Marine Natural Products

Importance of marine environment

- More than 70 % of the planet's surface is covered by oceans.
- The great biodiversity of marine environment.
- More than 300 000 species of plants and animals are described.
- Great number of marine organism have no terrestrial counterparts.

- **The very special living condition for marine organisms led them to adapt different physiological and behavioural characters which consequently resulted in novel biologically active molecules.**

- **Sea organisms are mostly unexplored reservoirs of new drugs.**

- **A small number of marine plants, animals, and microbes have already yielded more than 12000 novel chemicals.**

- **Hundreds of new compounds still being discovered every year**

Phases of work on marine chemistry

- **In the 1950's researchers were interested in studying the marine spines and shells of sea urchins with beautiful colors.**
- **In the 1970's interest of researchers was attracted to the halogenated metabolites from red algae.**
- **From the 1980's till now the marine chemistry was directed by the currently used sophisticated and smart biological assays.**
- **Interest switched from marine algae to marine invertebrates.**

Problems of marine research

1- The lack of trained personal.

2- Diving hazards.

3- The marine trips are effort, time and money consuming.

4- The time consuming experiments.

5- The scarcity of the starting organism to carry out the complete study.

6- Recollection problems of the same organisms in the dynamic environment.

7- **Difficulties in culturing** of marine organisms in the lab.

8- Most of the marine secondary metabolites are **polar** compounds, so additional difficulties with extraction, fractionation and separation are faced.

9- The marine organisms are usually associated with **parasitic commensal or symbiotic flora.**

10- The lack of **folk medicine** information or ethnobotanical documentation.

The marine biosphere

Marine organisms are classified into the following phyla:

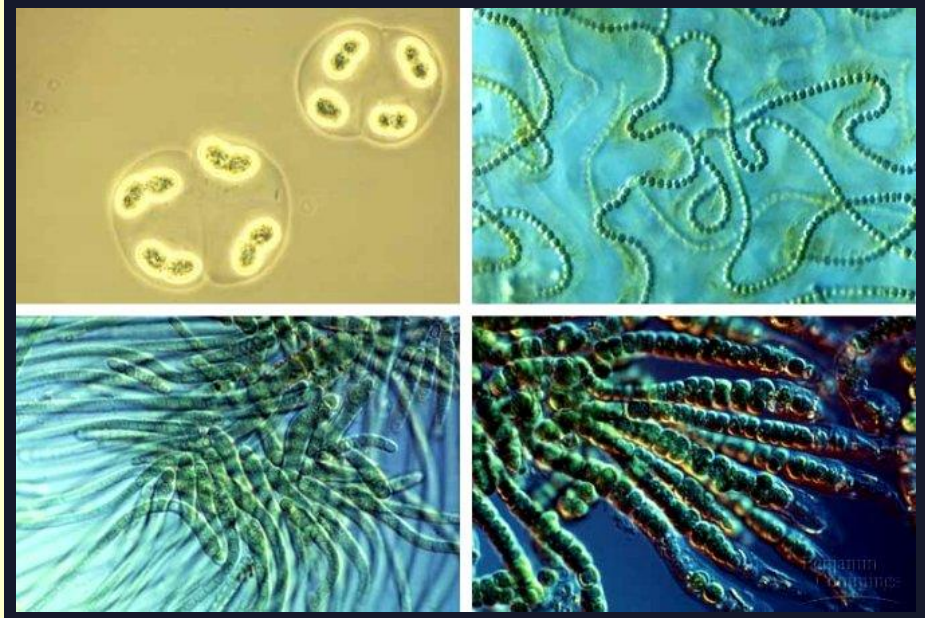
- **Monera**
- **Protista**
- **Metazoa**
- **Higher plants**

Monera

- **Monerans are one-celled organisms that have no nucleus or organelles.**
- **Monerans are individual cells that survive on their own.**
- **They do not work together in groups. However, they can be found in pairs, clumps, or in chains.**
- **The kingdom of Monera is divided into two types or organisms, bacteria and cyanobacteria.**

Cyanobacteria (blue-green algae)

- They make their own food through the process of **photosynthesis**.
- These cells are found in **oceans**, lakes, ponds, swimming pools, and **moist soil**.
- They are an important **food source** for many of the animals in the water.
- They can be found **alone, in colonies, or long thread** like chains.



