Marine Bacterial Natural Products

Subjects: Oceanography

Contributor: José Santos

Marine bacterial natural products are molecules produced by marine bacteria through secondary metabolism genes, which can provide them with competitive advantages. Certain natural products can have bioactive effects (e.g. antimicrobial properties) and thus can be used by humans as therapeutics or leads for novel therapeutics.

Keywords: antimicrobials ; anticancer ; antivirals ; drug discovery ; marine natural products ; bioactive bacteria

1. History

Nature has long been the most important source of therapeutics. The use of poultices and mixtures of plant material to treat infections goes back to the early bronze age civilizations[1]. Building on the prior knowledge acquired, early medicine, pharmacology and chemistry started to develop therapeutics by studying nature. For example, extracts of willow bark (genus *Salix*), containing salicylic acid, which was identified to be the bioactive molecule present in the bark in 1828, were already used by Sumerians and Egyptians to treat inflammation and pain. In 1852 acetylsalicylic acid was first synthesised and in 1899, Bayer patented it as aspirin[2]. Ever since then, many terrestrial organisms and in particular plants have been sought for use as natural products. It was only around the 1970s, that attention was first given to the ocean as a source of useful natural products. As the oceans cover most of the Earth's surface, they are home to a substantial portion of the world's biodiversity[3] which lives in distinctive and varied conditions and has evolved through a long period of metabolic adaptations. When exploration of the ocean's biodiversity and metabolic richness began, it resulted in the discovery of thousands of structurally unique bioactive marine natural products[4].

Initially, the exploitation of marine wildlife for natural bioactive products focused on a small number of organisms which included sponges, molluscs, tunicates and macroalgae[5]. These were shown to produce a very diverse range of unique molecular structures, like halogenated terpenes, polyketides and prostaglandins[6][7][8][9]. This diversity of bioactive structures is considered to be part of the defence, survival and predatorial strategies employed by these organisms, such as, for example, sponges, which are sessile, soft-bodied organisms, lacking morphological defences like biological armature or spines[10]. Thus, these organisms appeared to be a great source for the discovery of novel bioactive molecules. However, the bioactive molecules produced by these organisms can be present in quite small amounts. For example, halichondrin B (**1**) (Figure 1), a macrolide first isolated from *Halichondria okadai* that has potent anticancer activity, impeding mitotic division by targeting tubulin[11], is present in concentrations as low as 400 µg per kg wet weight of tissue of *Lissodendoryx* sp.[12]. Due to their low concentrations of bioactive molecules the use of these organisms poses environmental problems, because high quantities of organisms would be needed to produce enough molecules to even begin preclinical trials[13]. Yet, its structure inspired a synthetic analogue, eribulin mesylate, which is now used in breast cancer and lipocarcinoma treatment[14]. As such, sponges, molluscs, tunicates and macroalgae still remain relevant sources of new marine natural products[15].

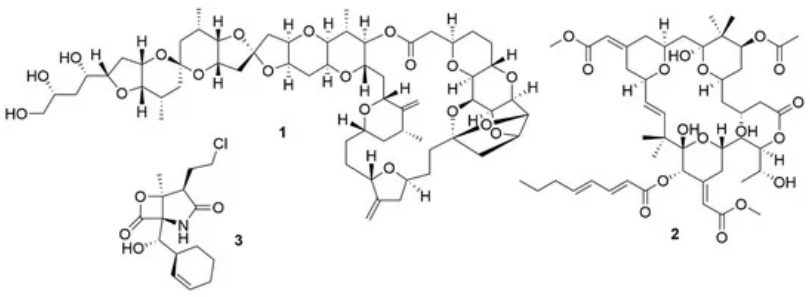

Figure 1. Bioactive metabolites isolated from marine organisms. Halichondrin B (**1**), a macrolide first isolated from *H. okadai* but also present in other sponges. Bryostatin 1 (**2**), which belongs to a family of polyketide macrolides first identified in the marine bryozoan *B. neritina*. Salinosporamide A (**3**), is a proteasome inhibitor isolated from bacteria from the genus *Salinospora* and is in phase III clinical trials for the treatment of multiple myeloma.

The exploitation of other sources of bioactive marine organisms, mainly microorganisms, has also led to the discovery of new promising leads. Indeed, some of the molecules associated with macroorganisms such as sponges, may have their origin in associated microorganisms[16]. This may be the case of bryostatins, found in the marine bryozoan *Bugula neritina*[17]. The bryostatins, exemplified by bryostatin 1 (**2**) are polyketide macrolactones with neurological and anticancer properties that work by modulating the activity of the protein kinase C family and they were first isolated from this bryozoan in 1982[18]. Yet, these macrolactones appear to be synthesised by a group of PKS genes of bacterial origin, indicating that bryostatins are produced by a bacterium[19] [56].

Marine microorganisms, like members of Actinobacteria, Proteobacteria, Firmicutes, Cyanobacteria, fungi and dinoflagellates, have shown to be great reservoirs of bioactive molecules[15]. Yet, even though initial predictions pointed to an immediate increase in the number of natural products discovered with the shift in focus from macroorganisms to microorganisms, this did not occur[20]. However, advances in the isolation of novel taxa, provided a boost in the discovery of novel bioactive molecules. Analysis of the literature reveals an increase in the number of new molecules discovered in all microorganisms from 2014 to 2018[15], with a special emphasis on fungi and bacteria. Members of the genus *Salinospora* (Actinobacteria) are examples of bacteria that lead to the discovery of salinosporamide A (**3**)[21]. This molecule has a potent cytotoxic activity due to a unique functionalisation of the core-fused γ-lactam-β-lactone bicyclic ring, which contributes significantly to its activity[22]. Salinosporamide A is now in phase III clinical trials for the treatment of multiple myeloma under the brand name Marizomib[23].

