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Marine Natural Product Peptides with Therapeutic Potential: Chemistry, Biosynthesis, and Pharmacology

Vedanjali Gogineni[a] and **Mark T. Hamann**[b,*]

[a]Department of BioMolecular Sciences, Division of Medicinal Chemistry, School of Pharmacy, The University of Mississippi, University, MS

[b]Department of Drug Discovery and Biomedical Sciences, College of Pharmacy and Public Health Sciences, Medical University of South Carolina, Charleston, SC

Abstract

The oceans are a uniquely rich source of bioactive metabolites, of which sponges have been shown to be among the most prolific producers of diverse bioactive secondary metabolites with valuable therapeutic potential. Much attention has been focused on marine bioactive peptides due to their novel chemistry and diverse biological properties. As summarized in this review, marine peptides are known to exhibit various biological activities such as antiviral, anti-proliferative, antioxidant, anti-coagulant, anti-hypertensive, anti-cancer, antidiabetic, antiobesity, and calcium-binding activities. This review focuses on the chemistry and biology of peptides isolated from sponges, bacteria, cyanobacteria, fungi, ascidians, and other marine sources. The role of marine invertebrate microbiomes in natural products biosynthesis is discussed in this review along with the biosynthesis of modified peptides from different marine sources. The status of peptides in various phases of clinical trials is presented as well as the development of modified peptides including optimization of PK and bioavailability.

Keywords

Marine organisms; bioactive peptides; challenges; peptide isolation; biosynthesis; therapeutic peptides

I. INTRODUCTION

The oceans represent a vast resource for new bioactive natural products with utility in basic research, biomedical sciences, and the development of therapeutics. Marine organisms and in particular sponges produce an unprecedented variety of chemical classes with a wide range of biological activities and are considered the largest remaining reservoir of undiscovered natural molecules. Marine organisms produce unique molecules due to conditions that differ significantly from terrestrial environments which include aggressive,

*Author to whom correspondence should be addressed; hamannm@musc.edu, Tel.: +1-843-876-2316; Fax: +1-843-876-2353.
Present Address: Medical University of South Carolina, 70 President Street, Room 406 DDB, MSC 140 Charleston, SC 29425

Notes

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exigent, and competitive surroundings that lead to the production of potent active molecules [1].

Peptides are promising drug candidates based on the significance of the bioregulatory role of various endogenous peptides and the unique molecular mechanisms of action of bioactive peptides obtained from marine natural sources [2]. Complex cyclic and linear peptides discovered from marine sources have expanded our knowledge about ion-channels, antimicrobial agents, cytotoxic mechanisms of action, and other properties that has led to the introduction of marine peptides as novel and innovative therapeutics [1]. Trends in marine natural products chemistry has shifted toward the study of the microbiome that live in association with marine macroorganisms and the sustainable production of these compounds. In this review, we focus largely on the diversity of complex bioactive modified peptides isolated from various marine sources and the biological aspects of these molecules.

II. BIOACTIVE PEPTIDES FROM VARIOUS MARINE SOURCES

A. Sponges

Sponges belong to a large and diversified group of colonial organisms comprising the phylum Porifera. With thousands of various species distributed widely ranging from shallow estuaries to deep waters of the ocean, sponges are a source of varied and novel bioactive metabolites that include nucleoside derivatives, terpenoids, polyethers, alkaloids, and macrolides, in addition to modified peptides [3]. Sponges are an abundant source of bioactive and structurally diverse peptides that include linear peptides, depsipeptides, and cyclic peptides with the residue numbers spanning from two to forty eight. The diverse biological activities and the novel structural features of these metabolites have engendered considerable interest [4].

Most of the active peptides from sponges have unique structures which can either be linear or cyclic, possessing unusual amino acids that are rarely seen in terrestrial systems [1]. The tetradecapeptide discodermins were the first novel peptides isolated from sponges that showed cell growth inhibition [5]. Discodermins A [6], B, C, D [5], E [7], F, G, and H [8] isolated from the genus *Discodermia* are cytotoxic peptides possessing a chain of amino acids, some of which are common and others extremely rare, along with a macrocyclic ring. All of these molecules were found to be cytotoxic with IC_{50} values ranging from 0.02–20 μg/mL against P388 murine leukemia cells and A549 human lung cell-lines [1]. Kasumigamide is a tetrapeptide that was initially isolated from *Microcystis aeruginosa*, a freshwater cyanobacterium [9], but was later isolated from *Discodermia calyx* [10]. Kasumigamide is known to possess an *N*-terminal α-hydroxy acid and displayed antialgal activity at a minimum inhibitory concentration (MIC) of 2 μg/mL [9]. Previous studies reported the presence of a filamentous microorganism *Entotheonella* sp. in the lithistid sponge *Discodermia* species. Schmidt *et al.* [11] initially reported the genus *Entotheonella* in the δ-subdivision of '*Candidatus* Entotheonella palauensis,' a Proteobacteria, isolated from the marine sponge *Theonella swinhoei* [12]. Exploration of *Entotheonella* symbionts in *T. swinhoei* revealed a large biosynthetic repertoire, including the potential for the production of polytheonamides, onnamide A, and theopederin A, along with cyclotheonamides, proteusins, nazumamide, and keramamides [13].

Phakellistatins are unique examples of proline-rich cycloheptapeptides that were isolated from *Phakellia* sp. where phakellistatin 1 was found to exhibit cell growth inhibition against P388 murine leukemia cell-line at ED_{50} of 7.5 μg/mL [14]. Phakellistatins 2 [15] and 14 [16] showed cell growth inhibitory activity against the murine P388 lymphocytic leukemia with ED_{50} values of 0.34 μg/mL and 5 μg/mL, respectively. Phakellistatin 3 and isophakellistatin 3 are two isomeric *cyclo*-heptapeptides of which phakellistatin 3 showed significant P388 inhibition at an ED_{50} of 0.33 μg/mL [17]. Phakellistatin 4 exhibited inhibition of L1210 leukemia, LNCAP lung carcinoma, KB human epidermoid carcinoma, and SK-OV-3 ovarian cancer cell-lines at concentrations of 31.6 μg/mL [18,19], while phakellistatin 5 showed GI_{50} value of 0.6 μM [20]. Phakellistatin 6 inhibited the growth of human cancer cell lines at GI_{50} values ranging between 0.1 to 0.01 μg/mL [21]. Phakellistatins 7–9 inhibited P388 cancer cell growth at ED_{50} values of 3.0, 2.9, and 4.1 μg/mL, respectively [22], while phakellistatins 10 and 11 exhibited inhibition at ED_{50} values of 2.1 and 0.2 μg/mL, respectively [23]. Phakellistatin 12 inhibited the P388 lymphocytic leukemia at an ED_{50} value of 2.8 μg/mL [24].

Phakellistatin 13 is a cyclic heptapeptide isolated from *Phakellia fusca* that showed significant cytotoxicity at an ED_{50} value of $< 10^{-2}$ μg/mL against the BEL-7404 human hepatoma cell-line [25]. Phakellistatin 15 is a cyclic octapeptide with three proline moieties (in *trans* form) [26] that exhibited antitumor activity against P388 cell-line at an IC_{50} value of 8.5 μM, while phakellistatin 16 inhibited both P388 and BEL-7402 cell-lines at IC_{50} values of 5.4 and 14.3 μM, respectively [27]. Phakellistatins 17 and 18 exhibited no antitumor activity [27], while phakellistatin 19 showed antimitotic activity at IC_{50} values ranging between 84 to 420 nM [28].

Geodiamolides A-I are a group of cyclodepsipeptides isolated from *Geodia* sp., of which geodiamolides A and B showed antifungal activity against *Candida albicans* [29], while geodiamolide H exhibited *in vitro* cytotoxicity against a number of human cancer cell-lines [30]. Geodiamolides A-F are cytotoxic peptides isolated from *Pseudaxinyssa* sp., that showed cytotoxicity at 3.2, 2.6, 2.5, 39.0, 14.0, and 6.0 ng/mL, respectively [31]. Geodiamolides A, B, H, and I were anti-proliferative against breast-cancer cells through the disorganization of the actin filaments of T47D and MCF7 cancer cells [32]. Geodiamolides J-P, and R are cyclic depsipeptides isolated from the *Cymbastela* sp., while geodiamolide TA and neosiphoniamolide A were reported from *Hemiastrella minor* and *Neosiphonia superstes*, respectively. Geodiamolide G exhibited weak *in vitro* cytotoxicity against U373 human glioblastoma/astrocytoma and HEY human ovarian carcinoma cell-lines at IC_{50} values of 7.7 mg/mL and 8.6 mg/mL, respectively [33]. Jaspamide or jasplakinolide isolated from *Jaspis johnstoni* is a cyclic depsipeptide with a 15-carbon macrocyclic ring and three amino-acid residues. Jasplakinolide exhibited apoptosis in Jurkat T cells along with increased caspase-3 activity. The apoptosis induced by jaspamide is connected with reduced Bcl-2 protein expression and caspase-3 activation, along with enhanced Bax levels. Jaspamide is known to induce caspases-independent pathway of cell-death that is considered to be responsible for membrane and cytoplasmic changes in apoptosis cells, and a caspase-dependent cell death, responsible for PARP proteolysis [34]. Pipestelides A-C are cyclodepsipeptides isolated from *Pipestela candelabra*, and are non-ribosomal peptide synthetase - polyketide synthase (NRPS-PKS) hybrid macrolides that are biosynthetically

related to jaspamide. Pipestelides AC hold a bromotyrosine [3-amino-3-(bromo-4-hydroxyphenyl)propanoic acid] unit, polypropionate with a double bond (*Z*), and 2-hydroxyquinolinone, respectively. Pipestelide A exhibited potent cytotoxicity at an IC_{50} value of 0.1 μM, while pipestelide B showed modest activity but these cytotoxicity's were low compared to jaspamide [35].

Milnamide D, hemiasterlin, scleritodermin A, and diazonamide A are other marine peptides that exhibited potent tubulin-polymerization in various cancer-cells. Milnamides A and D isolated from the *Cymbastela* sp., were found to be potent against two colorectal cancer cell-lines: p53-deficient and HCT-116 cell-lines with IC_{50} values of 1.65 μM and 66.8 nM, respectively. Milnamide C was isolated from *Auletta* sp., and exhibited activity against MDA-MB-435 cancer cell-line at an IC_{50} value of 1.48×10^{-4} μg/mL along with microtubule cytoskeletal activity [36]. Milnamides A and D also inhibited tubulin polymerization at IC_{50} values of 6.02 μM and 16.90 μM, respectively [34,37,38]. Hemiasterlin, also known as milnamide B [36], is a natural tripeptide isolated from *Hemiasterella minor*, *Cymbastela* sp., *Siphonochalina* sp., and *Auletta* sp., and binds to the vinca peptide site in tubulin, resulting in the disruption of the normal microtubule dynamics and microtubule depolymerization. Hemiasterlin was also found to be potent against p53 and HCT-116 colorectal cancer cell-lines at an IC_{50} value of 6.8 nM [34,37]. Milnamides E-G and hemiasterlins A & D were isolated from *Pipestela candelabra*. Milnamides A-G exhibited cytotoxicity against prostate cancer (PC3) and human neonatal foreskin fibroblast non-cancer (NFF) cell-lines at IC_{50} values of 11.0 & 70.6 nM, 0.05 & 0.40 nM, 31.7 & 188 nM, 0.38 & 1.19 μM, 34.2 & 123 nM, 2.18 & 5.65 μM, and 2.87 & > 10 μM, respectively, while hemiasterlins A and D showed cytotoxicity against PC3 and NFF cancer cell-lines at IC_{50} values of 0.27 & 1.03 nM and 2.20 & 8.16 nM, respectively [39]. Scleritodermin A isolated from *Scleritoderma nodosum*, a lithistid sponge, is a cyclic peptide with potential *in vitro* cytotoxicity against human tumor cell-lines and an inhibitor of the tubulin-polymerization. Scleritodermin A was found to induce apoptosis at an IC_{50} of 1.3 μM, and was found to be cytotoxic at an IC_{50} value of < 2 μM [34,40,41].

Mirabamides isolated from *Siliquariaspongia mirabilis* showed potent inhibition against HIV-1 fusion. Among these, mirabamide A showed inhibition in HIV-1 fusion and neutralization assays with IC_{50} values of 140 and 40 nM, respectively, while mirabamides C and D exhibited lower potential with IC_{50} values between 1.3 μM & 140 nM and 3.9 μM & 190 nM, respectively. Mirabamides are known to inhibit HIV-1 at membrane fusion level, presumably from interactions with the HIV-1 envelope glycoproteins [42,43]. Mirabamides E-H are depsipeptides isolated from *Stelletta clavosa* and exhibited strong HIV-1 inhibition at IC_{50} values of 121, 62, 68, and 41 nM, respectively, in a neutralization assay [44].

Celebesides A-C and theopapuamides B-D were isolated from *Siliquariaspongia mirabilis*. Celebesides are exceptional cyclic depsipeptides that included a polyketide moiety along with five other amino-acid residues comprising a phosphoserine residue and an uncommon 3-carbamoyl threonine. Theopapuamides B-D are undecapeptides that possessed an *N*-terminal fatty acid moiety with two unreported amino acids: 4-amino-2,3-dihydroxy-5-methylhexanoic acid and 3-acetamido-2-aminopropanoic acid. Celebeside A inhibited HIV-1 in the neutralization assay at an IC_{50} value of 1.9 ± 0.4 μg/mL, while celebeside C was

found to be inactive even at high concentrations (50 μg/mL). Theopapuamide A isolated from *Theonella swinhoei* and theopapuamides B-C isolated from *S. mirabilis* showed cytotoxicity against human colon HCT-116 carcinoma cell-line with IC_{50} values between 2.1 to 4.0 μg/mL along with strong antifungal activity against amphotericin-B resistant strains of *Candida albicans* at concentrations of 1–5 μg/disk [45].

Among the ten homophymines isolated from the *Homophymia* sp., homophymine A showed cytoprotective activity against HIV-1 infection with IC_{50} value of 75 nM [46]. Homophymines B-E and A1-E1 were other cyclodepsipeptides isolated from the same sponge and exhibited potent antiproliferative activity against a panel of human cancer cell-lines with IC_{50} values ranging between 2–100 nM [47].

Neamphamide A isolated from *Neamphius huxleyi* is a cyclic depsipeptide that included 11 amino-acid residues with an amide linked 3-hydroxy-2,4,6-trimethylheptanoic acid moiety. It showed potent cytotoxicity against HIV-1 infection at EC_{50} value of 28 nM [48,49]. Neamphamides B-D isolated from the same sponge exhibited cytotoxicity against human cancer cell-lines with IC_{50} values ranging between 88 to 370 nM, while neamphamide D displayed A549 cell-proliferation at sub-cytotoxic doses [50].

Callipeltins are cyclodepsipeptides isolated from the *Callipelta* sp. Callipeltin A is a decapeptide with three unusual amino-acid residues: (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid, (3*S*,4*R*)-3,4-dimethyl-L-glutamine, and β-methoxytyrosine and was found to exhibit anti-HIV and antifungal activities. Callipeltin A is also a potent selective inhibitor of Na/Ca exchanger and a positive inotropic-agent when tested in guinea pig left-atria [51]. Callipeltin B showed weak inhibition activity at 4 μM, while callipeltins C and D exhibited no significant inhibitory activity on Na/Ca exchanger. All three callipeltins B-D did not induce any positive inotropic effect [51,52].

Callipeltin E [53] is a truncated linear peptide isolated from *Latrunculia* sp., with unique amino acids such as D-allothreonine, D-arginine, leucine, *N*-methylglutamine, *N*-methylalanine, and β-methoxytyrosine, while callipeltins F-I were also isolated from the same sponge. Callipeltins F-I exhibited antifungal activities against *Candida* at 10^{-4} M [54]. Callipeltins J-M are antifungal peptides isolated from *Latrunculia* sp., as well, where callipeltins K and J inhibited the growth of *C. albicans* at MIC value of 10^{-4} M [55]. Callipeltins N-Q are callipeltin derivatives isolated from the *Asteropus* sp., where callipeltins P and Q are acyclic callipeltins, while callipeltins N and O are cyclic callipeltins. Callipeltins N and O exhibited significant cytotoxicity against various cell-lines at an IC_{50} value of 0.16 μM explaining the significance of macrocyclisation as well as amino-acid composition in biological activity [56].

Microspinosamide is a cyclic depsipeptide (tridecapeptide) isolated from *Sidonops microspinosa* with numerous unusual amino acids and was the first naturally occurring peptide to comprise a β-hydroxy-ρ-bromophenylalanine residue. Microspinosamide exhibited cytopathic effect against HIV-1 infection with an EC_{50} value of 0.2 μg/mL in a XTT-based *in vitro* assay [57]. Carteritins A and B are cyclic heptapeptides isolated from *Stylissa carteri*. Carteritin A exhibited cytotoxicity against human cervical cancer HeLa,

human colon cancer HCT116, and murine macrophage RAW264 cell-lines at IC_{50} values of 0.7, 1.3, and 1.5 μM, respectively [58].

Mycothiazole is a mixed polyketide/peptide derived compound isolated from *Spongia mycofijiensis* that exhibited *in vitro* anti-helminthic activity against *Nippostrongylus braziliensis* at 50 μg/mL. Mycothiazole was the first disubstituted thiazole that was known to inhibit the hypoxic HIF1 signal in tumor cells correlating with the HIF1 target gene suppression of VEGF expression. Mycothiazole is also known to selectively suppress the mitochondrial respiration at NADH-ubiquinone oxidoreductase [complex I] and can serve as a valuable molecular probe for HIF-mediated hypoxic signaling and mitochondrial biology. The only other examples of compounds with thiazole moiety are dysidenins [Ex. isodysidenin] isolated from *Dysidea herbacea* [34,59]. Dysideaprolines A-F and barbaleucamides A-B were isolated from *Dysidea* species. Dysideaprolines A-F are proline analogs of dysidenin, while barbaleucamides A-B are structural analogs of barbamide that were previously isolated from the marine cyanobacterium, *Lyngbya majuscula*. No biological activity was reported for either dysideaprolines A-F or barbaleucamides A-B [60]. Dysithiazolamide is a polychlorinated dipeptide which was also isolated from *Dysidea* species. Dysithiazolamide is a tetrachloro amino acid derivative with two leucine-like fragments with no reported biological activity [61].

Microcionamides A and B are linear peptides isolated from *Clathria (Thalysias) abietina*, a Philippine marine sponge. The *C*-terminus of these peptides is blocked by a 2-phenylethylenamine group with the peptides being cyclized via a cysteine moiety. Both these peptides showed inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Ra$ and displayed potential cytotoxicity against human breast cancer cell-lines: SKBR-3 and MCF-7. Microcionamide A was active against SKBR-3 and MCF-7 cell-lines with IC_{50} values of 98 and 125 nM, respectively, while microcionamide B was active with IC_{50} values of 172 and 177 nM, respectively. Microcionamides A and B also displayed MIC values of 5.7 μM against *M. tuberculosis* $H_{37}Ra$ [34,62,63].

Halicylindramides A-C are tetradecapeptides isolated from *Halichondria cylindrata*, a Japanese marine sponge with their *C*-terminus lactonized with a threonine residue and the *N*-terminus blocked by a formyl group. Halicylindramides A-C were found to be cytotoxic against P388 murine leukemia cells with IC_{50} values of 0.54, 0.2, and 0.2 μg/mL, respectively, and exhibited antifungal activity against *Mortierella ramanniana* at 7.5 μg/disk. A *seco*-methyl ester generated from the halicylindramide B was found to be antifungal at 120 μg/disk, and was cytotoxic at 10 μg/mL [34,64].

Haligramides A and B are two cyclic hexapeptides isolated from *Haliclona nigra* along with a known peptide waiakeamide. Haligramide A was found to be cytotoxic against lung A-549, colon HCT-15, CNS SF-539, and CNS SNB-19 human cancer cell-lines at 5.17, 15.62, 9.00, and 9.08 μg/mL respectively, while haligramide B was cytotoxic at 3.89, 8.82, 5.01, and 6.56 μg/mL, respectively, towards the same cell-lines [34,65]. Waiakeamide was previously isolated from *Ircinia dendroides* and included three proline residues along with one thiazolylphenylalanine and two methionine sulfoxides. Waiakeamide exhibited potent activity against P388 cell-line at an IC_{50} value of 0.054 μg/mL [66]. A hexapeptide which is

a sulfone derivative of waiakeamide was also isolated from *Haliclona* sp., along with waiakeamide, but did not exhibit any cytotoxicity [67].

Corticiamide A and cyclocinamide B are two halogenated cyclic peptides that were isolated from the Fijian sponge, *Corticium* sp. Corticiamide A is a member of a family with structural similarities to peptides including microspinosamide A, discodermins, polydiscamide A, and halicylindramides. Cyclocinamide A was isolated from the *Psammocinia* sp., [68] and exhibited potent *in vitro* selective cytotoxicity towards solid tumors while cyclocinamide B showed no cytotoxicity against HCT-116 cell-line [34,69]. Pembamide is an *N*-methylated linear peptide isolated from *Cribrochalina* species belonging to the family *Niphatidae*. Pembamide was found to exhibit cytotoxicity against human lung A-549 tumor, human colon HT-29, and human breast MDA-MB-231 cancer cell-lines at GI_{50} values of 2.46, 3.80, and 3.35 μM, respectively [70]. Kapakahines A-D are cyclic peptides that were isolated from a Pohnpei sponge, *C. olemda*. Kapakahines possessed a unique structural feature where the two tryptophan residues are linked with an N-C bond from the indole nitrogen of Trp-1, rather than an amide bond to the Trp-2 β-indole carbon. Kapakahines A, C, and D are octapeptides while kapakahine B is a hexapeptide. Kapakahines A-C exhibited moderate cytotoxicity against murine leukemia P388 cells at IC_{50} values of 5.4, 5.0, and 5.0 μg/mL, respectively, while kapakahine D did not show any cytotoxicity at 10 μg/mL. Kapakahine A was tested against several enzymes but possessed only 15% inhibition against protein phosphatase 2A (PP2A) at 30 μM [71]. Kapakahines E-G were also isolated from *C. olemda* where kapakahine E exhibited cytotoxicity against murine leukemia P388 cells at an IC_{50} value of 5.0 μg/mL, while kapakahines F and G showed weak cytotoxicity at this concentration [72].

Taumycins A and B are two related lipodepsipeptides that were isolated from the Madagascan sponge, *Fascaplysinopsis* sp., which possessed a 12-membered oxodepsipeptide ring-system. Both the taumycins were found to be toxic to brine-shrimp larvae at IC_{50} values of 10 μg/mL, but only taumycin A showed inhibition against human UT-7 leukemic cell-line at 1 μM [73].

Pipecolidepsins A and B are two cyclodepsipeptides isolated from *Homophymia lamellosa*. Of these, pipecolidepsin A exhibited cytotoxicity against A549 lung, HT29 colon, and MDA-MB-231 breast cancer cell-lines at GI_{50} values of 0.6, 1.12, and 0.7 μM, respectively, while pipecolidepsin B showed GI_{50} values of 0.04, 0.01, and 0.02 μM, respectively. The replacement of Asp2 residue in pipecolidepsin A with a HOAsp amino-acid gave rise to a 10-fold increase in bioactivity of pipecolidepsin B, revealing the key role of the hydrophilic nature and substitution at C-3 position of this amino-acid residue in the mode of action [74,75].

Halipeptins A-D [76,77] are cyclic depsipeptides isolated from the *Haliclona* sp. Halipeptin A is a 17-membered cyclic depsipeptide containing two alanines and three novel residues: 3-hydroxy-2,2,4-trimethyl-7-methoxydecanoic acid [HTMMD], *N*-methyl-δ-hydroxyisoleucine, and 1,2-oxazetidine-4-methyl-4-carboxylic acid. Halipeptin A exhibited potent *in vivo* anti-inflammatory activity at a dose of 300 μg/kg causing about 60% edema inhibition in mice [76]. Halipeptin D displayed strong *in vitro* inhibition against HCT-116

human colon cancer cell-line at IC_{50} value of 7 nM, and against BMS oncology diverse cell panel (ODCA) of tumor cell-lines at IC_{50} value of 420 nM [77].

Tausalarin C is a bioactive nitrogenous bismacrolide peptide isolated from the Madagascar sponge, *Fascaplysinopsis* sp. Tausalarin C was found to inhibit the proliferation of the K562 leukemia cell-line at 1 μM [78]. Arenastatin A is a cyclic didepsipeptide isolated from *Dysidea arenaria*, an Okinawan marine sponge that exhibited potent cytotoxicity at an IC_{50} value of 5 pg/mL against KB cell-line [79,80]. Axinastatins 1–3 are cycloheptapeptides isolated from *Axinella* species [81]. Pseudoaxinellin, also known as axinastatin 1 or malaysiatin [82] is a cyclic heptapeptide isolated from *Pseudoaxinella massa* [83]. Axinastatins-2 and -3 are cytostatic against six human cancer cell-lines at GI_{50} values ranging from 0.35 to 0.0072 μg/mL with axinastatin 3 being more potent against PS leukemia cell-line at an ED_{50} of 0.4 μg/mL [81].

Hymenamides A and B are proline rich cyclic heptapeptides having a prolylproline segment and were isolated from *Hymeniacidon* sp., an Okinawan marine sponge. Hymenamide A has an arginine residue, while hymenamide B possessed glutamic acid as hydrophilic moieties. Both hymenamides exhibited antifungal activity against *C. albicans* at MIC values of 33 and 66 μg/mL, respectively, and against *Cryptococcus neoformans* at > 133 and 33 μg/mL, respectively. Hymenamide B also showed cytotoxicity against *in vitro* human epidermoid KB carcinoma and murine lymphoma L1210 cell-lines with IC_{50} values of 6.0 and 3.2 μg/mL, respectively [84]. Hymenamides C-E are cyclic heptapeptides with two proline residues that were also isolated from the same sponge. Of these, hymenamides C and E exhibited antifungal activity against *C. neoformans* at MIC value of 133 μg/mL, but did not show any cytotoxicity against both human epidermoid KB carcinoma and murine lymphoma L1210 cell-lines at an IC_{50} value of > 10 μg/mL [85]. Hymenamide F was also isolated from *Hymeniacidon* sp., which is a cyclic heptapeptide with an arginine and prolylproline residues [86]. Hymenamides G, H, J, and K are cyclic octapeptides isolated from *Hymeniacidon* sp. Hymenamides G and K exhibited no cytotoxicity while hymenamide H showed cytotoxicity against L1210 cell-line at an IC_{50} value of 6.3 μg/mL. Hymenamide J showed cytotoxicity against human epidermoid KB carcinoma and murine leukemia L1210 cell-lines at IC_{50} values of 0.76 and 2.6 μg/mL, respectively. Hymenamides G and K also exhibited cytotoxicity against protein tyrosine-kinase *c-erbB*-2^{14} at IC_{50} values of 63 and 73 μg/mL, respectively [87].

Wainunuamide is an unusual cyclic heptapeptide isolated from *Stylotella aurantium*, a Fijian marine sponge. This peptide included three proline residues along with a histidine residue, which is usually rare in cyclic peptides isolated from marine sponges. Wainunuamide was previously reported from the cyanobacterium, *Oscillatoria agardhii*, and was found to be weakly cytotoxic against K562 leukemia cancer and A2780 ovarian tumor cell-lines at ID_{50} values of 18.36 and 19.15 μg/mL, respectively [88]. Axinellins A and B are bioactive cyclopeptides that were isolated from *Axinella carteri* [89], while axinellins B and C are cyclic octapeptides that were isolated from *Stylotella aurantium*. Axinellins A and B exhibited moderate antitumor activity against NSCLC-N6 human bronchopulmonary non-small cell lung carcinoma cell-line at IC_{50} values of 3.0 and 7.3 μg/mL, respectively [89]. Axinellin C showed weak cytotoxicity against K562 leukemia cancer and A2780 ovarian

tumor cell-lines at ID_{50} values of 4.46 and 13.17 μg/mL, respectively [90]. Cyclonellin is another cyclic octapeptide that was also isolated from *A. carteri*. Cyclonellin was found to be inactive when tested at 50 μg/mL against human colon COLO-205 and ovarian OVCAR-3 tumor cell-lines [91]. Stylopeptide 1 is a cycloheptapeptide that was also isolated from *Stylotella* sp. and *Phakellia costata* [92]. Stylopeptide 2 is a proline rich cyclodecapeptide isolated from the *Stylotella* sp., and exhibited inhibition against BT-549 and HS 578T breast cancer cell-lines at a dose of 10^{-5} M [93]. Stylostatin 1 is another cycloheptapeptide that has been isolated from *S. aurantium* which exhibited lymphocytic P388 leukemia cell-growth inhibition at an ED_{50} value of 0.8 μg/mL [94]. Stylostatin 2, also a cycloheptapeptide, was isolated from the *Stylotella* sp. and *P. costata* [95].

Fenestins A and B are cyclic peptides isolated from *Leucophloeus fenestrata*. Fenestin A is cyclo-[L-Pro-L-Pro-L-Leu-L-Ile], while fenestin B is cyclo-[L-Pro-L-Val-L-Pro-L-Leu-L-Ile]. Fenestins were tested against HT-29 and P388 cell-lines and were found to exhibit no activity at concentrations up to 20 μg/mL [96]. Hymenistatin 1 is an antineoplastic cyclic peptide isolated from *Hymeniacidon* sp., and exhibited cytotoxicity against NCI murine P388 lymphocytic leukemia cell-line at ED_{50} of 3.5 μg/mL [97].

Discobahamins A and B are bioactive peptides isolated from *Discodermia* and were found to exhibit weak antifungal activity against *C. albicans* [98]. Calyxamides A and B are thiazole and 5-hydroxytryptophan moieties containing cyclic peptides that were isolated from *Discodermia calyx* [99] with moderate cytotoxicity against murine leukemia P388 cell-line [100].

Microsclerodermins A-E [101,102] are cyclic hexapeptides isolated from the *Microscleroderma* sp. Microsclerodermins A and B exhibited antifungal activity against *C. albicans* at 2.5 μg/disk [101]. Microsclerodermins C-E and anhydromicrosclerodermin C were also isolated from *Theonella* sp., Microsclerodermins C-E and anhydromicrosclerodermin C were all found to exhibit antifungal activity against *C. albicans* with microsclerodermin C being the most active at 5 μg/disk, followed by microsclerodermin E at 10 μg/disk, anhydromicrosclerodermin C at 50 μg/disk, and microsclerodermin D at 100 μg/disk [102]. Microsclerodermins F-I are other cyclic peptides that were also isolated from *Microscleroderma* sp., and exhibited cytotoxicity against HCT-116 cell-lines with IC_{50} values of 1.8, 2.4, 1.0, and 1.1 μg/mL, respectively. Microsclerodermins F-I inhibited the growth of *Candida albicans* with microsclerodermin F being the most potent at 1.5 μg/disk, while microsclerodermins G-I were active at 3, 12, and 25 μg/disk, respectively [103]. Microsclerodermins J-K are cyclic hexapeptides with moderate antifungal activity [104].

Aciculitins A-C are cyclic peptides isolated from the lithistid sponge, *Aciculites orientalis* and were found to be cytotoxic against HCT-116 cell-line at an IC_{50} value of 0.5 μg/mL along with exhibiting antifungal activity against *C. albicans* at 2.5 μg/disk. Aciculitins included a bicyclic peptide with an unusual histidine-tyrosine bridge. To the bicyclic peptide, C_{13}-C_{15} 2,3-dihydroxy-4,6-dienoic acids bearing D-lyxose is attached at position 3. Aciculitamides A-B are artifacts obtained from the same sponge probably reacting to the methanol used in extraction, resulting in oxidation of the imidazole ring. Aciculitamide A

did not show any cytotoxicity against HCT-116 and/or antifungal activity even at loadings of < 500 μg/disk [105].

Polydiscamide A is a depsipeptide comprising of 13 amino acids including the 3-methylisoleucine and was isolated from the *Discodermia* sp., Polydiscamide A inhibited proliferation of A549 human lung cancer cell-line *in vitro* at an IC_{50} value of 0.7 μg/mL along with inhibition of *Bacillus subtilis* growth at an MIC value of 3.1 μg/mL [106]. Polydiscamides B-D are potent human sensory neuron specific G protein coupled receptor (SNSR) agonists isolated from the *Ircinia* sp., at EC_{50} values of 1.26, 3.57, and 2.80 μM, respectively [107].

Criamides A and B are cytotoxic peptides isolated from the *Cymbastela* sp., and were found to be potent cytotoxins, both *in vitro* and *in vivo*. Criamide B exhibited cytotoxicity against A549 human lung, LOVO human colon, HEY human ovarian carcinoma, U373 human glioblastoma/astrocytoma, MCF7 human breast cancer, and P388 murine leukemia cell-lines at ED_{50} values of 0.29, 0.15, 0.19, 0.27, 6.8, and 0.0073 μg/mL, respectively [108]. Gombamide A is a cyclic thiopeptide isolated from *Clathria gombawuiensis* that displayed weak cytotoxicity against A549 and K562 cell-lines at LC_{50} values of 7.1 and 6.9 μM, respectively, along with moderate inhibition of Na^+/K^+-ATPase action at an LC_{50} value of 9.4 μM [109].

Euryjanicins A-D and dominicin are cyclic peptides isolated from *Prosuberites laughlini*. Euryjanicins A-D are proline-rich cycloheptapeptides while dominicin is a cyclooctapeptide. These peptides were marginally active to inactive when screened against NCI-60 tumor cell-line panel. The lost activity was reported due to the conformational changes of the cyclic peptides during the isolation or due to the binding ability of the peptides in low concentrations to the potent antineoplastic substances making them detectable only in biological screenings [110]. Euryjanicins E-G are cyclic heptapeptides with poly-phenylalanine and poly-proline residues, which were also isolated from *P. laughlini* with no anticancer activity when tested at 10 μM against NCI-60 tumor cell panel [111].

Neopetrosiamides A and B are diastereomeric (differ only in the configuration at the sulfoxide functionality) tricyclic peptides isolated from the *Neopetrosia* sp. Neopetrosiamides A and B were found to be active at 6 μg/mL in the amoeboid invasion assay with the potential to find drug-targets for the inhibition of amoeboid invasion of tumor-cells [112]. *N*-sulfoureidylated lipopeptides named sulfolipodiscamides A-C are cytotoxic peptides isolated from *Discodermia kiiensis*. Sulfolipodiscamides A-C possessed a unique feature of having an unprecedented *N*-sulfoureidyl group on the D-citrulline residue which is not found in other structurally similar lipodiscamides A-C. Of the three sulfolipodiscamides A-C, sulfolipodiscamide A exhibited a 2.3 fold increase in cytotoxicity against P388 murine leukemia cell-line compared to the parent compound [113]. Lipodiscamides A-C are lipodepsipeptides that were also isolated from *D. kiiensis*, and possessed an unprecedented dilactone macrocycle. Lipodiscamides A-C are probably the only lipopeptides that included a 4*S*-hydroxy-*trans*-2-enoate along with non-canonical amino acids: D-citrulline, *E*-dehydronorvaline, and L-3-ureidoalanine. Lipodiscamides A-C exhibited moderate cytotoxicity against murine P388 leukemia cells at IC_{50} values of 23, 20,

and 31 μM, respectively, while showed weak to moderate cytotoxicity against HeLa cells at IC_{50} values of 18, 26, and 46 μM, respectively [114]. Jamaicensamide A is a cyclic peptide with a thiazole-homologated amino acid along with six other amino acids and was isolated from *Plakina jamaicensis*, a Bahamian sponge, with no known antifungal activity [115].

Stylissamides A-D are cyclic heptapeptides that were isolated from *Stylissa caribica* and included three proline residues in stylissamides A, C, & D and four proline residues in stylissamide B [116]. In addition, stylissamides E [117], F [117], G [118], and H [118] were also isolated from *S. caribica*. Stylissamide E included two proline residues while stylissamide F was a polar peptide with three proline residues [117]. Stylissamide H showed modest cytotoxicity against HCT-116 at an EC_{50} of 5.7 μM [118]. Stylissamide X is another proline-rich octapeptide isolated from the *Stylissa* sp. that showed inhibition of HeLa cell-migration at concentrations ranging between 0.1 to 10 μM and 75% cell viability [118]. Stylissatin A is another cyclic heptapeptide isolated from *Stylissa massa* and inhibited the nitric oxide production in LPS stimulated RAW264.7 murine macrophage cells at an IC_{50} value of 87 μM [119]. Stylissatins B-D were also isolated from *S. massa*, of which stylissatin B exhibited inhibition against a panel of human tumor cell-lines such as MCF7, HepG2, A2780, NCI-H1650, BGC-823, and HCT-116 at IC_{50} values ranging between 2.4 to 9.8 μM [120]. Apart from stylissamides, stylisins 1 and 2 were other cyclic heptapeptides that were isolated from *S. caribica* with no known anti-inflammatory, anti-microbial, anti-malarial, anti-cancer, anti-Mtb, and anti-HIV-1 activities [121].

Reniochalistatins A-E are cyclic peptides isolated from *Reniochalina stalagmitis* where reniochalistatins A-D are heptapeptides while reniochalistatin E is an octapeptide. Reniochalistatins C and D were closely related to phakellistatin 18 and stylissamide C with more than 70% similarity in their peptide sequences, while reniochalistatins A-E differed in more than 50% similarity within their peptide sequences. Reniochalistatin E exhibited cytotoxicity against RPMI-8226 myeloma and MGC-803 gastric cell-lines at IC_{50} values of 4.9 and 9.7 μM, respectively, with no activity against HeLa cervical, HepG2 hepatoma, and HL-60 leukemia cell-lines. Reniochalistins A-D did not possess any cytotoxicity [122]. Yaku'amides A and B are cytotoxic peptides that were isolated from *Ceratopsion* sp., which inhibited murine leukemia P388 cells at IC_{50} values of 14 and 4 ng/mL, respectively. When tested against a panel of 39 human cancer cell-lines, yaku'amide A was found to possess a unique mode of action in its growth-inhibition activity [123].

Chujamides A and B are cyclic cysteine-bridged peptides isolated from the Korean sponge, *Suberites waedoensis*. Chujamides A and B showed weak cytotoxicity against A549 cell-line at LC_{50} values of 10.1 and 26.4 μM, respectively, and against K562 cell-line at LC_{50} values of 37.0 and 55.6 μM, respectively. Chujamide B also showed moderate inhibition of Na^+/K^+-ATPase at an IC_{50} value of 17.2 μM [124]. Leucamide A is another bioactive cyclic heptapeptide that was isolated from *Leucetta microraphis*. Leucamide A included a distinct mixed 4,2-bisheterocycle tandem pair with a thiazole and methyloxazole subunit and exhibited moderate cytotoxicity against several tumor cell-lines such as Huh7, HepG2, and HM02 at GI_{50} values of 5.1, 5.9, and 5.2 μg/mL, respectively [125].

Azumamides A-E are cyclic tetrapeptides that were isolated from *Mycale izuensis*. Azumamides A-E were the first examples of marine cyclic peptides that exhibited histone deacetylase inhibition between the IC_{50} range of 0.045 – 1.3 μM. Azumamide A also exhibited moderate cytotoxicity against human leukemia K562 and human colon WiDr cancer cells at IC_{50} values of 4.5 and 5.8 μM, respectively [126]. Phoriospongins A-B are nematocidal depsipeptides that were isolated from *Phoriospongia* species and *Callyspongia bilamellata*. Phoriospongin A was structurally similar to cyclolithistide A and both the phoriospongins exhibited nematocidal activity with an LD_{99} of 8.3 μg/mL [127].

Callyaerins A-F and H are cytotoxic cyclic peptides that were isolated from *Callyspongia aerizusa*. Callyaerins included ring systems with 5–9 amino acids and side-chains of 2–5 amino acids in length. The ring closure has an unusual (*Z*)-2,3-diaminoacrylic acid unit template. All the peptides included three or more proline-residues with other hydrophobic residues where all the amino acids are in L form. Callyaerins E and H displayed strong activity against L5178Y cell-line with ED_{50} values of 0.39 and 0.48 μM, respectively, while the rest were less active with ED_{50} values between 2.92 to 4.14 μM. Callyaerin F was found to be inactive [128]. Callyaerin G was isolated from *C. aerizusa* and exhibited cytotoxicity against human cervix carcinoma HeLa, mouse lymphoma L5178Y, and rat brain tumor PC12 cell-lines at concentrations between 3–10 μg/mL [129].

Sponges are a generous source of compounds with unique chemical structures including peptides. The sponge *Theonella swinhoei* has been explored exhaustively for more than a decade yielding unprecedented peptide chemistry [4]. Motuporin, a cyclic pentapeptide possessed inhibitory activity towards protein phosphatase 1 at concentrations less than 1 nM [130]. It also showed cytotoxicity towards breast, brain, colon, ovarian, murine leukemia, and human lung cancer cell-lines at IC_{50} values of 12.4, 2.4, 2.3, 2.8, 6.0, and 2.4 μg/mL, respectively [131]. Theonellapeptolide Id showed moderate cytotoxicity towards L1210 at an IC_{50} of 2.4 μg/mL. It is also known to possess ion transport activities towards Na^+, K^+, and Ca^{2+} ions [132]. Nazumazoles A-F are cyclic pentapeptides that were isolated from *T. swinhoei*. Nazumazoles A-C displayed cytotoxicity against murine leukemia P388 cell-line at an IC_{50} value of 0.83 μM [133,134]. Nazumazoles D-F are protease inhibitors that cleaved amide-bonds adjacent to hydrophobic amino acid residues at IC_{50} values of 2, 3, and 10 μM, respectively, but did not show any inhibition against thrombin or trypsin nor exhibited P388 cytotoxicity at concentrations of 50 μM [134].

Orbiculamide A is a cyclic peptide that showed cytotoxicity at an IC_{50} of 4.7 μg/mL towards P388 murine leukemia cell-line [135]. Polytheonamides A, B, and C are cyclic peptides that showed cytotoxicity at IC_{50} values of 78, 68, and 68 pg/mL, respectively, against P388 leukemia cell-line. Polytheonamide A is an epimer of polytheonamide B which differ in the stereochemistry of the sulfoxide at the 44^{th} residue [136,137].

There are a huge number of cyclic peptides with potent activity which included pseudotheonamides [138], and cyclotheonamides A and B [139], that act as serine protease inhibitors. Cyclotheonamide A was the first macrocyclic peptide to belong to the class of serine protease inhibitors. It is known to be a potent inhibitor of streptokinase and trypsin at IC_{50} values of 0.023 and 0.035 μM, respectively, and is also a moderate inhibitor of α-

thrombin at an IC_{50} of 0.18 μM [140]. Cyclotheonamides E, E2, and E3 also showed inhibitory activities against thrombin at IC_{50} values of 2.9, 13.0, and 9.5 nM, respectively. They showed inhibition against trypsin at IC_{50} values of 30, 55, and 52 nM, respectively [139]. Nazumamide A is a linear tetrapeptide and is a thrombin inhibitor at an IC_{50} of 2.8 μg/mL. This was the first natural peptide with a *N*-2,5-dihydroxybenzoate terminus [141]. Pseudotheonamides A1, A2, B2, C, D, and dihydrocyclotheonamide A are all linear pentapeptides that have a rare piperidinoiminoimidazolone and piperazinone ring system. They inhibited thrombin at IC_{50} values of 1.0, 3.0, 1.3, 0.19, 1.4, and 0.33 μM, respectively. They also inhibited trypsin at 4.5, > 10, 6.2, 3.8, > 10, and 6.7 μM, respectively [138].

The common characteristics of the peptides isolated from *Theonella* spp. included high degree of isomerism and similarities represented in the peptide families of theonellamides, keramamides, and many more. Theonellamides are bicyclic peptides with bromine and carbohydrate substituents. Theonellamides A-E showed cytotoxicity towards P388 leukemia cell-line at IC_{50} values of 5.0, 1.7, 2.5, 1.7, and 0.9 μg/mL, respectively [142]. Theonellamide G was later isolated from *T. swinhoei* and was found to exhibit antifungal activity against wild and amphotericin-B resistant strains of *C. albicans* with IC_{50} values of 4.5 and 2.0 μM, respectively. Theonellamide G also displayed cytotoxicity against human colon adenocarcinoma HCT-16 cell-line at an IC_{50} value of 6.0 μM [143]. Keramamides are cyclic peptides containing oxazole or thiazole rings. Keramamide A is a cyclic hexapeptide with inhibitory activity against sarcoplasmic reticulum Ca^{2+}-ATPase at an IC_{50} value of 3×10^{-4} moldm^{-3} [144]. Keramamides B-D showed inhibition towards human neutrophil superoxide generation at 5×10^{-8} M [145]. Keramamide F is a cytotoxic cyclic peptide containing unusual amino acids including an isoserine residue, a didehydrotryptophan, an α-ketoamide function as part of 3-amino-4-methyl-2-oxo-hexanoic acid, and an *O*-methylserylthiazole derivative [146]. Keramamides E, G, H, and J are thiazole or oxazole containing cyclic peptides where keramamide E showed cytotoxicity against human epidermoid KB carcinoma and murine leukemia L1210 cell-lines at IC_{50} values of 1.55 and 1.60 μg/mL, respectively. Keramamides G, H, and J exhibited weak cytotoxicity at IC_{50} value of ~ 10 μg/mL [147]. Keramamides K and L are cyclic peptides with an unusual tryptophan; keramamide K is a thiazole-containing cyclic peptide while keramamide L possessed a 6-chloro-*N*-methyltryptophan residue and an ureido bond. Keramamides K and L displayed cytotoxicity against murine leukemia L1210 cell-line at IC_{50} values of 0.72 and 0.46 μg/mL, respectively, and against epidermoid KB carcinoma cell-line at IC_{50} values of 0.42 and 0.9 μg/mL, respectively [148]. Keramamides M and N are cyclic peptides with a sulfate ester that were known to exhibit cytotoxicity against epidermoid KB carcinoma cell-line at IC_{50} values of 6.0 and 7.5 μg/mL, respectively, and against murine leukemia L1210 cell-line at IC_{50} values of 2.4 and 2.8 μg/mL, respectively [149].

Numerous peptides have been reported from *Theonella* spp. exhibiting promising activities such as anti-HIV-1, immunomodulatory, antifungal, antibacterial, enzyme inhibitory, and others. The diverse structures of peptides isolated from *Theonella* sp. range from linear to cyclic peptides, depsipeptides, and large bicyclic peptides. Koshikamides [150] and highly cytotoxic polytheonamides [136] are examples of linear peptides isolated from *Theonella* sp. Koshikamide A1 is a linear decapeptide with moderate cytotoxicity towards P388 leukemia cell-line at IC_{50} of 2.2 μg/mL [150]. Koshikamide A2 is a linear undecapeptide that showed

moderate cytotoxicity towards P388 cell-line at IC_{50} of 6.7 μg/mL [151]. Koshikamide B is a cyclic peptide lactone and showed cytotoxicity towards human colon tumor and P388 leukemia cell-lines at IC_{50} values of 3.7 and 0.22 μM, respectively [152]. Koshikamides C-E, and G did not inhibit HIV entry [153], while koshikamides F and H showed entry inhibition at IC_{50} values of 2.3 and 5.5 μM, respectively. Koshikamide H exhibited cytotoxicity towards colon cancer at IC_{50} of 10 μM [152].

The depsipeptide nagahamide A exhibited antibacterial activity [154], while papuamides A-D are HIV-1 inhibitors [155]. Nagahamide A is also a weak antibacterial agent at 50 μg when applied to an inhibitory zone of 7 mm [154]. Papuamides A and B are cyclic depsipeptides that inhibited the human T-lymphoblastoid cell infection at EC_{50} of 4 ng/mL. Papuamide A also exhibited cytotoxicity towards human cancer cells at IC_{50} of 75 ng/mL [155]. Papuamides A and B showed 80% HIV viral entry inhibition at 710 nM, while papuamides C and D showed 30% and 55% entry inhibitions at approximate concentrations of 40- and 20-fold higher [156]. Two other depsipeptides, papuamides E and F were isolated from the marine sponge belonging to the genus *Melophlus* collected from the Solomon Islands along with known papuamides C and D. Papuamides E-F exhibited cytotoxicity against brine-shrimp with LD_{50} values of 92 and 106 μg/mL, respectively [157]. Bicyclic peptides theonellamide F and theonegramide were reported as antifungal agents [158]. Theonellamide F, a dodecapeptide exhibited cytotoxicity against P388 and L1210 leukemia cell-lines at IC_{50} values of 2.7 and 3.2 μg/mL, respectively [158]. Theonegramide is a glycopeptide combined with a bicyclic dodecapeptide that exhibited antifungal activity against *Candida albicans* at 10 μg/disk loading [159]. Cupolamide A is a cyclic heptapeptide isolated from *Theonella cupola* that included one D-Ser, one D-Leu, and two L-Val along with three uncommon amino-acid residues: L-2,4-diaminobutanoic acid [Dba], D-homoarginine [Har], and *trans*-4-hydroxy-L-proline [Hyp]. Cupolamide A exhibited cytotoxicity against murine leukemia P388 cells at an IC_{50} value of 7.5 μg/mL [160].

Theonella swinhoei collected from different regions of Indonesia is also a rich source of peptides. A series of cyclic peptides called barangamides were isolated from *T. swinhoei* collected at Barang Lompo Island, Indonesia. Barangamides A-D were reported as new cyclic undecapeptides with *N*-methylated amino acids and β-alanine [161]. Barangamides A, B, C, and D are cyclic peptides that were reported to lack cytotoxic and immunosuppressive activities [161,162]. In addition to barangamides, the sponge also included theonellapeptolides Ia, Id, Ie, IId, and IIe. Barangamide A showed sequence homology with the ring part of theonellapeptolide Id. Moreover, barangamides B, C, and D were derivatives of theonellapeptolides Ib, Ia, and Ic, respectively [162].

Theonellapeptolides possessed unique characteristics that were rich in β-, D, and *N*-methyl amino acids. Theonellapeptolides Ia, Ib, Ic, Id, and Ie were reported for the first time from the Okinawan sponge *Theonella swinhoei*. These are tridecapeptide lactones that showed moderate cytotoxicity against L1210 cell-line at IC_{50} values of 1.6, 1.3, 2.4, and 1.4 μg/mL respectively, except for theonellapeptolide Ia. These tridecapeptides inhibited the development of the fertilized eggs of the sea urchin, *Hemicentrotus pulcherrimus* [132], [163]. Theonellapeptolide Id [164] exhibited ion-transport activity for Na^+, K^+, and Ca^{2+} ions while theonellapeptolide Ie has activity for Na^+ and K^+ ions in erythrocyte membranes

of humans [132]. Theonellapeptolide Ie also caused malformation of starfish oocytes *Asterina pectinifera* [165]. Theonellapeptolides IId and IIe showed cytotoxicity at 9.4 μM. Of these two, theonellapeptolide IId exhibited the strongest immunosuppressive activity [152]. Theonellapeptolide IIIe, a 36-membered cyclic peptolide exhibited moderate cytotoxicity towards P388 at 7.4 μg/mL [166].

The crystal structures of theonellapeptolides Id and IIIe have been reported [166,167,168]. Theonellapeptolide IIIe was reported as a cytotoxic constituent of the deep water sponge, *Lamellomorpha strongylata*. This finding suggested that the sponge-associated microbes may be responsible for the biosynthesis of the peptides [166].

Two congeners of theonellapeptolides have been isolated from the Okinawan sponge, *Theonella* sp [170]. Congener **1** replaced the methoxyacetyl of theonellapeptolide with a methylsulfinylacetyl group at the *N*-terminus, while congener **2** possessed an acetyl group. Congeners 1 and 2 exhibited antifungal activity against *Trichophyton mentagrophytes* (4.0 & 8.0 μg/mL), *Aspergillus niger* (> 66 & 8.0 μg/mL), and antibacterial activity against *Staphylococcus aureus* (8.0 & > 16 μg/mL), *Micrococcus luteus* (8.0 μg/mL), *Bacillus subtilis* (8.0 & 16 μg/mL), and *Mycobacterium smegmatis* (16 & 66 μg/mL), respectively. They exhibited cytotoxicity towards L1210 leukemia cell-line at IC_{50} values of 9.0 and 7.5 μg/mL, respectively [170]. Solomonamides A and B are two unprecedented cyclic peptides isolated from *T. swinhoei* where solomonamide A exhibited anti-inflammatory activity at a dose of 100 μg/kg [171].

Cyclolithistide A along with motuporin and theonellapeptolide Id were isolated from *Theonella swinhoei* collected from the Sangihe Island, Indonesia. Cyclolithistide A included the unique amino acids: 4-amino-3,5-dihydrohexanoic acid, formyl-leucine, and chloroleucine. Cyclolithistide A is a cyclic depsipeptide that exhibited antifungal activity at 20 μg/disk [172]. In addition, it has been reported that *T. swinhoei* collected from the same location also possessed a series of swinholides A-G, theonellamine B, and theopalauamide A. Theonellamine B is used as a synonym for theonellapeptolide Id [173]. Theopalauamide differs from theonegramide in the presence of D-galactose instead of D-arabinose [174]. Theopalauamide is a bicyclic glycopeptide that showed inhibition towards *Candida albicans* at 10 μg/disk, while isotheopalauamide exhibited inhibition at 50 μg/disk. Isotheopalauamide is a stable conformational isomer of theopalauamide [174]. Oriamide is another cyclic peptide with a novel 4-propenoyl-2-tyrosylthiazole amino acid [PTT] that was also isolated from *T. swinhoei* [175].

Miraziridine A, paltolides A-C, perthamides B-F, and mutremdamide A are other peptides isolated from *Theonella*. Miraziridine A is a linear peptide with a rare aziridine-2,3-dicarboxylic acid residue, and was found to be a cathepsin B inhibitor at an IC_{50} value of 2.1 μM. Paltolides A-C are anabaenopeptin-type peptides. Anabaenopeptin class compounds included an *N*-methylated amino acid prior and adjacent to the *C*-terminal residue that is cyclized to the ε-amine of lysine residue. Paltolide A was the first reported anabaenopeptin-type peptide missing an *N*-methyl group at this site. Due to the presence of a *C*-terminal tryptophan residue linkage to the ε-amine of the *N*-terminal lysine residue, paltolides belong to the rare sub-group of anabaenopeptins. Other compounds in this subgroup are

carboxypeptidase U inhibitors. Paltolides A-B did not exhibit any biological activity in HCT-116 or HIV-1 entry assays, while the carboxypeptidase U inhibition has not been evaluated [152]. Perthamide B is a cyclic octapeptide with weak binding inhibition of [^{125}I]IL-1β to the intact EL46.1 cells at an IC_{50} value of 27.6 μM [177]. Perthamides C-E displayed anti-inflammatory activity that is known to mediate via TNF-α up-regulation [178]. Perthamides C and D displayed 60% and 46% edema reductions at a dose of 0.3 mg/kg. Similar to perthamide C, perthamides H, I, and K also exhibited similar behavior at 0.3 mg/kg [179]. Perthamides inhibited TNF-α and IL-8 release in the human primary keratinocyte cells, and hence could be the potential leads for psoriasis treatment [178]. Mutremdamide A was isolated from *T. swinhoei* and *T. cupola* and differs from perthamide C in the mutual presence of sulfation and carbamoylation of β-OH and N^{δ}-amide groups of β-OHAsn, respectively. Perthamide C had a *threo* configuration at C-2/C-3, while mutremdamide A displayed an *erythro* configuration [153]. Mutremdamide A is a sulfated cyclic depsipeptide similar to perthamide B exhibiting 60% edema inhibition at 0.3 mg/kg and is at least 100 times more potent than naproxen which has an ED_{50} of 40 mg/kg [152].

From a biological point of view, *Theonella swinhoei* is unique because it is a host to various microorganisms. Histological and ultra-structural investigation of *T. swinhoei* from the Red Sea and Indian Ocean revealed that the sponge may have ingested filamentous bacteria. In addition, the polychaete *Haplosyllis spongicola* was present in the aquiferous system of the sponge [180].

The metabolites reported from the Lithistid sponge including *Theonella* sp., revealed a degree of similarity with metabolites from microorganisms [Figure 45] [181,182,183]. This led to the suggestion that the metabolites from these sponges may be produced by symbiotic microorganisms, specifically cyanobacteria. This suggestion is also supported by the fact that these marine peptides included *D*- and unusual amino acids as well as additional side chains which are characteristic of microbial metabolites [130]. Cellular localization of metabolites along with analysis of the types of symbionts also supported the hypothesis. The presence of filamentous microorganisms in the interior of *T. swinhoei* correlated with the presence of theopalauamide, while the presence of unicellular bacteria correlated with the biosynthesis of swinholide A [184].

The structure of motuporin, an inhibitor of protein phosphatase 1 from *T. swinhoei* differs from nodularin isolated from the cyanobacteria, *Nodularia pumigena* only in the replacement of L-valine with L-arginine. Nodularin, a monocyclic pentapeptide exhibited inhibition towards protein phosphatases 1 and 2A at ED_{50} of 0.7 nM [185]. A cyclic peptide keramamide A isolated from the *Theonella* sp., [186] incorporated a 5-hydroxytryptophan residue and a ureido linkage, joining two amino acid residues that shared similarities with the main skeleton of ferintoic acids isolated from the fresh water cyanobacteria, *Microcystis aeruginosa* [187]. Keramamide A, a cyclic hexapeptide inhibited sarcoplasmic reticulum Ca^{2+}-ATPase at an IC_{50} of 3×10^{-4} moldm^{-3} [144]. Ferintoic acids A and B are two cyclic hexapeptides that did not exhibit any chymotrypsin inhibition at concentrations up to 1.5×10^{-4} M [187]. The structure of mozamide A isolated from the *Theonella* sp., [144] is closely related to brunsvicamides A and B isolated from a cyanobacterial strain. The difference is in the presence of hydroxylated tryptophan and the absolute configuration of some amino acid

residues [188]. Mozamides A and B are two cyclic peptides that did not exhibit any antimicrobial activity towards yeast or gram positive, and gram negative bacteria at low concentrations [189].

B. Marine Bacteria

Turnagainolides A and B isolated from *Bacillus* sp., are C-3 epimeric cyclic peptides where turnagainolide B stimulated the inositol 5-phosphatase SHIP1. Inositol 5-phosphatase SHIP1 is a negative regulator of PI3K (phosphatidylinositol-3-kinase) pathway, and its irregular functioning is associated with some cancers and inflammatory diseases [190]. Solonamides A and B are cyclic peptides isolated from a bacterial strain [tropical Pacific Ocean mussel] allied to *Photobacterium halotolerans* that hindered the *agr* quorum sensing system which controls the virulence gene expression in *S. aureus* [190]. Actinoramides A-C are modified peptides with unusual amino acids: 4-amino-3-hydroxy-2-methyl-5-phenylpentanoic acid and 2-amino-4-ureidobutanoic acid isolated from a bacterium closely associated to the genus *Streptomyces* [190]. Fijimycins A-C are three depsipeptides isolated from a *Streptomyces* strain that occurred as a complex conformational mixture and showed prominent activity against three MRSA strains [190]. Brunsvicamides A-C are cyclic hexapeptides isolated from the cyanobacterium of the *Tychonema* sp. Of these, brunsvicamides B and C showed selective inhibition against the protein tyrosine phosphatase B of *Mycobacterium tuberculosis* at IC_{50} values of 7.3 and 8.0 μM, respectively. However, brunsvicamide A exhibited weak inhibition at IC_{50} of 64.2 μM [191].

Malyngamide 2 isolated from a collection of *Lyngbya sordida* is a polyketide synthase-nonribosomal peptide synthetase [PKS-NRPS] derived metabolite that showed anti-inflammatory activity in LPS-induced [lipopolysaccharide] RAW macrophage cells with meek cytotoxicity within the cell-lines. Malyngamide 3 and cocosamides A and B, are three cyclic peptides isolated from *L. majuscula* with modest cytotoxicity against HT-29 colon and MCF7 breast cancer cell-lines [190,192]. Malyngamide 3 exhibited cytotoxicity against HT-29 and MCF7 cell-lines at IC_{50} values of 48 and 29 μM, respectively. Cocosamides A and B were cytotoxic against HT-29 at 24 and 11 μM, respectively, and against MCF7 at 30 and 39 μM, respectively [192]. Pitiprolamide is a proline-rich cyclic depsipeptide that was also isolated from *L. majuscula* and exhibited cytotoxicity against two HTCLs along with being weakly antibacterial against *B. cereus* and *M. tuberculosis* [190]. Pitipeptolides A and B isolated from *L. majuscula* and pitipeptolides C-F isolated from other collections were most active against *M. tuberculosis* and showed weak cytotoxicity against two HTCLs. Pitipeptolide C was formerly prepared as a hydrogenation artifact of pitipeptolides A and B [190,193].

Lagunamides A, B [194], and C [190] isolated from *L. majuscula* are cyclodepsipeptides with potent cytotoxicity towards HTCLs along with weak anti-swarming activity against *Pseudomonas aeruginosa* and significant anti-malarial activity against *Plasmodium falciparum* [190]. Wewakamide A and guineamide G are two cyclic depsipeptides [190] isolated from *L. semiplena* and *L. majuscula*, which showed potent toxicity to brine shrimp. Guineamide G was also found to be cytotoxic to mouse neuroblastoma cell lines [195]. Guineamides A-F are other cyclic depsipeptides isolated from *L. majuscula* [196].

Wewakazole is a cyclic dodecapeptide isolated from *Lyngbya majuscula* [197], while wewakazole B is a cytotoxic peptide isolated from the Red Sea *Moorea producens* (formerly *L. majuscula*). Wewakazole exhibited cytotoxicity against H460 human lung cancer cell-line at an IC_{50} value of 10 μM while wewakazole B displayed cytotoxicity against MCF7 human breast cancer and H460 human lung cancer cell-lines at IC_{50} values of 0.58 and 1.0 μM, respectively. Wewakazole and wewakazole B were the only isolated compounds from *M. producens* till date with both oxazole and methyloxazole moieties [198]. Wewakpeptins A-D are depsipeptides isolated from *L. majuscula*. Wewakpeptins have an unusual arrangement of hydroxy acid and amino subunits relative to well-known cyanobacterial peptides, along with a 2,2-dimethyl-3-hydroxyoctanoic acid or a 2,2-dimethyl-3-hydroxy-7-octynoic acid residue, a bis-ester, and a diprolyl group similar to dolastatin 15. Wewakpeptins A and B were the most cytotoxic peptides against human lung NCI-H460 tumor and neuro-2a mouse neuroblastoma cell-lines at an LC_{50} value of 0.4 μM [199].

Porpoisamides A and B isolated from *Lyngbya* sp., are two C-2 epimeric cyclic depsipeptides with weak cytotoxicity towards osteosarcoma U2OS and HCT-116 cell-lines [190]. Bisebromoamide [200,201,202] and its demethyl analog norbisebromoamide [202] isolated from the Okinawan *Lyngbya* sp., were found to be strongly anti-proliferative [202].

Somocystinamide A [ScA] and *C*-phycocyanin [*C*-PC] are other peptides isolated from the marine sources which exhibited potent caspases dependent anti-apoptotic activity in various cancer cell-lines. Somocystinamide A is a lipopeptide isolated from *Lyngbya majuscula*/*Schizothrix* sp., that stimulated apoptosis in angiogenic endothelial cells and various tumor cell-lines via both extrinsic and intrinsic pathways with the most effective mechanism being caspase 8 activation and its downstream-pathways [34,203]. *C*-phycocyanin is a major biliprotein (tetrapyrrole protein-complex) isolated from *Spirulina platensis*, *Agmenellum quadruplicatum*, and *Mastigocladus laminosus* that induced down regulation of anti-apoptotic gene-expression and pro-apoptotic gene activation facilitating the apoptosis signal-transduction resulting in *in vitro* HeLa cells apoptosis. *C*-PC also resulted in cytochrome-c release from mitochondria in to the cytosol when tested in *C*-PC treated HeLa cells [34].

Desmethoxymajusculamide C (DMMC) is a cyclic depsipeptide isolated from *Lyngbya majuscula* with selective and potent anti-solid tumor activity against HCT-116 human carcinoma cell-line, through the disruption of microfilament cellular networks at an IC_{50} value of 20 nM. There are significant differences in the anticancer activities of cyclic and linear DMMC where cyclic DMMC exhibited IC_{50} values of 0.02, 0.063, 0.22, and > 1.0 μM, and linear DMMC exhibited IC_{50} values of 0.016, 0.094, 0.23, and > 1.0 μM against HCT-116 human colon carcinoma, H-460 human large cell lung-carcinoma, MDA-MB-435 human carcinoma, and neuro-2A murine neuroblastoma cell-lines, respectively. The closely related compounds to DMMC include lyngbyastatins 1, 3, and dolastatin 12, which are considered to be mixtures of 4-amino-2,2-dimethyl-3-oxopentanoic acid unit [Ibu] epimers [*S* (minor) and *R* (major)], with majusculamide C being a single diastereomer with the *S*-Ibu unit [204]. Epilyngbyastatin 1 is a C-15 epimer of lyngbyastatin 1 which was also isolated from *L. majuscula*/*Schizothrix calcicola*. Epilyngbyastatin 1 displayed cytotoxicity against human nasopharyngeal KB carcinoma cell-line at MIC of 0.1 μg/mL, along with being a potent disrupter of cellular microfilament networks at concentrations of 2 and 0.2 μg/mL

[205]. Majusculamides A and B were isolated from *L. majuscula* which at low concentrations were found to increase sea hare feeding, while at high concentrations inhibited feeding [206]. Majusculamide C, dolastatins 11, and 12 are other cyclic depsipeptides that showed significant cytotoxicity stimulating the microfilament hyperpolymerization by arresting cells in a time- and dose-dependent manner [34,207]. Majusculamide C exhibited strong antifungal activity, while majusculamide D and deoxymajusculamide D are two acyclic lipopentapeptides that showed moderate cytotoxicity at 0.2 μg/mL in CCRF-CEM cell culture [208]. Lyngbyastatin 3 was also isolated from *L. majuscula* and exhibited activity against LoVo and KB cell-lines at IC_{50} values of 400 and 32 nM, respectively [209].

Apratoxins A-C are cyclodepsipeptides isolated from *Lyngbya majuscula* with *in vitro* cytotoxicity against LoVo cell-line at 0.36–10.8 nM and against KB cell-line at 0.52–21.3 nM [210]. Apratoxin D is another peptide isolated from *L. majuscula* and *L. sordida*. Apratoxin D was found to be cytotoxic against H-460 human lung cancer cell-line with an IC_{50} value of 2.6 nM. Apratoxin D included the same macrocycle as apratoxins A-C with an additional unprecedented 3,7-dihydroxy-2,5,8,10,10-pentamethylundecanoic acid as a polyketide moiety [204]. Apratoxin E is another peptide isolated from *L. bouillonii* and exhibited better cytotoxicity compared to its closest analog the semi-synthetic *E*-dehydroapratoxin A against various cancer cell-lines derived from bone, colon, and cervix with values ranging between 21–72 nM, but less active compared to apratoxin A. This was speculated to be due to the conformational alteration in apratoxin E resulting from the dehydration of the polyketide chain, thereby reducing its activity [204].

Dragomabin along with carmabin A and dragonamides A-E are acyclic peptides isolated from *Lyngbya majuscula* and *L. polychroa*. These peptides included an 8 or 10-carbon long terminal alkynamide. Among these peptides dragomabin, carmabin A, and dragonamide A exhibited good antimalarial activities at IC_{50} values of 6.0, 4.3, and 7.7 μM, respectively. Dragonamides A and E showed activity against *Leishmania donovani* at IC_{50} values of 6.5 and 5.1 μM, respectively. Dragonamide B lacked activity suggesting that the aromatic amino-acid at the carboxyl terminus was necessary for the antiparasitic activity [204]. Carmabins A-B are linear lipotetrapeptides isolated from *L. majuscula* [211]. Carmabin A was found to be more cytotoxic against Vero cells at IC_{50} value of 9.8 μM compared to dragomabin or dragonamide A that showed IC_{50} values of 182.3 and 67.8 μM, respectively. The increased cytotoxicity of carmabin A over dragomabin was due to the long and more branched alkynamide chain in carmabin A [204]. Carmabin B lacked any antiproliferative activity [211]. Dragonamides C-D exhibited weak cytotoxicity in cancer cell viability assays against U2OS osteosarcoma cells at GI_{50} values of 56 and 59 μM, respectively, against IMR-32 neuroblastoma cells at 49 and 51 μM, respectively, and against HT29 colon adenocarcinoma cells at 22 and 32 μM, respectively. Dragonamides C-D lacked any antiparasitic activity [204]. Herbamide A was isolated from the marine sponge *Dysidea herbacea* [212], while herbamide B was isolated from *L. majuscula* [213]. Herbamides are modified linear peptides where herbamide A was found to be inactive in the NCI cytotoxicity screen [212] while herbamide B displayed antileishmanial activity at an IC_{50} value of 5.9 μM [213].

Almiramides A-C are lipopeptides isolated from *L. majuscula*, a cyanobacterium of the Caribbean coast of Panama. Almiramides B-C were found to have antileishmanial properties. Almiramides B and C possessed an extra Ala residue when compared to dragonamide A along with opposite configuration of the α-carbon of lipophilic side-chain and absence of a methyl group on Val1. Almiramides B and C exhibited antileishmanial activity at IC_{50} values of 2.4 and 1.9 μM, respectively, but lacked antimalarial properties at concentrations up to 13.5 μM. Almiramide A lacked antileishmanial activity due to the absence of an unsaturated terminus on lipophilic side-chain that played a significant role in other almiramides and dragonamides [204].

Grassystatins A-C are three statin unit [γ-amino-β-hydroxyacid] containing linear peptides isolated from *Lyngbya confervoides*. Grassystatins A and B exhibited similar selectivity and potency against cathepsin D with IC_{50} values of 7.27 and 26.5 nM, respectively, and against cathepsin E with IC_{50} values of 354 and 886 pM, respectively. Grassystatins showed higher affinity for cathepsin E over cathepsin D due to the interaction of their polar asparagine-residue with glutamine-303 of cathepsin E which corresponded to the non-polar residue of methionine-307 in cathepsin D. Grassystatin A also showed antigen reduction by dendritic-cells; a process that relies on cathepsin E. Grassystatin C is a truncated peptide analog that included two fewer residues compared to grassystatins A and B, and hence was less potent against cathepsins D and E. However, grassystatin C showed selectivity towards cathepsin E. Grassystatins A-C were also found to be metalloprotease tumor necrosis factor α converting enzyme [TACE] inhibitors with IC_{50} values of 1.23, 2.23, and 28.6 μM, respectively [204].

Obyanamide is a cyclic depsipeptide isolated from *Lyngbya confervoides* and exhibited moderate cytotoxicity against KB and LoVo cell-lines at IC_{50} values of 0.58 and 3.14 μg/mL, respectively [214]. Lobocyclamides A-C are lipopeptides isolated from *L. confervoides*. Lobocyclamides B and C were the first peptides with a unique amino acid 4-hydroxythreonine along with the rare long chain β-amino acids: 3-aminooctanoic acid and homologous 3-aminodecanoic acid, respectively. Lobocyclamides A-C displayed moderate antifungal activity in disk diffusion assays when tested against fluconazole-resistant fungi, *Candida albicans* and *C. glabrata* at 150 μg/disk. In microbroth dilution assay, lobocyclamide A exhibited antifungal activity against *C. albicans* at an MIC of 100 μg/disk, while lobocyclamide B showed similar activity between 30–100 μg/disk [215].

Hantupeptins A-C are cyclodepsipeptides isolated from *Lyngbya majuscula*. Hantupeptins A-C exhibited 100% brine-shrimp mortality between 100 and 10 ppm. This activity was found to be significantly higher compared to its closest analog trungapeptin A isolated from the same cyanobacterium with mild toxicity to brine shrimp. Hantupeptins A-C exhibited *in vitro* cytotoxicity against MOLT-4 leukemia cell-line at IC_{50} values of 32, 0.2, and 3.0 μM, respectively, and against MCF-7 breast cancer cell-line at IC_{50} values of 4.0, 0.5, and 1.0 μM, respectively [204].

Trungapeptins A-C are cyclodepsipeptides isolated from *Lyngbya majuscula*. These three peptides are closely related to the antanapeptins, which are a series of depsipeptides isolated from the same cyanobacterium. Trungapeptin A exhibited mild toxicity towards brine-shrimp at 10 ppm and ichthyotoxicity at 6.25 ppm, with no activity against LoVo colon

carcinoma and KB cervical adenocarcinoma cell-lines at 10 μg/mL [216]. Antanapeptins A-D are other depsipeptides isolated from the same cyanobacterium with no antimicrobial activity at concentrations of 100 μg/disk [217].

Palmyramide A is an unusual cyclic depsipeptide isolated from *Lyngbya majuscula* which included three hydroxy acids and three amino acids. The 2,2-dimethyl-3-hydroxyhexanoic acid unit [Dmhha] found in palmyramide A was also found in guineamide F [196]. Palmyramide A is known to block the voltage-gated sodium channel in neuro-2a cells at an IC_{50} value of 17.2 μM, and exhibited mild cytotoxicity against human lung H-460 carcinoma cell-line at an IC_{50} value of 39.7 μM. Dudawalamides A-E are cyclic lipopeptides isolated from the *Lyngbya* sp. These depsipeptides are structurally similar to pitipeptolides A and B, antanapeptins, kulolides, and mantillamide A which were all isolated from the *Lyngbya* sp [218]. Dudawalamide A has a planar structure of 2,2-dimethyl-3-hydroxy-7-octynoic acid unit and was found to exhibit anti-parasitic activity [204]. Dudawalamides A-E displayed greatest biological activity when tested in Chagas, leishmania, anti-parasitic, and malarial assays. Dudawalamides A, B, D, and E displayed cytotoxicity against *Plasmodium falciparum* at IC_{50} values of 2.7, 7.6, 3.7, and 7.7 μM, respectively, and against *Leishmania donovani* at IC_{50} values of 25.9, 14.7, 2.6, and 2.6 μM, respectively. Dudawalamide E was cytotoxic against *Trypanosoma cruzi* at an IC_{50} value of 7.3 μM [218].

Grassypeptolide is a macrocyclic depsipeptide isolated from *Lyngbya confervoides* with one β-amino acid, an unusually high D-amino acid content, and two thiazolines. Grassypeptolide exhibited cytotoxicity against IMR-32 neuroblastoma, HeLa cervical carcinoma, HT29 colorectal adenocarcinoma, and U2OS human osteosarcoma cancer cell-lines with IC_{50} values ranging between 1.0–4.2 μM [204]. Carriebowmide is another cyclodepsipeptide isolated from *L. polychroa* and was previously isolated from *L. majuscula* along with two other depsipeptides: itralamides A and B. Carriebowmide included two rare amino acids: methionine sulfoxide and 3-amino-2-methylhexanoic acid. Carriebowmide was tested as a feeding deterrent whose effectiveness was not determined [204].

Hoiamide A is a bioactive cyclic depsipeptide isolated from *Lyngbya majuscula*. Hoiamide A possessed a 15 carbon subunit from C30 to C44 which was postulated to have been derived from the polyketide pathway. Hoiamide A is a partial agonist of the voltage-gated sodium channel α subunit at site-2 along with exhibiting modest cytotoxicity against cancer cells, and inhibiting batrachotoxin induced Na^+ elevation in a concentration-dependent manner [204].

Tiglicamides A-C were isolated from *Lyngbya confervoides* along with largamides A-C. Tiglicamides and largamides differed by only one amino acid residue in the cyclic core. This difference could result from the unusual relaxed specificity arising from the adenylation domains of the NRPS assembly or from a separate biosynthetic pathway. Tiglicamides A-C and largamides A-C are serine-protease inhibitors with elastase selectivity over trypsin and chymotrypsin. The carboxylic-acid residue present in the compounds showed little effect on the elastase inhibitory activity which was confirmed from the semi-synthetic methyl ester analogs of largamides that exhibited low micromolar inhibitory activities [204].

Itralamides A and B are two depsipeptides isolated from *Lyngbya majuscula*. Itralamide B exhibited significant cytotoxicity in HEK-293 human embryonic kidney cell-line at an IC_{50} value of 6 ± 1 μM while itralamide A showed a ten-fold lower potency. The cytotoxic difference between the two itralamides showed that the biological activities could be dramatically altered from minor structural modifications [204].

Lyngbyastatins 4–6 were isolated from *Lyngbya confervoides* while lyngbyastatins 8–10 were isolated from *L. semiplena*. Other peptides including lyngbyastatin 7, kempopeptins A and B, and somamide B were isolated from another *Lyngbya* sp., collected from the mangrove channel in Florida at Summerland Key. This class of compounds was known as serine protease inhibitors along with exhibiting varied selectivity and wide potency range. Extensive studies on the structure-activity relationships and the crystal structures of a related depsipeptide scyptolin A bound to the elastase and the cyanopeptolin (A90720A) bound to trypsin exposed significant interactions in the enzyme binding site, providing an insight into the selectivity of this class of inhibitors. Lyngbyastatins 8–10 showed weak inhibition against porcine pancreatic elastase when compared to lyngbyastatin 7 [204]. Somamides A and B are depsipeptides isolated from *L. majuscula* and *Schizothrix* sp., whose structures are analogous to symplostatin 2 and dolastatin 13 structures. The biological activities of somamides A and B have not been reported [219].

Lyngbyastatins 7–10 shared the same depsipeptide core, but the reduced potency of lyngbyastatins 8–10 could have been associated with the differences in the side-chain residues. These compounds were known to include hydrophobic residues, exclusively in the pendant chain which are considered to be responsible for the hydrophobic bonding and electrostatic interactions with the enzyme. Lyngbyastatin 6, a *O*-methylated [Amp] derivative was able to retain the protease-inhibitory activity explaining the fact that the presence of a hydroxyl group in the Ahp unit is not significant for the inhibition of chymotrypsin or elastase [204].

Lyngbyazothrins A-D, schizotrin A, and pahayokolides A-B were known to show structural similarity. Lyngbyazothrins A-D and pahayokolides A-B were produced from the cultured *Lyngbya* sp., and from freshwater *Lyngbya* sp., respectively. Schizotrin A was isolated from *Schizotrix* sp., while tychonamides were isolated from *Tchyonema* sp. These cyclic undecapeptides included the [Val/Ile/Dhb]-Ser-Dhb-[Ser/Thr]-[homo-Phe/homo-Tyr]-Pro-X-Gln-Gly-Pro-[Pro/Phe] sequence where X is an unusual long chain: α, γ-hydroxy-β-amino acid. In lyngbyazothrins, schizotrin A, and pahayokolides, the α, γ-hydroxy-β-amino acid is a 3-amino-2,5,7,8-tetrahydroxy-10-methylundecanoic acid [Athmu], while in tychonamides it is a 3-amino-2,5,7-trihydroxy-8-phenyloctanoic acid moiety [Atpoa]. The γ-hydroxy group has not been reported to decorate the ester linkage on the *N*-acetyl-*N*-methyl tyrosine [lyngbyazothrins], an *N*-butyroyl-*N*-methyl alanine [schizotrin A] or an *N*-acetyl-*N*-methyl leucine [pahayokolides and tychonamides]. The mixture of lyngbyazothrins A and B exhibited low antimicrobial activity against *Micrococcus flavus*, while the mixture of lyngbyazothrins C and D was found to be active against *Serratia marcescens*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli* at concentrations between 25–200 μg/disk [204,220]. The acyl residue present at the C-5 position of Athmu appears to play a critical role in the antimicrobial activity which has been supported from the structure and

activity of the pahayokolides A-B. Pahayokolide A showed acute toxicity towards zebrafish embryos at LC_{50} value of 2.15 μM, marginal toxicity against brine-shrimp at concentrations of 1 mg/mL, and inhibition against various cancer cell-lines at IC_{50} values ranging between 2.13 to 44.57 μM [204].

Grassypeptolides A-C are a group of closely related bis thiazoline containing cyclic depsipeptides [221] that were isolated from *Lyngbya confervoides* while grassypeptolides D-E and Ibu-epidemethoxylyngbyastatin 3 were isolated from *Leptolyngbya* collected off the Red Sea shipwreck, *SS Thistlegorm*. Grassypeptolide D exhibited cytotoxicity against neuro-2a mouse blastoma and HeLa cervical carcinoma cell-lines at IC_{50} values of 599 and 335 nM, respectively, while grassypeptolide E was cytotoxic at IC_{50} values of 407 and 192 nM, respectively. The cytotoxicity of grassypeptolide D was at least 1.5 times less compared to grassypeptolide E. Grassypeptolides D and E are threonine/*N*-methylleucine diastereomers while grassypeptolides A and C are *N*-methylphenylalanine epimers. Ibu-epidemethoxylyngbyastatin 3 showed low cytotoxicity to neuro-2a cell-line at an IC_{50} value of > 10 μM while grassypeptolides and dolastatin 12 were cytotoxic at an IC_{50} of > 1 μM [222].

Grassypeptolides F and G were isolated from *Lyngbya majuscula*. Grassypeptolides F and G are bis-thiazoline containing cyclic depsipeptides that included a rare β-amino acid, a large number of D-amino acids, and extensive *N*-methylation. Both grassypeptolides were found to exhibit moderate inhibition against the oncogenic AP-1 transcription factor at IC_{50} values of 5.2 and 6.0 μM, respectively [223].

Lyngbyapeptins A [224], B, C [225], and D [226] are tetrapeptides with a rare 3-methoxy-2-butenoyl moiety isolated from *Lyngbya bouillonii* [224,225]. All these peptides were found to be non-cytotoxic against LoVo and KB cell-lines at concentrations of < 5 μM [225]. Lyngbyabellin A [226], C [225], and J [226] are lipopeptides isolated from the same cyanobacterium. Lyngbyabellins A and C were found to be weakly cytotoxic against LoVo and KB cell-lines at IC_{50} values of 5.3 and 2.1 μM, respectively [225]. Lyngbyabellin B was isolated from *L. majuscula* along with lyngbyabellin A [227]. Lyngbyabellin B is a cyclic depsipeptide that was found to possess potent toxicity against the fungus *Candida albicans* at 100 μg/disk, and against brine shrimp at an LD_{50} value of 3.0 ppm [228]. Lyngbyabellins D-I were also isolated from *L. majuscula* where lyngbyabellins D, F, and H exhibited cytotoxicity against H460 and KB cancer cell-lines at LC_{50} or IC_{50} values ranging between 0.1 to 0.4 μM [229].

Lyngbyabellins K-N are lipopeptides isolated from two collections of extracts from marine cyanobacteria obtained from Palmyra Atoll. Lyngbyabellin L and its C-7 epimer, 7-*epi*-lyngbyabellin L, possessed a rare monochlorination on the 3-acyloxy-2-methyloctanoate residue while lyngbyabellin N included an unusual *N*,*N*-dimethylvaline terminus along with a leucine statin residue, showing strong cytotoxicity against HCT-116 colon cancer cell-line at an IC_{50} value of 40.9 ± 3.3 nM [230]. Alotamide A is another cyclic depsipeptide isolated from *Lyngbya bouillonii* which exhibited unique calcium-influx activation profile in the murine cyanobacterial metabolite at an EC_{50} value of 4.18 μM [231].

Barbamide is a chlorinated lipopeptide isolated from *Lyngbya majuscula* strain and is known for its potent molluscicidal activity [232]. Jamaicamides A-C are other lipopeptides isolated from *L. majuscula*. Jamaicamide A possessed a pyrrolinone ring, β-methoxy eneone system, alkynyl bromide, and vinyl chloride, and exhibited fish toxicity and sodium channel-blocking activity. All three jamaicamides exhibited cytotoxicity against neuro-2a mouse neuroblastoma and H-460 human lung cell-lines at an LC_{50} value of 15 μM along with sodium channel blocking activity at 5 μM. Jamaicamide C showed modest toxicity against brine shrimp at 10 ppm while jamaicamides A and B were inactive [233].

Hectochlorin is a lipopeptide isolated from *Lyngbya majuscula*. Hectochlorin exhibited potent antifungal activity against *Candida albicans* and antiproliferative activity in the NCI-60 cell-line assay. Hectochlorin also inhibited the human Burkitt lymphoma CA46 and actin cytoskeleton PtK2 cell-lines at IC_{50} values of 20 nM and 300 nM, respectively. Hectochlorin showed an 11 mm inhibition zone at 10 μg/disk against *C. albicans* and a 16 mm inhibition zone at 100 μg/disk but was inactive against *P. aeruginosa*, *E. coli*, *S. aureus*, *B. subtilis*, and *Salmonella choleraesuis*. Hectochlorin structurally resembled lyngbyabellins A and B, and dolabellin [234].

