

## **Marine-derived antimicrobial molecules from the sponges and their associated bacteria**

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### **Abstract**

Antimicrobial resistance (AMR) is one of the leading global health issues that demand urgent attention. Very soon the world will have to bear the consequences of increased drug resistance if new anti-infectives aren't pumped into the clinical pipeline in a short period. This presses on the need for novel chemical entities, and the marine environment is one such hotspot to look for. The Ocean harbours a variety of organisms, of which from this aspect, "Sponges (Phylum Porifera)" are of particular interest. To tackle the stresses faced due to their sessile and filter-feeding lifestyle, sponges produce various bioactive compounds, which can be tapped for human use. The sponges harbour several microorganisms of different types and in most cases; the microbial symbionts are the actual producers of the bioactive compounds. This review describes the alarming need for the development of new antimicrobials and how marine sponges can contribute to this. Selected antimicrobial compounds from the marine sponges & their associated bacteria have been described. Additionally, measures to tackle the supply problem have been covered, which is the primary obstacle in marine natural product drug discovery.

**Keywords:** sponge-associated microbes, chemical ecology, marine natural products, antibiotic resistance, antimicrobials

## **1. Introduction**

The discovery of certain microbes making antagonistic metabolites in the form of natural antibiotics toward other microbes brought about a transforming change in modern medicine (Schlatter and Kinkel 2014). As signalling agents at sub-biocidal concentrations, natural antibiotics are secondary metabolites, playing an essential role in microbial defence (Andersson and Huges 2014). They are drugs administered to treat infectious diseases and bring about this outcome by interfering with the crucial steps of the metabolic pathways in pathogens (Leekha et al. 2011). The breakthrough discovery of Penicillin by Alexander Fleming in 1928 was a starting point of the natural product antibiotic studies (Hutchings et al. 2019). Known as the ‘Golden Age of Antibiotics’, 1940 to 1960 was a sparkling period in antibiotic discovery (Katz and Baltz 2016). Many antibiotics were discovered during this period. However, the disheartening fact is that almost all the antibiotics developed so far have lost the game to the emerging resistant bacteria (Rather et al. 2017). One emerging global health and developmental threat, Anti-microbial resistance (AMR) demands a multisectoral approach to tackle the present situation. The transformation of pathogens into superbugs in globally connected ecosystems is rendering antibiotics ineffective (World Health Organization 2021). It also makes the treatment of infections like pneumonia, tuberculosis, etc. challenging (World Health Organization 2020). The best available antibiotics against MDR bacteria-carbapenems and third-generation cephalosporins have also lost the battle with superbugs (World Health Organization 2017). AMR is predicted to claim 10 million lives annually by 2050, imposing an economic burden of 100 trillion USD (O’Neill 2014). Improper use of antibiotics in terms of self-medication or therapy interruption and the extensive antibiotic usage in livestock farming as growth promoters are the leading causes that drive the emergence of multidrug-resistant pathogens (Rather et al. 2017).

## **2. Demand for new antimicrobials**

Though an increase in the development of resistant pathogenic strains has been observed, the number of antibiotic molecules in the pipeline is not increasing (Fair and Tor 2014). Out of the thirty-two antibiotics in clinical development that target the priority pathogens, WHO in 2019 classified only six as innovative. This depicts that the clinical pipeline of new antimicrobials is dry (World Health Organization 2021). Large pharmaceutical companies are turning away from research and development in antibiotics (Spellberg 2014). The cost factor is the primary reason, as antibiotic drugs fetch far fewer investment returns in comparison to other classes of drugs e.g, anti-hypertensive, etc. (Lewis 2013). The economic constraint impedes any antibiotic development programme as drug developers are reluctant to pump money into the R&D process (Renwick and Mossialos 2018). The

short duration of the antibiotic treatment further hampers revenue generation (Brogan and Mossialos 2013; Darrow et al. 2018). According to an estimate, if new drugs aren't developed by 2050, the world will have to bear the consequences of no antibiotic treatment (Rolain et al. 2016). Antibiotics with a novel mode of action and low rates of resistance development are the current requirement, this being the target of more than 70% of global projects (Theuretzbacher 2020).

### **3. Why turn towards the marine source?**

Covering about three-quarters of the earth's surface, the marine environment is home to many flora and fauna (Sutton et al. 2017; Barzkar et al. 2019). Variable physical parameters such as light, pressure, temperature, and nutrient conditions of the ocean challenge the marine living resource for producing complex bioactive compounds. These marine secondary metabolites are different from their terrestrial counterparts with high potency as an important characteristic due to the dilution factor of the ocean (Lindequist 2016; Wu et al. 2019; Paul and Ritson-Williams 2008). Since life originated in the sea and existed thrice as long as terrestrial life, marine life is evolutionarily far more diverse than its terrestrial counterpart (Blasiak et al. 2020). The marine secondary metabolites perform a wide range of functions. They protect the organisms from harmful UV radiations and other challenging physical conditions, protect them from predators and pathogens, help target the prey and also allow them to communicate with each other (Newman and Cragg 2020). Compounds of different chemical classes eg. Peptides, alkaloids, terpenes, polyketides, etc have been reported from marine organisms (Carroll et al. 2019; Shinde et al. 2019). A widely unexplored repository of living resources, marine biodiversity is a treasure attracting the pharmaceutical industries for drug discovery and other applications (Calado et al. 2018). Since the discovery of spongothymidine and spongouridine from the Caribbean sponge *Tethya crypta* by Bergmann et al. in 1950, many natural products from different marine sources have been isolated. With over 35,000 compounds discovered, the marine environment is a promising pool of novel entities for any drug discovery program (Carroll et al. 2020; Ghareeb et al. 2020; Antanasov et al. 2021; Carroll et al. 2021). During the five years from January 2016 to December 2016, 7547 new marine natural products have been reported (Carroll et al. 2022). Considering novel entities from marine invertebrates, 15,442 new metabolites were reported from 1990-2019. Phylum Porifera contributed 47.2% (2695) of the 5630 new compounds from 2010-2019 (Calado et al. 2022). Recently the depsipeptide from marine ascidian *Aplidium albicans*, Plitidepsin (Dehydrodemnin B) was found to be active against SARS-CoV-2 with 20 times more potency than Remdesivir (White et al. 2021). With a turnover of almost 400 million dollars, marine pharmaceutical products bagged the highest market share value in the 2020 European marine biotechnology sector (Absolute Report 2020). Many new and effective antimicrobial drugs

have been developed from natural products, especially the ones of marine origin (Indraningrat et al. 2016; Mehbub et al. 2016; Newman and Cragg 2016; Pye et al. 2017). In 2020, 1407 new compounds from marine sources were reported (Caroll et al. 2022). Fig 1 shows the natural products of marine origin available in the market.