Although salinosporamide A is the best example of the potential present in bacteria, many novel molecular structures are discovered each year. In fact, in 2016, 179 new natural products of marine bacterial origin were discovered[24], in 2017, the number rose to 242[25] and in 2018 a total of 240 new molecules were reported[15]. The upwards trend seen in the number of discovered molecules and the remarkable chemical diversity displayed, which ranges from peptides, siderophores and polyketides to esters, macrolactones, quinones and terpenes, shows the bacterial potential for the discovery of novel active principles.

2. Antimicrobial Marine Bacterial Natural Products

Bacteria are promising sources for novel antimicrobial natural product discovery. This is primarily due to two factors. One is their variable and malleable metabolism[26] and the other is their competitive pressure for resources against other microbes. Several recent examples of natural products from marine bacteria are provided below. The novel molecule bacicyclin (**4**) (Figure 2), which is a cyclic peptide, was isolated from a *Bacillus* sp. strain BC028 isolated from the common mussel (*Mytilus edulis*)[27]. It displays antibacterial activity against *E. faecalis* and *S. aureus* with minimal inhibitory concentration (MIC) values of 8 and 12 µM, respectively, and can help in the design of analogues with increased antibiotic efficacy[27]. Anthracimycin B (**5**), a polyketide with powerful anti-Gram-positive bacteria activity that was obtained from a marine-derived *Streptomyces cyaneofuscatus* M-169, has expanded the knowledge of how the methyl group at C-2 of anthracimycins plays a role in its antibacterial effect[28]. Taromycin B (**6**), a lipodepsipeptide with potent activity against methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* which was isolated from the marine actinomycete *Saccharomonospora* sp. CNQ-490, provides a promising start for the development of novel antibacterial scaffoldings[29]. Janthinopolyenemycin A (**7**) and B (**8**) are also polyketides and the first examples of molecules of their structural type. Janthinopolyenemycins were isolated from the proteobacterium *Janthinobacterium* spp., strains ZZ145 and ZZ148, and have activity against *Candida albicans*[30]. Streptoseomycin (**9**), a macrolactone isolated from the actinobacterium *Streptomyces seoulensis* A01, has specific activity against microaerophilic bacteria, specially the pathogen *H. pylori*[31]. This restricted activity makes streptoseomycin a good starting point for the discovery of antibiotics for the treatment of *H. pylori* infections. The polyketides ansalactams B (**10**), C (**11**) and D (**12**) are highly modified ansamycins that show weak and mild anti-methicillin-resistant *S. aureus* and were identified in cultures of *Streptomyces* sp. CNH189, isolated from marine sediments. Ansalactams B and D are cyclic polyketides with similarities to ansalactam A. However, ansalactam D shows evidence of an uncommon oxetane ring. Ansalactam C is an open polyketide chain resulting from a Baeyer–Villiger-type oxidation[32]. Micromonohalimanes A (**13**) and B (**14**) are rare halimane-type diterpenoids isolated from the actinobacterium *Micromonospora* sp. WMMC-218. Micromonohalimane A displays a very weak inhibitory effect on methicillin-resistant *S. aureus* while micromonohalimane B displays moderate bacteriostatic activity against it. Xestostreptin (**15**) is a modified diketopiperazine isolated from *Streptomyces* sp. S.4, resulting from the condensation of the aminoacids threonine and alanine[33]. Xestostreptin shows weak activity against the malarial agent *P. falciparum*. Two macrolides, branimycins B (**16**) and C (**17**) were identified from a fermentation of the actinobacterium *Pseudonocardia carboxydivorans* M-227, isolated from deep sea water[34]. Branimycin B shows moderate antibacterial activity against Gram-positive bacteria, while branimycin C displayed moderate antibacterial activity against Gram-negative bacteria.

