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Review

Bioactive natural products from marine cyanobacteria for drug discovery

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Abstract

The prokaryotic marine cyanobacteria continue to be an important source of structurally bioactive secondary metabolites. A majority of these molecules are nitrogen-containing compounds biosynthesized by large multimodular nonribosomal polypeptide (NRP) or mixed polyketide-NRP enzymatic systems. A total of 128 marine cyanobacterial alkaloids, published in the literature between January 2001 and December 2006, are presented in this review with emphasis on their biosynthesis and biological activities. In addition, a number of highly cytotoxic compounds such as hectochlorin, lyngbyabellins, apratoxins, and aurilides have been identified as potential lead compounds for the development of anticancer agents. A brief coverage on the distribution of natural product biosynthetic genes as well as the mechanisms of tailoring enzymes involved in the biosynthesis of cyanobacterial compounds will also be given.

Keywords: Marine cyanobacteria; Alkaloids; Polyketide-nonribosomal polypeptide; Drug discovery

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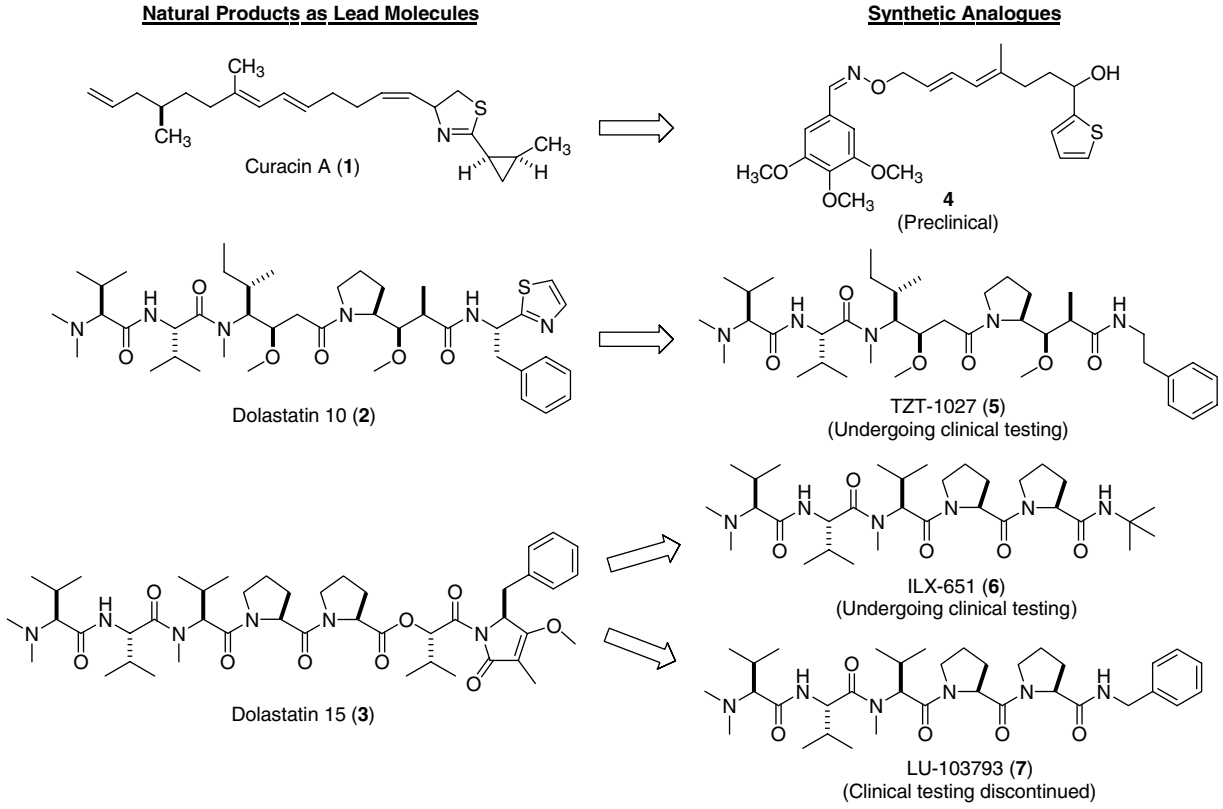


Fig. 1. Prominent anticancer marine cyanobacterial secondary metabolites and synthetic analogues.

1. Introduction

Over 300 nitrogen-containing secondary metabolites, represented by diverse structural types, have been reported from the prokaryotic marine cyanobacteria. A majority of these metabolites are biologically active and are products of either the nonribosomal polypeptide (NRP) or the mixed polyketide-NRP biosynthetic pathways. Biomolecules of the NRP and hybrid polyketide-NRP structural types are important subsets of natural products utilized as therapeutic agents. These include the antibiotic vancomycin, the immunosuppressive agent cyclosporine, and the anticancer agent bleomycin (Schwarzer et al., 2003). The discovery of these unique classes of natural products from marine cyanobacteria represents an important source of novel microbial secondary metabolites, in addition to the actinomycetes and fungi, for drug discovery efforts.

An increasing number of marine cyanobacterial compounds are found to target tubulin or actin filaments in eukaryotic cells, making them an attractive source of natural products as anticancer agents (Jordan and Wilson, 1998). Prominent molecules such as the anti-microtubule agents, curacin A (**1**) and dolastatin 10 (**2**), have been in preclinical and/or clinical trials as potential anticancer drugs (Gerwick et al., 2001). In addition, these molecules served as drug leads for the development of synthetic analogues, e.g. compound **4**, TZT-1027 (**5**), ILX-651 (**6**), and LU-103793 (**7**), usually with improved pharmacological and pharmacokinetic properties (Fig. 1) (Wipf et al., 2002; Mita et al., 2006; Watanabe et al., 2006). The antitumor activity of TZT-1027 (soblidotin), a synthetic derivative of dolastatin 10 (**2**), was found to be superior to existing anticancer drugs, such as paclitaxel and vincristine, and is currently undergoing Phase I testing for treating solid tumors (Watanabe et al., 2006). The third generation dolastatin 15 (**3**) analogue, ILX-651 (or tasidotin), is another antitumor agent currently undergoing Phase II trials after its successful run in Phase I trials (Mita et al., 2006).

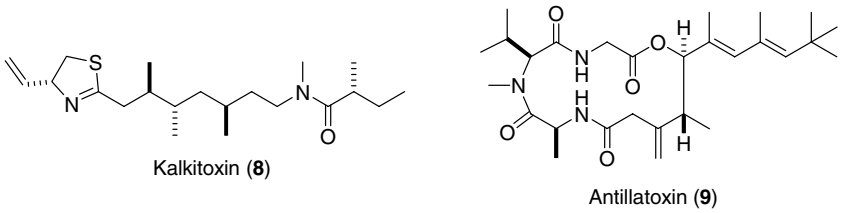


Fig. 2. Potent neurotoxins isolated from marine cyanobacteria.

Marine cyanobacteria are also a source of potent neurotoxins acting either as blockers [e.g. kalkitoxin (**8**) and jamaicamide A (**48**)] or activators [e.g. antillatoxin (**9**)] of the eukaryotic voltage-gated sodium (Na_v) channels (Figs. 2 and 6). Furthermore, the neurotoxic properties of these molecules are exquisitely potent, usually in the nanomolar range. Pharmacological studies have also showed the mechanistic novelty of certain molecules, such as antillatoxin (**9**), in modifying the activity of Na_v channels (Li et al., 2001). These cyanobacterial toxins are source of valuable molecular tools in functional characterization of Na_v channels as well as potential analgesics and neuroprotectants (Blumenthal and Seibert, 2003).

This review aims to showcase the structural diversity of marine cyanobacterial secondary metabolites with a comprehensive coverage of alkaloids published in the literature from January 2001 to December 2006. Previous coverage of nitrogen-containing compounds from marine cyanobacteria up to January 2001 was reviewed by Gerwick et al. (2001). Common metabolic themes and unique building blocks, especially on the incorporation of various ketide-derived moieties, used in the elaboration of these molecules will be highlighted. In addition, the distribution of natural product biosynthetic genes in cyanobacteria will be briefly discussed, followed by a summary of recent advances revealed from biosynthetic studies of novel tailoring enzymes involved in natural product biosynthetic pathways.

2. Secondary metabolites from marine cyanobacteria

2.1. Metabolic themes and building blocks

There are currently some 300 marine cyanobacterial alkaloids reported in the literature. Of these, 128 marine cyanobacterial nitrogen-containing secondary metabolites, covering literature from January 2001 to December 2006, are presented in this review (Table 1). Most of the cyanobacterial molecules discovered during this time frame were based on research conducted mainly at the laboratories of Professors Richard Moore (University of Hawaii) and William Gerwick (University of California, San Diego). As in the previous review (Gerwick et al., 2001), the majority of these biomolecules were isolated from the filamentous Order Nostocales, especially members belonging to the genera *Lyngbya*, *Oscillatoria*, and *Symploca*. The locations of the collection sites were mainly from the tropics, including Papua New Guinea and the Pacific islands, in particular Guam and Palau (Fig. 3).

The predominant metabolic theme of nitrogen-containing marine cyanobacterial compounds is the occurrence of mixed polyketide-nonribosomal polypeptide structural types. These are molecules containing acetate or propionate units as well as proteinogenic amino acids, forming as either linear or cyclic lipopeptides. The utilization of acetate-derived units in the construction of these hybrid compounds can be seen in several ways. Firstly, acetate-derived fatty acid chain can be coupled through amide bonds with a variety of functionalized amines in linear lipopeptides [e.g. malyngamides S (**41**)–W (**45**) in Fig. 6]. Further modifications on the fatty acid chain, such as methylation and halogenation, are common. Lipidation through amide bonds are also common in a number of oligopeptides, such as lyngbyabellin D (**118** in Fig. 12) and somamide A (**141** in Fig. 16). Single acetate unit or multiple ketides can also be utilized to extend amino acids. For instance, a unit of acetate is used in the extension of a variety of amino acids, such as Ala, Phe, Pro, and Gly. The extension can either be linear or undergo cyclization to form common moieties, such as pyrrolinone ring system in the jamaicamides (**48**–**50** in Fig. 6).

Polyketide-derived moieties occurring as β-hydroxy or amino acid residues are source of non-proteinogenic units in the construction of lipopeptides, especially cyclic depsipeptides. These macrocyclic molecules usually exhibit potent biological activities and this could in part due to the presence of β-amino or hydroxy acid moieties which are resistant to proteolysis as well as conferring unique structural properties in the molecules (Steer et al., 2002). The number of carbons of the β-hydroxy/amino acid units range from 4- [e.g. 3-amino-2-methyl-butanoic acid moiety in guineamide B (**78**)] to 12-carbons [e.g. 3-amino-2,5-dihydroxy-dodecanoic acid moiety in largamide H (**107**)] long. Furthermore, these β-amino or hydroxy polyketide-derived residues are characterized by methyl or dimethyl group at the α-C as well as alkene or alkyne functional group at the terminal end. Further modifications, including hydroxylation [e.g. largamide H (**107**) in Fig. 11] and dichlorination [e.g. lyngbyabellins (**114**–**116** and **118**–**123** in Fig. 12) and hectochlorins (**111**–**113** in Fig. 12)] can also take place along the carbon chain. Multiple ketide units can also be incorporated as part of the cyclic structures, such as in apratoxins (**126**–**128**) and palau'amide (**135**) (Fig. 14). Another unique feature of cyanobacterial compounds is the use of unusual starter units in polyketide extension and these include the proposed 2,2-dimethyl-propionic acid in antillatoxin B (**134**) and apratoxin A (**126**) (Fig. 14).

Proteinogenic amino acids used in the biosynthesis of marine cyanobacterial peptides are mainly neutral amino acids e.g. Val, Ala, Phe, Ile, Tyr, Pro, Cys, Ser, Leu, and Gly. Val or its derivatives is the predominant amino acid found in peptides, followed by Ala and Phe. A majority of these amino acids are incorporated as the L-form, although some undergo epimerization as the D-form. In addition, *N*- and *O*-methylation of amino acids, especially, *N*Me-Val, *N*Me-Phe, and *O*Me-Tyr, are common features in marine cyanobacterial molecules. A number of α-hydroxy acid residues are also frequently encountered as lactic acids [e.g. guineamide A (**77**) in Fig. 9], α-hydroxy isovaleric acids [e.g. guineamide D (**80**) in Fig. 9], α-hydroxy isoleucic acids [e.g. guineamide C (**79**) in Fig. 9], and phenyllactic acids [e.g. wewakpeptins C (**105**) and D (**106**) in Fig. 11]. Other amino acid modifications include hydroxylation [e.g. hydroxyproline and hydroxyleucine moieties in lobocyclamides B (**109**) and C (**110**) in

Table 1
Nitrogen-containing marine cyanobacterial and invertebrate-derived secondary metabolites published from January 2001 to December 2006

