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Review

Cyanobacteria-derived peptide antibiotics discovered since 2000

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ABSTRACT

Members of cyanobacteria, including *Moorea* spp., *Okeania* spp., *Lyngbya* spp., *Schizothrix* spp., *Leptolyngbya* spp., *Microcystis* spp., *Symploca* spp., *Hassallia* sp., *Anabaena* spp., *Planktothrix* sp., *Tychonema* spp., *Oscillatoria* spp., *Tolypothrix* sp., *Nostoc* sp., and *Hapalosiphon* sp. produce an enormously diverse range of peptide antibiotics with huge potential as pharmaceutical drugs and biocontrol agents following screening of structural analogues and analysis of structure-activity relationships (SAR). The need for novel antibiotic lead compounds is urgent, and this review summarizes 78 cyanobacteria-derived compounds reported since 2000, including 32 depsipeptides, 18 cyclic lipopeptides, 13 linear lipopeptides, 14 cyclamides, and one typical cyclic peptide. The current and potential therapeutic applications of these peptides are discussed, including for SAR, antituberculotic, antifungal, antibacterial, antiviral, and antiparasitic (anti-plasmodial, antitrypanosomal and antileishmanial) activities.

1. Introduction

In the recent era, drug discovery from marine microbes has increased annually [1]. Cyanobacteria, also known as blue-green algae, are a group of oxygenic photosynthetic prokaryotes that are widely distributed in nature. Over the past 50 years, cyanobacteria from different habitats, particularly marine environments, have been exploited as a source of surprisingly distinct and biologically active compounds exhibiting antibacterial, antiviral, antifungal, enzyme inhibition, immunostimulant, cytotoxic, anti-plasmodial, antitrypanosomal, antileishmanial, and insecticidal activities [2–4]. Among these antibiotic compounds, peptide and polyketide structural elements are predominant [5]. Short peptides comprising ~30 residues or fewer have received much attention due to their novel inhibitory mechanisms and recalcitrance to traditional modes of drug resistance [6]. They are produced by non-ribosomal peptide (NRP) synthetases and hybrid polyketide-NRP or ribosomal peptide-post-translationally modified biosynthetic pathways [4,6]. However, to date, none of these molecules have been approved as drugs, and none are in advanced clinical trials. Therefore, research on cyanobacteria-derived peptide antibiotic products appears to progress slowly, and this must be addressed if we are to successfully exploit this powerful resource. Since 2000, representative genera of cyanobacteria including *Moorea* spp. (*M. bouillonii* and *M. producens*) [7,8], *Okeania* spp. [9–11], *Lyngbya* spp. (*L. majuscula*, *L. semiplena* and *L. confervoides*) [12–34], *Schizothrix* spp. [13,35], *Leptolyngbya* spp. [36], *Microcystis* spp. (*M. ichthyoblabe* and *M. aeruginosa*) [37–43], *Symploca* spp. [44,45], *Hassallia* sp. [46,47], *Anabaena* spp. (*A. cylindrica* and *A. spiroides*) [48–53], *Planktothrix* sp. (*P. serta*) [54], *Tychonema* spp. [55,56], *Oscillatoria* spp. (*O. nigro-viridis*) [57–59], *Tolypothrix* sp. (*T. byssoidea*) [60], *Nostoc* sp. [61] and *Hapalosiphon* sp. [62] have been available for this purpose.

Cyanobacteria-derived peptide antibiotic products can be classified into four distinctive categories; depsipeptides, lipopeptides, cyclamides, and typical cyclic peptides. Both depsipeptides and lipopeptides have linear or cyclic structures with a lipophilic fatty acid, aromatic acid, or glycosylated hydrocarbon tail linked to the *N*-terminus of a short oligopeptide, and are usually produced by NRP or hybrid polyketide-NRP synthetases, but in depsipeptides, one or more of the amide groups are replaced by a corresponding ester [6,63]. Cyclamides are highly modified peptides of ribosomal origin, and this class encompasses hexa- and octameric cyclopeptides with alternating hydrophobic and hydrophilic amino acids, and the side chains can be heterocyclised to form oxazole, oxazoline, thiazole or thiazoline rings, resulting in rather planar, disk-like structures [40,64]. In recent years, several reviews have briefly

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Table 1
Depsipeptides from brine shrimp toxins.

