Chapter 6
Cytotoxic Cyclic Peptides from the Marine Sponges

Toshiyuki Wakimoto, Karen Co Tan, Hiroki Tajima and Ikuro Abe

Abstract To date, a significant number of cyclic peptides have been isolated from the marine sponges. Their structures often contain non-proteinogenic amino acids, some of which are derived from the biosynthetic pathway mixed with polyketides synthase. Halogenation, *N*-formylation, and racemaization to D-isomers were also frequently observed. Here we review the structural features of cytotoxic cyclic peptides from marine sponges. The cyclic peptides and depsipeptides were classified into different cyclization ways. The recent progress on the studies of their mode of action and biosynthesis was also included.

Keywords Cyclic peptide · Marine sponge · Nonribosomal peptide · Ribosomal peptide · Polyketide

6.1 Introduction

The marine sponges are prolific sources of cyclic peptides and depsipeptides (including ester bonds as part of their backbone) with unusual amino acids. The unique biological activity of these macrocycles originates from their structural complexity and ability to form rigid conformations in solution, which are therefore sought after as promising lead compounds for drug discovery. In particular, the reduction in conformational freedom brought about by macrocyclization often results in specific biological activities. Indeed, the fact that linearization abolishes the activity, has been known in some cyclic peptides. Although many reviews on natural compounds from marine environments have been published, we will focus here only on selected sponge-derived cytotoxic cyclic peptides and analogues either discovered or syn-

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thesized. Moreover, recent progress in biosynthetic studies on peptide secondary metabolites will also be described. It has become apparent that cyclic peptides were classified into ribosomal peptides and nonribosomal peptides. Nonribosomal peptide synthetases (NRPSs) are large multimodular biocatalysts, which are sometimes mixed with multimodular polyketide synthases (PKS) [1]. The hybrid pathway composed of NRPS and PKS often involves the biosynthesis of non-proteinogenic amino acids, leading to non-ribosomal peptide natural products with new and unusual structural motif. Most recently, the some modification processes of ribosomal peptides were also found to be comparable to those of nonribosomal peptides [2]. Taking into account the biosynthetic pathway, the cyclic peptides and depsipeptides are classified into two different cyclization ways, head-to-tail and head-to-side-chain, respectively. In addition, other unique cyclic peptides such as side-chain-to-tail heterodetic cyclopeptides, imidazole-bridged cyclopeptides, and dilactones are also included.

6.2 Cyclopeptides

6.2.1 Head-to-tail Cyclopeptides

This section aims to roughly classify the structurally diverse family of N-to-C-macrocylic peptides that have been characterized from marine sponges. Generally, natural product peptides can be subclassified on the basis of their biosynthetic origin: non-ribosomal (NRPS) and ribosomal peptides. Nonribosomally-produced peptides usually possess non-proteinogenic amino acids and the final product may be modified by tailoring enzymes via epimerization, hydroxylation, methylation, heterocyclization, and/or oxidative cross linking, among others, during or after the nonribosomal peptide assembly [3]. In this section, the following putative macrocyclic NRPS metabolites will be discussed: azumamides, barangamides, ceratospongamides, mutremdamides, and perthamides. On the other hand, ribosomally-synthesized cyclic peptides or cyanobactins consist exclusively of proteinogenic amino acids, and are produced by cyanobacteria, including *Prochloron* sp. and *Anabaena* sp. Many of them feature heterocyclized amino acids, such as thiazoline, methyloxazoline, and oxazoline, or their oxidized counterparts. However, homodetic cyanobactins or those which do not possess heterocyclized amino acids also exist, in which case, at least one proline residue is always present. Occasionally, post-translational modification may also involve prenylation of serine, threonine or tyrosine residues [4]. Under this category, the following putative cyanobactins from marine sponges shall be tackled: axinastatin, euryjanicins, hymenamides, malaysiatin, myriastramides, phakellistatins, and waiakeamide.

Azumamides are cyclic tetrapeptides isolated from the marine sponge *Mycale izuensis*. They were noted to possess an unusual β-amino acid, 3-amino-2-methyl-5-nonedioic acid (or 9-amide), and were found to potently inhibit histone deacetylase (HDAC), an enzyme involved in the regulation of DNA transcription.

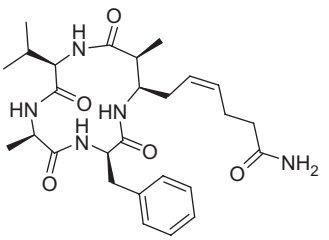
Consequently, HDAC is thought to be a potential target for anticancer agents, as demonstrated by the antiangiogenic effects of azumamide A *in vitro* [5].

Barangamides were first discovered from the marine sponge *Theonella swinhoei*, along with both new and known depsipeptides, theonellapeptolides. These cyclic undecapeptides have the same amino acid sequence as the cyclic portion of theonellapeptolides II, differing only in that the latter undergoes macrolactonization through the hydroxyl group of threonine, while the former forms the macrocycle through a peptide bond. Both peptide series bear several D-amino acids, N-methylated amino acids, as well as β-amino acids. Despite this, only the theonellapeptolides displayed cytotoxicity against L1210 tumor cells, while the barangamides were inactive [6, 7].

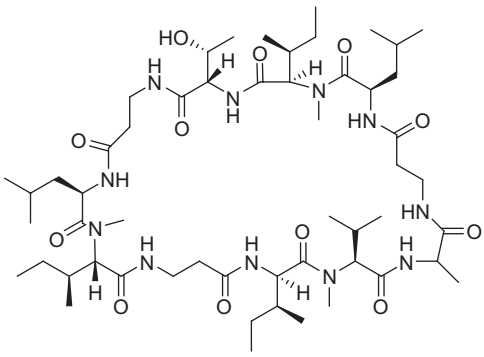
Ceratospongamides are cyclic heptapeptides having thiazole and methyloxazoline heterocycles. The *cis,cis*- and *trans,trans*-isomers were concomitantly obtained from the marine red alga *Ceratodictyon spongiosum* containing the symbiotic sponge *Sigmadocia symbiotica*. This was an unprecedented case of isolating two stable non-interconverting proline amide rotamers from nature. Although the real producer of these metabolites is still unknown, their biosynthesis is thought to proceed through a non-ribosomal pathway. This is well-suggested by the results of the synthetic studies conducted by Deng and Taunton, where if macrocyclization was carried out before threonine heterocyclization, only the *cis, cis*-isomer was synthesized. The chronology of this synthetic scheme mirrors that of the ribosomally-produced cyanobactins, where macrocylization precedes heterocyclization, and as a result, only one geometric isomer could be expected. In contrast, when heterocyclization was conducted before macrocylization, it became possible to obtain both geometric isomers, in a ratio that closely resembled their occurrence in nature. In terms of biological activity, only the *trans, trans*-isomer potently inhibited the secreted phospholipase A2 enzyme, suggesting its anti-inflammatory activity [8, 9].

Mutremdamide A (perthamide C) is a cyclic depsipeptide first characterized from deep-water specimens of *T. swinhoei*. Furthermore, it possesses a sulphated and carbamoylated asparginine, an unusual 3-amino-2-hydroxy-6-methylheptanoic acid (Ahmha), and a rare *o*-tyrosine residue. It is structurally similar to perthamide B isolated from the same species, in which the aforementioned residues have been replaced with β-hydroxyaspargine, 3-amino-2-hydroxy-6-methyloctanoic acid, and 3-bromotyrosine, respectively. Perthamide B has been reported to be cytotoxic, while perthramides C and D exhibited potent anti-inflammatory activity *in vivo* [10–12] (Fig. 6.1).

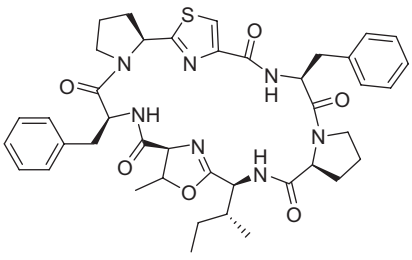
Axinastatins are N-to-C macrocyclic all-L-peptides that were isolated from the marine sponge *Axinella* sp. Axinastatins 1–4 are heptapeptides with two proline residues, while axinastatin 5 is an octapeptide having three proline residues. This group of peptides have been shown to be cytotoxic against murine and human cancer cell lines suggesting that the presence of high proportions of proline residues may be an important structural requirement for bioactivity. Moreover, conformational studies of axinastatins 1–4 indicated that the two prolines in common in positions two and six most strongly influenced the heptapeptide conformation, regardless of the solvent [13–18]. Two years after the discovery of axinastatin 1, another cyclic



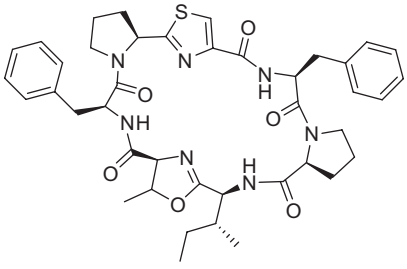
Azumamide A



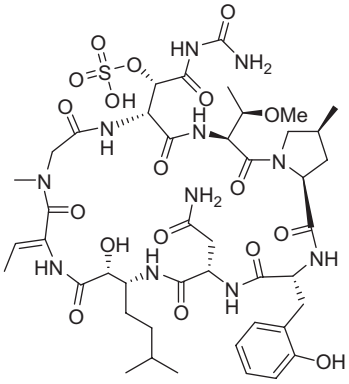
Barangamide A



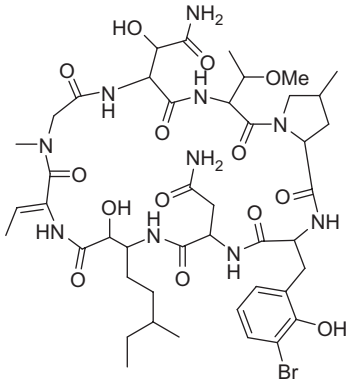
cis,cis-ceratospongamide



trans,trans-ceratospongamide



Mutremdamide A



Perthamide B

Fig. 6.1 Structures of head-to-tail cyclopeptides

heptapeptide, malaysiatin was reported from the marine sponge *Pseudoaxinyssa spongue*, whose concentrated extracts showed both cytotoxic and antimicrobial activities. The proposed structure was claimed to possess a unique valine homotripeptide and a prolylproline fragment: cyclo-(-Asn-Pro-Pro-Phe-Val-Val-Val) [19]. In comparison with axinastatin 1, cyclo-(-Asn-Pro-Phe-Val-Val-Pro-Val), the only difference was their amino acid sequence. However, through chemical synthesis of both peptides and comparison with the natural products, only the structure of axinastatin 1 was confirmed to be accurate, while malaysiatin's structure was found to be identical with that of axinastatin 1 [20].

