Major Antimicrobial Representatives from Marine Sponges and/or Their Associated Bacteria

Fei He, Linh H. Mai, Johan Gardères, Amjad Hussain, Vesna Erakovic Haber and Marie-Lise Bourguet-Kondracki

Abstract The rapid emergence of resistant bacteria during the last 20 years has stimulated research efforts in order to overcome this thorny problem. Marine sponges and their associated bacteria, which have been proven to be a source of bioactive natural products, have appeared as a promising opportunity to identify new antibiotic compounds. An overview of the major antibacterial compounds isolated from marine sponges and/or their associated bacteria is presented in this chapter, highlighting new potential antibiotics.

1 Introduction

The effectiveness of antimicrobial therapy is frequently mentioned as a great success story of modern medicine. The introduction of antibiotics into the medical practices has drastically changed the survival rates of human beings all around the world and has significantly increased the average life expectancy. Although one can be very happy, when one compares today's situation with that of 100 years ago, one should not forget that human pathogens are living organisms that have extraordinary capability to change and adapt to the new environment, including in the presence of antimicrobials. Therefore, emerging resistance to current antimicrobial therapy is all but surprising and presents serious threat to humans.

Fei He, Linh H. Mai, Johan Gardères, Amjad Hussain, Vesna Erakovic Haber, and Marie-Lise Bourguet-Kondracki are equally contributed.

F. He · L.H. Mai · J. Gardères · A. Hussain · M.-L. Bourguet-Kondracki (✉)
Laboratoire Molécules de Communication et Adaptation des Micro-organismes,
UMR 7245 MNHN-CNRS, Muséum National d'Histoire Naturelle,
57 rue Cuvier (C.P. 54), 75005 Paris, France
e-mail: bourguet@mnhn.fr

V. Erakovic Haber
Fidelta d.o.o., Prilaz baruna Filipovića 29, 10000 Zagreb, Croatia

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Antimicrobial resistance is a resistance of microorganisms, such as bacteria, fungi parasites, and viruses, to antimicrobial drugs. Lack of adequate clinical treatment can lead to serious and/or persistent infections of affected individuals, in some cases causing even lethal outcome.

World Health Organization, in its April 2015 Fact sheet, reported that 480,000 cases of multidrug-resistant tuberculosis happened during 2013, an appearance of resistance against artemisinin-based combination therapies for *falciparum* malaria in Great Mekong subregion. High proportions of antibiotic resistance in bacteria that cause common infections (e.g., urinary tract infections, pneumonia, bloodstream infections) are reported in almost all regions of the world, as well as resistance to treatment for gonorrhea in 10 countries (WHO Fact sheet No. 194).

Immuno-compromised patients, either suffering from diseases causing immunological incompetence or being treated with therapies that suppress activity of the immunological system, are particularly prone towards bacterial infections caused by organisms not particularly virulent such as *Pseudomonas aeruginosa*, *Stenotrophonomas maltophilia*, and *Acinetobacter* spp. Acquired drug resistance by such microorganisms presents extremely serious life-threatening medical situation.

The highly methicillin-resistant *Staphylococcus aureus* bacteria (MRSA) represent 18% of the isolated *S. aureus* in Europe, 44% in the United States (CDDEP 2015), 16% in Canada, 47% in India (2014), and 90% in Latin America hospitals (2013 PAHO) (CDDEP, The state of world's antibiotics 2015). In addition, an increased number of infections caused by Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, resistant to the current antibiotics, presents growing medical problem. Especially difficult to treat are extended-spectrum beta-lactamase (ESBL) producers which are resistant to third generation cephalosporins, whereas carbapenem-resistant enterobacteriaceae (CRE) are resistant even to the last resort antibiotic carbapenem (Glasner et al. 2013). During the year 2013, in 17 of 22 European countries, 85–100% of *E. coli* isolates were ESBL positive and five European countries reported an increase of carbapenem-resistant bacteria (CDDEP, The state of world's antibiotics 2015). The carbapenem resistance has been reported among 11% of *K. pneumoniae* and 2% of *E. coli* in USA hospitals during 2011. In India, resistance rate to carbapenem has been reported to be 13% among *E. coli* during 2013 and 57% among *K. pneumonia* during 2014 (CDDEP, The state of world's antibiotics 2015).

Unlike other drug classes, only two new classes of antibiotics have been discovered in the past couple of decades: oxazolidinones and cyclic lipopeptides, former being synthetic molecules and latter natural products. According to the PEW Charitable Trust, there are 39 new antibiotics with the potential to treat serious bacterial infections currently in clinical development for the U.S. market. Two new drugs, approved by FDA last year, are combinations of already existing drug classes: cephalosporins and beta-lactamase inhibitors (Zerbaxa: Ceftolzane/Tazobactam and Avycaz: Ceftazimide/Avibactam) (The PEW Charitable Trust 2015). They are approved for complicated urinary tract and intra-abdominal infections, hospital-acquired pneumonia, and ventilator associated pneumonia. These combinations are active against ESKAPE pathogens but not against carbapenem-resistant *Enterobacteriacae* and drug-resistant

Neisseria gonorrhoeae. Some of the compounds currently in Phase 3 of the clinical development demonstrate a potential to address carbapenem resistance; however all of them belong to already known antibiotic classes with no new mechanism of action (The PEW Charitable Trust 2015).

To cope with these issues, the search of novel antibiotics remains both urgency and a great challenge. Marine organisms have been found as a potential source of novel bioactive compounds and have been intensively explored, especially marine sponges with over 8600 valid species currently described. These metazoans, which live fixed on a substrate, are active filter feeders, which concentrate bacteria from environment for their nutrition. However, they also host various microbes such as heterotrophic bacteria, cyanobacteria, facultative anaerobes, archaea, unicellular protists, and fungi. They are now described as holobionts (Taylor et al. 2007; Webster and Taylor 2012). Their associated-bacteria have been particularly investigated because they can account up to 35% of the biomass of some demosponge species, reaching a density of bacterial population much greater than that of the surrounding water column. The mechanisms by which these sponge–microbe associations are established and maintained are still poorly understood. A complex process of acquisitions over time, both by vertical transmission through the embryos and/or by horizontal transmission through the filtration activity of environmental seawater by these animals, has been suggested (Schmitt et al. 2008; Bright and Bulgheresi 2010). The reported benefits that these associations may provide to the sponge include photosynthetic carbon fixation from symbiotic cyanobacteria, nitrogen fixation and nitrification, sulfate reduction, dehalogenation, anaerobic metabolism, contribution to sponge structural rigidity, or production of secondary metabolites for chemical defence (Webster and Blackall 2009; Roué et al. 2012). Those secondary metabolites, exactly because of their nature and function, are very likely to be of particular importance for novel antibiotic discovery.

Intensive chemical investigations during the last few decades on marine sponges collected from different geographical locations (The Bahamas, Indonesia, Mexico, Palau, Papua New Guinea, Philippines…) and/or from their associated microbes led to the discovery of thousands of bioactive compounds which revealed significant pharmacological activities such as anticancer, anti-kinase, antibacterial, antifungal, antimalarial, or anti-HIV activities.

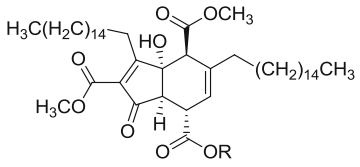
This chapter is an overview of the main antibacterial compounds isolated from marine sponges and/or their associated bacteria. The aim was not to be exhaustive but to present the major diverse antimicrobial representatives. From 2001 to 2010, 145 antibacterial compounds, isolated from marine sponges, have been reported, mainly from the order Dictyoceratida (Mehbub et al. 2014). So far, additional new molecules have enhanced this chemodiversity. The major antibacterial compounds from marine sponges presented in this chapter have been classified into different chemical classes including, lipids, polyketides, steroids, terpenoids, alkaloids, peptides, and miscellaneous brominated derivatives. This selection has been enriched by some representatives obtained from sponge-associated bacteria.

2 Antimicrobial Compounds from Marine Sponges

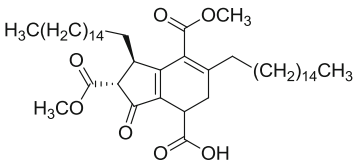
2.1 Lipids

The lipids are a broad and diverse group of naturally occurring organic compounds. Study of sponge lipids has been well documented (Bergé and Barnathan 2005; Barnathan 2009), and some sponge lipids have been reported as antimicrobials as illustrated by these few examples including fatty acid derivatives, glycolipids, and lysophospholipids.

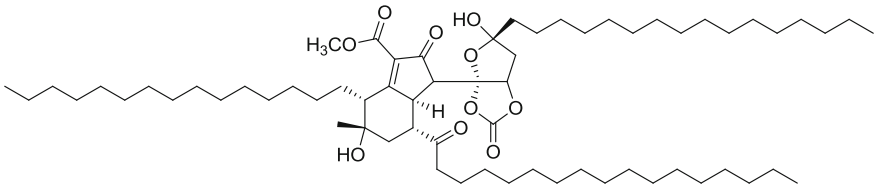
Three fatty acid derivatives, manzamenones L, M, and N were isolated from the Okinawan sponge *Plakortis* sp. These compounds consist of a tetrahydroindenone with three carboxyl groups and two hexadecanyl chains. Manzamenone M displayed moderate antimicrobial activities against the bacteria *E. coli* (MIC = 32 μg mL^{-1}) and *S. aureus* (MIC = 16 μg mL^{-1}) and against the yeasts *Candida albicans* (IC_{50} = 32 μg mL^{-1}) and *Cryptococcus neoformans* (IC_{50} = 8 μg mL^{-1}). Manzamenone N also exhibited moderate antimicrobial activities against *E. coli* (MIC = 32 μg mL^{-1}), *C. albicans* (IC_{50} = 32 μg mL^{-1}), and *C. neoformans* (IC_{50} = 4 μg mL^{-1}). According to the structure of the compounds, since Manzamenone L did not show any antimicrobial activity, the presence of a free carboxylic acid at C-5 position was reported as being important for the antimicrobial activities (Kubota et al. 2013a). The trimeric fatty acid Manzamenone O, with a novel skeleton consisting of C–C bonded octahydroindenone and dioxabicyclo[3.3.0]octane moieties and three long aliphatic chains, exhibited antimicrobial activities against *Micrococcus luteus*, *Aspergillus niger*, and *Trichophyton mentagrophytes* with MIC values of 4, 8, and 8 μg mL^{-1}, respectively (Tanaka et al. 2013a).



Manzamenone L: R = OCH_3
Manzamenone M: R = H

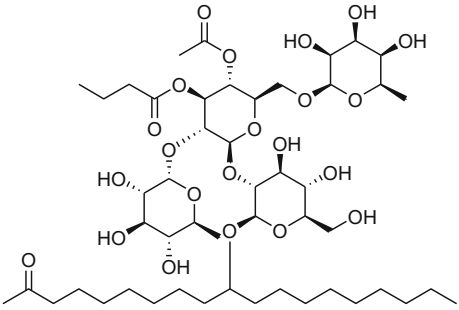


Manzamenone N



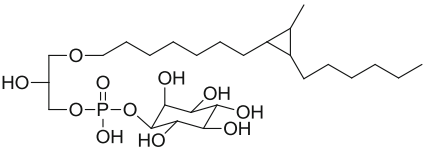
Manzamenone O

Bioassay-guided fractionation of the *Caminus sphaeroconia* extract led to the isolation of the antimicrobial glycolipid caminoside A (Linington et al. 2002). This was the first natural product known to be active (IC_{50} = 20 μM) in a bioassay designed to screen type III secretion inhibitors that potentially represent novel agents to control pathogenic *E. coli* by thwarting their pathogenicity without killing the bacteria. In addition, caminoside A showed potent in vitro inhibition against methicillin-resistant *S. aureus* (MIC = 12 μg mL^{-1}) and vancomycin-resistant *Enterococcus* (MIC = 12 μg mL^{-1}). It did not show any inhibition against the Gram-negative bacteria *E. coli*.

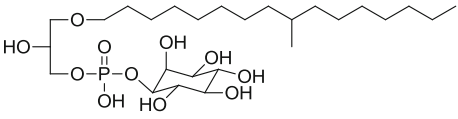


Caminoside A

Two antimicrobial lysoplasmanylinositols 1 and 2 were isolated from the marine sponge, *Theonella swinhoei* (Matsunaga et al. 2001). Lysoplasmanylinositol 1 was active against *E. coli*, showing a 12 mm inhibitory zone at 50 μg $disk^{-1}$, whereas lysoplasmanylinositol 2 was found only active in bioautography, used as a means of target-directed isolation of active molecules on chromatogram. Both compounds were inactive against the fungus *Mortierella rammaniana*.



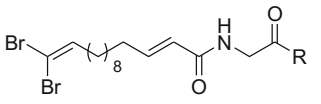
Lysoplasmanylinositol 1



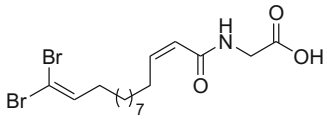
Lysoplasmanylinositol 2

Six brominated antibacterial lipids namely, motualevic acids A–F, were isolated from the Fijian sponge *Siliquariaspongia* sp. (Keffer et al. 2009). Motualevic acid F

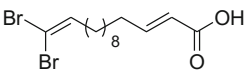
was reported as the first example of a long-chain 2*H*-azirine containing a C-2 carboxylic acid. Motualevic acids (A–D) are the first glycyl conjugates of the ω-brominated lipid (*E*)-14,14-dibromotetradeca-2,13-dienoic acid. Motualevic acids A and F, both containing a carboxylic acid, are the only compounds to inhibit the growth of *S. aureus* and methicillin-resistant *S. aureus* at 10.9–1.2 and 9.3–3.9 μg mL^{-1}, respectively. These results provided a starting point for optimization of new MRSA-inhibitors.



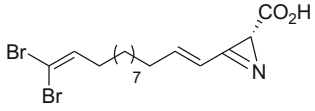
Motualevic acid A : R = OH
Motualevic acid C : R = NH_2
Motualevic acid D : R = $N(CH_3)_2$



Motualevic acid B

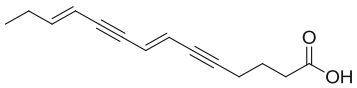


Motualevic acid E



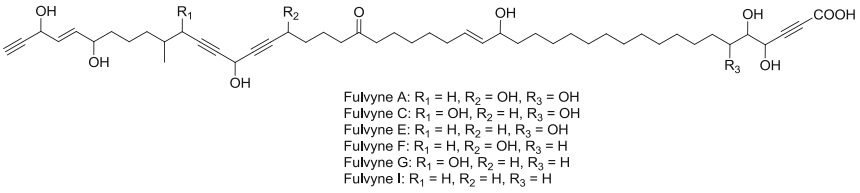
Motualevic acid F

The C_{14} acetylenic acid, isolated as an antimicrobial compound from a marine sponge *Oceanapia* sp. (Matsunaga et al. 2000), revealed inhibitory activity against both Gram-positive and Gram-negative bacterial strains, as well as various yeasts and fungi. In particular, this C_{14} unsaturated acetylenic fatty acid was moderately active against four mutants of *Saccharomyces cerevisiae* and *C. albicans*, but was inactive against *Penicillium chrysogenum* and *Mortierella ramanniana*.

