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Recent advances in deep-sea natural products

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REVIEW NPR

Recent advances in deep-sea natural products

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This review covers the 188 novel marine natural products described since 2008, from deep-water (50 - >5000 m) marine fauna including bryozoa, chordata, cnidaria, echinodermata, microorganisms, mollusca and porifera. The structures of the new compounds and details of the source organism, depth of collection and country of origin are presented, along with any relevant biological activities of the metabolites. Where reported, synthetic studies on the deep-sea natural products have also been included. Most strikingly, 75% of the compounds were reported to possess bioactivity, with almost half exhibiting low micromolar cytotoxicity towards a range of human cancer cell lines, along with a significant increase in the number of microbial deep-sea natural products reported.

1 Introduction

The deep sea is home to unprecedented biological diversity[1-7] and a myriad of marine species not encountered in shallow waters including carnivorous ascidians,[8, 9] mussels,[10] and sponges.[11, 12] Deep-sea organisms survive under extreme conditions in the absence of light, under low levels of oxygen and intensely high pressures, necessitating a diverse array of biochemical and physiological adaptations that are essential for survival. These adaptations are often accompanied by modifications to both gene regulation and to primary and secondary metabolic pathways,[13, 14] increasing the likelihood of finding structurally unique natural products that differ from those produced by shallow water organisms.

In recent years, several groups have reported astonishingly high hit-rates from screening deep-sea organisms, up to 74% by Schupp and co-workers for deep-sea sponges and gorgonians evaluated for anticancer activity.[15, 16] Furthermore, Blunt *et al.* 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 the Chasam Rise, New Zealand, compared to the average activity of >5000 shallow-water collections over the preceding 13 year period.[17] In our previous review of deep-sea natural products, 76% possessed biological activity, with over half exhibiting significant cytotoxicity towards a range of human cancer cell lines.[18] With multidrug resistance reaching critical point,[19] in particular in the case of antibiotic resistance,[20] it is imperative that the search for new chemical entities moves into unchartered waters.

The vast oceans cover 70% of the world's surface, with 95% greater than 1000 m deep.[21] The decade long Census of Marine Life, which assessed the diversity, distribution, and abundance of marine life expanded the number of known marine species from 230,000 to 250,000 and conjectured that the total number of marine species worldwide is at least one million, along with hundreds of millions of microbial species.[22] Further 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.[1-7] Yet, of the ~24,000 marine natural products described to date,[23] less than 2% derive from deep-water fauna, with a third of those compounds being described in the last five years. Although difficulty in accessing the deep sea has previously hindered research, improved acoustic technology and collaboration with marine-based industries is providing greater access to submersible technology giving momentum to the growing frontier of deep-sea research and uncovering a wealth of new species on continental shelves and seamounts worldwide (Fig. 1).[24]

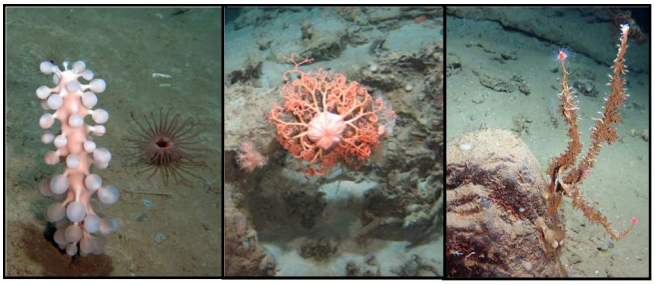


Fig 1. Deep-sea fauna. From left to right: the carnivorous giant club sponge *Chondrocladia gigantea* and cerianthid anemone in the background; the basket star *Gorgonocephalus caputmedusae*; and the hydroid *Tubularia* sp. All images from 920-930 m depth, Norway, courtesy of SERPENT Project, Southampton, UK.

In 2008, we published the first comprehensive review to focus solely on marine natural products isolated from deep-sea fauna

totalling almost 400 compounds.[18] Herein, this review describes a further 188 new deep-sea natural products reported in the last five years. The deep sea is variably defined as commencing at depths of anywhere between 100 and 1000 m; however for the purposes of this review deep-sea fauna are defined as those inhabiting depths of greater than 50 m (~164 ft), in order to include fauna beyond the depths of scuba. The majority of deep-sea natural products 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 from all regions around the world. Herein, where no biological activity or stereochemistry is ascribed to a particular metabolite (or stereochemical centre) it is because, to the best of our knowledge, no such data have yet been reported.

2 Reviews

In 2009,Wilson and Brimble reviewed molecules derived from the extremes of life, including some deep-sea examples.[25] In 2010, Thomas and Kavlekar *et al.* reviewed marine drugs from sponge-microbe associations, including some deep-sea examples.[26] A detailed review on the potential of deep-sea hydrothermal vents as hot spots for natural product discovery by Thornburg and co-workers appeared in 2010,[27] including biogeography and diversity of vent communities, and collection and cultivation of vent organisms. The culturability and diversity of extreme microbes was also covered in 2011 by Pettit.[28] In 2011, Winder and Pomponi *et al.* reviewed Lithistida sponge metabolites from both shallow and deep-water habitats reported since 2000,[29] while in 2012, Silva and Alves *et al.* published a review on polymeric and ceramic materials isolated from marine sources, which included deep-sea sponges.[30]

3 Deep-Sea Life

There are vastly different environmental conditions and oceanographic parameters operating in the deep-sea (Fig. 2).[31, 32] 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 bathyal 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[33, 34] and the salinity about 3.5% (35 g/kg) and therefore entirely marine, with a relatively low level of variability. Oxygen concentration drops from 7 $mL.L^{-1}$ at the surface to 3 $mL.L^{-1}$ at around 500 m, and to less than 0.1 $mg.L^{-1}$ in *oxygen minimum zones*. The sediment comprises weathered rock washed into the sea by wind and rivers, as well as planktonic material obtained from the water above, with intensified rates of microbial carbon turnover observed in the deepest oceanic trenches.[31, 32]

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 60s.[35-39] 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).

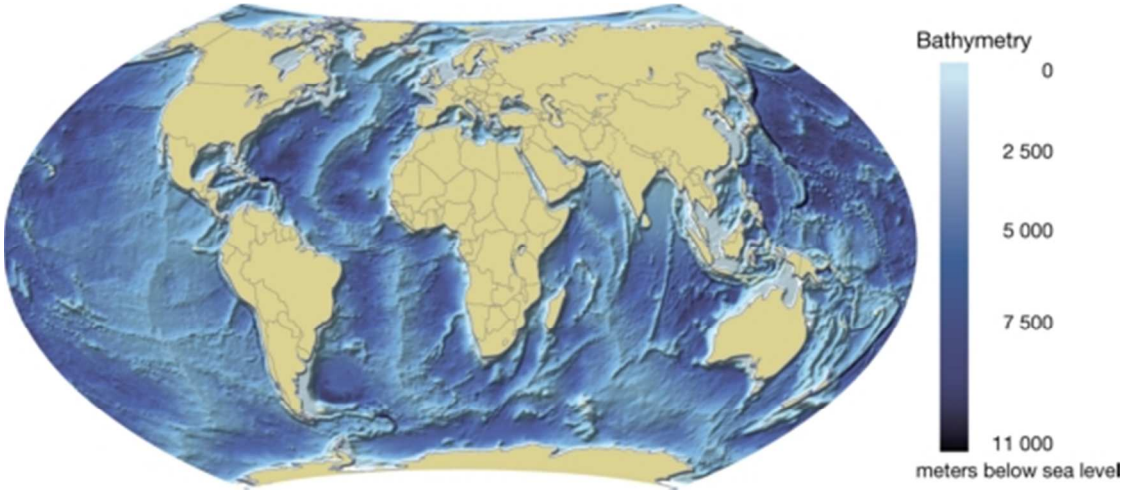


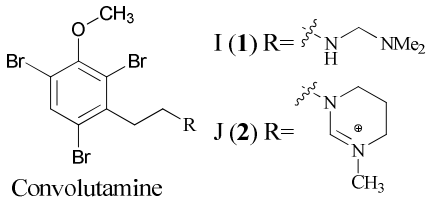
Fig. 2. World ocean bathymetric map.[58] The vast oceans cover 70% of the world's surface, with 95% greater than 1000 m deep.

At the species level, however, there are a high number of single rare species, with more than half being new to science, with some taxa possessing >95% of undescribed 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.[31, 32] Although abundance decreases with increasing depth, species richness appears to increases with the highest number of species found at depths of 3000 m and beyond.

A number of deep-sea psychrophilic (cold-loving) and thermophilic (heat-loving) microorganisms have been isolated, and their mechanisms of adapting to high pressure,[40-45] and either cold temperatures (in the majority of the deep-sea)[46-48] or high temperatures (around hydrothermal vents),[49-52] have been well documented. There is a multitude of recent papers detailing the characterisation, cloning, expression and function analysis of various genes from deep-sea organisms along with investigations into microbial diversity of deep-sea sponge-associated bacteria and other deep-sea sediment-derived microbes. [53-57] However, it is beyond the scope of this review to cover the diverse range of developments in the fields of marine biotechnology, ecology and biology. For an introductory overview of the biology of deep-sea life, see the earlier review in this series.[18]

4 Bryozoa

Bryozoans such as moss animals and lace corals are abundant in the marine environment with over 5000 species described to-date, ranging from shallow-water species to those living at depths of over 8500 m.[59-61] The secondary metabolites of bryozoans have been reviewed elsewhere.[62-64] Although shallow-water bryozoan species have produced such medicinally important compounds as the anti-cancer lead bryostatin 1 isolated from *Bugula neritina,*[65-67] there is only a single report on secondary metabolites from a deep-sea bryozoan. In 2011, Davis *et al.* described the first deep-water bryozoan metabolites, the brominated alkaloids convolutamine I (1) and J (2), isolated from *Amathia tortusa* collected by trawling at a depth of 63 m (Bass Strait, Tasmania, Australia). Compound 1 displayed cytotoxicity (IC_{50} of 22.0 μM) against the human embryonic kidney (HEK293) cell line, while both 1 and 2 were active against the parasite *Trypanosoma brucei* with IC_{50} values of 1.1 and 13.7 μM, respectively.[68]

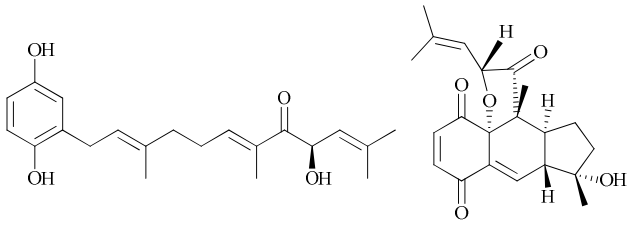


Convolutamine

5 Chordata

Ascidians comprise >2800 species and have yielded a diverse array of bioactive metabolites,[69, 70] including anticancer agents such as didemnin B from *Tridemnum solidum*, diazonamide from *Diazona angulata*, and the approved anticancer drug Ecteinascidin 743 (Yondelis™) from *Ecteinascidia turbinate.*[71,72] Deep-water ascidians from both the Atlantic and Pacific oceans are found at up to depths of over 8000 m,[73-75] and present a potentially rich source of interesting new metabolites. In 2008, Moser reviewed the cytotoxic cephalostatins and ritterazines isolated from the colonial marine worm *Cephalodiscus gilchristi* and the colonial marine tunicate *Ritterella tokioka,*[76] however, to date, only a small number of reports on the secondary metabolites of deep-water ascidians have been reported.

Rossinones A (**3**) and B (**4**) were isolated from an *Aplidium* ascidian species collected from Ross Sea, Antarctica by dredging at a depth of 200 m. While rossinone A (**3**) showed only modest biological activities, rossinone B (**4**) exhibited antileukemic, anti-inflammatory and antiviral properties.[77] Use of the Mosher ester method established the absolute configuration of rossinone A as 9'R, while a biomimetic synthesis of the racemic rossinone B has also been reported.[78]



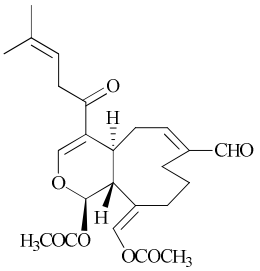
Rossinone A (**3**) Rossinone B (**4**)

A series of colonial ascidians belonging to the genera *Aplidium* and *Synoicum* collected in Antarctic waters at depths of 280 to 340 m, were recently evaluated for their chemical defensive properties towards the starfish *Odontaster validus* and the amphipod *Cheirimedon femoratus*. Four known meroterpenoids, rossinone B, 2,3-epoxy-rossinone B, 3-epi-rossinone B, and 5,6-epoxy-rossinone B, along with the indole alkaloids meridianins A–G, were isolated from several of the deep-water ascidian species.[79]

6 Cnidaria

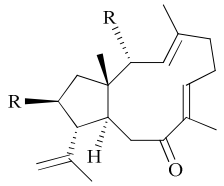
The phylum Cnidaria, comprising over 10,000 species, is divided into four classes: sessile Anthozoa (anemones, corals, sea pens), swimming Scyphoza (jellyfish), Hydrozoa (hydroids), and Cubozoa (box jellyfish). Cnidarians are the second largest source (after sponges) of new marine natural products reported each year, with a predominance of terpenoid metabolites[80-82] and are also well represented in the deep sea. In 2010, the stinging venoms of the Mediterranean scyphozoan jellyfish were reviewed by Mariottini *et al.*[25] In 2012, the chemical constituents and biological properties of the marine soft coral *Nephthea* were reviewed by Amir *et al.* including deep-sea species.[83, 84]

Anthozoans are the most abundant class of cnidarians with over 6500 species known. Since 2008, of the four cnidarian classes, only a small handful of reports on novel secondary metabolites have appeared, all from deep-sea anthozoans, from the order Alcyonacea (soft corals). The deep-sea cnidarian *Acanthoprimnoa cristata* collected by dredging at 138 m depth in the Yakushima-Shinsone, Kagoshima prefecture, Japan, yielded a new xenicane diterpenoid, cristaxenicin A (**5**) that exhibited potent antiprotozoal activities against *Leishmania amazonensis* and *Trypanosoma congolense* with IC_{50} values of 88 and 250 nM, respectively.[85]



