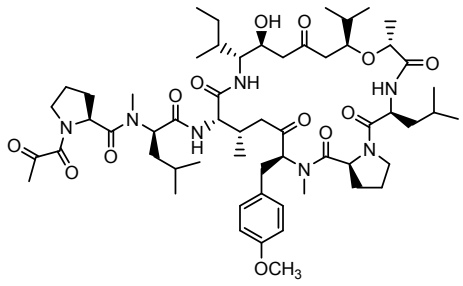
Dolastatin-10

Halichondrin B has been isolated from several different sponge genera in extremely low yield and it is the most potent member of the halichondrin family of polyether macrolides. Halichondrin B has also entered stage A clinical trials because of its potential as an effective anticancer agent. The laulimalides and discodermolide are of special interest to anticancer drug discovery researchers because they have been shown to remain active in cells over expressing multidrug-resistant P-glycoprotein [64,79].



Halichondrin B

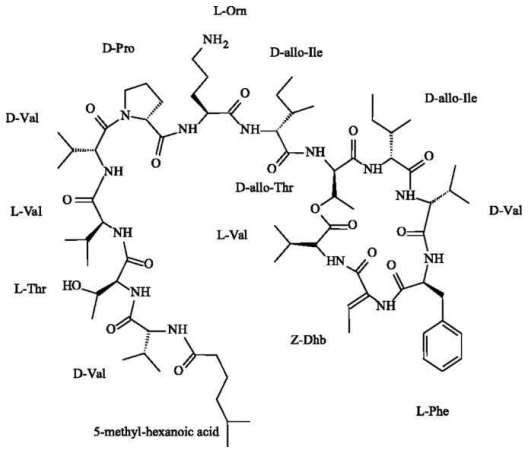
Aplidin (dehydrodidemnin B) is a novel marine-derived cyclic depsipeptide anti-tumour agent, originally isolated from the tunicate *Aplidium albicans* and currently obtained by total synthesis [2] and licensed to PharmaMar. The compound triggers rapid and persistent activation of the apoptotic process as a consequence of the induction of oxidative stress and the sustained activation of the protein kinases Jun N-terminal kinase, p38 stress-activated protein kinase, EGF receptor and Src [25,38]. Aplidin is currently in Phase II clinical evaluation for solid and hematologic malign neoplasias (Multiple Myeloma, Non-Hodgkin Lymphoma aggressive and indolent, and Acute Lymphoblastic Leucemia as single agent [10].



Aplidin

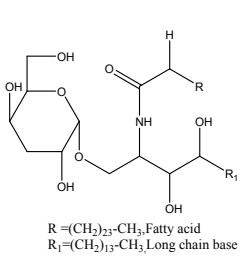
Kahalalide F, a depsipeptide derived from the sea slug *Elysia rufescens*, is the third marine natural product anticancer drug candidate in clinical development at PharmaMar [42]. Kahalalide F alters the function of the lysosomal membranes inducing cell death by oncosis. The antitumour activity of this compound may be by the action of interfering with lysosome function in prostate, colorectal and lung cancer cell lines as well as

in animal models of lung and breast cancer. Kahalalide F is currently in Phase II clinical trials in hepatocellular carcinoma, non-small cell lung cancer (NSCLC) and melanoma.

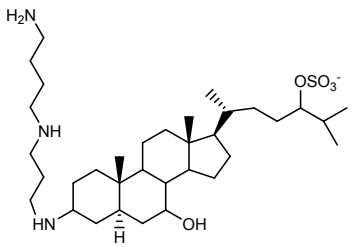


Kahalalide F

KRN7000, a novel α-galactosylceramide derived from agelasphin-9b, which, in turn, was isolated from the sponge *Agelas mauritianus*, for the potential treatment of cancer and other diseases [61].



KRN7000



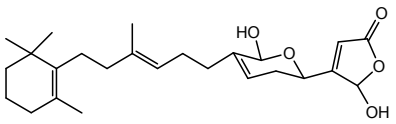
squalamine

Squalamine is a chemically synthesized aminosterol, originally isolated from the liver of the dogfish shark is currently in phase II clinical trials for ovarian and non-small cell lung cancer at Genaera and was granted Orphan Drug status for the treatment of ovarian cancer by the FDA [20,72].

Anti-inflammatory compounds

Inflammation is a one of the response to injury, resulting in the accumulation of cells and exudates in irritated tissues to protect from further damage. Natural products with anti-inflammatory activity have long been used as a folk remedy for inflammatory conditions such as fevers, pain, migraine and arthritis. Many natural products have been isolated from marine sponge as anti-inflammatory agent. Eighty four anti-inflammatory compounds mainly sesterterpenes have been isolated from marine sponges [53].

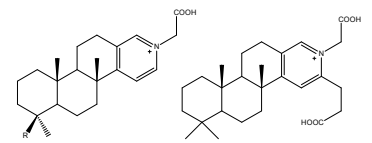
Manoalide originally isolated from the sponge *Luffariella variabilis* [56] is a well known anti-inflammatory products from sponge and has been studied extensively. The anti-inflammatory action of manoalide may be attributed to the irreversibly inhibition of PLA2 with the corresponding modification of a specific number of its lysine residues [30]. Manoalide licensed to Allergan entered clinical trials as a topical antipsoriatic with a company code name of AGN-190093.



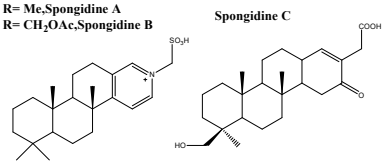
Monalide

Four pyridinium alkaloids named spongidines A-D, were isolated from a Vanuatu sponge of the genus *Spongia* exhibited anti-inflammatory action. They are considered as potential drugs for the treatment of a variety of inflammatory disorders because of their ability to inhibit human synovial enzyme phospholipase A_2 (PLA_2).

Spongidines A-D has exhibited inhibition against five secretory PLA2 enzymes and none of the compounds exhibited cytotoxic effects on human neutrophils at the tested concentrations [107]. Some compounds such as manoalide [30], spongidines A-D [107], petrosaspongiolides M-R [74] and dysidenones A, B and dysidine [96] are potent inhibitors of the enzyme PLA2, which is intimately involved in the initial step of the inflammatory response.