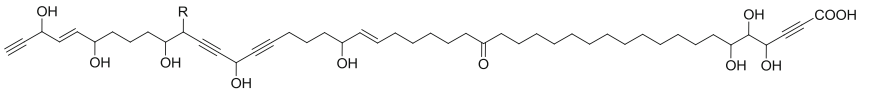


(7*E*,11*E*)-tetradeca-7,11-dien-5,9-diynoic acid

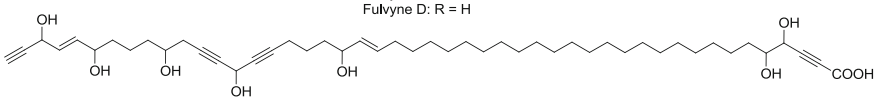
Nine linear polyoxygenated acetylene derivatives, named fulvynes A–I, exhibiting the uncommon propargylic acid terminal functionality, were isolated from the butanolic extract of the Mediterranean sponge *Haliclona fulva* (Nuzzo et al. 2012). All these fulvynes were found to be active against a chloramphenicol-resistant Gram-positive strain of *Bacillus subtilis* Cm (PY79) with IC_{50} values ranging from 12 to 60 μM; the fulvynes A, D, E, F, and I were the most active.



Fulvyne A: R_1 = H, R_2 = OH, R_3 = OH
Fulvyne C: R_1 = OH, R_2 = H, R_3 = OH
Fulvyne E: R_1 = H, R_2 = H, R_3 = OH
Fulvyne F: R_1 = H, R_2 = OH, R_3 = H
Fulvyne G: R_1 = OH, R_2 = H, R_3 = H
Fulvyne I: R_1 = H, R_2 = H, R_3 = H

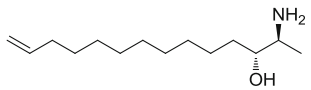


Fulvyne B: R = OH
Fulvyne D: R = H

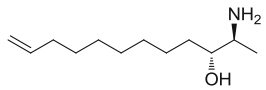


Fulvyne H

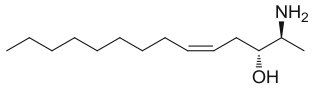
Halaminols A–C are three amino alcohols, reported as presumably derived from *L*-alanine from the tropical marine sponge *Haliclona* n. sp. They revealed antimicrobial activities against the growth of *E. coli*, *B. subtilis*, *C. albicans*, *T. mentagrophytes*, and *Cladosporium resinae*. Halaminols A and B were the most effective, showing antifungal activity against *T. mentagrophytes*, and *C. resinae* with a 10 mm zone of inhibition in a standard paper disk assay (0.12 mg disk^{-1}) (Clark et al. 2001). It is suggested that the antimicrobial activity of these linear amino alcohols may result from their detergent-like nature, which is likely to disrupt cell membranes. Authors reported that acetylation of these halaminols revealed a decrease of the antimicrobial activity, probably by altering the surfactant properties of the metabolites. Furthermore, they are presented as potential antifouling agents due to their capacity to disrupt the developmental processes of induced larval settlement of the ascidian *Herdmania curvata*.



Halaminol A



Halaminol B

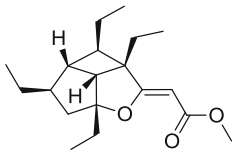


Halaminol C

2.2 Polyketides

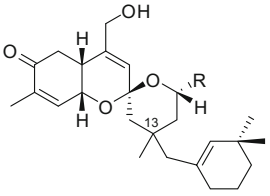
The polyketides are a structurally very diverse family of natural products. A wide range of biological activities have been reported for this class of metabolites, including antimicrobial activities.

Hippolachnin A, isolated from the sponge *Hippospongia lachne*, is an antifungal polyketide with an unusual carbon skeleton containing a four-membered ring. This compound was found active against *C. neoformans*, *Trichophyton rubrum,* and *Microsporum gypseum* with MIC values of 0.41 μM for each fungal strain. No significant cytotoxic activity was observed against the human colon carcinoma HCT116, the lung carcinoma A549, and the cervical cancer cell lines HeLa (Piao et al. 2013).



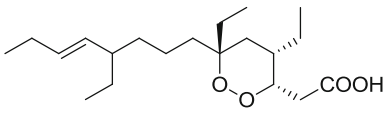
Hippolachnin A

The tetracyclic sesterterpene gombaspiroketal A and its corresponding hemiacetal C, isolated from the sponge *Clathria gombawuiensis*, exhibited activities against *S. aureus* ATCC6538p (MIC = 25.0 μg mL^{-1}, for both compounds), *B. subtilis* ATCC6633 (MIC = 6.25 μg mL^{-1}, for both compounds), *Kocuria rhizophila* NBRC 12708 (MIC = 12.5 and 25.0 μg mL^{-1}, respectively), *Salmonella enterica* ATCC14028 (MIC = 12.5 and 25.0 μg mL^{-1}, respectively), and *Proteus hauseri* NBRC3851 (MIC = 6.25 and 12.5 μg mL^{-1}, respectively). They also displayed cytotoxic activities against the human myelogenous leukemia cell line K562 and the carcinomic human alveolar basal epithelial cell line A549 with LC_{50} values from 0.70 to 4.65 μM (Woo et al. 2014).



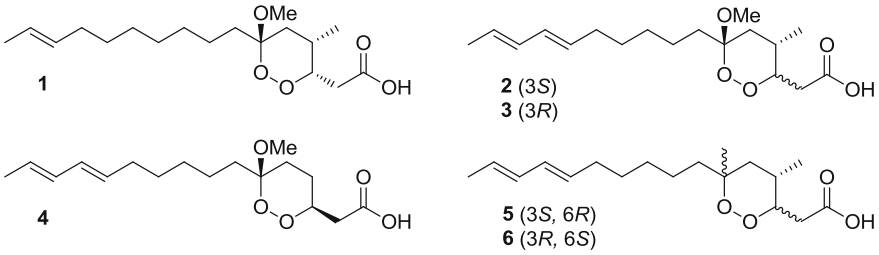
Gombaspiroketal A (R = OMe, 13*R*)
Gombaspiroketal C (R = OH, 13*R*)

Manadodioxan E, a polyketide endoperoxide isolated from the marine sponge *Plakortis bergquistae* collected from north Sulawesi, Indonesia, displayed antibacterial activities at the concentration of 10 μg disk^{-1} against *E. coli* (zone of inhibition of 16 mm) and *Bacillus cereus* (zone of inhibition of 9 mm), while its oxocongener was found inactive (Gushiken et al. 2015).



Manadodioxan E

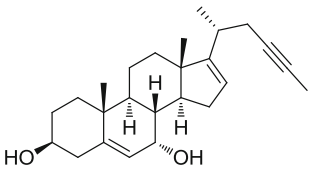
Cyclic peroxides **1**–**6**, isolated from the Korean sponge *Plakortis simplex*, showed interesting antifungal activities against *C. albicans* at the concentration of 10 μg disk^{-1} with growth inhibition zones from 16 to 20 mm, compared to the control amphotericin (15 mm). However, these compounds displayed a high cytotoxicity against the RAW264.7 cell line (murine macrophage cell line) with EC_{50} values from 2 to 4 μg mL^{-1} (Oh et al. 2013).



2.3 Steroids

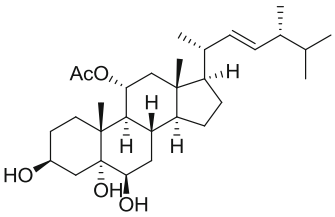
Polyhydroxylated sterols as well as some sulfated derivatives of revealed potential antimicrobial activities.

A sterol, gelliusterol E, was isolated from the Red Sea sponge *Callyspongia* aff. *implexa* (26,27-bisnorcholest-5,16-dien-23-yn-3*β*,7α-diol), which inhibited the formation and growth of *Chlamydia trachomatis* inclusions in a dose-dependent manner with an IC_{50} value of 2.3 μM (Abdelmohsen et al. 2015).

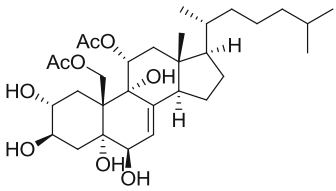


Gelliusterol E

The sponge *Haliclona crassibola* provided polyhydroxylated antimicrobial sterols. Halicrasterol D was efficient against the Gram-positive bacteria *Enterococcus faecalis* ATCC 29212 (MIC = 4.0 μg mL^{-1}). The polyhydroxylated sterol H (5α-cholest-7-ene-2α,3β,5α,6β,9α,11α,19-heptol 11,19-diacetate) revealed the same antibacterial activity (MIC value of 8.0 μg mL^{-1}) against both the methicillin-sensitive *S. aureus* strain ATCC 29213, and the methicillin-resistant *S. aureus* strains 43300. This sterol also exhibited a moderate activity against *B. subtilis* ATCC 21332, and *Bacillus licheniformis* ATCC 10716 with MIC values of 16 μg mL^{-1} (Cheng et al. 2013).

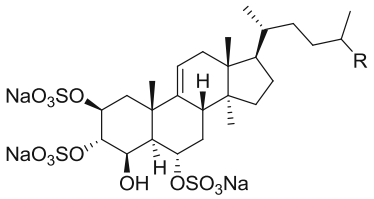


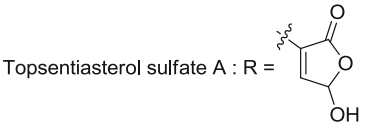
Halicrasterol D

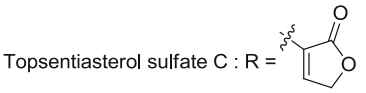


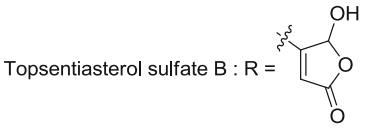
Polyhydroxylated sterol H

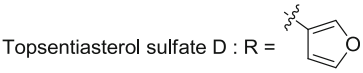
Topsentiasterol sulfates A–E were identified from a marine sponge *Topsentia* sp. collected at Ishigaki Island, Okinawa. The polysulfated sterols A–D have the particularity to possess a butenolide or a furan functionality at the end of the side chain. They all showed antibacterial activities against *P. aeruginosa* and *E. coli* at the concentration of 10 μg $disk^{-1}$, but only topsentiasterol sulfates D and E displayed antifungal activities against *M. ramanniana* and *C. albicans* at the same concentration (Fusetani et al. 1994).

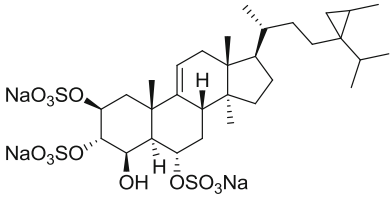






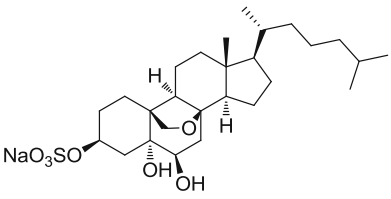




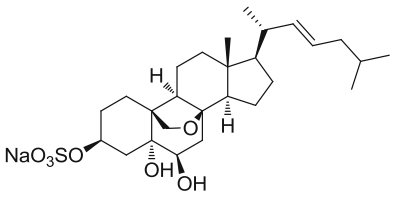


Topsentiasterol sulfate E

Two other steroid sulfates namely, eurysterols A and B, were isolated from an unidentified marine sponge of the genus *Euryspongia* collected in Palau (Boonlarppradab and Faulkner 2007). Both compounds exhibited the same antifungal activity against amphotericin B-resistant and wild-type strains of *C. albicans* with MIC values of 15.6 and 62.5 μg mL^{-1}, respectively. But they also displayed cytotoxicity against the human colon carcinoma cell line HCT116 with IC_{50} values of 2.9 and 14.3 μg mL^{-1}, respectively. These results predicted the presence of the double bond as a responsible factor for reducing the biological activities.



Eurysterol A

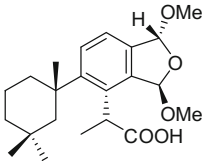


Eurysterol B

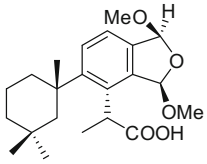
2.4 Terpenoids

Various terpenoids exhibiting the antimicrobial potential have been reported so far. Among the subclasses of terpenoids, sesquiterpenes, diterpenes are the most prominent ones. Some meroterpenes have also been found associated with antimicrobial activities.

Two diterpenes, named membranolides C and D, bearing a carboxylic group, were isolated from the Antarctic sponge *Dendrilla membranosa* (Ankisetty et al. 2004). Both exhibited moderate antibacterial activities against *E. coli*, and *C. albicans* with inhibitory zones ranging from 4 to 9 mm (200 μg disk^{-1}). At the same concentration, membranolide D was the only compound to show a 7 mm zone of inhibition against *S. aureus*.

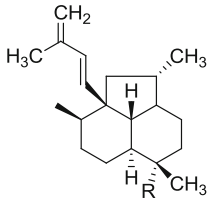


Membranolide C



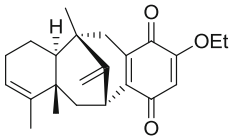
Membranolide D

The Caribbean sponge *Svenzea flava* provided three tricyclic marine diterpenes possessing the isoneoamphilectane backbone with antibacterial activities against *Mycobacterium tuberculosis* $H_{37}Rv$. The three natural compounds identified as 7-isocyanoisoneoamphilecta-1(14),15-diene, 7-methylaminoisoneoamphilecta-1(14),15-diene, and 7-formamidoisoneoamphilecta-1(14),15-diene revealed a MIC value of 8, 15, and 32 μg mL^{-1}, respectively. However, the most effective derivative was the semisynthetic compound 7-amidoisoneoamphilecta-1(14),15-diene with a MIC value of 6 μg mL^{-1} and no cytotoxicity has been shown against VERO cells (until 128 μg mL^{-1}). This data suggests that the isoneoamphilectane skeleton, and not the isocyanide functionality, that might be the molecular feature responsible for the antituberculosis activity (Avilés et al. 2013).