Dominicin is a cyclic octapeptide that was first characterized from the Caribbean marine sponge *Eurypon laughlini*. It was isolated again from another Caribbean marine sponge *Prosuberites laughlini*, along with the cycloheptapeptide euryjanicins. Dominicin was demonstrated to inhibit a leukemia and a renal cancer cell line, while euryjanicin A inhibited a non-small cell lung and renal cancer cell line. Euryjanicins B-D were only weakly cytotoxic against the 60-tumor cell line panel of the National Cancer Institute. Such loss in activity of proline-rich peptides was explained to may have been caused by conformational changes during the isolation process or otherwise their ability to complex with highly toxic natural products, which can only be detected by biological methods [21–25].

Hymenamides A–F are heptapeptides, while hymenamides G, H, J, and K are octapeptides isolated from the Okinawan marine sponge *Hymeniacidon* sp. Among this series of cyclic proline-rich peptides, hymenamides B and J demonstrated cytotoxicity against L1210 murine leukemia cells and KB human epidermoid carcinoma cells, while hymenamide H exhibited cytotoxicity only against the L1210 cells. On the other hand, hymenamides A, C, D, E, G and K did not show cytotoxicity against these cells. Furthermore, hymenamides A, B, C and E were shown to have antifungal activity against *Cryptococcus neoformans*, while hymenamides A and B were active against *Candida albicans* [26–29].

Myriastramides are cyclic octapeptides and were the first peptidic metabolites characterized from the Philippine marine sponge *Myriastra clavosa*. Myriastramides A and B are structurally similar, both possessing an isoprenyl ether group on tyrosine. However, whereas the former is directly prenylated, the latter bears an exomethylene and a chlorine atom. In contrast, the aromatic residue in myriastramide C is tryptophan, rather than tyrosine. Although the crude extracts of the sponge displayed selective toxicity towards NCI's 60-cell line human antitumor screen, myriastramide A failed to show any cytotoxicity, while the other two derivatives yielded insufficient amounts for further cytotoxicity screening [30].

Phakellistatins are proline-rich homodetic type macrocyclic peptides. The first one of this series, phakellistatin 1, is a heptapeptide obtained from two marine sponges, *Phakellia costata* and *Stylotella aurantium*. Phakellistatins 2–6, 13–14, and isophakellistatin 3 consist of 7 amino acids. Phakellistatin 2 from *P. carteri* has the same amino acid composition as phakellistatin 1, but the sequence is different. On the other hand, phakellistatin 3 and its isomer isophakellistatin 3 only differ on the hydroxyl group orientation at the photo-tryptophan indole ring juncture. These compounds discovered from *P. carteri* represent the first example of natural

product peptides with photo-oxidized tryptophan. Interestingly, between these two isomers, only phakellistatin 3 inhibited cancer cell growth. Furthermore, in contrast with other phakellistatins, which are generally all-L cyclopeptides, phakellistatin 4, characterized from *P. costata*, bears a threonine in D-form, confirmed by chiral GC analysis of its *N*-pentafluoropropionyl isopropyl ester-derivatized hydrolysate. Next, phakellistatin 5 and 14, isolated from *P. costata* and *Phakelli* sp., contain methionine and methionine sulfoxide units, respectively. In addition, phakellistatin 14 possesses a unique β-methoxyaspartic acid residue. Moreover, decapaptides, phakellistatins 7–9 and phakellistatin 12, have also been characterized from *P. costata* and *Phakellia* sp., respectively. They represent the first cyclic decapeptides with cell growth inhibitory activity. Lastly, octapeptides, phakellistatins 10–11 have also been characterized from *Phakellia* sp. All phakellistatins exhibited cancer cell growth inhibitory activities [31–41].

A cyclic hexapeptide, waiakeamide, was described from the sponge *Ircinia dendroides*. Its structure consists of a thiazolylphenylalanine and two methionine sulfoxides. Although it did not exhibit any biological activity, a few years later, it was re-isolated from another sponge *Haliclona nigra*, together with two other cytotoxic analogues, haligramides A and B. Haligramide A possesses two methionines in place of the methionine sulfoxides in waiakeamide, while haligramide B has one methionine and one methionine sulfoxide. The structures of these three peptides were eventually confirmed by their oxidation to a common bis-sulfone derivative. The haligramides demonstrated cytotoxicity against various tumor cell lines [42, 43] (Fig. 6.2).

6.2.2 Head-to-side-chain Cyclopeptides

This section focuses on some of the head-to-side chain cyclised peptides that have been described from marine sponges of the genus *Theonella*, *Discodermia*, *Microscleroderma*, *Psammocinia*, and *Ircinia*. The first two genera both belong to the family Theonillidae (Order Lithistida), the third one belongs to the family Scleritodermidae (Order Lithistida), while the latter two belong to family Irciniidae (Order Dictyoceratida). *Theonella* species have been an abundant source of bioactive peptides, including cyclotheonamides (A-E, E2, E3), orbiculamide, oriamides, keramamides, motuporin, and microsclerodermins. Meanwhile, under the *Discodermia* species, we shall be covering the calyxamides and discobahamins. Lastly, we shall also be discussing about the cyclocinamides and cycotheonamides E4-E5 from *Psammocinia* and *Ircinia*, respectively.

Cyclotheonamides A–E, E2 and E3 are potent serine protease inhibitors. These cyclic pentapeptides bearing a β-linked diaminopropionic acid (Dpr) have been reported from either *Theonella* sp. or *T. swinhoei*. The characteristic and rare amino acids, vinylogous tyrosine (V-Tyr) and α-ketohomoarginine (K-Arg), in their structures have been demonstrated by X-ray crystallography to be important for the binding of cyclotheonamide A with human α-thrombin, a serine protease crucial

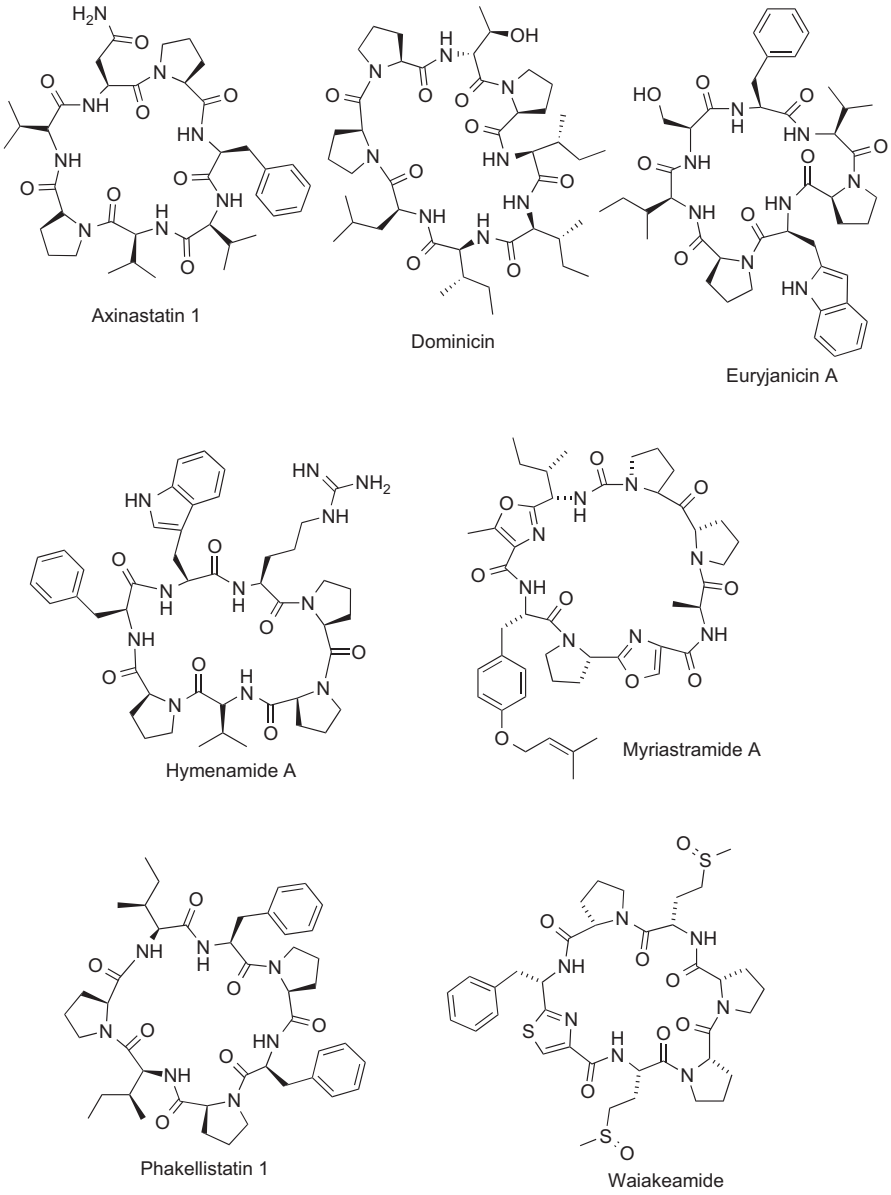


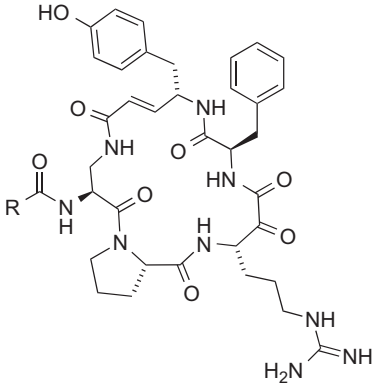
Fig. 6.2 Structures of head-to-tail cyclopeptides

for the regulation of thrombosis and hemostasis. Their ability to inhibit other serine proteases has also been reported, showing that cyclotheonamide A has enhanced specificity towards trypsin, while cyclotheonamides E-E3 prefer thrombin. Such difference in specificity was explained by the X-ray crystallography results and