The present pandemic of COVID-19 caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) necessitates the importance of obtaining new antiviral drugs and marine natural products can be an effective pool to screen for novel entities. Marine sponges also contribute to the secondary metabolite library being screened against the novel SARS-CoV-2 in recent in silico studies. Chhetri et al. 2022 have reported the antiviral activity of three compounds, Homofascaplysin A, (+)-aureol, and bromophycolide A to inhibit SARS-CoV-2 replications without any toxic activity toward human airway epithelial cells. Two of these three compounds, Homofascaplysin A and (+)-aureol have been reported from marine sponges. A study in 2021 by S. S. Elhady et al. mentions that the scalarane sesterterpenes from the sponge *Hyrtios erectus*, have potential SARS-CoV-2 inhibitory activity. The compound, esculetin-4 carboxylic acid ethyl ester was isolated from the marine sponge *Axinella cf. corrugata* (Lira et al. 2007). This group reported the inhibition potential of this compound against SARS-CoV (Severe acute respiratory syndrome coronavirus) 3CL protease and replication in Vero cells using an in-vitro assay. Further in 2020, by molecular docking studies, Vijayraj et al. showed the inhibitory potential of this compound against SARS-CoV-2 along with Hemigeran B isolated from the marine sponge *Hamigeran taragaensis* (Vijayraj et al. 2020). Another sponge metabolite, Ilimaquinone from the sponge *Hippospongia metachromia* (Luibrand et al. 1979), was a promising candidate targeting the crucial protein of SARS-CoV-2 by a computational dynamics study (Surti et al. 2020). Pseudotheonamide C and D from the marine sponge *Theonella swinhoei* are known to be serine protease inhibitors (Nakao et al. 1999). Virtual screening and molecular docking studies showed the inhibitory potential of these metabolites against SARS-CoV-2 (Gentile et al. 2020).

#### **4. The Sponge and its microbiome – A unique repository of diverse secondary metabolites**

Sponges are sessile freshwater and marine invertebrates widespread in tropical, temperate and polar habitats (Van Soest et al. 2012). Owing to the various microbial communities they harbour inside them, marine sponges are an excellent example of the holobiont concept (Thomas et al. 2016; Moitinho-Silva et al. 2017). Microbes from 39 different phyla and a candidate phyla are found to be associated with marine sponges (Pita et al. 2018). Microbial associates ensure the persistence of their sponge host by the various functional roles played by them eg. nutrient cycling, photosynthesis, and production of vitamins and secondary metabolites (Cardenas et al. 2019). Due to the challenging

conditions of the marine environment, marine sponges compared to their terrestrial counterparts are required to produce bioactive compounds for their successful survival and defence (Gogineni and Hamann 2018). Along with the low molecular weight antibacterial compounds, sponges are also known to produce proteins that can target microbes (Thakur et al. 2003). About 200 new molecules are reported from marine sponges every year, making them a treasure box for discovering novel therapeutic molecules (Ancheeva et al. 2017; Rane et al. 2014; Zhang et al. 2017). Selected antimicrobial compounds from sponges and sponge-associated bacteria have been described in Table number 1. Also when mentioning the novelty of the marine natural products discovered, Sponges and Cnidarians are noteworthy (Qi and Ma 2017; Blunt et al. 2018; Carroll et al. 2020).

## **5. Roles of associated microbes in the production of bioactive marine compounds**

In the marine world, predators, microbial pathogens, and fouling organisms are constantly on the look to attack the sponges. Sponges are exposed to various pathogenic microbes due to their filter-feeding nature. The lower rates of infections observed, even after such exposure; prove the potency of the sponge's chemical defences (Ruetzler 2003; Rohde et al. 2015; Thomas et al. 2006; Hernández-Delgado et al. 2008; Futch et al. 2011). In most of the cases, the chemical defence of the sponge host can be attributed to different bioactive compounds produced by its microbial partners (Lackner et al. 2017; Wilson et al. 2014). Environments that are nutrient-poor and antagonistic, such as marine sponges, demand the microbes living here to produce secondary metabolites to deal with the harsh conditions (Mearns-Spragg et al. 1998; Selvin et al. 2012). The symbionts are also exposed to pathogens, toxins, and incoming foreign DNA along with the sponge host. To deal with this, additional defensive functions are taken up by the microbes. This includes CRISPR-Cas systems to deal with viruses and toxin-antitoxin systems, and restriction modification systems to deal with foreign DNA (Thomas et al. 2010; Slaby et al. 2017; Horn et al. 2016). Sponges also have to deal with predation and the microbiome comes to the rescue. For example, cyanobacterial symbionts from the sponge *Lamellodysidea herbacea* produce compounds that deter fish feeding (Unson and Faulkner 1993). The bioactive compounds produced by the sponge microbiome are known to exhibit diverse activities eg. antimicrobial, antiviral, allelopathic, cytotoxic, and antipredatory (Florez et al. 2015; Taylor et al. 2007; Blunt et al. 2017; Pawlik 2011). Sponge symbionts are known to synthesize enzyme complexes such as Polyketide synthases (PKS) and Non-ribosomal peptide synthetases (NRPS) that are involved in the synthesis of many secondary metabolites (Rawlings 2001; Marahiel et al. 1997). Overall the sponge-associated microbes are a goldmine for exploring novel antimicrobials.

## 6. Selected antimicrobials from sponge and sponge-associated bacteria

### 6.1. Vidarabine

Gaining fame as one of the first successful antiviral compound to be licensed in 1977, Acyclovir now replaces this antibiotic. Its toxicity and poor solubility brought about this outcome. However, Vidarabine deserves special mention. A purine nucleoside analogue isolated from the sponge *Cryptotethya crypta*; this compound shows activity against Herpes simplex virus (HSV), Cytomegalovirus and Varicella Zoster virus (VZV) (Paintsil and Cheng 2009). Ara-A or Vidarabine, with improved antiviral activity, is a synthetic analogue of spongouridine (Privat de Garilhe and De Rudder 1964). In 1964, Privat de Garilhe and De Rudder first described the antiviral activity of this compound. The use of this compound for the treatment of Herpes encephalitis and other herpes infections sometimes occurring in neonates was confirmed by Whitley in 1976 (Field and Clercq 2004). Later, Acyclovir (Zovirax) was found to be a better alternative (Shepp et al. 1986; Whitley et al. 1980) for treating herpes virus infections. Nevertheless, the importance of Vidarabine is still reflected in its ability to inhibit acyclovir-resistant HSV and VZV (Kamiyama et al. 2001; Shiraki et al. 1990). Additionally, in the case of plaque reduction assays, Vidarabine was found to be 3-5 fold more active than Cidofovir (Vistide) against the vaccinia and cowpox viruses (Hilfinger et al. 2006). Though discontinued in the US, it is still used for ophthalmologic operations in the European Union (Mayer et al. 2010).

### 6.2. Mycalamide A and Mycalamide B

Mycalamide A and Mycalamide B are antiviral compounds derived from a New Zealand sponge belonging to *Mycale* sp. The in-vitro antiviral activity of these was first mentioned by Perry et. al. in 1988 (Perry et al. 1988) and 1990 (Perry et al. 1990) respectively. Moreover, these compounds were also found to have antitumor activity (Burres and Clement 1989). Both of these inhibited protein synthesis in a cell-free lysate of rabbit reticulocytes (Burres and Clement 1989). Also, in-vitro and in-vivo activities against murine coronavirus A59 have been reported (Perry et al. 1990). Burres and Clement described the mechanism of action of Mycalamide A and Mycalamide B in 1989. Here they showed that these compounds inhibited incorporation of [<sup>3</sup>H] leucine into protein when brome mosaic virus was used as an RNA substrate in lysed rabbit reticulocytes. The crude organic solvent extract of *Mycale* sp. containing just 2% Mycalamide A showed activity against the A59 coronavirus. Also at a concentration of 5ng/disc, Mycalamide A was active against *Herpes simplex* Type 1 and Polio Type 1 virus. A study by Hideto Fukui et. al. 1997 also reports Mycalamide A to show activity against VZV. Hagiwara et. al. 2010 reported four analogues of Mycalamide A that

inhibit the multiplication of the influenza virus by binding to its nucleoprotein (Hagiwara et al. 2010). Using molecular docking and molecular dynamics simulation studies, Demerdash et al. 2021 studied a group of thirty-four Mycalamide and related congeners structurally related to Pederin, for their binding activity against the main protease of SARS-CoV-2 and observed promising results (Demerdash et al. 2021).