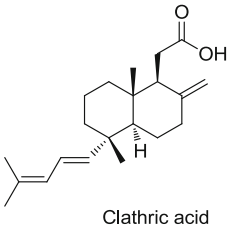
7-Isocyanoisoneoamphilecta-1(14),15-diene : R = NC
7-Methylaminoisoneoamphilecta-1(14),15-diene : R = $NHCH_3$
7-Formamidoisoneoamphilecta-1(14),15-diene : R = NHCHO
7- Amidoisoneoamphilecta-1(14),15-diene : R = NH_2

Dysidavarone A, a sesquiterpene quinone characterized by an unprecedented tetracyclic core, was initially isolated from the sponge, *Dysidea avara* (Jiao et al. 2012). The total synthesis of this compound was realized by a highly concise strategy in 10 steps (total yield of 11%) involving an advantageous intramolecular R-arylation of an elaborate ketone in order to access sufficient material for further biological evaluation of this important metabolite (Schmalzbauer et al. 2013). Dysidavarone A, revealed a potent inhibitory effects against Gram-positive bacterial strains, in particular against various *Staphylococci* even at very low concentrations (*S. aureus* DSM346: MIC = 7.1 μg mL^{-1}, multidrug resistant *S. aureus* DSM11822: MIC_{50} = 9.9 μg mL^{-1}, methicillin-resistant *S. aureus* N315: MIC_{50} = 4.0 μg mL^{-1}, *S. aureus* Newman MIC_{50} = 6.5 μg mL^{-1}, *Staphylococcus carnosus* DSM20501: MIC_{50} = 0.2 μg mL^{-1}). Furthermore, it also showed inhibitory activity against *M. luteus* (MIC_{50} = 5.5 μg mL^{-1}) but no inhibitory activity against various fungi/yeast and Gram-negative bacterial strains were observed. Dysidavarone A also showed antiproliferative activities against various human cancer cell lines by changing the morphology of the treated cells as well as inhibitory activities against protein tyrosine phosphatase 1B (PTP1B).

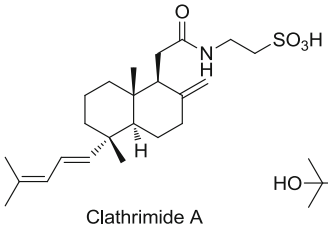


Dysidavarone A

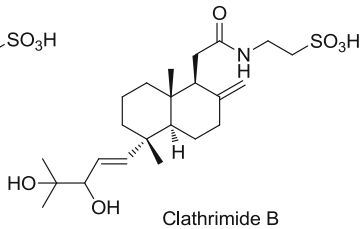
Three unusual bicyclicditerpene, clathric acid and two *N*–acyl taurine derivatives, clathrimides A and B, were isolated from the marine sponge *Clathria compressa* (Gupta et al. 2012). Clathric acid showed MIC values of 32 μg mL^{-1} against the *S. aureus* strain ATTC 6538P and 64 μg mL^{-1} against both *S. aureus* strains methicillin-resistant ATTC33591 and vancomycin-resistant *S. aureus*. Clathrimides A and B showed no activity at concentrations up to 128 μg mL^{-1}, revealing the importance of the acid function. None of the compounds was found active against the Gram-negative bacterial strains *E. coli* KCTC 1923 and *Klebsiella pneumonia* ATCC 10031 when tested at 128 μg mL^{-1}.



Clathric acid

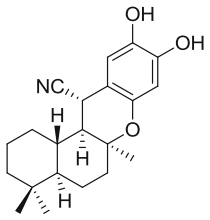


Clathrimide A

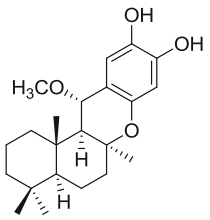


Clathrimide B

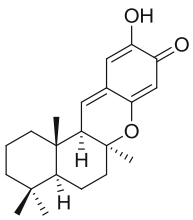
15-Cyanopuupehenol is an adduct of HCN and a mixed sesquiterpene—shikimate sponge metabolite of the order Dictyoceratida (Hamann and Scheuer 1991). It exhibited antimicrobial activity of 6 mm disk^{-1} at 5 μg mL^{-1} against *Penicillium notatum* (10 mm partial inhibition), *T. mentagrophytes* (9 mm), and *S. cerevisiae* (7 mm). The related compounds puupehenone and 15α-methoxypuupehenol were isolated from the newly identified Caledonian marine sponge *Hyrtios* sp. 15α-Methoxypuupehenol displayed similar antimicrobial activities as puupehenone against *S. aureus* (7 mm of growth inhibitory zone at 1 μg disk^{-1}) and *Candida tropicalis* (9 mm of growth inhibitory zone at 50 μg disk^{-1}). In addition, both compounds displayed cytotoxicity towards KB cells, with an IC_{50} value of 0.5 and 6 μg mL^{-1}, respectively (Bourguet-Kondracki et al. 1999). Recently, puupehenol and puupehenone, isolated from a Hawaiian deepwater sponge of *Dactylospongia* sp., revealed the same antimicrobial activities at the concentration of 10 μg disk^{-1} against the Gram-positive bacteria *S. aureus* (4 mm) and *B. cereus* (3 mm), respectively. Both were inactive against *E. coli* and *P. aeruginosa* at this concentration (Hagiwara et al. 2015).



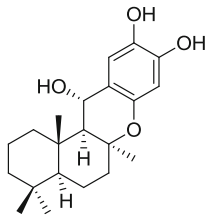
15-Cyanopuupehenol



15α-Methoxypuupehenol

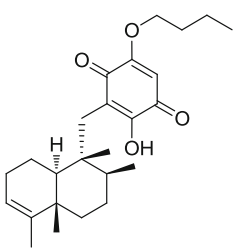


Puupehenone

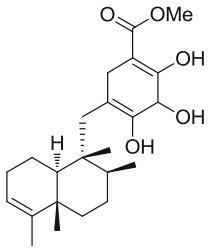


Puupehenol

Two meroterpenoids, nakijiquinone S and nakijinol C, isolated from an Okinawan of *Spongiidae* sp., consist of a clerodane-type decalin ring connected to 2-butoxy-5-hydroxy-benzoquinone unit or methyl 2,3,4-trihydroxybenzoate unit through a methylene, respectively. Both displayed antibacterial activities against several bacteria and fungi. Nakijiquinone S appeared to be the most efficient antimicrobial against *S. aureus*, *B. subtilis* and *M. luteus* (MIC values of 1 μg mL^{-1}) and showed a less activity against the Gram-negative bacteria *E. coli* (MIC from 8 μg mL^{-1}) but it also revealed antifungal activities against *A. niger*, *T. mentagrophytes* and *C. albicans* (IC_{50} from 4 to 16 μg mL^{-1}). Nakijinol C revealed activities against *S. aureus* and *M. luteus* (MIC values of 8 and 4 μg mL^{-1}, respectively) as well as against *A. niger* and *T. mentagrophytes* (IC_{50} = 8 μg mL^{-1}). Both compounds did not exhibit any cytotoxicity against the murine lymphoma L1210 and human epidermoid carcinoma KB cells (IC_{50} > 10 μg mL^{-1}) (Suzuki et al. 2014).



Nakijiquinone S

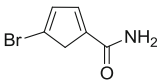


Nakijinol C

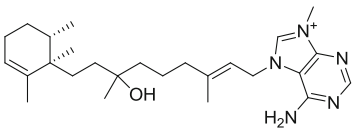
2.5 Alkaloids

Marine sponges have afforded a wide variety of alkaloids, usually with complex skeletons. Their antimicrobial activities have been frequently reported.

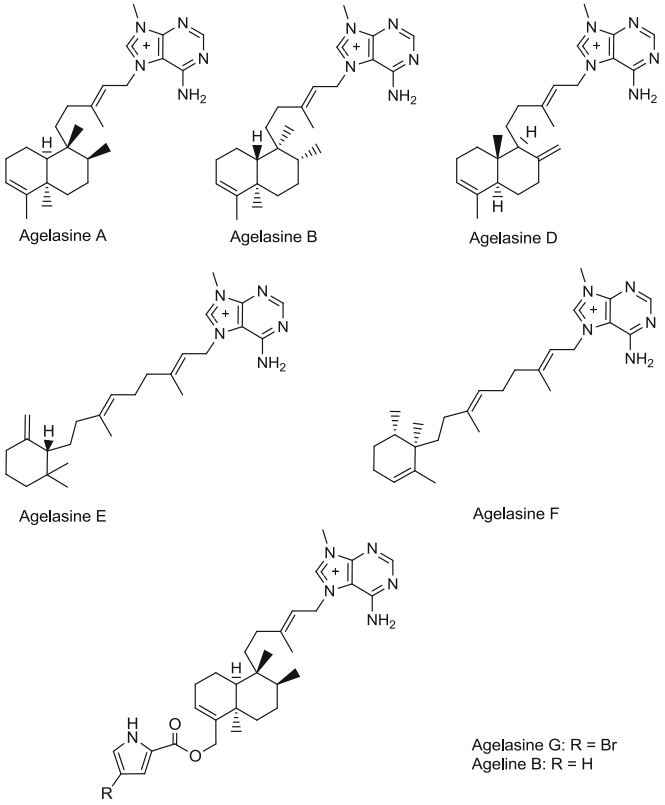
Sponges belonging to the genus *Agelas* have also proved to be a rich source of purinoditerpenes in addition to bromopyrrole derivatives. 5-Bromopyrrole-2-carboamide and agelasine B were initially isolated from the Guinean sponge, *Agelas nakamurai* (Iwagawa et al. 1998). Both compounds showed antimicrobial activity against Gram-positive bacteria and fungi. Therefore, both showed the same IC_{50} values of 6.25, 3.13, 0.78, and 3.13 μg mL^{-1} against *E. faecalis* 12964, *E. faecalis* 12367, *S. aureus* 12732MRSAa and *C. neoformans* TIMM0354, respectively. Agelasine B was more active than 5-bromopyrrole-2-carboamide against *S. epidermidis* 13889 (IC_{50} = 1.56 vs. 3.13 μg mL^{-1}) but less active against *C. albicans* IFO1269 (IC_{50} > 12.5 vs. 6.25 μg mL^{-1}). Recently, the compounds 10-hydro-9-hydroxyagelasine F, agelasines A, B, D, E, F, and G and the ageline B, isolated from the sponge *A. nakamurai*, were evaluated for their antibacterial activities against the bacterium *Mycobacterium smegmatis* showing antimycobacterial activities at the concentration of 20 μg $disk^{-1}$ with inhibition zones ranging from 10 to 18 mm, compared to 30 mm of the control streptomycin sulfate at the same concentration. None of these compounds exhibited any cytotoxic activity against the human hepatoma Huh7 and bladder EJ1 carcinoma (IC_{50} > 10 μM) (Abdjul et al. 2015).



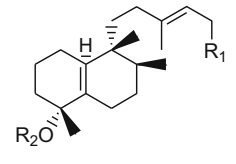
5-Bromopyrrole-2-carboamide



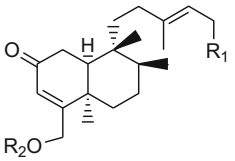
10-Hydro-9-hydroxyagelasine F



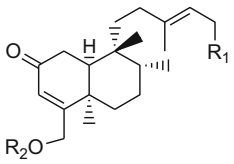
From an unidentified Okinawan marine sponge of *Agelas* sp. some diterpene alkaloids with a 9-*N*-methyladenine and a pyrrole units were isolated, especially agelasines O, P, Q, (Kubota et al. 2012). These latter showed potent growth inhibition activities against the bacteria *S. aureus*, *B. subtilis*, and *M. luteus* with MIC values ranging from 8.0 to 32.0 μg mL^{-1}, as well as against the fungi *A. niger*, *T. mentagrophytes*, *C. albicans*, and *C. neoformans* with more or less similar IC_{50} values.



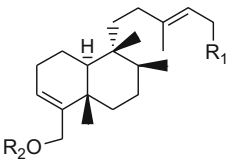
Agelasine O



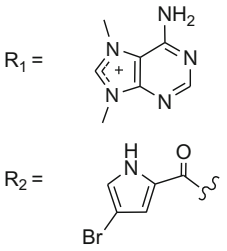
Agelasine P



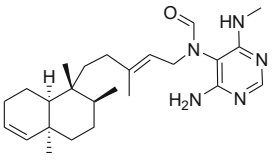
Agelasine Q



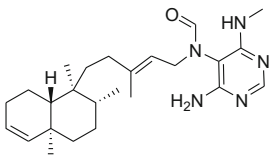
Agelasine R



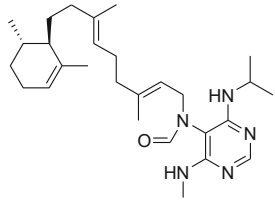
Three pyrimidine diterpenes, identified as axistatins 1, 2, and 3, were isolated from the marine sponge, *Agelas axifera* (Pettit et al. 2013). Axistatins 1, 2, and 3 have identical antimicrobial profiles, inhibiting Gram-positive bacteria, the sensitive Gram-negative pathogen *N. gonorrhoeae*, and the opportunistic fungus *C. neoformans* (ranges from 1 to 64 μg mL^{-1}).



Axistatin 1

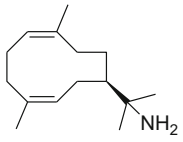


Axistatin 2



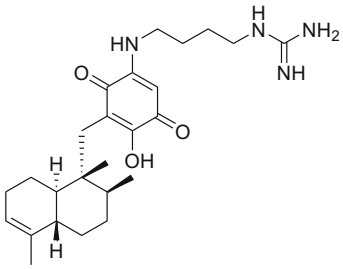
Axistatin 3

The germacrane sesquiterpene (1*Z*, 4*Z*)-7*αH*-11-aminogermacra-1(10),4-diene, isolated from a Thai marine sponge of *Axinyssa* n. sp., exhibited interesting antimicrobial activities at the concentration of 500 μg $disk^{-1}$ against *S. aureus*, *B. subtilis*, and *C. albicans* with inhibition zones of 23, 22, and 27 mm, respectively (Satitpatipan and Suwanborirux 2004).



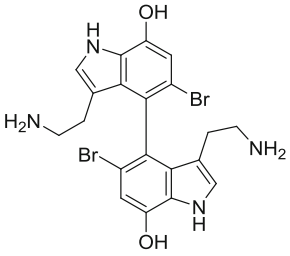
(1*Z*, 4*Z*)-7*αH*-11-Aminogermacra-1(10),4-diene

The original sesquiterpenoid quinone nakijiquinone H with an aminogroup derived from amino acids, was isolated from Okinawan marine sponges of the family *Spongiidae*. It showed antibacterial activity against *M. luteus* (MIC = 16.7 μg mL^{-1}), and antifungal activities against *C. neoformans* and *C. albicans* (same MIC values of 8.35 μg mL^{-1}), as well as against *A. niger* (MIC = 16.7 μg mL^{-1}) (Takahashi et al. 2008).