Name	Structural sequences	Brine shrimp	LD_{50}/ LC_{50}/ LC_{100}/MLC	Ref
Bouillonamide A	[1]Mhha*-[2]Mmaha-Val-*N*-Me-Phe-*N*-Me-Thr-*N*-Me-Phe*	*Artemia salina*	[a]9.0 μM	[7]
Odoamide	[3]Dtuea*-[4]Hmpa-Ala-*N*-Me-Phe-*N*-Me-Gly-Ile-*N*-Me-Ala*	*A. salina*	[a]13.0 μM	[9]
Odobromoamide	[5]Br-Hmoya*-Val-*N*-Me-Ile-[6]Hiva-Pro-*N*-Me-Val*	*A. salina*	[a]1.2 μM	[10]
Wewakamide A	Hiva*-Pro-*N*-Me-Ala-*N*-Me-Leu-*N*-Me-Ile-Val-[7]Maba-Leu-Phe*	*A. salina*	[b]5 ppm	[12]
Yanucamides A and B	[8]Dhoya*-Val/Ile-Hiva-*N*-Me-Phe-β-Ala*	*A. salina*	[a]5 ppm	[13]
Hantupeptins A–C	[9]Pla*-Pro-*N*-Me-Val-[10]Hmoya/[11]Hmoea/[12]Hmoaa-Val-*N*-Me-Ile*	*A. salina*	[c]10–100 ppm	[14,15]
Trungapeptin A	Pla*-Pro-Ile-Hmoya-Val-*N*-Me-Val*	Unknown	[d]10 ppm	[16]

1Mhha: 3-Me-5-hydroxy (Hy)-heptanoic acid; 2Mmaha: 2-methyl (Me)-6-methylamino-hex-5-enoic acid; 3Dtuea: 5,7-diHy-2,6,8-triMe-undec-2-enoic acid; 4Hmpa: 2-Hy-3-Me-pentanoic acid; 5Br-Hmoya: 8-Br-3-Hy-2-methyloct-7-ynoic acid; 6Hiva: 2-Hy-isovaleric acid; 7Maba: 3-amino-2-Me-butanoic acid; 8Dhoya: 2,2-diMe-3-Hy-7-octynoic acid; 9Pla: phenyllactic acid; 10Hmoya: 3-Hy-2-Me-7-octynoic acid; 11Hmoea: 3-Hy-2-Me-7-octenoic acid; 12Hmoaa: 3-Hy-2-Me-octanoic acid.

* denoting the linkage position of ring formation.

[a] median lethal dose (LD50).

[b] median lethal concentration (LC50).

[c] 100% lethal concentration (LC100).

[d] minimum lethal concentration (MLC).

mentioned bioactive natural peptides from cyanobacteria [2–4,65]. Herein, we provide a comprehensive review of progress on the source, structural sequence, and antibiotic activities of cyanobacteria-derived peptide products reported since 2000, with an emphasis on structure-activity relationships (SAR) to highlight the potential for exploration and exploitation as novel pharmaceutical drugs or biocontrol agents.

2. Depsipeptides from brine shrimp toxins

Brine shrimp (*Artemia salina*) is a wide-temperature and salt-tolerant aquatic organism. Because it is sensitive to poisons, and is small and easy to acquire and cultivate, *A. salina* is used in high-throughput screening of new pesticides to potentially alter current bioassays [66,67], and 10 active cyclic depsipeptides have been identified from this organism since 2000 (Table 1).

The coral-derived species *M. bouillonii* Hoffman and Demoulin produces bouillonamide A [7]. In addition to α-amino acid residues, this depsipeptide also contains two polyketide-derived moieties, namely a methylamino-enoic acid residue, and a 5-hydroxy alkanic acid unit. This compound exhibits a median lethal dose (LD_{50}) value of 9.0 μM against *A. salina*. Bioassay-guided fractionation of *Okeania* sp. (deposited in DDBJ/EMBL/GenBank databases under accession number LC155112) led to the isolation of odoamide and odobromoamide [9,10]. Odoamide includes five α-amino acid-derived units, a dihydroxy-enoic, and 2-hydroxy alkanic acid units within a complete 26-membered ring (belonging to the aurilide class) [9]. Odobromoamide, an analog of veraguamides A and B, has a terminal alkynyl bromide moiety and a 2-hydroxy alkanic acid unit [10]. Notably, both showed toxicity against brine shrimp (LD_{50} = 13.0 and 1.2 μM, respectively). In addition, research on two different structural analogues of veraguamide A, namely kulomoopunalide-1 and -2, suggests that the alkynyl bromide moiety may be an essential structural feature for potent activity [68]. Wewakamide A from shallow water-derived *L. semiplena* and *L. majuscula* includes a β-amino acid and an α-hydroxyalkanic acid residue [12]. This compound displays potent toxicity against brine shrimp with a median lethal concentration (LC_{50}) of 5 ppm. Yanucamides A and B were isolated from a mixed assemblage of shallow water-derived *Schizothrix* sp. and *L. majuscula* [13]. Both compounds contain a β-hydroxy alkynyl acid, a β-alanine, and an α-hydroxy alkanic acid moiety, and both exhibit strong toxicity against *A. salina* (LD_{50} = 5 ppm).