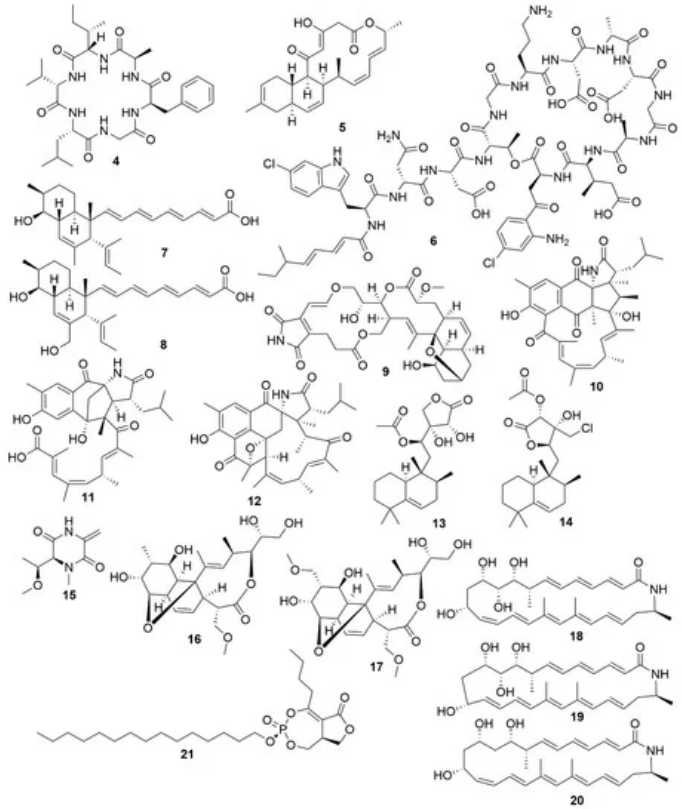

Figure 2. Examples of recently isolated antimicrobial natural products from marine bacteria. Bacicyclin (**4**), a cyclic peptide isolated from a *Bacillus* sp. BC028. Anthramicin B (**5**), a polyketide isolated from *S. cyaneofuscatus* M-169. Taromycin B (**6**), a lipopeptide from *Saccharomonospora* sp. CNQ-490. Janthinopolyenemycin A (**7**) and Janthinopolyenemycin B **(8**). The janthinopolyenemycins are polyketides isolated from two strains of the genus *Janthinobacterium*. Streptoseomycin (**9**), a macrolactone isolated from *S. seoulensis*. Ansalactam B (**10**), a pentacyclic polyketide. Ansalactam C (**11**), an open polyketide unlike ansalactam B. Ansalactam D (**12**), a hexacyclic polyketide. Ansalactams B, C and D were isolated from *Streptomyces* sp. CNH189. Micromonohalimane A (**13**). Micromonohalimane B (**14)**. Micromonohalimanes A and B are terpenes isolated from *Micromonospora* sp. WMMC-218. Xestostreptin (**15**), a diketopiperazine isolated from *Streptomyces* sp. S.4. Branimycin B (**16**) and Branimycin C (**17**) C are macrolides isolated from the deep-sea bacterium *P. carboxydivorans* M-227. Lobosamide A (**18**), Lobosamide B (**19**) and Lobosamide C (**20**) are macrolactams isolated from *Micromonospora* sp. RL09-050-HVF-A. Salinipostin A (**21**), a bicyclic phosphotriester isolated from *Salinispora* sp. RLUS08-036-SPS-B.

Utilizing a genome-assisted discovery strategy, three macrolactams, lobosamides A (**18**), B (**19**) and C (**20**), were isolated from *Micromonospora* sp. RL09-050-HVF-A[35]. Lobosamides A and B showed bioactivity against the microbial agent of African trypanosomiasis, *Trypanosoma brucei* in low concentrations. However, lobosamide C was not bioactive. Schulze and colleagues[36] also identified salinipostins A-K bicyclic phosphotriesters isolated from the actinobacterium *Salinispora* sp. RLUS08-036-SPS-B with potent and selective activity against *P. falciparum*. The salinipostin scaffold considerably differs from any of the known antimalarial compounds, representing a novel lead structure in the development of therapeutics for malaria. Experiments with salinipostin A (**21**), the most bioactive of the 11 salinipostins, indicate that it exhibits growth stage-specific effects and no apparent resistance could be identified in parasite populations. A hybrid peptide-polyketide, mollemycin A (**22**) (Figure 3) was isolated from the marine bacterium *Streptomyces* sp. CMB-M0244 and shows potent antimalarial and broad antibacterial activities[37]. Actinosporin A (**23**) is a glycosilated polyketide which shows antiparasitic activity against *T. brucei* and was isolated from a marine sponge associated *Actinokineospora* sp. EG49[38]. Likewise, actinosporin B, was also isolated but showed no bioactivity, suggesting that actinosporin A is acting selectively against the parasite. The linear lipopetides, gageopeptides A-D (**24**–**27**), gageotetrins A–C (**28**–**30**) and gageostatins A–C (**31**–**33**) were isolated from the marine *Bacillus subtilis* 109GGC020. These lipopetides showed a range of different antimicrobial bioactivities, with gageostatins A, B and C all showing good antimicrobial activity and moderate cytotoxic activity to lung cancer cell line NCI-H23[39]. Gageotetrins A, B and C showed potent antimicrobial bioactivities but not cytotoxic effect on human myeloid leukaemia K-562[40]. Furthermore, gageopeptides A, B, C and D all showed good antifungal and moderate broad antibacterial activity, while not showing cytotoxicity to human myeloid leukaemia K-562 and mouse leukemic macrophage RAW 264.7 cell lines[41].