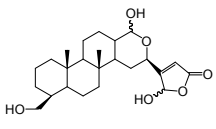


Spongidine C



Spongidine D

21-hydroxypetrosiaspongiolide K

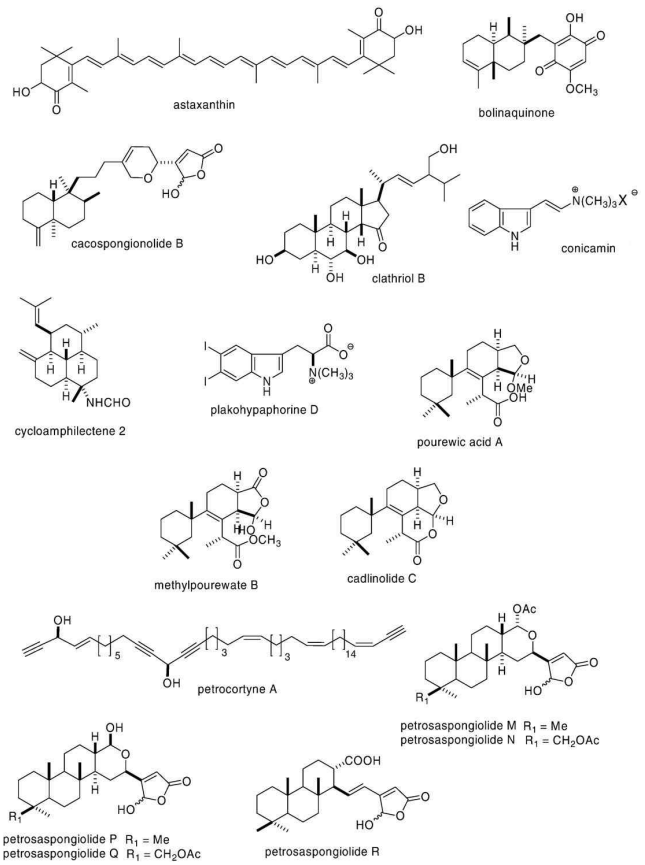


21-hydroxypetrosiaspongiolide P

Astaxanthin, a carotenoid found in crustacean cells, salmon and sea stars, has shown anti-inflammatory effect on lipopolysaccharide-induced uveitis in rats both *in vitro* and *in vivo* [79]. The mechanism of action determined for astaxanthin probably involved inhibition of nitric oxide, prostaglandin E2 and TNF-α generation.

Bolinaquinone, a sesquiterpenoid isolated from a *Dysidea* sp. sponge, significantly inhibited cytokine, iNOS expression and eicosanoid (LTB4, PGE2) generation *in vitro* and *in vivo* in several models of inflammation through secretory PLA2 inhibition [70]. These observation proposed the marine compound bolinaquinone as a potential anti-inflammatory agent.

Sesterterpene cacospongionolide B isolated from the Mediterranean sponge *Fasciospongia cavernosa*, showed anti-inflammatory activity in mouse peritoneal macrophages *in vitro*, as well as *in vivo* model of inflammation [94].



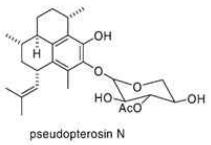
Cacospongionolide B inhibited nuclear factor-κ-DNA binding activity and enhanced IκB-α expression at the molecular level, cacospongionolide B also decreased nitric oxide, prostaglandin E2 and TNF-α generation as well as the corresponding gene expression.

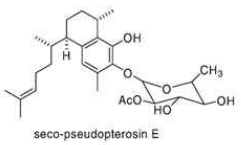
Cathriol B, a novel anti-inflammatory sterol, isolated from the New Zealand sponge *Clathria lissosclera* has been found to moderately inhibit production of superoxide anion from agonist stimulated human peripheral blood neutrophils [57]. Conicamin, another novel indole alkaloid histamine antagonist, isolated from the Mediterranean tunicate *Aplidium conicum* [1] demonstrated a concentration-dependent reduction of histamine-induced contractions in *ex vivo* studies with guinea pig ileum, by a non-competitive mechanism. Six new cycloamphilectenes isolated from the Vanuatu sponge *Axinella* sp. on murine macrophage have been found to reduce nitric oxide (NO) production in the submicromolar range [71]. A novel marine diterpene cycloamphilectene 2, isolated from the Vanuatu sponge *Axinella* sp. is an inhibitor of the NF-κB pathway and exhibits topical anti-inflammatory activity [58] . It also reduced NO production and elastase release without affecting TNF-α release, inhibited the nuclear factor-κB pathway and also exhibited *in vivo* activity. One iododinated plakohypaphorine plakohypaphorine D, with antihistamine activity was isolated from the Caribbean sponge *Plakortis simplex* [7] and the antihistamine activity was found to be related to the number and nature of the halogen atoms.

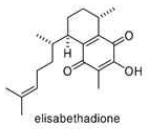
Three novel diterpenes pourewic acid A, methylpourewate B and cadlinolide C isolated from the New Zealand sponge *Chelonaplysilla violacea* [58], have moderately inhibited production of the inflammatory superoxide anion from human peripheral blood neutrophils stimulated with phorbol myristate acetate or *N*-formyl-methionine-leucine-phenylalanine. The marine sponge *Petrosia* sp. yielded a C46 polyacetylenicalcohol petrocortyne A that showed the anti-inflammatory activity [47]. Petrocortyne A inhibited release of both TNF-α (IC_{50}=2.35 μM) and nitric oxide from macrophages and induced homotypic aggregation of U937 human leukemic monocytes, a process that appears to involve phosphorylation of several intracellular signaling molecules.

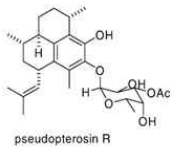
Bioactive sesterterpenes petrosaspongiolides M-R, isolated from the marine sponge *Petrosaspongia nigra* have exhibited anti-inflammatory activity[78]. The marine sesterterpenoid petrosaspongiolide M inhibited production of nitrite, prostaglandin E2 and TNF-α both in vitro and in vivo while concomitantly inhibiting NF-κB signalling suggesting that petrosaspongiolide M had "potentially wide therapeutic spectrum" in inflammatory

conditions[95]. The irreversible inhibition of bee-venom phospholipase A2 (PLA2) was investigated by mass spectrometry and molecular modelling approaches. These studies demonstrated that petrosaspongiolides N, O, P and R shared the same inhibition mechanism and covalent binding site as already reported for petrosaspongiolide M. Two new diterpenes pseudopterosin N and seco-pseudopterosin E along with hydroxyquinone elisabethadione isolated from the marine gorgonian *P. elisabethae* have shown *in vivo* anti-inflammatory activity [3]. In the search of novel agents to treat neuroinflammation, several novel diterpene glycoside pseudopterosins and seco-pseudopterosins from the Caribbean sea whip *P. elisabethae* were evaluated by *in vitro* anti-neuroinflammatory assay [97].







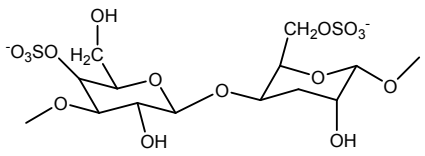


Pseudopterosin R proved to be the most promising compound by significantly inhibiting the generation of thromboxane B2 (IC_{50}=4.7 μM) from activated rat brain macrophages. Although the molecular mechanism of action of pseudopterosin R remains currently undetermined, it is expected to become a lead compound for anti-neuroinflammatory drug design.

