

REVIEW ARTICLE

Taking stock of *Nostoc*: Secondary metabolite analyses with an outlook for future therapeutic leadsKalyani Ajayan¹, Krishna Priya Sushaman¹, Nirmala Krishnamurthy^{2*},
and Rajesh Viswanathan^{1*}¹Department of Chemistry, Indian Institute of Science Education and Research, Tirupati, Andhra Pradesh, India²Department of Humanities and Social Sciences, Indian Institute of Science Education and Research, Tirupati, Andhra Pradesh, India(This article belongs to the *Special Issue: Medicinal and Pharmaceutical Chemistry*)

Abstract

Natural products derived from cyanobacteria have emerged as a prolific source of structurally diverse and biologically active compounds with significant therapeutic potential. This review summarizes the current literature on the isolation of natural products and their medicinal properties from the cyanobacterial genus *Nostoc*. It emphasizes the structural diversity of secondary metabolites biosynthesized by *Nostoc*. Based on the literature on the chemical characterization of natural products, we provide an outlook for harnessing the latent biocatalytic potential of this cyanobacterial genus to discover enzymes directly involved in the production of these diverse natural products. The review provides potential hints for future identification of enzymes with unique biochemistry and/or for the synthesis of novel natural product analogs from the families discussed herein.

Keywords: Cyanobacteria; Secondary metabolites; Natural products; *Nostoc****Corresponding authors:**Nirmala Krishnamurthy
(nirmala@labs.iisertirupati.ac.in)
Rajesh Viswanathan
(rajesh@labs.iisertirupati.ac.in)**Citation:** Ajayan K, Sushaman KP, Krishnamurthy N, Viswanathan R. Taking stock of *Nostoc*: Secondary metabolite analyses with an outlook for future therapeutic leads. *Innov Med Omics*. 2026;3(2):025490070. doi: 10.36922/IMO025490070**Received:** December 6, 2025**Revised:** January 22, 2026**Accepted:** February 5, 2026**Published online:** April 7, 2026**Copyright:** © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.1. Introduction: Cyanobacterial genus *Nostoc*

Cyanobacteria are one of the oldest life forms on Earth, having flourished for nearly 3.5 billion years.¹ Due to their evolutionary adaptation to a multitude of habitats, cyanobacteria are considered one of the largest, most diverse, and highly specialized groups of photosynthetic prokaryotes. Possessing the singular distinction of being the only prokaryotic organism capable of photosynthetically converting solar energy and CO₂ into organic matter, they are ecologically important members of the environment, food chain, and our biosphere.² In addition, many cyanobacteria contribute to the supply of reduced nitrogen in the environment; in some cases, they thrive as symbionts with other organisms, supplying them directly with reduced nitrogen. Cyanobacteria have also served as a significant source of medicinally active natural products.

In 2003, it was estimated that over 60–75% of cancer and infectious disease therapeutics were of natural origin.³ A more recent survey identified 1,184 new chemical entities spanning the period of 1981 to June 2006, of which 52% have a natural product

connection.⁴ Marching on, even between 2000 and 2010, the natural products field was still responsible for about 50% of all small-molecule new chemical entities.⁵ Among these, 41 of the 62 small-molecule drugs approved from 2011 to 2012 are derived from natural product structures as leads.⁶ Newman and Cragg's^{6–8} reviews cover these secondary divisions, and as of the 1981–2019 time frame, 64.9% of small-molecule drugs are either natural products or are natural product structure-inspired. With the increased capability of today's biotechnology tools, including genomics-based investigations, advanced activity screening, the use of genetically modified organisms or cell lines, and improved synthetic biology methods, it is predicted that natural sources will provide even more interesting compounds with exciting bioactivities in the years to come.⁹

It is therefore well documented that natural sources are highly attractive for the discovery of unique bioactive natural products,^{10,11} and cyanobacteria are no exception.¹² The aptitude of these organisms to inhabit almost every aquatic and terrestrial environment, and their unwavering survival, is attributed to their exceptionally diverse genetics. In turn, these attributes have enabled the successful evolution of metabolic pathways, allowing the majority of cyanobacteria to encode a variety of unique secondary metabolites^{13–18} with potent bioactivities.^{19–21} The exception to this observation is unicellular cyanobacteria, such as the genera *Prochlorococcus* and *Synechococcus*.²² Although cyanobacterial genomes vary greatly in size (1.4–9.1 Mb),²³ unicellular cyanobacteria typically possess genomes 5–6 Mb smaller than their filamentous or colonial counterparts, and, as a result, do not usually produce secondary metabolites.²²

While filamentous marine strains are better known for the sheer number of new isolated compounds (over 450 in 2013),²⁴ interest in filamentous terrestrial strains has gained momentum in recent years.^{22,25–29} The group IV genus *Nostoc* (family: Nostocaceae, order: Nostocales) is one of the most widespread phototrophic taxa known;³⁰ predominantly terrestrial strains,³¹ this genus also occupies marine and freshwater niches. *Nostoc* species are evolutionarily significant for their facultative lifecycle, which alternates between free-living and symbiotic associations with host organisms. Often, terrestrial species in symbiotic relation with plants form a stable microhabitat where they exchange biomaterials. Strains within the *Nostoc* genus are filamentous, capable of nitrogen fixation, and can thrive in macroscopic or microscopic colonies; they are also known for their characteristic morphologies³² and complicated life cycles.³³ Members of this genus produce metabolites ranging from hydrocarbons and

lipids to derivatives of amino acids, peptides, and lipopeptides. Recent application of genomics to natural product discovery has revealed the biosynthetic potential of these organisms. The use of appropriate genome-mining tools enables the identification of biosynthetic gene clusters (BGCs) and reveals the diversity and abundance of bioactive metabolites.³⁴ As a result, the biosynthetic prowess of these organisms is a hot topic in today's natural product field.³⁵ Irrespective of the vast number of reviews over the decades on *Nostoc*, they either broadly cover the isolates or particulars on biosynthetic aspects of a class of metabolites. Hence, this review serves as a repository of metabolite and related biosynthetic information regarding the *Nostoc* genus to better serve scientists exploring the potential of these organisms.

2. *Nostoc*-derived natural products

The medicinal activity of *Nostoc* species was exploited in 1500 BC when it was used to treat various forms of cancer, gout, and fistula; however, it was not until the 1990s that cyanobacteria, in general, were explored for their bioactive secondary metabolites.¹⁵ At the onset of cyanobacterial natural product discovery, crude extracts were screened for a desired biological activity using bioassay-guided screening, and the active component was purified and identified.^{36,37} For example, screening for protease inhibitors,³⁸ antimicrobials,³⁹ and antifungals⁴⁰ has led to the discovery of nostopeptins A and B, tenucyclamides A–D, and nostofungicidine, respectively. These molecules, along with microcystins (cyclic, hepatotoxic peptides),^{36, 41–43} cryptophycins (antimitotic, antitumor, cyclic depsipeptides),^{44,45} antiviral polysaccharide nostoflan^{46,47}, and various other metabolites produced by *Nostoc* species, were reviewed in 2005 by Dembitsky and Řezanka.¹⁸ Their review is a comprehensive overview of metabolites produced by *Nostoc* at that time. Another review in 2019 by Fidor *et al.*⁴⁸ extensively covered the structure, activity, and application of bioactive peptides from *Nostoc*. Thuan *et al.*⁴⁹ reviewed the literature on *Nostoc* (as well as *Lyngbya* and *Microcystis*) and highlighted multi-omics approaches and heterologous production of these metabolites. In the current review, we document ongoing characterizations of natural products alongside their biosynthetic classifications.

Bioassay-guided screening of cyanobacterial extracts remains one of the main tools for discovering new natural products. It is now complemented by powerful tools, such as peptidogenomic-based tandem mass spectrometry (MS/MS), metagenomic sequencing, and orphan gene cluster characterizations. Molecules that have been isolated post-2005 (since Dembitsky and Řezanka's¹⁸ publication) from this genus are summarized in Table 1. Selected molecules

from Table 1 are reviewed in the following subsections based on their recent isolations, interesting bioactivities, and unique structural features. Within the subsections reviewing individual natural products or families thereof, a brief history of the isolation of the metabolite is provided, followed by a description of its structural components. Natural product structures in this review were drawn from the respective primary literature; color coding illustrates various structural motifs or biosynthetic precursors that constitute the molecule.

2.1. Nostocarboline

2.1.1. Structure and isolation

Nostocarboline (Figure 1), the first quaternary carbolinium derivative extracted from a cyanobacterial strain, was first reported in 2005.⁵⁰ This natural product was isolated from *Nostoc* 78-12A, a freshwater isolate from a wastewater lagoon.⁵¹ Other carboline alkaloids had been isolated from cyanobacteria, such as baureines from *Dichothrix baueriana*⁵² and norharmane from *Nodularia harveyana*,⁵³ but none possess the quaternary structure characteristic of nostocarboline. In general, β -carboline alkaloids are nitrogen-containing pyrido[3,4-*b*]-indole heterocycles that display a signature tricyclic skeleton, as exemplified by nostocarboline.⁵⁴

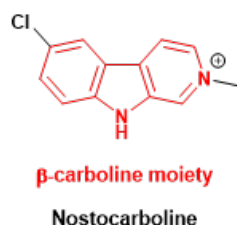


Figure 1. Chemical structure of nostocarboline

2.1.2. Bioactivity

Various β -carboline derivatives can be observed with substituents in both the pyrido and indole rings.⁵⁵ These molecules are known to have a wide range of bioactivity, from interacting with DNA and enzymatic systems to antitumor and antiviral activities. Curiosity in nostocarboline was sparked by its cholinesterase-inhibitory and anticyanobiotic activities.⁵⁶ The active component of the *Nostoc* 78-12A extract was isolated with aqueous CH₃CN and purified by high-performance liquid chromatography (HPLC). High-resolution matrix-assisted laser desorption/ionization (MALDI) and ¹⁵N-labeling supported the determination of the elemental composition of the natural product. The structure of nostocarboline was elucidated using various spectroscopic methods (¹H nuclear magnetic resonance [NMR], ¹³C NMR, heteronuclear single

quantum coherence [HSQC], heteronuclear multiple bond correlation [HMBC], and 1D nuclear overhauser effect spectroscopy [NOESY]) and confirmed by total synthesis.⁵⁰ Interest in the bioactive potential of this molecule led to the discovery that nostocarboline is an effective cholinesterase inhibitor, specifically acetylcholinesterase (AChE),⁵⁷ as well as a promising anti-biofouling compound.^{58,59} The cholinergic involvement in multiple system disorders was discussed in detail in the review by Ofek and Soreq.⁶⁰ With an IC₅₀ of 13.2 μ M, nostocarboline is comparable to the approved drug galanthamine (IC₅₀ of 16.9 μ M), which is used to treat Alzheimer's disease (AD).^{50,61,62} The bioactive potential of this molecule and its dimers or derivatives has only grown since its initial isolation through the use of both synthetic chemistry⁶³ and directed biosynthesis.⁶⁴ Nostocarboline derivatives are antiparasitodal,⁶³ antimalarial, antitubercular,⁶⁵ and antibacterial.⁶⁶

2.2. Insulapeptolides

2.2.1. Structure and isolation

Mehner *et al.*⁶⁷ were seeking inhibitors of a specific serine protease, human leukocyte elastase (HLE). They screened the crude extracts of 17 cyanobacterial strains using an HLE inhibition assay. Of the 17 strains tested, only *Nostoc insulare* showed noteworthy inhibition (IC₅₀ of 9 μ g/mL).⁶⁷ Further investigation using nonribosomal peptide synthetase adenylation domain-based degenerate polymerase chain reaction (PCR) revealed that *N. insulare* possesses genes involved in nonribosomal peptide biosynthesis. A subsequent PCR experiment based on genes involved in the biosynthesis of the unusual amino acid 4-methylproline (4-MePro) suggested that this amino acid is a component of the natural product. MALDI-time of flight analysis has discovered the active component of the *N. insulare* extract, and preparative reversed-phase HPLC has isolated insulapeptolides A–H (Figure 2). These natural product structures were elucidated using various spectroscopic methods, including 1D NMR (¹H, ¹³C, and distortionless enhancement by polarization transfer [DEPT]-135), 2D NMR (HSQC, correlation spectroscopy [COSY], HMBC, and NOESY/rotating frame nuclear overhauser effect spectroscopy [ROESY]), chiral gas chromatography–MS, and HPLC. The insulapeptolides belong to the family of cyanopeptolins,⁶⁸ a class of cyclic depsipeptides (peptides with a macrolide peptide architecture) characterized by the amino acid 3-amino-6-hydroxy-2-piperidone and the unique macrolactonization of the peptide ring.⁶⁹ Insulapeptolides A–D also contain *L*-citrulline, an unusual structural feature in cyanobacterial peptides, and the uncommon amino acid 3-hydroxy-4-methyl-proline (Hmp). Insulapeptolides E–H do not contain Hmp, but do possess another unusual amino acid,