Source	Location	Metabolite	Class	Biological activity
Lyngbya confervoides	Obyan Bay, Saipan	Obyanamide (**83**)	Lipopeptide	Cytotoxic against KB cells ($IC_{50} = 0.58$ μg/mL)
	Cay Lobos, Bahamas	lobocyclamides A (**108**)–C (**110**)	Lipopeptide	Mixtures of **108** and **109** exhibited synergistic activity against a panel of *Candida* sp.
L. majuscula	Crown Island, Papua New Guinea	Malyngamides U (**43**)–W (**45**)	Lipopeptide	
	Collado Reef, Puerto Rico	Malyngamide T (**42**), quinoline alkaloid (**46**), and tryptophan-derivative (**47**)	Lipopeptide/ alkaloids	
	Hector Bay, Jamaica	Jamaicamides A (**48**)–C (**50**), hectochlorin (**111**), and 23-deoxyhectochlorin (**112**)	Lipopeptide	**48**–**50** cytotoxic against H-460 human lung and neuro-2a mouse neuroblastoma cell lines; potent sodium channel blocking activity; **111** promote actin polymerization
	Seamount, Papua New Guinea	Guineamides A (**77**)–F (**82**)	Lipopeptide	**78** and **79** with moderate activity against neuroblastoma cell line
	Antany Mora, Madagascar	Antanapeptins A (**84**)–D (**87**) and dolastatin 16	Lipopeptide	
	Thailand	Trungapeptins A (**88**)–C (**90**)	Lipopeptide	
	Piti Bomb Holes, Guam	pitipeptolides A (**97**) and B (**98**)	Lipopeptide	Weak cytotoxicity against LoVo cancer cells; moderate antimycobacterial activity; stimulate eleastese activity
	Wasini Island, Kenya	Homodolastatin 16 (**100**)	Lipopeptide	Moderate activity against oesophageal and cervical cancer cell lines
	Apra Harbor, Guam	Lyngbyastatin 3 (**102**)	Lipopeptide	
	Alotau Bay, Papua New Guinea	lyngbyabellins E (**119**)–I (**123**) and dolabellin	Lipopeptide	Cytotoxic against H-460 human lung tumor and neuro-2a mouse neuroblastoma cell lines (LC_{50} between 0.2 and 4.8 μM)
	Wewak Bay, Papua New Guinea	Wewakazole (**125**)	Cyclic peptide	
	Apra Harbor, Guam	apratoxin A (**126**)	Lipopeptide	Cytotoxic against human tumor cell lines (0.36–0.52 nM)
	Collado Reef, Puerto Rico and Bush Key, Dry Tortugas, Florida	antillatoxin (**9**) and antillatoxin B (**134**)	Lipopeptide	**134** with sodium channel-activating ($EC_{50} = 1.77$ μM) and ichthyotoxic ($LC_{50} = 1.0$ μM) properties
	Alotau Bay, Papua New Guinea	Aurilides B (**137**) and C (**138**)	Lipopeptide	Cytotoxic against H-460 human lung tumor and neuro-2a mouse neuroblastoma cell lines (LC_{50} between 0.01 and 0.13 μM)
L. semiplena	Wewak Bay, Papua New Guinea	Semiplenamides A (**32**)–G (**38**)	Lipopeptide	All displayed weak to moderate toxicity in brine shrimp assay; **32**, **33**, and **38** showed weak affinity for the rat cannabinoid CB1 receptor; **32** showed moderate inhibitor of anandamide membrane transporter
	Wewak Bay, Papua New Guinea	Wewakpeptins A (**103**)–D (**106**)	Lipopeptide	**103** and **104** cytotoxic against H-460 human lung tumor and neuro-2a mouse neuroblastoma cell lines (LC_{50} about 0.4 μM)
L. majuscula and *Schizothrix* sp. assemblage	Taveuni and Yanuca Islands, Fiji	Taveuniamides A (**19**)–K (**29**)	*N*-containing lipids	Toxic in brine shrimp lethality assay
	Somo Somo, Fiji	Somocystinamide A (**30**)	Lipopeptide	Cytotoxic against neuro-2a neuroblastoma cells ($IC_{50} = 1.4$ μg/mL)
	Somo Somo and Taveuni Island, Fiji	Somamides A (**141**) and B (**142**)	Lipopeptide	
Lyngbya sp.	Various locations in Palau	palau'imide (**53**), lyngbyapeptins B (**56**), C (**57**), and lyngbyabellin C (**116**)	Lipopeptide	**53** and **116** cytotoxic against KB and LoVo cells
	Apra Harbor, Guam	15-Norlyngbyapeptin A (**55**) and lyngbyabellin D (**118**)	Lipopeptide	**118** cytotoxic to KB cell line ($IC_{50} = 0.1$ μM)
	Various locations, Palau	Ulongamides A (**91**)–F (**96**)	Lipopeptide	**91**–**95** with weak cytotoxic against KB cells
	Ulong Channel, Palau	ulongapeptin (**99**)	Lipopeptide	Cytotoxic against KB cell line ($IC_{50} = 0.63$ μM)
	Guam and Palau	Apratoxins B (**127**) and C (**128**)	Lipopeptide	Cytotoxic against KB and LoVo cells
	Ulong Channel, Palau	Palau'amide (**135**)	Lipopeptide	Strongly cytotoxic against KB cell line ($IC_{50} = 13$ nM)

(*continued on next page*)

Table 1 (*continued*)

Source	Location	Metabolite	Class	Biological activity
Microcoleus lyngbyaceus	Dublon Island, Chuuk Island Atoll	polychlorinated and nonchlorinated acetamides (**12**–**18**)	Lipopeptide	
Oscillatoria sp.	Key Largo, Florida	largamides A (**145**)–G (**151**) and H (**107**)	Lipopeptide	**148**–**151** inhibited chymotrypsin with IC_{50} values between 4 and 25 μM
Phormidium sp.	Bise, Okinawa	phormidinines A (**10**) and B (**11**)	*N*-containing lipids	
Symploca hydnoides	Kahe, Oahu, Hawaii	malevamide D (**52**)	Lipopeptide	Cytotoxic against P-388, A-549, HT-29, and MEL-28 cell lines
Symploca sp.	Fingers Reef, Guam	Guamamide (**40**) and micromide (**58**)	Lipopeptide	Cytotoxic against KB cell line
	Kaneohe Bay, Oahu, Hawaii	symplostatin 3 (**51**)	Lipopeptide	Cytotoxic against human tumor cell lines (3.9–10.3 nM); disrupt microtubules
	Salmedina Reef, Portobelo, Panama	belamide A (**54**)	Lipopeptide	Cytotoxic against HCT-116 cell line at IC_{50} 0.74 μM; tubulin destabilizing antimitotic properties
	Short Dropoff, Palau	Tasiamide (**59**) and tasiamide B (**60**)	Peptide/ lipopeptide	**59** cytotoxic against KB (IC_{50} = 0.48 μg/mL) and LoVo (IC_{50} = 3.47 μg/mL) cells; **60** cytotoxic against KB cell line (IC_{50} = 0.8 μM)
	Short Dropoff, Palau	Tasipeptins A (**143**) and B (**144**)	Lipopeptide	Cytotoxic against KB cell line
Trichodesmium erythraeum	Culture at Woods Hole Oceanographic Institute	trichamide (**124**)	Cyclic peptide	
Bursatella leachii	Eastern Beach, New Zealand	malyngamide S (**41**)	Lipopeptide	Exhibited cytotoxicity and anti-inflammatory activities
	Sichang Island, Thailand	Hectochlorin (**111**) and deacetylhectochlorin (**113**)	Lipopeptide	**113** cytotoxic against KB and NCI-H187 with ED_{50}'s of 0.31 and 0.32 μM, respectively
Philinopsis speciosa	Shark's Cove, O'ahu	Kulokekahilides-1 (**101**) and -2 (**139**)	Lipopeptide	Cytotoxic against various cancer cell lines, such as P388, SK-OV-3, MDA-MB-435, and A-10
Dysidea sp.	Bararin Island, Philippines	Dysideaprolines A (**63**)–F (**68**), barbaleucamides A (**69**) and B (**70**)	Peptide/ lipopeptide	
	Lizard Island, Australia	compounds **71**–**75**	Peptide	
	Mayo Island, Indonesia	Dysithiazolamide (**76**)	Lipopeptide	

Fig. 11], homo variants [e.g. homoserine and homotyrosine residues in lobocyclamide A (**108**) in Fig. 11 and largamide B (**146**) in Fig. 16, respectively], dehydrated amino acids [e.g. dehydro-threonine unit in largamide H (**107**) in Fig. 11], various oxidation states of Cys, Ser, and Thr [e.g. thiazole and oxazole residues in hectochlorin (**111**) and wewakazole (**125**), respectively], and halogenated derivatives [e.g. bromination and chlorination of Tyr units in largamides D (**148**) and E (**149**) in Fig. 16, respectively]. Furthermore, Cys, Ser, and Thr units can also undergo oxidative coupling with a number of amino acid residues [e.g. thiazole-alanyl unit in guineamide A (**77**) in Fig. 9].

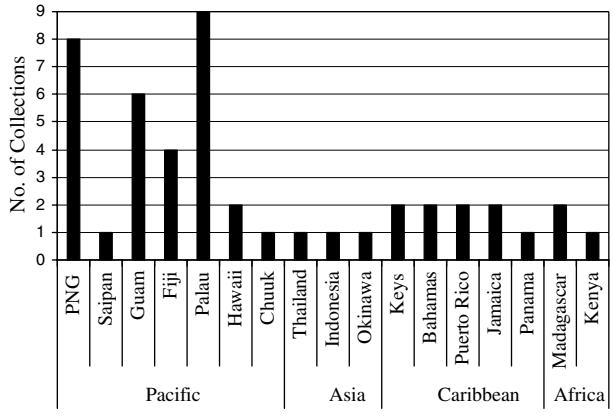


Fig. 3. Number of marine cyanobacterial collections by location based on publications from January 2001 to December 2006. (PNG = Papua New Guinea)

The incorporation of various forms of polyketide precursors along with modified proteinogenic building blocks via tailoring enzymes results in the structural diversification of marine cyanobacterial natural products. The following sections showcase the chemical diversity of these metabolites starting with nitrogen-containing lipids, followed by acyclic and cyclic lipopeptides.

2.2. Nitrogen-containing lipids

Two new 2-alkypyridine alkaloids, phormidinines A (**10**) and B (**11**), were reported from an Okinawan collection of the marine cyanobacterium, *Phormidium* sp. (Fig. 4) (Teruya et al., 2005). The structures and absolute stereochemistry of these compounds were determined based on 2D NMR spectra analysis and Mosher's method, respectively.

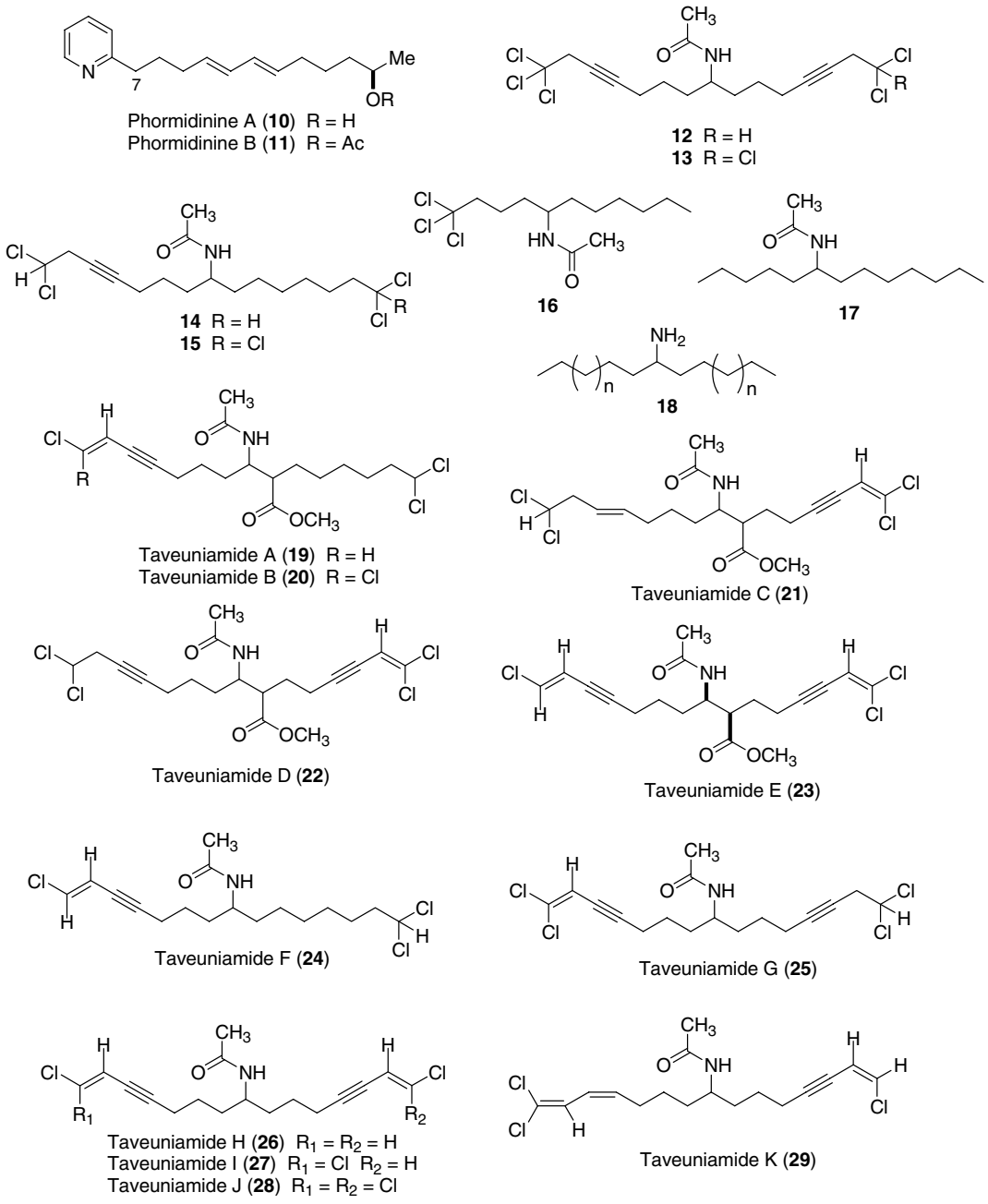


Fig. 4. Marine cyanobacterial nitrogen-containing lipids (**10**–**29**).

The occurrence of 2-alkylpyridines from marine sources is rare with pulo'upone from a marine mollusk being the only other example. The biosynthesis of the pyridine ring and C-7 was proposed by the authors to originate either from picolinic acid or from a linear 17-carbons chain.

A series of polychlorinated acetamides (**12**–**16** and **19**–**29**) and its dechlorinated derivatives (**17** and **18**) have been reported from *Microcoleus lyngbyaceus* and *Lyngbya majuscula*/*Schizothrix* assemblage collected at Chuuk Island and Fiji, respectively (Fig. 4) (Orsini et al., 2001; Williamson et al., 2004). These compounds were mainly isolated from the non-polar component or fractions of the organic extract and their chemical structures determined through a variety of spectroscopic methods. A majority of these unique molecules are characterized by having terminal mono, di, or trichlorinated functional groups. Other marine cyanobacterial metabolites, e.g. dysidenin-type compounds (e.g. **62**) and barbamide (**61**), having terminal di- and trichloromethyl groups were shown to derive from chlorination of Leu, possibly via free radical mechanism. The biogenesis of the taveuniamides (Williamson et al., 2004), isolated from Fijian *Lyngbya majuscula*/*Schizothrix* assemblage, has been proposed to occur either through the decarboxylation and methylation of an octaketide precursor or the C–C bond formation between the C-1 carboxyl carbon and C-2 of two tetraketide precursors. In

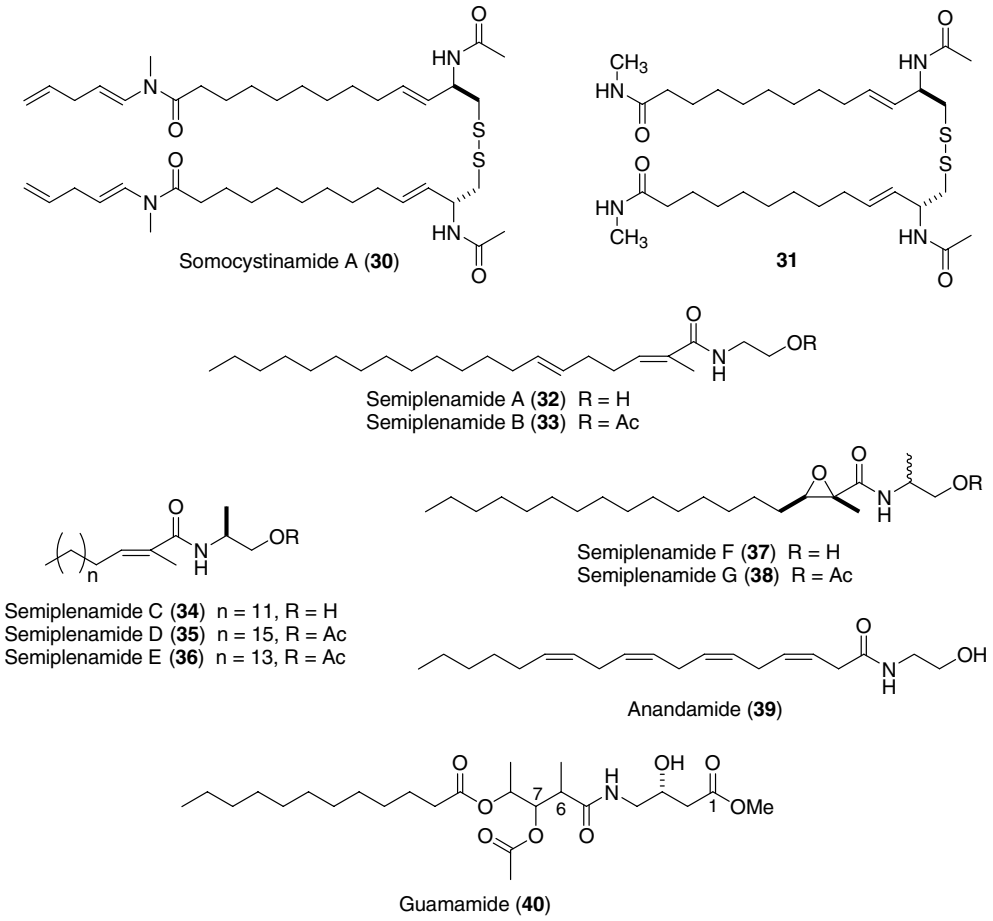


Fig. 5. Marine cyanobacterial linear lipopeptides (**30**, **32**–**38**, and **40**) and compounds **31** and **39**.

addition, terminal chlorination and the formation of triple bonds in the taveuniamides could involve novel halogenases and desaturases. The taveuniamides (**19**–**29**), in particular, showed significant biological activities in the brine shrimp toxicity assay with the more potent taveuniamides F (**24**), G (**25**), and K (**29**) having LD_{50}s of 1.8, 1.9, and 1.7 μg/mL, respectively. Compounds **12** and **13**, isolated from *M. lyngbyaceus*, on the other hand were not responsible for the initial HIV-active extract.