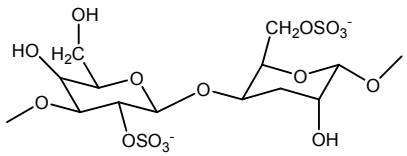
Antiviral compounds

A wide range of active compounds has been isolated and characterized from marine organism for antiviral activity. Even though sulphated polysaccharides from red algae show antiviral activities towards viruses responsible for human infectious diseases. *Aghardhiella tenera* and *Nothogenia fastigiata* are the most notable. A galactan sulphate from *Aghardhiella tenera* [27], and a xylomannan sulphate from *Nothogenia fastigiata* [28,63] exhibited good activity against human immunodeficiency virus (HIV), Herpes simplex virus (HSV) types 1 and 2 and respiratory syncytial virus (RSV). These polysaccharides are active during the first stage of the RNA virus replication when the virus adsorbs onto the surface of the cell [28,29]. An important requirement of an antiviral polysaccharide is that it must have very low cytotoxic activities towards mammalian cells. Most of the algal polysaccharides in general and galactan sulphate from *Aghardhiella tenera* and xylomannan sulphate from *Nothogenia fastigiata* are in particular have this characteristic [29].

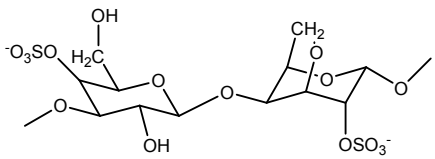
Λ-carrageenan and partially cyclised *μ/ι*-carrageenan from *Gigartina skottsbergii* were found to have potent antiviral effects against different strains of HSV types 1 and 2 during the virus adsorption stage [15,16,17] similar antiherpetic activity was shown by carrageenans from cystocarpic and tetrasporophytic stages of *Stenogramme interrupta*. Carrageenan and fucoidan, or fucoidin, were found to be good candidates for further development [13,119]. It is also important to note that none of these studies have shown that carrageenans exhibit significant levels of cytotoxicity or anti-



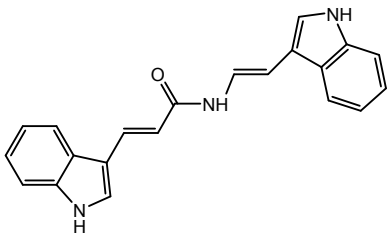
μ-carrageenan



λ–carrageenan



ι-carrageenan



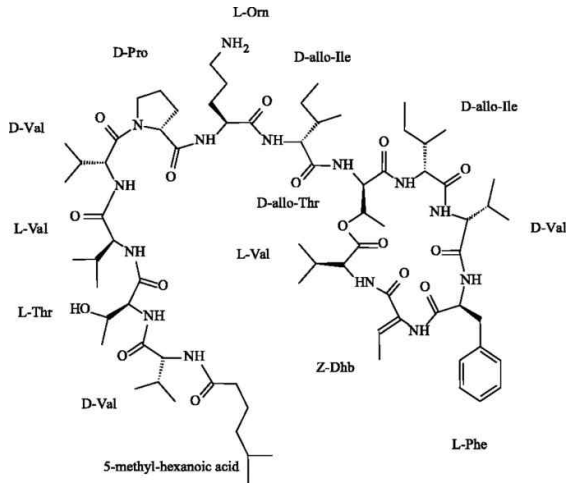
Chondriamide A

coagulant activity.

Carraguard, a carrageenan-based vaginal microbicide, has been shown to block HIV and other sexually transmitted diseases *in vitro*. Carraguard entered phase III clinical trials involving 6000 non-pregnant, HIV-negative women in South Africa and Botswana in 2003 [108]. A sulphated polysaccharide from *Schizymenia pacifica* inhibits HIV reverse transcriptase *in vitro* [80,81], a later stage in HIV replication. High molecular weight galactan sulphate from *Gracilaria corticata* agaroid, has antiviral properties against HSV types 1 and 2, and this action is likely due to an inhibition of the initial virus attachment to the host cell [77].

Fucoidan has been found to be a potent antiviral agent against viruses such as RSV [73], HIV [110], HSV types 1 and 2 and human cytomegalovirus [33,72,99]. The antiviral properties of fucoidan are due to the inhibiting binding of the viral particle to the host cell [4]. It has the additional benefit of inhibiting binding of sperm to the zona pellucida in humans [86], thus allowing the compound to be developed into a possible vaginal microbicide with contraceptive properties.

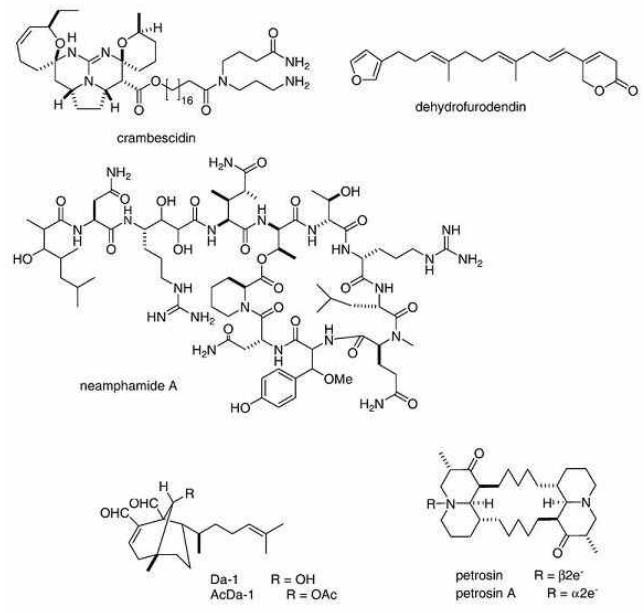
Chondriamide A isolated from *Chondria atropurpurea* shows antiviral activity against HSV type II [89]. Kahalalide F produced by a species of *Bryopsis* has also been found to be effective against HIV, and is under clinical trials [40,42].



Kahalalide F

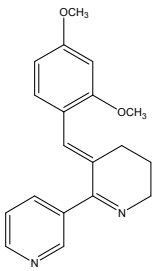
During the last two-year period 7 novel marine compounds were reported to have antiviral properties against the human immunodeficiency (HIV). A new polycyclic guanidine alkaloid crambescidin from the marine sponge *Monanchora* sp. was reported to inhibited HIV-1 envelope-mediated fusion *in vitro* [18], thus suggesting that this class of compounds might ultimately turn out to be a small molecule HIV-1fusion inhibitor. A new C_{22} furanoterpene designated dehydrofurodendin isolated from a Madagascan *Lendenfeldia* sponge, was reported to be active against HIV-1 reverse transcriptase-associated RNA- and DNA-directed DNA polymerase [21].