Cristaxenicin A (**5**)

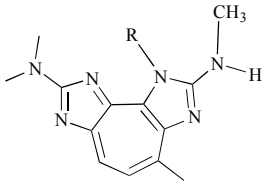
Two new dolabellane diterpenoids (**6** and **7**) were also reported from the cnidarian *Convexella magelhaenica* collected from the South Atlantic by dredging at a depth of 93 m. Both **5** and **6** exhibited significant cytotoxic activities against a human pancreatic adenocarcinoma cell line at micromolar concentrations.[86]

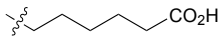


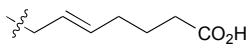
Dolabellane diterpenoids

(**6**) R=H
(**7**) R=$OCOCH_3$

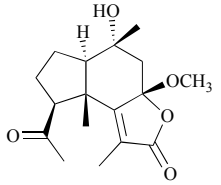
The cnidarian *Echinogorgia pseudossapo* (from Sanya, Hainan Province, P.R. China) was the source of two new alkaloids, pseudozoanthoxanthins III and IV (**8** and **9**) and two new sesquiterpenes (**10** and **11**). Compound **8** showed moderate anti-HSV-1 (Herpes simplex virus type-1) and anti-RSV (Anti-Respiratory Syncytial Virus) activity, while the guaiane **11** displayed significant antilarval activity towards *Balanus amphitrite* larvae.[87]



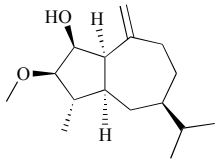
III (**8**) R= 

IV (**9**) R= 

Pseudozoanthoxanthins



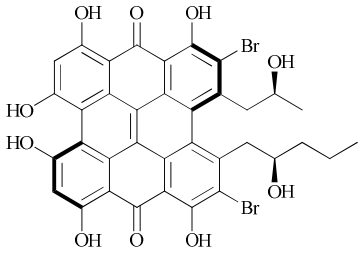
Sesquiterpene (**10**)



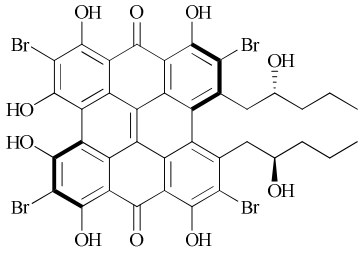
Sesquiterpene (**11**)

7 Echinodermata

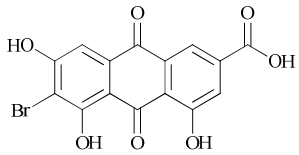
There are over 7000 living species of echinoderms worldwide, divided into five classes: Asteroidea (sea stars, starfish); Crinoidea (sea lilies, feather stars); Echinoidea (sea urhcins); Holothuroidea (sea cucumbers); and Ophiuroidea. Echinoderms are well known producers of bioactive glycosylated metabolites, dominated by steroidal metabolites, saponins and glycolipids.[80-82] They are the most abundant species of invertebrate fauna found in the deep sea, and while many new natural products have been described from deep-sea examples from the first four classes, new secondary metabolites from deep-water ophiuroids are yet to be described.



Gymnochrome E (**12**)



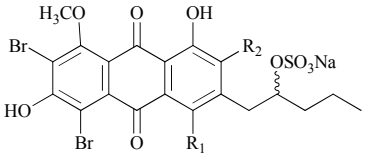
Gymnochrome F (**13**)



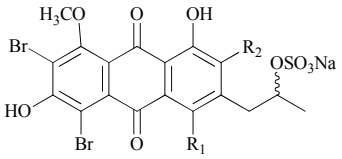
7-Bromoemodic acid (**14**)

Recently, gymnochromes E (**12**) and F (**13**) and 7-bromoemodic acid (**14**), together with anthraquinone metabolites and emodic acid were reported from the crinoid *Holopus rangii* collected from the south coast of Curaçao at a depth of 358 m. Gymnochrome E inhibited not only the proliferation of the NCI/ADRRes (multi-drug-resistant ovarian cancer cell line) with an IC_{50} value of 3.5 μM, but also histone deacetylase-1 (HDAC-1) with an IC_{50} value of 10.9 μM. Gymnochrome F was a moderate inhibitor of myeloid cell leukemia sequence 1 (MCL-1) binding to Bak with an IC_{50}value of 3.3 μM. Gymnochrome E exhibited minimum inhibitor concentrations (MICs) of 25 μg/mL against both *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA), while gymnochrome F exhibited MICs of 12.5 μg/mL against *S. aureus* and MRSA.[88]

Isolation work on the scarlet-coloured crinoid *Proisocrinus ruberrimus* obtained from Aguni Knoll, central Okinawa Trough, at a depth of approximately 1800 m, gave six new brominated anthraquinone pigments named proisocrinins A-F (**15-20**), all of which were present as optically active enantiomers, although their absolute configuration could not be assigned from the available data. This is the first report of tribromo- and tetrabromoanthraquinones isolated from a natural source.[89]

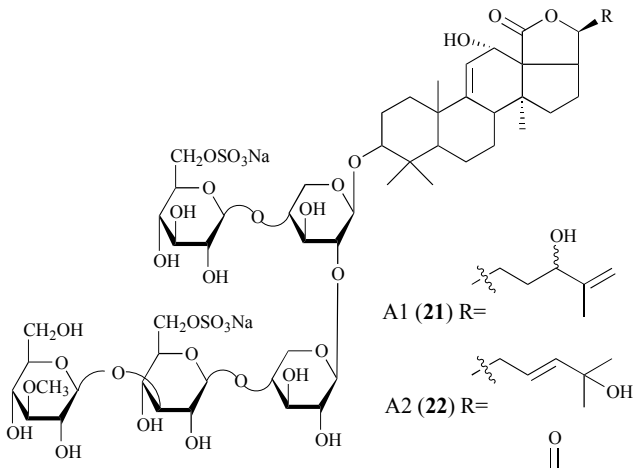


Proisocrinin A (**15**) R_1=R_2=Br
B (**16**) R_1=Br, R_2=H
C (**17**) R_1=H, R_2=Br



Proisocrinin D (**18**) R_1=R_2=Br
E (**19**) R_1=Br, R_2=H
F (**20**) R_1=H, R_2=Br

The Antarctic deep-sea cucumber *Achlionice* v*iolaecuspidata* collected by trawling at 1525 m depth, was the source of three new triterpene glycosides, achlioniceosides A_1 (**21**), A_2 (**22**), and A_3 (**23**). These disulfated pentaosides are branched at the first xylose residue with a sulfate attached to C-6 of the glucose residues, and constitute the first report of sea cucumber triterpene glycosides from the order Elasipodida.[90]



Achlioniceoside

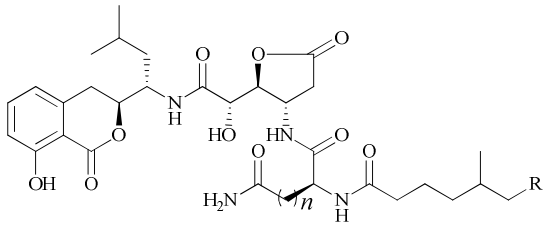
A1 (**21**) R=
A2 (**22**) R=
A3 (**23**) R=

8 Microorganisms

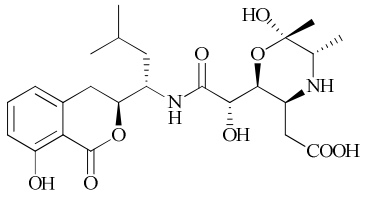
Marine microorganisms are a rich source of diverse and structurally unique metabolites.[91-93] Recently, the bioactive metabolites isolated from marine cyanobacteria with cytoxicity, anti-inflammatory and antibacterial activities were reviewed,[15] along with peptides isolated from the *Moorea* (formerly *Lyngbya)* genus of cyanobacteria[28] Marine drugs isolated from microbes associated with marine sponges of the class Demospongiae and the orders Halichondrida, Poecilosclerida and Dictyoceratida were also recently reviewed.[26]

8.1 Bacteria

The culture broth of the marine bacterium *Bacillus subtilis*, isolated from deep-sea sediment collected at a depth of 1000 m in the Red Sea, was found to yield four novel amicoumacins, lipoamicoumacins A–D (**24**–**27**), and one new bacilosarcin analogue (**28**) along with six known amicoumacins.[94] Two of the known amide-containing amicoumacin and bacilosarcin analogues were found to display both significant cytotoxicity against HeLa cells and antibacterial activity against *B. subtilis, S. aureus* and *L. hongkongensis*, with the amide group essential for activity.

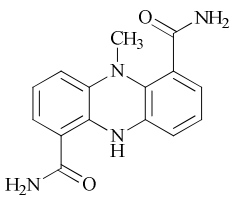


Lipoamicoumacin A (**24**) R=H, *n*=1
B (**25**) R=CH_3, *n*=1
C (**26**) R=H, *n*=2
D (**27**) R=CH_3, *n*=2

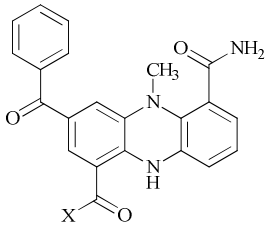


Bacilosarcin C (**28**)

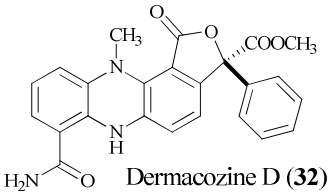
Seven dermacozines A–G (**29–35**) were reported from the actinobacteria *Dermacoccus abyssi* sp. nov., strains MT1.1 and MT1.2, isolated from Mariana Trench sediment collected at a depth of 10,898 m by the remotely operated submarine *Kaiko*. Dermacozines F (**34**) and G (**35**) displayed moderate cytotoxic activity against the leukaemia cell line K562 with IC_{50} values of 9 and 7 μM, respectively, while dermacozine C (**31**) also exhibited high radical scavenger activity with an IC_{50} value of 8.4 μM.[95]



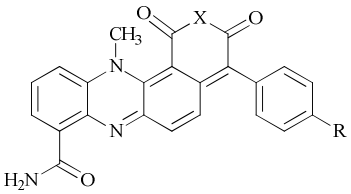
Dermacozine A (**29**)



Dermacozine B (**30**) X=NH_2
C (**31**) X=OH

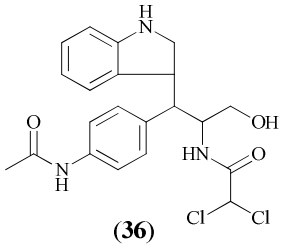


Dermacozine D (**32**)



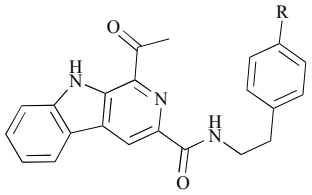
Dermacozine E (**33**) X=NH, R=H
F (**34**) X=O, R=H
G (**35**) X=O, R=OH

DNA extraction of sediment samples obtained at depths of 3006 m in the south western Indian Ocean, followed by metagenomic cloning and transformation into *E. coli*, has yielded eight known compounds along with the novel, optically active indole alkaloid (**36**), from the fermentation broth. The alkaloid, for which the stereochemistry at the chiral centre was not defined, exhibited some analgesic activity.[96]

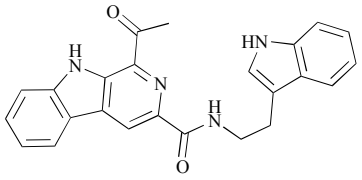


(**36**)

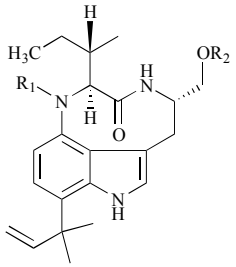
The culture broth of a *Verrucosispora* sp. actinomycete obtained from marine sediment collected at a depth of 3865 m in the northern South China Sea, was found to contain the unique *β*-carboline alkaloids, the marinacarbolines A−D (**37-40**), two new indolactam alkaloids, 13-*N*-demethyl-methylpendolmycin (**41**) and methylpendolmycin-14-*O*-*α*-glucoside (**42**), and the three known compounds 1-acetyl-*β*-carboline, methylpendolmycin and pendolmycin. The six new compounds exhibited strong antiplasmodial activities against *Plasmodium falciparum* lines 3D7 and Dd2, with IC_{50} values ranging from 1.9-36.0μM, but were inactive against a range of tumour cell lines.[97] The first total synthesis of marinacarbolines A-D was described in 2013,[98] along with discovery of an enzyme catalyzing the β-carboline skeleton construction in the marinacarboline biosynthetic pathway.[99]



Marinacarboline
A (**37**) R=OCH_3
B (**38**) R=OH
C (**39**) R=H

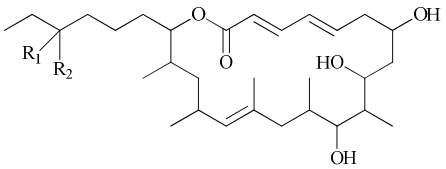


Marinacarboline D (**40**)



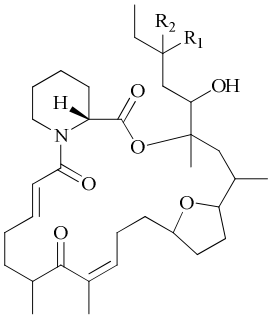
(**41**) R_1=H, R_2=H
(**42**) R_1=CH_3,
R_2=Glucose

Two novel 20-membered macrolides, levantilide A (**43**) and B (**44**), have been obtained from the actinobacterium *Micromonospora* strain M71-A77, recovered from a 4400 m deep-sea sediment sample from the Eastern Mediterranean Sea. Levantilide A exhibited moderate antiproliferative activity against several tumour cell lines.[100]