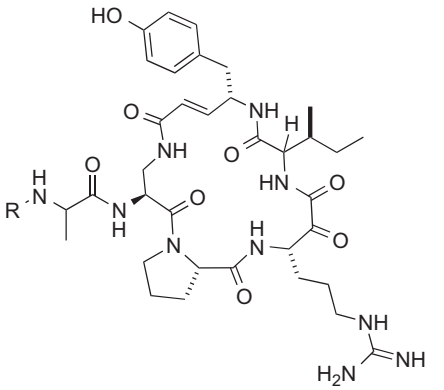
the structural differences among the analogues. The *N*-formyl group in cyclotheonamide A is replaced by an *N*-acetyl group in cyclotheonamide B. Cyclotheonamide C is a dehydrogenated analogue of cyclotheonamide A, where V-Tyr possesses an additional unsaturation. Next, the D-phenylalanine residue in cyclotheonamide A is replaced by a leucine residue in cyclotheonamide D. On the other hand, in cyclotheonamides E, E2, and E3, this D-phenylalanine residue is substituted with D-isoleucine, while the *N*-formyl group is replaced by an *N*-phenylacetylalanyl, an *N*-benzoylalanyl, and an *N*-isovalerylalanyl group, respectively. The phenylalanine-isoleucine substitution explains the loss of aromatic interaction of cyclotheonamides E-E3 with Tyr 39 and Tyr 41 in trypsin, while the presence of bulky acylated alanyl residue increases the hydrophobic interaction with Ile 174 in thrombin. Because of the potential of these compounds as antithrombotic agents, the total synthesis of cyclotheonamide A has also been described. Interestingly, four years after the discovery of cyclotheonamides E2 and E3, two other analogues, cyclotheonamides E4 and E5 were isolated from a different family of marine sponge, *Ircinia* sp. Both cyclotheonamides E4 and E5 bear an *N*-3-methylpentanoyl moiety in place of the *N*-isovaleryl group in cyclotheonamide E3. However, only cyclotheonamide E4 contains the characteristic V-Tyr residue, whereas cyclotheonamide E5 possesses an additional hydroxyl substitution ortho to V-Tyr's hydroxyl group. These two cyclotheonamides were reported to potently inhibit tryptase, which is a protease released from mast cells during allergic reactions. Consequently, these natural products are eyed for their potential use for the treatment of allergic diseases, including asthma [44–51].

Orbiculamide A is a cytotoxic cyclic peptide from *Theonella* sp. Its structure consists of three unique amino acid residues, 2-bromo-5-hydroxytryptophan (BhTrp), theonalanine, and theoleucine. Theoalanine contains an oxazole ring, which derives from the carbonyl of an alanine residue, while theoleucine is an α-keto-β-amino acid, which is reminiscent of the α-ketoamide, K-Arg, in cyclotheonamides. Aside from these, the cyclic portion of this peptide also consists of proline and δ-linked ornithine, while the side chain consists of a (*S*)-3-methylpentanoyl moiety [52]. Oriamide is another cytotoxic cyclic peptide from *Theonella* sp. Such as in the case of other cyclic peptides from *Theonella*, it was found to contain an α-ketoamide, 3-amino-2-keto-4-methyl hexanoic acid (AKMH). Furthermore, the presence of an unprecedented amino acid, 4-propenoyl-2-tyrosylthiazole (PTT), was established. Along with AKMH and PTT, the cyclic part of oriamide also includes cysteic acid, a β-linked Dpr, and norvaline. In addition, the side chain consists of one residue each of alanine and glycine, and a 2,5-dihydroxybenzoyl-protected *N*-terminus. However, this paper did not present their data regarding cytotoxicity [53] (Fig. 6.3).

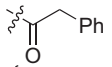
Keramamides are a series of tryptophan-containing head-to-chain cyclic peptides from the Okinawan marine sponge *Theonella* sp. We have classified them into the (1) oxazole-containing keramamides B–E and M–N, (2) thiazole-containing keramamides F–H, and J–K, and for the sake of completeness, we have also arbitrarily included (3) ureido-containing keramamides A and L. For the first subgroup, keramamides B–E are closely related to orbiculamide A, where the latter's (*S*)-3-methylpentanoyl side chain is changed to a (2*S*,3*S*)-2-hydroxy-3-methylpentanoyl moiety



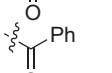
Cyclotheonamide A R = H
Cyclotheonamide B R = Me



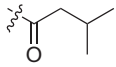
Cyclotheonamide E R =

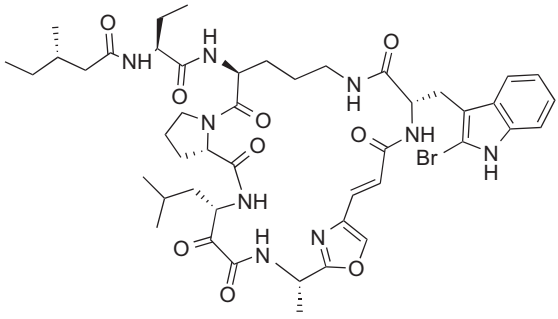


Cyclotheonamide E2 R =

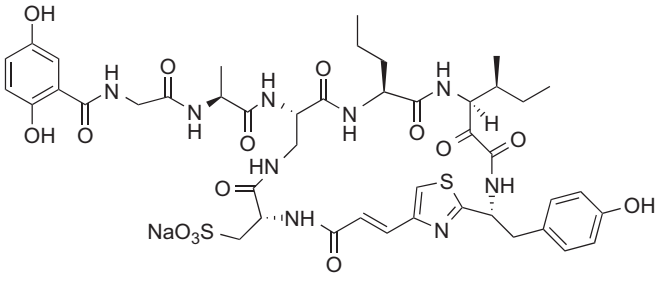


Cyclotheonamide E3 R =





Orbiculamide A



Oriamide

Fig. 6.3 Structures of head-to-side-chain cyclopeptides

(Hmp). On the other hand, keramamides M and N are rare sulphate ester congeners of the Hmp residue of keramamides D and E, respectively. For the next subgroup, all of them possess unusual amino acids, including isoserine (Ise), β-linked Dpr, AKMH, and (*O*-methylseryl)thiazole. In addition, keramamides F and G possess an α, β-dehydrotryptophan. The gross structures of these two keramamide congeners were judged to be the same, but with slight differences in the ^{13}C chemical shifts in the AKMH residue. Alkaline peroxidation, followed by acid hydrolysis of these two peptides converted AKMH to isoleucine in the D-form for keramamide F and in the L-form for keramamide G. Then, keramamides H and K contain rare modified tryptophan residues, BhTrp and (1-Me)Trp, respectively. Finally, for the third subgroup, keramamides A and L possess unusual features, such as the presence of a ureido bond and a 6-chloro-5-hydroxy-*N*-methyltryptophan (MeCtrp). In terms of bioactivities, keramamide A was reported to inhibit sarcoplamic reticulum Ca^{2+}-ATPase; keramamides B–D inhibited the superoxide generation response of human neutrophils; and keramamides E–F, K–N demonstrated cytotoxicity *in vitro* against KB human epidermoid carcinoma cells and L1210 murine leukemia cells, while keramamides G, H, and J displayed weak activity against these cell lines [54–59].

Motuporin (nodularin V) is a cytotoxic cyclic pentapeptide isolated from a Papua New Guinea marine sponge *T. swinhoei*. Its structure closely resembles that of an equipotent phosophatase inhibitor, nodularin (nodularin R), which was isolated from fresh-water blue-green cyanobacterium *Nodularia spumigena*. Both contain the β-amino acid, 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), which is also present in the structurally-related heptapeptide cyanobacterial toxin, microcystin-LR, from the cyanobacterium *Microcystis aeurigonsa*. The only difference between the two nodularins is the substitution of a polar arginine residue in nodularin R with a nonpolar valine residue in motuporin. These data suggest that the arginine residue is not significant for biological activity. Further details about the structural basis of how protein phosphatases are inhibited by motuporin and dihydromicrocystin were revealed by the crystal structure of these toxins complexed with human protein phosphatase-1c (γ-isoform). Indeed, phosphatase inhibitors are valuable tools for understanding these enzymes, which play important roles in regulating intracellular signalling pathways. Furthermore, as for motuporin, it is an especially attractive target for total synthesis because of its relative scarcity, high potency, and unique structure. Consequently, there have been a couple of reports for the total synthesis of motuporin. On the other hand, as for nodularin R and microcystin, their complete gene clusters, encoding integrated nonribosomal peptide-polyketide megasynthases, have been sequenced and characterized from their respective cyanobacterial producers [60–69] (Fig. 6.4).

