

Unit 2: Marine Natural Products

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2.1 The sea as a source of drugs

The oceans cover most of the planet's surface and hold an enormous range of living organisms, many of them unlike anything on land. Marine organisms, sponges, corals, algae, molluscs, sea squirts (tunicates), bryozoans, echinoderms and marine microorganisms among them, produce chemistry that terrestrial plants rarely make. Two features of marine life explain much of that chemistry. Many marine animals are soft bodied, slow moving or fixed in place, and chemical defence is their defence: they make potent compounds to deter predators, to stop other organisms growing over them, and to fight infection in a microbe rich medium. And seawater chemistry, rich in bromide and chloride, lets marine organisms build halogenated compounds, especially brominated ones, that are uncommon on land. The result is a library of structurally unusual molecules, some of them extremely potent, which is why marine natural products have supplied drug leads and approved medicines as well as research tools. The same features make the field difficult, and the last section of this unit is devoted to those difficulties and their solutions.

2.2 General methods of isolation and purification

The isolation of a marine natural product follows the same logic as the isolation of any natural product, adapted to material that is often wet, salty, scarce and chemically fragile. The standard sequence is as follows. The organism is collected, identified by a taxonomist, and a voucher specimen is preserved, because without a verified identity the work cannot be repeated. The material is preserved promptly, commonly by freezing or in a solvent, to stop enzymatic and microbial change. Extraction follows, typically with organic solvents such as methanol or a methanol and dichloromethane mixture, chosen to draw out a wide range of metabolite polarities. The crude extract is then partitioned between immiscible solvents of increasing polarity, a liquid-liquid fractionation that sorts the mixture roughly by polarity and concentrates the activity. From there, separation proceeds by chromatography in its several forms: column chromatography and vacuum liquid chromatography for bulk fractionation, flash chromatography, preparative thin layer chromatography, and high performance liquid chromatography (HPLC) for the final purification of individual compounds, with techniques such as gel filtration used where size separates the compounds. Throughout, the work is guided by testing: in bioassay guided fractionation, each fraction is tested for the activity of interest and only the active fractions are carried forward, so effort is spent where the chemistry is doing something. Structure determination then rests on spectroscopy, mass spectrometry for the molecular formula and fragmentation, nuclear magnetic resonance for the carbon and hydrogen framework, and ultraviolet and infrared spectra as supporting evidence, with the final compound characterised by its physical and spectral data. The figure below summarises the sequence.

Verified organism, voucher specimen preserved
|
Preservation (freezing or solvent) and extraction
|
Solvent partitioning by polarity
|
Chromatographic fractionation, bioassay guided
|
HPLC purification of the active compound
|
Structure elucidation: MS, NMR, UV, IR
|
Characterised pure marine natural product

Isolating a marine natural product



No voucher, no repeatability: identification comes before chemistry

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Figure: The general isolation and purification sequence for marine natural products. The voucher specimen and the bioassay guidance are the two steps students most often omit, and examiners notice both.

2.3 Marine toxins

Marine toxins are the poisonous compounds produced by marine organisms, and the syllabus asks for their study for two reasons: they are public health hazards in seafood, and they are some of the most precise pharmacological tools known, because a toxin that blocks one channel or one enzyme with great selectivity teaches physiology while it poisons. The standard named examples are these. Saxitoxin, produced by certain dinoflagellates and accumulated by shellfish, blocks voltage gated sodium channels and causes paralytic shellfish poisoning. Tetrodotoxin, found in puffer fish and some other marine animals and now understood to be associated with marine bacteria, also blocks voltage gated sodium channels and is a classic research tool for those channels. Ciguatoxins, from dinoflagellates and accumulated through reef food chains into large fish, act on sodium channels and cause ciguatera fish poisoning. Palytoxin, from zoanthid corals of the genus *Palythoa*, is among the most potent non protein toxins known and acts on the sodium potassium pump. Okadaic acid, a dinoflagellate polyether accumulated in shellfish, inhibits protein phosphatases and causes diarrhetic shellfish poisoning. Brevetoxins, from the dinoflagellate *Karenia brevis* of red tide fame, also act on sodium channels. The pattern to teach is mechanism: most of the famous marine toxins are ion channel or pump agents of extreme potency and selectivity, which is exactly why the laboratory values them and the clinic fears them.

2.4 Marine product families and drug leads

Marine research yields several kinds of product, and sorting them helps the student organise a large field. There are approved medicines whose origin is marine: cytarabine, the anticancer nucleoside whose design was inspired by nucleosides isolated from a Caribbean sponge, is the classic historical example, and the marine derived anticancer agent trabectedin, originally from a sea squirt, and the antibody drug conjugate component chemistry descended from the sea hare compound dolastatin 10 are standard modern examples. There are toxins used as research tools, covered in the previous section. There are compounds in development as analgesics and anticancer agents, of which the cone snail peptide ziconotide, a synthetic version of a *Conus* venom peptide used for severe chronic pain, is the best known approved peptide example. And there are the everyday marine products of the health market, such as fish oils rich in the polyunsaturated fatty acids of Unit 3 and algal products including *Spirulina*, which links this unit to the next. The figure below groups these families.