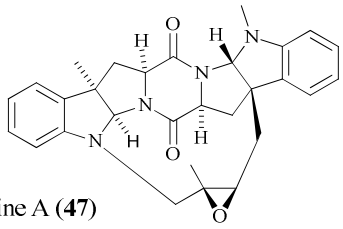


Levantilide A (**43**) R_1=H, R_2=OH
B (**44**) R_1, R_2= O

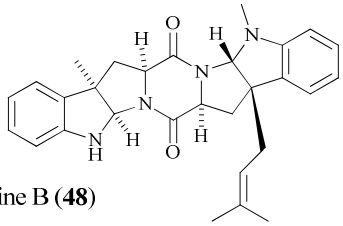
Nocardiopsins A (**45**) and B (**46**) have been isolated from a marine-derived actinomycete, *Nocardiopsis* sp. (CMB-M0232) cultured from deep-sea sediment collected at a depth of 55 m off the coast of Brisbane, Australia, in 2010, while a further two new prenylated diketopiperazines, nocardioazine A (**47**) and B (**48**) were isolated from the same sediment sample and reported in 2011. Compounds **45** and **46** were examined for their bioactivity and found to be neither antibacterial, antifungal nor cytotoxic, although they did exhibit binding to the immunophilin FKBP12.[101] Attempts at assigning absolute configuration at the C-5 centre via a Mosher ester were not successful, and only the partial absolute (15*Z*,21*E*,24*S*) and relative (9,12-*cis*) configurations were determined. Nocardioazine A (**47**) was found to be a non-cytotoxic inhibitor of the membrane protein efflux pump P-glycoprotein, reversing doxorubicin resistance in a multidrug resistant colon cancer cell line.[102] The total synthesis of nocardioazine B in an overall yield of 11.8% has been described, along with determination of the absolute configuration.[103]



Nocardiopsin
A (**45**) R_1, R_2=O
B (**46**) R_1=H, R_2=OH

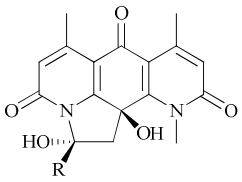


Nocardioazine A (**47**)

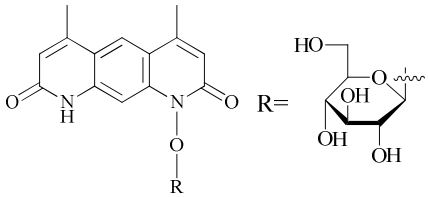


Nocardioazine B (**48**)

The actinobacterium *Pseudonocardia* sp. strain (SCSIO 01299) recovered from deep-sea sediment obtained at 3258 m depth in the South China Sea, yielded three new diazaanthraquinone derivatives, pseudonocardians A–C (**49**–**51**), along with a previously synthesized compound deoxynyboquinone. The pseudonocardians A–C exhibited cytotoxic activity against three tumour cell lines SF-268 (central nervous system cancer), MCF-7 (breast cancer) and NCI-H460 (lung cancer) with IC_{50} values ranging between 0.01 and 0.21 μM. The compounds also showed antibacterial activities against *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Bacillus thuringensis* SCSIO BT01, with MIC values of 1–4 μg/mL, [104] and are the subject of a recent Chinese patent.[105]

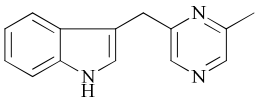


Pseudonocardian A (**49**) R=CH_3
B (**50**) R=CH_2CH_3



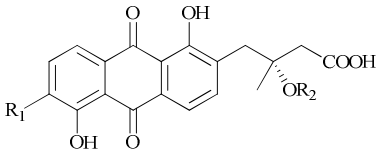
Pseudonocardian C (**51**)

The deep-sea actinomycete *Serinicoccus profundi* sp. isolated from deep-sea sediment from the Indian Ocean, yielded the new indole alkaloid (**52**), together with five known compounds. The new indole alkaloid displayed weak antimicrobial activity against *S. aureus* ATCC 25923 with an MIC value of 96 μg/mL, and was not cytotoxic when tested against a normal human liver cell line (BEL7402) and a human liver tumour cell line (HL-7702).[106]

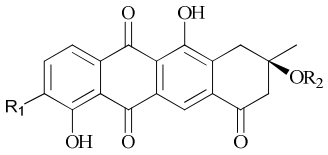


(**52**)

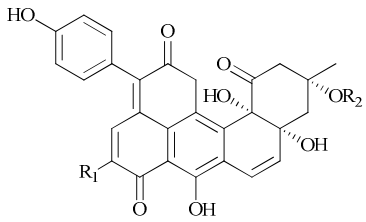
Fermentation of the actinobacteria *Streptomyces lusitanus* obtained from 3370 m deep sediment collected in the South China Sea, provided five new C-glycoside angucycline metabolites, grincamycins B−F (**53**−**57**), and a known angucycline antibiotic, grincamycin. With the exception of grincamycin F, all other compounds displayed in vitro cytotoxicities against the human cancer cell lines HepG2 (hepatocellular liver), SW-1990 (pancreatic), HeLa (epithelial carcinoma), NCI-H460 (lung), and MCF-7 (breast adenocarcinoma); and the mouse melanoma cell line (B16), with IC_{50} values ranging from 1.1 to 31 μM.[107] The gene cluster responsible for the biosynthesis of grincamycin derviatives in *Streptomyces lusitanus* SCSIO LR32 has been identified and patented.[108, 109]



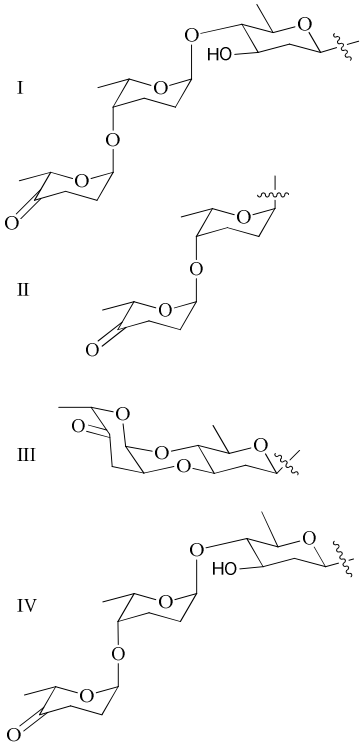
Grincamycin B (**53**) R_1= I, R_2= II
C (**54**) R_1= I, R_2= H
D (**55**) R_1= III, R_2= II



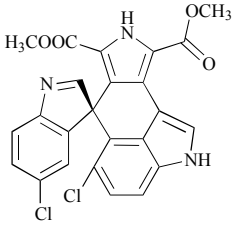
Grincamycin E (**56**)



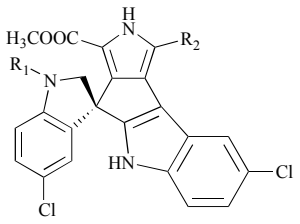
Grincamycin F (**57**)



A deep-sea-derived actinobacterium *Streptomyces* sp. SCSIO 03032, recovered from a sediment sample at 3412 m depth in the Indian Ocean, yielded four novel bisindole alkaloids spiroindimicins A-D (**58-61**), together with two known compounds, lynamicins A and D. Spiroindimicins B-D with a [5,5] spiro-ring displayed moderate cytotoxicities against several cancer cell lines[110] and are the subject of a recent patent on the application of using *Streptomyces* for the preparation of anti-tumour compounds.[111]

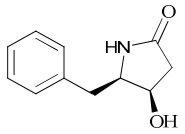


Spiroindimicin A (**58**)



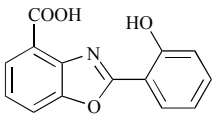
Spiroindimicin
B (**59**) R_1=CH_3, R_2=H
C (**60**) R_1=H, R_2=H
D (**61**) R_1=CH_3, R_2=CO_2CH_3

Another *Streptomyces* sp. (KORDI-3973), obtained from a deep-sea sediment sample collected at the Ayu Trough region in the Philippine Sea, was found to contain the unique benzyl pyrrolidine derivative, streptopyrrolidine (**62**), with significant anti-angiogenesis activity.[112] Stereoselective synthesis of the four possible isomers of streptopyrrolidine, established the absolute configuration as (4*S*,5*S*),[113] and there have been several other synthetic investigations into this novel but structurally unassuming antiangiogenic compound.[114-117]



Streptopyrrolidine (**62**)

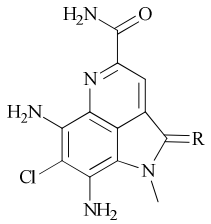
A further *Streptomyces* sp. (NTK 937), recovered from an Atlantic Ocean deep-sea sediment core collected at a depth of 3814 m, yielded a new benzoxazole antibiotic, caboxamycin (**63**), which exhibited inhibitory activity against Gram-positive bacteria and the enzyme phosphodiesterase, as well as cytotoxic activity towards gastric adenocarcinoma (AGS), hepatocellular carcinoma (Hep G2), and a breast carcinoma cell line (MCF7).[118] Caboxamycin has been synthesised using environmentally-friendly reagents,[119] and is also the subject of a recent patent on inhibitors of hepatitis C virus.[120]



Caboxamycin (**63**)

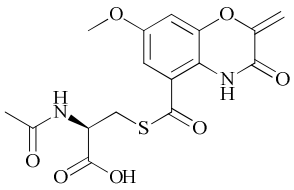
The highly coloured ammosamides A (**64**) and B (**65**) were isolated from a *Streptomyces* strain (CNR-698a) recovered from

deep-sea sediment collected at a depth of 1618 m off the Bahamas Islands.[121] The compounds exhibited potent cytotoxicity against the HCT-116 colon carcinoma cell line with IC_{50} values of 320 nM each, along with marked selectivity in a diverse cancer cell line panel. Fluorescent labelling of ammosamide B and subsequent cellular studies identified a member of the myosin family, which is important for cell cycle regulation and migration, as the ammosamide target[122] The ammosamides, and in particular ammosamide B, have been the subject of several synthetic investigations including by Hughes and Fenical in 17-19 steps from 4-chloroisatin in 2010,[123] later reviewed by Zurwerra;[124] in 9 steps and 7% overall yield by Reddy *et al.;*[125] in 5 steps by Wu *et al.* also in 2010; and by a Friedel-Crafts strategy by Takayama *et al.* reported earlier this year.[126] A series of ammosamide B analogues have been prepared and evaluated as inhibitors of quinone reductase 2 (QR2) by Reddy and co-workers in 2012. The natural product ammosamide B was the among the most potent QR2 inhibitor of the series, with potencies decreasing as structures diverged from ammosamide B, apart for methylation of the 8-amino group of ammosamide B, which led to an increase in activity from an IC_{50} of 61 nM to IC_{50} 4.1 nM.[127]



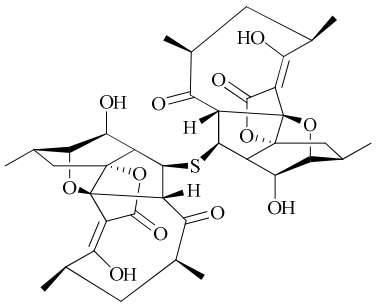
Ammosamides (A) **64** R=S
(B) **65** R=O

A *Streptomyces* sp. strain NTK 935, recovered from a deep-sea sediment sample collected at a depth of 3814 m in the Canary Basin, yielded a new 1,4-benzoxazine-type metabolite, benzoxacystol (**66**), which displayed inhibitory activity against the enzyme glycogen synthase kinase-3β and weak antiproliferative activity against a mouse fibroblast cell line.[128]

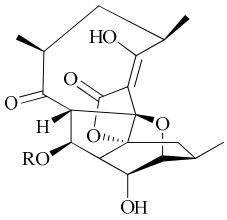


Benzoxacystol (**66**)

Bioassay-directed fractionation of a large-scale culture of the deep-sea, sediment-derived actinomycete, *Verrucosispora* sp. (MS100128), from the South China Sea (2733 m depth) yielded three new examples of a rare class of polyketides, abyssomicins J-L (**67-69**),[129] along with the four known abyssomicins B-D[130] and H.[131] The compounds were discovered by screening for growth inhibitory activity against *Bacille Calmette Guerin (BCG)*, a non-pathogenic strain of the bovine tuberculosis bacillus *Mycobacterium bovis*, with anti-BCG activities for abyssomisin J comparable to those of the known abyssomicin C, with MIC values of 3.13 and 6.25μg/mL, respectively.[129] The authors proposed that abyssomicin J acts a natural prodrug undergoing *in situ* reverse Michael addition to give the more active Michael acceptor containing derivative, *atrop*-abyssomicin C.[129] Abyssomicins B-D were originally described from the deep-sea *Verrucosispora* sp. (AB-18-032),[130, 132] now identified as the new taxon *Verrucosispora maris* sp. nov.,[133] however, it should be noted that the abyssomicin scaffold is not exclusive to the deep-sea and has also been found from terrestrial sources including abyssomicin E and I from the soil *Streptomyces* sp. HK10381[134] and CHI39[135] respectively, and ent-homoabyssomicins A and B from another soil *Streptomyces* sp. (Ank 210).[136]



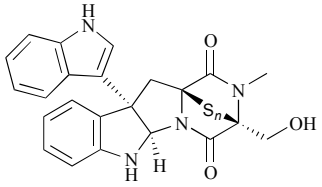
Abyssomicin J (**67**)



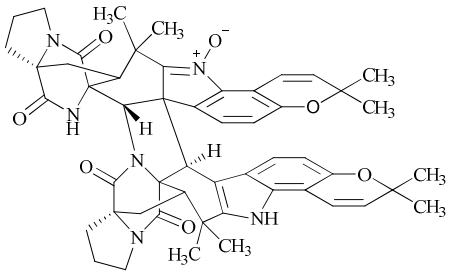
Abyssomicin K (**68**) R=H
L (**69**) R=Me

8.2 Fungi

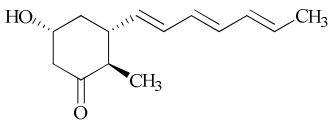
In the last five years, fungi derived from deep-water sediments have yielded and array of interesting new metabolites. Two new indole diketopiperazines, luteoalbusins A and B (**70** and **71**), along with eight known ones, T988A, gliocladines C–D, chetoseminudins B–C, cyclo(L-Trp-L-Ser-), cyclo(L-Trp-L-Ala-) and cyclo(L-Trp-*N*-methyl-L-Ala-), were isolated from the fungus *Acrostalagmus luteoalbus* SCSIO F457 originating from a deep-sea sediment sample collected at a depth of 2801 m in the South China Sea[137] The novel compounds displayed strong cytotoxic activities against four cancer cell lines (SF-268, MCF-7, NCI-H460 and HepG2) with IC_{50} values in the range of 0.23 – 1.31 μM, and were significantly more potent that the control cisplatin.