Apramides A-G are linear lipopeptides isolated from the lyngbyastatin-2 producing strain of *Lyngbya majuscula*. Apramides A-F were non-cytotoxic with no fungal, bacterial, or protease inhibiting activities but apramide A showed enhanced elastase-activity [235].

Aurilide is a potent cytotoxic cyclic depsipeptide isolated from *Dolabella auricularia*, a Japanese seahare [236], while aurilides B and C were isolated from *Lyngbya majuscula*. Aurilide induced apoptosis in human cells at picomolar to nanomolar range [236], while aurilides B and C exhibited cytotoxicity against neuro-2a mouse neuroblastoma and NCI-H460 human lung tumor cell-lines at LC_{50} values between 0.01 and 0.13 μM. Aurilide bound selectively to prohibitin-1 [PHB1] in mitochondria resulting in the activation of the proteolytic processing of optic-atrophy 1 [OPA1], thereby causing mitochondria induced apoptosis [236]. Aurilide B exhibited high level cytotoxicity against the NCI-60 cell-line with a GI_{50} concentration less than 10 nM, and was most active against prostate, leukemia, and renal cancer cell-lines [237]. Antillatoxin [238] is an ichthyotoxic cyclic lipopeptide isolated from *L. majuscula* at an LD_{50} value of 0.05 μg/mL, while barbaramide A [239] exhibited potent molluscicidal activity at an LD_{100} value of 10 μg/mL [240]. Kalkitoxin is another neurotoxic lipopeptide isolated from *L. majuscula* and was found to be a more potent ichthyotoxic towards common goldfish, *Carassius auratus*, at an LC_{50} value of 700 nM. Kalkitoxin also inhibited cell-division in fertilized sea-urchin embryo assay at an IC_{50} value of around 25 nM, and was potently toxic to brine shrimp at an LC_{50} value of 170 nM. Kalkitoxin was found to be a potent blocker of voltage sensitive sodium channel in mouse neuro-2a cell-line at an EC_{50} value of 1 nM [241].

Georgamide is a cyclic depsipeptide with an alkynoic acid residue and was isolated from the Australian cyanobacterium [242], while yanucamides A and B are two depsipeptides isolated from *Lyngbya majuscula* and *Schizothrix* sp. Both yanucamides possessed a unique 2,2-dimethyl-3-hydroxy-7-octynoic acid and exhibited strong brine-shrimp toxicity at an LD_{50} value of 5 ppm [243].

Dysidenamide, pseudodysidenin, and nordysidenin are lipopeptides isolated from *Lyngbya majuscula* while isodysidenin was isolated from the New Guinean and Australian sponge, *Dysidea herbacea*. Pseudodysidenin exhibited cytotoxicity against MEL-28, P-388, HT-29, and A-549 cell-lines at IC_{50} values of > 1 μg/mL [244].

Ulongamides A-F are cyclic depsipeptides isolated from *Lyngbya majuscula*. Ulongamides are β-amino acid containing depsipeptides where ulongamides A-E exhibited weak cytotoxicity against LoVo and KB cell-lines at IC_{50} values of 5 μM and 1 μM, respectively. Ulongamide F was inactive at < 10 μM against both the cell lines [245].

Malyngamides are a group of mixed polyketide-peptides isolated from *Lyngbya majuscula*. Malyngamides A and B, and isomalyngamides A and B were isolated from *L. majuscula*. Malyngamides A and B are chlorine-containing amides of 7(*S*)-methoxytetradec-4(*E*)-enoic acid. Isomalyngamides showed lethal toxicity towards crayfish [246]. Malyngamide C along with its stereoisomer 8-*epi*-malyngamide C were also isolated from *L. majuscula*. Both malyngamide C and 8-*epi*-malyngamide C exhibited cytotoxicity against HT29 colon cancer cell-line at IC_{50} values of 5.2 and 15.4 μM, respectively [247]. Malyngamides D and E are trans-7-methoxy-9-methylhexadec-4-enamides isolated from *L. majuscula* [248]. Malyngamide F was also isolated from *L. majuscula*. Malyngamide G is a chlorine containing 7(*S*)-methoxydodec-4(*E*)-enamide isolated from a blue-green alga, *Cystoseira crinite* [249] and from *L. majuscula* as well. Malyngamide F was found to be potent against NO assay at an IC_{50} value of 5.4 μM [250], while malyngamide G was found to be non-cytotoxic against KB cell-line but showed immunosuppressive activity at ED_{50} value of 6 μg/mL with lipopolysaccharide (LPS) and concanavaline K cells [251]. Malyngamides H-K were isolated from *L. majuscula* where malyngamides H, I, and K exhibited slight reduction of nitrite-production. Malyngamide I also exhibited brine shrimp toxicity at an LD_{50} value of 35 μg/mL, and goldfish toxicity at an LD_{50} of < 10μg/mL [252]. Malyngamides J and T did not show any anti-inflammatory activity due to their strong cytotoxicity of 60% and 9% cell-survival, respectively [250].

Malyngamides L and T were isolated from *Lyngbya majuscula*, while malyngamides M and N were isolated from *Gracilaria coronopifolia*, a Hawaiian red alga. Malyngamide N exhibited moderate cytotoxicity against mouse neuroblastoma (NB) cell-line at an IC_{50} value of 4.9 μg/mL, while malyngamide M showed weak cytotoxicity at an IC_{50} value of > 20 μM [253]. Malyngamides O and P were isolated from *Stylocheilus longicauda*, a marine sea hare. Malyngamide O exhibited moderate activity against human colon HT-29 carcinoma, lung A-549 carcinoma, and mouse P-388 lymphoma cell-lines at an IC_{50} value of 2 μg/mL [254]. Malyngamides Q and R were also isolated from *L. majuscula* where malyngamide Q did not show any biological activity due to its instability, while malyngamide R exhibited brine-shrimp toxicity at an LD_{50} value of 18 ppm [255]. Malyngamide S was isolated from *Bursatella leachii*, a New Zealand sea hare. Malyngamide S exhibited anti-proliferative activity against human leukemic HL60 cell-line at an IC_{50} value of ~ 6–8 μM and showed cytotoxicity towards P388 murine leukemia cell-line at an IC_{50} value of 29 μM and against NCI panel at LC_{50} value of 69.2 μM, GI_{50} value of 16.6 μM, and TGI value of 35.5 μM. Malyngamide S also exhibited cytotoxicity against BSC-1 cell-line at 120 μg/disk, and anti-tubercular activity at 6.25 μg/mL [256]. Malyngamides U-

W were isolated from *L. majuscula*, and did not show any brine shrimp toxicity [257]. Malyngamide X was the first (7*R*)-lyngbic acid with a novel tripeptide backbone which was isolated from *Bursatella leachii*, a Thai sea hare [258]. Malyngamide X was found to possess antimalarial activity against *P. falciparum*, and was found to be active against *M. tuberculosis* as well [259]. Malyngamide Y was isolated from *Moorea producens*, and exhibited anticancer activity. Malyngamide Y possessed four amino acid units including alanine, valine, proline, and *N*-methyl phenylalanine along with an unique unit: 2,2-dimethyl-3-hydroxy-octanoic acid [260].

Hermitamides A-B are lipopeptides isolated from *Lyngbya majuscula*. Hermitamides A-B represented the aromatized malyngamide type compounds and exhibited brine shrimp toxicity at LD_{50} values of 5 and 18 μM, respectively. Hermitamide A also displayed weak goldfish ichthyotoxicity at an LD_{50} value of 19 μM while hermitamide B was inactive at 25 μM. Both hermitamides were inactive in molluscicidal assay at a concentration of 10 ppm while showed cytotoxicity against neuro-2a-neuroblastoma cell-line at IC_{50} values of 2.2 and 5.5 μM, respectively [261]. Laxaphycins A [262] and B [262,263] are cyclic lipopeptides isolated from *L. majuscula*. Laxaphycin A is a cyclic undecapeptide, while laxaphycin B is a cyclic dodecapeptide. Laxaphycin A was found to be inactive at concentrations of 20 μM while laxaphycin B showed cytotoxic activities against drug sensitive CCRF-CEM human leukemic lymphoblasts at IC_{50} value of 1.1 μM along with preserving equal cytotoxicity against altered DNA-topoisomerase II associated MDR and Pgp-MDR cells [264].

Tasiamide and tasiamide B are cytotoxic peptides isolated from *Symploca* sp. Tasiamide is an acyclic peptide that exhibited cytotoxicity against LoVo and KB cell-lines at IC_{50} values of 3.47 and 0.48 μg/mL, respectively [265], while tasiamide B was cytotoxic against KB cell-line with an IC_{50} value of 0.8 μM [266]. Tasiamides C-E are lipopeptides which were also isolated from *Symploca* sp., and were found to be inactive against HCT-116 colon cancer cell-line at 25 μM [267]. Tasiamide F is a peptide isolated from *Lyngbya* sp., with a structure similar to pepstatin A, a natural aspartic protease inhibitor produced by Actinomycetes. Tasiamide F included a Phe-derived statin core and inhibited cathepsins D and E at IC_{50} values of 57 and 23 nM, respectively [268]. Tasipeptins A and B are cytotoxic depsipeptides isolated from *Symploca* sp., and exhibited cytotoxicity against KB cell-line at IC_{50} values of 0.93 and 0.82 μM, respectively [269].

Symplocamide A was isolated from *Symploca* sp., and exhibited potent cytotoxicity towards neuro-2a neuroblastoma and H-460 lung cancer cell-lines at IC_{50} values of 29 nM and 40 nM, respectively [270]. Symplocin A is a *N*,*N*-dimethyl-terminated peptide which was also isolated from *Symploca* sp., and was found to be a potent inhibitor of cathepsin E at an IC_{50} value of 300 pM [271]. Veraguamides A-G were isolated from *Symploca cf. hydnoides*, and were found to be moderately cytotoxic towards HTCLs [272].

Symplostatin 1 has been isolated from *Symploca hydnoides* and is a methyl derivative of dolastatin 10, which was also isolated from *S. hydnoides* apart from being initially isolated from the marine mollusk *Dolabella auricularia*. Symplostatin 1 induced proapoptotic stimuli in cancer cells similar to dolastatin 10 [273]. Symplostatin 2 is a cyclic depsipeptide and an

analog of dolastatin 13 that was isolated from *S. hydnoides* with no reported biological activity [274]. Symplostatin 3 is another analog of dolastatin 10 that differs only in the *C*-terminal unit where the 3-phenyllactic acid moiety replaces the dolaphenine. Symplostatin 3 exhibited IC_{50} values of 3.9 nM and 10.3 nM against KB and LoVo cell-lines respectively [275]. Symplostatin 4 [Sym4] is a cyanobacterial secondary metabolite isolated from *Symploca* sp. Sym4 was found to be a potent inhibitor of the malarial parasite, *P. falciparum* with IC_{50} values ranging between 36–100 nM. Symplostatin 4 was also known to cause a food vacuole phenotype in *Plasmodium* infected red blood cells and is known to inhibit the pathogen replication at an EC_{50} value of 0.7 μM [276].

Malevamides A-C are depsipeptides isolated from *Symploca laete-viridis* and were found to be inactive against human colon HT-29 carcinoma, mouse P388 lymphoma, and human lung A-549 carcinoma cell-lines at a concentration of 2 μg/mL. Malevamides A-C included structural features such as α-hydroxy acids, β-amino acids, and *N*-methylation [277]. Malevamide D and belamide A were isolated from *S. hydnoides*. Malevamide D is a highly cytotoxic peptide ester, while belamide A is a linear tetrapeptide belonging to similar compound class as dolastatin-10. Belamide A and malevamide D exhibited antiproliferative activity and subsequently, tubulin disrupting effects [273]. Largazole is another cytotoxic cyclodepsipeptide that was also isolated from *Symploca* sp. and included a substituted 4-methyl thiazoline, linearly fused to thiazole. Largazole exhibited cytotoxicity against human epithelial MDA-MB-231, murine mammary epithelial NMuMG, fibroblastic osteosarcoma U2OS, and nontransformed fibroblasts NIH3T3 cancer cell-lines at GI_{50} values of 7.7, 122, 55, and 480 nM, respectively [278].

Mitsoamide is a cytotoxic linear lipopeptide isolated from the Madagascar marine cyanobacterium, *Geitlerinema* sp., and included an unusual polyketide unit: 3,7-dimethoxy-5-methyl-nonanedioic acid [DMNA], along with a highly unusual piperidine aminal moiety, and a homolysine residue. Mitsoamide was found to be cytotoxic against NCI-H460 human lung tumor cell-line at an IC_{50} value of 460 nM [279]. Gallinamide A is an antimalarial peptide isolated from *Schizothrix* sp. Gallinamide A exhibited potent antimalarial activity against W2 chloroquine-resistant strain of *Plasmodium falciparum* at an IC_{50} value of 8.4 μM [280].

Nostocyclamide is a macrocyclic thiazole containing allelochemical isolated from the cyanobacteria belonging to the *Nostoc* sp. Nostocyclamide is cyclic peptide and an antialgal and an anticyanobacterial secondary metabolite with toxicity against *Brachionus calyciflorus*. Nostocyclamide also inhibited the growth of *Anabaena* P-9 at a concentration of 0.1 μM [281]. Tenuecyclamides A-D are cyclic hexapeptides isolated from *Nostoc spongiaeforme* var. *tenue*. Tenuecyclamide A inhibited sea-urchin embryos at an ED_{100} value of 10.8 μM, while tenuecyclamides C and D exhibited inhibition at ED_{100} values of 9.0 μM and 19.1 μM, respectively [282]. Cryptophycin was also isolated from *Nostoc* genus and is a cytotoxic dioxadiazacyclohexadecenetetrone exhibiting antifungal activity with unknown mechanism. Cryptophycin was a novel antimicrotubule compound and was a poor substrate for P-glycoprotein compared to *Vinca* alkaloids [283].

Microcystins are monocyclic heptapeptide liver-toxins from cyanobacteria of both marine and/or freshwater belonging to the genera *Nostoc*, *Oscillatoria*, *Anabaena*, and *Microcystis*. Over 50 different microcystins have been isolated so far that differ primarily in two L-amino acids plus demethylation and methylation on the two unusual amino acids. All microcystins included an Adda [(2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid] that is essential for the biological activity. Microcystins were found to be potent protein phosphatase types 1 and 2A inhibitors as well as tumor-promoters [284]. Raocyclamides A and B are two thiazole- and oxazole-containing cyclic hexapeptides isolated from *Oscillatoria raoi* where raocyclamide A exhibited moderate cytotoxicity against sea-urchin embryos [285]. Venturamides A-B are cyclic hexapeptides that were isolated from marine *Oscillatoria* species. Venturamides A-B exhibited antimalarial activity against W2 chloroquine-resistant strain of malaria, *Plasmodium falciparum* at IC_{50} values of 8.2 and 5.6 μM, respectively, while also exhibiting mild cytotoxicity against mammalian Vero cells at IC_{50} values of 86 and 56 μM, respectively [286].

Anabaenopeptins A and B are cyclic peptides isolated from *Anabaena flos-aquae*, and produced concentration dependent relaxations in rat aortic preparations with endothelium at concentrations of 10–400 μg/mL [287]. Anabaenopeptins C and D were isolated from the hepatotoxic cyanobacteria, *Anabaena* sp. [288], while anabaenopeptins E and F are ureido bond containing cyclic peptides isolated from *Oscillatoria agardhii* with no reported biological activities [289]. Anabaenopeptins G and H were also isolated from *O. agardhii* as potent carboxypeptidase-A [CPA] inhibitors at IC_{50} values of 0.0018 and 3.4 μg/mL, respectively, with no activity against proteases [290]. Pompanopeptins A and B were isolated from *L. confervoides*. Pompanopeptin A is a 3-amino-6-hydroxy-2-piperidone containing peptolide, while pompanopeptin B is a cyclic pentapeptide. Pompanopeptin B possessed *N*-methyl-2-amino-6-(4′-hydroxyphenyl) hexanoic acid [*N*-Me-Ahpha] and was structurally related to the carboxypeptidase A inhibitors: anabaenopeptins I and J, which were also isolated from the cyanobacterium *Aphanizomenon flos-aquae*. The *N*-methyl-*L*-Ahpha and *L*-Htyr in pompanopeptin B were replaced by the *N*-methyl-*L*-alanine and *L*-leucine/*L*-phenylalanine residues of anabaenopeptins J and I, respectively. Pompanopeptin A was found to selectively inhibit trypsin over chymotrypsin and elastase at an IC_{50} value of 2.4 μM which was due to the presence of the arginine residue in the cyclic core. There was no biological data reported for pompanopeptin B [204].

(+)-Floridamide is a cyclic depsipeptide isolated from *Moorea producens* and exhibited cancer cell cytotoxicity. The cyclic depsipeptide possessed four amino acid residues including proline, alanine, valine, and *N*-methyl phenylalanine [260]. Coibamide A [291] is a potent antiproliferative depsipeptide isolated from *Leptolyngbya* sp. Coibamide A exhibited potent cytotoxicity against mouse neuro-2a and NCI-H460 lung cancer cell-lines at LC_{50} values of < 23 nM but did not interfere with actin or tubulin in the cytoskeletal assays. Coibamide A was known to dose dependently increase the number of cells in G_1 phase of cell cycle with a little change in the G_2/M phase and a complete loss of cells in the S phase. Coibamide A was also evaluated against the *in vitro* panel of NCI 60 cancer cell-lines with high potency against MDA-MB-231, HL-60 (TB), SNB-75, and LOX IMVI at GI_{50} values of 2.8, 7.4, 7.6, and 7.4 nM, respectively, and showed good selectivity for CNS, ovarian, breast, and colon cancer cell-lines. Coibamide A could be a promising lead in the

drug discovery of cancer with potentially new mechanism of action [291]. Hormothamnin A is a lipophilic cyclic peptide isolated from *Hormothamnion enteromorphoides*, a tropical marine cyanobacterium. Hormothamnin A was an undecapeptide that exhibited antimicrobial and cytotoxic properties and resembled laxaphycin A with minute differences in the stereochemistry of the DHHA unit [292]. Trichamide is a small cyclic peptide isolated from a bloom-forming *Trichodesmium erythraeum* with no significant activity [293]. Scytonemin is a small molecule *polo*-like kinase 1 inhibitor isolated from *Stigonema* sp., and possessed a unique chemical structure with a potential scaffold, for further chemical modification that could be used for the development of therapeutically useful compounds in the treatment of hyperproliferative disorders due to its nontoxic and antiproliferative activity. Scytonemin is a natural product thought to stem from the condensation of tryptophan and phenylpropanoid derived subunits. Scytonemin inhibited the capability of GST-*polo*-like kinase 1 to phosphorylate GST-cdc25C at an IC_{50} value of 2.3 μM ± 3.6 in a concentration dependent manner [294].

Arenamides A-C are cyclohexadepsipeptides isolated from the marine bacterial strain, *Salinispora arenicola*. Arenamides A and B were known to block the TNF-induced activation in a time- and dose-dependent manner at IC_{50} values of 3.7 and 1.7 μM, respectively. These peptides also inhibited the PGE_2 and nitric oxide (NO) production with LPS-induced RAW 264.7 macrophages, but exhibited moderate cytotoxicity with HCT-116 human colon carcinoma cell-line [295]. Caldoramide is a linear pentapeptide isolated from *Caldora penicillata*. Caldoramide showed cytotoxicity against HCT116 KRAS cell-line at IC_{50} values of 3.9 μM to 5.2 μM [296].

Viequeamides A-F belonging to the kulolide superfamily of cyclic depsipeptides were isolated from the *Rivularia* sp., where viequeamide A was found to be extremely toxic to the human lung cancer H460 cell-line at an IC_{50} value of 60 ± 10 nM, while viequeamides B-F were found to be inactive. Viequeamides belonged to the 2,2-dimethyl-3-hydroxy-7-octynoic acid [Dhoya] comprising cyclic depsipeptides [297]. Companeramides A-B were cyclic depsipeptides with a 3-amino-2-methyl-7-octynoic acid [Amoya] and hydroxy isovaleric acid along with eight other α-amino acid units. Companeramides A-B were isolated from the same cyanobacteria as coibamide A and exhibited nanomolar *in vitro* anti-plasmodial activity, but were inactive against cancer cell-lines at concentrations of 1 μM [298].

Nodulapeptins A-B and spumigins A-C were isolated from the toxic *Nodularia spumigena*. Nodulapeptins A-B are cyclic peptides similar to anabaenopeptins that were isolated from *Anabaena* species, while spumigins A-C are linear peptides which were considered to be the precursors of aeruginosins containing agmatin, argininal, and argol isolated from the freshwater cyanobacteria, *Microcystis aeruginosa* [299]. Spumigins D-H were also isolated from *N. spumigena*. Spumigins are linear tetrapeptides with proteinogenic amino acids which included a *C*-terminal alcohol derivative of arginine [300]. Spumigin E and aeruginosins were also isolated from *N. spumigena*. Aeruginosins are a family of linear peptides that are known to be serine protease inhibitors [301].

Kailuins A-D are cyclic acyldepsipeptides that were isolated from the liquid cultures of BH-107, a Gram-negative bacterium collected from the Kailua beach. Kailuins A-D showed

mild cytotoxicity against A-549 lung cancer cell-lines at GI_{50} values of 3, 2, 3, and 2 μg/mL, respectively, MCF-7 breast cancer cell-lines at GI_{50} values of 3, 2, 4, and 3 μg/mL, respectively, and HT-29 colon cancer cell-lines at GI_{50} values of 3, 3, 3, and 2 μg/mL, respectively [302]. Kailuins E-H were also isolated from *Photobacterium halotolerans* similar to kailuins A-D. Kailuins B, C, D, E, G, and H exhibited cytotoxicity against HCT-116 cancer cell-line at IC_{50} values of 22, 50, 28, 18, 32, and 17 μM, respectively, while kailuin D showed cytotoxicity against MCF-7 breast cancer cell-line at IC_{50} value of 39 μM [303].

Ngercheumicins A-I [304,305] are other depsipeptides that were isolated from the *Photobacterium* strains. Ngercheumicins were found to be active against *Pseudovibrio denitrificans*. Of these, ngercheumicins A-B included a depsipeptide macrocycle with one Phe and two Leu residues with various fatty-acid tails while ngercheumicins C-E included a macrocycle with three Leu, two Thr, and one Ser with no fatty-acid tail [304]. Ngercheumicins F-I inhibited the regulatory *rnaIII* transcription in *S. aureus* which is an effector molecule of *agr* QS system, making these a novel class of peptide-signaling molecules in the marine environment [305]. Unnarmicins A and C are antibiotic depsipeptides that were isolated from the fermentation broth of *Photobacterium* species [306]. Unnarmicins A and C inhibited rhodamine 6G efflux at IC_{50} values of 3.61 and 5.65 μM, respectively, along with inhibition of the CaCdr1p ATPase activity (*in vitro*) with IC_{50} values of 0.495 and 0.688 μM, respectively. Unnarmicins A and C could be potential candidates as adjuvants for antifungal chemotherapy [307].

Ariakemicins A and B are linear hybrid polyketide nonribosomal peptide antibiotics that were isolated from the fermentation extract of *Rapidithrix* species. Ariakemicins A and B are positional isomers with a double bond and included a threonine, δ-isovanilloylbutyric acid, and two ω-amino-(ω−3)-methyl carboxylic acids with triene or diene units. Ariakemicins exhibited cytotoxicity against baby hamster BHK kidney and human lung A549 cancer cells at IC_{50} values of 15 and 25 μg/mL, respectively [308]. Mollemycin A is a glyco hexadepsipeptide-polyketide that was isolated from a marine derived *Streptomyces* species. Mollemycin A exhibited extremely selective and potent growth-inhibition against gram-negative and gram-positive bacteria at IC_{50} values of 10–50 nM and multi-drug resistant and drug-sensitive clones of *Plasmodium falciparum* at IC_{50} values of 9 and 7 nM, respectively [309]. Thiocoraline is a depsipeptide that was isolated from the marine actinomycete strain, L-13-ACM2-092 and exhibited potent cytotoxicity against MEL-28, P-388, and A-549 cell-lines at an IC_{50} value of 0.002 μg/mL along with strong anti-microbial activity against gram-positive microorganisms by binding to the super-coiled DNA and inhibiting the RNA-synthesis [310]. Cyclomarins A-C are cyclic heptapeptides that were isolated from *Streptomyces* sp. CNB-982. Cyclomarin A exhibited potent anti-inflammatory activity with 92% inhibition at a dose of 50 μg/ear [311]. Cyclomarin D along with cyclomarazines A and B are other cyclic peptides that were isolated from *Salinispora arenicola* CNS-205. Cyclomarazines A-B are diketopiperazine dipeptides [312].

Surugamides A-E are cyclic octapeptides that were isolated from the broth of a marine-derived *Streptomyces* species. Surugamides A-E included four D-amino acid residues and exhibited inhibition against bovine cathepsin-B at IC_{50} values of 21, 27, 36, 18, and 16 μM,

respectively [313]. Surugamide F is a linear decapeptide with a 3-amino-2-methylpropionic acid residue that was isolated from the mycelium extract of *Streptomyces* sp. JAMM992 [314]. Champacyclin is another cyclic octapeptide that was also isolated from the marine sediments of *Streptomyces champavatii* and exhibited antimicrobial activity against *Erwinia amylovora*, a phytopathogen, responsible for the fire-blight disease in plants. Champacyclin showed 40% inhibition of *E. amylovora* at 25 μM concentration [315].

Tumescenamides A and B are cyclic depsipeptides isolated from the marine bacterium *Streptomyces tumescens* YM23-260. The two tumescenamides differed in the replacement of 2,4-dimethylheptanoyl residue at α-NH_2 position in tumescenamide A with a 2,4,6-trimethylnonanoyl residue in tumescenamide B. Tumescenamide A induced reporter gene-expression under controlled insulin degrading enzyme (IDE) promoter and hence could be a promising candidate for the treatment of Alzheimer's disease [316]. Tumescenamide C is another cyclic lipodepsipeptide that was isolated from the broth of *Streptomyces* sp. KUSC_F05. Tumescenamide C is a congener of tumescenamides A and B and exhibited selective antimicrobial activity against *Streptomyces* strains with a growth inhibitory zone at 3.0 μg/disk [317]. Streptocidins A-D are cyclic decapeptide antibiotics that were isolated from the culture of *Streptomyces* sp. Tu 6071. Streptocidins possessed a distinct feature in that they included L-Leu at position 6 unlike loloatins and tyrocidines which possessed L-Trp or L-Phe [318,319]. Streptocidins C and D showed antimicrobial activity against *B. subtilis*, *S. aureus*, *S. viridochromogenes*, and *S.* sp. Tu 6071 at MIC values between 1–3 μg/mL [320].

Salinamides A-E are anti-inflammatory depsipeptides that were isolated from *Streptomyces* sp. CNB-091. Salinamides A and B exhibited 84% and 83% inhibition of edema at a testing dose of 50 μg/ear, respectively, and also showed moderate antibiotic activity against gram-positive bacteria *Streptomyces pyrogenes* and *S. pneumoniae* at MIC values of 4 μg/mL for salinamide A and 2 μg/mL for salinamide B [321]. Salinamide F was later isolated from the same *Streptomyces* strain on further exploration. Similar to salinamide A, salinamide F also exhibited significant antibacterial and RNA-polymerase (RNAP) inhibitory activities. Salinamide F displayed significant antibacterial activity against *E. coli* at MIC value of 0.20 μg/mL, *Enterococcus faecalis* and *Haemophilus influenzae* at MIC values of 12.5 μg/mL, *Neisseria gonorrhoeae* with MIC value of 25 μg/mL, *Enterobacter cloacae* with MIC value of 50 μg/mL, and *S. aureus* at MIC value of 100 μg/mL. Salinamide F exhibited potent gram-negative and gram-positive bacterial RNAP inhibition against *S. aureus* with an IC_{50} value of 4 μM and against *E. coli* RNAP with IC_{50} value of 2 μM [322].

Tauramamide is an antibiotic lipopeptide that was isolated from the marine bacterial cultures of *Brevibacillus laterosporus* PNG276. Tauramamide is acetylated at the *N*-terminus and included two D amino acids; the hallmarks indicating the non-ribosomal peptide synthase biosynthetic origin. Tauramamide exhibited selective and potent inhibition of the pathogenic *Enterococcus* sp. at minimum inhibitory concentration of 0.1 μg/mL [323]. Tupuseleiamides A and B are acyldipeptides that were also isolated from *B. laterosporus* PNG 276. Tupuseleiamides A and B had a nonprotein D configuration and differed only in the presence of a methyloctanoyl fragment [324]. Bogorols A-E are linear cationic peptides that were also isolated from *B. laterosporus* PNG276. Bogorols were the first known linear

cationic peptides with both *N*-terminal α-hydroxy acid and *C*-terminal aminol modifications. Bogorols A-E exhibited potent and selective activity against methicillin-resistant *Staphylococcus aureus* [MRSA] at MIC of 1–8 μg/mL range and also against vancomycin-resistant *Enterococcus* spp. [VRE] at MIC of 9–75 μg/mL range [325].

Loloatins A-D are cyclic decapeptide antibiotics that were isolated from a tropical marine bacterium MK-PNG-276A. Loloatins A-D showed potent antibiotic activity against MRSA, VRE, and the drug-resistant *Streptococcus pneumoniae*, but only loloatin C exhibited antibacterial activity against the gram-negative *E. coli*. Loloatin D was four fold less active against gram-positive bacteria compared to other loloatins [326]. Marthiapeptide A is a tristhiazole-thiazoline containing cyclic peptide that was isolated from *Marinactinospora thermotolerans* SCSIO 00652. Marthiapeptide A showed antibacterial activity against gram-positive bacteria between MIC values of 2.0 to 8.0 μg/mL, and exhibited anticancer activity between IC_{50} values of 0.38 to 0.52 μM [327].

Loihichelins A-F are amphiphilic peptide siderophores that were isolated from *Halomonas* sp. LOB-5 which is a heterotrophic Mn(II)-oxidizing bacterium [328]. Siderophores are high affinity iron (III) ligands with low molecular-weight, which are produced by bacteria in order to solubilize and promote the uptake of iron under low iron-conditions [329]. Loihichelins included a hydrophilic head group with an octapeptide comprising of a series of amino acids, appended by fatty acids ranging from tetradecanoic acid to decanoic acid [328]. Marinobactins are another class of marine bacterial siderophores with a distinct amphiphilic structure that were isolated from a *Marinobacter* sp. DS40M6. Marinobactins included a unique peptidic head-group which coordinates with iron (III) along with one series of fatty acid appendages. The membrane affinity of marinobactins and the changes due to iron-binding could help aid in the receptor-assisted iron acquisition process [330].

Aquachelins are other amphiphilic peptide siderophores that were isolated from *Halomonas aquamarina* and are characterized with a 7-aa peptide with *N*-terminal appendages that range from C-12 to C-14 fatty acids. The fatty acids present in both aquachelins and marinobactins included both unsaturated and saturated alkyl chains with one double bond in *cis* configuration [331]. Petrobactin is a photoreactive citrate based catecholate-type siderophore that was isolated from the culture of *Marinobacter hydrocarbonoclasticus*, an oil-degrading marine bacterium. Petrobactin is a bis-catecholate α-hydroxy acid siderophore which included a unique 3,4-dihydroxybenzoyl chelating subunit rather than the usual 2,3-dihydroxybenzoyl moiety [332]. Amphibactins are amphiphilic siderophores that were isolated from *Vibrio* sp. R-10, a γ-*Proteobacterium*. All amphibactins possessed similar Tris-hydroxamate containing peptidic headgroup with one serine residue and three ornithine residues but differed in the C-14 to C-18 acyl appendage, thereby varying in the degree of hydroxylation and saturation [331]. Aerobactin is a hydroxamate-siderophore that was isolated from the marine *Vibrio* sp. DS40M5 which was previously isolated from other organisms [333]. Amphi-enterobactin is another siderophore that was isolated from *V. harveyi* BAA-1116. Amphi-enterobactins are fatty acid derivatives with a fourth serine incorporated into the trilactone backbone to form a tetralactone ring. The presence of an acyl moiety increased the hydrophobicity of amphi-enterobactins causing them to associate with the cell [334].

Alterobactins A and B are other siderophores that were isolated from *Alteromonas luteoviolacea*. Alterobactins were the first natural products that included 4,8-diamino-3-hydroxyoctanoic acid known for its implication in peptide protease inhibition [335]. Pseudoalterobactins A and B are siderophores that were isolated from *Pseudoalteromonas* sp. KP20-4 collected from the marine sponge, *Cinachyrella australiensis*. Alterobactins and pseudoalterobactins resembled in the possession of a catechol and two β-hydroxy-Asp residues [336].

Trivanchrobactin, divanchrobactin, and vanchrobactin are catecholamide compounds isolated from *Vibrio* sp. DS40M4, a marine bacterium. Vanchrobactin included a L-serine, D-serine, and 2,3-dihydroxybenzoic acid, while trivanchrobactin is a trimer of vanchrobactin joined with two serine ester-linkages [337]. Anguibactin is another siderophore which belonged to the phenolate category isolated from *Vibrio anguillarum* 775 [338]. Anguibactin exhibited cytotoxicity against murine P388 leukemia cell-line at an IC_{50} value of 15 μM [337]. Vibrioferrin is another siderophore that was isolated from *V. parahaemolyticus* with the structure: 1-{2-[2[(5-carboxy-5-hydroxy-2-oxo-1-pyrrolidinyl)propionamide]ethyl} citrate existing in two epimeric forms that resulted from the cyclization of the keto group of 2-ketoglutaric acid residue and the amidic-nitrogen of the alanine residue. Vibrioferrin exhibited iron-uptake at V_{max} and K_m values of 54 pmol and 67 nM Fe/mg cell protein/min, respectively, showing that this was receptor-mediated [339].

Ochrobactins A-C are citrate-derived amphiphilic siderophores that were isolated from *Ochrobactrum* sp. SP18. Ochrobactins included a citric acid backbone amide that is linked to two lysine residues. Each ochrobactin had two appendages of which one is an acylated appendage: (*E*)-2-decenoic acid. The other acylated appendage is (*E*)-2-octenoic acid, octanoic acid, and (*E*)-2-decenoic acid for ochrobactins A, B, and C, respectively [340]. Synechobactins are other amphiphilic siderophores that were isolated from *Synechococcus* sp. PCC 7002. Synechobactins also possessed a citric acid backbone that is linked to two 1,3-diaminopropane units. Synechobactins A, B, and C differ in the terminal fatty-acid residues which were dodecanoic acid, decanoic acid, and octanoic acid, respectively [341].

C. Marine Fungi

Unguisins A, B [342], C [343], and D [344] are four cyclic heptapeptides isolated from a marine derived strain of *Emericella unguis*. Unguisin E is a γ-aminobutyric acid containing cyclic heptapeptide that was isolated from *Aspergillus* sp., [345,190] and unguisin F is another cyclic heptapeptide that was obtained from the endophytic fungus, *Mucor irregularis*, isolated from a medicinal plant *Moringa stenopetala* [346].

An inseparable mixture of two cyclic pentapeptides [2:1]: versicotides A-B [347], and the cyclopentapeptides: versicoloritides A-C were isolated from *Aspergillus versicolor*. Fellutamides A and B are cytotoxic peptides that were isolated from the cultured fungus, *Penicillium fellutanum* obtained from the gastro-intestine of the marine fish *Apogon endekataenia* [348]. Fellutamides C and D are two aldehyde peptides that were isolated from an undescribed species of *Metulocladosporiella* (Chaetothyriales), which are potent inhibitors of the fungal proteasome activity along with exhibiting substantial potency against human PC-3 tumor cell-line [349]. Fellutamide F is a lipopeptide that was isolated from *A.*

versicolor and exhibited cytotoxicity against a panel of HTCLs [190]. Asperterrestide A is another antiviral and cytotoxic cyclic tetrapeptide that was isolated from *Aspergillus terreus*. Asperterrestide A exhibited cytotoxicity against MOLT4 and U937 cell-lines at IC_{50} values of 6.2 and 6.4 μM, respectively, while displaying antiviral activity against H1N1 and H3N2 influenza strains at IC_{50} values of 15 and 8.1 μM, respectively [350].

Sansalvamide A is a cyclic depsipeptide isolated from the mycelium of the fungus belonging to *Fusarium* genus obtained from the surface of the sea-grass *Halodule wrightii*, and exhibited potent anticancer activity. An analog of sansalvamide A caused G-phase cell cycle arrest in CD18 and AsPC-1 human pancreatic cancer cell-lines. Sansalvamide A also caused topoisomerase I inhibition resulting in cell-death with some apoptotic characteristics in certain cancer cells. Sansalvamide A showed selective *in vitro* cytotoxicity towards SK-MEL-2 melanoma and COLO 205 colon cancer cell-lines at IC_{50} values of 5.9 μg/mL and 3.5 μg/mL, respectively [34,351]. Scopularides A and B are two cyclodepsipeptides isolated from *Scopulariopsis brevicaulis* obtained from the marine sponge *Tethya aurantium*. Scopularides showed weak activity against gram-positive bacteria and no activity against gram-negative bacteria, but exhibited significant activity against several tumor cell-lines at 10 μg/mL [352,353]. Exumolides A-B are cyclic depsipeptides that were isolated from the marine fungus belonging to *Scytalidium* genus and were found to display anti-microalgal activity at 20 μg/mL against the marine chlorophyte alga belonging to *Dunaliella* species [354].

Chemical analysis of *Penicillium bilaii*, an Australian marine derived fungi, yielded *cyclo*-(L-Phe-L-Pro), *cyclo*-(L-Pro-L-Tyr), *cyclo*-(L-Pro-L-Val), and *cis*-bis(methylthio)silvatin. *cis*-bis(methylthio)silvatin was found to be weakly cytotoxic at an LD_{99} value of 0.15 μM [355].

Penilumamide is a lumazine peptide which was the first and the only peptide isolated from a red algal derived *Penicillium* sp., (CNL-388 strain) fungus. Penilumamide is a linear peptide with an unusual 1,3 dimethyllumazine-6-carboxylic acid starter unit and did not exhibit any cytotoxicity [356]. Penilumamides B-D are other lumazine peptides isolated from a gorgonian-derived marine fungus *Aspergillus* sp., (XS-20090B15) which was obtained from the inner part of the gorgonian *Muricella abnormaliz* along with a cyclic pentapeptide asperpeptide A. Penilumamides A-D did not exhibit any antiviral and/or acetylcholinesterase inhibitory activities, while asperpeptide A displayed antibacterial activity against *Staphylococcus epidermidis* and *Bacillus cereus* at an MIC value of 12.5 μM [357].

Emericellamides A and B are cyclic depsipeptides isolated from the co-culture of the fungus belonging to *Emericella* sp., and *Salinispora arenicola*, an actinomycete. Emericellamide A exhibited antimicrobial activity against MRSA (methicillin-resistant *Staphylococcus aureus*) at an MIC of 3.8 μM, while also displaying cytotoxicity against human colon carcinoma HCT-116 cell-line at an IC_{50} value of 23 μM. Emericellamide B showed moderate cytotoxicity against MRSA at an IC_{50} value of 6.0 μM [358,359]. Guangomides A and B are cyclic depsipeptides isolated from an unidentifiable sponge-derived fungus cultured from salt-water. Along with guangomides A and B, homodestcardin which was the first example of a destruxin derivative was also isolated. Guangomides A and B exhibited weak

antibacterial activity against *Enterococcus durans* and *Staphylococcus epidermidis* at an MIC value of 100 μg/mL [360]. Azonazine is an unusual hexacyclic dipeptide isolated from *Aspergillus insulicola* which was a marine sediment-derived fungus. Azonazine displayed anti-inflammatory activity through NF-κB luciferase inhibition at an IC_{50} value of 8.37 μM and nitrite production at an IC_{50} value of 13.70 μM [361].

Endolides A-D and hirsutide were isolated from the sponge derived fungus *Stachylidium* sp. Hirsutide was previously isolated from the entomopathogenic fungus belonging to *Hirsutella* species. Endolides A and B were *N*-methylated peptides, while endolides C and D were tetrapeptide analogs. Endolides A and B showed affinity for vasopressin receptor 1A and serotonin receptor $5HT_{2B}$, respectively [362].

Dictyonamides A and B are peptides derived from the mycelium of the fungus isolated from the red alga *Ceratodictyon spongiosum* with no reported biological activity [363]. Simplicilliumtides A-H were linear tetrapeptides isolated from a deep-sea derived fungus *Simplicillium obclavatum*. Simplicilliumtides A-B are linear tetrapeptides with a 2-aminobenzoic acid residue, while simplicilliumtides C-H are acetylated linear di- or tri-peptides. Simplicilliumtides were evaluated for cytotoxic, acetylcholinesterase inhibition, antibacterial, and antifouling activities. Simplicilliumtides A and G exhibited weak cytotoxicity against human HL-60 leukemia cell-line at IC_{50} values of 64.7 and 100 μM, respectively, while simplicilliumtides E and H displayed cytotoxicity against K562 cell-line at IC_{50} values of 39.4 and 73.5 μM, respectively. Simplicilliumtide D displayed potent antifouling activity against *Bugula neritina* larvae settlement indicating its potential as a natural antifouling candidate [364].

Halolitoralin A is a cyclic hexapeptide while halolitoralins B-C are cyclic tetrapeptides isolated from the marine sediment derived *Halobacillus litoralis* along with three cyclic dipeptides: cyclo(Ile-Val), cyclo (Pro-Leu), and cyclo(Pro-Val). Halolitoralins A-C exhibited moderate antifungal activity along with weak anti-tumor activities *in vitro*, against human gastric BGC cell-line [365]. Sclerotides A-B were isolated from the marine derived halotolerant *Aspergillus sclerotiorum*. Sclerotides A-B are cyclic hexapeptides with dehydroamino acid and anthranilic acid units. Sclerotides A-B exhibited moderate antifungal activity against *Candida albicans* at MIC values of 7.0 and 3.5 μM, respectively, while sclerotide B also displayed weak cytotoxicity against HL-60 cell-line at an IC_{50} value of 56.1 μM and antibacterial activity against *Pseudomonas aeruginosa* at an MIC of 35.3 μM [366].

RHM1 and RHM2 were *N*-methylated linear octapeptides which were isolated from the fungus belonging to *Acremonium* species cultured from a marine sponge along with efrapeptin G. Efrapeptin G exhibited potent cytotoxicity while RHM1 and RHM2 displayed weak cytotoxicity against murine cancer cell-lines [367]. Efrapeptins are (peptides) potent inhibitors of mitochondrial ATPase isolated from the entomopathogenic fungus *Tolypocladium niveum* [368].

Cordyheptapeptides C-E were cycloheptapeptides that were isolated from *Acremonium persicinum*, a marine fungus. Cordyheptapeptides C and E exhibited cytotoxicity against

NCI-H460, SF-268, and MCF-7 tumor cell-lines with IC_{50} values between 2.5 to 12.1 μM [369]. Cordyheptapeptides A and B were isolated from an insect pathogenic fungus *Cordyceps* sp. BCC 16173. Cordyheptapeptide A possessed an *N*-methyl-L-tyrosine while cordyheptapeptide B has an *N*-methyl-L-phenylalanine residue. Cordyheptapeptide A showed antimalarial activity at an IC_{50} value of 3.8 μM, while cordyheptapeptide B was inactive. Cordyheptapeptides A and B also exhibited moderate cytotoxicity against NCI-H187 cells with IC_{50} values of 0.18 and 3.1 μM, BC cells with IC_{50} values of 0.20 and 0.66 μM, Vero cells with IC_{50} values of 14 and 1.6 μM, and KB cells with IC_{50} values of 0.78 and 2.0 μM, respectively [370]. Oryzamides A-E were cyclohexadepsipeptides that were isolated from the *Nigrospora oryzae* PF18, a marine fungus obtained from the sponge *Phakellia fusca*. Oryzamides did not exhibit any antiparasitic, NF-κB inhibition, cytotoxic, or antibacterial activities [371].

D. Ascidians

Cycloxazoline was a cyclic hexapeptide isolated from *Lissoclinum bistratum* and showed cytokinetic inhibition and HL-60 leukemia cell accumulation in G2/M. Cycloxazoline exhibited cytotoxicity against T24 and MRC5CV1 cell-lines at an IC_{50} value of 0.5 μg/mL [34,372]. Diazonamide A was a cytotoxic peptide isolated from *Diazona angulata* and possessed a unique binding-site on tubulin, differing from the dolastatin 10 and *Vinca* alkaloid binding-sites. Diazonamide A and its analog were also shown to strongly bind to the microtubule ends and weakly bind to the unpolymerized tubulin. Diazonamide A showed potent *in vitro* activity against B-16 murine melanoma and HCT-116 human colon carcinoma cell-lines with IC_{50} values of < 15 ng/mL while diazonamide B isolated from *D. chinensis* was found to be less active [34,373,374]. The structure of diazonamide A has been revised with the altered spectroscopic and physical characteristics relative to those of the original structure [375]. Diazonamides C-E were macrocyclic peptides isolated from *Diazona* sp., and displayed moderate cytotoxicity against human tumor cell-lines [376].

Vitilevuamide was a bicyclic 13 amino-acid residue isolated from *Didemnum cuculiferum* and *Polysyncranton lithostrotum*. Vitilevuamide exhibited inhibition of tubulin-polymerization at an IC_{50} value of 2 μM possibly through interaction at a unique site. Vitilevuamide showed *in vitro* activity against P388 lymphocytic leukemia at 30 μg/kg along with stabilizing colchicine binding to tubulin at 9 μg/mL. Vitilevuamide was also found to be cytotoxic against various human tumor cell-lines at LC_{50} values of 6–311 nM [34,377].

Thiazoline-, thiazole-, and oxazoline-based cyclic octa- and heptapeptides were isolated from *Lissoclinum patella*. Examples include lissoclinamides, patellamides, ulithiacyclamide A which included a disulfide-bridge, and ascidiacyclamide which incorporated a C_2-symmetry. Examples of compounds including oxazoline-based cyclic hexapeptides were bistratamides isolated from the Australian Great Barrier Reef and the Philippine ascidian *L. bistratum*. These hexapeptides were associated with the C_3-symmetric tris-oxazoline westiellamide isolated from *L. bistratum* [378,379]. Bistratamides A and B exhibited cytotoxicity against MRC5CV1 fibroblasts and T24 bladder carcinoma cell-lines at IC_{50} values of 50 and > 100 μg/mL, respectively. This toxicity was similar to certain cyclic hepta- and octapeptides isolated from *L. patella*: lissoclinamide 5 and patellamide D [380].

Bistratamides C and D were cyclic hexapeptides isolated from *Lissoclinum* sp., where bistratamide D exhibited depressant effects in mice at a dose of 65 μg [381]. Bistratamides E-J were moderate cytotoxic hexapeptides isolated from *L. bistratum*. Bistratamides E-J exhibited cytotoxicity against HCT-116 human colon tumor cell-line at IC_{50} values of 7.9, 28.0, 5.0, 1.7, 9.0, and 1.0 μg/mL, respectively [382]. Didmolamides A and B were bis-thiazole based compounds isolated from *Didemnum molle* collected from Madagascar [378].

Lissoclinamides isolated from the aplousobranch ascidian *Lissoclinum patella* showed anti-neoplastic properties against human bladder carcinoma and fibroblast cell-lines, and normal lymphocytes. Lissoclinamide 7 was the most potent compound with two thiazoline rings that rivaled *in vitro* didemnin B in cytotoxicity. Patellamides also displayed potent cytotoxicity [34,378,379].

N-methylamino acids are commonly found in marine peptides such as jaspamide, didemnins, and others. Didemnins A-E, M, N, X, Y, nordidemnin N, epididemnin A1, and acyclodidemnin A were cyclic depsipeptides that were isolated from a Caribbean tunicate *Tridemnum solidum* [383,384]. Didemnin B was a branched *N*-methylated cyclic peptolide and was shown to induce cell-death with apoptotic morphology, DNA fragmentation, and DNA ladder generation in a variety of transformed cells with no known mechanism. Many analogs of didemnin B were known to possess cytotoxicity, antiviral, and immunosuppressive properties [385]. Didemnin H was a cyclodepsipeptide isolated from *Tridemnum cyanophorum* [386]. Didemnins M, N, X, Y, A, and B exhibited cytotoxicity against P388 cell-line at IC_{50} values of 2.0, 50, 2.0, 2.0, 30, and 0.5 ng/mL, respectively. Epididemnin A1 and acyclodidemnin A also showed weak cytotoxicity at IC_{50} values of 2.0 and 0.2 μg/mL, respectively. Didemnin M expressed potent immunosuppressive activity in both graft vs host and lymphocyte reaction assays [384].

Styelin D was a *C*-terminal amidated 32-residue antimicrobial peptide isolated from the hemocytes of *Styela clava*, a solitary ascidian. Styelin D included two novel amino acids: dihydroxylysine and dihydroxyarginine, and two distinct unusual ones: 3,4-dihydroxyphenylalanine and 6-bromotryptophan. Styelin D was found to be cytotoxic and hemolytic to eukaryotic cells [34,387]. Eusynstyelamide was a modified dimer peptide isolated from *Eusynstyela misakiensis* and exhibited weak cytotoxicity at IC_{50} values of 100 μg/mL against human colon HCT-116 tumor cell-line [34,388]. Eudistomides A and B were five residue cysteine-linked cyclic peptides that were isolated from *Eudistoma* sp. Eudistomides were flanked with a 12-hydroxy- or 12-oxo-tetradecanoyl moiety and a *C*-terminal methyl ester and were reported to be the first ascidian derived peptides cyclized with a disulfide bridge [389].

Mollamide was a cytotoxic cyclic heptapeptide isolated from *Didemnum molle*. Mollamide was found to be cytotoxic against CV1 monkey kidney fibroblasts, A549 human lung carcinoma, and HT29 human colon carcinoma cell-lines at an IC_{50} value of 2.5 μg/mL, and against P388 murine leukemia cell-line at an IC_{50} value of 1 μg/mL [390]. Mollamide was also an RNA synthesis inhibitor at an IC_{50} value of 1 μg/mL. Mollamides -B and -C were two cyclic hexapeptides that were isolated from *D. molle* along with keenamide A. These peptides were previously reported from a notaspidean mollusk *Pleurobranchus forskalii*, and

shared peculiar reverse prenylated ethers of threonine and serine amino acids. Mollamide B and keenamide A were found to be cytotoxic against various cancer cell-lines. Mollamide B showed moderate anti-malarial activity against W2 and D6 clones of *Plasmodium falciparum* with IC_{50} values of 2.1 and 2.0 μg/mL, respectively, while marginal activity was seen with *Leishmania donovani* with IC_{90} and IC_{50} values of 35 and 18 μg/mL, respectively. Mollamide B also exhibited *in vitro* activity against HIV-1 with an EC_{50} value of 48.7 μM [34,391]. Keenamide A exhibited significant activity against MEL-20, P-388, and A-549 cell-lines at an IC_{50} value of 2.5 μg/mL, and showed activity against HT-29 cell-line at an IC_{50} value of 5.0 μg/mL [392]. Cycloforskamide was another macrocyclic peptide isolated from *P. forskalii* which exhibited cytotoxicity against murine P388 leukemia cell-line at an IC_{50} value of 5.8 μM [393].

Other marine peptides such as virenamides A-C, sansalvamide A, and cycloxazoline exhibited potent anti-apoptotic activity in various cancer-cells, but the exact targets of these compounds are unknown. Virenamides A-C were linear cytotoxic tripeptides isolated from a didemnid ascidian *Diplosoma virens*, and possessed modest cytotoxicity against a panel of cultured cells. Virenamide A was potent at an IC_{50} value of 10 μg/mL against CV1, A549, and HT29 cell-lines and against P388 cell-line at an IC_{50} value of 2.5 μg/mL. Virenamide A also exhibited topoisomerase II inhibition. Both virenamides B and C were potent at an IC_{50} value of 2.5 μg/mL against CV1, A549, HT29, and P388 cell-lines [34,394].

Cyclodidemnamide was a cyclic heptapeptide isolated from *Didemnum molle*, and was found to be weakly cytotoxic against human colon HCT-116 tumor cell-line at an ED_{50} value of 16 μg/mL [395]. Along with cyclodidemnamide, *D. molle* also yielded two cyclic hexapeptides: comoramides A and B, and two cyclic heptapeptides: mayotamides A and B [396]. Comoramides and mayotamide peptides were screened against various tumor cell-lines including MEL-28, A549, and HT29 and were found to be cytotoxic at IC_{50} values of 5–10 μg/mL [396]. Didmolamides A and B were isolated from *D. molle* along with prepatellamide A, and tamandarins A and B. Didmolamides A and B exhibited cytotoxicity against HT29, MEL28, and A549 at IC_{50} values of 10–20 μg/mL [397]. Prepatellamide A was initially isolated from *Lissoclinum patella* along with three cyclic peptides: patellamides A-C. Prepatellamide A and patellamides A-C exhibited cytotoxicity at an IC_{50} value of 5 μg/mL against murine leukemia P388 cell-line [398]. Tamandarin A inhibited protein-biosynthesis in the reticulocyte cell-lysates of rabbit at an IC_{50} value of 1.3 μM along with being more potent against various human cancer cell-lines compared to didemnin B [399].

Patellins 1–6 and trunkamide A were isolated from *Lissoclinum patella*. Patellins 1–2 were cyclic hexapeptides while patellins 3–6 were cyclic octapeptides; trunkamide A is a cyclic heptapeptide. Patellins 1–5 and trunkamide A did not exhibit any *in vitro* cytotoxicity, but patellin 6 displayed cytotoxicity against CV1, A549, HT29, and P388 cell-lines at an IC_{50} value of 2 μg/mL, and topoisomerase II inhibition at an IC_{50} value of 2.5 μg/mL [400].

Kulolides 1–3, kulokainalide-1, and kulomo'opunalides 1–2 were depsipeptides isolated from the marine mollusk *Philinopsis speciosa* along with the linear peptide, pupukeamide. Kulolide-1 exhibited cytotoxicity at a concentration of 50 μM in rat fibroblast cells. Similar

activity was also seen with other kulolides with the strongest activity seen with kulokainalide-1 at a concentration of 5 μM [401].

Ulicyclamide, preulithiacyclamide [402], ulithiacyclamide, and ulithiacyclamide B were small peptides that were isolated from *Lissoclinum patella* [403]. Ulithiacyclamide B exhibited cytotoxicity against solid tumor cells at an IC_{50} value of 17 ng/mL. Ulithiacyclamide and ulithiacyclamide B exhibited cytotoxicity against KB cell-line at IC_{50} values of 35 ng/mL and 17 ng/mL, respectively [404]. Ulithiacyclamide was also a potent inhibitor of Macrophage Scavenger Receptor (MSR) at an IC_{50} value of 98 nM, while ulicyclamide was inhibitor of MSR at 51 μM [402].

E. Other Marine Sources

A family of peptidic metabolites namely nobilamides A-E were isolated from the *Streptomyces* bacterial strain [*Chicoreus nobilis*] while nobilamides A and F-H were isolated from another *Streptomyces* strain [*Conus tribblei*] separated from molluscs [190]. A-3302-A and A-3302-B are related peptides which were previously obtained from the terrestrial *B. subtilis* and were later isolated from a marine source [190]. *N*-acetyl-L-phenylalanyl-L-leucinamide [405], a known synthetic peptide, was initially isolated from a natural source. Nobilamide B and A-3302-B are potent, long-acting antagonists of human and mouse transient receptor potential vanilloid-1 channels (TRPV1) as inflammation and pain mediators [406].

Aplidine is also known with several names such as aplidin, dehydrodidemnin B, and DDB, and was isolated from a Mediterranean tunicate *Alpidium albicans*. Low concentrations of aplidine were found to be sensitive against melanoma, non-small cell lung, and breast cancer cell-lines. Several mechanisms of action were involved such as inhibition of protein-synthesis and cell-cycle arrest. Aplidine resulted in a persistent and rapid activation of p38 MAPK phosphorylation and JNK activation resulting in the downstream release of cytochrome-c along with inducing early oxidative-stress. Aplidine also activated PARP cleavage and caspases-3 and -9 representing the mitochondrial apoptotic-pathway mediation during the process. Aplidine induced apoptosis in MDA-MB-231 breast cancer cell-line along with sustained activation of the serine/threonine kinases p38 MAPK and JNK, epidermal growth factor receptor [EGFR], and the non-receptor protein tyrosine kinase Src. Two proposed mechanisms regarding the JNK activation of aplidine included MKP-1 phosphatase down-regulation and Rac1 small GTPase activation. Aplidine is also known as plitidepsin, and following the completion of phase I clinical trials, has proceeded to phase II clinical trials well-tolerating the minor toxicity [34].

Dolastatin 3 was a cyclic peptide initially isolated from *Dolabella auricularia* and later from *Lyngbya majuscula*. Dolastatin 3 exhibited a GI_{50} value of < 1 μM against murine leukemia P388 cell-line [393]. Homodolastatin 3 and kororamide were other peptides isolated from *L. majuscula* with no known biological activity [407]. Dolastatin 10–15 were peptides isolated from a marine mollusk *D. auricularia* and included several unique amino-acid subunits. Dolastatin 10 was a linear pentapeptide known to inhibit the growth of L1210 murine leukemia-cell-line along with causing aggregation of cold-stable tubulin formation. Other properties of dolastatin 10 included tubulin-binding of *Vinca* alkaloids, inhibition of

microtubule assembly, and tubulin-dependent GTP hydrolysis. Dolastatin 10 was also known to prevent the loss of stabilizing effects on colchicine binding-activity of tubulin. A segment [tripeptide] of dolastatin 10 inhibited the GTP-hydrolysis and tubulin-polymerization, but did not show any significant inhibition towards nucleotide exchange or vincristine binding [34]. Dolastatin 11 exhibited a mean GI_{50} value of ~ 0.07 μM in the NCI-60 cell-line panel, while dolastatin 12 showed GI_{50} values ranging from ~ 1 nM in human NCI-H460 non-small cell lung cancer [NSCLC] to ~ 30 nM in human SF-295 CNS cancer when assayed in five different cancer cell-lines. Moreover, it showed GI_{50} values of > 1 μM in P388 leukemia cell-line and ~ 0.1 μM in mouse neuro-2a neuroblastoma cell-line. Dolastatins 13 and 14 displayed GI_{50} values of 14 nM and 20 nM in murine P388 leukemia cell-line, respectively [393]. Dolastatins 14 and 15 exhibited antineoplastic activity, with dolastatin 15 being the most potent [408]. Epidolastatin 12 was a C-15 epimer of dolastatin 12 that was isolated from *L. majuscula*/*Schizotrix calcicola*. Epidolastatin 12 exhibited cytotoxicity against human nasopharyngeal KB carcinoma cell-line at an MIC of < 0.05 μg/mL and disrupted the microfilament network at concentrations of 0.2 and 2 μg/mL [205].

Dolastatin 16 was another cyclic depsipeptide that was isolated from *Dolabella auricularia*, *Lyngbya majuscula*, and *Symploca* cf. *hydnoides*. Dolastatin 16 included two amino acids: dolaphenvaline and dolamethylleucine and displayed GI_{50} values in low nanomolar ranges in a panel of five leukemia cell-lines and four human solid cancer cell-lines with a mean GI_{50} value of ~ 0.3 μM [393]. Homodolastatin 16 was a cyclic depsipeptide which was also isolated from *L. majuscula* and was a higher homologue of dolastatin 16. Homodolastatin 16 exhibited moderate cytotoxicity against two oesophageal WHCO1 and WHCO6 cell-lines at IC_{50} values of 4.3 and 10.1 μg/mL, respectively, and against cervical ME180 cancer cell-line at an IC_{50} value of 8.3 μg/mL [409]. Dolastatin 17 was a cyclodepsipeptide that included dolayne (Doy), a novel acetylenic β-amino acid similar to onchidin. It showed submicromolar range of GI_{50} values when assayed in four cancer cell-lines. Dolastatin 18 was unique in the presence of a thiazole ring in its structure, and has submicromolar range GI_{50} values in the human NCI-H460 NSCLC and the mouse P388 lymphocytic leukemia cell-lines [393].

Dolastatin C was a depsipeptide structurally related to dolastatins 10 and 15 and was isolated from *Dolabella auricularia*. Dolastatin C exhibited weak cytotoxicity against HeLa S3 cell-line at an IC_{50} value of 17 μg/mL [410]. Dolastatin D was another cyclic depsipeptide that exhibited a GI_{50} value of ~ 4 μM in human cancer HeLa S3 cell-line, while dolastatin G and nordolastatin G were cyclic depsipeptides with GI_{50} values of ~ 1 and ~ 5 μM, respectively, against the same cancer cell-lines [393]. Dolastatin E was a cyclic hexapeptide with three five-membered heterocycles: thiazolone, thiazole, and oxazole isolated from *D. auricularia*. Dolastatin E exhibited cytotoxicity against HeLa S3 cell-line at IC_{50} values ranging between 22–40 μg/mL [411]. Lyngbyastatin 2 and norlyngbyastatin 2 were cytotoxic analogs of dolastatin G and nordolastatin G which were isolated from *L. majuscula*. Lyngbyastatin 2 exhibited toxicity at LD_{100} of 3 mg/kg in mice and this was hypothesized due to the presence of an enol ether functionality but was inactive at sub-lethal doses against *in vivo* C38 murine colon adenocarcinoma. Both lyngbyastatin 2 and norlyngbyastatin 2 were not inhibitors of microfilament assembly or microtubule, nor were topoisomerase I inhibitors [412]. Dolastatin H and isodolastatin H were linear peptides isolated from *D. auricularia* and

were closely related to dolastatin 10. Isodolastatin H exhibited *in vivo* antitumor activity against murine P388 leukemia and was slightly weaker than dolastatin 10, while synthetic dolastatin H displayed a GI_{50} value of 2 nM against human HeLa S3 cancer cell-line [393]. Dolastatin I was a cyclic hexapeptide with three five-membered heterocycles: oxazole, oxazoline, and thiazole isolated from *D. auricularia*. Dolastatin I displayed cytotoxicity against HeLa S3 cell-line at an IC_{50} value of 12 μg/mL [413].

Dolabellin was another novel cytotoxic metabolite isolated from the Japanese sea hare *Dolabella auricularia*. Dolabellin included a novel dechlorinated β-hydroxy acid along with two thiazole hydroxy-acids. Dolabellin exhibited cytotoxicity against HeLa S3 cell-line with an IC_{50} value of 6.1 μg/mL [414]. Doliculide was a cytotoxic cyclodepsipeptide that was isolated from the Japanese sea hare *D. auricularia*. Doliculide was a mixed peptide-polyketide having a 15-carbon polyketide unit, a unique D-amino acid, and glycine and showed potent cytotoxicity against HeLa S3 cell-line at an IC_{50} value of 0.001 μg/mL [415].

Kulokekahilide-1 was a cytotoxic depsipeptide that was isolated from a cephalaspidean mollusk *Philinopsis speciosa* and included two unusual amino acids: 3-amino-3-methylhexanoic acid and 4-phenylvaline. Kulokekahilide-1 was cytotoxic against P388 murine leukemia cell-line at an IC_{50} value of 2.1 μg/mL [416]. Kulokekahilide-2 was another cytotoxic depsipeptide that was isolated from the same cephalaspidean mollusk and was active against various cancer cell-lines such as A-10, P388, MDA-MB-435, and SK-OV-3 with IC_{50} values of 59.1, 4.2, 14.6, and 7.5 nM, respectively [417]. Aurilide was a cyclodepsipeptide that was isolated from a Japanese sea hare *Dolabella auricularia* and was similar to kulokekahilide-2. Aurilide was a potent cytotoxic peptide that may serve as a small molecule tool for studies of mitochondria-induced apoptosis [236]. Aurilide was a 26-membered cyclodepsipeptide that showed cytotoxicity against HeLa S3 cell-line at an IC_{50} value of 0.011 μg/mL [418].

Several bioactive peptides were isolated from the marine coral reef belonging to the *Okeania* genus. These included viridamides A-B [419] which were isolated from *Okeania comitata*; microcolins A-B [420,421] from *O. erythroflocculosa*; grassypeptolides A-C [221] and grassystatins A-B from *O. lorea*; tumonoic acids A-C, lyngbyastatin 1, and dolastatin 12 [205] from *O. plumata*; and malyngamide C, malyngamide C acetate [422], and lyngbic acid from *O. hirsuta* [423]. Microcolin A [Mic-1] induced apoptosis in murine-thymocytes at 10–100 nM [424], while microcolin B was found to be a potent immunosuppressant [421]. Other tumonoic acids D-I were isolated from the marine cyanobacterium *Blennothrix cantharidosmum* where tumonoic acid I exhibited moderate antimalarial activity at an IC_{50} value of 2 μM. Most of the tumonoic acids exhibited moderate bioluminescence inhibition with tumonoic acid F being the most active with an IC_{50} value of 62 μM. All the tumonoic acids were initially isolated from *L. majuscula* and *Schizothrix calcicola* [425]. Janadolide was a cyclic polyketide-peptide hybrid isolated from *Okeania* sp., and exhibited anti-trypanosomal activity at an IC_{50} value of 47 nM with no cytotoxicity towards human cells at 10 μM. Janadolide structure has a *tert*-butyl group similar to antillatoxins and apratoxins [426].

Onchidin and onchidin B were cyclic depsipeptides that were isolated from *Onchidium* sp., a pulmonate mollusk. The structure of onchidin included two identical halves of MeVal-Amo-Val-Hiv-Hiv with a novel β-amino acid: 3-amino-2-methyl-oct-7-ynoic acid (Amo). Onchidin was a cytotoxic depsipeptide that was found to be a rich source of γ-pyrone polypropionates [427]. Onchidin B included four α-amino acids: two units of proline and two units of *N*-methyl valine, two units of β-hydroxy acid: 3-hydroxy-2-methyloct-7-ynoic acid [Hymo], and four α-hydroxy acids: two 2-hydroxy-3-methylpentanoic acid moieties [Hmp] and two 2-hydroxyisovaleric acids [Hiv]. Onchidin B showed 97% inhibition of Kb cells at 10 μg/mL [428]. Norcardiamides A-B were cyclic hexapeptides that were isolated from the marine derived actinomycete *Nocardiopsis* species. Norcardiamides possessed a triple-Val subunit, and exhibited negligible antimicrobial activities with no cytotoxicity against human colon carcinoma HCT-116 cell-line [429].

Kahalalides were cyclic depsipeptides isolated from a sacoglossan mollusk *Elysia rufescens*. Kahalalides ranged from a C_{31} tripeptide to a C_{75} tridecapeptide. Kahalalides F and G included a rare dehydroaminobutyric acid that separated these from the other kahalalides, while the others included the same amino acids. Kahalalide A (KA) exhibited moderate antimalarial activity against *Plasmodium falciparum* while kahalalide E (KE) showed selectivity against HSV II (*Herpes simplex* virus II). Kahalalide F displayed selective activity against few AIDS opportunistic infections (OI) and solid tumors [430]. Kahalalide F (KF) also exhibited antitumor activity against human breast and prostate cancer cell-lines at IC_{50} values ranging from 0.07 μM to 0.28 μM while being less sensitive to non-tumor human cells at IC_{50} values ranging from 1.6–3.1 μM [431]. Of the different kahalalides, only kahalalides A, E, F, isoKF, R_1, isoKA, and 5OH-KF showed significant biological activities. Kahalalides R_1 and F exhibited cytotoxicity against MCF-7 cell-line at IC_{50} values of 0.14 and 0.22 μM, respectively, while kahalalide R_1 displayed cytotoxicity against L1578 Y cell-line at an IC_{50} value of 4.3 nM [432]. KA exhibited antimicrobial activity with 83% growth inhibition against *Mycobacterium tuberculosis* at 12.5 μg/mL. KF showed antifungal activity against *Aspergillus fumigatus* at IC_{50} value of 3.2 μM, *Cryptococcus neoformans* at 1.5 μM, and *Candida albicans* at 3.0 μM, along with antiviral activity against HSV II at 0.5 μg/mL, immunosuppressive activity at an IC_{50} value of 3 μg/mL, and antileishmanial activity. Kahalalide R_1 displayed antifungal activity with inhibition zones of 16 and 24 mm [432].

Two isomers of bioactive thiazole containing cyclic heptapeptides: *cis,cis*-ceratospongamide and *trans,trans*-ceratospongamide were isolated from the marine red alga, Rhodophyta: *Ceratodictyon spongiosum* with the symbiotic sponge *Sigmadocia symbiotica*. *trans,trans*-Ceratospongamide exhibited anti-inflammatory activity with potent $sPLA_2$ expression inhibition at an ED_{50} value of 32 nM while the *cis,cis* isomer was inactive. The *trans, trans* isomer also exhibited the human-$sPLA_2$ promoter based inhibition by 90% [433]. Mebamamides A-B were lipopeptides isolated from the green alga *Derbesia marina*. Mebamamides included a 3,8-dihydroxy-9-methyldecanoic acid residue along with four D-amino acid residues. Mebamamide A did not display any growth-inhibition against HL60 and HeLa cells at 10 μM while mebamamide B did not exhibit any growth inhibition at 100 μM. Mebamamide B also persuaded the differentiation of HL60 cells into macrophage like cells at 100 μM [434]. Galaxamide was a cyclic pentapeptide that was isolated from *Galaxaura filamentosa*, a marine alga, and exhibited antiproliferative activity. Galaxamide

included two *N*-methyl leucines and three leucines [435]. Galaxamide showed cytotoxicity against human cancer U87 and MCF-7 cell-lines with IC_{50} values of 10.6 and 14.9 μg/mL, respectively [436].

Conantokin G and conotoxin GV were isolated from a fish eating snail *Conus geographus* [437], while conantokin T was isolated from the venom of a fish hunting cone snail *Conus tulipa* [438]. Conantokin G was a 17 amino acid and possessed *N*-methyl-D-aspartate (NMDA) antagonist activity blocking the NMDA induced cGMP elevation at an IC_{50} value of 171 nM [437]. Conantokin-T was a 21 amino acid peptide that included 4 residues of a modified amino acid: γ-carboxyglutamate. Conantokin T exhibited NMDA antagonist activity [438]. Conotoxin GV was a sleeper heptadecapeptide whose structure was determined to be Gly-Glu-Gla-Gla-Leu-Gln-Gla-Asn-Gln-Gla-Leu-Ile-Arg-Gla-Lys-Ser-Asn-NH_2. Low doses of this peptide induced a sleep-like state in mice under 2 weeks old at doses of 4–30 pmol/g while older mice tended to be more hyperactive [439]. *Actinia equine* equinatoxin II [EqT-II] represented a family of basic, pore-forming, polypeptide toxins isolated from the sea-anemones which are now called as actinoporins. Actinoporins are 15–20 kDa cytolytic polypeptides that were isolated from the sea-anemones *Actiniaria* and exhibited pore forming activity in model and natural lipid membranes. Of the three isotoxins: actinoporins, sphingomyelin, and equinatoxin II, EqT-II was found to be highly lethal in mammals at an LD_{50} value of 35 μg/kg and also strongly hemolytic [440]. A mitogenic hexapeptide named SECMA 1 isolated from the alga belonging to *Ulva* sp., with the sequence Glu-Asp-Arg-Leu-Lys-Pro was found to be active against human foreskin fibroblasts at 4 μg/mL [441,442].

Arasin-1 was a proline-arginine rich antimicrobial peptide that was isolated from the hemocyte extracts of *Hyas araneus*, a spider crab. Arasin-1 included 37 amino acids with a *C*-terminal domain having two disulfide linkages and an *N*-terminal domain rich in arginine and proline. The amino acid sequence of arasin-1 is SRWPSPGRPRPFPGRPKPIFRPRPCNCYAPPCPCDRW with an average mass of 4345.10 Da and a calculated monoisotopic mass of 4342.06 Da. Aracin-1 exhibited activity against *Corynebacterium glutamicum* at an MIC value of 0.8 μM, while showing antibacterial activity at higher concentrations [443]. Arenicins 1 and 2 were antimicrobial peptides with 21-residues that were isolated from the coelomocytes of *Arenicola marina*, a marine polychaeta. Arenicin-1 has a molecular mass of 2758.3 Da with the amino acid sequence: RWCVYAYVRVRGVLVRYRRCW, while arenicin-2 has a molecular mass of 2772.3 Da with the amino acid sequence: RWCVYAYVRIRGVLVRYRRCW. Arenicins 1 and 2 exhibited antimicrobial activity at 25 μg/mL. Arenicins showed activity against *Listeria monocytogenes* at an MIC value of 0.6 μg/mL at low salt conditions and were less potent against *E. coli* and *C. albicans* at MIC values of 4.0 and 4.5 μg/mL, respectively [444].

III. CHALLENGES INVOLVED WITH PEPTIDE ISOLATION

Peptides are an interesting class of therapeutics that shows growing interest. Peptides are used in various therapeutic areas like anti-infectives, arthritis, allergy, cardiovascular, oncology, obesity, and diabetes besides others. Peptides also possess various advantages such as specificity, potency, minimized drug-drug interactions, high activity, less tissue

accumulation; thereby low toxicity, and also offer a significant chemical and biological diversity. Along with advantages, peptides do have some disadvantages limiting their success. The major disadvantage is the stability of peptides in the body that could result in lesser bioavailability and shorter half-life along with other limitations such as formulation challenges and expensive synthesis. Solubility and pH signify important characteristics that should be considered for drug-formulation. During synthesis, one can encounter problems such as aggregation and solubility hurdles. There is only an 11 per cent success rate for peptides to reach from phase I clinical trials to drug approval, which could be higher with cardiovascular peptide-drugs and lower with anticancer peptide-drugs [445]. A total of 19 peptides were approved between 2001 and 2012, while in 2012 alone five of the 40 drugs approved were peptides [446].

One of the major challenges in peptide-based drug development is the optimization between the required peptide length and the pharmacologically useful levels for receptor-activation. The numerous variables that are considered include: (1) size and accessibility of ligand binding surfaces; (2) possible induced fit; (3) receptor residency time and ligand-stability. Another drawback with peptide drugs is their increased proteolytic instability compared to other small-molecule drugs which can be overcome by altering both the side-chains and amide-bonds making the peptidomimetics resistant to proteolytic degradation. Serum stability assay helps measure the peptide stability along with other important pharmacokinetic behavior of drugs [446].

In order to overcome the challenges of lower bioavailability and shorter half-life, the peptide backbone can be modified by introducing D-amino acids or unnatural amino acids or the peptide bonds can be altered with reduced amide bonds or β-amino acids in order to constrain the backbone by introducing cyclization or using constrained amino acids to induce less flexibility and enzyme-digestion. With some peptides, a fatty-acid attachment might result in increased bioavailability and half-life along with more target-specific binding, thereby resulting in fewer side-effects [445].

There are drug-delivery technologies (DDT) to improve the pharmacokinetics of the peptides and recent advancements to modulate their *in vivo* stability. Most peptides work by exerting their action on the cell-surface by binding to the membrane-proteins and hence various techniques were developed for intracellular delivery of peptides. One of the techniques is to fuse the peptides with nanoparticles or liposomes in order to penetrate the cell-membrane for the release of their contents in to the intracellular-domain, while the other technique involves the use of protein transduction domains (PTD) which are short peptide sequences, in order to allow the peptide-delivery into the cell. However, the challenge involved with liposomal formulation involves the inefficiency of encapsulation of the active pharmaceutical ingredient (API) into the liposomes; however this technology is still one of the best solutions with certain drug-formulations. Some of the achievements with this technology are Exubera® and inhaled insulin, opening the doors for further market-growth [445].

The process development of peptide synthesis is costly. This depends on the specifications or requirements and targeted volumes, which in turn affect the manufacturing costs.

Delivering expected purities and yields is another problem associated with peptides along with identifying critical process parameters and proven acceptable ranges. The costs can also increase during drug-development. Peptide synthesis involves either solid-phase or liquid-phase or a combination of both. Liquid phase peptide synthesis (LPPS) is suitable for shorter peptide sequences (< 15 residues) and gives higher purity compared to solid-phase peptide synthesis (SPPS). LPPS process is often longer than an SPPS process. SPPS is used for longer peptide sequences (> 20 residues). The major drawbacks with SPPS involve waste volumes, solvents, and high raw-material costs. Along with these, the coupling reagents, choice of the resins, etc. should also be optimized [445].

Another challenge involved in peptide synthesis is aggregation. Some peptide sequences tend to self-associate due to aggregation [β-sheet formations]. This problem could be resolved by using pseudoprolines that tend to break the structures since the amide bond adopts a *cis* conformation (similar to proline residues in peptide sequences), which further leads to better solvation and chain-accessibility for further couplings. But the use of cysteine pseudoprolines shows limitations in peptide synthesis due to the high thiazolidine ring-stability which could require stronger acidic-conditions for deprotection. Hence, the deprotection conditions depend on the peptide sequences present and so require a case to case study [445].

Chemical biology comes into play to increase the sensitivity of the quantitative analysis of peptides. Another limitation is the oral bioavailability of peptides. The chemical and physical modifications that improve the oral bioavailability of peptides include conjugation to active and passive transport enhancers. Chemical biology has twofold function: to improve or solve suboptimal parameters such as poor pharmacokinetics of peptides or lack of oral activity, along with educating biotechnology investors the misconceptions of peptide-based therapeutics, which in reality are highly active and safe therapy options [446].

One noteworthy example of a peptide which was led from discovery to clinical development is caspofungin acetate, a parenteral antifungal agent. Caspofungin was a semisynthetic derivative of a natural, lipophilic cyclic peptide, pneumocandin B_0, isolated from the fungus *Glarea lozoyensis*. There were many challenges faced by caspofungin to get approved for clinical use, starting with its discovery to final approval. These included the discovery of pneumocandin B_0, fermentation development of pneumocandin B_0, semisynthetic modifications of pneumocandin B_0 using medicinal chemistry approaches to improve its properties, purification, formulation-development, commercial synthesis, and clinical development for the final approval of caspofungin as an antifungal drug [447].

Initially echinocandin B, a cyclic lipopeptide, was reported by Sandoz in 1974. The screening efforts at Merck's natural products led to the discovery of pneumocandin series with two structural differences to echinocandins. In 1987, the structural characterization and biological evaluation of pneumocandin A_0 as an antifungal agent was established. During the same year, pneumocandin B_0, a desmethyl congener of pneumocandin A_0, was identified. The actual structure of pneumocandin B_0 was not established due to insufficient amounts of natural product and also based on the fact that the pneumocandin A_0 lead was discontinued due to the lack of antifungal activity, poor water solubility, and oral

bioavailability. When pneumocandin A_0 was tested in an immunosuppressed rat model of *Pneumocystis carinii* pneumonia, it exhibited superior activity compared to the existing trimethoprim/sulfamethoxazole therapy. This led to reinstate pneumocandin B_0 as a lead compound in order to improve its properties using medicinal chemistry program and make it a successful drug [447].

The complete structure of pneumocandin B_0 was established, followed by its relative stereochemistry by X-ray crystallography and the absolute stereochemistry from acid hydrolysis and HPLC analysis. The challenge that was faced with the determination of relative stereochemistry was the presence of a large portion of fatty side chain that was disordered, making the dataset acquisition process slow. This also prevented the establishment of relative stereochemistry of two methyl groups in the side chain. Following this, the next major challenge was with the purification of pneumocandin B_0. The purification of pneumocandin B_0 was a challenge due to its structural similarity to not only pneumocandin A_0, but also to its regioisomer, pneumocandin C_0. Pneumocandin B_0 was purified in a silica gel thin layer chromatography using a combination of dichloromethane, methanol, and water. For commercial scale production of pneumocandin B_0, a normal phase silica-gel based HPLC method is being used [447].

Since pneumocandin A_0 was the dominant product, efforts were made to improve the fermentation development of pneumocandin B_0 to selectively increase the production and purity of pneumocandin B_0. This was done using environmental approach which included optimizing the medium composition, pH, temperature, oxygen transfer, and carbondioxide concentrations. The other approach used was the genetic approach where the selective mutant for pneumocandin B_0 was isolated. The optimization of the physicochemical and pharmacological properties of pneumocandin B_0 followed the discovery, isolation, and fermentation of pneumocandins. These included stability, solubility, pharmacokinetic properties, and antifungal spectrum of pneumocandin B_0. This is where the medicinal chemistry approaches come into play. In order to enhance the water solubility, pneumocandin B_0 prodrugs with charged groups were developed. At a pH range of 5 to 8, pneumocandin B_0 underwent accelerated ionization or ring-opening at hemiaminal. Under acidic conditions, both the benzylic hydroxyl groups and hemiaminal were ionized and hydride was delivered with improved acid and base stability. This chemistry was used for further discovery of caspofungin analogs to improve the stability. Various structural modifications on pneumocandin B_0 to improve the pharmacokinetic parameters along with pharmacology, drug metabolism studies, and minimizing the toxicity led to MK-0991, which was later named as caspofungin [447].

Caspofungin synthesis involved modifications at two sites on the pneumocandin B_0 peptide core: reduction of the primary amide of 3-hydroxyglutamine to an amine, and the condensation of the hemiaminal moiety with ethylenediamine. These transformations led to significant synthetic challenges where the need for the control of the region-, chemo-, and stereoselectivity during the peptide core modification on an industrial scale was required. Though the starting material pneumocandin B_0 was purified to 90%, it still retained close to 20 analogs that were difficult to remove. Standard workups were impossible due to the detergent-like physical properties of the compounds with a lipophilic side chain and a polar

peptide core. Non-conventional workups and purification processes were required. Finally, the compound was unstable without any crystalline intermediates or final product availability when the compound entered development [447].

As mentioned before, medicinal chemistry approaches came into play during the peptide core modification, to an analog with improved water solubility, half-life, and potency. Following the identification of the lead candidate, the process chemistry group helped in the development of a scalable and practical process, defining a route that was economically viable, green, and robust. The synthesis of the final compound was a 5-step route with an overall yield of 6–8% and poor α:β selectivity at the hemiaminal center. Even after the development of caspofungin acetate, there were significant challenges faced by the pharmaceutical scientists with regards to its instability. Caspofungin acetate decomposed by oxidation and hydrolysis even at neutral pH and also underwent dimerization. Hence caspofungin acetate is commercialized as a lyophilized powder as it is the only viable option. It took more than a decade from the start of the discovery to the entry of caspofungin into clinical development. Caspofungin serves as an example to understand the various challenges of getting a peptide to be approved for therapeutic use [447].

IV. BIOSYNTHESES OF MARINE PEPTIDES

Marine invertebrate derived natural products have biosynthetic origins that are not always clear, and increasing evidence shows the involvement of associated microorganisms. The following highlights the marine source biosyntheses based on the cellular localization studies [182]. Feeding experiments with isotope-labelled precursors were used to evaluate the biosynthetic pathways. For deeper understanding of complex marine microbial pathways, modern molecular techniques concerning recombinant technology and bioinformatics were used. Most biosynthetic pathways were initially elucidated from marine bacteria and cyanobacteria to complex peptides, polyketides, and hybrids, opening the door for novel research opportunities engaging metabolic biocatalysis and engineering [448].

Nonribosomal peptides and polyketides are a diverse group of natural products possessing complex chemical structures and vast pharmaceutical potential. These are synthesized by a conserved thiotemplate mechanism on the modular non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) enzyme complexes. NRPS and PKS are known for their involvement across three domains of life from the discovery of 3,339 gene clusters from 991 organisms with a total of 2,699 genomes. A total of 1,147 hybrid NRPS/PKS clusters were discovered, explaining their widespread occurrence. Sequence analysis indicated NRPS evolution from a combination of common descent and horizontal gene transfer. Related siderophore NRPS gene clusters have been identified, which were known to encode modular and non-modular NRPS enzyme organization in a gradient. Higher frequencies of NRPS and PKS gene clusters were detected from bacteria in comparison to archaea or eukarya along with common occurrence in the phyla of *Actinobacteria*, *Cyanobacteria*, *Firmicutes*, and *Proteobacteria* in bacteria and the phylum of *Ascomycota* in fungi [449]. Most of these NRPS and PKS gene clusters have unknown end products (referred to as orphan gene clusters) [450], emphasizing the significance of genome mining

in the identification of novel genetic machinery for the biosynthesis of secondary metabolites [449].

