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Marine derived pharmaceuticals- Development of natural health products from marine biodiversity

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Abstract: Marine derived pharmaceuticals have been used as sources of chemical diversity in drug discovery programs. Marine biotechnology is an emerging field encompassing marine biomedicine and it also plays an increasing role in developing and producing new products, particularly in the pharmaceutical industry. The fundamental enthusiasm for this discipline is clearly derived from the enormous biodiversity and genetic uniqueness of life in the sea. Pushed by the accelerating search for new marine natural products and biomaterials as potential pharmaceuticals, pharmaceutical companies are actively screening marine sources potential new active substances. Marine-derived pharmaceuticals are the result of a breakthrough application of biotechnology to marine sources to enable them to produce therapeutic agents that could ultimately be used by the medical community to combat life-threatening illnesses. Some examples of commercially available marine bioproducts are Ara-A (acyclovir) as antiviral drug used in herpes infections from marine sponges, *Tethya crypta.* Ara-C (cytosar-U, cytarabine) as anticancer drug used in leukemia and non-Hodkin's lymphoma from marine sponge, *Tethya crypta* etc. There are several marine-derived compounds currently in clinical trials and it is likely that many more will advance to the clinic as more scientists look to the sea for these biotechnological uses. Marine derived pharmaceutical products need much basic and applied research in order to put this resource on the same level as the patented pharmaceutical products so achieving acceptation by the medical system, and satisfying the requisite of efficacy, safety and quality.

Key words: Marine-derived pharmaceuticals, chemical diversity, marine biotechnology,pharmaceutical potential, marine organisms.

Introduction

Oceans cover seventy percent of the surface of the planet. Countless marine plants and animals contain biochemical secrets that, if unlocked, can provide new insights and understanding of human diseases and their treatment. Today, with the modern tools of molecular biology and advanced technology, the potential for marine environment to provide new drugs to treat human illnesses has never offered greater promise. Just as plants have provided numerous medical drugs, from aspirin to morphine, marine organisms are another vast reservoir of original molecules that could prove to have therapeutic properties[1].

Although large numbers of novel compounds have been isolated from marine organisms and many of these substances have pronounced biological activity, only very few have been marketed as pharmaceutical products. A few have also been valuable as 'lead' compounds, which have led to derivatives of them being marketed. Some compounds with cytotoxic properties either have been or are undergoing various phases of clinical trial and thus have the prospect of being new pharmaceutical products[2].

The term "marine biotechnology" denotes a potentially wide variety of activities, which may be divided into the following broad categories:

- Genetically engineered marine organisms
- Manufacture of pharmaceuticals and nutraceuticals
- Chemicals produced by or found in marine organisms have been shown to have a wide variety of applications as pharmaceuticals for humans and other animals. Uses have included antibacterial, analgesic, anti-inflammatory, antimalarial, anticancer, antiparasitic and antiviral agents[3].

Pharmaceutical Potentials from Marine Sources

Despite the much compounds isolated from marine organisms and the biological activities attributed to many of them, those that have either been marketed or are under development are very few. The potential for marine natural products as pharmaceutical was first developed in the 1950s which led to two marine-derived pharmaceuticals that are still in use today. Ara-C is an anti-cancer drug (used against acute myelocytic leukemia and non-Hodgkin's lymphoma) and Ara-A used as an antiviral drug for treating herpes. More and more medicines are developed from natural products. About 15,000 natural products have been described and about 30% of these natural products have been isolated from sponges[4].

Table 1 Shows different drugs with their therapeutic categories and sources

S. No.	Drugs	Therapeutic Category	Source
1	Prialt™,	Analgesic	*Conus magus*
2	Squalimine KRN 7000 Eleutherobin E7389 Discodermolide Dictyostatin 1 Salinosporamide A Apratoxin Bryostatins 1 And 2 Dolastatin H Isodolastatin H Auripyrone A and B Niphatesine D Clavepictine A and B Amphidinolides G and H Lejimalides A-D Sporiolides A and B Spongiostatin 4 Cephalostatin 1 Sorbicillactone A and B	Anticancer	*Shark* *Agelas mauritianus* *Eleutherobia sp.* *Halicondria okadai* *Discodermia dissolute* *Spongia genus* *Salinospora* *Lyngbya sp.* *Bugula neritina* *Dolabella auricularia* *Dolabella auricularia.* *Dolabella auricularia* *Niphates species* *Clavelina picta* *Amphidinium sp.* *Eudistoma cf. rigida* *Cladosporium sp.* *Spirasrella spinispirulifer* *Cephalodiscus gilchristi* *Ircinia fasciculote*
3	Topsentin	Anti-inflammatory	*Spongosporites ruetzleri*

	Sesterterpene, palaulol Sesquiterpene furan Tsitsixenicin A 5α-pregna-1,20-dien-3-one Tsitsixenicin B		*Fascaplysinopsis sp.* *Sinularia sp.* *Capenella thyrsoidea* *Capenella thyrsoidea* *Alcyonium valdivae*
4	Manzamine A Axisonitrile 3 Kalihinol A	Antimalarial	*Haliclona sp.* *Acanthella klethra* *Acanthella sp.*
5	Cephalosporins Istamycin Speradine A Modiolides A and B Seragakinone A 2*S*-acetamido-3s-acetoxy-5E	Antimicrobial	*Cephalosporium acremonium* *Streptomyces tenjimariensi* *Aspergillus tamari* *Paraphaeosphaeria sp.* *Cocodinium sp.* *Pseudodistoma sp.*
6	Ara A Didemnin B Rietone Avarol and Avarone	Antiviral	*Tethya crypta.* *Tridemnum sp.* *Alcyonium fauri* *Disidea avara*
7	α-Kainic acid	Antiparasitic	*Digenia simplex*
8	Orthopedic implants	Bone grafting	*Coral (Family Isididae)*
9	Okadaic acid	Molecular probe	*Prorocentrum belizeanum*
10	Polyketide synthase	Enzyme	*Pseudoceratina clavata*
11	Speradine A	Ca^{2+}-ATPase and histone deacetylase ihibitor	*Aspergillus tamari*

Many of the compounds shown to have promising biological properties have complicated structures and it would be impossible in a limited survey to include all the compounds considered to have significant biological activity. So, in this review, few examples given of biologically active compounds to illustrate the range of structures reported and also the variety of marine source from which they have been isolated.

Antimicrobial Agents

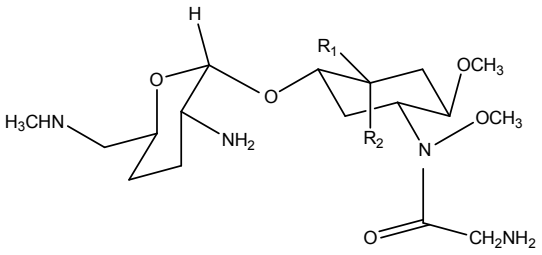
The cephalosporins are good example of antimicrobial agents which owe their origin to a marine source. Cephalosporin C was isolated from marine fungus, *Cephalosporium acremonium*. A semi-synthetic derivative of this, cephalothin sodium, has been widely used as an antibiotic.

Marine microorganisms which can be grown in culture to yield valuable compounds would be of interest to the pharmaceutical industry. Examples of those compounds which have been obtained by fermentation are the istamycins produced by the marine actinomycete *Streptomyces tenjimariensis* SS-939. These compounds were reported to have *in vitro* activity against both Gram-negative and Gram-positive bacteria, including those with known resistance to the aminoglycoside antibiotics[5]. Modiolides A and B, 10-

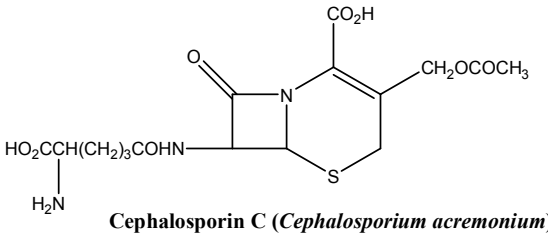
membered macrolides, were isolated from the cultured broth of a fungus *Paraphaeosphaeria sp.*[6]. Modiolides A and B show antibacterial activity against *Micrococcus luteus* and antifungal activity against *Neurospora crassa*.