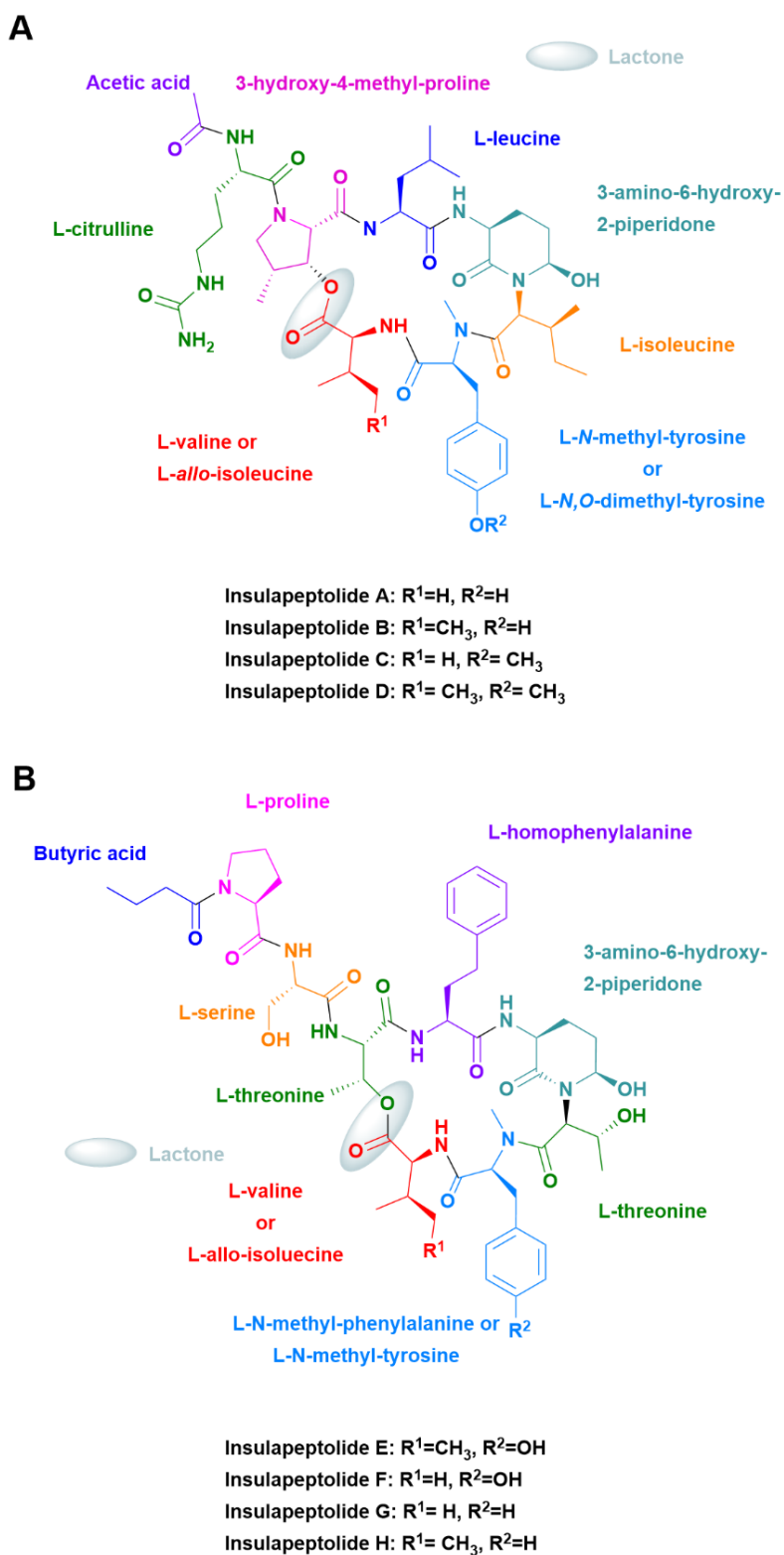


Figure 2. Chemical structures of (A) insulaeptolide A–D and (B) insulaeptolide E–H

L-homophenylalanine. The naming of the cyanopeptolin family of natural products is slightly confusing because some members share the same name (e.g., cyanopeptolins A, B, and C) and others have synonyms (e.g., nostocyclin and nostopeptin).⁷⁰

2.2.2. Bioactivity

The bioactivity-based isolation of insulapeptolides from *N. insulare* identified insulapeptolide D as the most potent inhibitor of HLE, with an IC₅₀ value of 85 nM. This class of compounds demonstrates high selectivity for HLE, with significantly weaker inhibition of related neutrophil serine proteases, such as proteinase 3 and cathepsin G. Advancing research on insulapeptolides is highly significant because sivelestat remains the only selective synthetic inhibitor of HLE available on the market.

Biosynthetic information is rather limited for the insulapeptolides in *Nostoc* beyond the putative gene fragment sequences documented earlier. Gene cluster information for cyanopeptolins is available from other cyanobacterial strains, such as the anabaenopeptilides from *Anabaena* strain 90.⁷¹

2.3. Carbamidocyclophanes

2.3.1. Structure and isolation

The [m.n]-paracyclophanes were first described by Cram *et al.*⁷² in 1951. They refer to a class of organic compounds with two benzene rings bridged by alkane chains of lengths *m* and *n*, creating a strained, stacked structure with unique electronic properties.⁷³ They are used in asymmetric synthesis and materials science (e.g., polymers and dyes), as well as used as photoswitches, with [2.2]-paracyclophane being a classic example featuring two ethylene bridges and strong transannular interactions. This class of macrocyclic compounds, also known as *caged compounds* due to their interesting structures, originated as the lead molecules to function as hosts for aromatic and aliphatic compounds, providing a cavity of finite shape and size for *guests*. It triggered a mammoth research area, broadly termed *host-guest* chemistry, and eventually earned a Nobel Prize in 1987.⁷⁴

Initially known only through synthesis, paracyclophanes were not observed in nature until 1990, when Moore *et al.*⁷⁵ isolated and identified [7.7]paracyclophanes from two species of the *Nostocaceae* family. A subsequent study has investigated these compounds and determined their biosynthetic origins.⁷⁶ An excellent review was published in 2012, covering strained macrocyclization in natural products and the difficulties it presents to synthetic chemists; it provides a brief historical perspective on cyclophanes in both natural product isolation and total

synthesis.⁷⁷

2.3.2. Bioactivity

To date, several cyclophanes have been isolated from cyanobacteria with interesting bioactivities, including the cylindrocyclophanes (antitumor, cytotoxic),^{76,78} nostocyclophanes (antitumor, cytotoxic),⁷⁹ nostocycline A (antimicrobial),⁸⁰ merocyclophanes,⁸¹ and carbamidocyclophanes (cytotoxic, antibiotic, anti-*Mycobacterium tuberculosis* activity).^{82,83} The alkylresorcinol scaffold, in particular, has garnered significant interest due to its diverse biological properties and potential effects on human health, especially when consumed as part of a whole grain diet.⁸⁴ Dietary alkylresorcinols function as autoregulators in microbial communities, influencing the gut microbiome composition and potentially impacting gut-immune and gut-nervous systems. Meanwhile, 4-hexylresorcinol has been shown to enhance the efficacy of antibiotics and combat antibiotic resistance by integrating into cell walls and acting as a structural modifier of biopolymers, thereby increasing membrane permeability. Other notable bioactive properties include neuroprotective potential through antioxidant activity and anti-aging potential by activating sirtuins, which are involved in DNA repair, stress responses, and wound healing, thereby promoting epithelization and collagen regeneration by suppressing inflammatory factors such as tumor necrosis factor- α .

The carbamidocyclophanes were originally isolated by Rui *et al.*⁸³ in 2007 when northern Vietnamese cyanobacterial isolates were screened for antibiotic activity. The methanol extract prepared from the biomass of *Nostoc* sp. CAVN 10 showed inhibitory activity against Gram-positive bacteria, yeast, and, notably, coagulase-negative methicillin-resistant *Staphylococcus aureus*. Analysis of the extract led to the identification of five new paracyclophanes, carbamidocyclophanes A–E (Figure 3). These polyketides contain the [7.7]paracyclophane ring, but differ in chlorination of their butyl side chains (except for carbamidocyclophane E, which does not contain chlorine) and contain different carbamido substituents in the 1, 14-positions.

A few years later, carbamidocyclophanes F, G,⁸⁴ and H–L⁸⁵ were added to this collection of natural products. The extract of a field sample of *Nostoc* sp. (UIC 10274) showed inhibitory activity against *M. tuberculosis*; analysis of the extract showed known molecules, carbamidocyclophanes A–C, as well as two new polyketides, carbamidocyclophanes F and G. These new paracyclophanes follow the same structural scaffold as described above, with the [7.7]paracyclophane ring and various chlorinated side chains,

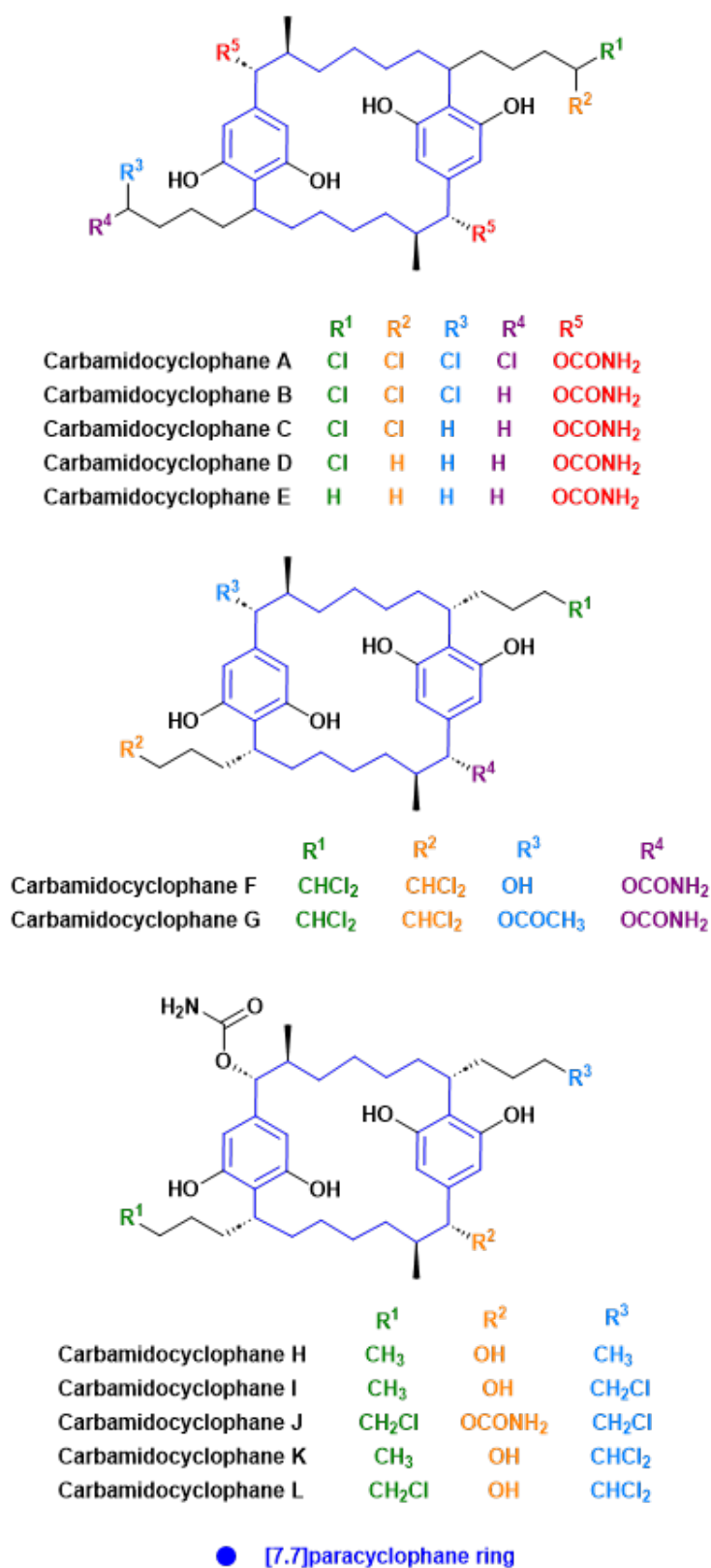


Figure 3. Chemical structures of carbamidocyclophane A–L

but have only one carbamate moiety (at C-14), opposed to two in carbamidocyclophanes A–E (at C-1 and C-14). Carbamidocyclophanes H–L were discovered following the evaluation of several cyanobacterial strains for cytotoxicity against several cell lines. They exhibit favorable selectivity indices, with their therapeutic concentrations well below those that cause toxicity to human cells. Similar to their F and G congeners, carbamidocyclophanes H–L are monocarbamoylated. Interestingly, carbamidocyclophane J is the first of the carbamidocyclophanes to possess a monochlorine at both butyl residues. Feeding studies with KCl and KBr in culture medium resulted in upregulation of carbamidocyclophane production in *Nostoc* sp. CAVN2.⁸⁶ NMR (proton, heteronuclear multiple quantum coherence [HMQC]–DEPT, and HMBC), attenuated total reflectance–infrared spectroscopy, and electronic circular dichroism (ECD) analysis showed the presence of nine carbamidocyclophanes M–U in the isolate. Although biosynthetic information is available for [7.7] paracyclophanes,⁷⁷ no biosynthetic literature is available for the carbamidocyclophanes, particularly. However, it has been hypothesized that the biosynthesis of these metabolites will be similar to that of the cylindrocyclophanes, based on structural similarities.⁸⁴