A. Marine Cyanobacteria

Cyanobacteria include slow-growing photosynthetic bacteria [451] and hence produce diverse natural products, some of which possess potential pharmaceutical activities while others are toxic [450]. Most of the biosynthetic mechanisms are unique to cyanobacteria and are rarely described from other organisms [451]. Genome mining is one way of enabling the characterization and identification of natural product gene clusters; yet the present number of cyanobacterial genomes is low compared to other phyla. This issue has been overcome by increasing the sequenced cyanobacterial genomes, enabling the identification of biosynthetic gene clusters for structurally distinct metabolites including ribosomal peptides, non-ribosomal peptides, alkaloids, fatty acids, terpenes, and UV-absorbing compounds. Various bioinformatic tools have been used for the prediction of the orphan gene clusters; however the prediction could be problematic in cases of complexity of the cyanobacterial pathways. Use of mass spectrometry guided natural product genome mining and/or heterologous expression helped solve this issue exploring the cyanobacterial natural product gene cluster [450]. The above studies demonstrate the role of cyanobacteria in encoding huge diverse cryptic gene clusters for natural product production, and the known chemical diversity is only a fraction of the true biosynthetic capabilities of this ancient group of organisms [451].

Marine blue-green algae/cyanobacteria are considered to be the prolific producers of bioactive natural products, most of which originate from the mixed polyketide-peptide biosynthetic pathways. The biosynthesis of microcystin LR, a cyclic heptapeptide, isolated from the alga *Microcystis aeruginosa* originated from the hybrid PKS-NRPS. The first cluster that represented the complete characterization of a complex cyanobacterial secondary metabolic-pathway belonged to *M. aeruginosa* PCC7806, which was about 55-kb and included 10 bi-directionally transcribed open reading frames (ORFs) arranged in two operons [*mcy*ABC and *mcy*DEFGHIJ]. The microcystin synthetase included a loading di-domain, adenylation-peptidyl carrier protein (A-PCP) at PKS McyG, which was the *N*-terminus that was known to activate and load phenylacetate, the starter unit for consequent extension by six amino-acids and four malonate residues to McyC-bound linear microcystin-precursor. *C*-terminal thioesterase (TE) of NRPS McyC catalyzed the hydrolysis and cyclization of microcystin-LR. McyF was the tailoring racemase enzyme that reported the preliminary probing of microcystin pathway. Characterizing the microcystin synthetase genes allowed for the study of pathway regulations, elucidation of genetic-variants correlating different microcystin isoforms, and detection of microcystin producing cyanophytes from various environmental samples. The cyclic pentapeptide nodularin is structurally related to microcystins, and the nodularin biosynthetic gene-cluster identified from *N. spumigena* was found to proceed through a similar pathway to that of microcystin-LR [448].

In general, *Lyngbya majuscula* is a prolific producer of structurally diverse natural-products with broad biological activities. The biosynthesis of barbamide was chemically probed with labeled precursors as well as genetically probed *via* sequence analysis of the biosynthetic

gene cluster. Previous studies revealed that barbamide was derived from one molecule each of acetate, L-cysteine, L-phenylalanine, and L-leucine along with two methyl-groups from *S*-adenosyl-L-methionine [SAM]. The direct precursor of this polyketide-peptide molecule was 5,5,5-trichloroleucine formed from the chlorination of the inactivated *pro-R* methyl-group of leucine. Sequence analysis of the 12 ORF cluster, which extended to 26-kb, exposed a co-linear genetic arrangement of barbamide cluster. L-leucine undergoes chlorination on the PCP [BarA]-bound leucine molecule by BarB1 and BarB2 halogenases before the transfer of 5,5,5-trichloroleucine to the PCP domain of NRPS BarE. An uncharacterized one carbon truncation of 5,5,5-trichloroleucine into a trichloroisovaleryl moiety precedes a malonate extension on BarE-BarF complex with an *E*-double bond to a diketide. The pathway was completed when cysteine and phenylalanine were added to PCP-bound diketide-dipeptide intermediate on the bimodular NRPS BarG undergoing the formation of a novel thiazole ring catalyzed by BarG *C*-terminal TE. The intermediacy of L-leucine, 5,5,5-trichloroleucine, and L-cysteine amino acids was supported by the biochemical characterization of the adenylation domains of BarD, BarE, and BarG, respectively. The related barbaleucamide supported the presumption that many *Dysidea* natural products are of cyanobacterial origin [448].

Jamaicamide A was a mixed polyketide-peptide with a number of unique structural features including a vinyl chloride, pyrrolinone ring, and alkynyl bromide. Jamaicamide A was known to be derived from ten acetate units, L-alanine, β-alanine, and two methyl groups from SAM. Jamaicamide A was a ~ 58-kb biosynthetic gene-cluster that revealed a high integrated PKS-NRPS system on 17 ORFs that were organized co-linearly with regards to its biosynthetic utilization. A β-keto diketide intermediate was formed from the ligation of 5-hexynoic acid to ACP *JamC* by acyl ACP synthetase *JamA*, followed by the extension of malonate on hexadomain PKS *JamE*. The *N*-terminal region of *jamJ* product and *jamFGHI* led to a “β-keto modifying gene cassette,” which was involved in the formation of pendent carbon-atom having vinyl chloride functionality. The addition of acetate to β-keto intermediate was catalyzed by the HMG-CoA synthase like homolog: JamH. The nascent polyketide underwent two rounds of NRPS and five rounds of PKS extension after the formation of vinyl (chloride). JamQ, an NRPS condensation (C)-related protein, facilitated the cyclization reaction, resulting in ACP-bound linear-intermediate on PKS JamP and the formation of pyrrolinone ring residue [448].

The biosynthesis of lyngbyatoxin was established from the molecular cloning of its biosynthetic gene-cluster of 11.3-kb with four ORFs [448]. A copy control fosmid vector pCC1FOS has been used to include a genomic fosmid library made from a lyngbyatoxin producing strain of *L. majuscula*. (–)-Indolactam V was the core structure of lyngbyatoxins A, B, and C, which was partially assembled using an NRPS system with a *C*-terminal reductase domain. Based on the Red1 motif of NRPS-associated Red-domains and the A3 motif of the adenylation (A)-domains, a highly specific probe was isolated by PCR from the genomic DNA of *Lyngbya* strain using degenerate primers. The probe was 1.4 kilobase (kb) and was used to isolate the fosmid clones that were analyzed by Southern blot and restriction mapping experiments. For DNA sequencing, a single fosmid clone fos-DE3-86 was chosen. The *ltx* gene cluster was then sequenced using fragments that were subcloned into pBluescript II SK(+) and a 17.1 kb region [452].

The *ltx* gene cluster was an 11.3 kb region and had four open reading frames (ORFs) that were all transcribed in a similar direction. *ltxA* was the first ORF that encoded for a two module NRPS protein. The first module included an A-domain specific for L-Val based on the traditional A-domain binding pocket designations, an *N*-methylation domain (NM), and a peptidyl carrier protein (PCP). There was a second module that included a condensation (C) domain, A-domain specific for L-Trp, a PCP, and a Red domain responsible for NADPH-dependent reductive release of *N*-Me-L-Val-L-Trp from NRPS for the generation of **5**. *ltxB* was the second ORF that encoded for the cytochrome P450 monooxygenase that included an *N*-terminal with 80 amino acids, which was similar to MbtH, an unknown domain seen in numerous diverse NRPS containing pathways. LtxB was known for its involvement in the oxidation of the indole-ring of **5** and in subsequent cyclization for the formation of **4**. *ltxC* was the third ORF that encoded proteins with little resemblance to other known enzymes. *ltxD* was the fourth ORF that encoded for proteins related to diverse families of oxidase or reductase-type proteins. LtxD might be responsible for the conversion of lyngbyatoxin A into minor metabolites: lyngbyatoxins B and C [452].

The dolastatins are hybrid polyketide-peptides produced by cyanobacteria and isolated from the sea-hares. Due to the low isolation yields of dolastatins from molluscs, cyanobacterial fermentation and subsequent bioengineering afforded new opportunities for the drug discovery and development of these promising anti-cancer agents [448].

Recently, molecular networking was employed, especially in industrial settings, to help expedite the discovery of innovative small molecule therapeutic leads from complex marine sources. Sirenas LLC has integrated chemometrics-based bioactivity predictions with molecular networking in a drug discovery platform that has been successful over the years in identifying new classes of molecules, especially with the well-studied dolastatin 10 structural class. A new member belonging to the dolastatin 10 structural class has been discovered with better physicochemical profile and increased potency using molecular networking. This was done by screening the marine fraction library against several cancer cell-lines, followed by the LC-MS/MS analysis. Following this, activity scores were assigned to all the metabolites found to exhibit cytotoxic activity that were generated from the relative abundance of each metabolite. Sometimes a single metabolite could be present across multiple fractions in varying abundances, resulting in rank-order correlations between the strength of the biological activity and the relative abundance of the metabolite. An activity score or a correlative value was yielded by the global analysis of the fraction that falls between 0 and 1, where 1 represents a perfect correlation between the biological activity of the fraction and the abundance of the metabolite. Mapping the scores to their corresponding metabolites in a molecular network provides visualization between the bioactivity and the structural relationship between molecules. Interrogation of the above network resulted in revealing a molecular family with strong activity scores, and numerous member nodes were de-replicated as dolastatin 10 along with the related symplostatins 1 and 3, malevamide D family members, and a novel analog SMD5041 [453].

Anabaenopeptins are assembled on a NRP synthetase enzyme complex coded by a 32 kb *apt* gene cluster encoded with two alternative starter modules arranged in separate bimodular proteins. The starter modules exhibited strong substrate specificity for L-Arg/L-Lys and L-

Tyr, respectively, allowing specific biosynthesis of various anabaenopeptin variants. NRPSs are huge enzymes with modular structures where in each module catalyzed the activation and incorporation of an amino acid or in some instances a carboxylic acid to the growing peptide in a stepwise fashion. The modules included catalytic domains for amino acid condensation, activation, and thiolation. Additional modifications on the amino acids included *N*-methylation, epimerization, and heterocyclization. The collinearity rule is applied to the NRPSs where the substrate specificity and the module number reflect the product composition. In the NRPS enzyme complexes, the adenylation domains determined the amino acid selection while the condensation domains played a selective role in the non-ribosomal peptide synthesis. Discrete NRPS enzyme complexes are capable of synthesizing sets of peptides simultaneously. Incomplete modification and lack of substrate specificity are a few reasons for natural variation in the non-ribosomal peptide chemical structures [454].

Anabaena species included a 32.5 kb gene cluster with five ORFs: *aptA*$_1$, *aptA*$_2$, *aptB*, *aptC*, and *aptD* with the amino acid sizes of 2195, 2174, 1069, 2565, and 1403, respectively. Each AptA$_1$ and AptA$_2$ was comprised of two NRPS modules, both of which had an adenylation and thiolation domains, one epimerization, and one condensation domain. AptB and AptD included a single module containing an adenylation, thiolation, and condensation, while AptD also included a thioesterase domain. AptC included two modules; each with an adenylation, thiolation, and condensation domain. The latter module also included an *N*-methyltransferase domain embedded in the adenylation domain. The gene cluster also included two genes: *aptE* and *aptF*, which did not code for NRPS. The catalytic domain order and the modular structure matched the NRPS organization for the assembly of anabaenopeptins from *Anabaena* species [454].

The genome of *Nodularia spumigena* included a 17.6 kb gene cluster for aeruginosin (*aer*) as a single contig that encoded a peptide synthetase with reductive release mechanism as reactive peptide aldehydes. Aeruginosins and spumigins are structurally similar families with linear peptide aldehydes utilizing separate peptide synthetases. The spumigin gene cluster was located at 11 kb and 133 kb apart from the nodulapeptin gene cluster and *aer* gene cluster, respectively. Eight proteins were encoded by the *aer* gene cluster that was organized in a single operon. The substrate specificities predicted for AerB, AerG, and AerM peptide synthetases were L-Tyr, Choi, and L-Arg from comparison with other biosynthetic pathways. Similar to other non-ribosomal biosynthetic pathways, aeruginosin biosynthesis started from loading short chain fatty acids by the AerB condensation domain. The condensation domain resulted in lipidation of aeruginosins. Genes that encoded AerD, AerE, and AerF enzymes have been located on the *aer* gene cluster along with AerI, which encoded a putative glycosyltransferase. The reductase domain AerM resulted in the release of the *C*-terminal arginine as reactive aldehyde [301].

Spumigins are linear peptides with an *N*-terminal hydroxyphenyl lactic acid exclusively with D-homotyrosine, 4-methylproline (mPro) or proline, and an arginine derivative or a *C*-terminal lysine. Spumigins were assembled on the NRPS enzyme complex, offloading the peptides as reactive aldehydes. Necessary enzymatic steps for the unusual mPro were encoded in the 21-kb gene cluster along with the peptide synthetases [301].

The biosynthesis of thiocoraline involved at least one initiation module and four modules for amino-acid incorporation. The starter unit can be activated in two ways. When the starter unit was an amino-acid, the first module included an adenylation (A) and a peptidyl carrier protein (P) domain. When the starter unit was an aromatic compound (not an amino-acid), an adenosine monophosphate (AMP) ligase and an aryl-carrier protein were found. An AMP-ligase containing module was expected since the starter unit of thiocoraline was 3HQA. TioJ and TioO proteins formed the initiation module. There was no candidate for an aryl-carrier protein in the thiocoraline cluster while TioJ was expected to be the 3HQA AMP-ligase. TioO was expected to play the role of 3HQA-carrier protein. TioK was an NRP related enzyme formed by P8 and A8 domains, which were also known to involve in 3HQA activation. The P domain present was unusual and independent. TioX was involved in the methylation of sulfhydryl groups in two cysteine residues in thiocoraline [455].

The biosynthetic gene cluster of thiocoraline was a 64.6 kbp DNA region sequence with 36 complete ORFs and two incomplete ones. The NRPS that was involved in the biosynthesis of thiocoraline backbone constituted TioR and TioS. Thiocoraline included two moieties of 3-hydroxy-quinaldic acid [3HQA], which might have acted as the starter unit during biosynthesis and was derived from tryptophan. *tioF*, *tioG*, *tioH*, and *tioI* were the genes involved in the biosynthesis of 3HQA [455]. The role of TioN, which was initially thought to be inactive, was identified in the formation of 3HQA [456]. TioG was similar to kynurenine transaminases and aspartate aminotransferases. TioH was the only oxidoreductase in the cluster that had similarity with several $NADP^+$ and NAD^+ oxidoreductases. TioI was similar to cytochrome P450s and acted as quinaldate-3-hydroxylase for the conversion of quinaldic acid to 3HQA, which was the starter unit in biosynthesis of thiocoraline. TioF was involved in the conversion of L-tryptophan to *N*-formyl-L-kynurenine. *tioL* or *tioM* encoded formamidase resulting in the generation of L-kynurenine that was later transformed to kynurenic acid by TioG. TioH and TioI were responsible for 3HQA formation with an oxido-reduction step by eliminating the 4-hydroxy group in kynurenic acid followed by a hydroxylation step for the introduction of 3-hydroxy group [455].

The biosynthetic gene cluster of thiocoraline also included TioN. TioN was the A domain and a potential candidate for *S*-Me-L-Cys formation. An A domain included 10 core signature sequences, and in a variety of natural products, it is usually interrupted between a8 and a9 core signature sequences. Contrary to this, the interruption of A domain by M domain occurred between a2 and a3 core signature sequences in TioN. A domain could be involved in the *S*-methylation of L-Cys. TioN was also unique in that it was the only A domain that was interrupted. Initially TioT was found to be inactive, but later it was found that TioT was essential for TioN enzymatic activity. TioT was not required for the TioN expression in its soluble form. TioN was involved in the methylation of both L-Cys-AMP and L-Cys-*S*-TioS. *TioN* was a bifunctional [adenylating and methylating] stand-alone A domain that was interrupted in an NRPS complex [456].

There were four modules responsible for the biosynthesis of the thiocoraline backbone with four A domains that activated L-cysteine, glycine, L-cysteine, and L-cysteine. An epimerization (E) domain should be present in the first module as the first amino-acid in the

peptide backbone was a D-cysteine. The last two modules must include a proper *N*-methyltransferase (M) domain since the last two L-cysteines were *N*-methylated. The last module ends up with a thioesterase (TE) domain for the peptide chain release and cyclization [455].

Cyclomarin A was a marine microbial peptide that was largely derived non-ribosomally from the nonproteinogenic amino-acid residues. *Salinispora arenicola* has a 5.8 Mb long DNA sequence analysis with a circular genome and a 47 kb biosynthetic gene-cluster (*cym*) with 23 open reading frames. The *cym* locus is controlled by the largest ORF with 23,358 bp *cymA*, which encoded the 7-module (heptamodular) NRPS and led to the assembly of the full length cyclomarin heptapeptides and also truncated cyclomarazine dipeptides. The megasynthetase CymA possessed an unprecedented biosynthetic feature that helped synthesize different sized peptides *in vivo*, which was triggered by the β-oxidation level of the priming tryptophan-residue. This tryptophan residue was unoxidized in cyclomarazines and oxidized in the cyclomarin series. Prior to the release of the cyclic peptide from CymA, the tryptophan residue was reverse prenylated by CymD while the cytochrome P450 CymV introduced the epoxide group on the cyclomarin C isoprene post NRPS assembly. Lastly, the 2-amino-3,5-dimethylhex-4-enoic acid in the cyclomarin series was derived from the condensation of the isobutyraldehyde and pyruvate followed by the *S*-adenosylmethionine methylation. Hence, the biosynthesis of cyclomarins started with the tryptophan derivative and ended with ADH yielding a linear heptapeptide intermediate that was bound to the thiolation (T) domain. The *C*-terminal thioesterase (TE) then helped in subsequent release and macrocyclization. In case of cyclomarazines, the diketopiperazines (DKPs) were yielded from module-2 bound diketide that was cleaved from CymA, which in turn was facilitated by type II TE CymQ [312].

The *cym* cluster included four oxygenases: *cymO*, *cymS*, *cymV*, and *cymW* along with an *O*-MT (*cymP*), a putative PTase (*cymD*), a four gene operon (*cymE-H*) involved with ADH biosynthesis, four other genes putatively involved in resistance and regulation, and two in phosphoenolpyruvate metabolic flux. The *cym* locus was flanked with pseudogenes including fragments of transposases and integrases suggesting this cluster to be horizontal [312].

The putative gene cluster of the surugamides included four NRPS genes: *surA*, *surB*, *surC*, and *surD*. Surugamides A-E were produced by the *surA* and *surD* NRPS genes while surugamide F was produced by *surB* and *surC* NRPS genes. The modular compositions of SurA and SurB were similar, and vice versa with SurC and SurD. While SurA and SurB started with a A-domain and ended with a peptidyl carrier protein, SurC and SurD started with a condensation (C) domain and ended with an epimerization (E) domain [314].

Four contiguous NRPS genes encoding 18 A-domains had the biosynthetic genes for SA-SE present at their head and tail. The enzymes responsible for SA-SE and SF production lacked domains such as condensation, thioesterase, or terminal reductase for chain termination. Hence, the biosynthesis was expected to be terminated by a putative α/β-hydrolase (Orf2) or a putative β-lactamase (Orf9) that encoded upstream of *surA* – *surD* [314].

The gene cluster for the biosynthesis of salinamides was 47.6 kbp encoding 14 sequences. This is a NRPS-PKS hybrid gene cluster designated in the *sln* locus. The *sln* cluster included four genes coding the NRPS proteins and one gene coding the PKS/NRPS hybrid along with enzymes involved in the precursor biosynthesis and post-NRPS tailoring enzymes. The genes supporting the biosynthesis of *ρ*-HPG, which is a non-proteinogenic amino-acid residue, were sub-clustered in the *sln1-3* gene cassette. The *sln* cluster also included two genes: *sln6* and *sln9*, which encoded the tetra-domain NRPS modules comprising the *C*-terminal TE domain. This suggested that one of the type I TE domains played a significant role in the addition of (4-methylhexa-2,4,-dienoyl)-glycine moiety to the Ser-OH [457].

Sln9 was a nonribosomal peptide synthetase that played a central role in the construction and installation of a distinctive acyl-glycine “basket” handle to salinamides. Sln9 was a thioesterase domain that resulted in the transesterification of the serine residue in desmethylsalinamide E with acylated glycyl thioesters in order to yield the desmethylsalinamide C. The construction of salinamides involved ATP-dependent activation by multifunctional assembly-line proteins, and their amino-acid precursors were transferred to the arrayed carrier protein (CP) domains. NRPS assembled the mature peptide intermediate and then the peptide product was released by a myriad of protein off-loading reactions. The terminal reaction was catalyzed by the thioesterase (TE) proteins that occupied the NRPS terminal domain, and the product was released as linear or macrocyclized peptides [457].

The biosynthesis of amphibactins involved a genome with two putative NRPSs: ABO_2093 and ABO_2092, which in turn possessed four classical NRPS modules. The M1 of ABO_2093 started with an *N*-terminal condensation domain, suggesting the presence of an external ligase that activated the fatty acid in order to be incorporated into the peptidic headgroup. There was no ACP domain present in ABO_2092 to tether and transport this activated fatty acid. The biosynthesis then proceeded in a linear fashion, ending with a thioesterase domain which was preceded by a domain with unknown function [458].

There are two putative NRPSs involved in the biosynthesis of marinobactins: ENO16763 and ENO16762. ENO16763 was the first module that encoded a unique domain with high homology to fatty acyl-AMP ligases (FAALs). This module activated the fatty acid to get it incorporated into the peptidic headgroup. The biosynthesis of marinobactins also occurred in a linear fashion and was terminated by a thioesterase domain. Hence the biosynthesis of marinobactins started with an *N*-terminal acyl AMP-ligase starter domain that activated the fatty acid, thereby initiating the biosynthesis [458].

The biosynthetic pathway of amphi-enterobactin involved six genes: *aebA-F*, to encode the homologous proteins similar to enterobactin biosynthetic machinery. EntA, EntB (*N*-terminal domain), and EntC converted the chorismate to 2,3-dihydroxybenzoic acid (DHBA). EntB (*C*-terminal domain), EntD, EntE, and EntF were four NRPS proteins that catalyzed the formation of the DHBA L-Ser unit, polymerized three units, and cyclized the trimer to form the lactone-backbone. In *Vibrio harveyi*, the presence of a proximal *aebG* gene was a distinct feature that encoded a long-chain fatty acid CoA ligase (FACL). The FACL enzymes activated the fatty acids to fatty acyl-CoA thioesters prior to their

incorporation on to the acylated non-ribosomal peptides. Hence, it was predicted that the gene cluster *aebA-F* was responsible for the formation of the amphi-enterobactin core-structure, and the *aebG* gene was involved in acylation of the serine residue. AebB and AebE were necessary for the DHBA activation, AebE for DHBA-AMP ligase, and AebB as DHBA carrier protein [334].

B. Marine Fungi

The biosynthesis of scopulariside A isolated from the marine fungi *Scopulariopsis brevicaulis* is discussed here. Scopulariside A is a lipopeptide. Lipopeptides are usually linear or cyclic compounds having a fatty acid attached to the *N*-terminal amino-acid of the peptide portion with hydroxyl acids or amino acids. This peptide core was synthesized by the NRPSs consisting of modules that enabled the sequential synthesis of the growing peptide chain. The NRPS module usually included an amino acid substrate recognizing adenylation [A] domain and a peptide acyl carrier [T or PCR] domain that transferred amino acid to condensation [C] domain where peptide-bond formation occurred. The lipid portion attached to the peptide core could be derived from various sources, including the PKSs or the primary lipid metabolism. Similar to NRPSs, PKSs were multi-domain enzymes with three core domains: β-ketosynthase [KS], acyltransferase [AT], and acyl-carrier protein [ACP]. The carbon chain in lipopeptides provided by the PKSs included additional reducing domains such as ketoreductase [KR], enoylreductase [ER], dehydratase [DH], and an optional methylation domain [MET]. During biosynthesis, the reduced carbon chain was merged into the peptidyl backbone by a process called lipoinitiation. Scopulariside A is structurally similar to emericellamide A produced by a marine *Aspergillus* sp [353].

The gene clusters in both *S. brevicaulis* and *A. nidulans* included a CoA-ligase and an acyltransferase. The two enzymes were considered to be responsible for the activation and loading of the reduced polyketide to the NRPS. There was an additional gene between the NRPS and PKS in *A. nidulans* with unknown function, and was not involved in the biosynthesis of emericellamide. There were five additional genes between *NRPS1* and *PKS2* in *S. brevicaulis*. These genes were expected to encode a transporter, a copper amide oxidase, a mannosyl transferase, transcription factor, and a gene with unknown function [353].

The proteins that are involved in the biosynthesis of a specific secondary metabolite are frequently encoded by genes located in close proximity, forming a cluster. The responsible gene clusters for emericellamide A have been identified. The carbon chains in emericellamide A were provided by PKSs that included the reducing and methylation domains. The resultant reduced polyketides were then transformed to CoA thioesters by acyl-CoA ligases and were loaded on to acyltransferases that shuttled the polyketide intermediates to first thiolation [T] domain of NRPSs [353].

The most probable biosynthetic gene cluster in the production of scopulariside A was *NRPS1/PKS2* based on the *in silico* analyses of the *S. brevicaulis* genome. This was indirectly proven from the enhanced production of scopularides in two transformants TF1-5-1 and TF5-2, which included the gene that encoded the putative transcription factor from a gene cluster under a constitutive promoter. Based on the emericellamide model, the following

biosynthesis of scopularide A was proposed where the reduced polyketide that was produced by the *PKS2* was loaded to the *NRPS1* via the CoA ligase and the acyl transferase [353].

The biosynthetic origin of the *N*-methyl-3-(3-furyl)alanine moiety of the cyclic peptide endolide A was described by König *et al* in 2016. The initial hypothesis of the 3-(3-furyl)alanine biosynthesis was based on its structural relationship to a phenylalanine skeleton. Both erythrose-4-phosphate and phosphoenolpyruvate were the precursor molecules, and the shikimate pathway was established to be the biosynthetic route for the 3-(3-furyl)alanine moiety in endolide A, where the *N*-methyl group was known to originate from methionine [362].

C. Sponges

Entotheonella sp., was found to be responsible for the production of kasumigamide from *Discodermia calyx* when a single-cell analysis was conducted in conjunction with PCR. This bacterial phylotype was reported to be a symbiotic producer of multiple natural products in *Theonellidae* sponges. Four different kasumigamide gene clusters were detected in four different bacterial species, namely Entotheonella [a marine sponge symbiont], *Microcystis aeruginosa* [a free-living cyanobacterium], *Delftia acidovorans* [a human oral bacterium], and *Herbaspirillum* sp. [the endosphere of *Populus deltoids* tree] [10].

The biosynthetic gene cluster included a hybrid PKS-NRPS cluster with 9 ORFs, of which the *kasA-C* formed the PKS-NRPS core. KasA had an adenylation (A) domain [KasA-A1], a ketoreductase (KR) domain, and a peptidyl carrier protein (PCP) domain. KasB included three modules [2–4], where the first two coded for NRPSs and the latter encoded a PKS. Modules 5–6 were encoded in *kasC*. From the NRPS codes, the substrates for five A domains were predicted, which were KasA-A1, KasB-A1, A2, KasC-A1, and A2, with the exception of KasA-A1, which was annotated to A domain employing phenyl pyruvic acid [PP]. Kasumigamide that was initially isolated from a fresh water cyanobacterium *M. aeruginosa* was predicted to be the chemical structure of PKS and NRPS hybrid compound [10].

There were some peculiar features in the module or domain organization of the *kas* family gene clusters. One of the noteworthy points was the shift of PKS module in the *M. aeruginosa kas*-cluster [*makas*A-D] while in other *kas* genes the PKS module was located on module 4. D-*erythro*-PS was the *C*-terminal residue of kasumigamide. L-Phe was initially hydroxylated by MakasD for the generation of L-*threo*-PS. Subsequently the L-*threo*-PS was loaded onto the PCP domain by MakasC-A2. Finally MakasC-E1 epimerized L-*threo*-PS to D-*erythro*-PS that was encoded between modules 4 and 5 [10].

Other unusual features of *kas* family genes included the likely chain termination by a condensation (C) domain and the absence of a thioesterase (TE) domain. Due to the fact that some C domains functioned as a TE domain, it was expected that the *C*-terminal C domain encoded in *kasC*, *hkasC*, and *dakasC* served as a thioesterase. The release mechanism of *makas* pathway remained uncertain because the *C*-terminal C domain was absent in *makasA-D* [10].

Polytheonamides are the largest among the known NRPS-synthesized secondary metabolites. A ribosomal pathway was also necessary to introduce multiple D-configured and *C*-methylated residues. The DNA region included 11 additional genes that were clustered around the ORF. *poy* genes *poyA-I* were nine ORFs that formed the operon that was known from the short or absent intergenic regions. The 3′ terminus of the *poyA* included 48 codons, which matched with the complete polytheonamide precursor. The three 3-hydroxyvaline units originated from two residues: *C*-methylation of residue 16 from threonine (Thr) and hydroxylation of residues 23 and 31 from valine (Val). There was also a long 5′ sequence in *poyA* exhibiting homology to nitrile-hydratases. The production of polytheonamides from proteinogenic residues involved four hydroxylations, 18 epimerizations, and at least 21 methylations. PoyB, PoyC, and PoyD were homologous to the radical *S*-adenosylmethionine (rSAM) superfamily members; PoyE was homologous to the SAM-dependent methyltransferases; PoyF was homologous to dehydratase domain of lantibiotic LanM-type synthetases; and PoyI was homologous to the Fe(II)/α-ketoglutarate oxidoreductases. The cluster also encoded other proteins on the basis of homologies that were involved in transport, regulation, and proteolytic removal of the leader region: PoyJGH. The homology of PoyK is unknown. Individual enzymes converted structurally and positionally diverse residues [459].

The biosynthetic genes of keramamides isolated from *Theonella swinhoei* Y (*ker*) were homologous to the keramamide (*krm*) genes isolated from *T. swinhoei* WA. The keramamide gene-cluster *krm* included the unusual 5-hydroxytryptophan 6-halogenase gene. The notable differences between the two clusters included *krmR* and *krmI*. An *O*-methylserine extension similar to keramamide H was exhibited by the keramamides identified from *T. swinhoei* WA while *krmR* encoded the NRPS module that activated and incorporated *O*-methylserine. The *krmI C*-terminal region resembled the flavin-dependent tryptophan halogenases [FDTHs] and functionalized position-6 of indole. FDHs usually encoded in the natural product biosynthetic pathway gene-cluster and halogenated phenol, pyrrole, and indole motifs. A second *N*-terminal domain was also present in *krmI* with a distinct homology to ThiF enzyme family members. These were the enzymes that utilized ATP by adenylation to activate the carboxylic acids [460].

The key difference between the *ker* and *krm* genes was the presence of *krmI*. *krmI* was a flavin-dependent halogenase that generated the 6-halo containing keramamides and was the first halogenase to use the L-5-hydroxytryptophan as its preferred substrate. KrmI also exhibited promising broad substrate-specificity and accommodated a series of indole-derived substrates. Following protein engineering, krmI can also be a promising starting point for the generation of brominated and chlorinated products because of its inherent substrate-flexibility [460].

The biosynthesis of microsclerodermins involved a multi-modular PKS/NRPS system with the involvement of a set of enzymes for the biosynthesis of side-chains and post-assembly line modification. The enzymes that were involved in the side-chain biosynthesis were responsible for modifications such as oxidation or halogenation of the pyrrolidone ring. The gene cluster was about 60 kbp in length. The gene *mscK* encoded a major facilitator superfamily transporter followed by *mscJ*, a type-II thioesterase located upstream to *mscA*.

The core biosynthetic assembly covered three PKS modules and five NRPS modules encoded on genes *mscA* to *mscI*. *mscL* encoded an additional halogenase near the downstream boundary [461].

The biosynthesis of microsclerodermin was initiated with the build-up of a phenyl group in conjugation to a double-bond at the side-chain. In such a case, benzoyl-CoA or *trans*-cinnamoyl-CoA was the activated starter unit that was recruited by the enzyme. But the observed biosynthesis suggested otherwise, and so phenylacetyl-CoA was found to be the starter unit in the biosynthesis of microsclerodermin. MscA and MscC modules helped in the elongation of the phenylacetate unit, using two times 3-hydroxymalonate and three times malonate as extender units. The modules 2 (MscB) and 4 (MscD) exhibited a combination of functional KS domain attached to an inactive AT domain. The PKS derived unit was then forwarded to the module MscF: the first PCP domain. MscF module harbored two additional uncommon domains that showed high homology to the amino-transferase (AMT) and monooxygenase families located downstream to the PCP domain. This domain resulted in the oxidation of the β-hydroxyl group of bound intermediate to β-keto functionality, followed by conversion to the β-amino moiety, which underwent macrocyclization [461].

The biosynthesis continued with a set of PKS- and NRPS-based reaction cycles. The A domain of the MscF module was specific for asparagine activation. Such an asparagine-derived pyrrolidone system was only found in koshikamides and microsclerodermins. The protein MscE was responsible for the cyclization step and was similar to the amidohydrolase class. Tryptophan halogenation as well as pyrrolidone ring oxidation was catalyzed by the tailoring enzymes. MscL was a halogenase located downstream and was responsible for tryptophan chlorination. MscN belonged to the SAM-dependent methyl transferase family, while MscM showed homology with Fe(II)/α-ketoglutarate dependent dioxygenases. Hence, MscM and MscN were responsible for the oxidation and methylation of the pyrrolidone ring, respectively [461].

D. Ascidians

A single coding sequence (CDS) was identified that was found to include the required sequence necessary for patellamide C. This gene was found to be a candidate for *patE*: a patellamide precursor peptide. The presence of two peptide products on a single CDS proposed the importance of synergy in the mechanism of action of patellamides. There were several other CDSs surrounding *patE* which included *patA* – *patG* genes in a 11-kbp cluster. *patE* was surrounded by *patA:* a protease enzyme, *patD:* an adenylating enzyme-hydrolase hybrid, and *patG:* an oxidoreductase-protease hybrid. This cluster also included *patB*, *patC*, and *patF*, which were other CDSs with low or no similarity to other proteins; and the cluster ended with a gene that was assigned to primary metabolism, which was a DNA-photolyase homolog and a putative structural gene on the other side extending to approximately 1 kbp which was upstream of *patA* [462].

patE encoded a peptide of 71 aa of which the first 37 served as a leader sequence for processing. Of the remaining 34 aa, 16 encoded patellamide C and A sequences while 18 make up motifs directed the cyclization of patellamides. The patellamide C was 8 aa upstream of the patellamide A sequence. Prior to the two peptides, there was a 5 aa

conserved region that included G(L/V)E(A/P)S. The patellamide A sequence was terminated by AYDGE sequence and preceded the stop codon directly. An 8 aa sequence AYDGVEPS encoded between the two patellamides for both start and stop cyclization sequences with the consensus stop sequence being AYDG(E/V). The start consensus motif in PatE was G(L/)E(A/P)S, which resembled the consensus sequence (GAEPR) in some lantibiotics [462].

The *pat* cluster included 7 genes: *patA* – *patG* which were all transcribed in the same direction and included an operon. *patA* was involved in the cleavage of the PatE precursor peptide. Similar to PatA, PatD also included two domains: an *N*-terminal and a *C*-terminal domain. There were two proposed roles for PatD: the involvement of PatD2 in the cyclization of threonine and cysteine residues of PatE that resulted in oxazoline and thiazoline ring formation, and activation of cleaved patellamide precursors as adenylated by PatD1, which were then cyclized to final patellamide structures. PatG was a large multidomain protein involved in the oxidation and maturation of PatE. PatB, PatC, and PatF have no obvious roles in the biosynthesis of patellamides while epimerization was possible in tandem with heterocycle oxidation [462].

PEPTIDES IN THE DEVELOPMENT PIPELINE—The marine pharmaceutical pipelines include few FDA [Food and Drug Administration] approved drugs along with some natural products in various phases of clinical trials. Several hundred marine derived compounds with potential value moved into the preclinical pipeline. Hence, the marine pharmaceutical pipeline remains active and now has enough momentum to deliver novel compounds to the near future [463].

The initial marine derived natural products that entered into the pharmacopeia include cytarabine [Ara C] and vidarabine [Ara A] in 1974, following which it took at least 30 years before more marine derived natural products gained approval and became part of the pharmacopeia. The following marine compounds were either accepted or are in various phases of clinical trials [464,465].

Ziconotide was the first marine drug isolated from *Conus magus*, a fish eating cone snail, which has been approved by the FDA. Ziconotide is a neuroactive peptide that is synthetically equivalent to ω-MVIIA [ω-conotoxin], a component of marine snail venom. Ziconotide is known to selectively block the neuronal N-type voltage sensitive calcium channels [NVSCCs], thereby inhibiting the activity of a subset of pain sensing primary nociceptor neurons and providing a unique mechanism of action [466,467].

Leconotide is a 27-residue, similar to ziconotide, which is currently in Phase I clinical trials sponsored by Relevare Pharmaceuticals, previously known as CNSBio. Leconotide includes three internal CYS-CYS bonds and was developed for the treatment of cancer related pain. Leconotide is a ω-conotoxin that blocks the neuronal voltage sensitive calcium channels [468] and is used via systemic administration [469].

Xen-2174 is a naturally occurring χ-conotoxin isolated from the venom of a marine cone snail, *Conus marmoreus*. Xen-2174 is a modified 13-residue chi-conopeptide that selectively

inhibits the neuronal norepinephrine transporter. Xen-2174 was developed for the treatment of chronic pain and postoperative pain including cancer pain and is currently in phase-II clinical trials [470,469].

Brentuximab vedotin (adcetris®) originated from a mollusk associated cyanobacteria and is known to treat Hodgkin's lymphoma and patients with systemic anaplastic large cell lymphoma [467, 471]. Brentuximab vedotin is an immunoconjugate derived from dolastatin 10, monomethylauristatin E (MMAE), which is a secondary metabolite from *Symploca* species and is approved for the treatment of CD30 positive lymphoproliferative disorders [469].

Soblidotin and tasidotin [ILX-651] are synthetic analogs of dolastatin 10 [472]. Soblidotin differs from dolastatin 10 in the replacement of the thiazole moiety of dolaphenine in dolastatin 10 to a phenylalanine methyl ester. Soblidotin was found to possess *in vivo* anticancer activity in murine P388 leukemia, Lewis Lung carcinoma, M5076 sarcoma, B16 melanoma, human MX-1 breast cancer, and Colon26 colon cancer cell-lines and SBC-3 SCLC and LX-1 xenografts, but was found to be ineffective as a single agent and hence was discontinued from Phase II clinical trials [393]. Cemadotin is a synthetic water-soluble analog of dolastatin 15 and is known to inhibit the cell-proliferation and the growth of human tumor xenografts. Cemadotin is also in clinical trials as a potential cancer chemotherapeutic agent. Cemadotin binds to tubulin by strongly suppressing the microtubule dynamics and thereby blocking mitosis. Cemadotin binds to tubulin with affinity to two binding sites with K_d values of 19.4 and 136 μM [473].

Elisidepsin or isokahalalide F is a cyclic peptide that belongs to the kahalalide family of compounds, which was previously in clinical trials. Elisidepsin was found to be cytotoxic against a panel of human NSCLC [non-small cell lung cancer] cell-lines [474] along with inducing rapid oncosis in ErbB3 expressing cells [475].

HTI-286 is a synthetic analog of the tripeptide hemiasterlin and was found to inhibit tubulin polymerization along with the disruption of microtubule organization in cells and induced mitotic arrest and apoptosis. HTI-286 was a potent inhibitor of human tumor cell proliferation at an IC_{50} value of 1.16 μM, with less P-glycoprotein interaction compared to the current anti-microtubule agents [476].

Glembatumumab vedotin [CR-011-vc-MMAE] is a monoclonal antibody (mAb)-drug conjugate developed by Celldex Therapeutics Inc., for treatment of glycoprotein non-metastatic melanoma protein-B [GPNMB] expressing cancers. MMAE is a full human mAb directed against extracellular GPNMB domain expressed in human breast melanomas and cancers. Glembatumumab is conjugated to the monomethylauristatin E, a potent microtubule inhibitor, with a cathepsin cleavable valine-citrulline [vc] dipeptide linker. While glembatumumab did possess potent antitumor activity, the most common toxicity associated is skin rash due to GPNMB expression in healthy skin [477].

ABT-414 is an antibody drug conjugate (ADC) linked to the anti-Epidermal Growth Factor Receptor (EGFR) ABT-806 antibody, where monomethylauristatin F (MMAF) is used.

Abbvie, renamed Abbott Pharmaceutical Division, developed this ADC, which is currently extended to Phase II clinical trials and was developed as an anti-EGFR mAb [469].

There are many monoclonal antibodies coupled to either MMAE or MMAF that are currently in various phases of clinical trials with different therapeutic applications. PSMA-ADC is a human mAb against prostate specific antigen coupled via the valine-citrulline dipeptide linker to MMAE, which was designed to release via proteolysis by human cathepsin B and is currently in Phase II clinical trials. DCDT-2980S is an IgG1 antibody against CD22 epitope with MMAE, a potent microtubule disrupting agent, linked to the antibody on the sulfhydryl groups (reduced cysteines) via a protease cleavable linker, maleimidocaproyl valine-citrulline-ρ-aminobenzoyloxycarbonyl (MC-vc-PAB). DCDT-2980S is currently in Phase II clinical trials. DCDS-4501A is another ADC with MMAE linked to anti-CD79b monoclonal for the treatment of follicular B cell lymphoma. DCDS-4501A was developed by Genentech/Roche pharmaceuticals and is currently in Phase II clinical trials. Enfortumab vedotin is another human IgG1k antibody linked to MMAE with a valine-citrulline linker and is also known as AGS-22MSE and AGS-22ME [469]. Enfortumab vedotin was developed to target Nectin-4, which is found in many cancers including pancreatic, breast, urothelial, and breast [478]. Enfortumab vedotin was developed by Astellas Pharma and Agensys, Seattle Genetics and is currently in Phase I clinical trials [469].

Vorsetuzumab Mafdotin is an ADC developed by Seattle Genetics, which is a MMAF linked to anti-CD70 mAb 1F6 through a non-cleavable maleimidocaproyl linker, where the release relies on invagination followed by proteolytic digestion. This is used against relapsed and refractory non-Hodgkin’s lymphoma and metastatic renal cancer expressing CD70 epitope and is currently in Phase I trials. SGN-19A is another ADC developed by Seattle Genetics with an anti-CD19 antibody linked to MMAF via a maleimidocaproyl valine-citrulline linker. SGN-19A is used for the treatment of lymphomas including Burkitt’s lymphoma and is currently in Phase I clinical trials. BAY 79-4620 is an ADC with a MMAE linked to an antibody against human carbonic anhydrase IX. BAY 79-4620 was developed by Seattle Genetics for the determination of maximum tolerated dose (MTD) with advanced solid tumors and is currently in Phase I clinical trials. AGS-16C3F is IgG2k mAb against AGS-16 antigen, conjugated to MMAF with a non-cleavable maleimido caproyl linker. AGS-16C3F is used against liver and renal carcinomas from AGS-16 antigen and has currently completed Phase I clinical trials [469].

DMUC-5754A is a mAb against MUC16 epitope linked to MMAE, which is used for the treatment against ovarian carcinomas and is currently under Phase I clinical trials. DNIB-0600A is an IgG1 mAb against NaPi2b epitope linked to MMAE. DNIB-0600A is currently in Phase I trials for treatment against non-small cell lung cancer (NSCLC) and platinum resistant ovarian cancer. A1-mcMMAF is an ADC with MMAF linked to the maleimidocaproyl to a mAb against 5T4 tumor antigen. A1-mcMMAF exhibited potent antitumor activity. DMOT-4039A is a mAb identified as MMOT-0530A against antigen overexpressed in ovarian and pancreatic cancers, which is conjugated to MMAE. DMOT-4039A is currently in Phase I clinical trials. RG-7600 is an ADC developed by Genentech and is currently in Phase I trials for the treatment of ovarian cancers.

DEDN-6526A is an ADC currently in Phase I trials for unresectable melanoma. The warhead is expected to be a auristatin derivative with the antibody directed against endothelin ETB receptors [469].

DSTP-3086S is an ADC developed by Genentech/Roche with an antibody against anti-STEAP1 IgG1 antibody modified with reactive thiols modification and coupled to MMAE. The antibody is directed against a six transmembrane epithelial antigen of prostate 1 (STEAP1) and is currently in Phase I clinical trials for its use in metastatic castration resistant prostate cancer. MLN-0264 is an ADC with monoclonal IgG antibody [5F9] against guanylyl cyclase (GCC), conjugated to MMAE with a cleavable linker. MLN-0264 is currently in Phase I clinical trials for its use in gastrointestinal tumors expressing GCC. RG-7598 is an ADC currently in Phase I trials for its use in multiple myeloma with a auristatin warhead. SGN-LIV1A is an anti-LIV-1 mAb linked to MMAE, which was developed by Seattle Genetics. The LIV-1 epitope is also known as ZIP6 or SLC39A6 and is a member of zinc transporter family. SGN-LIV1A is currently in Phase I trials for its use that leads to significant delay of tumor growth [469].

ASG-15E is also known as ASG-15ME and is an ADC with IgG2 mAb [AGS15 which targets SLITRK6]. ASG-15E is conjugated to MMAE via a maleimidocaproyl valine-citrulline linker. This antibody targets SLITRK6, a member of SLITRK family of neuronal transmembrane proteins. ASG-15E was developed by Seattle Genetics and is currently in Phase I clinical trials for its use in human bladder transitional cell carcinomas and advanced primary and metastatic tumors [469]. AGS67E is an anti-CD37 antibody, AGS67C, which has been linked through reduced cysteine to MMAE, with maleimidocaproyl valine-citrulline ρ-aminobenzyloxycarbonyl, a protease linker. AGS67E is known to induce cell-cycle arrest and apoptosis in various cell-lines [479].

ABBV-399 is another ADC that has been generated with c-Met targeting ABT-700 antibody. This led in delivering a potent cytotoxin to the c-Met overexpressing tumor cells, resulting in cell-death without relying on MET signaling. ABBV-399 is currently in Phase I clinical trials where it is well tolerated and producing positive responses in c-Met expression in non-small cell lung cancer [NSCLC] patients [480]. GSK2857916 is an IgG1 anti-BCMA antibody that has been conjugated to MMAF, a microtubule disrupter, via a maleimidocaproyl linker that is stable and protease resistant. GSK2857916 exhibited enhanced antibody dependent cell mediated cytotoxicity, and this is the result of afucosylation of the FC domain that is known to increase the FCγRIIIa affinity expressed on the immune effector cells. GSK2857916 is currently in Phase I clinical trials for its use in relapsed/refractory multiple myeloma [481].

There are few ADC’s currently in advanced preclinical trials with minimal information. CDX-014 [CR-014-vcMMAE] is hypothesized to be a valine-citrulline linked MMAE to an anti-TIM1 mAB CR-014 based on the code name. This antibody targets a type I transmembrane (TIM 1) protein that is known to be expressed on the surface of the renal and ovarian carcinoma cells. HuMax-CD74 is an auristatin linked ADC with HuMax-CD74 antibody known to target the HLA class II histocompatibility antigen gamma chain [CD74] and is used in solid tumors and hematological malignancies. HuMab-TF-011-vcMMAE is

an ADC developed for its use in solid tumors. It includes a human tissue factor [TF] specific antibody [TF-011] linked to valine-citrulline cleavable linker and MMAE [469].

V. CONCLUSION

Marine natural products provide tremendous opportunities for the study of unique and diverse secondary metabolites including modified peptides, providing opportunities for expansion of the pharmaceutical pipeline. Marine natural products have escalated beyond their original role in the identification of novel prototype drug-leads to studies involving the design of unique molecules and utilizing biosynthesis in association with synthesis. As mentioned in this review, there are several marine peptides that have been placed in the market as therapeutic agents contributing to improved human health. Enhanced methods in fermentation technologies to grow bacteria/fungi in addition to biosynthesis and syntheses have opened new doors to both generate and supply drug-leads from various marine sources. Examples include ziconotide, the first FDA approved marine peptide for pain treatment while dolastatin-derived agent (adcetris®) [484] is a treatment for cancer which was approved by the FDA as well, suggesting the importance of marine derived peptides in the field of science. Hence, the potential for marine based compounds in various diseases is immense, and there are approximately 25,000 defined chemical compounds that have been reported thus far [484] supporting the significance of drug-discovery from marine sources.

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Highlights

- Peptides from marine sources
- Challenges involved with peptide isolation
- Biosynthesis of peptides from marine cyanobacteria, sponges, fungi, and ascidians
- Therapeutic peptides approved by FDA or in clinical trials

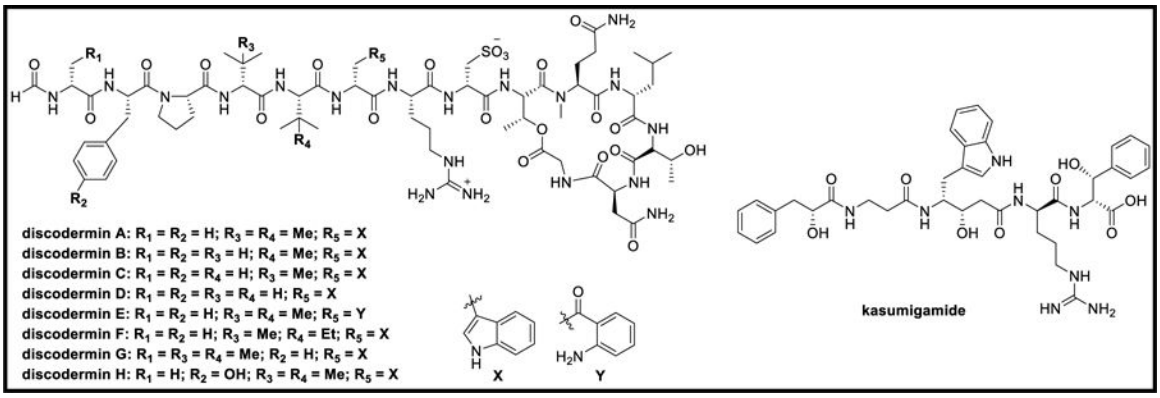


Figure 1.
Chemical structures of discodermins A-H and kasumigamide

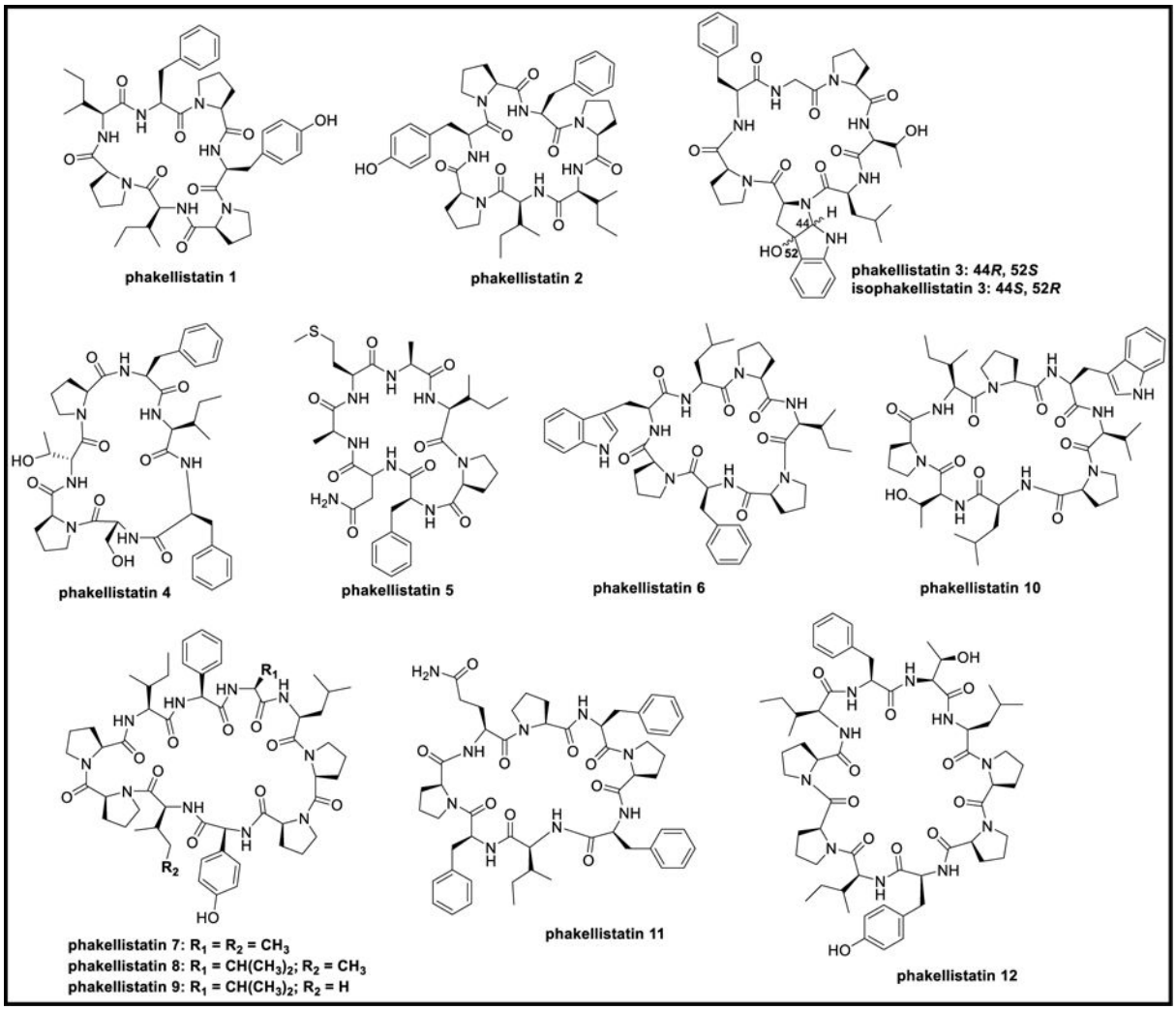


Figure 2.
Chemical structures of phakellistatins 1–12 and isophakellistatin 3

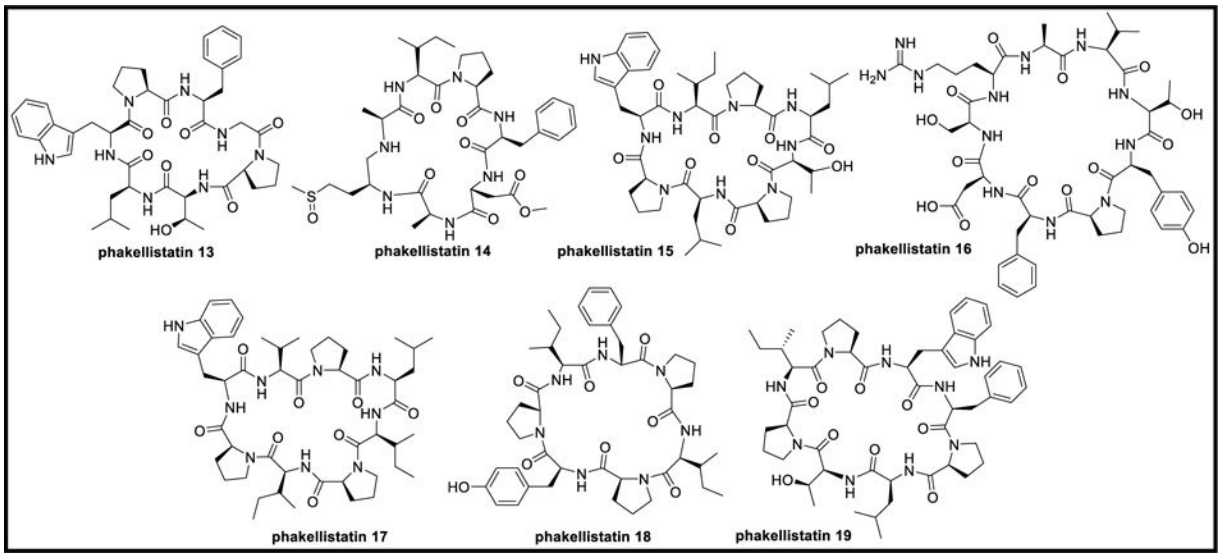


Figure 3.
Chemical structures of phakellistatins 13–19

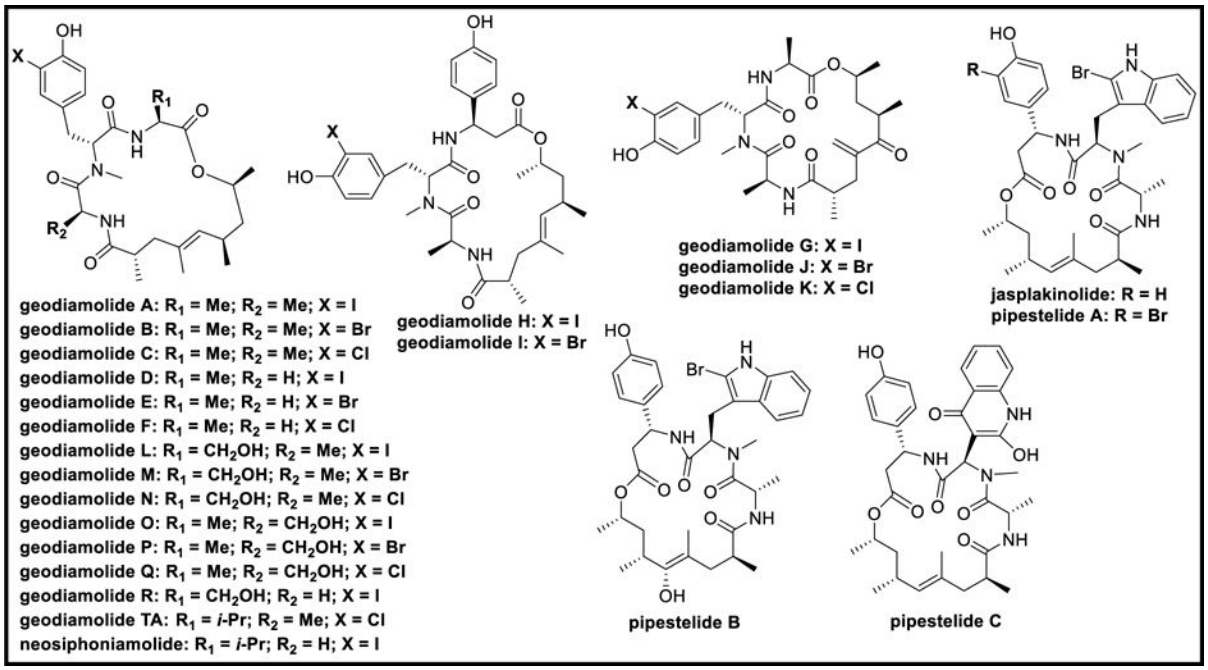


Figure 4.

Chemical structures of geodiamolides A-R, geodiamolide-TA, neosiphoniamolide, jasplakinolide, and pipestelides A-C

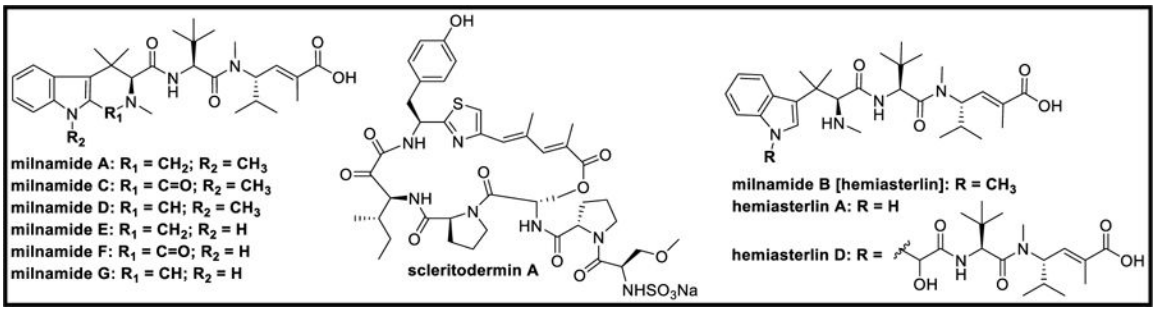


Figure 5.
Chemical structures of milnamides A-G, hemiasterlins A, D, and scleritodermin A

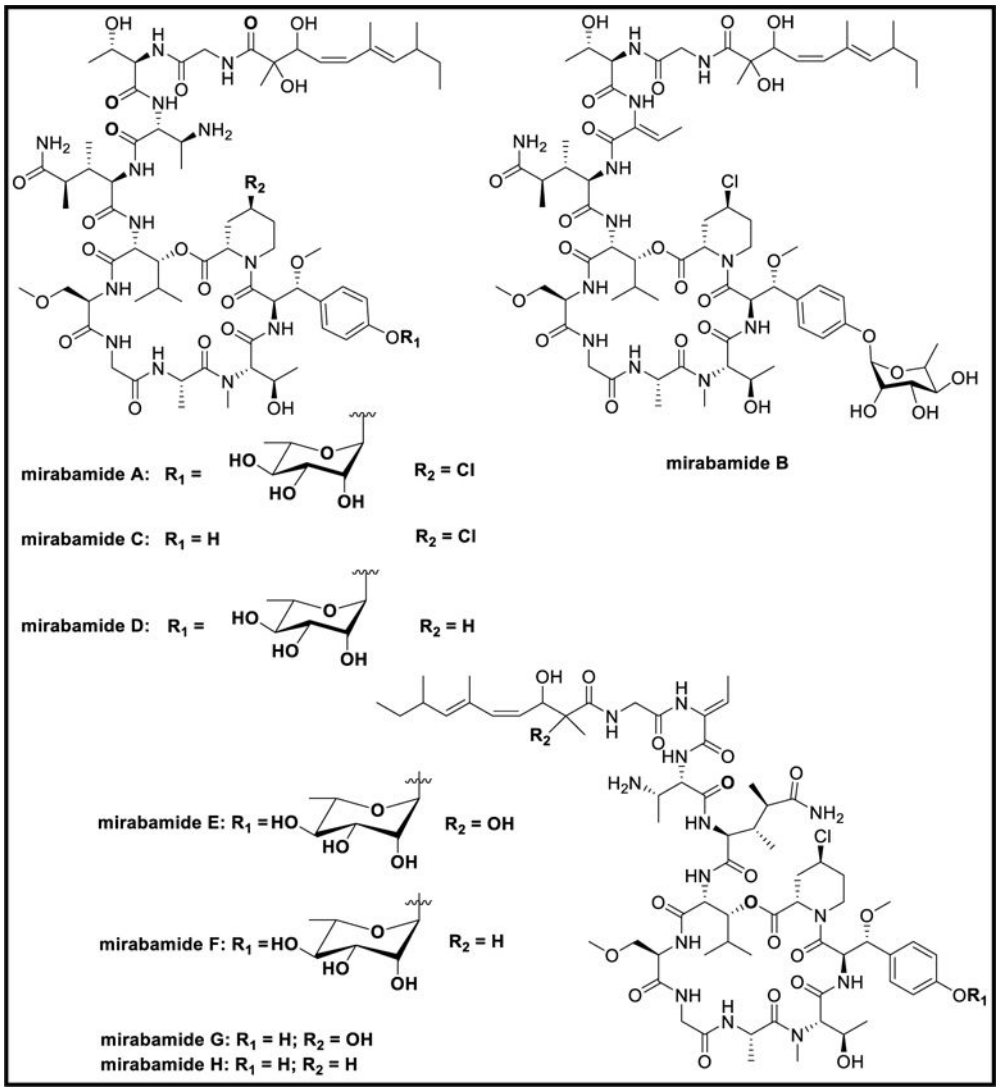


Figure 6.
Chemical structures of mirabamides A-H

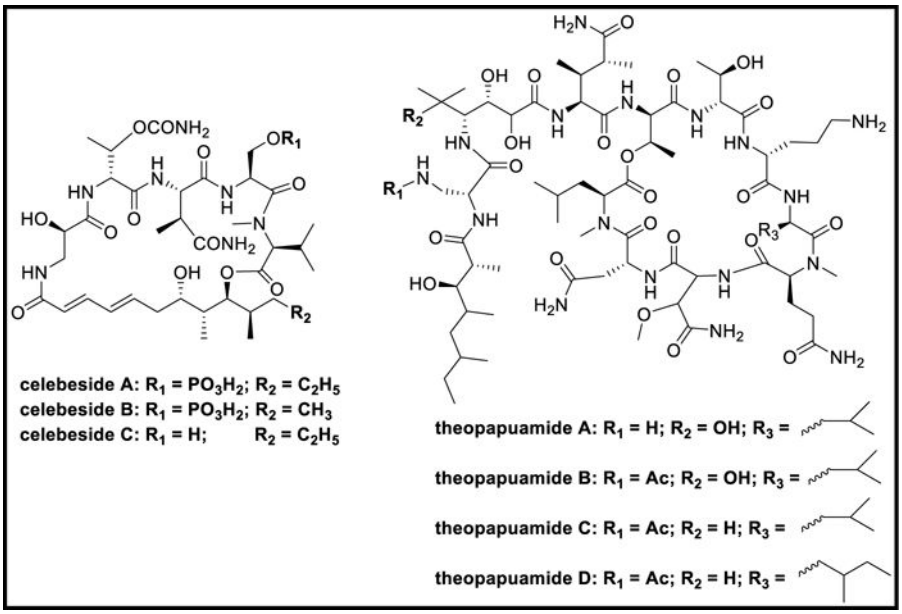


Figure 7.
Chemical structures of celebesides A-C and theopapuamides A-D

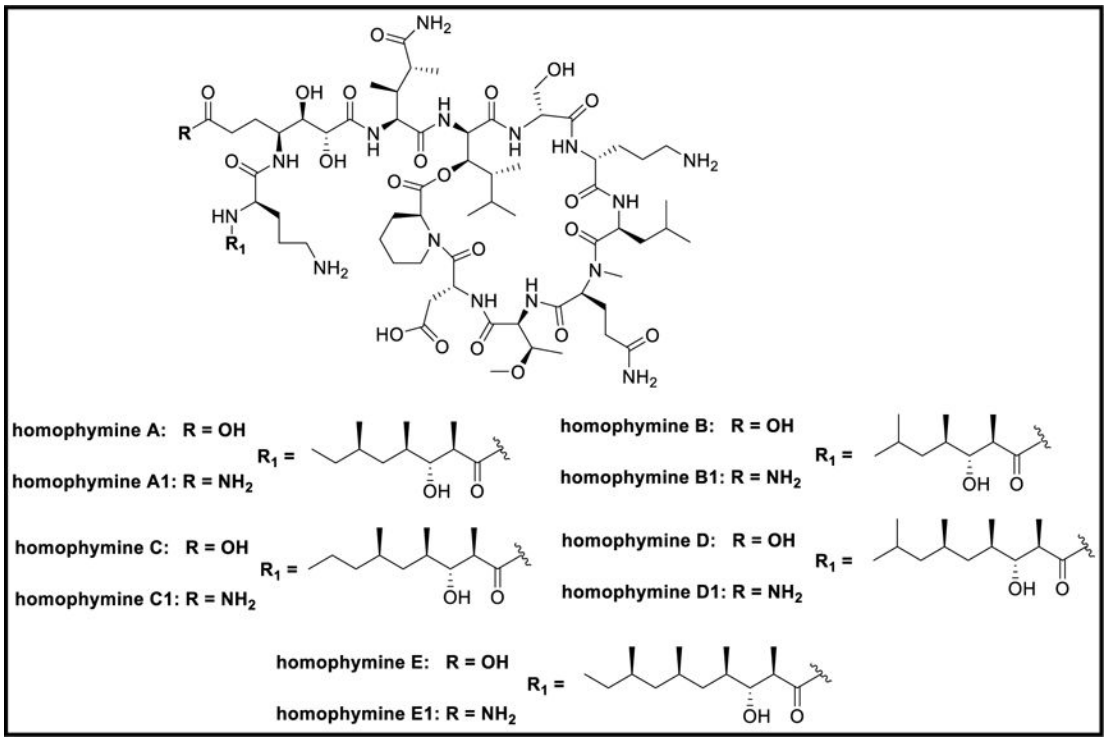


Figure 8.
Chemical structures of homophymines A-E and A1-E1

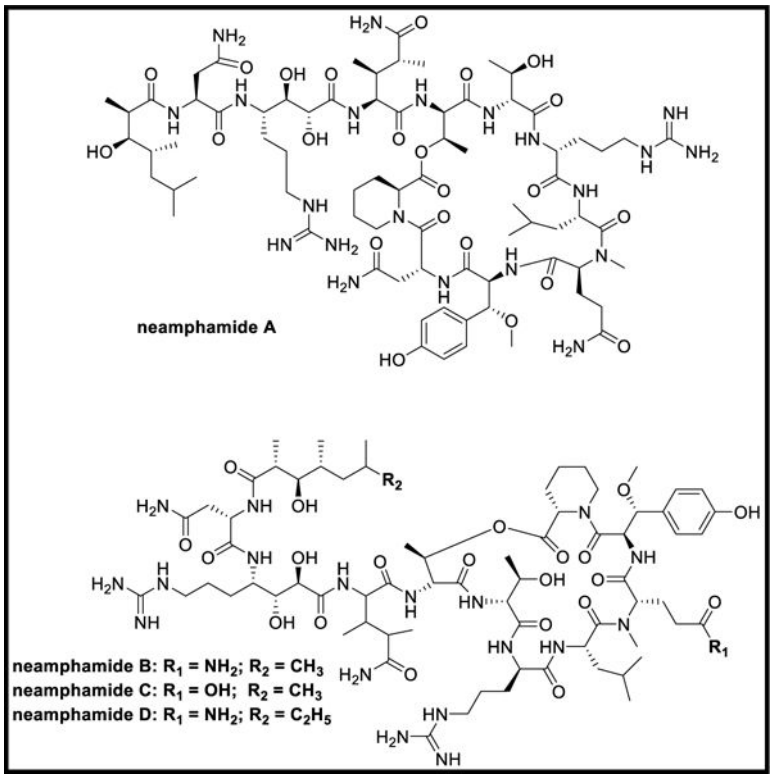


Figure 9.
Chemical structures of neamphamides A-D

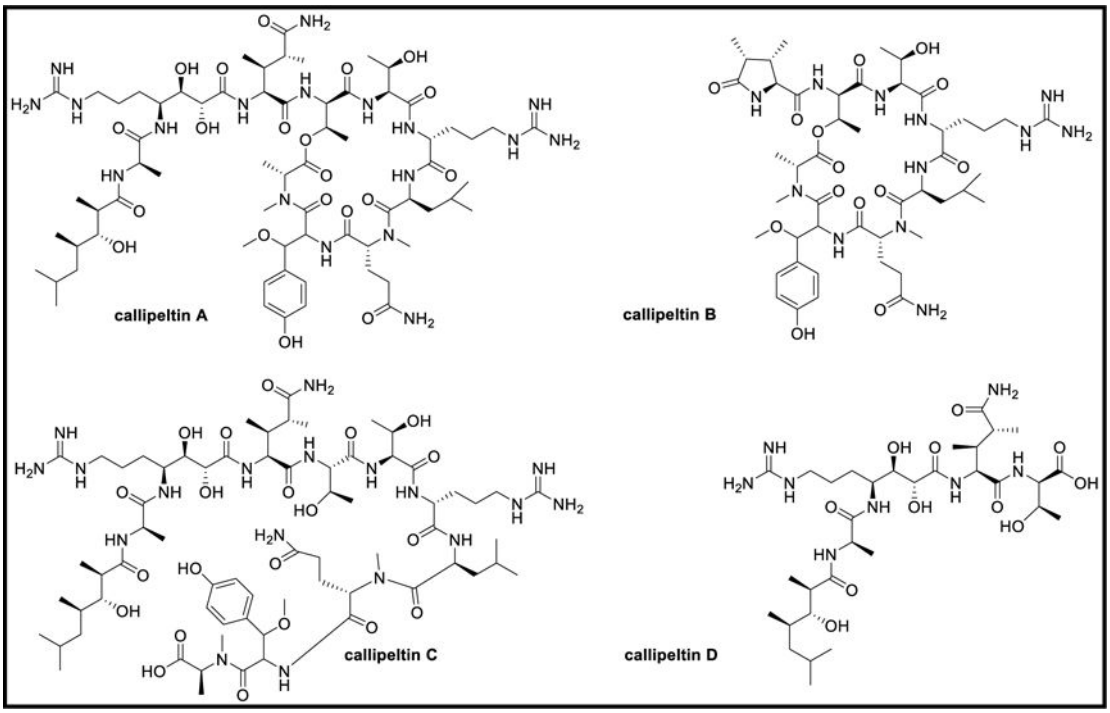


Figure 10.
Chemical structures of callipeltins A-D

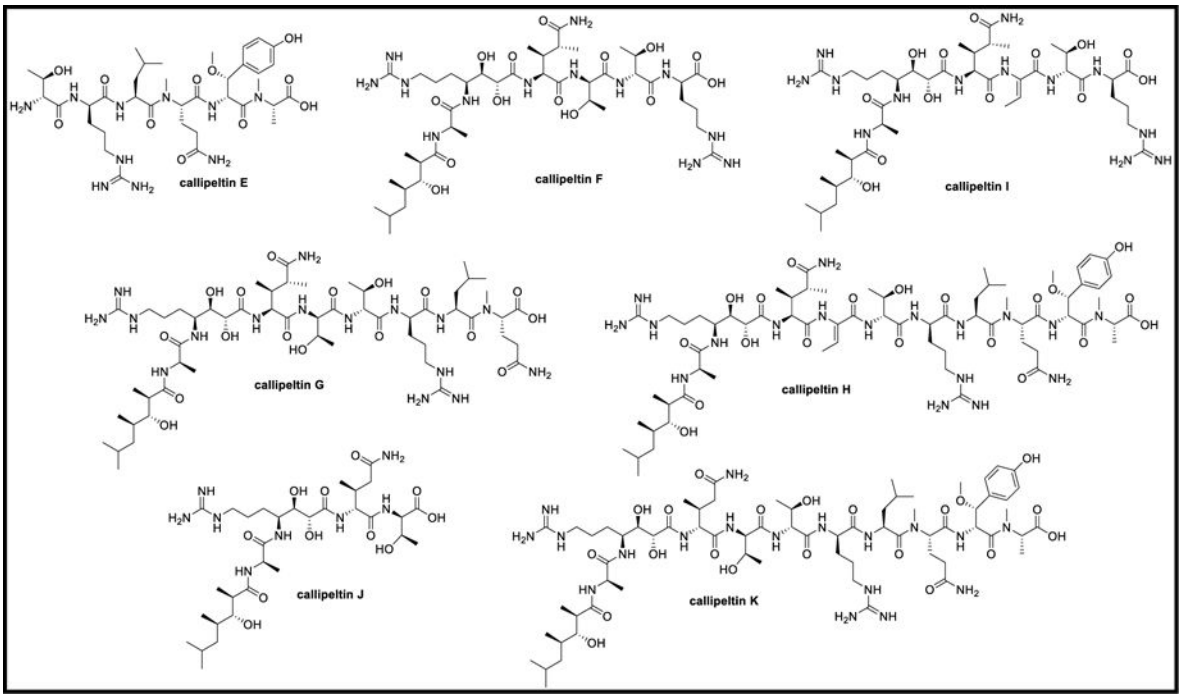


Figure 11.
Chemical structures of callipeltins E-K

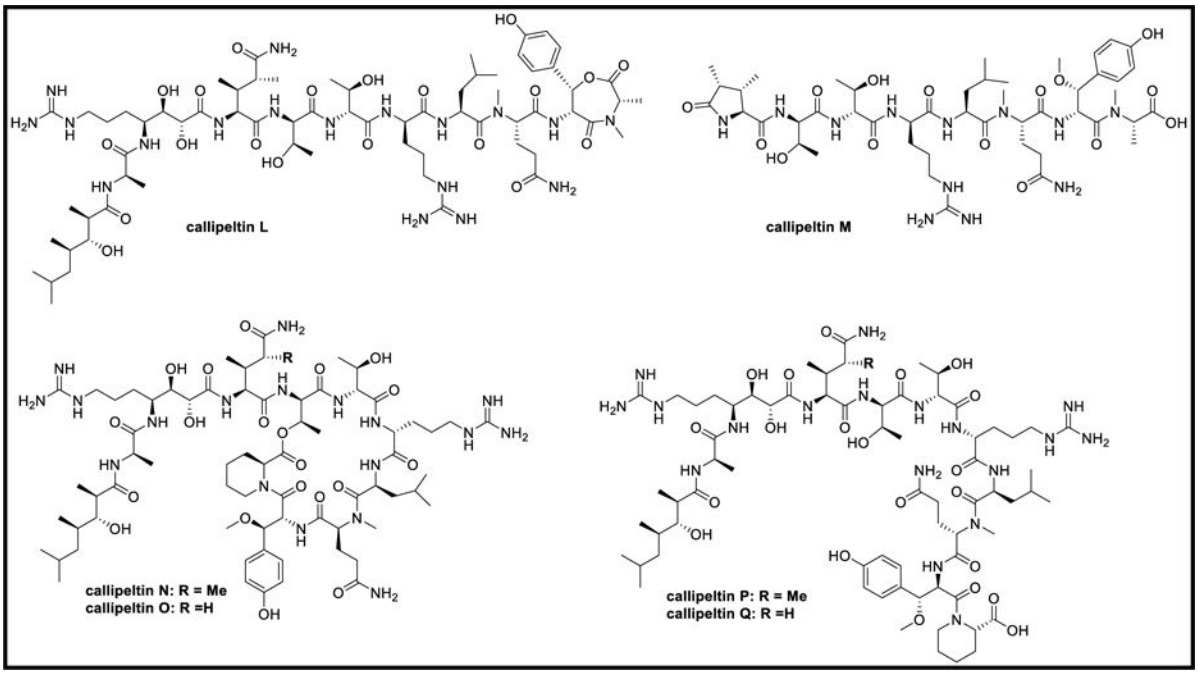


Figure 12.
Chemical structures of callipeltins L-Q

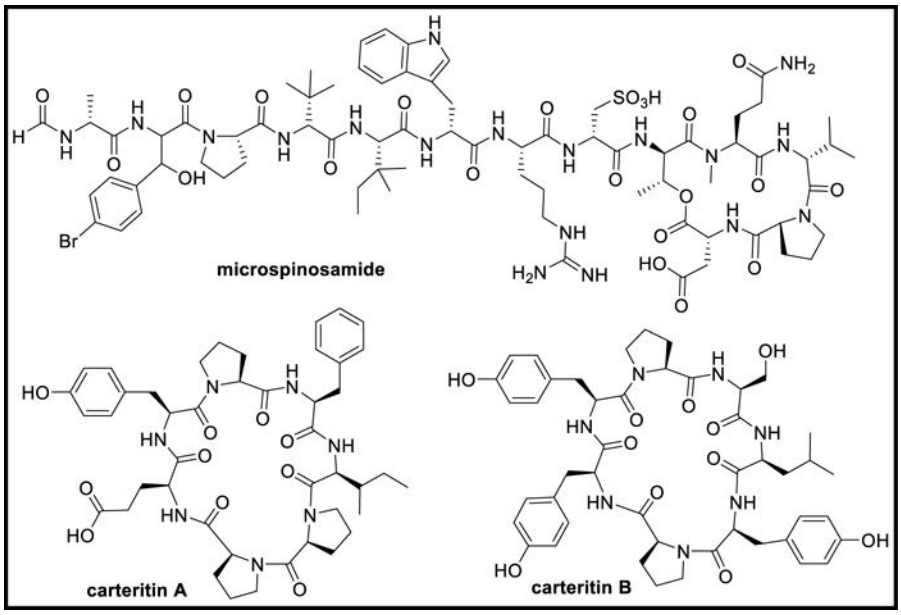


Figure 13.
Chemical structures of microspinosamide and carteritins A-B

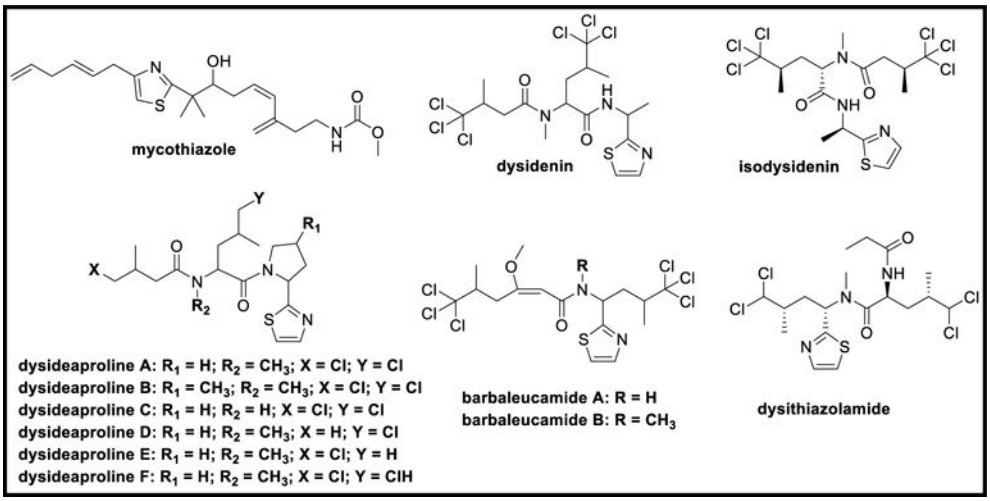


Figure 14.