Seragakinone A is an anthracycline derived pentacyclic metabolite isolated from the mycelium of a fungus *Cocodinium sp*., which was separated from the rhodophyta *Ceratodictyon spongiosum*[7-8]. Seragakinone A exhibits antimicrobial activity against *Staphylococcus aureus*, *Micrococcus luetus*, *Corynebacterium xerosis* and *Bacillus subtilis*.

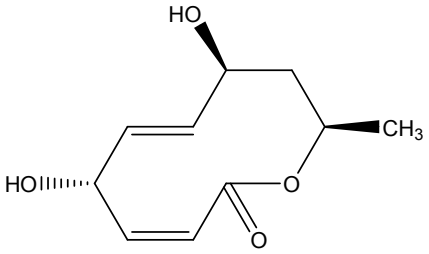
2*S*-acetamido-3S-acetoxy-5E,13-tetradacadiene, is peracetylated derivative of acyclic amino acid isolated from *Pseudodistoma sp*. show antimicrobial activity due to their ability to disrupt bacterial cell walls[9].



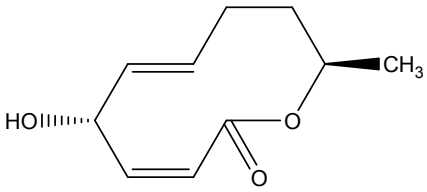
Istamycin A R_1 = H, R_2 = NH_2
Istamycin B R_1 = NH_2, R_2 = H
***(Streptomyces tenjimariensis*)**



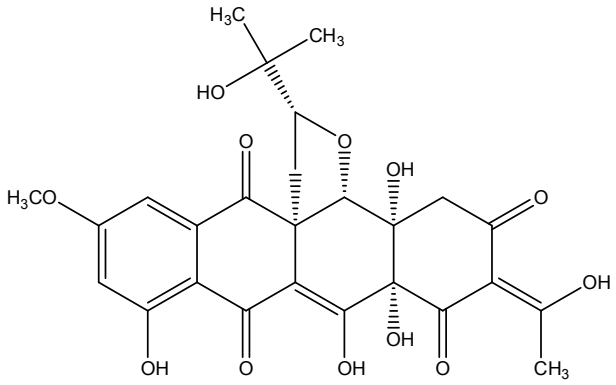
Cephalosporin C (*Cephalosporium acremonium*)



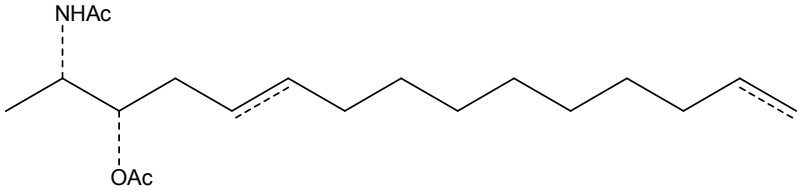
Modiolide A (*Paraphaeosphaeria sp.*)



Modiolide B (*Paraphaeosphaeria sp.*)



Seragakinone A (*Ciratodictyon spongiosum*)



2S-acetamido-3s-acetoxy-5E,13-tetradacadiene (*Pseudodistoma sp*.)

Fig 1. It shows different examples of antimicrobial agents with their structures.

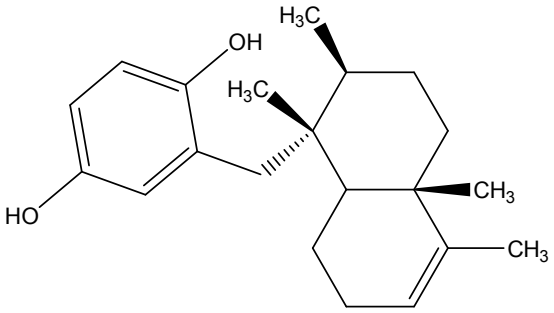
Antiviral Agents

The first compound reported to have significant antiviral activity is Ara-A which is a semi-synthetic substance based on the arabinosyl nucleosides isolated from the sponge *Tethya crypta*. Other compounds reported to have antiviral properties include the didemnins, which are cyclic depsipeptides isolated from *Tridemnum sp*. (tunicates). Didemnin B an antiviral, also shows pronounced antitumor activity[10]. Patellazole B isolated from the tunicate, *Lissoclinum patella* has very potent *in vitro* activity against herpes simplex viruses[11].

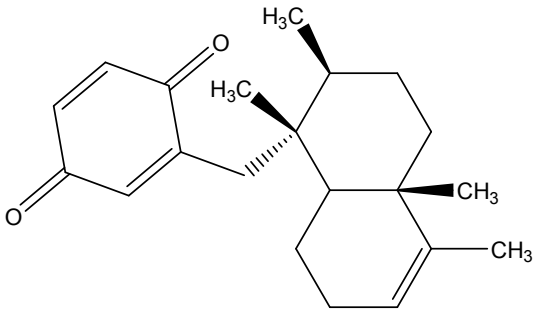
Seulezonones A and B are metabolites containing a phenalenone-dione nucleus isolated from the broth of *Penicillium sp*., which was separated from a marine bivalve *Mytilus coruscus*[12]. Seulezonones A and B inhibit bovine DNA polymerase α and γ[13].

The endemic red soft coral, *Alcyonium fauri*, is one of the most conspicuous shallow water octocorals found along the southeast coast of Southern Africa[14]. Specimens of this species collected near Port Alfred yielded three related sesquiterpenes including the major metabolite rietone. Rietone exhibited activity in the NCI's CEM-SS cell line screen; a general screen designed to identify metabolites acting any stage in the reproductive cycle of the human immunodeficiency virus (HIV)[15].

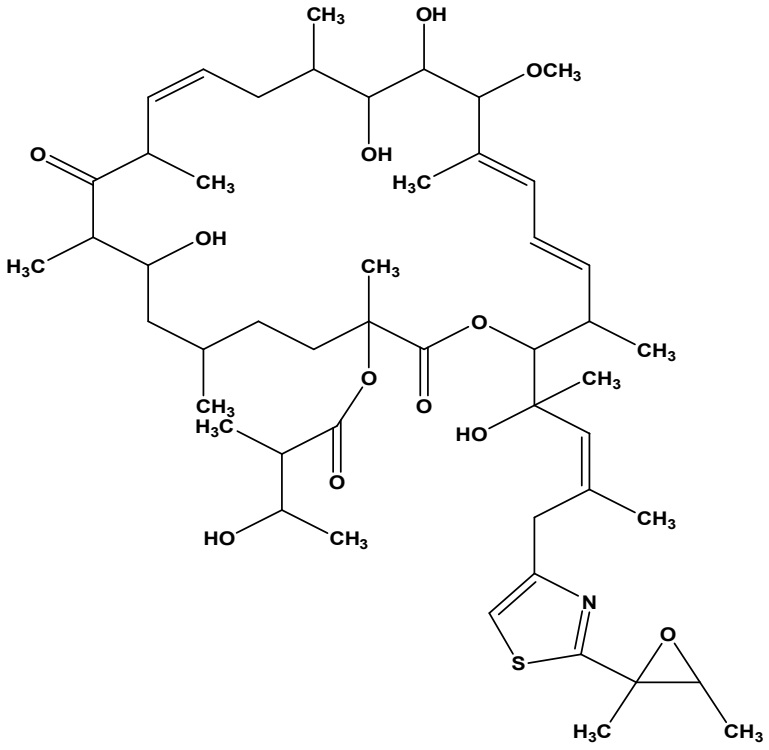
Other antiviral compounds include avarol and avarone isolated from a sponge, *Disidea avara*. These compounds inhibit the immunodeficiency virus; have high therapeutic indices and the ability to cross the blood–brain barrier[16].



