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Deep-sea Natural Products

Danielle Skropeta
University of Wollongong, skropeta@uow.edu.au

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Abstract

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Keywords

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Disciplines

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Danielle Skropeta*

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School of Chemistry, University of Wollongong, Wollongong, Australia. E-mail: skropeta@uow.edu.au; Fax: +61 24221 4287; Tel: +61 24221 4360
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Danielle Skropeta

Danielle Skropeta obtained her BSc(Hons) degree from Monash University and her PhD degree from the Australian National University. She has held postdoctoral appointments in marine natural products with F. Pietra at Trento University, Italy, and in carbohydrate chemistry with R. R. Schmidt at Konstanz University, Germany, as well as at the University of Sydney and the Heart Research Institute. In 2006 she took up a lectureship at Wollongong University, where she now leads a research team in marine natural products chemistry, with particular interests in deep-sea natural products.

1 Introduction

Over the past 50 years, approximately 20 000 natural products have been reported from marine flora and fauna, and yet less than 2% of those derive from deep-water marine organisms.[1] The vast oceans cover 70% of the world's surface, with 95% greater than 1000 m deep.[2] Although difficulty in accessing these depths has previously hindered deep-sea research, today with improved acoustic technology and greater access to submersibles, deep-sea exploration is uncovering extensive deep-water coral reefs that are home to a wealth of species on continental shelves and seamounts world-wide (Fig. 1).[3] It has been estimated that the number of species inhabiting the world's oceans may be as high as 10 million,[4] and the ocean fringe with its high concentration of competing species was always thought to have the highest species diversity. On the contrary, recent analyses have shown that the deep sea is one of the most biodiverse and species-rich habitats on the planet, rivalling that of coral reefs and rainforests.[4–9]

With over 60% of drugs on the market of natural origin, natural products can be considered the foundation of the pharmaceutical industry.[10] Although in recent years the pharmaceutical industry decreased its activity in this area, today natural product-based drug discovery is experiencing a renaissance.[11] In particular, the marine environment, a rich source of structurally unique, bioactive metabolites, has produced a number of drug candidates that are currently in clinical trials.[12–16] In the ever-expanding search for sources of new chemical diversity, the exploration of deep-sea fauna has emerged as a new frontier in drug discovery and development.

Novel marine actinomycetes obtained from deep oceanic sediments such as the Mariana trench (10 898 m), are a promising source of new and unexplored chemical diversity for drug discovery.[17–19] Blunt *et al.*[20] have recorded an approximate doubling in the frequency of cytotoxicity towards the P388 murine tumour cell line from a single deep-water collection at a depth of 100 m off Chasam Rise, New Zealand, compared to the average activity of >5000 shallow-water collections over a 13 year period. Deep-sea hydrothermal vents[21] and cold-seeps[22] where nutrient-rich fluid seeps from the sea floor, are host to high levels of microbial diversity that are currently being explored as sources of unique biocatalysts able to withstand high pressure and variable temperatures.[23–25]

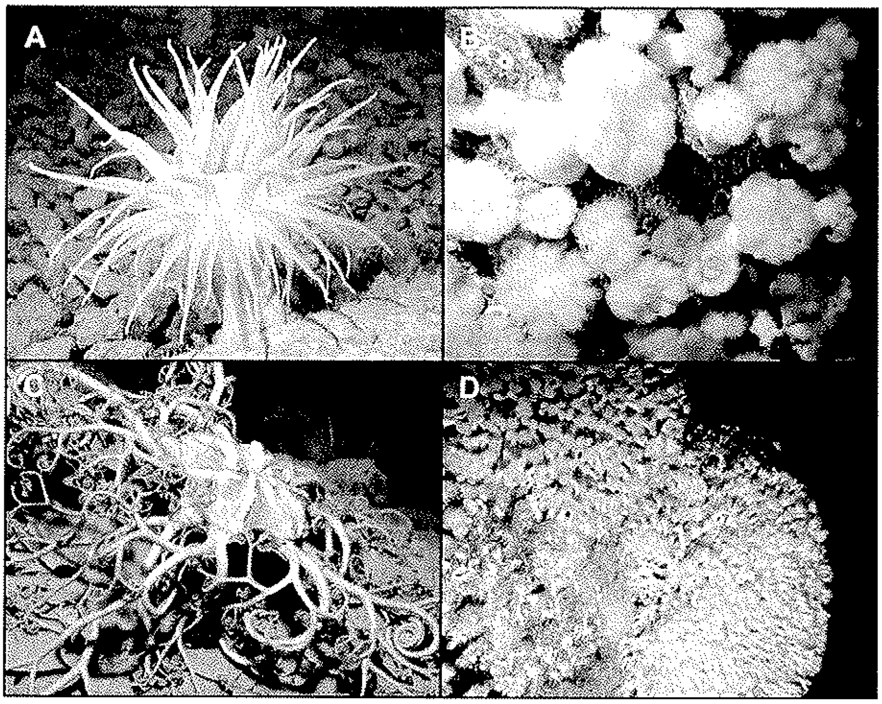


Fig. 1 Deep-sea marine fauna. (A) A *Bolocera* sp. anemone (500 m depth, Barents Sea, Norway); (B) A community of anemones, hydroids and corals (100 m depth, North Sea, UK); (C) The basket star *Gorgonocephalus caputmedusae* (930 m depth, Norway); (D) A colony of the deep-water coral *Lophelia pertusa* (100 m depth, North Sea, UK). [Images courtesy of SERPENT Project, Southampton, UK].

There are vastly different environmental conditions and oceanographic parameters at play in the deep-sea (Fig. 2).[26,27] Pressure increases by 1 atm for every 10 m below sea level, thereby varying from 10 atm at the shelf-slope interface to >1000 atm in the deepest part of the trenches. Consequently, species inhabiting these depths must adapt their biochemical machinery to cope with such pressures. Temperatures taper off rapidly with increasing depth down to ~2 °C at bathal depths of >2000 m. As lower temperatures reduce the rates of chemical reactions, deep-sea species must adjust their biochemical processes to function at depressed temperatures. Light penetration decreases exponentially with depth, such that below 250 m essentially no light penetrates. In the dark, cold depths of the ocean, vision becomes less important, and it is presumed that chemoreception and mechanoreception play greater roles. The near-bottom current is much slower in the deep sea compared to shallow-water with speeds of around 10 cm s^{-1} at bathyal depths and 4 cm s^{-1} at abyssal depths. The average metabolic rates and growth rates are lower than shallow-water species, however the latter is closely aligned to food availability. In the deep-sea the pH is typically around 8[28,29] and the salinity about 35% and therefore entirely marine, with a relatively low level of variability. The sediment comprises weathered rock washed into the sea by wind and rivers, as well as planktonic material obtained from the water above.[26,27]

Deep-sea organisms survive under extreme conditions in the absence of light, under low levels of oxygen and intensely high pressures, all of which may affect their primary metabolic pathways and consequently their secondary metabolites.[31,32] For this reason, deep-sea fauna are expected to have a greater genetic diversity than their shallow-water counterparts, and a higher probability of containing structurally unique metabolites.

The extraordinarily high level of diversity of deep-sea benthic fauna has been well known, and the mechanism to explain it hotly debated, since the 1960s.[5,33–36] Soft-bottom deep-sea fauna are found to be similar at the higher taxonomic level to shallow-water fauna and consist primarily of megafauna such as echinoderms (sea cucumbers, star fish, brittle stars) and anemones; macrofauna such as polychaetes, bivalve molluscs, isopods, amphipods and other crustacea; and meiofauna which primarily comprise foraminifers, nematodes and copepods, while hard-bottom deep-sea fauna are dominated by sponges and cnidarians (soft corals, gorgonians). At the species level, however, deep-sea fauna are found to contain a high number of single rare species, with more than half being new to science, and with some taxa comprising almost entirely of new species. In addition, many of the species are found to exclusively inhabit the deep sea, with high levels of biodiversity extending to abyssal depths of 5000 m.[26,27]

Recent sampling expeditions by the ANDEEP (Antarctic benthic deep-sea biodiversity) project in the Southern Ocean deep sea revealed extremely high levels of biodiversity across a range of taxa including meio-, macro- and megafauna, with the highest levels of species richness amongst the first two. In general, abundance decreased with increasing depth, while species richness increased with the highest number of species found at bathyal depths of 3000 m. Depth and biogeography trends were found to vary between taxa, and there was an apparent higher

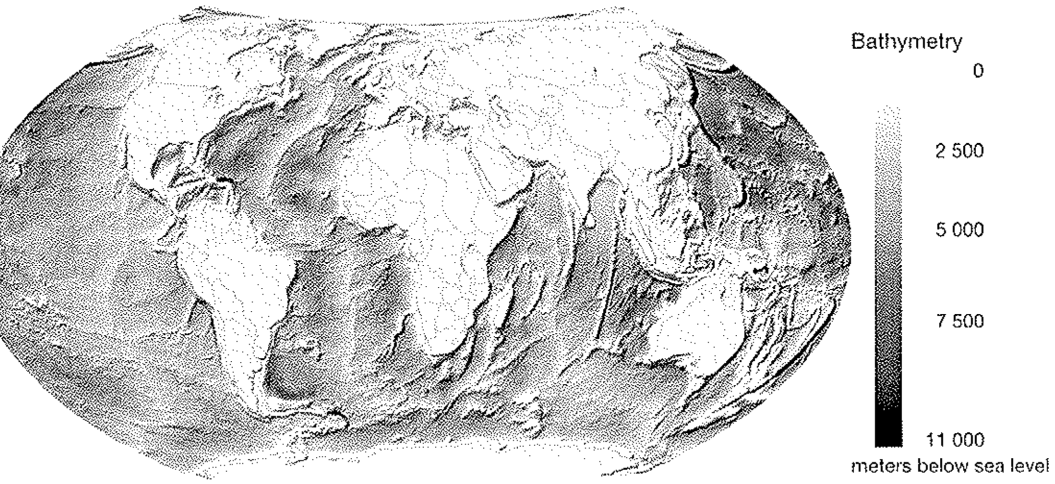


Fig. 2 World ocean bathymetric map.[30] The vast oceans cover 70% of the world's surface, with 95% greater than 1000 m deep.

species richness for many taxa of the Southern ocean compared to the Arctic deep sea.[7]

This review describes the 390 novel natural products isolated to date from deep-sea fauna. The deep sea is variably defined as commencing at depths of anywhere between 100 and 1000 m;[2] however, for the purposes of this review deep-sea fauna are defined as those inhabiting depths of greater than 50 m, in order to include those fauna beyond the depths of scuba. The majority of deep-sea natural products included in this review have been isolated from deep-sea sponges, echinoderms and microorganisms obtained using manned submersibles, or from commercial and scientific dredging and trawling operations, and emanate from tropical, temperate and polar regions. Herein, where no biological activity is ascribed to a particular metabolite it is because no such data have yet been reported.

2 Reviews

Cold-water marine natural products isolated from organisms collected from habitats below 4 °C were covered for the first time in 2007 by Baker *et al.* in a review that included some deep-water examples.[37,‡] In 2004, Laurent and Pietra reviewed the natural product diversity of the New Caledonian marine ecosystem, including deep-water sponges.[38] In 2001, a list of deep-water marine natural products appears in Pietra's book *Biodiversity and Natural Product Diversity*.[39] In 2001, Capon published a minireview on natural products isolated from Australian marine sponges obtained from trawling operations.[40] In 1998, Bewley and Faulkner reviewed lithistid sponge metabolites from both shallow and deep-water habitats.[41] To the best of the author's knowledge, this is the first comprehensive review to focus solely on marine natural products isolated from deep-sea (>50 m) fauna.

3 Deep-sea life

Life in the deep sea involves exposure to high hydrostatic pressures and low temperatures, requiring its inhabitants to adapt their genetic, biochemical and physiological processes and presenting unique challenges in terms of gene regulation, structure and function of proteins and other cellular components, and metabolism and physiology.[42,43] A number of deep-sea psychrophilic (cold-loving) and thermophilic (heat-loving) microorganisms have been isolated, and their mechanisms of adapting to high pressure,[44–49] and either cold temperatures (in the majority of the deep sea)[50–52] or high temperatures (around hydrothermal vents),[21,53–55] have been well documented. In contrast, there is a paucity of literature surrounding the adaptation of marine invertebrates to deep-sea life. It is beyond the scope of this review to cover the diverse range of adaptive mechanisms reported for deep-sea fauna; however, some of the key data that has emerged regarding gene regulation, macromolecular structure and metabolism in the deep sea have been summarized below.

Intense investigation into the piezophilic psychrophile *Shewanella violacea*, a bacterium isolated from deep-sea sediment from the Ryukyu Trench at a depth of 5110 m,[56] has revealed much about its metabolic pathways. *Shewanella violacea* survives at atmospheric pressure, but as with several other piezophilic microorganisms, it shows enhanced growth at pressures above atmospheric pressure. Isolation of the genes encoding for the biosynthesis of a number of enzymes, including cytochromes (bd, c_A, c_B),[57,58] glutamine synthetase,[59] and RNA polymerase[60] have revealed that the expression of these components is pressure-regulated. A terminal oxidase (d-type cytochrome) in the respiratory pathway of *S. violacea* is also expressed at high pressure, resulting in an altered lipid membrane composition that it is

‡ Some of the cold-water marine natural products reviewed by Baker *et al.*[37] were isolated from deep-water habitats, and those compounds, paesslerins A–B (**17–18**), the 10-hydroxydocosapolyenoic acids (**40–42**), carolisterols A–C (**66–68**), guaymasol (**108**) and epiguaymasol (**109**), a cyclic tetrapeptide (**111**), streptokordin (**112**), γ-indomycinone (**113**), caprolactins A–B (**120–121**), macrolactins A–F (**122–129**), (+)-formylanserinone B (**135**), (−)-epoxyserinone A (**136**) and its enantiomer, hydroxymethylanserinone B (**137**) and deoxyanserinone B (**138**), have been included here for completeness.

more pressure resistant,[61] while dihydrofolate reductase isolated from the bacteria has shown increasing activity with increasing pressures up to 100 MPa.[62] Pressure-regulated genes have also been discovered in the deep-sea bacterium *Photobacterium* sp. (strain SS9), including the genes for the outer membrane protein ompH and the porin-like protein ompL.[63,64] Furthermore, computational studies on the polyketide synthase pathway have revealed that high pressure may have a beneficial effect on certain secondary metabolic pathways over others.[65]

The high pressures experienced by deep-sea organisms are expected to affect the conformational shape of proteins and membranes, and their associated activity and binding processes. A range of thermophilic and psychrophilic enzymes have been isolated from deep-sea microorganisms, including α-glucosidase from the deep-sea bacterium *Geobacillus* from the Mariana Trench,[66] α-amylase and lipase from the actinomycete *Nocardiopsis* and the bacterium *Psychrobacter* respectively (both obtained from deep-sea sediment from Prydz Bay, Antarctica[67,68]) and the genes encoding the cold-adapted chaperones DnaK and DnaJ from the deep-sea psychrotrophic bacterium *Pseudoalteromonas* sp. SM9913, have also been characterised.[69]

It has been found that proteins in thermophilic organisms, relative to their mesophilic counterparts, show differences in amino acid sequences and 3D structure, such as increased stabilization of α-helices, a greater fraction of proline and β-branched residues and fewer uncharged polar residues, along with increased protein stabilization through crucial electrostatic interactions and a heightened role for molecular chaperones, in particular the heat shock proteins.[48,49,70,71] Conversely, psychrophilic proteins and enzymes display a reduced number of interactions involved in protein stability such as decreased proline residues and salt bridges, thereby leading to increased flexibility.[51,52,72] Other mechanisms of cold-adaptation[42] include the presence of antifreeze proteins[73,74] increased levels of trimethylamine oxides[75,76] and incorporation of exopolysaccharides into microbial cell membranes.[74,77]

Membranes comprising tetraether lipids such as those found in deep-sea archaea appear more resistant to higher temperatures than bacterial lipids consisting of labile ester linkages. Moreover, deep-sea organisms have been found to modulate their membrane fluidity and stabilization, through elements such as the incorporation of high levels of polyunsaturated fatty acids,[48] and the bacterial genes responsible for the biosynthesis of polyunsaturated fatty acids in deep-sea bacteria have also been reported.[78]

In the absence of photosynthesis, chemosynthesis is the dominant metabolic pathway in the deep sea. The genome sequence of the deep-sea γ-protobacterium *Idiomarina loihiensis* reveals that the organism obtains its energy from catabolism of amino acids rather than sugar fermentation.[74] Other deep-sea invertebrates are involved in highly specialized symbiotic associations, such the hydrothermal-vent-inhabiting tube worm *Riftia pachyptila*, which is entirely dependent on a sulfur-oxidizing, endosymbiotic bacterium for the *de novo* biosynthesis of pyrimidines,[79] and the deep-sea nematode *Stilbonema* sp., which relies on nitrate reduction by ectosymbiotic bacteria as an alternative electron acceptor to oxygen, thereby allowing it to inhabit deeper, anoxic sediments.[80] Taken together, the above adaptions to deep-sea life and their effect on gene regulation and primary and secondary metabolic pathways are certain to give rise to a wealth of interesting new marine natural products.

4 Bryozoa

The colonial bryozoans (moss animals, lace corals) are well represented in the marine environment, with over 5000 species described, ranging from shallow-water species to those living at depths of over 4000 m.[81–83] The secondary metabolites of bryozoans have been reviewed elsewhere,[84–86] and although shallow-water species have furnished such medicinally important compounds as the anti-cancer agent bryostatin 1 isolated from *Bugula neritina*,[87–89] there appear to be no reports as yet on the isolation, characterisation or bioactivity of secondary metabolites from deep-sea bryozoans.

5 Chordata (ascidians)

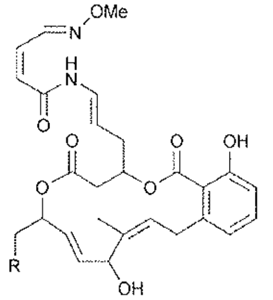
Shallow-water ascidians, comprising over 2000 known species, have yielded a diverse array of biologically important metabolites[90,91] including anticancer agents such as didemnin B from *Trididemnum solidum*, diazonamide from *Diazona angulata*, and the recently approved anticancer drug ectinascidian 743 from *Ecteinascidia turbinata*.[12,92] Deep-water ascidians, which have been well documented from both the Atlantic and Pacific oceans and up to depths of over 8000 m,[93–95] present a potentially rich source of interesting new metabolites. To date, only two reports on the secondary metabolites of deep-water ascidians have been reported.

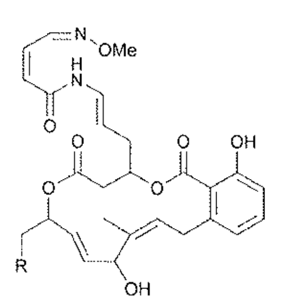
A deep-water tunicate belonging to the genus *Aplidium*, collected by trawling in the Great Australian Bight, has yielded the novel macrolides lobatamides A–F (**1–6**).[96,97] The structures of aplidites E–G, described earlier from the same sponge specimen,[14] were revised and the metabolites renamed as the lobatamides G–I (**7–9**).[13] The lobatamides are structurally related to the salicylihalamides isolated from a *Haliclona* species of sponge, but differing by the presence of the unique conjugated oxime methyl ether. The lobatamides, which were also obtained from shallow-water collections of *Aplidium lobatum* (SW Australia) and an unidentified Philippine ascidian, exhibited significant cytotoxicity in the NCI 60 human tumour cell line screen, and are the subject of several recent total syntheses.[98,99]

The deep-sea ascidian *Ritterella rete*, collected by dredging at a depth of 300 m on the Norfolk Ridge, New Caledonia, was found to contain six new cytotoxic dendrolasin-type hydroxylated sesquiterpenes (**10–15**), which are the first examples of furanoterpenes from a marine tunicate.[100]

6 Cnidaria

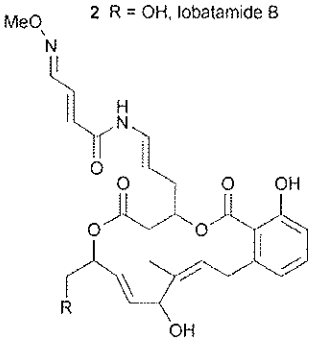
The phylum Cnidaria, comprising of the four classes Hydrozoa (hydroids), Anthozoa (anemones, corals, sea pens), Scyphoza (jellyfish), and Cuboza (box jellyfish), are well represented in the deep sea. Cnidarians are the second largest source (after sponges) of new marine natural products reported each year, with a predominance of terpenoid metabolites.[101–103] Herein, of the four cnidarian classes, only a small handful of examples have been reported on the secondary metabolites produced by

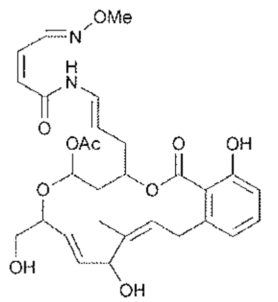




1 R = H, lobatamide A   3 R = H, lobatamide C

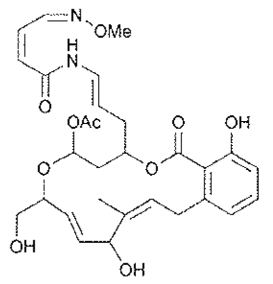
2 R = OH, lobatamide B   4 R = OH, lobatamide D

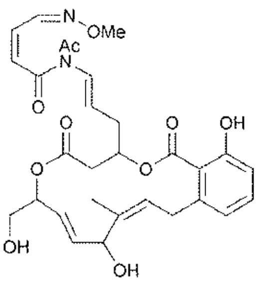




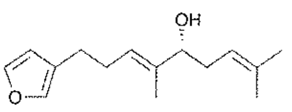
5 R = H, lobatamide E   7 lobatamide G

6 R = OH, lobatamide F





8 lobatamide H   9 lobatamide I



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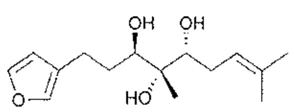

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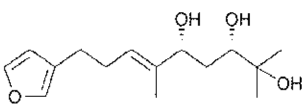

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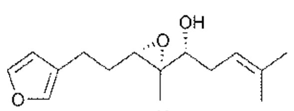

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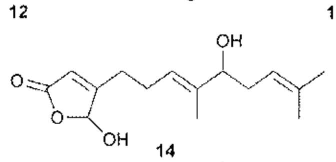

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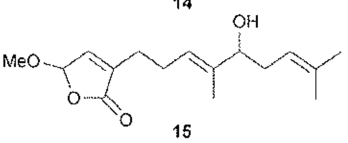


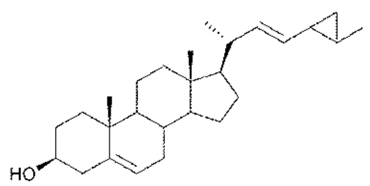
15

deep-sea anthozoans, namely from the orders Alcyonacea (octocorals, soft corals, gorgonians), Scleractinia (stony corals), along with one example from the class Scyphoza.