### 6.3. Andrimid

Widely diverse in its origin, Andrimid was confirmed to be a peptide antibiotic having anti-bacillus activity. The marine source of this compound was the *Hyatella sp.* sponge extract. When a homogenate of the same sponge was studied, bacterial isolate M22-1, belonging to the genus *Vibrio* was isolated. The same compound was produced by culturing this bacterium in marine agar (Oclarit et al.1994). Another source of this compound comes from the marine bacterium *Pseudomonas fluorescens* wherein it was found to be active against MRSA (Methicillin-resistant *Staphylococcus aureus*) (Needham et al. 1994). Widespread in delta-Proteobacteria, (Oclarit et al. 1994; Graff et al. 2013; Wietz et al. 2010) this antibiotic shows a wide spectrum of antibacterial activity towards Gram-positive and Gram-negative bacteria (Singh et al. 1997). Wietz et al. 2010 studied the antibacterial activity of this compound further, wherein it was found to inhibit bacterial pathogens like *Bacillus cereus*, *Salmonella enteritidis*, *Yersinia enterocolitica*, *Yersinia ruckeri*, *Vibrio harveyi* and *Vibrio vulnificans* (Wietz et al. 2010). The likely explanation for the widespread occurrence of this antibiotic is Horizontal Gene Transfer (Fischbach et al. 2008).

### 6.4. Trisindoline

Responsible for the antibacterial, anti-biofilm and cytotoxic activity of *Callyspongia siphonella* crude extracts, these two compounds, 5-bromotrisindoline and 6-bromotrisindoline have a significant role to play in the development of new anti-infective agents (El-Hawary et al. 2019). By combining bioactivity-guided fractionation and LC-HRESIMS (Liquid chromatography-high resolution electrospray ionization mass spectrometry) assisted chemical investigation of this red sea sponge, El-Hawary et al. 2019 claimed the isolation of these two antibacterial brominated oxindole alkaloids for the first time from a natural source with other known metabolites (El-Hawary et al. 2019). In this study, 5-bromotrisindoline and 6-bromotrisindoline inhibited *S. aureus* with a MIC of 8 and 4µg/ml respectively. Also, *B. subtilis* was inhibited by 5-bromotrisindoline and 6-bromotrisindoline with an MIC of 16 and 4µg/ml respectively. A previous report by Kobayashi et al. in 1994 mentions the isolation of Trisindoline from the Okinawan marine sponge *Hyrtios altum*-associated bacterium of *Vibrio sp* (Kobayashi et al. 1994). Trisindoline showed activity against *E.coli*, *Bacillus subtilis* and

*Staphylococcus aureus* (Kobayashi and Kitagawa 1994; Kobayashi et al. 1994; Braekman and Daloz 2004).

#### 6.5. Aurantoside K

Isolated from the marine sponge of *Melophlus* sp., Aurantoside K showed inhibitory activity towards a broad range of pathogenic fungi. It inhibited wild-type *C. albicans* and Amphotericin B (AmB) resistant *C. albicans* with a minimum inhibitory concentration (MIC) value of 1.95 and 31.25mg/L respectively. It was also active against the pathogenic yeast *Cryptococcus neoformans* at a concentration of 100µg/disc showing a clear inhibition zone of 14mm diameter. Also at the same concentration (100µg/disc), Aurantoside K inhibited *A. niger*, *Penicillium* sp., *R. sporangia* and *Sordaria* sp. with zones of inhibition of 28, 21, 31 and 29mm respectively (Kumar et al. 2012).

Fig. 2 shows the chemical structures of some antimicrobial compounds from sponge and sponge-associated bacteria.

### 7. PM181104 – An emerging wonder drug

Obtained by the fermentation of the microorganism belonging to *Kocuria* sp., PM181104 is a potent thiazolyl cyclic peptide antibiotic showing antibacterial activity against MRSA and several other bacterial pathogens. The *Kocuria* sp. culture has been isolated from the marine sponge *Spirastralla inconstans* var. *digitata* from PalkBay, Tamil Nadu, India. The novel purified compound PM181104 (Molecular formula: C<sub>69</sub>H<sub>66</sub>N<sub>18</sub>O<sub>13</sub>S<sub>5</sub> and molecular weight 1514amu) has been characterized by HPLC, MS, UV, IR and NMR (Mahajan et al. 2007). Fig. 3 shows the chemical structure of PM181104. The antibiotic PM181104 is a potent inhibitor of Gram-positive bacteria and is known to inhibit bacterial protein synthesis at the translational level. Structural relationship studies of this antibiotic compound with some key peptide antibiotics depict its binding to 23s rRNA of the 50S ribosomal subunit (Mahajan et al. 2011).

#### 7.1. In-Vitro activity of PM181104

This compound PM181104 was tested against 261 test organisms including Vancomycin-resistant and Vancomycin-sensitive *Enterococci*, *Staphylococcus epidermidis*, *Bacillus* sp., 17 Gram-negative strains and most importantly Methicillin-resistant and methicillin-sensitive *S. aureus*. This antibiotic's inhibition of *S. aureus* is worth mentioning, both resistant and sensitive strains with a MIC range of 0.008 to 2.048 µg/ml and an MIC<sub>90</sub> value of 0.064 µg/ml which depicts its potent inhibitory activity. This compound was also effective against Linezolid-resistant strains of *S. aureus* and *S. aureus* carrying the *cfr* gene. Also against *S. epidermidis*, this compound showed a MIC range of 0.008 to 1.024 µg/ml and a MIC<sub>90</sub> value of 0.128 µg/ml. Also in the case of VRE and VSE strains,



PM181104 showed good potential with a MIC range of 0.004 to 1.024  $\mu\text{g/ml}$  and an MIC<sub>90</sub> value of 0.016  $\mu\text{g/ml}$ . It also showed good activity against the clinical strain of *Enterococci* and *Bacillus* strains, though it did not show any activity against fungi or Gram-negative bacteria. This compound was found to be non-toxic up to 100 $\mu\text{g/ml}$  on mammalian cell lines (Lung fibroblast cells WI-38) (Mahajan et al. 2013).

Daptomycin and Linezolid are the present drugs of choice for treating MRSA infections. But the increasing cases of resistance to these antibiotics alarm the need for developing novel chemical entities with antibacterial activity (Mutnick et al. 2003; Skiest 2006) and PM181104 is one of these emerging antibiotics with outstanding potential, particularly against drug-resistant non-treatable pathogens.

## 7.2. In-Vivo activity of PM181104

In the case of general-purpose efficacy testing models of disseminated septicemia, wherein mice were treated intraperitoneally with a lethal dose of MRSA strain E710, the compound PM181104 showed 100% protection at a dose of 5mg/kg. In the case of anti-infective activity of PM181104 for organ or tissue-specific infections in skin abscess or lung infection model, PM181104 proved promising. Its efficacy was comparable to the standard antibiotic Linezolid in some models. In the case of treating the kidney infection model, PM181104 was comparable to the standard antibiotics Linezolid at 25mg/kg and Vancomycin at 150mg/kg. This promising in-vivo activity translates to the development and use of PM181104 as an anti-infective therapeutic agent (Mahajan et al. 2013). Significant characteristics of this antibiotic are depicted in Fig. 4.