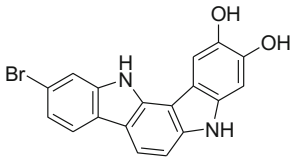
Nakijiquinone H

A unique C_2-symmetrical 4,4′-bis (7-hydroxy) indole alkaloid, dendridine A, was isolated from an Okinawan marine sponge *Dictyodendrilla* sp. Dendridine A exhibited inhibitory activities against both Gram-positive bacteria *B. subtilis* and *M. luteus* with MIC values of 8.3 and 4.2 μg mL^{-1}, respectively and the fungus *C. neoformans* with MIC value of 8.3 μg mL^{-1} (Tsuda et al. 2005).



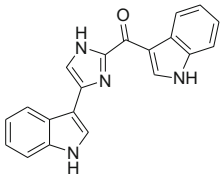
Dendridine A

An antimicrobial compound, indolo[3,2-*a*]carbazole, was discovered from a deepwater sponge *Ateropus* sp. It also displayed antimicrobial activities against *C. albicans* with a MIC value of 25 μg mL^{-1} and methicillin-resistant *S. aureus* with a MIC value of 50 μg mL^{-1}. No cytotoxicity was observed against the human PANC1 pancreatic carcinoma and NCI/ADR-Res ovarian adenocarcinoma cell lines at 5 μg mL^{-1} (Russell et al. 2013).

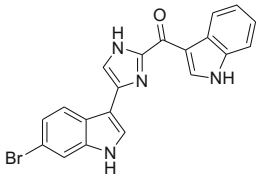


Indolo[3,2-*a*]carbazole

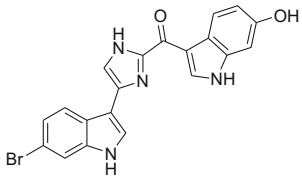
Bis-indole alkaloids, of the topsentin and hamacanthin classes, isolated from the sponge *Spongosorites* sp. were evaluated for their antimicrobial activities against various bacterial and fungi strains (Oh et al. 2006). Compounds of the hamacanthin class exhibited more potent antibacterial activity against medically important pathogenic fungi than those of the topsentin class. Deoxytopsentin and hamacanthin A also exhibited significant antibacterial activity against methicillin-resistant *S. aureus*, with MIC values less than 12.5 μg mL^{-1}. In addition, hamacanthin A also showed potent antifungal activity against *C. albicans*, *T. rubrum*, *T. mentagrophytes*, and *Aspergillus fumogatus* with MIC values ranging from 6.25 to 50 μg mL^{-1}.



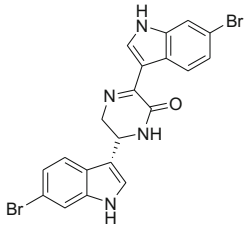
Deoxytopsentin



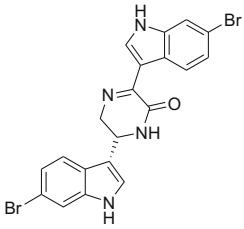
Bromodeoxytopsentin



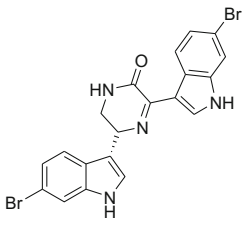
Bromotopsentin



trans-4,5-Dihydro-hamacanthin A



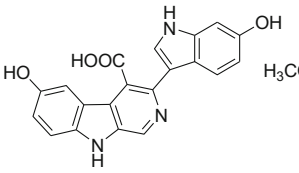
Hamacanthin A



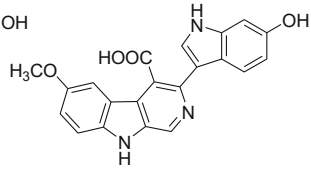
Hamacanthin B

Hyrtioerectines D, E, and F, isolated from a Red Sea sponge belonging to the genus *Hyrtios* are rare alkaloids possessing an indole nucleus and a *β*-carboline skeleton linked through C-3/C-3' of both fragments. They displayed moderate antifungal activities against *C. albicans* at the concentration of 10 μg $disk^{-1}$ with inhibition zones of 17, 9, and 14 mm, respectively, compared to 35 mm at the same concentration for the control clotrimazole. They also showed to inhibit the growth

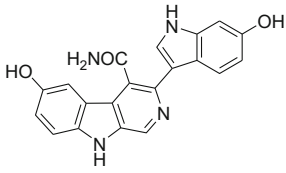
of *S. aureus* with inhibition zones of 20, 10, and 16 mm, respectively, compared to the control ampicillin (30 mm). But they were inactive against *E. coli*. It was reported that the three compounds exhibited low cytotoxic activity against the lung carcinoma A549, colorectal carcinoma HT29, and breast adenocarcinoma MDAMB231 with GI_{50} (concentration required to achieve 50% growth inhibition of the cells) from 25 to 100 μM; hyrtioerectines D and F being slightly more cytotoxic than hyrtioerectine E (Youssef et al. 2013).



Hyrtioerectine D

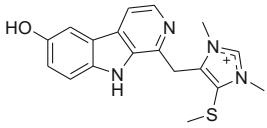


Hyrtioerectine E



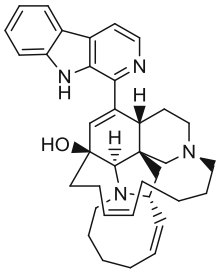
Hyrtioerectine F

A *β*-carboline alkaloid with an imidazole ring, gesashidine A (Iinuma et al. 2005), was isolated from an Okinawan marine sponge of the family *Thorectidae*. This compound showed antibacterial activity against *M. luteus* (MIC = 16.6 μg mL^{-1}).

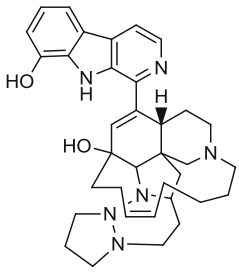


Gesashidine A

Keramamine A and B are *β*-carboline alkaloids having a 13-membered ring, which were isolated from the Okinawan marine sponge *Pellina* sp. as antimicrobial substances (Nakamura et al. 1987). Their MIC values against *S. aureus* were established as being 6.3 and 25 μg mL^{-1}, respectively.

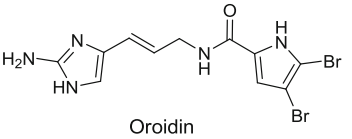


Keramamine A

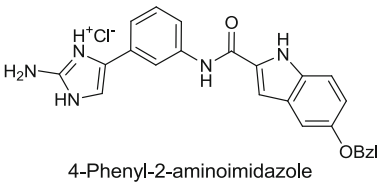


Keramamine B

Marine sponges have produced diverse bromopyrrole alkaloids, in particular from the genus *Agelas*. The marine alkaloid oroidin, isolated from an unidentified sponge of the genus *Agelas*, as well as the preparation of an oroidin derivative series, were evaluated for their antimicrobial potencies. Oroidin showed to inhibit the growth of the Gram-positive bacterial strain *S. aureus* with a MIC_{90} value of 100 μM. Interestingly, the 4-phenyl-2-aminoimidazole was found to have a MIC_{90} value of 12.5 μM against both *S. aureus* and *E. faecalis* and 50 μM against *E. coli*. This latter alkaloid revealed no cytotoxic activity at the highest tested concentration (IC_{50} > 100 μM) against the human hepatocellular carcinoma Huh-7 cell line whereas oroidin showed an IC_{50} value of 21.2 μM (Zidar et al. 2014).

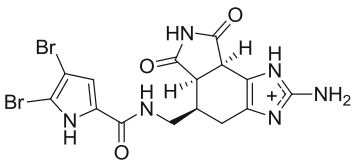


Oroidin

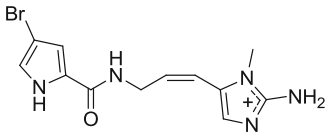


4-Phenyl-2-aminoimidazole

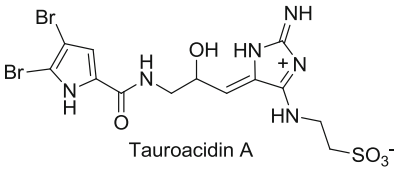
A series of bromopyrrole alkaloids, purified from an Okinawan marine sponge *Agelas* sp., were evaluated for their antimicrobial activities against diverse Gram-positive and Gram-negative bacterial strains as well as yeasts and fungi. The new bromopyrrole alkaloid mukanadin G, which has a tricyclic skeleton consisting of a fused tetrahydrobenzaminoimidazole and 2,5-dioxopyrrolidine functions, was the only one to show moderate antifungal activities against *C. albicans* and *C. neoformans* with IC_{50} values of 16 and 8.0 μg mL^{-1}, respectively. Both known alkaloids keramadine and tauroacidin A exhibited antibacterial activity against *M. luteus* with MIC values of 4.0 and 8.0 μg mL^{-1}, respectively (Kusama et al. 2014c).



Mukanadin G

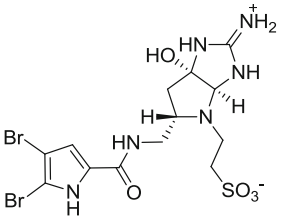


Keramadine

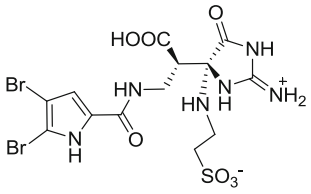


Tauroacidin A

Nagelamides M and N are two additional bromopyrrole alkaloids isolated from an Okinawan marine sponge *Agelas* species (Kubota et al. 2008). Nagelamide M carries a 2-amino-octahydropyrrolo[2,3-*d*] imidazole ring with a taurine unit, while nagelamide N consists of a 2-amino-tetrahydroimidazole-4-one ring with a taurine unit and 3-(dibromopyrrole-2-carboxamido) propanoic acid moiety. Both compounds showed inhibitory activity against *A. niger*, each with a MIC value of 33.3 μg mL^{-1}.

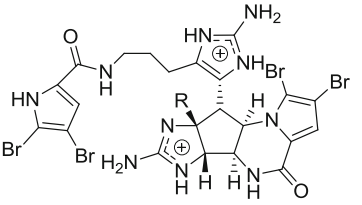


Nagelamide M

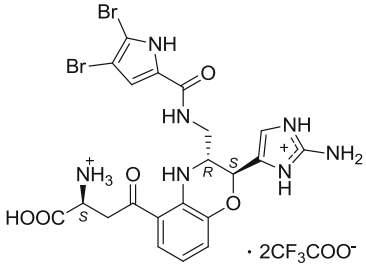


Nagelamide N

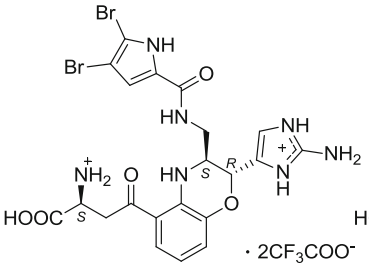
Bromopyrrole alkaloids derived from oroidin, hymenidin, and clathrodin monomers have also gained sufficient great interest due to their fascinating complex chemical structures with a high N to C ratio (∼1:2) and promising biological activities, including significant antimicrobial activities. Agelamadins A-B, isolated from an *Agelas* sp. sponge, are bromopyrrole alkaloids consisted of agelastatin-like tetracyclic and oroidin-like linear moieties, while agelamadins C, D, and E present an original structure combining oroidin structure coupled to a 3-hydroxykynurenine through a dihydro-1,4-oxazine moiety. Agelamadins D and E are a C-9/C-10 diastereomer and a 10-epimer of Agelamadin C, respectively. Both agelamadins A and B have exhibited the same antibacterial activity against *B. subtilis* (MIC = 16 μg mL^{-1}) and a MIC value of 4.0 and 8.0 μg mL^{-1} against *M. luteus*, respectively. All compounds showed antifungal activities against *C. neoformans* with IC_{50} values from 4.0–32 μg mL^{-1}. No cytotoxic activity was shown by agelamadins A and B (IC_{50} > 10 μg mL^{-1}) against the murine lymphoma L1210 and human epidermoid carcinoma cell lines (Kusama et al. 2014a, b).



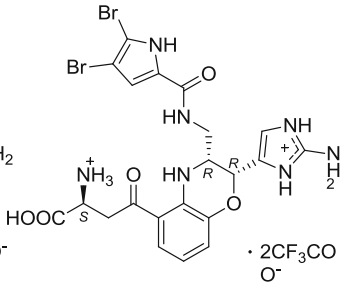
Agelamadin A : R = OMe
Agelamadin B : R = OH



Agelamadin C

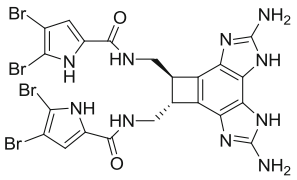


Agelamadin D



Agelamadin E

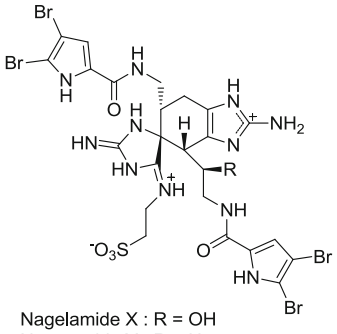
A dimeric bromopyrrole alkaloid, consisting of a benzocyclobutane ring, named bromosceptrin C, was isolated from an Okinawan marine sponge *Agelas* sp. It has shown antimicrobial activities against *B. subtilis*, *E. coli*, *M. luteus*, *S. aureus*, *T. mentagrophytes C. neoformans*, *C. albicans*, and *A. niger* with MIC values ranging from 6.0 to 13.0 μg mL^{-1} (Kubota et al. 2009).



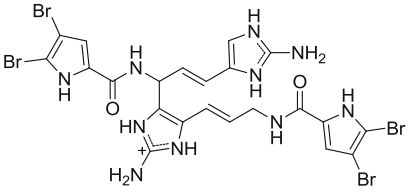
Bromosceptrin C

More recently, three dimeric bromopyrrole alkaloids, namely nagelamides X–Z, consisting of a novel tricyclic skeleton with spiro-bonded tetrahydrobenzaminoimidazole and aminoimidazolidine moieties, were isolated from the sponge *Agelas* sp. Nagelamines X and Z exhibited antibacterial activities against *S. aureus* and *M. luteus* with MIC values ranging from 8.0 to 16.0 μg mL^{-1}. All the three

compounds showed significant activities against *C. albicans* with MIC values ranging from 0.25 to 2 μg mL^{-1}. Nagelamide Z also displayed broad antifungal activities against *A. niger*, *T. mentagrophytes*, and *C. neoformans* with IC_{50} values of 4.0 and 2.0 μg mL^{-1}, respectively (Tanaka et al. 2013b).