2.4. Nostotrebin 6

2.4.1. Structure and isolation

Zelík *et al.*⁸⁷ searched for new AChE inhibitors for potential AD therapeutics. They screened for this inhibitory activity in *Nostoc* species from different niches. *Nostoc* sp. str. Lukešová 27/97 was identified as one of the most active cyanobacterial strains. The methanol extract of this strain yielded an active fraction containing a novel compound, nostotrebin 6, with a 2,2'-bis(cyclopentenedione [CPD]) skeleton, including a cyclopentene double bond substituted by two *p*-hydroxybenzyl groups (Figure 4A).⁸⁸

2.4.2. Bioactivity

Nostotrebin 6 was determined to be an S-parabolic, I-parabolic noncompetitive inhibitor of AChE ($IC_{50} = 5.5 \mu M$), and an S-parabolic, I-parabolic mixed-type inhibitor of butyrylcholinesterase ($IC_{50} = 6.1–7.5 \mu M$).⁸⁸ Both AChE and BChE have multiple binding sites for nostotrebin 6. Although this was one of the earliest studies to address AChE inhibitory activity in cyanobacteria, the insufficient inhibitory activity of nostotrebin 6 relative to reference standards suggested that it would not be worth pursuing as an AD therapeutic. The reference standards, galanthamine and tacrine, possess IC_{50} values for AChE inhibition that are lower than that of nostotrebin 6 by 10-fold and 100-fold, respectively. Interestingly for BChE activity, nostotrebin 6 displays an IC_{50} value slightly lower than that

of galanthamine ($6.1–7.5 \mu M$ compared to $8.6–37.9 \mu M$), but higher than that of tacrine by roughly 400-fold.⁸⁸ Also, recent studies have classified nostotrebin 6 as a potential pan-assay interference compound (PAINS) candidate. Its broad inhibitory activity across unrelated targets is not driven by its unique bis(CPD) core but rather by its phenolic substructures. Therefore, it shows a significant lack of selectivity between therapeutic targets and human proteins, such as cathepsin L.

Nostotrebin 6 skeleton can serve as a base for potent antibacterial agents against multidrug-resistant Gram-positive bacteria, but it has a narrow antibacterial spectrum, with no activity against Gram-negative bacteria or yeast.⁸⁹ In that study, nostotrebin 6 was isolated from *Nostoc* sp. str. Lukešová 27/97 cultivated in a large-scale photobioreactor using high-performance counter-current chromatography combined with gel permeation chromatography. Gram-positive bacteria were more susceptible to nostotrebin 6, with minimal inhibitory concentrations ranging from 6.25 to 15.6 $\mu g/mL$. There is no biosynthetic information available for this natural product; however, biosynthetic investigations could benefit the search for AD therapeutics by enabling the production of analogs of nostotrebin-6 with higher inhibitory activity.

Along with nostotrebin 6 (homodimeric CPD), new monomeric, dimeric, and higher oligomeric CPDs were identified in *Nostoc* sp. CBT1153 extract (Figure 4B), and were further isolated and structure elucidated by 1D and 2D NMR experiments.⁹⁰ Among the isolated compounds, the monomer with an additional hydroxy group at C-2 was named nostotrebinol 3, the monomer with a lactone core and a hydroxy group at C-14 was named nostolactone 4, nostotrebin with an additional hydroxy group at C-14 was named nostotrebin 7, and the dimeric structure with one lactone core and one CPD monomer was named nostotrebinlactone 7. Nostotrebin has a broad spectrum of bioactivity, making it a PAINS compound. Comparative activity testing of monomer, homodimer, and heterodimer CPDs suggested that their bioactivity is not determined by the CPD core but by the number of free phenolic hydrogens per molecule.

2.5. Cylindrocyclophanes

2.5.1. Structure and isolation

The isolation of [m.n]paracyclophanes from cyanobacteria was already discussed earlier. Among those isolated are the cylindrocyclophanes. Cylindrocyclophane A was isolated from a non-*Nostoc* species, *Cylindrospermum licheniforme* Kützing.⁷⁶ A few years later, cylindrocyclophanes B–F were isolated from three strains of the same species (*C. licheniforme* ATCC 29204, ATCC 29412, and UTEX

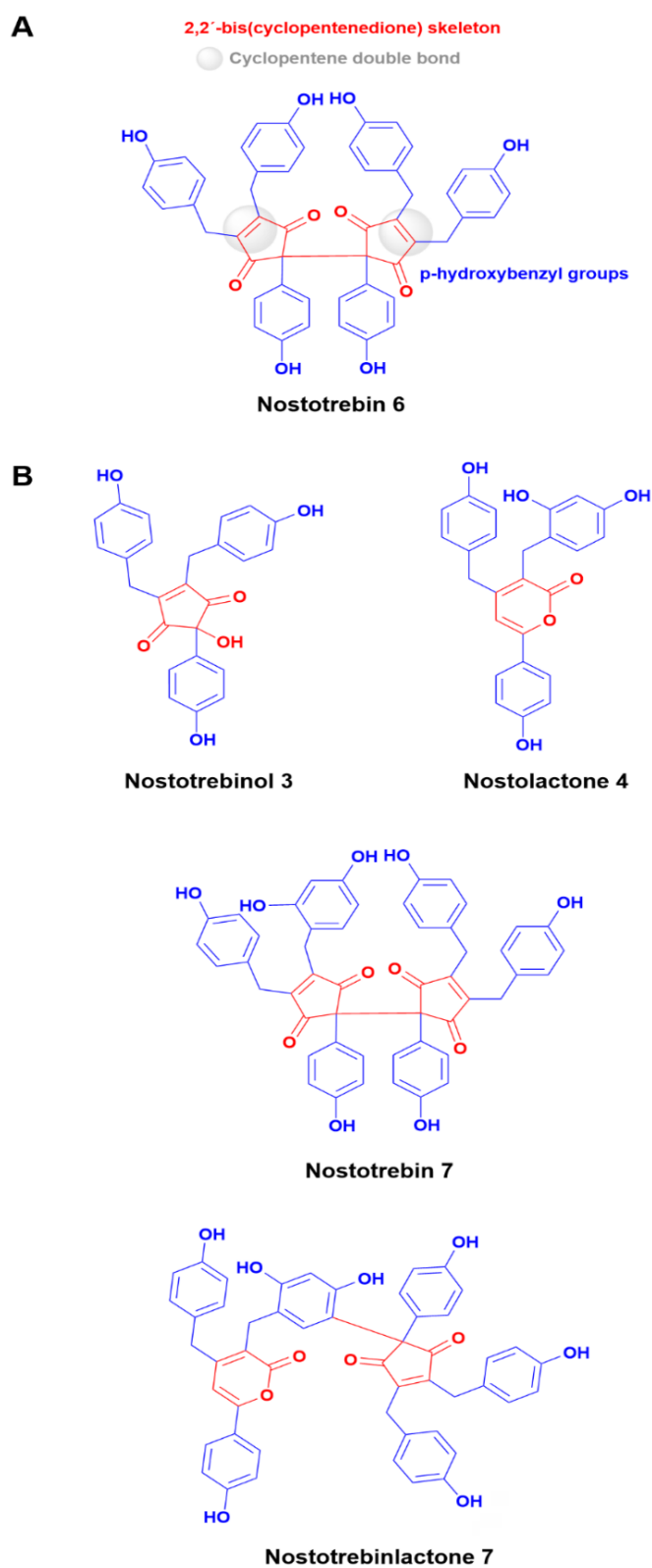


Figure 4. Chemical structure of (A) nostotrebin 6 and (B) monomeric, dimeric, and higher oligomeric cyclopentenediones identified in *Nostoc* sp. CBT1153 extract

2014).⁷⁹ It was not until 2010 that this class of molecules was isolated from a *Nostoc* species; three known (A, C, F), nine new (A₄-A₁, C₄-C₁, F₄), and one unnatural variant (A_{B4}) of cylindrocyclophanes were isolated from *Nostoc* sp. (UIC 10022A) (Figure 5).⁹¹

2.5.2. Bioactivity

Cylindrocyclophanes were discovered following screening of cyanobacterial strains for inhibition of the 20S proteasome, the catalytic core of the 26S proteasome that catalyzes protein degradation.⁹² Assays measuring inhibitory activity showed that cylindrocyclophanes A₂-A₄ were the most potent, with IC₅₀ values ranging from 2.55 to 3.93 μM, indicating high anticancer potency. [7.7]Paracyclophane often serves as a benchmark for structural complexity, and the total synthesis of (-)-cylindrocyclophanes A and F is seen as a yardstick for probing new C-H functionalization.^{93,94}

The biosynthesis of this family has not been investigated in any *Nostoc* species. However, biosynthetic information is available from other sources. In the early 1990s, Bobzin and Moore⁷⁷ reported the biosynthetic origins of the [7.7]paracyclophanes through feeding studies with *Nostoc linckia*, which produces nostocyclophane D, and *C. licheniforme*, which produces cylindrocyclophane D. Their study showed an acetate-derived β-methyl group incorporated into the structural scaffold of the cylindrocyclophanes. Since 2012, studies have identified a biosynthetic gene cluster in *C. licheniforme* (UTEX B 104) using PCR to probe for putative 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase homologs.^{95,96} The hypothesized involvement of HMG-CoA synthase was based on the feeding study by Bobzin and Moore.⁷⁷ Once the gene cluster was identified, it was associated with the cylindrocyclophanes after multiple *in vitro* characterization of enzymatic activities.⁹⁵ Additional feeding studies with *C. licheniforme* and d₁₉-decanoic acid showed incorporation of the isotopically labeled precursor into both halves of the molecule, confirming decanoic acid as a precursor to the cylindrocyclophanes and providing insight into the formation of the natural product.⁹⁵ Further investigations by Nakamura *et al.*^{97,98} described an off-loading mechanism for polyketide assembly line termination by a type III polyketide synthase, which generates a resorcinol intermediate, quantified using HPLC assays. Also, they reported the complete mechanism of paracyclophane ring formation via CylC catalyzing a cryptic chlorination, followed by CylK, an enzyme that alkylates the resorcinol aromatic ring.

2.6. Nostocyclopeptides

2.6.1. Structure and isolation

Cyclic peptides constitute a major class of natural products

isolated from cyanobacteria and possess a broad spectrum of bioactivities.⁹⁹⁻¹⁰² The structures of nostocyclopeptides, a class of cyclic heptapeptides, were introduced in 2000 when two *Nostoc* species were compared genetically and biochemically.^{18,103} Nostopeptolides are produced by *Nostoc* sp. GSV224, whereas *Nostoc* sp. ATCC53789 produces nostocyclopeptides (specifically, nostocyclopeptides A1 and A2; Figure 6A). The discovery of these natural products highlights the importance of genomic data in natural product discovery, which is further supported by many examples in the literature.¹⁰⁴⁻¹⁰⁸ The nostocyclopeptides are unique in that they possess an uncommon imino linkage, rather than all typical peptide bonds, within their structural backbone. This type of linkage is rarely seen in natural product cores. In addition, the nostocyclopeptides contain the rare amino acids 4-MePro and D-glutamate.