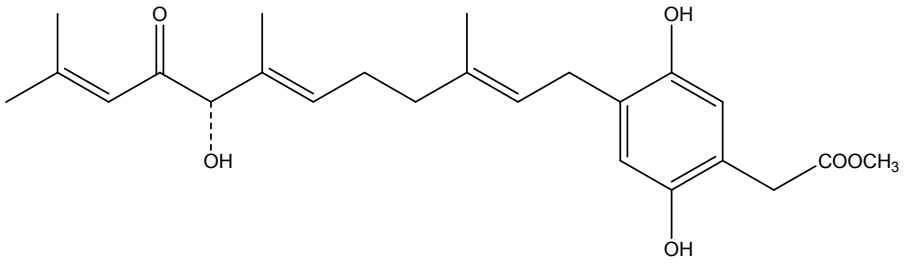
Avarol (*Disidea avara*)



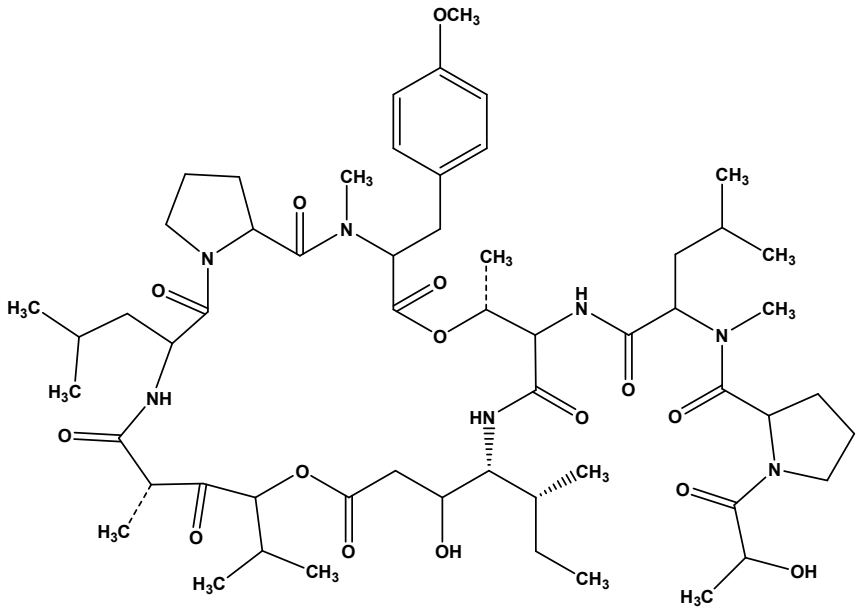
Avarone (*Disidea avara*)



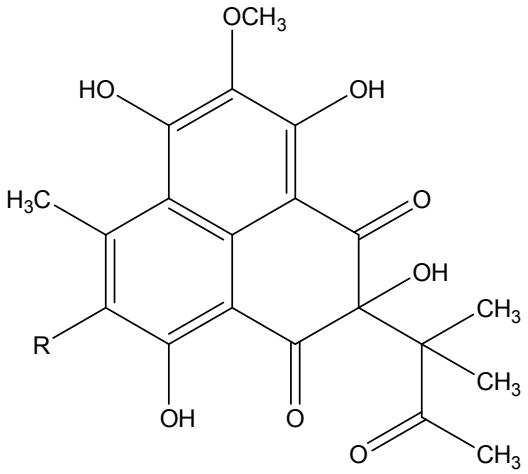
Patellazole B (*Lissoclinum patella*)



Rietone (*Acyonium fauri*)



Didemnin B (*Tridemnum sp.*)



R= H, Sculezonones A (*Mytilus coruscus*)
R= OH, Sculezonones B (*Mytilus coruscus*)

Fig 2. It shows different examples of antiviral agents with their structures.

Anticancer Agents

Many compounds isolated from marine organisms have been tested for cytotoxicity in the search for drugs active against cancer. Probably the best known compounds with potential as anticancer drugs are the macrolides known as bryostatins, isolated primarily from the bryozoan, *Bugula neritina*, although some have been extracted from sponges and tunicates. Bryostatin-1 triggers activation and differentiation of peripheral blood cells from lymphocytic leukaemia patients[17].

A family of cyclic and linear peptides and depsipeptides known as dolastatins has been isolated from the sea hare, *Dolabella auricularia.* Dolastatin-10 when first reported was claimed to be the most active neoplastic substance known[18]. More recently, other dolastatins have been isolated and both Dolastatin-H (*Dolabella auricularia*), Isodolastatin-H (*Dolabella auricularia*) as highly cytotoxic agent[19]. Other cytotoxic agents are the polypropionates, auripyrone-A and B which have also been extracted from *Dolabella auricularia*[20].

α-Galactosylceramide (α-Gal-Cer ; KRN7000), an agelasphin derivative, is a biological response modifier (BRM). Agelasphins was isolated from an extract of the marine sponge, *Agelas mauritianus*, as active substances. α-Gal-Cer ; KRN7000, a chemically synthesized α - Galactosylceramide, is a specific ligand for human and mouse natural killer T (NKT) cells, KRN7000 exhibits potent antitumor activity in various kinds of *in vivo* murine experimental models including subcutaneously implanted model and metastatic models in the liver and lung[21-22].

E7389 is a cell-killing derivative of halichondrin B, one of a number of compounds originally isolated in 1985 from the Japanese sponge *Halicondria okadai*. Developed E7389 is a synthetic compound that is currently in its first phase of human trials (Phase I) for the treatment of non-small cell lung cancer and other cancers[23].

Discodermolide isolated from the sponge *Discodermia dissolute*, most promising natural products discovered to date. Discodermolide has been shown to be more potent than taxol and is being tested for use against solid tumors[24]. Dictyostatin-1 is an anticancer compound was originally isolated in 1993 from a shallow-water sponge in the Spongia[25].

Salinosporamide A, isolated from the microbe *Salinospora tropica* exhibits strong cytotoxicity against melanoma, colon cancer, breast cancer, and non-small cell lung cancer[26-27]. It also shows potency 35 times greater than that of omuralide, a powerful anticancer agent with a new way of controlling cancer cell growth[28].

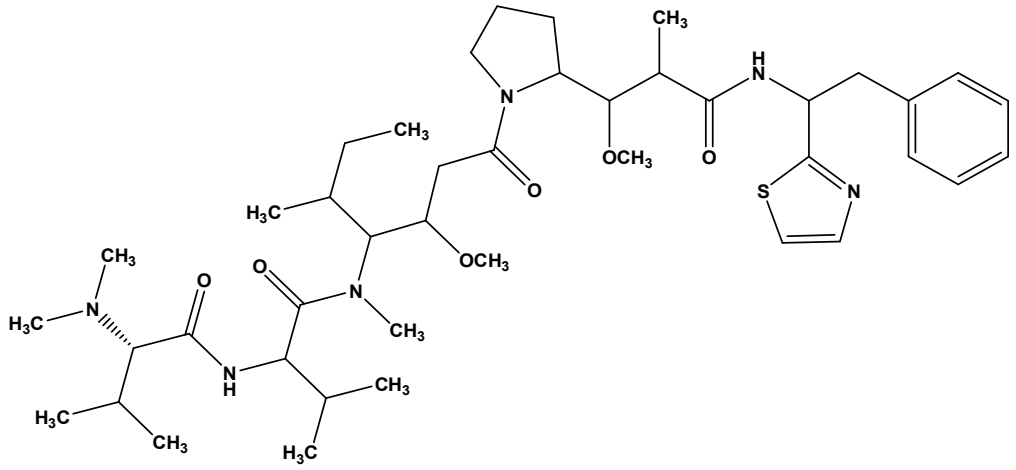
Amphidinolides G and H isolated from the marine dinoflagellate *Amphidinium sp*. (Y-25 strain) are potent cytotoxic 27 and 26 membered macrolides, respectively, having structural unique features such as an allyl epoxide and vicinally located one carbon branches[29].

Sporiolides A and B, two new twelve-membered macrolides, were isolated from the cultured broth of a fungus *Cladosporium sp*. which was separated from brown alga *Actinotrichia fragilis*[30-31]. Sporiolides A and B, exhibit cytotoxicity against L1210 cells.

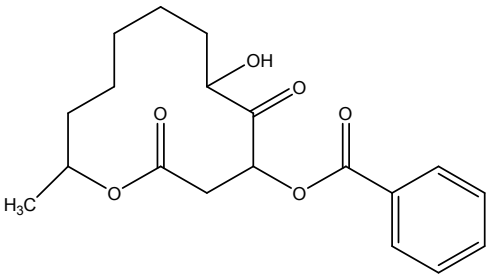
Lejimalides (A-D) obtained from a marine tunicate *Eudistoma cf. rigida* are unique 24-membered polyene macrolides having two methoxy groups, four dienes units, and a *N*-formyl-L-serine terminus, and exhibit potent *in vitro* cytotoxic activity[32-33].