Microsclerodermins are antifungal cyclic peptides from Lithistid sponges, *Microscleroderma* sp. and *Theonella* sp. Microsclerodemins are a family of hexapeptides, having only three amino acids, glycine, *N*-methylglycine and (3*R*)-4-amino-3-hydroxybutyric acid (GABOB), in common for all members. The variable units include (1) tryptophan, which is formoylated in microsclerodermins A, B, and E, chlorinated in microsclerodermins C-D, and α,β-desaturated in microsclerodermins G and I; (2) the unusual 3-amino-pyrrolidone-4-acetic acid, which is either hydrox-

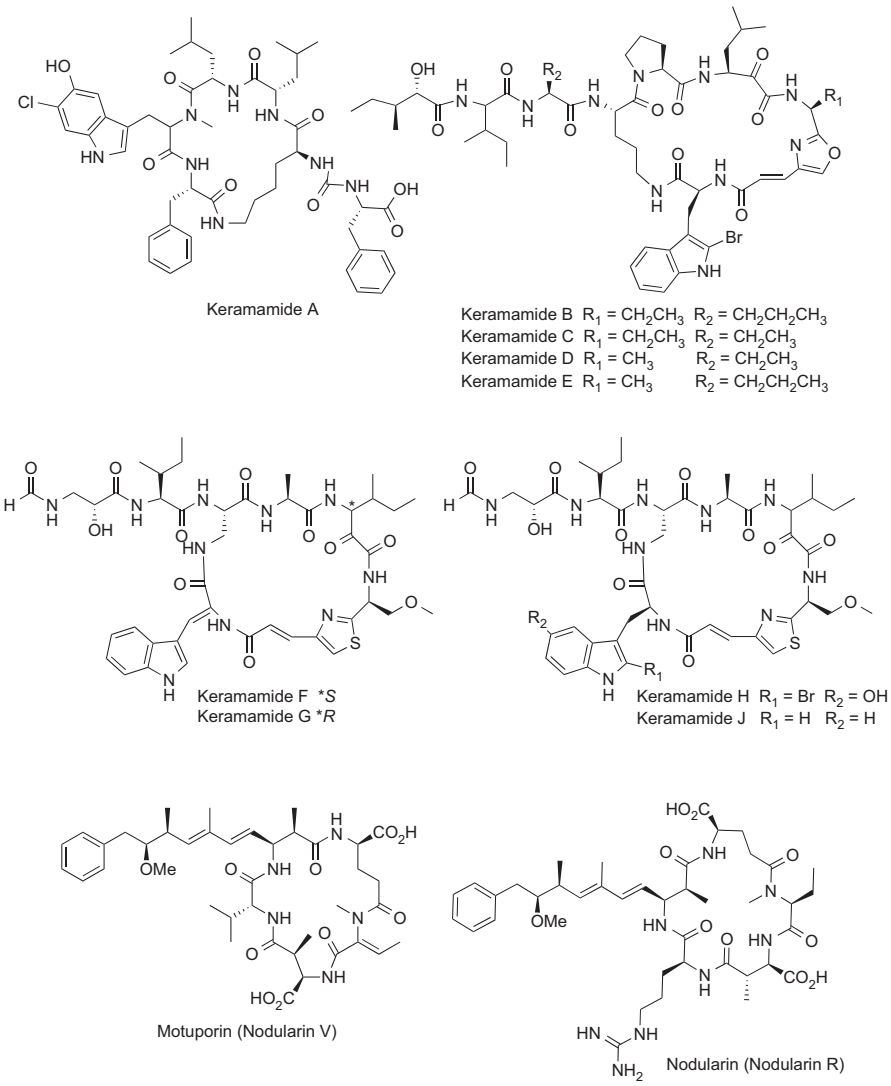


Fig. 6.4 Structures of head-to-side-chain cyclopeptides

ylated or dehydrated; and (3) different ω-aromatic 3-amino-2,4,5-trihydroxyacids. With respect to bioactivity, aside from antifungal activity, microsclerodermins F-I also displayed antitumor activity against HCT-116 cell line. Finally, their production has been attributed to a filamentous bacterium of the family Beggiatoaceae, which occurs as mats in deep-water environments [70–72].

Calyxamides are cytotoxic cyclic peptides isolated from the marine sponge *Discodermia calyx*. Their structures are very similar to the thiazole-containing keramamides, in which the components of the cyclic portion are entirely the same,

except for the tryptophan moiety, which is 5-hydroxytryptophan for calyxamides. In addition, the *N*-terminal amino acid in the side chain is glutamine, instead of Ise, but is also *N*-formylated. Another similar point is that calyxamides A and B possess the same planar structure, but are isomeric at the 3-position of the AKMH residue, just as in the case of keramamides F and G. The microbial producer of the calyxamides is suspected to be *Candidatus* Endotheonella sp., whose presence in *D. calyx* was confirmed by 16s rDNA sequence analysis of the sponge DNA metagenome. This endosymbiont has also been identified from *T. swinhoei*, which may rationalize the similarity of the secondary metabolites from these two sponges [73].

Discobahamins are structurally similar to calyxamides and oxazole-containing keramamides, wherein the BhTrp unit in the latter is changed for a 5-hydroxytryptophan. The Hmp-protected *N*-terminus is common among the discobahamins and keramamides B-E and M-N, while the characteristic (*O*-methylseryl)thiazole, AMKH, and δ-linked ornithine are common among these two series of compounds, as well as the calyxamides. Lastly, the discobahamins are reported to possess weak antifungal activity against *Candida albicans* [74].

Cyclocinamides A and B are minor head-to-side chain cyclohexapeptides, which were isolated at different times and by separate groups from two distinct marine sponges *Psammocinia* and *Corticium*, respectively. Their unique β2αβ2α tetrapeptide cyclic core includes a β-linked Dpr, aspargine, isoserine, and 5-bromotryptophan, while the side chain consists of a glycine unit protected by a distinct proline-derived *N*-methylchloropyrrole for cyclocinamide A or *N*-methyldichloropyrrole for cyclocinamide B. During the first isolation of cyclocinamide A in 1997 by Crews' group, the determination of its absolute structure could not be completed by chiral TLC analysis of its hydrolysate, where only two of the four chiral centers' stereochemistries were identified as 7*S*, 14*S* for 5-bromotryptophan and aspargine, respectively. From the two remaining chiral centers, there were still four possibilities, (4*S*, 11*S*), (4*S*, 11*R*), (4*R*, 11*R*), and (4*R*, 11*S*). In efforts to elucidate cyclocinamide A's complete structure, Grieco and Reilly successfully synthesized nominal (4*R*, 11*R*)-cyclocinamide A, while Postema and Liu were able to synthesize the nominal (4*R*, 11*S*)-diastereomer. Both synthetic studies concluded that the natural product was different from the synthetic materials. Years later, in 2008, recollection of the cyclocinamide-containing sponge lead to the isolation of a little more of the compound, whose acid hydrolysate was derivatized by Marfey's method. This resulted to the supposed complete assignment of the absolute structure of cyclocinamide A as all-*S*. However, in 2012, Konopelski et al., who prepared the two remaining unsynthesized nominal cyclocinamide A's, suggested that the natural product did not match the spectra of either the 4*S*, 11*S*- or 4*S*, 11*R*-diastereomer. Moreover, cyclocinamide B characterized by Ireland et al. (2007) [79], was assigned a 4*S*, 7*R*, 11*S*, 14*R* stereochemistry by Marfey's and modified Marfey's analyses. Because of these conflicting results, the complete structures of the cyclocinamides remain elusive. As for biological activity, only cyclocinamide A demonstrated potent cytotoxicity and selective cytotoxicity against solid tumors, while cyclocinamide B exhibited no cytotoxicity against HCT-116 cells [75–80] (Fig. 6.5).

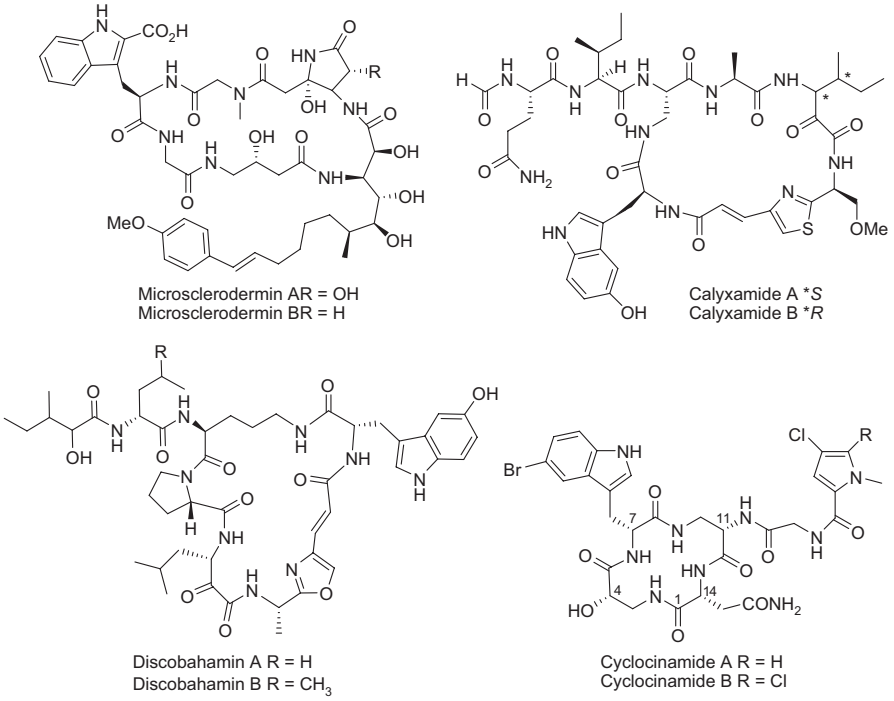


Fig. 6.5 Structures of head-to-side-chain cyclopeptides

6.3 Cyclodepsipeptides

6.3.1 Head-to-tail Cyclodepsipeptides

Jasplakinolide, also known as jaspamide, is a cytotoxic cyclodepsipeptide from the marine sponge, *Jaspis splendens*. Its characterization was first reported in 1986 by two separate groups, Crews et al. [81], and the Ireland–Faulkner–Clardy consortium [82]. Since then, it has also been isolated from taxonomically distinct sponges, *Auletta* [83, 84] and *Hemiastrella minor* [84, 85]. The structure of this polyketide-peptide (PKS-NRPS) metabolite consists of a 19-membered macrocylic lactone, containing an L-Ala-D-N-Me-2-BrTrp-L-β-Tyr tripeptide fragment, linked to an ω-hydroxyacid. Its complete structure was elucidated by NMR spectral [81] and X-ray crystallographic analyses [81, 82], and later confirmed by total synthesis [86].