Neamphamide A a new HIV-inhibitory depsiundecapeptide was isolated from the Papua New Guinea marine sponge *Neamphius huxleyi* [88]. Neamphamide A potently inhibited the cytopathic effect of HIV-1infection in a cell-based in vitro assay (EC_{50}=28 nM). An extensive study on the mechanism of action of two diterpenes, Da-1 and AcDa-1, isolated from the marine alga *Dictyota menstrualis*, showed that these two diterpenes inhibited HIV-1 virus replication in the PM-1 cell line *in vitro* [92]. Although both diterpenes did not affect viral attachment nor internalization of the virus into PM-1 cells, they inhibited the RNA-dependent DNA polymerase activity of the viral reverse transcriptase enzyme in a cell-free *in vitro* assay. These results strongly suggested that "inhibition of synthesis of the proviral DNA by the diterpenes" was the probable mechanism involved in HIV replication inhibition in PM-1 cells. Two bis-quinolizidine alkaloids petrosins isolated from the Indian marine sponge *Petrosia similis* have shown inhibition of HIV [39]. The study revealed that both petrosins inhibited HIV-1 replication formation of giant cells and recombinant reverse transcriptase *in vitro*.



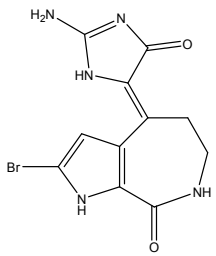
Anti-Alzheimer's compounds

GTS21, 3-(2,4-dimethoxybenzylidene)-anabaseine, is a selective α7 nAChR partial agonist in clinical development at Taiho to treat Alzheimer's disease and schizophrenia. GTS21 was isolated from the nemertine worm *Amphiporus lactifloreus*. The compound has been shown to improve learning performance and memory retention in passive avoidance models in nucleus basalis magnocellularis (NbM)-lesioned rats as well as in active avoidance models in aged rats. It also reduced neocortical cell loss in NbMlesioned rats and cell death induced by β-amyloid or glutamate in cultures of neuronal cells (http://www.iddb3.com; http://www.prous.com). GTS-21-anabaseine (also known as DMXB)[54,55] is currently in clinical trials for possible treatment of Alzheimer's dementia.



GTS21, 3-(2,4-dimethoxybenzylidene)-anabaseine

Hymenialdisine is a sponge alkaloid named after *Hymeniacidon aldis*. The compound inhibited the *in vitro* phosphorylation of human microtubule-associated protein tau, which is implicated in the pathogenesis of Alzheimer's disease, and in Sf9 cells expressing the protein [112].



Hymenialdisine

Concluding remarks

With few drugs from the marine organism, the cephalosporins, cytarabine (Ara-C) and vidarabine (Ara-A), already well-established on the market, the granting of Orphan Drug status to bryostatin-1, squalamine and ET743 in the past years, and more than a dozen marine compounds or their derivatives are currently in clinical trials, the marine natural products will have a promising future in drug development. Even though the drug development from marine natural product has begun recently it has already yielded several thousand novel molecules. As the biochemical diversity in the marine organisms is higher than the terrestrial plants or animals, there is good reason to believe that approval of the above-mentioned drugs will only be the beginning and a larger number of marine natural products, or compounds derived from them to follow, for the improved treatment of human illnesses.

Acknowledgements

The authors acknowledge Marine Bioprocess Research center of Marine Bio 21 project, funded by the Ministry of Maritime Affairs and Fisheries, Republic of Korea, for the support provided through the research grant, m-2008-1.

References

1. Aiello A., Borrelli F., Capasso R., Fattorusso E., Luciano P., Menna M. 2003. Conicamin, a novel histamine antagonist from the Mediterranean tunicate *Aplidium conicum*. *Bioorg. Med. Chem. Lett*. **13**, 4481-4483.
2. Anthoney, D. A. and Twelves, C. J. 2001. DNA: still a target worth aiming at? A Review of new DNA-interactive agents. *Am. J .Pharmacogenomics* **1**, 67-81.
3. Ata A., Kerr R. G., Moya C. E., Jacobs R. S., 2003. Identification of anti-inflammatory diterpenes from the marine gorgonian *Pseudopterogorgia elisabethae*. *Tetrahedron* **59**, 4215-4222.
4. Baba M., Snoeck R., Pauwels R., De Clercq E. 1988. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stromatitis virus, and human immunodeficiency virus. *Antimicrob. Agents Chemother*. **32**, 1742-1745.
5. Balunas M. J., Kinghorn A. D. 2005. Drug discovery from medicinal plants. *Life Sci.* **78,** 431-441.
6. Bhadury P., Mohammad B. T., Wright P. C. 2006. The current status of natural products from marine fungi and their potential as anti-infective agents. *J. Ind. Microbiol. Biotechnol.* **33**, 325-337
7. Borrelli F., Campagnuolo C., Capasso R., Fattorusso E., Taglialatela-Scafati O. 2004. Iodinated indole alkaloids from *Plakortis simplex* — new plakohypaphorines and an evaluation of their antihistamine activity. *Eur. J. Org. Chem*. **15**, 3227-3232.
8. Buchanan G. O., Williams P. G., Feling R. H., Kauffman