## 8. Hindrances in marine natural product development

Even though the marine environment has been an origin of a vast number of structurally diverse bioactive metabolites, (Newman and Cragg 2016; Pye et al. 2017; Blunt et al. 2017; Blunt et al. 2018) very few of them have been approved for clinical use. The supply issue is the main reason most marine natural product drugs do not make it to the counter. This even hinders the availability of the drug to be used for clinical trials. With regards to marine organisms, their distribution is uneven and the biomass available is limited. This hampers further studies and the development of drugs, even though many compounds of pharmacological importance have been isolated from different marine organisms (Proksch et al. 2002). For example, to obtain 1g of ET-743, which has anti-cancer properties, around one metric tonne of *E. turbinata* has to be harvested (Mendola 2000). Even after the availability of the X-ray analysis configurations, in the case of (+)Merochlorin A, an MRSA active tetracyclic chlorinated mero-sesquiterpene; the absolute configurations for a total synthesis

took an additional seven years (Brandstätter et al. 2019). The case is more problematic for Halichondrin B, a cytotoxic polyketide. After harvesting 1 metric tonne of the sponge *Lissodendoryx sp.*, only 300 mg of two Halichondrin analogue mixtures can be obtained. If the drug is launched in the market, the requirement would be around 1-5kg per year. It translates to harvesting 3000 to 16000 metric tonnes of sponge biomass annually which is a hard-to-achieve task, not to mention the environmental damage that can be caused (Ollivera 2000). Lack of efficacy (43%) and drug toxicity (33%) have been the principal causes of molecules getting withdrawn from clinical trials (Schuster et al. 2005). It has been hypothesized that the microbiome of the invertebrates is the source of many bioactive metabolites. Such microbial symbionts are crucial in producing many marine invertebrate natural products (Piel 2009). But when these symbionts are not capable of growing outside their hosts, i.e when they are obligatory, a major roadblock sets in (Kwan 2018).

## **9. Chemical ecology-driven bioprospecting**

Along with the constant availability of the source organisms being a major impediment (Hart et al. 2000), chemical variation within the organism itself poses a further challenge (Page et al. 2005). Predation, space constraints leading to competition and epibiont controls are some of the stressors which require many invertebrates, including sponges to have chemical defences. Habitats with high competition and feeding pressures demand more of the destructive chemicals. Other factors such as life-history strategies, non-native species and the time of the year may also play a role. Hence the species collected from the very same location might show a variation in the metabolites obtained. This indicates that chemical ecology-driven bioprospecting is a way to tackle this problem (Deshpande and Thakur 2020). De. Caralt et. al., 2013 have shown chemical variation in the sesquiterpenoids with medicinal value (avarol and derivatives) from the sponge *Dysidea avara*. This group studied the relationship of chemical variability with external factors such as seasonality and interaction with neighbours and reproductive stages as internal factors. Their findings suggested that, depending on the nature of their neighbours, sponges can enhance the accumulation or, production of the bioactive compounds in their peripheral zone. Also, brooding periods showed the highest concentrations of avarol (De. Caralt et al. 2013) Another example of the geographic variation in secondary metabolite production is the sponge *Mycale hentscheli*. Even though this sponge is found all over New Zealand's exclusive economic zone, the cytotoxic compound Peloruside A is produced only by a specific population growing in Pelorus Sound (Page et al. 2005).

## 10. What can be done to resolve the supply issue?

Even though the supply problem is a major hurdle in any marine natural product research and development, various measures have been considered to tackle the same. (Fig. 5.)

### 10.1. Chemical Synthesis

Chemical synthesis of pharmacologically active compounds is one of the options, but the complex molecular structures make the job more challenging. Also, in this case, the final yield obtained is meagre, making it economically unfeasible. Nevertheless, success has been obtained in the case of total synthesis. An example is the painkilling  $\omega$ -conotoxin MVIIA (SNX-111) (Generic name Ziconotide) from the marine mollusc *Conus magnus*. It can be obtained in large amounts by synthesis due to its peptide nature (Ollivera 2000). Also, isolated from the sponge, *Halichondria okadai* in 1986, Eribulin mesylate (Halaven) is a synthetic analogue of Halichondrin B. Halaven is used for metastatic breast cancer treatment and is a microtubule depolymerising agent (Dybdal-Hargreaves et al. 2015). A total synthesis requiring 60 steps solved the supply issue for this drug (Austad et al. 2013; Melvin et al. 2013).

### 10.2. Partial Synthesis

When there is a chemical similarity between the desired drug and a related metabolite, partial synthesis becomes a favourable option. In the case of ET-743, the chemical similarity of its structure to Safracin B, a metabolite of *Pseudomonas fluorescens* has proved beneficial (Ikeda et al. 1983). This paved the way for PharmaMar to successfully develop ET-743 by a semisynthetic process beginning with Cyanosafracin B, an antibiotic produced by *Pseudomonas fluorescens* on fermentation (Ikeda et al. 1983; Cuevas et al. 2000). Puupehedione was isolated from the Verongid sponge (Hamman et al. 1993) and displayed anti-tumour, anti-angiogenic, antimicrobial and immunomodulatory activities (Martínez-Poveda et al. 2017). To ensure enough supply for detailed studies, semi-synthesis from the natural product sclareolide was attained through 7 steps (Martínez-Poveda et al. 2017).

### 10.3. Heterologous expression of biosynthetic gene clusters (BGCs)

Another upcoming approach to resolve the marine natural product supply issue is the heterologous expression of biosynthetic gene clusters (BGCs). Success has been achieved in the case of compounds like polyketides, non-ribosomal peptide-polyketide and isoprenoids (Zhang et al. 2011). The halophilic myxobacterium *Haliangium ochraceum* SMP-2 was a source of Haliangicin, the first marine myxobacterial antibiotic (Fudou et al. 2001). A 10-fold enhancement in the production of

Haliangicin was observed when its biosynthetic gene cluster was expressed heterologously in *Myxococcus xanthus* (Sun et al. 2016).

#### 10.4. Mariculture

Mariculture is another option where marine organisms can be cultured and then harvested for use. In the case of the tunicate *E. turbinata* which is a source of the antitumor compound ET-743 and the bryozoan *Bugula neritina* which produces Bryostatins, progress has been made. Hence this technique holds a promising opportunity in the future (Mendola 2000; Mutter and Wills 2000). Also, the Mariculture of the sponge species *Negombata magnifica* producing Latrunculin B, an actin polymerization inhibitor was reported by Bergman et. al. in 2011.

#### 10.5. Fermentation

When a microbe is the source of the desired natural product, fermentation comes to the rescue. The desired quantity of Salinosporamide A for clinical trials was made available by fermentation. Scientists at San Diego Nereus Pharmaceuticals in collaboration with Industrial Research Limited (IRL), New Zealand brought about this outcome. This was the first time a marine-sourced microbe was fermented on a large scale (Jensen et al. 2007).

### 11. Tackling other challenges

Automated data collection technology could recognize high biodiversity zones and the sample collection from places inaccessible to humans can be done by remotely operated vehicles (Hurst et al. 2016). Using novel techniques for isolation, purification and characterization of compounds along with exploration and sampling of new organisms would help to increase the drug discovery rate (Kasanah and Triyanto 2019). Applying high throughput screening methods to identify new marine leads can significantly reduce the cost and time required for conventional screening programs (Mishra et al. 2008). Another alternative to discover new leads and resolve the supply issue is function-oriented synthesis (FOS). This considers the structure-activity relationship to enhance the activity and simplify the structure (Liu et al. 2018; Gao et al. 2020). Sustainable production methods like Aquaculture help protect the marine ecosystem and avoid the use of toxic chemicals (Leal et al. 2013; Vlachou et al. 2018). Directing the isolation of molecules in parallel to bacterial culturing is crucial. This gets difficult when stimulation is required, even though the symbiont has the desired machinery to produce more than 20 different molecules. The particular pathways must be switched on as the molecules remain “cryptic entities” (Udwary et al. 2007; Walsh and Fischbach 2010). A deeper understanding of the sponge/tunicate-microorganism intricate relationships is necessary. Thorough knowledge of these symbiotic interactions will lead to better simulation of these processes

in a laboratory setting. This will promote the production of novel metabolites and enhanced biosynthetic yields. Molecular genetics' tools are the key to unlocking the secrets in marine natural product research. This may help suggest new speculations for the biosynthetic pathways of such molecules, particularly the amino acid-containing natural products. This may also help in producing a structurally diverse range of biosynthetic natural products through coordination between gene clusters from sponge, tunicate, and bacteria metagenomes. Molecular genetics, genome mining of the whole genome sequences (WGS) of the actinomycetes, and analytical spectrometry with the application of Synthetic biology etc. may unfold these mysteries for an inexhaustible supply of novel natural products and their translation into effective therapeutics (McCauley 2020).