2.3. Linear lipopeptides

A novel class of cytotoxic marine cyanobacterial metabolite, somocystinamide A (**30**), was isolated from a Fijian *Lyngbya majuscula*/*Schizothrix* mixed assemblage (Fig. 5) (Nogle and Gerwick, 2002a). Compound **30** displayed toxicity activity against the mouse neuro-2a neuroblastoma cells with IC_{50} of 1.8 μM. However, the molecule was acid sensitive and it was converted to compound **31** due to traces of HCl and H_2O in deuterated $CDCl_3$. The biosynthesis of **30** was hypothesized to be derived from L-Cys, followed by ketide extension with five acetate units and amide linkage with *N*MeGly and further extension by two acetate units. Further modifications involving decarboxylation and dimerization lead to the formation of terminal olefin and the dimeric structure of **30**. Terminal olefinic carbon in somocystinamide A is also present in curacin A (**1**) and kalkitoxin (**8**) and is speculated to derive from C-2 of acetate unit.

New anandamide-like derivatives, the semiplenamides (**32**–**38**), were isolated from a Papua New Guinea strain of *Lyngbya semiplena* (Fig. 5) (Han et al., 2003). Due to the structural similarity with anandamide (**39**), an endogenous cannabinoid neurotransmitter, the molecules were evaluated in a number of bioassays based on the endocannabinoid system. Weak affinity of the rat cannabinoid CB_1 receptor was reported for semiplenamides A (**32**), B (**33**), and G (**38**) while compound **32** displayed moderate inhibitory activity with IC_{50} at 18 μM in the anandamide membrane transporter. In addition, the semiplenamides showed weak to moderate toxicity in the brine shrimp lethality assay with LD_{50}s ranging from 1.4 to 19 μM. Of the series, semiplenamide C (**34**) was recently synthesized using a novel *syn*-aldol/dehydration method (Davies et al., 2005).

A 12-carbons fatty acid chain-containing cytotoxic molecule, guamamide (**40**), was isolated together with micromide (**58**) from *Symploca* sp. collected from Guam (Figs. 5 and 7) (Williams et al., 2004). The structure of **40** was determined by 1D and 2D NMR spectrometry while the

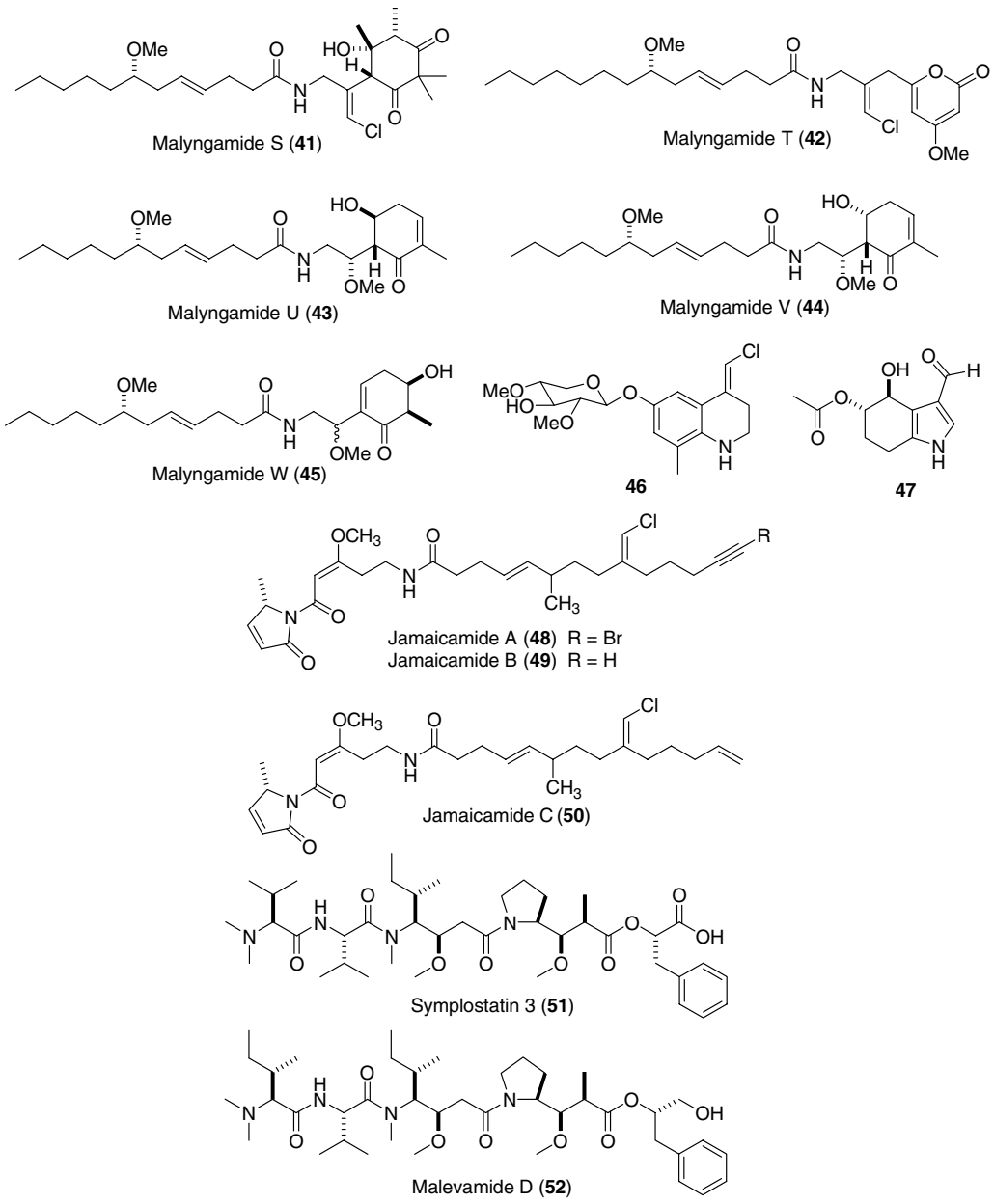
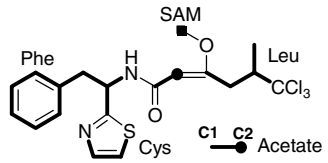
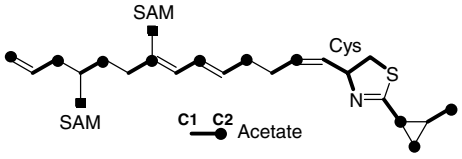
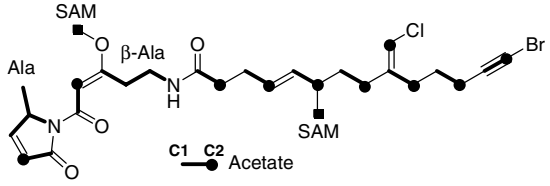
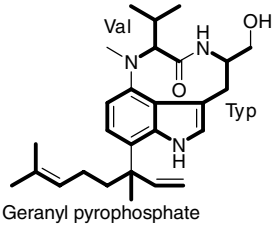


Fig. 6. Marine cyanobacterial linear lipopeptides (**41**–**45** and **48**–**52**) and alkaloids (**46** and **47**).

absolute stereochemistry of the hydroxyl group was established from ^{1}H NMR comparison between the (*R*)- and (*S*)-α-methoxyphenylacetic acid derivative of **40**. The biogenesis of guamamide could derive from carbonyl ester linkage of a 12-carbons fatty acid with lactic acid followed by a ketide extension and amide linkage with Gly. Further ketide extension on Gly and methylations at C-6 and C-1, as well as acetylation at C-7 deriving from SAM and acetate unit, respectively yield compound **40**. The cytotoxicity of guamamide (**40**) against KB cell lines was reported at IC_{50} of 1.2 μM.

A predominant class of linear lipopeptides that has become a signature of marine cyanobacterial secondary metabolism is the malyngamides (Gerwick et al., 2001). Five additional compounds [malyngamides S (**41**) to W (**45**) in Fig. 6] have been discovered since 2001, bringing the total to 34 of such molecules isolated mainly from *Lyngbya* sp. A Puerto Rican and a Papua New Guinea collection of *L. majuscula* provided malyngamides T (**42**) and U (**43**)–W (**45**), respectively, while a mollusk, *Bursatella leachii*, was the source of malyngamide S (**41**) (McPhail and Gerwick, 2003; Nogle and Gerwick, 2003a; Appleton et al., 2002). Although malyngamide S (**41**) was purified from a sea hare, its origin is possibly from the invertebrate cyanobacterial diet. A new chlorinated quinoline alkaloid (**46**) and a tryptophan derivative (**47**) were also isolated together with malyngamide T (**42**) (Fig. 6) (Nogle and Gerwick, 2003a). These malyngamides consisted of either a 12-carbons (e.g. **41** and **43**–**45**) or 14-carbons (e.g. **42**) fatty acid moiety termed as lyngbic acid with a methoxy and

Table 2
Notable genetic and biochemical features of the biosynthetic gene clusters of marine cyanobacterial molecules

Marine cyanobacterial molecules	Gene size	Unique genetic and biochemical features
Barbamide 	26 kb	1. Biotransformation of Leu to the trichloroisovaleric residue 2. Terminal thiazole ring formation via oxidative decarboxylation 3. Two separate ORFs coding of a PKS module 4. Separate ORFs coding of peptidyl carrier and adenylation domain of one NRPS module
Curacin A 	64 kb	1. Involvement of HMG-CoA in formation of cyclopropyl ring 2. Unique chain termination involving product release and dehydration and decarboxylation processes yielding a terminal methylene group
Jamaicamide A 	58 kb	1. Tight integration of mixed PKS/NRPS pathway 2. Involvement of HMG-CoA in formation of vinyl/vinyl chloride group 3. Biotransformation and incorporation of unique alkynyl starter unit 4. Unique chain termination yielding pyrrolinone ring moiety
Lyngbyatoxin A 	11 kb	1. Prenylation process leading to the formation of lyngbyatoxin A

trans double bond at C-7 and C-4, respectively. Chain extension on lyngbic acid by a variety of amino acids (e.g. β-Ala and Gly) and malonyl-CoA-derived acetate units with further modifications, including methylation and chlorination, give rise to compounds **41**–**45**. The present of a vinyl chloride group could derive from C-2 of acetate group via tailoring enzymes such as hydratases and halogenases. Malyngamides S (**41**) displayed anti-inflammatory activities in an activated human peripheral blood neutrophil assay by inhibiting superoxide production induced by inflammation-promoting compounds. In addition, **41** exhibited weak to moderate cytotoxicity properties in bioassays based on human leukemic HL60 cells, P388 murine leukemia, BSC-1 cells, and the NCI human tumor activity assay. No antimicrobial and antitubercular activities were detected for this molecule.

The jamaicamides (**48**–**50**) are a series of potent neurotoxins isolated from a chemically rich Jamaican strain of *L. majuscula* (Fig. 6) (Edwards et al., 2004). These lipopeptides are highly functionalized with pyrrolinone ring system, vinyl chloride, and a terminal alkynyl bromide (e.g. **48**) or olefinic carbon (e.g. **50**). In addition to the jamaicamides, the cytotoxic hectochlorin (**111**) and its derivative (**112**) were also isolated from the same cyanobacterium strain (see Section 2.5). The jamaicamides exhibited sodium channel blocking properties at 5 μM as well as moderate cytotoxicity activities against the H-460 human lung and neuro-2a mouse neuroblastoma cell lines with LC_{50}s about 15 μM. Jamaicamide B (**49**) was the most active molecule in the goldfish toxicity assay at 100% lethality at 5 ppm after 90 min of observation. Due to the amenability of this marine

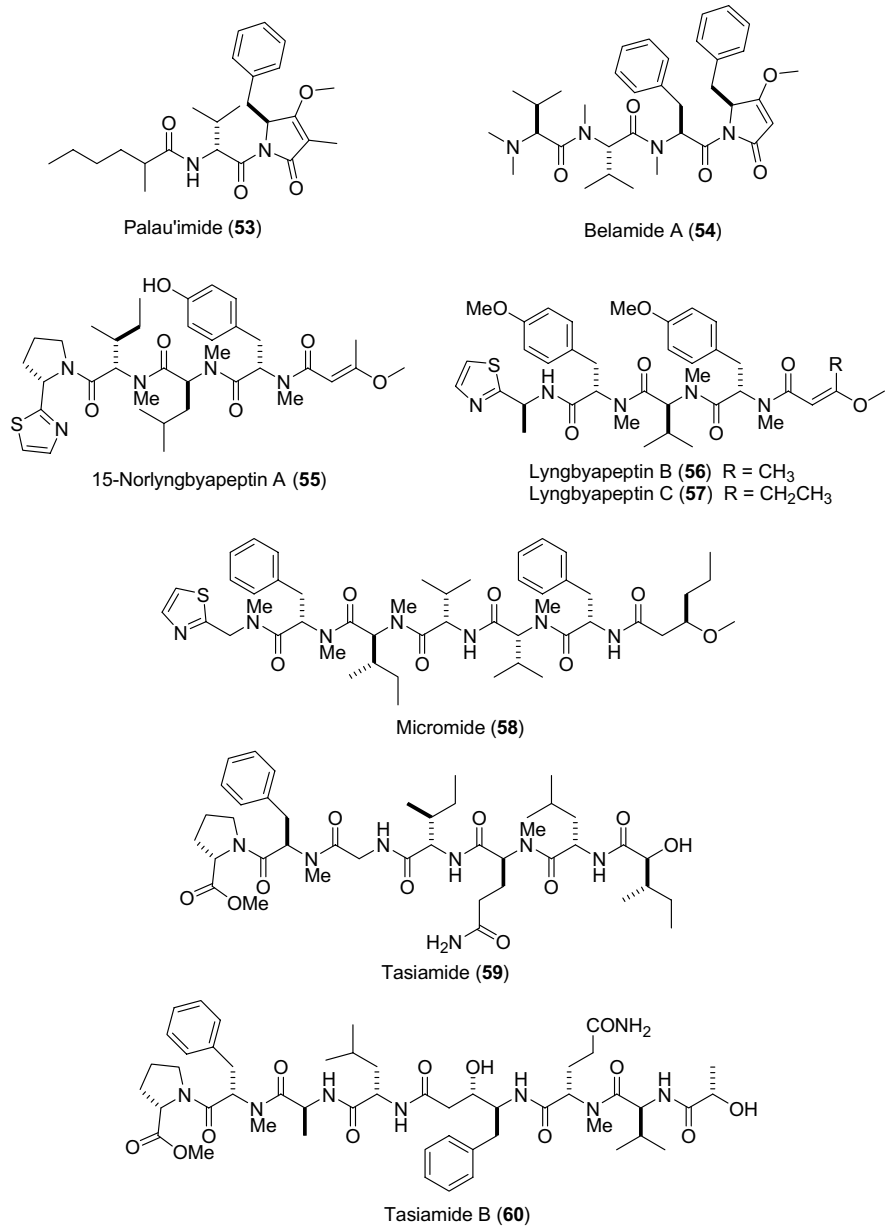


Fig. 7. Marine cyanobacterial linear lipopeptides (**53**–**60**).

cyanobacterium strain to laboratory culture, a series of feeding experiments using stable isotope precursors as well as molecular genetic studies on the biosynthetic gene cluster were carried out. The results of these studies are summarized in Section 3.2 and Table 2. The discovery of the jamaicamides adds to the growing number of novel neurotoxic compounds from marine cyanobacteria.