Chemical structures of mycothiazole, dysidenin, isodysidenin, dysideaprolines A-F, barbaleucamides A-B, and dysithiazolamide

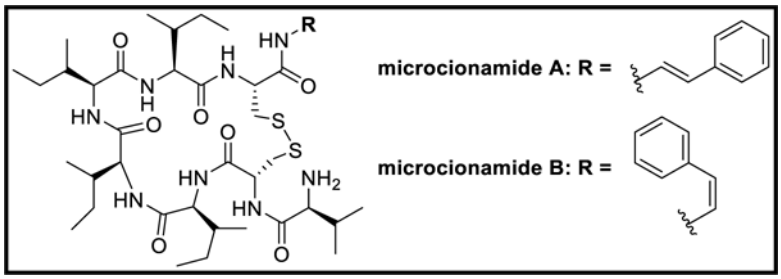


Figure 15.
Chemical structures of microcionamides A-B

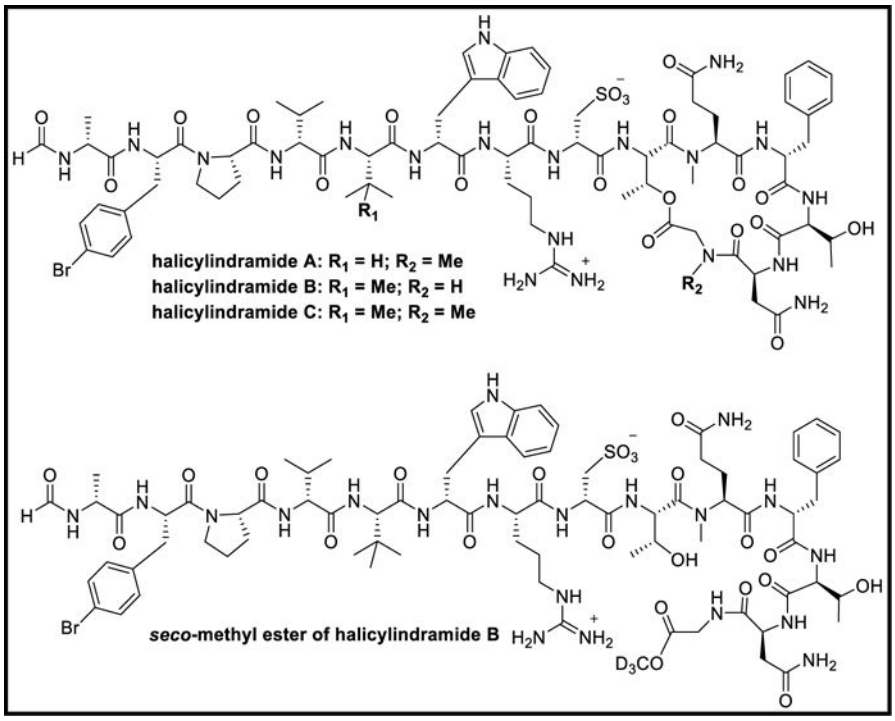


Figure 16.
Chemical structures of halicylindramides A-C and *seco*-methyl ester of halicylindramide B

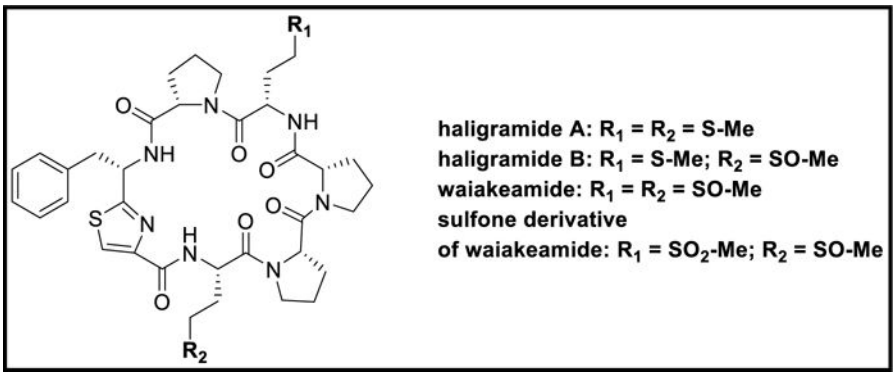


Figure 17.
Chemical structures of haligramides A-B, waiakeamide, and sulfone derivative of waiakeamide

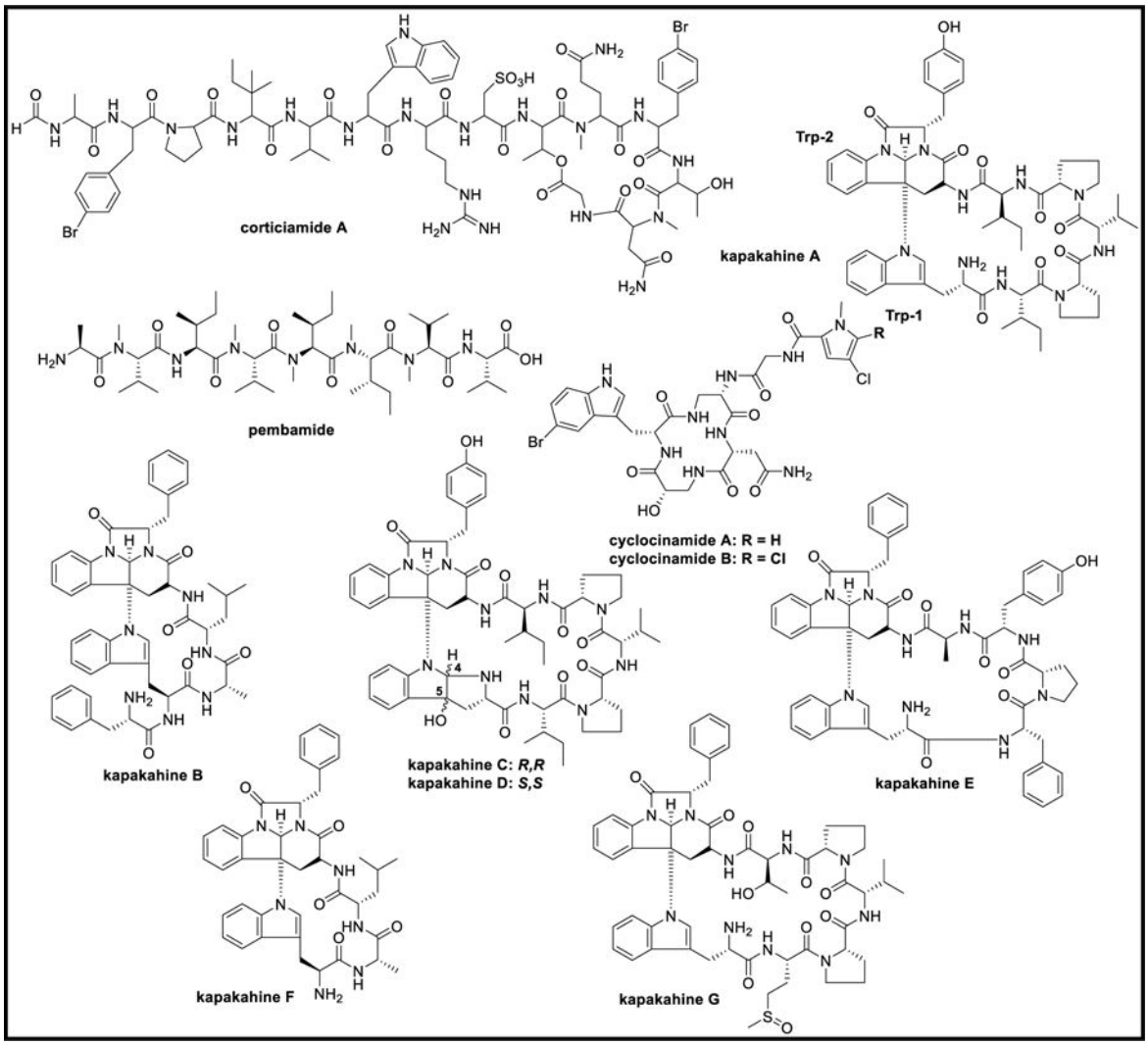


Figure 18.

Chemical structures of corticiamide A, pembamide, cyclocinamides A-B, and kapakahines A-G

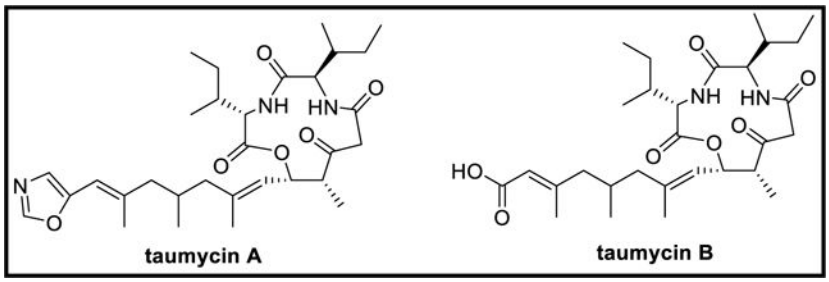


Figure 19.
Chemical structures of taumycins A-B

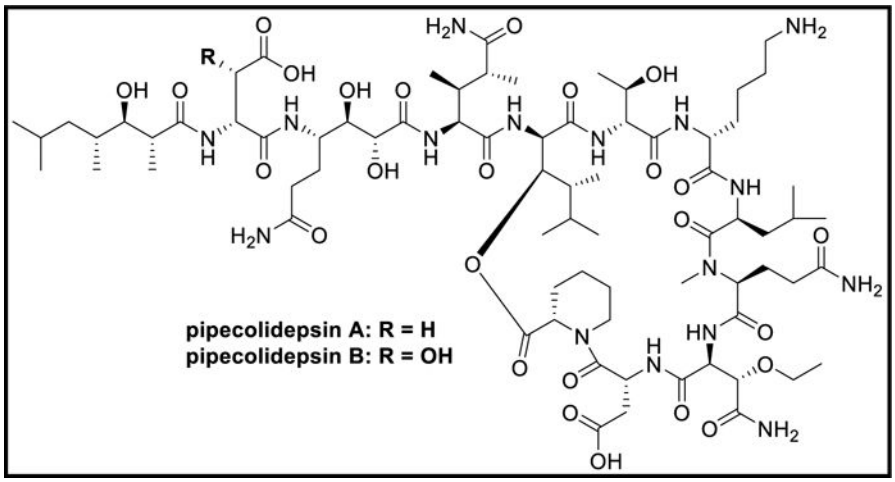


Figure 20.
Chemical structures of pipecolidepsins A-B

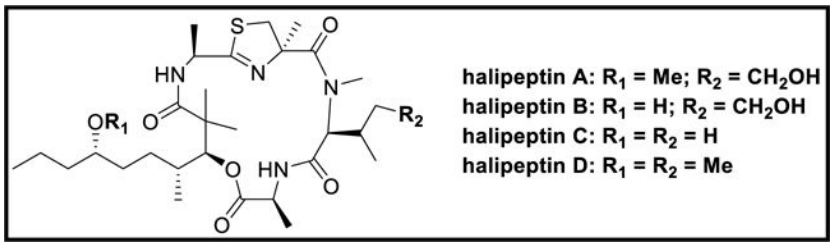


Figure 21.
Chemical structures of halipeptins A-D

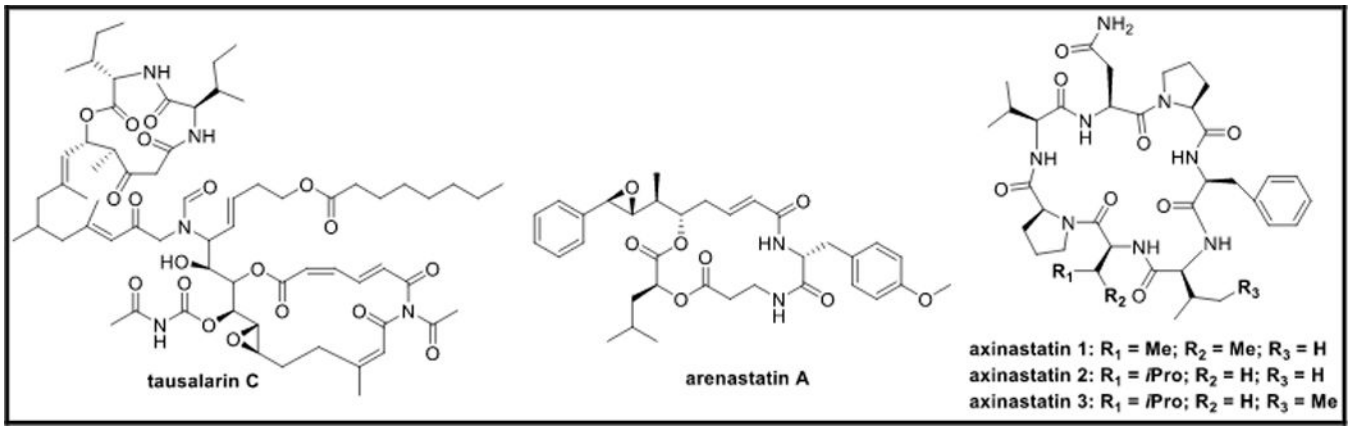


Figure 22.
Chemical structures of tausalarin C, arenastatin A, and axinastatins 1–3

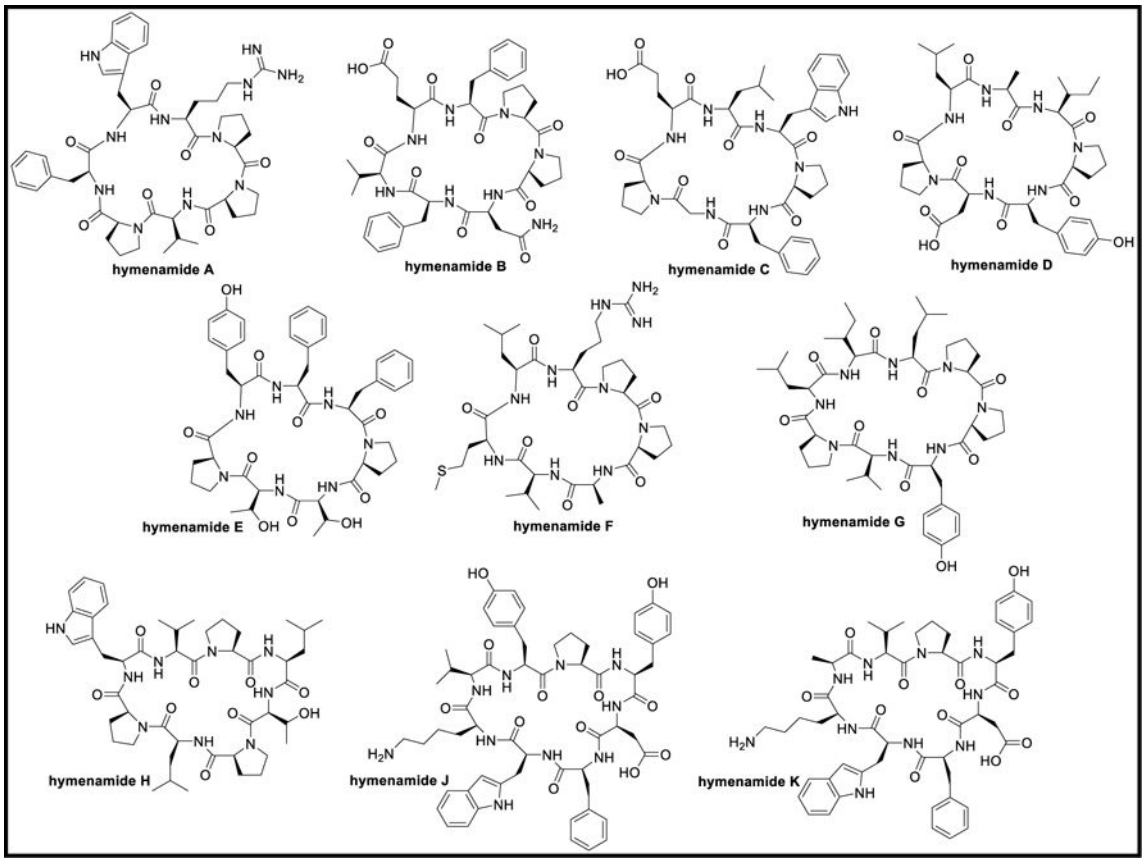


Figure 23.
Chemical structures of hymenamides A-H and J-K

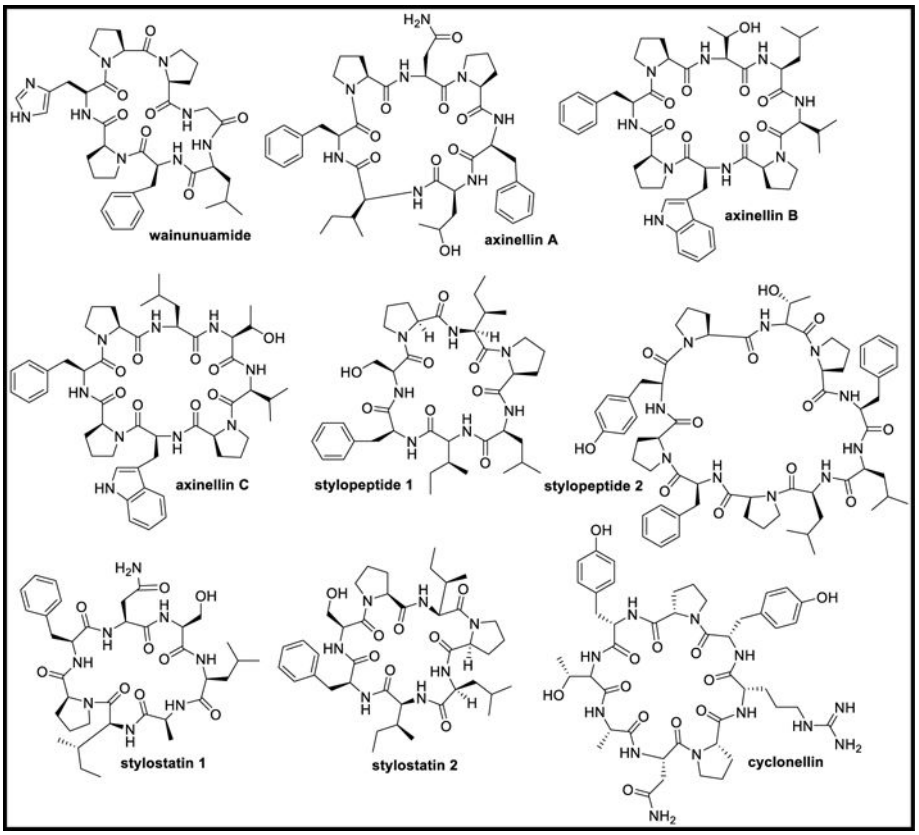


Figure 24.

Chemical structures of wainunuamide, axinellins A-C, stylopeptides 1–2, stylostatins 1–2, and cyclonellin

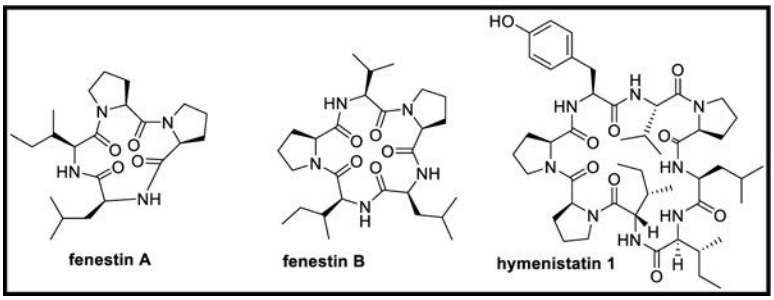


Figure 25.
Chemical structures of fenestins A-B and hymenistatin 1

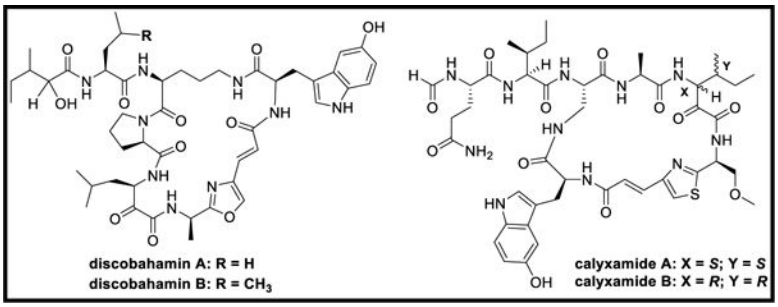


Figure 26.
Chemical structures of discobahamins A-B and calyxamides A-B

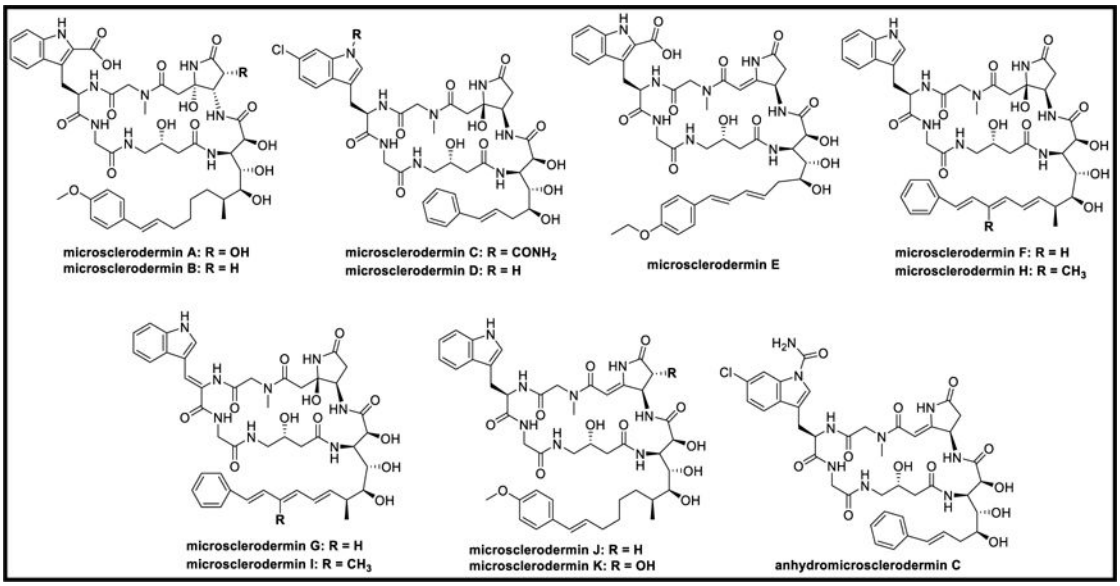


Figure 27.
Chemical structures of microsclerodermins A-K and anhydromicrosclerodermin C

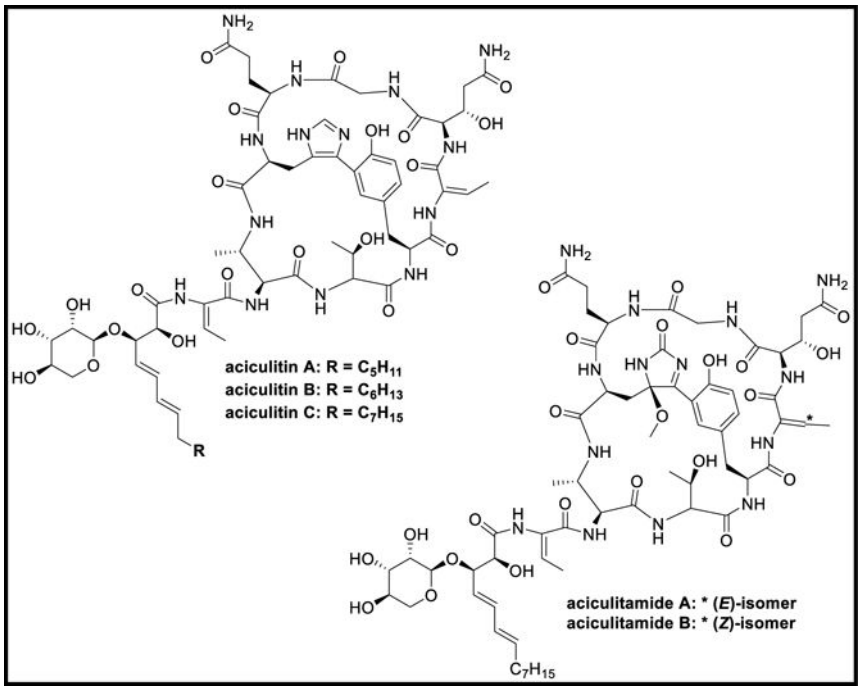


Figure 28.
Chemical structures of aciculitins A-C and aciculitamides A-B

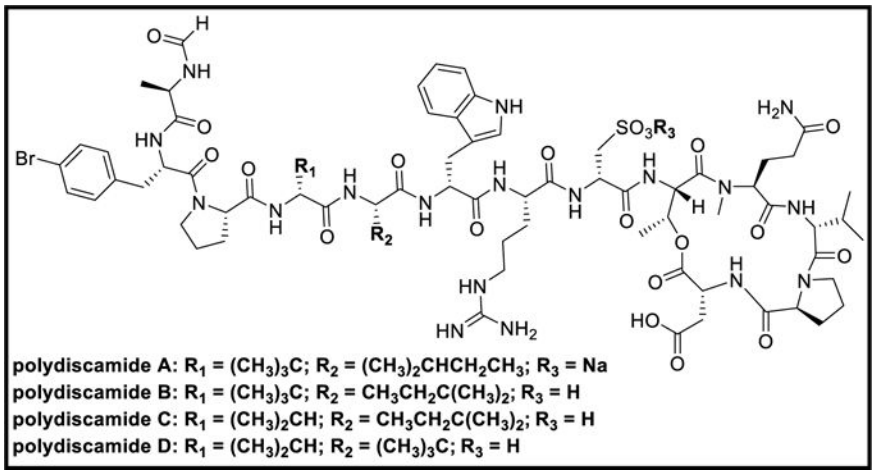


Figure 29.
Chemical structures of polydiscamides A-D

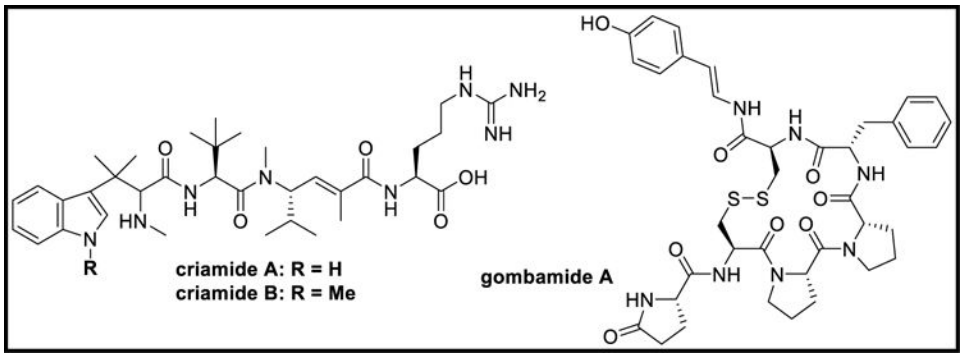


Figure 30.
Chemical structures of criamides A-B and gombamide A

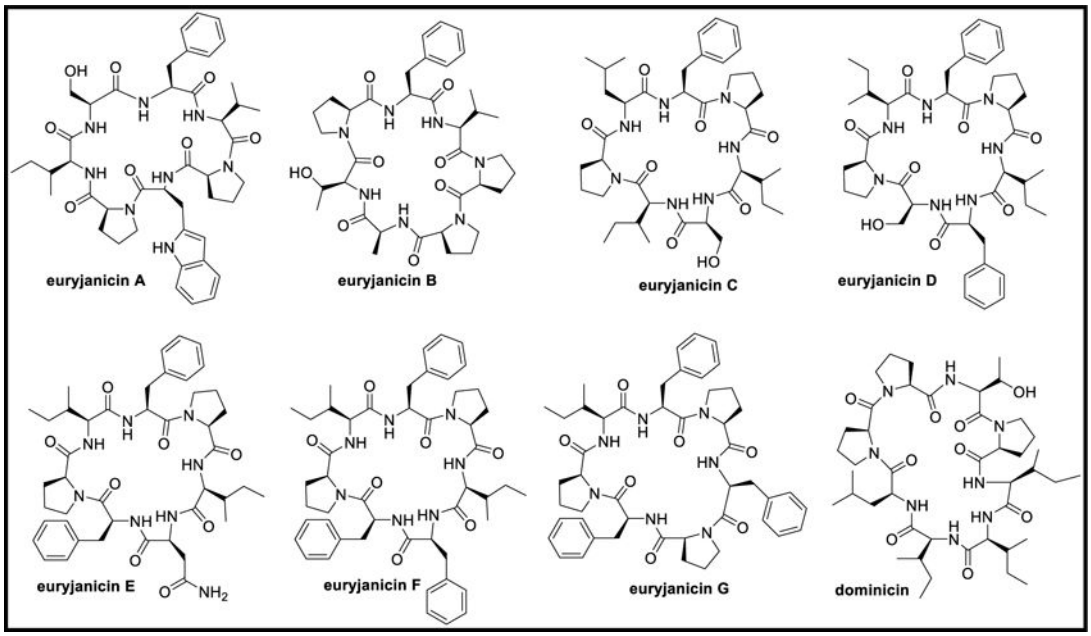


Figure 31.
Chemical structures of euryjanicins A-G and dominicin

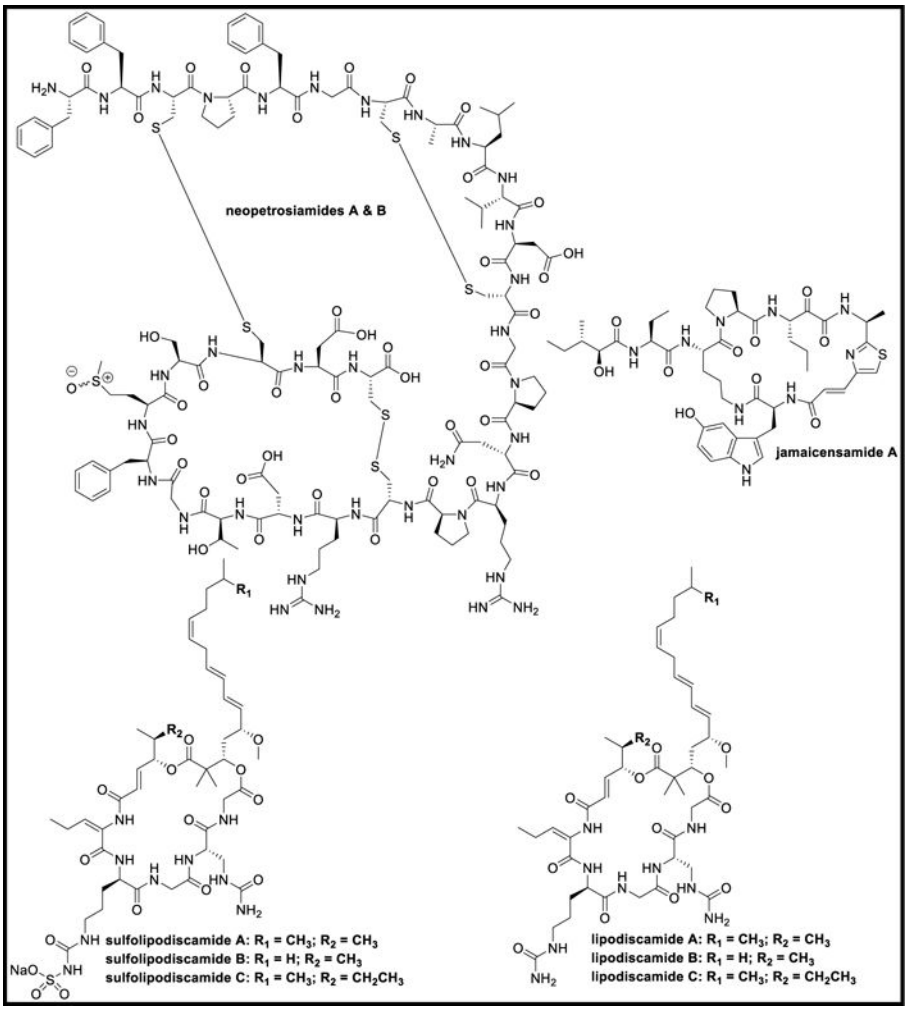


Figure 32.

Chemical structures of neopetrosiamides A-B, jamaicensamide A, sulfolipodiscamides A-C, and lipodiscamides A-C

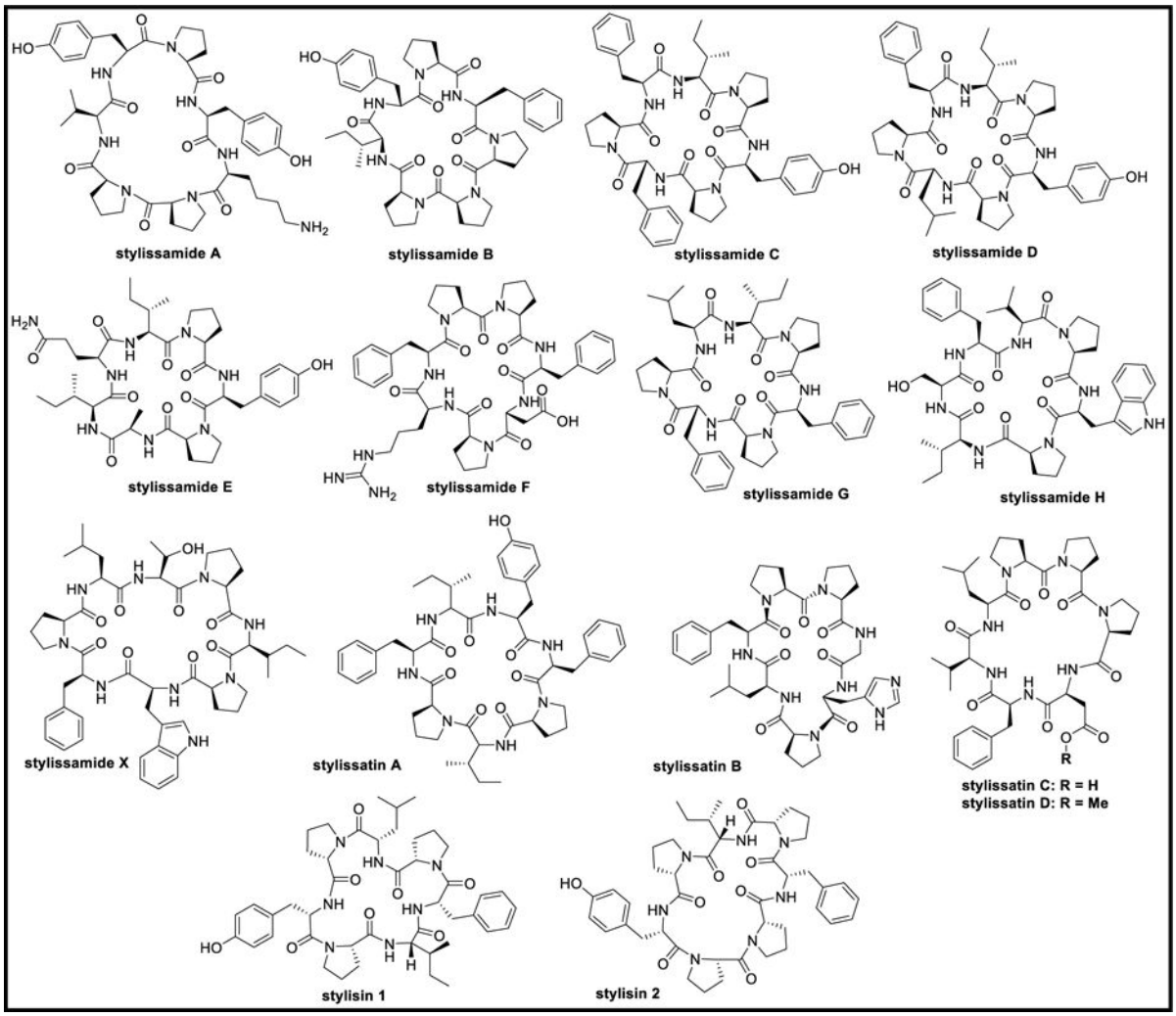


Figure 33.
Structures of stylissamides A-H, X, stylissatins A-D, and stylisins 1–2

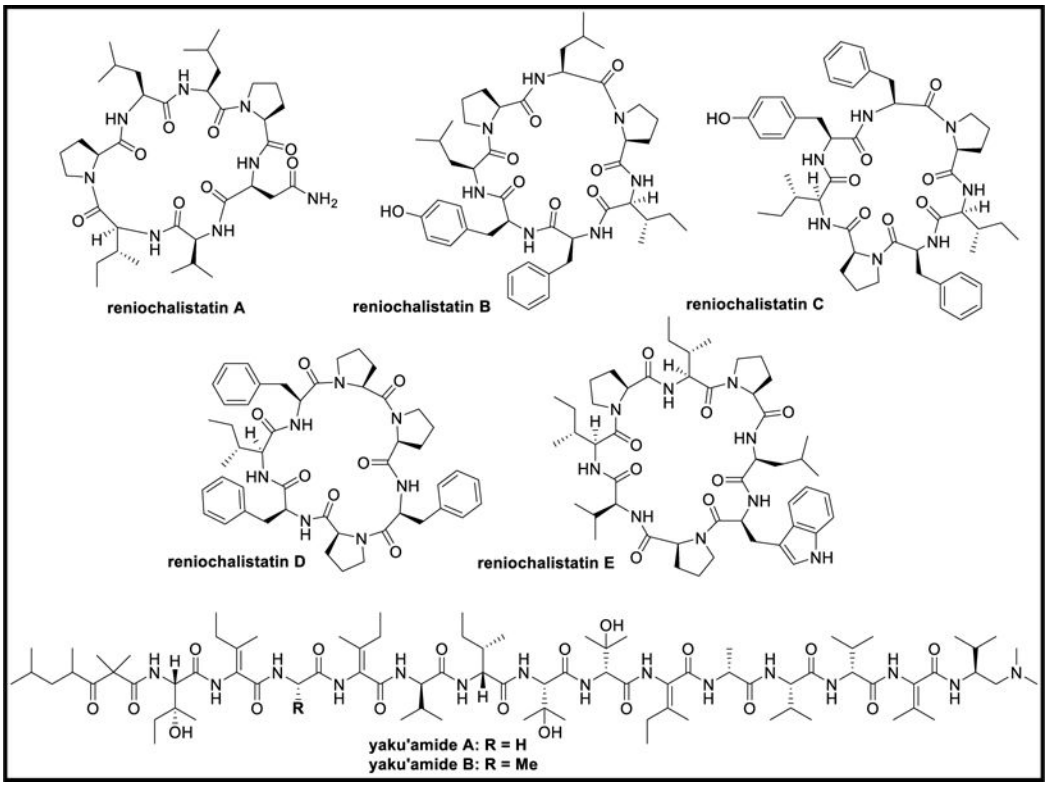


Figure 34.
Chemical structures of reniochalistatins A-E and yaku’amides A-B

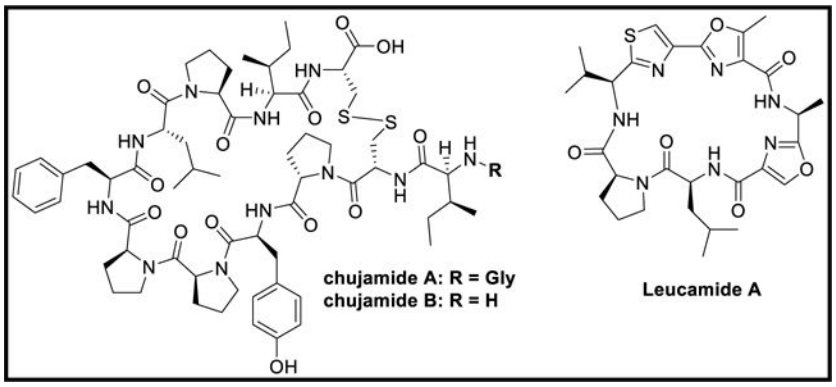


Figure 35.
Chemical structures of chujamides A-B and leucamide A

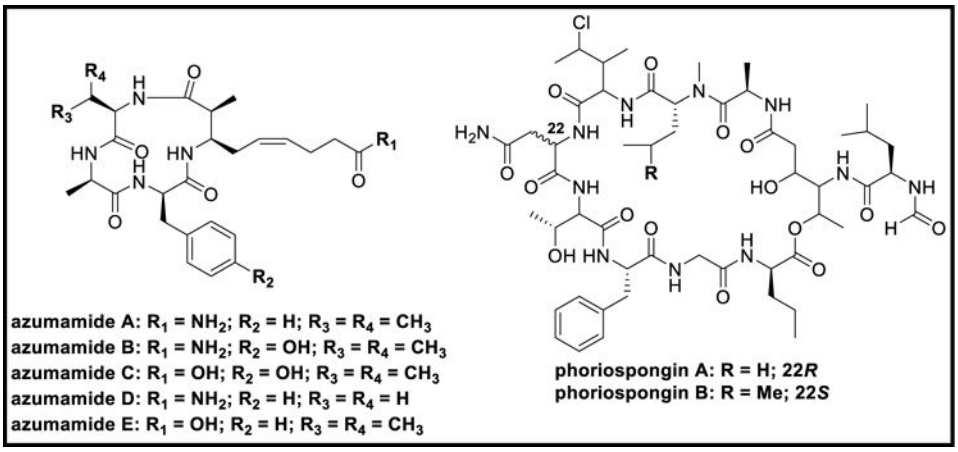


Figure 36.
Chemical structures of azumamides A-E and phoriospongins A-B

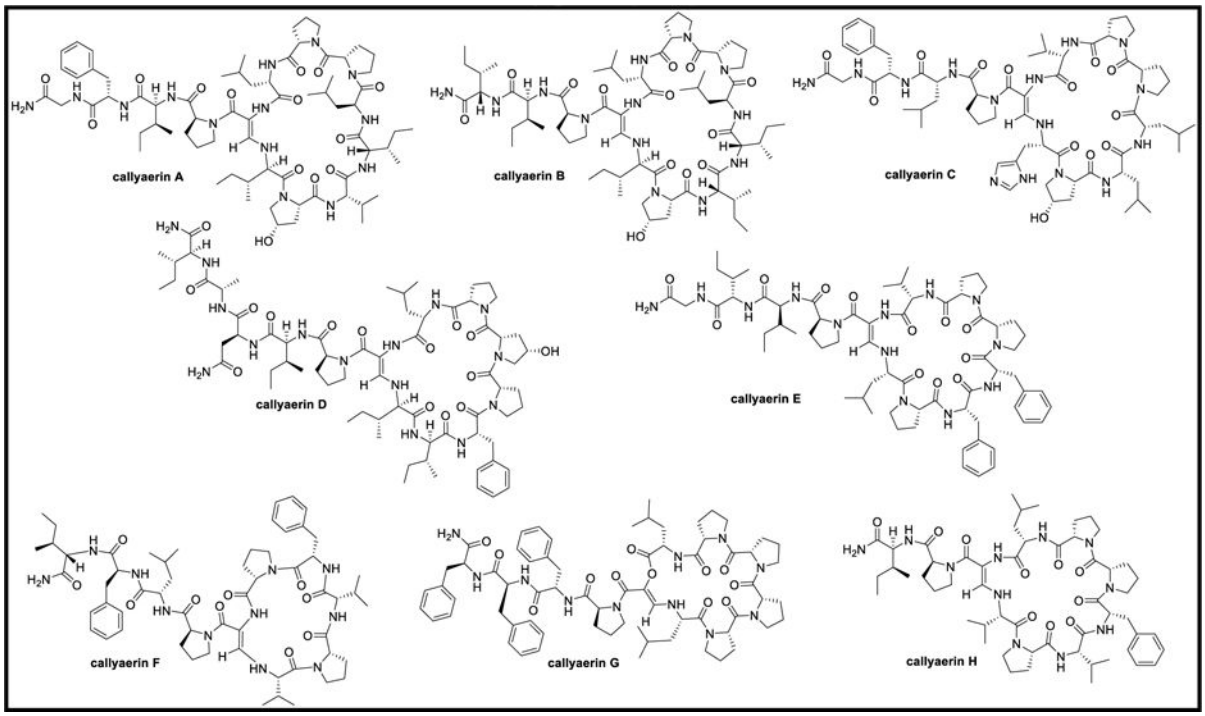


Figure 37.
Chemical structures of callyaerins A-H

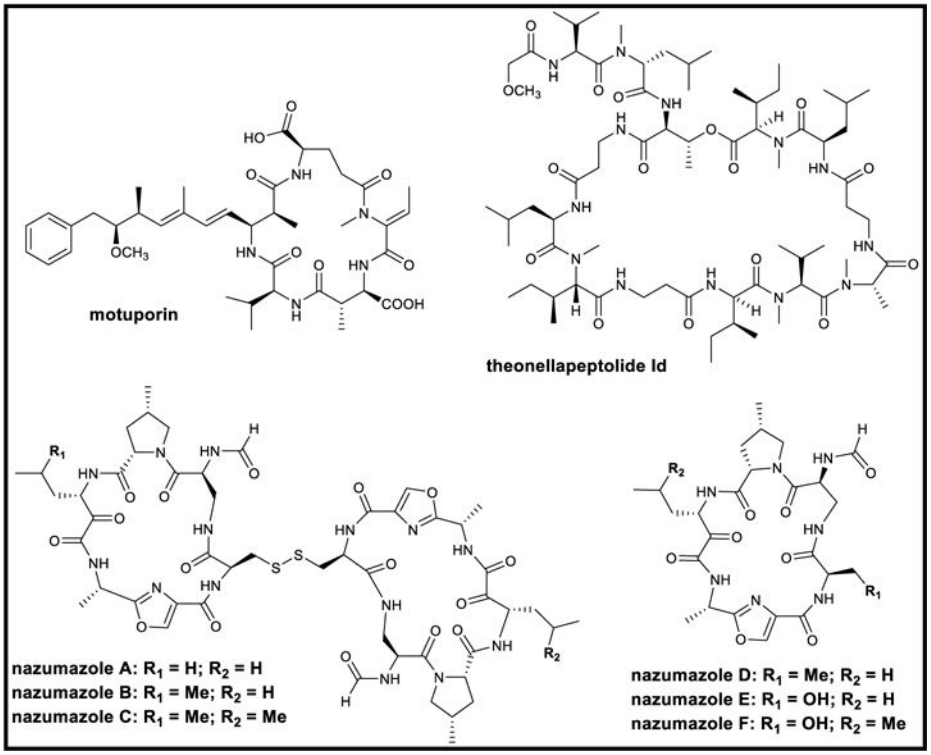


Figure 38.
Chemical structures of motuporin, theonellapeptolide Id, and nazumazoles A-F

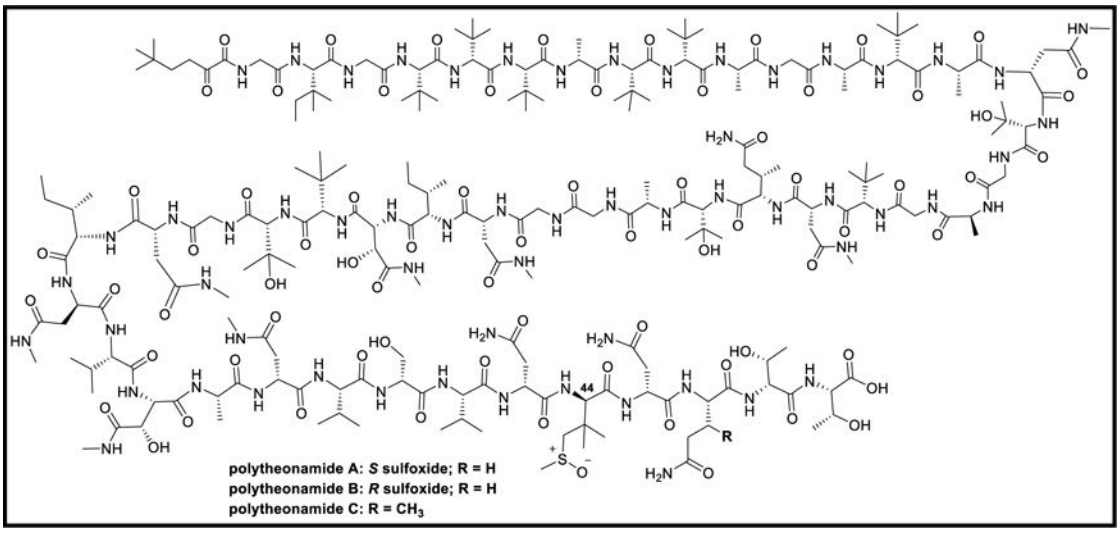


Figure 39.
Chemical structures of polytheonamides A-C

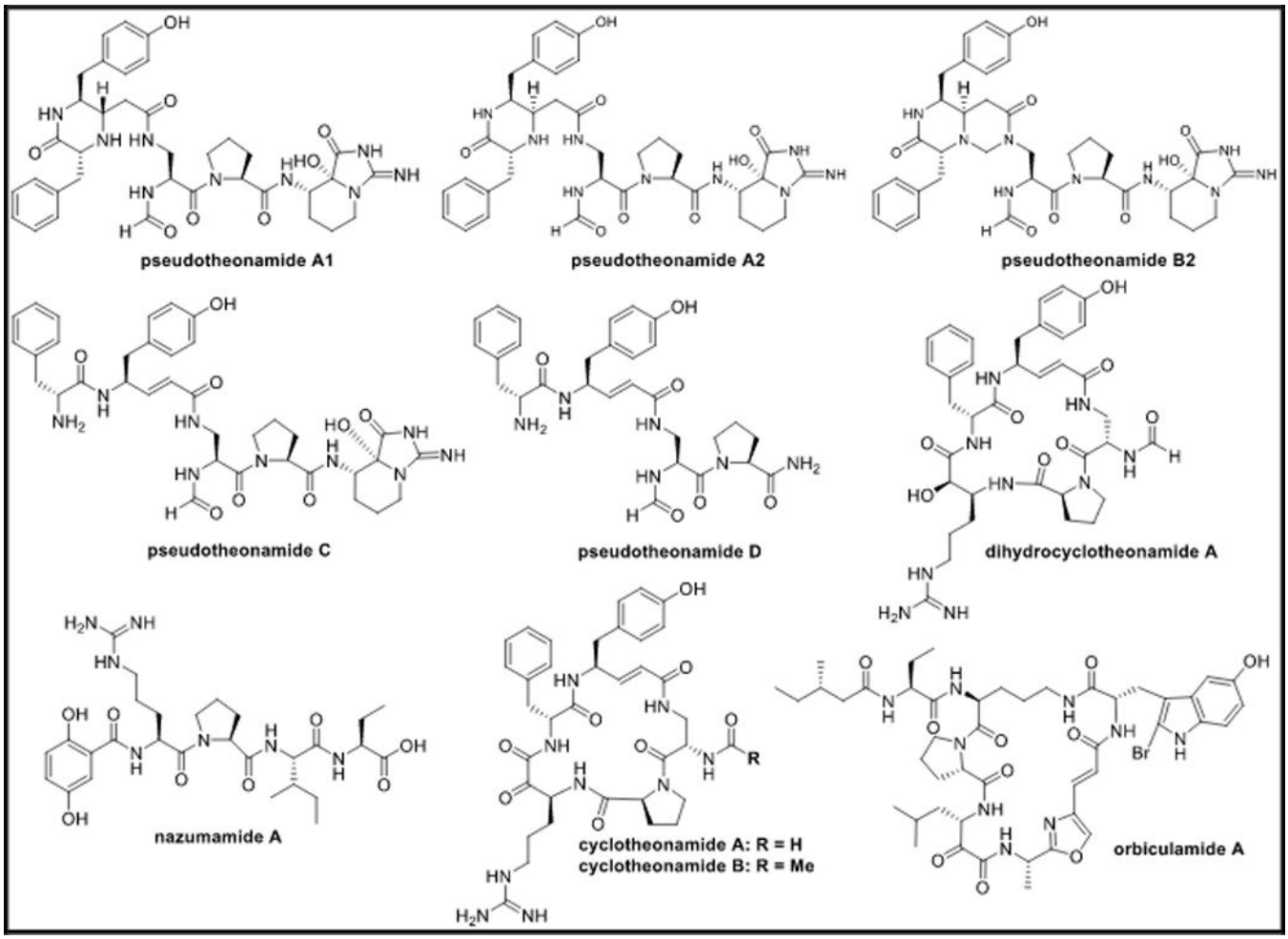


Figure 40.

Chemical structures of pseudotheonamides A1-A2, B2, C-D, dihydrocyclotheonamide A, nazumamide A, cyclotheonamides A-B, and orbiculamide A

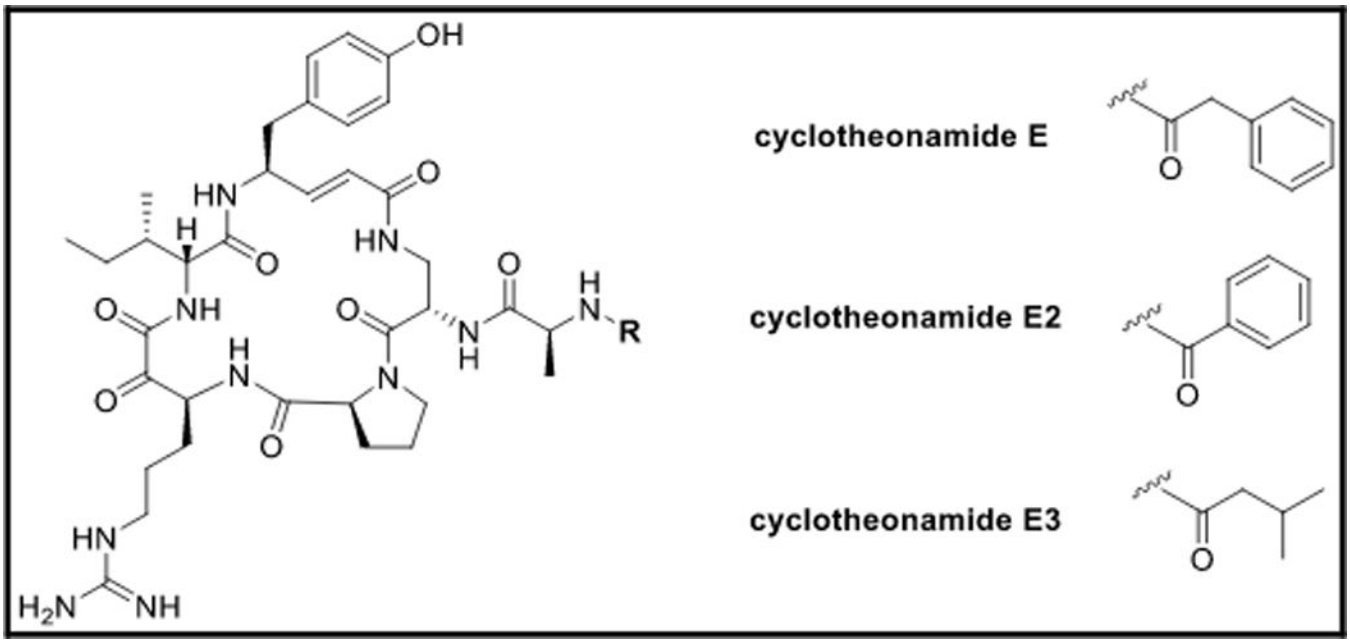


Figure 41.
Chemical structures of cyclotheonamides E, E2, and E3

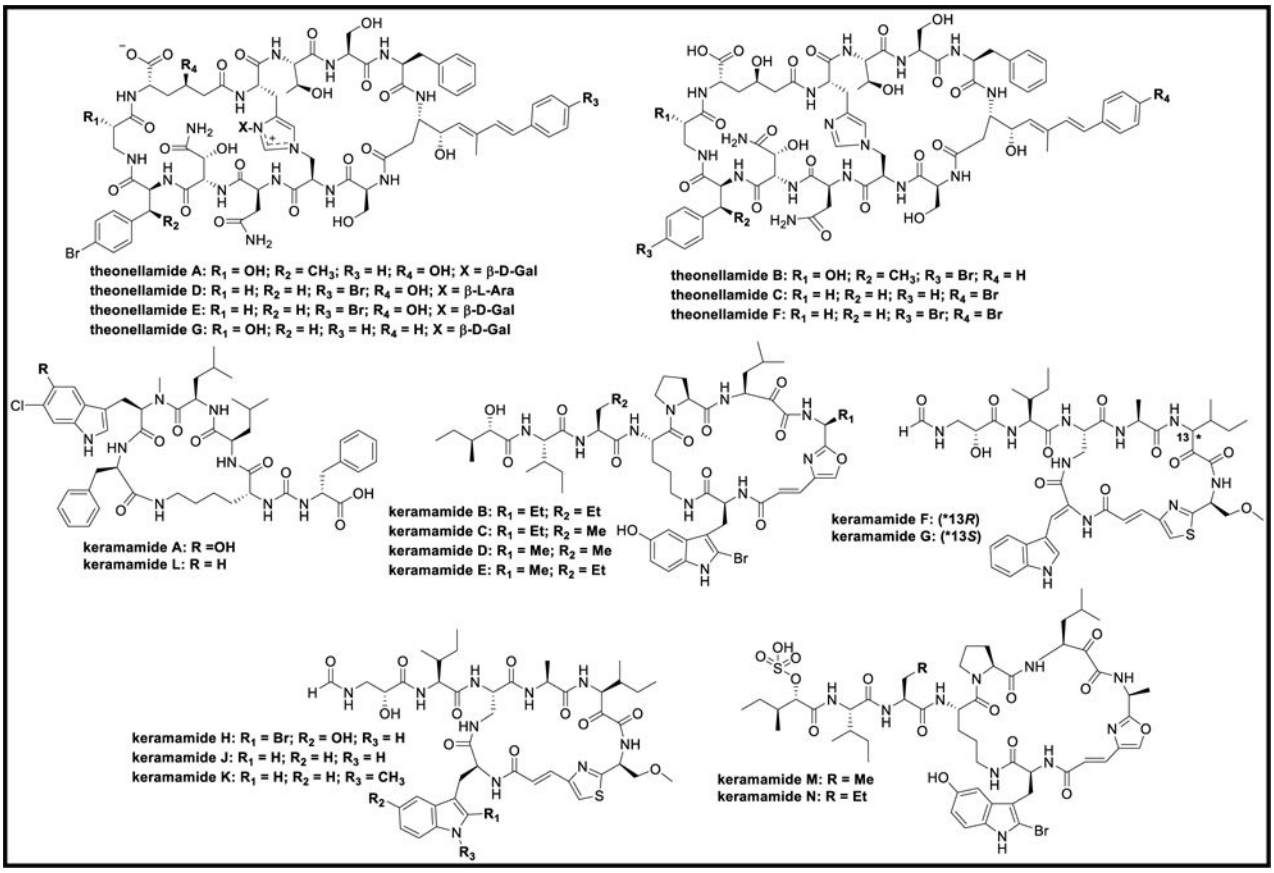


Figure 42.
Chemical structures of theonellamides A-G, keramamides A-H, and J-N

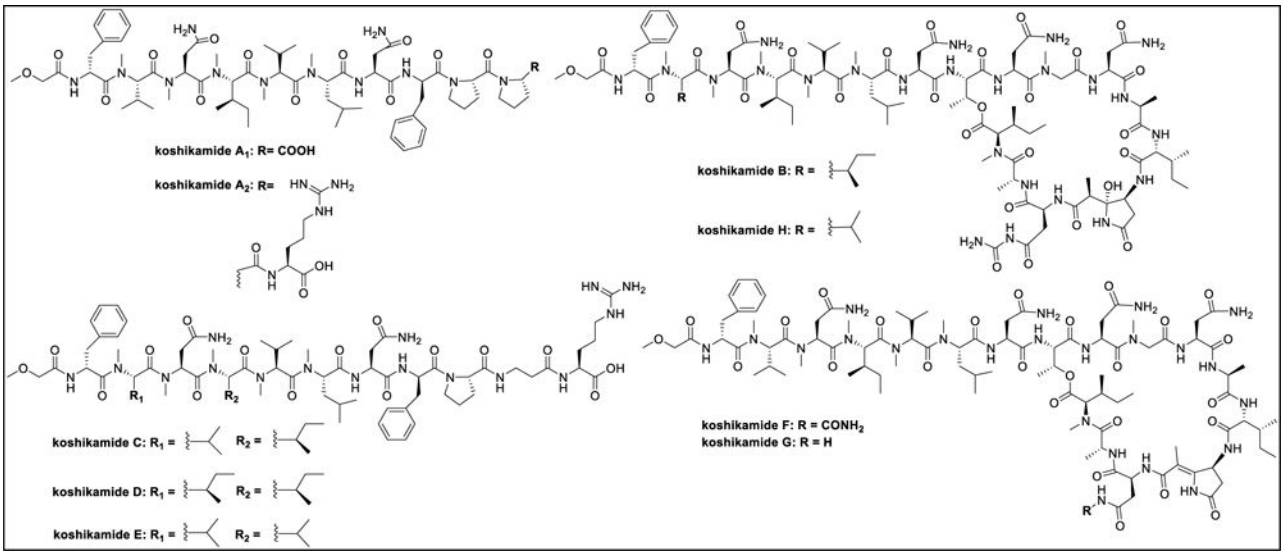


Figure 43.
Chemical structures of koshikamides A1-A2 and B-H

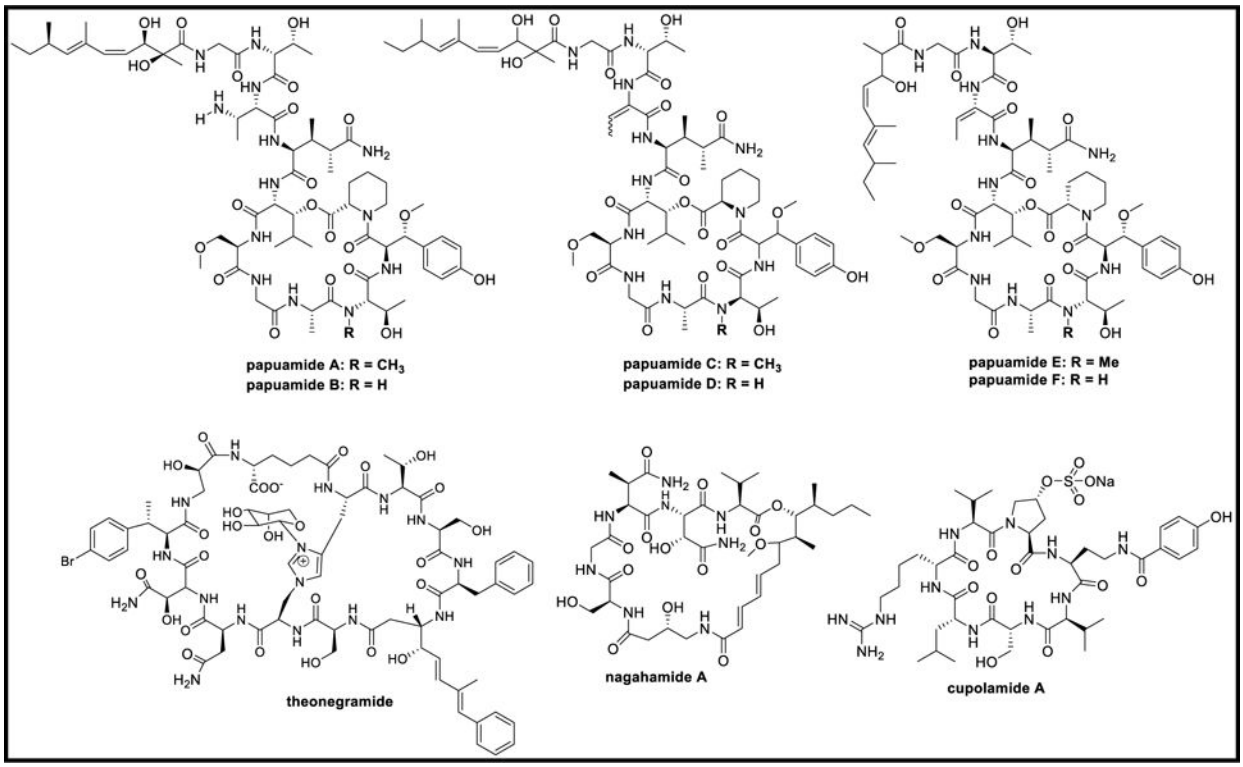


Figure 44.
Chemical structures of papuamides A-F, theonegramide, nagahamide A, and cupolamide A

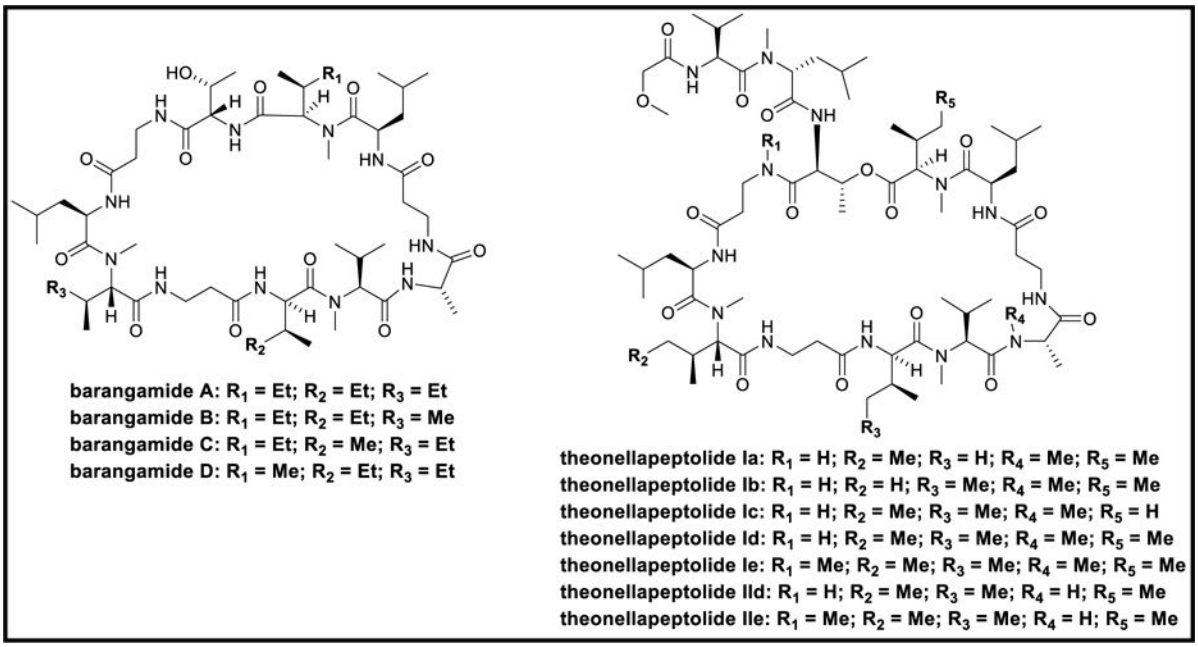


Figure 45.
Chemical structures of barangamides A-D, theonellapeptolides Ia-Ie, and IId-IIe

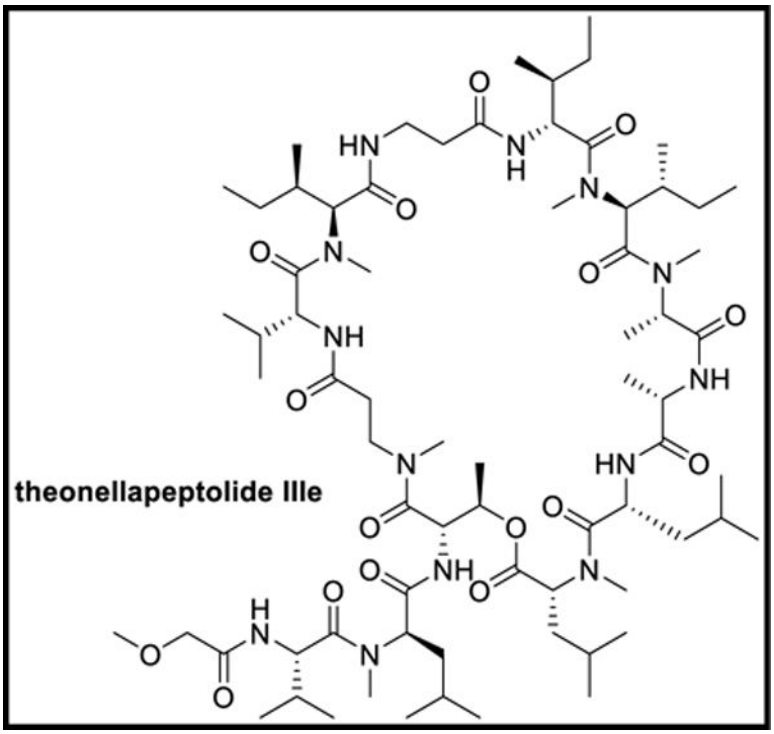


Figure 46.
Chemical structure of theonellapeptolide IIIe [169]

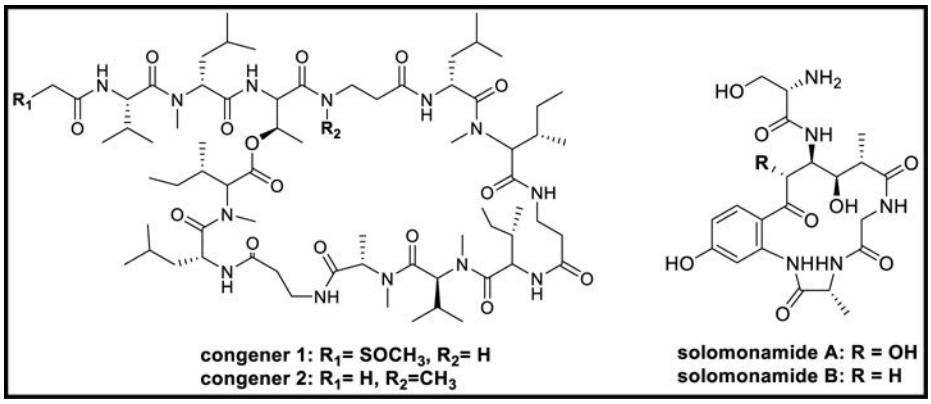


Figure 47.
Chemical structures of congeners 1–2 and solomonamides A-B

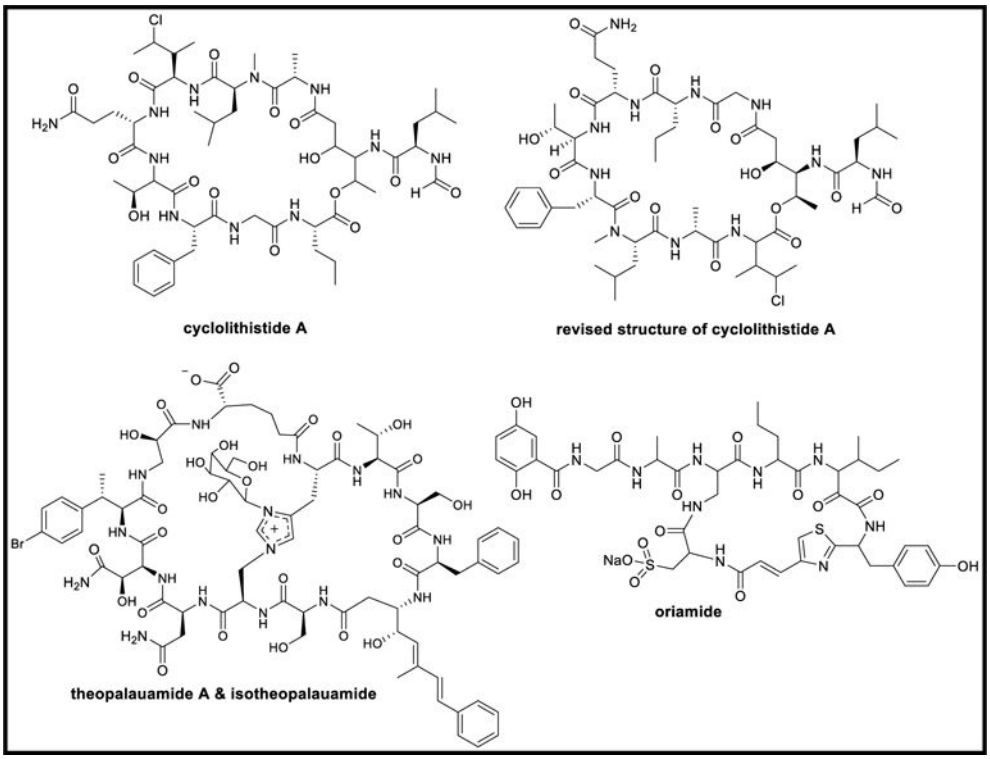


Figure 48.

Chemical structures of cyclolithistide A, revised structure of cyclolithistide A [176], theopalauamide A, isotheopalauamide, and oriamide

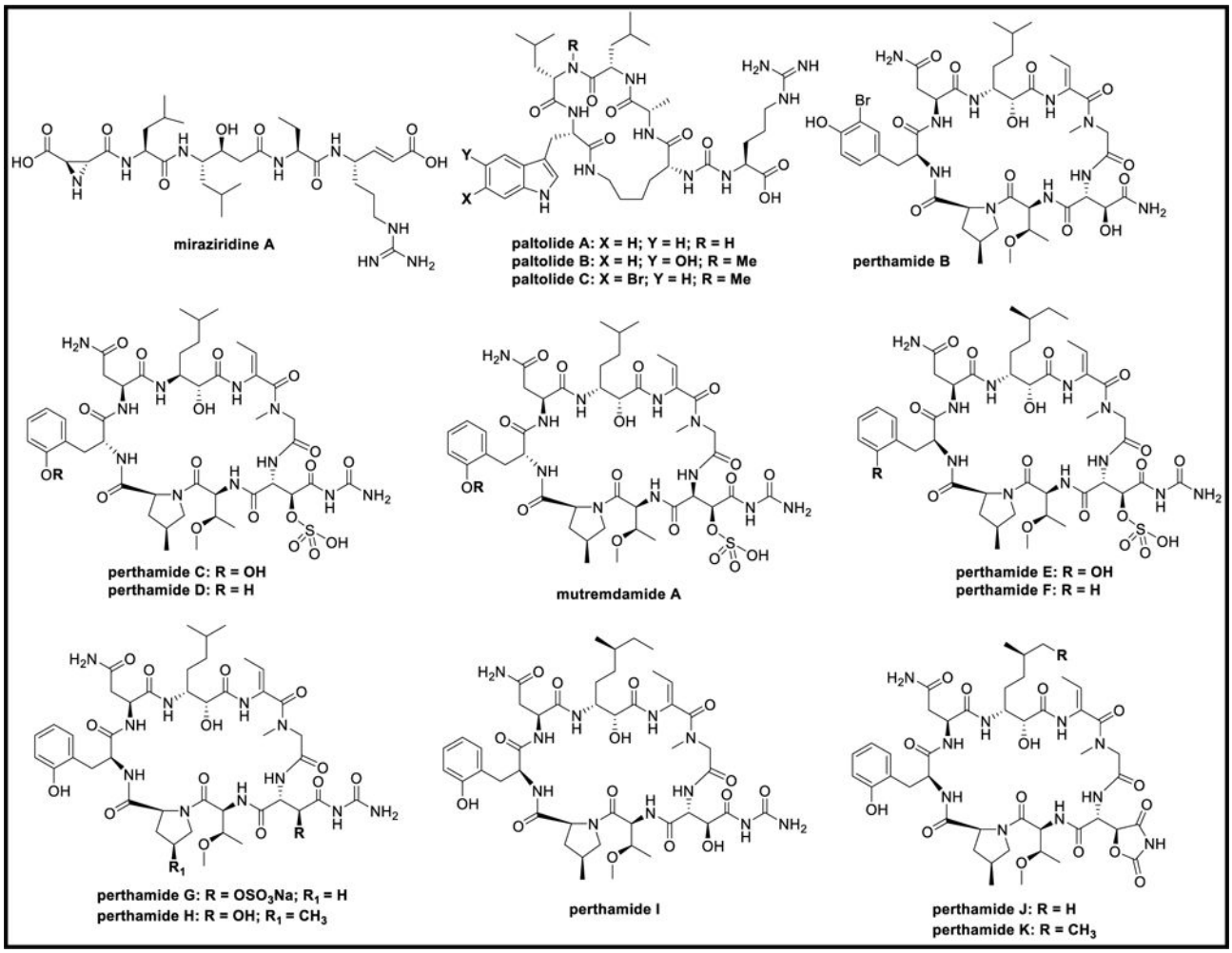


Figure 49.

Chemical structures of miraziridine A, paltolides A-C, perthamides B-K, and mutremdamide A

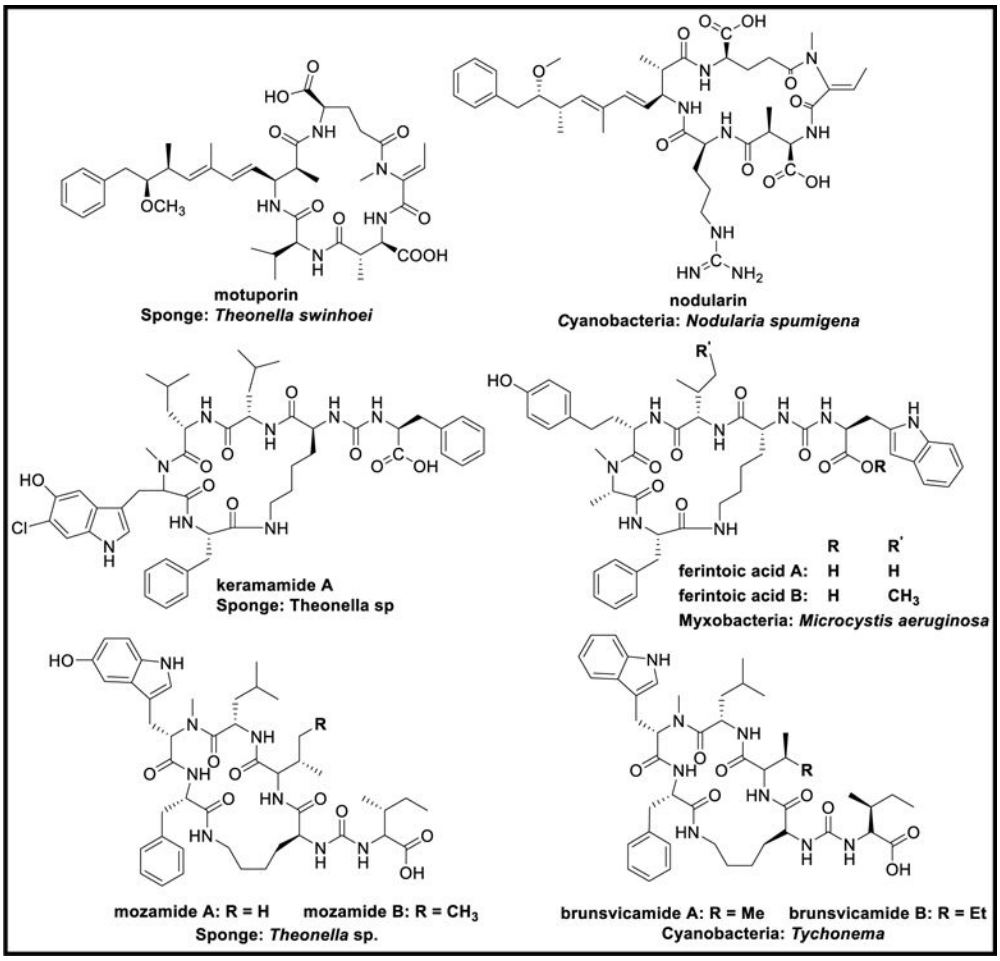


Figure 50.
Structural similarity of peptides isolated from *Theonella* sp., and microorganisms

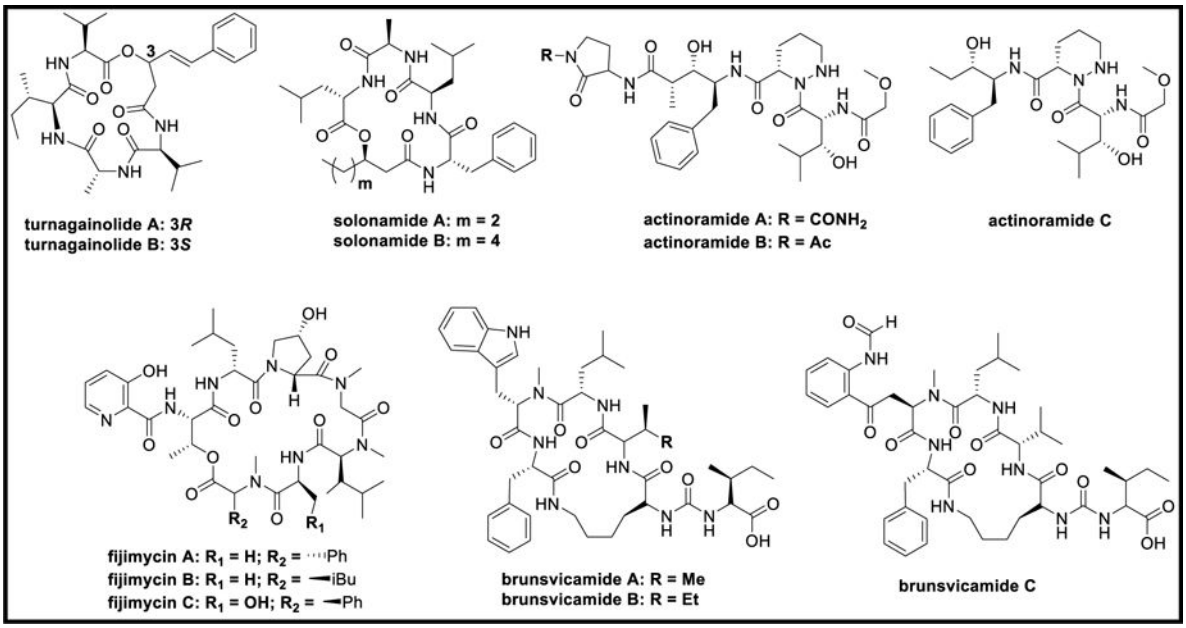


Figure 51.