Protista

- a diverse group of **eukaryotic** microorganisms.
- unicellular, or multicellular without specialized tissues.
- They include marine **fungi and algae**.

1- Marine fungi

- live **saprophytic** on algae, plants or animals.
- **parasites** on shells, crabs, sponges, in the GIT of fishes.
- Source of **antibacterial, antifungal, cytotoxic and anti-inflammatory agents**.
- produce several **secondary metabolites** e.g. alkaloids, terpenoids and polyketides.

2- Algae

- are a large and diverse group of simple, typically autotrophic organisms, ranging from unicellular to multicellular forms.
- They are photosynthetic and simple.
- There are nearly 30,000 algae species.
- They could be divided into the following groups:

1- Red algae (Rhodophyta)

2- Brown algae (Phaeophyta)

3- Green algae (Chlorophyta)

4- Golden brown algae

5- Yellow algae and diatoms (Chrysophyta)

6- Euglenophyta

7- Blue green algae

8- Dinoflagellates (Pyrrophyta)

Chlorophyta (green algae)

- About 8000 species.
- Mostly live in fresh water.
- Chlorophyll a and c.

Rhodophyta (red algae)

- About 5000 – 6000 species.
- 95% are marine.
- Chlorophyll a, phycoerythrin.

Phaeophyta (brown algae)

- **About 1500-2000 species.**
- **99% are marine.**
- **Chlorophyll a, c and phycoerythrin.**

Marine animals (Metazoa)

- Marine vertebrates and invertebrates were subjected to chemical study.
- These studies covered representative phyla:
- **Porifera**
- **Cnidaria**
- **Mollusca**
- **Echinodermata**
- **Annelida**
- **Chordata**

Porifera (Sponges الأسفنج)

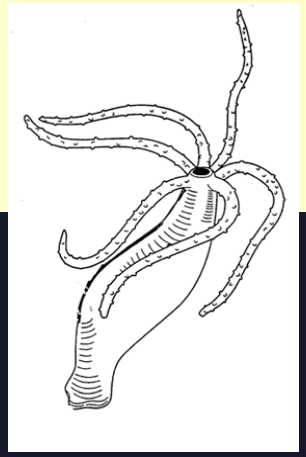
- Over 9000 known species and as many species not yet described.
- Aquatic sessile filter feeders.
- Simplest animals, multicellular organisms with specialized cells found in a various forms, no organs.
- 50% of the natural products reported from marine invertebrates.
- About 2600 metabolites were isolated.

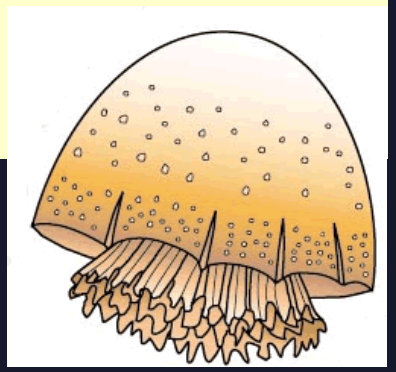
Cnidaria

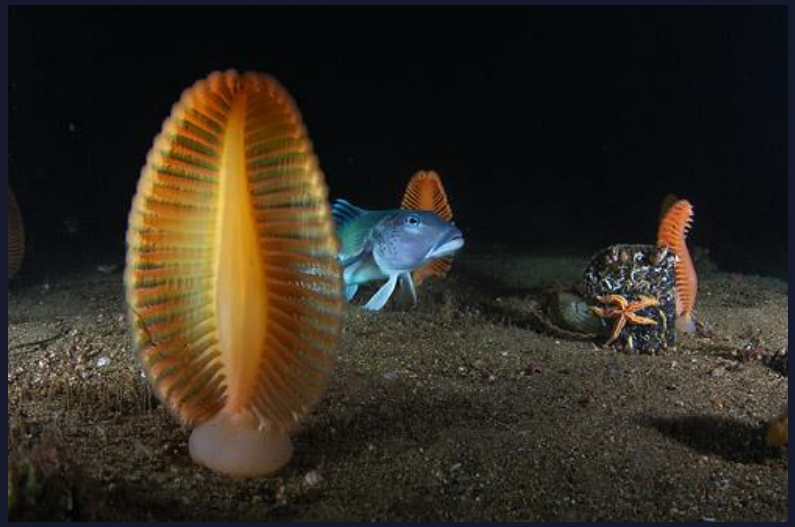
- This phylum include: soft and hard corals المرجان, gorgonians المرجان المروحي, sea pens اقلام البحر, jellyfish قنديل البحر , sea wasps دبور البحر and sea anemones شقائق النعمان.
- Simple structure: a sac-like body with single opening that functions as both mouth and anus, one or more circles of tentacles surrounding the mouth, an internal space called the coelenteron, which serves for digestion and circulation.