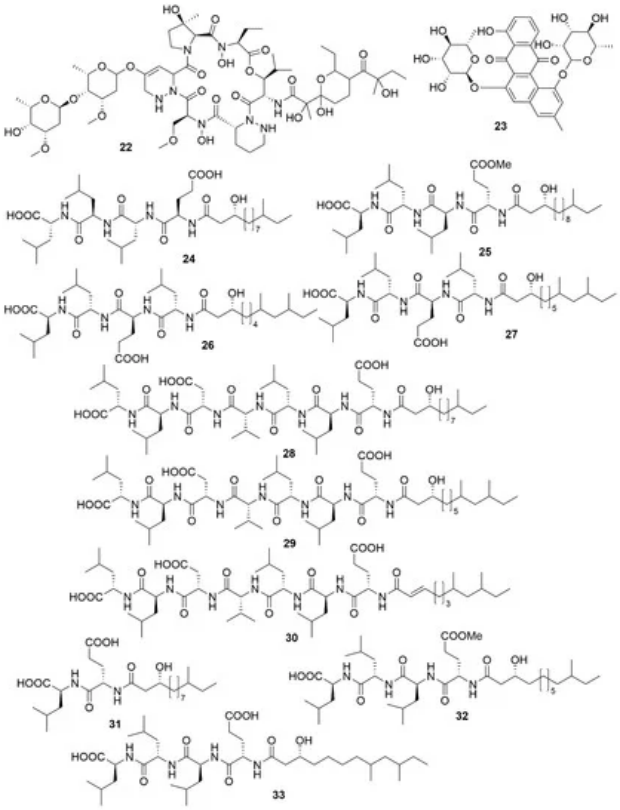

Figure 3. Examples of recently isolated antimicrobial natural products from marine bacteria. Mollemycin A (**22**) is a hybrid peptide-polyketide isolated from *Streptomyces* sp. CMB-M0244. Actinosporin A (**23**), a polyketide isolated from *Actinokineospora* sp. EG49. Gageopeptide A (**24**). Gageopeptide B (**25**). Gageopeptide C (**26**), Gageopeptide D (**27**), Gageotetrin A (**28**). Gageotetrin B (**29**). Gageotetrin C (**30**). Gageostatin A (**31**). Gageostatin B (**32**). Gageostatin C (**33**). The gageopeptides, gageotetrins and gageostatins are linear lipopeptides isolated from *B. subtilis* 109GGC020.

3. Antiviral Marine Bacterial Natural Products

It is estimated that as many as 10^{31} viruses inhabit the oceans[42], with concentrations ranging from 3×10^6 viruses mL^{-1} in deep sea waters to 10^8 viruses mL^{-1} in coastal waters[43], many of which are bacteriophages. Consequently, marine bacteria are subjected to evolutionary pressure to develop defences against viral attacks. As such, marine bacteria may be great reservoirs of antiviral leads.

A number of examples of marine bacterial natural products with antiviral bioactivities have been recently reported. Three novel abyssomicin monomers, neoabyssomicins D (**34**) (Figure 4), E and A2 and two dimers—neoabyssomicins F (**35**) and G (**36**)—were isolated from the marine *Streptomyces koyangensis* SCSIO 5802, with neoabyssomicin D showing moderate anti-herpes simplex virus activity, and neoabyssomicins F and G showing low activity against vesicular stomatitis virus[44]. *Streptomyces* sp. OUCMDZ-3434, isolated from the marine alga *Enteromorpha prolifera*, was shown to produce five new phenolic polyketides[45]. Of these molecules, wailupemycin J (**37**) and (*R*)-wailupemycin K (**38**) proved to be bioactive against the influenza A virus (H1N1). The indolosesquiterpenoids xiamycins C (**39**), D (**40**) and E (**41**) were isolated from the marine-derived *Streptomyces* sp. #HK18, and showed strong inhibitory effect against the coronavirus porcine epidemic diarrhoea virus[46]. As such, xiamycins may provide useful leads in the development of antivirals with broader spectrum activity against other coronaviruses.

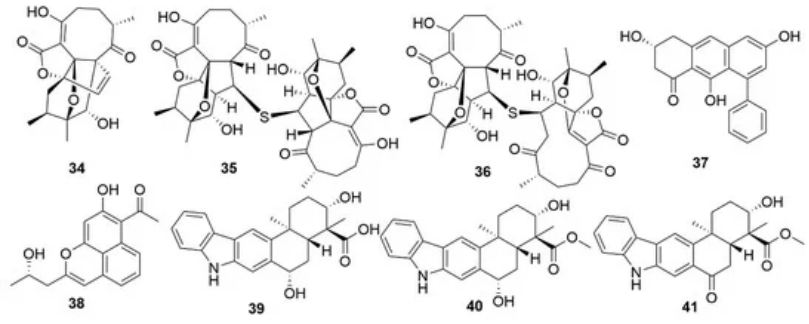

Figure 4. Examples of recently isolated natural products from marine bacteria with antiviral activity. Neoabyssomicin D (**34**). Neoabyssomicin F (**35**) and Neoabyssomicin E (**36**) are polycyclic polyketides isolated from *S. koyangensis* SCSIO 5802. Wailupemycin J (**37**) and (*R*)-wailupemycin K (**38**) are phenolic polyketides isolated from *Streptomyces* sp. OUCMDZ-3434. Xiamycin C (**39**), Xiamycin D (**40**) and Xiamycin E (**41**) were isolated from *Streptomyces* sp. #HK18.