Collections of the ubiquitous wall sponge *Spirasrella spinispirulifer*, a source of spongiostatin 4 and additional collection of the marine tube worm, *Cephalodiscus gilchristi*, which had yielded cephalostatin 1. Both compounds are undoubtedly the most significant potential anticancer compounds yet to be discovered from South African marine organisms[34-37].

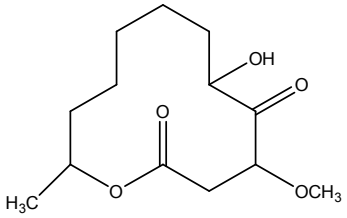
Sorbicillin-derived alkaloids sorbicillactone A and its 2',3'-dihydro analog sorbicillactone B from a salt-water culture of a *Penicillium chrysogenum* strain isolated from a specimen of the mediterranean sponge *Ircinia fasciculata* is active against leukemia cells without showing notable cytotoxicity[38]. (Fig 3.)



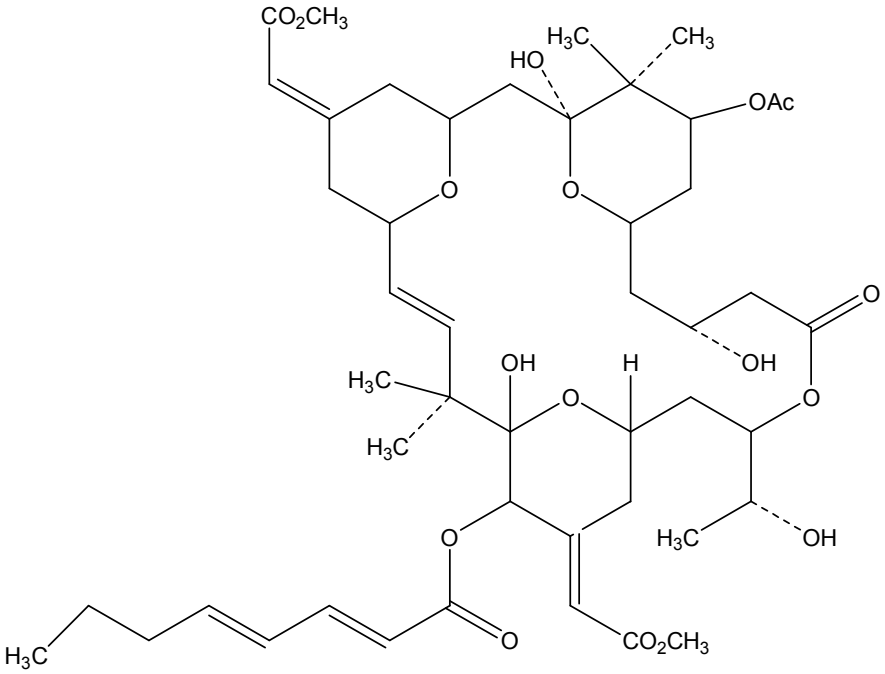
Dolastatin-10 (*Dolabella auricularia*)



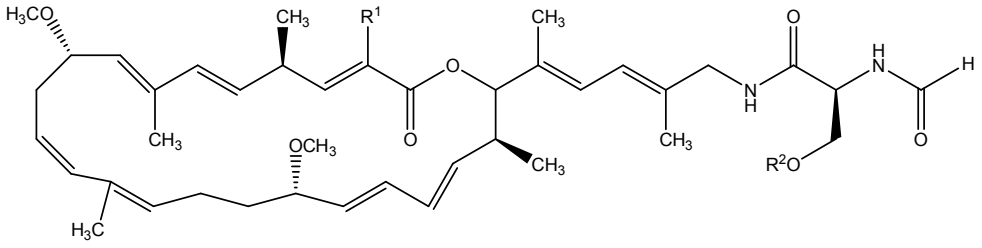
Sporiolide A (*Actinotrichia fragilis*)



Sporiolide B (*Actinotrichia fragilis*)

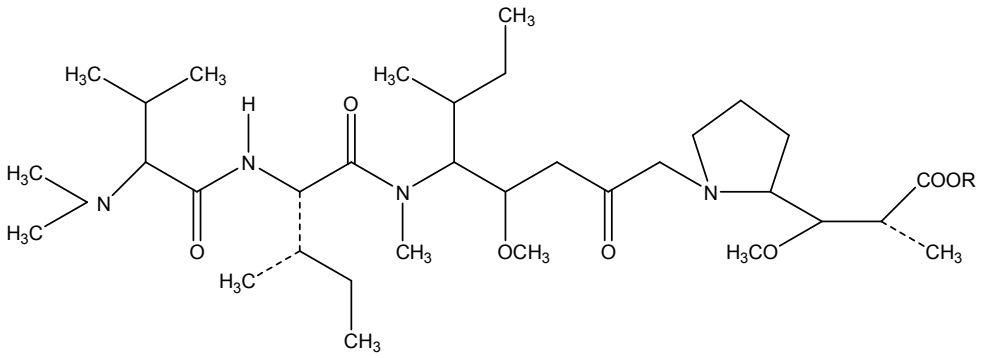


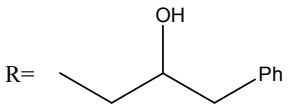
Bryostatin (*Bugula neritina*)



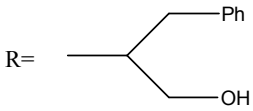
Lejimalides A-D (*Eudistoma cf. rigida*)

A: R^1=R^2=H
B: R^1=CH3, R^2=H
C: R^1=H, R^2=SO_3H
D: R^1=CH_3, R^2=SO_3H

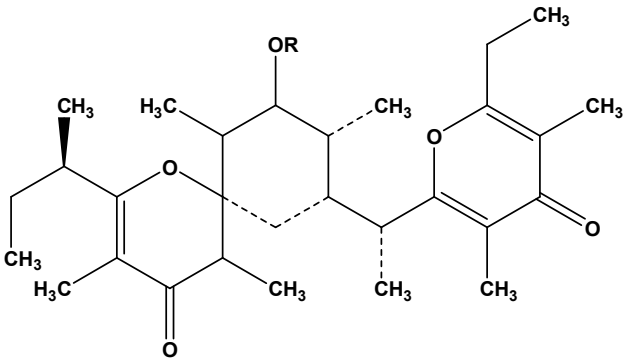




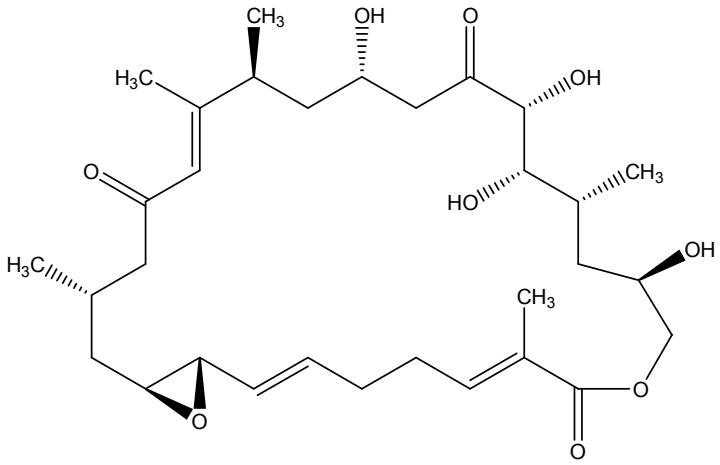
Dolastatin H (*Dolabella auricularia*)



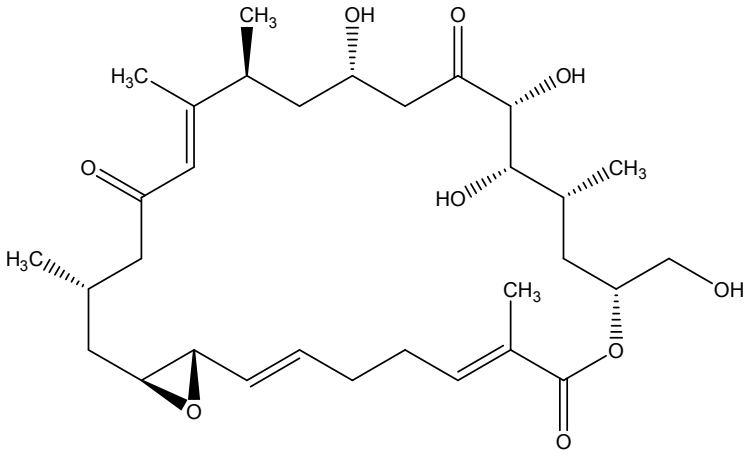
Isodolastatin H (*Dolabella auricularia*)