2.6.2. Bioactivity

Nostocyclopeptides A1 and A2 showed weak cytotoxicity against various cancer cell lines and did not possess antifungal or antibacterial activities against the fungi/bacteria tested.¹⁰³ Additionally, Jokela *et al.*¹⁰⁹ discovered nostocyclopeptide M1 when examining the shortcomings of a microcystin assay technique (Figure 6B). Nostocyclopeptide M1 is structurally similar to the previously isolated nostocyclopeptides A1 and A2. It contains the same uncommon imino linkage in the backbone and 4-MePro; however, unlike A1 and A2, which contain D-glutamate, M1 contains D-homoserine. Nostocyclopeptide M1 is a non-toxic, potent antitoxin against microcystin and a potent, non-toxic inhibitor of the hepatocyte drug transporters organic anion transporting polypeptide 1B3 (OATP1B3) and OATP1B1.¹¹⁰ Nostocyclopeptides are also identified as novel inhibitors of the 20S proteasome. The distinct selectivity of nostocyclopeptides in inhibiting specific proteasome activities, such as linear aldehyde forms targeting the chymotrypsin-like activity and a cyclic variant affecting the trypsin-like site, makes them the perfect scaffold to replace drugs that cause resistance and severe side effects, including bortezomib, carfilzomib, and ixazomib.

2.7. Suomilides and banyasides

2.7.1. Structure and isolation

Banyasides and suomilides are glycosylated leucine-containing peptides with an azobicyclononane core and a 1-amino-2-(N-amidino-Δ³-pyrrolinyl) ethyl (Aeap) moiety. They have a striking similarity to aeruginosin with a tricyclic core and Aeap attachments. In 2005, Pluotno *et al.*¹¹¹ identified novel modified peptides, banyaside A and banyaside B, along with the cyclic peptide banyasin A, from the freshwater bloom of *Nostoc* sp. IL 235 (Figure 7A).¹¹¹

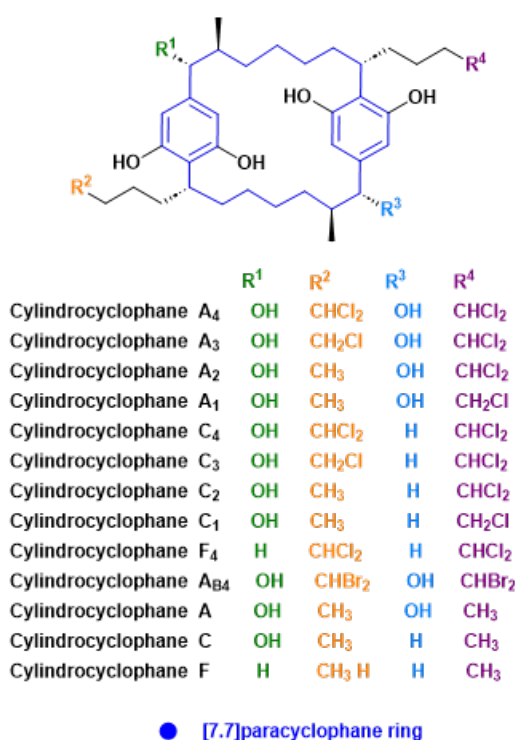


Figure 5. Chemical structures of cylindrocyclophanes A, C, and F

The banyaside peptides are structurally similar to another modified peptide, suamilide, which was first isolated from the cyanobacterium *Nodularia spumigena* HKVV in 1997.¹¹² The banyaside peptides were obtained as colorless glassy solids with optical activity and were characterized using fast atom bombardment mass spectrometry, NMR, COSY, total correlation spectroscopy (TOCSY), HMQC, and HMBC.¹¹²

2.7.2. Bioactivity

Prompted by the antiproliferative activity of crude extracts from *Nostoc* sp. KVJ20, four new suamilides (B–E) were identified (Figure 7B).¹¹³ Isolation of the compounds was performed using semi-preparative HPLC, followed by ultra-performance liquid chromatography–high-resolution MS/MS analysis. Suamilides were obtained as white crystalline solids. NMR characterization using HSQC, HMBC, ROESY, and COSY identified isoleucine, azobicyclononane, Aeap, carbamic acid, and hexanoic acid moieties.

Banyaside A and B showed serine protease inhibitory activity, with IC₅₀ of 1.48 µg/mL for trypsin and 0.39 µg/mL for thrombin.¹¹¹ This introduced a new class of pharmacophore unit that can be targeted in the synthesis of protease inhibitors. Though suamilides were tested for anti-biofilm activity and cytotoxicity, they did not show

promising results. Additionally, previous results showed that suamilides inhibit cancer cell invasion rather than proliferation. Nonetheless, it is worth studying their protease-inhibitory activity, as they share structural units with banyasides.

2.8. Merocyclophanes A and B

2.8.1. Structure and isolation

A new [7.7]paracyclophane skeleton was introduced with the discovery of merocyclophanes A and B, isolated from the terrestrial *Nostoc* sp. (UIC10062) (Figure 8).⁸² [7.7] Paracyclophanes contain various R groups at C-1 and C-14; the merocyclophanes contain simple α-branched methyl groups, representing the first observation of this structural scaffold within this family of natural products. The merocyclophanes were discovered for their antiproliferative activity against the HT-29 human colon cancer cell line, with the cellular extract from *Nostoc* sp. (UIC10062) displaying an IC₅₀ of 13.1 µg/mL. Bioactivity-guided fractionation of the cellular extract and liquid chromatography (LC)–MS analysis identified these natural products, and their structures were elucidated using various spectroscopic techniques and NMR analysis, including high-resolution electrospray ionization mass spectrometry (HRESIMS), ¹H NMR, COSY, HSQC, and HMBC.

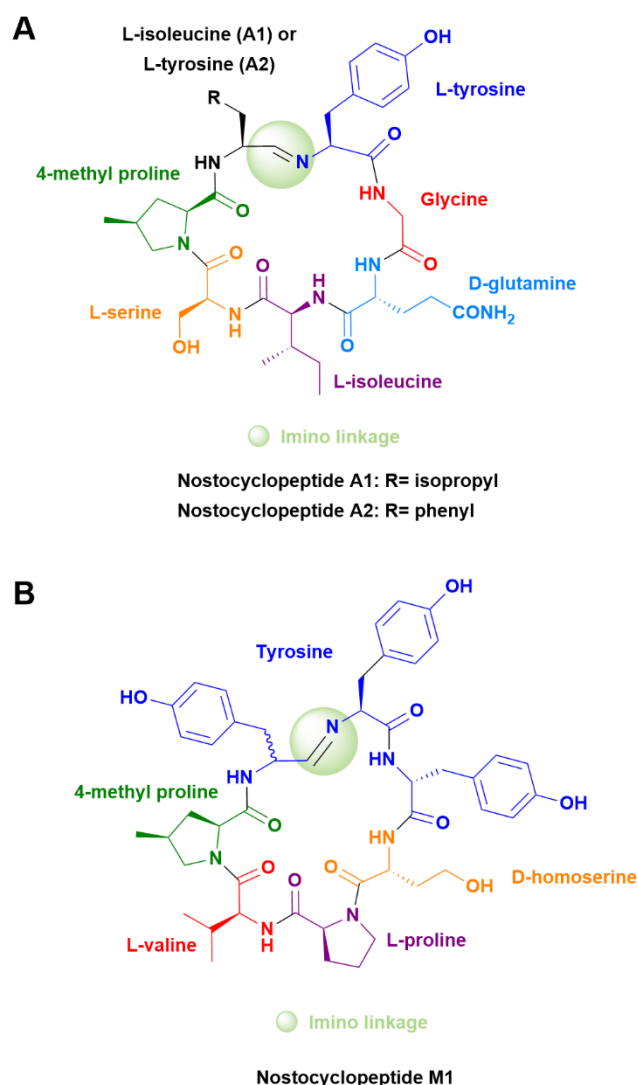


Figure 6. Chemical structures of nostocyclopeptides (A) A1 and A2 and (B) M1

The feeding study by Bobzin and Moore⁷⁷ shed light on the biosynthesis of merocyclophanes, just as it did for all [7.7]paracyclophanes. However, no genes or gene clusters have yet been associated with the biosynthesis of these natural products. The unique structural scaffold of merocyclophanes could potentially be generated using biocatalysts if their biosynthetic pathway were elucidated. A strategy similar to the identification of the cylindrocyclophane gene cluster⁹⁶—possibly using degenerate PCR primers to target putative HMG-CoA synthase homologs—may prove useful. The only known analogs of the merocyclophane core, merocyclophanes C and D, were first reported by May *et al.* in 2017.¹¹⁴

2.8.2. Bioactivity

A high-throughput cytotoxicity screen for freshwater

cyanobacterial strains identified UIC 10110 as producing two antiproliferative agents against the MDA-MB-435 cell line, with IC_{50} values of 1.6 and 0.9 μ M, respectively.¹¹⁴ HRESIMS data indicated that these compounds are structural analogs of merocyclophane A, each containing an additional oxygen atom. Both merocyclophanes C and D were isolated by reversed-phase semi-preparative HPLC and their structures elucidated using ¹H NMR, DEPT with quadrature detection, COSY, HSQC, HMBC, and IR spectroscopy. The absolute configurations were determined using ECD spectroscopy.

2.9. Aeruginosins

Aeruginosin was first isolated from a *Microcystis* strain and was found to be a trypsin and thrombin inhibitor

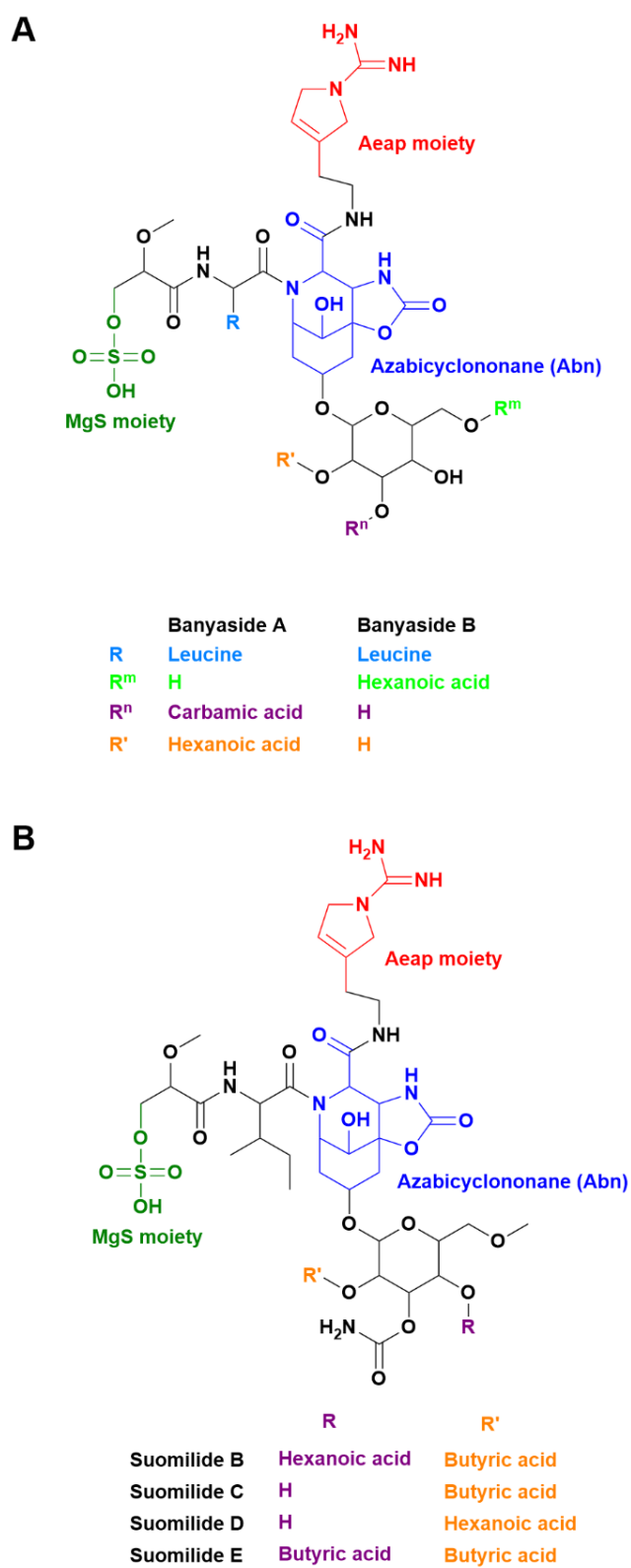


Figure 7. Chemical structures of (A) banyasides A and B and (B) suomilides B–E

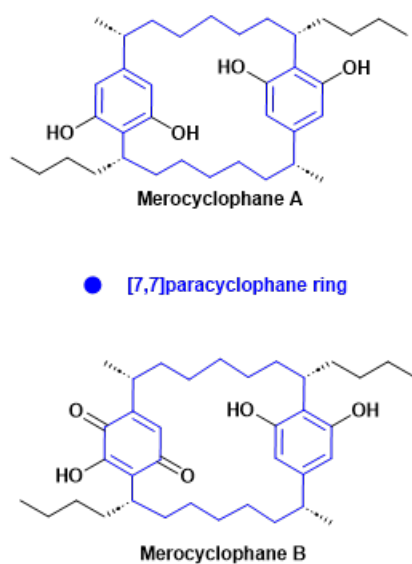


Figure 8. Chemical structures of merocyclophanes A and B

(Figure 9A).¹¹⁵ Aeruginosins are modified linear peptides characterized by a 2-carboxy-6-hydroxyoctahydroindole moiety and a hydroxyphenyl lactic acid derivative. These molecules inhibit serine proteases with varying efficacies.