4. Anticancer Marine Bacterial Natural Products

As with antimicrobials, it is ascertained that marine bacteria are great reservoirs for cytotoxic natural products. While salinosporamide A, already mentioned above, is a great example of marine cytotoxic drug discovery [58], every year, novel anticancer bioactive structures are discovered. Actinobacteria, especially those of the genera *Streptomyces* and *Micromonospora*, have been a very prolific source of cytotoxic compounds. There are several recent examples of structures isolated from these bacteria. Dentigerumycin E (**42**) (Figure 5), is a cyclic hexapeptide bearing three piperazic acids and a pyran-bearing polyketide acyl chain, isolated from the marine actinoabcterium *Streptomyces albogriseolus* JB5[47]. It showed moderate cytotoxicity against lung carcinoma A549, colorectal cancer HCT116, breast cancer MDA-MB-231, liver cancer SK-HEP-1 and stomach cancer SNU638 cell lines, while not being cytotoxic to the normal human breast epithelial cell line MCF-10A [84]. Likewise, neothioviridamide (**43**) is a polythioamide cyclic peptide with strong cytotoxicity against human ovarian adenocarcinoma (SKOV-3), malignant pleural mesothelioma (Meso-1) and immortalized human T lymphocyte (Jurkat) cell lines[48]. It was isolated after discovery of a novel biosynthetic cluster (thioviridamide-like biosynthetic gene) in *Streptomyces* sp. MSB090213SC12 by genome mining and heterologous expression of a bacterial artificial chromosome in *Streptomyces avermitilis* SUKA. Three cyclic depsipeptides, rakicidins G-I (**44**–**46**), isolated from the marine actinobacterium *Micromonospora chalcea* FIM 02–523, have potent cytotoxic activity against the human pancreatic cancer cell line PANC-1 and human colon carcinoma cell line HCT-8[49]. Rakicidins G-I differ in the length of their β-hydroxy fatty acid moiety. The 26-membered polyene macrolactam, FW05328-1 (**47**), isolated from *Micromonospora* sp. FIM05328, has potent bioactivity against three cells lines of human oesophageal squamous cell carcinoma (KYSE30, KYSE180 and EC109)[49]. The integration of genomic data in association with nuclear magnetic resonance (NMR) analysis allowed the determination of the stereostructure of neaumycin B, a cytovaricin-ossamycin-oligomycin macrolide, that was isolated from *Micromonospora* sp. CNY-010[50]. Neaumycin B (**48**) has shown potent anti-human glioblastoma cell line U87 activity but it is unstable. Through genetic manipulation of promoters, six new polyketides, pactamides A–F, were isolated from *Streptomyces pactum* SCSIO 02999. Pactamides B-F showed low to moderate cytotoxic activity against human glioblastoma cell line (SF-268), human breast cancer cell (MCF-7), human large-cell lung carcinoma (NCI-H460) and human liver cancer cell (HepG2) while pactamide A (**49**) showed potent activity[51]. Two cyclodepsipeptides, streptodepsipeptides P11A (**50**) and P11B (**51**), were isolated from *Streptomyces* sp. P11-23B and displayed potent anti-proliferative bioactivity in four cell lines of human glioblastoma (U251, U87-MG, SHG-44 and C6)[52]. Research with *Streptomyces* sp. strain THS-55 yielded four new antimycin alkaloids, antimycins E-H (**52**–**55**), which showed potent cytotoxic effect on HPV-transformed human cervix adenocarcinoma (HeLa) cells and moderate anti-proliferative activity in human cervical cancer cell SiHa, human myelogenous leukaemia cell line K562, and human leukaemia cell line HL-60[53]. However, cytotoxic effects were shown in healthy human embryonic kidney cells 293T. In a knockout mutant of *Streptomyces* sp. CHQ-64, two new alkaloids, geranylpyrrol A and piericidin F (**56**), were discovered[54]. Of these, piericidin F showed potent anti-proliferative activity against several cancer cell lines, including HeLa, human acute promyelocytic leukaemia (NB4) and human lung carcinoma (A549 and H1975).