Cnidarians have two body forms:

- 1- Poly - stationary, vase-shaped e.g. hydra, coral, sea anemone
- 2- Medusa - swimming, cup-shaped e.g. jellyfish
- More than 10000 described species.
- Only 12% were chemically investigated.
- About 1500 metabolites were isolated.





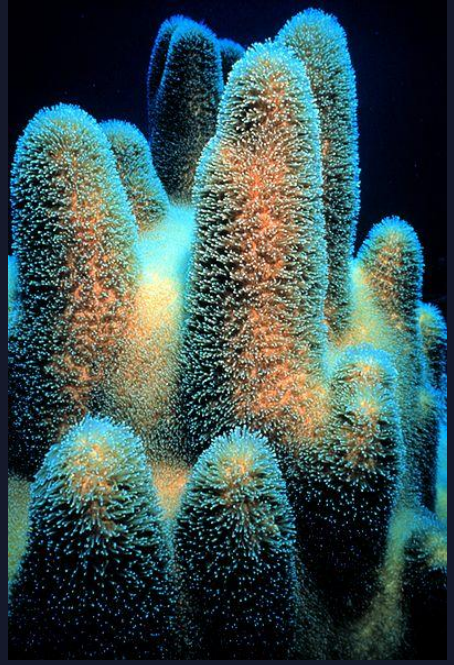


Sea pens

Jellyfish قنديل البحر

Sea anemones شقائق النعمان

Portuguese man of war



المرجان Corals

Jellyfish

Mollusca الرخويات

- This phylum contains a highly diverse group of animals including 50000 species and 60000 fossil molluscs.
- vary greatly in physical appearance, size, and feeding habits.
- include snails الحلزون , tusk shells, shellfish المحار, octopus الإخطبوط, squids حبار, mussels بلح البحر

Mussels بلح البحر

Octopus

Squids حبار

Chordata حبليات

- This phylum includes tunicates and **vertebrates.**
- The most distinctive morphological features of chordates are the notochord, nerve cord, and visceral clefts and arches.
- About 1500 species of tunicates.

Tunicates

Echinodermata قنفذيات او شوكيات

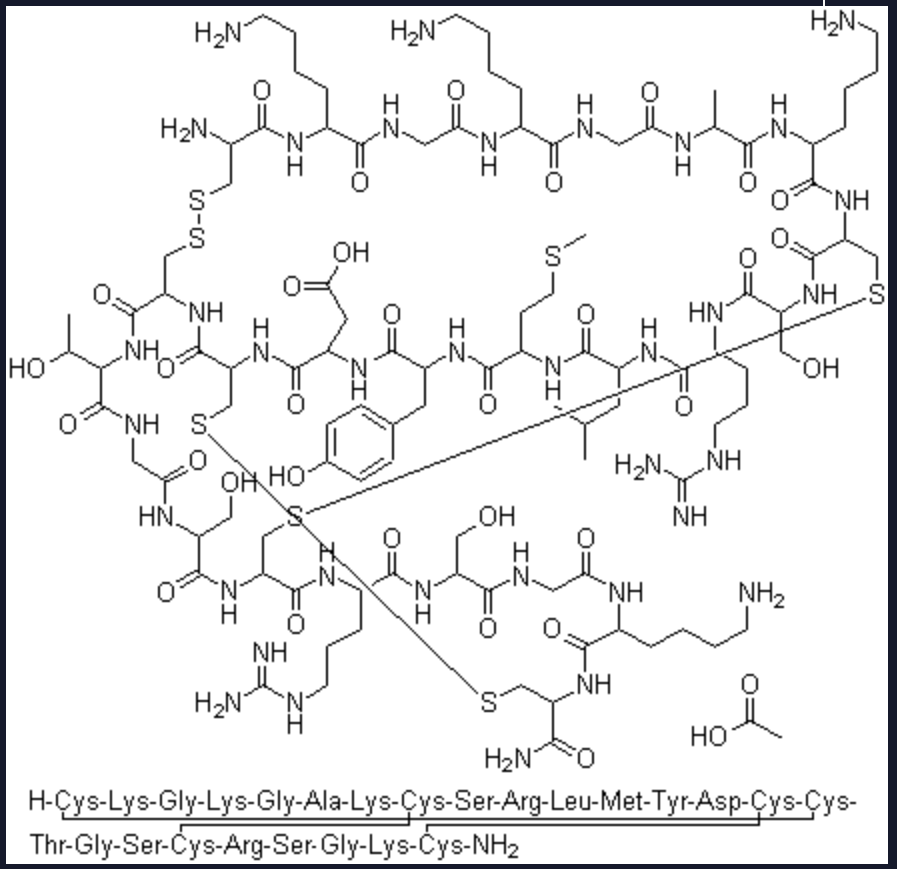
- With 7000 extant and 13000 extinct species.
- They are deuterostomes, a deuterostom being an animal in which the anus is formed from the blastopore during development and the mouth arises as a secondary invagination.