The deep-sea fungus *Aspergillus* sp. obtained from a soil sample collected at a depth of 50 m near Waikiki Beach (Honolulu, Hawaii), was found to produce two novel metabolites, a new complex prenylated indole alkaloid named waikialoid A (**72**), and a polyketide metabolite, waikialide A (**73**). Waikialoid A, inhibited *C. albicans* biofilm formation with an IC_{50} value of 1.4 μM, while waikialide A was less potent with an IC_{50} value of 32.4 μM.[138]

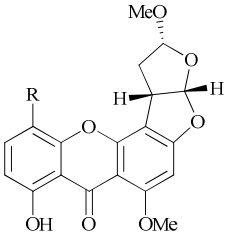


Waikialoid A (**72**)

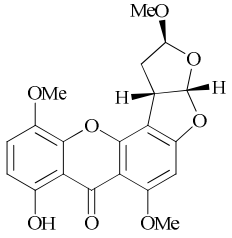


Waikialide A (**73**)

The deep-sea-derived fungus *Aspergillus versicolor* obtained from 800 m depth in the Pacific Ocean, has furnished three new sterigmatocystin derivatives, oxisterigmatocystin A-C (**74-76**), along with the known compound, 5-methoxysterigmatocystin.[139] The compounds were evaluated for cytotoxicity towards the A-549 and HL-60 cell lines, with only the known compound shown to exhibit moderate low micromolar cytotoxicity.

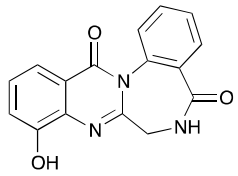


Oxisterigmatocystin A (**74**) R = OMe
C (**76**) R = H

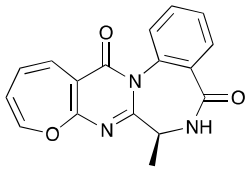


Oxisterigmatocystin B (**75**)

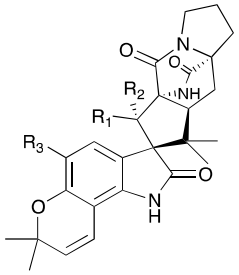
A rich collection of both novel and known alkaloids were also obtained from *Aspergillus westerdijkiae* DFFSCS013, obtained from South China Sea at a depth of 2918 m. The metabolites included two new benzodiazepine alkaloids, circumdatins K and L (**77** and **78**); two new prenylated indole alkaloids, 5-chlorosclerotiamide (**79**) and 10-epi-sclerotiamide (**80**); a novel amide, aspergilliamide B (**81**); and six known alkaloids. The compounds were evaluated against a range of human cancer cell lines (A549, HL-60, K562, and MCF-7) but did not exhibit any cytotoxicity.[22]



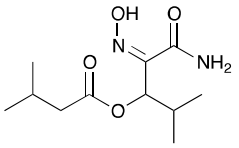
Circumdatin K (**77**)



Circumdatin L (**78**)

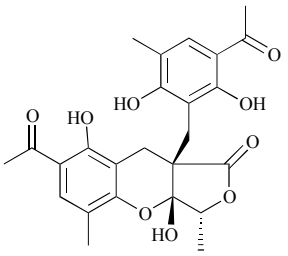


5-Chlorosclerotiamide (**79**) R_1=H, R_2=OH, R_3=Cl
10-Epi-sclerotiamide (**80**) R_1=OH, R_2=H, R_3=H

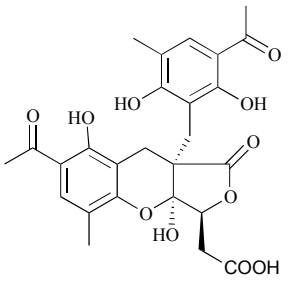


Aspergilliamide B (**81**)

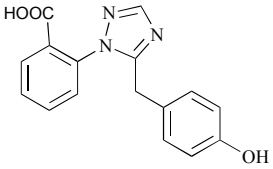
In 2012, two highly oxygenated polyketides, penilactones A and B (**82** and **83**) of related structure but opposite absolute stereochemistry, were isolated from the Antarctic deep-sea derived fungus *Penicillium crustosum* PRB-2, along with five known compounds.[140] The penilactones contain a new carbon skeleton formed from two 3,5-dimethyl-2,4-diol-acetophenone units and a γ-butyrolactone moiety, and have been prepared by a biomimetic synthesis reported the following year.[141] The novel triazole carboxylic acid, penipanoid A (**84**), two new quinazolinone alkaloids, penipanoids B (**85**) and C (**86**), and a known quinazolinone derivative were isolated from the marine sediment derived fungus *Penicillium paneum* SD-44 obtained at a depth of 201 m in the South China Sea.[142] The cytotoxic and antimicrobial activities of the compounds were evaluated, and found to possess mid- to low micromolar activity towards SMMC-7721 (liver), BEL-7402 (liver), and A-549 (lung) cancer cell lines, but no activity when screened against two bacteria and five plant-pathogenic fungi. Penipanoid A is reportedly the first example of a triazole derivative from marine sediment-derived fungi, while pnipanoid B is a rare quinazolinone-derivative containing a dihydroimidazole ring system.



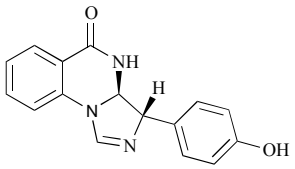
Penilactone A (**82**)



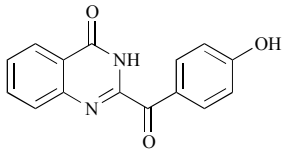
Penilactone B (**83**)



Penipanoid A (**84**)

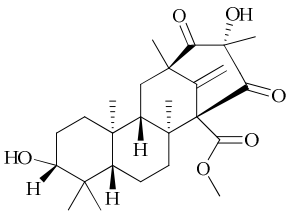


Penipanoid B (**85**)

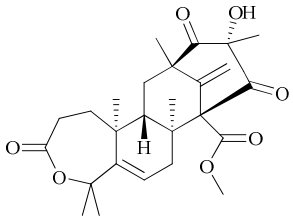


Penipanoid C (**86**)

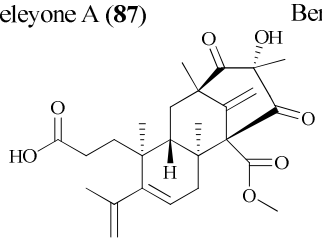
In 2011, berkeleyones A-C (**87-89**) along with the known preaustinoid A and A1, were obtained from the deep-water fungus *Penicillium rubrum* from sediment obtained at 270 m depth from the acid mine waste Berkeley Pit Lake, in Montana, USA.[143] The compounds were evaluated for inhibition of the signaling enzyme caspase-1 and for mitigation of interleukin-1β production in induced THP-1 cells, with activity comparable to that of the commercially supplied inhibitor Ac-YVAD-CHO, in the latter assay.



Berkeleyone A (**87**)

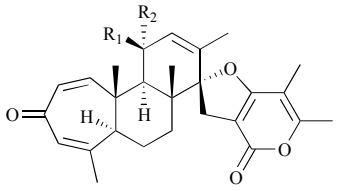


Berkeleyone B (**88**)

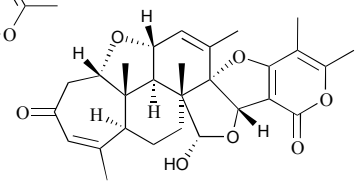


Berkeleyone C (**89**)

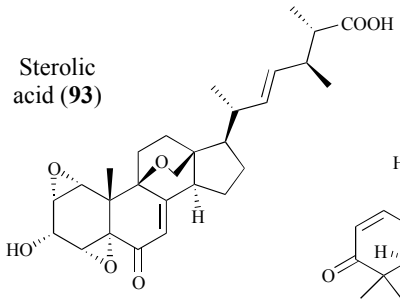
In 2009, Capon's group reported the isolation and characterization of three new bioactive breviane spiroditerpenoids, breviones F-H (**90-92**), from the deep-sea sediment derived fungus *Penicillium* sp. (MCCC 3A00005) collected at a depth of 5115 m in the East Pacific.[144] In 2012, the same group reported the isolation of breviones I–K (**94**–**96**), a novel polyoxygenated sterol, sterolic acid (**93**), along with four known breviones, from the same fungal strain. Brevione I exhibited significant cytotoxicity against MCF-7 cells.[145] Earlier members of the brevione family (A-C) have been the subject of several recent synthetic studies,[146, 147] along with the synthesis of the western half of brevione C, D, F and G by Macias in 2010.[148] Synthetic studies on breviones and structurally related natural products have been reviewed by Takikawa.[149]



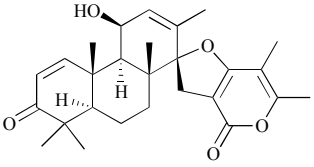
Breviones
F (**90**) R_1=OH, R_2=H
G (**91**) R_1=H, R_2=OH



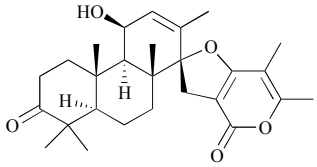
Brevione H (**92**)



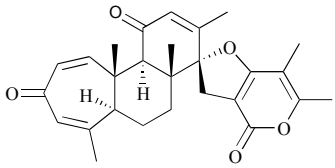
Sterolic
acid (**93**)



Brevione I (**94**)

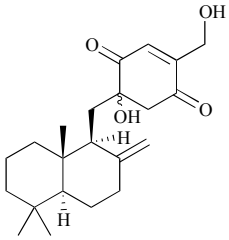


Brevione J (**95**)



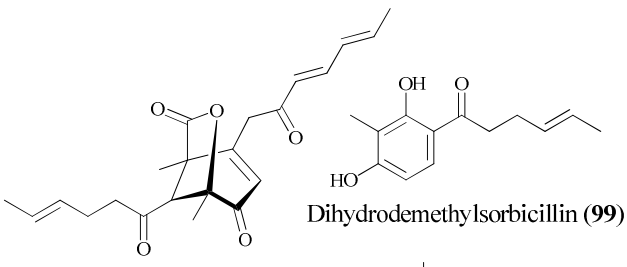
Brevione K (**96**)

The fungus *Penicillium* sp. (F00120) recovered from deep-sea sediment obtained at a depth of 1300 m from northern South China Sea, yielded the new sesquiterpene quinone, penicilliumin A (**97**), along with known ergosterol and ergosterol peroxide. Penicilliumin A moderately inhibited in vitro proliferation of mouse melanoma (B16), human melanoma (A375), and human cervical carcinoma (Hela) cell lines.[150]



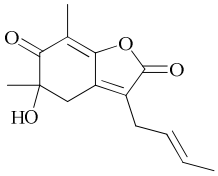
Penicilliumin A (**97**)

The fungus *Phialocephala* sp. isolated from deep-sea sediment obtained from the east Pacific at a depth of 5059 m, was the source of two new sorbicillinoids (**98** and **99**), together with a novel benzofuranone derivative named phialofurone (**100**). All compounds displayed cytotoxicity towards P388 murine leukemia (IC_{50} values of 11.5, 0.1, and 0.2 μM, resp.) and K562 human erythromyeloblastoid leukemia (IC_{50} values of 22.9, 4.8 and 22.4 μM, resp.) cell lines.[151]



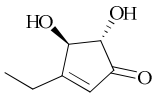
Dihydrodemethylsorbicillin (**99**)

Dihydrotrichodermolide (**98**)



Phialofurone (**100**)

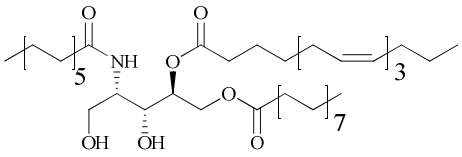
A novel cytotoxic cyclopentenone, trichoderone (**101**) was isolated from a marine-derived fungus *Trichoderma* sp. obtained from deep-sea sediment collected in the South China Sea. Trichoderone displayed potent activity against six cancer cell lines, with a selectivity index of over 100 compared to normal cells. The compound also exhibited activities against HIV protease and Taq DNA polymerase.[152]



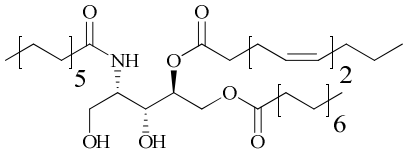
Trichoderone (**101**)

9 Mollusca

The deep-sea mollusc *Bathymodiolus thermophilus*, collected using a deep submergence vehicle at a depth of 1733 m from an active hydrothermal vent in the north of Lucky Strike in the Mid-Atlantic Ridge, has furnished the first reported molluscan deep-sea small molecular metabolites, two novel ceramide derivatives, bathymodiolamides A (**102**) and B (**103**), both of which exhibited apoptosis induction and potential anticancer activity.[153]



Bathymodiolamide A (**102**)



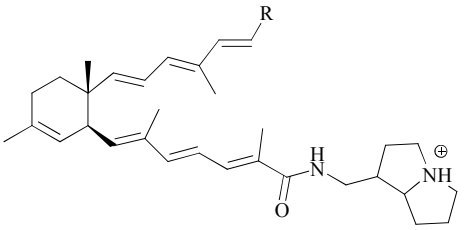
Bathymodiolamide B (**103**)

10 Porifera

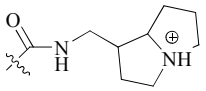
Sponges are extremely well represented in the marine environment, with over 8000 species ranging from shallow-water to those inhabiting depths of over 8800 m, with some deep-water species adopting carnivorous behaviour.[11, 154] Marine sponges are the largest source of new marine natural products reported annually[80-82] and have provided a rich array of biologically important compounds,[155] 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*.[71, 156] Sponge metabolites, predominantly from shallow-water species, have been reviewed previously,[154, 157] while in 2011, Winder *et al.* reviewed the natural products isolated from Lithistid sponges collected since 2000 including deep-sea species.[29] Deep-water species of marine sponges have already provided important anticancer leads such as halichondrin and discodermolide[71] and are certain to be a rich new source of biologically and structurally interesting molecules.