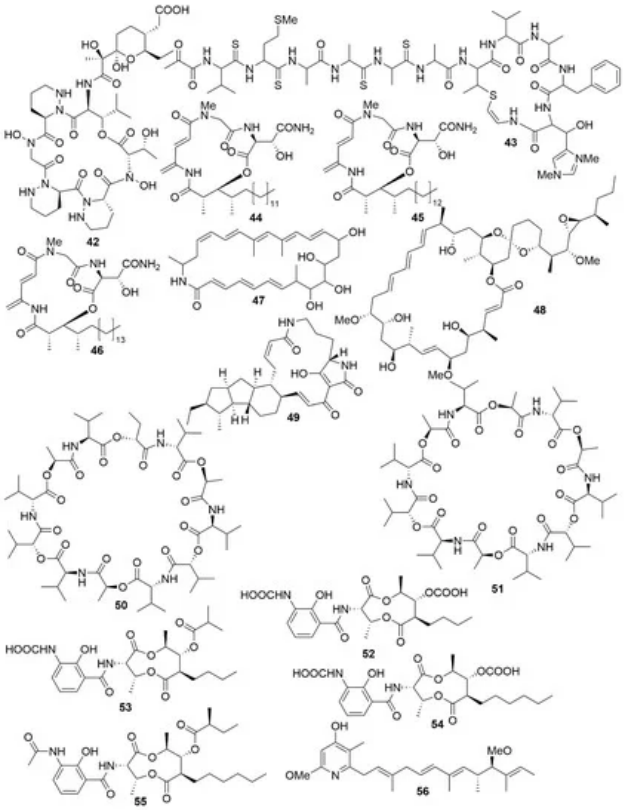

Figure 5. Examples of recently isolated cytotoxic natural products from marine bacteria. Dentigerumycin E (**42**), a cyclic hexapeptide isolated from *S. albogriseolus* JB5. Neothioviridamide (**43**), a cyclic peptide from *Streptomyces* sp. MSB090213SC12. Rakicidin G (**44**), Rakicidin H (**45**) and Rakicidin I (**46**) are cyclic depsipeptides isolated from *M. chalcea* FIM 02–523. FW05328-1 (**47**), a polyene macrolactam isolated from *Micromonospora* sp FIM05328. Neaumycin B (**48**), a macrolide from *Micromonospora* sp. CNY-010. Pactamide A (**49**), a polyketide isolated from *S. pactum* SCSIO 02999. Streptodepsipeptide P11A (**50**) and Streptodepsipeptide P11B (**51**) are cyclodepsipeptides from *Streptomyces* sp. P11-23B. Antimycin E (**52**), Antimycin F (**53**), Antimycin G (**54**) and Antimycin H (**55**) are alkaloids isolated from *Streptomyces* sp. THS-55. Piericidin F (**56**) is an alkaloid isolated *Streptomyces* sp. CHQ-64.

Two new chromodepsipeptides, neo-actinomycin A (**57**) (Figure 6) and neo-actinomycin B (**58**) were isolated from a marine-derived *Streptomyces* sp. IMB094[55]. They showed strong cytotoxic effect on human colorectal carcinoma cell line HCT116 and human lung carcinoma cell line A549.

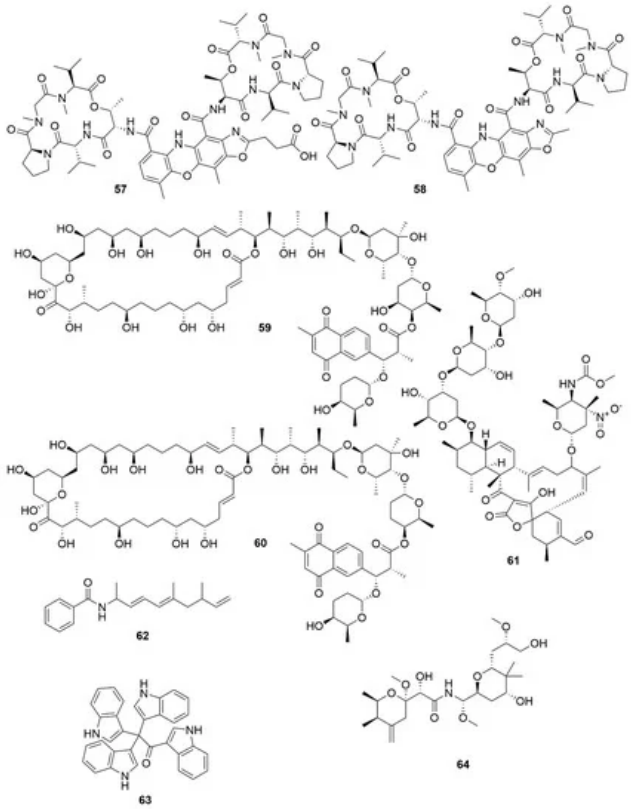

Figure 6. Examples of recently isolated cytotoxic natural products from marine bacteria. Neo-actinomycin A (**57**) and Neo-actinomycin B (**58**) are chromopeptides from *Streptomyces* sp. IMB094. PM100117 (**59**) and PM100118 (**60**) are macrolides isolated from *S. caniferus* GUA-06-05-006A. Lobophorin I (**61**), a spirotetronate isolated from *Streptomyces* sp. 1053U.I.1a.3b. Haliamide (**62**), a hybrid of a polyketide synthase from *H. ochraceum* SMP-2. Tetra(indol-3-yl)ethenone (**63**), an indole isolated from *P. denitrificans* BBCC725. O-Demethylpederin (**64**), a polyketide with a tetrahydropyran-core from *Labrenzia* sp. PHM005.

Two new macrolides, PM100117 (**59**) and PM100118 (**60**) were isolated from a marine *Streptomyces caniferus* GUA-06-05-006A[56]. Both PM100117 and PM100118 show potent cytotoxic effect on human breast adenocarcinoma (MDA-MB-231), human lung carcinoma (A549) and human colorectal carcinoma (HT-29) cell lines. The study of a symbiotic *Streptomyces* sp. (strain 1053U.I.1a.3b) of cone snails lead to the isolation of two lobophorins, H and I[57]. Lobophorins are a large family of spirotetronates with antimicrobial and cytotoxic bioactivities. Of these, lobophorin I (**61**) showed potent cytotoxic activity against human T-cell leukaemia cell line CEM-TART.

Besides Actinobacteria, other marine bacterial phyla are also proving to be relevant for the isolation of novel bioactive molecules. As a result of a hybrid polyketide synthase (PKS) and non-ribosomal peptide synthetase (NRPS) biosynthesis, haliamide (**62**) was isolated from a marine myxobacterium, *Haliangium ochraceum* SMP-2, and shows moderate cytotoxicity towards the HeLa cell line[58]. A novel cytotoxic indole, tetra(indol-3-yl)ethenone (**63**) was isolated from the marine proteobacterium *Pseudovibrio denitrificans* BBCC725[59]. Tetra(indol-3-yl)ethenone has moderate cytotoxicity to human lung carcinoma cell line A549 and the mouse fibroblasts cell line L929. Another marine proteobacterium, *Labrenzia* sp. PHM005 produced a new tetrahydropyran-core polyketide and analogue of pederin[60]. This novel pederin, 18-O-demethylpederin (**64**) shows potent anti-proliferative activity against four cell lines: human lung carcinoma cell line A549, human colon adenocarcinoma cell line HT-29, human breast adenocarcinoma cell line MDA-MB-231 and human pancreas adenocarcinoma cell line PSN-1.