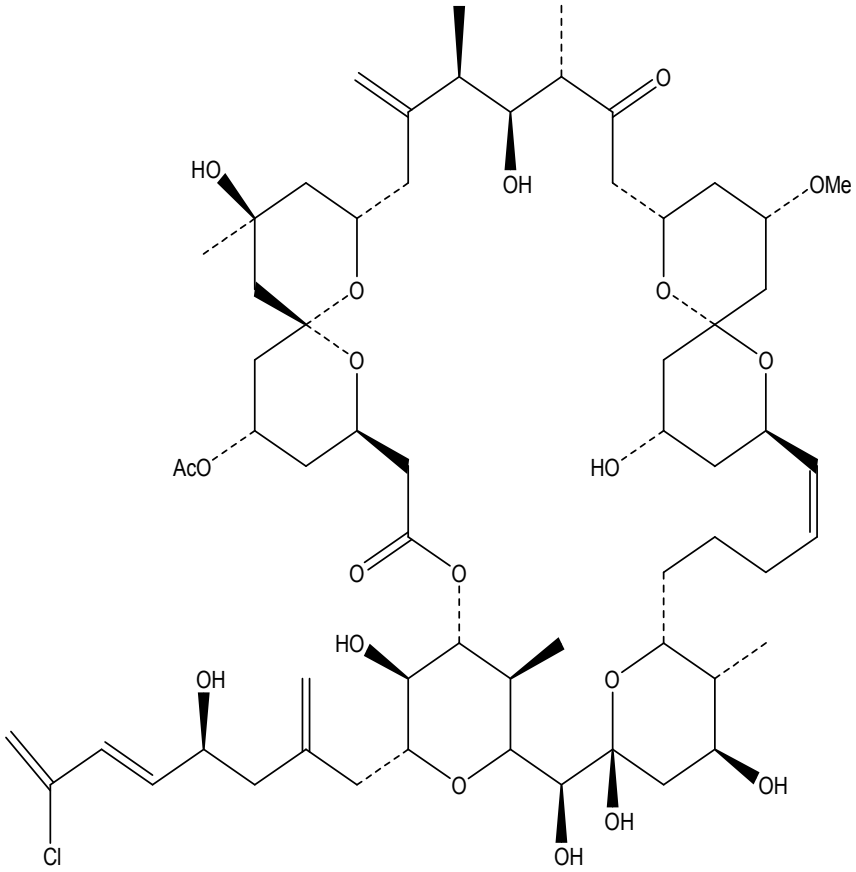
R = $COCH_2CH(CH_3)_2$ = Auripyrone A (*Dolabella auricularia*)
R = $COCHCH_3(C_2H_5)$ = Auripyrone B (*Dolabella auricularia*)



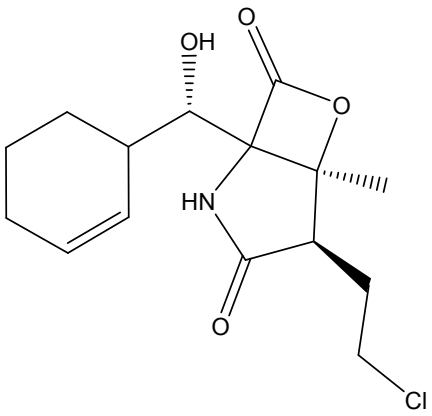
Amphidinolide G (*Amphidinium sp.*)



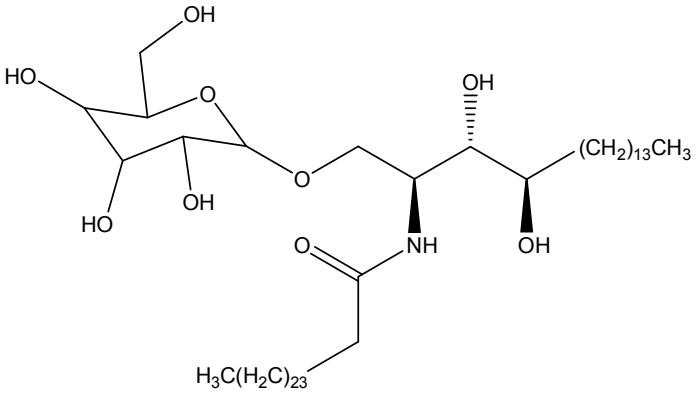
Amphidinolide H (*Amphidinium sp.*)



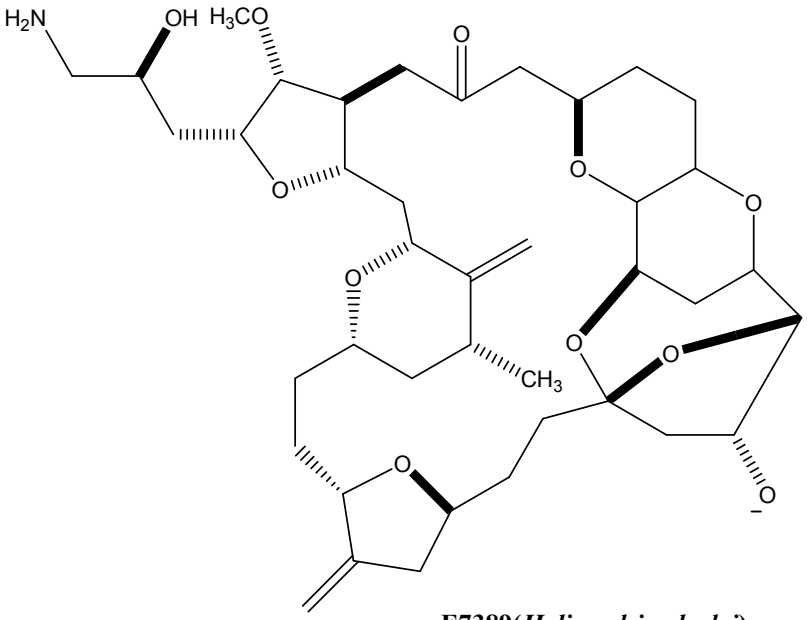
Spongistatin 4 (*Spirastrella spinispirulifer*)



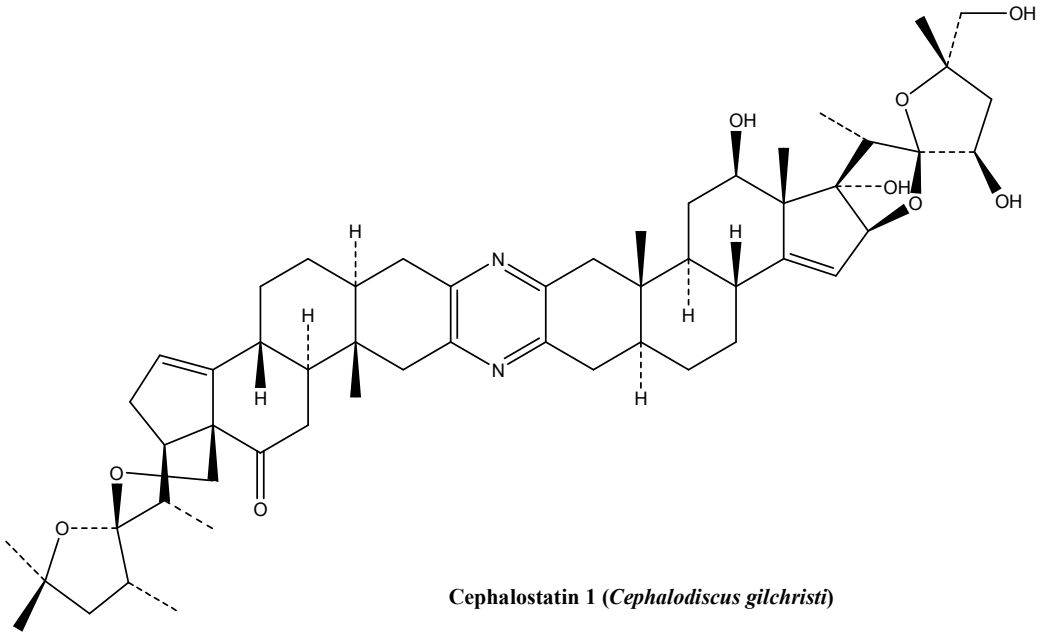
Salinosporamide A (*Salinispora tropica*)