Two of the more potent members of this family, namely chlorodysynisin A and oscillarin, inhibit trypsin with an IC_{50} value of $0.037 \mu M$.¹¹⁶ It is well known that cyanobacterial strains can produce aeruginosin-type peptides;¹¹⁷⁻¹²¹

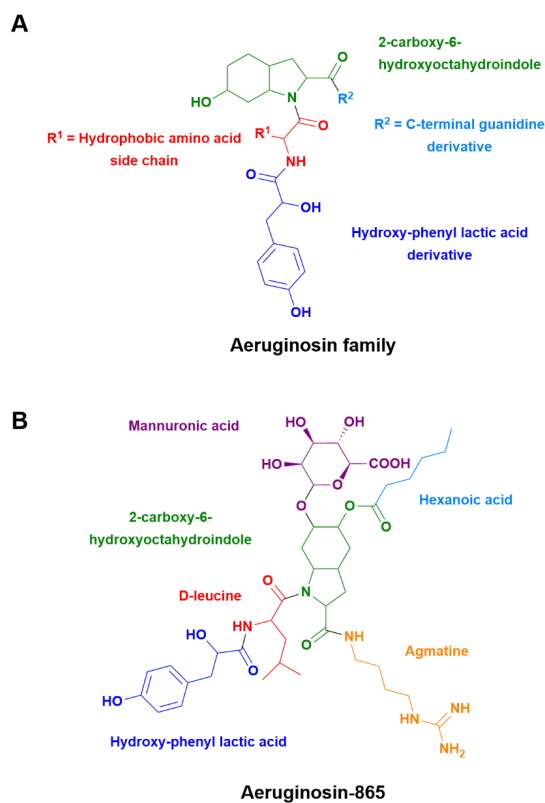


Figure 9. Structures of aeruginosins. (A) Generalized structure of aeruginosin. (B) Chemical structure of aeruginosin-865

however, these peptides had not been isolated from a *Nostoc* strain until 2013, when aeruginosin-865 was first isolated from *Nostoc* sp.¹²² Furthermore, aeruginosin-865 is also the first identified aeruginosin-type peptide to contain both a fatty acid and a carbohydrate moiety (Figure 9B). Biosynthetic investigations on aeruginosins have been successful in other cyanobacterial strains, including *Planktothrix agardhii* CYA126/8¹¹⁷, *Planktothrix rubescens*,¹²³ and three *Microcystis aeruginosa* strains (PCC 7806, NIES-98, and NIES-843).¹¹⁷

2.10. Nostosins A and B

2.10.1. Structure and isolation

Nostosins A and B were isolated from the methanol extract of the biomass of a hydrophilic extract of *Nostoc* sp. strain

FSN.¹²⁴ LC-MS analysis of the extract from a ¹⁵N-labeled culture, compared with an unlabeled culture, provided insights into the structural components, revealing the presence of isoleucine or leucine and argininal or argininol (Figure 10). The complete structures were then elucidated using NMR spectroscopy, including ¹H NMR, ¹H-¹H double-quantum filtered COSY, ¹H-¹H TOCSY, ¹³C and ¹⁵N gradient-selected HSQC, and ¹³C gradient-selected HMBC. Nostosins comprise three moieties: 2-hydroxy-4-(4-hydroxyphenyl)-butanoic acid, *L*-isoleucine, and *L*-argininal (nostosin A) or argininol (nostosin B).

2.10.2. Bioactivity

Trypsin inhibitors typically contain guanidino groups from arginine derivatives, which are crucial for interacting with

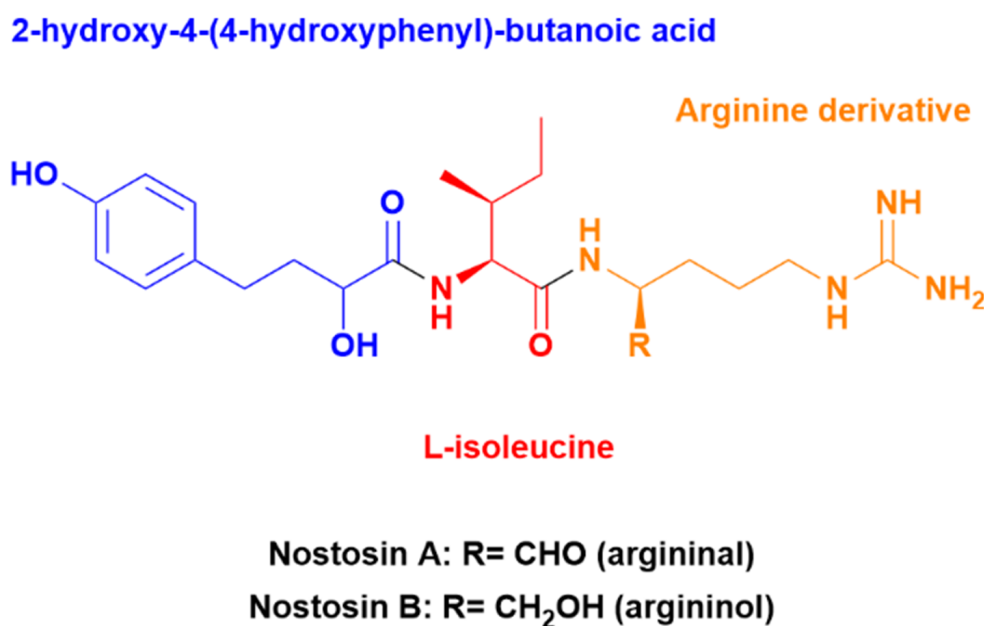


Figure 10. Chemical structures of nostosins A and B

the trypsin active site.¹²⁵ Both nostosins A and B contain arginine derivatives, suggesting that these natural products are potential trypsin inhibitors. Evaluation using a trypsin inhibition assay revealed IC₅₀ values of 0.35 and 55 μM, respectively, against porcine trypsin. For comparison, the commercially available trypsin inhibitor leupeptin exhibited an IC₅₀ value of 0.5 μM.¹²⁶ Notably, nostosin A is the first three-subunit natural product to display trypsin-inhibitory activity comparable to leupeptin. Although no biosynthetic investigations have yet been conducted, elucidating the biosynthesis of nostosins could expand the biocatalytic toolbox for trypsin inhibitors.

3. Conclusion

The *Nostoc* genus has already provided the scientific

community with a plethora of novel natural products exhibiting unique bioactivities. Advances in sequencing technologies and genome mining have significantly improved our understanding of cyanobacterial genomes. Currently, five *Nostoc* genomes are available; five sizable gene clusters have been characterized enzymatically; one gene cluster has been identified in an available genome, another has been partially sequenced; and an additional biosynthetic pathway has been proposed via feeding studies. As more genomic information becomes available, the potential for biocatalysis in these organisms will only grow.

For example, nostotrebin 6 has been identified as a potential AD therapeutic. Elucidating the gene cluster

Table 1. Bioactive secondary metabolites isolated from members of the *Nostoc* genus (post 2005)

Source	Compound	Activity	Structural class
<i>Nostoc</i> 78-12A freshwater) ^{50,57,58,59,63,66}	Nostocarboline ^a	Butyrylcholinesterase, acetylcholinesterase (AChE), and trypsin inhibitors, antiplasmodial, algicidal, antibacterial, antifouling	β -carboline indole alkaloid
<i>Nostoc insulare</i> 53,67,127,128	4,4'-dihydroxybiphenyl ^a 9H-pyrido(3,4-b)indole (a.k.a. norharmane)	Algicidal, antibacterial, antifungal, cytotoxic	Phenolic compound, β -carboline indole alkaloid
	Insulaeptolides A–H ^a	Selective and potent inhibitors of human leukocyte elastase	Peptolide
<i>Nostoc muscorum</i> (terrestrial) ^{129,130}	4-hydroxy-3-methoxy-3-methylbutyl 4-cyano-3-hydroxybenzoate ^a	Antimicrobial	Phenolic compound
	Microcystin variants	-	Cyclic heptapeptide
<i>Nostoc</i> sp. strain CAVN 10 ⁸³	Carbamidocyclophanes A–E ^a	Cytotoxic, antibiotic	Chlorinated paracyclophane
<i>Nostoc commune</i> 131,132,133	β -D-galactofuranosyl-(1 \rightarrow 6)-[β -D-galactofuranosyl-(1 \rightarrow 6)] ₂ - β -D-1,4-anhydrogalactitol ^a	Preventive against desiccation damage in <i>Escherichia coli</i> , preventative against heat inactivation of a phosphogluco-mutase	Galactooligosaccharides
	β -(1 \rightarrow 6)-galactofuranosylated homologs		
	Norharmane	Algicidal, antibacterial, antifungal, cytotoxic	β -carboline indole alkaloid
<i>Nostoc commune</i> NIES-24 (IAM M-13) ¹³⁷	Mycosporine-like amino acids (porphyra-334 derivative, palythine-threonine derivative)	Radical scavenging activities	Mycosporine-like amino acid
<i>Nostoc carneum</i> ¹³³	Norharmane	Algicidal, antibacterial, antifungal, cytotoxic	β -carboline indole alkaloid
<i>Nostoc</i> CCC 537 (Antarctic) ¹³⁴	4-[(5-carboxy-2-hydroxy)-benzyl]-1,10-dihydroxy-3,4,7,11,11-pentamethyloctahydrocyclopenta-naphthalene ^a	Antibacterial	Hybrid terpenoid–polyketide
<i>Nostoc</i> sp. BHU001 ¹³⁵	Microcystin variants	-	Cyclic heptapeptide
<i>Nostoc</i> sp. strain UK18 ¹³⁶	Microcystin variants	-	Cyclic heptapeptide
<i>Nostoc commune</i> NIES-24 (IAM M-13) ¹³⁷	β -carotene β -carotene hydroxyl derivatives (3R)-b-cryptoxanthin, (3R,30R)-zeaxanthin, (2R,3R,30R)-caloxanthin, and (2R,3R,20R,30R)-nostoxanthin β -carotene keto derivatives echinenone and canthaxanthin (3R,20S)-myxol 20-fucoside and (2R,3R,20S)-2-hydroxymyxol 20-fucoside	-	Carotenoid
<i>Nostoc</i> sp. strain Lukešová 27/97 ^{88,89,138}	Nostotrebin 6 ^a	AChE inhibitor, cytotoxic, pro-apoptotic	Bis(cyclopentenedione)
<i>Nostoc</i> sp. (UIC 10022A) ⁹²	Cylindrocyclophanes (A, C, F, A ₁ -A ₄ , C ₁ -C ₄ , F ₄ , and A _{B4}) ^a	Proteasome inhibitor, antiproliferative against several cancer cell lines	Paracyclophane
<i>Nostoc</i> sp. CENA88 (freshwater) ¹³⁹	Microcystin variants	-	Cyclic heptapeptide
<i>Nostoc</i> sp. XSPORK 13A ^{111,140}	Nostocyclopeptide M1 ^a	Antitoxin, hepatocyte drug transporter (OATP1B3 and OATP1B1) inhibitor	Cyclic heptapeptide

(Cont'd...)