Chemical structures of turnagainolides A-B, solonamides A-B, actinoramides A-C, fijimycins A-C, and brunsvicamides A-C

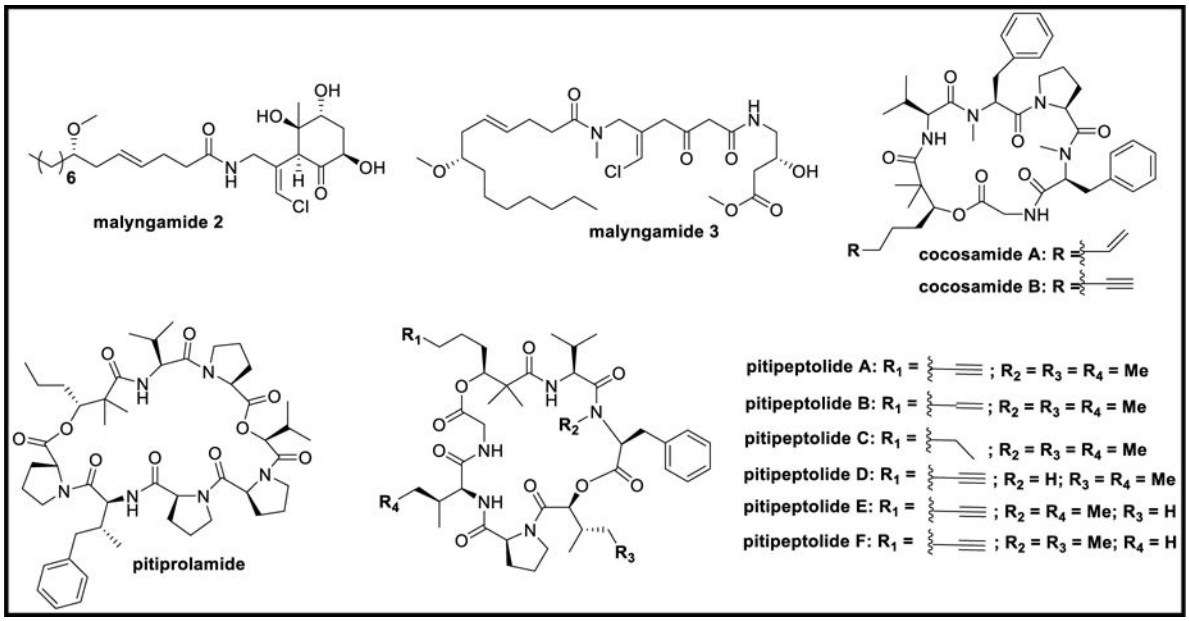


Figure 52.
Chemical structures of malyngamides 2–3, cocosamides A-B, pitiprolamide, and pitipeptolides A-F

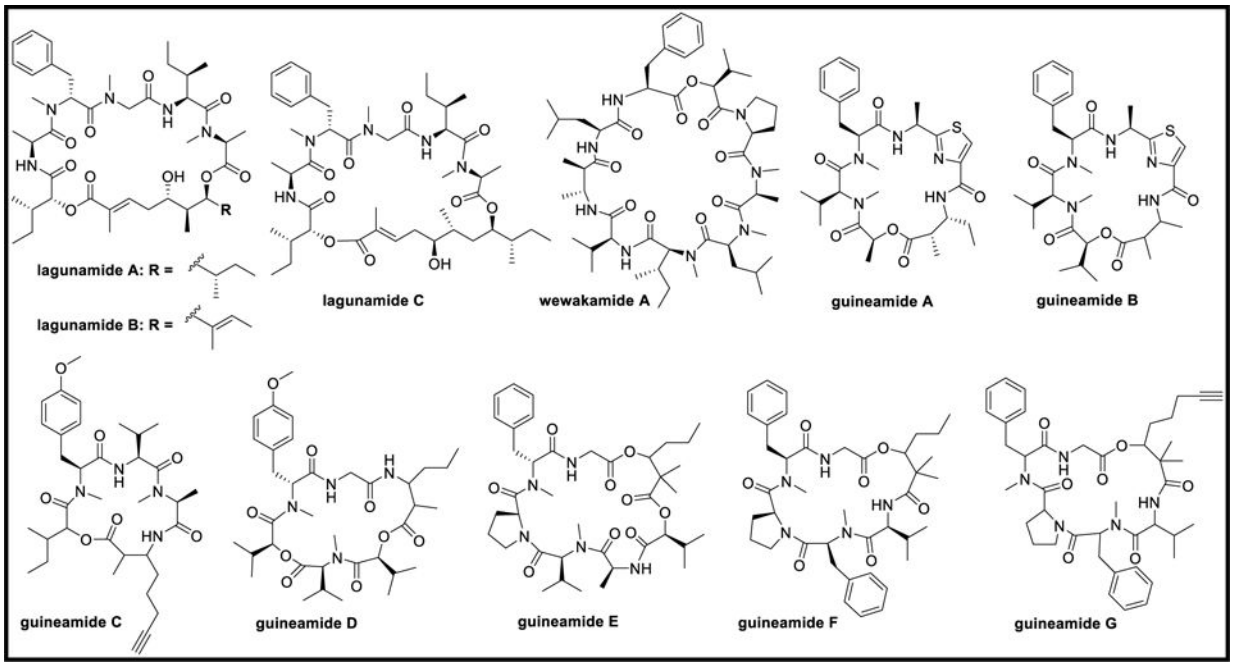


Figure 53.
Chemical structures of lagunamides A-C, wewakamide A, and guineamides A-G

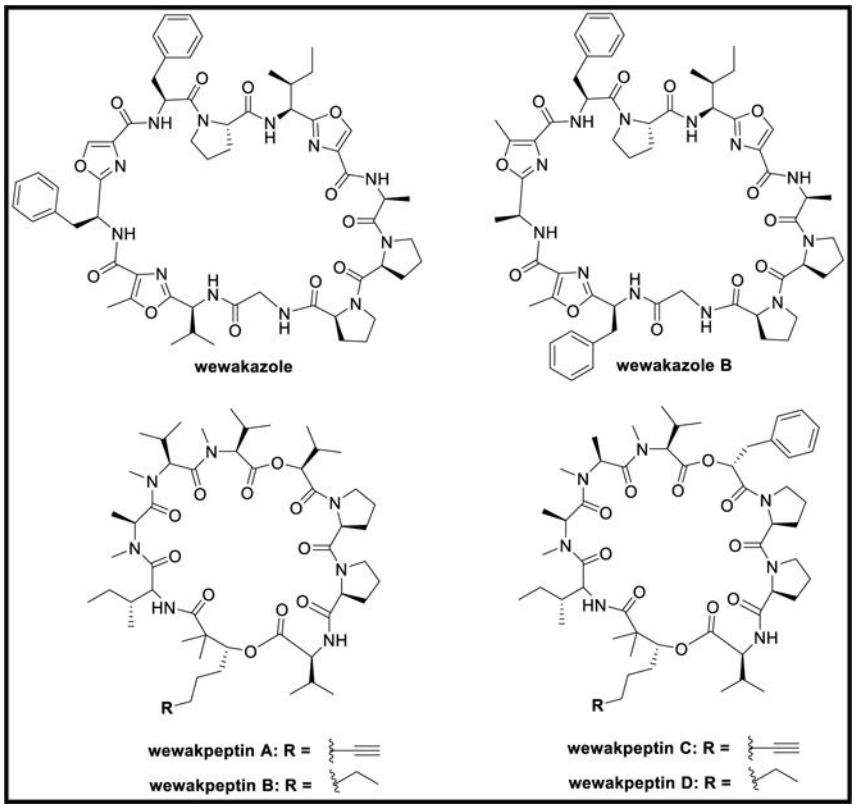


Figure 54.
Chemical structures of wewakazole, wewakazole B, and wewakpeptins A-D

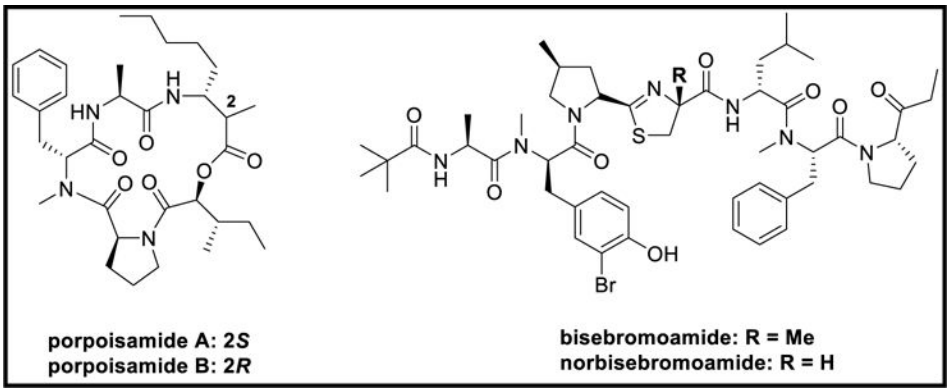


Figure 55.
Chemical structures of porpoisamides A-B, bisebromoamide, and norbisebromoamide

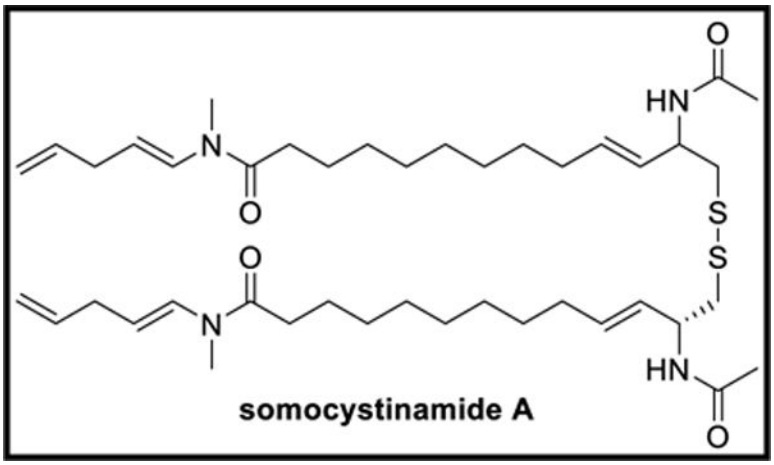


Figure 56.
Chemical structure of somocystinamide A

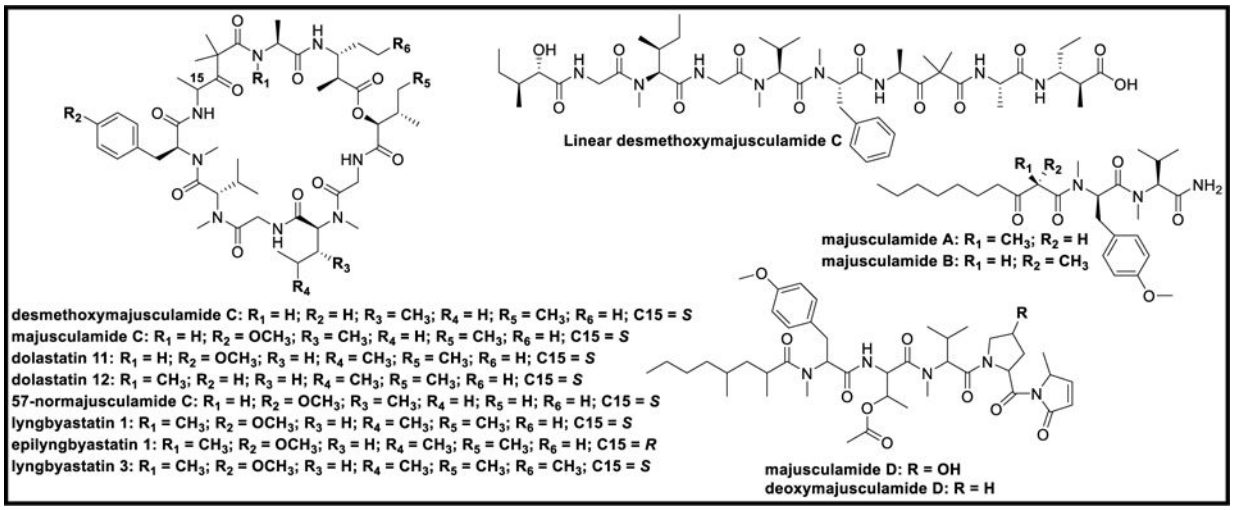


Figure 57.

Chemical structures of cyclic desmethoxymajusculamide C, linear desmethoxymajusculamide C, majusculamides A-D, dolastatins 11–12, 57-normajusculamide C, lyngbyastatins 1, 3, epilyngbyastatin 1, and deoxymajusculamide D

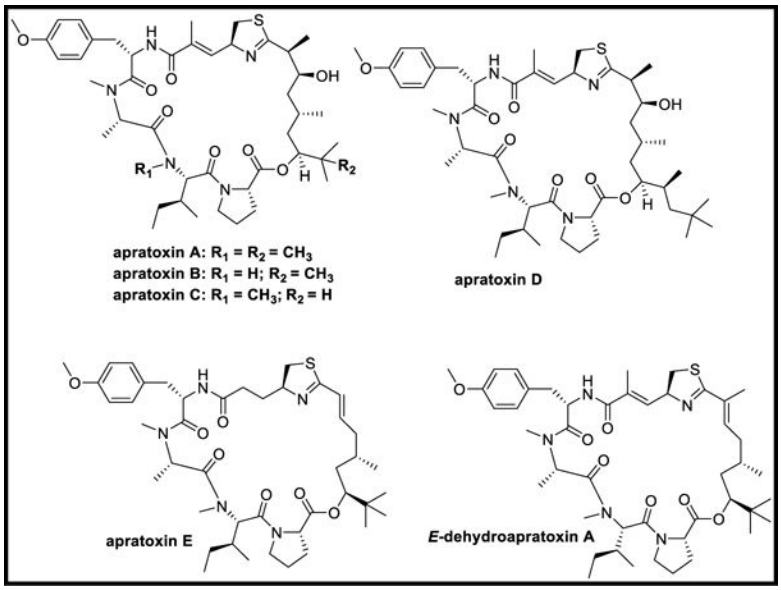


Figure 58.
Chemical structures of apratoxins A-E and dehydroapratoxin A

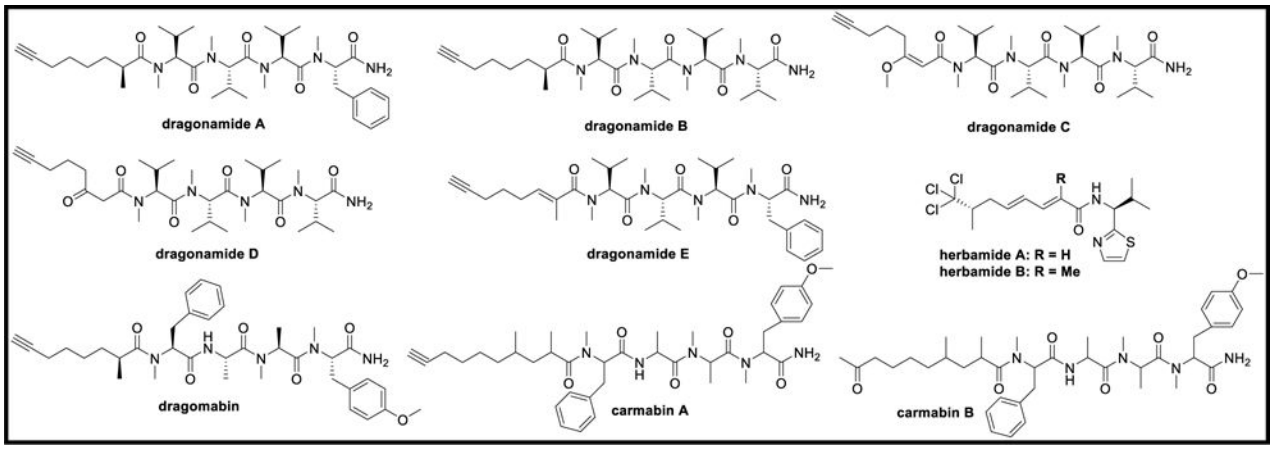


Figure 59.
Chemical structures of dragonamides A-E, herbamides A-B, dragomabin, and carmabins A-B

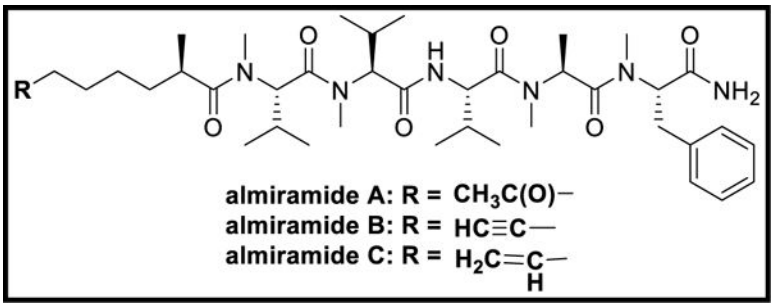


Figure 60.
Chemical structures of almiramides A-C

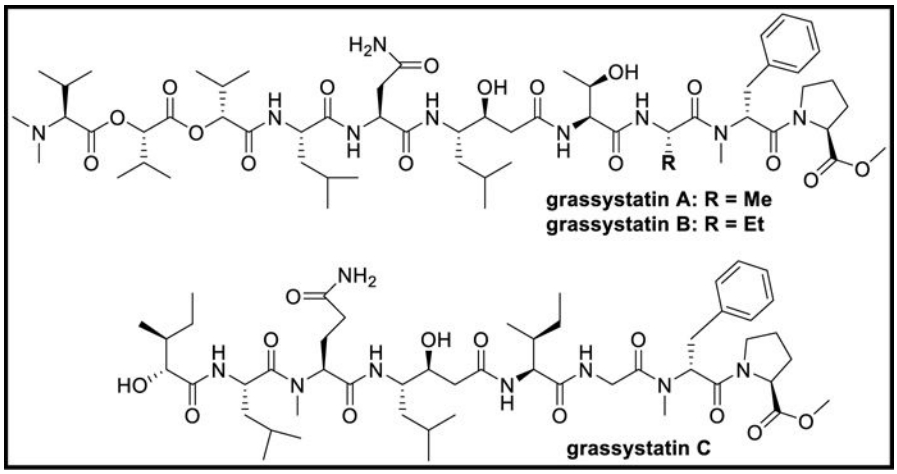


Figure 61.
Chemical structures of grassystatins A-C

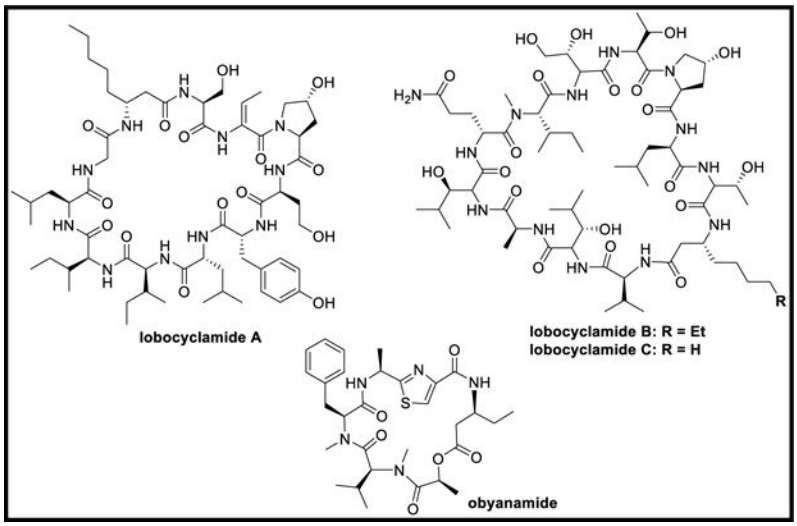


Figure 62.
Chemical structures of lobocyclamides A-C and obyanamide

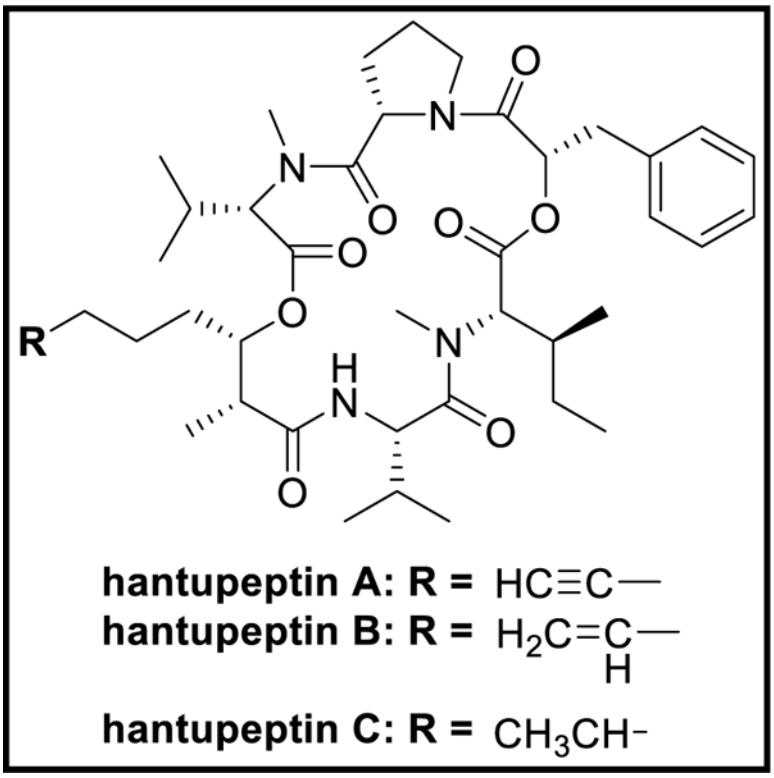


Figure 63.
Chemical structures of hantupeptins A-C

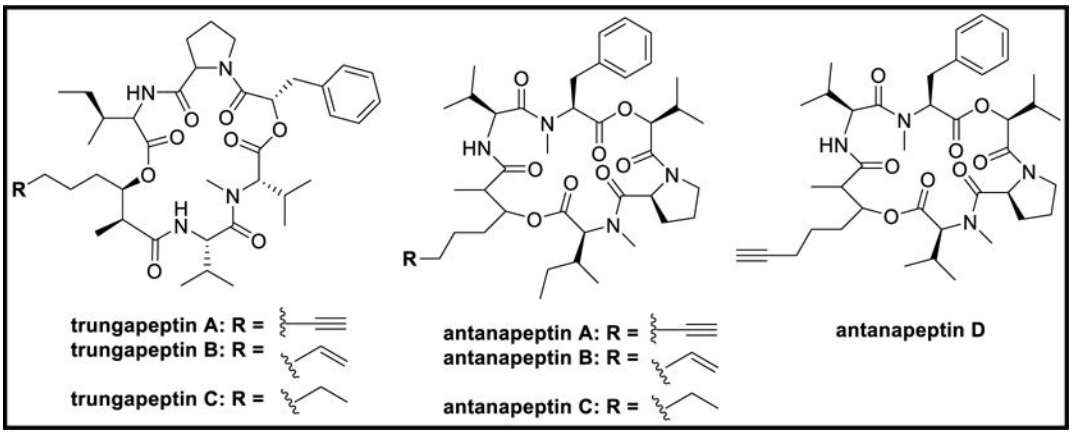


Figure 64.
Chemical structures of trungapeptins A-C and antanapeptins A-D

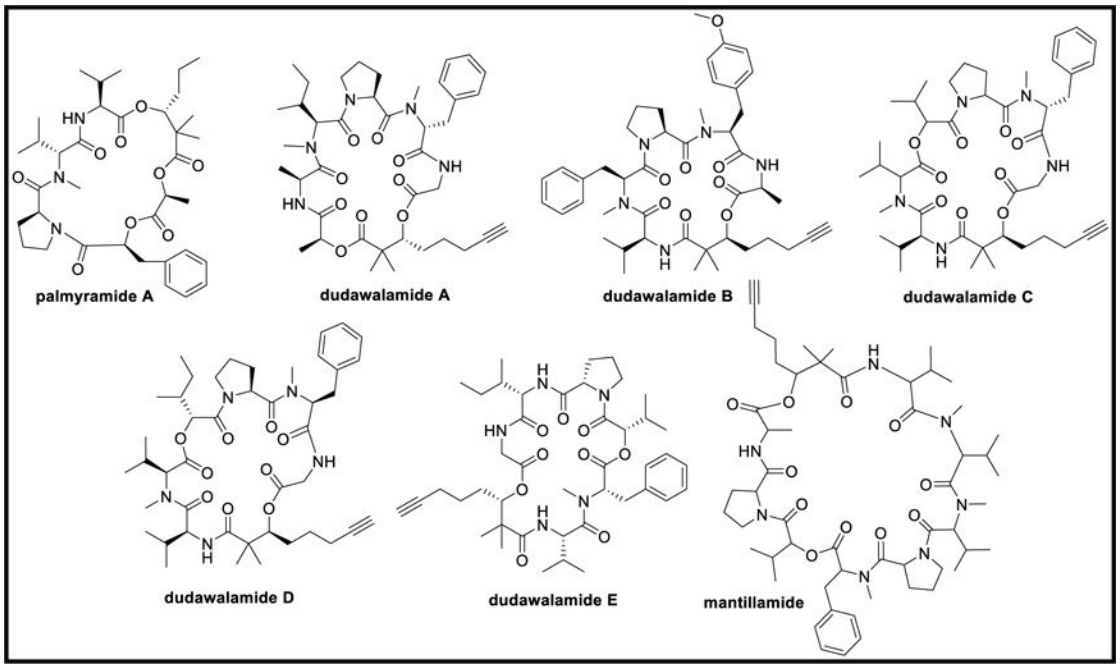


Figure 65.
Chemical structures of palmyramide A, dudawalamides A-E, and mantillamide

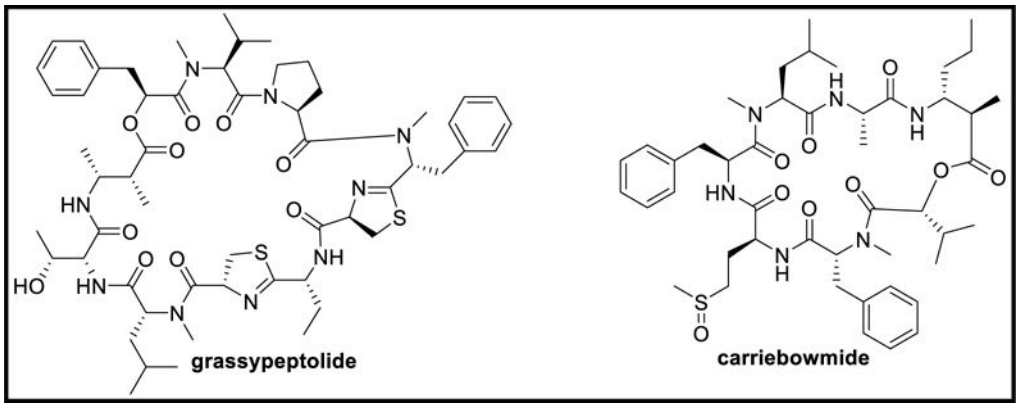


Figure 66.
Chemical structures of grassypeptolide and carriebowmide

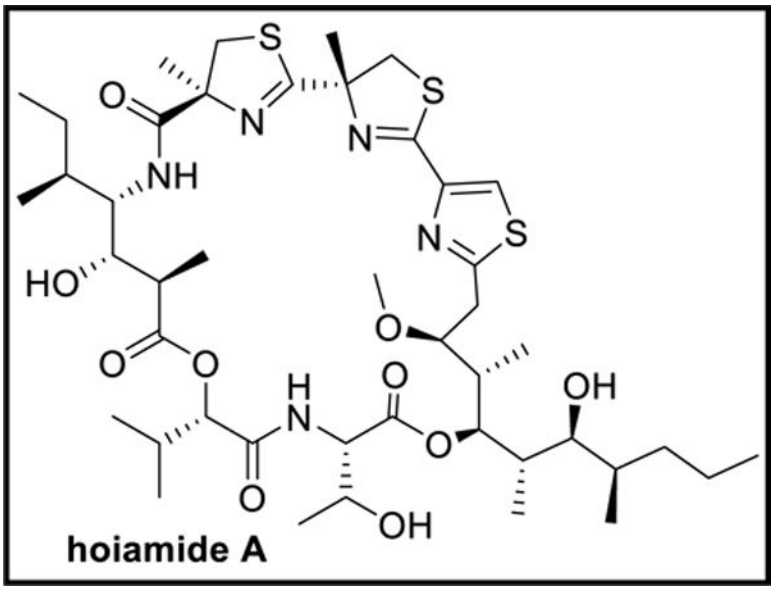
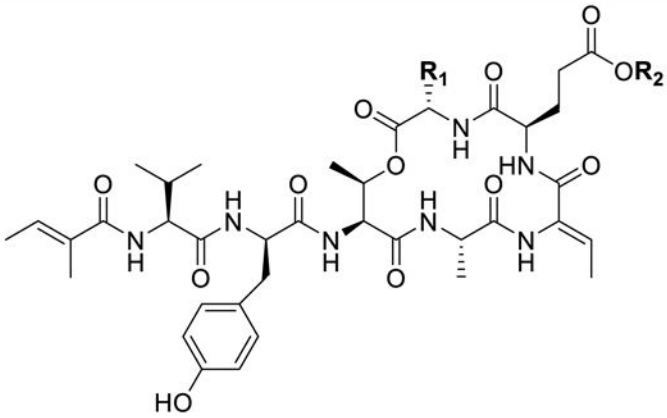


Figure 67.
Chemical structure of hoiamide A



Name	R_1	R_2
tiglicamide A	4-OH-PhC_2H_4-	H
tiglicamide B	PhCH_2	H
tiglicamide C	CH_3-SO-C_2H_4-	H
largamide A	*i*-Bu	H
largamide B	4-OH-PhC_3H_6-	H
largamide C	4-OH-PhC_4H_8-	H
largamide A methyl ester	*i*-Bu	Me
largamide B methyl ester	4-OH-PhC_3H_6-	Me
largamide C methyl ester	4-OH-PhC_4H_8-	Me

Figure 68.

Chemical structures of tiglicamides A-C, largamides A-C, and methyl esters of largamides A-C

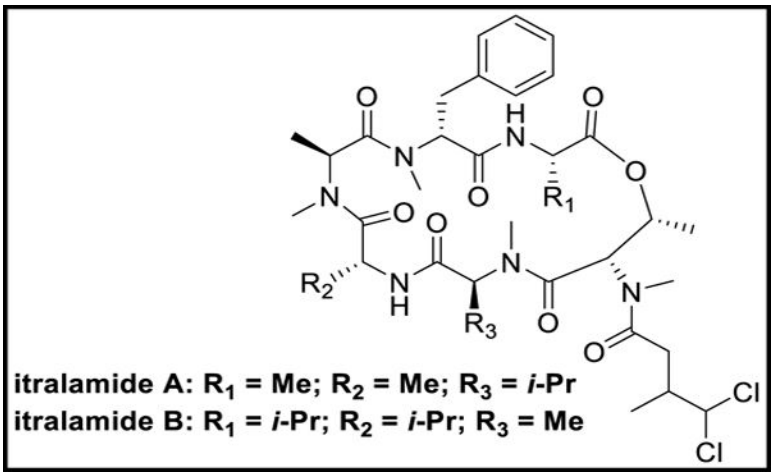
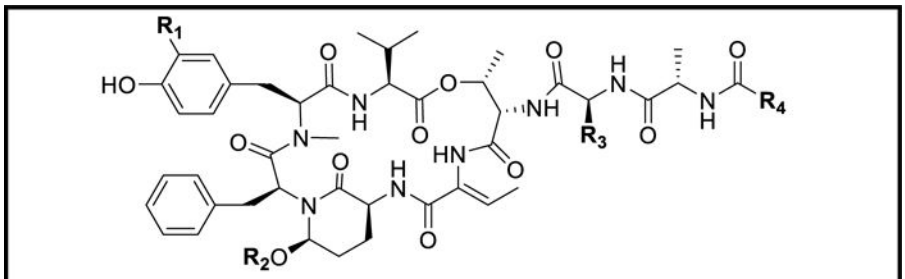


Figure 69.
Chemical structures of itralamides A-B



Name	R_1	R_2	R_3	R_4
lyngbyastatin 4	H	H	4-OH-PhC_2H_4-	HO_3SO-CH_2-CH(OH)-
lyngbyastatin 5	H	H	4-OH-PhC_2H_4-	HO-CH_2-CH(OH)-
lyngbyastatin 6	H	Me	4-OH-PhC_2H_4-	NaO_3SO-CH_2-CH(OH)-
lyngbyastatin 8	H	H	*i*-Pr	Me
lyngbyastatin 9	H	H	*i*-Pr	Pr
lyngbyastatin 10	Br	H	*i*-Pr	Pr

Figure 70.
Chemical structures of lyngbyastatins 4–6 and 8–10

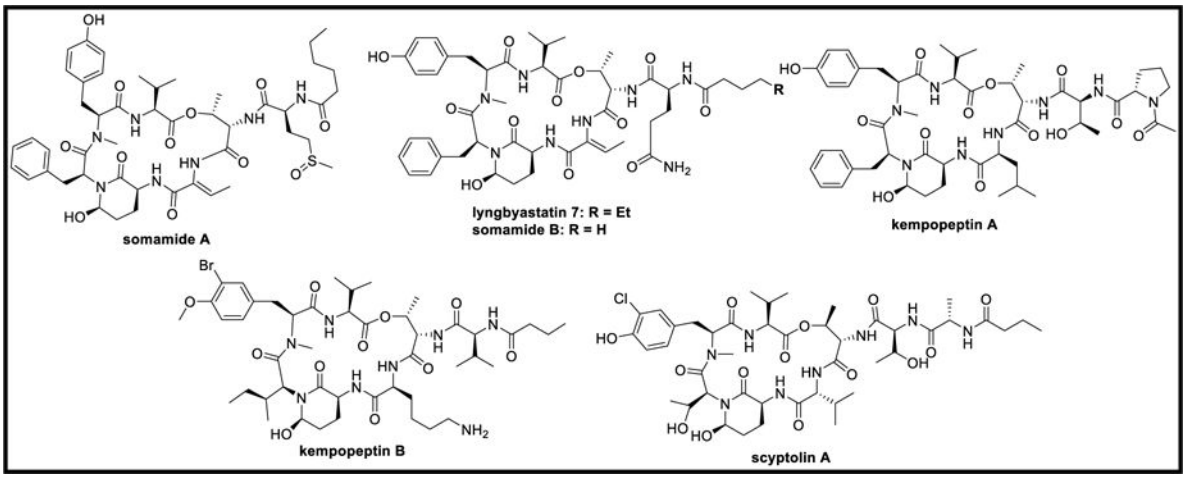


Figure 71.

Chemical structures of somamides A-B, lyngbyastatin 7, kempopeptins A-B, and scyptolin A

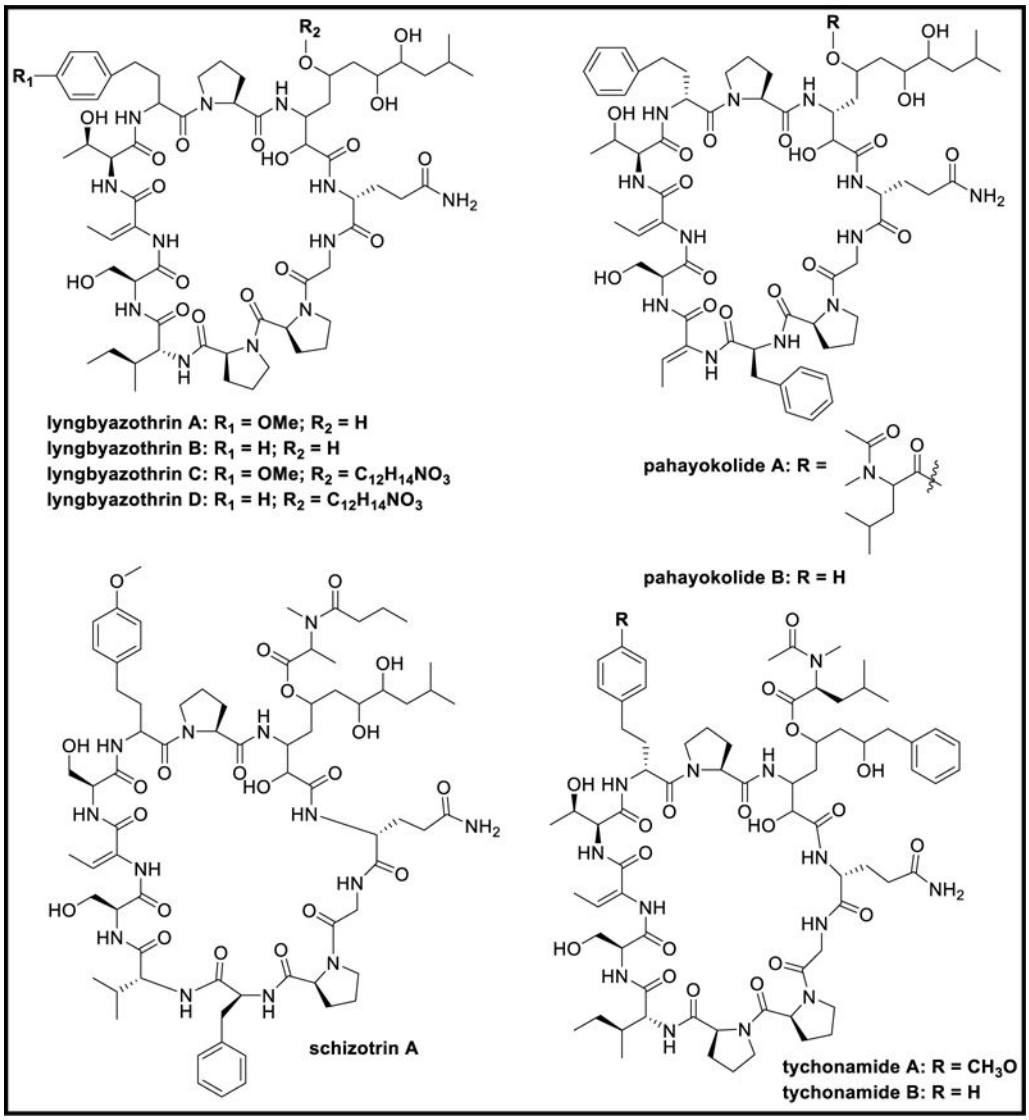


Figure 72.
Chemical structures of lyngbyazothrins A-D, pahayokolides A-B, schizotrin A, and tychonamides A-B

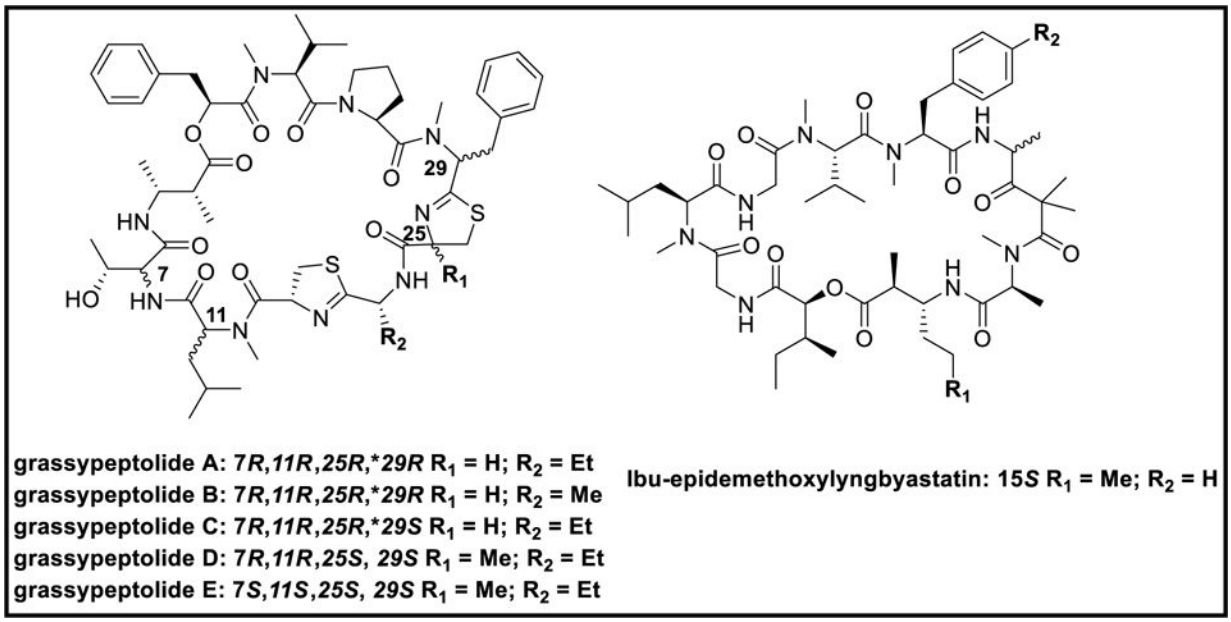


Figure 73.
Chemical structures of grassypeptolides A-E and ibu-epidemethoxylyngbyastatin

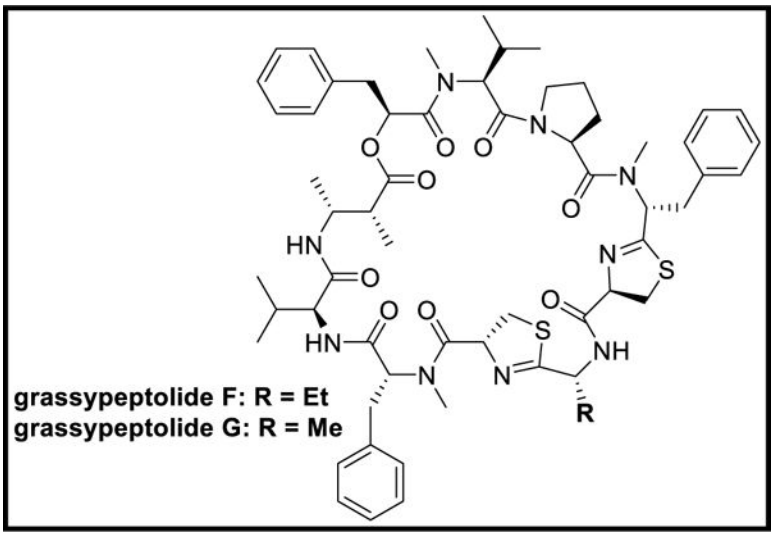


Figure 74.
Chemical structures of grassypeptolides F-G

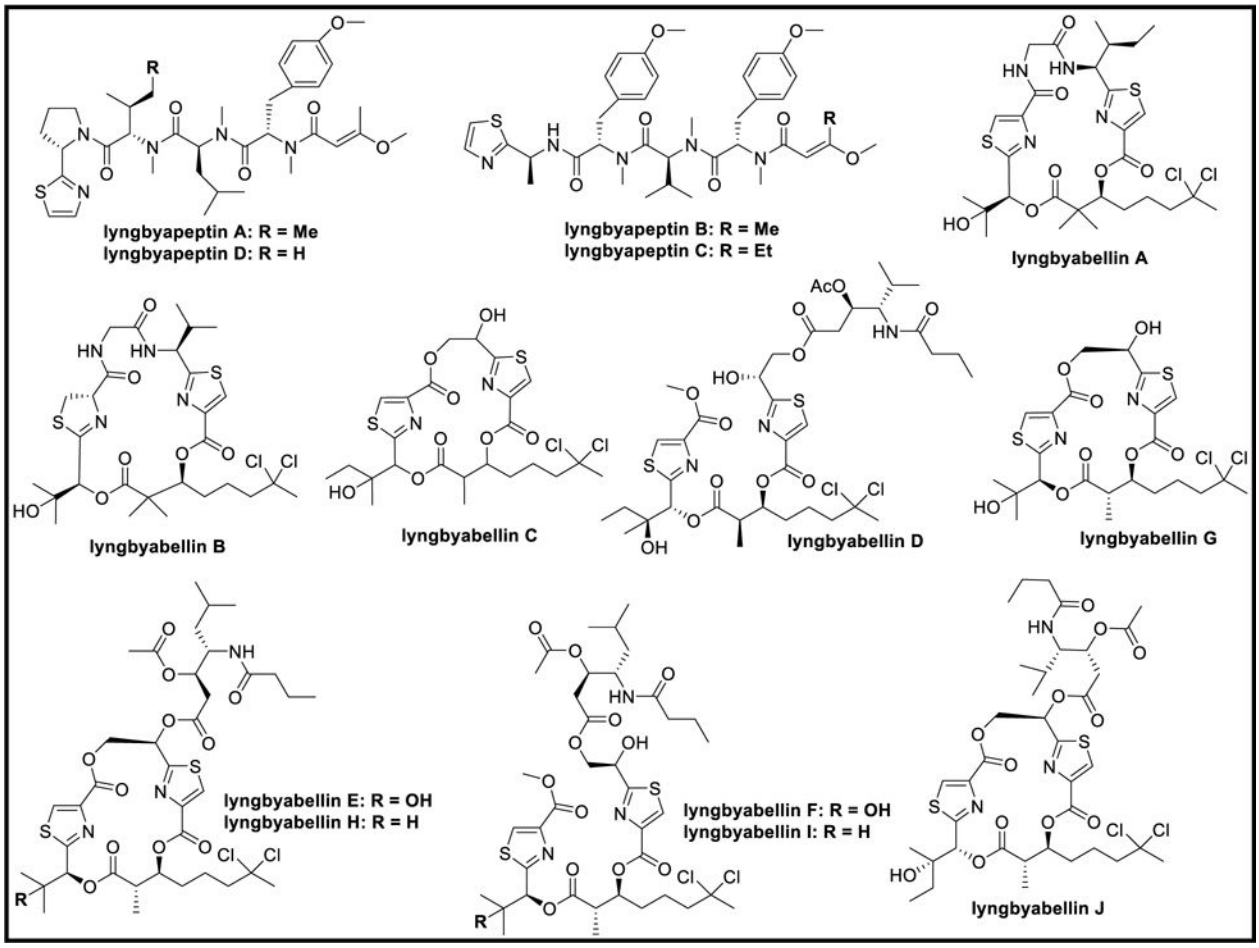


Figure 75.
Chemical structures of lyngbyapeptins A-D and lyngbyabellins A-J

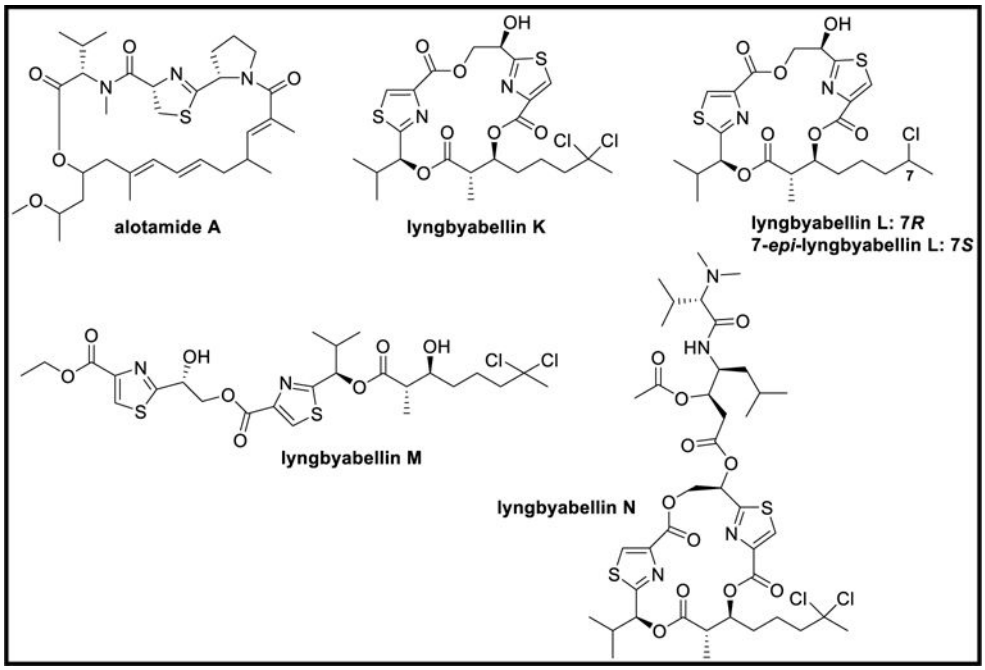


Figure 76.
Chemical structures of alotamide A, lyngbyabellins K-N, and 7-*epi*-lyngbyabellin L

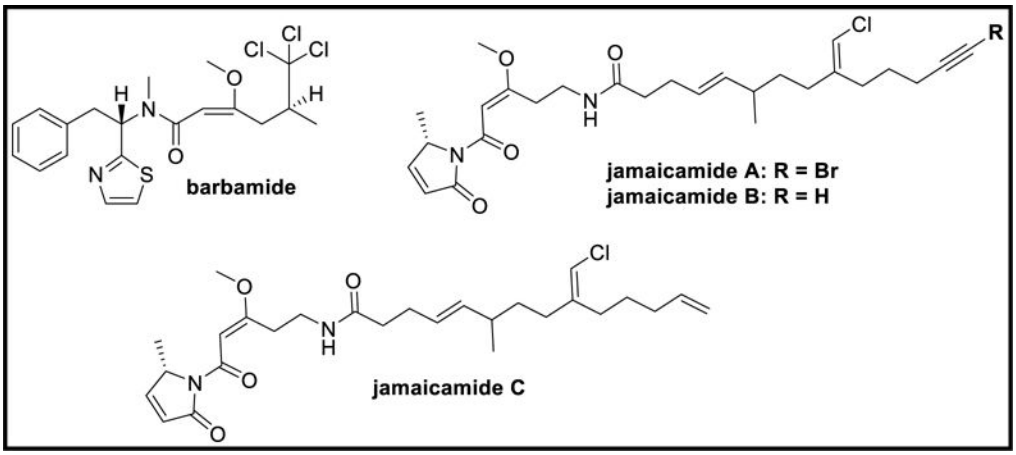


Figure 77.
Chemical structures of barbamide and jamaicamides A-C

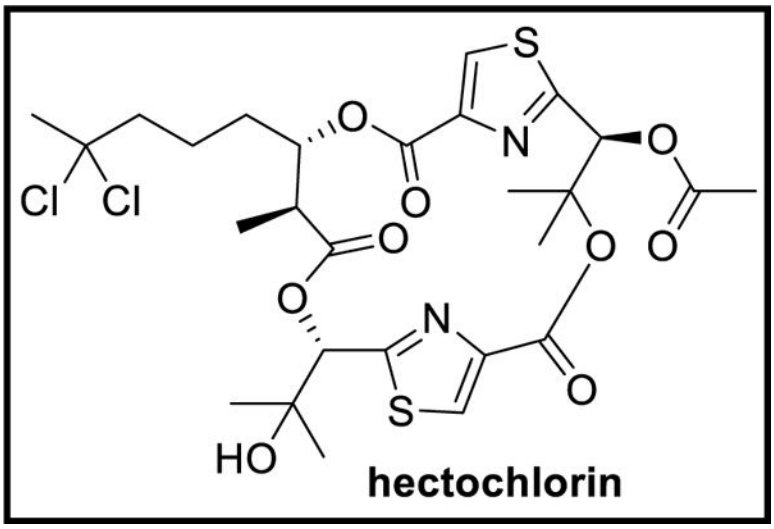


Figure 78.
Chemical structure of hectochlorin

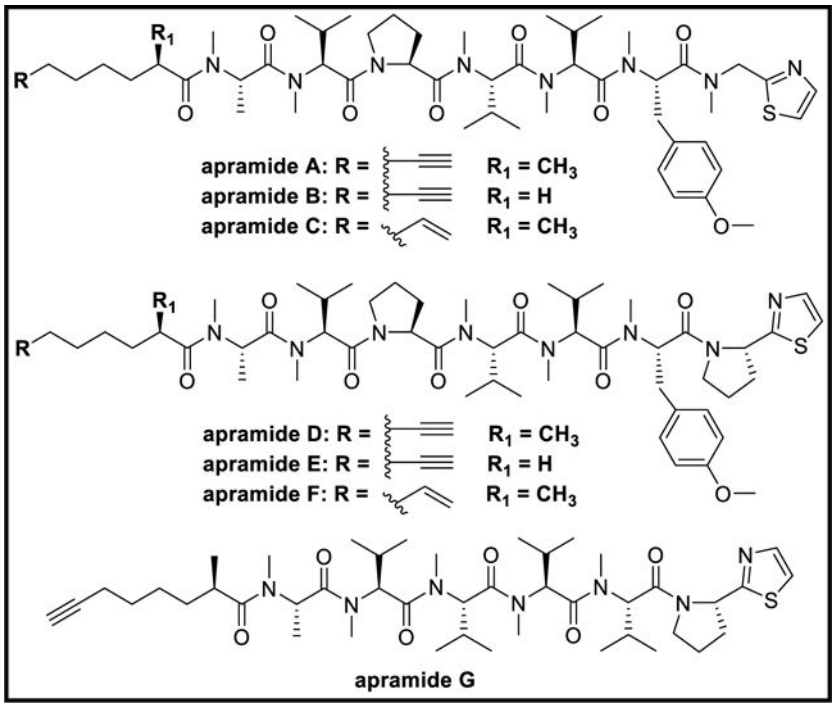


Figure 79.
Chemical structures of apramides A-G

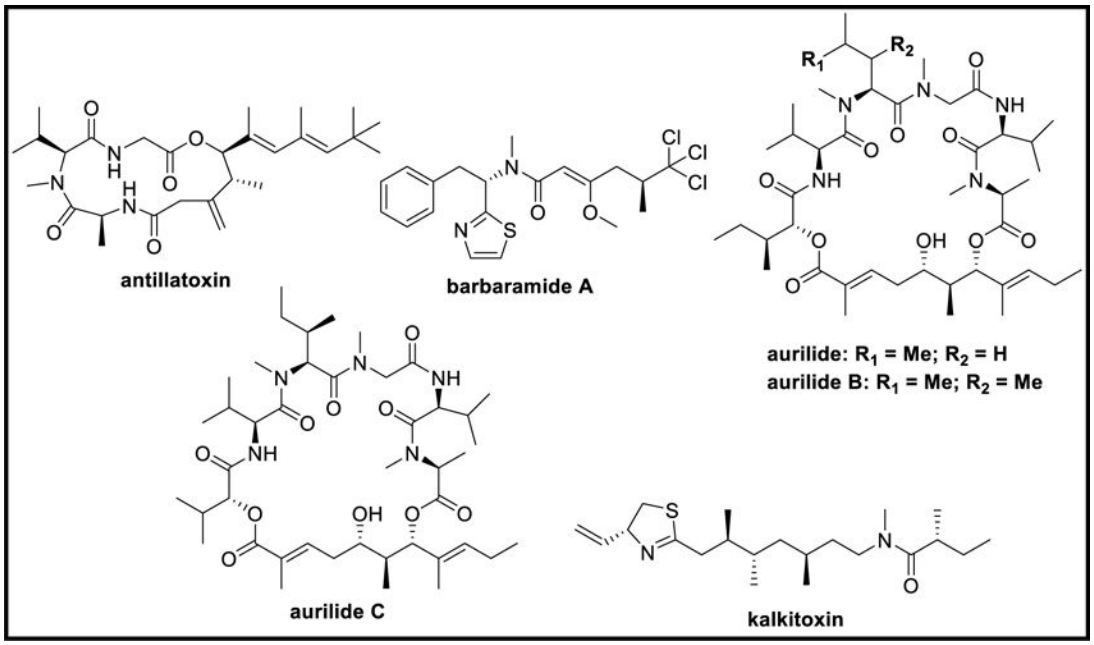


Figure 80.
Chemical structures of antillatoxin, barbaramide A, aurilide, aurilides B-C, and kalkitoxin

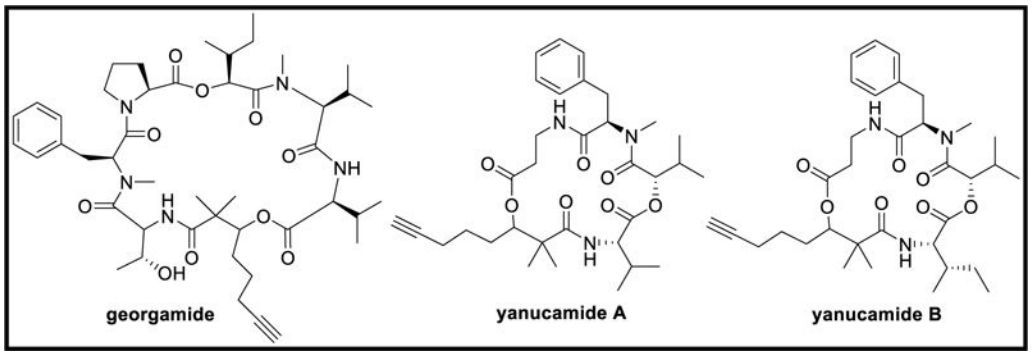


Figure 81.
Chemical structures of georgamide and yanucamides A-B

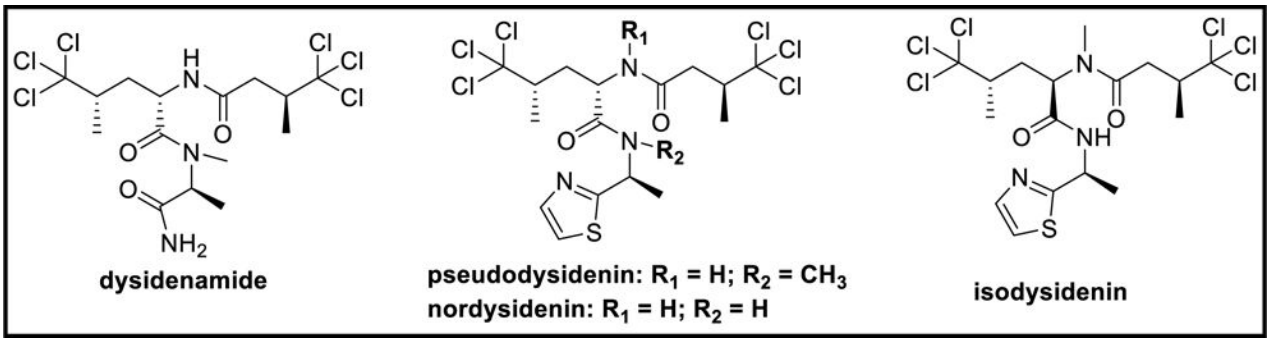


Figure 82.
Chemical structures of dysidenamide, pseudodysidenin, nordysidenin, and isodysidenin

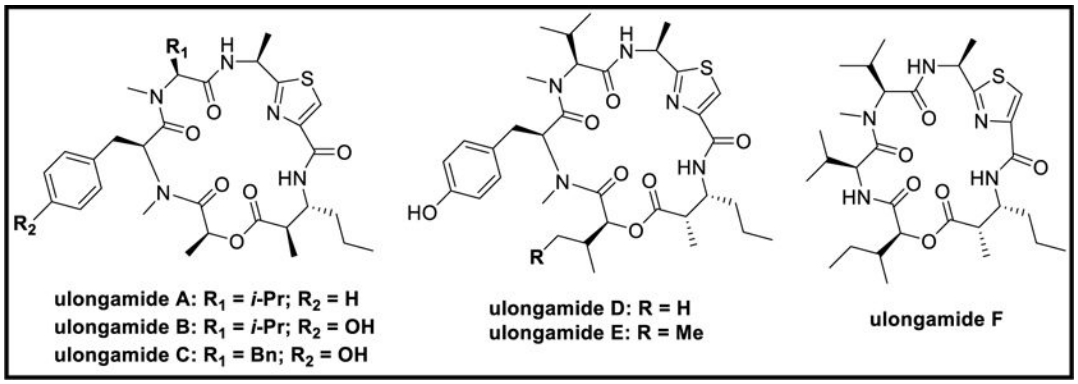


Figure 83.
Chemical structures of ulongamides A-F

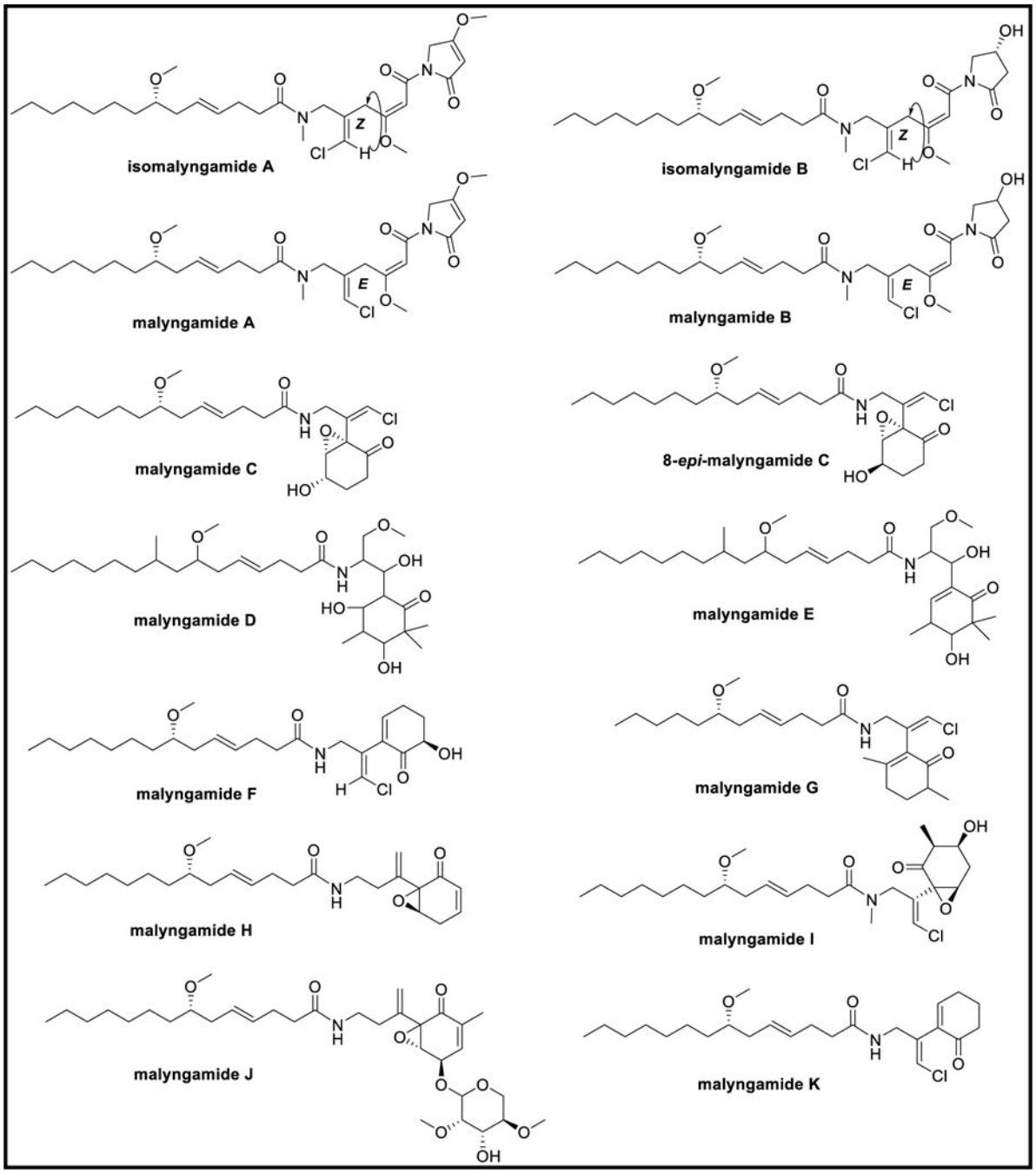


Figure 84.
Chemical structures of isomalyngamides A-B, malyngamides A-K, and 8-*epi*-malyngamide C

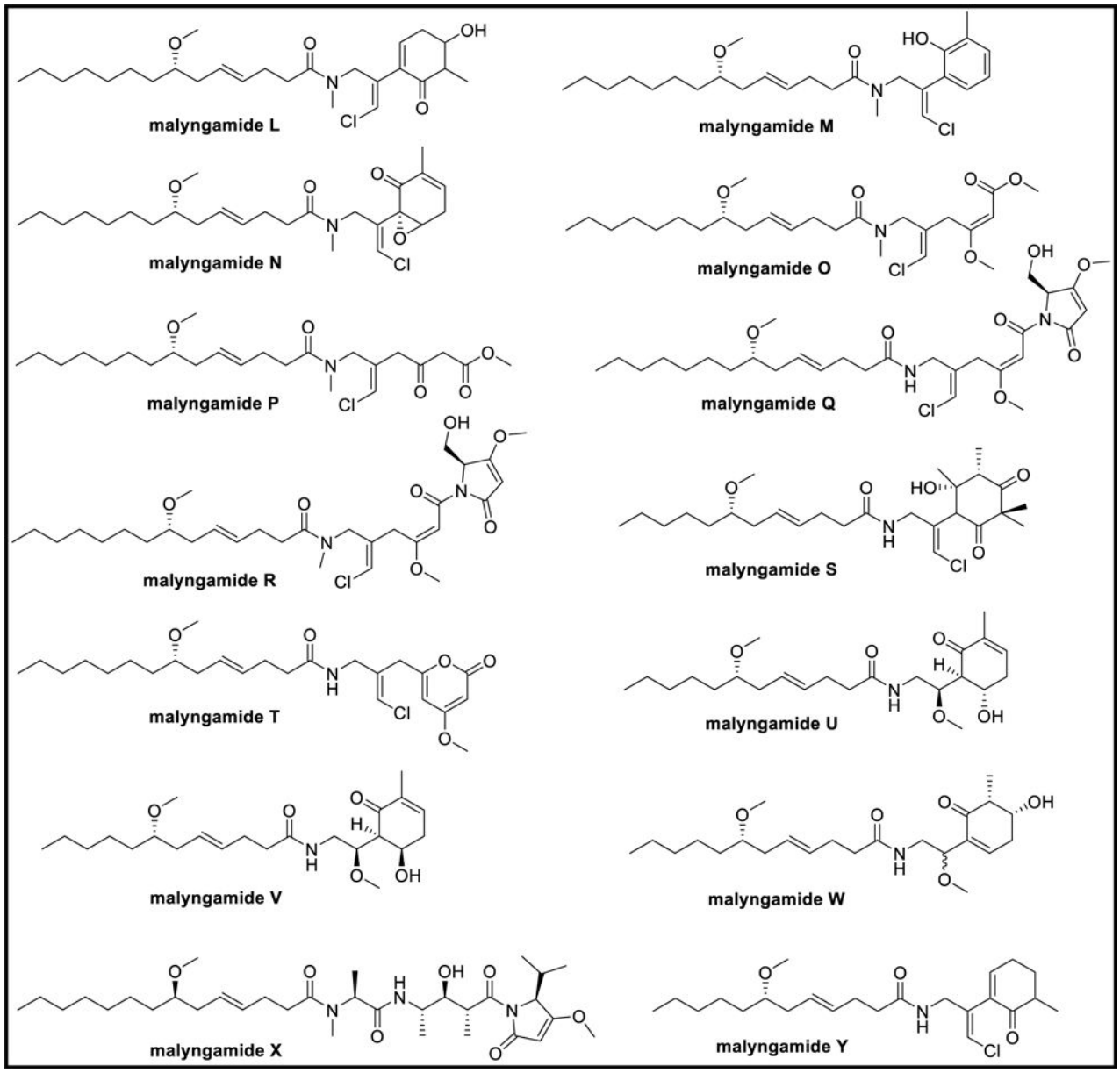


Figure 85.
Chemical structures of malyngamides L-Y

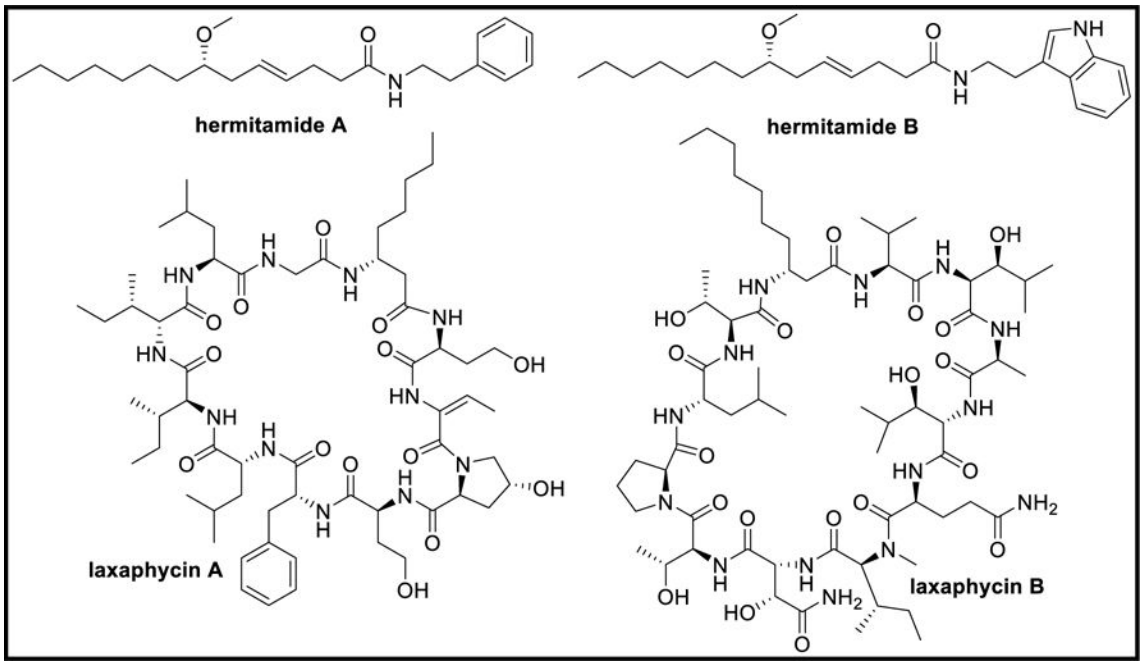


Figure 86.
Chemical structures of hermitamides A-B and laxaphycins A-B

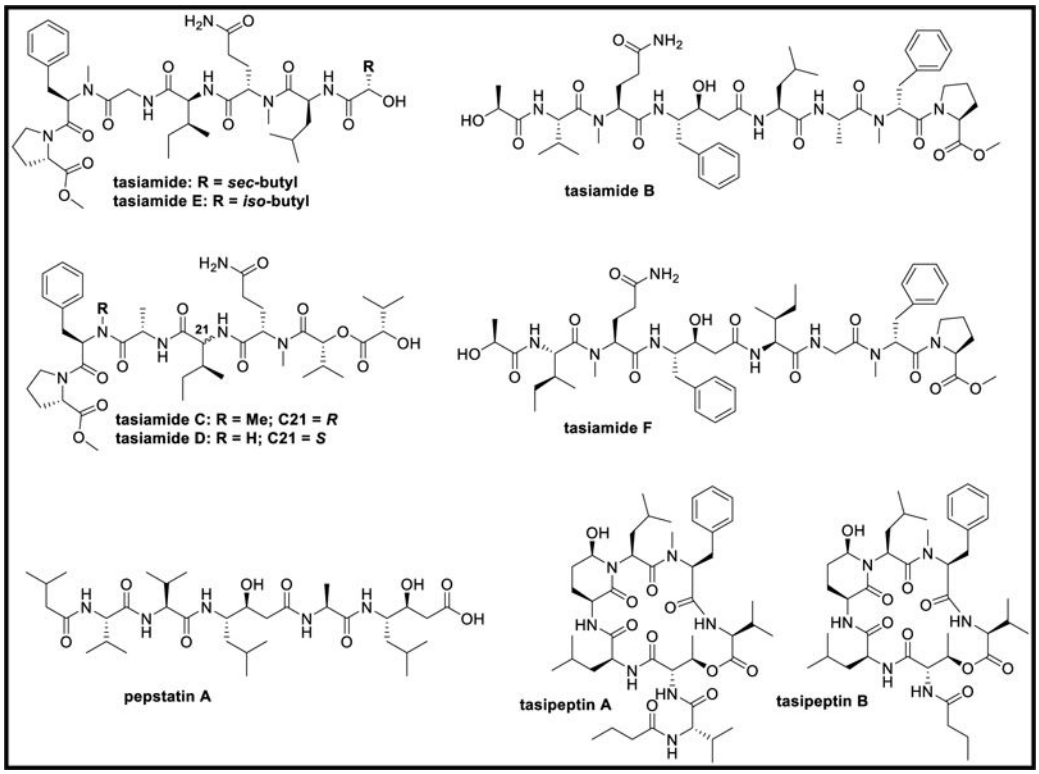


Figure 87.
Chemical structures of tasiamide, tasiamides B-F, pepstatin A, and tasipeptins A-B

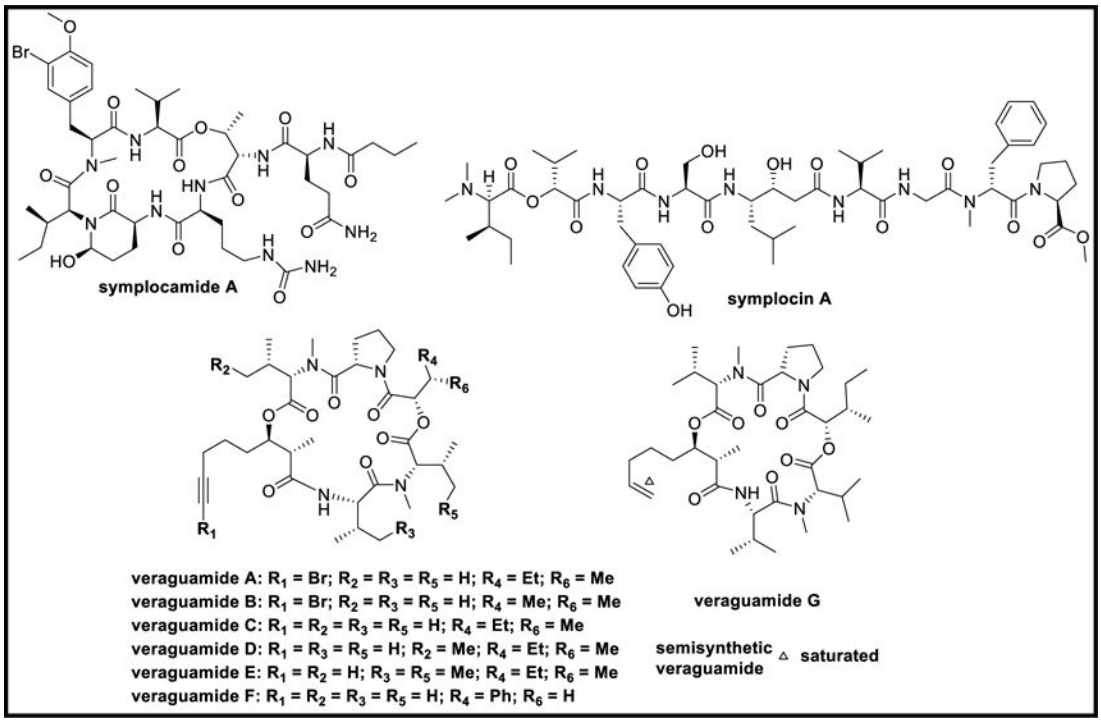


Figure 88.

Chemical structures of symplocamide A, symplocin A, veraguamides A-G, and semisynthetic veraguamide

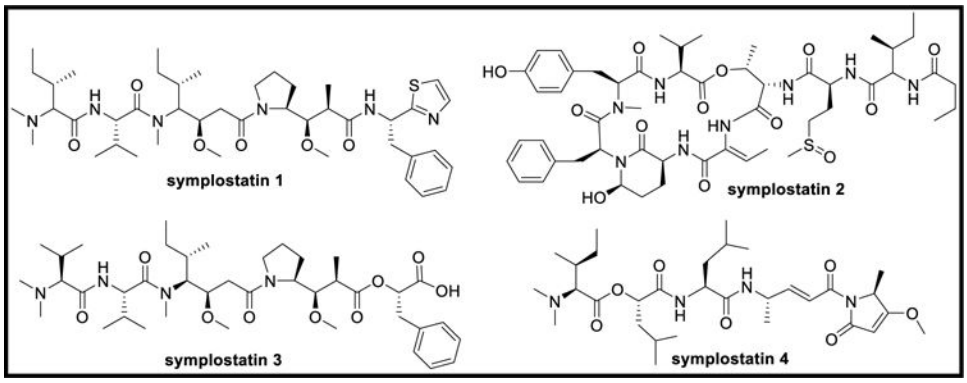


Figure 89.
Chemical structures of symplostatins 1–4

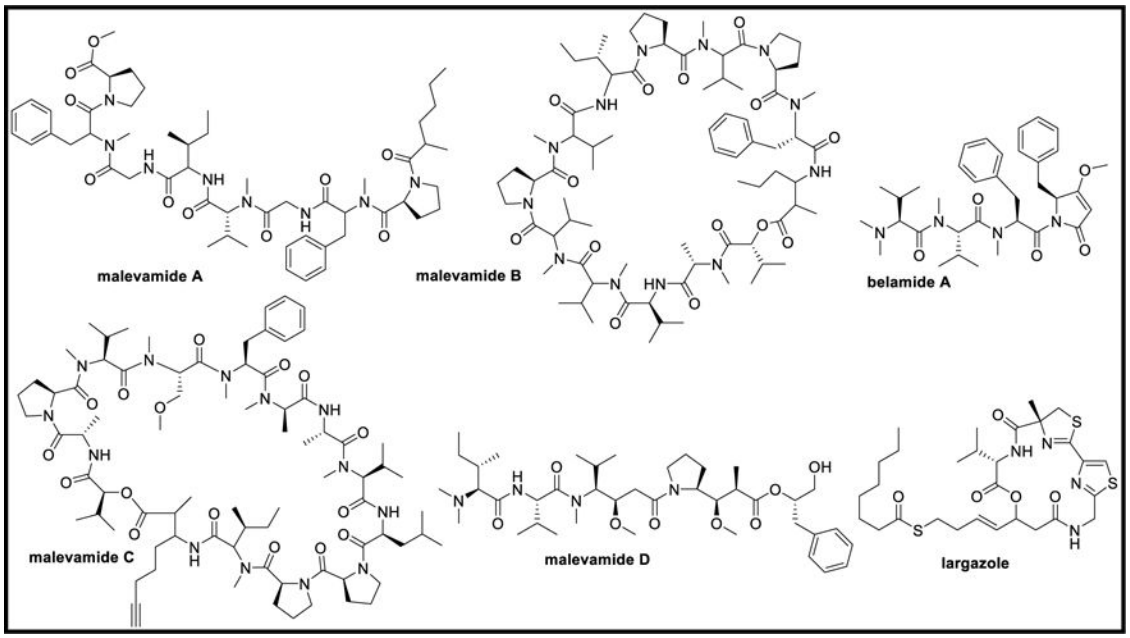


Figure 90.
Chemical structures of malevamides A-D, belamide A, and largazole

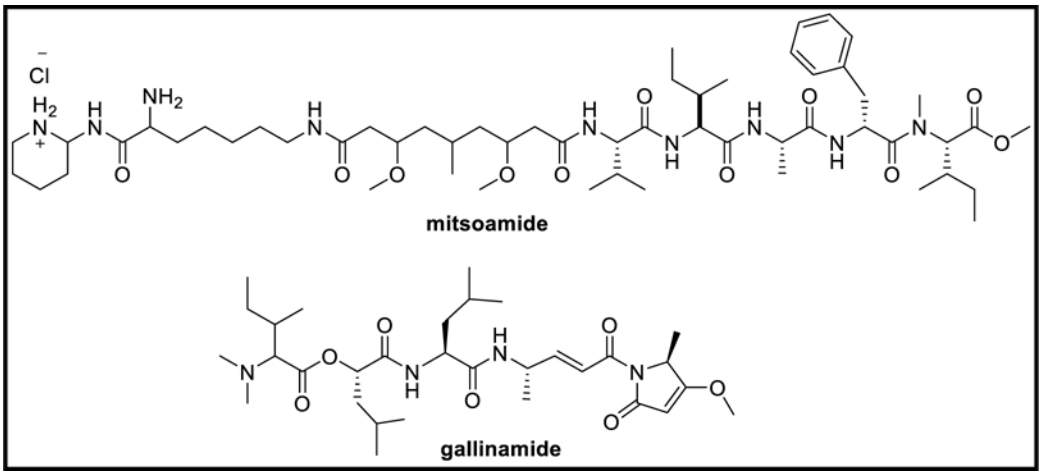


Figure 91.
Chemical structures of mitsoamide and gallinamide

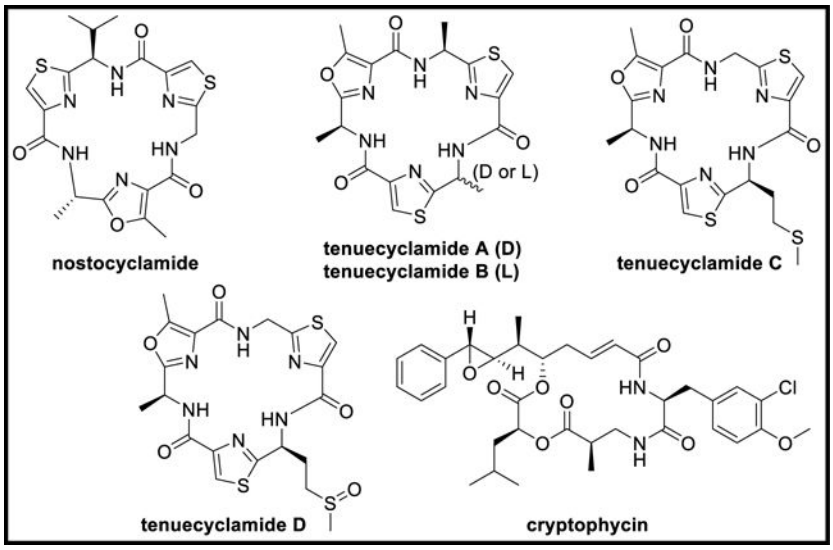


Figure 92.
Chemical structures of nostocyclamide, tenuecyclamides A-D, and cryptophycin

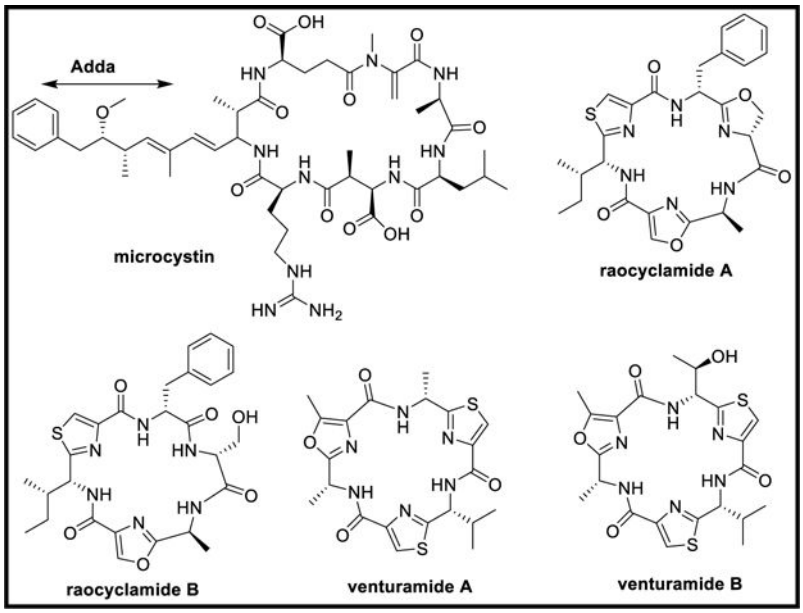


Figure 93.
Chemical structures of microcystin, raocyclamides A-B, and venturamides A-B

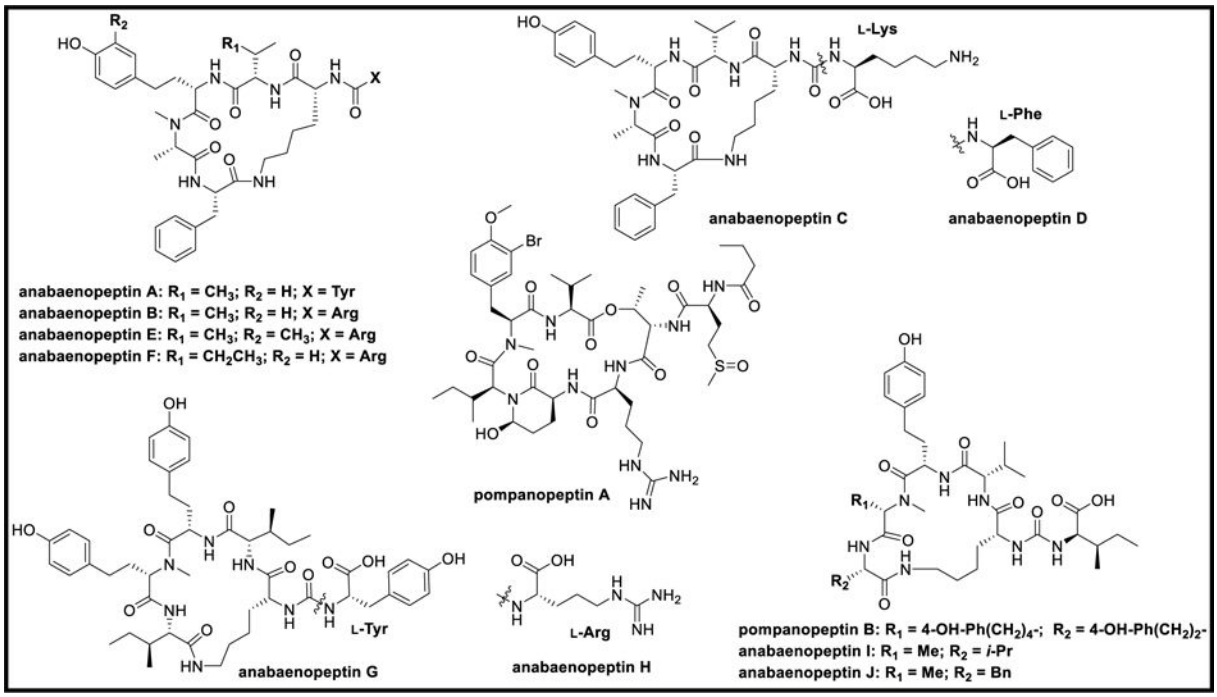


Figure 94.
Chemical structures of anabaenopeptins A-J and pompanopeptins A-B

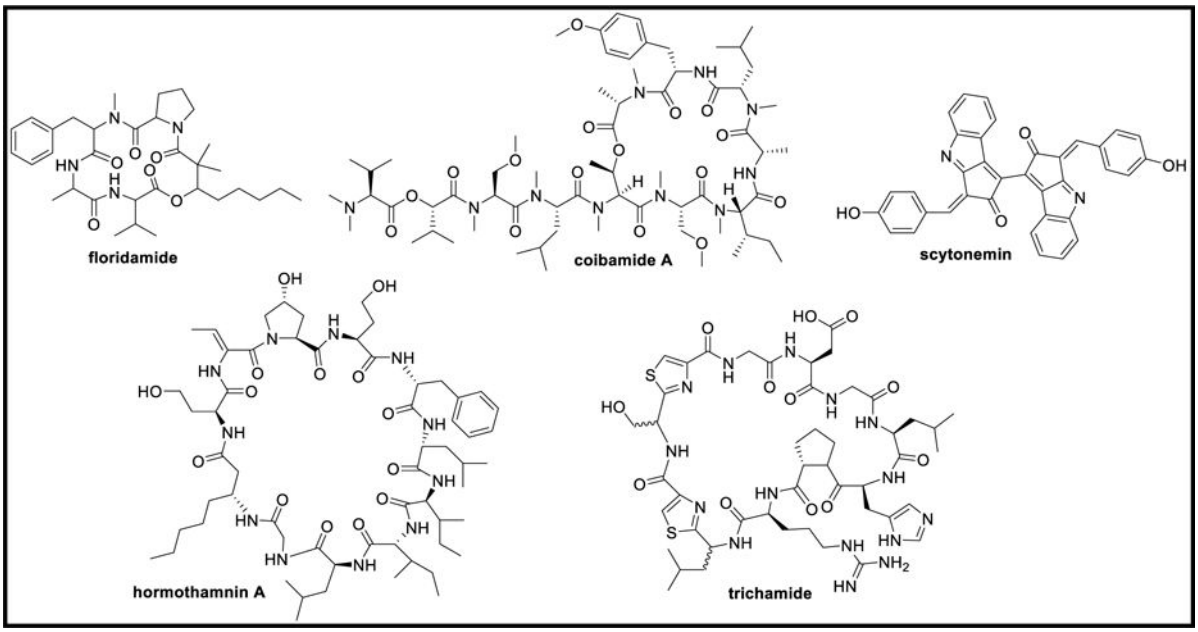


Figure 95.
Chemical structures of floridamide, coibamide A, scytonemin, hormothamnin A, and trichamide,

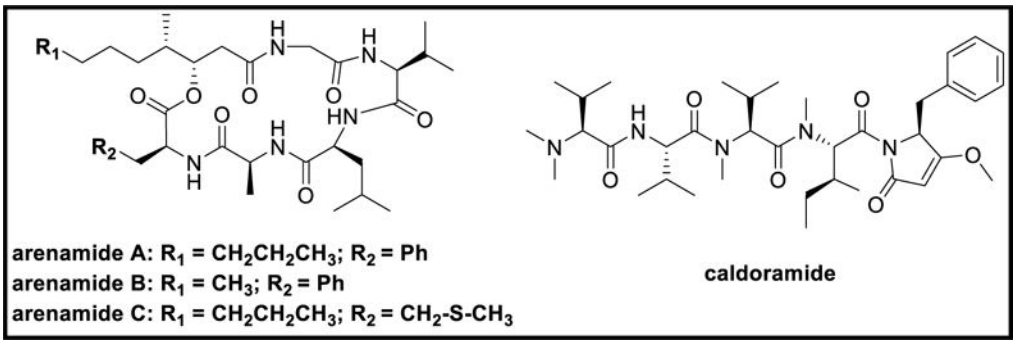


Figure 96.
Chemical structures of arenamides A-C and caldoramide

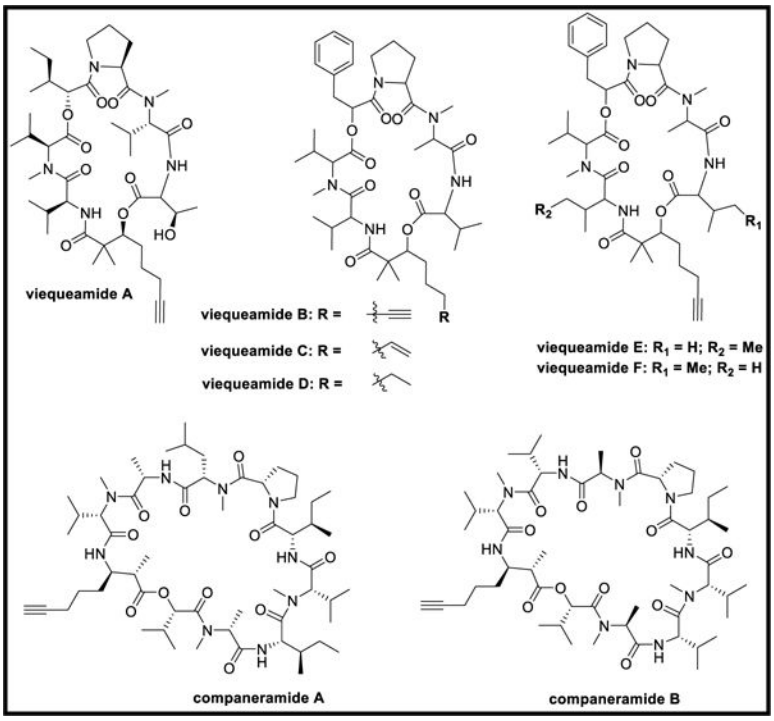


Figure 97.
Chemical structures of viequeamides A-F and companeramides A-B

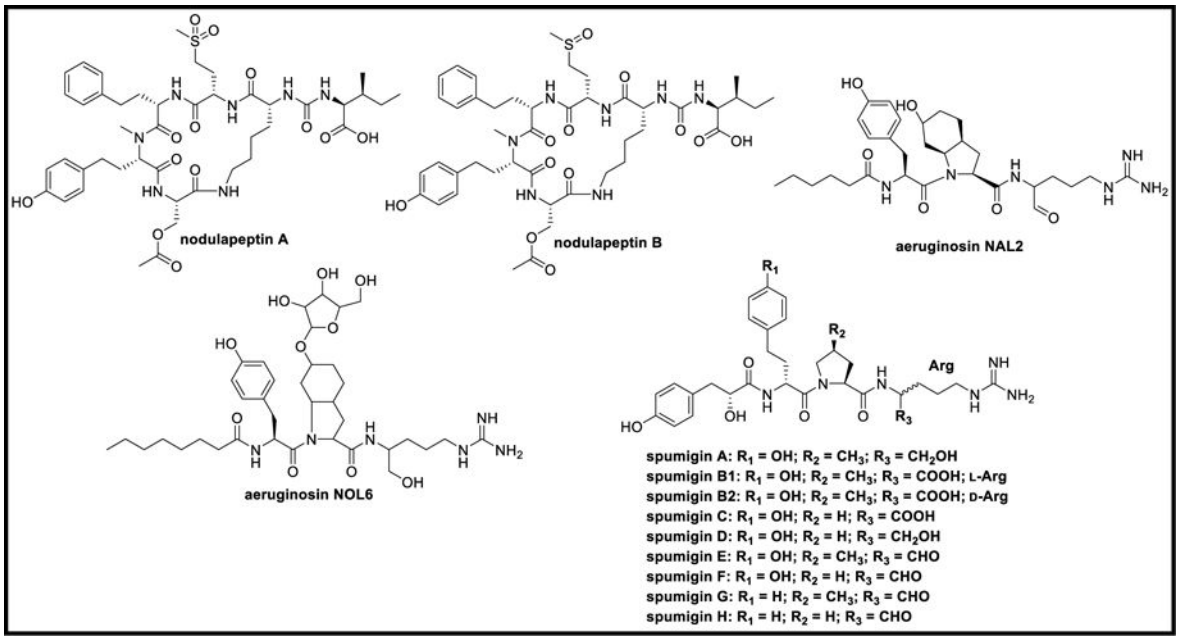


Figure 98.