## **12. Conclusion & way forward**

With the emergence of resistant bacteria on the rise, antimicrobial resistance has become a significant health issue worldwide. Along with making the treatment of infectious diseases difficult, it poses a substantial economic burden on the patients. This problem if not paid urgent attention to, might claim a million lives soon. Hence it is the need of the hour to search for unique chemical entities with novel modes of action. But to the dismay, not many new antimicrobials are pumped into the clinical pipeline. The cost factor is the primary reason for big pharma turning away from antibiotic research and development. Nevertheless, adequate measures must be taken to tackle this issue and the marine biota can come to the rescue. The marine environment is a largely unexplored reserve of novel secondary metabolites. Challenging ocean conditions demand marine organisms to have unique chemical defences in the form of bioactive compounds. Marine sponges (Phylum Porifera) are one such example. They are sessile invertebrates harbouring various microbial symbionts within them. The sponge and its microbiome form a unique repository with different natural products having various effective therapeutic properties. With several compounds in clinical trials and on the market, sponges have showcased their exceptional potential. However, the journey of an emerging drug from the ocean to the drug store is extremely challenging, with the supply problem being one of the major hindrances. Potential solutions to this problem have been stated in this article. Various measures must be taken to solve the underlying bottlenecks in commercializing a compound. Unexplored areas of the ocean have to be dwelled into for sampling unique biota. Novel techniques can be used to isolate previously unknown compounds. Chemical ecology-driven bioprospecting should be considered to avoid the non-availability of the desired compound. Finally, new biosynthetic pathways must be activated and the intricate relationships between the invertebrate and its microbial symbionts need to be understood deeply.

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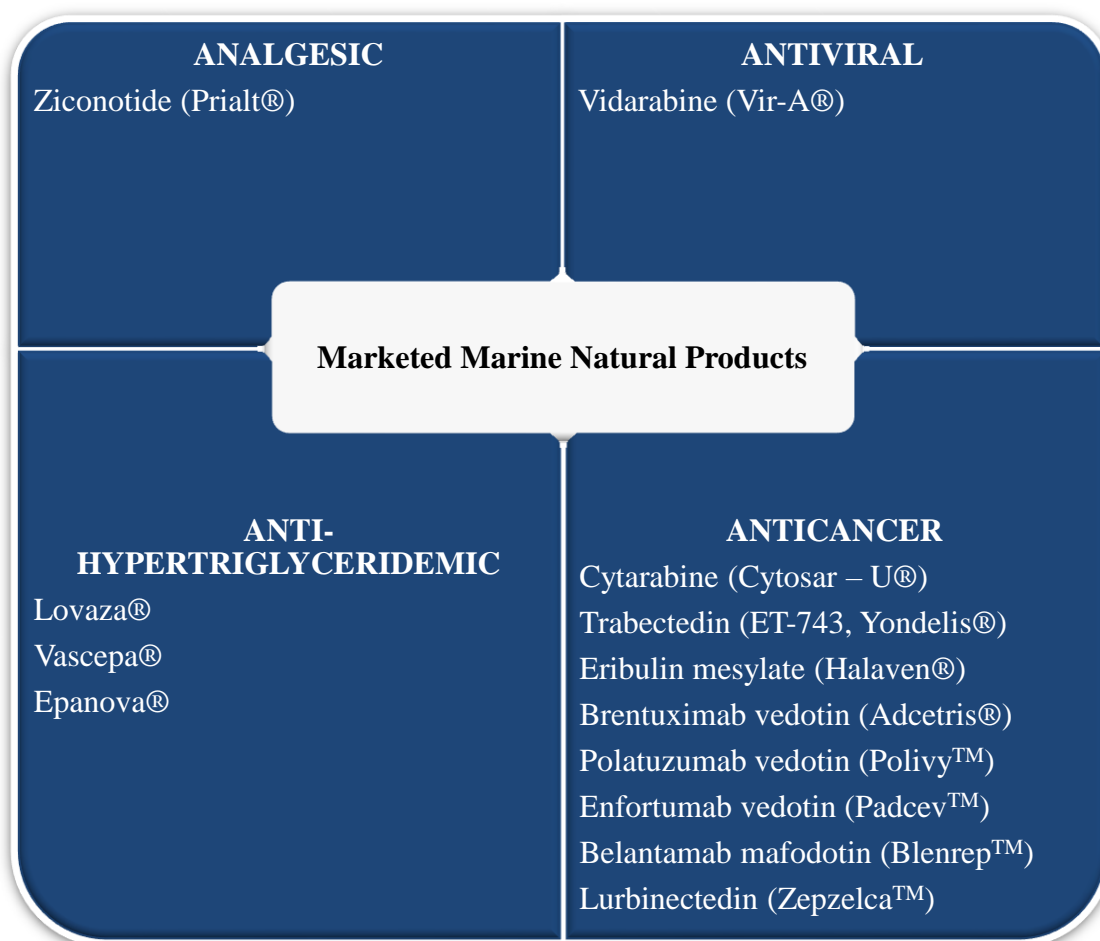
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**Table 1 Selected examples of antimicrobial compounds from sponge and sponge associated bacteria**

Sr. No	Compound	Source	Active against	Reference
<b>Antibacterials</b>				
1	Pseudoceroxime B	<i>Pseudoceratina sp</i>	MRSA <sup>a</sup> (MIC 5.2µM)	(Chen et al. 2020)
2	Myrindole A	<i>Myrmekioderma sp.</i>	<i>E. coli</i> (MIC 37.5µM) and <i>B. subtilis</i> (MIC 18.5µM)	(Moosmann et al. 2021)
3	3-(3,5-dichloro-4-hydroxyphenyl) propanoic acid	<i>Streptomyces coelicolor</i> (LY001) associated with <i>Callyspongia siphonella</i>	<i>E. coli</i> (MIC 16µg/ml) and <i>S.aureus</i> (MIC 32µg/ml)	(Shaala et al. 2020)
4	Xishaeleganin B	<i>Dactylospongia elegans</i>	<i>S. aureus</i> (MIC 1.5µg/ml) <i>S. pyogenes</i> (MIC 1.5µg/ml) and <i>E. faecium</i> (3µg/ml)	(Chen et al. 2022)
5	Macfarlandin D	<i>Chelonaplysilla sp.</i>	<i>M. tuberculosis</i> (1.2±0.4µg/ml)	(Oliveira et al. 2020)
<b>Antifungals</b>				
6	Poecillastrosides D and E	<i>Poecillastra compressa</i>	<i>A. fumigatus</i>	(Calabro et al. 2017)
7	Haliscosamine	<i>Haliclona viscosa</i>	<i>C. albicans</i> (0.4-0.8µg/ml) <i>C. tropicalis</i> (0.4-0.8µg/ml) <i>C. neoformans</i> (0.2-0.4µg/ml)	(El-Amraoui et al. 2013)
8	Ceratinine N	<i>Pseudoceratina arabica</i>	<i>C. albicans</i> (MIC 16µg/ml)	(Shaala and Youssef 2020)
9	Cyclo (L-Phe-trans-4-OH-L-Pro) and Cyclo (L-Phe-cis-4-OH-D-Pro)	<i>Streptomyces coelicolor</i> (LY001) associated with <i>Callyspongia siphonella</i>	<i>C. albicans</i> (MIC 32µg/ml)	(Shaala et al. 2020)
10	(-)-Ageloxime D	<i>Agelas maurutiana</i>	<i>C. neoformans</i>	(Yang et al. 2012)