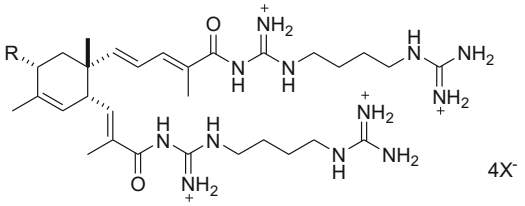


Nagelamide X : R = OH
Nagelamide Y : R = H



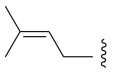
Nagelamide Z

Two other dimeric alkaloids, namely bistellettadines A and B, were isolated from *Stelletta* sp. collected from Shikine-jima island, located at 200 kms from South of Tokyo. These compounds inhibited the growth of the bacterium *E. coli* at 10 μg $disk^{-1}$ (Tsukamoto et al. 1999).

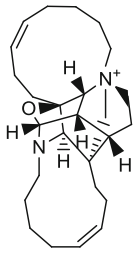


Bistellettadine A R=H

Bistellettadine B R=

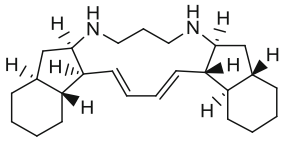


A manzamine-related alkaloid, zamamiphidin A, possessing an original heptacyclic ring system was isolated from an Okinawan marine sponge *Amphimedon* sp. (Kubota et al. 2013b). Zamamiphidin A showed a specific antibacterial activity against *S. aureus* with a MIC value of 32 μg mL^{-1}, while no activity was observed neither against *E. coli*, *B. subtilis*, and *M. luteus*, nor against diverse yeasts and fungi.

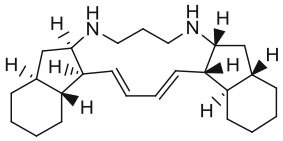


Zamamiphidin A

Marine sponge of *Haliclona* sp. collected from Papua New Guinea showed the existence of an unsymmetrical diastereoisomer of papuamine, namely haliclonadiamine, as the major antimicrobial alkaloid produced by the sponge along with the minor amount of papuamine. The structure of haliclonamine was established by X-ray crystallography. Both of the compounds inhibited the growth of *C. albicans*, *B. subtilis*, and *S. aureus* in the standard disk assay at the concentrations of 1.0–5.0 μg disk^{-1} (Fahy et al. 1988).



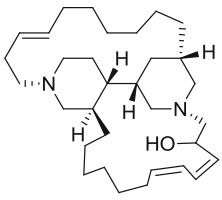
Haliclonadiamine



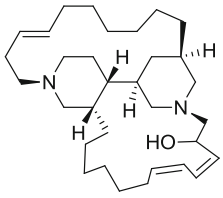
Papuamine

Arenosclerins A–C and haliclonacyclamine E, tetracyclic alkyl-bis-piperidine alkaloids isolated from the marine sponge, *Arenosclera brasiliensis*, were evaluated for antimicrobial activities against 14 microorganisms including the Gram-positive bacterial strains *S. aureus* ATCC 6538 as well as 9 MRSA strains isolated in hospital environment, the Gram-negative bacterial strain *E. coli* ATCC 25922, the antibiotic-resistant strain *P. aeruginosa*, and the yeast *C. albicans* (Torres et al. 2002). The four compounds displayed antibacterial activity against the bacterial strains methicillin-resistant *S. aureus* and *P. aeruginosa*, showing an inhibition zone between 7 and 13 mm, but did not show any effect against *E. coli* and *C. albicans*. Arenosclerin A and haliclonacyclamine E, which differ by the presence of one additional hydroxyl group, showing the same MIC value of 10 μg mL^{-1} against one MRSA bacterial strain, indicating that the hydroxyl group does not play any significant role in the antibacterial activity. In contrast, the modification of the stereochemistry of the bis-piperidine ring system seems to have a major influence on the activity. Both arenosclerins B and C exhibited the same MIC value of

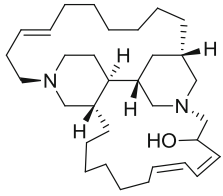
5 μg mL^{-1}, a much lower than those of arenosclerin A and haliclonacyclamine E. Another closely related bis-piperidine alkaloid, namely halicyclamine A, was isolated from the Australian sponge of the genus *Haliclona*. Halicyclamine A was also reported as a lead antituberculosis agent from a marine sponge of *Haliclona* sp. (Arai et al. 2008). It showed a growth inhibition against *M. smegmatis*, *Mycobacterium bovis* BCG, and *M. tuberculosis* H37Ra with the same MIC values of 2.5, 1.0, and 5.0 μg mL^{-1}, respectively, under both aerobic and hypoxic conditions namely in growing and dormant states. Another bis-piperidine alkaloid, identified as neopetrosiamine A from the Caribbean marine sponge *Neopetrosia proxima* (Wei et al. 2010), also showed a good MIC value of 7.5 μg mL^{-1} when tested in vitro against a pathogenic strain of *M. tuberculosis* $H_{37}Rv$ in a microplate Alamar Blue assay (MABA). It also displayed antiplasmodial activity against *Plasmodium falciparum* with an IC_{50} value of 2.3 μM as well as cytotoxic activities against a panel of cancer cell lines.



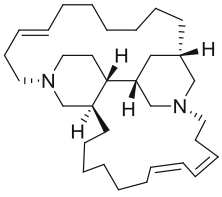
Arenosclerin A



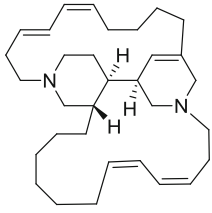
Arenosclerin B



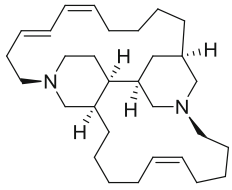
Arenosclerin C



Haliclonacyclamine E

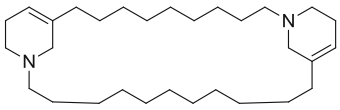


Halicyclamine A

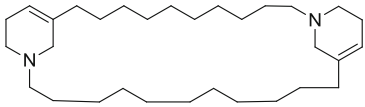


Neopetrosiamine A

Haliclamines C and D are 3-alkyl tetrahydropyridine alkaloids isolated from the Arctic marine sponge, *Haliclona viscosa* (Volk et al. 2004). Such compounds are of special interest as possible precursors in the biosynthesis of the bioactive manzamine alkaloids (Baldwin et al. 1999). When tested at the concentration of 5 mg mL^{-1}, they showed strong inhibition against *Polaribacter* spp. (inhibition zones of the bacterial growth from 3 to 7 mm) or very strong inhibition (inhibition zones of the bacterial growth from 7 to 15 mm) against *Planococcus* spp.

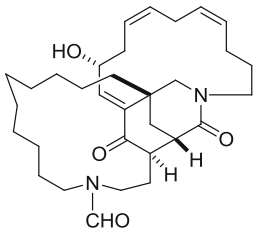


Haliclamine C



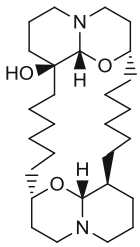
Haliclamine D

Haliclonin A is an original macrocyclic diamide metabolite isolated from the marine sponge, *Haliclona* sp. collected from Korean waters (Jang et al. 2009). When tested against Gram-positive and Gram-negative bacteria, haliclonin A exhibited moderate antibacterial activities with MIC values of 25.0, 6.25, 12.5, and 12.5 μg mL^{-1} against the strains *S. aureus* ATCC 6538p, *B. subtilis* ATCC 6633, *M. luteus* IFO12708 and *Proteus vulgaris* ATCC3851, respectively. It did not show any activity against *E. coli* ATCC25922 up to 100 μg mL^{-1}. It also displayed moderate cytotoxicity against the K562 leukemia cell lines with an IC_{50} value of 15.9 μg mL^{-1}.



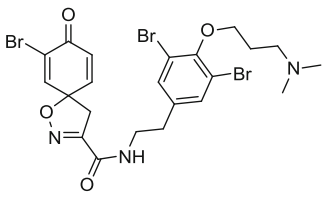
Haliclonin A

In 1996, Pettit's group reported the occurrence of the racemic (±)-Xestospongin D from the Singapore marine sponge *Niphates* sp. (Pettit et al. 1996). Previously, the natural macrocyclic 1-oxaquinolizidine (+)-xestospongin D was reported from the Australian marine sponge *Xestospongia exigua* (Nakagawa et al. 1984). Xestospongin D was found to inhibit the growth of the Gram-positive opportunist *M. luteus* with a MIC value ranging from 12.5–25 μg $disk^{-1}$. *M. luteus*, a part of normal human skin flora, has been shown to cause prosthetic value endocarditis in immuno-compromised patients (Dürst et al. 1991).

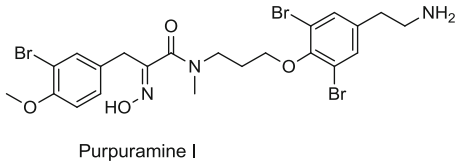


(+)- Xestospongin D

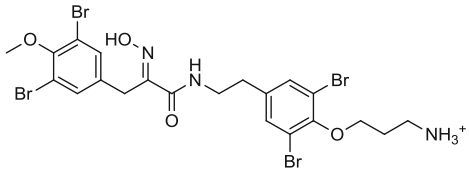
Three bromotyrosine alkaloids purpurealidin B, purpuramine I, and 16-debromoaplysamine-4, isolated from the marine sponge *Psammaplysilla purpurea*, exhibited a moderate or a weak in vitro antimicrobial activity against *E. coli*, *S. aureus*, and *Vibrio cholerae* (Tilvi et al. 2004) with the exception of purpurealidin B, which showed a good activity against *S. aureus* (MIC = 10 μg mL^{-1}) and *V. cholerae* (MIC = 25 μg mL^{-1}).



Purpurealidin B

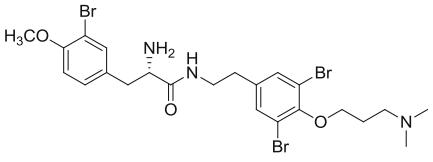


Purpuramine I

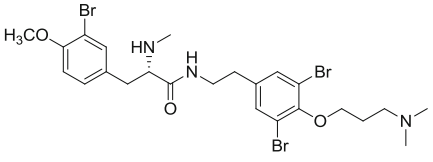


16-Debromoaplysamine-4

Two rare antimicrobial bromotyrosine alkaloids having a primary amino or an *N*-methyl amino group at the α-carbon, namely suberedamines A and B, were isolated from an Okinawan marine sponge *Suberea* sp. Each one of them showed antimicrobial activity against *M. luteus* with MIC values of 12.6 μg mL^{-1} (Tsuda et al. 2001).

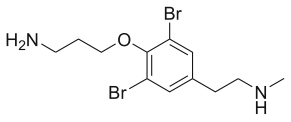


Suberedamine A

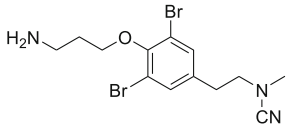


Suberedamine B

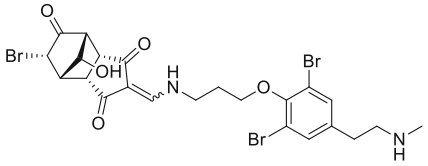
Three bromotyrosine derivatives, 11-*N*-methylmoloka'iamine, 11-*N*-cyano-11-*N*-methylmoloka'iamine and kuchinoenamine, were isolated as antibacterial constituents from a marine sponge *Hexadella* sp. (Matsunaga et al. 2005). They showed antibacterial activity in disk agar diffusion assay against the fish pathogenic bacteria *Aeromonas hydrophila* at the concentration of 100 µg disk^{-1} with the zone of inhibition of 7.5, 8.0, and 7.0 mm, respectively.



11-*N*-methylmoloka'iamine

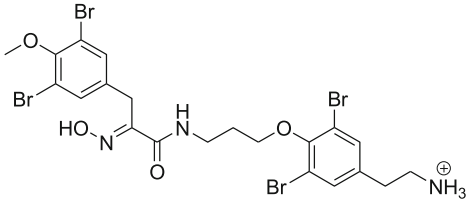


11-*N*-eyano-11-*N*- methylmoloka'iamine



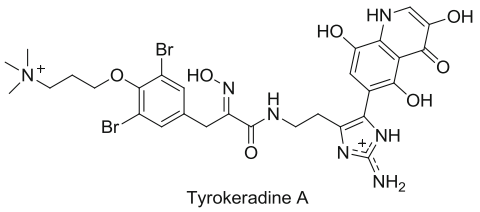
Kuchinoenamine

Another bromotyrosine compound, namely aplysamine 8, was isolated from the marine sponge *Pseudoceratina purpurea*, collected from the Australian coasts. This compound showed a moderate activity against *S. aureus* (MIC = 31 µg mL^{-1}) and *E. coli* (MIC = 125 µg mL^{-1}) (Gotsbacher and Karuso 2015).

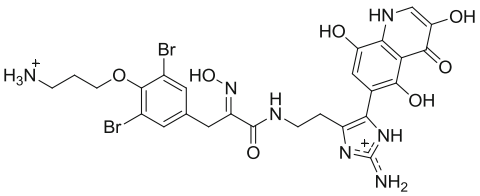


Aplysamine 8

Tyrokeradines A and B are two rare bromotyrosine alkaloids (Mukai et al. 2009) possessing an imidazolyl-quinolinone moiety isolated from an Okinawan marine sponge of the order Verongida. The alkaloid tyrokeradine B showed inhibitory activity against *M. luteus*, *S. aureus*, and *T. mentagrophytes* (MIC value of 25.0 µg mL^{-1}, each), and against *C. neoformans*, *C. albicans*, and *A. niger* (MIC value of 12.5 µg mL^{-1}, each). In contrast, tyrokeradine A did not show any activity up to 25 µg mL^{-1}.