Class Anthozoa

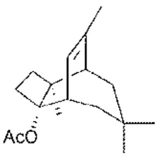
The Anthozoan class comprises anemones, soft corals, and sea pens, with around 6500 species known across the world, mostly from the tropics. Shallow-water anthozoans have produced a range of biomedically important compounds including the sarcodictyins from the Mediterranean coral *Sarcodictyon roseum*, eleutherobin from the Australian octacoral *Eleutherobia* sp., and the pseudopterosins from the soft coral *Pseudopterogorgia elisabethae*.[12,15]

Order Alcyonacea. Papakusterol (**16**), from the Hawaiian "*papaku*" for ocean floor, is a cyclopropyl-containing 22-dehydro-24,26-cyclocholesterol obtained from a deep-sea gorgonian mixture, including an *Acanthagorgia* species, collected by mini-submersible off Makapuu, Hawaii, at a depth of 300–350 m.[104]

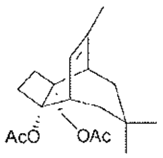


16 papukasterol

The sub-Antarctic soft coral *Alcyonium paessleri*, collected from the South Georgia islands by deep-water netting at a depth of 200 m, has yielded the novel sesquiterpenes paesslerins A and B (**17**, **18**), comprising a previously unreported tricyclic skeleton and exhibiting moderate cytotoxicity.[105] However, the total synthesis of **17** has cast doubts on its proposed structure.[106]



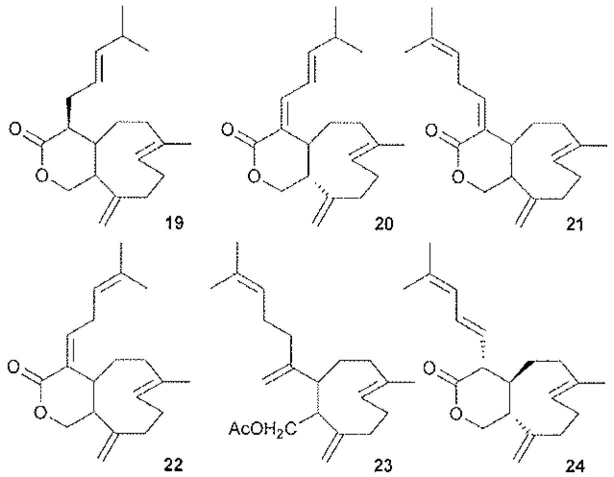
17 paesslerin A



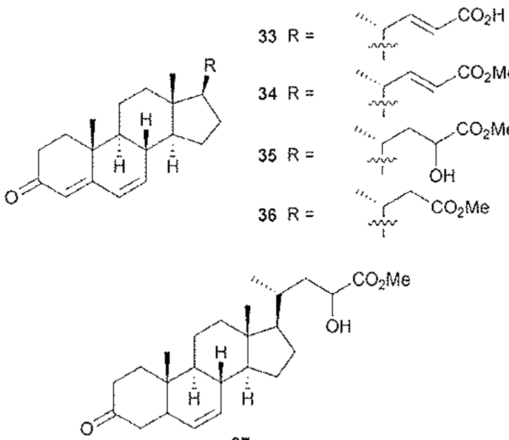
18 paesslerin B

The deep-sea gorgonian *Corallium* sp., collected at 350 m depth off Makapuu, Oahu, Hawaii, was found to contain five new diterpenes, coraxeniolide A–C (**19–21**), coraxeniolide C′ (**22**) and corabohcin (**23**), which are structurally related to the xenicins, isolated from soft corals and brown algae.[107] The total synthesis of coraxeniolide A (**19**) has been reported.[108] Another novel xeniolide, the diterpene arboxeniolide-1 (**24**), was isolated from the gorgonian *Paragorgia arborea*, recovered from a depth of 280 m by trawling operations west of the Crozet Islands, South Indian Ocean.[109]

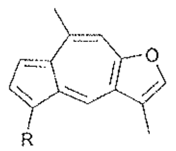
A deep-sea gorgonian of the genus Paramuricea, collected off the northwest coast of Curaçao at a depth of 342 m by manned submersible, has furnished the known compound linderazulene (**25**), along with two new members of the series, **26** and **27**.[110] The linderazulenes **25–27** exhibited mild cytotoxicity against the murine P388 leukemia cell line.



19 20 21 22 23 24



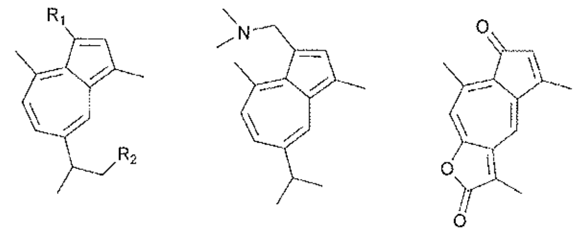
33 R = 34 R = 35 R = 36 R = 37



linderazulenes

25 R = Me
26 R = CO_2Me
27 R = CHO

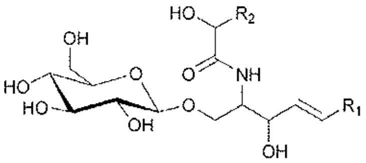
Three novel halogenated azulenes (**28–30**), along with *N*,*N*-dimethylamino-3-guaiazulenylmethane (**31**), were isolated from a blue gorgonian (Paramuriceidae family), collected from Oahu, Hawaii, at 350 m depth using a submersible,[111,112] while the yellow pigment (**32**), was isolated as a minor metabolite of the gorgonian *Placogorgia* sp., retrieved from the same location.[113]



28 R_1 = Cl, R_2 = H
29 R_1 = Br, R_2 = H
30 R_1 = H, R_2 = Br
31
32

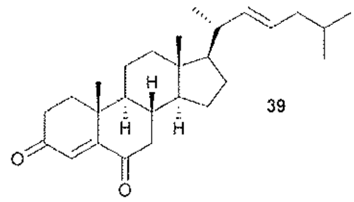
Order Scleractinia. The scleractinian stony corals are reef-building corals with around 800 species described world-wide, predominantly from shallow waters.[3] Scleractinians have a wide distribution and have been recorded from Antarctica to Norway, and down to depths of 6200 m.[114] The first secondary metabolites described from a deep-water scleractinian coral were the novel cholic-acid-type 3-keto steroids **33–37** isolated from the Pacific coral species *Deltocyathus magnificus* collected by trawling near the Loyalty Islands at a depth of 463 m.[114] Along with the novel steroids **33–37**, three other known steroidal natural products were obtained. It should be noted that all compounds apart from **33** were obtained after diazomethane treatment.

The same group found that the Mediterranean scleractinian coral *Dendrophyllia cornigera* contained a complex mixture of β-glucosylceramides (β-GlcCer) (**38**) with a high degree of heterogeneity in both the sphingoid moiety (Δ18:2, 19:2, 20:2, 20:3) and the α-hydroxy fatty acid chain (C19–C24).[115] Four of the major β-GlcCer metabolites of the dendrophylliid coral, collected by dredging at 162 m in northern Corsica, Ligurian Sea, corresponded to the ophidiacerebrosides A–D isolated from the shallow-water sea star *Ophidiaster ophidiamus* from the Balearic Islands, Spain.[116]



38 R_1, R_2 = aliphatic chain

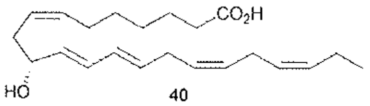
A further specimen of *D. cornigera*, collected at a depth of 80 m near the island of Serifos, Mediterranean Sea, was found to contain the novel (20*R*)-22*E*-cholesta-4,22-diene-3,6-dione (**39**), together with three known 3-keto steroids.[117]



39

Deep-water corals belonging to the genus *Lophelia* (Fig. 1) and *Madrepora* are found at depths of 50 to 2000 m, ranging from the Atlantic to the Indian Ocean, and have been well studied, in terms of their range, distribution and phylogeny.[118,119] A specimen of *Madrepora oculata* recovered near St. Paul Island (S Indian Ocean) by trawling at a depth of 290 m, has yielded the novel 10-hydroxydocosapolyenoic acids **40–42**, along with other known 10-hydroxydocosa- and 8-hydroxyeicosa-polyenoic acids,[120] while the same coral species collected in Trondheimsfjord, Norway, by dredging at 350–380 m depth, gave **40** and **42**. Of the other deep-water scleractinians surveyed in the same study, including *Letepsammia formosissima* (depth 430 m), *Deltocyathus magnificus* (depth 463 m), *Stephanocyatus spiniger*

(depth 480 m), and *Javania lamprotichum* (depth 561 m) from the Loyalty Islands (Pacific Ocean), only the NE Atlantic *Lyophelia pertusa* (depth 765 m) was found to contain hydroxypolyenoic acids.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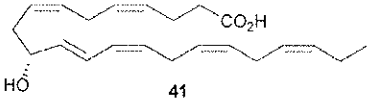
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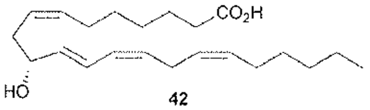
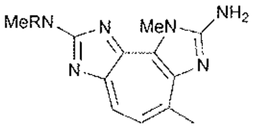
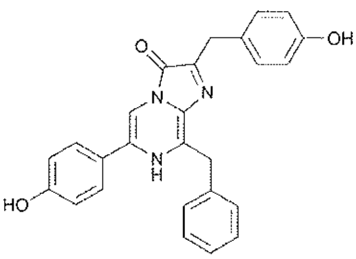

42

Order Zoanthidea. The Pacific gold coral, the colonial anemone *Gerardia* sp., collected at a depth of 350 m from Hawaii by minisubmersible, has been reported to produce two new fluorescent nitrogenous pigments, pseudozoanthoxanthins I and II (**43–44**), both derivatives of tetraazacyclopentazulene.[121]


43 R = Me
44 R = H

Class Scyphoza

The scyphozan class consists of around 250 known species of jellyfish. Coelenterazine (**45**) is an imidopyrazinone-containing metabolite connected to the luminescence of several deep-sea fauna, including the bioluminescent jellyfish *Auquorea auquorea*,[122] the sea pansy *Renilla reniformis*,[123] and the deep-sea shrimp *Oplophorus gracilorostris*.[124] Coelenterazine possesses strong antioxidant properties and provides protection from oxidative stress to cells,[125] and is a key component of several chemiluminescent assays.[126]


45

An analysis of the lipid component of 81 specimens of deep-sea corals revealed six major lipid classes, including sterols, free fatty acids, triacylglycerols, monoalkyldiacyl glycerol, wax, and sterol esters. Compared to their shallow-water counterparts, the deep-sea corals contained fewer lipids.[127]

7 Echinoderms

The most abundant species of invertebrate fauna found in the deep sea are the echinoderms (sea urchins, sea cucumbers, sea stars), which are considered to be among the most numerous species on earth based on the sheer volume of deep-sea floor. Echinoderms, of which there are over 6000 species known worldwide, are a prolific source of bioactive glycosylated metabolites, in particular saponins and glycolipids.[101,128,129] As with shallow-water echinoderms, the deep-water echinoderms are dominated by steroidal metabolites.

Class Asteroidea

Asteroids (sea stars, starfish) have a wide geographical spread, ranging from the poles to the tropics, and from shallow-water to depths of over 4700 m. Shallow-water asteroids are well known as a rich source of steroidal metabolites, in particular steroidal oligoglycosides.[130,131] Deep-sea asteroids have also proven a rich source of novel sterols. For example, the starfish *Henricia downeyae*, retrieved from offshore waters (90 m depth) in the northern Gulf of Mexico, was found to produce thirteen novel (**46–58**) steroidal glycosides, all containing a glucuronic acid moiety atypical for echinoderm glycosides. A further seven known steroidal metabolites were isolated, and the extract of the starfish showed potent antimicrobial activity.[132,133]

The Pacific starfish *Mediaster murrayi*, obtained from dredging in the Philippine Sea at 400–600 m depth, was found to contain four new steroidal glycosides, the mediasterosides M_1 (**59**), M_2 (**60**), M_3 (**61**), and M_4 (**62**), and the known 5α-cholestane-3β,6β,8,15α,16β,26-hexaol. Mediasterosides **59–62** contain rare 1→5 glycosidically linked carbohydrate moieties, and mediasterosides **59** and **60** were found to inhibit the division of fertilized sea urchin eggs.[134]

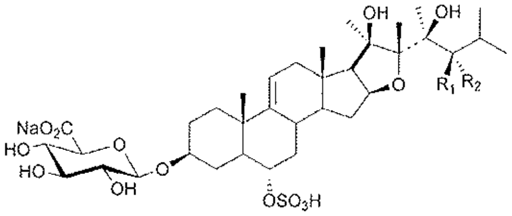
Three new polyhydroxylated sterols (**63–65**), along with two known steroids, were isolated from a Pacific deep-water starfish, *Rosaster* sp., obtained at a depth of 400–500 m off Noumea, New Caledonia.[135] Steroid **64** displayed moderate antifungal activity towards *Cladosporium cucumerinum*.

Specimens of the deep-water starfish *Styracaster caroli* collected at 2000 m depth in New Caledonian waters were found to contain a complex mixture of novel polyhydroxysteroids, including the carolisterols A–C (**66–68**),[136] various 3β,5,6β-trihydroxysteroids (**69–76**)[137] and two minor metabolites with a novel 24-ethyl-25-hydroxy-26-sulfoxycholestane skeleton (**77–78**).[138]

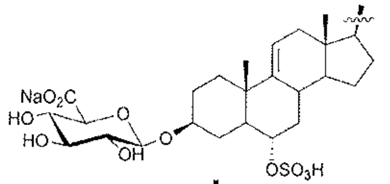
The "living fossil" starfish *Tremaster novaecaledoniae*, collected at a depth of 530 m (New Caledonia), has furnished a range of novel polyhydroxysteroids including the steroids **79–81**, four 3β,6α-disulfated steroids **82–85**, and four unique polyhydroxysteroids, the steroid **86** and the glycosylated tremasterols A–C (**87–89**), possessing both sulfation and phosphorylation.[139,140]

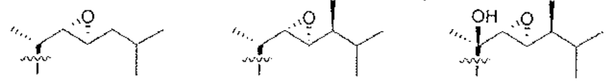
Class Crinoidea

The class Crinoidea comprises around 100 species of sea lilies (stalked crinoids) and feather stars (stalkless crinoids), which have been found from Antarctica to the tropics, and from shallow-water to hadal depths.[141] The so-called "living fossil"

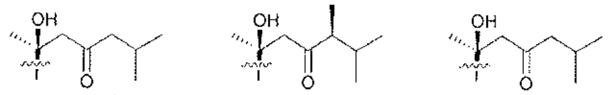


46 $R_1 = CH_3$, $R_2 = H$ downeyoside A
47 $R_1 = H$, $R_2 = CH_3$ downeyoside B

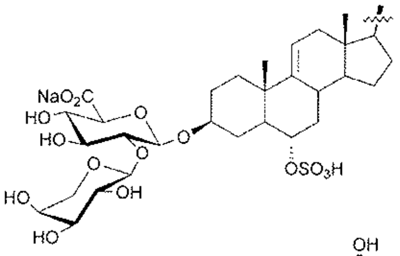


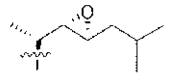


48 downeyoside C **49** downeyoside D **50** downeyoside E

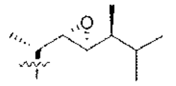


51 downeyoside F **52** downeyoside G **53** 9(11)-dihydro downeyoside J

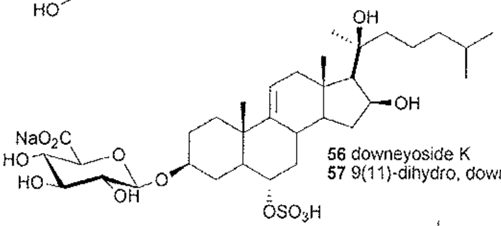




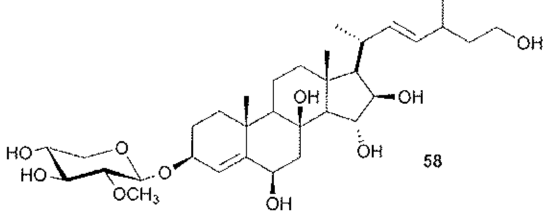
54 downeyoside H



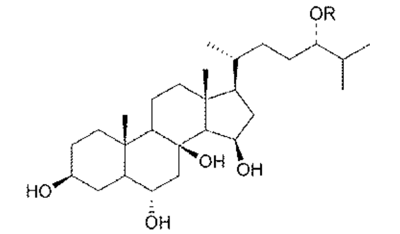
55 downeyoside I



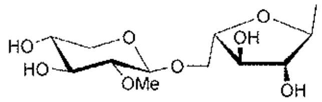
56 downeyoside K
57 9(11)-dihydro, downeyoside L



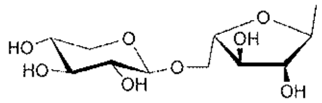
58



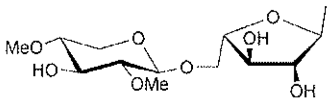
59 R =



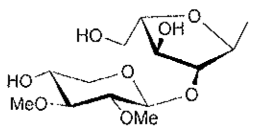
60 R =

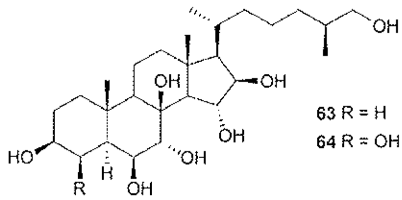


61 R =

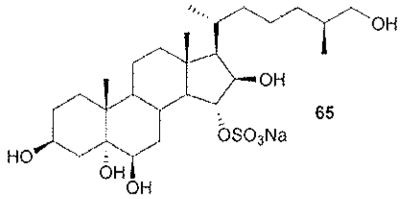


62 R =





63 R = H
64 R = OH



65

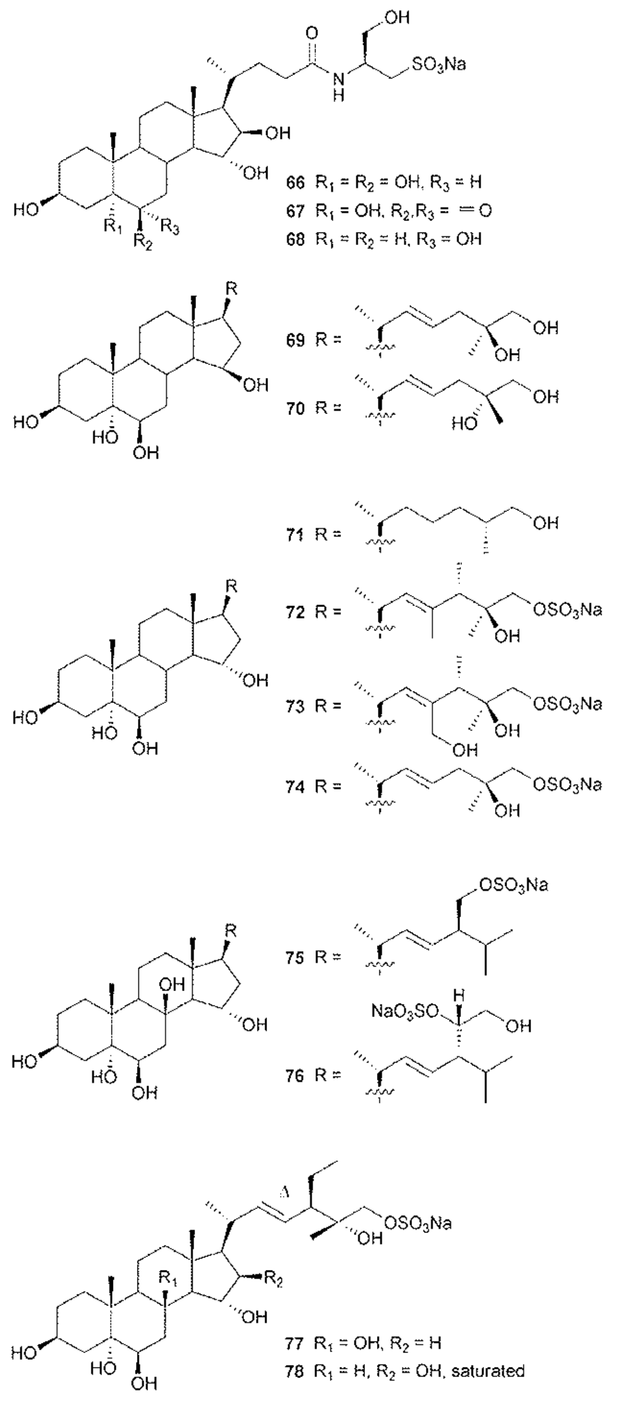
stalked crinoid *Gymnocrinus richeri*, retrieved from bathal depths of 520 m, from Norfolk Ridge, New Caledonia, yielded the novel brominated phenanthroperylenequinone pigments, gymnochromes A–D (**90–93**) and isogymnochrome D (**94**), considered to be conserved traits from Jurassic crinoids.[142]