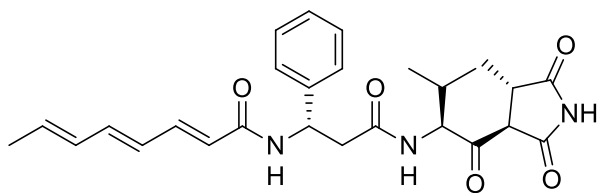
Antivirals				
11	Microspinosamide	<i>Sidonops microspinosa</i>	HIV <sup>b</sup> (EC <sub>50</sub> 0.2µg/ml)	(Rashid et al. 2001)
12	4-methylaaptamine	<i>Aaptos aaptos</i>	HSV-1 <sup>c</sup> (EC <sub>50</sub> 2.4µM)	(Souza et al. 2006)
13	Dragmacidin F	<i>Halicortex sp.</i>	HSV-1 (EC <sub>50</sub> 95.8µM) and HIV-1 (EC <sub>50</sub> 0.91µM)	(Cutignano et al. 2000)
14	Raspadiene	<i>Raspailia bouryesnaultae</i>	Herpes Simplex Virus Type I (Inhibited replication of strain KOS by 83% and 29R by 74% )	(Lhullier et al. 2019)
15	Ansellone J	<i>Phorbas sp.</i>	HIV-1 (In vitro and In-vivo HIV-1 latency reversal)	(Wang et al. 2022)
Antimalarials				
16	Tsitsikammamine C	<i>Zyzya sp.</i>	<i>P. falciparum</i> 3D7 (IC <sub>50</sub> 13nM) and <i>P. falciparum</i> Dd2 (IC <sub>50</sub> 18nM)	(Davis et al. 2012)
17	Bisaprasin	<i>Aplysinella rhax</i>	<i>P. falciparum</i> 3D7 (29 ± 6µM)	(Oluwabusola et al. 2020)
18	Friomaramide	<i>Inflatella coelosphaeroides</i>	<i>P. falciparum</i> (Blocks >90% liver stage parasite development at 6.1µM)	(Knestrick et al. 2019)
19	Kaimanol and Saringosterol	<i>Xestospongia sp.</i>	<i>P. falciparum</i> 3D7 (IC <sub>50</sub> 359 and 0.250nM)	(Murthihapsari et al. 2021)
20	(-)-Ircinianin	<i>Ircinia wistarii</i>	<i>P. falciparum</i> (IC <sub>50</sub> 25.4µM)	(Majer et al. 2022)

<sup>a</sup>MRSA: Methicillin-resistant *Staphylococcus aureus*; <sup>b</sup>HIV-Human Immunodeficiency Virus; <sup>c</sup>HSV-1: Herpes Simplex Virus type I