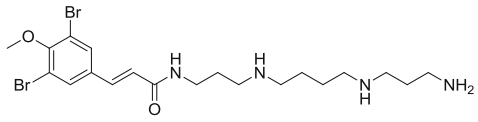


Tyrokeradine A

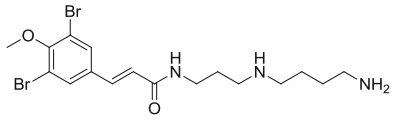


Tyrokeradine B

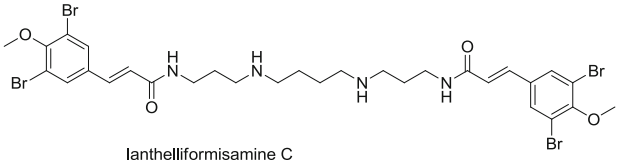
Only few bromotyrosine derivatives contain spermine or spermidine moiety as illustrated with ianthelliformisamines A-C isolated from the marine sponge *Suberea ianthelliformis* (Xu et al. 2012). Ianthelliformisamine A revealed a selective activity against *P. aeruginosa* PAO1 with an IC_{50} value of 6.8 μg mL^{-1} (MIC = 35 μg mL^{-1}), and 77% inhibition against *S. aureus* O1A1095 at 175 μg mL^{-1}. Ianthelliformisamine B showed only a minor inhibition (80% at 87.5 μg mL^{-1}) against *P. aeruginosa*, while ianthelliformisamine C showed IC_{50} values of 8.9 (MIC = 17.5 μg mL^{-1}) and 4.1 μg mL^{-1} (MIC = 8.75 μg mL^{-1}) against both *P. aeruginosa* and *S. aureus*, respectively.



Ianthelliformisamine A

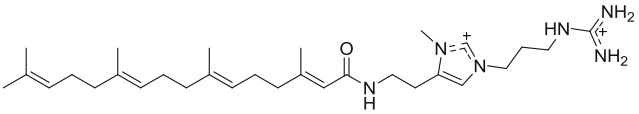


Ianthelliformisamine B

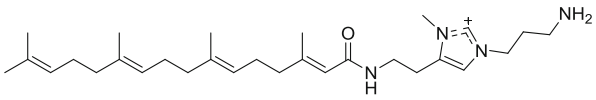


Ianthelliformisamine C

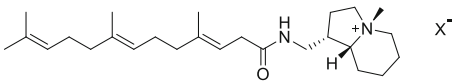
From a marine sponge of the genus *Stelletta*, three highly polar alkaloids, namely stellettazole B, stellettazole C, and stellettamide C, were isolated as antibacterial compounds against *E. coli*, showing inhibitory zones of 6.1, 6.2, and 10.5 mm at 20 μg disk^{-1}, respectively (Matsunaga et al. 1999).



Stelletazole B

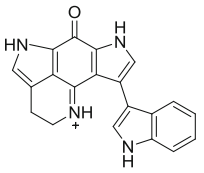


Stelletazole C

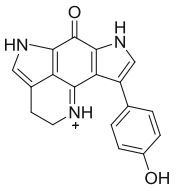


Stelletamide C

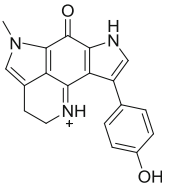
Two bis-pyrroloiminoquinone alkaloids, namely tsitsikammamines A and B along with both brominated discorhabdin C derivatives named 14-bromodiscorhabdin C and 14-bromodihydrodiscorhabdin C, isolated from an undescribed South African Latrunculid sponge, exhibited antimicrobial activity against *B. subtilis* comparable with that of wakayin (MIC = 0.3 μg mL^{-1}), previously isolated from the ascidian *Clavelina* sp. While tsitsikammamines A and B and related derivatives showed murine cell line cytotoxicity, they did not reveal, in contrast to wakayin, any topoisomerase II inhibition (Copp et al. 1991; Hooper et al. 1996).



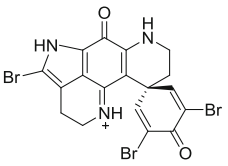
Wakayin



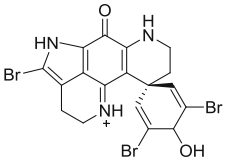
Thetsitsikammamine A



Thetsitsikammamine B

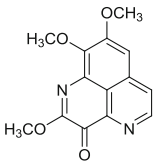


14-Bromodiscorhabdin C

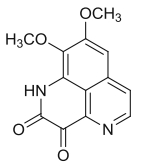


14-Bromodihydrodiscorhabdin C

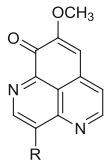
From the sponge *Aaptos* sp. collected at Kupang, Indonesia, the aaptamine alkaloid 2-methoxy-3-oxoaaptamine was isolated along with other known aaptamines, including 2,3-dihydro-2,3-dioxoaaptamine, demethyl(oxy)aaptamine, 3-aminodemethyl-aaptamine and 3-(methylamino)demethyl(oxy)aaptamine, as antimicrobials. Under active growing aerobic condition, 2-methoxy-3-oxoaaptamine and both amino derivatives showed antimicrobial activity against dormancy-induced *M. smegmatis* with a MIC value of 6.25 μg mL^{-1}, while both 2,3-dihydro-2,3-dioxoaaptamine and demethyl(oxy)aaptamine exhibited a moderate activity with a MIC value of 25 μg mL^{-1}, revealing the positive effect of the presence of the carbonyl in C-3 position. Under hypoxic condition, both amino derivatives appeared as the most promising with a MIC value of 1.5 μg mL^{-1}, in contrast to the others derivatives, for which a MIC value of 6.25 μg mL^{-1} was observed (Arai et al. 2014).



2-Methoxy-3-oxoaaptamine

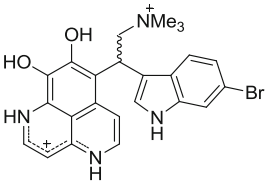


2,3-Dihydro-2,3-dioxoaaptamine

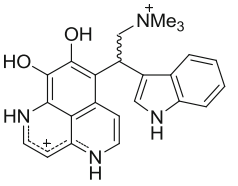


Demethyl(oxy)aaptamine : R = H
3-Aminodemethyl(oxy)aaptamine : R = NH_2
3-(Methylamino)demethyl(oxy)aaptamine : R = $NHCH_3$

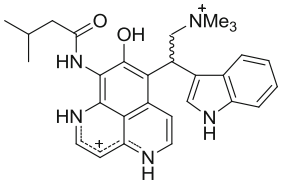
Out of seven secondary metabolites isolated from the Okinawan marine sponge, *Suberites* sp., the three bromodiscorhabdin derivatives, nakijinamines A, B, and F showed antimicrobial activities (Takahashi et al. 2012). Nakijinamine A exhibited activities against *C. albicans* (IC_{50} = 0.25 μg mL^{-1}), *C. neoformans* (IC_{50} = 0.5 μg mL^{-1}), *T. mentagrophytes* (IC_{50} = 0.25 μg mL^{-1}), *S. aures* (MIC = 16 μg mL^{-1}), *B. subtilis*), (MIC = 16 μg mL^{-1}), and *M. luteus* (MIC = 2 μg mL^{-1}), while both nakijinamines B and F showed activity against *C. albicans* (IC_{50} = 8 μg mL^{-1}). The three alkaloids did not show any cytotoxic activity against the murine lymphoma L1210 and human epidermoid carcinoma KB (IC_{50} > 10 μg mL^{-1}).



Nakijinamine A

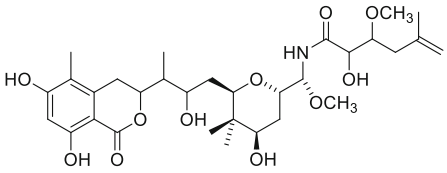


Nakijinamine B



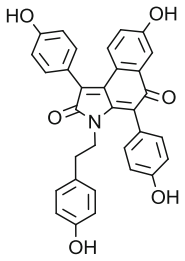
Nakijinamine F

Irciniastatin A, isolated from the Indo-Pacific marine sponge *Ircinia ramosa*, revealed antifungal and antibacterial activities, with MIC values of 16 and 64 μg mL^{-1} against *C. neoformans* and *N. gonorrhoeae*, respectively (Pettit et al. 2004). It also exhibited strong activities against the murine P388 leukemia cell line and diverse human cancer cell lines with GI_{50} values of 10^{-3}–10^{-4} μg mL^{-1}.



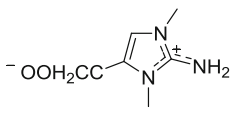
Irciniastatin A

Out of the three 3,4-diaryl pyrrole alkaloids isolated from the marine sponge *Dendrilla nigra*, denigrin C, isolated as an antimycobacterial compound against *M. tuberculosis* H37Rv (MIC = 4.0 μg mL^{-1}), is the only compound found active against both *B. subtilis* ATCC6633 and *S. aureus* ATCC25923 bacterial strains with the same MIC value of 6.25 μg mL^{-1} (Kumar et al. 2014).

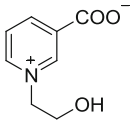


Denigrin C

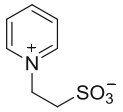
Three betaine alkaloids, aminozooanemonin, pyridinebetaine A, and pyridinebetaine B, were isolated from the Caribbean sponge *Agelas dispar* (Cafieri et al. 1998). Evaluation of their antibacterial activities against Gram-positive bacterial strains, *B. subtilis* ATCC6633 and *S. aureus* ATCC 6538 as well as the Gram-negative bacterial strain *Salmonella typhi* ATCC 19430 showed activities against Gram-positive bacteria for aminozooanemonin and pyridinebetaine with MIC values ranging from 2.5 to 8 μg mL^{-1}.



Aminozooanemonin

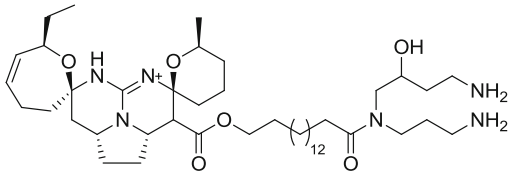


Pyridinebetaine A



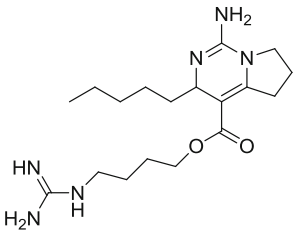
Pyridinebetaine B

Crambescidin 800 was isolated from the marine sponge *Clathria cervicornis*. This pentacyclic guanidine compound showed significant activities against *Acinetobacter baumannii*, *Klebesiella pneumonia* and *P. aeruginosa* with MIC values of 2.0, 1.0, and 1.0 μg mL^{-1}, respectively (Sun et al. 2015b).



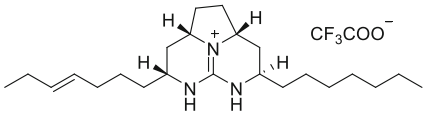
Crambescidin 800

The antibacterial bicyclic bis-guanidine type of alkaloid, namely sch 575948, isolated from the marine sponge *Ptilocaulis spiculifer*, exhibited antibacterial activity against a super sensitive strain of *S. aureus*, with inhibition zones of 13, 15, and 18 mm at the concentrations of 25, 50, and 100 μg disk^{-1}, respectively (Yang et al. 2003).

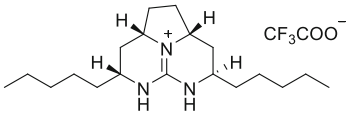


Sch 575948

Merobatzelladines A and B are tricyclic guanidine derivatives isolated from a marine sponge *Monanchora* sp. as antibacterial constituents (Takishima et al. 2009). They exhibited of a moderate antimicrobial activity against *Vibrio anguillarum* with inhibitory zones of 9–10 mm at 50 μg disk^{-1} (6 mm diameter).



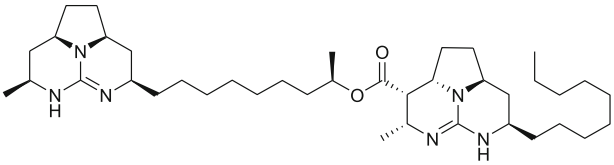
Merobatzelladine A



Merobatzelladine B

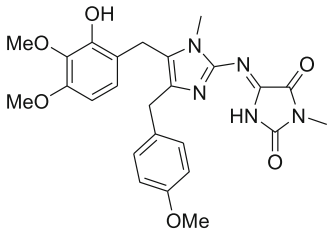
Interestingly is also the promising activity of the polycyclic guanidine alkaloid batzelladine L. This latter, isolated from the sponge *Monanchora arbuscula*, exhibited antifungal activities with MIC values ranging from 1.9 to 7.8 μg mL^{-1} against different strains of *Aspergillus flavus*, isolated from stored peanuts. Furthermore, batzelladine L showed significant antifungal activities against two resistant strains (MIC value of 3.9 μg mL^{-1} against both), in comparison with cercobin (MIC values of 15 and >250 μg mL^{-1}, respectively), an antifungal agent used in agriculture for a wide range of fungal diseases. As the world production of shelled peanuts (*Arachis hypogaea*) is around 38.6 and 5.8 million tons of peanut oil, we can

evaluate the impact of such result! Indeed, contamination of peanuts by aflatoxigenic fungi is an important economic problem in many tropical and subtropical areas of the world. Batzelladine L and derivatives could be useful constituents to overcome the thorny problem of aflatoxigenic strains (Arevabini et al. 2014).



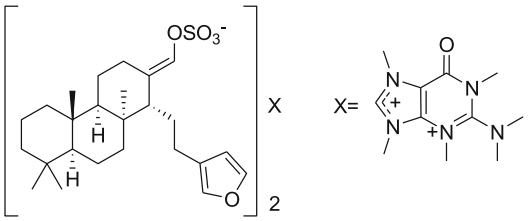
Batzelladine L

The imidazole alkaloid pyronaamidine (Plubrukarn et al. 1997), isolated from the Northern Mariana island sponge *Leucetta* sp. cf. *chagosensis* exhibited antimicrobial activities against *B. subtilis* and *C. albicans* at a concentration of 100 μg disk^{-1} (zones of inhibition of 10 and 7 mm, respectively).



Pyronaamidine

The suvanine *N*,*N*-dimethyl-1,3-dimethylherbipoline salt was isolated from a sponge of *Coscinoderma* sp. collected from Chuuk Island, Micronesia. This sulfated sesterterpene derived suvanine displayed antibacterial activities against the Gram-positive bacterial strains *S. aureus* ATCC6538, *B. subtilis* ATCC 6633, *K. rhizophila* NBRC12708 with MIC values of 6.25, 0.78, 6.25 μg mL^{-1} and against the Gram-negative strains *S. enterica* ATCC14028 and *P. hauseri* NBRC3851 with MIC values of 0.78 and 6.25 μg mL^{-1}, respectively. It was also reported having a moderate cytotoxicity against the human erythroleukemic cell line K562 and the adenocarcinomic human alveolar basal epithelial cell line A549 with LC_{50} values of 2.2 and 1.9 μM, respectively (Kim et al. 2014).