Chemical structures of nodulapeptins A-B, aeruginosins NAL2, NOL6, spumigins A, C-H, and spumigins B1-B2

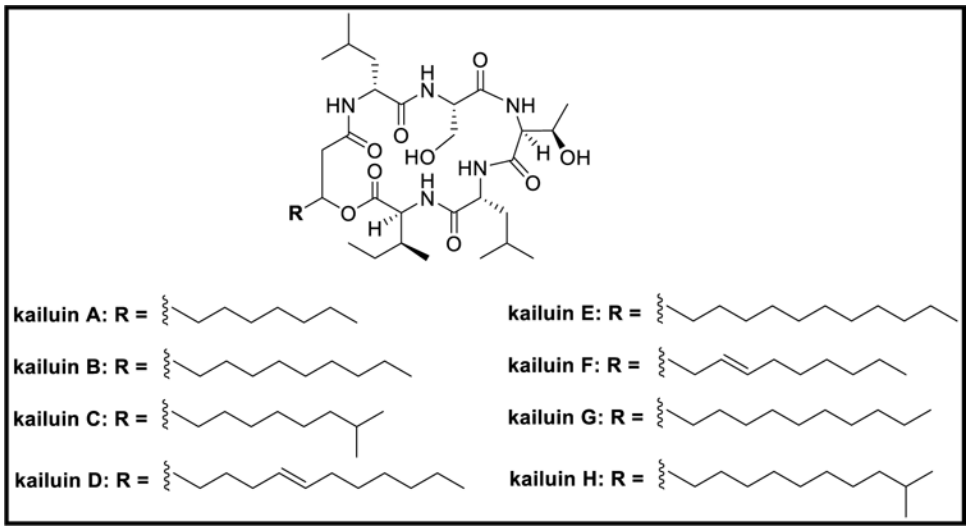


Figure 99.
Chemical structures of kailuins A-H

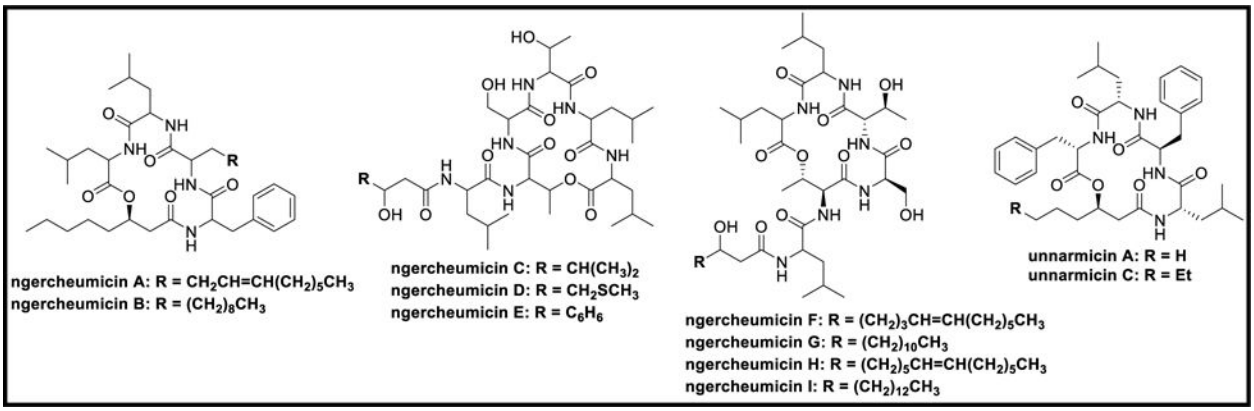


Figure 100.
Chemical structures of ngercheumicins A-I, unnarmicins A and C

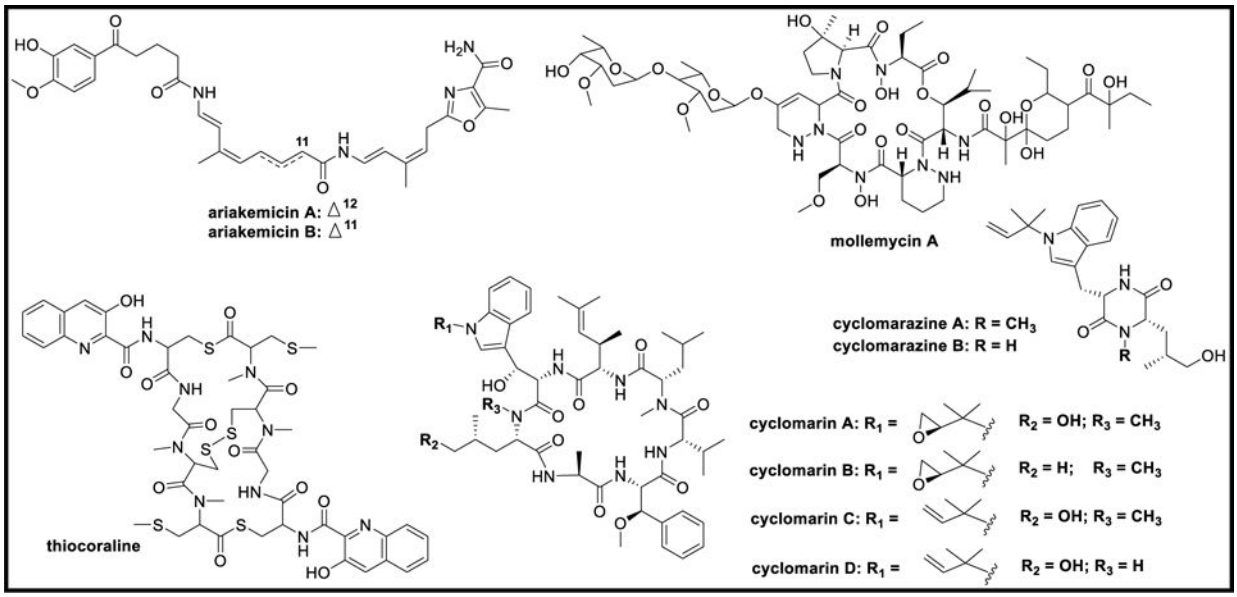


Figure 101.

Chemical structures of ariakemicins A-B, mollemycin A, thiocoraline, cyclomarins A-D, and cyclomarazines A-B

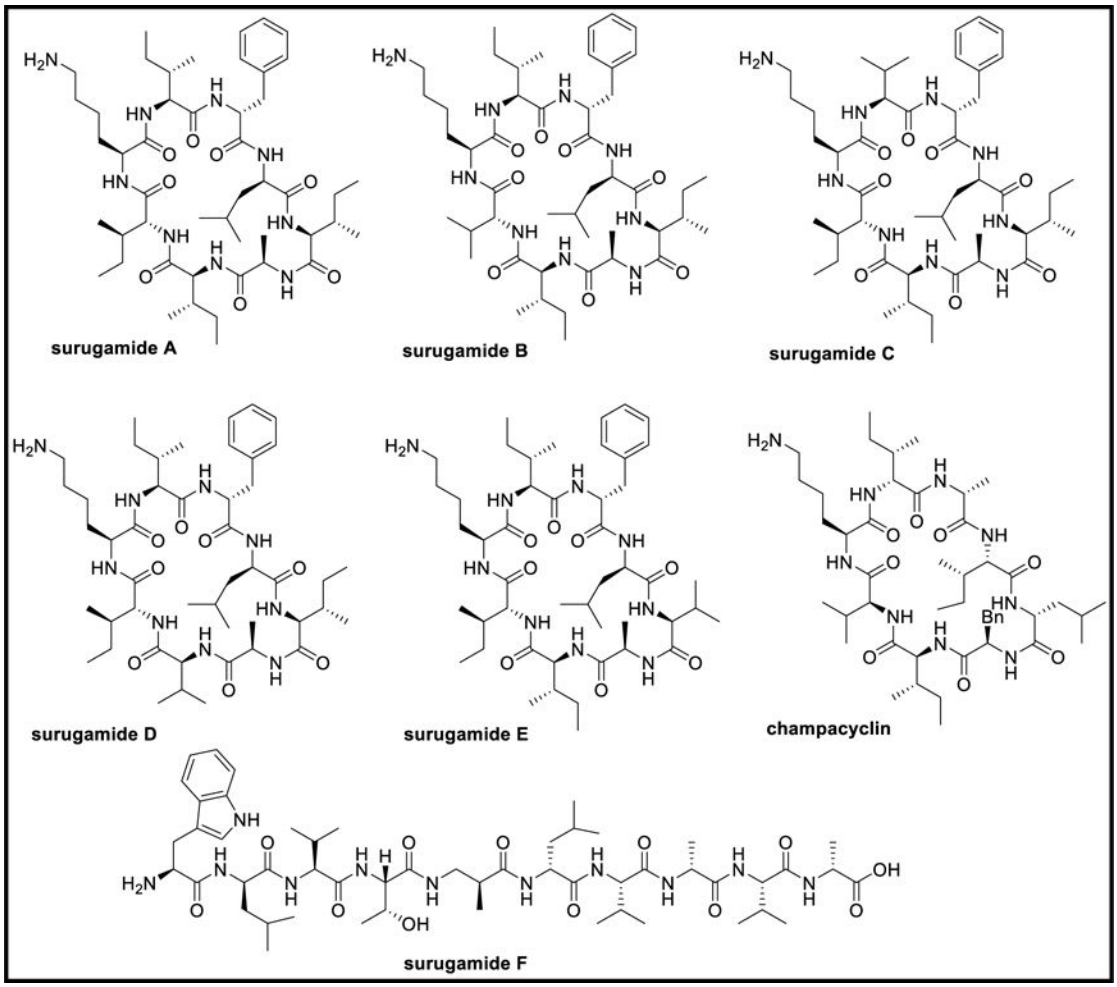


Figure 102.
Chemical structures of surugamides A-F and champacyclin

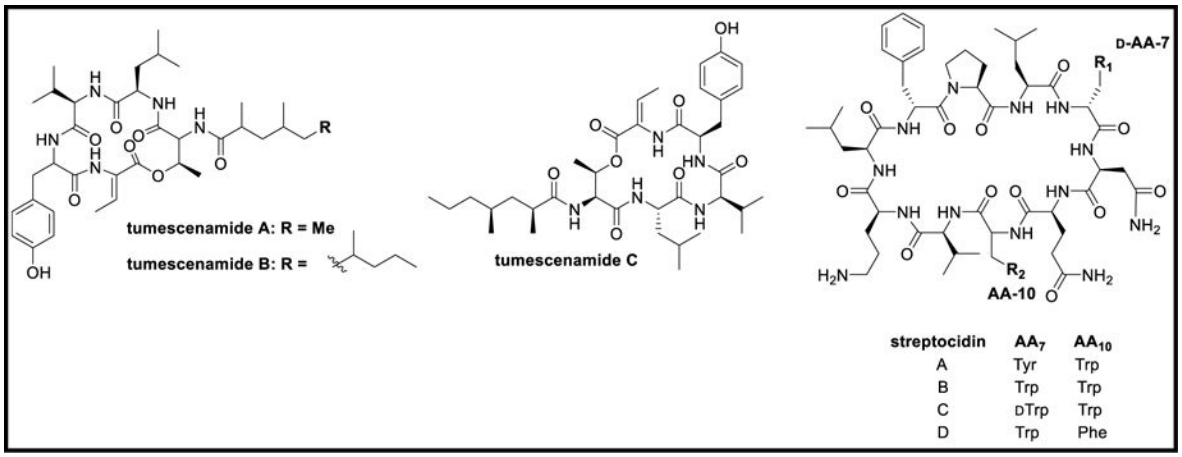


Figure 103.
Chemical structures of tumescenamides A-C and streptocidins A-D

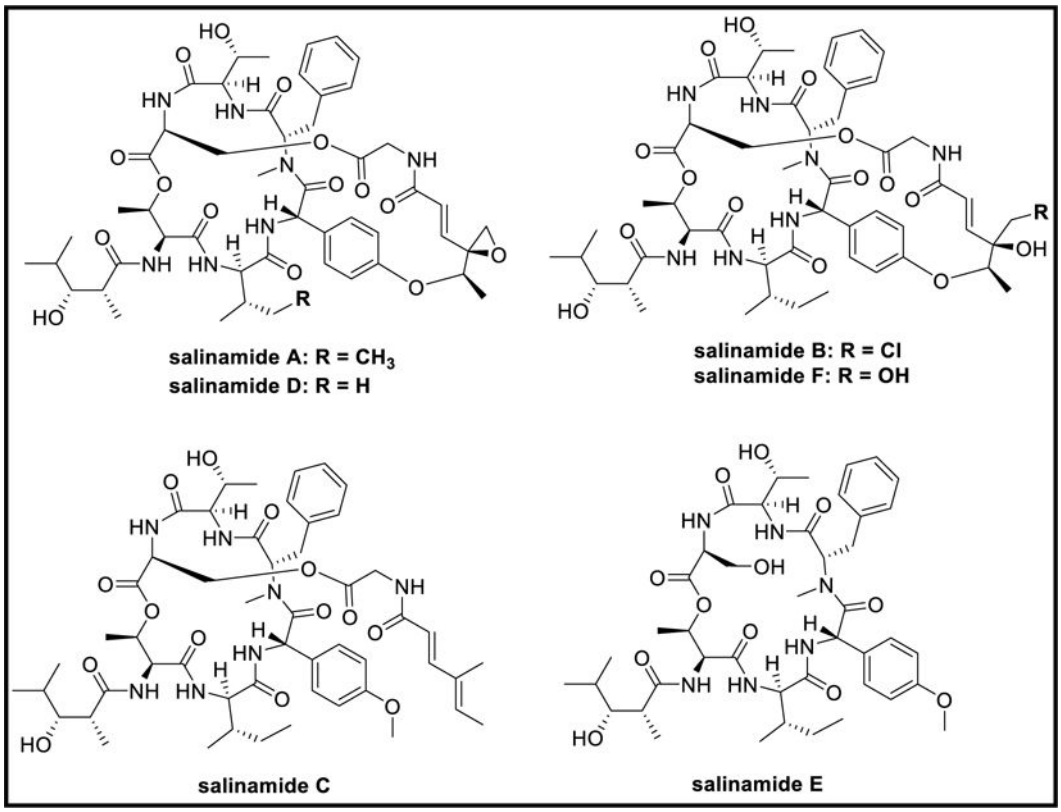


Figure 104.
Chemical structures of salinamides A-F

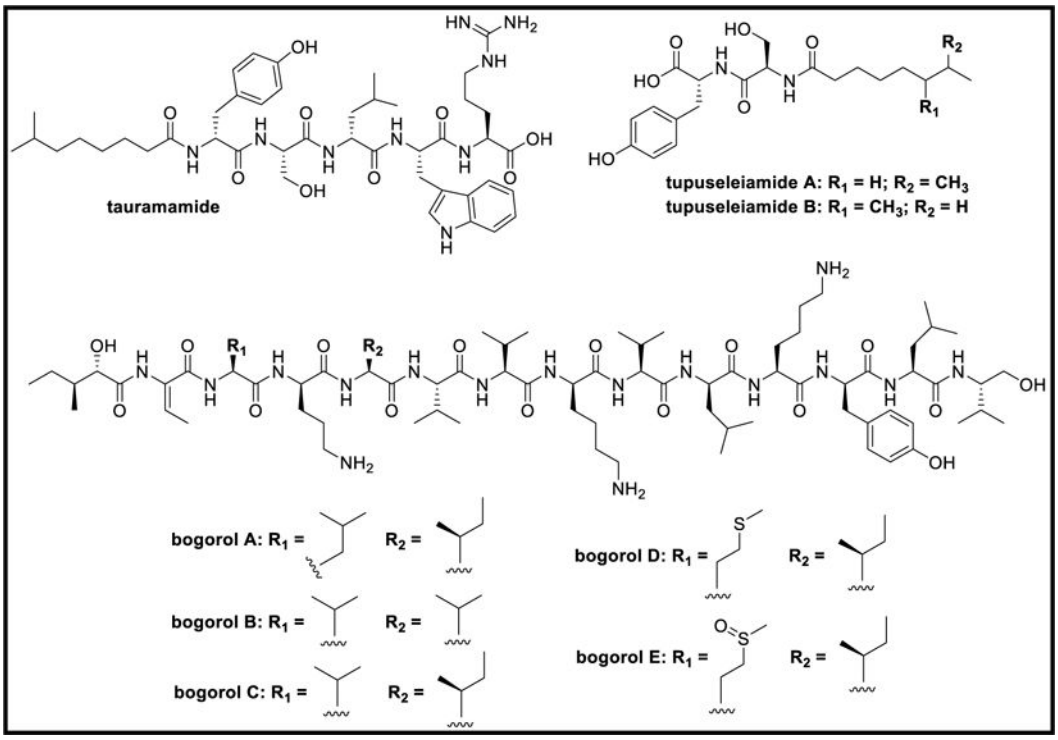


Figure 105.
Chemical structures of tauramamide, tupuseleiamides A-B, and bogorols A-E

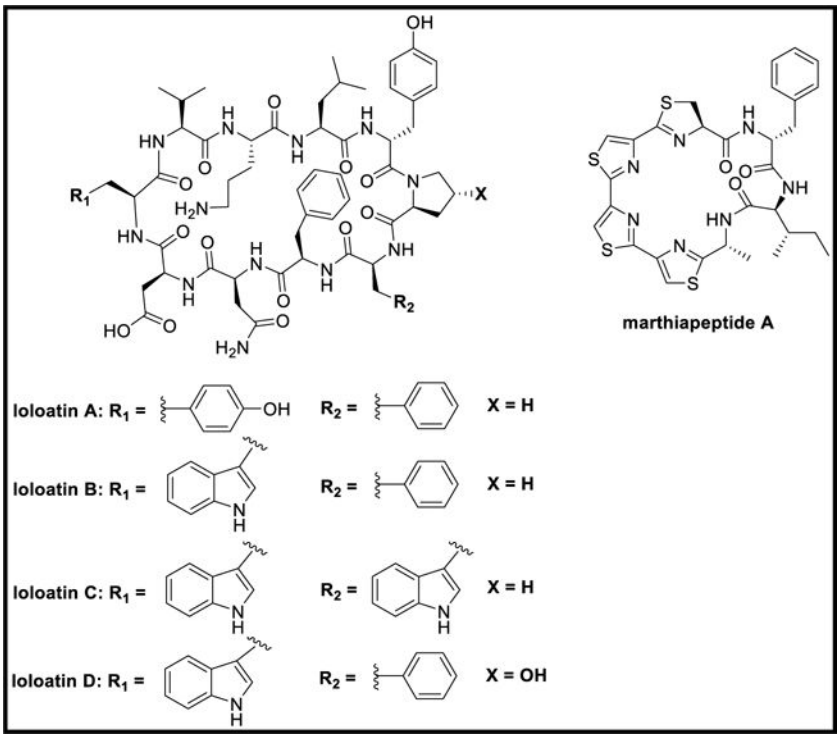


Figure 106.
Chemical structures of loloatins A-D and marthiapeptide A

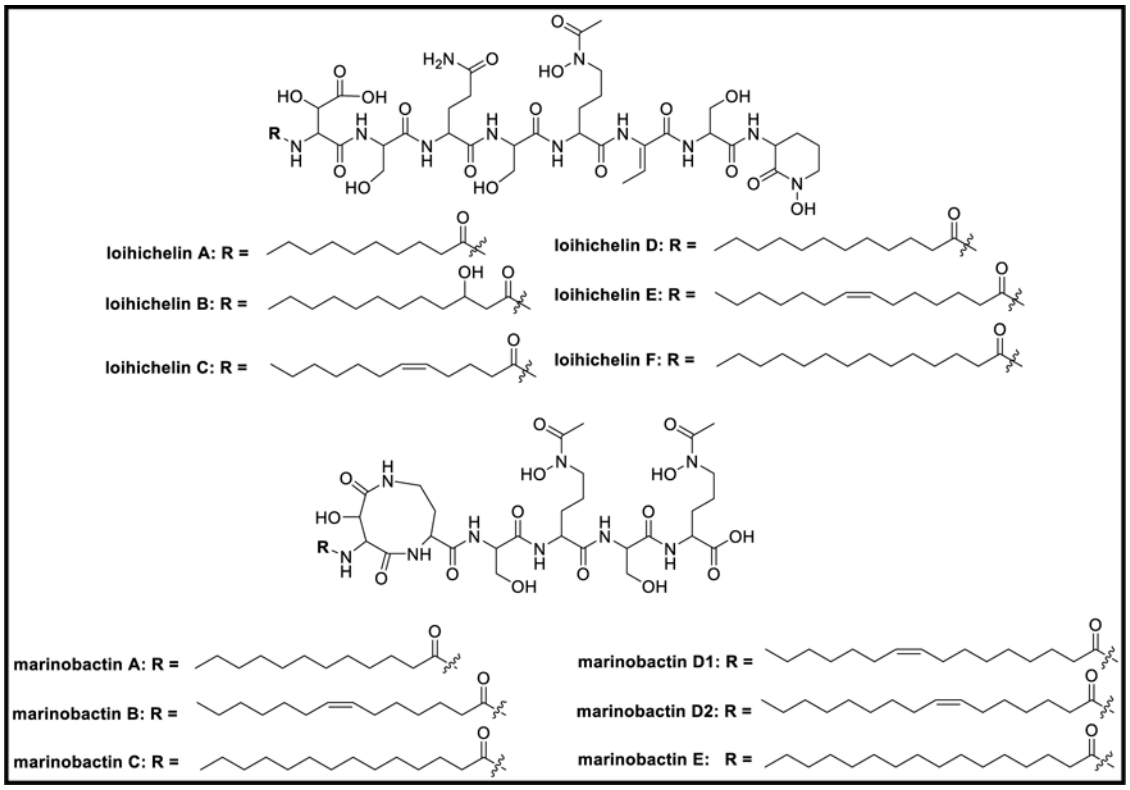


Figure 107.
Chemical structures of loihichelins A-F, marinobactins A-C, D1, D2, and E

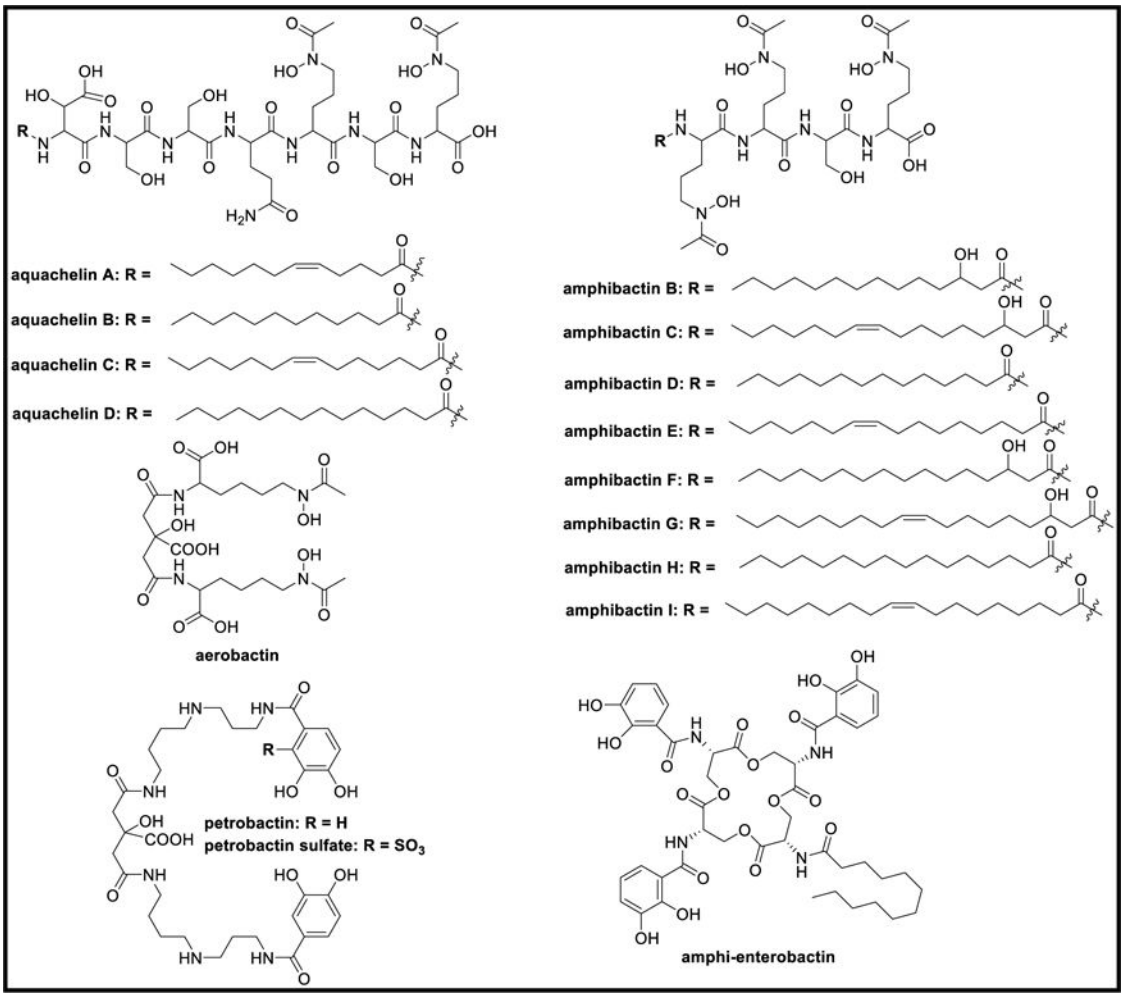


Figure 108.

Chemical structures of aquachelins A-D, amphibactins B-I, petrobactin, petrobactin sulfate, aerobactin, and amphi-enterobactin

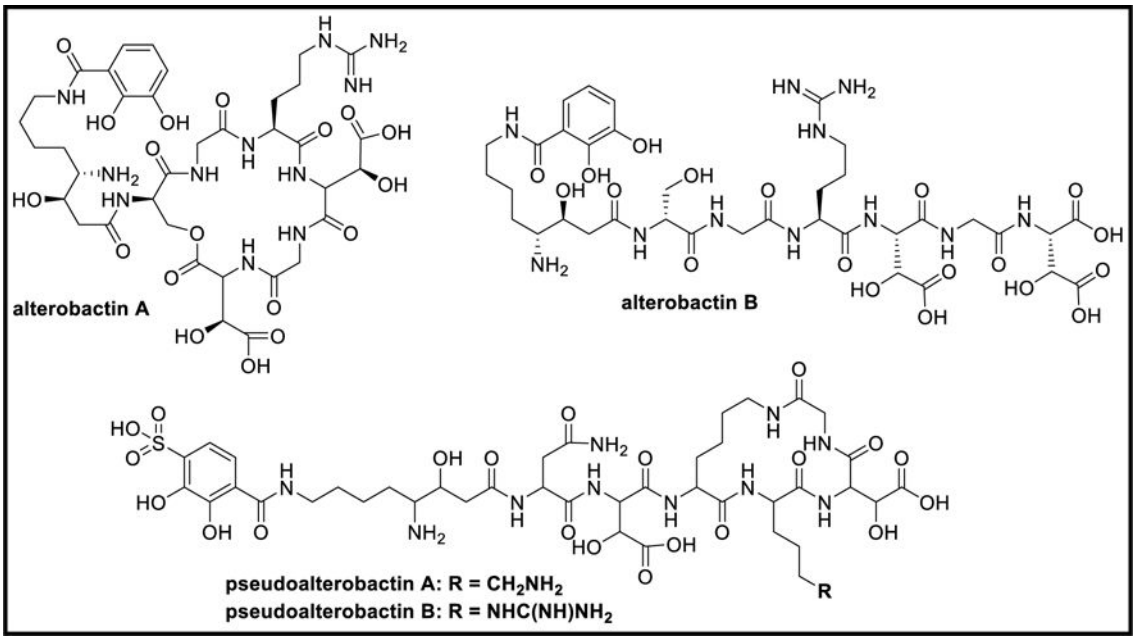


Figure 109.
Chemical structures of alterobactins A-B and pseudoalterobactins A-B

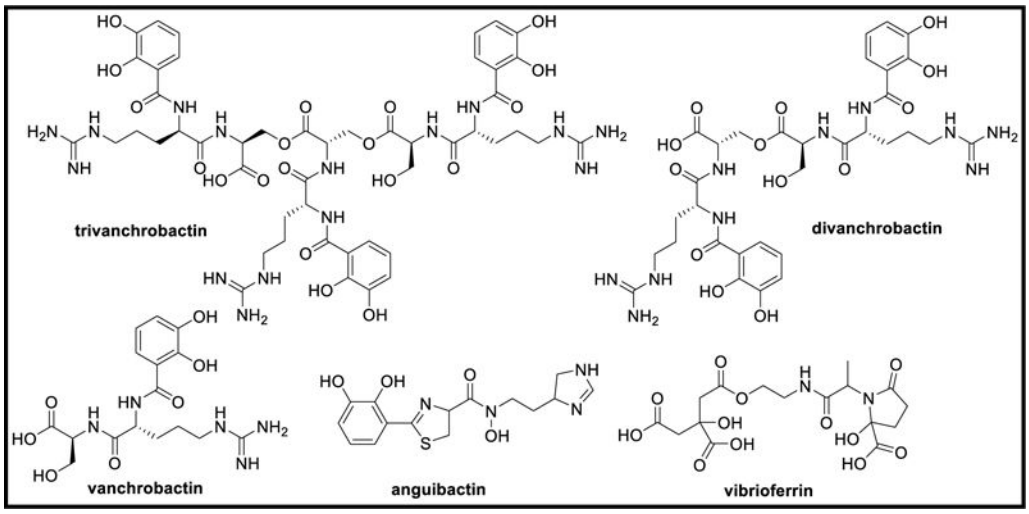


Figure 110.

Chemical structures of trivanchrobactin, divanchrobactin, vanchrobactin, anguibactin, and vibrioferrin

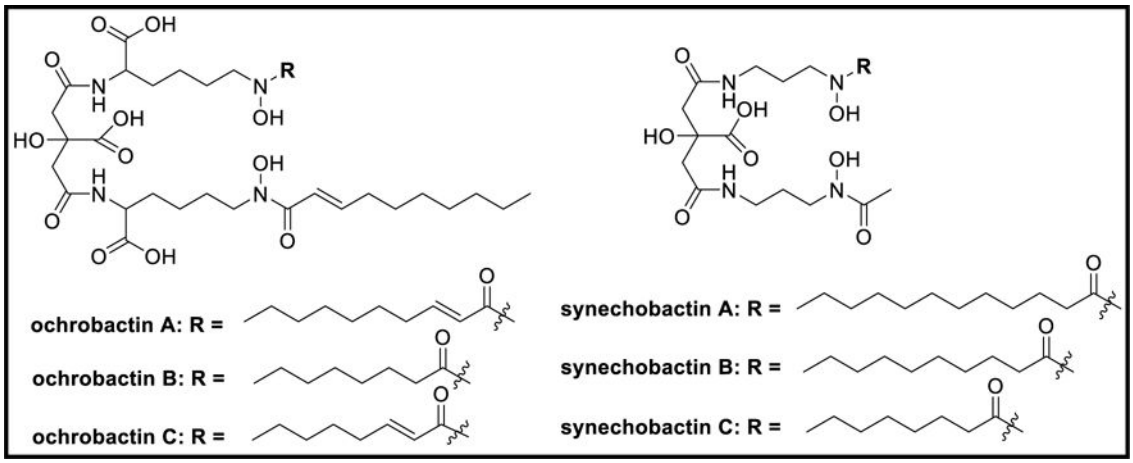


Figure 111.
Chemical structures of ochrobactins A-C and synechobactins A-C

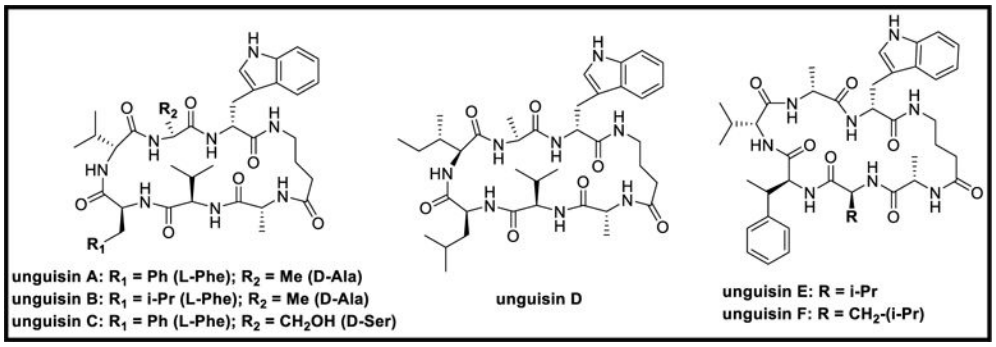


Figure 112.
Chemical structures of unguisins A-F

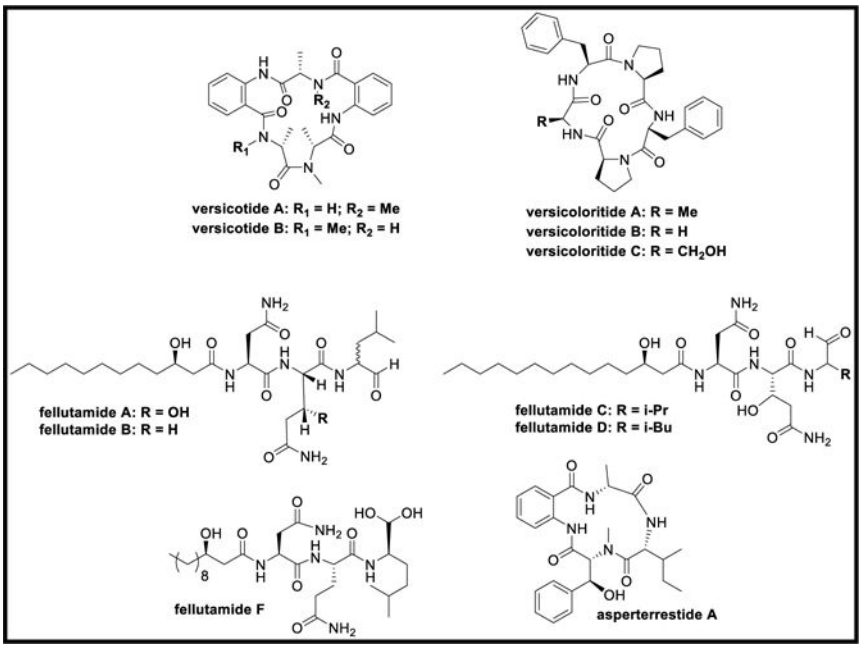


Figure 113.

Chemical structures of versicotides A-B, versicoloritides A-C, fellutamides A-D, F, and asperterrestide A

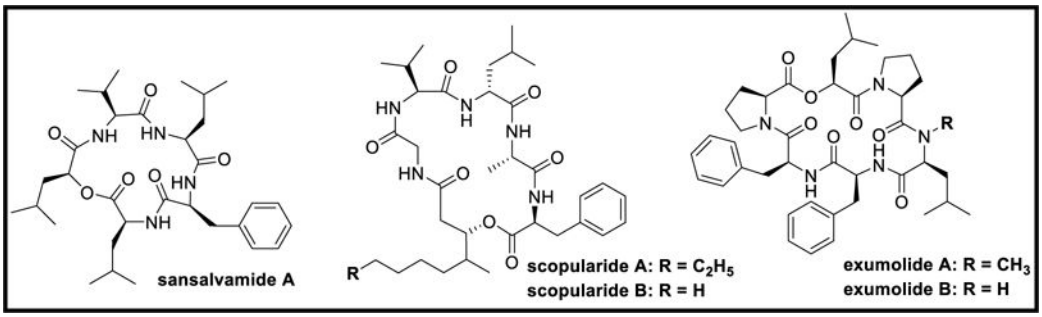


Figure 114.
Chemical structures of sansalvamide A, scopularides A-B, and exumolides A-B

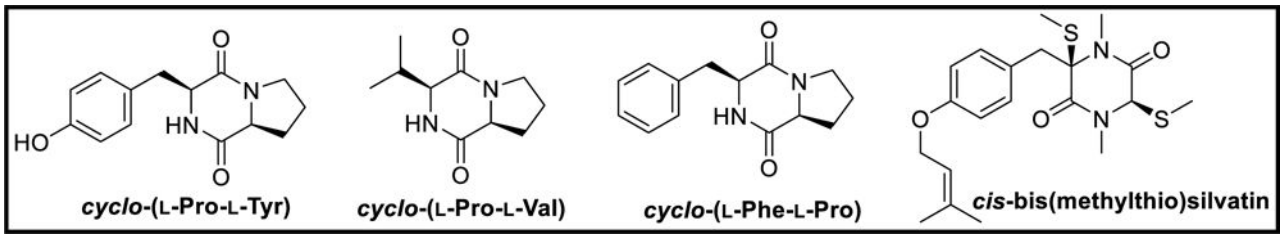


Figure 115.
Chemical structures of *cyclo*-(L-Pro-L-Tyr), *cyclo*-(L-Pro-L-Val), *cyclo*-(L-Phe-L-Pro), and *cis*-bis(methylthio)silvatin

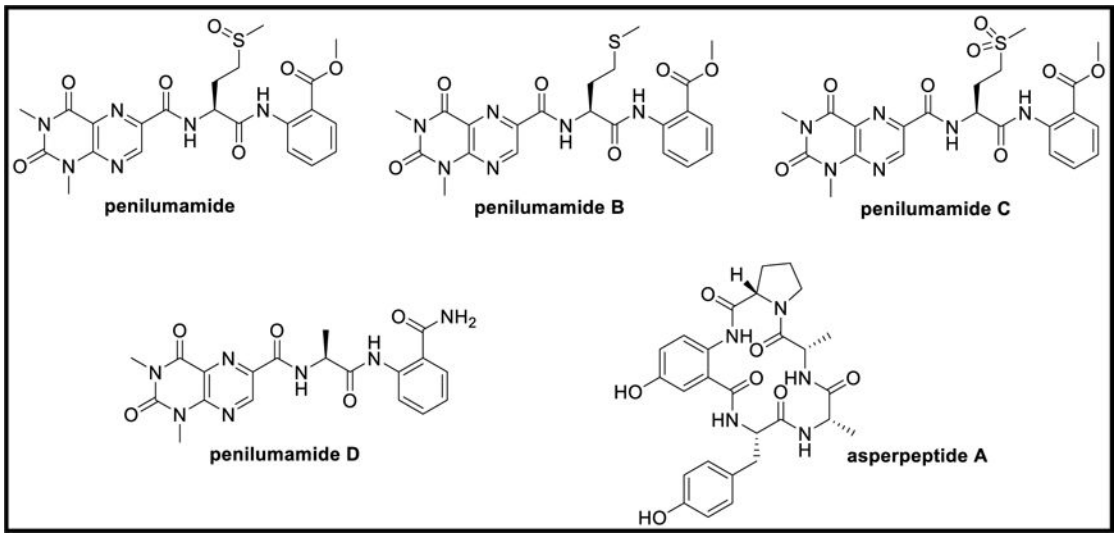


Figure 116.
Chemical structures of penilumamide, penilumamides B-D, and asperpeptide A

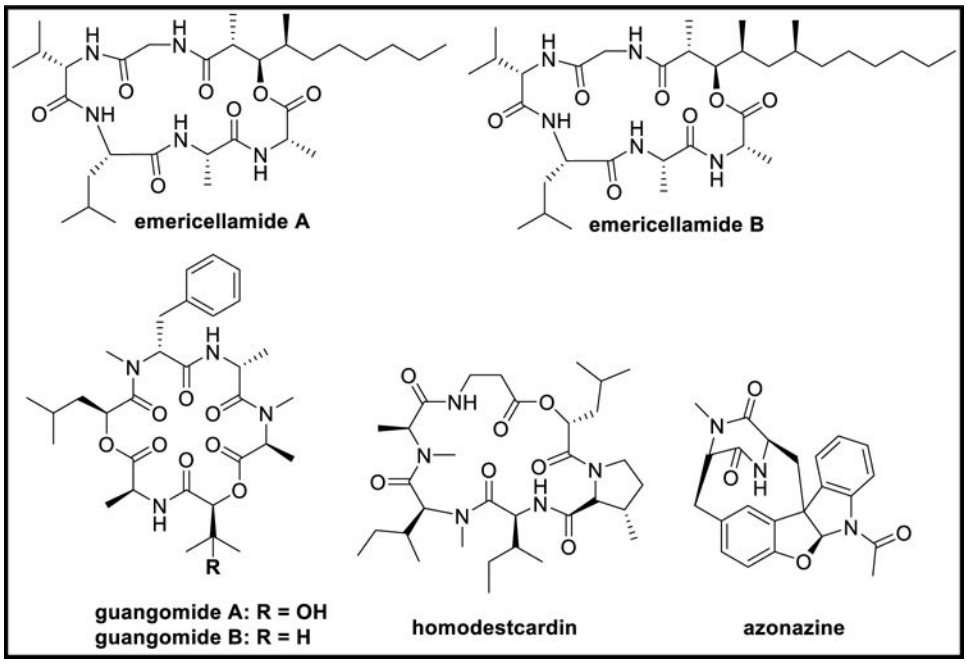


Figure 117.
Chemical structures of emericellamides A-B, guangomides A-B, homodestcardin, and azonazine

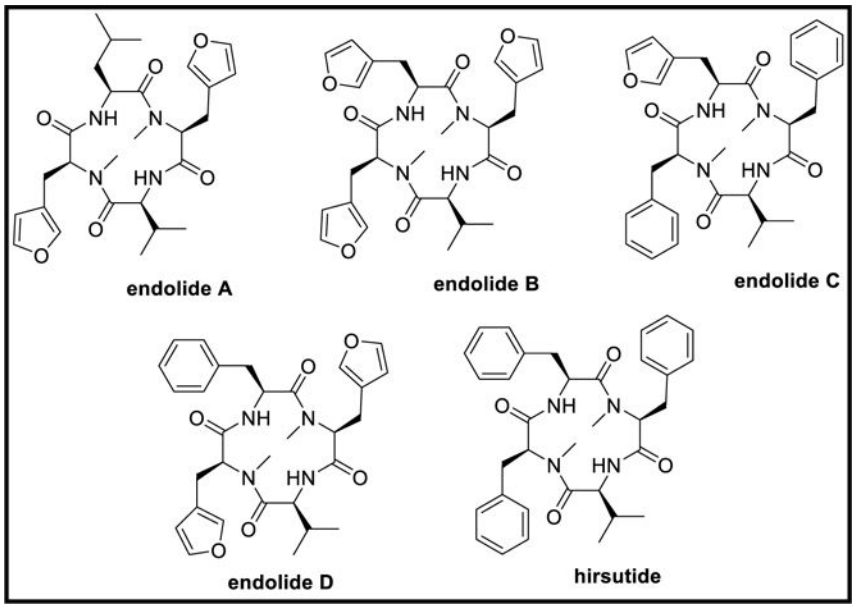


Figure 118.
Chemical structures of endolides A-D and hirsutide

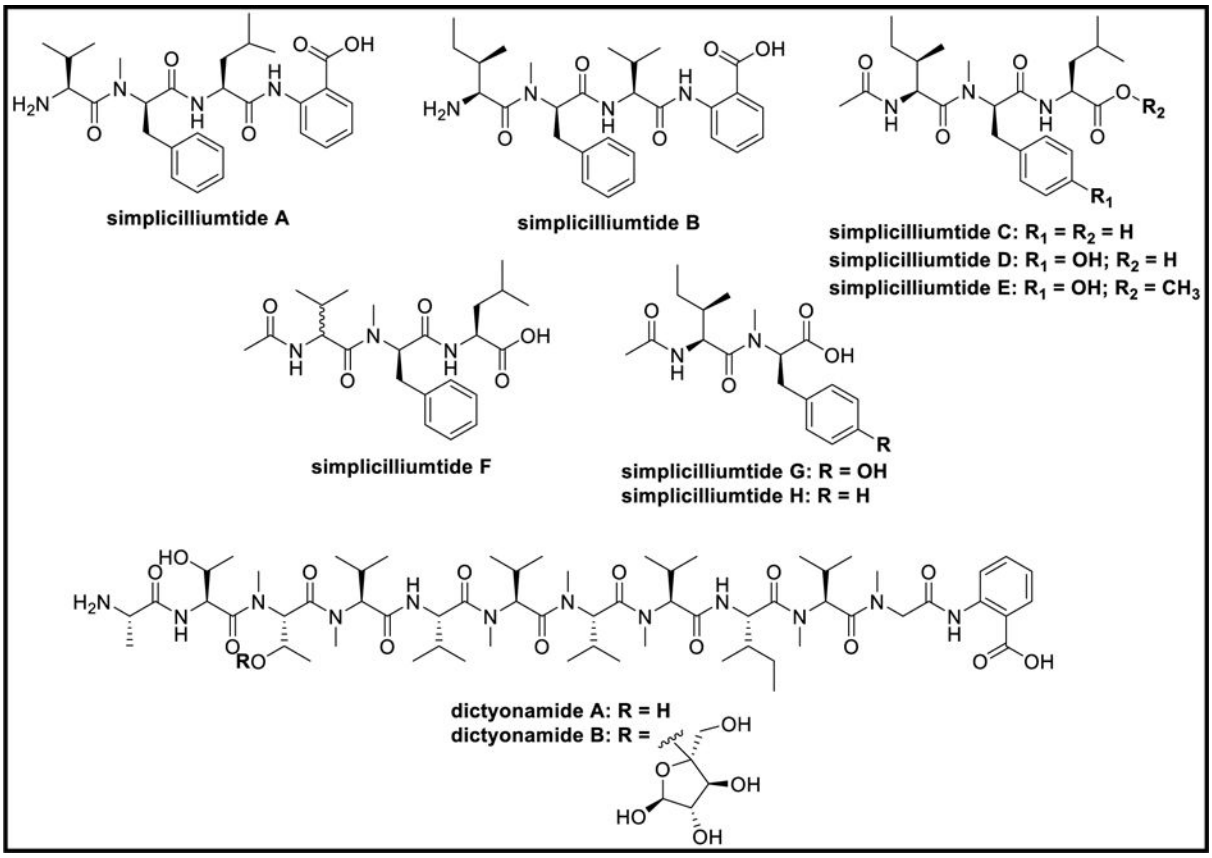


Figure 119.
Chemical structures of simplicilliumtides A-H and dictyonamides A-B

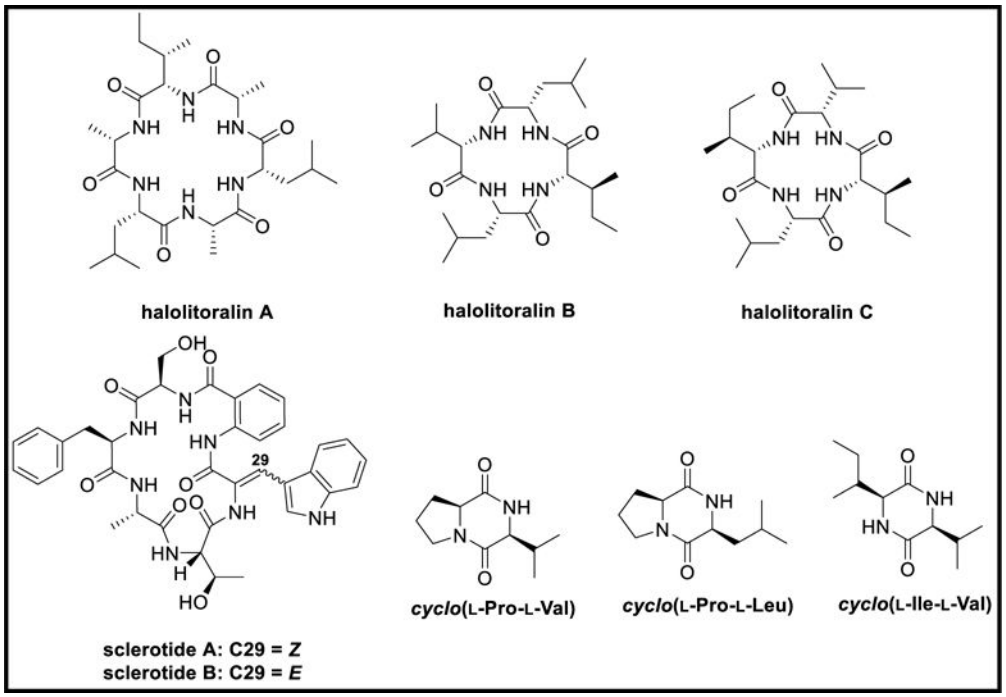


Figure 120.

Chemical structures of halolitoralins A-C, sclerotides A-B, *cyclo*(L-Pro-L-Val), *cyclo*(L-Pro-L-Leu), and *cyclo*(L-Ile-L-Val)

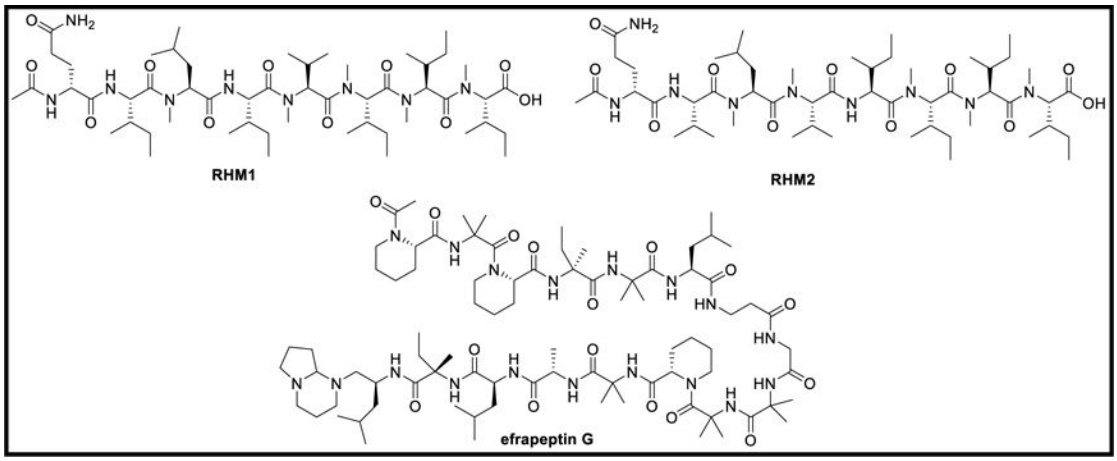


Figure 121.
Chemical structures of RHM1, RHM2, and efrapeptin G

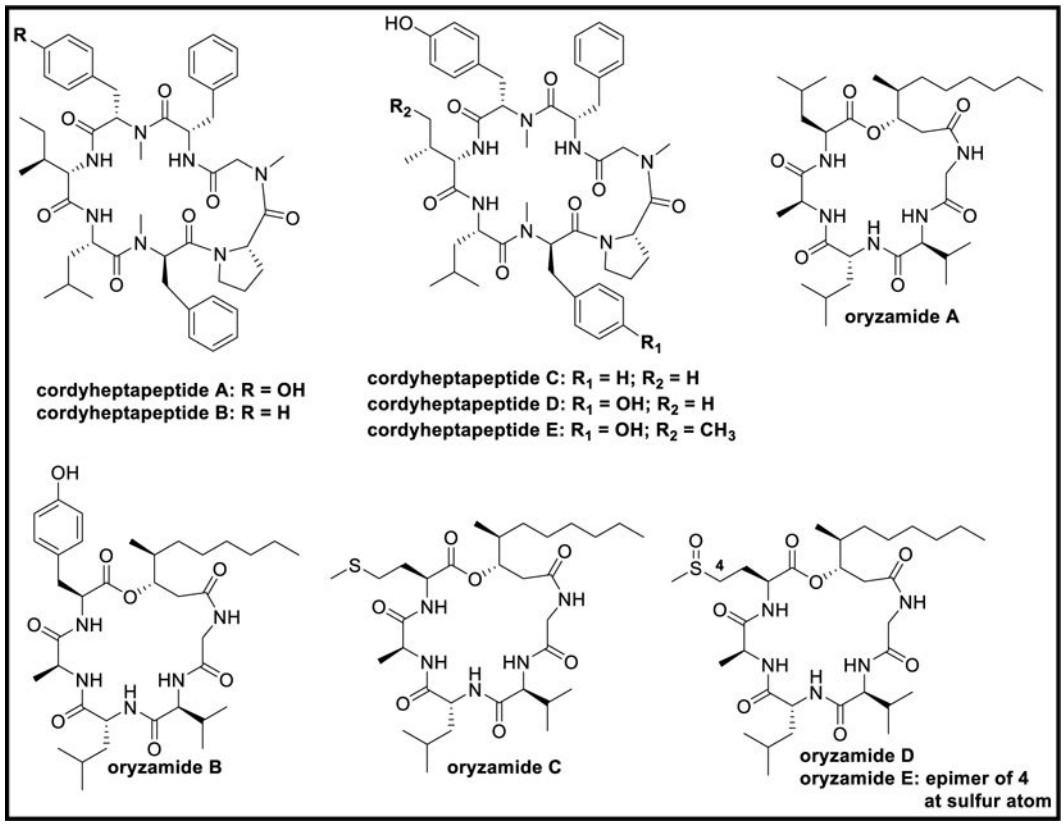


Figure 122.
Chemical structures of cordyheptapeptides A-E and oryzamides A-E

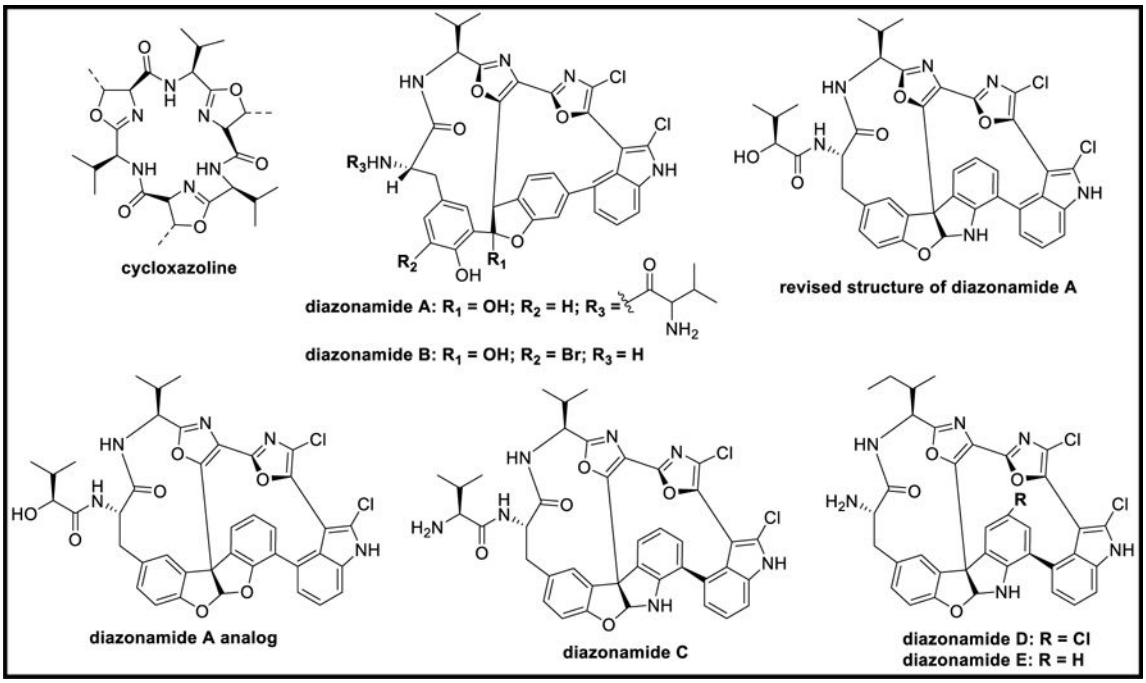


Figure 123.

Chemical structures of cycloxazoline, diazonamides A-E, revised structure of diazonamide A, and diazonamide A analog

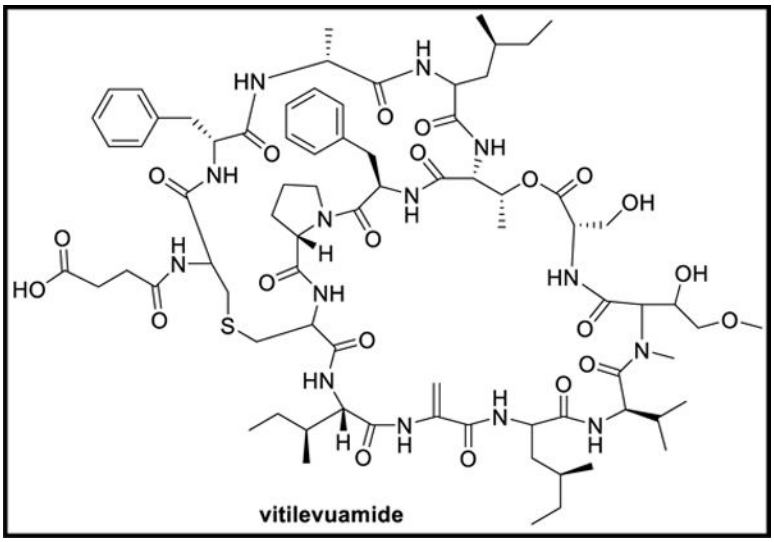


Figure 124.
Chemical structure of vitilevuamide

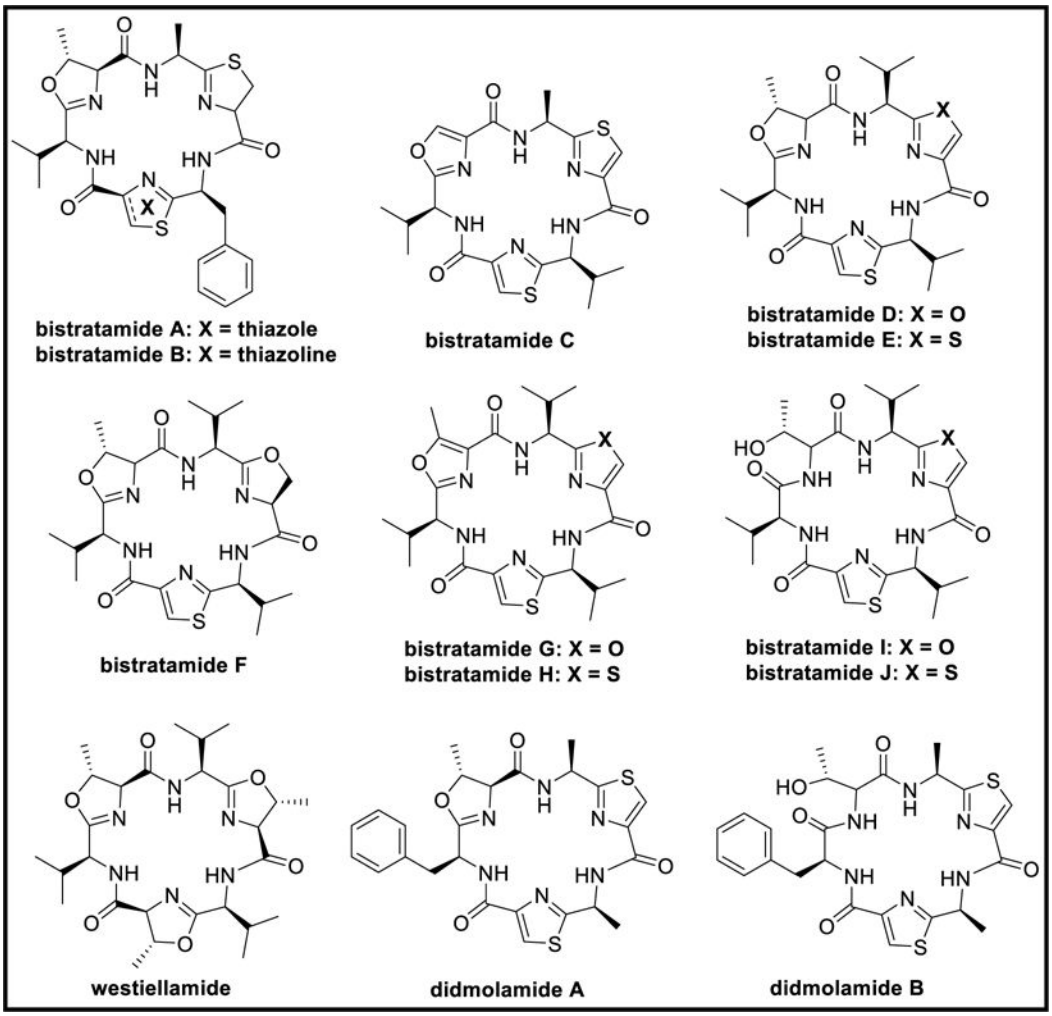


Figure 125.
Chemical structures of bistratamides A-J, westiellamide, and didmolamides A-B

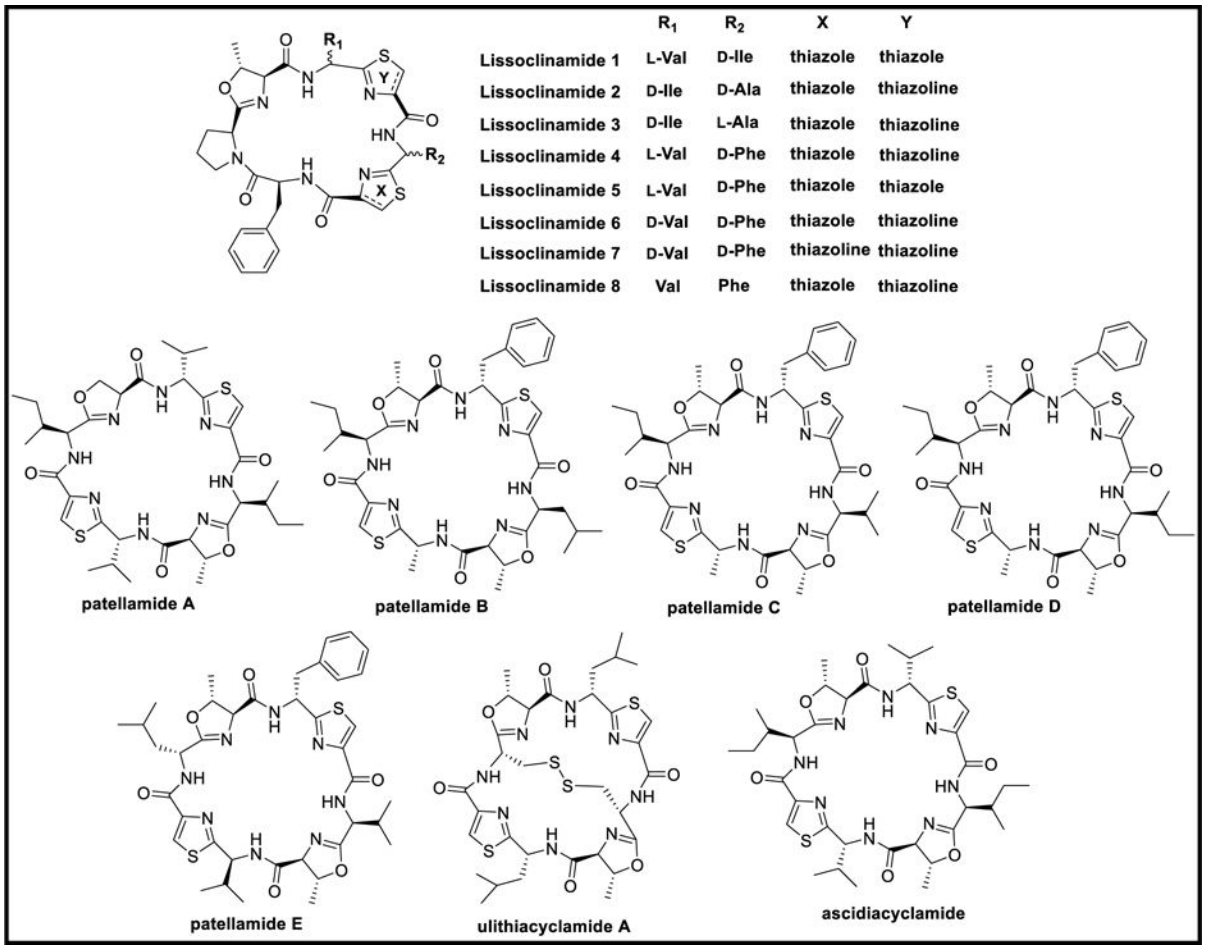


Figure 126.

Chemical structures of lissoclinamides 1–8, patellamides A-E, ulithiacyclamide A, and ascidiacyclamide

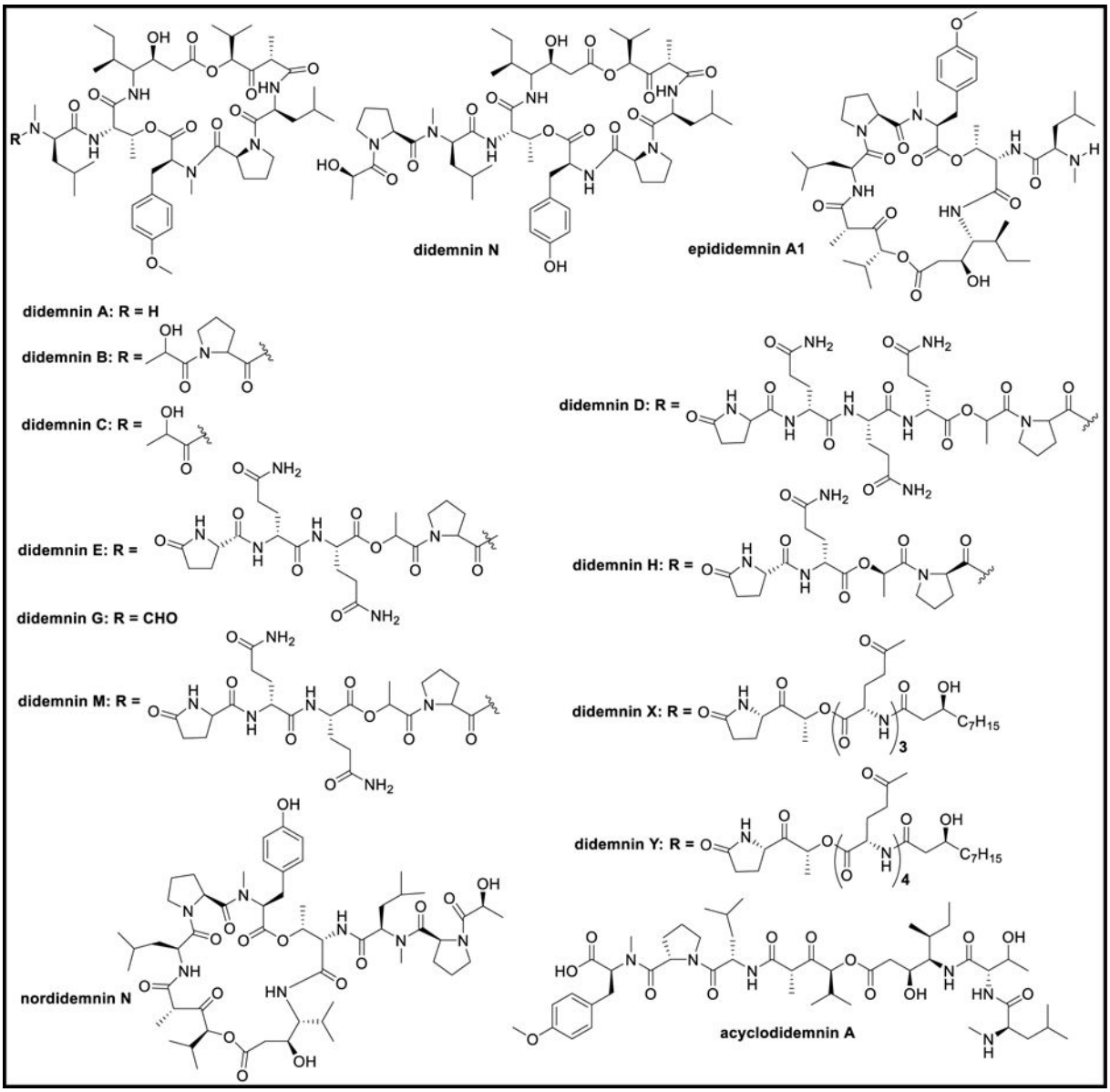


Figure 127.

Chemical structures of didemnins A-E, G-H, M-N, X-Y, epididemnin A1, nordidemnin N, and acyclodidemnin A

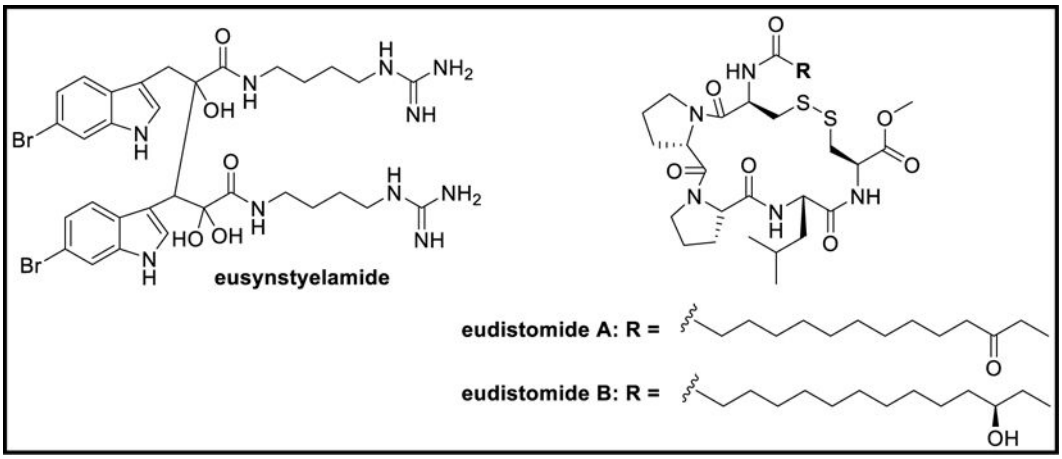


Figure 128.
Chemical structures of eusynstyelamide and eudistomides A-B

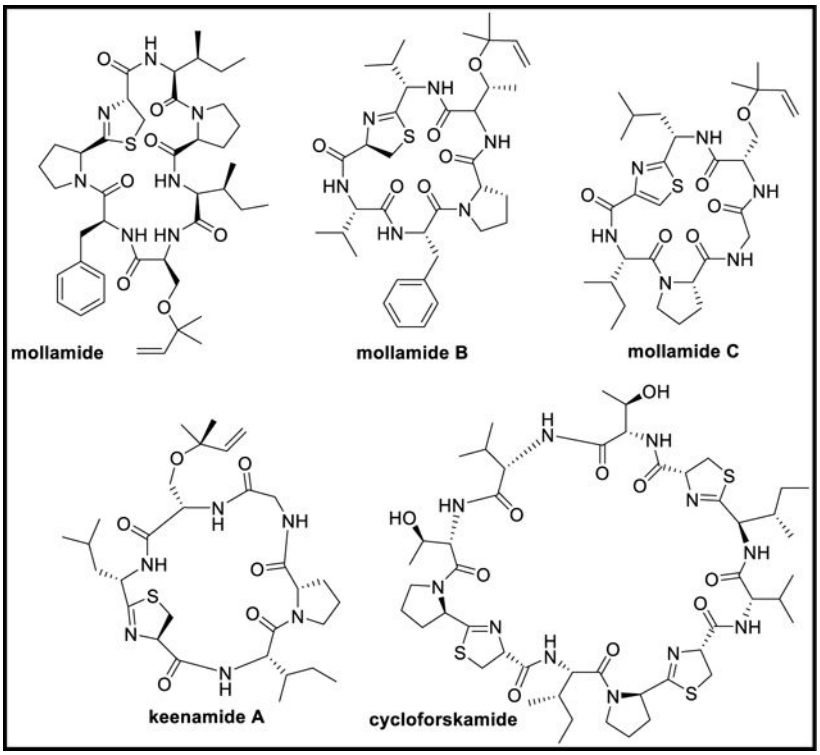


Figure 129.
Chemical structures of mollamide, mollamides B-C, keenamide A, and cycloforskamide

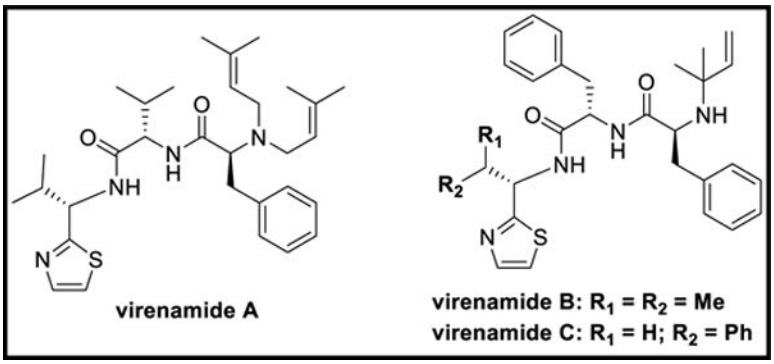


Figure 130.
Chemical structures of virenamides A-C

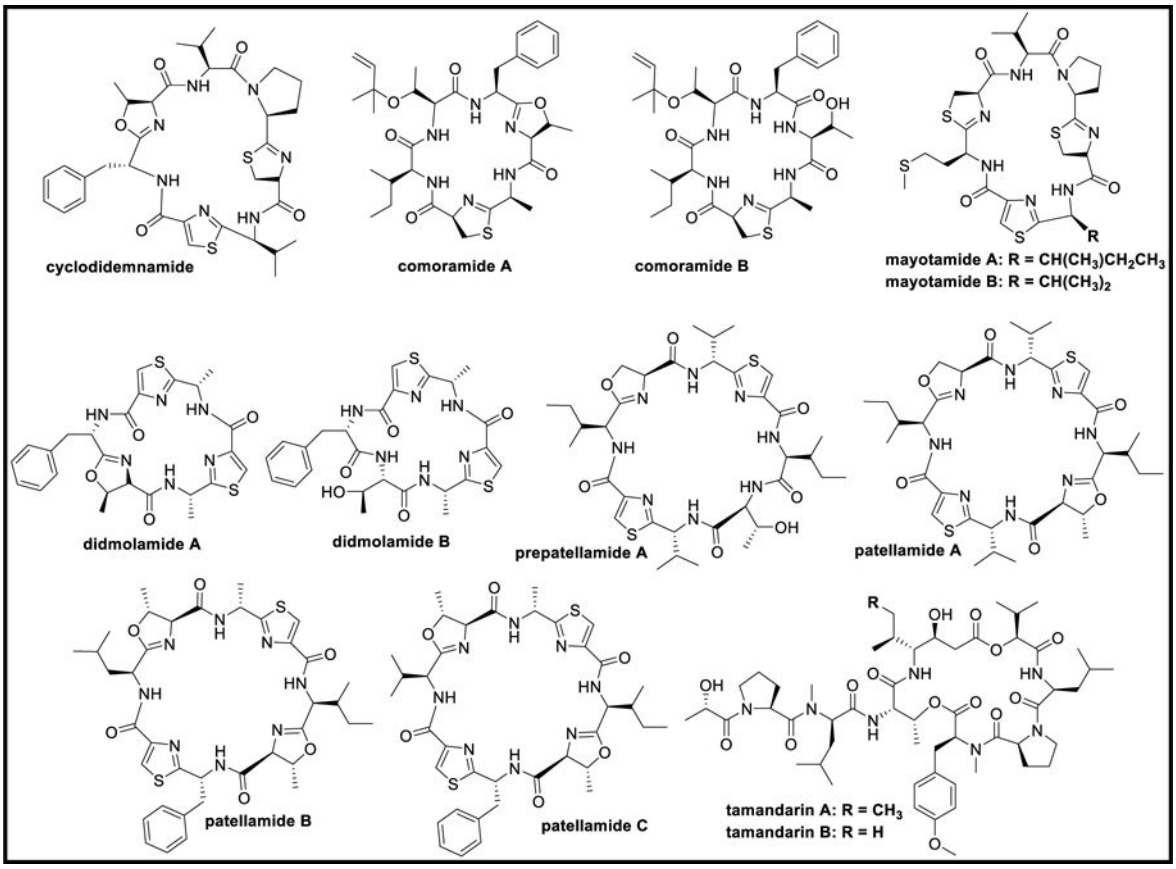


Figure 131.

Chemical structures of cyclodidemnamide, comoramides A-B, mayotamides AB, didmolamides A-B, prepatellamide A, patellamides A-C, and tamandarins A-B

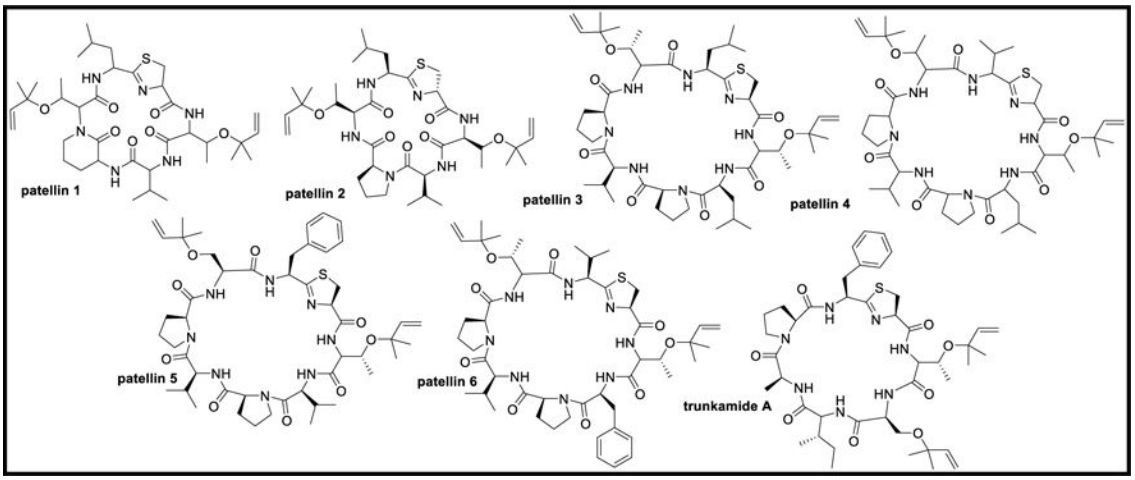


Figure 132.
Chemical structures of patellins 1–6 and trunkamide A

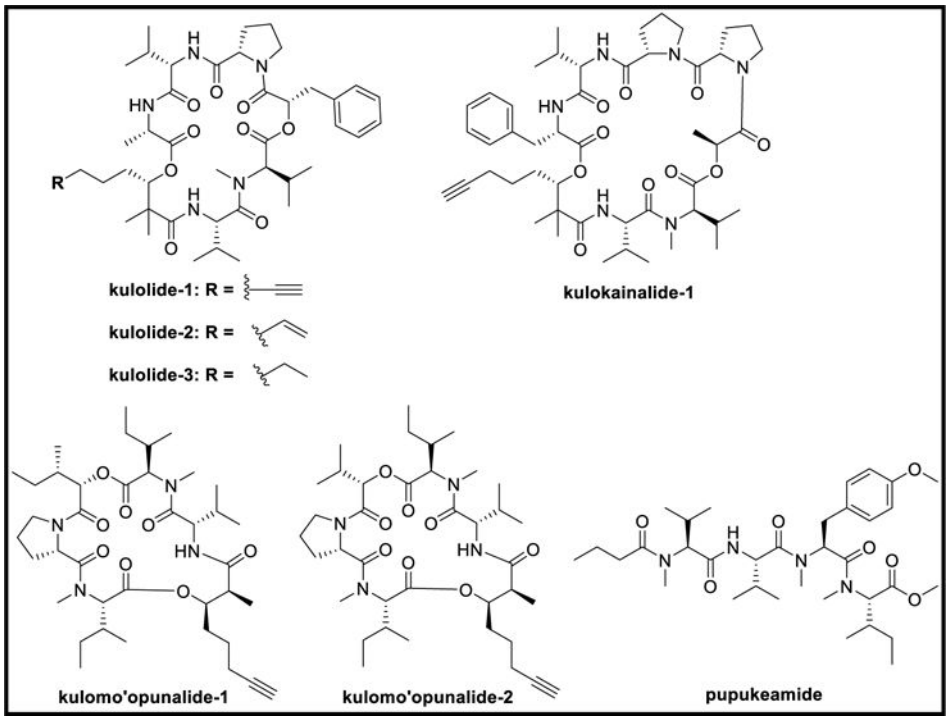


Figure 133.