Order Astrophorida

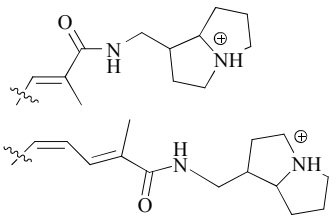
Four novel alkaloids, the bistellettazines A-C (**104-106**) and the bistellettazole A (**107**), were described from a deep-water Pacific sponge belonging to the genus *Stelletta*, retrieved from 90 m depth from the Great Australian Bight.[158]

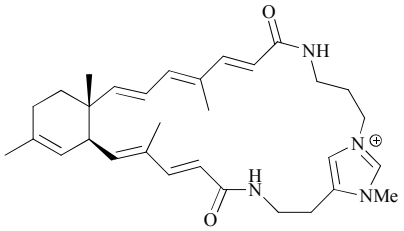


Bistellettazine A (**104**) R=



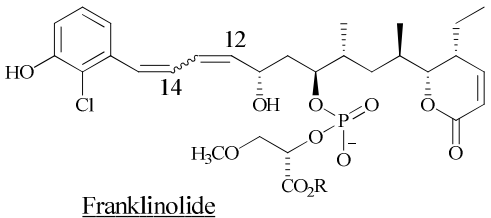
B (**105**) R=





Bistellettazole A (**107**)

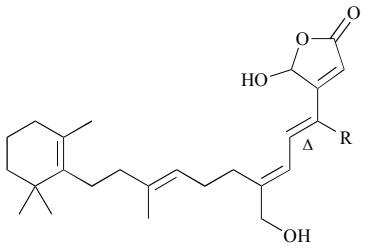
From the same Order, three cytotoxic polyketides, franklinolides A–C (**108-111**), were isolated from the deep-sea sponge, *Geodia* sp. thinly encrusted with a *Halichondria* sp., collected at a depth of 105 m, also from trawling operations in the Great Australian Bight.[159]



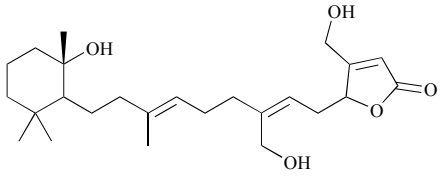
Franklinolide
A (**108**) 12*Z*, 14*Z,* R=H
A methyl ester (**109**) 12*Z*, 14*Z,* R=CH_3
B (**110**) 12*E*, 14*E*, R=H
C (**111**) 12*E*, 14*Z,* R=H

Order Dictyoceratida

The marine sponge *Aplysinopsis digitata*, obtained during deep-sea dredging at a depth of 150 m at Oshima-shinsone, Kagoshima Prefecture, Japan, was found to produce the three novel sesterterpenoids, aplysinoplides A-C (**112-114**) with cytotoxic activity against the P388 murine leukemia cell line.[160]

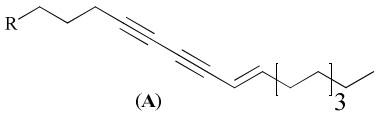


Aplysinoplide A (**112**) R=H
B (**113**) R=OH, Δ saturated



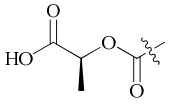
Aplysinoplide C (**114**)

Bioassay directed fractionation of a deep-sea collection of the sponge *Spongia* (*Heterofibria*) sp. at 125 m depth in the Great Australian Bight by Capon's group, led to the isolation of six new compounds, the fatty acid heterofibrins A1 (**115**) and B1 (**118**), along with related monolactyl and dilactyl esters, heterofibrins A2 (**116**), B2 (**119**), A3 (**117**) and B3 (**120**).[161] Subsequent studies by the same group demonstrated that heterofibrin A1 inhibited lipid droplet biogenesis in A431 cells and AML12 hepatocytes and also significantly reduced intracellular accumulation of fatty acids in both cultured cells and zebrafish (*Danio rerio*) embryos.[162] Zivanovic *et al.* described the fatty acid profile of a mixed specimen of *Ircinia/Sarcotragus* sp. from 84 m depth from the North West Shelf of Australia, reporting a greater proportion of saturated fatty acids than their shallow-water counterparts and an absence of the C_{24}-$C_{25}\Delta^{5,9}$ demospongic acids typical of marine sponges.[163]

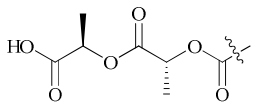


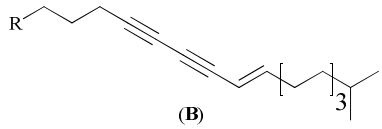
Heterofibrin A1 (**115**) R=

A2 (**116**) R=



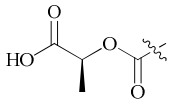
A3 (**117**) R=



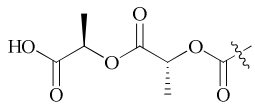


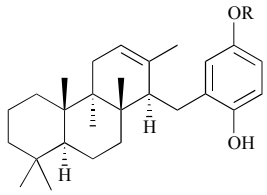
Heterofibrin B1 (**118**) R=

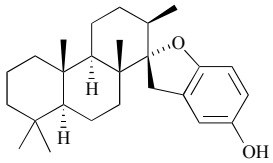
B2 (**119**) R=



B3 (**120**) R=

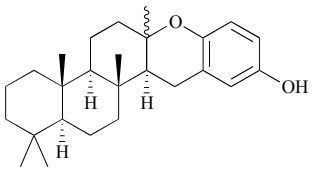




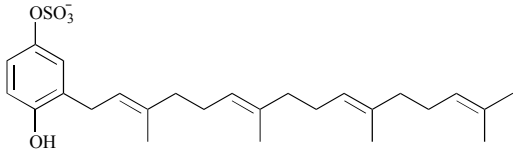


Fascioquinol A (**121**) R=SO_3^-
B (**122**) R=H

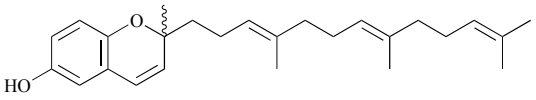
Fascioquinol C (**123**)



Fascioquinol D (**124**) α-CH_3
Strongylophorine-22 (**125**) β-CH_3



Fascioquinol E (**126**)

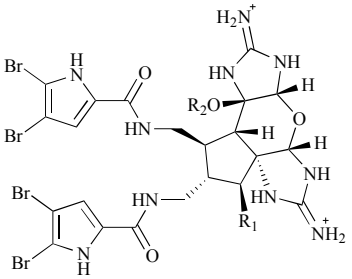


Fascioquinol F (**127**)

A deep-water sponge of the genus *Fasciospongia*, collected during scientific trawling operations at a depth of 100 m, west of Cape Leeuwin, Western Australia, has yielded the ew meroterpene sulfate fascioquinol A (**121**) together with a series of acid mediated hydrolysis/cyclization products, fascioquinols B-D (**122**-**124**), and strongylophorine-22 (**125**). Additional co-metabolites include the new meroterpenes fascioquinol E (**126**) and fascioquinol F (**127**), together with the known sponge metabolite geranylgeranyl 1,4-hydroquinone. By contrast, while the fascioquinols displayed little or no inhibitory activity towards human cancer cell lines, fascioquinols A and B displayed promising Gram-positive selective antibacterial activity towards *S. aureus* with IC_{50} values ranging from 0.9 to 2.5 μM and *B. subtilis* with IC_{50} values ranging from 0.3 to 7.0 μM.[164]

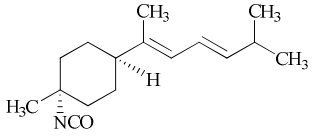
Order Halichondrida

Three new bromopyrrolo-2-aminoimidazoles, 14-*O*-sulfate massadine (**128**), 14-*O*-methyl massadine (**129**), and 3-*O*-methyl massadine chloride (**130**), together with the known metabolites massadine chloride, massadine, stylissadine B, axinellamines A–C, hymenin, stevensine (also known as odiline), tauroacidin A, hymenidin, taurodispacamide A, oroidin, debromohymenialdisine, hymenialdisine, and aldisin, were isolated from a deep-sea sponge, *Axinella* sp. obtained at a depth of 85 m in the Great Australian Bight[165] Compound **130** displayed significant growth inhibitory activity against the Gram positive bacteria *S. aureus* and *B. subtilis*; Gram negative bacteria *E. coli* and *P. aeruginosa*; and the fungus*C. albicans*. The massadines with their complex architecture and interesting biological activities have been the subject of several synthetic pursuits including an enantioselective total synthesis of (-)-palau'amine, (-)-axinellamines, and (-)-massadines from Baran's group,[166-168] and by an Ugi four-component coupling by Carreira's group.[169-172]

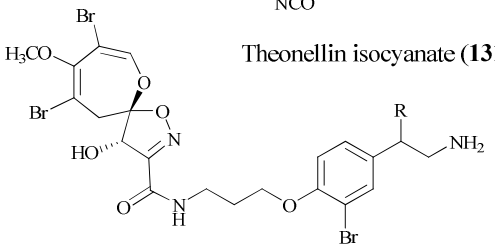


(**128**) R_1=OSO_3^- R_2=H
(**129**) R_1=OCH_3 R_2=H
(**130**) R_1=Cl R_2=CH_3

Wright and co-workers screened the extracts of 65 sponges, gorgonians, hard corals and sponge-associated bacteria from depths of 50 and 1000 m, giving rise to a 42% bioactivity hit rate overall, and an impressive 72% for sponge and gorgonian extracts.[15] From this screening, two sponges were chosen at random for further investigation. The sponges *Suberea* sp. (family Aplysinellidae) and *Rhaphoxya* sp. (family Halichondriidae), retrieved from a depth of 60 m and 90 m from the Black Coral Kingdom, and Blue Hole, Guam, respectively, yielded a vast array of compounds including the novel theonellin isocyanate (**131**) and novel bromotyrosine-containing psammaplysins I and J (**132** and **133**), along with six previously reported compounds.[16]



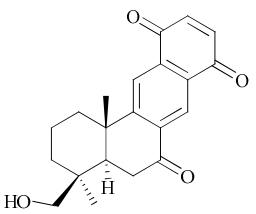
Theonellin isocyanate (**131**)



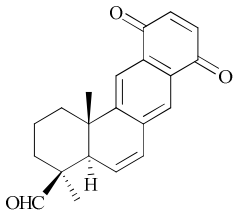
Psammaplysin I (**132**) R=H
J (**133**) R=OH

Order Haplosclerida

Two new marine-derived sesquiterpene benzoquinones, neopetrosiquinones A (**134**) and B (**135**), have been isolated from a deep-water sponge *Neopetrosia proxima* collected at a depth of 140 m off the north coast of Jamaica, St. Ann's Bay. While both compounds inhibited in vitro proliferation of the DLD-1 human colorectal adenocarcinoma cell line with IC_{50} values of 3.7 and 9.8 μM, respectively, and the PANC-1 human pancreatic carcinoma cell line with IC_{50} values of 6.1 and 13.8 μM, respectively, neopetrosiquinone A also inhibited the in vitro proliferation of the AsPC-1 human pancreatic carcinoma cell line with an IC_{50} value of 6.1 μM.[173]

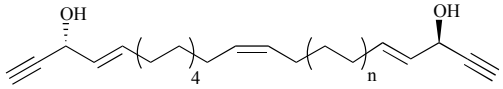


Neopetrosiquinone A (**134**)

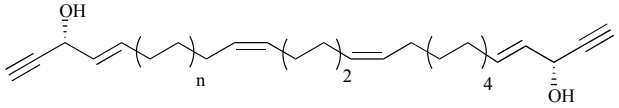


Neopetrosiquinone B (**135**)

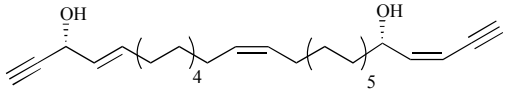
Six linear acetylenes, (-)-duryne (**136**) and (-)-durynes B-F (**137-141**) have been reported from the marine sponge *Petrosia* sp. collected by remotely operated vehicle (ROV) from a depth of 415 m at Miyako sea-knoll, southwestern Japan. The compounds (**136-137**) exhibited cytotoxicity against HeLa cells with IC_{50} values between 80 and 500 nM.[174] An enantioselective synthesis of (+)-duryne via a one-pot organocatalyzed hydroxylation/Ohira-Bestmann and Grubbs cross-metathesis/selective cis-Wittig reaction has been reported, with the potential to access other members of the family by this route.[175] Earlier syntheses had established the geometry of the central double bond and the absolute configuration of the chiral centres in (+)- and (-)-duryne.[176]



(-)-Duryne (**136**) *n*=4
B (**137**) *n*=5

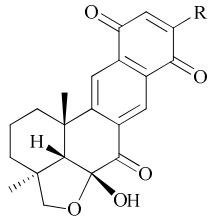


(-)-Duryne C (**138**) *n*=2
D (**139**) *n*=3
E (**140**) *n*=4

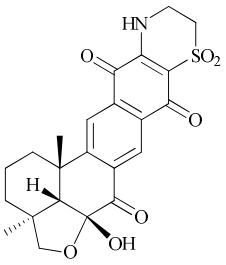


(-)-Duryne F (**141**)

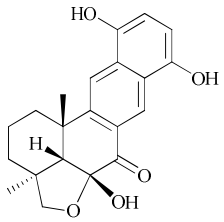
Four new meroterpenes, alisiaquinones A-C (**142-144**) and alisiaquinol (**145**), were isolated from a New Caledonian deep water sponge, *Xestospongia* sp. collected by trawling on a deep-sea mount between depths of 250 and 400 m in the South of New Caledonia, Norfolk Rise. The compounds exhibited micromolar inhibitory activity towards plasmodial kinase Pfnek-1 and protein farnesyl transferase, both important antimalarial targets. Alisiaquinone C (**144**) displayed potent activity on *P. falciparum* and competitive selectivity towards different plasmodial strains.[177]