Marine secondary metabolites

Potent Analgesic drug (Ziconotide)

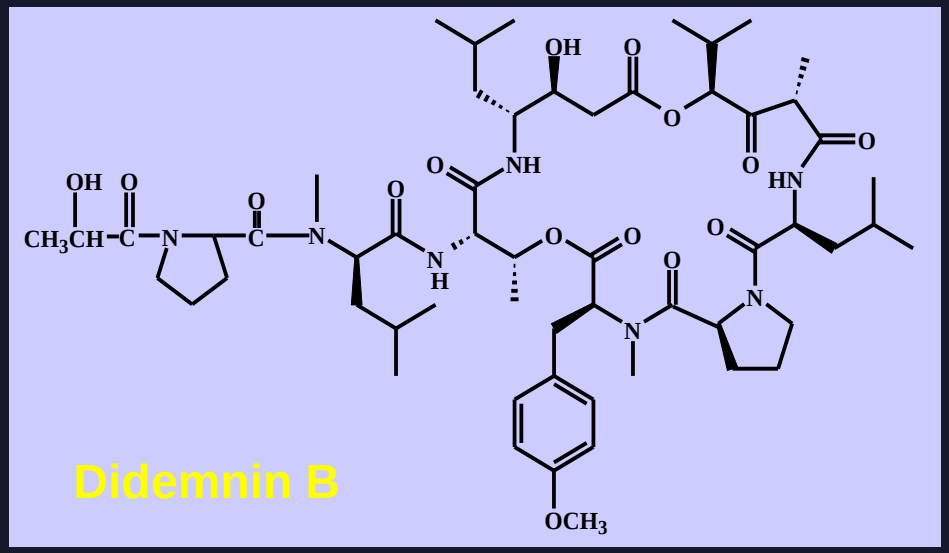
- **Ziconotide** (**Prialt**) is a non-opioid and non-NSAID analgesic agent used for the treatment of severe and chronic pain. Derived from *Conus magus* (Cone Snail), it is the synthetic form of an ω-conotoxin peptide.
- A **conotoxin** is one of a group of neurotoxic peptides isolated from the venom of the marine cone snail, genus *Conus*
- Conotoxins, which are peptides consisting of 10 to 30 amino acid residues, typically have one or more disulfide bonds.
- In December 2004 the Food and Drug Administration approved ziconotide when delivered as an infusion into the cerebrospinal fluid using an intrathecal pump system.
- Amino acid sequence
- H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH2

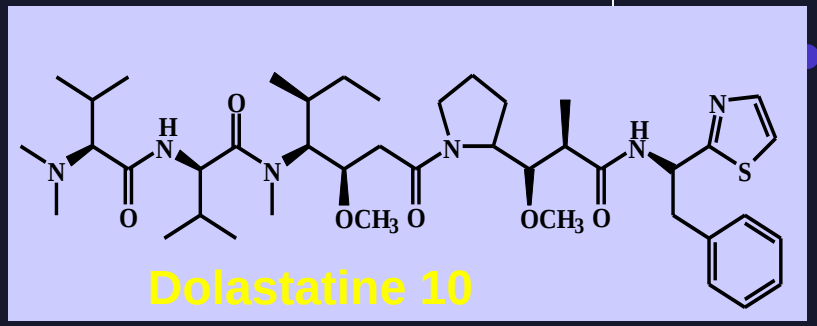
Dorsal (left) and ventral (right) views of a shell of *Conus magus*