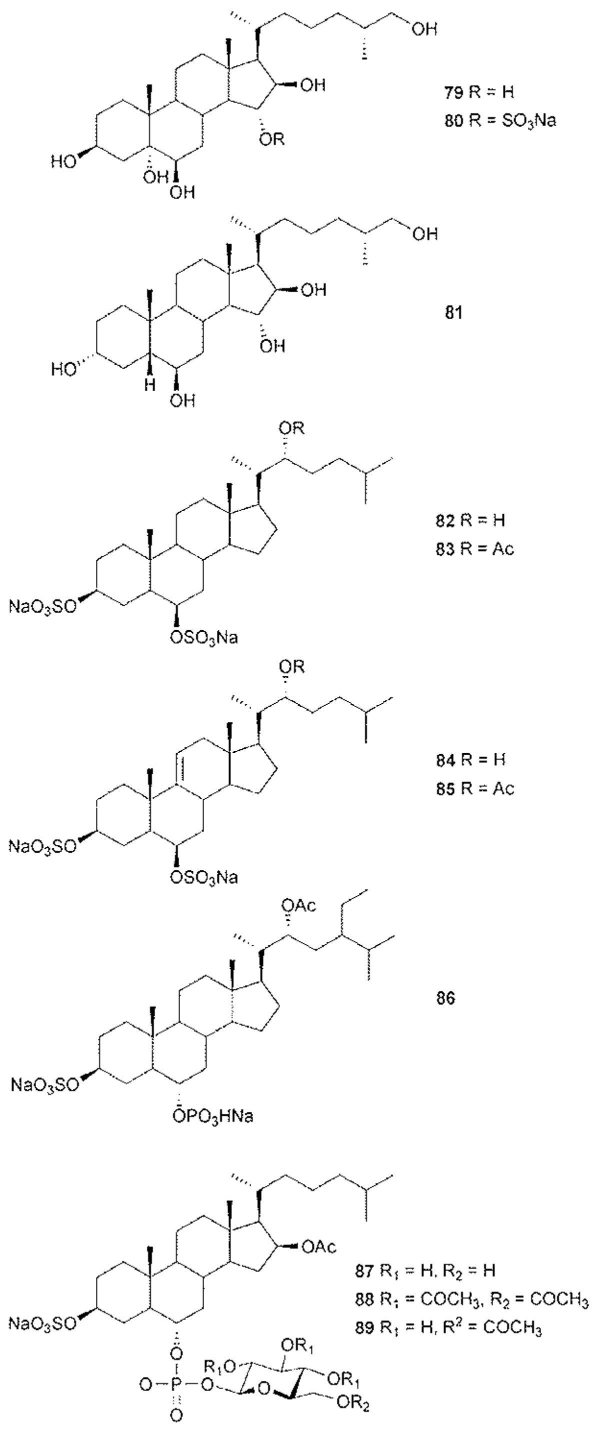
Class Echinoidea

Echinoids (sea urchins) are found in both shallow- and deep-water and are widely distributed from the polar regions to the tropics. Although several shallow-water urchin metabolites have been described, to date there is only one example from the deep sea. The sea urchin *Echinocardium cordatum*, collected at 400 m depth off the Heda coast of the Izu Peninsula, Japan, was found to produce the novel hedathiosulfonic acids A (**95**) and B (**96**), constituting the first isolation of thiosulfonic acids from echinoderm species.[143,144] The sulfur-oxidising bacteria *Thiothrix* sp. has, however, been demonstrated as having a symbiotic relationship with *E. cordatum*[145] and may be the actual source of the novel compounds, which have been patented due to their potent antibacterial, antitumour and antifouling activities.[146]

Class Holothuroidea

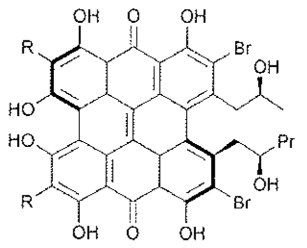
Holothuroids (sea cucumbers) have a wide geographical distribution, ranging from Antarctica to the tropics and from



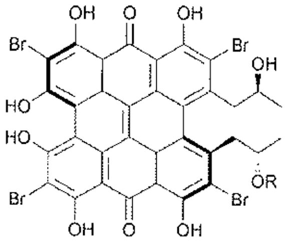


shallow-water to abyssal depths of 5400 m.[147] The secondary metabolites of shallow-water holothuroids have been reviewed,[130] and two examples of deep-sea cucumber metabolites have appeared in the literature. The North Pacific sea cucumber *Pseudostichipus trachus*, collected by deep-water trawling at 300 m in the Pacific Ocean near the Kuril Islands, was found to contain a novel sulfated triterpene glycoside, pseudostichoposide B (**97**), along with the known pseudostichoposide A (**98**).[148,149]

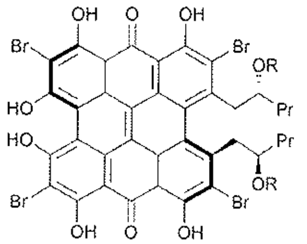
The same group described another specimen of Northern Pacific sea cucumber, *Synallactes nozawai*, obtained at 540 m depth by bottom trawling in the Sea of Japan, which yielded the synallactosides A1 (**99**), A2 (**100**), B1 (**101**), B2 (**102**), and C (**103**), the first report of triterpene glycosides from the family Synallactidae. The novel synallactosides A2–C (**100–103**) possess carbohydrate chains that were previously undescribed among sea cucumber glycosides.[150]



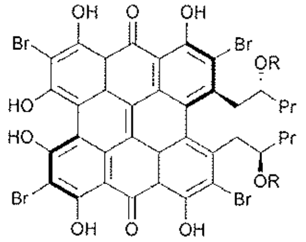
90 $R_1 = R_2$ = Br gymnochrome A
91 R_1/R_2 = H/Br gymnochrome B



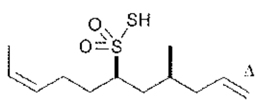
92 R = SO_3H gymnochrome C



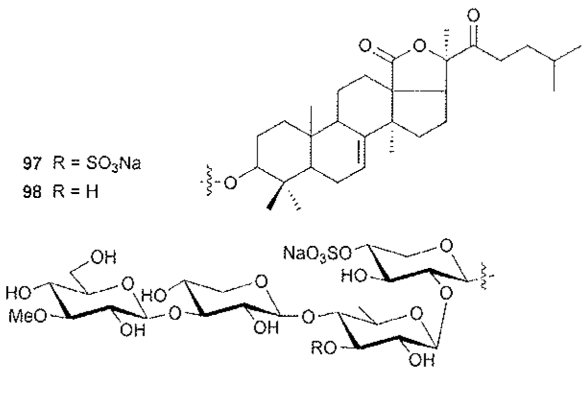
93 R = SO_3H gymnochrome D



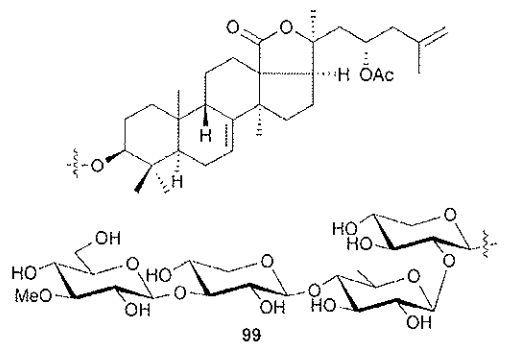
94 R = SO_3H isogymnochrome D



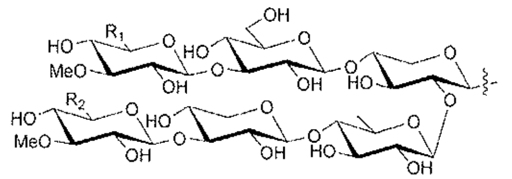
hedathiosulfonic acids
95 Δ, saturated
96



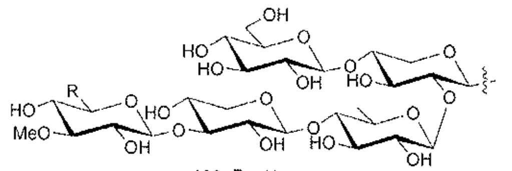
97 R = SO_3Na
98 R = H



99



100 $R_1 = R_2$ = H
101 R = H, R_2 = CH_2OH



102 R = H
103 R =CH_2OH

Class Ophiuroidea

Deep-water ophiuroids were first reported in the early 19th century, and have since been found to inhabit all oceans, and down to depths of over 7000 m.[151] Although shallow-water ophiuroids are well known,[130] up until now there have been no secondary metabolites described from deep-water ophiuroids.

8 Microorganisms

Marine microorganisms are well known as a rich source of diverse and structurally unique metabolites.[13,152,153] In recent years, development of methods for sampling, identification and successful culturing of deep-sea microorganisms have uncovered a new resource for drug discovery.[154]

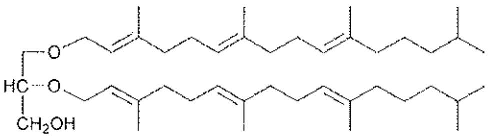
Archaea

An anaerobic culture of the archaeon *Thermococcus* sp., collected from a deep-sea hydrothermal vent, has yielded the novel glycerol ether lipid 2,3-di-*O*-dihydro-14,15-geranylgeranylglycerol (**104**), accompanied by the known lipids, diphytanyl glycerol and dibiphytanyl diglycerol,[155] while the lipid fraction of further species of hydrothermal vent archae, such as *Thermococcus hydrothermalis* isolated from an active chimney on the East Pacific Rise, were also found to comprise diphytanylglycerol and dibiphytanyldiglycerol ethers.[156,157] Another deep-sea hydrothermal vent archaeon, the methanogen *Methanococcus jannaschii* isolated from black smoker sediment at the East Pacific Rise, was found to contain the novel macrocyclic ether **105**,[158] with variable lipid compositions at different temperatures and pressure.[159,160]

Bacteria

In 1987, the culture broth of the marine bacteria *Alteromonas haloplanktis*, isolated from deep-sea mud collected at a depth of 3300 m off the coast of Aomori Prefecture, Japan, was found to produce the novel siderophore bisucaberin (**106**), which rendered tumour cells sensitive to macrophage-mediated cytolysis.[161,162] Bisucaberin has been the subject of a total synthesis,[163] and its method of production and use as a antitumour agent has been patented.[164]

The culture broth of a *Bacillus* deep-sea floor species obtained from a sediment core at 124 m deep near the Guaymas Basin, Mexico, was found to contain the novel moderately cytotoxic



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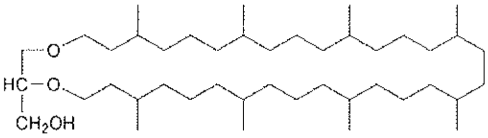
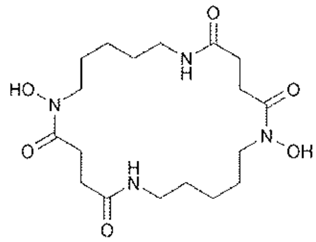
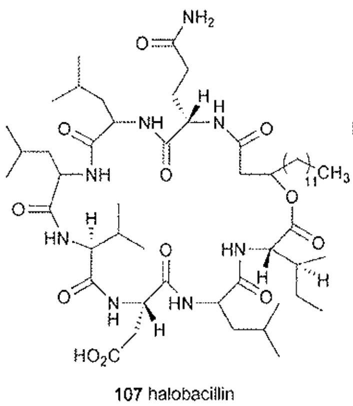


105

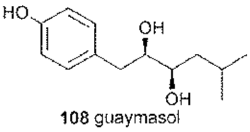


106 bisucaberin

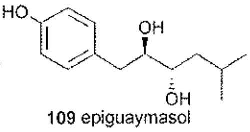
cyclic acylpeptide halobacillin (**107**), a member of the iturin class of natural products,[165] while the same group identified two novel aromatic triols, guaymasol (**108**) and epiguaymasol (**109**), along with the known ketodiol guaymasone, from a second *Bacillus* sediment species obtained by drilling at 1834 m in the Guaymas Basin.[166] A further Pacific sediment *Bacillus* sp. (5059 m depth) yielded the novel cytotoxic phenazine derivative (**110**) with a unique [4,2,2] ring system, accompanied by six known compounds.[167]



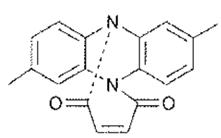
107 halobacillin



108 guaymasol

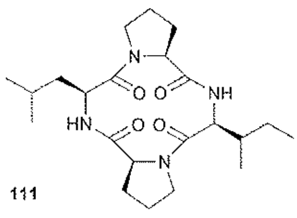


109 epiguaymasol



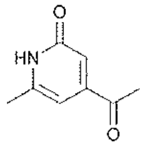
110

The culture broth of a *Nocardiopsis* sp. actinomycete obtained from 3000 m deep, benthic sediment from the Clarion–Clipperton Fracture Zone, yielded a novel cyclic tetrapeptide, cyclo(L-isoleucyl-L-prolyl-L-leucyl-L-prolyl) (**111**), along with several diketopiperazines.[168] Although the crude extract showed significant cytotoxicity, the purified metabolite was inactive.

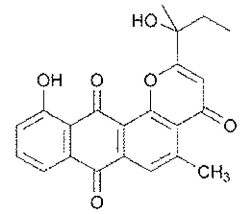


111

The culture broth of an actinomycete strain belonging to the *Streptomyces* genus collected from deep-sea sediment at Ayu Trough, Pacific Ocean, was found to contain the novel methylpyridine streptokordin (**112**), along with the known compounds nonactic acid, dilactone, trilactone, and nonactin.[169] Streptokordin (**112**) displayed significant cytotoxicity against seven human cancer cell lines (IC_{50} <10 µg mL^{-1}) but did not exhibit antibacterial or antifungal activity. Fermentation of another *Streptomyces* sp. obtained from a 4680 m deep sediment core off the coast of Majuro, Marshall Islands, provided a new pluramycin metabolite, γ-indomycinone (**113**), along with the known metabolites rubiflavinone C-1 and β-indomycinone.[170] The pluramycin class of antibiotics had only previously been isolated from terrestrial *Streptomyces* spp.



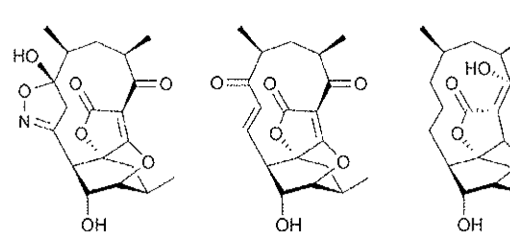
112 streptokordin



113 γ-indomycinone

An actinomycete, *Verrucosispora* sp., obtained at a depth of 289 m in the Sea of Japan, was found to contain the unique polycyclic antibiotics, the abyssomicins B–D **114–116**.[171] The structure and relative stereochemistry of the abyssomicins was confirmed by X-ray crystallography, and the absolute stereochemistry deduced using the Mosher and Helmchen method. Abyssomicin C (**116**) was found to inhibit the *para*-aminobenzoic acid/tetrahydrofolate biosynthetic pathway, and exhibited strong activity towards Gram-positive bacteria.[172]

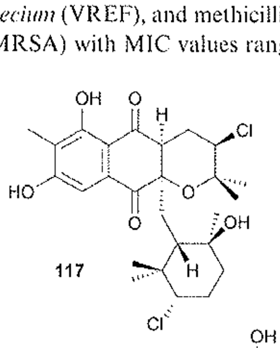
abyssomicins



114 115 116

A new genus of actinomycete isolated from 152 m deep-sea sediment (La Jolla, California) has furnished the cytotoxic chloro-dihydroquinones **117–119**, with IC_{50} values of 2.40 and 0.97 µg mL^{-1} for **117** and **118** respectively, against human HCT-116 colon carcinoma cells, along with two known chlorinated dihydroquinones.[173–175] The compounds also displayed potent antibacterial activity towards vancomycin-resistant *Enterococcus*

faecium (VREF), and methicillin-resistant *Staphylococcus aureus* (MRSA) with MIC values ranging from 1.95–15.6 μg mL^{-1}.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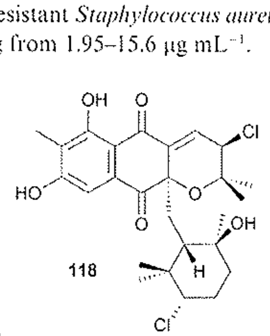
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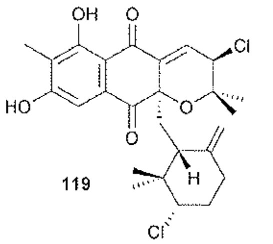
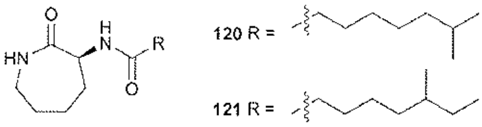
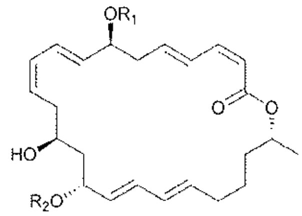
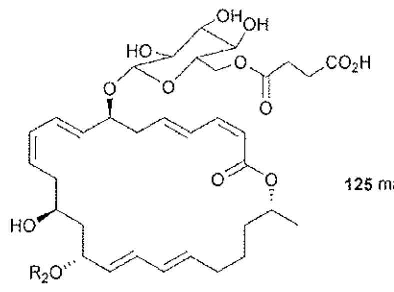

119

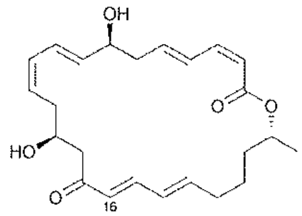
Two new cytotoxic caprolactams, caprolactins A (**120**) and B (**121**), were isolated as an inseparable mixture from the culture broth of an unidentified Gram-positive bacterium obtained from 5065 m deep ocean sediment from the Central Pacific Basin, the deepest reported sample from which a new natural product has been isolated.[176] The structure of the caprolactins has been confirmed by synthesis, and both exhibit significant cytotoxicity against human KB (epidermal) and LoVo (colorectal) tumour cell lines, as well as moderate antiviral activity against Herpes simplex virus-II (HSV-II).

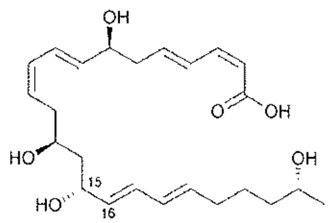


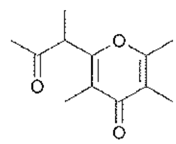
The antimicrobial macrolactins A–F (**122–127**), along with macrolactinic acid (**128**) and isomacrolactinic acid (**129**), were isolated from an unclassifiable deep-sea bacterium obtained from a 980 m deep sediment sample from the North Pacific.[177] The macrolactins have been elegantly reviewed by Baker *et al.*[37]

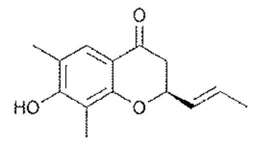

macrolactin A-C
122 $R_1 = R_2 = H$
123 R_1 = β-glucosyl, R_2 = H
124 R_1 = H, R_2 = β-glucosyl


125 macrolactin D


126 macrolactin E
127 16,17-dihydro macrolactin F


128 macrolactinic acid
129 15-keto-16,17-dihydro isomacrolactinic acid

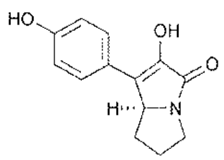

130


131

Fungi

The deep-sea fungus *Aspergillus sydowi*, obtained at a depth of 1000 m, was found to produce two novel pyranone (**130**) and chromenone (**131**) metabolites, with the latter compound exhibiting significant cytotoxicity towards the murine P388 cell line (IC_{50} 0.14 μM).[178] Six known natural products were also isolated from the same sample.