All these examples show the great potential displayed by marine bacteria which reveals the extraordinary chemical diversity of their metabolism. When analysing the bioactive bacteria and their taxonomic groups, Actinobacteria proved to be the most prolific and diverse producers (Tables 1–3). However, ignoring other less studied phyla denies access to valuable chemical diversity, which is essential in the drug discovery process. Moreover, marine bacterial metabolites have shown to have potential as treatment in both human and animal pathologies. Thus, marine bacterial natural products have great significance under the “One Health” framework.

Table 1. Recently isolated bioactive molecules from marine bacteria with antimicrobial properties.

Molecule	**Bacterial Origin**		**Chemical Structure**	**Bioactivity**	
	Strain Identification	**Phyla**		**Effect**	**Target**
Actinosporin A	*Actinokineospora* sp. EG49.	Actinobacteria	Polyketide	AP	TBB
Lobosamide A	*Micromonospora* sp. RL09-050-HVF-A	Actinobacteria	Polyketide	AP	TBB
Lobosamide B	*Micromonospora* sp. RL09-050-HVF-A	Actinobacteria	Polyketide	AP	TBB
Micromonohalimane A	*Micromonospora* sp. WMMC-218	Actinobacteria	Polyketide	AB	MRSA
Micromonohalimane B	*Micromonospora* sp. WMMC-218	Actinobacteria	Polyketide	AB	MRSA
Branimycin B	*Pseudonocardia carboxydivorans* M-227	Actinobacteria	Polyketide	AB	G+

Branimycin C	*Pseudonocardia carboxydivorans* M-227	Actinobacteria	Polyketide	AB	G-
Taromycin B	*Saccharomonospora* sp. CNQ-490	Actinobacteria	Peptide	AB	MRSA; VRE
Salinipostin A	*Salinispora* sp. RLUS08-036-SPS-B	Actinobacteria	Polyketide	AP	PF
Anthracimycin B	*Streptomyces cyaneofuscatus* M-169	Actinobacteria	Polyketide	AB	G+
Streptoseomycin	*Streptomyces seoulensis* A01	Actinobacteria	Polyketide	AB	H. pylori
Mollemycin A	*Streptomyces* sp. CMB-M0244	Actinobacteria	Peptide-polyketide	AB/AP	Broad spectrum/PF
Ansalactam B	*Streptomyces* sp. CNH189	Actinobacteria	Polyketide	AB	MRSA
Ansalactam C	*Streptomyces* sp. CNH189	Actinobacteria	Polyketide	AB	MRSA
Ansalactam D	*Streptomyces* sp. CNH189	Actinobacteria	Polyketide	AB	MRSA
Xestostreptin	*Streptomyces* sp. S.4	Actinobacteria	Peptide	AP	PF
Bacicyclin	*Bacillus* sp. BC028	Firmicutes	Peptide	AB	G+
Gageopeptide A	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Gageopeptide B	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Gageopeptide C	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Gageopeptide D	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Gageotetrin A	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AF	Broad spectrum
Gageotetrin B	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AF	Broad spectrum
Gageotetrin C	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AF	Broad spectrum

Gageostatin A	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Gageostatin B	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Gageostatin C	*Bacillus subtillis* strain 109GGC020	Firmicutes	Peptide	AB/AF	Broad spectrum
Janthinopolyenemycin A	*Janthinobacterium* spp. ZZ145 and ZZ148	Proteobacteria	Polyketide	AF	CA
Janthinopolyenemycin B	*Janthinobacterium spp.* ZZ145 and ZZ148	Proteobacteria	Polyketide	AF	CA

AB = Antibacterial, AF = Antifungal AP = Antiparasitic; CA = *Candida albicans*; G+ = Gram-positive bacteria; G- = Gram-negative bacteria; MRSA = Methicillin-resistant *S. aureus*; PF = *Plasmodium falciparum*; TBB = *Trypanosoma brucei;* VRE = Vancomycin-resistant *E. faecium*

Table 2. Recently isolated bioactive molecules from marine bacteria with antiviral properties.

Molecule	**Bacterial Origin**		**Chemical Structure**	**Bioactivity**
	Strain Identification	**Phyla**		**Target**
Neoabyssomicin D	*S. koyangensis* SCSIO 5802	Actinobacteria	Polyketide	HSV
Neoabyssomicin F	*S. koyangensis* SCSIO 5802	Actinobacteria	Polyketide	VSV
Neoabyssomicin G	*S. koyangensis* SCSIO 5802	Actinobacteria	Polyketide	VSV
Wailupemycin J	*Streptomyces* sp. OUCMDZ-3434	Actinobacteria	Polyketide	H1N1
R-wailupemycin K	*Streptomyces* sp. OUCMDZ-3435	Actinobacteria	Polyketide	H1N1
Xiamycin C	*Streptomyces* sp. #HK18	Actinobacteria	Polyketide	PEDV
Xiamycin D	*Streptomyces* sp. #HK18	Actinobacteria	Polyketide	PEDV
Xiamycin E	*Streptomyces* sp. #HK18	Actinobacteria	Polyketide	PEDV

HSV = Herpes simplex virus; VSV = vesicular stomatitis virus; H1N1 = influenza A virus; PEDV = porcine epidemic diarrhea virus

Table 3. Recently isolated bioactive molecules from marine bacteria with cytotoxic properties.