Alisiaquinones A (**142**) R=H
B (**143**) R=OMe



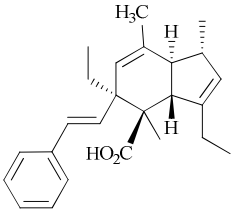
Alisiaquinone C (**144**)



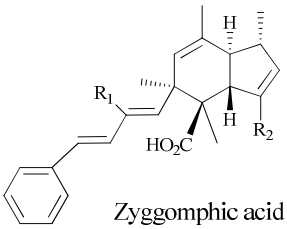
Alisiaquinol (**145**)

Order Homoscleropherida

The deep reef Caribbean sponges *Plakortis angulospiculatus*, obtained by mixed gas scuba at a depth of 58 m from Little Cayman Island, Bahamas, was found to produce a new compound, 23-*nor*-spiculoic acid B (**146**) along with known spiculoic acid B. Four other new compounds, zyggomphic acid B (**147**), 27-*nor*-zyggomphic acid B (**148**), 22-*nor*-zyggomphic acid B (**149**) and 22,27-*dinor*-zyggomphic acid B (**150**), were isolated from a second sample of the same sponge species collected at 62 m from Exuma Cays, Bahamas, with compounds **146** and **148** found to inhibit NFκB activity with IC_{50} values of 0.5 and 2.3μM, respectively.[178]



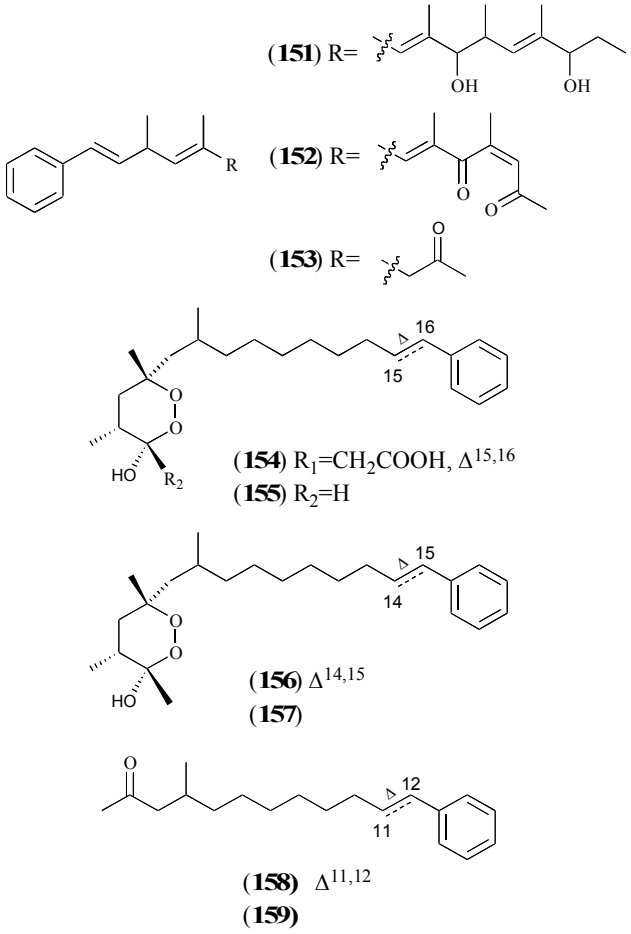
(**146**)



Zyggomphic acid B

(**147**) R_1=CH_3, R_2=CH_2CH_3
(**148**) R_1=CH_3, R_2=CH_3
(**149**) R_1=H, R_2=CH_2CH_3
(**150**) R_1= H, R_2=CH_3

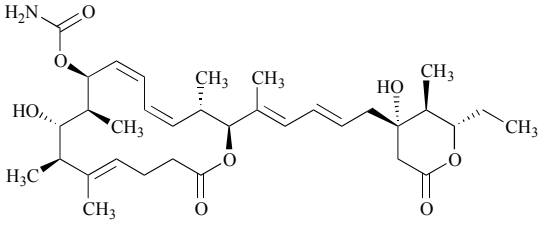
A third sample collected at a depth of 91 m from Exuma Cays, Bahama, and identified as *Plakortis halichondrioides,* yielded three new aromatic compounds (**151-153**). While, another deep-sea *Plakortis* sp. obtained at a depth of 96 m, near Blue Hole, Orote Peninsula, Guam, yielded a further six new aromatic metabolites (**154-159**), along with the known compounds dehydrocurcuphenol and manoalide. The new compounds were evaluated for antifungal and antibacterial activity with the cyclic peroxides **154** and **155** showing weak activity against *S. aureus.*[179]



(**151**) R=
(**152**) R=
(**153**) R=
(**154**) R_1=CH_2COOH, $\Delta^{15,16}$
(**155**) R_2=H
(**156**) $\Delta^{14,15}$
(**157**)
(**158**) $\Delta^{11,12}$
(**159**)

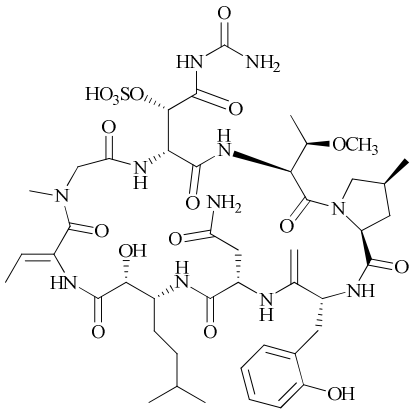
Order Lithistida

Bioassay-guided isolation of the deep-water sponge *Leiodermatium* sp., collected at a depth of 618 m off Wemyss Bight in the Bahamas, furnished leiodermatolide (**160**), with a previously unreported 16-membered macrolide skeleton. The structurally unique compound exhibited potent antimitotic activity (IC_{50}<10 nM) against human A549 lung adenocarcinoma, PANC-1 pancreatic carcinoma, DLD-1 colorectal carcinoma, and murine P388 leukemia cell lines.[180] The structurally unique macrolide has attracted much interest and is the subject of a patent by Wright and co-workers,[181] and several total synthesis studies including by the research groups of Paterson,[182, 183] Roush[184] and Maier.[185, 186]

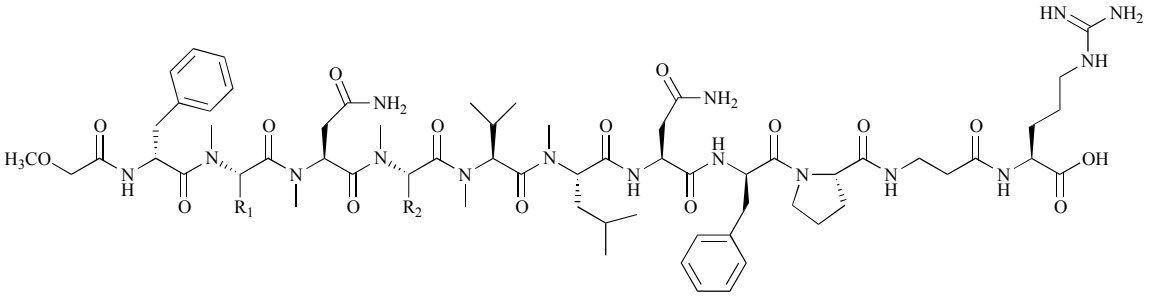


Leiodermatolide (**160**)

The deep-sea sponges *Theonella swinhoei* and *Theonella cupola* obtained at a depth of 100-120 m and 90 m, respectively, yielded the new sulfated cyclic depsipeptide, mutremdamide A (**161**), and six new highly *N*-methylated peptides, koshikamides C-H (**162-167**). The cyclic koshikamides F and H were found to inhibit HIV-1 entry at low micromolar concentrations, while their linear counterparts were inactive.[187]



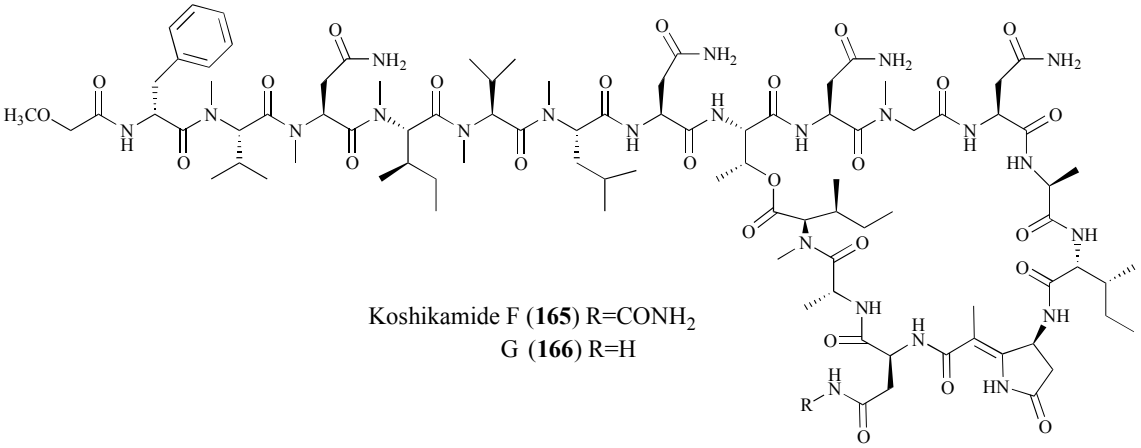
Mutremdamide A (**161**)



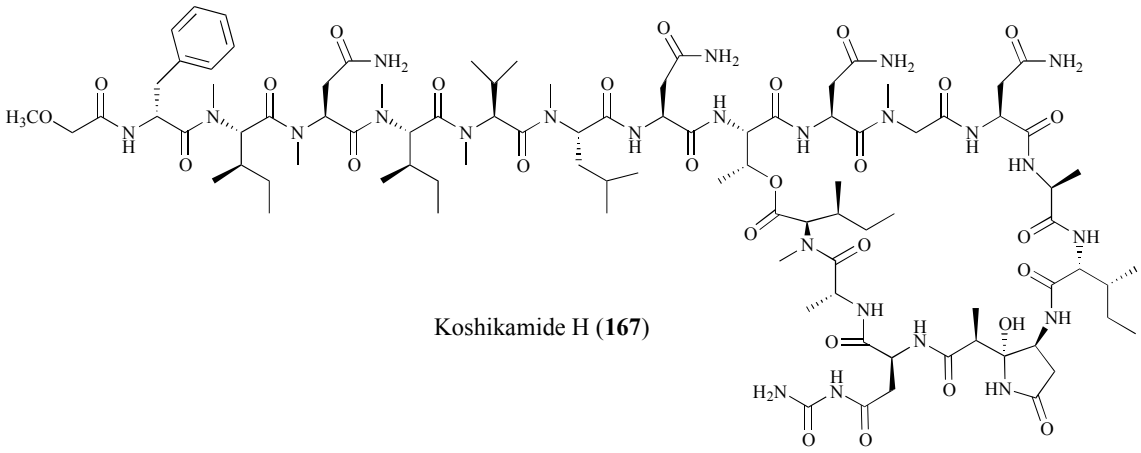
Koshikamide C (**162**) R_1=  R_2= 

D (**163**) R_1=  R_2= 

E (**164**) R_1=  R_2= 

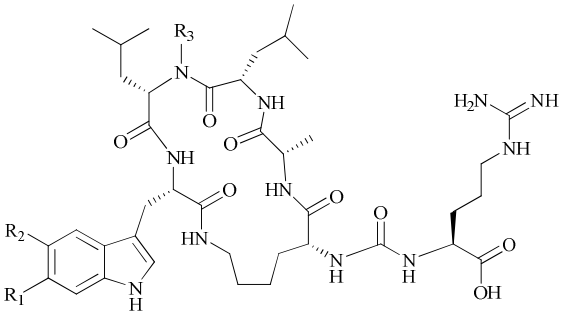


Koshikamide F (**165**) R=$CONH_2$
G (**166**) R=H



Koshikamide H (**167**)

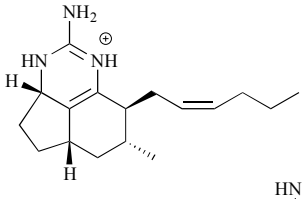
The marine sponge *Theonella swinhoei,* obtained from Uchelbeluu Reef in Palau at a depth of 100 m, was reported to produce three new anabaenopeptin-like peptides, paltolides A-C (**168-170**).[188] The compounds were investigated for inhibition of HIV-1 entry and cytotoxicity towards HCT-116, but were not active in either assay.