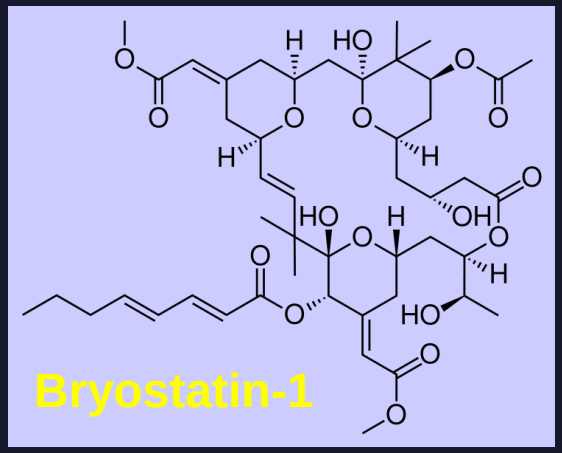


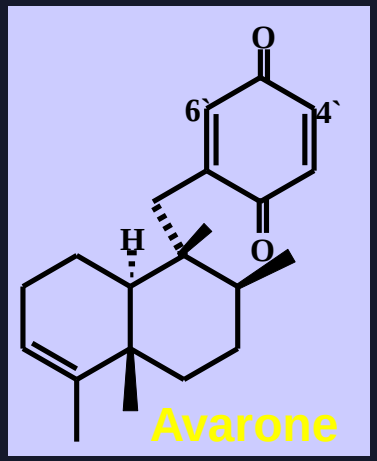
Ziconotide acetate

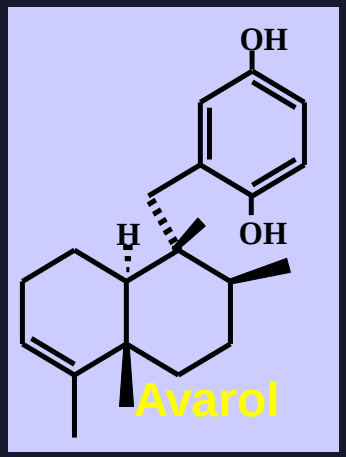
Product	Source	Composition	Uses	
Didemnins A, B, C, D, E, G, X and Y	*Tridemnum* sp.	cyclic depsipeptides	cytotoxic, antiviral and immunosuppressive	Antitumor and Cytotoxic Agents
Dolastatins	*Dollabella* sp	cyclic and linear peptides and depsipeptides	mitotic inhibitors	
Bryostatins	*Bugula neritina*, sponges and tunicates	macrolide lactones	a potent activator of protein kinase C	
Didemnins A, B, C, D, E, G, X and Y (as above)				Antiviral active compounds
Avarol and avarone	a sponge, *Disidea avara*	Sesquiterpenes attached to quinone or hydroquinone unit	inhibit the human immunodeficiency virus have high therapeutic indices and the ability to cross the blood–brain barrier	
Cyanovirin-N (CV-N)	cyanobacterium that *Nostoc ellipsosporum*	protein	virucidal activity against several viruses, including HIV	
Ara-A	semi-synthetic	arabinosyl adenine	antileukemic	