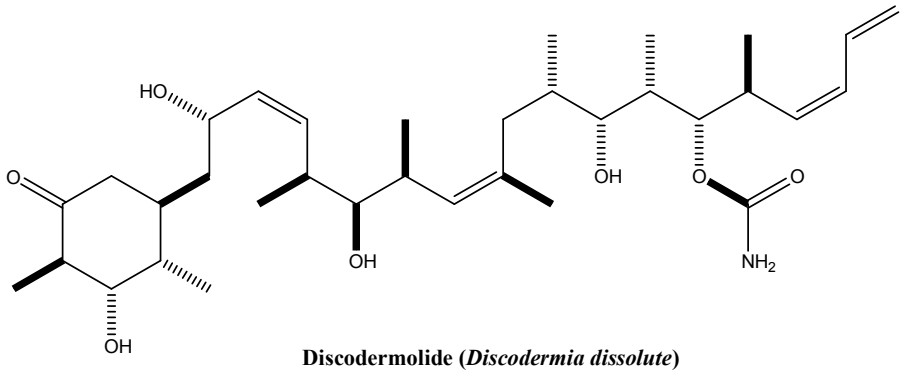
KRN7000 (*Agelas mauritianus*)



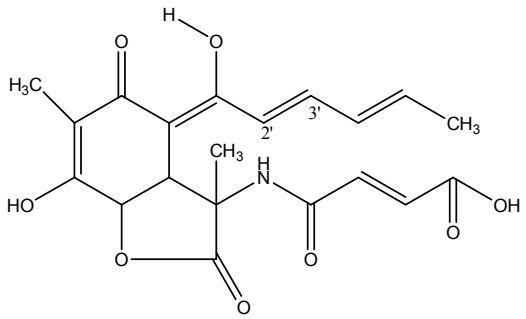
E7389(*Halicondria okadai*)



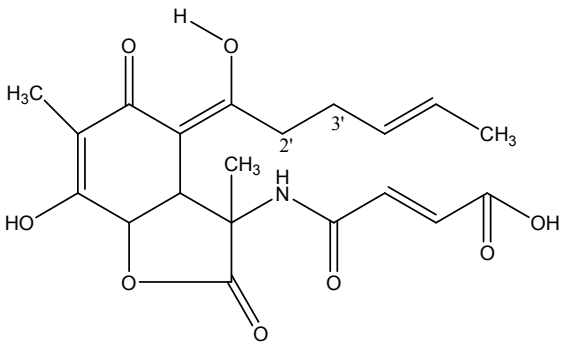
Cephalostatin 1 (*Cephalodiscus gilchristi*)



Discodermolide (*Discodermia dissolute*)



Sorbicillactone A (*Penicillium chrysogenum*)



Sorbicillactone B (*Penicillium chrysogenum*)

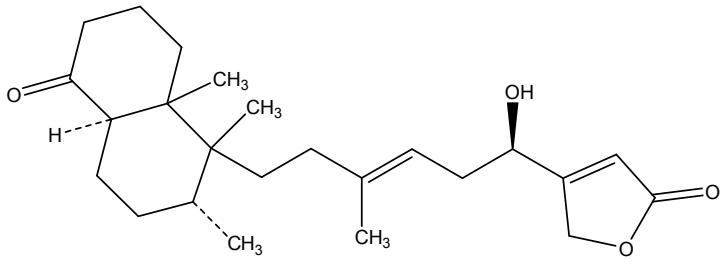
Fig 3. It shows examples of different anticancer agents with their structures.

Anti-inflammatory Agents

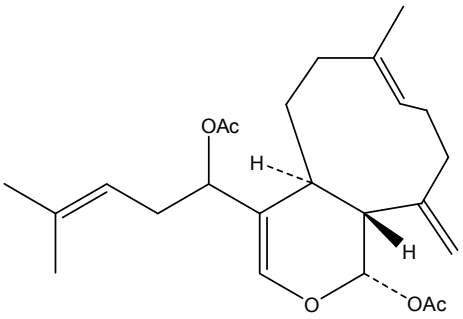
In more recent years, interesting anti-inflammatories have been isolated from marine animals. Examples are the sesterpene, palaulol from the sponge *Fascaplysinopsis sp*.[39] and a sesquiterpene furan from the coelenterate, *Sinularia s*p. this has subsequently been synthesized[40].

Terpenoid containing natural products predominates in soft corals, *Capenella thyrsoidea*, collected in the Tsitsikamma Marine Reserve, yielded a series of xenicane diterpenes, e.g. tsitsixenicin A and pregnadiene sterols, e.g. 5α-pregna-1,20-dien-3-one. Anti-inflammatory activity also shown by the diterpene secondary metabolites, tsitsixenicin B isolated from another Southern African soft coral, *Alcyonium valdivae*[41-42].

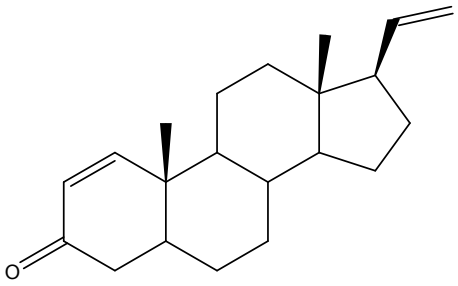
The compound topsentin, a substance isolated from the deep-water sponge *Spongosporites ruetzleri*, shows promise as an anti-inflammatory agent to treat arthritis and skin irritations. Topsentin is also being investigated as a treatment for Alzheimer's disease and to prevent colon cancer[43]. (Fig 4.)



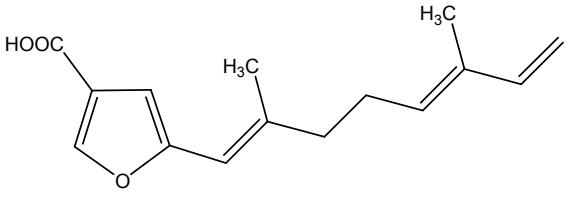
Palaulol (*Fascaplysinopsis sp.*)



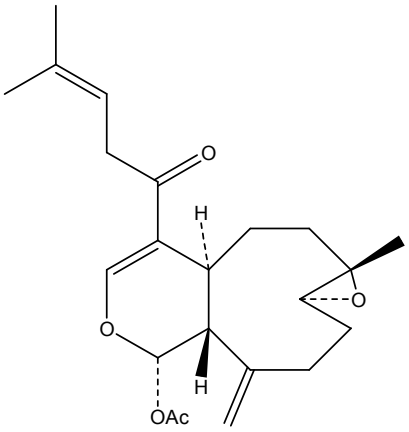
Tsitsixenicin A (*Capnella thyrsoidea*)



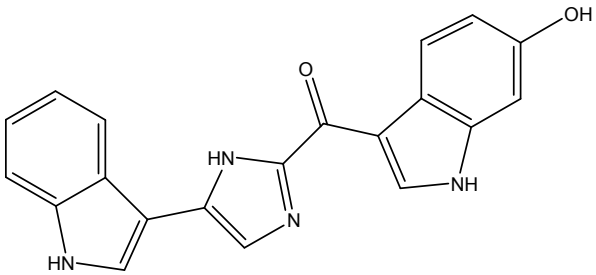
5α-pregna-1,20-dien-3-one (*Capnella thyrsoidea*)



Sesquiterpene furan (*Sinularia sp.*)



Tsitsixenicin B (*Acyonium valdivae*)

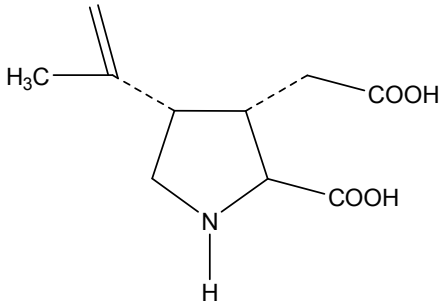


Topsentin (*Spongosporites ruetzleri*)

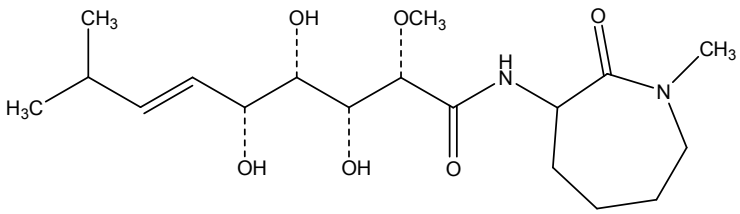
Fig 4. It shows different examples of anti-inflammatory agents with their structures.