C. A., Jensen P. R. Fenical W. 2005. Sporolides A and B: structurally unprecedented halogenated macrolides from the marine actinomycete Salinispora tropica. *Org. Lett.* **7**, 2731.
9. Burja A.M., Banaigs B., Abou-Mansour E., Burgess J.G., Wright P.C. 2001. Marine cyanobacteria-a prolific source of natural products. *Tetrahedron* **57**, 9347-9377.
10. Burkhard Haefner. 2003. Drugs from the deep: marine natural products as drug candidates. *Drug discovery Today* **8**,536-544.
11. Burnett A. R., Thomson R. H. 1968. Naturally occurring quinones. Part XIV. The quinonoid constituents of *Pyrola media* Sw. (Pyrolaceae) *J. Chem. Soc. C*, 857-860.
12. Butler M. S. 2005. Natural products to drugs: natural products derived compounds in clinical trials. *Nat. Prod. Rep*. **22** ,162-195.
13. C´aceres P. J., Carlucci M. J., Damonte E. B., Matsuhiro B., Z´u˜niga E. A. 2000. Carrageenans from Chilean samples of *Stenogramme interrupta* (Phyllophoraceae): Structural analysis and biological activity. *Phytochemistry* **53**, 81-86
14. Capon R. J. 2001. Marine bioprospecting-trawling for treasure and pleasure. *Eur. J. Org. Chem*. 633-645.
15. Carlucci M. J., Ciancia M., Matulewicz M. C., Cerezo A. S., Damonte E. B. 1999. Antiherpetic activity and mode of action of natural carrageenans of diverse structural types. *Antivir. Res*. **43**, 93-102.
16. Carlucci M. J., Pujol C. A., Ciancia M., Noseda M. D., Matulewicz M. C., Damonte E. B., Cerezo A. S. 1997. Antiherpetic and anticoagulant properties of carrageenans from the red seaweed *Gigartina skottsbergii* and their cyclized derivatives: correlation between structure and biological activity. *Int. J. Biol. Macromol.* **20**, 97-105.
17. Carlucci M. J., Scolaro L. A., Damonte E. B. 1999. Inhibitory action of natural carrageenans on *Herpes simplex* virus infection of mouse astrocytes. *Chemotheraphy* **45**, 429-436.
18. Chang L., Whittaker N. F., Bewley C. A. 2003. Crambescidin 826 and dehydrocrambine A: new polycyclic guanidine alkaloids from the marine sponge *Monanchora* sp. that inhibit HIV-1 fusion. *J. Nat. Prod*. **66**, 1490-1494.
19. Chelossi E., Mancini I., Sepc˘ic´ K., Turk T., Faimali M. 2006. Comparative antibacterial activity of polymeric 3-alkylpyridinium salts isolated from the Mediterranean sponge *Reniera sarai* and their synthetic analogues *Biomolecular Engineering* **23**, 317-323
20. Chen Q, William J. I, **A**nderson M., Kinney W. K., Zasloff M. 1999. The angiostatic sterol squalamine is a calmodulin chaperone. *Clin. Cancer Res.* **5** (Suppl.), 3768-3797.
21. Chill L., Rudi A., Aknin M., Loya S., Hizi A., Kashman Y. 2004. New sesterterpenes from Madagascan *Lendenfeldia* sponges. *Tetrahedron* **60**, 10619-10626.
22. Chin Y. W., Balunas M. J., Chai H. B., Kinghorn A. D. 2006. Drug discovery from natural sources. *AAPS Journal* **8 (2)**, E 239-253.
23. Clamp A., Jayson G. C. 2002. The clinical development of the bryostatins. *Anticancer Drugs* **13**, 673-683.
24. Closse A., Mauli R., Sigg H. P., Sandoz A. G. 1965. Structure of epoxydon. *Helv. Chim. Acta* **49**, 204-213.
25. Cuadrado A., Gracia Fernandez L. F.,Ganzalez L., Saurez Y., Losada A., Alcaide V., Martinez T., Maa Fernandez-Sousa J., Sanchez- Puelles, J. M. Munoz A. 2003. AplidinTM induces apoptosis in human cancer cells via glutathione depletion and sustained activation of the epidermal growth factor receptor, Src, JNK, and p38 MAPK. *J. Biol. Chem.* **278,** 241-250.
26. da Rocha A. B, Lopes R. M, Schwartsmann G. 2001. Natural produ cts in anticancer therapy. *Current Opinion in Pharmacology* **1**, 364-369.
27. Damonte E. B., Neyts J., Pujol C. A., Snoeck R., Andrei G., Ikeda S., Witvrouw M., Reymen D., Haines H., Matulewicz M. C., Cerezo A., Coto C. E., De Clercq E. 1994. Antiviral activity of a sulfated polysaccharide from the red seaweed *Nothogenia fastigiata*. *Biochem. Pharmacol*. **47**, 2187-2192.
28. De Clercq E. 1996. Chemotheraphy of human immunodeficiency virus (HIV) infection: anti-HIV agents targeted at early stages in the virus replicative cycle. *Biomed. Pharmacother.* **50**, 207-215.
29. De Clercq E. 2000. Current lead natural products for the chemotheraphy of human immunodeficiency virus (HIV) infection. *Med. Res. Rev*. **20**, 323-349.
30. De Silva E. D., Scheuer P. J. 1980. Manoalide, an antibiotic sesterterpenoid from the marine sponge *Luffariella variabilis* (Poleajaeff) *Tetrahedron Lett*. **21**, 1611-1614.
31. De Souza M.V.N. 2006. Marine Natural Products against Tuberculosis. *The Scientific World* **6**, 847-861.
32. Edler, M. C.Fernandez A. M. Lassota P., Ireland C. M., Barrows L. R. 2002. Inhibition of tubulin polymerisation by vitilevuamide, a bicyclic marine peptide, at a site distinct from colchicine, the vinca alkaloids, and dolastatin-10. *Biochem. Pharmacol.* **63**, 707-715.
33. Feldman S. C., Reynaldi S., Stortz C. A., Cerezo A. S., Damont E. B. 1999. Antiviral properties of fucoidan fractions from *Leathesia difformis*. *Phytomed.* **6**, 335-340.
34. Feling R. H., Buchanan G. O., Mincer T. J., Kauffman C. A., Jensen P. R. Fenical W. 2003. Salinosporamide A: A highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus *Salinospora*. *Angew. Chem. Int. Ed.* **42**, 355-357.
35. Fukuda D. S., Mynderse J. S., Yao R. C. 1990. U.S. Patent 4904590.
36. Fukuda D. S., Mynderse J. S., Baker P. J., Berry D. M., Boeck L. D., Yao R. C., Mertz F. P., Nakatsukasa W. M., Mabe J., Ott J. 1990. A new antibiotic complex produced by *Streptomyces aculeolatus*. Discovery, taxonomy, fermentation, isolation, characterization, and antibacterial evaluation. *J. Antibiot.* **43**, 623-633.
37. Gamble W. R., Durso N. A., Fuller R. W., Westergaard C. K.,Johnson T. R., Sackett D. L., Hamel E., ….Boyd M.R. 1999. Cytotoxic and tubulin-interactive hemiasterlins from *Auletta* and *Siphonochalina* spp. sponges. *Bioorg. Med. Chem.* **7**, 1611-1615.