Chemical structures of kulolides 1–3, kulokainalide-1, kulomo'opunalides 1–2, and pupukeamide

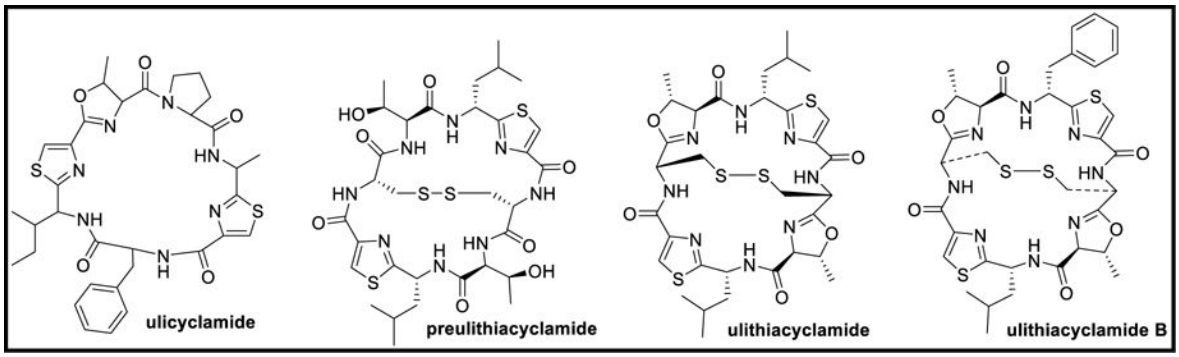


Figure 134.
Chemical structures of ulicyclamide, preulithiacyclamide, ulithiacyclamide, and ulithiacyclamide B

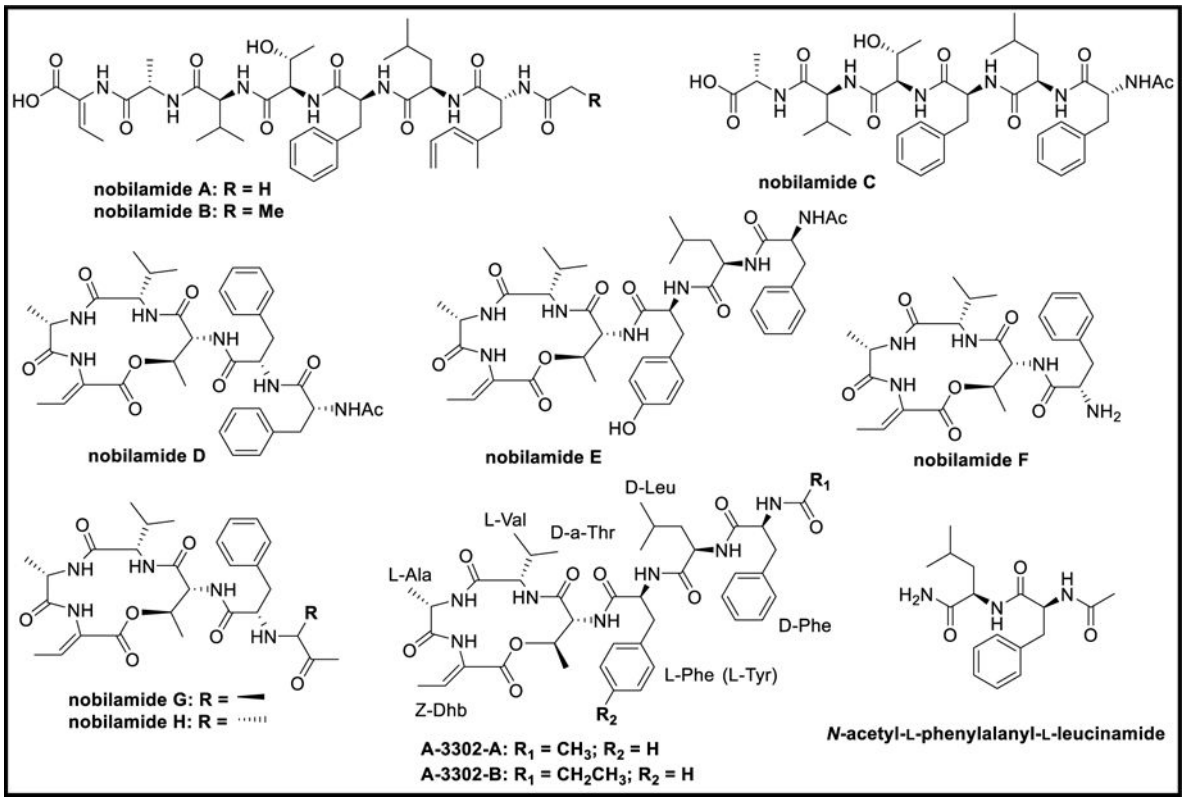


Figure 135.

Chemical structures of nobilamides A-H, A-3302 A-B, and *N*-acetyl-L-phenylalanyl-L-leucinamide

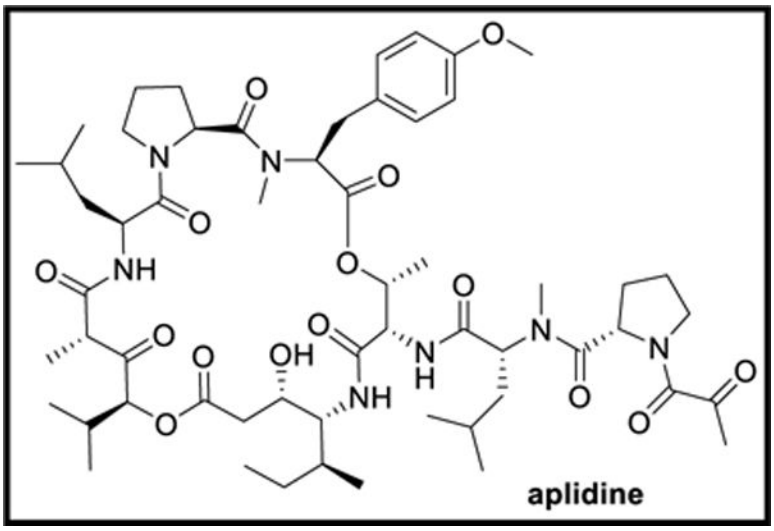


Figure 136.
Chemical structure of aplidine

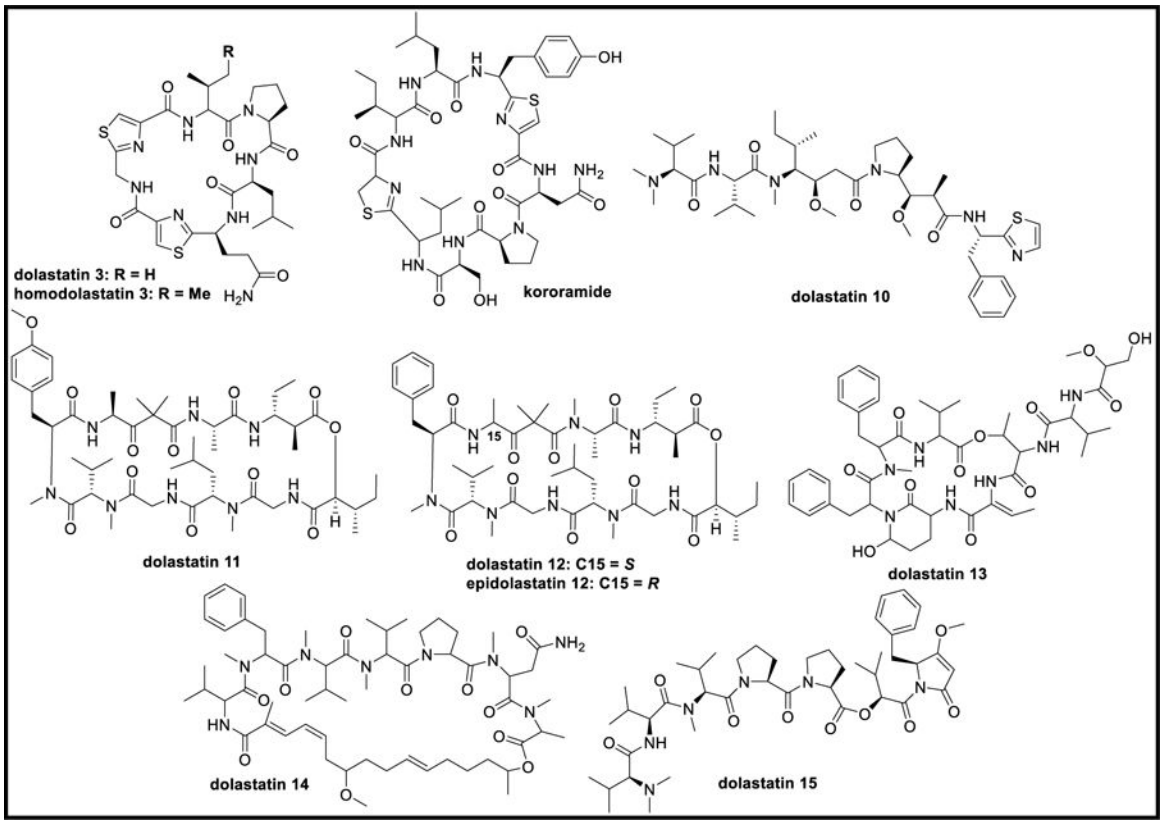


Figure 137.

Chemical structures of dolastatins 3, 10–15, homodolastatin 3, kororamide, and epidolastatin 12

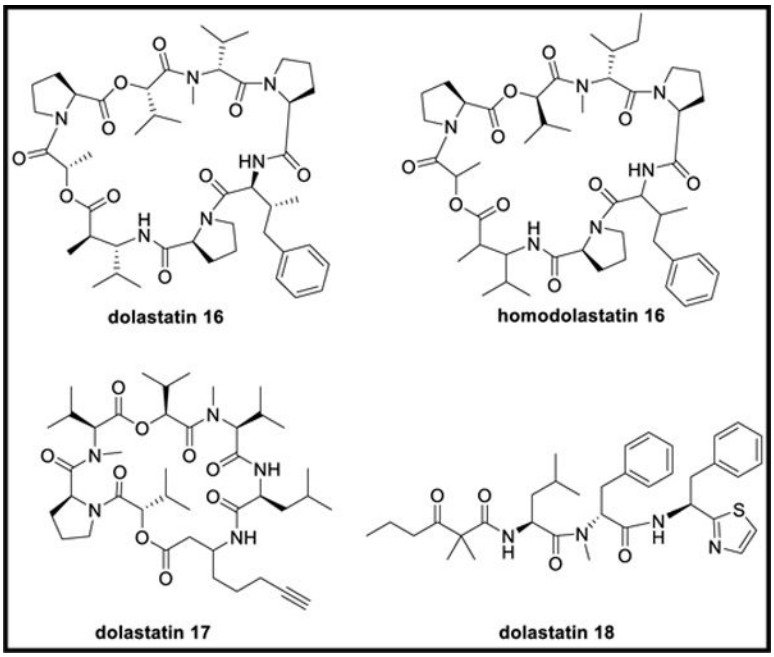


Figure 138.
Chemical structures of dolastatins 16–18 and homodolastatin 16

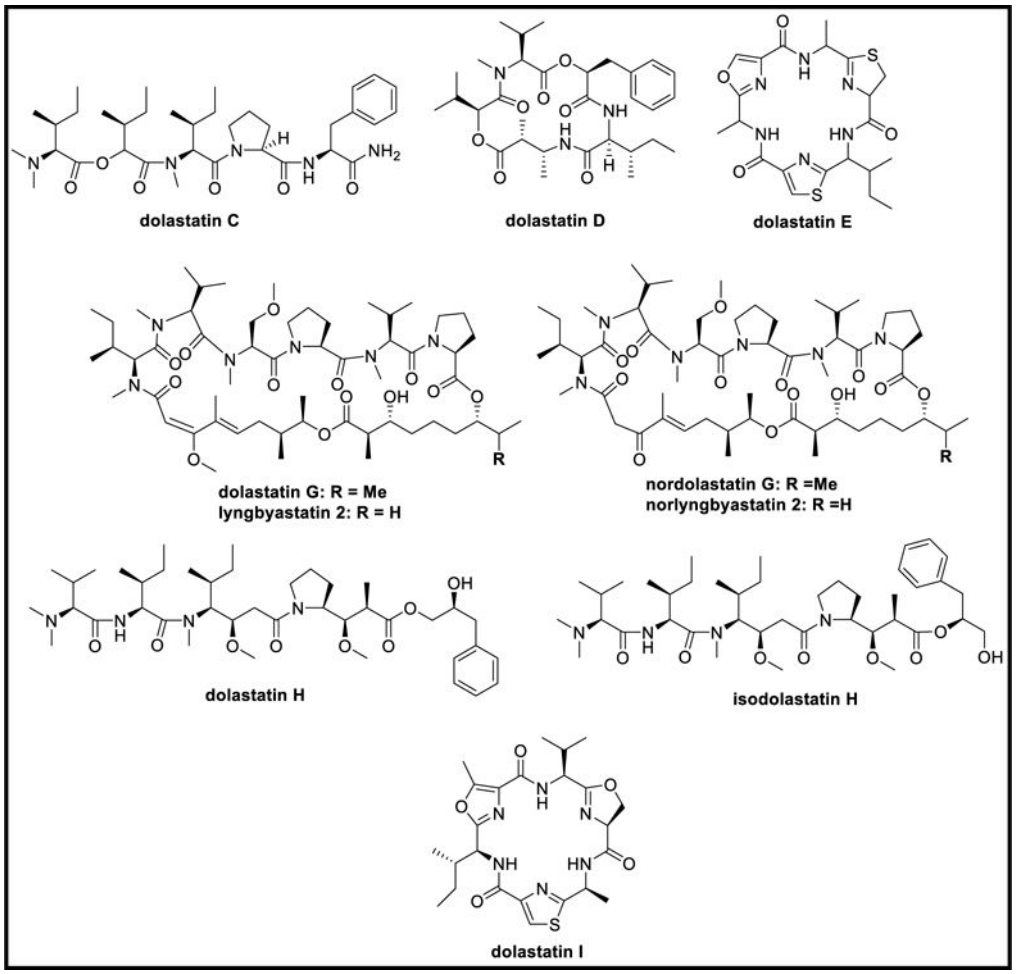


Figure 139.

Chemical structures of dolastatins C-E, G-I, nordolastatin G, isodolastatin H, lyngbyastatin 2, and norlyngbyastatin 2

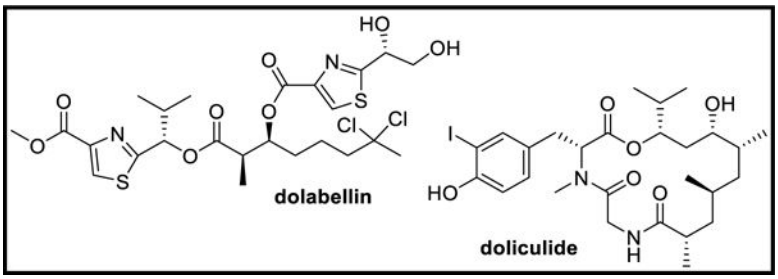


Figure 140.
Chemical structures of dolabellin and doliculide

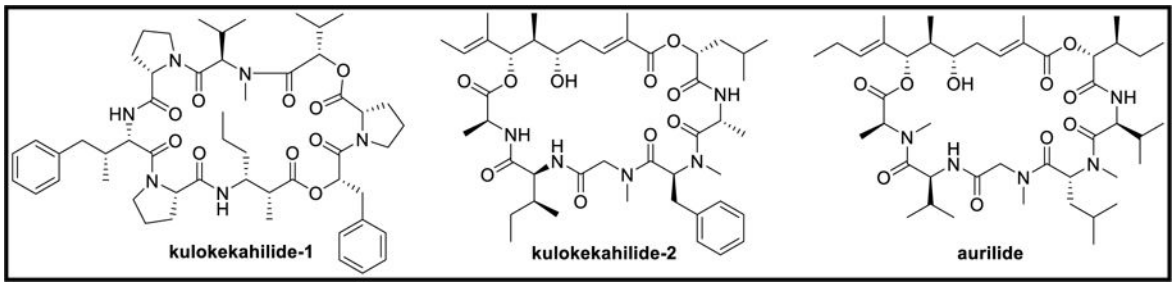


Figure 141.
Chemical structures of kulokekahilides 1–2 and aurilide

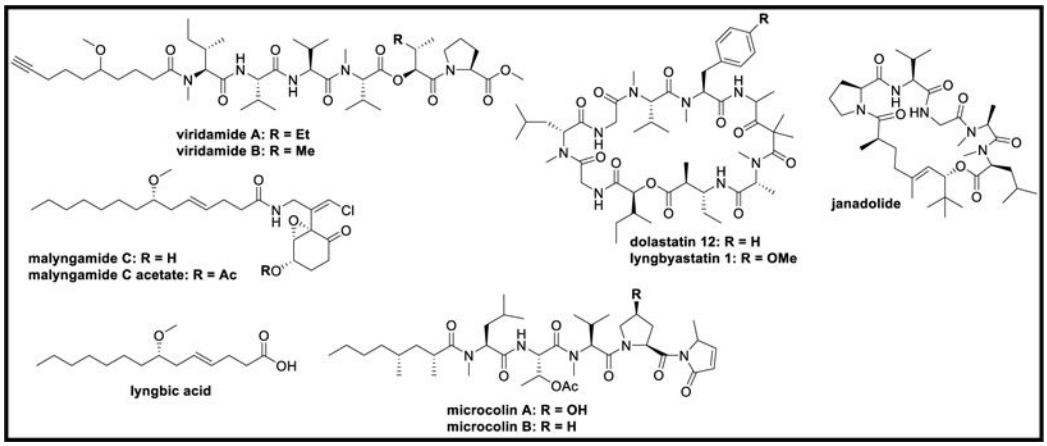


Figure 142.
Chemical structures of viridamides A-B, dolastatin 12, lyngbyastatin 1, malyngamide C, malyngamide C acetate, lyngbic acid, janadolide, and microcolins A-B

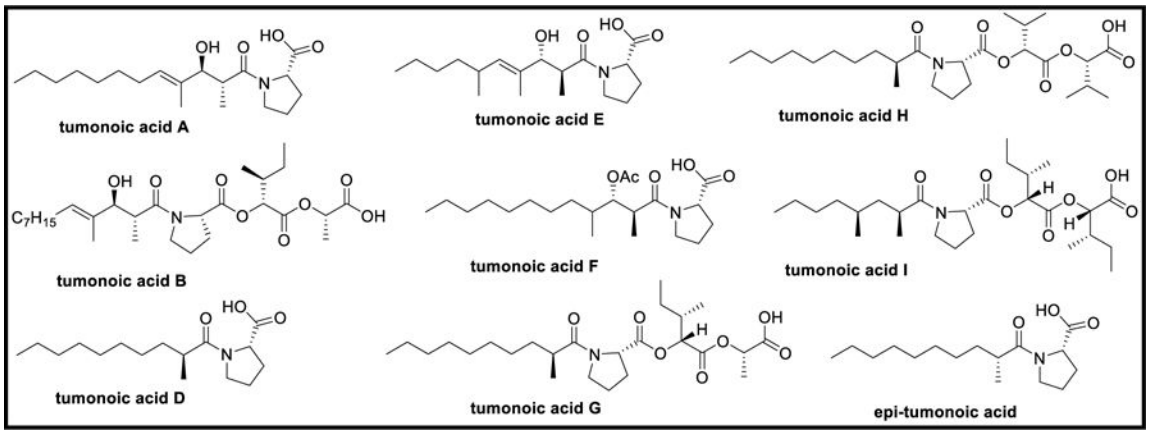


Figure 143.
Chemical structures of tumonoic acids A-B, D-I, and *epi*-tumonoic acid

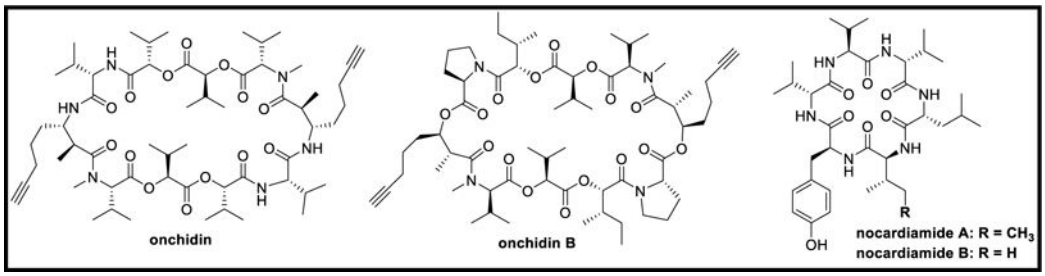


Figure 144.
Chemical structures of onchidins A-B and nocardiamides A-B

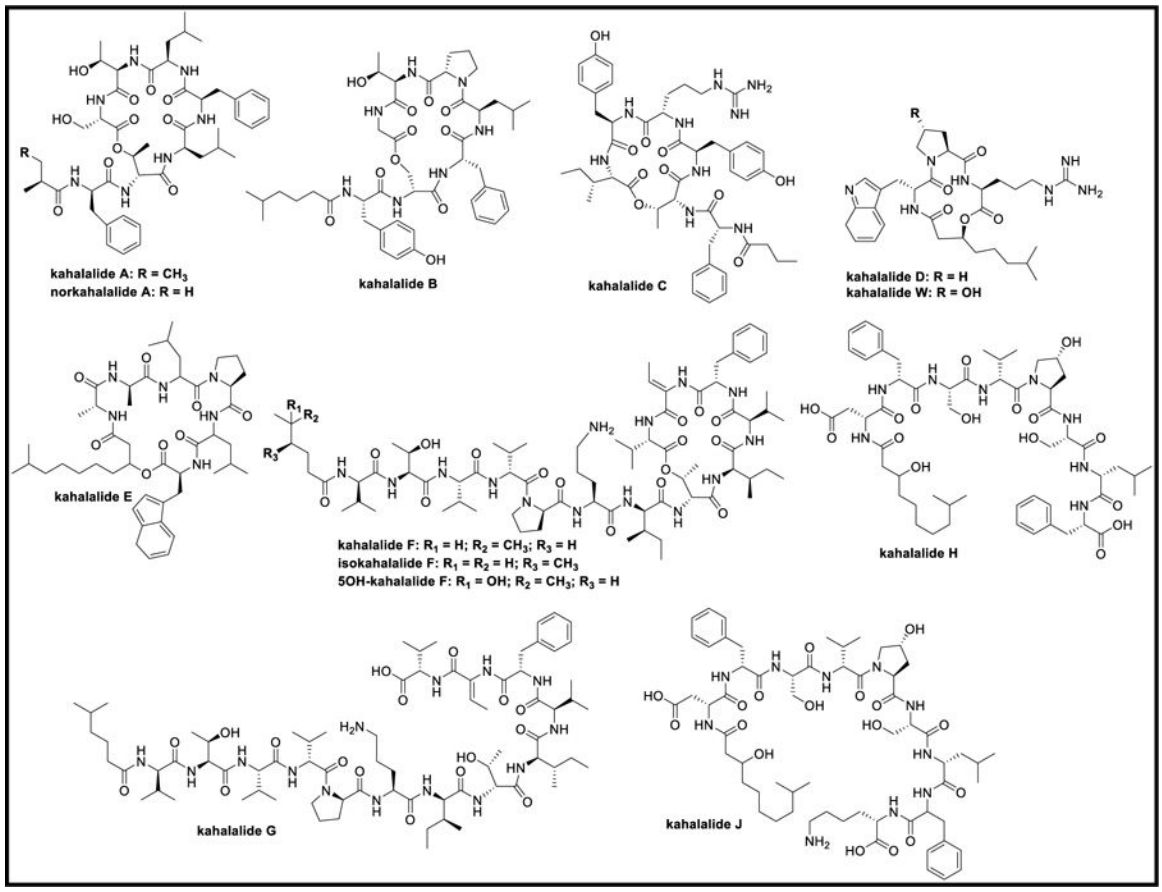


Figure 145.
Chemical structures of kahalalides A-H, J, W, norkahalalide A, isokahalalide F, and 5OH-kahalalide F

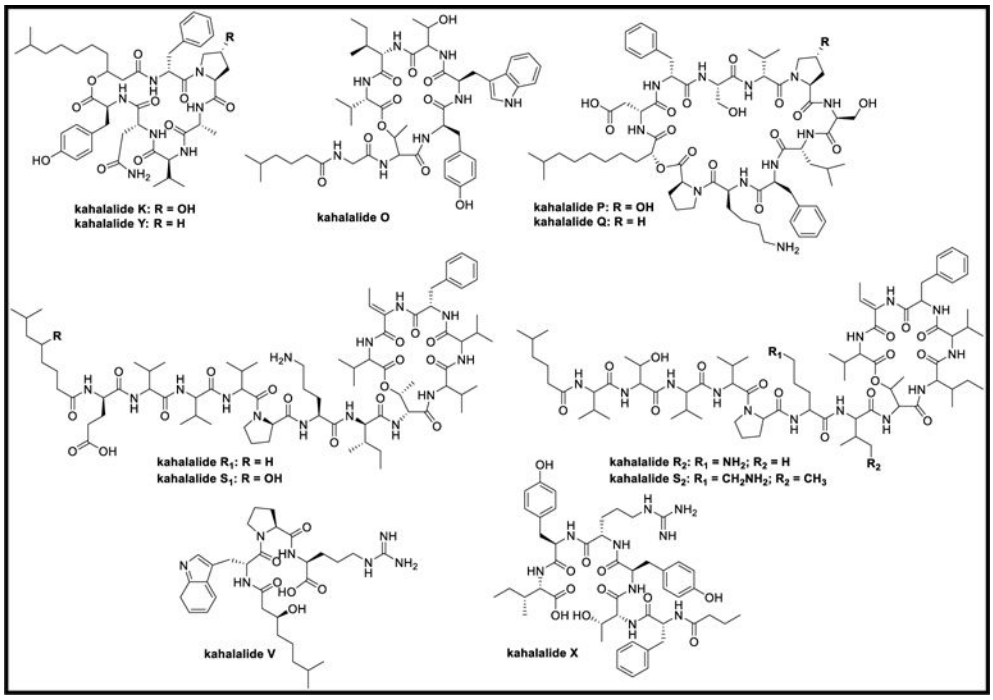


Figure 146.
Chemical structures of kahalalides K, O-Q, R_1-R_2, S_1-S_2, V,X, and Y

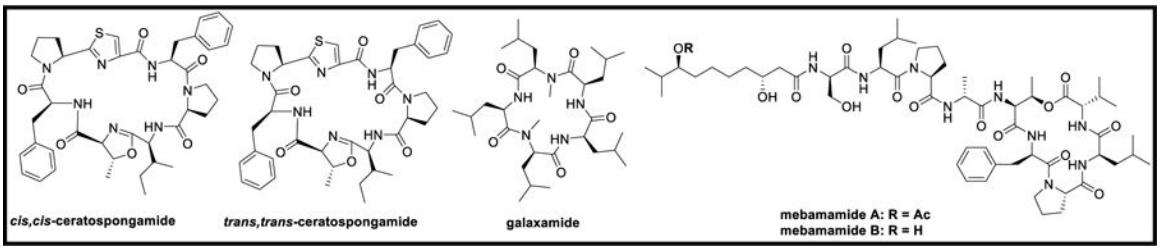


Figure 147.
Chemical structures of *cis,cis*-ceratospongamide, *trans,trans*-ceratospongamide, galaxamide, and mebamamides A-B

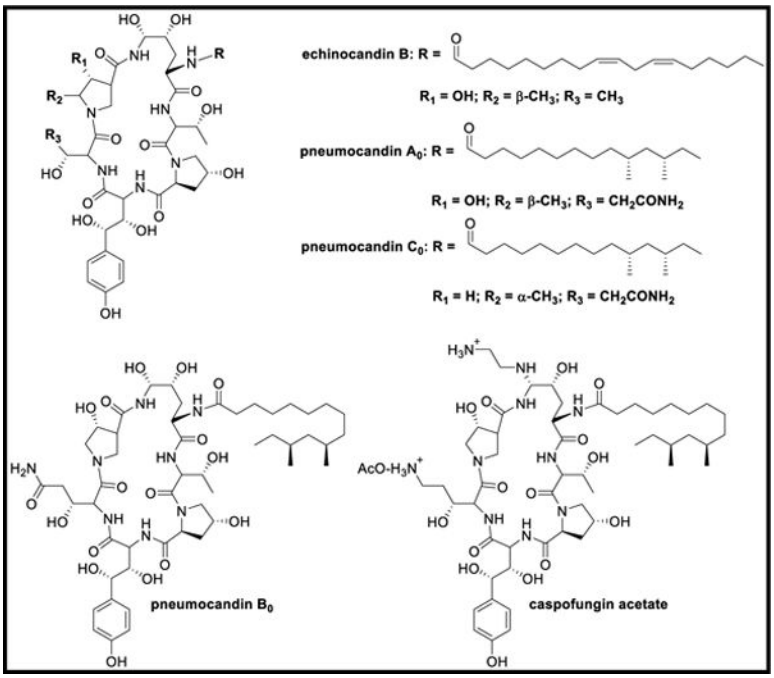


Figure 148.

Chemical structures of echinocandin B, pneumocandins A_0, B_0, C_0, and caspofungin acetate

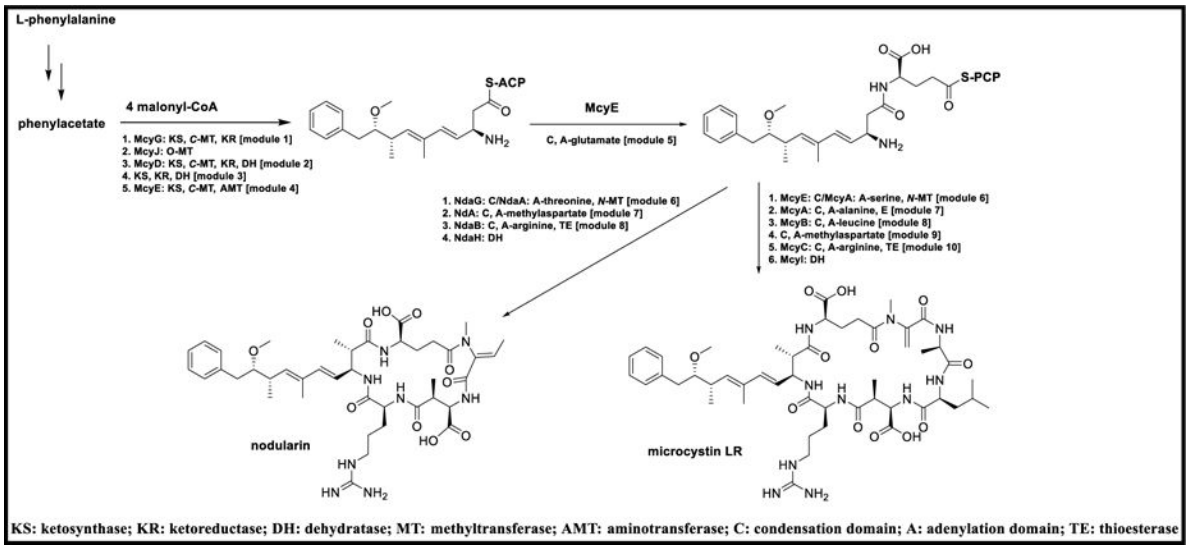


Figure 149.
Biosynthesis of nodularin

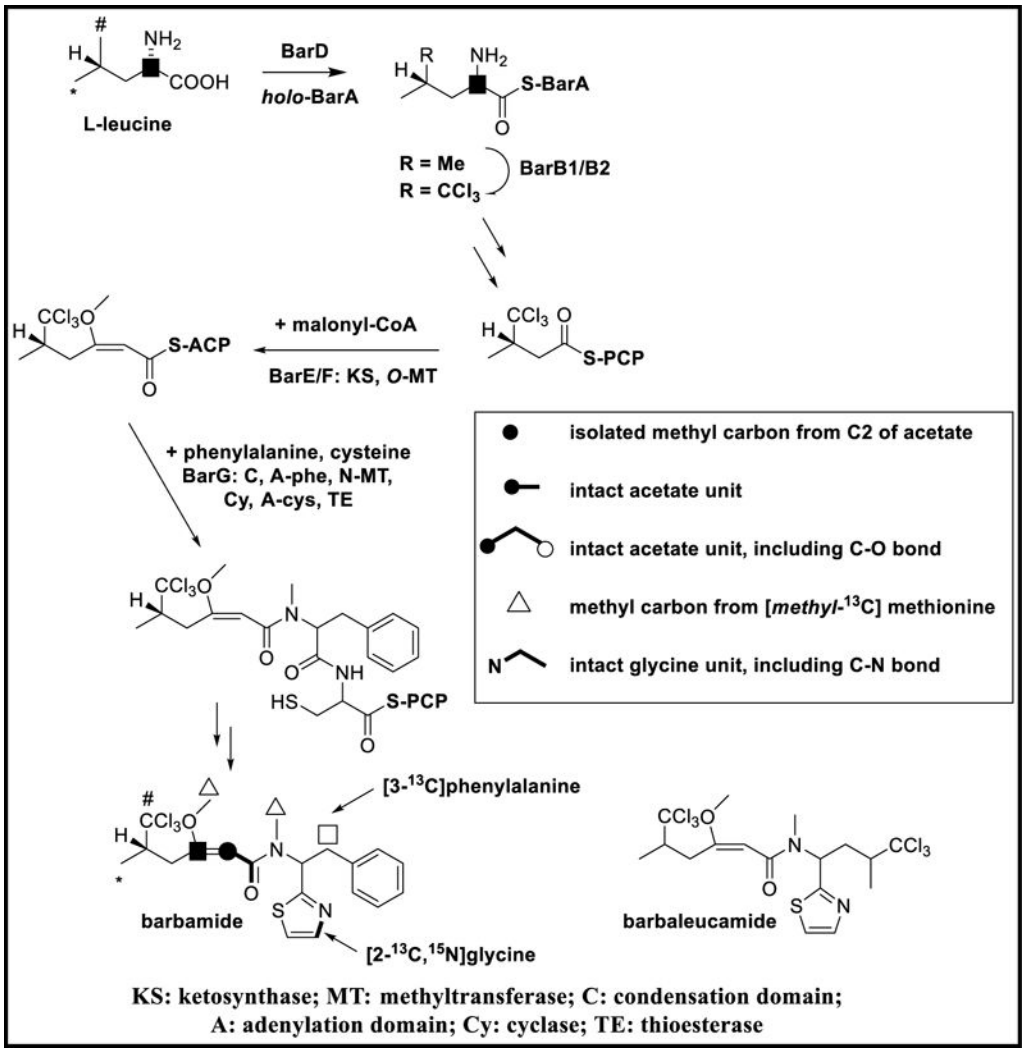


Figure 150.
Biosynthesis of barbamide & barbaleucamide

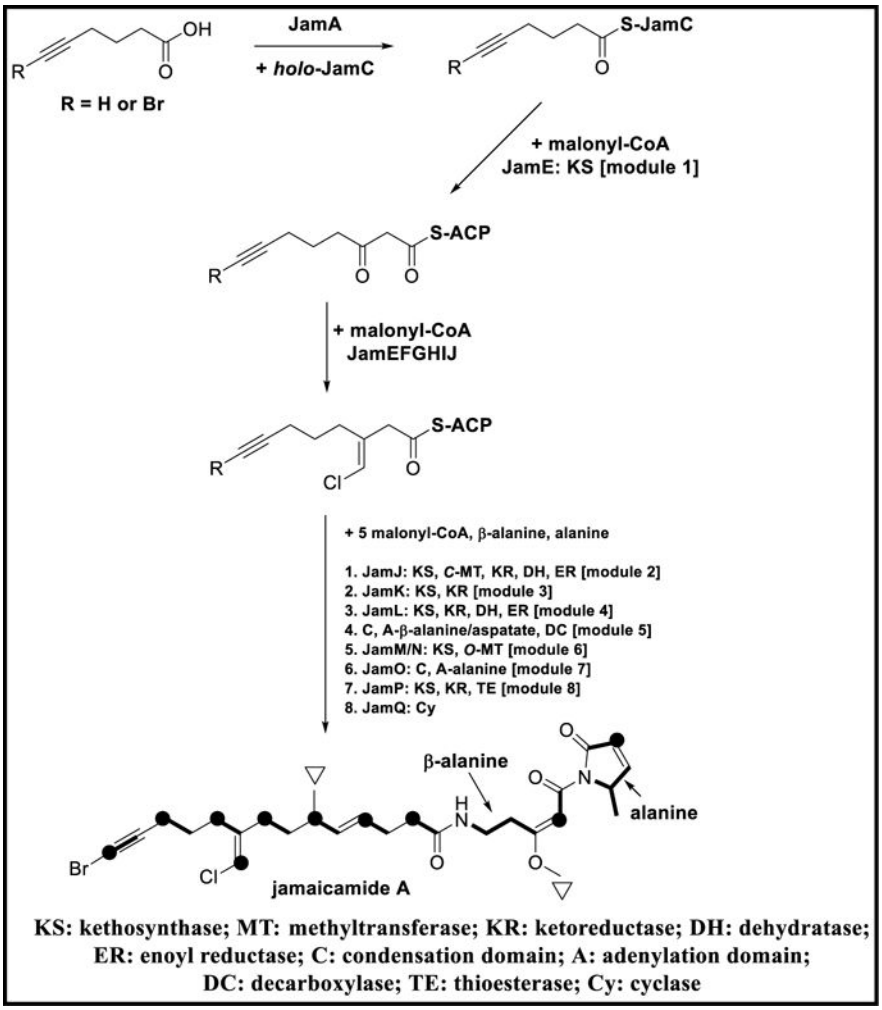


Figure 151.
Biosynthesis of jamaicamide A

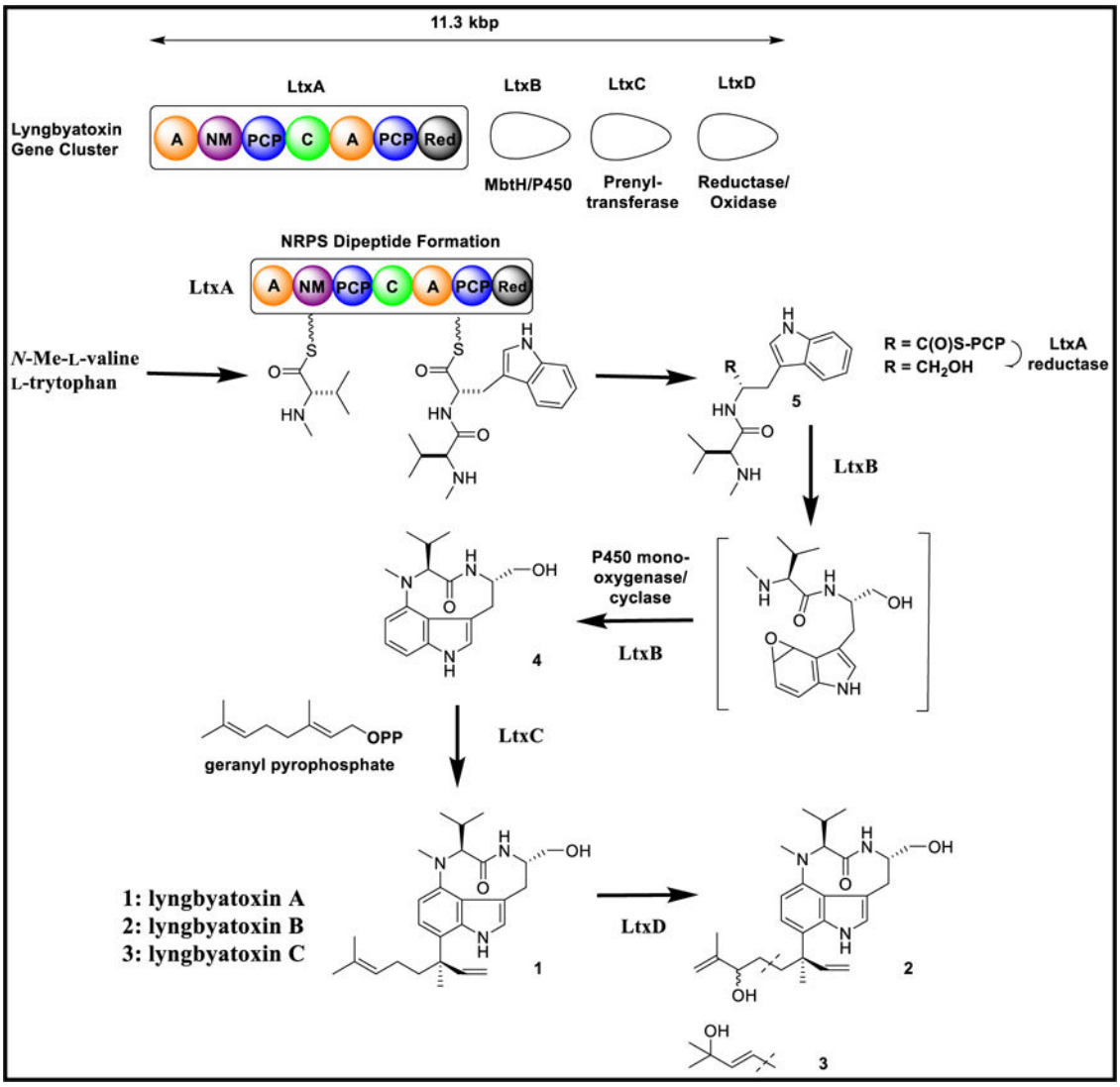


Figure 152.
Biosynthesis of lyngbyatoxins [452]