Antiparasitic Agents

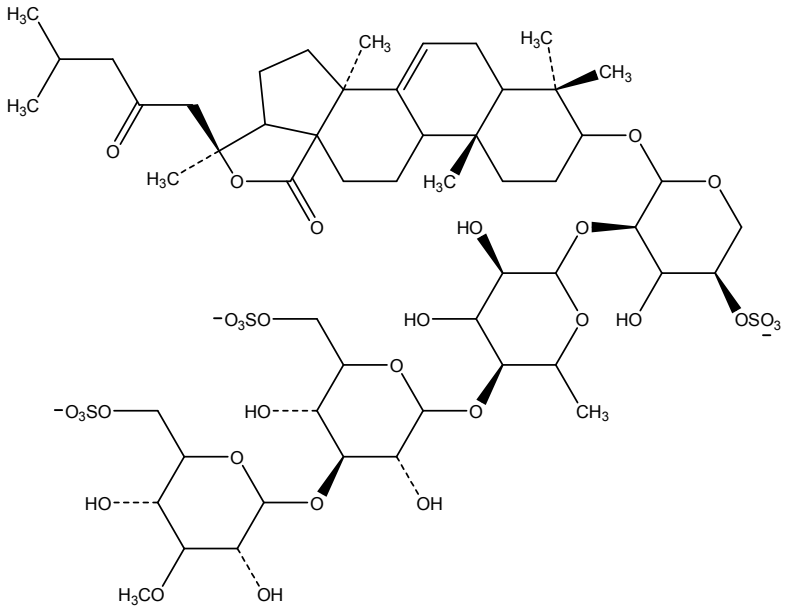
Digenia simplex, a red alga, has been used as a vermifuge for very many years. Its active component, α-kainic acid is marketed for the treatment of parasitic round worm, whip worm and tape worm. Marine animals have been tested as sources of antiparasitic compounds and this work has led to the isolation and for characterization example, bengamide F which has anthelmintic properties and cucumechinoside F from sea cucumber which has antiprotozoal activity[44].(Fig 5.)



α -Kainic acid (*Digenia simplex*)



Bengamide F



Cucumechinoside F

Fig 5. It shows different examples of antiparasitic agents with their structures.

Ca^{2+}-ATPase and Histone Deacetylase Inhibitors

Speradine A, a pentacyclic oxindole alkaloid isolated from the cultured broth of a fungus *Aspergillus tamari*. Speradine A with a 1-*N*-methyl-2-oxindole ring is a new congener of cyclopiazonic acid. Speradine A exhibits inhibitory activity against Ca^{2+}-ATPase and histone deacetylase, and also exhibited antibacterial activity against *Mycrococcus luteus*[45]. (Fig 6.)

Antimalarial Activity

Isonitrile-containing antimalarial derivatives have been isolated from the Japanese sponge *Acanthella sp*. These molecules belong to the class of the kalihinane diterpenoids, which comprises also antifungal, anthelmintic and antifouling compounds. Isonitrile kalihinanes showed a potent antiplasmodial activity in the very low nanogram range (e.g. kalihinol A IC50 = 0.4 ng/mL)[46-47].

Axisonitrile-3 was isolated from the sponge *Acanthella klethra* Pulitzer-Finali and found to possess a potent antimalarial activity both on chloroquine-sensitive (D6, 142 ng/mL) and chloroquine resistant (W2, 17 ng/mL) *P. falciparum* strains[48-49].

Manzamines are undoubtedly the most important and potent antimalarial alkaloids isolated from marine sources. They are very complex polycyclic (7-8 rings or more) alkaloids first reported by Higa and coworkers in 1986 from an Okinawan sponge belonging to the genus *Haliclona*[50-51]. These molecules are characterized by an intricate pentacyclic heterocyclic system attached to a β-carboline moiety. Since the first report of manzamine A, at least 60 additional manzamine-type alkaloids have been reported from taxonomically unrelated sponges belonging to different genera (e.g.*Xestospongia*, *Ircinia*, and *Amphimedon*) and different orders. (Fig 7.)

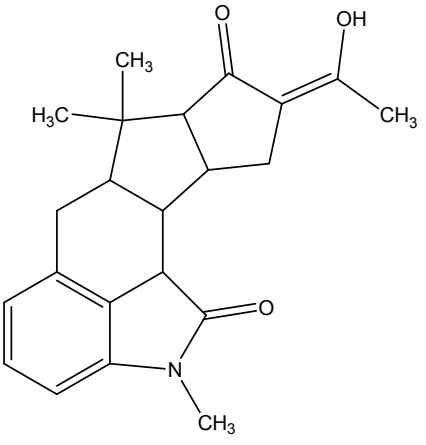
Analgesic Agents

Ziconotide, also known as Prialt was isolated from the marine snail *Conus magus* and recently approved by the FDA to treat pain. The mechanism of ziconotide has not yet been discovered in humans. Results in animal studies suggest that ziconotide blocks the *N*-Type calcium channels on the primary nociceptive nerves in the spinal cord[52].

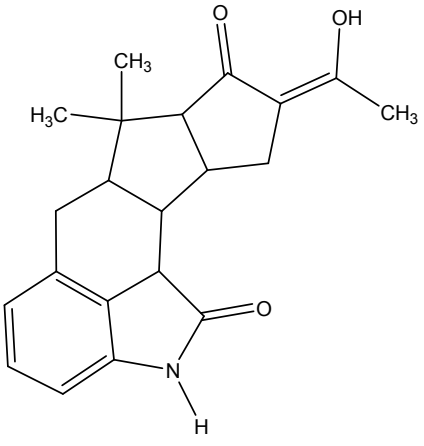
Bone grafting Agents

Bone grafts to help repair fractures are the second most common medical transplant, after blood transfusions. Natural coral has been used as a bone substitute for more than 10 years in orthopedic, trauma, craniofacial, dental, and neurosurgeries. Corals have a structure similar to that of human bone, with a hard outer sheath and a spongy inner core[53].

At present, the tropical coral genera Porites, Alveopora, Acropora, and Goniopora are being used as bone substitutes; these are the only families known to have the correct pore diameter and the ability to connect properly with bone[54].

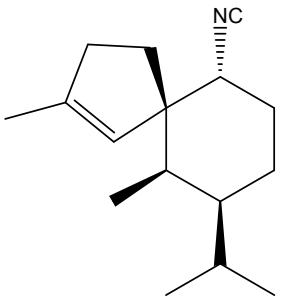


Speradine A (*Aspergillus tamarii*)

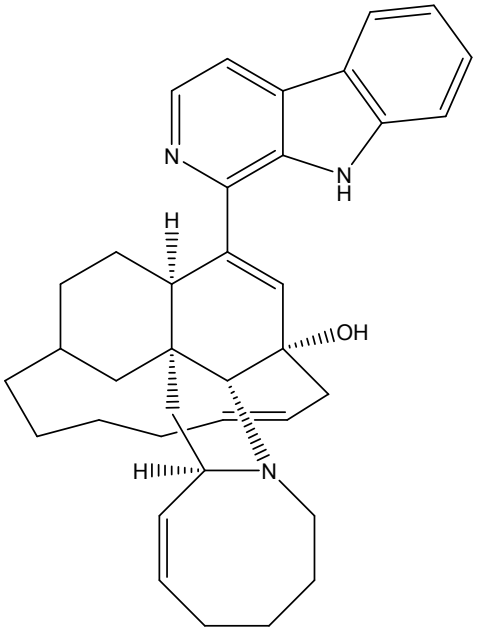


Cyclopiazonic acid (*Aspergillus tamarii*)

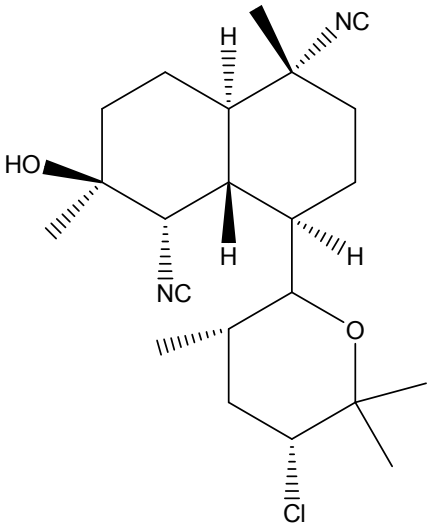
Fig 6. It shows examples of Ca^{2+}-ATPase and histone deacetylase inhibitors with their structures.