Table 1. (Continued)

Source	Compound	Activity	Structural class
<i>Nostoc commune</i> Vauch ¹⁴¹⁻¹⁴⁴	Nostocionone	Antioxidative, antimicrobial, anti-inflammatory, <i>Propionibacterium acnes</i> growth inhibitor	β -ionone derivative
	3-oxo- β -ionone	--	β -ionone derivative
	Scytonemin Reduced scytonemin	Radical scavenging, antioxidative, induces autophagic cell death in the human T-lymphoid cell line Jurkat cells	Indole alkaloid
<i>Nostoc</i> sp. (UIC10062) ^{82,145}	Merocyclophanes A and B ^a	Antiproliferative against the HT-29 human colon cancer cell line	Heteroglycan, paracyclophane
<i>Nostoc</i> sp. 'Macrozamia serpentina 73.1' ¹⁴⁶ <i>Nostoc</i> sp. 'Macrozamia riedlei 65.1' ¹⁴⁷	Nodularin	Protein phosphatase 2A inhibitor	Cyclic pentapeptide
<i>Nostoc calcicola</i> (ISC89) ¹⁴⁷	β -carotene Lycopene Lutein Zeaxanthin	-	Carotenoid
<i>Nostoc</i> sp. CENA89 ¹⁴⁸	Aeruginosin Microcystin	-	Linear peptide, cyclic heptapeptide
<i>Nostoc</i> sp. Lukešová 30/93 (terrestrial) ¹²³	Aeruginosin-865	Anti-inflammatory	Linear peptide
<i>Nostoc</i> sp. (UIC 10274) (freshwater) ⁸⁴	Carbamidocyclophanes A, B, C, F, G	Anti-mycobacterium tuberculosis	Chlorinated paracyclophane
<i>Nostoc</i> sp. strain FSN ¹²⁵	Nostosins A and B	Trypsin inhibitor	Peptide
<i>Nostoc</i> sp. CENA543 ¹⁰² <i>Nostoc edaphicum</i> strain CCNP1411 ¹⁰³	Anabaenopeptins Namalides	Proteases, phosphatases, and carboxypeptidases inhibitors	Cyclic hexapeptides
<i>Nostoc</i> sp. strain UHCC 0450 ¹⁴⁹	Swinholide A	Antifungal	Polyketide
<i>Nostoc</i> sp. IL235 ¹¹³	Banyasides A and B	Protease inhibitors	Nonribosomal peptides

Notes: ^aNovel compounds. Fatty acids and some hydrocarbons are not included. Entries are organized chronologically based on the natural product isolation report. The exception to this occurs if more than one molecule is isolated from an individual strain. The first metabolite listed for the strain will be in chronological order as stated, but any other natural products associated with that strain may be out of order.

responsible for its biosynthesis could enable the production of more potent AD treatments. Additionally, identifying the gene cluster for nostocarboline could enrich the natural-product biosynthesis toolbox by providing a promiscuous tryptophan halogenase. Such an enzyme would not only advance nostocarboline research but could also be combined with other tryptophan-modifying biosynthetic enzymes to generate diverse natural product analogs.

Addressing the potential for natural product analogs from the *Nostoc* genus is a significant opportunity. Several enzymes within these biosynthetic pathways exhibit potential for substrate promiscuity, which could be harnessed to create molecules with rare and

unique structural features. For example, enzymes in the nostopeptolide gene cluster could be exploited to generate novel 4-MePro-containing analogs. Similarly, investigating the substrate flexibility of the unusual R domain of NcpB (from the nostocyclopeptide gene cluster) could yield a library of imino-linked, MePro-containing analogs. Furthermore, exploiting ScyA from the scytonemin cluster could enable catalysis of acyloin condensations between various precursors. Enzymes involved in nostophycin biosynthesis have already demonstrated relaxed substrate specificity, offering further opportunities for the development of novel analogs. Finally, while the exceptional flexibility of cryptophycin

and microcystin biosynthesis has been explored, it remains a promising avenue for expansion. In conclusion, natural product chemists, synthetic biologists, and researchers across disciplines should be enthusiastic about the future potential of the *Nostoc* genus in producing novel bioactive compounds and advancing biocatalytic applications.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Rajesh Viswanathan, Nirmala Krishnamurthy

Visualization: All authors

Writing—original draft: All authors

Writing—review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Castenholz RW. Species usage, concept, and evolution in the cyanobacteria (blue-green algae). *J Phycol.* 1992;28(6):737-745.
doi: 10.1111/j.0022-3646.1992.00737.x
2. Hess WR. Cyanobacterial genomics for ecology and biotechnology. *Curr Opin Microbiol.* 2011;14(5):608-614.
doi: 10.1016/j.mib.2011.07.024
3. Newman DJ, Cragg GM, Snader KM. Natural Products as Sources of New Drugs over the Period 1981–2002. *J Nat Prod.* 2003;66(7):1022-1037.
doi: 10.1021/np030096l
4. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Last 25 Years. *J Nat Prod.* 2007;70(3):461-477.
doi: 10.1021/np068054v
5. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010. *J Nat Prod.* 2012;75(3):311-335.
doi: 10.1021/np200906s
6. Newman D J, Cragg GM. Natural Products as Drugs and Leads to Drugs: An Introduction and Perspective as of the End of 2012. In: Hanessian S, ed. *Natural Products in Medicinal Chemistry*. Weinheim, DE: Wiley-VCH; 2014:1-42.
7. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs from 1981 to 2014. *J Nat Prod.* 2016;79(3):629-661.
doi: 10.1021/acs.jnatprod.5b01055
8. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J Nat Prod.* 2020;83(3):770-803.
doi: 10.1021/acs.jnatprod.9b01285
9. Cragg GM, Newman DJ. Natural products: A continuing source of novel drug leads. *Biochim Biophys Acta.* 2013;1830(6):3670-3695.
doi: 10.1016/j.bbagen.2013.02.008
10. Ganesan A. The impact of natural products upon modern drug discovery. *Curr Opin Chem Biol.* 2008;12(3):306-317.
doi: 10.1016/j.cbpa.2008.03.016
11. Butler MS, Capon RJ, Blaskovich MAT, Henderson IR. Natural product-derived compounds in clinical trials and drug approvals. *Nat Prod Rep.* 2026; 43: 20-88.
doi: 10.1039/D5NP00031A
12. Gerwick WH, Grindberg RV, Coates RC, Engene N, Jones AC, Sorrels CM, et al. Giant Marine Cyanobacteria Produce Exciting Potential Pharmaceuticals. *Microbe Mag.* 2008;3(6):277-284.
doi: 10.1128/microbe.3.277.1
13. Kehr JC, Picchi DG, Dittmann E. Natural product biosyntheses in cyanobacteria: A treasure trove of unique enzymes. *Beilstein J Org Chem.* 2011;7:1622-1635.
doi: 10.3762/bjoc.7.191
14. Patterson GML, Larsen LK, Moore RE. Bioactive natural products from blue-green algae. *J Appl Phycol.* 1994;6(2):151-157.
doi: 10.1007/bf02186069
15. Burja AM, Banaigs B, Abou-Mansour E, Burgess JG, Wright PC. Marine cyanobacteria- a prolific source of natural products. *Tetrahedron.* 2001;57(46):9347-9377.
doi: 10.1016/s0040-4020(01)00931-0
16. Gademann K, Portmann C. Secondary Metabolites from Cyanobacteria: Complex Structures and Powerful Bioactivities. *Curr Org Chem.* 2008;12(4):326-341.

- doi: 10.2174/138527208783743750
17. Chlipala GE, Mo S, Orjala J. Chemodiversity in freshwater and terrestrial cyanobacteria – a source for drug discovery. *Curr Drug Targets*. 2011;12(11):1654-1673.
doi: 10.2174/138945011798109455
18. Dembitsky VM, Řezanka T. Metabolites produced by nitrogen-fixing Nostoc species. *Folia Microbiol*. 2005;50(5):363-391.
doi: 10.1007/bf02931419
19. Jones AC, Gu L, Sorrels CM, Sherman DH, Gerwick WH. New tricks from ancient algae: natural products biosynthesis in marine cyanobacteria. *Curr Opin Chem Biol*. 2009;13(2):216-223.
doi: 10.1016/j.cbpa.2009.02.019
20. Tan LT. Bioactive natural products from marine cyanobacteria for drug discovery. *Phytochemistry*. 2007;68(7):954-979.
doi: 10.1016/j.phytochem.2007.01.012
21. Singh S, Kate BN, Banerjee UC. Bioactive Compounds from Cyanobacteria and Microalgae: An Overview. *Crit Rev Biotechnol*. 2005;25(3):73-95.
doi: 10.1080/07388550500248498
22. Méjean A, Ploux O. A Genomic View of Secondary Metabolite Production in Cyanobacteria. In: *Advances in Botanical Research*. Elsevier; 2013:189-234.
doi: 10.1016/b978-0-12-394313-2.00006-8
23. Larsson J, Nylander JA, Bergman B. Genome fluctuations in cyanobacteria reflect evolutionary, developmental and adaptive traits. *BMC Evol Biol*. 2011;11(1):187.
doi: 10.1186/1471-2148-11-187
24. Tan LT. Pharmaceutical agents from filamentous marine cyanobacteria. *Drug Discov Today*. 2013;18(17-18):863-871.
doi: 10.1016/j.drudis.2013.05.010
25. Hrouzek P, Tomek P, Lukešová A, et al. Cytotoxicity and secondary metabolites production in terrestrial Nostoc strains, originating from different climatic/geographic regions and habitats: Is their cytotoxicity environmentally dependent? *Environ Toxicol*. 2010;26(4):345-358.
doi: 10.1002/tox.20561
26. Micallef ML, Sharma D, Bunn BM, Gerwick L, Viswanathan R, Moffitt MC. Comparative analysis of hapalindole, ambiguine and welwitindolinone gene clusters and reconstitution of indole-isonitrile biosynthesis from cyanobacteria. *BMC Microbiol*. 2014;14(1):213.
doi: 10.1186/s12866-014-0213-7
27. Hillwig ML, Zhu Q, Liu X. Biosynthesis of Ambiguine Indole Alkaloids in Cyanobacterium Fischerella ambigua. *ACS Chem Biol*. 2013;9(2):372-377.
doi: 10.1021/cb400681n
28. Hillwig ML, Fuhrman HA, Ittiamornkul K, Sevco TJ, Kwak DH, Liu X. Identification and Characterization of a Welwitindolinone Alkaloid Biosynthetic Gene Cluster in the Stigonematalean Cyanobacterium Hapalosiphon welwitschii. *Chembiochem*. 2014;15(5):665-669.
doi: 10.1002/cbic.201300794
29. Sharma D. Harnessing genome and building molecules for investigating biosynthetic mechanism in the model group V cyanobacteria. Dissertation. Case Western Reserve University; 2016.
30. Dodds WK, Gudder DA, Mollenhauer D. The ecology of Nostoc. *J Phycol*. 1995;31(1):2-18.
doi: 10.1111/j.0022-3646.1995.00002.x
31. Potts, M. Nostoc. In: Whitton BA, Potts M, editors. *The Ecology of Cyanobacteria*. Dordrecht, NL: Springer; 2002:465-504.
32. Mollenhauer D, Büdel B, Mollenhauer R. *Approaches to species delimitations in the genus Nostoc Vaucher 1803 ex Bornet et Flahault 1888*. *Algol Stud*. 1995;75:189-209.
doi: 10.1127/algol_stud/75/1995/189
33. Komárek J, Anagnostidis K. Modern approach to the classification system of Cyanophytes 4-Nostocales. *Algol Stud*. 1989;73(3):247-345.
34. Micallef ML, D'Agostino PM, Sharma D, Viswanathan R, Moffitt MC. Genome mining for natural product biosynthetic gene clusters in the Subsection V cyanobacteria. *BMC Genom*. 2015;16(1):669.
doi: 10.1186/s12864-015-1855-z
35. Rawat D, Bhargava S. Bioactive Compounds from Nostoc Species. *Curr Res Pharm Sci*. 2011;02:48-54.
36. Schwartz RE, Hirsch CF, Sesin DF, et al. Pharmaceuticals from cultured algae. *J Ind Microbiol Biotechnol*. 1990;5(2-3):113-123.
doi: 10.1007/bf01573860
37. Parker CN, Ottl J, Gabriel D, Zhang JH. Advances in Biological Screening for Lead Discovery. In: Buss AD and Butler MS, eds. *Natural Product Chemistry for Drug Discovery*, Cambridge, UK: Royal Society of Chemistry; 2010: 243-271.
38. Okino T, Qi S, Matsuda H, Murakami M, Yamaguchi K. Nostopeptins A and B, Elastase Inhibitors from the Cyanobacterium Nostoc minutum. *J Nat Prod*. 1997;60(2):158-161.
doi: 10.1021/np960649a
39. Banker R, Carmeli S. Tenuocyclamides A–D, Cyclic Hexapeptides from the Cyanobacterium Nostoc spongiaeforme var. tenue. *J Nat Prod*. 1998;61(10):1248-1251.