Marine cyanobacteria continue to be a source of novel linear and cyclic dolastatin-type molecules. The dolastatins are a series of potent cytotoxic molecules initially isolated from the sea hare, *Dolabella auricularia*, and are generally accepted that they are sequestered through the invertebrate cyanobacterial diet. Evidence of its cyanobacterial origins has been substantiated by the discovery of a number of dolastatins (e.g. dolastatins 3, 10, 12, and 16) from marine cyanobacteria (see Luesch et al., 2002c, for review). Additional new dolastatin 10 analogues, symplostatin 3 (**51**) and malevamide D (**52**), and dolastatin 15 analogues, palau'imide (**53**) and belamide A (**54**) have been reported since 2001 (Figs. 6 and 7).

Symplostatin 3 (**51**) was purified from a tumor selective organic extract of the marine cyanobacterium, *Symploca* sp. VP452, collected from Hawaii (Fig. 6) (Luesch et al., 2002a). The complete structure elucidation of **51** was based on extensive 2D NMR spectrometry, MS/MS data comparison with dolastatin 10 (**2**), and chemical manipulation. This molecule differs from dolastatin 10 (**2**) only in the C-terminal unit where the dolaphenine unit in the latter compound is replaced by a 3-phenyllactic acid moiety. Due to this structural difference, the biological activity of

symplostatin 3 was found to be about 100-fold less active in comparison with **2** against the KB and LoVo cell lines with IC_{50} of 3.9 and 10.3 nM, respectively. In addition, symplostatin 3 was found to cause microtubule depolymerization in A-10 cells. The cytotoxic malevamide D (**52**) is another dolastatin 10 analogue isolated together with the known molecules, curacin D and symplostatin 1, from a Hawaiian strain of marine cyanobacterium, *Symploca hydnoides* (Fig. 6) (Horgen et al., 2002). Malevamide D (**52**) differs from dolastatin 10 by having a L-Ile and a 3-phenyl-1,2-propanediol units at the N- and C-terminal ends, respectively. The biological activity of **52** was found to be in the subnanomolar range when tested against a panel of different cell lines including P-388, A-549, HT-29, and MEL-28 cells.

Two truncated analogues of dolastatin 15 (**3**), palau'imide (**53**) and belamide A (**54**) were isolated from a Palauan strain of *Lyngbya* sp. (most likely to be *L. bouillonii*) and a Panamanian strain of *Symploca* sp., respectively (Fig. 7) (Luesch et al., 2002b; Simmons et al., 2006). The common structural feature in these molecules is the presence of the pyrrolinone functional group. Palau'imide (**53**) is one of several structural classes of secondary metabolites purified from the Palauan strain of *Lyngbya* sp. (Luesch et al., 2002b). Compound **53** exhibited in vitro cytotoxicity against KB and LoVo cells with IC_{50} of 1.4 and 0.36 μM, respectively, while belamide A (**54**) displayed toxicity against the MCF7 breast cancer and HCT-116 cells with IC_{50} of 1.6 and 0.74 μM, respectively. In addition, the tubulin destabilizing property of the latter compound was demonstrated in A-10 cells. The discovery of these novel dolastatin 10 and 15 related molecules from marine cyanobacteria contributes to SAR studies as well as the development of potential drug leads as anticancer agents.

Structural variation of the dolaphenine unit in dolastatin 10 (**2**) is observed in four other marine cyanobacterial linear lipopeptides, mainly 15-norlyngbyapeptin A (**55**), lyngbyapeptins B (**56**) and C (**57**), and micromide (**58**), purified from three filamentous marine cyanobacterial strains (Fig. 7). The 15-norlyngbyapeptin A (**55**) was isolated from a Guamanian *Lyngbya* sp. (Williams et al., 2003a). Additional members, lyngbyapeptins B (**56**) and C (**57**), were also isolated from another strain of *Lyngbya* sp. procured from Palau (Luesch et al., 2002b). It was observed that the morphology of this Palauan marine cyanobacterial strain was similar to that of *L. bouillonii*. The lyngbyapeptin class of lipopeptides is biosynthetically derived from five amino acid residues and a combination of acetate and possible propionate units giving rise to the terminal polyketide chain. Lyngbyapeptins B (**56**) and C (**57**) were found to be not toxic when tested at <5 μM against KB and LoVo cells. A collection of *Symploca* sp. from Guam yielded another thiazole-containing linear lipopeptide, micromide (**58**), along with guamamide (**40**) (Williams et al., 2004). Compounds **58** consisted of seven amino acid residues as well as a unique β-methoxy acid unit, 3-methoxy-hexanoic acid, which could be derived from three acetate units. Micromide (**58**) displayed IC_{50} value at 0.26 when tested against KB cell line. These three cyanobacterial strains were found to be prolific source of secondary metabolites as molecules from several classes of lipopeptides, such as the apramides and lyngbyabellins, were also isolated from these extracts.

Further collections of *Symploca* sp. from Palau yielded two novel linear peptides, tasiamide (**59**) and tasiamide B (**60**) (Fig. 7) (Williams et al., 2002a; Williams et al., 2003b). The former molecule comprised of seven amino acid-derived residues while tasiamide B (**60**) is longer with an additional amino acid unit. In addition, tasiamide B (**60**) has an unusual residue, 4-amino-3-hydroxy-5-phenylpentanoic acid residue, which could be biosynthetically derived from an acetate unit extension of a Phe unit. Both compounds **59** and **60** were cytotoxic against KB cells at IC_{50} of 0.58 and 0.80 μM, respectively. In addition, **59** exhibited toxicity activity against LoVo cells at IC_{50} of 3.47 μg/mL.

2.4. Polychlorinated peptides from Dysidea species

A series of polychlorinated peptides (**63**–**76**) isolated from the sponge, *Dysidea* sp., are included in this review due to their structural similarities with a number of marine cyanobacterial metabolites, e.g. barbamide (**61**) and nordysidinin (**62**) (Fig. 8). Several studies, including cell separation and the recently reported methodology using catalyzed reporter deposition fluorescence in situ hybridization (CARD-FISH) techniques, revealed that these sponge-derived peptides are actually produced by the filamentous cyanobacterial symbiont, *Oscillatoria spongeliae*. Genetic probes based on the barbamide biosynthetic gene cluster were used to amplify a *barB1* homolog (*dysB1*) from *Dysidea herbacea* genomic samples (Flatt et al., 2005). Subsequently, the *dysB1* probes hybridized to genetic sequences in the cyanobacterial symbiont *O. spongeliae* based CARD-FISH analysis.

Since 2001, a total of 14 polychlorinated peptides (**63**–**76**) have been reported from *Dysidea* sp. collected at various locations. Dysideaprolines A (**63**)–F (**68**) and barbaleucamides A (**69**) and B (**70**) were isolated from *Dysidea* sp. collected off Bararin Island, Philippines (Fig. 8) (Harrigan et al., 2001). In addition, five related polychlorinated peptides (**71**–**75**) and dysithiazolamide (**76**) were reported from two collections of *Dysidea* sp. from Lizard Island, Australia (Stapleton et al., 2001) and Mayo Island, Indonesia (Arda et al., 2005), respectively (Fig. 8). The *J*-based configuration method was particularly useful in determining the relative stereochemistry of the two Leu-derived units in dysithiazolamide (**76**). This is perhaps the first report on extending the *J*-based method to determine stereochemistry of nitrogen-containing natural molecule. No biological activities were reported for these sponge-derived compounds.

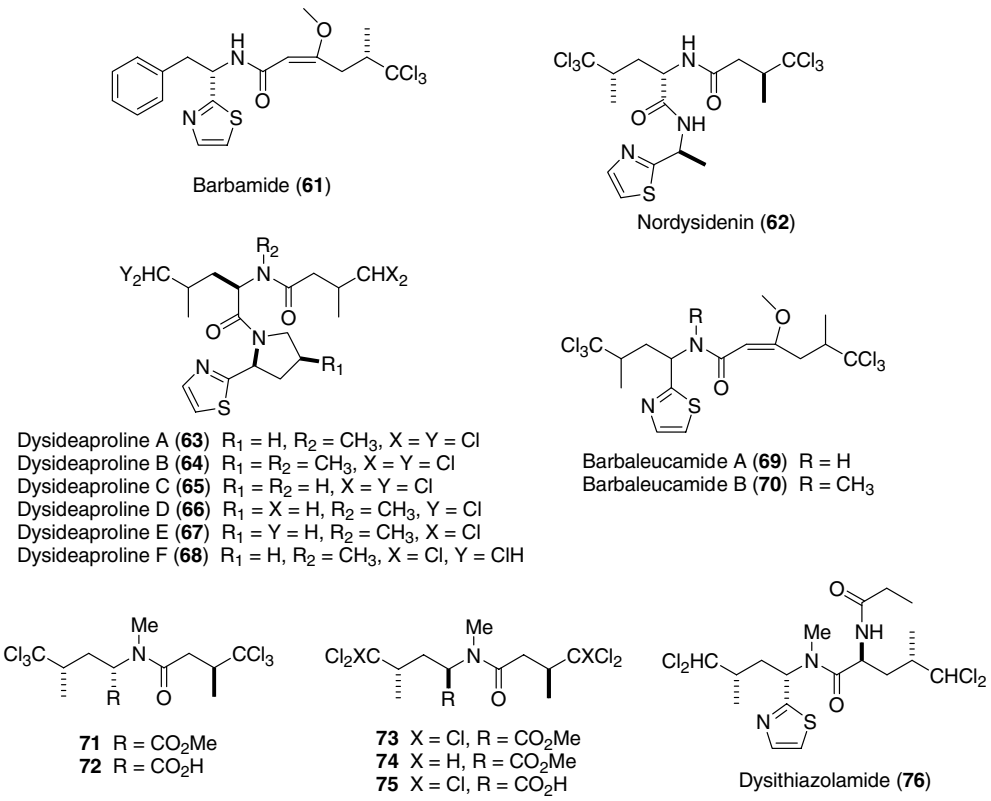


Fig. 8. Marine cyanobacterial and sponge-derived linear lipopeptides (**61**–**76**).

2.5. Cyclic lipopeptides and peptides

A broadly common structural feature amongst marine cyanobacterial cyclic lipopeptides of various ring sizes, ranging from 5 to 12 residues, is the occurrence of either β-hydroxy or amino acid residue. The marine cyanobacterial strain, *L. majuscula*, collected from Papua New Guinea yielded seven such cyclic lipopeptides, named the guineamides (**77**–**82** in Fig. 9) (Tan et al., 2003). The chemical structures of these molecules were determined using an extensive array of 1D and 2D NMR spectrometry and chemical manipulations including the advanced Marfey's method. The ring sizes of the guineamides ranged from five [e.g. guineamide C (**79**)] to seven [guineamide E (**81**)] residues and are represented by several structural types. In addition to the β-amino acid residues, guineamides A (**77**) and B (**78**) also contained a thiazole unit each. An analogue of guineamide A, obyanamide (**83**), was discovered from another cyanobacterial species, *Lyngbya confervoides*, collected from Saipan (Fig. 9) (Williams et al., 2002b). This molecule differs from **77** by having a 3-amino-pentanoic acid unit instead of a 2-methyl-3-amino-pentanoic acid residue in guineamide A. Guineamides B (**78**) and C (**79**) possessed moderate cytotoxicity to a mouse neuroblastoma cell line with IC_{50} values of 15 and 16 μM, respectively while obyanamide (**83**) displayed cytotoxicity property against KB cells with IC_{50} of 0.9 μM. The discovery of the β-amino/hydroxy-containing guineamides with various ring sizes underscores the genetic capacity of biosynthetic gene clusters in producing combinatorial-like metabolites.

A series of related compounds, the antanapeptins A (**84**) to D (**87**) and trungapeptins A (**88**) to C (**90**), were reported from *L. majuscula* obtained from Madagascar and Thailand, respectively (Fig. 9) (Nogle and Gerwick, 2002b; Bunyajetpong et al., 2006). These cyclic depsipeptides comprised of six residues and are characterized by the presence of β-hydroxy acids with different degree of unsaturations at the tail end of the acetate-derived carbon chain. A known compound, dolastatin 16, was isolated in addition to the antanapeptins from the Madagascan strain of *L. majuscula*. The antanapeptins were inactive in several bioassays, including the brine shrimp toxicity, sodium channel modulation, and antimicrobial assays. In contrast, trungapeptin A (**88**) showed mild brine shrimp toxicity and ichthyotoxicity properties at 10 and 6.25 ppm, respectively.

The ulongamides (**91**–**96**) are additional examples of cyclic depsipeptides containing six residues including β-amino acids as 3-amino-2-methyl-hexanoic acid and thiazole residues (Fig. 10) (Luesch et al., 2002d). These molecules were purified from an extract of *Lyngbya* sp. obtained from Palau. This particular strain of *Lyngbya* is another prolific source of secondary metabolites with the isolation of other bioactive compounds such as the cytotoxic apratoxins (see below). Moderate cytotoxicity activities were reported for compounds **91** to **95** when tested against KB and LoVo cell lines with IC_{50}s ranging from 1 to 5 μM.