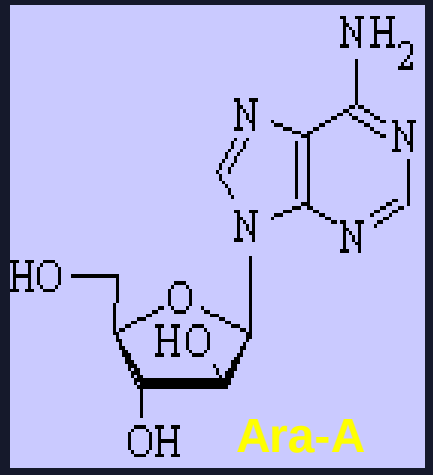

Didemnin B


Dolastatine 10

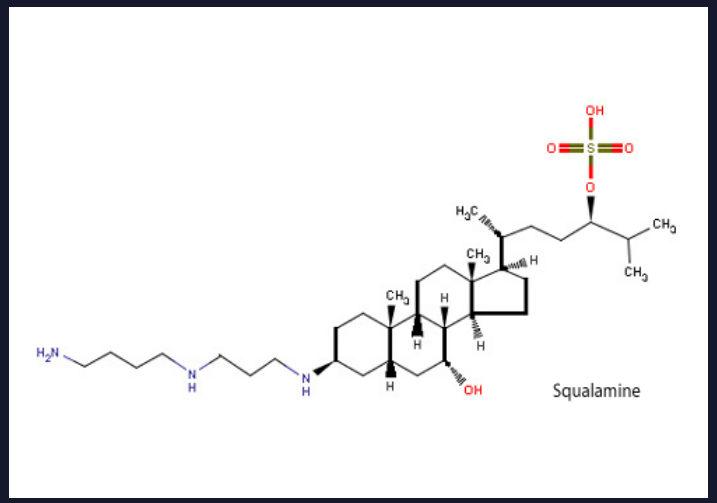

Bryostatin-1

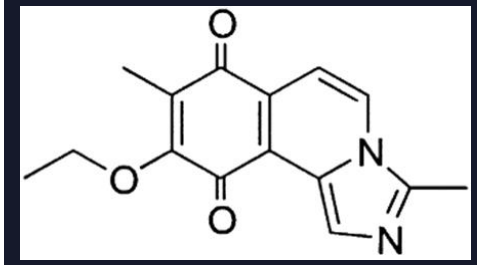

Avarone


Avarol

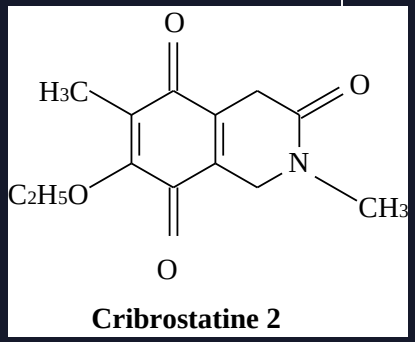

Ara-A

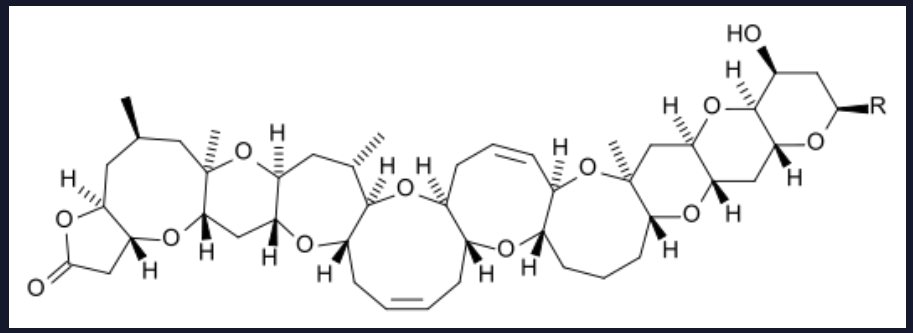
Product	Source	Composition	Uses	
Squalamine	dogfish shark *Squalus acanthias* (F Squalidae).	aminosterol	selective in-vitro antimicrobial activity against *Candida albicans*	Antibacterial active compounds
Cribrostatins	blue sponge *Cribrochalina* sp.	Isoquinoline dion	antineoplastic and antimicrobial. Cribrostatin 3 has potent inhibitory activity against penicillin- resistant *Neisseria gonorrheae*	
Jasplakinolide (Jaspamide)	sponge (*Jaspis* sp.)	19-membered macrocyclic cyclodepsipeptide	selective in-vitro antimicrobial activity against *Candida albicans*	Antifungal active compounds Most antifungal compounds from marine origin are cytotoxic. Could not be used clinically
Gambieric acids	epiphytic marine dinoflagellate *Gambierdiscus toxicus.*	the first antifungal representatives of the brevetoxin-type (fused polyether rings)	inhibits the growth of *Aspergillus niger* The potency of gambieric acids exceeds that of amphotericin B by 2000-fold.	