Hantupeptins A–C, from lagoon and shallow water-derived *L. majuscula*, consists of a phenyllactic acid and β-hydroxy acid unit with different degrees of unsaturation at the terminal end of each molecule. These compounds exhibit 100% toxicity against brine shrimp at 10–100 ppm [14,15]. Trungapeptin A from *L. majuscula* contains a β-hydroxy alkynyl acid and phenyllactic acid residues, and is closely related to the antanapeptins [16]. Interestingly, it is only mildly toxic to brine shrimp at 10 ppm, and is significantly less active than its close analogues hantupeptins A–C.

3. Other depsipeptides

In addition, since 2000, another 32 depsipeptide products with antibiotic activity have been reported (Table 2).

Two cyclic depsipeptides, companeramides A and B, from an assemblage of reef pinnacle-derived *Leptolyngbya* spp. (GenBank acc. no. KM882611), contain similar structural moieties consisting of a β-amino alkynyl acid and an α-hydroxy alkanic acid [36]. These compounds exhibit differential activity against chloroquine-sensitive (D6) and -resistant (Dd2 and 7G8) strains of *Plasmodium falciparum*, with median inhibitory concentration (IC_{50}) values of 220–1100 nM, less than the chloroquine control, but neither are overtly cytotoxic to mammalian cells. It is interesting to speculate that nontoxic cyclic alkynoic depsipeptides may be used as a precursor in the biosynthesis of anti-malaria drugs. Similarly, a family of a β-hydroxy alkynyl acid (Dhoya)-containing dudawalamides A–D from shallow marine habitat-derived *M. producens* (DDBJ/EMBL/GenBank acc. no. EU492878.1) have been characterised as the 'kulolide-like superfamily' [8]. These compounds exhibit a broad spectrum of activity against *P. falciparum*, *Leishmania donovani* and *Trypanosoma cruzi*. Interestingly, A and D possess the most potent activity against *P. falciparum* (IC_{50} = 3.6 and 3.5 μM, respectively), and D is relatively potent against the other two parasites, with IC_{50} = 2.6 μM and a growth inhibition rate (GIR) of 60% at 10 μg/mL, respectively. Intriguing SAR analysis revealed that minor changes in both the configuration and sequence of residues strongly impacts the bioactivity of these depsipeptides, and the Dhoya residue is considered a molecular fingerprint of cyanobacterial peptides.

Ichthyopeptins A and B, from lake water-derived *M. ichthyoblabe* BM Mi/13, contain a *p*-hydroxy phenyllactic acid and 3-amino-6-hydroxy-2-piperidone (Ahp) unit [37]. These compounds display antiviral activity against influenza A virus (IC_{50} = 12.5 μg/mL), essentially at the same level as amantadine at 15 μg/mL. In addition, their mode of action may be based on protease inhibition. Janadolide, a polyketide-peptide hybrid possessing a *tert*-butyl-containing 7-hydroxyl-enoic acid, was isolated from coast-derived *Okeania* sp. 1504-15 (DDBJ/EMBL/GenBank acc. no. LC149728) [11]. This compound has potent anti-trypanosomal activity against *Trypanosoma brucei brucei* (IC_{50} = 47 nM) without cytotoxicity against human cells, which is more potent than the commonly used therapeutic drug suramin (IC_{50} = 1.2 μM). Thus, synthetic analogs of janadolide could be developed as new anti-trypanosomal drugs. Lagunamides A–C are members of the aurilide class isolated from benthic shallow water-maintained *L. majuscula* from the National Institute of Education under code TLT/PHB/002 [17,18]. These compounds display significant antimalarial properties, with IC_{50}