38. Garcia-Fernandez, L. F. Losada A., Alcaide V., Alvarez A. M., Cuadrado A., Gonzalez L., Nakayama K. I., Fernandez-Sousa J. M., Munoz A., Sanchez-Puelles J. M. 2002. AplidinTM induces the mitochondrial apoptotic pathway via oxidative stress-mediated JNK and p38 activation and protein kinase Cδ. *Oncogene* **21**, 7533-7544.
39. Goud T. V., Reddy N. S., Swamy N. R., Ram T. S., Venkateswarlu Y. 2003. Anti-HIV active petrosins from the marine sponge *Petrosia similis*. *Biol. Pharm. Bull*. **26**, 1498-1501.
40. Haefner B. 2003. Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today* **8**, 536-544.
41. Hale K. J., Hummersone M. G., Manaviazar S., Frigerio M. 2002. The chemistry and biology of the bryostatin antitumour macrolides. *Nat. Prod. Rep.* **19**, 413-453.
42. Hamann, M. T., Otta C. S., Scheuer P. J. 1996. Kahalalides: bioactive peptides from a marine mollusk *Elysia rufescens* and its algal diet *Bryopsis sp. J. Org. Chem.* **61**, 6594-6600.
43. Han X. X., Cui C. B., Gu Q. Q., Zhu W. M., Liu H. B., Gu J. Y., Osada H. 2005. ZHD-0501, a novel naturally occurring staurosporine analog from *Actinomadura* sp. 007. *Tetrahedron Lett.* **46**, 6137-6140.
44. Herbst R. S., Hammond L. A., Carbone D. P., Tran H. T., Holroyd K. J., Desai A., Williams J.I., Bekele B. N., Hait H., Allgood.V., Stephen Solomon S., Schiller J. H. 2003. A phase I/IIA tTrial of continuous five-day infusion of squalamine lactate (MSI-1256F) plus carboplatin and paclitaxel in patients with advanced non-small cell lung cancer[1]. *Clinical Cancer Research* **9**, 4108–4115
45. Higgs M. D., Vanderah D. J., Faulkner D. J. 1977. Polyhalogenated monoterpenes from *Plocamium cartilagineum* from the British coast. *Tetrahedron* **33**, 2775-2780.
46. Hinterding, K. Knebel A., Herrlich P. Waldmann H. 1998. Synthesis and biological evaluation of aeroplysinin analogues: a new class of receptor tyrosine kinase inhibitors. *Bioorg. Med. Chem.* **6**, 1153-1162.
47. Hong S., Kim S. H., Rhee M. H., Kim A. R., Jung J. H., Chun T., Yoo E. S., Cho J. Y. 2003. *In vitro* anti-inflammatory and pro-aggregative effects of a lipid compound, petrocortyne A, from marine sponges. *Naunyn-Schmiedeberg's Arch. Pharmacol*. **368**, 448-456.
48. Hood, K. A. Backstrom B. T., West L. M., Northcote P. T. West L. M., Northcote P. T. Berridge M. V., Miller J. H. 2001. The novel cytotoxic sponge metabolite peloruside A, structurally similar to bryostatin-1, has unique bioactivity independent of protein kinase C. *Anticancer Drug Des.* **16**, 155-166.
49. Iinuma Y., Kozawa S., Ishiyama H., Tsuda M., Fukushi E., Kawabata J., Fromont J., Kobayashi J. 2005. Gesashidine A, a beta-carboline alkaloid with an imidazole ring from a *Thorectidae* sponge. *J. Nat. Prod.* **68**, 1109-1110.
50. Ireland C., Stallard M. O., Faulkner D. J., Finer J., Clardy J. 1976. Some chemical constituents of the digestive gland of the sea hare *Aplysia californica. J. Org. Chem.* **41**, 2461.
51. Jensen P. R., Fenical W. 2000. Marine microorganisms and drug discovery: current status and future potential. In: Fusetani N., ed. *Drugs from the Sea.* New York, Karger, pp 6-29.
52. Jones W. P., Chin Y. W., Kinghorn A. D. 2006. The role of pharmacognosy in modern medicine and pharmacy. *Curr. Drug Targets* **7**, 247-264.
53. Jung H. J., Kim S. G., Nam J. H., Park K. K., Chung W. Y., Kim W. B., Lee K. T., Won J. H., Choi J. W., Park H. J. 2005. Isolation of saponins with the inhibitory effect on nitric oxide, prostaglandin E2 and tumor necrosis factor-α production from *Pleurospermum kamtschaticum. Biol. Pharm. Bull.* **28**, 1668-1671.
54. Kem W. R., Mahnir V. M., Lin B. and Prokai-Tartarai K. 1996. Two primary GTS-21 metabolites are potent partial agonists at alpha7 nicotinic receptors expressed in the *Xenopus* oocyte. *Soc. Neurosci. Abstr*. **22**, 268.
55. Kem W. R., Mahnir V. M., Papke R. L., Lingle C. J. 1997. Anabaseine is a potent agonist on muscle and neuronal *alpha*-bungarotoxin-sensitive nicotinic receptors. *The Journal of Pharmacology and Experimental Therapeutics* **283**, 979-992.
56. Keyzers R. A., Davies-Coleman M. T. 2005. Anti-inflammatory metabolites from marine sponges. *Chem. Soc. Rev.* **34**, 355-365.
57. Keyzers R. A., Northcote P. T., Berridge M. V. 2003. Clathriol B, a new 14 beta marine sterol from the New Zealand sponge *Clathria lissosclera*. *Aust. J. Chem*. **56**, 279-282.
58. Keyzers R. A., Northcote P. T., Zubkov O. A. 2004. Novel anti-inflammatory spongian diterpenes from the New Zealand marine sponge *Chelonaplysilla violacea*. *Eur. J. Org. Chem.* 419-425.
59. Kladi M., Vagias C., Furnari G., Moreau D., Roussakis C. Roussis V. 2005. Cytotoxic cuparene sesquiterpenes from *Laurencia microcladia* . *Tetrahedron Lett.* **46**, 5723-5726.
60. Knott M. G., Mkwananzi H., Arendse C. E., Hendricks D. T., Bolton J. J., Beukes D. R. 2005. Plocoralides A-C, polyhalogenated monoterpenes from the marine alga *Plocamium corallorhiza*. *Phytochemistry* **66**, 1108-1112.
61. Kobayashi, E. Motoki K., Uchida T., Fukushima H., Koezuka Y. 1995**.** KRN7000, a novel immunomodulator, and its antitumor activities. *Oncol. Res.* **7**, 529-534.
62. Koehn F. E., Carter G. T. 2005. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov.* **4**, 206-220.
63. Kolender A. A., Matulewicz M. C., Cerezo A. S. 1995. Structural analysis of antiviral sulfated *a* -D-(1,3)-linked mannans. *Carbohyd. Res*. **273**, 179-185.
64. Kowalski, R. J. Giannakakou P., Gunasekera S. P., Longley R. E., Day B. W., Hamel E. 1997. The microtubule-stabilizing agent discodermolide competitively inhibits the binding of paclitaxel (Taxol) to tubulin polymers, enhances tubulin nucleation reactions more potently than paclitaxel, and inhibits growth of paclitax-