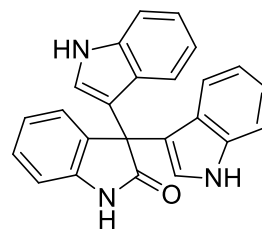


**Fig. 1: Marine natural products in the market**

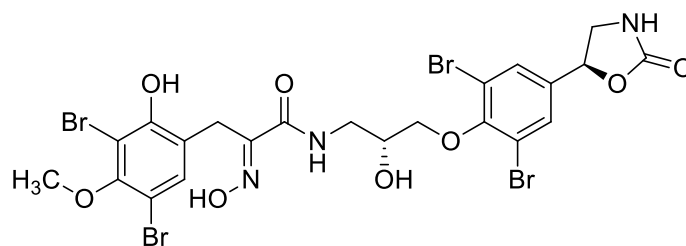
Antibacterials



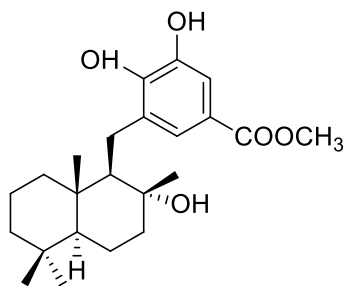
Andrimid



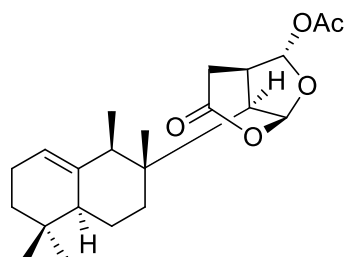
Trisindoline



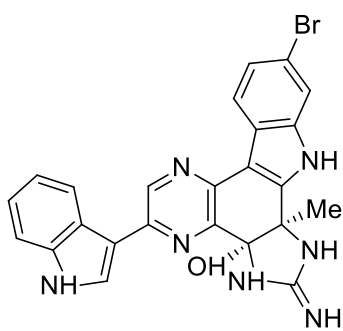
Pseudoceroxime B



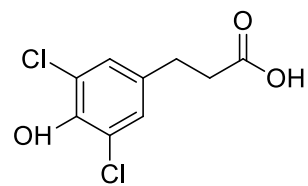
Xishaeleganin B



Macfarlandin D

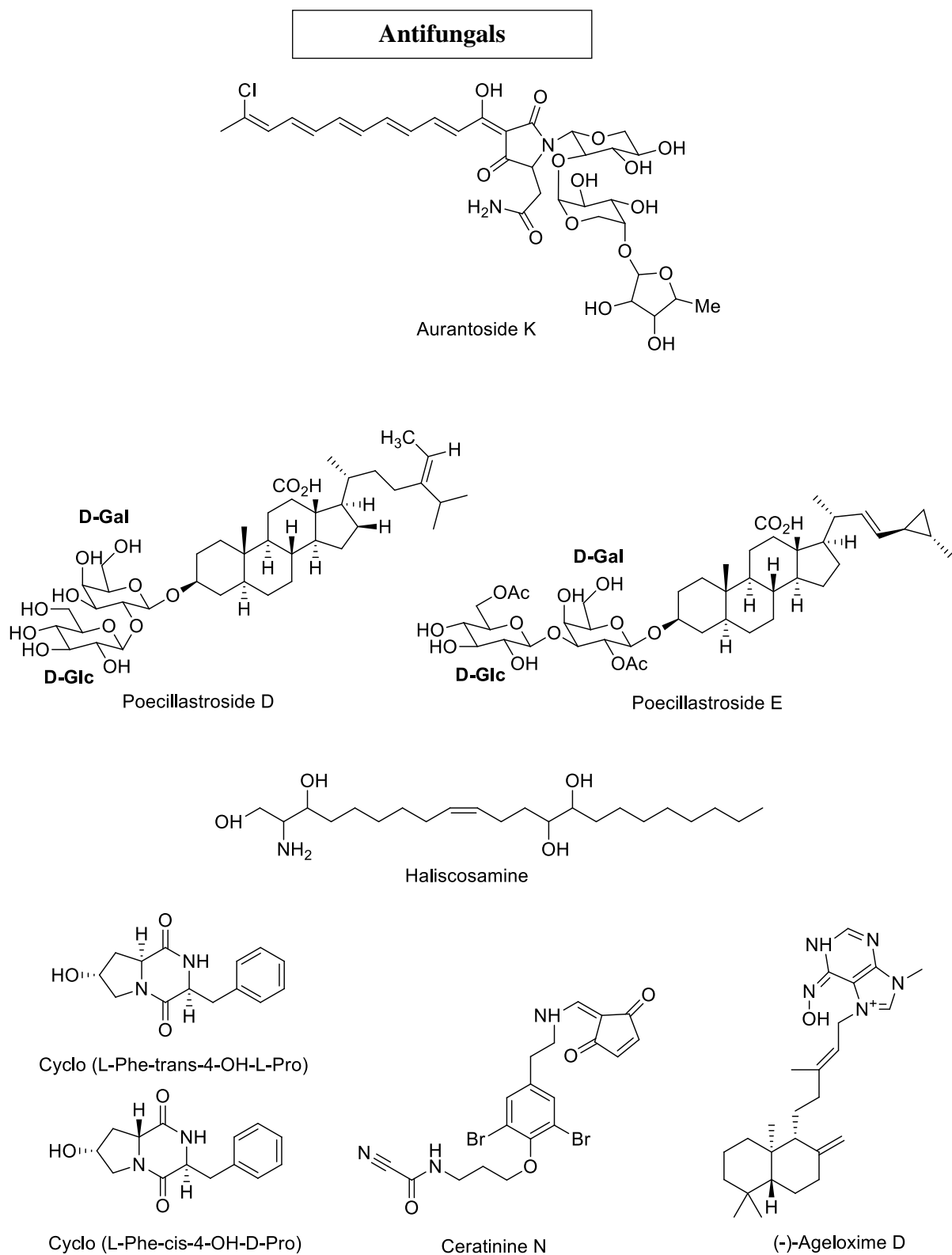


Myrindole A



3-(3,5-dichloro-4-hydroxyphenyl) propanoic acid

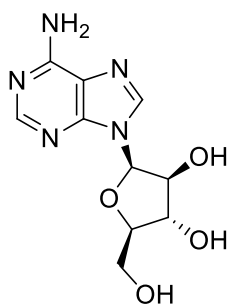
Fig. 2: Chemical structures of some antimicrobial compounds from sponge and sponge-associated bacteria



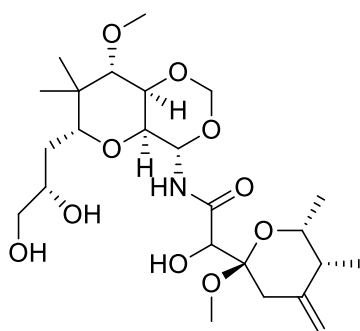
**Fig. 2: Chemical structures of some antimicrobial compounds from sponge and sponge-associated bacteria**