This unique cytotoxin possesses several bioactivities, such as antifungal, insecticidal, and anthelmintic properties [81, 82]. Most notably, its antiproliferative activity is attributed to its ability to alter actin assembly, inducing cell death. Actin is a cytoskeletal protein ubiquitously found in eukaryotic cells. Its dynamic interconversion between its two forms, filamentous (F-actin) and globular (G-actin) states, is suggested to be crucial for regulating various cellular functions including

cell division [84, 87–88]. Previous reports have provided evidence that jasplakinolide, binds competitively *in vitro* with phalloidin to F-actin. Phalloidin, on the other hand, is a bicyclic heptapeptide derived from the poisonous mushroom *Amanita phalloides*. Although bearing little structural resemblance, the Ala-Trp fragment present in both phalloidin and jasplakinolide are implicated in their actin filament-stabilizing ability, and are representative examples of this class of actin-targeting natural products [87, 89]. Jasplakinolide, in contrast to other actin-targeting substances, has exhibited selective induced apoptosis towards transformed cell lines than normal, nontransformed cells. In addition, its cytotoxicity against HL-60 (human promyelocytic leukemia) cells, Jurkat T (immortalized human T lymphocytes) cells, EL-4 (murine lymphoma) cells, SP-2/0 (mouse hybridoma: B lymphocyte) cells, and J774.1 (mouse ascites reticulum) cells has been demonstrated [84, 90]. It has also exhibited cytotoxicity against breast and prostatic cancers [87]. As such, it was considered to be a potential antineoplastic agent until it was withdrawn from preclinical evaluation due to severe toxicity [91, 92]. Consequently, investigations on both natural and synthetic analogues of jasplakinolide still continue in hope of finding a pharmacologically useful drug.

The jasplakinolide family so far consists of nearly 20 analogues and has been classified into two groups based on the hybridization of C-31, i.e. sp^3-hybridized in Group 1 and sp^2-hybridized in Group 2 [83, 93, 94]. In addition, related actin-targerting cyclodepsipeptides have been characterized from other marine sponges, such as geodiamolides from *Geodia* [95] and *Cymbastela* and seragamides from *Suberites* [96]. Interestingly, a structurally similar family of 18-membered cyclodepsipeptides, the chondramides, have been isolated from terrestrial myxobacterium [94, 97]. Furthermore, similarly bioactive congeners have been synthesized [92], persistently providing insights to structure-activity relationships, substrate binding mechanisms, and drug optimization studies. Based on these, a number of generalizations about the structure-bioactivity patterns of jasplakinolide congeners have been summarized by Crews et al., citing the importance of the *S*-configuration at C-9 to maintain optimal activity and the β-tyrosine unit for protein binding, among others [94]. These valuable pieces of information contribute to overcoming the challenges of drug development and to the further optimization of modified jasplakinolide analogues that hold promise for cancer chemotherapy (Fig. 6.6).

6.3.2 Head-to-side-chain Cyclodepsipeptides

The depsipeptide is defined as the peptides containing ester bonds in place of at least one of the amide bonds. Usually, the ester bond is involved in the macrocycle linkage between the carboxyl group in C-terminal amino acid and an amino acid bearing hydroxyl group such as serine and threonine. When serine or threonine is located at an internal position of the peptide sequence, the macrocyclic ring can be closed in a head-to-side-chain fashion. The first head-to-side chain cyclodepsipeptides from marine sponge was discodermin A originally isolated from the

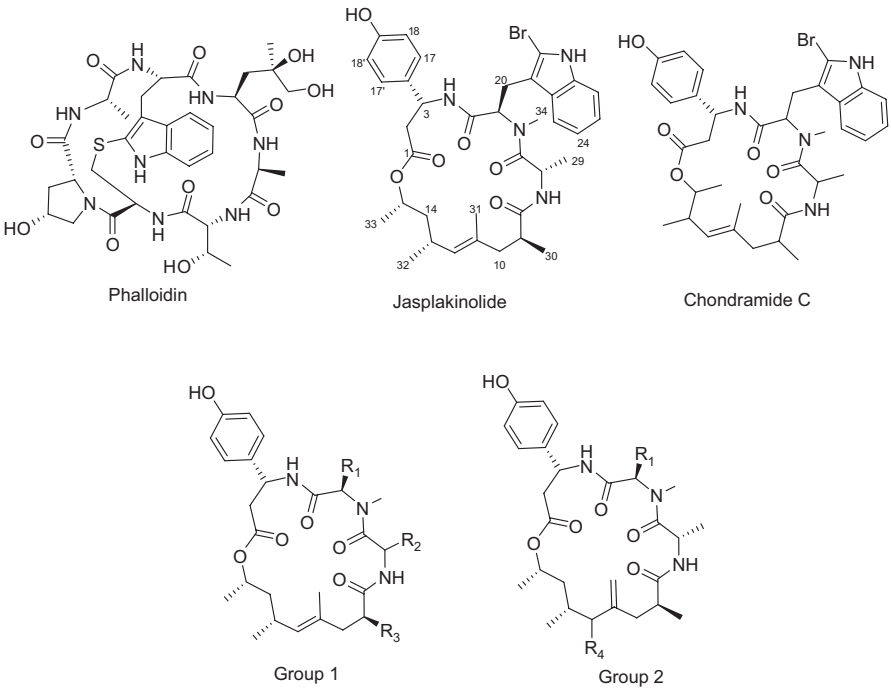


Fig. 6.6 Structures of head-to-tail cyclodepsipeptides

marine sponge *Discodermia kiiensis* in 1984 [98, 99]. Since then, the related derivatives with high structural similarity had been isolated from taxonomically remote sponges. Discodermins [99–102] and polydiscamide A [103] were from the genus *Discodermia*; polydiscamides B–D [104] from the genus *Ircinia*; halicylindramides [105, 106] from the genus *Halichondria*; microspinosamide [107] from the genus *Sidonops*; corticiamide [79] from the genus *Corticium*. Their structures can be classified into two groups; discodermins, halicylindramides and corticiamide are tetradecapeptides with 19-membered macrolactone, and polydiscamides and microspinosamide are tridecapeptides with 16-membered macrolactone. The presence of formyl group on N-terminus, L-The residue on the branching point and adjacent D-cysteic acid residue are identical in both tetradecapeptides and tridecapeptides. Both L- and D-forms, as well as *N*-Me amino acids such as Sar are found in the structures. Discodermins and halicylindramides show cytotoxicity against P388 cells with IC_{50} in the sub-micromolar range as well as antimicrobial activity. The hydrophobic *N*-terminal sequence composed of six successive amino acids such as L-*t*-Leu and L-β-MeIle resemble the *N*-terminal portion of 48-mers polytheoneamides, which exhibit potent cytotoxicity by forming unimolecular ion channel in cell membranes [108, 109]. As alluded to this, Karaki and co-workers demonstrated that discodermin A enhanced the permeability of the plasma membrane [110]. On the other hand, the linear analogs, secohalicylindramide B and halicylindramide E were

no longer cytotoxic, which suggested that the macrolactone ring is also essential for the cytotoxicity [105]. More recently, tridecapeptides, polydiscamides B-D were disclosed to be potent agonists against human sensory neuron-specific G protein coupled receptor [104]. Microspinosamide has cytoprotective activity against HIV-1 *in vitro* [107] (Fig. 6.7).