A series of guineamide E analogues comprising of seven residues known as the pitipeptolides (**97**–**98**) and ulongapeptin (**99**) have been isolated from a Guamanian *L. majuscula* and a Palauan *Lyngbya* sp., respectively (Fig. 10) (Luesch et al., 2001a; Williams et al., 2003c). The structures of these molecules were established through 2D NMR spectrometry, chemical synthesis, and Marfey's method. Pitipeptolides A (**97**) and B (**98**) were weakly cytotoxic against LoVo cells with IC_{50} values of 2.78 and 2.40 μM, respectively while ulongapeptin (**99**) showed significant activity with IC_{50} of 0.63 μM against KB cells. In addition, the pitipeptolides displayed weaker antimycobacterial properties compared to streptomycin in the antimycobacterial diffusion susceptibility assay.

Pitipeptolide A (**97**) was recently found to chemically defend *L. majuscula*, tested at natural concentration, from a range of generalized and specialized marine grazers, including *Echinometra mathaei* (sea urchin), *Menaethius monoceros* (herbivorous crab), *Parhyale hawaiensis* (amphipod), and *Cymadusa imbroglio* (amphipod) . The compound, however, did not prevent feeding of the sea hare, *Stylocheilus striatus* (Cruz-Rivera and Paul, 2007).

Beta-hydroxy/amino acid-containing macrocyclic structures comprising of eight and nine residues have also been

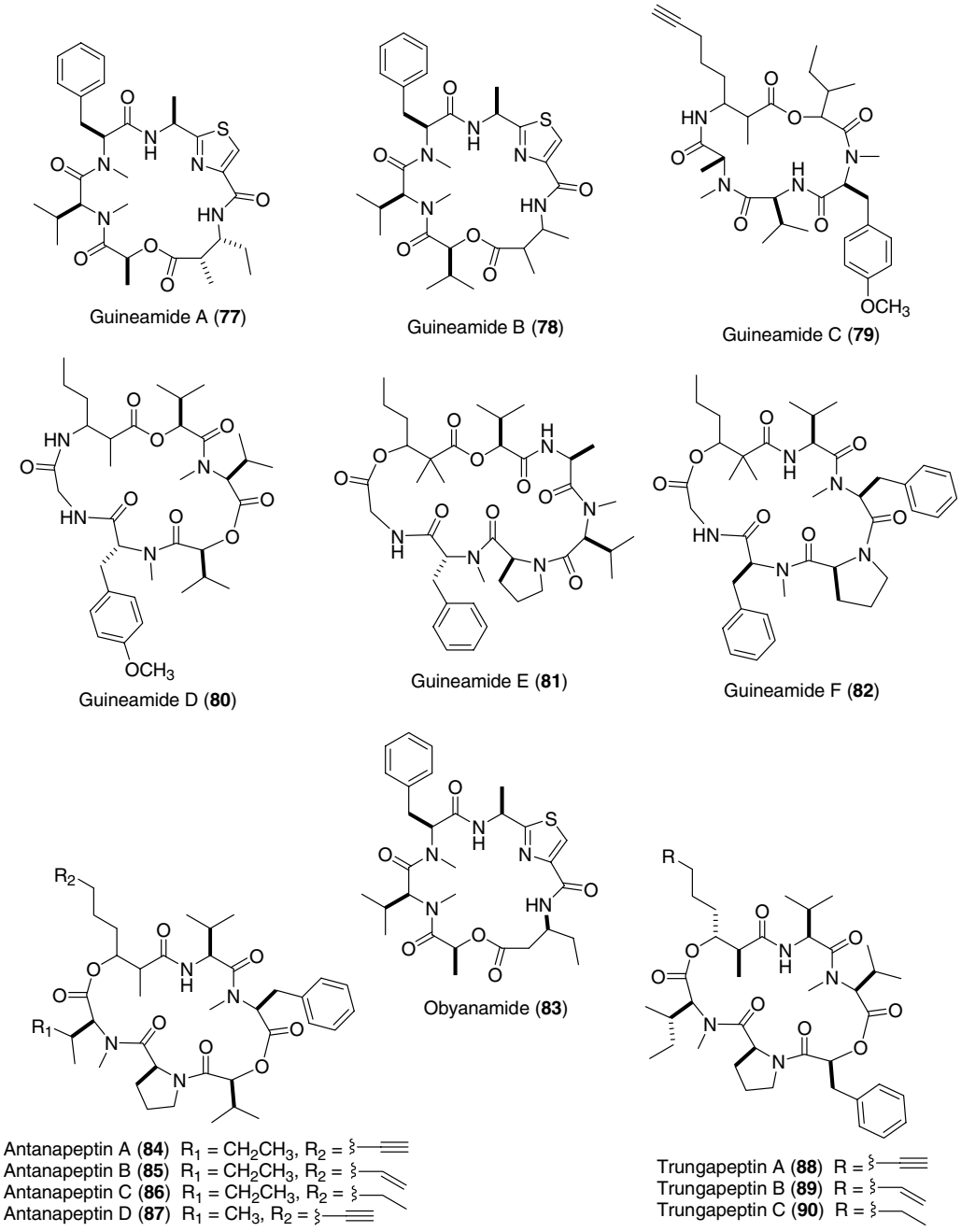


Fig. 9. Marine cyanobacterial β-hydroxy/amino-containing cyclic lipopeptides (**77**–**90**).

reported with the discovery of the dolastatin 16 analogue, homodolastatin 16 (**100**), dolastatin 12 analogue, lyngbyastatin 3 (**102**), and the wewakpeptins (**103**–**106**) (Figs. 10 and 11). The isolation of homodolastatin 16 (**100**), an eight residue-containing cyclic lipopeptide, from a Kenyan marine cyanobacterium, *L. majuscula*, provided further evidence that the sea-hare derived class of dolastatins are truly of cyanobacterial origins (Fig. 10) (Davies-Coleman et al., 2003). An analogue of homodolastatin 16, kulokekahilide-1 (**101**), was isolated from the mollusk, *Philinopsis speciosa*, and its origin is highly likely to be from the invertebrate cyanobacterial diet (Fig. 10) (Kimura et al., 2002). Homodolastatin 16 showed moderate activity against two oesophageal and cervical cancer cells lines with IC_{50} ranging from 4.3 to 10.1 μg/mL, while compound **101** exhibited cytotoxicity against P388 murine leukemia cells with IC_{50} of 2.1 μg/mL.

The nine residue-containing cyclic depsipeptides, the wewakpeptins (**103**–**106**), were isolated from the cyanobacterial species, *Lyngbya semiplena*, collected from Papua New Guinea (Fig. 11) (Han et al., 2005a). Complete structural determination of these cyclic lipopeptides was based on 2D NMR spectral analysis, including HSQC-TOCSY and ROESY, mass spectrometry, and chiral HPLC methods. Of the wewakpeptins, compounds **103** and **104** exhibited significant cytotoxicity against the NCI-H460 human lung tumor and the neuro-2a mouse neuroblastoma cell lines with LD_{50}s averaged at about 0.4 μM. Lyngbyastatin 3 (**102**) was isolated from *L. majuscula* collected from the Tokai Maru shipwreck located in Guam (Fig. 11) (Williams et al., 2003d). In addition to the β-amino acid unit, **102** contained an unusual 4-amino-2,2-dimethyl-3-oxopentanoic acid (Ibu) residue which could derive from Ala with extension of one acetate unit and further dimethylation at

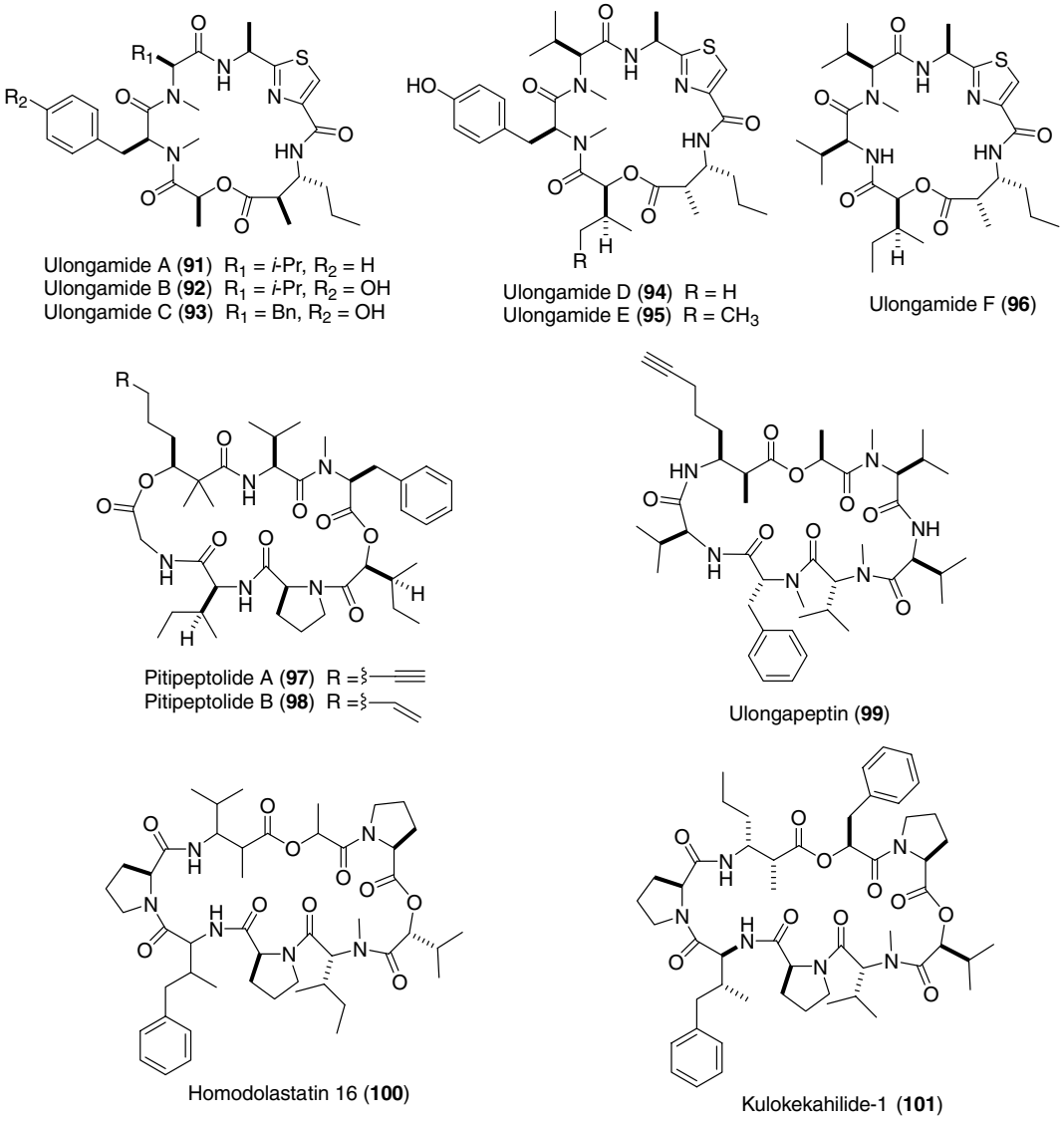


Fig. 10. Marine cyanobacterial β-hydroxy/amino-containing cyclic lipopeptides (**91**–**101**).

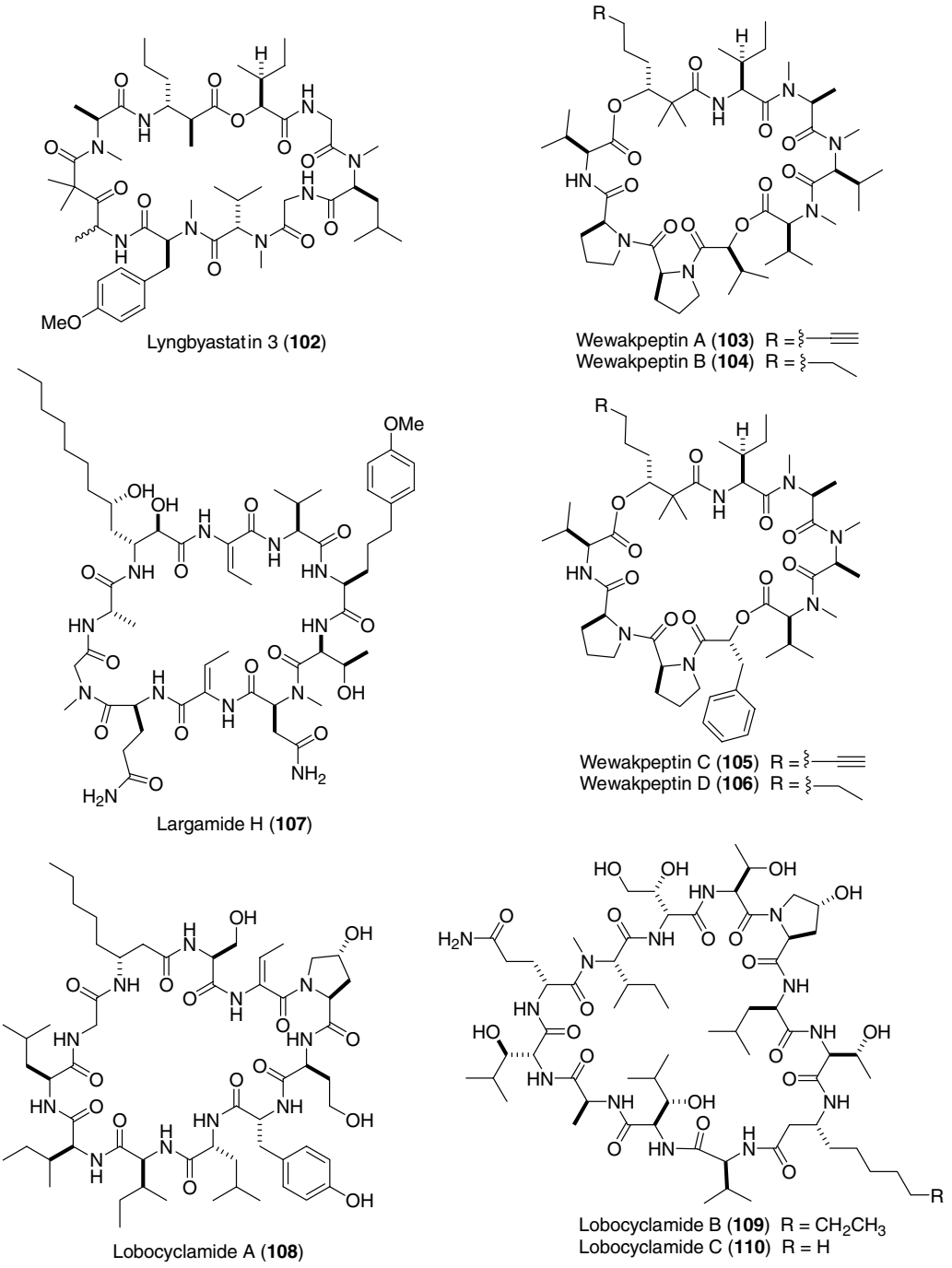


Fig. 11. Marine cyanobacterial β-hydroxy/amino-containing cyclic lipopeptides (**102**–**110**).