Three new compounds, *p*-hydroxyphenopyrrozin (**132**) and the diketopiperazines (**133–134**), have been obtained from the culture broth of a marine-derived fungus *Chromocleista* sp. isolated from 70 m deep sediment from the Gulf of Mexico.[179] Other known natural products, including phenopyrrozin, four diketopiperazines, *N*-acetyltryptamine and agathic acid, were obtained from the same sample.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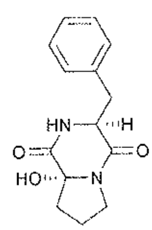
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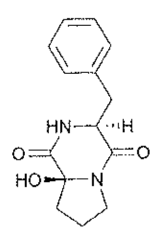
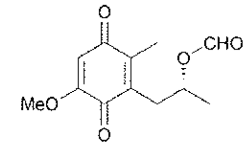

134

The cytotoxic pentaketides (+)-formylanserinone B (**135**) and (−)-epoxyserinone A (**136**) (and its enantiomer) along with minor amounts of hydroxymethylanserinone B (**137**) and deoxyanserinone B (**138**) and the known anserinones A and B, were isolated from a salt-water culture of two *Penicillium corylophilum* fungal strains obtained from a 1335 m deep sediment grab between Fiji and Matuka.[180–182]



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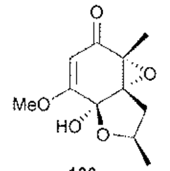

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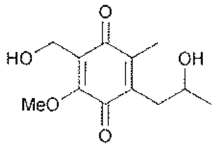

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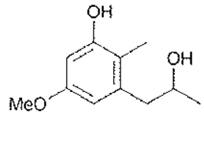
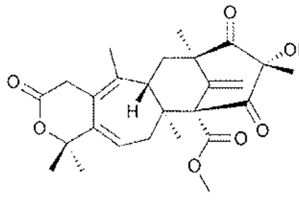


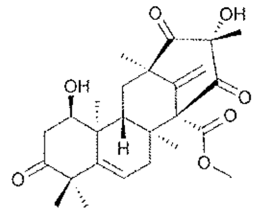
138

The culture broth of a deep-water fungus *Penicillium rubrum* Stoll, obtained at a depth of 270 m from Berkeley Pit Lake, an open-pit copper mine in Montana, USA, has yielded several novel metabolites, including berkeleydione (**139**) and berkeleytrione (**140**);[183] the berkeleyacetals A–C (**141–143**);[184] and the berkeleyamides A–D (**144–147**).[185] All seven of the hybrid polyketide–terpenoid metabolites (**139–147**) were found to inhibit MMP-3 and caspase-1 activity.

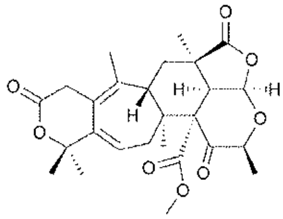
A deep-sea fungus, *Phialocephala* sp., obtained at a depth of 5059 m, has yielded the novel metabolite trisorbicillinone A (**148**), bearing a unique trimeric sorbicillin skeleton, and exhibiting significant cytotoxicity towards murine P388 and HL60 cells (IC_{50} 9.10 and 3.14 μM, respectively).[186,187] The same group identified a further two new antineoplastic antibiotic bisorbicillinoids from the same sample, designated oxosorbiquinol (**149**) and dihydrooxosorbiquinol (**150**).[188]



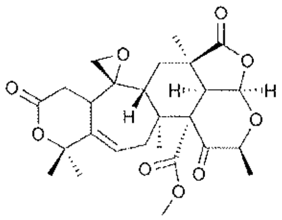
139 berkeleydione



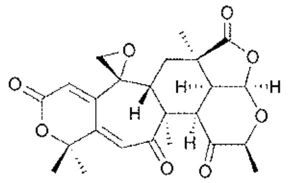
140 berkeleytrione



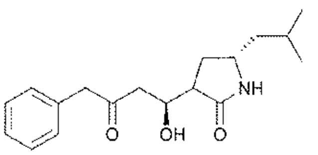
141 berkeleyacetal A



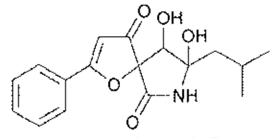
142 berkeleyacetal B



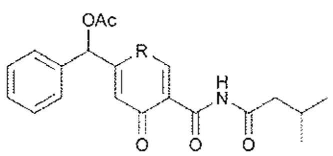
143 berkeleyacetal C



144 berkeleyamide A



145 berkeleyamide D



146 R = O berkeleyamide B

147 R = NCH_2CH_2OH berkeleyamide C

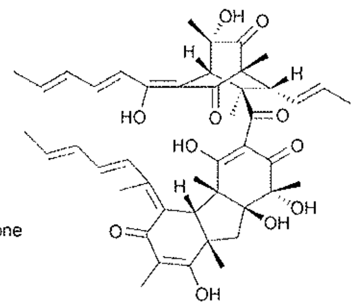
9 Mollusca

The deep-sea bivalve *Calyptogena soyoae*, collected at a depth of 1100 m from a cold seep in Sagami Bay, Japan, has furnished the known phytosterols 24-methylenecycloartanal, cycloeucalenol, and obtusifoliol, while the bivalve *Bathymodiolus septemdierum*, retrieved from 1244 m deep hydrothermal vents at Myojin Knoll, Japan, was found to contain more diverse sterols, including 6α-chlorostigmastane-3β,5β-diol, 5α,8α-epidioxycholest-6-en-3β-ol and 5α,6β-dihydroxystigmastan-3-*O*-β-glycopyranoside, along with cholesterol, cholestanol and lathosterol.[189]

10 Porifera (sponges)

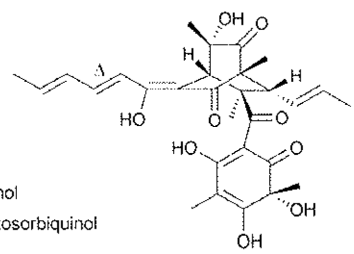
Sponges are the largest source of new marine natural products reported annually[101–103] and they have been providing a smorgasbord of bioactive compounds for the pharmaceutical industry since the 1950s, including the natural product analogue cytosine arabinoside from the Caribbean sponge *Tethya crypta*, halichondrin B from the Japanese sponge *Halichondria okadai*, discodermolide from the Caribbean sponge *Discodermia dissoluta* and agelasphin from *Agelas mauritianus*.[12,190] Sponges are extremely well represented in the marine environment, with over 7000 species described, ranging from shallow-water to those inhabiting depths of over 8000 m, with some deep-water species adopting carnivorous behaviour.[191,192] Sponge metabolites, predominantly from shallow-water species, have been reviewed previously.[192,193] Deep-water species of marine sponge, having

148 trisorbicillinone



149 oxosorbiquinol

150 Δ, dihydrooxosorbiquinol



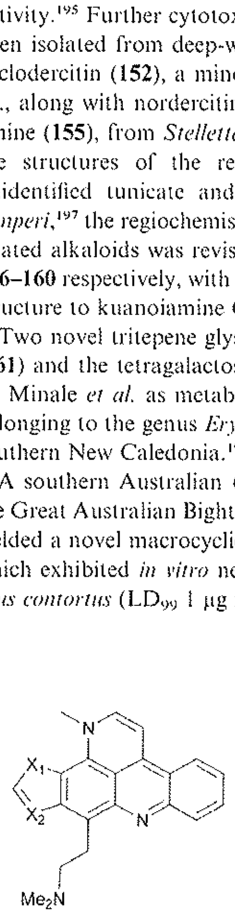
already provided important anticancer agents such as halichondrin and discodermolide,[12] are certain to be a rich new source of biologically and structurally interesting molecules.

Order Astrophorida

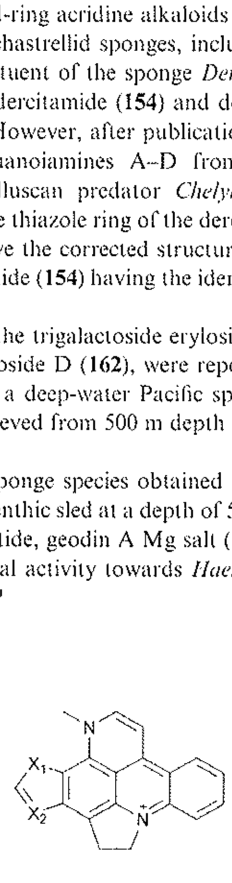
A purple-coloured, cytotoxic acridine alkaloid, dercitin (**151**), was isolated from a Caribbean marine sponge, *Dercitus* sp., collected at a depth of 160 m from Goulding Cay, Bahamas, using a manned submersible.[194] Dericitin (**151**), a pentacyclic aromatic alkaloid with a unique thiazole-containing fused-ring, was found to possess potent *in vitro* antitumour, antiviral and immunomodulatory activity, along with *in vivo* antitumour activity.[195] Further cytotoxic, fused-ring acridine alkaloids have been isolated from deep-water pachastrellid sponges, including cyclodercitin (**152**), a minor constituent of the sponge *Dercitus* sp., along with nordercitin (**153**), dercitamide (**154**) and dercitamine (**155**), from *Stelletta* sp.[196] However, after publication of the structures of the related kuanoiamines A–D from an unidentified tunicate and its molluscan predator *Chelynotus semperi*,[197] the regiochemistry of the thiazole ring of the dercitin-related alkaloids was revised to give the corrected structures as **156–160** respectively, with dercitamide (**154**) having the identical structure to kuanoiamine C.[198]

Two novel tritepene glysosides, the trigalactoside eryloside C (**161**) and the tetragalactoside eryloside D (**162**), were reported by Minale *et al.* as metabolites of a deep-water Pacific sponge belonging to the genus *Erylus*, retrieved from 500 m depth from southern New Caledonia.[199]

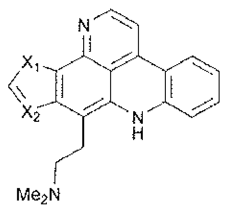
A southern Australian *Geodia* sponge species obtained from the Great Australian Bight by epibenthic sled at a depth of 51 m, yielded a novel macrocyclic polyketide, geodin A Mg salt (**163**), which exhibited *in vitro* nematocidal activity towards *Haemonchus contortus* (LD_{99} 1 μg mL^{-1}).[200]



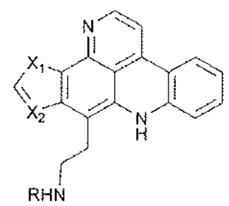
151 X_1 = S, X_2 = N
156 X_1 = N, X_2 = S



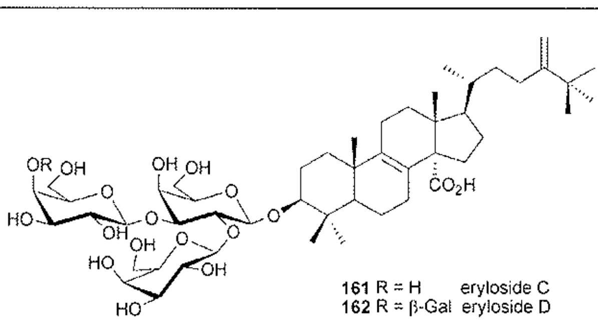
152 X_1 = S, X_2 = N
157 X_1 = N, X_2 = S



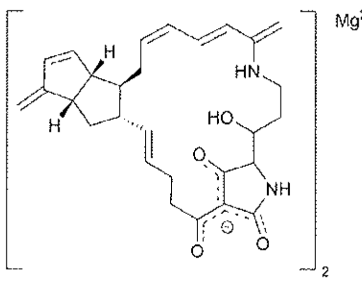
153 X_1 = S, X_2 = N
158 X_1 = N, X_2 = S



154 X_1 = S, X_2 = N, R = COEt
155 X_1 = S, X_2 = N, R = Me
159 X_1 = N, X_2 = S, R = COEt
160 X_1 = N, X_2 = S, R = Me



161 R = H eryloside C
162 R = β-Gal eryloside D



163 geodin A Mg salt

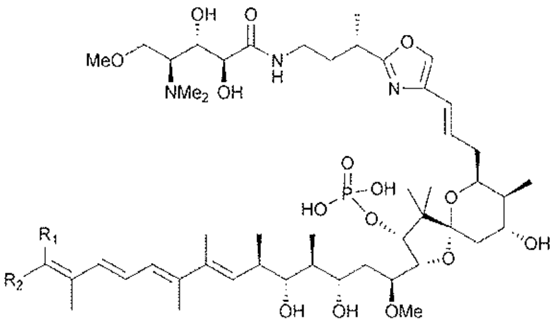
The pachastrellid sponge *Lamellomorpha strongylata*, obtained by benthic dredging at a depth of 80–100 m off the Chatham Rise, New Zealand, has yielded three distinct classes of cytotoxic compounds: the first characterised by the known calyculins A, B, E, and F,[201,202] and the novel derivatives calyculinamides A (**164**) and B (**165**); the second by the novel swinholide derivative swinolide H (**166**); and the third by a 36-membered ring cyclic peptolide, theonellapeptolide IIe (**167**).[20,203] The related theonellapeptolides I and II were isolated from the shallow-water sponge *Theonella swinhoei*.[204]

Bioassay-guided isolation of the deep-water sponge *Poecillastra laminaris*, collected at a depth of 750 m in the Philippine Sea, furnished the novel sulfated steroid annasterol sulfate (**168**), a potent inhibitor of glucanase activity.[205]

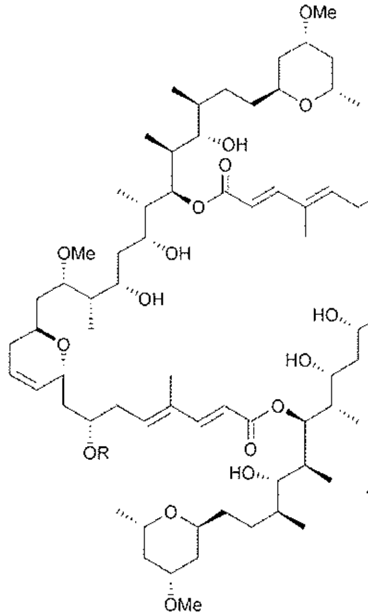
Bioassay-guided purification of extracts of the deep-water marine sponge *P. sollasi* led to the isolation of six new sesquiterpene-derived compounds, the sollasins A–F (**169–174**), which display both antifungal and cytotoxic activity when tested against *Candida albicans* and *Cryptococcus neoformans*, and murine P388 (leukemia) and human A549 (lung) tumour cell lines respectively. The marine sponge sample was collected at a depth of 375 m from Little Inagua Island, Bahamas, using a manned submersible.[206]

The deep-water sponge *Poecillastra* sp., collected from Grand Bahama Island at a depth of 359 m by manned submersible, has furnished the potent antitumour macrolide lactam poecillastrin A (**175**),[207] along with trace amounts of poecillastrin B (**176**) and C (**177**).[208] Poecillastrin D (**178**) was obtained, along with poecillastrin C (**177**), from the deep-sea sponge *Jaspis serpentina*, collected by dredging in Japanese waters.[209] The poecillastrins, novel 33-membered polyketide-derived macrolide lactams displaying potent cytotoxicity, are structurally related to the chondropsin lactams, which have been isolated from a variety of sponge genera, including *Ircinia* and *Chondropsis* sp.[210,211]

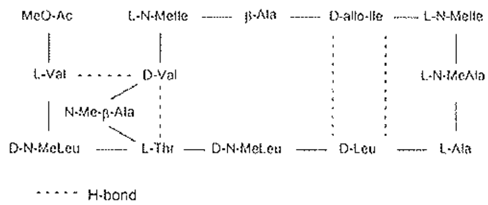
The pachastrellid sponge *Stoeba extensa*, collected by dredging at 160 m depth at Oshima-Shinsone, Japan, has yielded a novel



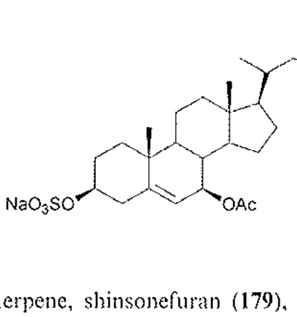
164 R_1 = $CONH_2$, R_2 = H, calyculinamide A
165 R_1 = H, R_2 = $CONH_2$, calyculinamide B



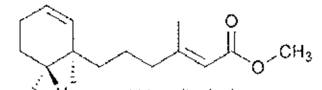
166 swinholide H



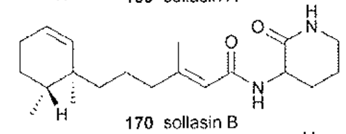
167 theonellapeptolide IIIe



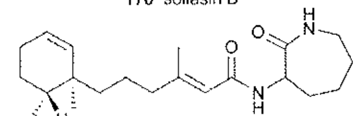
168 annasterol



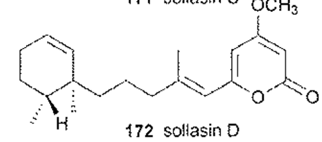
169 sollasin A



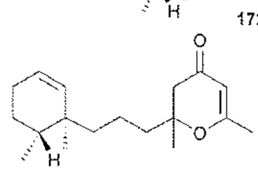
170 sollasin B



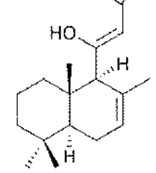
171 sollasin C



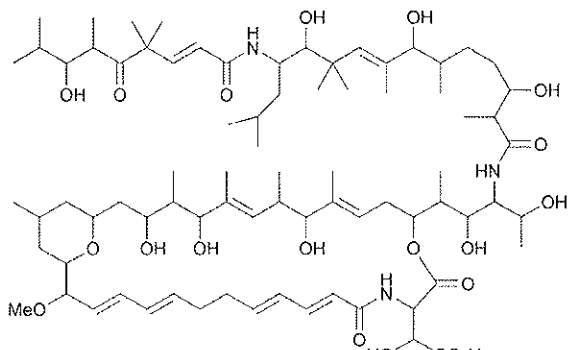
172 sollasin D



173 sollasin E



174 sollasin B



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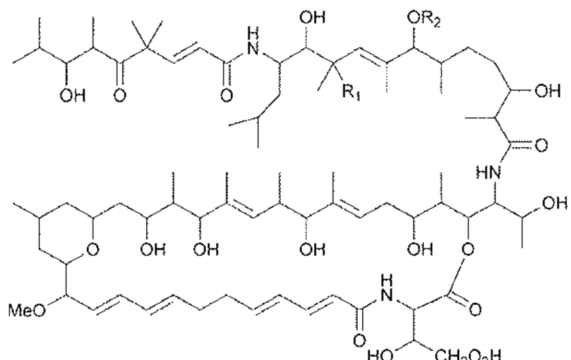
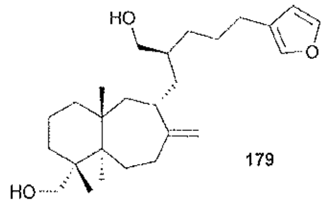


176 R_1 = Me, R_2 = H
177 R_1 = H, R_2 = H
178 R_1 = H, R_2 = Me

furanosesterpene, shinsonefuran (**179**), which possesses a new carbon skeleton and significant cytotoxic activity towards HeLa cells (IC_{50} 16 μg mL^{-1}).[212]

The deep-water sponge *Stelleta* sp., retrieved from a depth of 700 m in the Coral Sea, was found to elaborate stigmastane-type sterones and sterols, stigmasta-4,24(25)-dien-3-one ((+)-**180**), and stigmasta-4,24(25)-diene-3,6-dione ((−)-**181**), with a C24–C25 double bond, unprecedented in marine sterols.[213]



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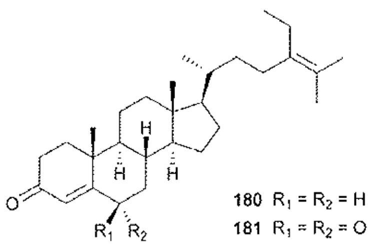
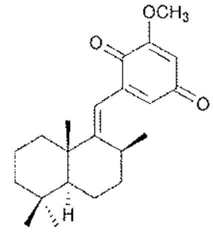


180 $R_1 = R_2 = H$
181 $R_1 = R_2 = O$



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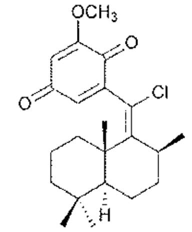

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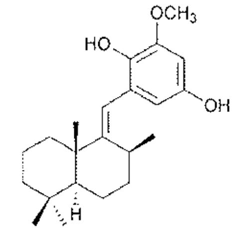

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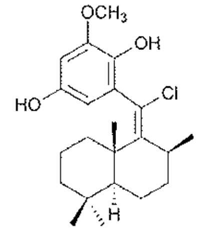
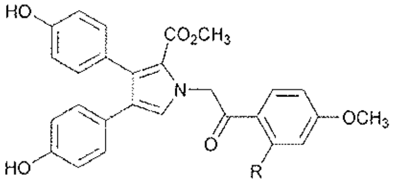


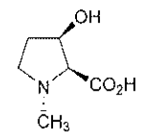
188

Order Dendroceratida

The sponge *Dendrilla cactos*, obtained during deep-sea trawling operations in Bass Strait, Australia, was found to produce the novel alkaloids lamellarin O (**182**) and P (**183**) with moderate antibiotic activity,[214] while another specimen of *Dendrilla* sp., collected at a depth of 1000 m by trawling in the Great Australian Bight, was found to elaborate the new amino acid *cis*-3-hydroxy-*N*-methyl-L-proline (**184**), as a highly abundant metabolite.[215]



182 R = H lamellarin O
183 R = OH lamellarin P



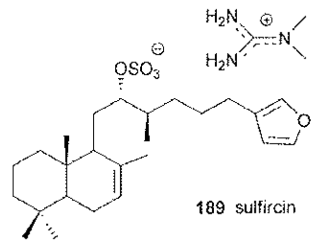
184

Bioassay-guided fractionation of the sponge *Euryspongia* sp., retrieved from a depth of 150 m from the Great Australian Bight, has yielded the new sesquiterpene quinones (**185–186**) and sesquiterpene hydroquinones (**187–188**), with moderate growth inhibitory activity towards the Gram-positive bacterium *Micrococcus lutea*.[216]

Order Dictyoceratida

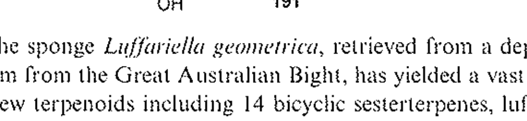
A deep-water marine sponge of the genus *Ircinia*, collected at a depth of 119 m off Fresh Creek, Andros, Bahamas, has yielded a novel sesterterpene sulfate, sulfircin (**189**), constituting a rare example of an *N,N*-dimethylguanidinium salt from a marine source.[217] Sulfircin (**189**), which is an unusual furan-bearing bicyclic structure with sulfation at C12, displays inhibitory activity against the fungal pathogen *C. albicans* (MIC = 25 μg mL^{-1}).