Molecule	**Bacterial Origin**		**Chemical Structure**	**Bioactivity**
	Strain Identification	**Phyla**		**Target**

Dentigerumycin E	*Streptomyces albogriseolus* JB5	Actinobacteria	Peptide	HCT116; A549; MDA-MB-231; SK-HEP-1; SNU638
Neothioviridamide	*Streptomyces* sp. MSB090213SC12	Actinobacteria	Peptide	SKOV-3; Meso-1; Jurkat
Rakicidin G	*Micromonospora chalcea* FIM 02-523	Actinobacteria	Peptide	PANC-1; HCT-8
Rakicidin H	*Micromonospora chalcea* FIM 02-523	Actinobacteria	Peptide	PANC-1; HCT-8
Rakicidin I	*Micromonospora chalcea* FIM 02-523	Actinobacteria	Peptide	PANC-1; HCT-8
FW05328-1	*Micromonospora* sp. FIM05328	Actinobacteria	Polyketide	KYSE30; KYSE180; EC109
Neaumycin B	*Micromonospora* sp. CNY-010	Actinobacteria	Polyketide	U87
Pactamide A	*Streptomyces pactum* SCSIO 02999	Actinobacteria	Polyketide	SF-268; MCF-7; NCI-H460; Hep-G2
Pactamide B	*Streptomyces pactum* SCSIO 02999	Actinobacteria	Polyketide	SF-268; MCF-7; NCI-H460; Hep-G2
Pactamide C	*Streptoyces pactum* SCSIO 02999	Actinobacteria	Polyketide	SF-268; MCF-7; NCI-H460; Hep-G2
Pactamide D	*Streptomyces pactum* SCSIO 02999	Actinobacteria	Polyketide	SF-268; MCF-7; NCI-H460; Hep-G2
Pactamide E	*Streptomyces pactum* SCSIO 02999	Actinobacteria	Polyketide	SF-268; MCF-7; NCI-H460; Hep-G2
Pactamide F	*Streptomyces pactum* SCSIO 02999	Actinobacteria	Polyketide	SF-268; MCF-7; NCI-H460; Hep-G2
Streptodepsipeptide P11A	*Streptomyces* sp. P11-23B	Actinobacteria	Peptide	U251; U87; SHG-44; C6

Streptodepsipeptide P11B	*Streptomyces* sp. P11-23B	Actinobacteria	Peptide	U251; U87; SHG-44; C6
Antimycin E	*Streptomyces* sp. THS-55	Actinobacteria	Polyketide	HeLa; SiHa; K562; HL-60; 293T
Antimycin F	*Streptomyces* sp. THS-55	Actinobacteria	Polyketide	HeLa; SiHa; K562; HL-60; 293T
Antimycin G	*Streptomyces* sp. THS-55	Actinobacteria	Polyketide	HeLa; SiHa; K562; HL-60; 293T
Antimycin H	*Streptomyces* sp. THS-55	Actinobacteria	Polyketide	HeLa; SiHa; K562; HL-60; 293T
Piericidin F	*Streptomyces* sp. CHQ-64	Actinobacteria	Polyketide	HeLa; NB4; A549; H1975
Neo-actinomycin A	*Streptomyces* sp. IMB094	Actinobacteria	Peptide	HCT116; A549
Neo-actinomycin B	*Streptomyces* sp. IMB094	Actinobacteria	Peptide	HCT116; A549
PM100117	*Streptomyces caniferus* GUA-06-05-006A	Actinobacteria	Polyketide	A549; MDA-MB-231; HT-29
PM100118	*Streptomyces caniferus* GUA-06-05-006A	Actinobacteria	Polyketide	A549; MDA-MB-231; HT-29
Lobophorin I	*Streptomyces* sp. 1053U.I.1a.3b	Actinobacteria	Polyketide	CEM-TART
Haliamide	*Haliangium ochraceum* SMP-2	Myxobacteria	Polyketide	HeLa
Tetra(indol-3-yl)ethanone	*Pseudovibrio denitrificans* BBCC725	Proteobacteria	Polyketide	L929; A549
18-O-demethylpederin	*Labrenzia* sp. PHM005	Proteobacteria	Polyketide	A549; HT-29; MDA-MB-231; PSN-1;

HCT116 = HCT-8 = HT-29 = human colorectal carcinoma; A549 = H1975 = human lung carcinoma; MDA-MB-231 = MCF-7 = human breast adenocarcinoma; SK-HEP-1 = Hep-G2 = human hepatic adenocarcinoma; SNU638 = human gastric carcinoma; SKOV-3 = human ovarian adenocarcinoma; Meso-1 = malignant pleural mesothelioma; Jurkat = immortalized human T lymphocyte; PANC-1 = PSN-1 = human pancreas adenocarcinoma; KYSE30 = KYSE180 = EC109 = human

oesophageal squamous cell carcinoma; U251 = U87 = SHG-44 = C6 = SF-268 = human glioblastoma cell line; HeLa = SiHa = human cervix adenocarcinoma; K562 = HL-60 = NB4 = human leukaemia cell line; 293T = human embryonic kidney cells; L929 = mouse fibroblasts cell; CEM-TART = human T-cell leukaemia

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