C-2 by SAM. Lyngbyastatin 3 is related to the dolastatin 11 class of molecules with potent actin stabilizing properties (Bai et al., 2001). These molecules, especially dolastatin 11, are potential drug leads and a number of potent derivatives have been synthesized based on the natural scaffolds for SAR studies and lead optimization as anticancer agents (Ali et al., 2005).

Beta-amino acid-containing cyclic lipopeptides with 10 or more residues have been reported in largamide H (**107**) and the lobocyclamides (**108**–**110**) (Fig. 11). Largamide H (**107**) contained 10 residues and it belongs to a series of structural diverse cyclic lipopeptides isolated recently from the filamentous marine cyanobacterium, *Oscillatoria* sp. obtained from Key Largo, Florida (Plaza and Bewley, 2006). This molecule has a number of unique structural features including the dihyroxylated β-amino acid, 2, 5-dihydroxy-3-amino-dodecanoic acid, a 2-amino-5-(4′-methoxyphenyl)pentanoic acid unit, and two dehydro-2-aminobutanoic acid (Dab) residues. The structure of **107** was determined through extensive 2D NMR spectrometry,

J-based configuration analysis, and the advanced Marfey's method. The lobocyclamides (**108**–**110**) are examples of β-amino-containing cyclic lipopeptides with more than 10 residues (MacMillan et al., 2002). A number of structural features distinguish the lobocyclamides from the rest of the β-amino/hydroxy-containing cyclic lipopeptides. For instance, lobocyclamides B (**109**) and C (**110**) consisted of six hydroxygenated amino acid residues, including the first report of a γ-hydroxythreonine unit, as well as the rare 3-amino-octanoic acid and 3-amino-decanoic acid units. These cyclic lipopeptides when tested individually exhibited moderate antifungal activity against *Candida albicans* and *C. glabrata*. Synergistic activity was observed when mixtures of **108** and **109** were tested.

A group of structurally related potent actin-disrupting agents known as the hectochlorins and lyngbyabellins are bithiazole-containing cyclic depsipeptides possessing the unusual dichlorinated β-hydroxy acid residue, 7,7-dichloro-3-hydroxy-2-methyl-octanoic acid (Dhmoc). Since the discovery of lyngbyabellins A (**114**) and B (**115**) in 2000, nine additional new analogues have been reported from marine cyanobacteria (Fig. 12). Hectochlorin (**111**) was purified from an isolate of *L. majuscula* collected from Hector Bay, Jamaica (Fig. 12) (Marquez et al., 2002). 1D and 2D NMR spectrometry were employed to determine its planar structure while X-ray crystallography was used to establish the absolute stereochemistry. A unique feature of this molecule, in addition to the Dhmoc unit, is the absence of any amide functional groups. The biological activity of hectochlorin was similar to that of jaspamide, a sponge-derived molecule, with regards to the hyperpolymerization of actin protein. Evaluation of hectochlorin in the NCI 60 cancer cell lines revealed significant cytotoxicity against colon, melanoma, ovarian, and renal cell lines with an average GI_{50} of 5.1 μM. In addition, **111** exhibited potent inhibitory activity against the fungus, *C. albicans*.

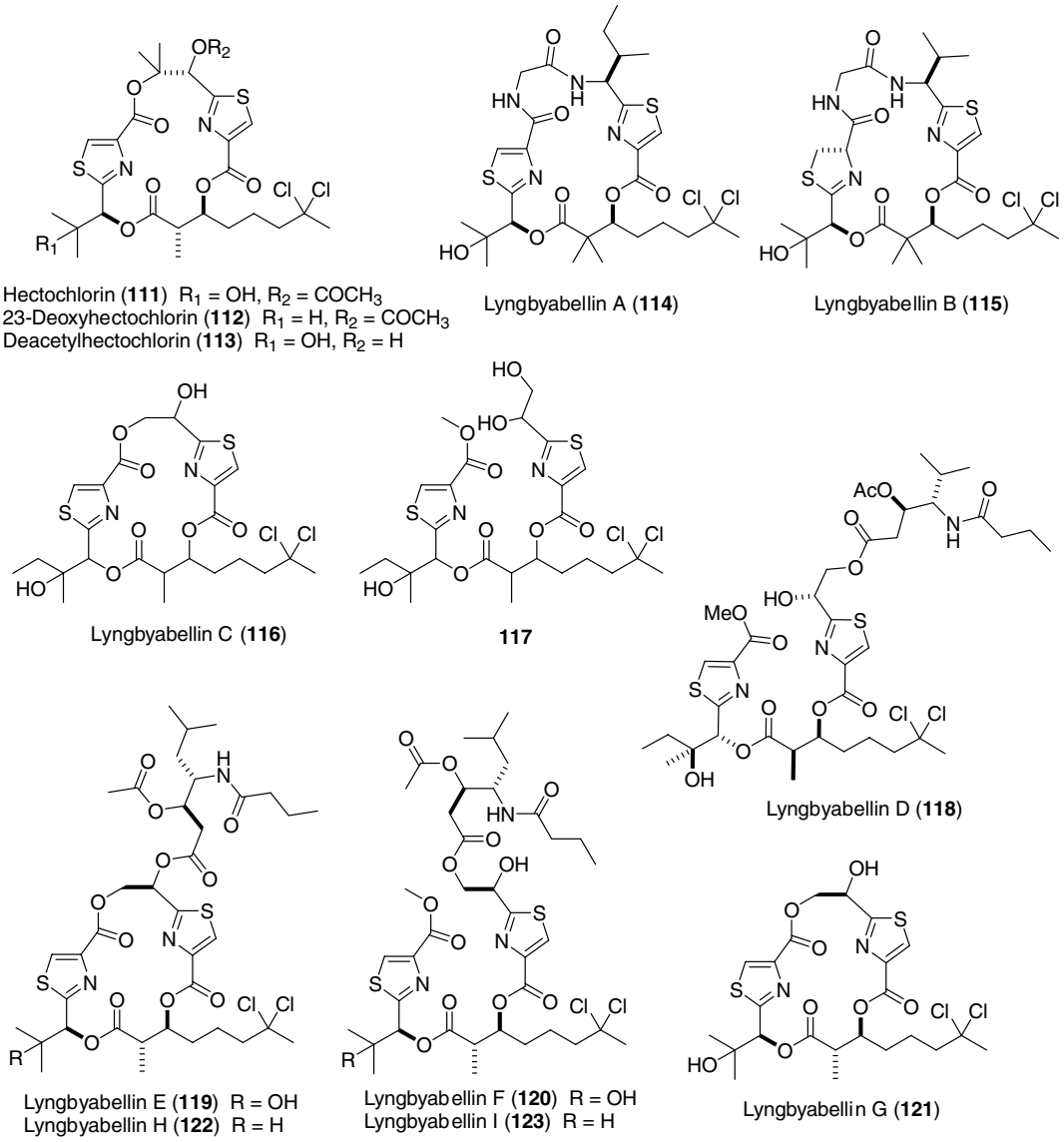


Fig. 12. Marine cyanobacterial β-hydroxy-containing lipopeptides (**111**–**116** and **118**–**123**) and compound **117**.

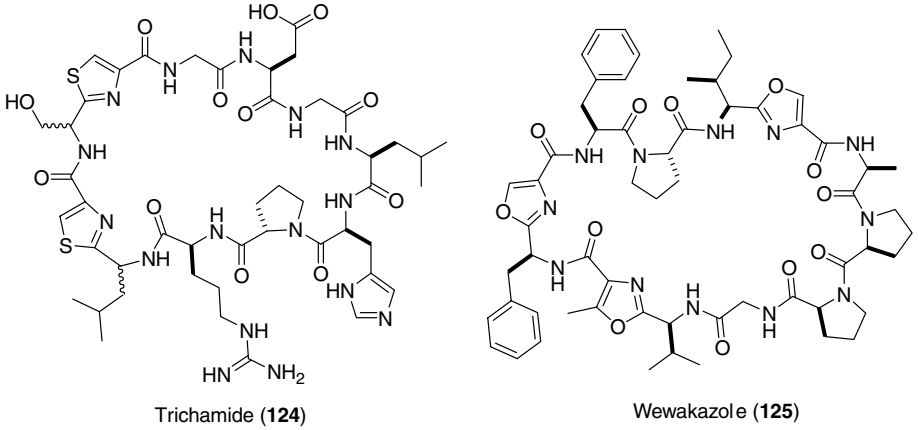
A more potent deacetylated derivative, deacetylhectochlorin (**113**), has also been reported from the sea hare, *B. leachii* (Fig. 12) (Suntornchashwej et al., 2005). This hectochlorin analogue exhibited cytotoxicity properties against KB and NCI-H187 cells with ED_{50}'s of 0.31 and 0.32 μM, respectively. Hectochlorin, on the other hand, displayed ED_{50}'s values of 0.86 and 1.20 μM against the former and latter cell lines, respectively.

Seven additional new cytotoxic lyngbyabellin analogues (**116** and **118**–**123**) were isolated from *Lyngbya* sp. (most likely to be *L. bouillonii*) and *L. majuscula* collected from Palau, Guam, and Papua New Guinea (Fig. 12). The Palauan and Guamanian strains of *Lyngbya* sp. were particularly rich in secondary metabolites. A total of 12 alkaloids [representing five distinct structural types, including lyngbyabellin C (**116**)] and over 25 compounds [representing eight unique structural types, including lyngbyabellin D (**118**)] were reported from *Lyngbya* sp. collected from Palau and Guam, respectively (Luesch et al., 2002b; Williams et al., 2003a). A recent collection of *L. majuscula* from Papua New Guinea yielded five new lyngbyabellins E (**119**)–I (**123**) along with a related molecule, dolabellin, originally reported from the sea hare, *D. auricularia* (Han et al., 2005b). During the isolation of lyngbyabellin C (**116**), it was found that the ester linkage at C-16 was proned to methanolysis, yielding compound **117**. Such conversion led to the speculation that the acyclic forms of lyngbyabellins (e.g. **120** and **123**) could derived from methanolysis of the cyclic forms (e.g. **119** and **122**). Lyngbyabellins D (**118**), F (**120**), and H (**122**) displayed significant cytotoxicity against various cell lines, including KB and H460 cancer cells with IC_{50} or LC_{50} values ranging from 0.1 to 0.4 μM. Due to the structural novelty and its potential as anticancer agents, two members of the lyngbyabellin class, lyngbyabellins A (**114**) and B (**115**), and hectochlorin (**111**) were the target of total synthesis for further biological evaluation (Cetusic et al., 2002; Yokokawa et al., 2001, 2002a).

In addition to the lyngbyabellins and hectochlorins, cyclic peptides containing heterocyclic moieties, namely trichamide (**124**) and wewakazole (**125**) have also been isolated since January 2001. The discovery of the cyclic peptide, trichamide (**124**), from the bloom-forming marine cyanobacterium *Trichodesmium erythraeum* was based on analysis of the cyanobacterial genome sequence (Fig. 13) (Sudek et al., 2006). Trichamide (**124**) consists of 11 amino acid residues including two Cys-derived thiazole units and despite its unique features, its biosynthesis is ribosomal. The presence of the gene cluster for trichamide was detected using genetic information of a recently characterized patellamide biosynthetic gene cluster. The patellamides are biosynthesized ribosomally in *Prochloron didemni*, a unicellular cyanobacterial symbiont of the tunicate *Lissoclinum patella* (Schmidt et al., 2005). The structure of trichamide was determined based mainly on the analysis of MS/MS fragmentation pattern. The natural molecule was isolated in minute quantity and was not responsible for the neurotoxic effect found in the methanolic extracts. This study underscores the importance of the availability of genomic information for potential mining of novel natural products for drug discovery.

The Cys-derived thiazole unit is the predominant heterocyclic ring system in many marine cyanobacterial secondary metabolites. Oxazole-containing metabolites, although not as common, have also been reported from cyanobacteria. An example is the discovery of wewakazole (**125**), a cyclic dodecapeptide containing three oxazole unit, from a Papua New Guinea *L. majuscula* (Fig. 13) (Nogle et al., 2003b). Complete structure determination of wewakazole (**125**) was based on extensive 1D, 2D NMR, MS/MS data, HPLC analysis using Marfey's method, and chiral GCMS analysis. In addition, spectral data from 1D HMBC spectrometry was essential in the connectivity of three amino acid fragment in **125**. No biological activity was reported for this structurally impressive molecule. Despite a number of metabolic themes, the wewakazole could also be biosynthesized by ribosomal pathway.

Another distinct class of marine cyanobacterial cyclic lipopeptides is the linking of polyketide chain ($\geqslant 2$ acetate units) with proteinogenic amino acids in the overall construction of the macrocyclic structure. Such metabolic



Trichamide (**124**) Wewakazole (**125**)

Fig. 13. Marine cyanobacterial heterocyclic-containing cyclopeptides (**124** and **125**).

theme is observed in the cytotoxic apratoxins (**126**–**128**), antillatoxin B (**134**), palau'amide (**135**), as well as the aurilides (**137**–**138**) (Fig. 14).

The apratoxins (**126**–**128**) are a novel class of potent cytotoxic cyclic depsipeptides isolated from chemically rich strains of *Lyngbya* sp. (morphology of these strain were reported to be similar to *L. bouillonii*) collected from Guam and Palau (Fig. 14) (Luesch et al., 2001b, 2002e). These molecules are characterized by having five amino acid residues and a polyketide chain as part of the cyclic carbon skeleton. The chemical structure of apratoxin A (**126**), the first molecule of this series, was determined through extensive 2D NMR techniques as well as chemical manipulations. The relative stereochemistry of the unique polyketide chain, 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid, was established using the *J*-based configuration analysis (Luesch et al., 2001b). Apratoxin A was found to be acid sensitive and it decomposed to its dehydro-derivative, **129**, in traces of HCl present in $CDCl_3$.