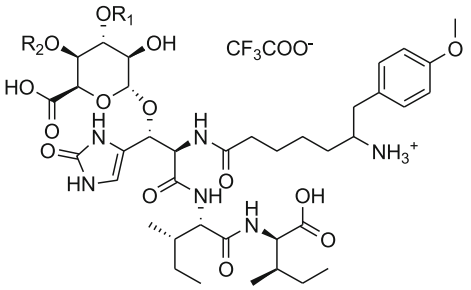


Suvanine salt

2.6 Peptides

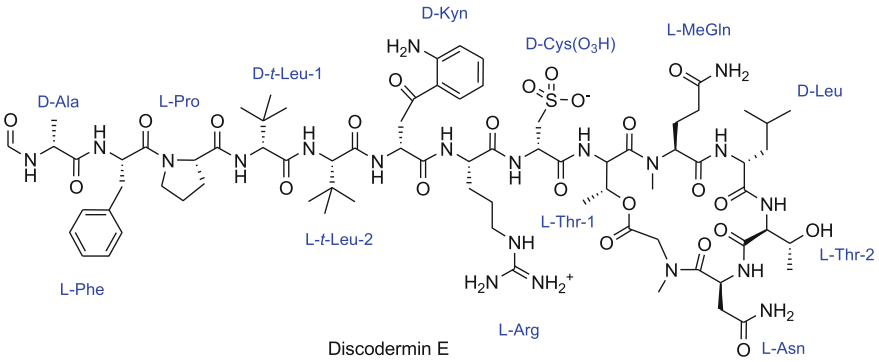
Marine peptides are structurally diverse and display a broad spectrum of bioactivities (Cheung et al. 2015). Recently, they have been reported as an alternative for innovative medicines (Da Costa et al. 2015). Cyclic peptides have been particularly studied because they provide potential anti-infective drug candidates (Kang et al. 2015), in particular as novel antifungal agents.

Two linear tetrapeptides, citronamides A and B, were isolated from the Australian sponge *Citronia astra* (Carroll et al. 2009). The peptides contained two previously unreported amino acids, 3-(2-oxo-2,3-dihydro-1*H*-imidazol-4-yl) serine and 6-amino-7-(4-methoxyphenyl) heptanoic acid, and α-iduronic acid modified at either C-3 or C-4 with a carbamate. Citronamide A showed moderate antifungal activity against *S. cerevisiae*.



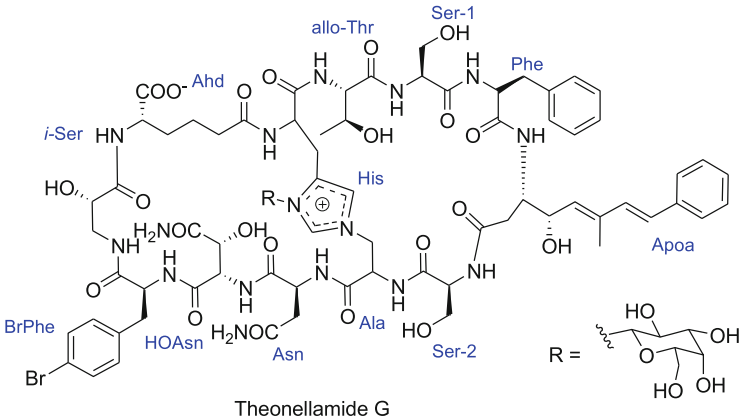
Citronamide A R_1 = $CONH_2$, R_2 = H
Citronamide B R_1 = H, R_2 = $CONH_2$

Discodermin E, was initially isolated from the marine sponge, *Discodermia kiiensis* as a cytotoxic compound against P388 leukemia cells (IC_{50} = 0.02 μg mL^{-1}). It also showed inhibition of the growth of *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa* at 2.5 μg $disk^{-1}$, and *Mortierella ramannianus*, *C. albicans*, and *P. chrysogenum* at 25 μg $disk^{-1}$. This tetradecapeptide also inhibited the development of *Asterinu pectiniferu* starfish embryo at 5 μg mL^{-1}.



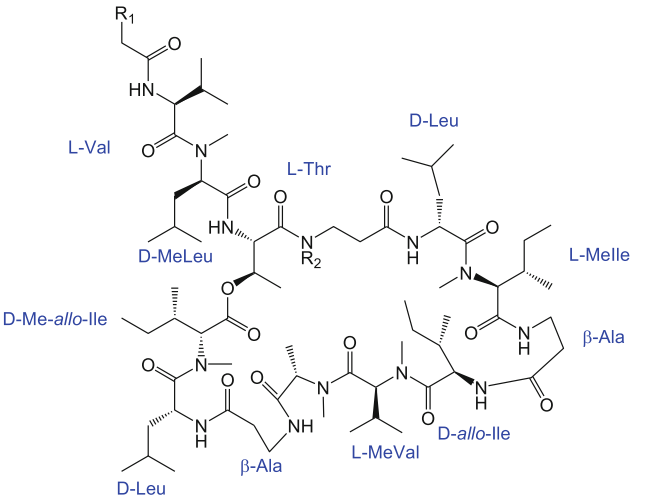
Discodermin E

A bicyclic glycopeptide, theonellamide G, purified from the Red Sea sponge *T. swinhoei*, showed antifungal activities against wild (ATCC 32354) and amphotericin B-resistant (ATCC 90873) *C. albicans* strains with IC_{50} values of 4.5 and 2.0 μM, respectively. It also displayed a cytotoxic activity against the human colon adenocarcinoma cell line HCT-16 with an IC_{50} of 6.0 μM (Youssef et al. 2014).

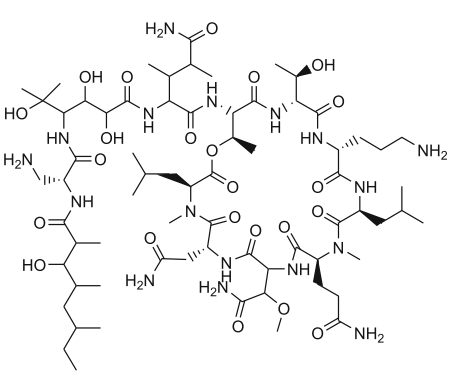


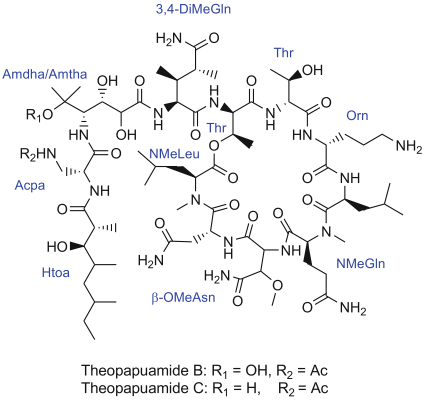
Theonellamide G

The following two theonellapeptolide-related cyclic depsipeptides have been isolated from an Okinawan marine sponge *Theonella* sp. (Tsuda et al. 1999). These depsipeptides showed moderate antimicrobial activities against some Gram-positive bacteria such as *S. aureus* (MIC = 8.0, and > 16 μg mL^{-1}, respectively), *M. luteus* (MIC = 8.0 μg mL^{-1} for both compounds), *B. subtilis* (MIC = 8.0 and 16.0 μg mL^{-1}, respectively), *M. smegmatis* (MIC = 16 and 66 μg mL^{-1}, respectively), and against fungi such as *T. mentagrophytes* (MIC = 4.0 and 8.0 μg mL^{-1}, respectively), and *A. niger* (MIC > 66 and 8.0 μg mL^{-1}, respectively).



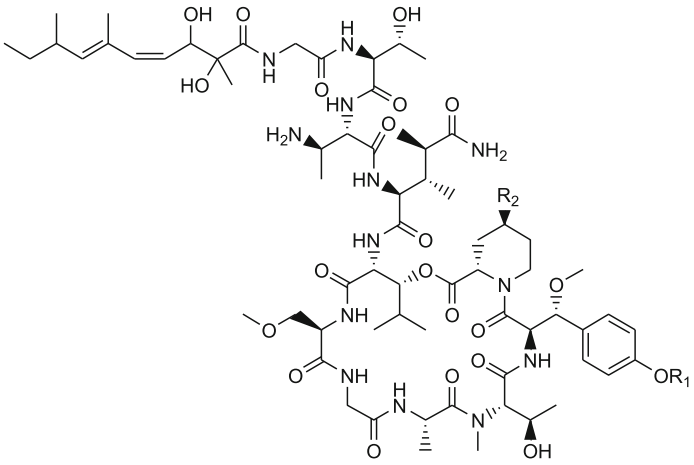
Theopapuamides A–C are depsipeptides isolated from the Indonesian marine sponge *Siliquariaspongia mirabilis*. The undecapeptides theopapuamides B–C revealing an *N*-terminal fatty acid moiety containing two original amino acids, 3-acetamido-2-aminopropanoic acid and 4-amino-2,3-dihydroxy-5-methylhexanoic acid. Theopapuamides A–C exhibited strong antifungal activities against wild-type and amphotericin B-resistant strains of *C. albicans* at the concentration of 1–5 μg $disk^{-1}$. They also showed cytotoxicity against human colon carcinoma HCT-116 cells with IC_{50} values ranging from 2.1 to 4.0 μg mL^{-1} (Ratnayake et al. 2006; Plaza et al. 2008).

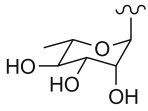




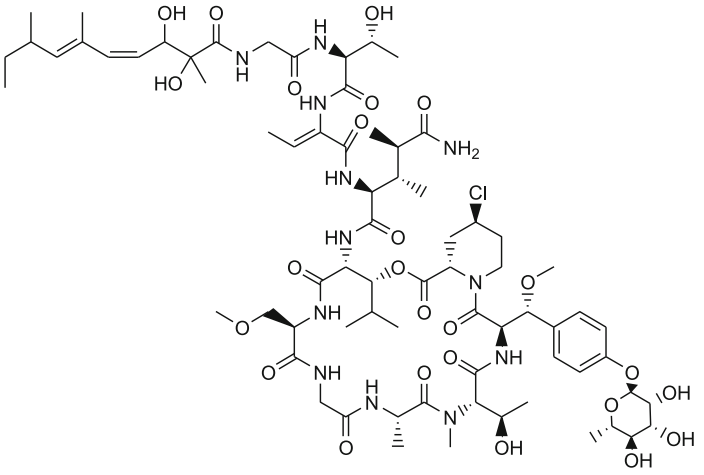
Theopapuamide B: R_1 = OH, R_2 = Ac
Theopapuamide C: R_1 = H, R_2 = Ac

Mirabamides A–C, are other depsipeptides previously isolated from the same sponge, that inhibited the growth of *B. subtilis* and *C. albicans* at 1–5 μg disk^{-1} in disk diffusion assays (Plaza et al. 2007). They are also reported as inhibitors of the envelope-mediated membrane fusion (HIV-fusion).



Mirabamide A: R_1 =  R_2 = Cl

Mirabamide C: R_1 = H, R_2 = Cl

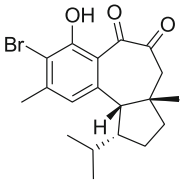


Mirabamide B

2.7 Miscellaneous Brominated Derivatives

Marine sponges have also provided various brominated organic compounds, especially diverse polybrominated ethers.

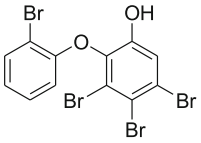
Hamigerans constitute a diverse structural family of brominated derivatives isolated from the sponge *Hamigera tarangaensis* (collected off New Zealand). Out of them, Hamigeran G was reported as an antifungal agent against the budding yeast *S. cerevisiae* (Singh et al. 2013).



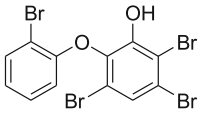
Hamigeran G

The marine sponge *Dysidea herbacea* collected from Indonesia yielded four tribrominated diphenyl ether congeners as well as known tetrabromo and dibromoderivatives (Handayani et al. 1997). All of the compounds were active against the Gram-positive bacteria *B. subtilis* and the phytopathogenic fungus *Cladosporium cucumerinum*. The isolated polybrominated compounds were also active in the brine shrimp lethality assay. Both 3,4,5,6- and 2,3,4,5-tetrabromo

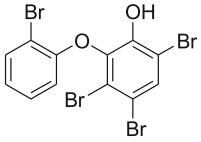
derivatives were found as the most active with IC_{50} values of 0.96 and 0.94 μg mL^{-1}, respectively.



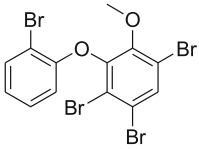
3,4,5-Tribromo-2-(2'-bromophenoxy)phenol



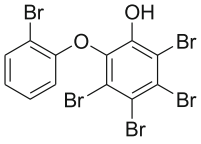
3,5,6-Tribromo-2-(2'-bromophenoxy)phenol



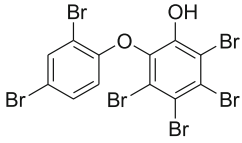
3,4,6-Tribromo-2-(2'-bromophenoxy)phenol



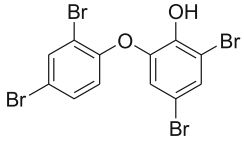
3,5,6-Tribromo-1-(2'-bromophenoxy)-2-benzene methyl ether



3,4,5,6-Tetrabromo-2-(2'-bromophenoxy)phenol

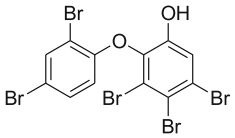


2,3,4,5-Tetrabromo-6-(2',4'-dibromophenoxy)phenol

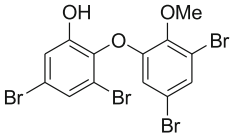


4,6-Dibromo-2-(2',4'-dibromophenoxy)phenol

The 2,3,4,5-tetrabromo-6-(2',4'-dibromophenoxy)phenol, previously mentioned, as well as the polybrominated compounds 3,4,5-tribromo-2-(2',4'-dibromophenoxy)phenol and 3,5-dibromo-2-(3',5'-dibromo-2'-methoxyphenoxy)phenol, isolated from unidentified marine sponges, exhibited a high activity against *S. aureus* (MIC_{100} = 0.36, 0.36, 0.15 μg mL^{-1}, respectively) and *T. mentagrophytes* (MIC_{100} = 3.12, 3.12, 1.56 μg mL^{-1}, respectively). They were found inactive towards *E. coli* and *Saccharomyces carlsbergensis* strains (Popov et al. 1999).