Axisonitrile-3 (*Acanthella klethra*)



Manzamine A (*Micronosphora sp*.)



Kalihinol A (*Acanthella sp*.)

Fig 7. It shows different examples of antimalarial agents with their structures.

Marine Biotechnology in the Pharmaceutical Industry:

In order to understand the potential growth of marine biotechnology, it is first important to understand the ways marine biotechnology contributes to the larger biotechnology, biomedical and pharmaceutical industries. It is clear that the term "marine biotechnology" is misleading. Companies view themselves as part of the much larger biotechnology industry, and they face the same research, technical and financial obstacles as other companies in the biotechnology field. The term "marine biotechnology" creates perceptions of a specialty market or field when in fact their products are targeted for the same markets as other biotech companies. Marine biotechnology has direct outputs to the pharmaceutical just as the larger biotechnology industry does. (Fig 8.)

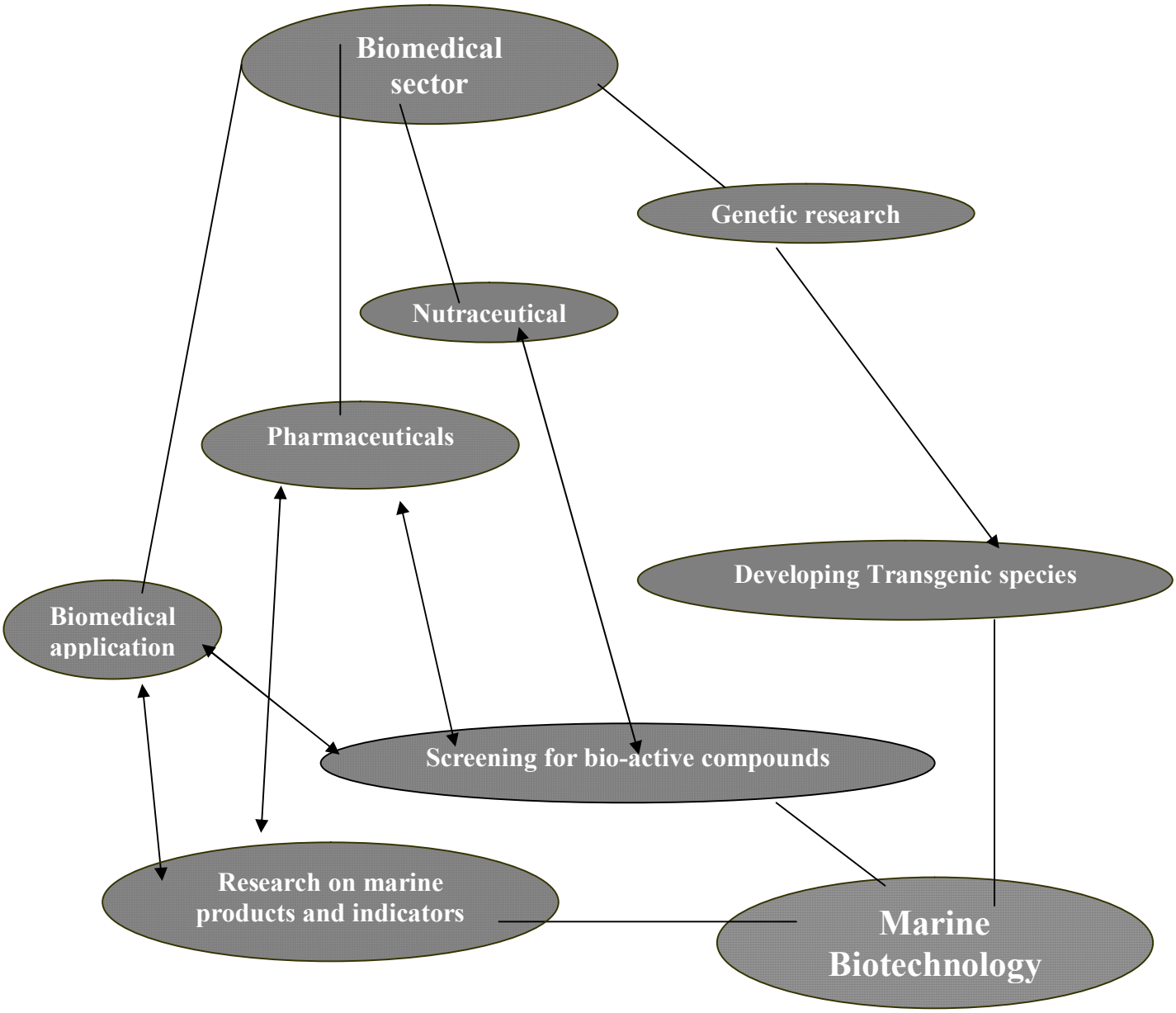


Fig 8. It shows pharmaceutical industrial structure

Demand for New Drugs: Opportunities for Marine Biotechnology

In the last few years, interest in the ocean as a source of bioactive compounds and drugs has increased dramatically, as many of the most useful compounds from the terrestrial ecosystems have been commercialized (for example, penicillin, actinomycin, cyclosporin, and streptomycin are all derived form terrestrial microbes). While identification of compounds from terrestrial plants (i.e. tamoxifen and others) receives much publicity, in fact the unidentified reservoir of bioactive compounds from microbes
and higher life forms in marine systems is considered to be much larger than terrestrial systems, and remains largely unexplored. The demand for new drugs for the U.S. and global markets is very strong, and the outlook is for continued growth over the next five years. This demand for new drugs has created opportunities in marine biotechnology[55].

Recommendations for monitoring & supporting the growth of marine biotechnology

There are some recommendations which can be easily applied to the larger field of marine biotechnology development[56]:

- Maintaining and developing R&D base
- Scientific understanding of marine biotechnology and marketing
- Stimulate training and education
- Sustaining networking
- Commercialization and R&D funding
- Expansion of existing companies
- Development of new entrepreneurial companies
- Organizing biotech and marine biotech
- Setting regulatory policies

Conclusion

To appreciate the impact of marine biotechnology in pharmaceutical sciences understanding of some basics of genetics is necessary. The backbone of this technology has been largely the progress made in genetics and genetic engineering. Research programs in different countries are active in the investigation of marine sources. There are many possibilities for research, but priority should be given to tropical infectious and chronic diseases for which current medications have severe drawbacks, and to the scientific appraisal of marine-based remedies that might be safer, cheaper, and less toxic for self-medication than existing prescription medicines.

Marine derived pharmaceuticals provide a novel and rich source of chemical diversity that can contribute to design and development of new and potentially useful pharmaceutical agents. Unfortunately, these secondary metabolites are usually present in trace amounts, and natural stocks are too small to sustain the development of widely available medicines. The development of ways to obtain large quantities of the secondary metabolites is therefore currently the most important quest.

The available survey demonstrates that the marine ecosystem is a tool to identify new cellular targets for therapeutic intervention. A better understanding of the molecular determinants of therapeutic response will help identify patients at risk for severe toxicities. A proactive interaction between researchers, the pharmaceutical marine biotech sector and government regulating agencies is crucial to the incorporation of this challenging new tool in clinical medicine.

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