The biosynthesis of apratoxin A (**126**) could be rationalized by the involvement of a unique starter unit, 2,2-dimethyl-propionic acid (Dpa), followed by polyketide extension with three acetate units catalyzed by polyketide synthase (PKS). A Cys and acetyl unit will then be added

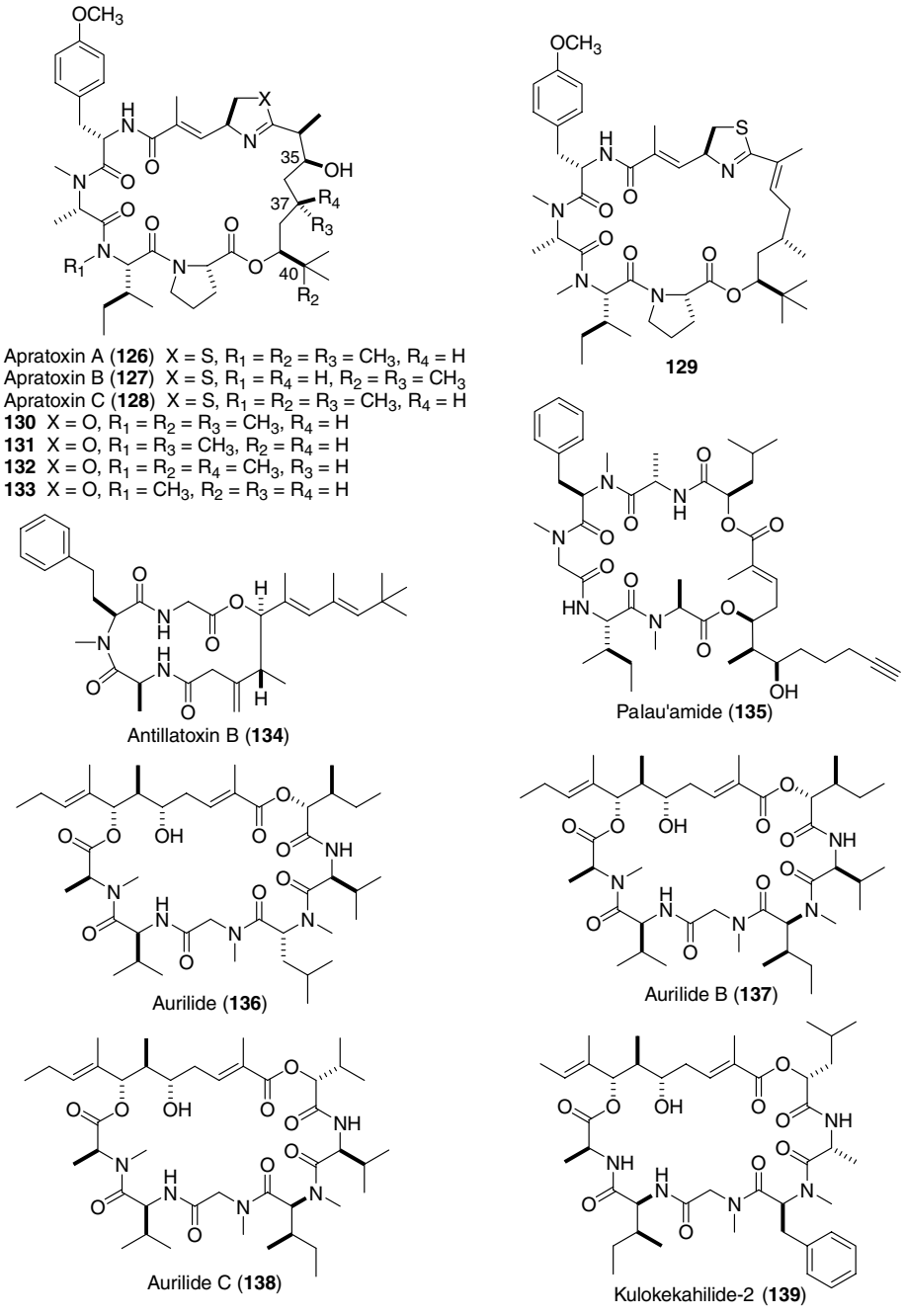


Fig. 14. Marine cyanobacterial and sea hare-derived cyclic lipopeptides (**126**–**139**).

onto this linear intermediate carbon chain via nonribosomal polypeptide synthetase (NRPS) and PKS enzyme, respectively. This is followed by the addition of four amino acids, Tyr, Ala, Ile, and Pro, to the growing intermediate chain using NRPS. Heterocyclization of Cys, methylation by SAM, and ring closure between Pro and Dpa would yield compound **126** (Fig. 15). Apratoxin A exhibited exquisite in vitro cytotoxicity in various human tumor cell lines with IC_{50} values ranging from 0.36 nM in LoVo cancer cells to 0.52 nM in KB cancer cells (Luesch et al., 2001b). Furthermore, the presence of *N*-methylated Ile and hydroxyl group at C-35 are important features for biological activities (Luesch et al., 2002e).

Due to the structural novelty, coupled with the exceptional biological activities of apratoxin A (**126**), three organic synthetic research groups initiated total synthesis of this molecule and its analogues (**130**–**133**) for SAR studies (Chen and Forsyth, 2003a,b, 2004; Zou et al., 2003; Doi et al., 2006; Ma et al., 2006). Compound **130**, an oxazoline analogue of apratoxin A (**126**), was found to be slightly lower in potency against HeLa cells when compared with the natural compound, **126** (Ma et al., 2006). Further SAR studies on synthetic oxazole-containing analogues of apratoxin A (e.g. **131**–**133**) revealed the importance of methyl groups at C-37, C-40, as well as the stereochemistry at C-37 for biological activity (Ma et al., 2006). In terms of the mechanism of action, apratoxin A inhibited cell division by arresting cell cycle at the G1 phase. In addition, the use of functional genomic methods revealed apratoxin A blocks the FGFR (fibroblast growth factor receptor) pathway by preventing the phosphorylation and activation of STAT3, which is a downstream effector of the FGFR pathway (Luesch et al., 2006).

The neurotoxic antillatoxin B (**134**), an analogue of antillatoxin (**9**), is another cyclic depsipeptide with the unique *tert*-butyl functional group, isolated from *L. majuscula* obtained from Collado Reef, Puerto Rica and Bush Key, Dry Tortugas (Fig. 14) (Nogle et al., 2001a). Compound **134** is also the first marine cyanobacterial secondary metabolite possessing the homophenylalanine residue. The

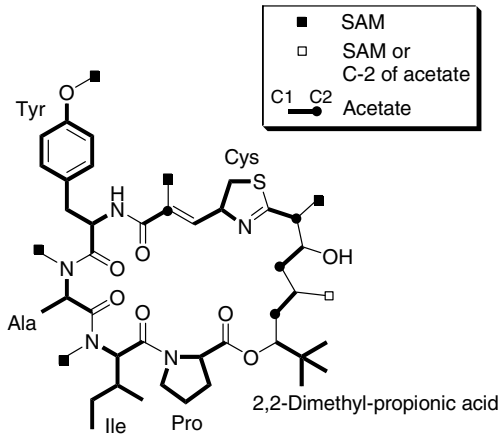


Fig. 15. Proposed biosynthesis of apratoxin A (**126**).

biogenesis of this neurotoxin could be initiated by the unique starter unit, Dpa, extended by four acetate-derived units and further coupling with three proteinogenic amino acid residues. Methylations along the polyketide chain and *N*-methylation of the homophenylalanine unit by SAM/C-2 of acetate and final macrocyclization lead to the formation of **134**. Antillatoxin B (**134**) is a sodium channel-activator with EC_{50} value of 1.77 μM. In addition, it is highly ichthyotoxic to goldfish with LC_{50} of 1.0 μM. It was further observed that the replacement of the *N*-methyl Val unit in antillatoxin (**9**) with homophenylalanine unit in **134** gave a 10-fold decrease in biological activities in both biological assays. The discovery of **134** joins a growing class of important marine cyanobacterial metabolites with sodium channel-activating property.

A highly potent cytotoxin, palau'amide (**135**), was isolated from a Palauan strain of *Lyngbya* sp. (Fig. 14) (Williams et al., 2003e). The planar structure of **135** was based on NMR data recorded in $CDCl_3$ and MeOH-d_4 and its stereochemistry determined by ^1H NMR analysis of the α-methoxyphenylacetic acid derivatives and chiral HPLC. In addition to the six amino acid-derived residues, **135** contained a polyketide chain with a terminal alkyne functional group. The biosynthesis of this lipid portion could derive from a hex-5-ynoic acid starter unit with ketide extension by three acetate units, followed by methylations along the carbon chain. The free hex-5-enoic or hex-5-ynoic acid has also been suggested to be the starter unit for the biosynthesis of the jamaicamides (**48**–**50** in Fig. 6) (Edwards et al., 2004). Palau'amide (**135**) is highly cytotoxic against KB cells with IC_{50} of 13 nM.

Two aurilide analogues, aurilides B (**137**) and C (**138**), have been recently isolated from the Papua New Guinea *L. majuscula* (Fig. 14) (Han et al., 2006). Aurilide (**136**) was previously reported from the sea hare *D. auricularia* and the discovery of these new analogues further supports their cyanobacterial origin. Another recently reported sea hare-derived cytotoxic cyclic depsipeptide, kulokekahilide-2 (**139**), from *Philinopsis speciosa* shares structural similarities with the aurilides and its biosynthetic origin is again highly to be of cyanobacterial source (Nakao et al., 2004). The biogenesis of the aurilides could be conceived from either a 2-methyl-but-2-enoic acid or 2-methyl-pent-2-enoic acid starter unit extended by three acetate-derived units. Further methylations on the lipid chain and coupling with six proteinogenic amino acids follow by macrocyclization would result in the formation of these cyclic molecules. Aurilide B (**137**) was found to be the more potent compound when tested in the NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cell lines with LC_{50} of 10 and 40 nM, respectively. In addition, the evaluation of **137** in the NCI panel of 60 cell lines displayed significant growth inhibitory properties against leukemia, renal, and prostate cancer cells. Furthermore, aurilide B exhibited tumor cell killing activity in the NCI's in vivo model hollow fiber assay. Kulokekahilide-2 (**139**) was selectively cytotoxic against a panel of cancer cell lines, including

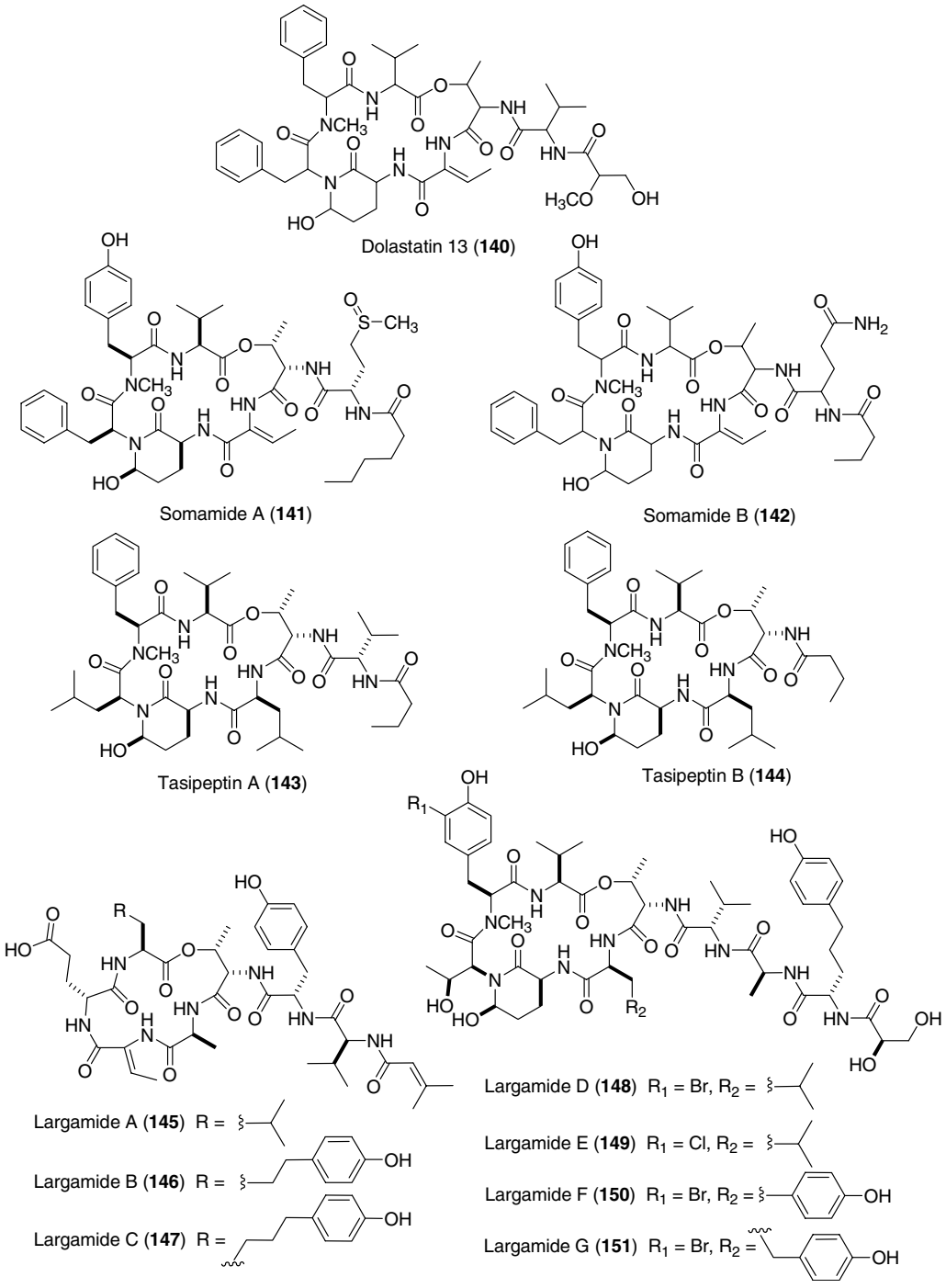


Fig. 16. Marine cyanobacterial lariat-type lipopeptides (**140**–**151**).

P388, SK-OV-3, MDA-MB-435, and A-10, with IC_{50} values ranging from 4.2 to 59.1 nM. Due to the significant cytotoxic properties of this class of unique cyclic lipopeptides, compound **136** and its analogues were synthesized for further biological and pharmacological studies (Suenaga et al., 2004; Takahashi et al., 2003).

Another prominent class of marine cyanobacterial cyclic depsipeptides consists of lariat type structures with Thr residue serving as the branching unit. These macrocycles are usually characterized with the presence of a 3-amino-6-hydroxy-2-piperidone (Ahp) unit and they include the somamides (**141**–**142**), the tasipeptins (**143**–**144**), and largamides D (**148**) to G (**151**) (Fig. 16). New structural variants have also been reported in largamides A (**145**) to C (**147**) (Fig. 16).

The somamides (**141**–**142**) and the tasipeptins (**143**–**144**) were isolated from a mixed collection of *Lyngbya majuscula*/*Schizothrix* sp. and *Symploca* sp. obtained from Somo Somo, Fiji and Palau, respectively (Fig. 16) (Nogle et al., 2001b; Williams et al., 2003f). Structure elucidations of

these molecules were achieved using a combination of 2D NMR spectral analyses, fragmentation data from FABMS, Marfey's method, and chiral HPLC. In addition, the structure of somamide A was confirmed by its total synthesis reported by Yokokawa and Shioiri (2002b). These cyclic lipopeptides are analogues of the sea hare- derived molecule, dolastatin 13 (**140**). The discovery of somamides and tasipeptins as well as other dolastatin analogues discussed in other sections of the review support the notion that the entire dolastatin class of molecules is possibly derived from marine cyanobacteria. Tasipeptins A (**143**) and B (**144**) were cytotoxic against KB cells with IC_{50} of 0.93 and 0.82 μM, respectively. No biological activities were reported for the somamides.

A collection of the marine cyanobacterium, *Symploca* sp., from Florida Keys yielded an impressive array of cyclic lipopeptides known as the largamides (**145–151** and **107**) (Figs. 11 and 16) (Plaza and Bewley, 2006). Largamides D (**148**) to G (**151**) are Ahp-containing molecules while largamides A (**145**) to C (**147**) represent new structural variants comprising of five residues and the absence of Ahp unit in the macrocyclic structures. Largamide H (**107**), a β-amino acid-containing cyclic depsipeptides was discussed above. The planar structures of these cyclic molecules were determined using NMR experiments and ESI-MS while its absolute configurations were established through Marfey's method, chiral HPLC, analysis of ROE and homonuclear and heteronuclear $^{2,3}J$ couplings. A number of highly unusual amino acid units are featured in the largamides, such as the 2-amino-5-(4′-hydroxyphenyl)pentanoic acid, the 2-amino-6-(4′-hydroxyphenyl)hexanoic acid, and the monochlorination or monobromination of the Tyr units. Of the largamides, compounds **148–151** are inhibitors of chymotrypsin with IC_{50} values between 4 and 25 μM.