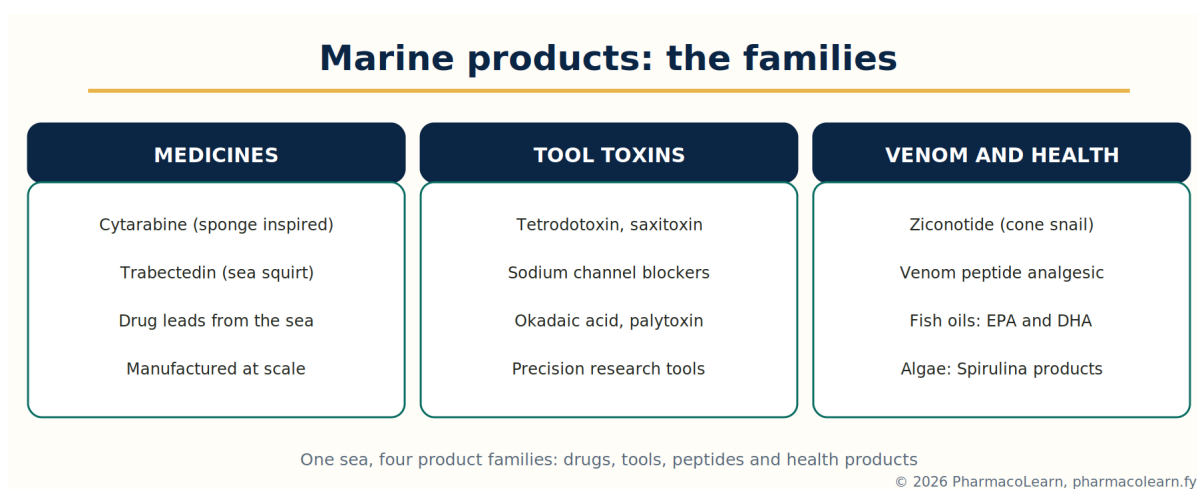


Figure: The families of marine products, from approved medicines and research tool toxins to venom peptide drugs and marine health products such as fish oils and algae.

2.5 Recent advances in research in marine drugs

Recent advances in marine drug research have come less from sailing further than from solving the field's standing problems with new methods, and the strongest examination answers name the method and the problem it answers together. Genome mining and metagenomics read the DNA of marine organisms and of their microbial communities, and can reveal the gene clusters for compounds produced in amounts too small to isolate, or not produced at all in the laboratory. That work has also settled a long standing question of origin: many compounds isolated from sponges and sea squirts are actually made by symbiotic microorganisms, and knowing the true producer opens the way to making the compound by fermentation. Aquaculture of the source organism and culture of the producing microbe are the accompanying supply side advances. In chemistry, total synthesis and simpler analogues have repeatedly converted an unobtainable compound into a manufacturable drug. In screening, high throughput methods, spectroscopy that works on very small amounts, and dereplication, the early identification of already known compounds so effort is not wasted rediscovering them, have made the work far faster. The direction is constant: from collecting tonnes of an organism for milligrams of a compound, towards identifying the producer, reading its genes, and making the compound, or a better analogue, by culture or synthesis.

2.6 Problems faced in research on marine drugs, and their solutions

The syllabus names two problems directly, taxonomical identification and chemical screening, and a complete answer sets them in the wider problem list. Taxonomical identification is hard at sea: many marine invertebrates are difficult to identify to species, similar looking organisms may be different species with

different chemistry, the producing organism may really be a symbiont, and a misidentified source makes the whole study unrepeatable. The solutions are expert taxonomic examination with a preserved voucher specimen, photographic and collection records, and increasingly DNA barcoding, in which a standard gene sequence identifies the organism objectively. Chemical screening is hard because a crude marine extract is an extreme mixture, often salty, frequently containing very small amounts of very many compounds, with known nuisance compounds recurring again and again. The solutions are dereplication by LC-MS and NMR comparison against databases of known compounds, bioassay guided fractionation to follow activity rather than bulk, and prefractionation so that screens test simpler mixtures. Around these two named problems stand three more that the student should know. Supply: the active compound may be a trace fraction of an organism that cannot be collected again in quantity, answered by aquaculture, fermentation of the true microbial producer, total synthesis and analogue design. Structural complexity: marine compounds are often large and intricate, making synthesis and even structure determination slow, answered by modern high field NMR, mass spectrometry and computational assistance. And variability: chemistry varies with place, season and depth, answered by careful collection records and by moving production into controlled culture as soon as a lead is confirmed.

2.7 Unit 2 in one view

Marine natural products are the chemically distinctive products of sea organisms, often halogenated, often potent, and frequently made as chemical defence. Isolation follows verified collection, extraction, solvent partitioning, bioassay guided chromatography and spectroscopic structure determination. The toxins are chiefly selective ion channel and pump agents. The field's advances are genetic, cultural and synthetic answers to its standing problems of identification, screening and supply.

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