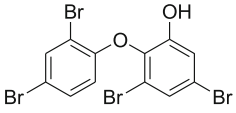


3,4,5-Tribromo-2-(2',4'-dibromophenoxy)phenol



3,5-Dibromo-2-(3',5'-dibromo-2'-methoxyphenoxy)phenol

More recently, the new 3,5-dibromo-2-(2′,4′-dibromophenoxy)phenol as well as the 3,4,5-tribromo-2-(2′,4′-dibromophenoxy)phenol were isolated as powerful antimicrobial compounds from the marine sponge *Dysidea granulosa*. These polybrominated diphenyl ethers revealed a broad spectral antimicrobial activity with MIC values in the range of 0.1–4.0 and 0.1–16.0 mg mL^{-1} against Gram-positive and -negative bacteria, respectively. In particular, they showed a MIC value of 0.1 mg L^{-1} against MRSA bacteria. Furthermore, the dibromophenol revealed a MIC value of 0.1 μg mL^{-1} against the Gram-negative bacterial strain *K. pneumoniae*. This result is particularly exciting since this activity is comparable and even stronger than the available antibiotics such as ciprofloxacin (MIC = 0.125 μg mL^{-1}), cefoxitin (MIC = 0.25 μg mL^{-1}), and imipenem (MIC = 0.25 μg mL^{-1}), used as positive controls in the assays. As *K. pneumoniae* can cause different types of healthcare-associated infections and have developed resistance to multiple antimicrobial drugs, especially to the class of carbapenems, 3,5-dibromo-2-(2′,4′-dibromophenoxy)phenol appeared as a lead compound for clinical applications. In addition, both compounds also inhibited a wide variety of Gram-negative pathogens, which the treatment options are greatly limited (Sun et al. 2015a).



3,5-Dibromo-2-(2',4'-dibromophenoxy)phenol

3 Antimicrobial Compounds from Sponge-Associated Bacteria

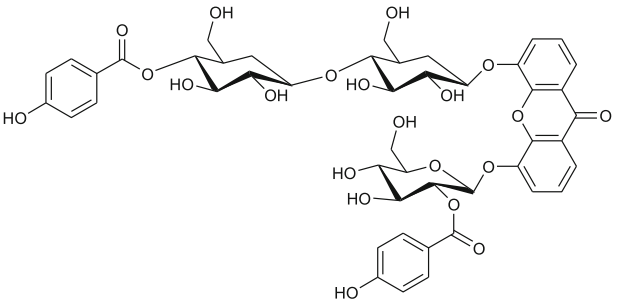
Intriguingly, close inspection of the structures of pharmacologically active natural products isolated from sponges and other marine invertebrates have revealed striking chemical similarities to known microbial metabolites. These observations, combined with those of the pioneer microscopic studies of sponge tissues from Vacelet and Wilkinson in the early 70s of the twentieth century, have attracted the attention of scientists towards sponge-associated bacteria in view of their potential involvement in the production of molecules of interest, in particular of antimicrobial molecules. So far, more than 30 bacterial phyla have been identified in Demospongiae such as Actinobacteria, Acidobacteria, Chloroflexi, Planctomycetes, Proteobacteria, Nitrospira, Cyanobacteria, Bacteroidetes, Verrucomicrobia, and Poribacteria (Taylor et al. 2007); some of them appearing specific to the Porifera, as illustrated with the bacterial phylum Poribacteria.

Although it is difficult to state with full surety about the biosynthetic marine natural products due to the complexity of the associations, the research of their localization within sponge-microorganisms associations has been conducted. Genome sequencings and heterologous expression of biosynthetic pathways can provide the ultimate proof for the production of secondary metabolites by associated microbes.

Using differential centrifugation experiment followed by chemical analysis of the different fractions, Faulkner and coworkers brought the first experimental evidence of the production of natural products by sponge-associated microbiome. Therefore, they demonstrated that the cytotoxic macrolide swinholide A was localized in unicellular heterotrophic bacteria and that the antifungal cyclic peptide theopalauamide was found within filamentous heterotrophic bacteria (Bewley et al. 1998).

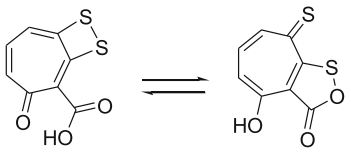
A cultivation of sponge-associated bacteria has been emerged as a novel source for obtaining novel chemical skeletons in large quantity and to overcome the thorny problem of supply of molecules of interest. However, it has been estimated that less than 1% of bacteria can be cultivated in laboratory conditions (Bernard et al. 2000). Therefore, novel strategies will have to be developed in order to cultivate so far uncultivable organisms. Several attempts have been made to improve the situation by changes in culture media and introduction of up-to-date technologies within cultivation procedures (Vartoukian et al. 2010; Stewart 2012; Rocha-Martin et al. 2014).

Microluside A, a *O*-glycosylated substituted xanthone, was obtained from the actinobacterium *Micrococcus* sp. EG45 isolated from the Red Sea marine sponge *Spheciospongia vagabunda*. This compound displayed antibacterial activities against *S. aureus* NCTC 8325 (MIC = 13 μM) and *E. faecalis* JH 212 (MIC = 10 μM), enterococci being common causes of nosocomial infections. No cytotoxicity against J774.1 macrophages was detected (IC_{50} > 200 μM) (Eltamany et al. 2014).



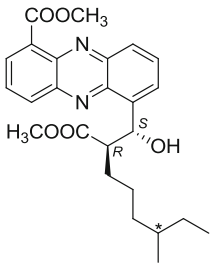
Microluside A

Pseudovibrio species are ubiquitous bacteria in the marine environment, especially within marine sponges. *Pseudovibrio* isolates from the sponges *Axinella dissimilis*, *Polymastia boletiformis* and *Haliclona simulans* showed to produce the antibacterial sulfur containing compound tropodithietic acid (TDA). This latter is formed by a dithiet moiety fused to tropone-2-carboxylic acid, which can coexist with its tautomer thiotorpocin. A bacterial extract containing 95% TDA was effective against a range of human-pathogenic bacteria, including both Gram-negative and -positive bacteria. TDA has shown to have a strong inhibitory activity against a wide range of marine bacteria, such as *S. enterica* serovar Typhimurium SL 1344, *E. coli*, NCTC 10538, *P. aeruginosa* NCTC 10662, *S. aureus* NCTC 8532, and *V. anguillarum* 90-11-287 (MIC from 3 to 25 μg mL^{-1}) (Porsby et al. 2011; Harrington et al. 2014).

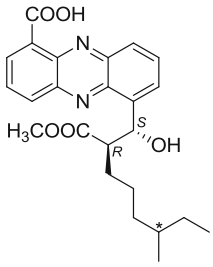


Tropodithietic acid Thiotropocin

A *Streptomyces* bacterium, *Streptomyces* sp. HB202, was isolated from the sponge *Halichondria panicea* collected from the Baltic Sea. Eight streptophenazines were purified from in vitro cultures of this bacterium using a dereplication strategy. Among these compounds, streptophenazine G and K displayed moderate antibacterial activities against *Staphylococcus epidermidis* (MIC = 8.4 and 14.5 μM, respectively) and *B. subtilis* (MIC = 8.2 μM and 21.6 μM, respectively) (Kunz et al. 2014).



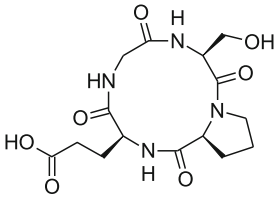
Streptophenazine G



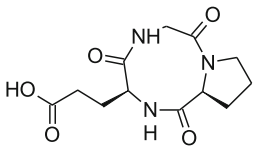
Streptophenazine K

The lantibiotic (e.g., a ribosomally synthetized and posttransiationally modified peptide with potent antimicrobial activities), namely subtilomycin, was isolated from the *B. subtilis* strain MMA7 isolated from the marine sponge *H. simulans*. This peptide, confirmed as T-W-A-T-I-G-K-T-I-V-Q-S-V-K-K, displayed antibacterial activities against Gram-positive and Gram-negative pathogens (*B. cereus*, *Bacillus megaterium*, *Listeria monocytogenes* and *Listeria innocua*) and against the fungus *Candida sporogenes* (Phelan et al. 2013).

Two cyclic peptides, identified as cyclo-(glycyl-L-seryl-L-prolyl-L-glutamyl) and cyclo-(glycyl-L-prolyl-L-glutamyl), were isolated from the *Ruegeria*, SDC-1 strain associated with cell cultures of *Suberites domuncula* (Mitova et al. 2004). Both peptides showed moderate effects against *B. subtilis* (MIC = 25 and 50 μg mL^{-1}, respectively) and no activity against *E. coli* and *S. cerevisiae*.

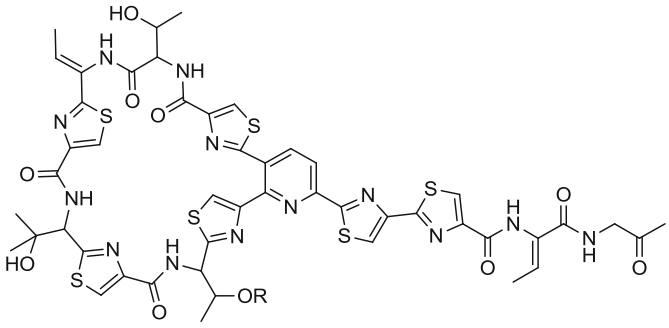


Cyclo- (glycyl-*L*-seryl-*L*-prolyl-*L*-glutamyl)



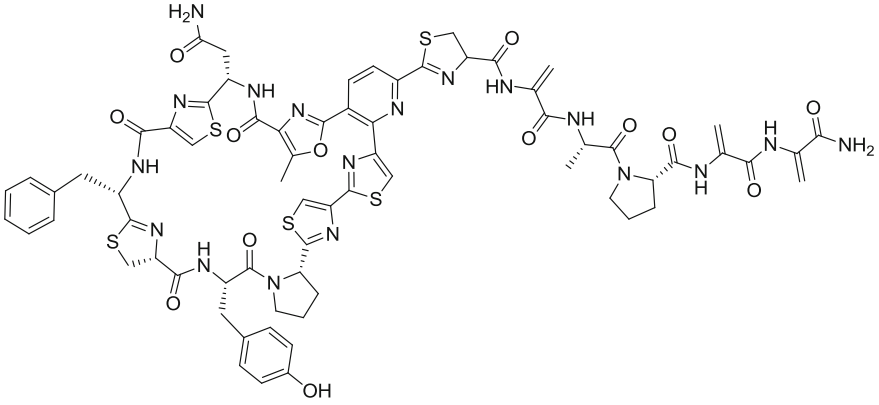
Cyclo-(glycyl-*L*-prolyl-*L*-glutamyl)

Novel antibiotics, YM-266183 and YM-266184, were found in the culture broth of *B. cereus* QN03323 which was isolated from the marine sponge *Halichondria japonica*. These thiopeptides exhibited potent antibacterial activities against the Gram-negative staphylococci and enterococci including multiple drug-resistant strains, whereas they were inactive against Gram-negative bacteria (Suzumura et al. 2003).



YM-266183: R= H
YM-266184: R= CH_3

Fourty four *Micrococcus* and *Kocuria* bacterial strains were collected from Florida Keys, Fort Lauderdale and Maryland sponges. Three isolates showed to produce in vitro a thiazolyl peptide, kocurin, of which the antimicrobial activity profile has shown to have extremely potent activities against Gram-positive bacteria with MIC values of 0.25–0.5 μg mL^{-1} against MRSA and no activity against the Gram-negative bacterial pathogens, *A. baumannii*, *P. aeruginosa*, and *E. coli*. None of these compounds exhibited cytotoxicity against human promyelocytic leukemia HL-60, human lung carcinoma A549, cervical carcinoma HeLa, and chronic leukemia K562 cell lines (Palomo et al. 2013).



Kocurin

4 Conclusions and Future Challenges

In the light of current medical need, activity against methicillin-resistant *S. aureus* (MRSA), extended-spectrum beta-lactamase producers (ESBL), carbapenem-resistant enterobacteriaceae (CRE), and drug-resistant *N. gonorrhoeae*, as well as discovery of novel druggable antimicrobial mechanisms of action, are of the great importance. Even if we are able to tackle the current challenges, some new resistances are likely to develop by the bacteria, which will devalue all the available antimicrobial drugs. Therefore, constant efforts are required for the introduction of new potent antibacterials. The value of natural products in such efforts is well recognized (Payne et al. 2007).

Marine sponge research produces more than 200 new compounds each year (Laport et al. 2009), providing an exceptional source of diverse marine bioactive compounds, especially, antibacterials. Activity against MRSA has been reported for sponges, as illustrated with the glycolipid caminoside A, the brominated lipids motualevic acids, the steroids halicrasterol H, the terpenes dysidavarone A, clathric acid, the tetracyclic alkylpiperidine haliclonacyclamine E, arenosclerins A–C, the indolo [3,2-*a*] carbazole, and the bis-indole alkaloid deoxytopsentin. Activities of those marine natural molecules span between 1.2 to 136.6 μg mL^{-1} and there is an obvious need for better understanding their mechanisms of action. Some indication of activity against *E. coli* has been detected with several reviewed molecules, nevertheless, no data is presented in relationship to ESBL producers. Axistatins are the only reviewed molecules that have been tested and demonstrated activity against *N. gonorrhoeae* in the concentration range which also influenced eukaryotic cells. Two polybrominated diphenylethers, namely 3,5-dibromo-2-(2′,4′-dibromophenoxy)phenol and 3,4,5-tribromo-2-(2′,4′-dibromophenoxy)phenol have shown nice potency against *K. pneumonia* and definitely should be tested against ESBL producers and CRE strains since such activities would be of great medical interest.

Vast majority of the currently used antibiotics came from nature and medicinal chemists working on novel antibiotic projects are painfully aware how hard it is to make better molecules. Therefore, it is most likely that next generation of great antimicrobial molecules will come from nature, too. It is just the extent and duration of optimization that nature did that one cannot adequately compete within the laboratory.

Obvious next step is to look at places in nature which were less accessible before, such as seas and oceans, and use techniques that humans were not able to use in last century when first generations of antibiotics have been discovered.

It is very important to test systematically and promptly all newly discovered natural molecules against resistant pathogens of medical interest and to elucidate their antimicrobial mode of action. Even if not being optimal drugs themselves, because of their relatively poor potency, lack of selectivity against human cells, or our inability to produce such molecules in significant quantities, they could be

excellent starting point for synthesis of analogues, biotechnological chemical investigations, and/or bioengineering. Furthermore, such novel molecules with potential novel modes of action could shed the light on still undiscovered mechanisms that play significant role in bacterial survival and virulence and that could be exploited as potential novel drug targets. Furthermore, quorum sensing, which controls many virulence factors responsible for bacterial infections appears to be a new promising path in the search of alternative antibiotic drugs (Saurav et al. 2016). Addressing quorum sensing has remarkable potential to weaken bacterial virulence and still does not put such pressure on bacteria that pushes them towards further mutations/changes. Therefore, anti-virulence therapy emerges as a new alternative that might be able to unlock the drug resistance threat and extensive research of symbiotic microbes could provide the clue where the right therapeutic interventions should be.

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