3. Natural product biosynthetic genes in marine cyanobacteria

3.1. Distribution and diversity of natural product biosynthetic genes

A majority of the nitrogen-containing marine cyanobacteria metabolites discussed above are products of either the NRPS or hybrid PKS-NRPS biosynthetic pathways. These assembly-lined enzymatic systems are large, usually 200–2000 kDa, multifunctional proteins organized in a modular fashion (Dittmann et al., 2001). The detection of these secondary metabolic pathways in cyanobacteria is accomplished using degenerate primer sets designed from conserved gene sequences of the adenylation and ketosynthase domains in NRPS and PKS gene clusters, respectively.

Although studies on the distribution of natural products genes were conducted mostly on freshwater cyanobacterial strains, results have indicated its wide occurrence and diversity. The PKS and NRPS genes appeared to be more prevalent in undifferentiated filamentous and heterocystous cyanobacterial strains (Christiansen et al., 2001; Burns et al., 2005; Ehrenreich et al., 2005). For instance, of the 146 axenic cyanobacterial strains, represented by 35 genera, obtained from the Pasteur Culture Collection (PCC), about 75% indicated the presence of NRPS genes predominantly in members of pleurocapsalean and oscillatorian strains. In contrast, NRPS genes were not detected in unicellular cyanobacteria belonging to the genera *Synechococcus* and *Synechocystis* (Christiansen et al., 2001). In another study involving both marine and freshwater cyanobacterial cultures, about 50% of the strains contained both NRPS and/or PKS genes (Ehrenreich et al., 2005). High genetic diversity in the sequenced NRPS and PKS fragments were also observed amongst closely related cyanobacterial strains. Furthermore, analysis of 14 sequenced cyanobacteria genomes revealed the presence of multiple NRPS and PKS genes, particularly in *Nostoc punctiforme* ATCC 29133 containing at least 17 NRPS and 10 PKS genes. In addition, significant correlation between genome size and total number of biosynthetic genes was observed. However, phylogeny studies amongst different cyanobacteria strains did not reveal insights into the distribution and diversity of natural product genes. A recent study conducted by Thacker and Paul (2004) showed that 16S rDNA from closely related marine cyanobacterial species, such as *L. majuscula* and *L. bouillonii*, do not correlate with secondary metabolite variability. This could be due to a number of factors involved in the generation of diverse secondary metabolites within and among cyanobacterial species such as higher degree of evolution, horizontal gene transfer amongst different genotypes as well as environmental factors (Thacker and Paul, 2004).

The presence of natural products genes have also been detected in symbiotic marine cyanobacteria associated with various invertebrates such as tunicates and sponges (Schmidt et al., 2004; Flatt et al., 2005). For instance, molecular techniques, such as the fluorescence in situ hybridization (FISH) methods, have been used to detect genes responsible for the production of halogenated lipopeptides in *O. spongeliae*, a filamentous cyanobacterial symbiont of the sponge *Dysidea herbacea*. Such studies resulted in the discovery of novel biosynthetic genes with high identity with the barbamide biosynthetic gene cluster (Flatt et al., 2005). Furthermore, it was found that different sponge species harbor distinct strains of cyanobacterial symbiont producing different sets of natural products (Ridley et al., 2005). Ribosomally encoded natural product genes have also been detected in the unicellular cyanobacterium, *Prochloron* sp., a symbiont of a number of didemnid tunicates. These ribosomally produced natural products belong to a large class of heterocyclic-containing cyclopeptides known as the patellamides (Schmidt et al., 2005). Recent genetic studies have shown that the generation of combinatorial-type patellamide class of molecules arises from a small genetic cassette with high variability

within a mostly conserved biosynthetic gene clusters (Donia et al., 2006).

3.2. Biosynthesis of marine cyanobacterial compounds – tailoring enzymes

To date, the biosynthetic gene clusters of several marine cyanobacterial metabolites, including barbamide, curacin A, jamaicamide A, lyngbyatoxin A, trichamide, and patellamide class of molecules, have been elucidated. A recent review by Ramaswamy et al. (2006) provided an excellent account on the biosynthesis of barbamide, curacin A, jamaicamide A, and lyngbyatoxin A. Notable biochemical and genetic features revealed from the biosynthetic studies of these molecules are summarized in Table 2. Since the review of Ramaswamy et al. (2006), recent biochemical studies provided further insight into the mechanisms and functions of tailoring enzymes involved in the early biosynthetic stages of curacin A and barbamide pathways. These relate mainly to the biotransformation of L-Leu to the trichloroisovaleric residue and the formation of 3-methylcrotonyl precursor to the cyclopropane unit in the biosynthetic pathways of barbamide and curacin A, respectively (Galonic et al., 2006; Gu et al., 2006; Flatt et al., 2006).

In the biosynthesis of barbamide, biochemical experiments revealed the tandem activity of two non-heme Fe^{II} halogenases, BarB1 and BarB2, in the trichlorination of the methyl group of L-Leu precursor (Galonic et al., 2006; Flatt et al., 2006). These tailoring enzymes join a growing class of novel halogenases, including CmaB and SyrB2 from *Pseudomonas syringae*, in the halogenation of unactivated aliphatic carbons (Vaillancourt et al., 2005a,b). BarB1 and BarB2 are O_2-dependent halogenases requiring α-ketoglutarate as cofactor and Cl^- to form a highly oxidative Fe^{IV}=O species to facilitate the abstraction of a hydrogen radical from an unactivated methyl group in L-Leu. The Cl ligand on the Fe^{III} complex will then be transferred to the CH_2 radical on L-Leu to complete the halogenation process. It was further reported that BarB1 catalyzed the dichlorination while BarB2 enzyme was involved in the addition of the third Cl atom leading to the formation of the trichloroisovaleric residue. Similar enzymatic mechanism using iron halogenase has been proposed to be involved in the en route formation of the vinyl chloride group and cyclopropyl moiety in the jamaicamides and curacin A, respectively (Fig. 17) (Vaillancourt et al., 2006).

The initial enzymatic steps in the formation of the cyclopropane unit in curacin A pathway have also been characterized recently. Biosynthesis of the cyclopropyl group involves the intermediate, 3-methylcrotonyl, formed via the dehydration and decarboxylation of (*S*)-3-hydroxy-3-methylglutaryl-unit, catalyzed by a pair of enoyl-Co hydratases (ECH), ECH_1 and ECH_2 (Gu et al., 2006). Further reduction, halogenation (possibly by Fe-halogenase), and cyclization of the 3-methylcrotonyl precursor could lead to the formation of the cyclopropane moiety. The ECH_1–ECH_2 enzyme pair is coded by *curE* and *curF* genes which are part of a novel 3-hydroxy-3-methylglutaryl (HMG)-CoA synthase (HCS)-like gene cassette. The HCS-like gene cassette is also present in the jamaicamide gene cluster and it has been proposed that the addition of C-2 from acetate on the polyketide chain is formed via enzymes coded by this novel gene cassette (Fig. 17).

Genetic and biochemical studies on the biosyntheses of marine cyanobacterial metabolites have revealed tremendous

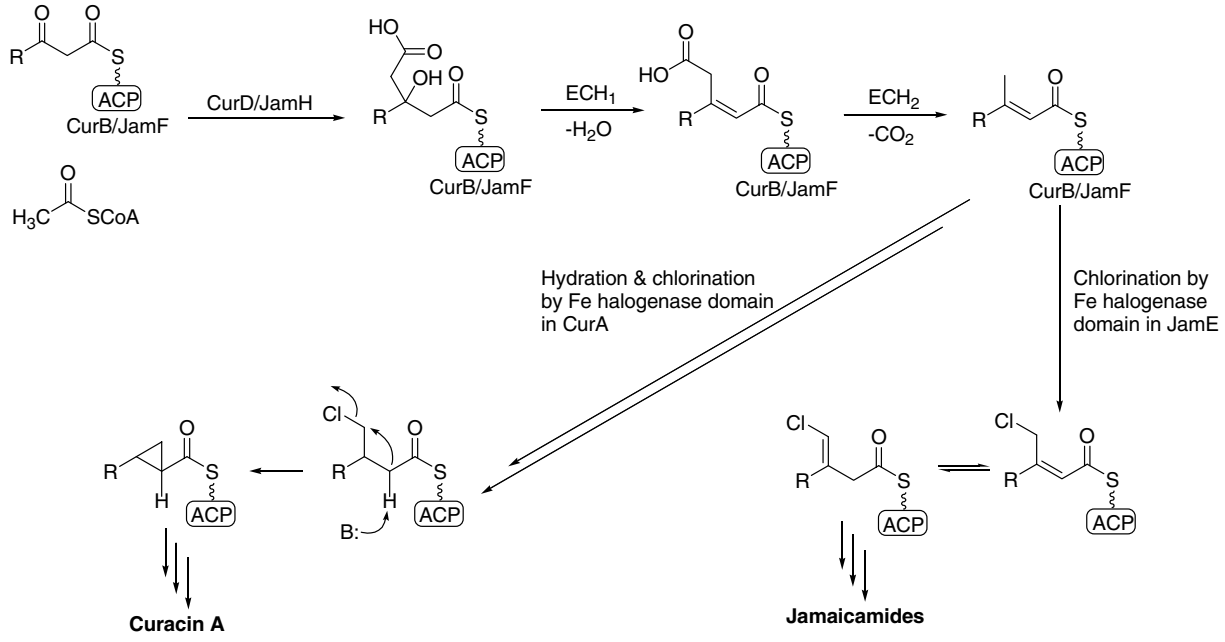


Fig. 17. Proposed biosynthesis of cyclopropyl unit and vinyl chloride moiety in curacin A and the jamaicamides, respectively (adapted from Vaillancourt et al., 2006 and Gu et al., 2006).

novelty and versatility of tailoring enzymatic systems in the creation of diverse functional groups. It is therefore highly anticipated that novel enzymatic mechanisms of tailoring enzymes will be revealed from further biochemical studies of marine cyanobacterial secondary metabolic pathways.

4. Conclusion and perspective

This review presented a total of 128 nitrogen-containing secondary metabolites, belonging mainly to the mixed PKS-NRPS structural class, isolated from filamentous marine cyanobacteria. The overall structural diversity of these alkaloids is highly impressive and could probably match those of the actinomycetes and myxobacteria. Single species such as *L. majuscula* has been reported to be a cornucopia of secondary metabolites, usually represented by several structural types. Single strain of marine cyanobacterium has been shown to produce a variety of combinatorial type molecules and this could be due to the versatility of adenylation domains in the modular enzymatic systems. A number of striking structural features of many marine cyanobacterial metabolites include high degree of *N*-methylated amino acids, aromatic heterocyclic moieties, such as thiazole, halogenation at unactivated aliphatic groups, and lipidation of peptides. These unique features not only generate structural diversity but also confer biological activities through structure rigidification and chemical stability.

A number of highly potent cyanobacterial natural products have been uncovered as potential lead compounds for further drug development, especially in the area of anticancer agents. An increasing number of lipopeptides, such as symplostatin 3 (**51**), lyngbyastatin 3 (**102**), hectochlorin (**111**), and lyngbyabellins (**114–116** and **118–123**), have been reported to target eukaryotic cytoskeletal macromolecules, such as actin and microtubule filaments. These are attractive biological features for the development of potential anticancer drugs with specific cellular targets. Apratoxin A (**126**) is another potent cytotoxic compound worthy of further biological investigation as anticancer agent due to it mechanism of action in attenuating the FGF (fibroblast growth factor) signaling pathway. Synthetic analogues based on the scaffolds of these cyanobacterial natural products can be developed for SAR studies as well as lead optimization for drug development.

It is evident that certain classes of invertebrate-derived lipopeptides, e.g. the dolastatins, are of cyanobacterial origins due to the reports of identical compounds or its derivatives from these microbes. This includes a number of polyketides from sponges and nudibranchs, such as the aurisides and swinholides from *D. auricularia* and *Theonella swinhoei*, respectively. The isolation of their structural counterparts from cyanobacteria e.g. lyngboulloside and swinholide A, have been reported from *L. majuscula* and *Geitlerinema* sp., respectively (Tan et al., 2002; Andrianasolo et al., 2005).

An advantage of natural products research on marine cyanobacteria is the high discovery rate (>95%) of novel compounds as compared to other traditional microbial sources. This is due largely to the unexplored nature of this group of microalgae (Olaizola, 2003). One of the key areas to further tap these microalgae for new chemical entities is the collection of cyanobacterial strains from unexplored localities, especially from Africa and Asia (Fig. 3). In view of this, a pilot project on drug discovery from marine organisms was recently initiated in Singapore and biological data indicated significant cytotoxic activities in extracts prepared from *Lyngbya* sp. (Seng et al., 2007). Furthermore, preliminary chemical analysis indicated the presence of unique PKS-NRPS type molecules in the extracts/fractions and work is currently underway to determine their chemical structures. In addition to the procurement of marine cyanobacteria from unexplored locales, the amenability of field collected strains to laboratory culture is an important factor in the drug discovery process. The culturability of marine cyanobacteria would ensure a constant supply of potent secondary metabolites for further biological evaluation, chemical and biosynthetic studies. However, as indicated by Ramaswamy et al. (2006), the culturing of marine cyanobacteria has several significant challenges, including physical parameters, sampling techniques, and issues associated with slow growing filamentous strains.

Another research area to exploit marine cyanobacteria as source of new therapeutics is to harness the genetic versatility of its biosynthetic gene clusters. The modularity and colinearity of the cyanobacterial PKS-NRPS gene clusters are attractive features for the heterologous expression of natural products and genetic manipulation for combinatorial biosynthesis of new hybrid chemical entities. In order to achieve success in genetic applications to produce compounds, it is important to have a better understanding at the molecular level of these gene clusters and the underlying enzymology associated with the biosynthetic pathways. For instance, a recent study by Copp and Neilan (2006) revealed unique function-based phosphopantetheinyl transferases in cyanobacteria through phylogenetic analysis. Such information would have important implications in the heterologous production of cyanobacterial secondary metabolites. In addition to the discovery and production of novel compounds, the presence of unique tailoring enzymes, such as halogenases and desaturases, involved in the formation of functional groups in marine cyanobacterial compounds has applications in biotechnology. Such individual enzymes when expressed from genetic domains are of great utility especially in chemoenzymatic reactions. A recent study by Beck et al. (2005) demonstrated the successful utility of thioesterase, isolated from the cryptophycin biosynthetic pathway, in the macrocyclization of a series of linear synthetic precursors in generating 16-membered cyclic depsipeptides as potential anticancer agents.

In spite of the challenges pertaining to the exploitation of marine cyanobacteria as potential drug source, they

are not insurmountable due to advances in molecular biology and culturing technologies. It is therefore without doubt that natural products research involving these deceptively simple marine microbes will result in high degree of success in uncovering products useful in the biomedical and biotechnology arena.

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