Further samples from the genus *Ircinia*, collected from the Norfolk Ridge, New Caledonia, at a depth of 425–500 m, have been shown to produce the novel sulfated C_{31} furanoterpenol, ircinol sulfate (**190**) and hydroxylated

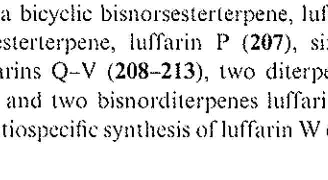


189 sulfircin

2-heptaprenylhydroquinone (**191**), the latter showing tyrosine protein kinase and HIV-integrase inhibitory activity.[218] In addition, a range of prenylhydroquinone-4-sulfates, prenylated benzopyran sulfates, prenylated hydroquinones, corresponding quinones and three chromenols were isolated from the same material, with the majority of the metabolites either known or closely related to known marine natural products.[218]

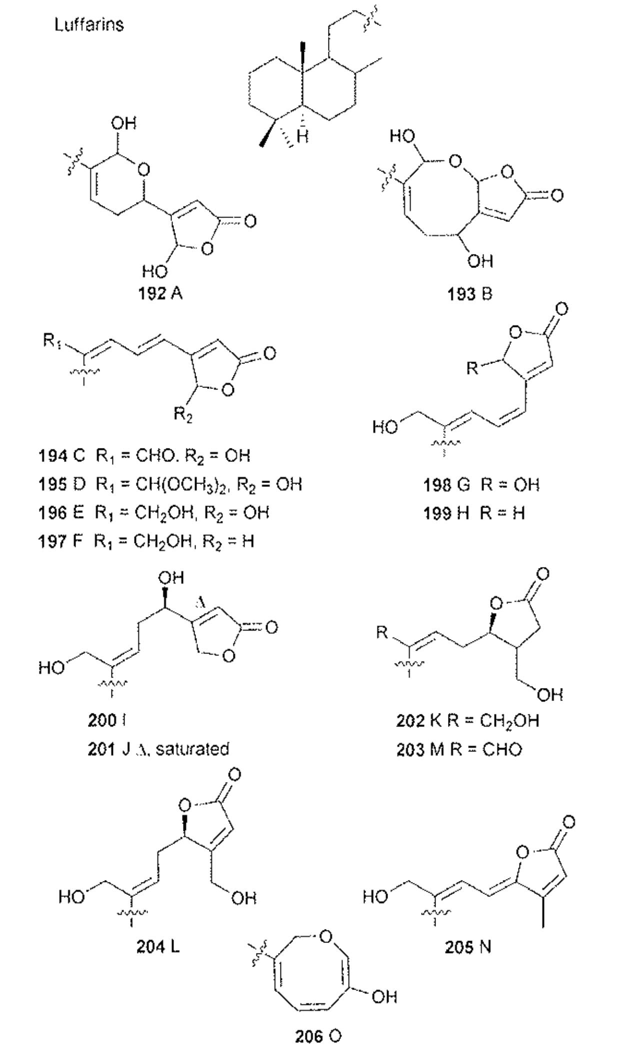


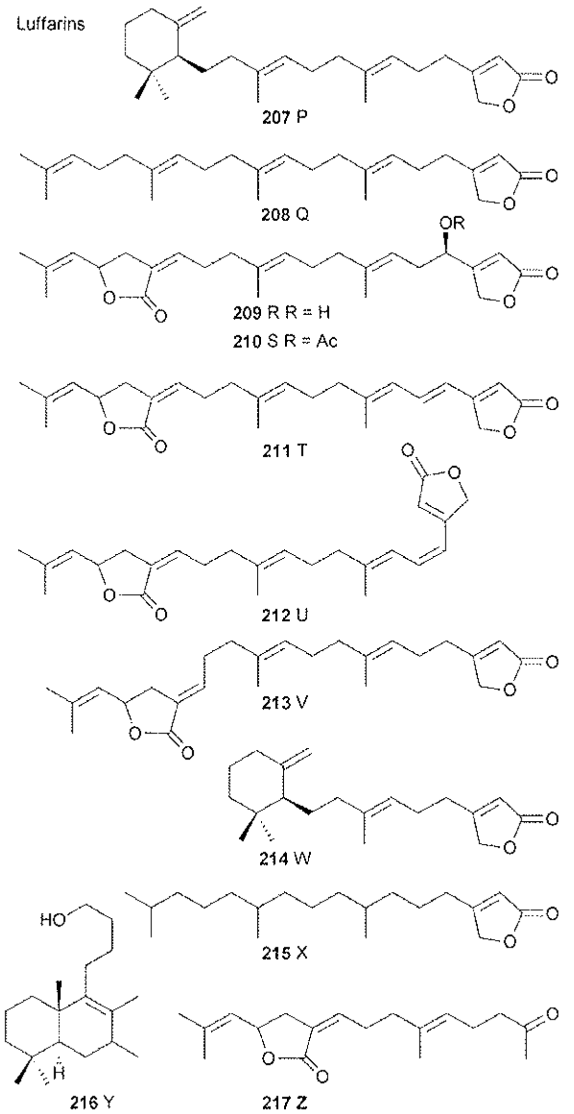
190 ircinol sulfate



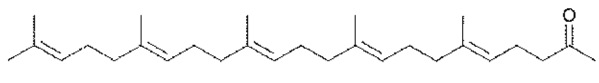
191

The sponge *Luffariella geometrica*, retrieved from a depth of 350 m from the Great Australian Bight, has yielded a vast array of new terpenoids including 14 bicyclic sesterterpenes, luffarins A–N (**192–205**), a bicyclic bisnorsesterterpene, luffarin O (**206**), a monocyclic sesterterpene, luffarin P (**207**), six acyclic sesterterpenes, luffarins Q–V (**208–213**), two diterpenes, luffarins W–X (**214–215**), and two bisnorditerpenes luffarins Y–Z (**216–217**).[219] The enantiospecific synthesis of luffarin W (**214**) has been reported.[220]

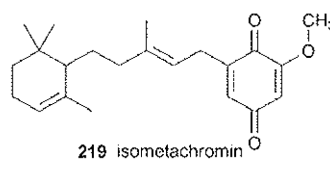




The sponge *Sarcotragus spinulosus*, obtained from trawling operations at 400 m depth in the Tasman Sea, was found to contain the new nortriterpenoid geranylfarnesylacetone (**218**),[221] while a sponge belonging to the family Spongiidae, collected from Chub Cay, Bahamas, at a depth of 800 m, was found to elaborate the new sesquiterpene–quinone, isometachromin (**219**), along with the known metabolites, ilimaquinone and 5-*epi*-ilimaquinone.[222] Isometachromin (**219**) displayed antimicrobial activity, as well as *in vitro* cytotoxicity towards human A549 (lung) tumour cells (IC_{50} 2.6 μg ml^{-1}), but not against murine P388 (leukemia) cells.[222]



218 geranylfarnesylacetone



219 isometachromin

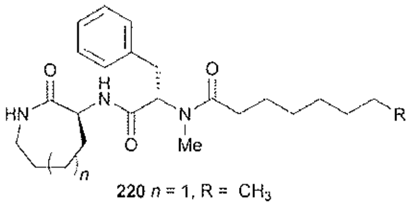
Order Hadromerida

The sponge *Aaptos ciliata*, collected by deep-sea dredging at 150 m off Oshima-Shinsone, Japan, has yielded three new anti-leishmanial lipopeptides, ciliatamides A–C (**220–222**).[223]

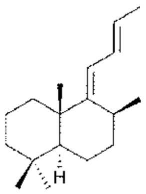
A novel bisnorditerpene, sigmosceptrin A (**223**), and two new norditerpenes, sigmosceptrins B (**224**) and C (**225**), were obtained from the deep-sea sponge *Sigmosceptrella* sp., collected during trawling operations at depths of around 70 m in the Great Australian Bight.[224]

Order Halichondrida

The sesquiterpene phenols (*S*)-(+)-curcuphenol (**226**) and (*S*)-(+)-curcudiol (**227**) were isolated from the sponge *Didiscus*



220 $n = 1$, R = CH_3
221 $n = 1$, R = $CH_2CH{=}CH_2$
222 $n = 0$, R = CH_3



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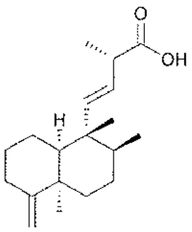

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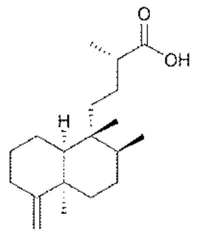
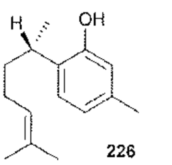


225

flavus obtained from three different collections at depths of 3 m (Long Island, Bahamas), 15 m (Turneffe Islands, Belize), and 139 m (Hogsty Reef, Bahamas), respectively.[225] (*S*)-(+)-Curcuphenol (**226**) was found to exhibit antifungal activity towards *C. albicans* (MIC 8 μg mL^{-1}), as well as *in vitro* cytotoxicity towards murine P388 (leukemia) cells (IC_{50} 7 μg mL^{-1}) and against human A549 (lung), HCT-8 (colon), and MDAMB (mammary) tumour cell lines (MIC 10, 0.1, and 0.1 μg mL^{-1}, respectively).[225] In a later article, **226** was also reported as exhibiting potent antimalarial and antimicrobial activity, including against resistant bacterial strains.[226] A sample of **226** isolated from the same genus of sponge (*D. oxeata*) collected at a depth of 80 m (Rio Bueno, Jamaica) underwent microbial transformations when treated with *Kluyveromyces marxianus* var. *lactis* to yield six new hydroxycurcuphenols, while incubation with *Aspergillus alliaceus* gave another three new derivatives, and fermentation with *Rhizopus arrhizus* and *Rhodotorula glutinus* produced a glycosylated derivative.[226]



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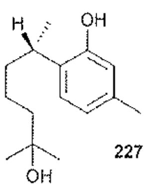
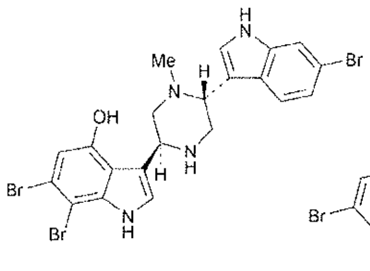
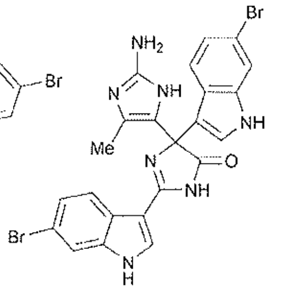


227

A Caribbean axinellid sponge, *Dragmacidon* sp., collected at 148 m depth by manned submersible from Sweetings Cay, Bahamas, has yielded the unique bis(indole) alkaloid, dragmacidin (**228**), comprising two indole rings and an unoxidized piperazine ring.[227] This novel compound exhibited picomolar cytotoxicity towards murine P388 (leukemia) cell lines, as well as against human A549 (lung), HCT-8 (colon) and MDAMB (mammary) tumour cell lines.[227] A further specimen of *Dragmacidon*, collected by dredging at 300 m at Mont Sous Marin, New Caledonia, has produced the novel bis(indole) alkaloid nortopsentin D (**229**).[228] Although other topsentin-type alkaloids (*e.g.* **239–241**, see later) often display potent cytotoxic and antifungal activity, nortopsentin D (**229**) was inactive when tested *in vitro* against human KB epidermal tumor cells.[228]

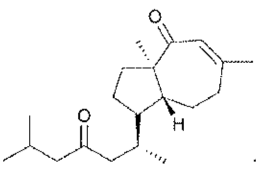


228 dragmacidin

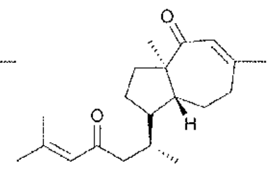


229 nortopsentin D

In 1987, the sponge *Epipolasis reiswigi*, collected by manned submersible at a depth of 330 m from Venezuelan waters, was reported to contain the novel antiviral diterpenes reiswigins A (**230**) and B (**231**), which exhibited potent *in vitro* activity against HSV-1 and murine A59 hepatitis virus.[229] The absolute and relative configurations were later assigned through an 8-step enantiospecific synthesis.[230]



230 reiswigin A

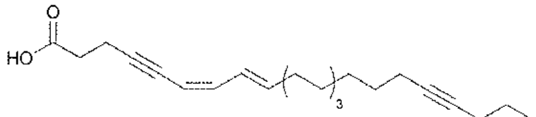


231 reiswigin B

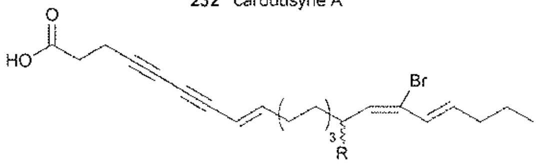
The axinellid sponge *Phakellia carduus*, obtained from a depth of 350 m during commercial trawling operations in the Great Australian Bight, was found to contain five new C_{23} acetylenic acids, carduusynes A–E (**232–236**), which displayed antimicrobial activity towards the Gram-positive bacteria *Staphylococcus aureus* and a *Micrococcus* sp.[231]

The bis(indole) alkaloids topsentin (**237**) and bromotopsentin (**238**) were isolated from a halichondrid sponge belonging to the genus *Spongosorites* Topsent 1896, collected at a depth of 174 m from Chub Cay, Bahamas, using a manned submersible.[232] The topsentins, which were found to display both antitumour and antiviral activities,[232] had previously been reported as metabolites of the Mediterranean shallow-water sponge *Topsentia genitrix*.[233] A further sponge specimen, *S. ruetzleri*, collected at a depth of 460 m off Nassau, Bahamas, by manned submersible, has yielded three unique cytotoxic and antifungal alkaloids, nortopsentins A–C (**239–241**), along with topsentin (**237**) and bromotopsentin (**238**),[234] while another deep-water sample of *Spongosorites* sp., retrieved from the South Australian coast using a benthic sled, gave the novel isobromotopsentin (**242**).[235] The nortopsentins A–D (**239–241**, **229**) have been the subject of much synthetic effort,[236] as have their analogues.[237,238]

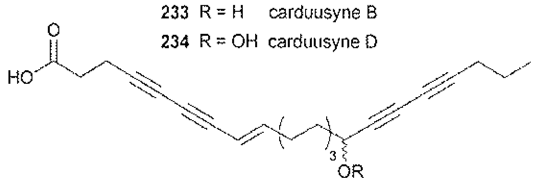
The bis(indole) alkaloid dragmacidin D (**243**) was obtained from a *Spongosorites* sponge species collected by manned



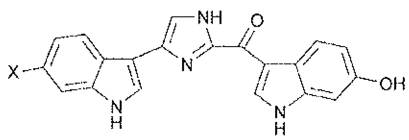
232 carduusyne A



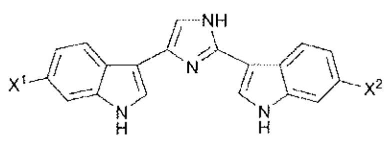
233 R = H carduusyne B
234 R = OH carduusyne D



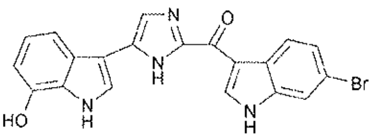
235 R = CH_3 carduusyne C
236 R = H carduusyne E



237 X = H topsentin
238 X = Br bromotopsentin



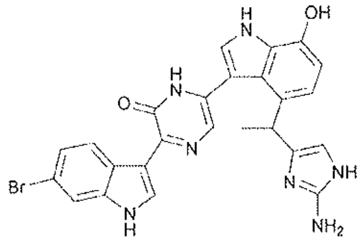
239 X^1 = X^2 = Br nortopsentin A
240 X^1 = Br, X^2 = H nortopentin B
241 X^1 = H, X^2 = Br nortopsetin C



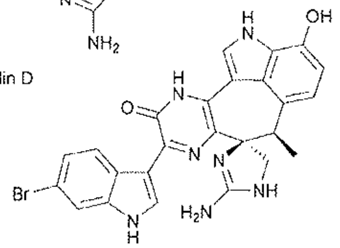
242 isobromotopsentin

submersible at 70 m depth from York Bay, St Vincents, Grenadines.[239] Dragmacidin D (**243**), which exhibits broad-spectrum antimicrobial activity (against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Cryptococcus neoformans*) as well as significant cytotoxicity towards P388 and A549 cell lines (IC_{50} = 1.4 and 4.4 μg mL^{-1}, respectively),[239] has been the subject of several syntheses.[240,241] A further specimen of *Spongosorites* sponge, collected by trawling at 90 m depth off the S Australian coast, yielded a fluorescent yellow pigment, dragmacidin E (**244**), a potent inhibitor of serine–threonine protein phosphatase.[242]

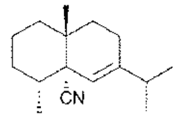
A relatively simple sesquiterpene isocyanide, stylotelline (**245**), was obtained from a halchondrid sponge belonging to the genus *Stylotella*, collected to the south-east of New Caledonia at a depth of 250 m.[243]



243 dragmacidin D

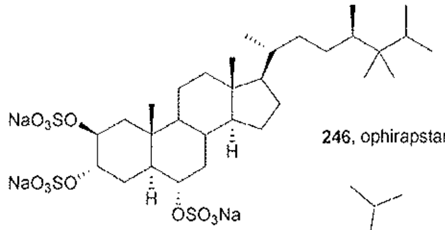


244 dragmacidin E

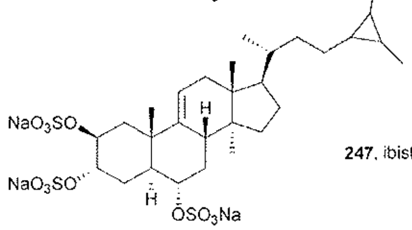


245 stylotelline

The deep-sea sponge *Topsentia ophiraphidites* acquired from the Gulf of Mexico (168 m depth), has provided the bioactive steroid ophirapstanol trisulfate (**246**), which was found to inhibit the guanosine diphosphate/G-protein RAS exchange,[244] while another Caribbean *Topsentia* species, collected at a depth of 359 m off Grand Bahama Island, Bahamas, has yielded the novel HIV-inhibitory sterol ibisterol sulfate (**247**), containing a $\Delta^{9(11)}$ olefin and C14 methylation.[245]



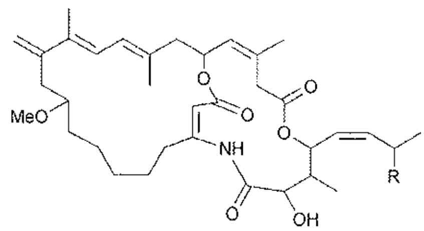
246, ophirapstanol trisulfate



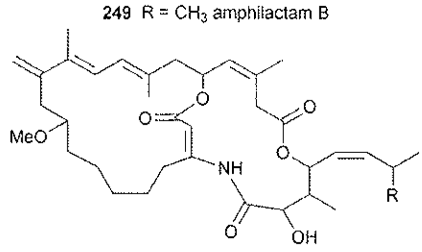
247, ibisterol trisulfate

Order Haplosclerida

A sponge belonging to the genus *Amphimedon*, obtained from a depth of 50 m by trawling operations in the Great Australian Bight, was found to produce the novel macrocyclic lactone/lactams amphilactams A–D (**248–251**), with an unprecedented carbon skeleton.[246] The amphilactams exhibited *in vitro* nematocidal activity.