el-resitant cell lines. *Mol. Pharmacol.* **52**, 613-622.
65. Kreuter M. H., Leake R. E., Rinaldi F., Muller-Klieser W., Maidhof A., Muller W. E. G., Schroder H. C. 1990 Inhibition of intrinsic protein tyrosine kinase activity of EGF-receptor kinase complex from human breast cancer cells by the marine sponge metabolite (+)-aeroplysinin-1. *Comp. Biochem. Physiol. B* **97**, 151-158.
66. Kubanek J., Prusak A. C., Snell T. W., Giese R. A., Hardcastle K. I., Fairchild C. R., Aalbersberg W., Raventos-Suarez C., Hay M. E. 2005 Antineoplastic diterpene－benzoate macrolides from the Fijian red alga *Callophycus serratus*. *Org. Lett.* **7**, 5261.
67. Kubota T., Takahashi A., Tsud a M., Kobayashi J. 2005. Luteophanol D, new polyhydroxyl metabolite from marine dinoflagellate *Amphidinium* sp. *Mar. Drugs* **3**, 113-118.
68. Li F., Maskey R. P., Qin S., Sattler I., Fiebig H. H., Maier A., Zeeck A., Laatsch H. 2005. Chinikomycins A and B: Isolation, structure elucidation, and biological activity of novel antibiotics from a marine *Streptomyces* sp. isolate M045. *J. Nat. Prod.* **68**, 349-353.
69. Liu, R., Cui, C. B., Duan, L., Gu, Q. Q. und Zhu, W. M. 2005. Potent *in vitro* anticancer activity of metacycloprodigiosin and undecylprodigiosin from a sponge-derived actinomycete *Saccharopolyspora* sp. nov. *Arch Pharm. Res.* **28**, 1341-1344.
70. Lucas R., Giannini C., D'Auria M. V., Paya M. 2003. Modulatory effect of bolinaquinone, a marine sesquiterpenoid, on acute and chronic inflammatory processes. *J. Pharmacol. Exp. Ther.* **304**, 1172-1180.
71. Lucas, R., Casapullo, A., Ciasullo, L., Gomez-Paloma, L., Paya, M. 2003. Cycloamphilectenes, a new type of potent marine diterpenes: inhibition of nitric oxide production in murine macrophages. *Life Sci.* **72**, 2543-2552.
72. Majczak G. A. H., Richartz R. R. T. B., Duarte M. E. R., Noseda M. D. 2003. Antiherpetic activity of heterofucans isolated from *Sargassum stenophyllum* (Fucales, Phaeophyta). In Chapman ARO, Anderson R. J., Vreeland V. J., Davison I. R. (eds), Proceedings of the 17th International Seaweed Symposium, Oxford University Press, Oxford, pp. 169-174.
73. Malhotra R., Ward M., Bright H., Priest R., Foster M. R., Hurle M., Blair E., Bird M. 2003. Isolation and characterisation of potential respiratory syncytial virus receptor(s) on epithelial cells. *Microbes Infect.* **5**, 123-133.
74. Marino S. D., Iorizzi M., Zollo F., Debitus C., Menou J. L., Luis F. O., Alcaraz M. J., Payá M. 2000. New pyridinium alkaloids from a marine sponge of the genus *Spongia* with a human phospholipase A2 inhibitor profile. *J. Nat. Prod.* **63**, 322-326.
75. Matsunaga S., Kobayashi H., van Soest R. W. M., Fusetani N. 2005. Novel bromotyrosine derivatives,which inhibit the growth of the fish pathogenic bacterium *Aeromonas hydrophyla*, from the marine sponge *Hexadella sp*. *J. Org. Chem.* **70**, 1893-1896.
76. Mayer A. M. S., Rodríguez A. D., Berlinck R. G. S., Hamann M. T. 2007. Marine pharmacology in 2003 – 4: Marine compounds with anthelmintic antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. *Comparative Biochemistry and Physiology* **145**, 553-581.
77. Mazumder S., Ghosal P. K., Pujol C. A., Carlucci M. J., Damonte E. B., Ray B. 2002. Isolation, chemical investigation and antiviral activity of polysaccharides from *Gracilaria corticata* (Gracilariaceae, Rhodophyta). *Int. J. biol. Macromol.* **31**, 87-95.
78. Monti M. C., Casapullo A., Riccio R., Gomez-Paloma L. 2004. Further insights on the structural aspects of PLA(2) inhibition by gammahydroxybutenolide-containing natural products: a comparative study on petrosaspongiolides M-R. *Bioorg. Med. Chem.* **12**, 1467-1474.
79. Mooberry, S. L., Tien G., Hernandez A. H., Plubrukarn A., Davidson B. S. 1999. Laulimalide and isolaulimalide, new paclitaxel-like microtubule-s tabilizing agents. *Cancer Res.* **59**, 653-660.
80. Nakashima H., Kido Y., Kobayashi N., Motoki Y., Neushul M., Yamamoto N. 1987. Antiretroviral activity in a marine red alga; reverse transcriptase inhibition by an aqueous extract of *Schizymenia pacifica*. *J. Cancer Res. Clin. Onc*. **113**, 413-416.
81. Nakashima H., Kido Y., Kobayashi N., Motoki Y., Neushul M., Yamamoto N. 1987. Purification and characterization of an avian myeloblastosis and human immunodeficiency virus reverse transcriptase inhibitor, sulfated polysaccharides extracted from sea algae. *Antimicrob. Agents Chemotheraphy* **31**, 1524-1528.
82. Newman D. J., Cragg G. M. 2004. Advanced preclinical and clinical trials of natural products and related compounds from marine sources. *Curr. Med. Chem*. **11**, 1693-1713.
83. Newman D. J., Cragg G. M. 2004. Marine natural products and related compounds in clinical and advanced preclinical trials. *J. Nat. Prod*. **67**, 1216-1238.
84. Newman D. J., Cragg G. M., Snader K. M. 2000. The influence of natural products upon drug discovery. *Nat. Prod. Rep.* **17**, 215-234.
85. Newman D. J., Cragg G. M., Snader K. M. 2003. Natural products as sources of new drugs over the period 1981-2002. *J. Nat. Prod.* **66**, 1022-1037.
86. Oehninger S., Clark G. F., Acosta A. A., Hodgen G. D. 1991. Nature of the inhibitory effect of complex saccharide moieties on the tight binding of human spermatozoa to the human zona pellucida. *Fertil. Steril*. **55**, 165-169.
87. Ohgami K., Shiratori K., Kotake S., Nishida T., Mizuki N., Yazawa K., Ohno S. 2003. Effects of astaxanthin on lipopolysaccharide-induced inflammation *in vitro* and *in vivo*. *Invest. Ophthalmol. Visual Sci*. **44**, 2694-2701.
88. Oku N., Gustafson K. R., Cartner L. K., Wilson J. A., Shigematsu N., Hess S., Pannell L. K., Boyd M. R., McMahon, J. B. 2004. Neamphamide A, a new HIV-inhibitory depsipeptide from the Papua New Guinea marine sponge *Neamphius huxleyi*. *J. Nat. Prod*. **67**, 1407-1411.