Callipeltins A–C were originally isolated from the New Caledonian Lithistida sponge *Callipelta* sp. by Minale and co-workers [111]. Noteworthy is the acylation of the *N*-terminal unit with unique polyketide-derived hydroxyacid moieties and the presence of previously unknown amino acid residues such as 3,4-dimethylglutamine. Callipeltin A was first reported to exhibit anti-HIV and anti-fungal activities [111]. Later, it was reported that callipeltins A and B exhibit broad-spectrum cytotoxicity against the tumor cell lines [112]. However, cytotoxicity of the acyclic congener, callipeltin C was significantly diminished [112], thus suggesting that the macrolactone ring is important for the cytotoxicity as is the case for halicylindramides. Recently it was found that callipeltin A is a selective and powerful inhibitor of the Na/Ca exchanger and a positive inotropic agent in guinea pig left atria [113]. In addition to callipeltins A-C, more congeners callipeltins D–M were isolated from a different sponge, *Latrunculia* sp. [114, 115]. All these new derivatives were truncated and linear in structure except for callipeltin L, which contains a unique 8-membered ring formed between carboxyl group at C-terminal and β-hydroxyl group on tyrosine residue. The unusual structural features of these peptide metabolites and the interesting biological activities have attracted considerable interest among the synthetic chemistry community, culminating in the total synthesis of callipeltin B, D and E [116–118]. The Papua New Guinea marine sponge *Neamphius huxleyi* contained closely related depsipeptide, neamphamide A [119]. Another congener, neamphamide B, was isolated from a Japanese marine sponge *Neamphius* sp., [120] and neamphamides B–D from Australia collection of the marine sponge *Neamphius huxleyi* [121]. Whereas the macrocyclic region of neamphamide A is composed of a 25-membered ring, both callipeltin A and neamphamides B-D share the same ring size of 22-memebers. All neamphamides bear a unique L-homoproline reside in place of L-*N*-MeAla residue at the C-terminal of callipeltin A and inhibited the growth of human cell lines with IC_{50} of sub-nanomolar range. The homoproline residue is also found in similar depsipeptides, papuamides and mirabamide. Papuamides A-D are cytotoxic, antiviral cyclic depsipeptides isolated from the marine sponge *Theonella swinhoei* and *mirabilis* [122]. New derivatives papuamides E and F were also isolated from the genus *Melophlus* [123]. Mirabamides, isolated from the Micronesian sponge *Siliquariaspongia mirabilis* represent the a recent example of this class. The distinguishable feature of all these depsipeptides is β-methoxytyrosine (β-MeOTyr) present in callipeltin A–C, neamphamide, papuamide and mirabamides. This unique substructure evoked the formation of a quinone methide intermediate by elimination of methanol from β-MeOTyr, which might be the principal source of the cytotoxicity. However, synthetic desmethoxylcallipeltin B lacking β-methoxy group at the tyrosine residue also showed cytotoxicity comparable to that of callipeltin B, leading to the conclusion that the quinone methide intermediate is unlikely to be essential for the cytotoxicity [124]. This is rather