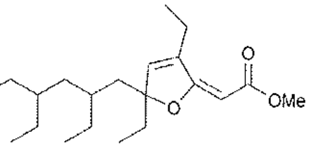


248 R = H amphilactam A
249 R = CH_3 amphilactam B

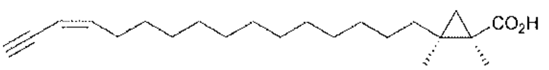


250 R = H amphilactam C
251 R = CH_3 amphilactam D

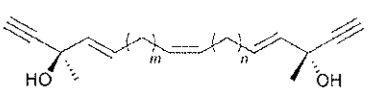
The novel polyketides cladocrocin A (**252**) and cladocroic acid (**253**) were isolated from the sponge *Cladocroce incurvata*, obtained by dredging at 500 m in southern New Caledonian waters,[247] while cytotoxicity-guided fractionation of the Caribbean sponge *Cribrochalina vasculum*, recovered from a depth of 174 m off Egg Island, Bahamas, gave a new long-chain acetylenic alcohol, vasculyne (**254**).[248]



252 cladocrocin A



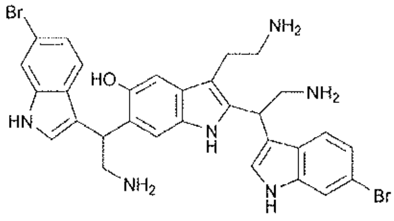
253 cladocroic acid



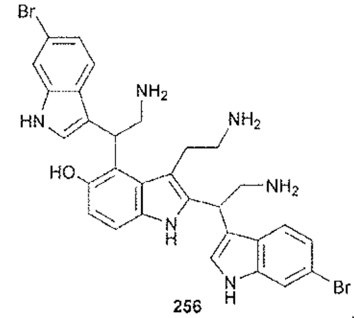
254 $m + n = 31$ vasculyne

A deep-sea sponge (*Gellius* or *Orina* sp.) collected at a depth of 255–285 m to the north of New Caledonia (Grand Passage), has yielded two new cytotoxic brominated tris-indole alkaloids, gelliusines A and B (±)-(**255**) as an enantiomeric pair.[249] Further studies on the same sample revealed four novel brominated indole alkaloids **256**–**259**, along with the known indole, 2,2-bis(6′-bromo-3′-indolyl)ethylamine, previously obtained from the tunicate *Didemnum candidum*.[250]

A previously undescribed species of the sponge *Phloeodictyon*, retrieved from a depth of 235 m by dragging operations at Kaimon Mara Mountain, New Caledonia, has furnished the novel cytotoxic antibacterial alkaloids phloeodictines A (**260**) and B (**261**), containing an unprecedented 6-hydroxy-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidinium skeleton.[251] The same group reported the isolation of further cytotoxic guanidine



(+/-)-**255** gelliusines A and B



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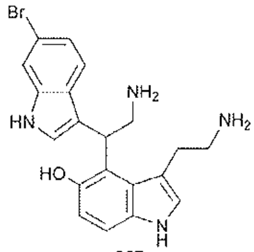

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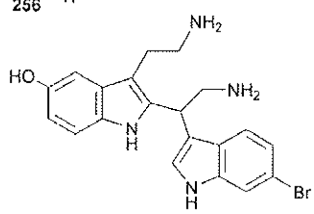

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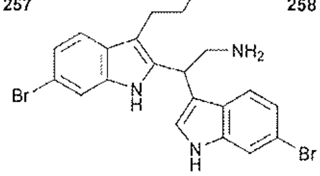

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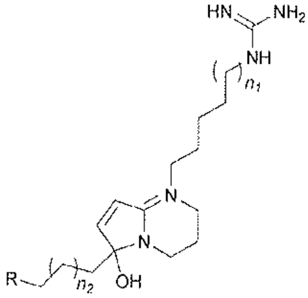
alkaloids, phloeodictines A1–A7 (**262**–**268**) and phloeodictines C1–C2 (**269**–**270**) from the same sponge specimen,[252] while additional phloeodictines have been reported from the shallow-water haplosclerid sponge *Oceanapia fistulosa*.[253] The seven-step synthesis of phloeodictine A1 (**262**) has been reported.[254]

The sponge *Siphonodictyon coralliphagum*, collected at a depth of 60 m off the coast of San Salvador, Bahamas, has yielded bis(sulfato)cyclosiphonodictyol A (**271**),[255] while the sponge *Stronglyohpora hartmani* from Goulding Cay, Bahamas (225 m depth) gave a cytotoxic sesquiterpene–methylene quinone, puupehenone (**272**), previously isolated from shallow-water sponges (*Heteronema* and *Hyrtios*).[256]

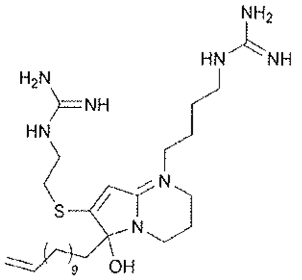
A unique cyclopropyl-containing sterol ester (**273**), was reported as a metabolite of the Caribbean deep-water sponge *Xestospongia* sp., which was collected at a depth of 52 m in the Bahamas, using a manned submersible.[257] The sterol ester (**273**) was inactive against P388 cells, *C. albicans* and HSV-1.

Order Homosclerophorida

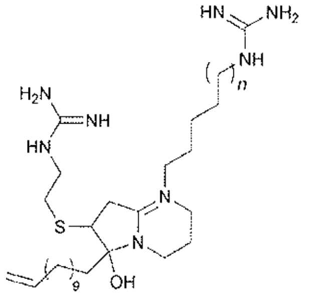
The plakinid sponge *Corticium* sp., obtained at 137 m depth from Great Inagua Island, Bahamas, has yielded an antitumour pentacyclic aromatic alkaloid, meridine (**274**), earlier isolated



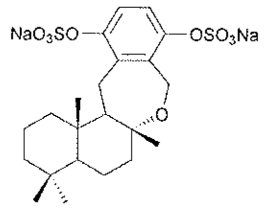
Phloeodictine		n_1	n_2	R
260	A	0	9	$CH_2CH{=}CH_2$
262	A1	1	7	$CH_2CH{=}CH_2$
263	A2	0	7	$CH_2CH{=}CH_2$
264	A3	1	5	$CH_2CH{=}CH_2$
265	A4	0	5	$CH_2CH{=}CH_2$
266	A5	1	4	$CH_2CH{=}CH_2$
267	A6	1	8	$CHMe_2$
268	A7	0	8	$CHMe_2$



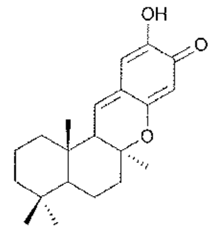
261 phloeodictine B



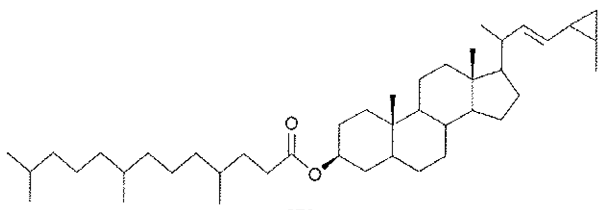
269 n = 1 phloeodictine C1
270 n = 0 phloeodictine C2



271 bis(sulfato)cyclosiphonodictyol A



272 puupehenone



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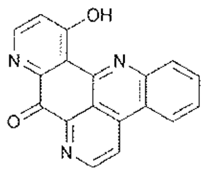
from the South Australian shallow-water ascidian *Amphicarpa meridiana*.[258] While early studies reported that **274** exhibited antifungal activity against *C. albicans*, as well as activity against *Trichophyton mentagrophytes* and *Epidermophyton floccosum*,[259] recent studies have revealed that **274** also intercalates DNA with a significant preference for quadruplex DNA.[260] Several syntheses of **274** and its analogues have been described.[261–263]

The first natural product study on the sponge *Plakinastrella onkodes*, collected from the Gulf of Mexico by trawling at 73 m, has revealed three new peroxylactones, plakortolides B–D (**275–277**), and a new peroxy ester, epiplakinic acid E methyl ester (**278**), along with a mixture of steroidal peroxides. Compounds **275**, **277**, and **278** exhibited cytotoxicity towards the human A549 lung and murine P388 leukemia cell lines.[264] Additional peroxide and peroxylactone derivatives have been isolated from a shallow-water *Plakinastrella* species.[265]



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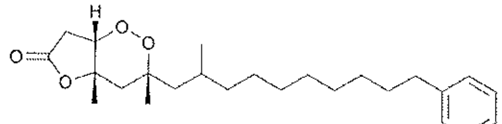
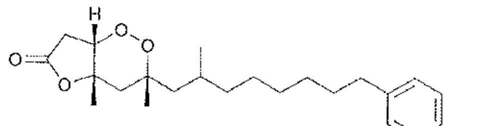
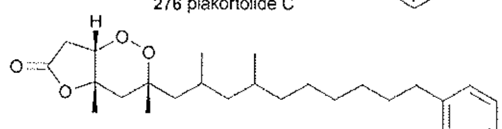


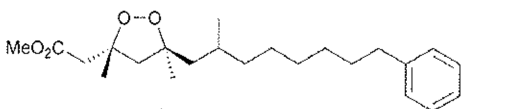
275 plakortolide B



276 plakortolide C



277 plakortolide D



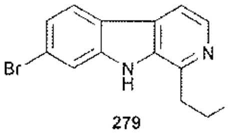
278 epiplakinic acid E methyl ester

The Palaun sponge *Plakortis nigra*, collected at a depth of 116 m, was found to produce the β-carbolines plakortamines A–D (**279–282**), along with the cyclic peroxides, epiplakinic acids G and H (**283–284**), and related γ-lactones, (**285–286**), the majority exhibiting cytotoxicity towards the human HCT-116 colon carcinoma cell line (IC_{50} 0.16–15.0 μM).[266]

Order Lithistida

Lithistid sponges are well known as a prolific source of biologically active compounds, including a diverse range of sterols, macrolides, acetogenins, alkaloids, and peptides.[41] Lithistid sponges are widely represented amongst the deeper water sponge species, including from the genera *Aciculites*, *Corallistes*, *Discodermia*, *Leiodermatium*, *Macandrewia*, *Microscleroderma*, *Neosiphonia*, *Pleroma* and *Reidispongia*.

In 1983, Djerassi *et al.* described the isolation of pulchrasterol (**287**) and other related sterols from the deep-water lithistid sponge *Aciculites pulchra*, collected at a depth of 100–200 m by dredging near Cape Reinga off the north-eastern coast of New Zealand.[267]



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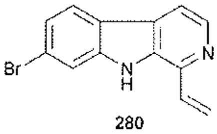

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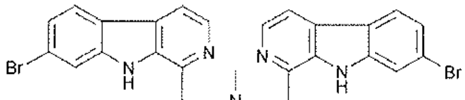

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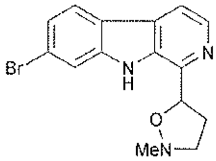

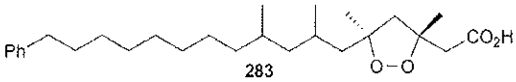

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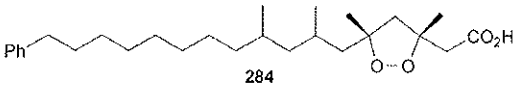

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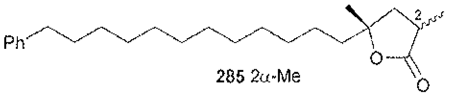
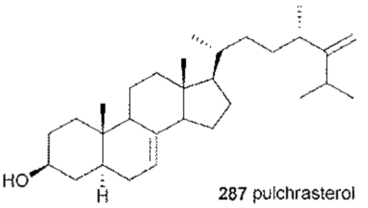


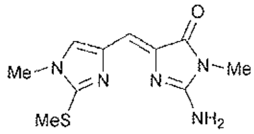
285 2α-Me
286 2β-Me



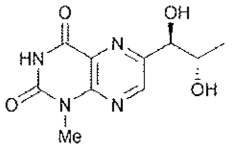
287 pulchrasterol

In 1989, the isolation of a new polynitrogen metabolite, corallistine (**288**), was reported from the sponge *Corallistes fulvodesmus*, obtained by dredging at a depth of 500 m in southern New Caledonian waters.[268] Around the same time, a further 300 m deep New Caledonian species of *Corallistes* was described, which yielded five porphyrin pigments, characterised by corallistin A (**289**), which showed some *in vitro* cytotoxicity towards the human KB cell line (65% inhibition at 100 μg mL^{-1}).[269,270] In later studies by the same group, *Corallistes undulatus*, collected at a depth of 510 m (New Caledonia), was found to contain the novel pteridine (1′*R*,2′*S*)-6-(1′,2′-dihydroxypropyl)-1-methylpteridine-2,4-dione ((−)-**290**), along with other known pteridines, sterols and indole metabolites.[271] The total synthesis of corallistin A has been described.[272]

A novel brominated aminoimidazolinylindole, discodermindole (**291**), was isolated from the Carribean lithistid sponge *Discodermia polydiscus*, collected at a depth of 185 m off Chub Cay, Berry Islands, Bahamas.[273] Discodermindole (**291**) exhibited significant *in vitro* cytotoxicity against murine P388 and human A549 and HT-29 tumour cell lines. Other specimens of *D. polydiscus*, obtained from the Bahamas at a depth of 170–



288 corallistine



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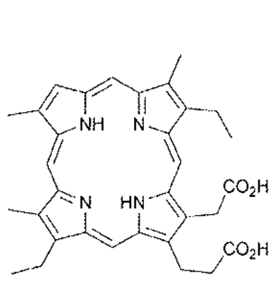
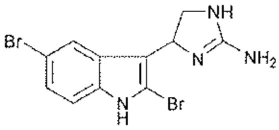
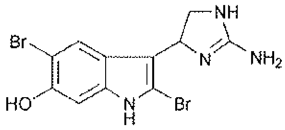


289 corallistin A

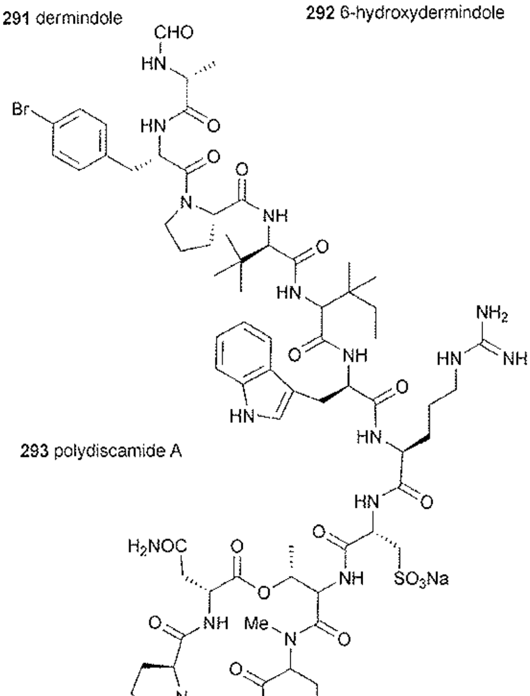
181 m, have yielded a new cytotoxic indole analogue, 6-hydroxydiscodermindole (**292**).[274] Another Caribbean sample of *Discodermia* sp., collected from St. Lucia, Lesser Antilles, at a depth of 274 m, produced a cytotoxic depsipeptide, polydiscamide A (**293**), which was found to inhibit *in vitro* proliferation of the A549 (human lung) cancer cell line.[275]



291 dermindole

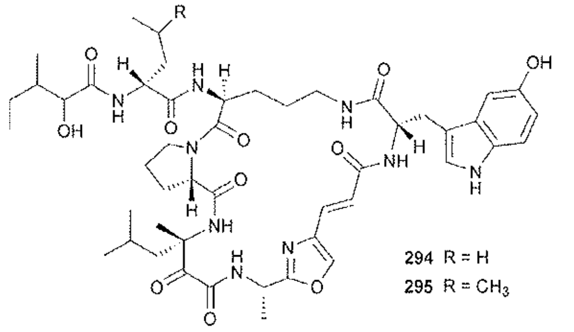


292 6-hydroxydermindole



293 polydiscamide A

A new species of deep-water lithistid sponge belonging to the *Discodermia* genus collected by manned submersible at a depth of 180 m from Gouldings Cay, Bahamas, has yielded two novel peptides, the discobahamins A (**294**) and B (**295**), which showed weak antifungal activity against *C. albicans*.[276]



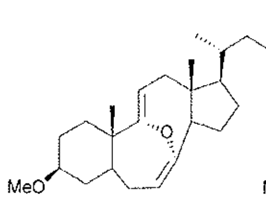
The deep-water sponge *Jereicopsis graphidiophora*, collected in northern New Caledonia (225 m depth) and identified as a new genus, was found to produce two new, rare 3β-methoxy secosteroids, jereisterols A (**296**) and B (**297**).[277] A number of novel 3β-methoxysteroids with various nuclei (Δ^5, Δ^7, $\Delta^{7,9(11)}$, Δ^8, $\Delta^{8,14}$) coupled with common C_8–C_{10} side chains (**298–311**), were subsequently obtained from the lipid fraction of the same sample, along with five novel 3β-methoxysteroids containing oxygenated nuclei such as Δ^7-9α,11α-epoxy (**312**), $\Delta^{9(11)}$-8α,14α-epoxy (**313**), Δ^8-7-one (**314**), Δ^7-9-hydroxy (**315**), and Δ^8-14-hydroxy (**316**).[278]

A new species of the rare deep-water marine sponge *Leiodermatium*, collected at a depth of 229 m in Palau using a manned submersible, has yielded two cytotoxic macrolides, leiodolides A (**317**) and B (**318**), the first metabolites from this genus representing a new class of 19-membered ring macrolides.[279] Leiodolide A (**317**) exhibited significant *in vitro* cytotoxicity in the National Cancer Institute's 60 cell line panel with highest activity against the HL-60 leukemia and OVCAR-3 ovarian cancer cell lines.[279]

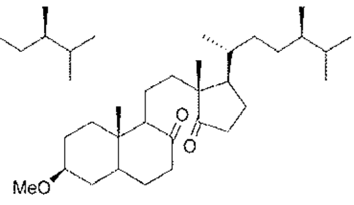
The deep-water lithistid sponge *Macandrewia azorica*, collected at a depth of 600 m from the edge of Gettysburg and Ormonde Sea Mount, North Atlantic, has yielded the unusual azoricasterol (**319**), along with *S*-methylergothioneine, as the first reported metabolites from this genus.[280]

The lithistid sponge *Microscleroderma* sp. has yielded the microsclerodermins A–I, a family of antifungal cyclic peptides containing glycine, *N*-methylglycine and (3*R*)-4-amino-3-hydroxybutyric acid, and various moieties such as a modified tryptophan, a 3-aminopyrrolidone-4-acetic acid and ω-aromatic 3-amino-2,4,5-trihydroxyacids. Microsclerodermin A (**320**) and B (**321**) were isolated from a specimen collected at 300 m depth by dredging on the Norfolk Rise, New Caledonia,[281] whereas the microsclerodermins C–E (not shown) were isolated from shallow-water *Theonella* sp. and *Microscleroderma* sp. from the Philippines.[282] A further specimen of *Microscleroderma* sp. collected at 125 m depth in Palau yielded the microsclerodermins F–I (**322–325**).[283] All members of the family showed significant antifungal activity against *C. albicans*, while microsclerodermins F–I also displayed significant cytotoxicity against the HCT-116 (human colon) carcinoma cell line with IC_{50} values ranging from 1.0–2.4 μg mL^{-1}.

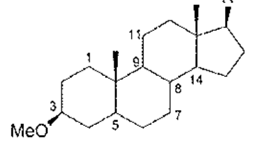
The novel macrolide neopeltolide (**326**) was recently obtained from a lithistid sponge (family Neopeltidae) acquired at 442 m depth off the NW coast of Jamaica. Neopeltolide (**326**) exhibited potent inhibitory activity against both the fungal pathogen *C. albicans* (MIC 0.62 μg mL^{-1}) and *in vitro* proliferation of murine

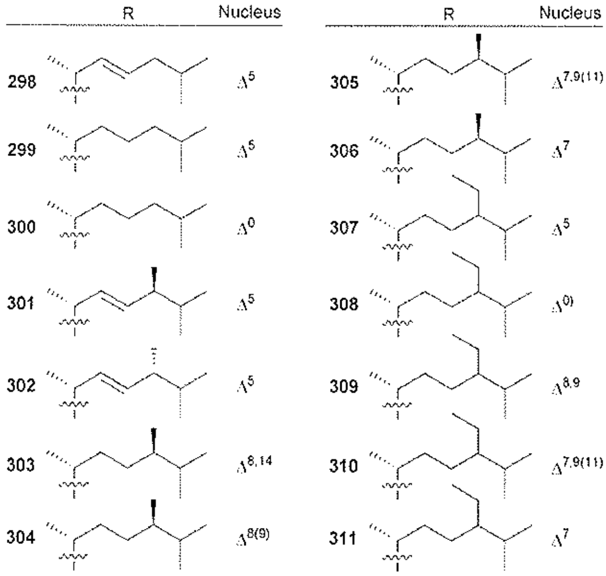


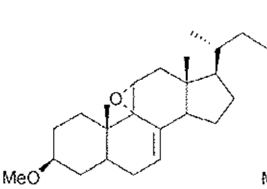
296 jereisterol A



297 jereisterol B







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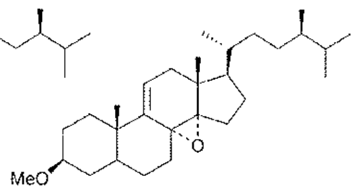

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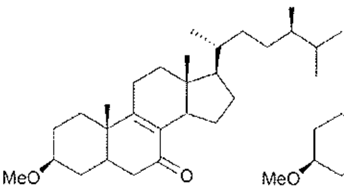

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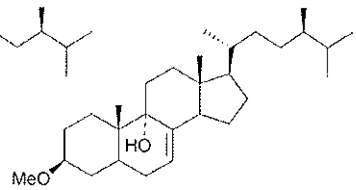

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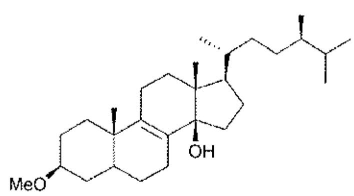

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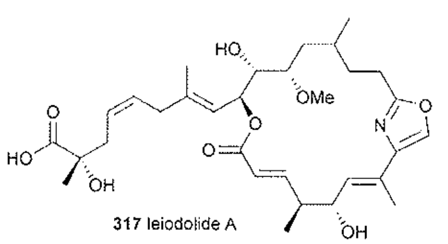
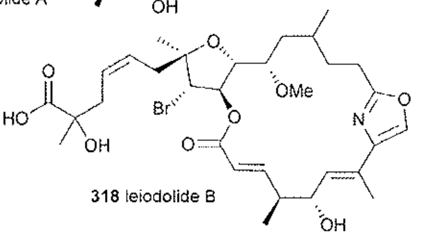
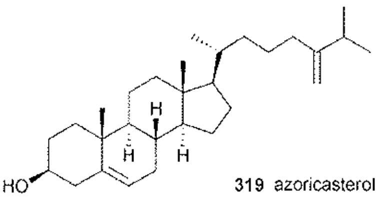