89. Palermo J. A., Flower B. P., Seldes A. M. 1992. Chondriamides A and B, new indolic metabolites from the red alga *Chondria* sp.. *Tetrahedron Lett*. **33**, 3097-3100.
90. Paterson I., Anderson E. A. 2005. The renaissance of natural products as drug candidates. *Science* **310**, 451-453.
91. Patrzykat A., Douglas S. E. 2003. Gone gene fishing: how to catch novel marine antimicrobials. *Trends in Biotechnology* **21**, 362-369.
92. Pereira H. S., Leao-Ferreira L. R., Moussatche N., Teixeira V. L., Cavalcanti D. N., Costa L. J., Diaz R., Frugulhetti I. C. 2004. Antiviral activity of diterpenes isolated from the Brazilianmarine alga *Dictyota menstrualis* against human immunodeficiency virus type 1 (HIV-1). *Antivir. Res.* **64**, 69-76.
93. Ponce N. M. A., Pujol C. A., Damonte E. B., Flores M. L., Stortz C. A. 2003. Fucoidans from the brown seaweed *Adenocystis utricularis*: extraction methods, antiviral activity and structural studies. *Carbohyd. Res*. **338**, 153-165.
94. Posadas I., De Rosa S., Terencio M. C., Paya M., Alcaraz M. J. 2003. Cacospongionolide B suppresses the expression of inflammatory enzymes and tumour necrosis factor-alpha by inhibiting nuclear factor-kappa B activation. *Br. J. Pharmacol*. **138**, 1571-1579.
95. Posadas I., Terencio M. C., Randazzo A., Gomez-Paloma L., Paya M., Alcaraz M. J. 2003. Inhibition of the NF-kappaB signaling pathway mediates the anti-inflammatory effects of petrosaspongiolide M. *Biochem. Pharmacol*. **65,** 887-895.
96. Randazzo A., Debitus C., Minale L., Pastor P. G., Alcaraz M. J., Payá M., Gomez-Paloma L. 1998. Petrosaspongiolides M-R: new potent and selective phospholipase A2 inhibitors from the new Caledonian marine sponge *Petrosaspongia nigra*. *J. Nat. Prod.* **61**, 571-575.
97. Rodríguez I. I., Shi Y. P., Garcia O. J., Rodriguez A. D., Mayer A. M., Sanchez J. A., Ortega-Barria E., Gonzalez J. 2004. New pseudopterosin and seco-pseudopterosin diterpene glycosides from two Colombian isolates of *Pseudopterogorgia elisabethae* and their diverse biological activities. *J. Nat. Prod*. **67**, 1672-1680.
98. Rodriguez-Nieto, S. Gonzalez-Iriarte M., Carmona R., Munoz Chapuli R., Medina M. A., Quesada A. R. 2002. Antiangiogenic activity of aeroplysinin-1, a brominated compound isolated from a marine sponge. *FASEB J.* **16**, 261-263.
99. Sasaki M., Tsuda M., Sekiguchi M., Mikami Y., Kobayashi J. 2005. Perinadine A, a novel tetracyclic alkaloid from marine-derived fungus *Penicillium citrinum. Org. Lett.* **7**, 4261-4264.
100. Sata N., Abinsay H., Yoshida W. Y., Horgen F. D., Sitachitta N., Kelly M., Scheuer P. J. 2005. Lehualides A-D, metabolites from a Hawaiian sponge of the genus *Plakortis*. *J. Nat. Prod.* **68**, 1400-1403.
101. Sequin-Frey M., Tamm C. 1971. Gentisyl acetal and chlorgentisyl alcohol, two new metabolites from a *Phoma* species *Helv. Chim. Acta*, **54**, 851-861.
102. Shizuri Y. Yamada K. 1985. Laurebiphenyl, a dimeric sesquiterpene of the cyclolaurane-type from the red alga *Laurencia nidifica. Phytochemistry* **24**, 1385-1386.
103. Shubina L. K., Fedorov S. N., Radchenko O. S., Balaneva N. N., Kolesnikova S. A., Dmitrenok P. S., Bode A., Dong Z. Stonik V. A. 2005 Desmethylubiquinone Q2 from the far-Eastern ascidian *Aplidium glabrum*: structure and synthesis. *Tetrahedron Lett.* **46**, 559-562.
104. Simmons T. L., Andrianasolo E., Kerry McPhail K., Patricia Flatt P., William H. Gerwick W. H. 2005. Marine natural products as anticancer drugs. *Mol. Cancer Ther.* **4(2)**, 333-342.
105. Simon-Levert A., Arrault A., Bontemps-Subielos N., Canal C., Banaigs B. 2005. New meroterpenes from the ascidian *Aplidium aff.* Densum. *J. Nat. Prod.* **68**, 1412-1415.
106. Soria-Mercado I. E., Prieto-Davo A., Jensen P. R., Fenical W. 2005. Antibiotic terpenoid chloro-dihydroquinones from a new marine actinomycete. *J. Nat. Prod.* **68**, 904-910.
107. Soriente A., De Rosa M.M., Scettri A., Sodano G., Terencio M. C., Payá M., Alcaraz M. J. 1999. Manoalide. *Curr. Med. Chem*. **6**, 415-431.
108. Spieler R. 2002. Seaweed compound's anti-HIV efficacy will be tested in southern *Africa. Lancet*. **359**, 1675
109. Stierle D. B., Wing R. M., Sims J. J. 1979. Marine natural products-XVI polyhalogenated acyclic monoterpenes from the red alga *Plocamium* of antarctica *Tetrahedron* **35**, 2855-2859.
110. Sugawara I., Itoh W., Kimura S., Mori S., Shimada K. 1989. Further characterization of sulfated homopolysaccharides as anti-HIV agents. *Experientia* **45**, 996-998.
111. Sun J., Shi D., Ma M., Li S., Wang S., Han L., Yang Y., Fan X., Shi J. He L. 2005. Sesquiterpenes from the red alga *Laurencia tristicha***.** *J. Nat. Prod.* **68**, 915-919.
112. Tasdemir D., Mallon R., Greenstein M., Feldberg L. R., Kim S. C., Collins K., Wojciechowicz D., Mangalindan G. C., Con- cepcio´ n G. P., Harper M. K., *et al.* 2002. Aldisine alkaloids from the Philippine sponge *Stylissa massa* are potent inhibitors of mitogen-activated protein kinase kinase-1 (MEK-1). *J. Med. Chem.* **45**, 529-532.
113. Terracciano S., Aquino M., Rodriguez M., Monti M. C., Casapullo A., Riccio R., Gomez-Paloma L. 2006 Chemistry and biology of anti-inflammatory marine natural products: molecules interfering with cyclo-oxygenase, NF-kB and other unidentified targets. *Current Medicinal Chemistry* **13**, 1947-1969.
114. Tsuda M., Sasaki M., Mugishima T., Komatsu K., Sone T., Tanaka M., Mikami Y., Kobayashi J. 2005. Scalusamides A~C, new pyrrolidine alkaloids from marine-derived fungus. *J. Nat. Prod.* **68**, 273-76.
115. Wasserman H. H., Rodgers G. C. and Keith D. D. 1969. Metacycloprodigiosin, a tripyrrole pigment from *Streptomyces longisporusruber*. *J. Am. Chem. Soc.* **91**, 1263-1264.
116. Williams P. G., Buchanan G. O., Feling R. H., Kauffman C. A., Jensen P. R., Fenical W. 2005. New

cytotoxic salinosporamides from the marine actinomycete *Salinispora tropica*. *J. Org. Chem.* **70**, 6196-6203.

117. Witvrouw M., Este J. A., Mateu M. Q., Reymen D., Andrei G., Snoeck R., Ikeda S., Pauwels R., Bianchini N. V., Desmyter J., de Clercq E. 1994. Activity of a sulfated polysaccharide extracted from the red seaweed *Aghardhiella tenera* against human immunodeficiency virus and other enveloped viruses. *Antiviral Chem. Chemotheraphy* **5**, 297-303.
118. Yuan G., Wahlqvist M. L., He G., Yang M., Li D. 2006. Natural products and anti-inflammatory activity. *Asia Pacific J. Clin. Nutr*. **15**, 143-152.
119. Zeitlin L., Whaley K. J., Hegarty T. A., Moench T. R., Cone R. A. 1997. Tests of vaginal microbicides in the mouse genital herpes model. *Contraception* **56**, 329-335.