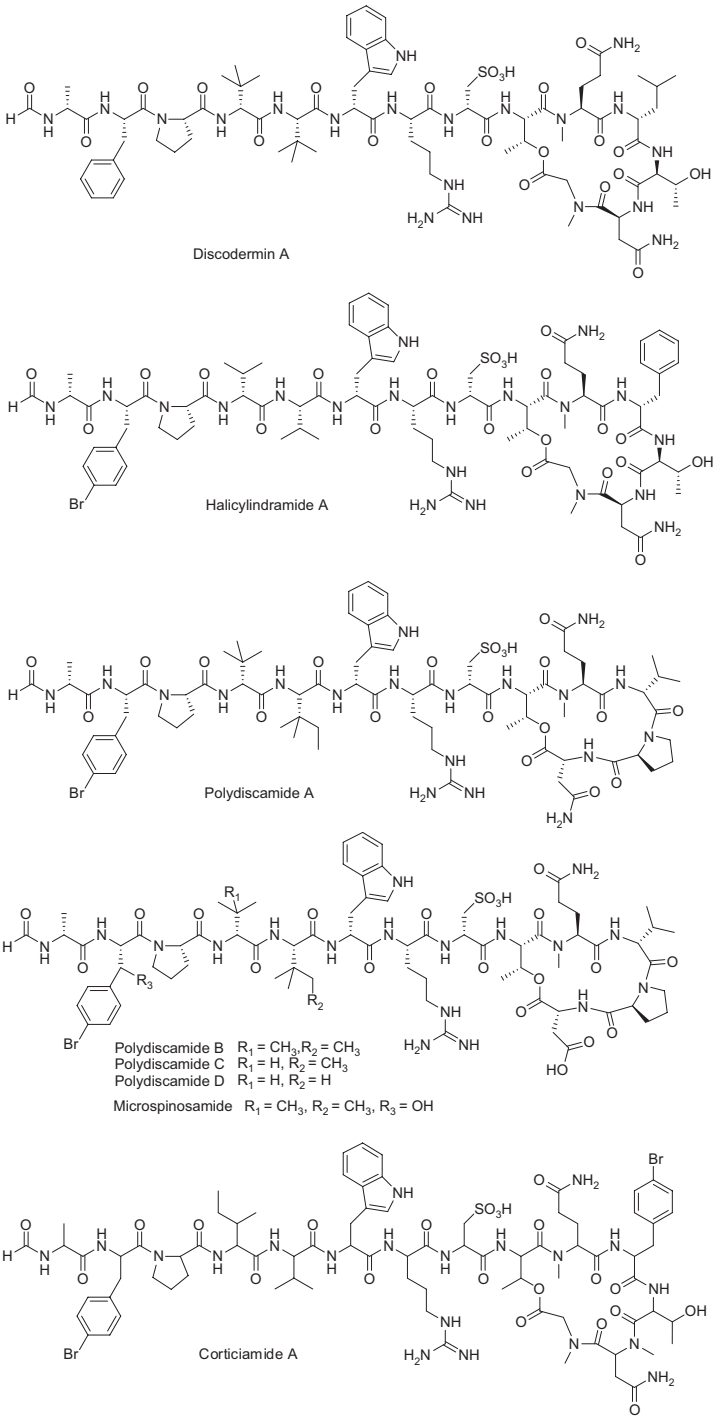


Fig. 6.7 Structures of head-to-side-chain cyclodepsipeptides

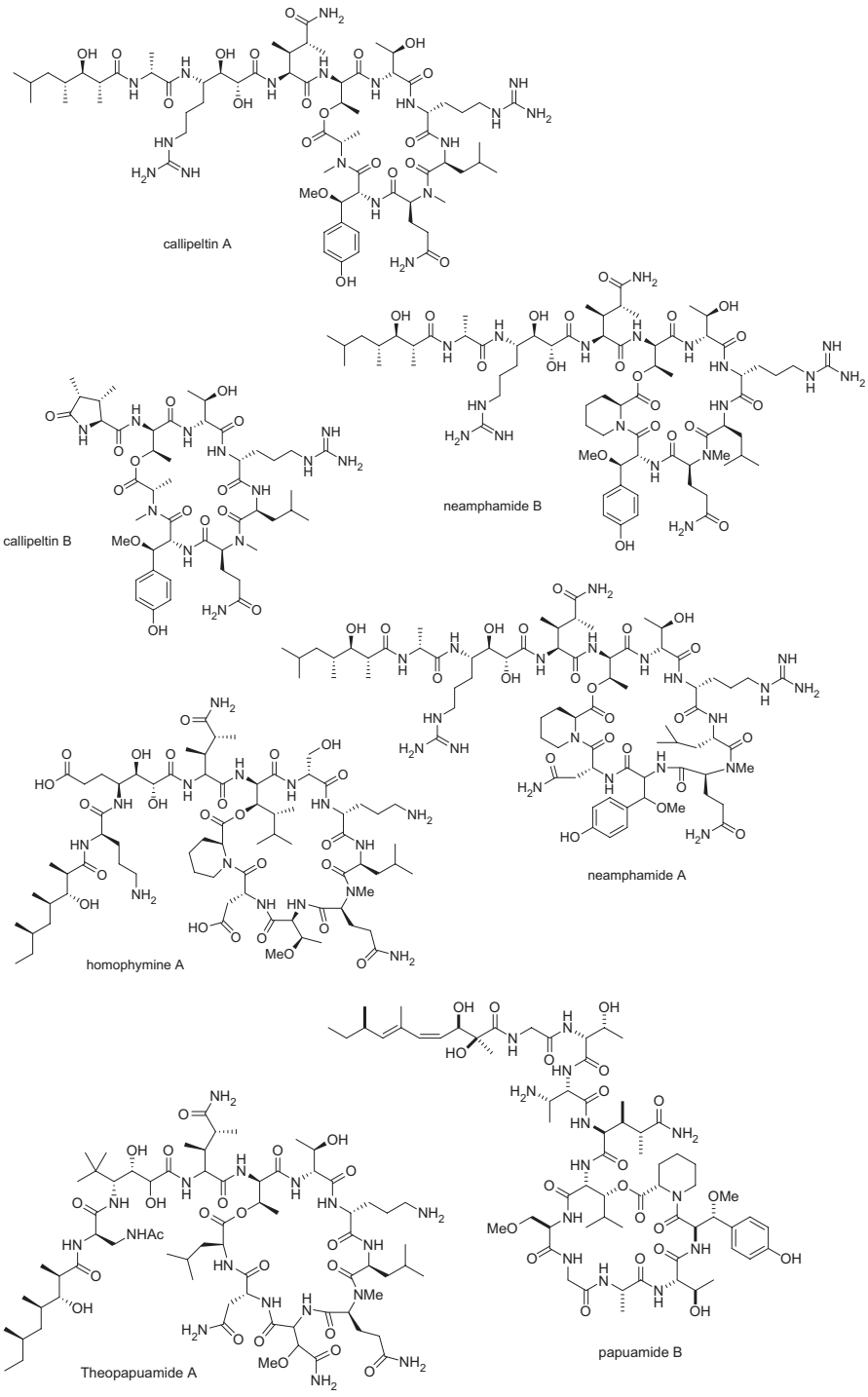


Fig. 6.8 Structures of head-to-side-chain cyclodepsipeptides

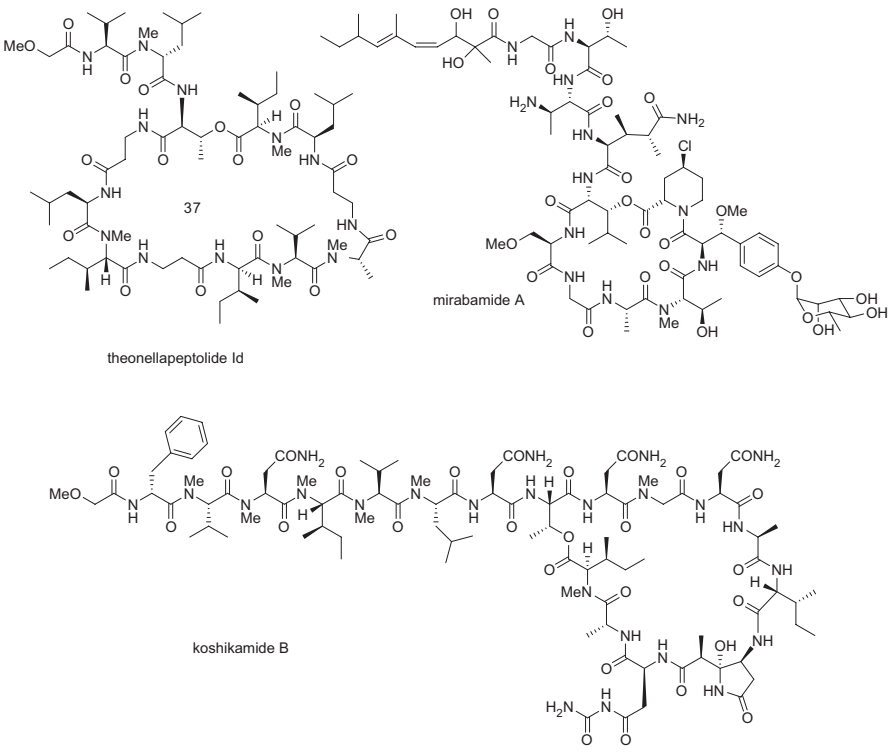


Fig. 6.8 (continued)

reasonable because the related depsipeptides, both homophymine and theopapuamide lacking β-MeOTyr, retain considerable cytotoxicity.

Other classes of head-to-side chain cyclodepsipeptides are theonellapeptolides and koshikamides, both of which were orginally isolated from the genus *Theonella*. Theonellapeptolides are tridecapeptide containing a 37-membered lactone ring. They constitute the members of a growing class of depsipeptides from sponges. Of note, apart from sponge-derived head-to-side-chain cyclodepsipeptides, there are several other important cytotoxic peptides including kahalalides from mollusk and didemnins from tunicates (Fig. 6.8).

6.4 Others

6.4.1 Side-chain-to-tail Cyclopeptides

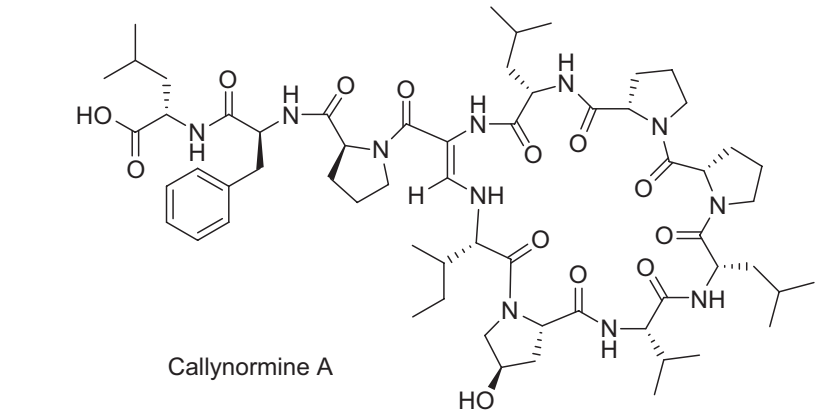
The side chain-to-tail type cyclopeptides are rarely-observed in natural sources. In 2004, callynormine A was reported as a new class of peptides by Kashman and co-workers [125]. Callynormine A was isolated from a Kenyan marine sponge,

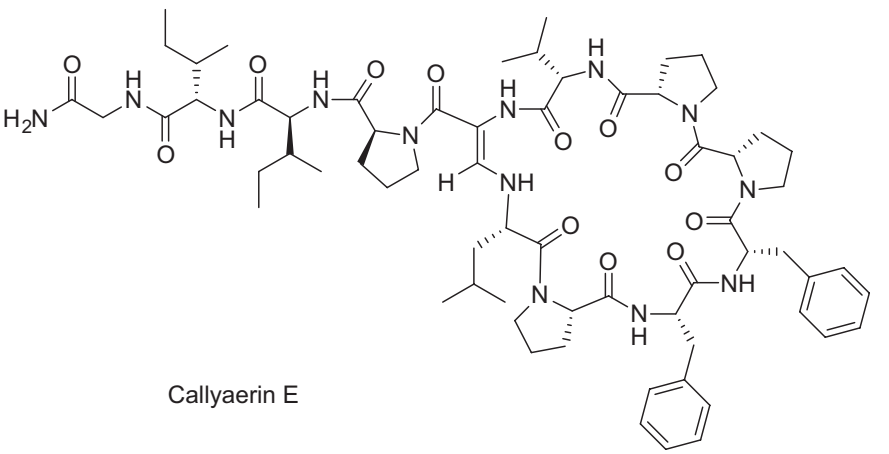
Callyspongia abnormis. The undecapeptide structure was composed of three Leu, three Pro, Phe, Val, Ile and two non-proteinogenic amino acids including γ-hydroxyproline and latent formylglycine. All amino acids were determined to be L-forms based on Murphy's analysis. The most unprecedented feature of the structure is the α-amido-β-aminoacrylamide functionality for the linkage of macrocylization, which was confirmed by X-ray structure. It was envisioned that the formylglycine embedded in the nascent linear peptide chain is a suitable acceptor of the amino group on the *N*-terminal residue, Ile. The condensation between aldehyde and *N*-terminal amino group generates the conjugated acrylamide functionality through Schiff base formation. Thus, callynormine A is a novel class of side-chain-to-tail cyclopeptide in which the endiamino moiety served as a heterodetic linkage. Although no biological activity of callynormine A was reported, same class of peptides was reported to be cytotoxic, soon later. In 2008, Proksch and co-workers reported callyaerin G as an analogue of callynormine A, from the Indonesian sponge *Callyspongeia aerizusa* [126]. The succeeding report by same group included the isolation and structure elucidation of callyaerin A-F and H. All callyaerins contain several proline residues, of which one proline was always positioned at the side chain and adjacent to macrocyclic ring. The basic structural unit of the callyaerins comprises a cyclic peptide with a linear peptide side chain, both of variable size, linked through an α-amido-β-aminoacrylamide functionality. This functional group in a peptide has to date only been described from the sponge of the genus *Callyspongia* [127]. Among eight derivatives, callyaerin E exhibited the most potent cytotoxicity against the L5178Y cell line with ED_{50} values of 0.39 μM. Considering lesser activity of the remaining congeners, increasing the number of proline residues in the cyclic moiety seemed to enhance the cytotoxicity, while replacement of a proline with a hydroxyproline would reduce the cytotoxicity (Fig. 6.9).

6.4.2 Imidazole-bridged Peptides

Aciculitins are cytotoxic and antifungal cyclopeptides isolated from the lithistid sponge *Aciculites orientalis* by Faulkner et al. in 1996 [128]. The structural feature of these peptides is a bicyclic peptide moiety containing an unusual histidinotyrosine bridge, to which C13-C15 2,3-dihydroxy-4,6-dienoic acids having D-lyxose at 3-position are attached. At the same time, aciculitamides, artifacts generated during the isolation process, were also found in the same sponge. In aciculitamides, the imidazole ring is oxygenated at 2′-position and methanol is added to the same ring at 4′-position. Interestingly, while aciculitins are cytotoxic to HCT-116 cell line (IC_{50}: 0.5 μg/mL), aciculitamides didn't show any cytotoxicity. This fact suggests the importance of the imidazole ring for bioactivity.

Theonellamides are cytotoxic and antifungal cyclopeptides from marine sponge *Theonella* sp., which was reported by Fusetani et al. in 1989 and in 1995 [129, 130]. Similarly, two related compounds have been isolated from the sponge *Theonella swinhoei*; theonegramide [131] and theopalauamide [132]. Their structures





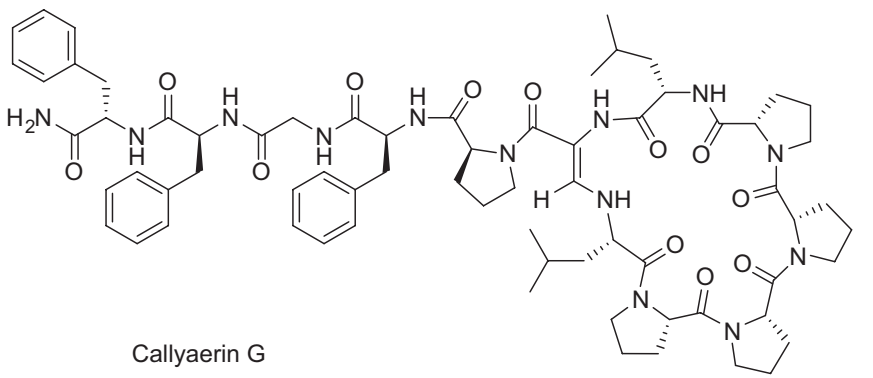
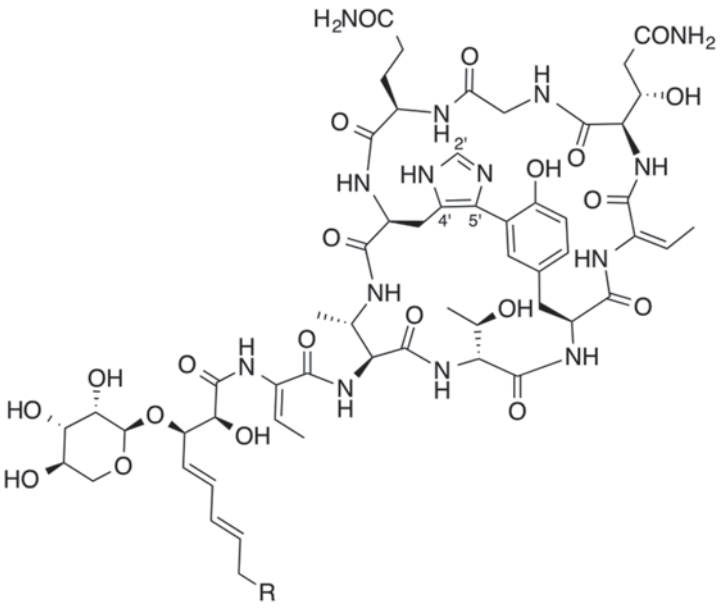