317 leiodolide A



318 leiodolide B



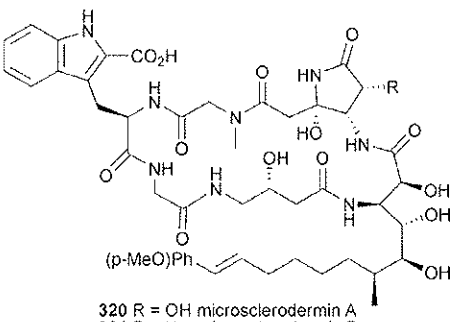
319 azoricasterol

P388 and human A549 tumour cell lines (IC_{50} = 0.56 and 1.2 nM, respectively).[284]

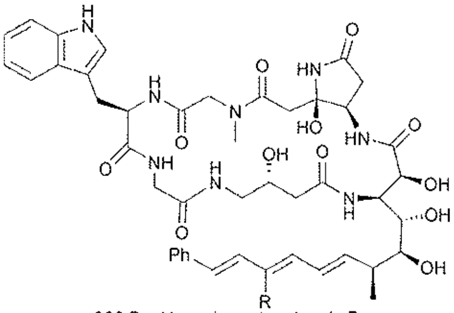
The cyclodepsipeptide neosiphoniamolide A (**327**),[285] along with the cytotoxic macrolides, superstolide A and B (**328–329**), were isolated from the deep-water lithistid sponge *Neosiphonia superstes*, obtained by dredging at a depth of 500–515 m, off the southern coast of New Caledonia.[286,287]

The same species of *Neosiphonia* collected at 500–515 m on the Norfolk Rise, New Caledonia, was found to contain the known sphinxolide[288] as the major component, along with known sphinxolides B–D[289] and two novel 26-membered macrolides, designated as sphinxolides E–F (**330–331**).[290] A sample of another lithistid sponge, *Reidispongia coerulea*, collected at the same time, produced the known metabolites reidispongiolides A–B,[291] sphinxolides B–D, and minor amounts of two novel macrolides, sphinxolide G (**332**) and reidispongolide C (**333**).[290] The sphinxolides and reidispongolides were found to be potent *in vitro* cytotoxic agents in the NCI human 60 cancer cell line panel, and are both the subject of several ongoing synthetic studies.[292–294]

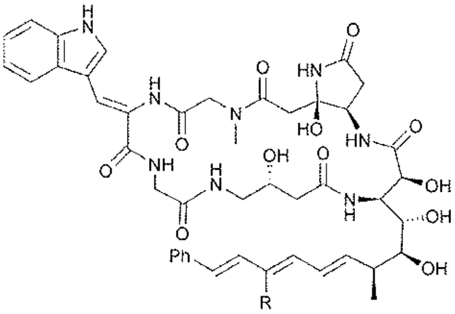
Two novel bromindoles, ethyl 6-bromo-3-indolcarboxylate (**334**) and 3-hydroxyacetal-6-bromoindole (**335**), were obtained from the lithistid sponge *Pleroma menoui* collected at a depth of 500 m from the Coral Sea, Noumea.[295]



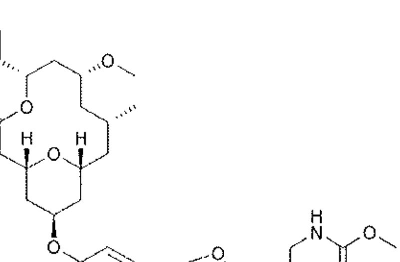
320 R = OH microsclerodermin A
321 R = H microsclerodermin B



322 R = H microsclerodermin F
323 R = CH_3 microsclerodermin G



324 R = H microsclerodermin H
325 R = CH_3 microsclerodermin I

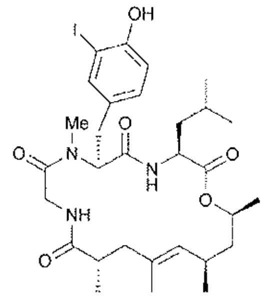


326

Order Poecilosclerida

The sponge *Arenochalina* sp., collected at a depth of 350–400 m during a trawling expedition in the Great Australian Bight, yielded the new alkaloid metabolites mirabilins A–F (**336–341**),[296] while mirabilin G (**342**) was isolated from the deep-water sponge *Clathria* sp., retrieved off the coast of Cape Arid, Western Australia, using an epibenthic sled.[297]

Discorhabdin P (**343**), a new member of the growing discorhadbin family which comprise an iminquinone and either a spiro-enone or spiro-dieneone unit, was isolated from a sponge belonging to the *Batzella* genus collected at a depth of 141 m from the western Great Bahama Bank, Bahamas.[298] Discorhabdin P (**343**), displays *in vitro* cytotoxicity against murine P388 and human A549 cancer cell lines, and inhibits both the



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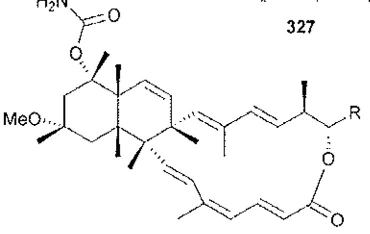
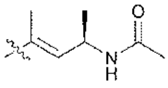
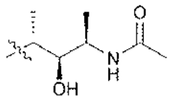
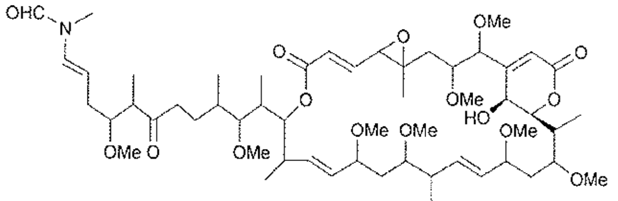
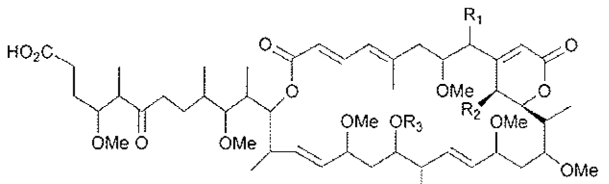


328 

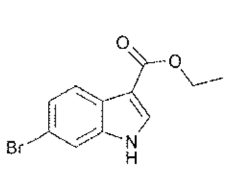
329 



330 sphinxolide E



331 R_1 = OMe, R_2 = OH, R_3 = H sphinxolide F
332 R_1 = H, R_2 = OH, R_3 = Me sphinxolide G
333 R_1 = H, R_2 = H, R_3 = Me redispongiolide C



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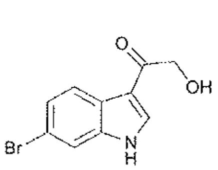

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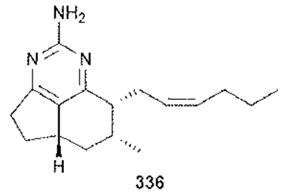

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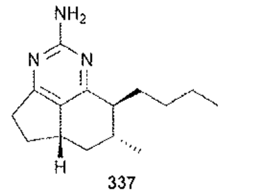

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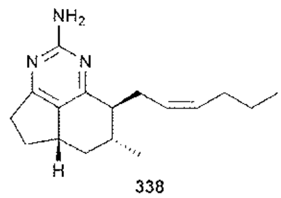

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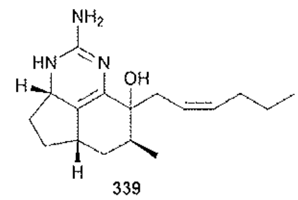

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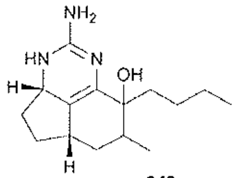

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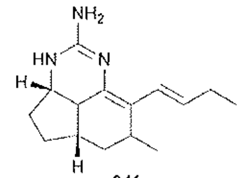

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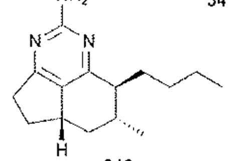

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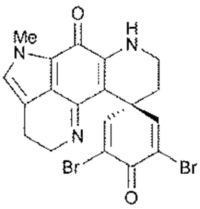
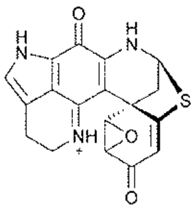
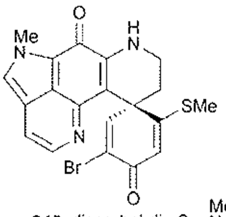


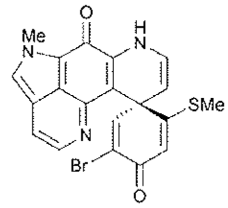
343 discorhabdin P



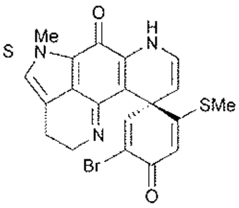
344 discorhabdin R



345 discorhabdin S



346 discorhabdin T

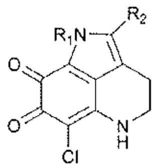


347 discorhabdin U

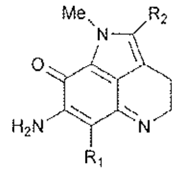
phosphatase activity of calcineurin and the peptidase activity of caspase CPP32.[298] The antibacterial discorhabdin R (**344**) has been isolated from two distinct marine sponges, an Antarctic *Latrunculia* sp. and a southern Australian *Negombata* sp., collected at depths of 544 m and 20 m respectively.[299] The cytotoxic 5-*S*-methyl discorhabdins S–U (**345–347**), were obtained from a further specimen of sponge from the *Batzella* genus also collected at a depth of 141 m (Ocean Cay, Bahamas).[300] Both discorhabdin P and U were recently obtained *via* a semi-synthetic route.[301]

Various specimens of poecilosclerid sponge belonging to the *Batzella* genus collected in the Bahamas, using a manned submersible at depths ranging from 120 to 152 m, have been found to contain an array of novel highly functionalized pyrroloquinoline alkaloids. These include the aminoquinone-containing batzellines A–C (**348–350**),[302] and the amino-iminoquinone-containing isobatzellines A–D (**351–354**)[303] and secobatzelline A (**355**), the latter accompanied by a probable isolation artifact, secobatzelline B (**356**).[304] The batzellines, isobatzellines and secobatzellines all displayed significant

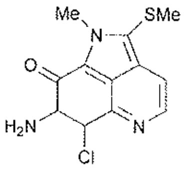
cytotoxicity against murine P388 tumour cells, with the batzellines and secobatzellines were also active against human A549 tumour cell lines.[303–305] The isobatzellines (**351–354**) also exhibited moderate antifungal activity against *C. albicans*,[303] while the secobatzellines were found to inhibit calcineurin's phosphatase activity.[304] Secobatzelline A also inhibited the peptidase activity of caspase CPP32.[304]



348 R_1 = Me, R_2 = SMe
349 R_1 = H, R_2 = SMe
350 R_1 = Me, R_2 = H



351 R_1 = Cl, R_2 = SMe
352 R_1 = H, R_2 = SMe
353 R_1 = Cl, R_2 = H



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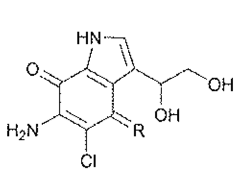
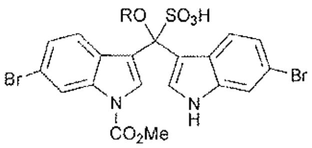
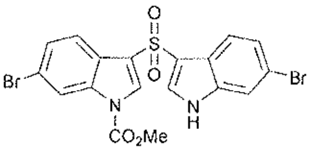


355 R = NH
356 R = O

A deep-sea sponge belonging to the genus *Echinodictyum*, obtained during trawling operations at 65 m depth in the Great Australian Bight, was found to contain four novel antibacterial bromoindole dimers, echinosulfonic acids A–C (**357–359**) and echinosulfone A (**360**).[306]



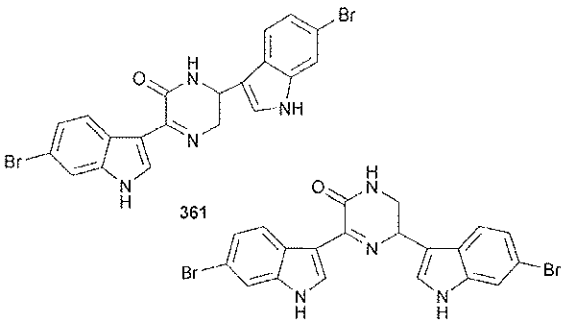
357 R = Et echinosulfonic acid A
358 R = Me echinosulfonic acid B
359 R = H echinosulfonic acid C



360 echinosulfone A

The antifungal bis(indole) alkaloids hamacanthin A (**361**) and B (**362**) were reported in 1994 from a new species of deep-water sponge belonging to the genus *Hamacantha*, collected by manned submersible at a depth of 548 m off the Madeiran SE coast.[307] The synthesis of hamacanthin B led to the assignment of (*S*)- to the stereogenic carbon (**362**).[308]

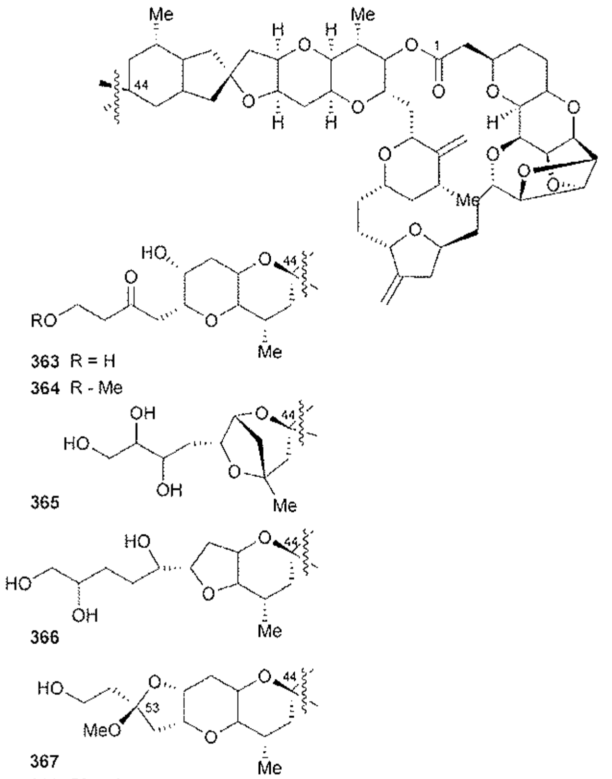
The bright yellow myxillid sponge *Lissodendoryx* sp., obtained by dredging off the Kaikoura Peninsula, New Zealand, at a depth of >100 m, was found to produce the known halichondrin B, homohalichondrin B and the new derivative,



361

362

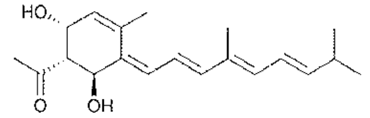
isohomohalichondrin B (**363**), which displayed potent cytotoxicity towards the murine P388 leukaemia cell line and selective cytotoxicity in the NCI primary screen.[309] The same group reported on a larger-scale collection (200 kg) of the same species obtained at 100 m depth, from Kaikoura Peninsula, which yielded an additional five antitumour polyether macrolides, neonor-, neohomo-, 55-methoxyisohomo-, 53-methoxyneoisohomo- and 53-*epi*-methoxyneoisohomo-halichondrin B (**364–368**).[310]



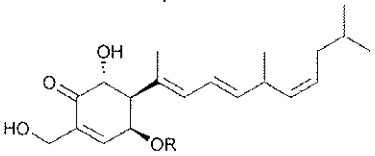
363 R = H
364 R - Me
365
366
367
368 53-*epi*

A southern Australian sponge belonging to the genus *Phorbas*, collected by epibenthic sled at a depth of 90–100 m, was found to contain the novel diterpenes phorbasins A–C (**369–371**), bearing a unique carbon skeleton.[311,312]

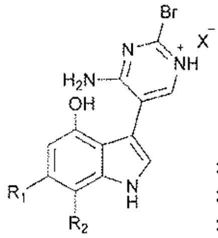
Antarctic sponge specimens belonging to the genus *Psammopemma*, collected from Prydz Bay by bottom trawling at a depth of 251–266 m, were found to contain three novel brominated 4-hydroxyindole alkaloids, psammopemmins A–C (**372–374**), which contain a unique 2-bromopyridine unit.[313]



369 phorbasin A

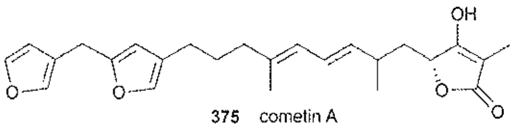


370, R = H phorbasin B
371, R = Ac phorbasin C

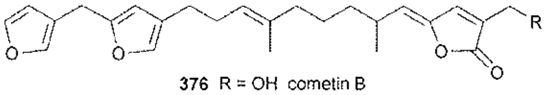


372 R_1 = H, R_2 = H
373 R_1 = H, R_2 = Br
374 R_1 = Br, R_2 = H

The marine sponge *Spongia* sp., collected at a depth of 150 m during commercial trawling operations in the Great Australian Bight, yielded three new furanosesterterpenes, cometins A–C (**375–377**), along with a known furanosesterterpene, furospinosulin 1. Cometin A exhibited antibiotic activity towards *S. aureus* and a *Serratia* sp.[314]



375 cometin A

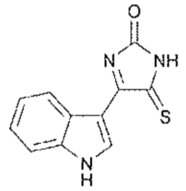


376 R = OH cometin B
377 R = H cometin C

The tricyclic imidazolthione zyzzin (**378**), along with minor amounts of the indolyl amides **379** and **380**, was isolated from the poecilosclerid sponge *Zyzza massalis*, collected from the Norfolk Ridge seamounts, New Caledonia, by dredging at a depth of 235 m. The major metabolite, the orange alkaloid **378**, was accompanied by several isolation artefacts, including the yellow tricyclic derivative **381**, which resulted from S→O exchange during aqueous work-up. Furthermore, incorporation of either water or methanol into **381** at ambient temperature gave the colourless products **382–383**, which reverted to compound **381** upon heating, representing the first thermochromic systems of marine origin.[315]

Order Spirophorida

The deep-water marine sponge *Scleritoderma* sp. cf. *paccardi*, retrieved from Cay Bokel, Turneffe Islands, Belize (293 m depth) using a manned submersible, has yielded the cytotoxic sterol **384**,



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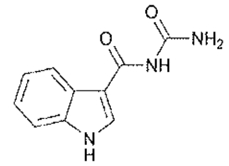

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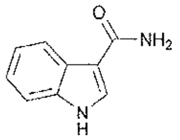

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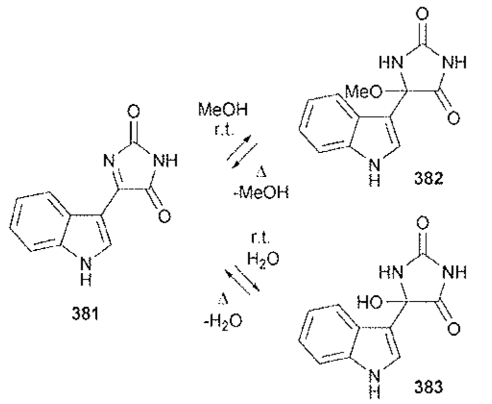
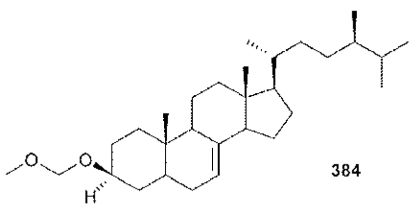


381 **382** **383**

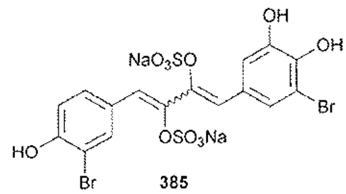
the first reported methoxymethyl ether sterol from Nature (IC_{50} 2.3 μg mL^{-1} *vs.* the P388 tumour cell line).[316]



384

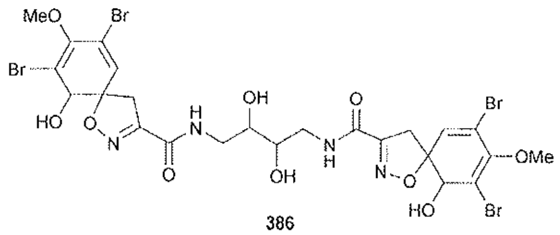
Order Verongida

Aplysillin A (**385**) was isolated from the sponge *Aplysina fistularis fulva*, collected using a manned submersible at a depth 113 m off Sweetings Cay, Grand Bahama Island, Bahamas.[317] The unusual 1,4-diphenyl-1,3-butadiene disulfate ester displays weak thrombin receptor antagonistic activity.[317]



385

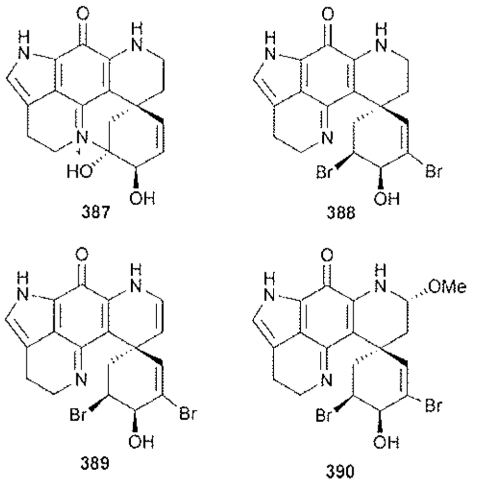
The first bromotyrosine-derived metabolites from the *Verongula* genus are the novel dihydroxyaerothionin (**386**) and known aerophobin 1, isolated from the sponge *Verongula rigida* collected from Sweetings Cay, Bahamas, at a depth of 70 m using a manned submersible.[318] Aerophobin 1 had previously been isolated from the shallow-water Mediterranean sponge *Verongia aerophoba*.[319]



386

Unidentified marine sponge species

The novel pyrroloiminoquinone alkaloids epinardins A–D (**387–390**) have been isolated from unidentified spinach-green pre-Antarctic sponge samples collected by trawling at a depth of 115 and 200 m near the Crozet islands in the South Indian Ocean.[320] Potent *in vitro* cytotoxicity against doxorubicin-resistant L1210/DX murine lymphocytic leukemia cells was detected for epinardin C (**389**).[320] The epinardins A–D are related to the discorhabdin/prianosin metabolites, which have been isolated from diverse sponge taxa including the *Batzella*, *Latrunculia*, *Negombata* and *Prianos* genera.[299,300,321–323]



387 388 389 390

11 Conclusions

Deep-water natural products have been discovered from the cold waters of Antarctica to the tropical waters of the Caribbean (Table 1). Over a quarter of the metabolites reported emanate from New Caledonia and just under 20% from Australian waters, followed by the Bahamas, the Gulf of Mexico, Japan and the Phillippine Sea (Fig. 3). This is certain to be linked to the historical level of access to manned submersibles and trawling operations in these areas, rather than an indication of the geographical distribution of natural products in deeper water. Expanded access to submersibles and remotely operated vehicle technology through new collaborations, including with the oil and gas industry,[324,275] are providing researchers today with the tools they need to further explore and map deep-sea fauna and their natural products.