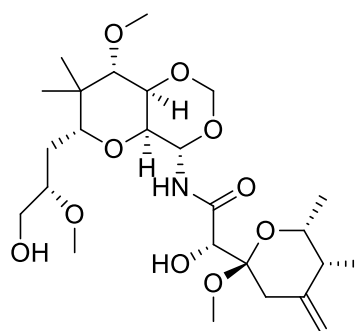
**Antivirals**



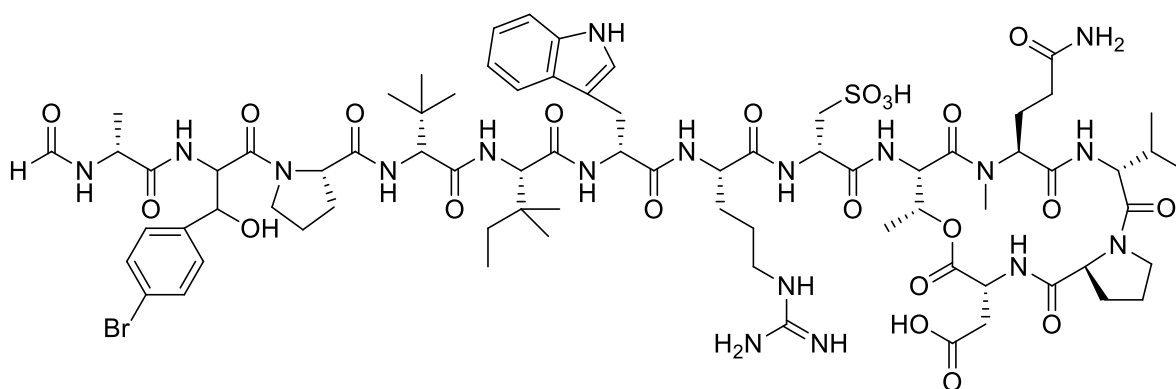
Vidarabine



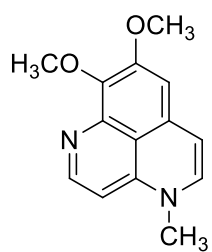
Mycalamide A



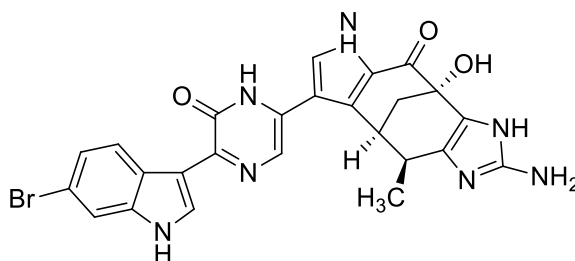
Mycalamide B



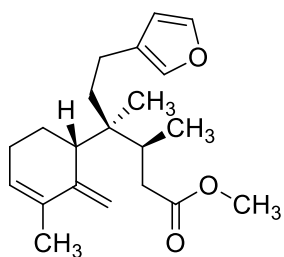
Microspinosamide



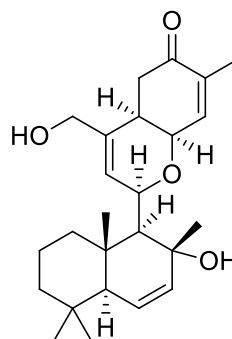
4-methylaaptamine



Dragmacidin F

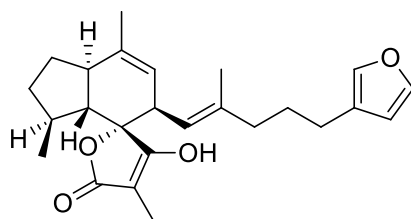
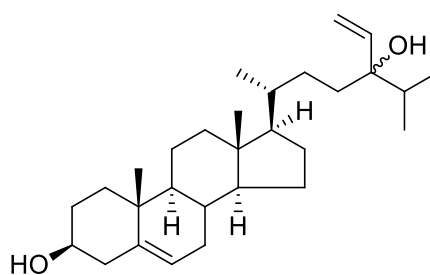
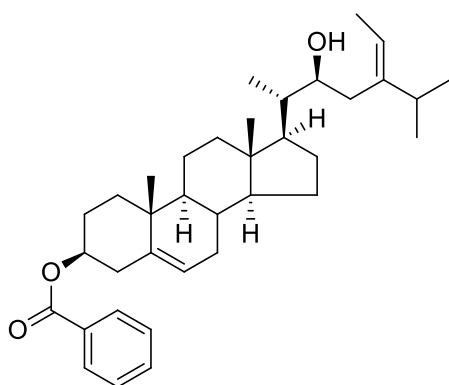
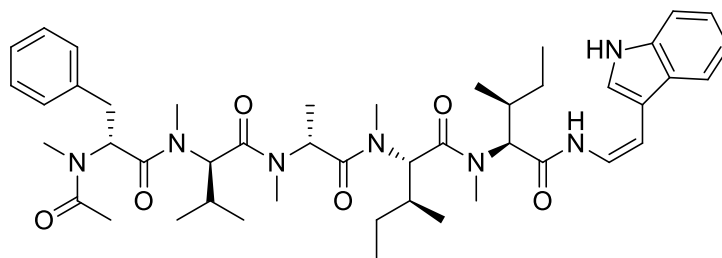
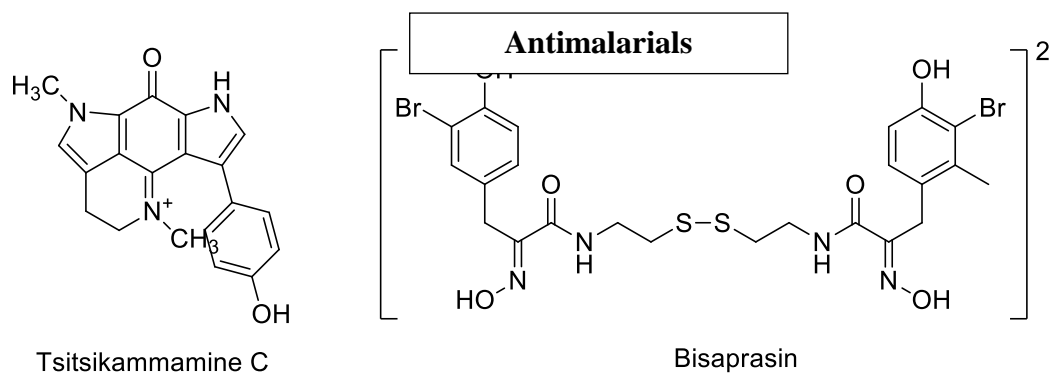


Raspadiene

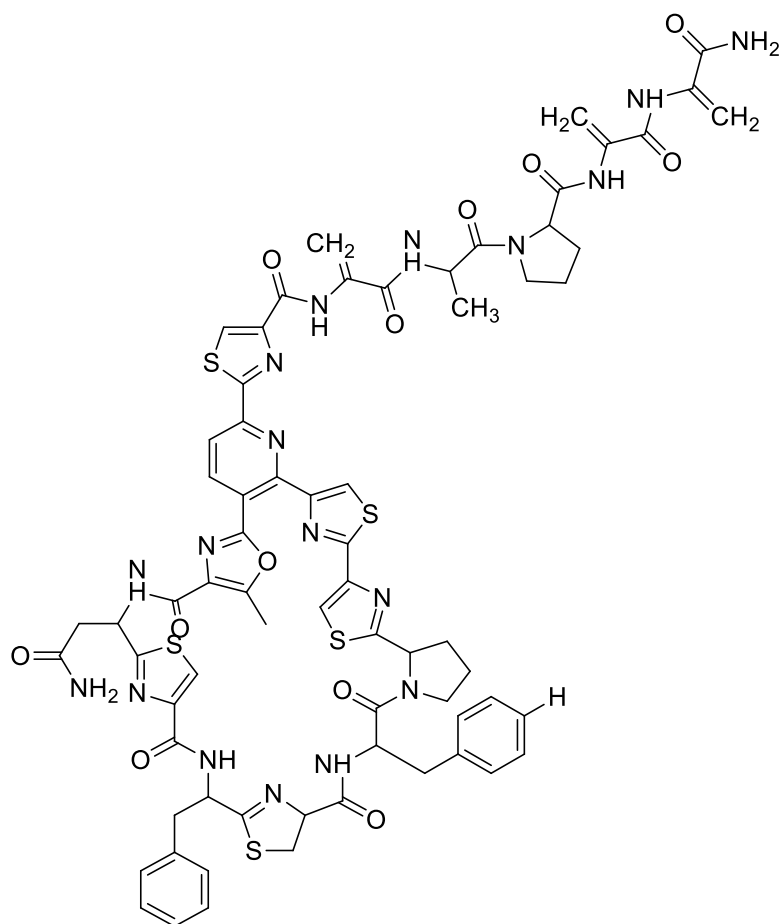


Ansellone J

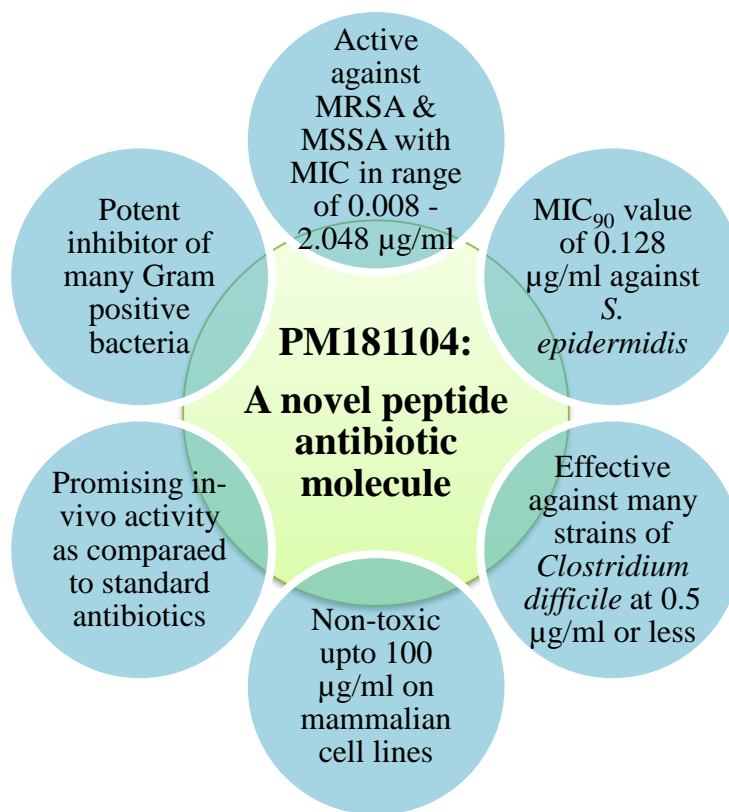
**Fig. 2: Chemical structures of some antimicrobial compounds from sponge and sponge-associated bacteria**



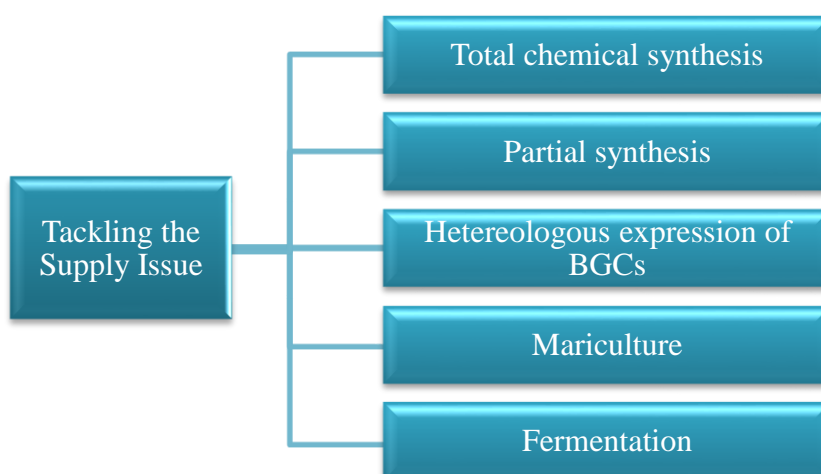
**Fig. 2: Chemical structures of some antimicrobial compounds from sponge and sponge-associated bacteria**



**Fig. 3: Chemical Structure of PM181104**



**Fig. 4: Significant characteristics of the antibiotic PM181104**



**Fig. 5: Measures to tackle the supply problem in marine natural product development**