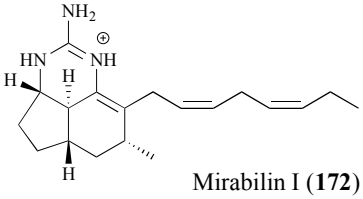
Paltolide A (**168**) R_1=H, R_2=H, R_3=H
B (**169**) R_1=H, R_2=OH, R_3=CH_3
C (**170**) R_1=Br, R_2=H, R_3=CH_3

Order Poecilosclerida

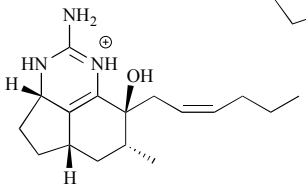
Three new polycyclic guanidine-containing mirabilins H–J (**171-173**), together with the known mirabilins C, F and G,[189, 190] were isolated from a Southern Australian marine sponge *Clathria* sp., retrieved by epibenthic sled at a depth of 60 m in the Great Australian Bight.[191] Although the original *n*-BuOH extract exhibited cytotoxicity against a range of human cancer cell lines (HT-29, A549, MDA-MB-232), the purified mirabilins displayed only modest activity (>30 μM). Mirabilins have also been isolated from the marine sponges *Batzella* sp.[192] and *Monanchora unguiferax,*[193] and the synthesis of mirabilin B, along with the a biosynthetic proposal, has been recently reported from Snider's group.[194]



Mirabilin H (**171**)

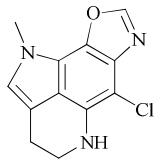


Mirabilin I (**172**)



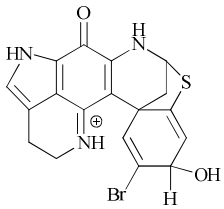
Mirabilin J (**173**) R=OH

A novel batzelline derivative featuring a benzoxazole moiety, citharoxazole (**174**), along with the known batzelline C, was isolated as a dark purple solid from the deep-sea Mediterranean sponge *Latrunculia (Biannulata) citharistae* obtained by remotely operated vehicle (ROV) at 103 m depth off La Ciotat, Banc de Banquiere in France.[195]

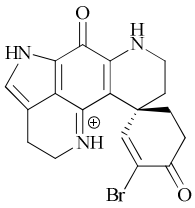


Citharoxazole (**174**)

Bioassay- and LC-MS-guided fractionation of a new species of deep-sea sponge belonging to the genus *Latrunculia*, collected by dredging at a depth of 230 m off the Aleutian Islands, Alaska, led to the isolation of two new brominated pyrroloiminoquinones, dihydrodiscorhabdin B (**175**) as a dark green solid and discorhabdin Y (**176**) as a purple solid, along with six known pyrroloiminoquinone alkaloids, discorhabdins A, C, E, and L, dihydrodiscorhabdin C, and a benzene derivative.[196] The absolute configuration of **176** was assigned as 6R from CD spectroscopy, but could not be assigned for **175** due to sample decomposition during the collection of optical rotation and CD data. The highly cytotoxic discorhabdins were first reported from the sponge *Latrunculia* sp. in 1988 by Blunt and Munro.[197-199] Their potent biological activity (including antitumour, antimicrobial, and antiviral) and exquisite architecture has attracted the attention of several research groups over the years, with numerous synthetic endeavours reported including by the groups of Kita,[200] Cava[201] and Heathcock,[202] and a recent semi-synthesis by Copp and co-workers.[203] The discorhabdin family of alkaloids have been reviewed by Molinksi in 1993,[204] Harayama and Kita in 2005,[205] by Wada and co-workers in 2010[206] and by Hu and co-workers in 2011.[207] Although they possess an impressive array of biological activities, the discorhabdins have proven too non-selective for further drug development.

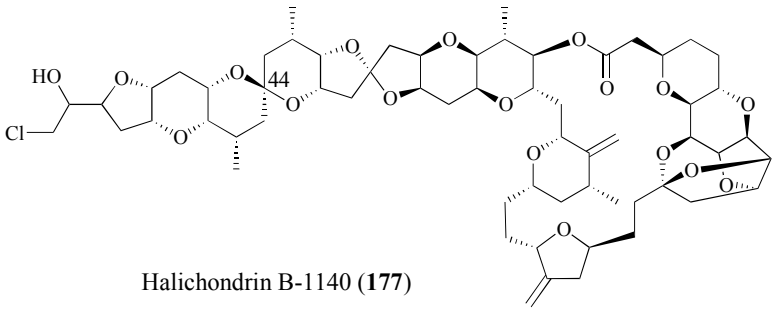


Dihydrodiscorhabdin B (**175**)

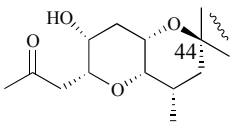


Discorhabdin Y (**176**)

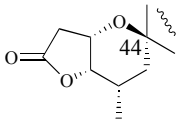
On-going investigations of a large (1 tonne) collection of the bright yellow deep-sea sponge *Lissodendoryx*sp. (family Poecilosclerida), collected by trawling at a depth of 100 m off the Kaikoura coast of New Zealand back in 1995 to supply halichondrin B for earlier preclinical trials, has furnished four new variants of the halichondrin B skeleton, halichondrin B-1140 (**177**), halichondrin B-1092 (**178**), halichondrin B-1020 (**179**) and halichondrin B-1076 (**180**), with comparable potency towards P388 murine leukemia cell line as halichondrin B.[208]



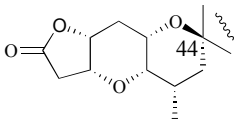
Halichondrin B-1140 (**177**)



Halichondrin B-1092 (**178**)

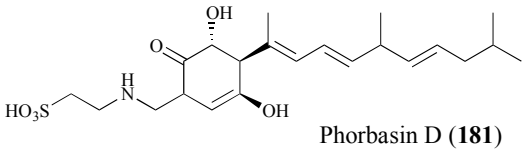


Halichondrin B-1020 (**179**)

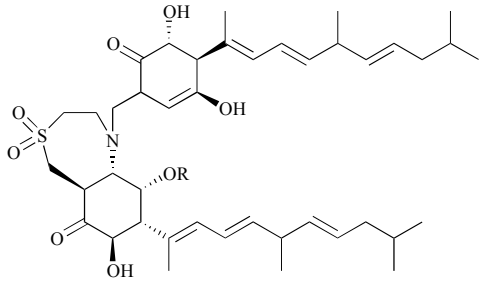


Halichondrin B-1076 (**180**)

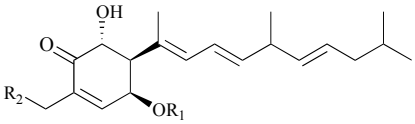
Three novel diterpenyltaurines, phorbasins D-F (**181-183**), together with the known phorbasins B and C, were isolated by bioassay-guided fractionation of an Australian deep-sea sponge, *Phorbas* sp. obtained by epibenthic sled at a depth of 65 m in the Great Australian Bight.[209] A further five new members of the phorbasin family, phorbasins G–K (**184-188**) were isolated from the same marine source, although I and J are likely to be solvolysis artefacts.[210] The phorbasins show low micromolar cytotoxicity towards a range of human cancer cell lines including A549, HT29 and MM96L cell lines.



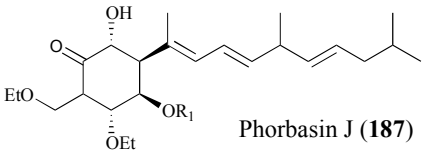
Phorbasin D (**181**)



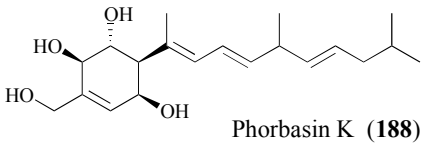
Phorbasin E (**182**) R=H
F (**183**) R=Ac



Phorbasin G (**184**) R_1=H, R_2=H
H (**185**) R_1=Ac, R_2=H
I (**186**) R_1=Ac, R_2=OEt



Phorbasin J (**187**)



Phorbasin K (**188**)

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

	Species	Natural Products (or *Compound Type*)	Depth (m)	Region	Ref
BRYOZOA					
Ctenostomata	*Amathia tortusa*	Convolutamines I and J (**1, 2**)	63	Australia	68
CHORDATA					
Ascidiacea					
Enterogona	*Aplidium*sp.	Rossinones A and B (**3, 4**)	200	Antarctica	77
CNIDARIA					
Anthozoa					
Alcyonacea	*Acanthoprimnoa cristata*	Cristaxenicin A (**5**)	138	Japan	85
	Convexella magelhaenica	*Dolabellanediterpenoids* (**6, 7**)	93	Atlantic	86
	Echinogorgia pseudossapo	Pseudozoanthoxanthins III-IV (**8, 9**) Sesquiterpenes (**10, 11**)	n.s.	S China Sea	87
ECHINODERMATA					
Crinoidea					
Cyrtocrinida	*Holopus rangii*	Gymnochromes E and F (**12, 13**) 7-Bromoemodic acid (**14**)	358	Caribbean	88
	Proisocrinus ruberrimus	Proisocrinins A-F (**15-20**)	1800	Japan	89
Holothuroidea					
Elasipodida	*Achlionice violaecuspidata*	Achlioniceosides A1-3 (**21-23**)	1525 &407	Weddell Sea	90
MICROORG.					
Bacteria	*Bacillus subtilis*	Lipoamicoumacins A–D (**24-27**) Bacilosarcin C (**28**)	1000	Red Sea	94
	Dermacoccus abyssi	Dermacozines A–G (**29-35**)	10898	Philippine Sea	95
	Clone-derived *E. coli*	Alkaloid (**36**)	3006	Indian Ocean	96
	Marinactinospora thermotolerans	Marinacarbolines A−D (**37-40**) Indolactam alkaloid (**41, 42**)	3865	S China Sea	97
	Micromonospora sp.	Levantilides A and B (**43, 44**)	4400	Mediterranean	100
	Nocardiopsis sp.	Nocardiopsins A and B (**45, 46**)	55	S Molle Island	101
	Nocardiopsis sp.	Nocardioazines A and B (**47, 48**)	55	S Molle Island	102
	Pseudonocardia sp.	Pseudonocardians A–C (**49-51**)	3258	S China Sea	104
	Serinicoccus profundi	Alkaloid (**52**)	n.s.	Indian Ocean	106
	Streptomyces lusitanus	Grincamycins B−F (**53-57**)	3370	S China Sea	107
	Streptomyces sp.	Spiroindimicins A-D (**58-61**)	3412	Indian Ocean	110
	Streptomyces sp.	Streptopyrrolidine (**62**)	n.s.	Ayu Trough	112
	Streptomyces sp.	Caboxamycin (**63**)	3814	Atlantic	118
	Streptomyces sp.	Ammosamides A and B (**64, 65**)	1618	Bahamas	121
	Streptomyces sp.	Benzoxacystol (**66**)	3814	Atlantic	128
	Verrucosispora sp.	Abyssomicins J-L (**67-69**)	2733	S China Sea	129
Fungi	*Acrostalagmus luteoalbus*	Luteoalbusins A, B (**70, 71**)	2801	S China Sea	137
	Aspergillus sp.	Waikialoid A (**72**); Waikialide A (**73**)	50	Hawaii	138
	Aspergillus versicolor	OxisterigmatocystinA-C (**74-76**)	800	Pacific Ocean	139
	Aspergillus westerdijkiae	Circumdatins K and L (**77, 78**), 5-Chlorosclerotiamide (**79**), 10-Epi -sclerotiamide (**80**), Aspergilliamide B (**81**)	2918	S China Sea	22
	Penicillium crustosum	Penilactones A and B (**82, 83**)	526	Antarctica	211
	Penicillium paneum	Penipanoids A-C (**84-86**)	201	S China Sea	142
	Penicillium rubrum	Berkeleyones A-C (**87-89**)	n.s.	USA	143
	Penicillium sp.	Breviones F-H (**90-92**) Sterolic acid (**93**)	5115	E Pacific	145
	Penicillium sp.	Breviones I–K (**94-96**)	5115	E Pacific	144
	Penicillium sp.	Penicilliumin A (**97**)	1300	S China Sea	150

Table 3 (*Contd.*)

PHYLA/ Class/Order	Species	Natural Products (Or Compound Type)	Depth/m	Region	Ref
Fungi	*Phialocephala malorum*	Dihydrotrichodermolide (**98**) Dihydrodemethylsorbicillin (**99**), Phialofurone (**100**)	5059	E Pacific	151
	Trichoderma sp.	Trichoderone (**101**)	n.s.	S China Sea	152
MOLLUSCA **Bivalvia**					
Mytiloida	*Bathymodiolus thermophilus*	Bathymodiolamides A and B (**102, 103**)	1733	Mid-Atlantic Ridge	153
PORIFERA **Demospongiae**					
Astrophorida	*Stelletta* sp.	Bistellettazines A-C (**104-106**) Bistellettazole A (**107**)	90	Australia	158
	Geodia sp.	Franklinolide A (**108**) Franklinolide A methyl ester (**109**) Franklinolides B and C (**110, 111**)	105	Australia	159
Dictyoceratida	*Aplysinopsis digitata*	Aplysinoplides A-C (**112-114**)	150	Japan	160
	Spongia sp.	Heterofibrins A1-A3 and B1-B3 (**115-120**)	125	Australia	161
	Fasciospongia sp.	Fascioquinols A-D (**121-124**) Strongylophorine-22 (**125**) Fascioquinols E and F (**126, 127**)	100	Australia	164
Halichondrida	*Axinella* sp.	14-*O*-Sulfate massadine (**128**) 14-*O*-Methyl massadine (**129**) 3-*O*-Methyl massadine chloride (**130**)	85	Australia	165
	Halichondria sp.	Franklinolides A–C (**108, 110, 111**)	105	Australia	159
	Rhaphoxya sp.	Theonellin isocyanate (**131**) Psammaplysins I, J (**132**, **133**)	90	Guam	16
Haplosclerida	*Neopetrosia proxima*	Neopetrosiquinones A, B (**134, 135**)	140	Jamaica	173
	Petrosia sp.	(−)-Duryne (**136**) (−)-Durynes B–F (**137-141**)	415	Japan	174
	Xestospongia sp.	Alisiaquinones A-C (**142-144**) Alisiaquinol (1**45**)	250-400	Australia	177
Homosclerophorida	*Plakortis angulospiculatus*	23-*nor*-Spiculoic acid B (**146**) Zyggomphic acid B (**147**) 27-*nor*-Zyggomphic acid B (**148**) 22-*nor*-Zyggomphic acid B (**149**) 22,27-*dinor*-Zyggomphic acid B (**150**)	58 62	Caribbean Bahamas	178
	Plakortis halichondrioides	Aromatic metabolites (**151-153**)	91	Bahamas	
	Plakortis sp.	Aromatic metabolites (**154-159**)	96	Guam	179
Lithistida	*Leiodermatium* sp.	Leiodermatolide (**160**)	401	USA	180
	Theonella swinhoei *Theonella cupola*	Mutremdamide A (**161**) Koshikamides C-H (**162-167**)	100-120 90	Palau	187
	Theonella swinhoei	Paltolides A-C (**168-170**)	101	Palau	188
Poecilosclerida	*Clathria* sp.	Mirabilins H–J (**171-173**)	60	Australia	191
	Latrunculia sp.	Citharoxazole (**174**)	103	France	195
	Latrunculia sp.	Dihydrodiscorhabdin B (**175**) Discorhabdin Y (**176**)	230	Alaska	196
	Lissodendoryx sp.	Halichondrin B-1140, 1092, 1020, 1076 (**177-180**)	100	New Zealand	208
	Phorbas sp.	Phorbasins D-F (**181-183**)	65	Australian	209
	Phorbas sp.	Phorbasins G–K (**184-188**)	65	Australia	210
Verongida	*Suberea* sp.	Psammaplysins I, J (**132, 133**)	60	Guam	16

[a]n.s. = not specified.