Fig. 6.9 Structures of side-chain-to-tail heterodetic cyclopeptides

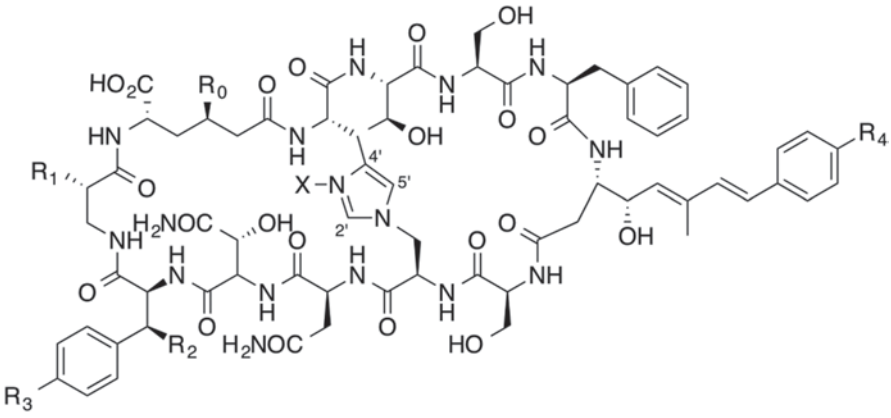
are characterized by a histidinoalanine residue that bridges the macrocyclic peptide ring. Notably, while the carbon atom at 5′-position in the imidazole ring is connected to a tyrosine residue in aciculitins, the nitrogen at 1′-position is connected in theonellamide analogues. Four of the eight analogues including theonegramide and theopalauamide are glycosylated at the π-nitrogen of the imidazole ring. Theonellamides A–F showed moderate cytotoxicity against P388 murine leukemia cells with IC_{50} values of 5.0, 1.7, 2.5, 1.7, 0.9, and 2.7 μg/mL, respectively [129, 130]. This suggests that the glycosyl groups show little effect on cytotoxicity and that the characteristic bicyclic peptide framework is responsible for biological activity. Recently, it has been revealed that theonellamides recognize 3β-hydroxysterol-containing membranes, induce glucan overproduction, and damage cellular membrane [133]. Further study turned out that they directly recognize the 3β-OH moiety and facilitate their binding to bilayer membranes [134] (Fig. 6.10).

6.4.3 Dilactones

Arenastatin A is a potent cytotoxic cyclodepsipeptide isolated from the Okinawan marine sponge *Dysidea arenaria* by Kitagawa et al. in 1994 [135]. The structure of this compound is characterized by a 16-membered macrocyclic dilactone, in which both of the ester linkages are formed by an L-leucic acid. This macrocycle exhibits extremely potent cytotoxicity (IC_{50}:5 pg/mL) against KB cells [135]. Synthetic approach of this compound has elucidated the cytotoxicity to be ascribable to inhibition of microtubule assembly through binding to rhizoxin/maytansine site [136, 137]. On the other hand, it possesses little *in vivo* anti-tumor activity through intravenous administration due to its lability in mouse serum arising from the cleavage of a 15,20-ester bond [138]. In addition, structure-activity relationship studies have revealed that each epimer of 7,8-epoxide, 6-methyl, and OMe-tyrosine lost cytotoxicity at concentration below 0.1 μg/mL [139]. In contrast, a 15-epimer synthesized from D-Leu showed moderate cytotoxicity (IC_{50}: 20 ng/mL). Therefore, several analogues derived from changing the L-leucic acid moiety or the 15,20-ester bond were synthesized, including a 15,20-triamide analogue (IC_{50}: 6 ng/mL, [138], a carba analogue (IC_{50}: 70 ng/mL, [140]), a deoxo analogue (IC_{50}: 40 ng/mL, [140]), and a 15-*t*-butylanalogue (IC_{50}: 10 ng/mL, [141]). All of these analogues turned out to be more stable than arenastatin A, while the 15,20-triamide analogue was almost insoluble in polar solvents. Thereafter, some soluble triamide analogues have been synthesized with polar substituents on the phenyl ring [142]. Among them, two analogues with diethylamine and piperazine moieties on the phenyl group have shown the strongest cytotoxicity (IC_{50}: 0.18 and 1.5 ng/mL, respectively) with good solubility and stability. The *in vivo* anti-tumor activity assay of the diethylamine analogue through intraperitoneal administration in subcutaneously implanted murine sarcoma S180 cells has revealed that it inhibited tumor growth at a dose of 1 mg/kg without acute toxicity, the efficacy of which was comparable to that of doxorubicin (positive control).



Aciculitin A R = C_5H_{11}
Aciculitin B R = C_6H_{13}
Aciculitin C R = C_7H_{15}



	R_0	R_1	R_2	R_3	R_4	X
Theonellamide A	OH	OH	Me	Br	H	β-D-Gal
B	OH	OH	Me	Br	H	
C	OH	H	H	H	Br	
D	OH	H	H	Br	Br	β-L-Ara
E	OH	H	H	Br	Br	β-D-Gal
F	OH	H	H	Br	Br	
Theonegramide	H	OH	Me	Br	H	β-D-Ara
Theopalauamide	H	OH	Me	Br	H	β-D-Gal

Fig. 6.10 Structures of imidazole-bridged cyclopeptides

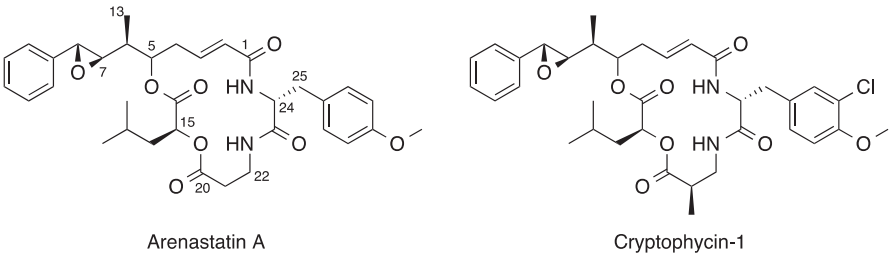


Fig. 6.11 Structures of dilactones

Arenastatin A is also known as cryptophycin-24, which belongs to the cryptophycin natural product family consisting of more than 25 analogues [143–145]. Cryptophycin-1 has firstly been reported as an antifungal depsipeptide from a cultured cyanobacterium of *Nostoc* sp. by Merck Sharp & Dohme Research Laboratories, which has shown antifungal activity against the genus *Cryptococcus* [146]. Cryptophycin-1 shows not only *in vitro* cytotoxicity but also *in vivo* anti-tumor activity because a C21-methyl group prevents hydrolysis of the 15,20-ester linkage. Recently, Sherman and co-workers identified the biosynthetic gene cluster of cryptophycin from the cyanobacterium *Nostoc* sp. ATCC 53789 [147]. The gene cluster encoded mixed NRPS and PKS biosynthetic enzymes, in which the thioesterase (TE) was isolated and its function was evaluated with a series of linear intermediate substrates. The TE substrate flexibility as well as its ability to catalyze hydrolysis or macrocyclization between C-2 ester and C-16 hydroxyl groups demonstrated an efficient chemoenzymatic synthesis of cryptophycins and arenastatins (Fig. 6.11).

6.5 Summary and Future Prospects

In the past three decades, numerous cyclic peptides have been discovered from marine sponges as described above, which attracted growing interest due to unique chemical structures as well as due to pronounced biological activities. In addition, some of them exhibit potential value as primary structures for the development of anti-cancer agents. The frequent occurrence of bioactive peptides, especially in sessile marine invertebrates such as sponges, is usually interpreted as chemical defense that protects these organisms against biotic stress factors such as predation, infection by pathogens, or overgrowth by fouling organisms [148]. It has long been deduced that the real producer of these peptides could be symbiont bacteria rather than sponge itself [149, 150]. The recent progress in biosynthetic research makes it possible to investigate the biosynthesis gene cluster of sponge-derived peptides or polyketides, revealing that they are most likely of bacterial origin [151–154]. Even though the symbiont bacteria would usually be difficult to be cultivated in standard laboratory conditions, the biosynthetic gene clusters might be useful for heterologous expression in a suitable cultivable host. If engineering technology of

biosynthetic enzymes such as non-ribosomal peptide synthetase becomes generally available, a vast variety of unique peptides would be generated according to the scaffolds of sponge-derived bioactive peptides. This was exemplified to some extent, by the pioneering works on some ribosomal peptides [2] and non-ribosomal peptides [147]. Furthermore, the solid phase peptide synthesis has culminated in advancement highly efficient synthesis of complex peptides composed of non-proteinogenic amino acids [155, 156]. In future, the combination of chemical synthetic and biosynthetic technologies has been anticipated to accelerate the development of anticancer drugs derived from the defensive peptides evolving from sponge-microbe association.

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