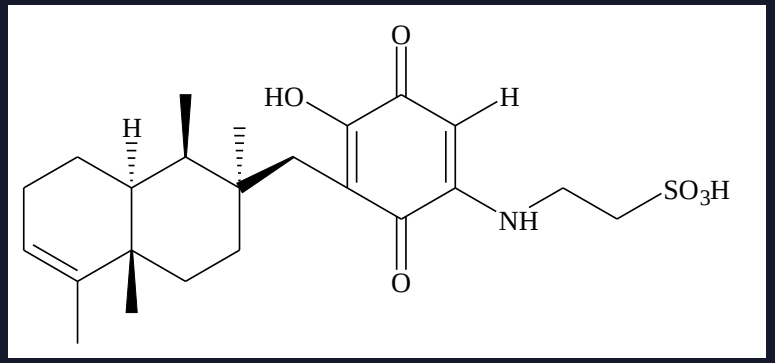


Cribrostatin 6

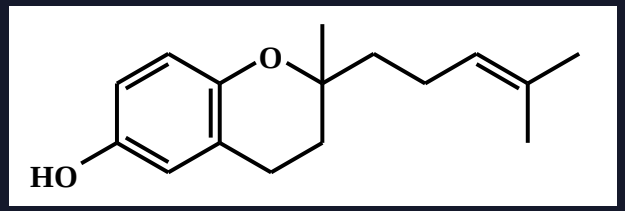




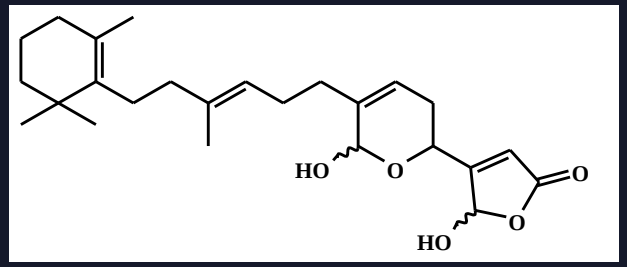
brevetoxin-type



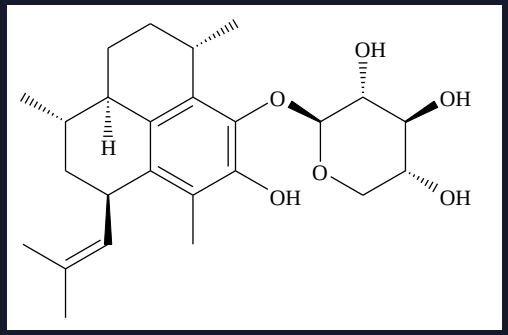
Dysidine



Cordiachromen A



Manoalide



Pseudopterosin A

Product	Source	Composition	Uses	
Cyclic peroxides	**sponges (*Plakortis sp.*)**		**Two isolated peroxides are active against *Leishmania mexicana***	**Antiprotozoal active compounds**
Manzamine A	marine sponges of the genus Haliclona	**alkaloid**	**70% inhibition of the *Toxoplasma gondii* parasite, at 0·054 g/mL concentration, without cell toxic effects.**	
Manoalide	***Luffariella variabilis***		**Irreversibly inhibits phospholipase A2**	**Anti-inflammatory Agents**
Dysidine	***Dysidea* sp.**		**Exerts higher potency and selectivity toward phospholipase A2 than manoalide.**	
Cordiachromen A	***Aplidium multiplicatum***		**Strong anti-inflammatory effect similar to that of indomethacin**	
Pseudopterosins	***Pseudopterogorgia bipinnata.***		**They inhibit PGs biosynthesis It exhibited potent anti-inflammatory and analgesic activities**	

Some Marine Products In Use

Product	Source	Composition	Uses
Agar Agar	Red algae	polymer of subunits of galactose	Bacteriological media
Cod liver oil	Cod livers	Omega-3 fatty acids	wasting diseases
Protamine SO4	Salmon	polycationic protein	Heparin antagonist
Algenate & alginic acid	Sea weed(giant kelp) *Macrocystis pyrifera*	linear copolymer	Textile ,food & cosmetics, pharmaceutical prep.
Carrageenan	Red seaweeds *Kappaphycus*	linear sulphated polysaccharides	Food industry & cosmetics
Spermaceti	Cavities in head of sperm whale	cetyl palmitate (ester of cetyl alcohol and palmitic acid)	Ointments, cosmetics
Laminarin	Brown algae (kelp)	polysaccharide	Anticoagulant, food thickener