- p>doi: 10.1021/np980138j
40. Kajiya SI, Kanzaki H, Kawazu K, Kobayashi A. Nostofungicidine, an antifungal lipopeptide from the field-grown terrestrial blue-green alga *Nostoc commune*. *Tetrahedron Lett.* 1998;39(22):3737-3740.
doi: 10.1016/s0040-4039(98)00573-5
41. Sivonen K, Carmichael WW, Namikoshi M, Rinehart KL, Dahlem AM, Niemelä SI. Isolation and characterization of hepatotoxic microcystin homologs from the filamentous freshwater cyanobacterium *Nostoc* sp. strain 152. *Appl Environ Microbiol.* 1990;56(9):2650-2657.
doi: 10.1128/aem.56.9.2650-2657.1990
42. Oksanen I, Jokela J, Fewer DP, Wahlsten M, Rikkinen J, Sivonen K. Discovery of Rare and Highly Toxic Microcystins from Lichen-Associated Cyanobacterium *Nostoc* sp. Strain IO-102-I. *Appl Environ Microbiol.* 2004;70(10):5756-5763.
doi: 10.1128/aem.70.10.5756-5763.2004
43. Chaganty S, Golakoti T, Heltzel C, Moore RE, Yoshida WY. Isolation and Structure Determination of Cryptophycins 38, 326, and 327 from the Terrestrial Cyanobacterium *Nostoc* sp. GSV 224. *J Nat Prod.* 2004;67(8):1403-1406.
doi: 10.1021/np0499665
44. Smith CD, Zhang X, Mooberry SL, Patterson GM, Moore RE. Cryptophycin: a new antimicrotubule agent active against drug-resistant cells. *Cancer Res.* 1994;54(14):3779-3784.
45. Shih C, Teicher B. Cryptophycins: a novel class of potent antimitotic antitumor depsipeptides. *Curr Pharm Des.* 2001;7(13):1259-1276.
doi: 10.2174/1381612013397474
46. Kanekiyo K, Lee JB, Hayashi K, *et al.* Isolation of an Antiviral Polysaccharide, Nostoflan, from a Terrestrial Cyanobacterium, *Nostoc flagelliforme*. *J Nat Prod.* 2005;68(7):1037-1041.
doi: 10.1021/np050056c
47. Kanekiyo K, Hayashi K, Takenaka H, Lee JB, Hayashi T. Anti-herpes Simplex Virus Target of an Acidic Polysaccharide, Nostoflan, from the Edible Blue-Green Alga *Nostoc flagelliforme*. *Biol Pharm Bull.* 2007;30(8):1573-1575.
doi: 10.1248/bpb.30.1573
48. Fidor A, Konkel R, Mazur-Marzec H. Bioactive peptides produced by cyanobacteria of the genus *Nostoc*: a review. *Mar Drugs.* 2019;17(10):561.
doi: 10.3390/md17100561
49. Thuan NH, An TT, Shrestha A, Canh NX, Sohng JK, Dhakal D. Recent advances in exploration and biotechnological production of bioactive compounds in three cyanobacterial genera: *Nostoc*, *Lyngbya*, and *Microcystis*. *Front Chem.* 2019;7:604.
doi: 10.3389/fchem.2019.00604
50. Becher PG, Beuchat J, Gademann K, Jüttner F. Nostocarboline: isolation and synthesis of a new cholinesterase inhibitor from *NosTOC78-12A*. *J Nat Prod.* 2005;68(12):1793-1795.
doi: 10.1021/np050312l
51. Flores E, Wolk CP. Production, by filamentous, nitrogen-fixing cyanobacteria, of a bacteriocin and of other antibiotics that kill related strains. *Arch Microbiol.* 1986;145(3):215-219.
doi: 10.1007/bf00443648
52. Larsen LK, Moore RE, Patterson GML. β -Carbolines from the Blue-Green Alga *Dichothrix baueriana*. *J Nat Prod.* 1994;57(3):419-421.
doi: 10.1021/np50105a018
53. Volk RB. Screening of microalgal culture media for the presence of algicidal compounds and isolation and identification of two bioactive metabolites, excreted by the cyanobacteria *Nostoc insulare* and *Nodularia harveyana*. *J Appl Phycol.* 2005;17(4):339-347.
doi: 10.1007/s10811-005-7292-7
54. Allen JRF, Holmstedt BR. The simple β -carboline alkaloids. *Phytochemistry.* 1980;19(8):1573-1582.
doi: 10.1016/s0031-9422(00)83773-5
55. Cao R, Peng W, Wang Z, Xu A. β -Carboline Alkaloids: Biochemical and Pharmacological Functions. *Curr Med Chem.* 2007;14(4):479-500.
doi: 10.2174/092986707779940998
56. Gademann K. Natural product hybrids. *CHIMIA.* 2006;60(12):841.
doi: 10.2533/chimia.2006.841
57. Becher PG, Baumann HI, Gademann K, Jüttner F. The cyanobacterial alkaloid nostocarboline: an inhibitor of acetylcholinesterase and trypsin. *J Appl Phycol.* 2008;21(1):103-110.
doi: 10.1007/s10811-008-9335-3
58. Blom JF, Brüttsch T, Barbaras D, *et al.* Potent algicides based on the cyanobacterial alkaloid nostocarboline. *Org Lett.* 2006;8(4):737-740.
doi: 10.1021/ol052968b
59. Gademann K. Cyanobacterial natural products for the inhibition of biofilm formation and biofouling. *CHIMIA.* 2007;61(6):373.
doi: 10.2533/chimia.2007.373
60. Ofek K, Soreq H. Cholinergic involvement and manipulation approaches in multiple system disorders. *Chem Biol Interact.* 2013;203(1):113-119.
doi: 10.1016/j.cbi.2012.07.007

61. Lilienfeld S. Galantamine - a Novel Cholinergic Drug with a Unique Dual Mode of Action for the Treatment of Patients with Alzheimer's Disease. *CNS Drug Rev.* 2002;8(2):159-176.
doi: 10.1111/j.1527-3458.2002.tb00221.x
62. Scarpini E, Schelterns P, Feldman H. Treatment of Alzheimer's disease; current status and new perspectives. *Lancet Neurol.* 2003;2(9):539-547.
doi: 10.1016/s1474-4422(03)00502-7
63. Barbaras D, Kaiser M, Brun R, Gademann K. Potent and selective antiplasmodial activity of the cyanobacterial alkaloid nostocarboline and its dimers. *Bioorg Med Chem Lett.* 2008;18(15):4413-4415.
doi: 10.1016/j.bmcl.2008.06.049
64. Portmann C, Prestinari C, Myers T, Scharte J, Gademann K. Directed biosynthesis of phytotoxic alkaloids in the cyanobacterium *Nostoc* 78-12A. *Chembiochem.* 2009;10(5):889-895.
doi: 10.1002/cbic.200800837
65. Bonazzi S, Barbaras D, Patiny L, *et al.* Antimalarial and antitubercular nostocarboline and eudistomin derivatives: Synthesis, in vitro and in vivo biological evaluation. *Bioorg Med Chem.* 2010;18(4):1464-1476.
doi: 10.1016/j.bmc.2010.01.013
66. Locher HH, Ritz D, Pfaff P, *et al.* Dimers of Nostocarboline with Potent Antibacterial Activity. *Chemotherapy.* 2010;56(4):318-324.
doi: 10.1159/000320033
67. Mehner C, Müller D, Kehraus S, Hautmann S, Gütschow M, König GM. New Peptolides from the Cyanobacterium *Nostoc insulare* as Selective and Potent Inhibitors of Human Leukocyte Elastase. *Chembiochem.* 2008;9(16):2692-2703.
doi: 10.1002/cbic.200800415
68. Weckesser J, Martin C, Jakobi C. Cyanopeptolins, depsipeptides from cyanobacteria. *Syst Appl Microbiol.* 1996;19(2):133-138.
doi: 10.1016/s0723-2020(96)80038-5
69. Martin C, Oberer L, Ino T, König WA, Busch M, Weckesser J. Cyanopeptolins, new depsipeptides from the cyanobacterium *Microcystis* sp. pcc 7806. *J Antibiot.* 1993;46(10):1550-1556.
doi: 10.7164/antibiotics.46.1550
70. Welker M, Von Döhren H. Cyanobacterial peptides - Nature's own combinatorial biosynthesis. *FEMS Microbiol Rev.* 2006;30(4):530-563.
doi: 10.1111/j.1574-6976.2006.00022.x
71. Rouhiainen L, Paulin L, Suomalainen S, *et al.* Genes encoding synthetases of cyclic depsipeptides, anabaenopeptolides, in *Anabaena* strain 90. *Mol Microbiol.* 2000;37(1):156-167.
doi: 10.1046/j.1365-2958.2000.01982.x
72. Cram DJ, Steinberg H. Macro Rings. I. Preparation and spectra of the paracyclophanes. *J Am Chem Soc.* 1951;73(12):5691-5704.
doi: 10.1021/j⁰¹¹⁵⁶059
73. Martins TP, Rouger C, Glasser NR, *et al.* Chemistry, bioactivity and biosynthesis of cyanobacterial alkylresorcinols. *Nat Prod Rep.* 2019;36(10):1437-1461.
doi: 10.1039/c8np00080h
74. Koga K, Odashima K. Cyclophanes as hosts for aromatic and aliphatic guests. *J Incl Phenom Macrocycl Chem.* 1989;7(1):53-60.
doi: 10.1007/bf01112782
75. Moore BS, Chen JL, Patterson GML, *et al.* [7.7] Paracyclophanes from blue-green algae. *J Am Chem Soc.* 1990;112(10):4061-4063.
doi: 10.1021/j00166066
76. Bobzin SC, Moore RE. Biosynthetic origin of [7.7] paracyclophanes from cyanobacteria. *Tetrahedron.* 1993;49(35):7615-7626.
doi: 10.1016/s0040-4020(01)87237-9
77. Gulder T, Baran PS. Strained cyclophane natural products: Macrocyclization at its limits. *Nat Prod Rep.* 2012;29(8):899.
doi: 10.1039/c2np20034a
78. Moore BS, Chen JL, Patterson GML, Moore RE. Structures of cylindrocyclophanes a-f. *Tetrahedron.* 1992;48(15):3001-3006.
doi: 10.1016/s0040-4020(01)92244-6
79. Chen JL, Moore RE, Patterson GML. Structures of nostocyclophanes A-D. *J Org Chem.* 1991;56(14):4360-4364.
doi: 10.1021/jo00014a008
80. Ploutno A, Carmeli S. Nostocycline A, a Novel Antimicrobial Cyclophane from the Cyanobacterium *Nostoc* sp. *J Nat Prod.* 2000;63(11):1524-1526.
doi: 10.1021/np0002334
81. Kang HS, Santarsiero BD, Kim H, *et al.* Merocyclophanes A and B, antiproliferative cyclophanes from the cultured terrestrial Cyanobacterium *Nostoc* sp. *Phytochemistry.* 2012;79:109-115.
doi: 10.1016/j.phytochem.2012.03.005
82. Bui HTN, Jansen R, Pham HTL, Mundt S. Carbamidocyclophanes A-E, Chlorinated Paracyclophanes with Cytotoxic and Antibiotic Activity from the Vietnamese Cyanobacterium *Nostoc* sp. *J Nat Prod.* 2007;70(4):499-503.
doi: 10.1021/np060324m
83. Luo S, Kang HS, Kronic A, *et al.* Carbamidocyclophanes F and G with anti-*Mycobacterium tuberculosis* activity