11 Recent advances in the development of deep-sea derived drugs

Natural product derived drugs account for 50% of the drugs used for the treatment of cancer and over 75% of the drugs used for treating infectious diseases.[156, 212, 213] At the time of writing, six marine-derived drugs have been approved for clinical use for cancer, pain and, HIV (see Table 2), with tens more in different phases of clinical trials, hundreds in preclinical trials and thousands under development.[213, 214] The six approved drugs are the sponge-derived nucleosides cytarabine and vidarabine; the cone snail peptide ziconotide; the complex ascidian alkaloid trabectedin; the antibody-drug conjugate brentuximab vedotin involving a synthetic derivative of the cyanobacterial-derived molluscan metabolite dolastatin; and eribulin mesylate, a synthetic macrocyclic ketone of the marine sponge natural product halichondrin-B.[215, 216]

Table 2. Approved drugs derived from marine natural products:[214]

Year	Compound	Tradename	Source	Compound type	Indication	Company
1969	Cytarabine	Cytosar-U®	Sponge	Nucleoside	Cancer	Bedford, Enzon
1976	Vidarabine	Vira-A®	Sponge	Nucleoside	Antiviral	King Pharmaceuticals
2004	Ziconotide	Prialt®	Cone snail	Peptide	Pain	Elan Corporation
2007	Trabectedin	Yondelis®	Tunicate	Alkaloid	Cancer	Pharmamar
2010	Eribulin mesylate	Halaven®	Deep-sea sponge	Macrocyclic ketone	Cancer	Eisai
2011	Brentuximab vedotin	Adcetris®	Mollusc	Antibody drug conjugate (MM auristatin E)	Cancer	Seattle Genetics

Halichondrin-B is a natural mitotic inhibitor with a unique mechanism of action as a non-taxane microtubule dynamics inhibitor[217, 218] originally isolated by Hirata and Uemura from a 600 kg collection of the black shallow-water sponge *Halichondria okadai* from coastal Japan in 1986.[219] Blunt and Munro later isolated halichondrin-B and a series of other halichondrin derivatives from a 200 kg collection of the unrelated bright yellow, deep-sea Poecilosclerid sponge *Lissodendoryx* sp.,[220] from trawling at >100 m depth off the Kaikoura Peninsula, New Zealand. The deep-sea sponge was found to produce halichondrins in a much greater amount (~10-fold) than any of the shallow-water halichondrin producing sponge species, and a massive 1-tonne scale collection of *Lissodendoryx* sp. was undertaken in 1995 (under Government licence after surveys established there was approx. 300 tonne in the area) to furnish 200 mg of halichondrin B and 300 mg of isohomohalichondrin B for further biological investigation at the time.[221, 222] This, coupled with the pioneering total synthesis of halichondrin-B reported by Kishi and co-workers in 1992,[223] enabled further drug development[224] and although the natural product halichondrin-B eventually proved too toxic for clinical use, eribulin mesylate E7389 (Halaven™), a synthetic truncated analogue of halichondrin-B was successfully brought to market by Eisai in 2010 for the treatment of metastatic breast cancer for patients who have received at least two relevant chemotherapeutic regimens, including an anthracycline and a taxane.[225]

Today, halichondrins have been reported from a range of both shallow- and deep-water sponge species, including by Pettit and co-workers from an Eastern Indian Ocean shallow reef sponge *Phakellia carteri*[226] and a Western Pacific marine sponge *Axinella* sp. collected at 40 m depth,[227] raising the possibility that these highly active compounds are of microbial origin. Furthermore, the 1995 1-tonne collection of deep-sea *Lissodendoryx* sp. continues to provide new halichondrin derivatives as described herein (see *Porifera*, section)[208]. The halichondrin story, elegantly reviewed by Jackson and colleagues in 2009,[228] exemplifies the drug development potential of those deep-sea natural products bearing unusual architectures and unique modes of action.

Conclusions

Deep-sea fauna have yielded an impressive array of novel compounds (Table 1) with exquisite and complex structures and potent (nanomolar) biological activities including the antiprotozoal xenicane diterpenoid, cristaxenicin A (**5**) from the Japanese cnidarian *Acanthoprimnoa cristata* (138 m depth);[85] the cytotoxic chlorinated pyrrolo[4,3,2-de]quinolones, ammosamides A (**64**) and B (**65**) from a Caribbean sediment-derived *Streptomyces* sp. (1618 m depth);[121] the cytotoxic indole diketopiperazines, luteoalbusins A (**70**) and B (**71**) from the South China Sea fungus *Acrostalagmus luteoalbus* (2800 m depth);[137] the highly cytotoxic and structurally unique macrolide, leiodermatolide (**160**) from the Caribbean sponge *Leiodermatium* sp. (618 m depth);[180] and new cytotoxic discorhadbin derivatives (**175** and **176**) from a new species of Alaskan sponge belonging to the genus *Latrunculia* (230 m depth).[196] There have also been new additions to some well known natural product families that have already attracted attention due to their structural complexity and range of biological activities including the rare actinomycete-derived abyssomicins J-L (**67-69**) from 2733 m depth in the South China Sea;[129-131] the benzodiazepine alkaloids, circumdatins K and L (**77** and **78**) from the Pacific sediment-derived fungus *Aspergillus versicolor* (800 m depth);[139] new massadine derivatives (**128-130**) from the Australian sponge *Axinella* sp. (85 m depth);[165] and new sponge-derived psammaplysin derivatives I and J (**132-133**) from 60-90 m depth, Guam.

Most strikingly, deep-sea natural products appear to have a particularly high hit rate regarding biological activity. Herein, 75% of the compounds were reported to possess bioactivity (i.e. 141 of 188 compounds), with almost half (i.e. 81 of 188 compounds) exhibiting low micromolar cytotoxicity towards a range of human cancer cell lines, as found previously.[18] Under 18% of the compounds (33 from 188) were described as either not active or only weakly or moderately active in the bioassays utilised, while the remaining 7% of the compounds (14 of 188) had no biological results reported.

Almost a quarter of the metabolites (24%) reported emanate from Australia, as found previously. However, the main difference in the regional analysis of samples is the marked increase in reports of metabolites from deep-sea sediment sampling from the South China Sea (18%) and the Pacific Ocean (17%, including Guam and Palau) (Fig. 3). Currently, the level of access to manned submersibles and trawling operations in different regions will be the greatest influence on any regional analysis, rather than an indication of the geographical distribution of marine fauna (and their natural products) in deeper water. In addition to using research-class deep-sea sampling equipment, expanded access to submersibles, remotely operated vehicles and trawling technology through collaboration with deep-sea industries is enabling researchers to further explore deep-sea fauna and their natural products.[229, 230]

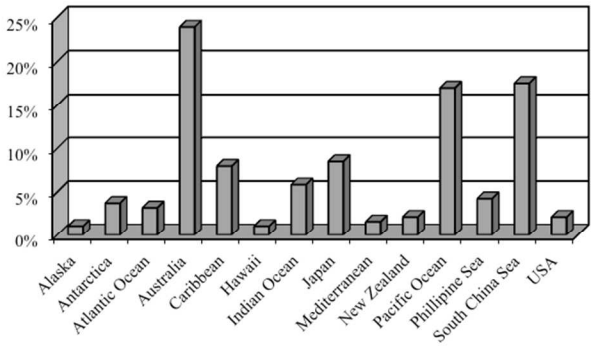


Fig 3. Geographic origins of deep-sea natural products reported since 2008.

Compared to the previous review, where over 50% of the metabolites were found in depths ranging from 100–400 m, the depth profile of the metabolites in this review are more polarised with 44% of the compounds obtained from organisms inhabiting the twilight zone of 50-200 m and 37% originating from organisms found at depths of over 1000 m (Fig. 4, top chart). The latter, which has increased from just 8% in the previous review, may be a reflection of expanded access to deep-sea submersibles and other deep-sea research opportunities enabling further exploration of these unchartered waters. Overall, the depth profile of all reported deep-sea natural products shows that depth is inversely correlated with the number of novel compounds reported (Fig. 4, bottom chart).

Pleasingly there is typically more information provided in recent papers regarding collection and identification of the organisms, although there is still no depth information provided for a small number of papers. The deepest reported sample, from which new natural products have been isolated, is a 10,898 m deep ocean sediment from the Philippine Sea, from which the marine bacterium *Dermacoccus abyssi* was cultured, to give seven novel, cytotoxic compounds, the dermacozines A–G (**29-35**).

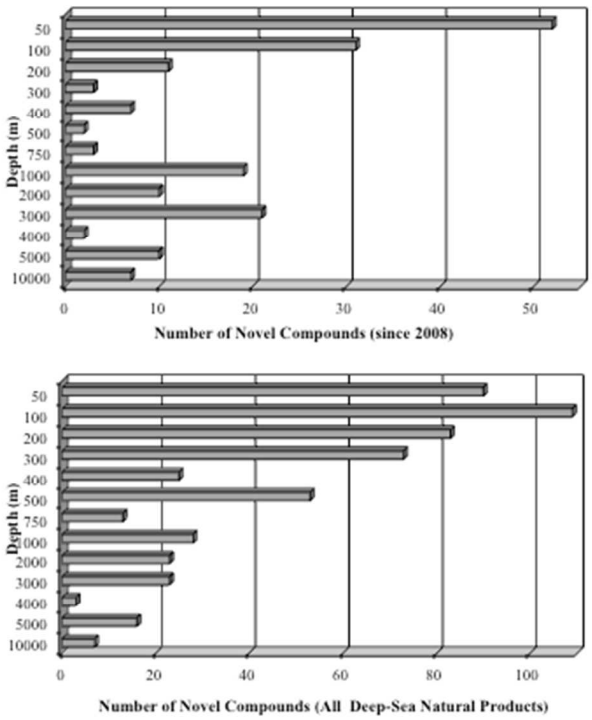


Fig 4. Top chart: Depth profile of novel deep-sea natural products reported since 2008; Bottom chart: All reported deep-sea natural product.

Deep-sea sponges are the largest source of new deep-water metabolites, accounting for over 45% of the metabolites described, with specimens down to 400 m depth (Table 3). Compared to the previous review, there has been a shift to a larger number of microbial metabolites (42% compared to 12% previously), reflecting the different degrees of difficulty in sampling deep-sea macro-invertebrates compared to sampling of deep-sea sediment and subsequent culturing of the microbial flora at sea level. Deep-sea bacteria, accounting for over 25% of the natural products reported, have been cultured from sediment obtained down to 10,898 m depth, while deep-sea fungi, which account for over 17% of the reported metabolites have been cultured from sediment collected down to 5115 m depth. Bryozoa, Cnidarians, Chordata, Echinodermata and Mollusca make up the remainder of the Phyla, including the first examples of deep-sea bryozoan metabolites, the brominated convolutamines I (**1**) and J (**2**) from *Amathia tortusa,*[68] and the first reported deep-sea molluscan metabolites, the bathymodiolamides A (**102**) and B (**103**) from *Bathymodiolus thermophiles.*[153]

Deep-sea natural products represent just a fraction (<2%) of the marine natural products reported to-date,[23] and yet there is already a deep-sea natural product derived drug (Eribulin mesylate) that has advanced to market. This coupled with the high hit rates (~75%) from screening programs indicate that deep-sea natural products are a potentially rich source of structurally diverse, biologically active compounds just waiting to be explored

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Table 3. Deep-sea marine species collected at different depths since 2008.

Depth (m)	Phyla	Species	Depth (m)	Phyla	Species
50	Bryozoa	*Amathia tortusa*	**200**	Chordata	*Aplidium* sp.
	Cnidaria	*Convexella magelhaenica*		Porifera	*Latrunculia* sp.
	Bacteria	*Nocardiopsis* sp.	**300**	Echinodermata	*Holopus rangii*
	Fungi	*Aspergillus* sp.	**400**	Porifera	*Petrosia* sp.
	Porifera	*Stelletta* sp.		Porifera	*Leiodermatium* sp.
	Porifera	*Axinella* sp.	**500**	Fungi	*Penicillium crustosum*
	Porifera	*Rhaphoxya* sp.	**800**	Fungi	*Aspergillus versicolor*
	Porifera	*Theonella cupola*	**1000**	Echinodermata	*Proisocrinus ruberrimus*
	Porifera	*Clathria*		Mollusca	*Bathymodiolus thermophilus*
	Porifera	*Phorbas* sp.		Bacteria	*Bacillus subtilis*
	Porifera	*Plakortis angulospiculatus*		Fungi	*Penicillium* sp.
	Porifera	*Plakortis halichondrioides*	**2000**	Fungi	*Acrostalagmus luteoalbus*
	Porifera	*Plakortis* sp.		Bacteria	*Verrucosispora* sp.
100	Cnidaria	*Acanthoprimnoa cristata*	**3000**	Bacteria	*Escherichia coli*
	Porifera	*Geodia* sp.		Bacteria	*Marinactinospora thermotolerans*
	Porifera	*Spongia (Heterofibria)* sp.		Bacteria	*Pseudonocardia* sp.
	Porifera	*Fasciospongia* sp.		Bacteria	*Streptomyces lusitanus*
	Porifera	*Halichondria* sp.		Bacteria	*Streptomyces* sp.
	Porifera	*Neopetrosia cf. proxima*	**4000**	Bacteria	*Micromonospora* sp.
	Porifera	*Theonella swinhoei*	**5000**	Fungi	*Penicillium* sp.
	Porifera	*Latrunculia* sp.		Fungi	*Phialocephala malorum*
	Porifera	*Lissodendoryx* sp.	**10000**	Bacteria	*Dermacoccus abyssi*
	Porifera	*Aplysinopsis digitata*			
	Porifera	*Aaptos ciliata*			

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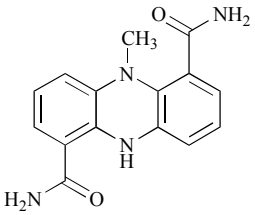

Dermacozine A (10,898 m depth)
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