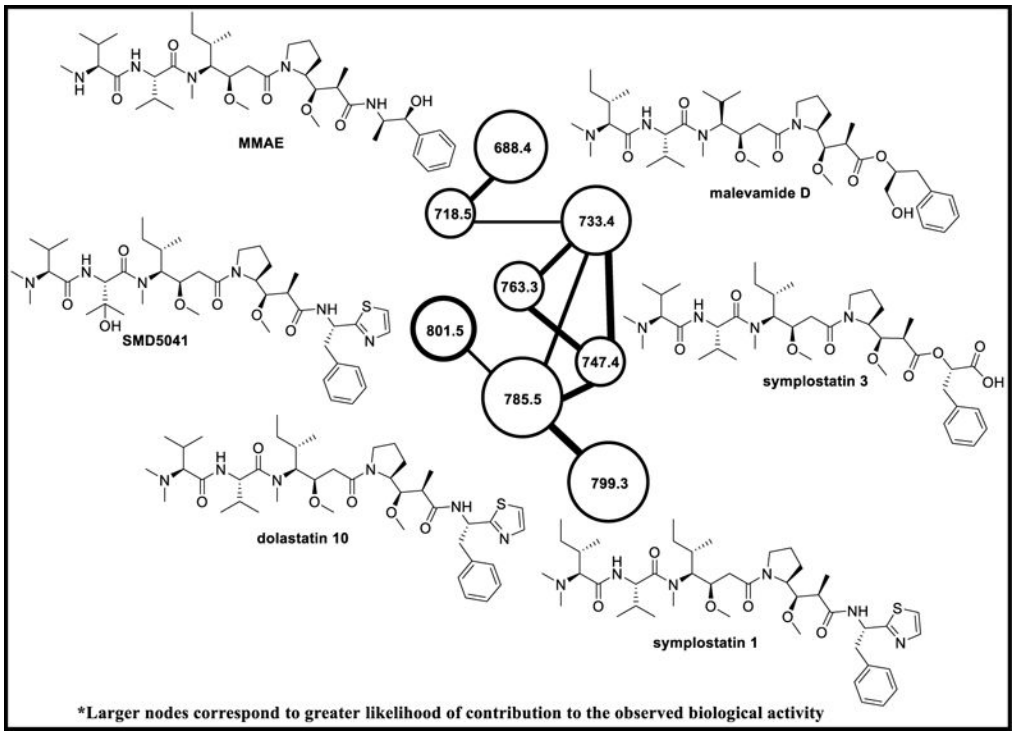


Figure 153.
Molecular networking of dolastatin 10 tetrapeptide molecular family

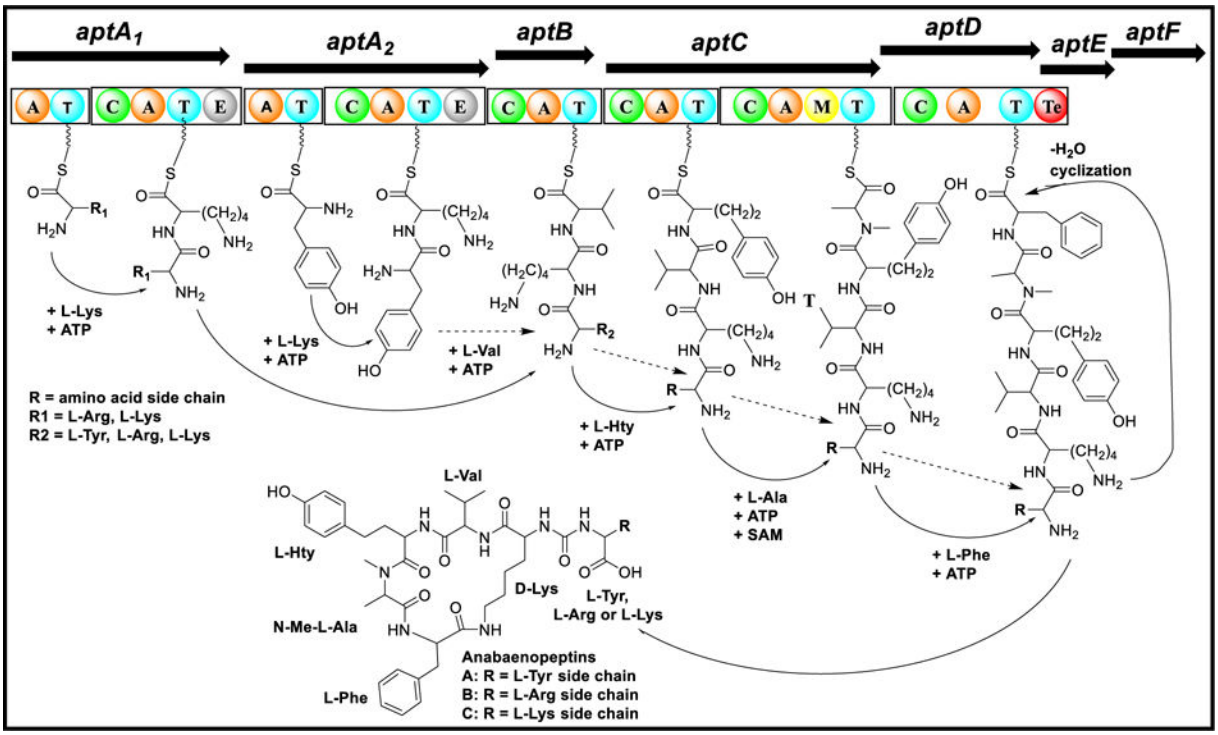


Figure 154.
Biosynthesis of anabaenopeptins

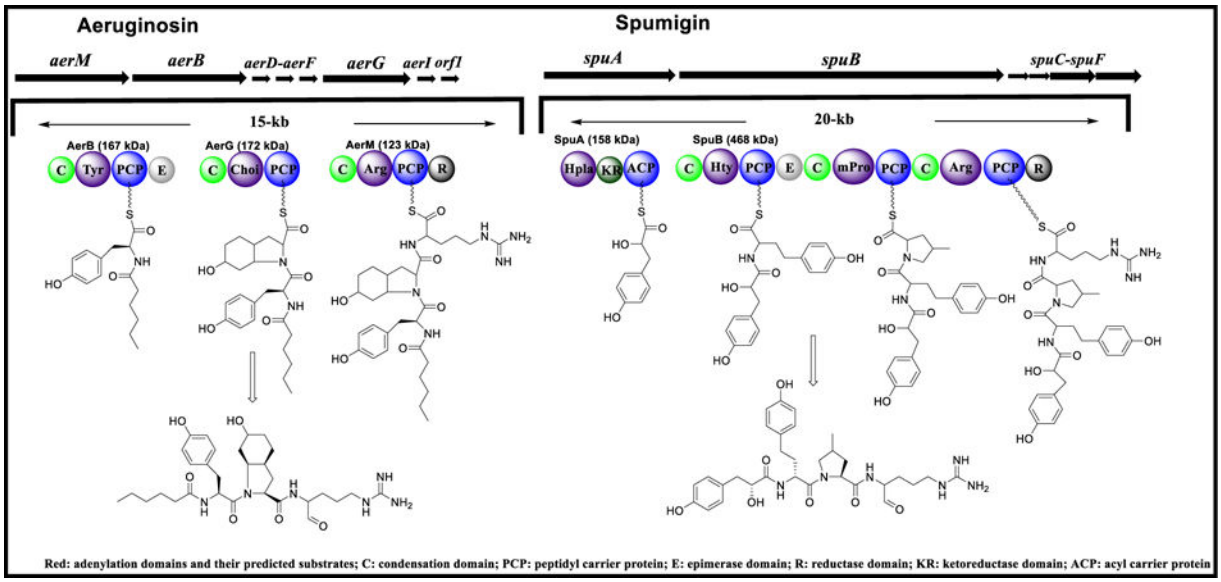


Figure 155.
Biosyntheses of aeruginosin and spumigin

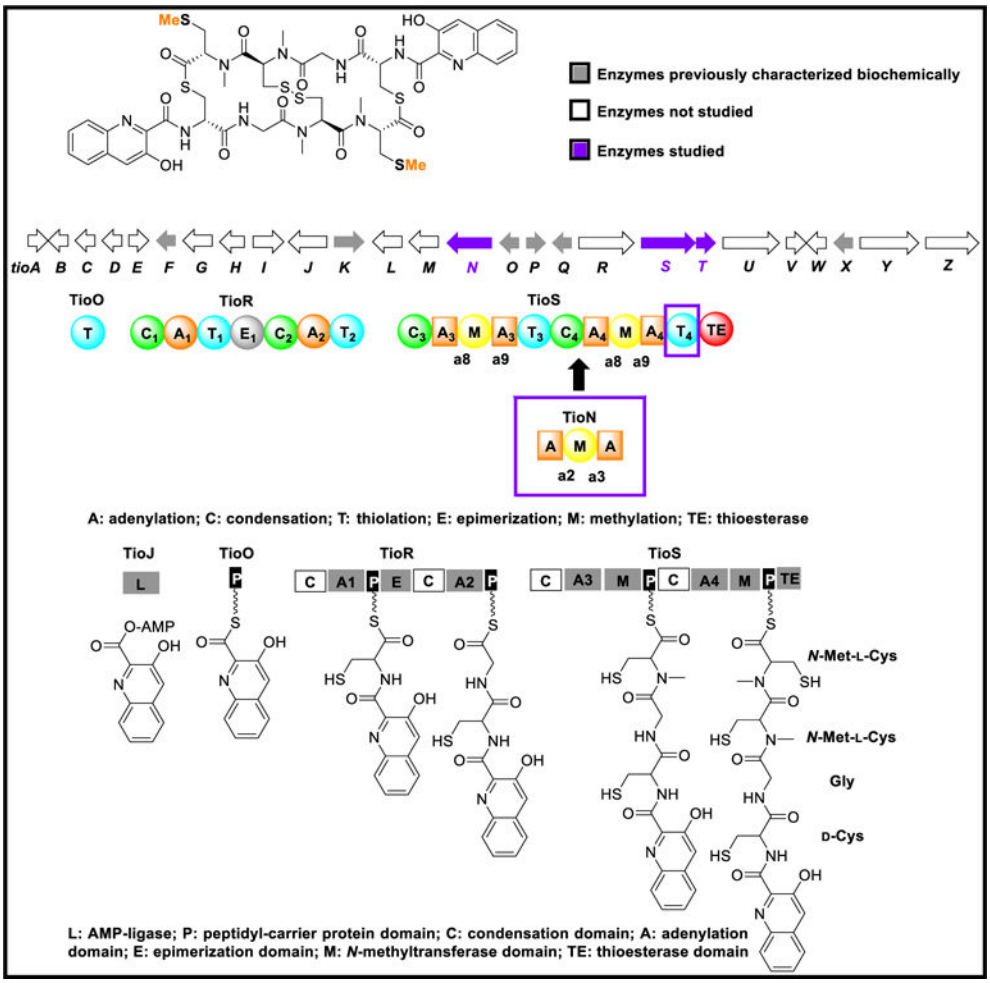


Figure 156.
Biosynthesis of thiocoraline

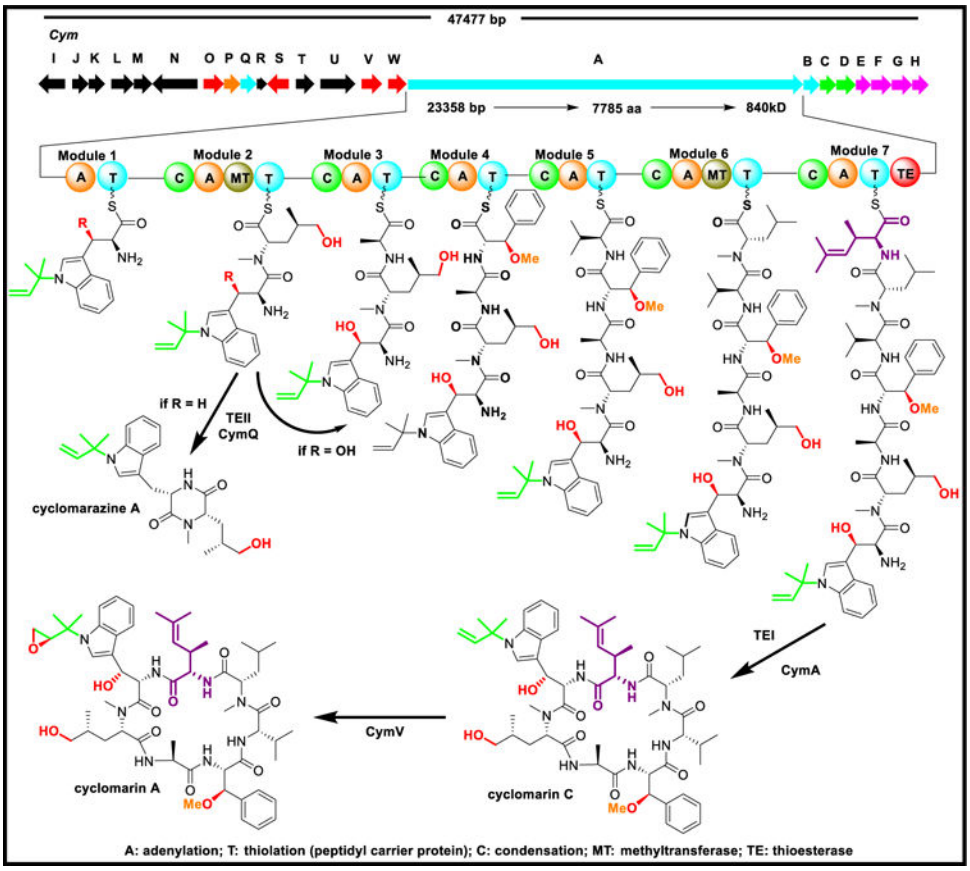


Figure 157.
Biosynthesis of cyclomarin A and cyclomarazine A

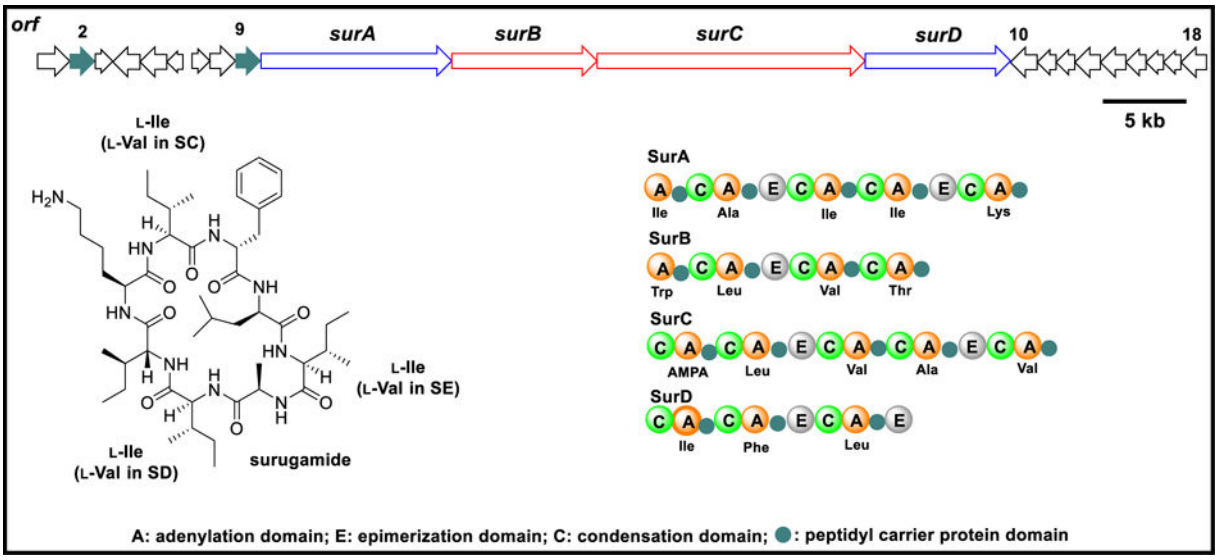


Figure 158.
Biosynthesis of surugamides

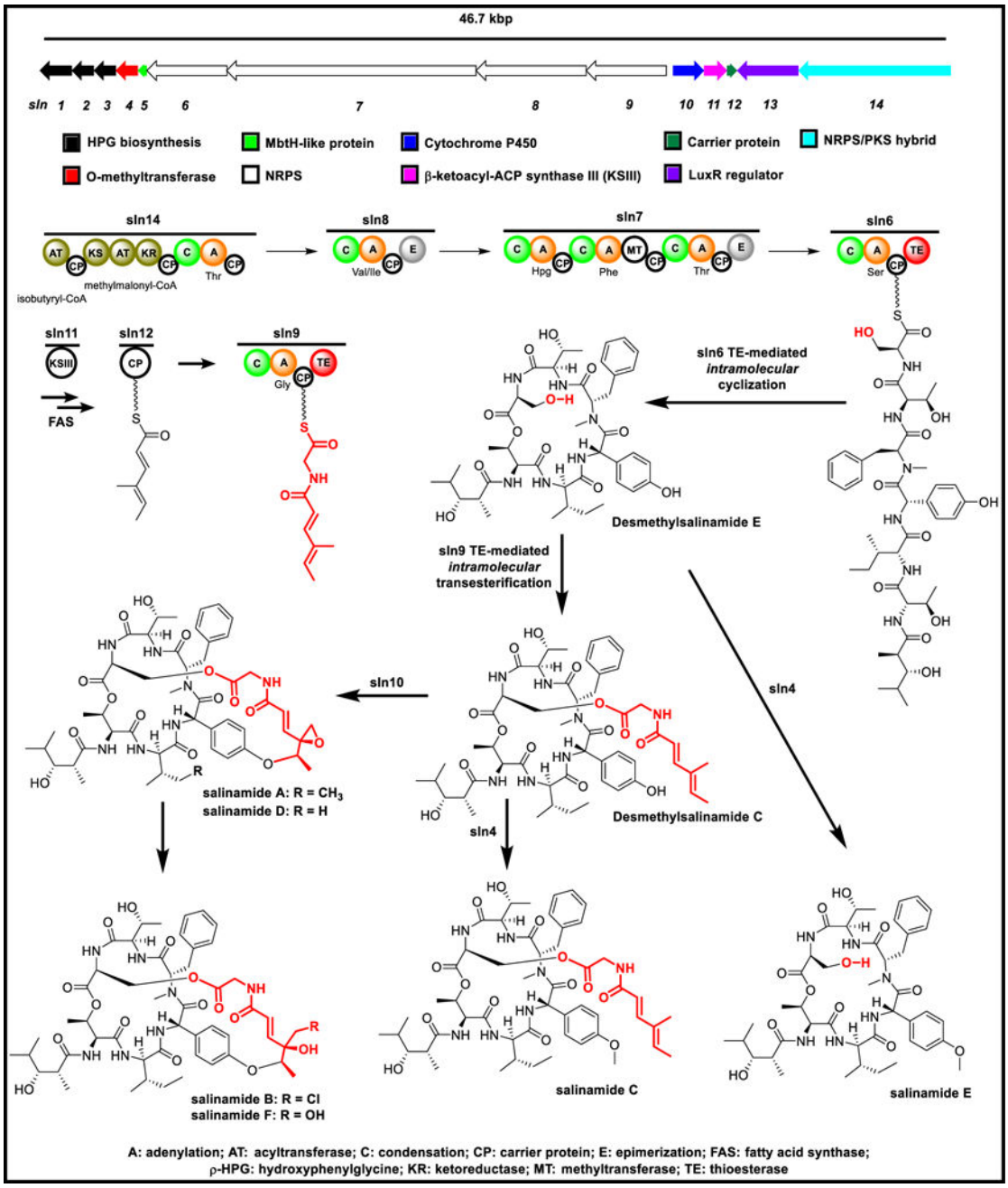


Figure 159.
Biosynthesis of salinamides

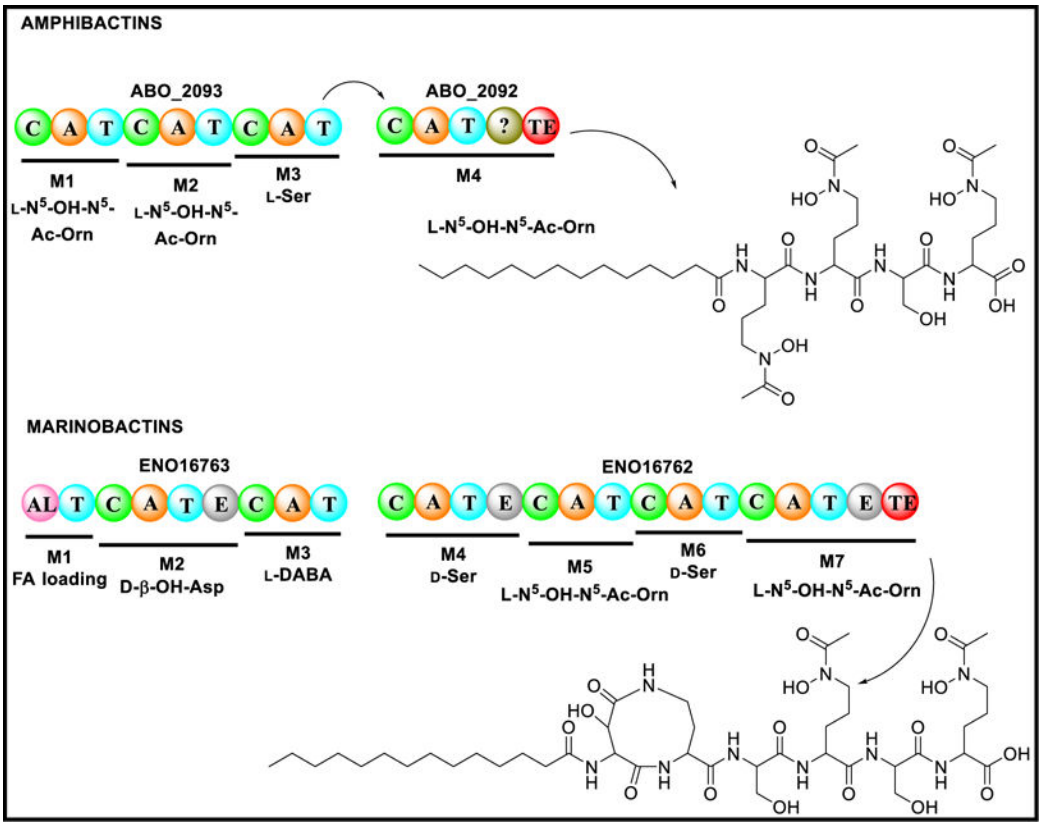


Figure 160.
Biosyntheses of amphibactins and marinobactins

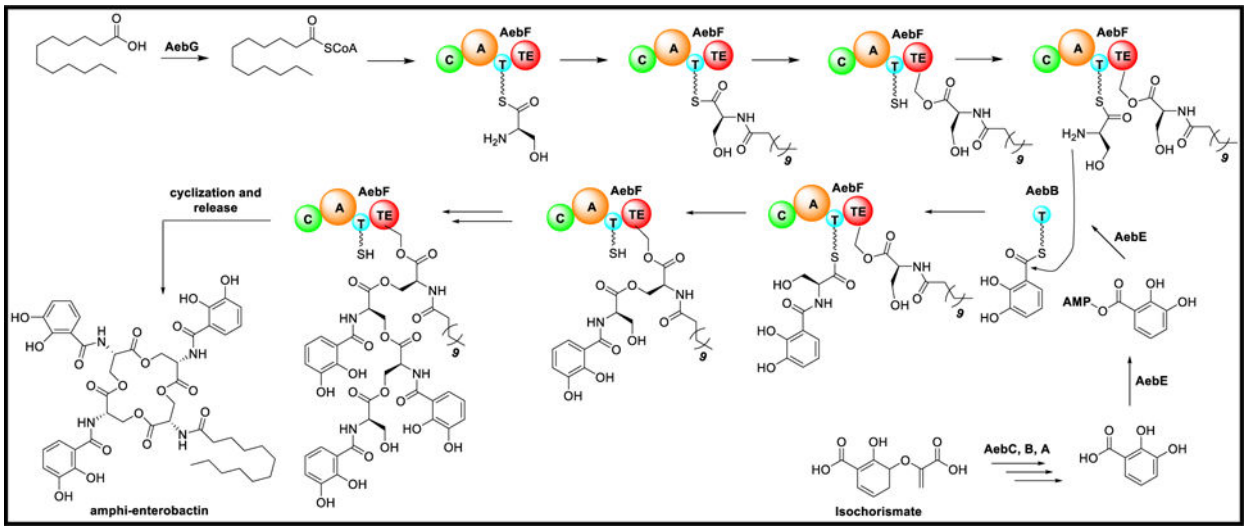


Figure 161.
Biosynthesis of amphi-enterobactin

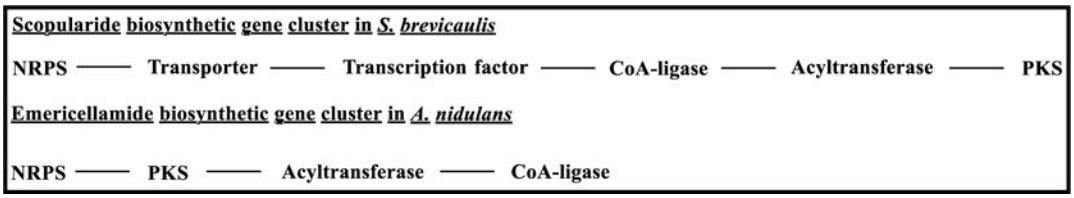


Figure 162.
Biosynthetic gene clusters of scopularide and emericellamide

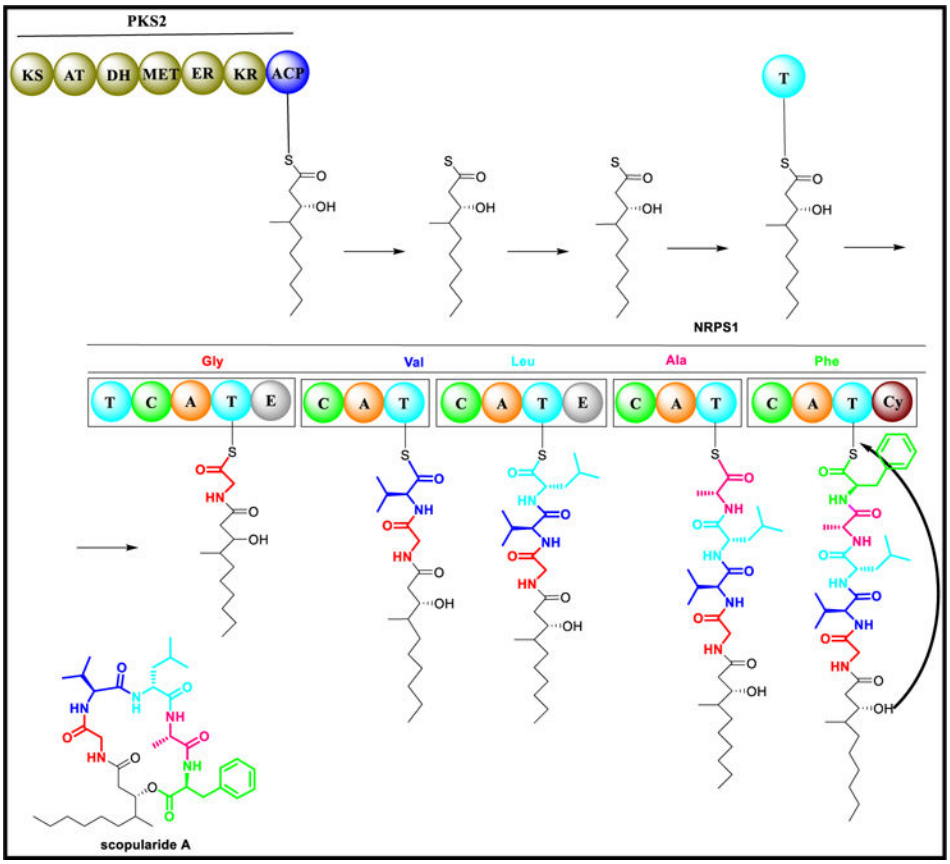


Figure 163.
Biosynthesis of Scopularide in *Scopulariopsis brevicaulis*

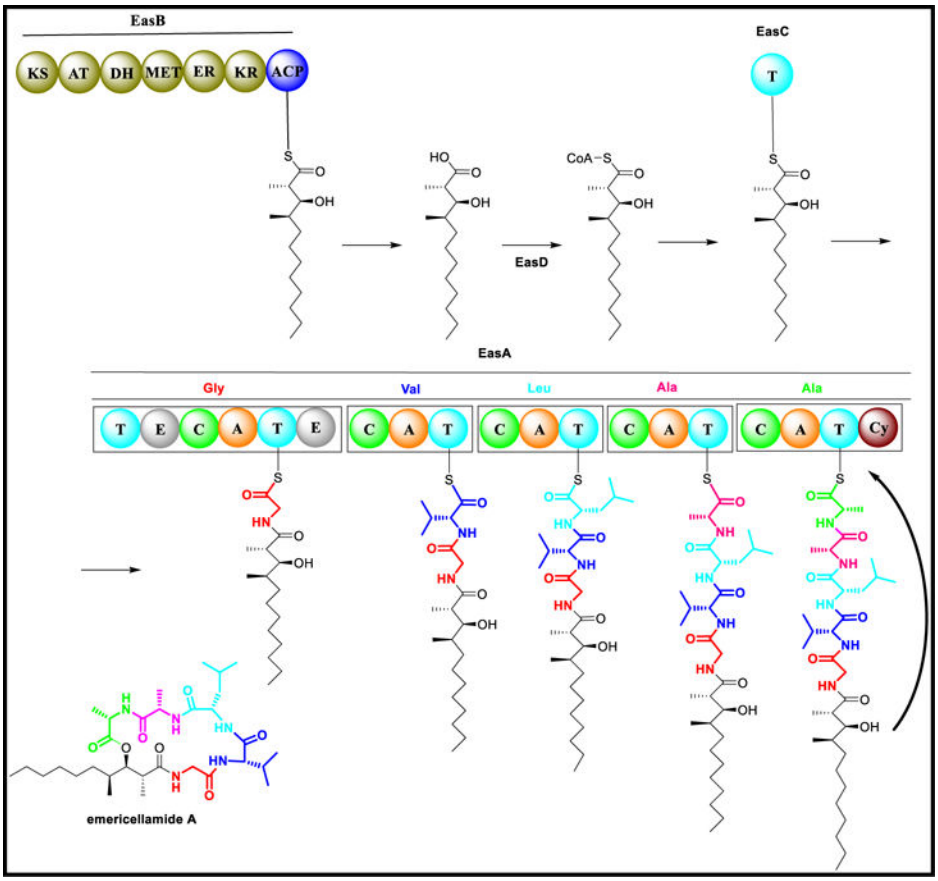


Figure 164.
Biosynthesis of emericellamide in *Aspergillus nidulans*

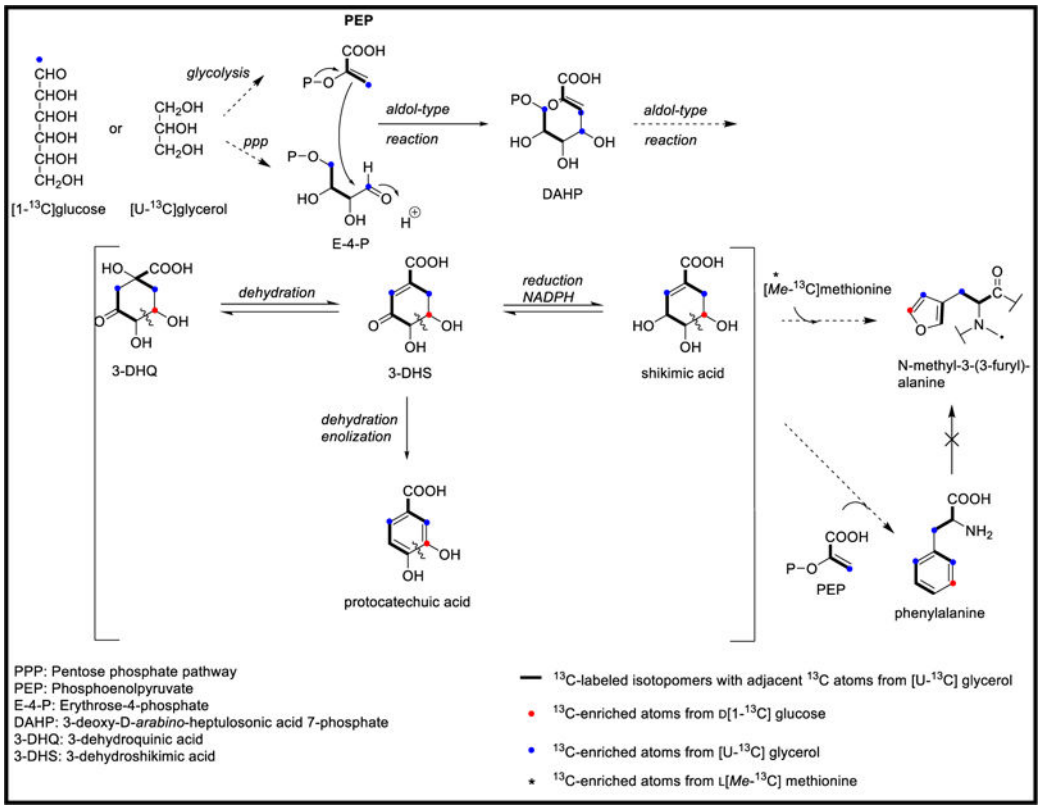


Figure 165.
Biosynthesis of *N*-methyl-3-(3-furyl)alanine

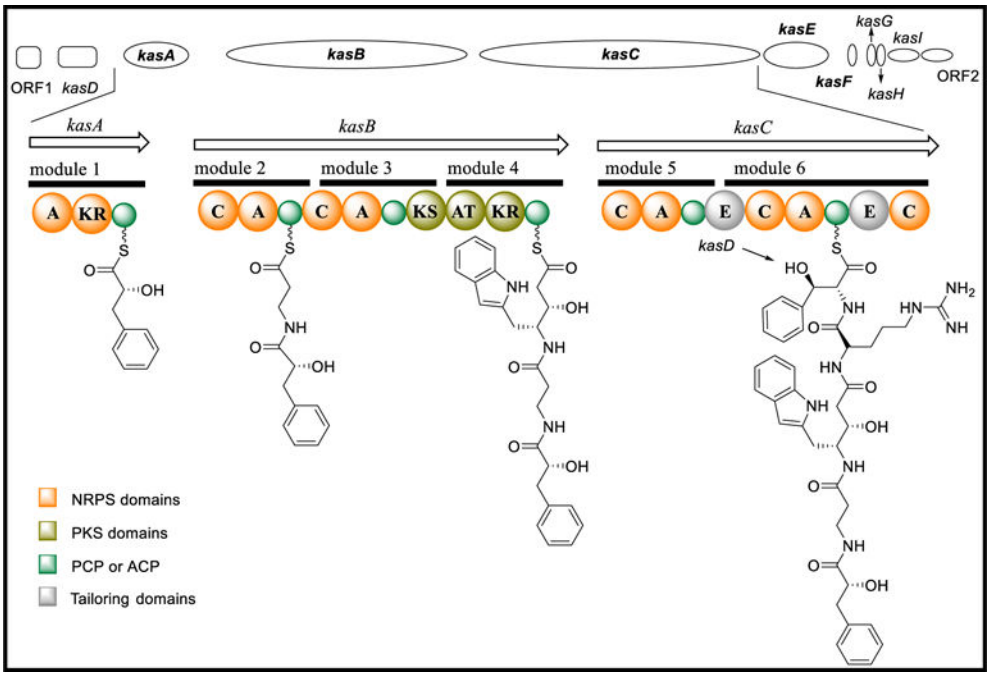


Figure 166.
Biosynthesis of kasumigamide

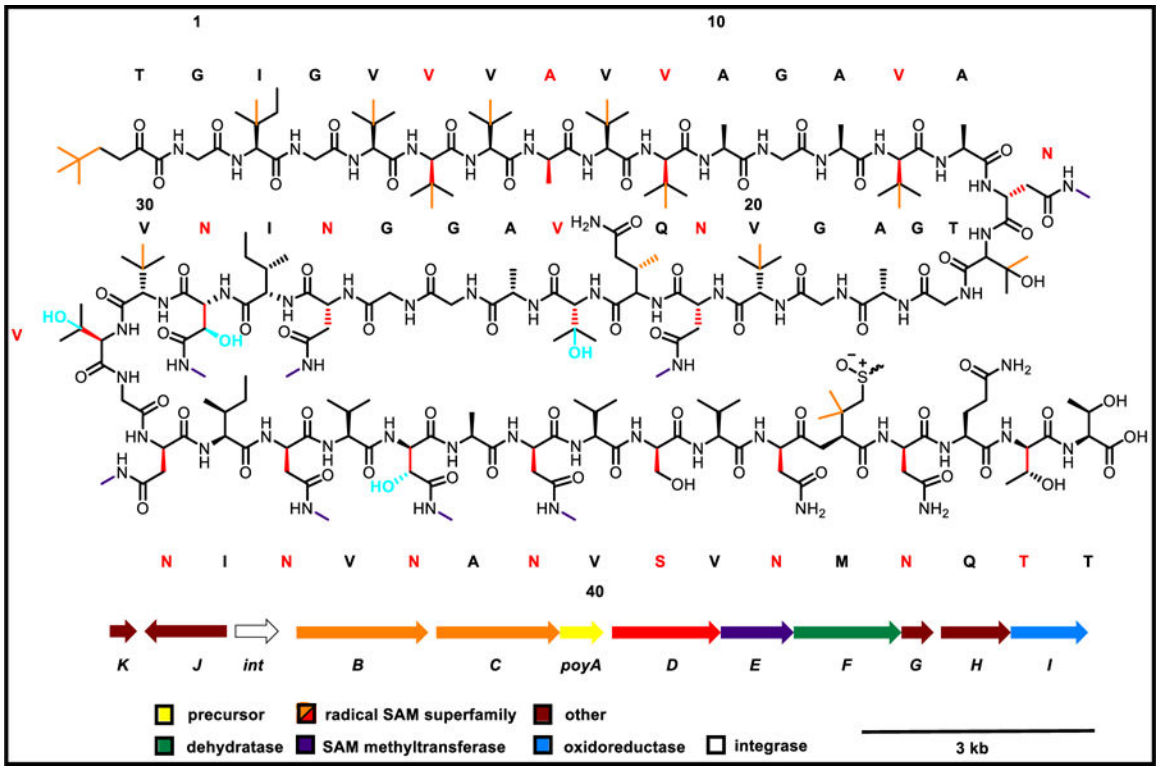


Figure 167.
Biosynthesis of polytheonamides

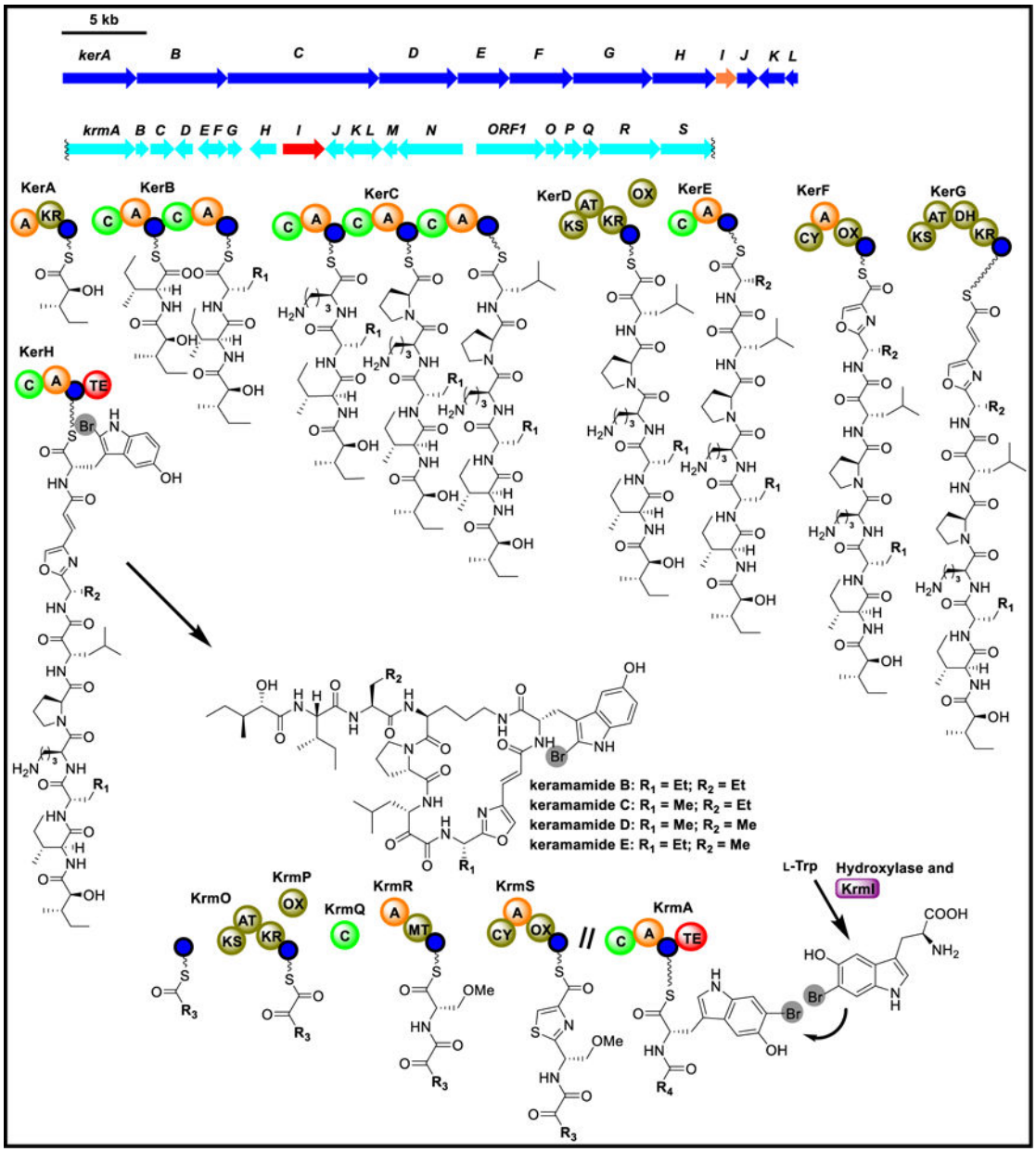


Figure 168.
Biosynthesis of keramamides

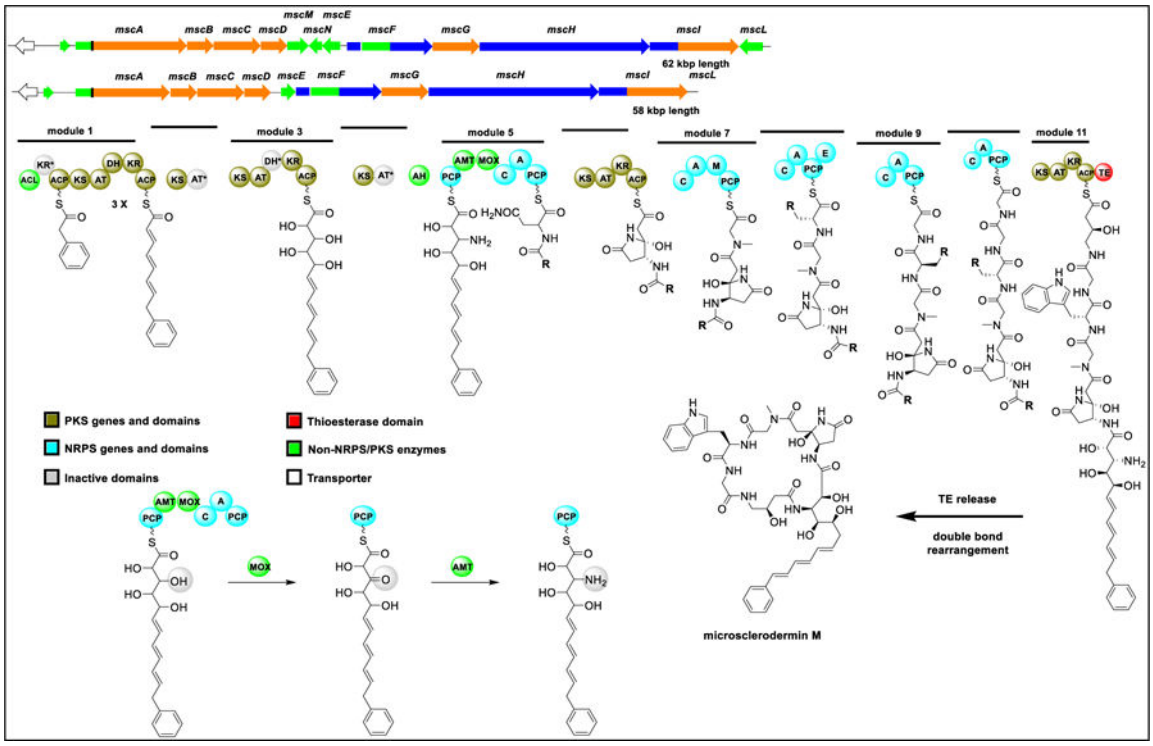


Figure 169.
Biosynthesis of microsclerodermins

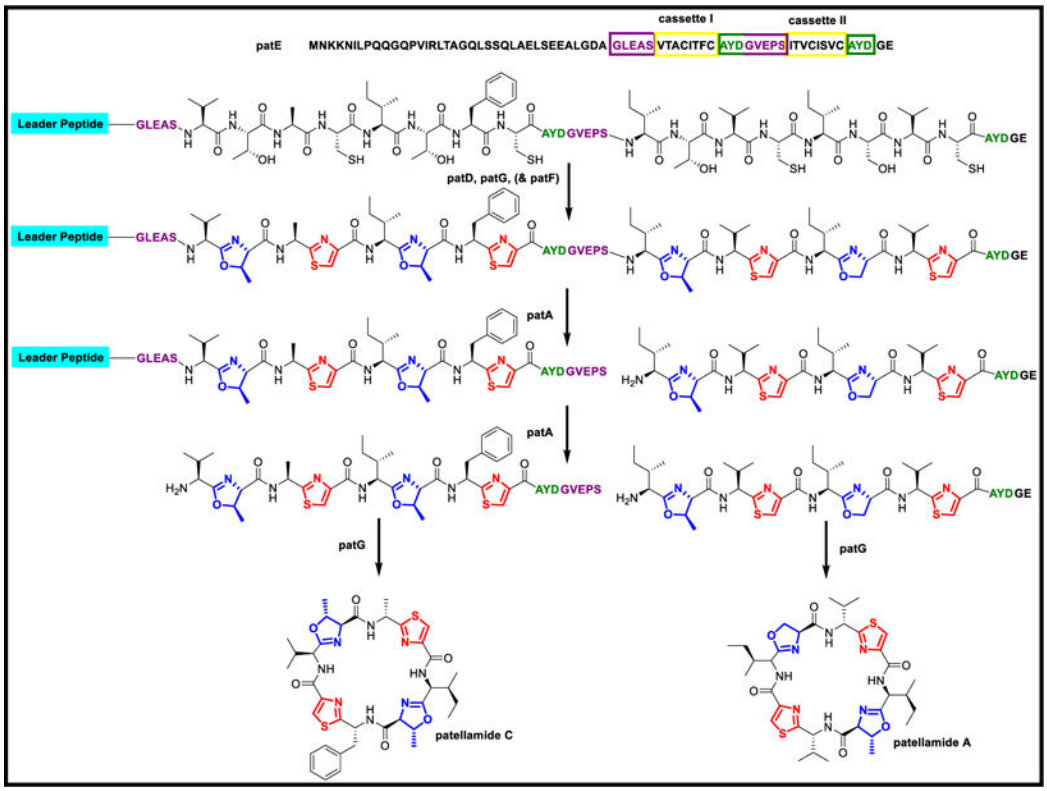


Figure 170.
Biosynthesis of patellamides

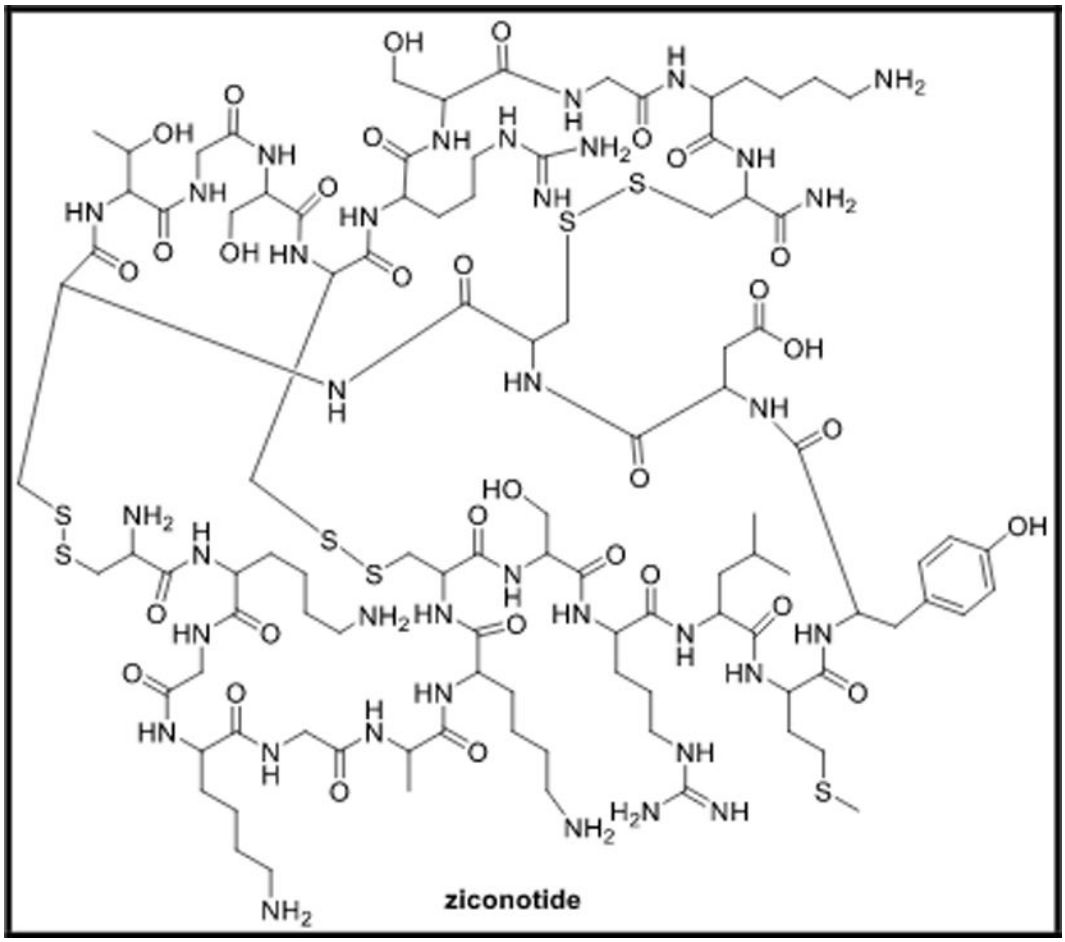


Figure 171.
Chemical structure of ziconotide

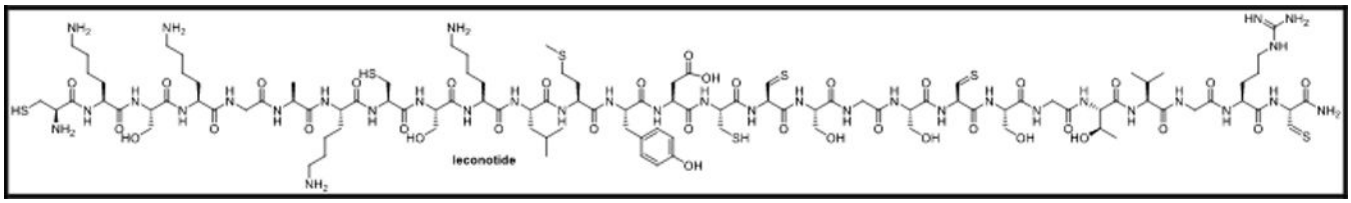


Figure 172.
Chemical structure of leconotide

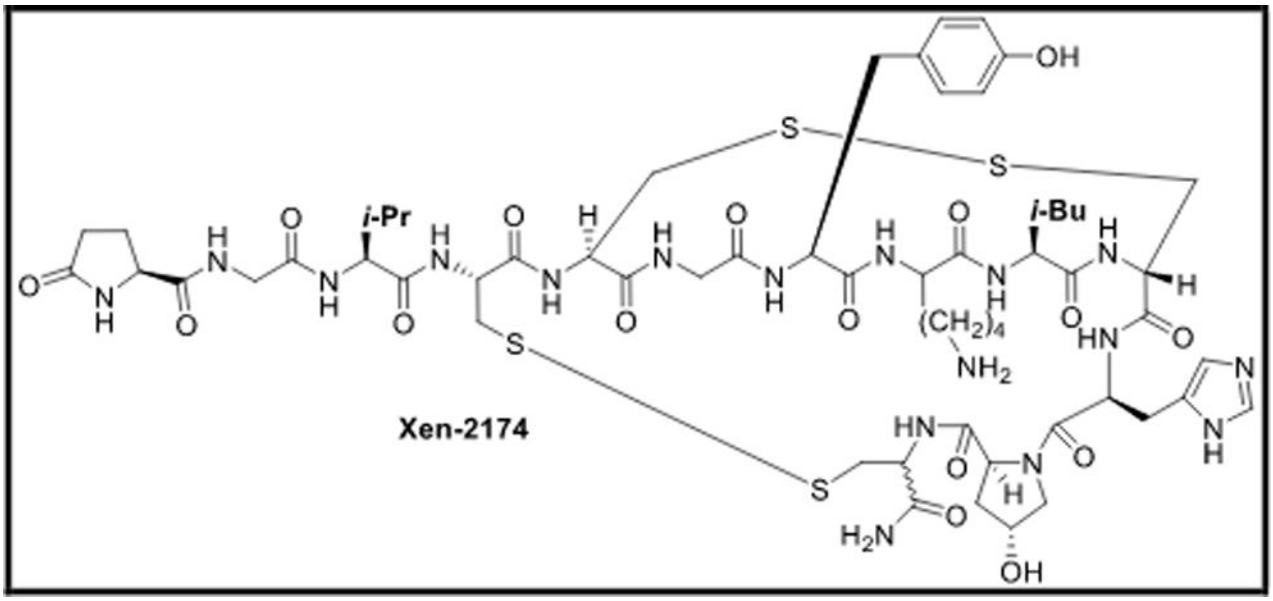


Figure 173.
Chemical structure of Xen-2174

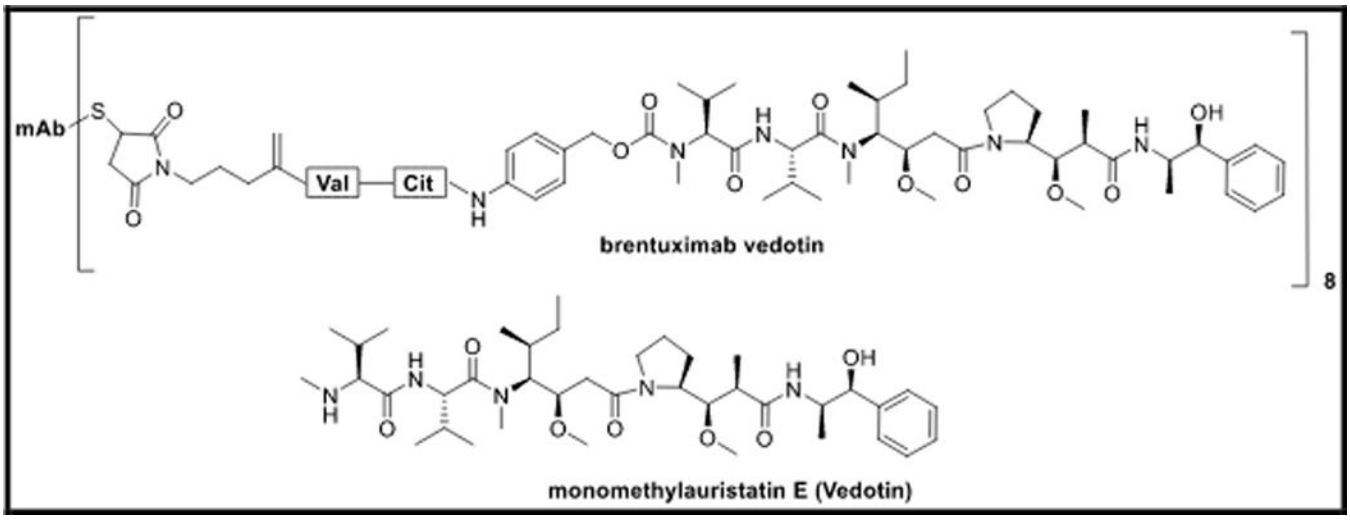


Figure 174.
Chemical structures of brentuximab vedotin and monomethylauristatin E

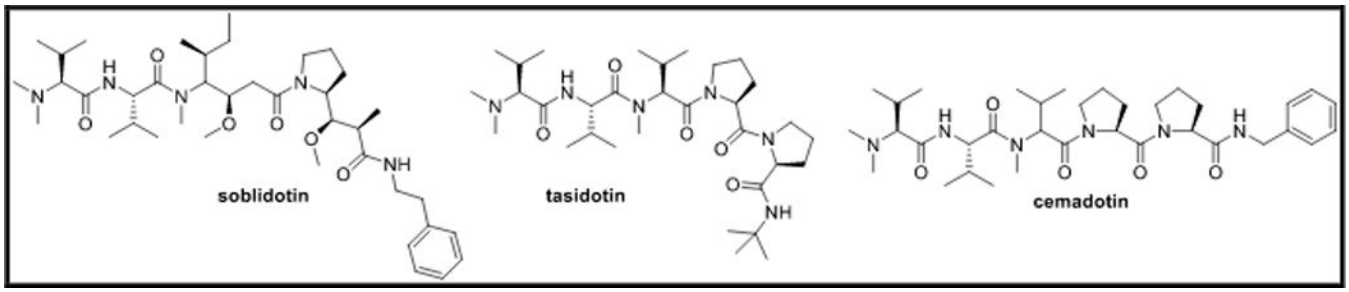


Figure 175.
Chemical structures of soblidotin, tasidotin, and cemadotin

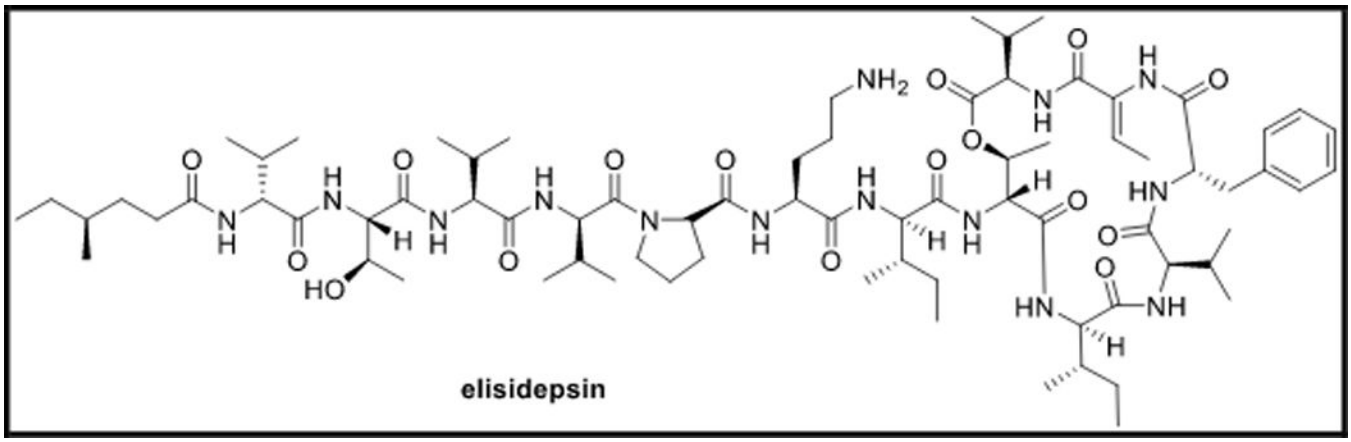


Figure 176.
Chemical structure of elisidepsin

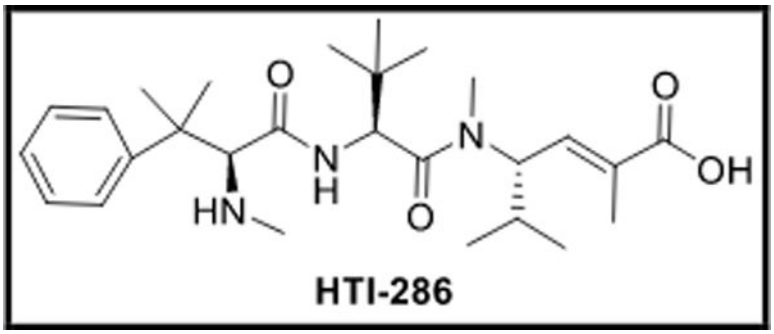


Figure 177.
Chemical structure of HTI-286

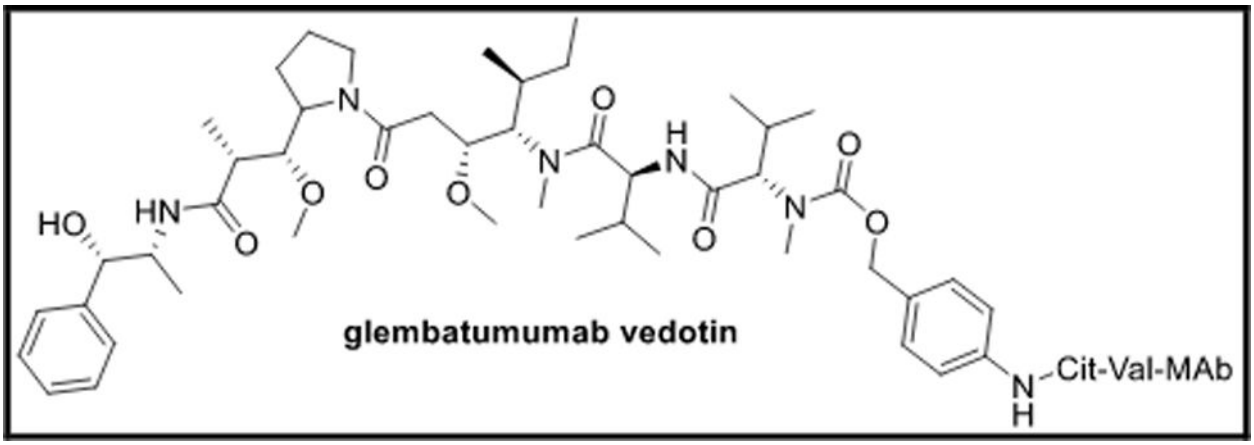


Figure 178.
Chemical structure of glembatumumab vedotin

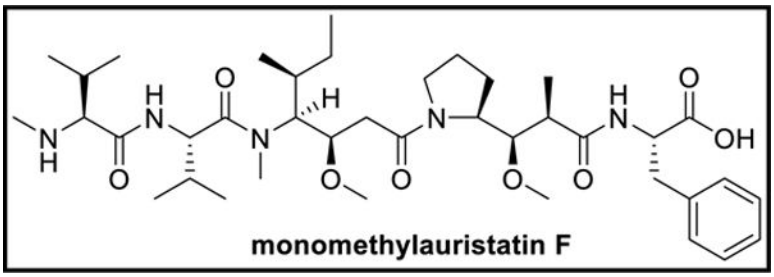


Figure 179.
Chemical structure of monomethylauristatin F

Table 1

Peptides from Marine Sponges

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Discodermins A–H	*Discodermia*	Cytotoxic	IC_{50} 0.01 – 11.9 μM	5–8
Kasumigamide	*D. calyx*	Antialgal	MIC 2.54 μM	9–10
Phakellistatins 1–3	*Phakellia* sp.	Cytotoxic	ED_{50} 0.4 – 9.1 μM	14–15, 17
Phakellistatin 4	*Phakellia* sp.	Cytotoxic	ED_{50} 40 μM	18–19
Phakellistatin 5	*Phakellia* sp.	Cytotoxic	GI_{50} 0.6 μM	20
Phakellistatin 6	*Phakellia* sp.	Cytotoxic	GI_{50} 11.8 – 117.5 nM	21
Phakellistatins 7–14	*Phakellia* sp.	Cytotoxic	ED_{50} 0.01 – 6.4 μM	16, 22–25
Phakellistatin 15	*Phakellia* sp.	Antitumor	IC_{50} 8.5 μM	26–27
Phakellistatin 16	*Phakellia* sp.	P388 & BEL-7402 cytotoxicity	IC_{50} 5.4 & 14.3 μM	27
Phakellistatin 19	*Phakellia* sp.	Antimitotic	IC_{50} 420 to 84 nM	28
Geodiamolides A–F	*Pseudaxinyssa*	Cytotoxic	4.99, 4.37, 4.54, 62.15, 24.11, & 11.19 nM	31
Geodiamolide G	*Geodia*	Human glioblastoma/astrocytoma U373 cytotoxicity HEY human ovarian carcinoma cytotoxicity	IC_{50} 11.75 mM IC_{50} 13.12 mM	33
Jasplakinolide	*Jaspis johnstoni*	Apoptosis	–	34
Pipestelide A	*Pipestela candelabra*	Cytotoxic	IC_{50} 0.1 μM	35
Milnamide A	*Cymbastela*	Cytotoxic Tubulin polymerization PC3 & NFF cytotoxic	IC_{50} 1.65 μM IC_{50} 6.02 μM IC_{50} 11.0 & 70.6 nM	34, 36–39
Milnamide B/Hemiasterlin	*Hemiasterella, Cymbastela, Siphonochalina* & *Auletta*	Cytotoxic PC3 & NFF cytotoxic	IC_{50} 6.8 nM IC_{50} 0.05 & 0.40 nM	34, 37, 39
Milnamide C	*Auletta*	Anticancer PC3 & NFF cytotoxic	IC_{50} 267.77 pM IC_{50} 31.7 & 188 nM	36, 39
Milnamide D	*Cymbastela*	Cytotoxic Tubulin polymerization PC3 & NFF cytotoxic	IC_{50} 66.8 nM IC_{50} 16.9 μM IC_{50} 0.38 & 1.19 μM	34, 36–39
Milnamide E	*Pipestela candelabra*	PC3 & NFF cytotoxic	IC_{50} 34.2 & 123 nM	39
Milnamide F	*P. candelabra*	PC3 & NFF cytotoxic	IC_{50} 2.18 & 5.65 μM	39
Milnamide G	*P. candelabra*	PC3 cytotoxic	IC_{50} 2.87 μM	39
Hemiasterlin A	*P. candelabra*	PC3 & NFF cytotoxic	IC_{50} 0.27 & 1.03 nM	39
Hemiasterlin D	*P. candelabra*	PC3 & NFF cytotoxic	IC_{50} 2.20 & 8.16 nM	39
Scleritodermin A	*Scleritoderma nodosum*	Apoptosis Cytotoxic	IC_{50} 1.3 μM IC_{50} < 2 μM	34, 40–41
Mirabamide A	*Siliquariaspongi a mirabilis*	HIV-1 fusion & neutralization	IC_{50} 140 & 40 nM	42–43
Mirabamide C	*S. mirabilis*	HIV-1 fusion & neutralization	IC_{50} 1.3 μM & 140 nM	42–43
Mirabamide D	*S. mirabilis*	HIV-1 fusion & neutralization	IC_{50} 3.9 μM −190 nM	42–43
Mirabamides E–H	*Stelletta clavosa*	HIV-1 inhibition	IC_{50} 121, 62, 68, & 41 nM	44

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Celebeside A	*S. mirabilis*	HIV-1 neutralization assay	IC_{50} 2.1 μM	45
Theopapuamides A–C	*T. swinhoei* & *S. mirabilis*	Cytotoxic Antifungal	IC_{50} 1.3 – 2.6 μM 1-5 μg/disk	45
Homophymine A	*Homophymia* sp.	HIV-1 cytoprotective activity	IC_{50} 75 nM	46
Homophymines B–E	*Homophymia* sp.	Antiproliferative	IC_{50} 2–100 nM	47
Homophymines A1–E1	*Homophymia* sp.	Antiproliferative	IC_{50} 2-100 nM	47
Neamphamide A	*Neamphius huxleyi*	HIV-1 cytotoxicity	EC_{50} 28 nM	48–49
Neamphamides B–D	*N. huxleyi*	Anticancer	IC_{50} 88–370 nM	50
Callipeltin A	*Callipelta*	Anti-HIV, antifungal, inhibition of Na/Ca exchanger	–	51
Callipeltin B	*Callipelta*	Inhibition of Na/Ca exchanger	4 μM	51–52
Callipeltins F–I	*Callipelta*	Antifungal activity	MIC 10^{-4} M	54
Callipeltin K	*Callipelta*	Antifungal activity	MIC 10^{-4} M	55
Callipeltin J	*Callipelta*	Antifungal activity	MIC 10^{-4} M	55
Callipeltins N–O	*Asteropus*	Cytotoxic	IC_{50} 0.16 μM	56
Microspinosamide	*Sidonops microspinosa*	HIV-1 cytopathic effect	EC_{50} 115.8 nM	57
Carteritin A	*Stylissa carteri*	HeLa, HCT116, & RAW264 cytotoxicity	IC_{50} 0.7, 1.3, & 1.5 μM	58
Mycothiazole	*Spongia mycofijiensis*	Anti-helminthic	123.59 μM	34, 59
Microcionamide A	*Clathria abietina*	SKBR-3 & MCF-7 activity Anti-tubercular	IC_{50} 98 & 125 nM MIC 5.7 μM	34, 62–63
Microcionamide B	*C. abietina*	SKBR-3 & MCF-7 activity Anti-tubercular	IC_{50} 172 & 177 nM MIC 5.7 μM	34, 62–63
Halicylindramides A–C	*Halichondria cylindrata*	Cytotoxic Anti-fungal	IC_{50} 0.3, 0.1, & 0.1 μM MIC 7.5 μg/disk	34, 64
Halicylindramide B methyl ester	*H. cylindrata*	Antifungal Cytotoxic	120 μg/disk 5.5 μM	34, 64
Haligramide A	*Haliclona nigra*	A549, HCT-15, SF-539, SNB-19 cytotoxicity	6.6, 19.9, 11.5, & 11.6 μM	34, 65
Haligramide B	*H. nigra*	A549, HCT-15, SF-539, SNB-19 cytotoxicity	4.9, 11.0, 6.3, & 8.2 μM	34, 65
Waiakeamide	*Ircinia dendroides*	Cytotoxic	IC_{50} 66.2 nM	66
Cyclocinamide A	*Psammocinia* sp.	Cytotoxic	–	34, 68–69
Pembamide	*Cribrochalina*	A-549, HT-29, MDA-MB-231 cytotoxicity	GI_{50} 2.46, 3.80, & 3.35 μM	70
Kapakahines A–C	*C. olemda*	Cytotoxic	IC_{50} 5.1, 5.9, & 4.7 μM	71
Kapakahine E	*C. olemda*	Cytotoxic	IC_{50} 5.0 μM	72
Taumycin A	*Fascaplysinopsis*	Brine shrimp toxicity Anti-leukemic	IC_{50} 17.9 μM 1 μM	73
Taumycin B	*Fascaplysinopsis*	Brine shrimp toxicity	IC_{50} 17.9 μM	73
Pipecolidepsin A	*Homophymia lamellosa*	A549, HT29, MDA-MB-231 cytotoxicity	GI_{50} 0.6, 1.12, & 0.7 μM	74–75
Pipecolidepsin B	*H. lamellosa*	A549, HT29, MDA-MB-231 cytotoxicity	GI_{50} 0.04, 0.01, 0.02 μM	74–75

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Halipeptin A	*Haliclona* sp.	Anti-inflammatory	0.3 mg/kg	76–77
Halipeptin D	*Haliclona* sp.	Cytotoxic Anti-tumor	IC_{50} 7 nM IC_{50} 420 nM	77
Tausalarin C	*Fascaplysinopsis*	Anti-leukemic	1 μM	78
Arenastatin A	*Dysidea arenaria*	Cytotoxic	IC_{50} 8.2 pM	79–80
Axinastatin 2	*Axinella* sp.	Cytostatic	GI_{50} 9.4 – 456.4 nM	81
Axinastatin 3	*Axinella* sp.	Cytostatic Anti-leukemic	GI_{50} 9.2 – 448.2 nM ED_{50} 512.2 nM	81
Hymenamide A	*Hymeniacidon*	Anti-fungal	MIC 37.5 μM	84
Hymenamide B	*Hymeniacidon*	Anti-fungal Cytotoxic to KB cells and murine lymphoma L1210 cells	MIC 79.4 μM IC_{50} 7.2 & 3.8 μM	84
Hymenamides C & E	*Hymeniacidon*	Antifungal	MIC 160.7 & 155.7 μM	85
Hymenamide H	*Hymeniacidon*	Cytotoxic	IC_{50} 6.96 μM	87
Hymenamide J	*Hymeniacidon*	KB & L1210 cytotoxicity	IC_{50} 691.2 nM & 2.4 μM	87
Hymenamides G & K	*Hymeniacidon*	Cytotoxic	IC_{50} 70.5 & 72.5 μM	87
Wainunuamide	*Stylotella aurantium*	Cytotoxic against K562 & A2780	ID_{50} 24.6 & 25.7 μM	88
Axinellins A–B	*Axinella carteri*	Antitumor	IC_{50} 3.7 & 7.8 μM	89
Axinellin C	*A. carteri*	K562 & A2780 cytotoxicity	ID_{50} 4.8 & 14.0 μM	90
Stylopeptide 2	*Stylotella* sp. &	Anticancer	10^{-5} M	93
Stylostatin 1	*S. aurantium*	Anti-leukemic	ED_{50} 1.1 μM	94
Hymenistatin 1	*Hymeniacidon*	Cytotoxic	ED_{50} 3.9 μM	97
Discobahamins A–B	*Discodermia*	Antifungal	–	98
Calyxamides A–B	*D. calyx*	Cytotoxic	–	99–100
Microsclerodermins *A*. A–B	*Microscleroderma*	Antifungal	2.5 μg/disk	101
Microsclerodermin C	*Theonella*	Antifungal	5 μg/disk	102
Microsclerodermin D	*Theonella*	Antifungal	100 μg/disk	102
Microsclerodermin E	*Theonella*	Antifungal	10 μg/disk	102
Microsclerodermins F–I	*Microscleroderma*	Cytotoxic Antifungal	1.9, 2.6, 1.1, & 1.2 μM 1.5, 3.0, 12.0, & 25.0 μg/disk	103
Microsclerodermins J–K	*Microscleroderma*	Antifungal	–	104
Anhydromicrosclerode rmin C	*Theonella*	Antifungal	50 μg/disk	102
Aciculitins A–C	*Aciculites orientalis*	Cytotoxic Antifungal	IC_{50} 0.4 μM 2.5 μg/disk	105
Polydiscamide A	*Discodermia* sp.	Anticancer Antimicrobial	IC_{50} 403.8 nM MIC 1.8 μM	106
Polydiscamides B–D	*Ircinia*	SNSR agonists	EC_{50} 1.26, 3.57, & 2.80 μM	107
Criamide B	*Cymbastela*	A549, LOVO, HEY, U373, & P388 cytotoxicity MCF7 cytotoxicity	ED_{50} 424.3, 219.5, 277.9, 395.0, & 10.2 nM ED_{50} 9.9 μM	108
Gombamide A	*Clathria gombawuiensis*	A549 & K562 cytotoxicity	LC_{50} 7.1 & 6.9 μM	109

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
		Na^+/K^+-ATPase inhibition	LC_{50} 9.4 μM	
Neopetrosiamides A & B	*Neopetrosia* sp.	Inhibition of amoeboid invasion of tumor cells	1.95 μM	112
Sulfolipodiscamides A–C	*Discodermia kiiensis*	Cytotoxicity	–	113
Lipodiscamides A–C	*D. kiiensis*	P388 cytotoxic HeLa cytotoxic	IC_{50} 23, 20, & 31 μM IC_{50} 18, 26, & 46 μM	114
Stylissamide H	*Stylissa caribica*	Cytotoxic	EC_{50} 5.7 μM	118
Stylissamide X	*Stylissa* sp.	Inhibition of HeLa cell-migration	0.1– 10 μM	118
Stylissatin A	*S. massa*	NO Inhibition	IC_{50} 87 μM	119
Stylissatin B	*S. massa*	Antitumor	IC_{50} 2.4 – 9.8 μM	120
Reniochalistatin E	*Reniochalina stalagmitis*	RPMI-8226 & MGC- 803 cytotoxicity	IC_{50} 4.9 & 9.7 μM	122
Yaku'amides A–B	*Ceratopsion* sp.	Cytotoxic	IC_{50} 8.5 & 2.4 nM	123
Chujamide A	*Suberites waedoensis*	A549 & K562 cytotoxicity	LC_{50} 10.1 & 37.0 μM	124
Chujamide B	*S. waedoensis*	A549 & K562 cytotoxicity Na^+/K^+-ATPase inhibition	LC_{50} 26.4 & 55.6 μM IC_{50} 17.2 μM	124
Leucamide A	*Leucetta microraphis*	Huh7, HepG2, & HM02 cytotoxic	GI_{50} 8.3, 9.6, & 8.5 μM	125
Azumamide A	*Mycale izuensis*	Histone deacetylase inhibition K562 & WiDr cytotoxic	IC_{50} 0.045 μM IC_{50} 4.5 & 5.8 μM	126
Azumamides B-E	*M. izuensis*	Histone deacetylase inhibition	IC_{50} 0.11, 0.11, 1.3 & 0.064 μM	126
Phoriospongins A-B	*Phoriospongia* sp. & *Callyspongia bilamellata*	Nematocidal	LD_{99} 7.2 μM	127
Callyaerins E	*C. aerizusa*	Cytotoxic	ED_{50} 0.39 μM	128
Callyaerin H	*C. aerizusa*	Cytotoxic	ED_{50} 0.48 μM	128
Callyaerin G	*C. aerizusa*	Cytotoxic	2.3 – 7.7 μM	129
Motuporin	*T. swinhoei*	Protein phosphatase-1 inhibitor & Cytotoxic	IC_{50} < 1.0 nM IC_{50} 3.1 – 16.2 μM	130–131
Theonellapeptolide Id	*T. swinhoei*	Cytotoxic	IC_{50} 1.7 μM	132
Nazumazoles A-C	*T. swinhoei*	Cytotoxic	IC_{50} 0.8 μM	133–134
Nazumazoles D-F	*T. swinhoei*	Protease inhibitors	IC_{50} 2.0, 3.0, & 10.0 μM	133–134
Orbiculamide A	*Theonella sp.*	Cytotoxic	IC_{50} 4.8 μM	135
Polytheonamides A–C	*T. swinhoei*	Cytotoxic	IC_{50} 15.5, 13.5, & 13.5 pM	136–137
Cyclotheonamide A	*T. swinhoei*	Serine protease inhibitor	Streptokinase: IC_{50} 0.02 μM Trypsin: IC_{50} 0.04 μM α-thrombin: IC_{50} 0.18 μM	140
Cyclotheonamides E, E2 & E3	*T. swinhoei*	Thrombin inhibitor Trypsin inhibitor	IC 50 2.9, 13.0 & 9.5 nM IC_{50} 30.0, 55.0 & 52.0 nM	139
Nazumamide A	*T. swinhoei*	Thrombin inhibitor	IC_{50} 4.6 μM	141
Pseudotheonamides A1, A2, B2, C, D	*T. swinhoei*	Thrombin inhibitors Trypsin inhibitors	IC_{50} 1.0, 3.0, 1.3, 0.2, & 1.4 μM IC_{50} 4.5, > 10, 6.2, 3.8, & > 10 μM	138

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Dihydrocyclotheonami de A	*T. swinhoei*	Thrombin inhibitor Trypsin inhibitor	IC_{50} 0.33 μM IC_{50} 6.7 μM	138
Theonellamides A–C	*Theonella* sp.	Cytotoxic	IC_{50} 2.8, 1.1, 1.6 μM	142
Theonellamides D-E	*Theonella* sp.	Cytotoxic	IC_{50} 953.2, & 496.3 nM	142
Theonellamide G	*T. swinhoei*	Antifungal Cytotoxic	IC_{50} 4.5 & 2.0 μM IC_{50} 6.0 μM	143
Keramamide A	*T. swinhoei*	Ca^{2+}-ATPase inhibitor	IC_{50} 3×10^{-4} moldm^{-3}	144
Keramamides B–D	*T. swinhoei*	Inhibition of human neutrophil superoxide generation	5×10^{-8} M	145
Keramamide E	*T. swinhoei*	KB & L1210 cytotoxicity	IC_{50} 1.37 & 1.42 μM	147
Keramamide F	*T. swinhoei*	Cytotoxic	–	146
Keramamide G–H	*T. swinhoei*	Cytotoxic	~ 10 μM	147
Keramamide J	*T. swinhoei*	Cytotoxic	~ 10 μM	147
Keramamides K–L	*T. swinhoei*	L1210 cytotoxicity KB cytotoxicity	IC_{50} 768.1 & 495.9 nM IC_{50} 448.0 & 970.4 nM	148
Keramamides M–N	*T. swinhoei*	KB cytotoxicity L1210 cytotoxicity	IC_{50} 5.1 & 6.2 μM IC_{50} 2.0 & 2.3 μM	149
Koshikamide A1	*T. swinhoei*	Cytotoxic	IC_{50} 1.7 μM	150
Koshikamide A2	*T. swinhoei*	Cytotoxic	IC_{50} 4.6 μM	151
Koshikamide B	*T. swinhoei*	Human colon tumor & P388 cytotoxicity	IC_{50} 3.7& 0.2 μM	152
Koshikamide F	*T. swinhoei*	HIV entry inhibition	IC_{50} 2.3 μM	152
Koshikamide H	*T. swinhoei*	HIV entry inhibition Cytotoxic	IC_{50} 5.5 μM IC_{50} 10 μM	152
Nagahamide A	*Theonella* sp.	Antibacterial	50 μg	154
Papuamide A	*Theonella* sp.	Anti-infective Cytotoxic HIV entry	EC_{50} 2.8 nM IC_{50} 52.9 nM 710 nM	155–156
Papuamide B	*Theonella* sp.	Anti-infective HIV-entry inhibition	EC_{50} 2.8 nM 710 nM	155–156
Papuamides C–D	*Theonella* sp.	HIV entry	28.4 & 14.2 μM	156
Papuamides E–F	*Melophlus*	Brine shrimp toxicity	LD_{50} 66.5 & 77.4 μM	157
Theonellamide F	*Theonella* sp.	P388 & L1210 cytotoxicity	IC_{50} 1.6 & 1.9 μM	158
Theonegramide	*Theonella sp.*	Antifungal	10 μg/disk	159
Cupolamide A	*T. cupola*	Cytotoxic	IC50 7.2 μM	160
Theonellapeptolide Ib–Ie	*T. swinhoei*	Cytotoxic	IC50 1.2, 0.9, 1.7, & 0.9 μM	163
Theonellapeptolide IId–IIe	*T. swinhoei*	Cytotoxic	9.4 μM	152
Theonellapeptolide IIIe	*T. swinhoei*	Cytotoxic	4.8 μM	166
Congeners 1–2	*Theonella sp.*	Cytotoxic	IC50 6.3 & 5.4 μM	170
Solomonamide A	*T. swinhoei*	Anti-inflammatory	0.1 mg/kg	171
Cyclolithistide A	*T. swinhoei*	Antifungal	20 μg/disk	172
Theopalauamide	*T. swinhoei*	Antifungal	10 μg/disk	174

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Isotheopalauamide	*T. swinhoei*	Antifungal	50 μg/disk	174
Miraziridine A	*Theonella*	Cathepsin B inhibitor	IC50 2.1 μM	152
Perthamide B	*Theonella*	[125I]IL-1β inhibition	IC50 27.6 μM	177
Perthamide C–D	*Theonella*	Anti-inflammatory Edema reduction	– 0.3 mg/kg	178–179
Perthamide E	*Theonella*	Anti-inflammatory	–	178
Perthamides H–I	*Theonella*	Edema reduction	0.3 mg/kg	179
Perthamide K	*Theonella*	Edema reduction	0.3 mg/kg	179
Mutremdamide A	*Theonella*	Edema inhibition	0.3 mg/kg	152

Table 2

Peptides isolated from Marine Cyanobacteria

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Nodularin	*Nodularia pumigena*	Protein phosphatases 1 & 2A inhibitor	ED_{50} 0.7 nM	185
Turnagainolide B	*Bacillus* sp.	Inositol 5-phosphatase stimulator	–	190
Solonamides A-B	*Photobacterium halotolerans*	Viral gene expression controller	–	190
Fijimycins A-C	*Streptomyces*	Antibacterial	–	190
Brunsvicamide A	*Tychonema* sp.	Antitubercular	IC_{50} 64.2 μM	191
Brunsvicamides B-C	*Tychonema* sp.	Antitubercular	IC_{50} 7.3 & 8.0 μM	191
Malyngamide 2	*L. sordida*	Anti-inflammatory	–	190, 192
Malyngamide 3	*L. majuscula*	HT-29 & MCF7 cytotoxicity	IC_{50} 48 & 29 μM	192
Cocosamides A-B	*L. majuscula*	HT-29 cytotoxicity MCF7 cytotoxicity	IC_{50} 24 & 11 μM IC_{50} 30 & 39 μM	192
Pitiprolamide	*L. majuscula*	Cytotoxic & antibacterial	–	190
Pitipeptolides A-F	*L. majuscula*	Anti-tubercular & cytotoxicity	–	190, 193
Lagunamides A-C	*L. majuscula*	Cytotoxic, anti-swarming & antimalarial	–	190, 194
Wewakamide A	*L. semiplena*	Brine shrimp toxicity	–	190, 195
Guineamide G	*L. majuscula*	Brine shrimp toxicity & cytotoxic	–	190, 195
Wewakazole	*L. majuscula*	Cytotoxic	IC_{50} 10 μM	197–198
Wewakazole B	*Moorea producens*	MCF7 & H460 cytotoxicity	IC_{50} 0.58 & 1.0 μM	197–198
Wewakpeptins A-B	*L. majuscula*	Cytotoxic	LC_{50} 0.4 μM	199
Porpoisamides A-B	*Lyngbya* sp.	Cytotoxic	–	190
Bisebromoamide	*Lyngbya* sp.	Anti-proliferative	–	200–202
Norbisebromoamide	*Lyngbya* sp.	Anti-proliferative	–	200–202
Somocystinamide A	*L. majuscula/Schizothrix* sp.	Apoptosis	–	34, 203
C-phycocyanin	*S. platensis, A. quadruplicatum* & *M. laminosus*	Apoptosis	–	34
Desmethoxymajusc ulamide C	*L. majuscula*	Antitumor	IC_{50} 20 nM	204
Epilyngbyastatin 1	*L. majuscula/Schizothr ix calcicola*	Cytotoxic Cellular microfilament disrupter	MIC 0.1 μM 2.0 & 0.2 μM	205
Majusculamide C	*L. majuscula*	Cytotoxic & antifungal	–	34, 207–208
Majusculamide D	*L. majuscula*	Cytotoxicity	0.25 μM	208
Deoxymajusculamid e D	*L. majuscula*	Cytotoxicity	0.3 μM	208
Lyngbyastatin 3	*L. majuscula*	LoVo & KB cytotoxicity	IC_{50} 400 & 32 nM	209
Apratoxins A-C	*L. majuscula*	LoVo cytotoxic KB cytotoxic	IC_{50} 0.36–10.8 nM IC_{50} 0.52–21.3 nM	210
Apratoxin D	*L. majuscula* & *L. sordida*	Cytotoxic	IC_{50} 2.6 nM	204
Apratoxin E	*L. bouillonii*	Cytotoxic	21–72 nM	204

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Dragomabin	*L. majuscula*/*L. polychroa*	Antimalarial Cytotoxic	IC_{50} 6.0 μM IC_{50} 182.3 μM	204
Dragonamide A	*L. majuscula*/*L. polychroa*	Antimalarial Antileishmanial Cytotoxic	IC_{50} 7.7 μM IC_{50} 6.5 μM IC_{50} 67.8 μM	204
Dragonamide C	*L. majuscula*/*L. polychroa*	U2OS, IMR-32, & HT29 cytotoxicity	GI_{50} 56, 49, 22 μM	204
Dragonamide D	*L. majuscula*/*L. polychroa*	U2OS, IMR-32, & HT29 cytotoxicity	GI_{50} 59, 51, 32 μM	204
Dragonamide E	*L. majuscula*/*L. polychroa*	Antileishmanial	IC_{50} 5.1 μM	204
Carmabin A	*L. majuscula*/*L. polychroa*	Antimalarial Cytotoxic	IC_{50} 4.3 μM IC_{50} 9.8 μM	204
Herbamide B	*L. majuscula*	Antileishmanial	IC_{50} 5.9 μM	213
Almiramides B-C	*L. majuscula*	Antileishmanial	IC_{50} 2.4 & 1.9 μM	204
Grassystatins A-B	*L. confervoides*	Cathepsin D inhibitor Cathepsin E inhibitor TACE inhibitor	IC_{50} 7.3 & 26.5 nM IC_{50} 354 & 886 pM IC_{50} 1.2 & 2.2 μM	204
Grassystatin C	*L. confervoides*	TACE inhibitor	IC_{50} 28.6 μM	204
Obyanamide	*L. confervoides*	KB & LoVo cytotoxicity	IC_{50} 0.97 & 5.20 μM	214
Lobocyclamide A	*L. confervoides*	Antifungal	MIC 100 μg/disk	215
Lobocyclamide B	*L. confervoides*	Antifungal	MIC 30–100 μg/disk	215
Lobocyclamide C	*L. confervoides*	Antifungal	MIC 150 μg/disk	215
Hantupeptins A-C	*L. majuscula*	Brine shrimp toxicity MOLT-4 cytotoxicity MCF-7 cytotoxicity	100–10 ppm IC_{50} 32.0, 0.2, & 3.0 μM IC_{50} 4.0, 0.5, & 1.0 μM	204
Trungapeptin A	*L. majuscula*	Brine shrimp toxicity Ichthyotoxicity	10 ppm 6.25 ppm	216
Palmyramide A	*L. majuscula*	Sodium-channel blocker Cytotoxic	IC_{50} 17.2 μM IC_{50} 39.7 μM	196, 218
Dudawalamide A	*Lyngbya*	Anti-parasitic Antimalarial Antileishmanial	– IC_{50} 2.7 μM IC_{50} 25.9 μM	204, 218
Dudawalamide B	*Lyngbya*	Antimalarial Antileishmanial	IC_{50} 7.6 μM IC_{50} 14.7 μM	218
Dudawalamide D	*Lyngbya*	Antimalarial Antileishmanial	IC_{50} 3.7 μM IC 2.6 μM 50	218
Dudawalamide E	*Lyngbya*	Antimalarial Antileishmanial Antitrypanosomal	IC_{50} 7.7 μM IC_{50} 2.6 μM IC_{50} 7.3 μM	218
Grassypeptolide	*L. confervoides*	Cytotoxic	IC_{50} 1.0–4.2 μM	204
Carriebowmide	*L. majuscula*/*L. polychroa*	Feeding deterrent	–	204
Hoiamide A	*L. majuscula*	Sodium channel agonist & cytotoxic	–	204
Tiglicamides A-C	*L. confervoides*	Serine protease inhibitors	–	204
Largamides A-C	*L. confervoides*	Serine protease inhibitors	–	204

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Itralamide B	*L. majuscula*	Cytotoxic	IC_{50} 6.0±1.0 μM	204
Lyngbyastatins 4–6	*L. confervoides*	Serine protease inhibitors	–	204
Lyngbyastatin 7	*Lyngbya* sp.	Serine protease inhibitors	–	204
Lyngbyastatins 8–10	*L. semiplena*	Serine protease inhibitors	–	204
Kempopeptins A-B	*Lyngbya* sp.	Serine protease inhibitors	–	204
Lyngbyazothrins AB	*Lyngbya* sp.	Antimicrobial	–	204, 220
Lyngbyazothrins C-D	*Lyngbya* sp.	Antimicrobial	25–200 μg/disk	204, 220
Pahayokolide A	*Lyngbya* sp.	Zebra fish toxicity Brine shrimp toxicity Anticancer	LC_{50} 2.2 μM 679.0 μM IC_{50} 2.1–44.6 μM	204
Grassypeptolides D-E	*Leptolyngbya*	Neuro-2a mouse blastoma cytotoxic HeLa cervical carcinoma cytotoxic	IC_{50} 599 & 407 nM IC_{50} 335 & 192 nM	222
Grassypeptolides F-G	*L. majuscula*	AP-1 inhibitor	IC_{50} 5.2 & 6.0 μM	223
Ibuepidemethoxylyn gbyastatin 3	*Leptolyngbya*	Cytotoxic	IC_{50} > 10 μM	223
Lyngbyabellin A	*L. bouillonii*	Cytotoxic	IC_{50} 5.3 μM	225–226
Lyngbyabellin B	*L. majuscula*	Antifungal Brine shrimp toxicity	100 μg/disk LD_{50} 3.0 ppm	227–228
Lyngbyabellin C	*L. bouillonii*	Cytotoxic	IC_{50} 2.1 μM	225
Lyngbyabellin D	*L. bouillonii*, *L. majuscula*	Cytotoxic	IC_{50} 0.1–0.4 μM	229
Lyngbyabellin F	*L. majuscula*	Cytotoxic	IC_{50} 0.1–0.4 μM	229
Lyngbyabellin H	*L. majuscula*	Cytotoxic	IC_{50} 0.1–0.4 μM	229
Lyngbyabellin N	*L. majuscula*	Cytotoxic	IC_{50} 40.9±3.3 nM	230
Alotamide A	*L. bouillonii*	Calcium influx activator	EC_{50} 4.18 μM	231
Barbamide	*L. majuscula*	Molluscicidal	–	232
Jamaicamide A	*L. majuscula*	Cytotoxic Sodium channel blocker	LC_{50} 15 μM 5 μM	233
Jamaicamide B	*L. majuscula*	Cytotoxic Sodium channel blocker	LC_{50} 15 μM 5 μM	233
Jamaicamide C	*L. majuscula*	Cytotoxic Sodium channel blocker Brine shrimp toxicity	LC_{50} 15 μM 5 μM 10 ppm	233
Hectochlorin	*L. majuscula*	Antifungal CA46 & PtK2 cytotoxicity	10–100 μg/disk IC_{50} 20 & 300 nM	234
Apramide A	*L. majuscula*	Elastase activity	–	235
Aurilide	*Dolabella auricularia*	Apoptosis	–	236
Aurilides B-C	*L. majuscula*	Cytotoxic	LC_{50} 0.01–0.13 μM	236
Antillatoxin	*L. majuscula*	Ichthyotoxic	LD_{50} 99.3 nM	238
Barbaramide A	*L. majuscula*	Molluscicidal activity	LD_{100} 21.6 μM	239–240
Kalkitoxin	*L. majuscula*	Ichthyotoxic Cell division inhibitor Brine shrimp toxicity	LC_{50} 700 nM IC_{50} 25 nM LC_{50} 170 nM	241

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
		Sodium channel blocker	EC_{50} 1 nM	
Yanucamides A-B	*L. majuscula/Schizothrix* sp.	Brine shrimp toxicity	LD_{50} 5 ppm	243
Pseudodysidenin	*L. majuscula*	Cytotoxic	IC_{50} > 1.8 μM	244
Ulongamides A-E	*L. majuscula*	LoVo & KB cytotoxic	IC_{50} 5.0 & 1.0 μM	245
Isomalyngamides	*L. majuscula*	Crayfish toxicity	–	246
Malyngamide C	*L. majuscula*	Cytotoxic	IC_{50} 5.2 μM	247
8-*epi*-malyngamide C	*L. majuscula*	Cytotoxic	IC_{50} 15.4 μM	247
Malyngamide F	*L. majuscula*	NO inhibition	IC_{50} 5.4 μM	250
Malyngamide G	*L. majuscula*	Immunosuppressive	ED_{50} 14.2 μM	251
Malyngamides H-I	*L. majuscula*	Reduction of nitrite production	–	250–251
Malyngamide I	*L. majuscula*	Brine shrimp toxicity Goldfish toxicity	LD_{50} 72.3 μM LD < 20.7 μM 50	252
Malyngamide K	*L. majuscula*	Reduction of nitrite production	–	251
Malyngamide R	*L. majuscula*	Brine shrimp toxicity	LD_{50} 18 ppm	255
Malyngamide Y	*Moorea producens*	Anticancer	–	260
Hermitamide A	*L. majuscula*	Brine shrimp toxicity Ichthyotoxicity Cytotoxic	LD_{50} 5 μM LD_{50} 19 μM IC_{50} 2.2 μM	261
Hermitamide B	*L. majuscula*	Brine shrimp toxicity Cytotoxic	LD_{50} 18 μM IC_{50} 5.5 μM	261
Laxaphycin B	*L. majuscula*	Cytotoxic	IC_{50} 1.1 μM	262–264
Tasiamide	*Symploca* sp.	LoVo & KB cytotoxic	IC_{50} 4.2 & 0.6 μM	265
Tasiamide B	*Symploca* sp.	Cytotoxic	IC_{50} 0.8 μM	266
Tasiamide F	*Lyngbya* sp.	Cathepsin D & E inhibitor	IC_{50} 57 & 23 nM	268
Tasipeptins A-B	*Symploca* sp.	Cytotoxic	IC_{50} 0.9 & 0.8 μM	269
Symplocamide A	*Symploca* sp.	Neuro-2a neuroblastoma & H-460 cytotoxicity	IC_{50} 29 & 40 nM	270
Symplocin A	*Symploca* sp.	Cathepsin E inhibitor	IC_{50} 300 pM	271
Veraguamides A-G	*Symploca cf. hydnoides*	Cytotoxic	–	272
Symplostatin 1	*Symploca hydnoides*	Proapoptosis	–	273
Symplostatin 3	*S. hydnoides*	KB & LoVo cytotoxicity	IC_{50} 3.9 & 10.3 nM	275
Symplostatin 4	*Symploca* sp.	Antimalarial Pathogen replication inhibitor	IC_{50} 36–100 nM EC_{50} 0.7 μM	276
Malevamide D	*S. hydnoides*	Cytotoxic, antiproliferative & tubulin disruption	–	273
Belamide A	*S. hydnoides*	Antiproliferative & tubulin disruption	–	273
Largazole	*Symploca* sp.	MDA-MB-231, NMuMG, U2OS, & N1H3T3 cytotoxic	GI_{50} 7.7, 122.0, 55.0, & 480.0 nM	278
Mitsoamide	*Geitlerinema* sp.	Cytotoxic	IC_{50} 460 nM	279
Gallinamide A	*Schizothrix* sp.	Antimalarial	IC_{50} 8.4 μM	280

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Nostocyclamide	*Nostoc* sp.	Antialgal & anticyanobacterial *Anabaena* P-9 growth inhibitor	– 0.1 μM	281
Tenuecyclamide A	*Nostoc spongiaeforme*	Sea-urchin embryo inhibitor	ED_{100} 10.8 μM	282
Tenuecyclamides C-D	*N. spongiaeforme*	Sea-urchin embryo inhibitors	ED_{100} 9.0 & 19.1 μM	282
Cryptophycin	*Nostoc*	Antifungal Antimicrotubule	–	283
Microcystins	*Nostoc*	Protein phosphatase 1 & 2A inhibitors Tumor promoters	–	284
Raocyclamide A	*Oscillatoria raoi*	Cytotoxic	–	285
Venturamides A-B	*Oscillatoria* sp.	Antimalarial Cytotoxic	IC_{50} 8.2 & 5.6 μM IC_{50} 86 & 56 μM	286
Anabaenopeptins A-B	*Anabaena flos-aquae*	Rat aortic relaxations	11.8 – 477.3 μM	287
Anabaenopeptins G-H	*O. agardhii*	Carboxypeptidase A-inhibitors	IC_{50} 2.2 nM & 3.7 μM	290
Anabaenopeptins I-J	*Aphanizomenon flos-aquae*	Carboxypeptidase-A inhibitors	–	205
Pompanopeptin A	*L. confervoides*	Trypsin inhibitor	IC_{50} 2.4 μM	205
(+)-floridamide	*Moorea producens*	Anticancer	–	260
Coibamide A	*Leptolyngbya* sp.	Cytotoxic MDA-MB-231, HL-60, SNB-75 & LOX IMVI cytotoxicity	LC_{50} < 23 nM GI_{50} 2.8, 7.4, 7.6, & 7.4 nM	291
Hormothamnin A	*Hormothamnion enteromorphoides*	Antimicrobial & cytotoxic	–	292
Scytonemin	*Stigonema* sp.	GST-*polo*-like kinase 1 inhibitor	IC_{50} 2.3 μM ± 3.6	294
Arenamides A-B	*Salinispora arenicola*	TNF-induced activation blockers PGE_2 inhibitors NO production inhibitors Anticancer	IC_{50} 3.7 & 1.7 μM	295
Caldoramide	*Caldora penicillata*	Cytotoxic	IC_{50} 3.9 – 5.2 μM	296
Viequeamide A	*Rivularia* sp.	Anticancer	IC_{50} 60 ± 10 nM	297
Companeramides A-B	*Leptolyngbya* sp.	Anti-plasmodial	–	298
Aeruginosins	*Nodularia spumigena*	Serine protease inhibitors	–	301
Kailuin A	BH-107	A-549, MCF-7, & HT-29 cytotoxicity	GI_{50} 4.3 μM	302
Kailuin B	BH-107	A-549, MCF-7, & HT-29 cytotoxicity HCT-116 cytotoxicity	GI_{50} 2.8, 2.8, & 4.1 μM IC_{50} 22 μM	302–303
Kailuin C	BH-107	A-549, MCF-7, & HT-29 cytotoxicity HCT-116 cytotoxicity	GI_{50} 4.1, 5.5, & 4.1 μM IC_{50} 50 μM	302–303
Kailuin D	BH-107	A-549, MCF-7, & HT-29 cytotoxicity HCT-116 cytotoxicity	GI_{50} 2.7, 3.9, & 2.7 μM IC_{50} 28 μM	302–303
Kailuin E	*Photobacterium halotolerans*	HCT-116 cytotoxicity	IC_{50} 18 μM	303
Kailuins G & H	*Photobacterium halotolerans*	HCT-116 cytotoxicity	IC_{50} 32 & 17 μM	303
Ngercheumicins F-I	*Photobacterium* sp.	Inhibition of *rnaIII* transcription	–	305
Unnarmicin A	*Photobacterium* sp.	Rhodamine 6G efflux inhibition CaCdr1p ATPase inhibition	IC_{50} 3.6 μM IC_{50} 0.5 μM	307

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Unnarmicin C	*Photobacterium* sp.	Rhodamine 6G efflux inhibition CaCdr1p ATPase inhibition	IC_{50} 5.6 μM IC_{50} 0.7 μM	307
Ariakemicins A-B	*Rapidithrix* sp.	Cytotoxic	IC_{50} 25.4 & 42.4 μM	308
Mollemycin A	*Streptomyces* sp.	Antibacterial Antimalarial	IC_{50} 10–50 nM IC_{50} 7–9 nM	309
Thiocoraline	L-13-ACM2-092	Cytotoxic	IC_{50} 1.7 nM	310
Cyclomarin A	*Streptomyces* sp.	Anti-inflammatory	50 μg/ear	311
Surugamides A-E	*Streptomyces* sp.	Cathepsin-B inhibitors	IC_{50} 21, 27, 36, 18, & 16 μM	313
Champacyclin	*S. champavatii*	Antimicrobial	25 μM	315
Tumescenamide A	*S. tumescens*	Alzheimer's disease	–	316
Tumescenamide C	*S. tumescens*	Antimicrobial	3.0 μg/disk	317
Streptocidins C-D	*Streptomyces* sp. Tu 6071	Antimicrobial	MIC 0.8 – 2.4 μM	320
Salinamide A	*Streptomyces* sp. CNB-091	Edema Antibiotic	50 μg/ear MIC 3.9 μM	321
Salinamide B	*Streptomyces* sp. CNB-091	Edema Antibiotic	50 μg/ear MIC 1.9 μM	321
Salinamide F	*Streptomyces* sp.	Antibacterial RNAP inhibiton	MIC 0.2 – 96.3μM IC_{50} 2 – 4 μM	322
Tauramamide	*Brevibacillus laterosporus* PNG276	Antibacterial	MIC 0.12 μM	323
Bogorols A-E	*B. laterosporus*	MRSA inhibition VRE inhibition	MIC 0.6 – 5.1 μM MIC 5.6 – 48.2 μM	325
Loloatins A-B	MK-PNG-276A	Antibiotics	–	326
Loloatin C-D	MK-PNG-276A	Antibiotic & antibacterial	–	326
Marthiapeptide A	*Marinactinospora thermotolerans*	Antibacterial Anticancer	MIC 3 – 12 μM IC_{50} 0.4–0.5 μM	327
Anguibactin	*Vibrio anguillarum*	Cytotoxic	IC_{50} 15 μM	337–338

Table 3

Peptides isolated from Marine Fungi

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Fellutamides A-B	*Penicillium fellutanum*	Cytotoxic	–	348
Fellutamides C-D	*Metulocladosporiella*	Fungal proteasome inhibitors Antitumor	–	349
Fellutamide F	*Aspergillus versicolor*	Cytotoxic	–	190
Asperterrestide A	*Aspergillus terreus*	MOLT4 & U937 cytotoxicity H1N1 & H3N2 antiviral	IC_{50} 6.2 & 6.4 μM IC_{50} 15.0 & 8.1 μM	350
Sansalvamide A	*Fusarium*	Anticancer, Topoisomerase I inhibition SK-MEL-2 & COLO 205 colon cancer cells cytotoxicity	– IC_{50} 10.1 & 5.9 μM	34, 351
Scopularides A-B	*Scopulariopsis brevicaulis*	Antitumor	15.0 – 15.5 μM	352–353
Exumolides A-B	*Scytalidium*	Anti-microalgal	28 μM	354
Cis-bis(methylthio)silvatin	*Penicillium bilaii*	Cytotoxic	LD_{99} 0.15 μM	355
Asperpeptide A	*Aspergillus* sp.	Antibacterial	MIC 12.5 μM	357
Emericellamide A	*Emericella* sp. & *Salinispora arenicola*	Antimicrobial Cytotoxic	MIC 3.8 μM IC_{50} 23 μM	358–359
Emericellamide B	*Emericella* sp. & *S. arenicola*	Cytotoxic	IC_{50} 6.0 μM	358–359
Guangomides A-B	Unidentifiable fungus	Antibacterial	MIC 166 μM	360
Azonazine	*Aspergillus insulicola*	Anti-inflammatory Nitrite production	IC_{50} 8.4 μM IC_{50} 13.7 μM	361
Endolides A-B	*Stachylidium* sp.	Affinity for vasopressin receptor 1A & serotonin receptor $5HT_{2B}$	–	362
Simplicilliumtide A	*Simplicillium obclavatum*	Cytotoxic	IC_{50} 64.7 μM	364
Simplicilliumtide D	*S. obclavatum*	Antifouling	–	364
Simplicilliumtide E	*S. obclavatum*	Cytotoxic	IC_{50} 39.4 μM	364
Simplicilliumtide G	*S. obclavatum*	Cytotoxic	IC_{50} 100 μM	364
Simplicilliumtide H	*S. obclavatum*	Cytotoxic	IC_{50} 73.5 μM	364
Halolitoralins A-C	*Halobacillus litoralis*	Antifungal	–	365
Sclerotide A	*Aspergillus sclerotiorum*	Antifungal	MIC 7.0 μM	366
Sclerotide B	*A. sclerotiorum*	Antifungal Cytotoxic Antibacterial	MIC 3.5 μM IC_{50} 56.1 μM MIC 35.3 μM	366
RHM1	*Acremonium*	Cytotoxic	–	367
RHM2	*Acremonium*	Cytotoxic	–	367
Efrapeptin G	*Acremonium*	Cytotoxic Mitochondrial ATPase inhibitor	–	367–368
Cordyheptapeptide A	*Cordyceps* sp.	Antimalarial Cytotoxic	IC_{50} 3.8 μM IC_{50} 0.2–14.0 μM	370
Cordyheptapeptide B	*Cordyceps* sp.	Cytotoxic	IC_{50} 0.6–3.1 μM	370
Cordyheptapeptides C-E	*A. persicinum*	Cytotoxic	IC_{50} 2.5–12.1 μM	369

Table 4

Peptides from Marine Ascidians

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Cycloxazoline	*Lissoclinum bistratum*	Cytotoxic	IC_{50} 0.9 μM	34, 372
Diazonamide A	*Diazona angulata*	Cytotoxic	IC_{50} < 19.6 nM	34, 373–374
Diazonamides C-E	*Diazona* sp.	Cytotoxic	–	376
Vitilevuamide	*Didemnum cuculiferum* & *Polysyncranton lithostrotum*	Tubulin polymerization inhibition Lymphocytic leukemia inhibition Colchicine binding stabilization Cytotoxic	IC_{50} 2 μM IC_{50} 30 μg/kg IC_{50} 5.6 μM LC_{50} 6–311 nM	34, 377
Bistratamides A-B	*Lissoclinum bistratum*	Cytotoxic	IC_{50} 87.6 & > 175.8 μM	380
Bistratamide D	*Lissoclinum* sp.	Depressant	65 μg	381
Bistratamides E-J	*L. bistratum*	Cytotoxic	IC_{50} 14.4, 51.4, 9.5, 3.1, 16.4, & 1.8 μM	382
Lissoclinamide 7	*L. patella*	Anti-neoplastic	–	34, 378–379
Patellamides	*L. patella*	Cytotoxic	–	34, 378–379
Didemnin A	*Tridemnum solidum*	Cytotoxic	IC_{50} 0.03 μM	383–384
Didemnin B	*T. solidum*	Cytotoxic Apoptosis	IC_{50} 0.5 nM –	383–385
Didemnin M	*T. solidum*	Cytotoxic Immunosuppressive	IC_{50} 1.5 nM –	383–384
Didemnin N	*T. solidum*	Cytotoxic	IC_{50} 46.1 nM	383–384
Didemnins X-Y	*T. solidum*	Cytotoxic	IC_{50} 1.2 & 1.1 nM	383–384
Epididemnin A1	*T. solidum*	Cytotoxic	IC_{50} 2.1 μM	383–384
Acyclodidemnin A	*T. solidum*	Cytotoxic	IC_{50} 0.2 μM	383–384
Styelin D	*Styela clava*	Cytotoxic & hemolytic	–	34, 387
Eusynstyelamide	*Eusynstyela misakiensis*	Cytotoxic	IC_{50} 126.6 μM	34, 388
Mollamide	*Didemnum molle*	A549 & HT29 cytotoxicity P388 cytotoxicity RNA synthesis inhibitor	IC_{50} 3.1 μM IC_{50} 1.2 μM IC_{50} 1.2 μM	34, 390–391
Mollamide B	*D. molle* & *Pleurobranchus forskalii*	Anti-malarial against W2 and D6 of *P. falciparum* Antileishmanial HIV-1 inhibition	IC_{50} 3.0 & 2.9 μM IC_{90} 50.2 μM & IC_{50} 25.8 μM EC_{50} 48.7 μM	34, 391
Keenamide A	*D. molle* & *P. forskalii*	MEL-20, P-388 & A-549 cytotoxicity HT-29 cytotoxicity	IC_{50} 4.0 μM IC_{50} 8.0 μM	392
Cycloforskamide	*P. forskalii*	Cytotoxic	IC_{50} 5.8 μM	393
Virenamide A	*Diplosoma virens*	CV1, A549, & HT29 cytotoxicity P388 cytotoxicity Topoisomerase-II inhibition	IC_{50} 18.6 μM IC_{50} 4.6 μM –	34, 394
Virenamides B-C	*D. virens*	Cytotoxic	IC_{50} 4.8 μM	34, 394
Cyclodidemnamide	*Didemnum molle*	Cytotoxic	ED_{50} 23.1 μM	395
Comoramides A-B	*D. molle*	Cytotoxic	IC_{50} 7.5 – 14.9 μM	396

Compound	Biological Source	Biological Activity	Inhibitory Concentration	Ref
Mayotamides A-B	*D. molle*	Cytotoxic	IC_{50} 7.4 – 14.7 μM	396
Didmolamides A-B	*D. molle*	Cytotoxic	IC_{50} 18.0 – 37.1 μM	397
Prepatellamide A	*Lissoclinum patella* & *D. molle*	Cytotoxic	IC_{50} 6.6 μM	398
Patellamides A-C	*L. patella* & *D. molle*	Cytotoxic	IC_{50} 6.4 – 6.6 μM	398
Tamandarin A	*Didemnidae* Family	Reticulocyte cell-lysate protein biosynthesis inhibition	IC_{50} 1.3 μM	399
Patellin 6	*L. patella*	Cytotoxic Topoisomerase II inhibition	IC_{50} 2.1 μM IC_{50} 2.6 μM	400
Kulolide-1	*Philinopsis speciosa*	Cytotoxic	50 μM	401
Kulokainalide-1	*P. speciosa*	Cytotoxic	5 μM	401
Ulithiacyclamide	*L. patella*	Cytotoxic Macrophage Scavenger Receptor (MSR) inhibitor	IC_{50} 0.04 μM IC_{50} 98 nM	402–404
Ulithiacyclamide B	*L. patella*	Cytotoxic	IC_{50} 21.3 nM	403–404
Ulicyclamide	*L. patella*	Macrophage Scavenger Receptor (MSR) inhibitor	IC_{50} 51 μM	402–403

Table 5

Peptides from Other Marine Sources

Compound	Biological Source	Source	Biological Activity	Inhibitory Concentration	Ref
Malyngamide M	*Gracilaria coronopifolia*	Red alga	Cytotoxic	IC_{50} > 20 μM	253
Malyngamide N	*G. coronopifolia*	Red alga	Cytotoxic	IC_{50} 10.5 μM	253
Malyngamide O	*Stylocheilus longicauda*	Sea hare	Cytotoxic	IC_{50} 4.2 μM	254
Malyngamide S	*Bursatella leachii*	Sea hare	Antiproliferative Cytotoxic Antitubercular	IC_{50} ~ 6–8 μM IC_{50} 29 μM IC_{50} 12.9 μM	256
Malyngamide X	*B. leachii*	Sea hare	Antimalarial & antitubercular	–	258–259
Nobilamide B	*Chicoreus nobilis*	Mollusk/cyanobacteria	Anti-inflammatory & pain mediator	–	190, 406
A-3302-B	Unknown	–	Anti-inflammatory & pain mediator	–	190, 406
Aplidine	*Alpidium albicans*	Tunicate	Anticancer	–	34
Dolastatin 3	*Dolabella auricularia*/*Lyngbya majuscula*	Mollusk/cyanobacteria	Cytotoxic	GI_{50} < 1 μM	393
Dolastatin 10	*D. auricularia*	Mollusk	Growth inhibition of L1210 murine leukemia cells, inhibition of microtubule assembly, & tubulin-dependent GTP hydrolysis	–	34
Dolastatin 11	*D. auricularia*	Mollusk	Anticancer	GI_{50} ~ 0.07 μM	34, 393
Dolastatin 12	*D. auricularia*	Mollusk	Anticancer	GI_{50} ~1 to ~30 nM	34, 393
Epidolastatin 12	*L. majuscula*/*S. calcicola*	Cyanobacteria	Cytotoxic Microfilament disruption	MIC < 0.05 μM 0.2 – 2.1 μM	206
Dolastatin 13	*D. auricularia*	Mollusk	Anticancer	GI_{50} 14 nM	34, 393
Dolastatin 14	*D. auricularia*	Mollusk	Anticancer Antineoplastic	GI_{50} 20 nM –	34, 393, 408
Dolastatin 15	*D. auricularia*	Mollusk	Antineoplastic	–	34, 408
Dolastatin 16	*D. auricularia*/*L. majuscula*/*Symploca*	Mollusk/Cyanobacteria	Antileukemic & anticancer	GI_{50} ~ 0.3 μM	393
Homodolastatin 16	*L. majuscula*	Cyanobacteria	WHCO1 & WHCO6 cytotoxicity ME180 cytotoxicity	IC_{50} 4.8 & 11.3 μM IC_{50} 9.3 μM	409
Dolastatin 17	*D. auricularia*	Mollusk	Anticancer	–	393
Dolastatin 18	*D. auricularia*	Mollusk	Antileukemic	–	393
Dolastatin C	*D. auricularia*	Mollusk	Cytotoxic	IC_{50} 26.4 μM	410

Compound	Biological Source	Source	Biological Activity	Inhibitory Concentration	Ref
Dolastatin D	*D. auricularia*	Mollusk	Anticancer	GI_{50} ~ 4.0 μM	393
Dolastatin E	*D. auricularia*	Mollusk	Cytotoxic	IC_{50} 44.8 – 81.5 μM	411
Dolastatin G	*D. auricularia*	Mollusk	Anticancer	GI_{50} ~ 1.0 μM	393
Nordolastatin G	*D. auricularia*	Mollusk	Anticancer	GI_{50} ~ 5.0 μM	393
Lyngbyastatin 2	*L. majuscula*	Cyanobacteria	Cytotoxic	LD_{100} 3 mg/kg	412
Norlyngbyastati n 2	*L. majuscula*	Cyanobacteria	Cytotoxic	–	412
Isodolastatin H	*D. auricularia*	Mollusk	Antitumor	–	393
Dolastatin H	*D. auricularia*	Mollusk	Anticancer	GI_{50} 2 nM	393
Dolastatin I	*D. auricularia*	Mollusk	Cytotoxic	IC_{50} 23.2 μM	413
Dolabellin	*D. auricularia*	Mollusk	Cytotoxic	IC_{50} 9.97 μM	414
Doliculide	*D. auricularia*	Mollusk	Cytotoxic	IC_{50} 1.6 nM	415
Kulokekahilide-1	*Philinopsis speciosa*	Mollusk	Cytotoxic	IC_{50} 2.2 μM	416
Kulokekahilide-2	*P. speciosa*	Mollusk	A-10, P388, MDA-MB-435, & SK-OV-3 cytotoxicity	IC_{50} 59.1, 4.2, 14.6, & 7.5 nM	417
Aurilide	*Dolabella auricularia*	Japanese sea hare	Cytotoxic	IC_{50} 13.2 nM	237, 418
Microcolin A	*Okeania erythroflocculosa*	Coral reef	Apoptosis in murine thymocytes	10–100 nM	420–421, 424
Microcolin B	*O. erythroflocculosa*	Coral reef	Immunosuppressant	–	420–421
Tumonoic acid F	*L. majuscula/S. calcicola*	Cyanobacteria	Bioluminescence inhibition	IC_{50} 62 μM	425
Tumonoic acid I	*Blennothrix cantharidosmum*	Cyanobacteria	Antimalarial	IC_{50} 2.0 μM	425
Janadolide	*Okeania* sp.	Cyanobacteria	Anti-trypanosomal	IC_{50} 47 nM	426
Onchidin	*Onchidium* sp.	Pulmonate mollusk	Cytotoxic	–	427
Onchidin B	*Onchidium* sp.	Pulmonate mollusk	Kb cells inhibition	IC_{97} 8.7 μM	427–428
Norcardiamides A-B	*Nocardiopsis*	Actinomycete	Antimicrobial	–	429
Kahalalide A	*Elysia rufescens*	Sacoglossan mollusk	Antimalarial activity Antimicrobial	– 13.98 μM	430, 432
Kahalalide E	*E. rufescens*	Sacoglossan mollusk	HSV-II inhibition	–	430
Kahalalide F	*E. rufescens*	Sacoglossan mollusk	Antitumor activity Cytotoxic HIV OI inhibitor Antifungal HSV-II inhibition	IC_{50} 0.07 – 0.28 μM IC_{50} 0.22 μM – IC_{50} 1.5 – 3.2 μM	430–432

Compound	Biological Source	Source	Biological Activity	Inhibitory Concentration	Ref
			Immunosuppressive Antileishmanial	IC_{50} 0.3 μM IC_{50} 2.03 μM –	
Kahalalides R_1	*E. rufescens*	Sacoglossan mollusk	MCF-7 cytotoxicity L1578 cytotoxicity Antifungal	IC_{50} 0.14 μM IC_{50} 4.3 nM –	432
Trans,trans-ceratospongami de	*Ceratodictyon spongiosum*	Red alga/sponge	Anti-inflammatory Inhibition of human-$sPLA_2$ promoter	ED_{50} 32 nM –	433
Mebamamide B	*Derbesia marina*	Green alga	HL60 differentiation	100 μM	434
Galaxamide	*Galaxaura filamentosa*	Alga	U87 & MCF-7 cytotoxicity	IC_{50} 17.8 & 25.1 μM	436
Conantokin G	*Conus geographus*	Cone snail	NMDA antagonist	IC_{50} 171 nM	437
Conantokin T	*C. tulipa*	Cone snail	NMDA antagonist	–	438
Conantokin GV	*C. geographus*	Cone snail	Sleep-inducer	4–30 pmol/g	437, 439
Actinoporins	*Actiniaria*	Sea-anemone	Pore forming	–	440
Equinatoxin II	*Actinia equine*	Sea anemone	Lethal	LD_{50} 35 μg/kg	440
SECMA 1	*Ulva* sp.	Alga	Human foreskin fibroblast inhibitor	5.3 μM	441–442
Arasin-1	*Hyas araneus*	Spider crab	Antibacterial	MIC 0.8 μM	443
Arenicins 1-2	*Arenicola marina*	Polychaeta	Antimicrobial	9.1 μM	444

Table 6

Peptides in the Clinical Pipeline [482,483]

Clinical Status	Compound Name	Chemical Class	Source	Disease area
Approved	Ziconotide	Peptode	Cone snail	Pain
	Brentuximab vedotin [SGN 35]	ADC [MMAE]	Mollusk/cyanobacterium	Hodgkin lymphoma & systemic anaplastic large cell lymphoma
Phase III	Plitidepsin/aplidine	Depsipeptide	Tunicate	Relapsed/refractory multiple myeloma
Phase II	Soblidotin [TZT-1027]	Dolastatin 10 derivative	Mollusk/cyanobacterium	Sarcoma & lung cancer
	Xen-2174	chi-conopeptide	Cone snail	Pain
	Elisidepsin; PM02734; erlotinib	Cyclic depsipeptide	Mollusk	Advanced malignant solid tumors
	Tasidotin/synthadotin [ILX-651]	Dolastatin 15 derivative	Mollusk/cyanobacterium	Melanoma, non-small cell lung carcinoma, & hormone refractory prostate cancer
	ABT-414	ADC [MMAF]	Mollusk/cyanobacterium	Glioblastoma, gliosarcoma, & glioblastoma multiforme
	Glembatumumab vedotin	ADC [MMAE]	Mollusk/cyanobacterium	Squamous cell carcinoma of lung, recurrent osteosarcoma, recurrent uveal melanoma, stage IV uveal melanoma, melanoma, metastatic gpNMB over-expressing triple negative breast cancer, breast cancer, & unresectable stage III or stage IV melanoma
	AGS-16C3F	ADC [MMAF]	Mollusk/cyanobacterium	Metastatic renal cell carcinoma
	PSMA-ADC	ADC [MMAE]	Mollusk/cyanobacterium	Prostate cancer, glioblastoma multiforme, & gliosarcoma
Phase I/II	Pinatuzumab vedotin [DCDT-2980S]	ADC [MMAE]	Mollusk/cyanobacterium	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, lymphoma, follicular, & diffuse large B-cell lymphoma
	Polatuzumab vedotin [DCDS-4501A]	ADC [MMAE]	Mollusk/cyanobacterium	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, lymphoma, follicular, & diffuse large B-cell lymphoma
	Tisotumab vedotin [HuMax-TF-ADC or HuMab-TF-011-vcMMAE]	ADC [MMAE]	Mollusk/cyanobacterium	Ovary cancer, cervix cancer, endometrium cancer, bladder cancer, prostate cancer, esophagus cancer, lung cancer, & squamous cell carcinoma of the head and neck
	Lifastuzumab vedotin [DNIB0600A; RG-7599]	ADC [MMAE]	Mollusk/cyanobacterium	Ovarian cancer, epithelial tumors, malignant, fallopian tube cancer, peritoneal neoplasms, & non-squamous non-small cell lung cancer
	CDX-014	ADC [MMAE]	Mollusk/cyanobacterium	Renal cell carcinoma, clear-cell renal cell carcinoma, papillary renal cell carcinoma, kidney diseases, kidney neoplasms, & metastatic renal cell carcinoma
Phase I	Leconotide [CNSB004; AM336]	Peptode	Cone snail	Calcium channel blocker
	Taltobulin [HTI-286; SPA-110]	Hemiasterlin analog	Sponge	Cancer
	Enfortumab vedotin [ASG-22CE; AGS-22M6E]	ADC [MMAE]	Mollusk/cyanobacterium	Metastatic urothelial cancer, other malignant solid tumors, tumors, medical oncology, & neoplasms
	Vorsetuzumab Mafdotin [SGN-75]	ADC [MMAF]	Mollusk/cyanobacterium	Non-Hodgkin's lymphoma & renal cell carcinoma

Clinical Status	Compound Name	Chemical Class	Source	Disease area
	Telisotuzumab vedotin [ABBV-399]	ADC [MMAE]	Mollusk/cyanobacterium	Advanced solid tumor & cancer
	GSK2857916	ADC [MMAF]	Mollusk/cyanobacterium	Multiple myeloma
	ASG-15ME; AGS15E	ADC [MMAE]	Mollusk/cyanobacterium	Metastatic urothelial cancer
	AGS-67E	ADC [MMAE]	Mollusk/cyanobacterium	Relapsed/refractory lymphoid malignancy, acute myeloid leukemia
	MLN-0264	ADC [MMAE]	Mollusk/cyanobacterium	Gastrointestinal malignancies
	SGN-19A; SGN-CD19A	ADC [MMAF]	Mollusk/cyanobacterium	Burkitt's lymphoma & follicular lymphoma
	SGN-LIV1A	ADC [MMAE]	Mollusk/cyanobacterium	Breast cancer
	BAY79-4620	ADC [MMAE]	Mollusk/cyanobacterium	Neoplasms
	DMUC-5754A	ADC [MMAE]	Mollusk/cyanobacterium	Ovarian & pancreatic cancers
	DMOT4039A; RG-7600	ADC [MMAE]	Mollusk/cyanobacterium	Ovarian cancer
	DEDN6526A; RG-7636	ADC [MMAE]	Mollusk/cyanobacterium	Malignant melanoma
	Vandortuzumab vedotin; DSTP3086S; RG7450; MSTP2109A	ADC [MMAE]	Mollusk/cyanobacterium	Prostate cancer
	DFRF4539A; RG-7598	ADC [MMAE]	Mollusk/cyanobacterium	Multiple myeloma
Preclinical Trials	HuMax-CD74	ADC [MMAE/MMAF]	Mollusk/cyanobacterium	Solid tumors & hematological malignancies
Discontinued	Cemadotin	Dolastatin 15 analog	Mollusk/cyanobacterium	Cancer
	Kahalalide F	Depsipeptide	Alga	Cancer
	PF-06263507; A1-mcMMAF	ADC [MMAF]	Mollusk/cyanobacterium	Neoplasms, carcinoma, non-small cell lung, breast neoplasms & ovarian neoplasms