The depth profile of the 390 marine natural product described in this review reveals that over 50% of the metabolites were found in depths ranging from 100–400 m, with another 10% retrieved from depths of 500–600 m (see Fig. 4). Due to the greater difficulty in accessing bathyl and abyssal depths, only 8% of the compounds reported were obtained at depths below 1000 m. The deepest reported sample from which a new natural product has been isolated is a 5065 m deep ocean sediment from the Central Pacific Basin that contained an unidentified Gram-positive bacterium, which was found to produce two cytotoxic caprolactams, caprolactins A (**120**) and B (**121**).

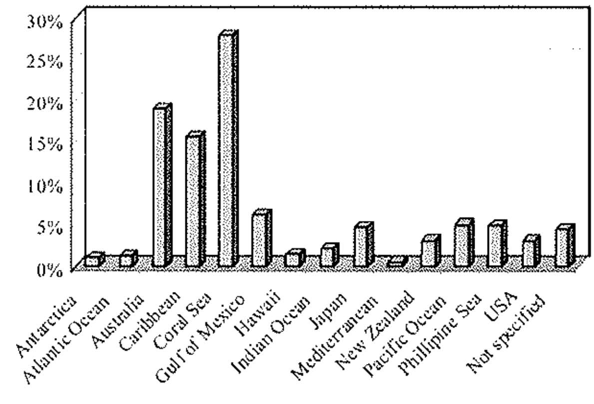


Fig. 3 Geographic origins of reported novel deep-sea natural products.

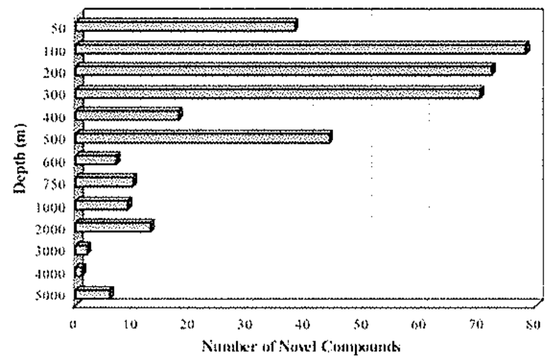


Fig. 4 Depth profile of novel deep-water marine natural products.

Deep-sea metabolites have been reported from a diverse range of phyla including Chordata, Cnidaria, Echinodermata and Porifera, along with a range of microorganisms such as archaea, bacteria and fungi. Deep-sea sponges are by far the largest source of new deep-water metabolites, accounting for over 60% of those reported to date, with examples down to 1000 m depth. The next largest source of deep-sea metabolites are the echinoderms, accounting for 15% of the natural products reported with specimens obtained down to 2000 m, followed closely by microorganisms, which account for 12% and have been cultured from sediment collected at 5065 m depth. Cnidarians and Chordata make up the remainder, with samples from depths of 300 and 463 m, respectively.

As for shallow-water sponges, their deep-water cousins have proven to be a rich source of metabolites from a diverse variety of structural classes including alkaloids (in particular bromoindoles), amino acids, polyketides, fatty acids, macrolides, terpenes (including oxygenated derivatives), sterols, glyosides,

Table 1 Novel natural products isolated from deep-water marine sources[a]

PHYLA/Class/Order	Species	Natural product (or *compound type*)	Depth/m	Region	Ref.
CHORDATA					
Ascidiacea	*Aplidium* sp.	Lobatamides A–F (**1–9**)	n.s.	Australia	96
	Ritterella rete	*Hydroxylated furanosesquiterpenes* (**10–15**)	300	New Caledonia	100
CNIDARIA					
Anthozoa					
Alcyonacea	*Acanthagorgia* sp. (mixed)	Papakusterol (**16**)	350	Hawaii	104
	Alcyonium paessleri	Paesslerins A and B (**17, 18**)	200	South Georgia Islands	105
	Corallium sp.	Coraxeniolides A–C and C′ (**19–22**), corabohcin (**23**)	350	Hawaii	107
	Paragorgia arborea	Arboxeniolide (**24**)	280	Crozet Island	109
	Paramuricea sp.	Linderazulenes (**25–27**)	342	Curacao	110
	Paramuriceidea family	*Azulene derivatives* (**28–31**)	350	Hawaii	111,112
	Placogorgia sp.	*Azulene derivative* (**32**)	350	Hawaii	113
Scleractinia	*Deltocyathus magnificus*	*Cholic-acid-type sterones* (**33–37**)	463	Loyalty Islands	114
	Dendrophyllia cornigera	β-Glucosylceramides (**38**)	162	Corsica	115
	Dendrophyllia cornigera	Cholestadiene-3,6-dione (**39**)	80	Greece	117
	Madrepora oculata	*Hydroxypolyenoic acids* (**40–42**)	290	St. Paul Island	120
	Madrepora oculata	*Hydroxypolyenoic acids* (**40, 42**)	380	Norway	120
	Gerardia sp.	Pseudozoanthoxanthins I and II (**43, 44**)	350	Hawaii	121
Scyphoza	*Auquorea auquorea*	Coelenterazine (**45**)	n.s.	n.s.	122
ECHINODERMATA					
Asteroidea	*Henricia downeyae*	*Steroidal glycosides* (**46–58**)	90	Gulf of Mexico	133
	Mediaster murrayi	Mediasterosides M_1–M_4 (**59–62**)	600	Philippine Sea	134
	Rosaster sp.	*Polyhydroxysteroids* (**63–65**)	500	New Caledonia	135
	Styracaster caroli	Carolisterols A–C (**66–68**), *hydroxysteroids* (**69–78**)	2000	New Caledonia	136–138
	Tremaster novaecaledoniae	*Polyhydroxysteroids* (**79–89**)	540	New Caledonia	139,140
Crinoidea	*Gymnocrinus richeri*	Gymnochromes A–D (**90–93**), isogymnochrome D (**94**)	520	New Caledonia	142
Echinoidia	*Echinocardium cordatum*	Hedathiosulfonic acids A, B (**95, 96**)	400	Japan	144
Holothuroidea	*Pseudostichopus trachus*	Pseudostichoposide A, B (**97, 98**)	300	Kuril Islands	148
	Synallactes nozawai	Synallactosides A_1, A_2, B_1, B_2, C (**99–103**)	540	Japan	150
MICROORGANISMS					
Archaea	*Thermococcus* sp.	*Glycerol ether* (**104**)	n.s.	East Pacific Rise	155
	Methanococcus jannaschii	*Glycerol ether* (**105**)	n.s.	East Pacific Rise	158
Bacteria	*Alteromonas haloplanktis*	Bisucaberin (**106**)	3300	Japan	162
	Bacillus sp.	Halobacillin (**107**)	124	Mexico	165
	Bacillus sp.	Guaymasol (**108**), epiguaymasol (**109**)	1834	Mexico	166
	Bacillus sp.	*Phenazine derivative* (**110**)	5059	West Pacific Ocean	167
	Nocardiopsis sp.	*Cyclic tetrapeptide* (**111**)	3000	Clarion-Clipperton Zone	168
	Streptomyces sp.	Streptokordin (**112**)	n.s.	Ayu Trench	169
	Streptomyces sp.	γ-Indomycinone (**113**)	4680	Marshall Islands	170
	Verrucosispora sp.	Abyssomicins B–D (**114–116**)	n.s.	Japan	172
	Unidentified	Chlorinated dihydroquinones (**117–119**)	152	USA	173–175
	Unidentified	Caprolactins (**120, 121**)	5065	Central Pacific Basin	176
	Unidentified	Macrolactins A–F (**122–129**)	980	North Pacific	177
Fungi	*Aspergillus* sp.	*Chromenones* (**130, 131**)	1000	n.s.	178
	Chromocleista sp.	*p*-Hydroxyphenopyrrozin (**132–134**)	70	Gulf of Mexico	179
	Penicillium corylophilum	*Anserinone derivatives* (**135–138**)	1335	Fiji	180–182
	Penicillium rubrum	Berkeleydione (**139**) and berkeleytrione (**140**)	270	USA	183
	Penicillium rubrum	Berkeleyacetals (**141–143**), berkeleyamides (**144–147**)	270	USA	184,185

Table 1 (*Contd.*)

PHYLA/Class/Order	Species	Natural product (or *compound type*)	Depth/m	Region	Ref.
	Phialocephalo sp.	Trisorbicillinone A (**148**), *bisorbicillinoids* (**149, 150**)	5059	n.s.	187,188
PORIFERA					
Astrophorida	*Dercitus* sp.	Dercitin (**151–160**)	160	Bahamas	194
	Erylus sp.	Erylosides C and D (**161, 162**)	500	New Caledonia	199
	Geodia sp.	Geodin A Mg salt (**163**)	51	Australia	200
	Jaspis serpentina	Poecillastrin D (**178**)	n.s.	Japan	209
	Lamellomorpha strongylata	Calyculinamides A and B (**164, 165**), swinholide H (**166**)	100	New Zealand	20
	Lamellomorpha strongylata	Theonellapeptolide IIIe (**167**)	100	New Zealand	203
	Poecillastra laminaris	Annasterol sulfate (**168**)	750	Philippines	205
	Poecillastra sollasi	Sollasins A–F (**169–174**)	375	Bahamas	206
	Poecillastra sp.	Poecillastrins A–C (**175–177**)	359	Bahamas	207,208
	Stoeba extensa	Shinsonefuran (**179**)	160	Japan	212
	Stelleta sp.	*Stigmastane sterols* (**180, 181**)	700	New Caledonia	213
Dendroceratida	*Dendrilla cactos*	Lamellarins O and P (**182, 183**)	n.s.	Australia	214
	Dendrilla sp.	*cis*-3-Hydroxy-*N*-methyl-L-proline (**184**)	1000	Australia	215
	Euryspongia sp.	*Sesquiterpene quinones* (**185–188**)	150	Australia	216
Dictyoceratida	*Ircinia* sp.	Sulfircin (**189**)	119	Bahamas	217
	Ircinia sp.	*Hydroquinone* (**190**), ircinol sulfate (**191**)	500	New Caledonia	218
	Luffariella geometrica	Luffarins A–Z (**192–217**)	350	Australia	219
	Sarcotragus spinulosus	Geranylfarnesylacetone (**218**)	400	Tasman Sea	221
	Spongiidae family	Isometachromin (**219**)	800	Bahamas	222
Hadromerida	*Aaptos ciliata*	Ciliatamides A–C (**220–222**)	150	Japan	223
	Latrunculia sp.	Discorhabdin R (**344**)	544	Antarctica	299
	Sigmosceptrella sp.	Sigmosceptrins A–C (**223–225**)	70	Australia	224
Halichondrida	*Didiscus flavus*	(+)-Curcuphenol (**226**), (+)-Curcudiol (**227**)	139	Bahamas	225
	Didiscus oxeata	(+)-Curcuphenol (**226**), (+)-Curcudiol (**227**)	80	Jamaica	226
	Dragmacidon sp.	Dragmacidin (**228**)	148	Bahamas	227
	Dragmacidon sp.	Nortopsentin D (**229**)	300	New Caledonia	228
	Epipolasis reiswigi	Reiswigins A and B (**230, 231**)	330	Venezuela	229
	Phakellia carduus	Carduusynes A–E (**232–236**)	350	Australia	231
	Spongosorites sp.	Topsentin (**237**), bromotopsentin (**238**)	174	Bahamas	232
	Spongosorites ruetzleri	Nortopsentins A–C (**239–241**)	460	Bahamas	234
	Spongosorites sp.	Isobromotopsentin (**242**)	n.s.	Australia	235
	Spongosorites sp.	Dragmacidin D (**243**)	70	Grenadines	239
	Spongosorites sp.	Dragmacidin E (**244**)	90	Australia	242
	Stylotella sp.	Stylotelline (**245**)	250	New Caledonia	243
	Topsentia ophiraphidites	Ophirapstanol (**246**)	168	Gulf of Mexico	244
	Topsentia sp.	Ibisterol sulfate (**247**)	359	Caribbean	245
Haplosclerida	*Amphimedon* sp.	Amphilactams A–D (**248–251**)	50	Australia	246
	Cladocroce incurvata	Cladocrocin A (**252**), cladocroic acid (**253**)	500	New Caledonia	247
	Cribrochalina vasculum	Vasculyne (**254**)	174	Bahamas	248
	Orina sp.	Gelliusines A and B (**255**), *bromoindoles* (**256–259**)	285	New Caledonia	249,250
	Phloeodictyon sp.	Phloeodictines A, B, A1–7, C1–2 (**260–270**)	235	New Caledonia	251,252
	Siphonodictyon coralliphagum	Bis(sulfato)-cyclosiphonodictyol A (**271**)	60	Bahamas	255
	Stronglyophora hartmani	Puupehenone (**272**)	225	Bahamas	256
	Xestospongia sp.	*Sterol ester* (**273**)	52	Bahamas	257

Table 1 (*Contd.*)

PHYLA/Class/Order	Species	Natural product (or *compound type*)	Depth/m	Region	Ref.
Homosclerophorida	*Corticium* sp.	Meridine (**274**)	137	Bahamas	258
	Plakinastrella onkodes	Plakortolides B–D (**275–277**), epiplakinic acid E (**278**)	73	Gulf of Mexico	264
	Plakortis nigra	Plakortamines A–D (**279–282**)	116	Palau	266
	Plakortis nigra	Epiplakinic acids G and H (**283**, **284**), *γ-lactones* (**285–286**)	116	Palau	266
Lithistida	*Aciculites pulchra*	Pulchrasterol (**287**)	200	New Zealand	267
	Corallistes fulvodesmus	Corallistine (**288**)	500	New Caledonia	268
	Corallistes sp.	Corallistin A (**289**)	300	New Caledonia	269
	Corallistes undulates	*Pteridine* (**290**)	510	New Caledonia	271
	Discodermia polydiscus	Discodermindole (**291**)	185	Bahamas	273
	Discodermia polydiscus	6-Hydroxydiscodermindole (**292**)	170	Bahamas	274
	Discodermia sp.	Polydiscamide A (**293**)	274	Lesser Antilles	275
	Discodermia sp.	Discobahamins A and B (**294**, **295**)	180	Bahamas	276
	Jereicopsis graphidiophora	Jereisterols A and B (**296**, **297**), *sterols* (**299–316**)	225	New Caledonia	277
	Leiodermatium sp.	Leiodolides A and B (**317**, **318**)	226	Palau	279
	Macandrewia azorica	Azoricasterol (**319**)	600	North Atlantic	280
	Microscleroderma sp.	Microsclerodermins A and B (**320**, **321**)	300	New Caledonia	281
	Microscleroderma sp.	Microsclerodermins F–I (**322–325**)	125	Palau	283
	Neopeltidae family	Neopeltolide (**326**)	442	Jamaica	284
	Neosiphonia superstes	Neosiphoniamolide A (**327**)	515	New Caledonia	285
	Neosiphonia superstes	Superstolides A and B (**328**, **329**)	515	New Caledonia	286,287
	Neosiphonia superstes	Sphinxolides E and F (**330**, **331**)	515	New Caledonia	290
	Pleroma menoui	*Bromoindoles* (**334**, **335**)	500	Noumea	295
	Reidispongia coerulea	Reidispongolide C (**332**), sphinxolide G (**333**)	515	New Caledonia	290
Poecilosclerida	*Arenochalina mirabilis*	Mirabilins A–F (**336–341**)	400	Australia	296
	Batzella sp.	Discorhabdin P (**343**), Discorhabdins R–U (**344–347**)	141	Bahamas	298,300
	Batzella sp.	Batzellines A–C (**348–350**)	120	Bahamas	302
	Batzella sp.	Isobatzellines A–D (**351–354**)	120	Bahamas	303
	Batzella sp.	Secobatzelline A and B (**355**, **356**)	152	Bahamas	304
	Clathria sp.	Mirabilin G (**342**)	n.s.	Australia	297
	Echinodictyum sp.	Echinosulfonic acids A–C, echinosulfone (**357–360**)	65	Australia	306
	Hamacantha sp.	Hamacanthins A and B (**361**, **362**)	548	Madeira	307
	Lissodendoryx sp.	Halichondrin derivatives (**363–368**)	100	New Zealand	309,310
	Phorbas sp.	Phorbasins A–C (**369–371**)	100	Australia	311,312
	Psammopemma sp.	Psammopemmins A–C (**372–377**)	266	Antarctica	313
	Spongia sp.	Cometins A–C (**375–377**)	150	Australia	314
	Zyzza massalis	Zyzzin (**378**) and derivatives (**379–383**)	235	New Caledonia	315
Spirophorida	*Scleritoderma* sp.	*Methoxymethyl ether sterol* (**384**)	293	Belize	316
Verongida	*Aplysina fistularis fulva*	Aplysillin A (**385**)	113	Bahamas	317
	Verongula rigida	Dihydroxyaerothionin (**386**)	70	Bahamas	318
Undetermined	Spinach-green demosponge	Epinardins A–D (**387–390**)	200	Crozet Islands	320

[a] n.s. = not specified.

and products of mixed biosynthetic pathways. The metabolites of deep-water echinoderms are found to be dominated by sulfated and glycosylated sterols, as are their shallow-water counterparts.

Nitrogen-containing compounds are found at all depths down to 5000 m and account for around 40% of the metabolites described here (152 compounds), with common alkaloid type structures such as bromoindoles found down to depths of 500 m. Polyketide metabolites are also reported at all depths. Sterols have so far been found at all depths down to 2000 m, and account for almost a quarter of the deep-sea natural products reported (61 compounds). A third of these sterols are glycosylated, with the deepest glycoside appearing at 600 m depth. Halogen-containing deep-sea natural products are obtained from species collected down to 500 m depth, with 14% of those reported containing bromine and 2% containing chlorine. Sulfur-containing metabolites are richly presented in the deep-sea, predominantly in the form of sulfated sterols, accounting for just over 15% of the metabolites reported, and from samples obtained down to depths of 2000 m. On the other hand, there are some structural classes that appear scarce in the deep sea, for example only one isocyanide, stylotelline (**245**), has been reported.

A range of unique and structurally complex ring systems are found across all depths from the abyssomicins A–D (**114–116**) from 289 m depth to trisorbicillinone (**148**) from a fungus collected at 5059 m depth. Likewise, relatively simple yet novel structures are also found across all depths from the phorbasins A–C (**369–371**) from 100 m to the caprolactins A–B (**120–121**) obtained from abyssal depths.

Around 60% of the deep-sea natural products are reported to possess bioactivity, with over half exhibiting significant cytotoxicity towards a range of human cancer cell lines. This raises the question of whether deep-sea fauna are a richer source of bioactive metabolites than their shallow-water counterparts. However, to answer this there would need to be many more studies that compared statistically relevant numbers of samples from related shallow- and deep-water species. It must also be kept in mind that the deep sea is an immense area, covering approximately 70% of the planet, and the relative amount of sampling is low (<5%), and therefore theories on which processes are at play in the deep sea and any trends observed should be treated with caution.

Does the high-pressure environment of the deep sea result in the production of certain secondary metabolites at the expense of others, due to the preferential involvement of enzymes or pathways that have adapted to life at high pressure? To date, there have been few biosynthetic studies on deep-sea natural products. Does the extremely high level of biodiversity in the deep sea equate to a high level of chemical diversity? As a consequence of adapting to the severe conditions of the deep sea, do deep-sea fauna hold the potential for the discovery of inhibitors or activators of stress-related pathways that may play a key role in a number of diseases including cancer? These and many more questions about deep-sea fauna and their secondary metabolites remain unanswered. However, one thing is certain. The deep sea, which covers 70% of the earth's surface, is a vast and relatively untapped reservoir of unique molecular, structural and biological diversity waiting to be discovered.

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