- from the cultured freshwater cyanobacterium *Nostoc* sp. *Tetrahedron Lett.* 2013;55(3):686-689.
doi: 10.1016/j.tetlet.2013.11.112
84. Zabolotneva AA, Shatova OP, Sadova AA, Shestopalov AV, Roumiantsev SA. An overview of Alkylresorcinols Biological Properties and Effects. *J Nutr Metab.* 2022;2022:1-12.
doi: 10.1155/2022/4667607
85. Preisitsch M, Harmrolfs K, Pham HT, *et al.* Anti-MRSA-acting carbamidocyclophanes H-L from the Vietnamese cyanobacterium *Nostoc* sp. CAVN2. *J Antibiot.* 2015;68(3):165-177.
doi: 10.1038/ja.2014.118
86. Preisitsch M, Heiden S, Beerbaum M, *et al.* Effects of Halide Ions on the Carbamidocyclophane Biosynthesis in *Nostoc* sp. CAVN2. *Mar Drugs.* 2016;14(1):21.
doi: 10.3390/md14010021
87. Zelík P, Lukešová A, Voloshko LN, Štys D, Kopecký J. Screening for acetylcholinesterase inhibitory activity in cyanobacteria of the genus *Nostoc*. *J Enzyme Inhib Med Chem.* 2009;24(2):531-536.
doi: 10.1080/14756360802234836
88. Zelík P, Lukešová A, Čejka J, *et al.* Nostotrebins 6, a bis(cyclopentenenedione) with cholinesterase inhibitory activity isolated from *Nostoc* sp. str. Lukešová 27/97. *J Enzyme Inhib Med Chem.* 2010;25(3):414-420.
doi: 10.3109/14756360903213481
89. Cheel J, Bogdanová K, Ignatova S, *et al.* Dimeric cyanobacterial cyclopent-4-ene-1,3-dione as selective inhibitor of Gram-positive bacteria growth: Bio-production approach and preparative isolation by HPLC. *Algal Res.* 2016;18:244-249.
doi: 10.1016/j.algal.2016.06.022
90. Kossack R, Breinlinger S, Nguyen T, *et al.* Nostotrebins 6 Related Cyclopentenenediones and δ -Lactones with Broad Activity Spectrum Isolated from the Cultivation Medium of the Cyanobacterium *Nostoc* sp. CBT1153. *J Nat Prod.* 2020;83(2):392-400.
doi: 10.1021/acs.jnatprod.9b00885
91. Chlipala GE, Sturdy M, Kronic A, *et al.* Cyliindrocyclophanes with Proteasome Inhibitory Activity from the Cyanobacterium *Nostoc* sp. *J Nat Prod.* 2010;73(9):1529-1537.
doi: 10.1021/np100352e
92. Voges D, Zwickl P, Baumeister W. The 26S proteasome: a molecular machine designed for controlled proteolysis. *Annu Rev Biochem.* 1999;68(1):1015-1068.
doi: 10.1146/annurev.biochem.68.1.1015
93. Berthold D, Breit B. Total Synthesis of (–)-Cyliindrocyclophane F: A yardstick for probing new catalytic C–C Bond-Forming methodologies. *Chemistry.* 2018;24(63):16770-16773.
doi: 10.1002/chem.201804585
94. Bosse AT, Hunt LR, Suarez CA, *et al.* Total synthesis of (–)-cyliindrocyclophane A facilitated by C–H functionalization. *Science.* 2024;386(6722):641-646.
doi: 10.1126/science.adp2425
95. Nakamura H, Hamer HA, Sirasani G, Balskus EP. Cyliindrocyclophane biosynthesis involves functionalization of an unactivated carbon center. *J Am Chem Soc.* 2012;134(45):18518-18521.
doi: 10.1021/ja308318p
96. Balskus EP, Nakamura H. Using chemical knowledge to uncover new biological function: Discovery of the cyliindrocyclophane biosynthetic pathway. *Synlett.* 2013;24(12):1464-1470.
doi: 10.1055/s-0033-1338879
97. Nakamura H, Wang JX, Balskus EP. Assembly line termination in cyliindrocyclophane biosynthesis: discovery of an editing type II thioesterase domain in a type I polyketide synthase. *Chem Sci.* 2015;6(7):3816-3822.
doi: 10.1039/c4sc03132f
98. Nakamura H, Schultz EE, Balskus EP. A new strategy for aromatic ring alkylation in cyliindrocyclophane biosynthesis. *Nat Chem Biol.* 2017;13(8):916-921.
doi: 10.1038/nchembio.2421
99. Moore RE. Cyclic peptides and depsipeptides from cyanobacteria: A review. *J Ind Microbiol.* 1996;16(2):134-143.
doi: 10.1007/bf01570074
100. Sainis I, Fokas D, Vareli K, Tzakos A, Kounnis V, Briasoulis E. Cyanobacterial cyclopeptides as lead compounds to novel targeted cancer drugs. *Mar Drugs.* 2010;8(3):629-657.
doi: 10.3390/md8030629
101. Shishido TK, Jokela J, Fewer DP, Wahlsten M, Fiore MF, Sivonen K. Simultaneous Production of Anabaenopeptins and Namalides by the Cyanobacterium *Nostoc* sp. CENA543. *ACS Chem Biol.* 2017;12(11):2746-2755.
doi: 10.1021/acschembio.7b00570
102. Konkel R, Grabski M, Ceglowska M, Wiczerzak E, Węgrzyn G, Mazur-Marzec H. Anabaenopeptins from *Nostoc edaphicum* CCNP1411. *Int J Environ Res Public Health.* 2022;19(19):12346.
doi: 10.3390/ijerph191912346
103. Golakoti T, Yoshida WY, Chaganty S, Moore RE. Isolation and Structure Determination of Nostocyclopeptides A1 and A2 from the Terrestrial Cyanobacterium *Nostoc* sp. ATCC53789. *J Nat Prod.* 2001;64(1):54-59.

- doi: 10.1021/np000316k
104. Bok JW, Hoffmeister D, Maggio-Hall LA, Murillo R, Glasner JD, Keller NP. Genomic mining for *Aspergillus* natural products. *Chem Biol.* 2006;13(1):31-37.
doi: 10.1016/j.chembiol.2005.10.008
105. Corre C, Challis GL. New natural product biosynthetic chemistry discovered by genome mining. *Nat Prod Rep.* 2009;26(8):977.
doi: 10.1039/b713024b
106. Kalaitzis JA, Lauro FM, Neilan BA. Mining cyanobacterial genomes for genes encoding complex biosynthetic pathways. *Nat Prod Rep.* 2009;26(11):1447.
doi: 10.1039/b817074f
107. Osbourn A. Secondary metabolic gene clusters: evolutionary toolkits for chemical innovation. *Trends Genet.* 2010;26(10):449-457.
doi: 10.1016/j.tig.2010.07.001
108. Cimermanic P, Medema MH, Claesen J, *et al.* Insights into Secondary Metabolism from a Global Analysis of Prokaryotic Biosynthetic Gene Clusters. *Cell.* 2014;158(2):412-421.
doi: 10.1016/j.cell.2014.06.034
109. Jokela J, Herfindal L, Wahlsten M, *et al.* A Novel Cyanobacterial Nostocyclopeptide is a Potent Antitoxin against Microcystins. *Chembiochem.* 2010;11(11):1594-1599.
doi: 10.1002/cbic.201000179
110. Herfindal L, Myhren L, Kleppe R, *et al.* Nostocyclopeptide-M1: a potent, nontoxic inhibitor of the hepatocyte drug transporters OATP1B3 and OATP1B1. *Mol Pharm.* 2011;8(2):360-367.
doi: 10.1021/mp1002224.
111. Pluotno A, Carmeli S, Banyasin A and banyasides A and B, three novel modified peptides from a water bloom of the cyanobacterium *Nostoc* sp. *Tetrahedron.* 2005;61(3):575-583.
doi: 10.1016/j.tet.2004.11.016.
112. Fujii, K, Sivonen, K, Adachi, K, *et al.* Comparative study of toxic and non-toxic cyanobacterial products: A novel glycoside, suomilide, from non-toxic *Nodularia spumigena* HKVV. *Tetrahedron Lett.* 1997;38(31):5529-5532. doi: 10.1016/S0040-4039(97)01193-3
113. Schneider YK, Liaimer A, Isaksson J, *et al.* Four new suomilides isolated from the cyanobacterium *Nostoc* sp. KVJ20 and proposal of their biosynthetic origin. *Front Microbiol.* 2023;20(14):1130018.
doi: 10.3389/fmicb.2023.1130018.
114. May DS, Chen WL, Lantvit DD, *et al.* Merocyclophanes C and D from the Cultured Freshwater Cyanobacterium *Nostoc* sp. (UIC 10110). *J Nat Prod.* 2017;80(4):1073-1080.
doi: 10.1021/acs.jnatprod.6b01175
115. Banker R, Carmeli S. Inhibitors of serine proteases from a waterbloom of the cyanobacterium *Microcystis* sp. *Tetrahedron.* 1999;55(35):10835-10844.
doi: 10.1016/s0040-4020(99)00597-9
116. Ersmark K, Del Valle JR, Hanessian S. Chemistry and biology of the aeruginosin family of serine protease inhibitors. *Angew Chem Int Ed Engl.* 2007;47(7):1202-1223.
doi: 10.1002/anie.200605219
117. Ishida K, Welker M, Christiansen G, *et al.* Plasticity and evolution of aeruginosin biosynthesis in cyanobacteria. *Appl Environ Microbiol.* 2009;75(7):2017-2026.
doi: 10.1128/aem.02258-08
118. Raveh A, Carmeli S. Two novel biological active modified peptides from the cyanobacterium *Microcystis* sp. *Phytochem Lett.* 2008;2(1):10-14.
doi: 10.1016/j.phytol.2008.10.002
119. Elkobi-Peer S, Faigenbaum R, Carmeli S. Bromine- and Chlorine-Containing Aeruginosins from *Microcystis aeruginosa* Bloom Material Collected in Kibbutz Geva, Israel. *J Nat Prod.* 2012;75(12):2144-2151.
doi: 10.1021/np3005612
120. Elkobi-Peer S, Singh RK, Mohapatra TM, Tiwari SP, Carmeli S. Aeruginosins from a *Microcystis* sp. Bloom Material Collected in Varanasi, India. *J Nat Prod.* 2013;76(6):1187-1190.
doi: 10.1021/np4001152
121. Adiv S, Carmeli S. Protease Inhibitors from *Microcystis aeruginosa* Bloom Material Collected from the Dalton Reservoir, Israel. *J Nat Prod.* 2013;76(12):2307-2315.
doi: 10.1021/np4006844
122. Kapuścik A, Hrouzek P, Kuzma M, *et al.* Novel Aeruginosin-865 from *Nostoc* sp. as a Potent Anti-inflammatory Agent. *ChemBioChem.* 2013;14(17):2329-2337.
doi: 10.1002/cbic.201300246
123. Rounge TB, Rohrlack T, Nederbragt AJ, Kristensen T, Jakobsen KS. A genome-wide analysis of nonribosomal peptide synthetase gene clusters and their peptides in a *Planktothrix rubescens* strain. *BMC Genomics.* 2009;10(1):396.
doi: 10.1186/1471-2164-10-396
124. Liu L, Jokela J, Wahlsten M, *et al.* Nostosins, Trypsin Inhibitors Isolated from the Terrestrial Cyanobacterium *Nostoc* sp. Strain FSN. *J Nat Prod.* 2014;77(8):1784-1790.
doi: 10.1021/np500106w

125. Iyaguchi D, Kawano S, Takada K, Toyota E. Structural basis for the design of novel Schiff base metal chelate inhibitors of trypsin. *Bioorg Med Chem*. 2010;18(6):2076-2080.
doi: 10.1016/j.bmc.2010.02.016
126. Aoyagi T, Miyata S, Nanbo M, Kojima F, Matsuzaki M. Biological activities of Leupeptins. *J Antibiot*. 1969;22(11):558-568.
doi: 10.7164/antibiotics.22.558
127. Volk RB, Mundt S. Cytotoxic and non-cytotoxic exometabolites of the cyanobacterium *Nostoc insulare*. *J Appl Phycol*. 2006;19(1):55-62.
doi: 10.1007/s10811-006-9110-2
128. Volk RB, Furkert FH. Antialgal, antibacterial and antifungal activity of two metabolites produced and excreted by cyanobacteria during growth. *Microbiol Res*. 2006;161(2):180-186.
doi: 10.1016/j.micres.2005.08.005
129. El-Sheekh MM, Osman ME, Dyab MA, Amer MS. Production and characterization of antimicrobial active substance from the cyanobacterium *Nostoc muscorum*. *Environ Toxicol Pharmacol*. 2006;21(1):42-50.
doi: 10.1016/j.etap.2005.06.006
130. Oudra B, Andaloussi MDE, Vasconcelos VM. Identification and quantification of microcystins from a *Nostoc muscorum* bloom occurring in Oukaïmeden River (High-Atlas mountains of Marrakech, Morocco). *Environ Monit Assess*. 2008;149(1-4):437-444.
doi: 10.1007/s10661-008-0220-y
131. Wieneke R, Klein S, Geyer A, Loos E. Structural and functional characterization of galactooligosaccharides in *Nostoc commune*: β -D-galactofuranosyl-(1 \rightarrow 6)-[β -D-galactofuranosyl-(1 \rightarrow 6)] β -D-1,4-anhydrogalactitol and β -(1 \rightarrow 6)-galactofuranosylated homologues. *Carbohydr Res*. 2007;342(18):2757-2765.
doi: 10.1016/j.carres.2007.09.003
132. Volk RB. Screening of microalgae for species excreting norharmane, a manifold biologically active indole alkaloid. *Microbiol Res*. 2008;163(3):307-313.
doi: 10.1016/j.micres.2006.06.002
133. Nazifi E, Wada N, Yamaba M, Asano T, Nishiuchi T, Matsugo S, Sakamoto T. Glycosylated porphyra-334 and palythine-threonine from the terrestrial cyanobacterium *Nostoc commune*. *Mar Drugs*. 2013;11(9):3124-3154.
doi: 10.3390/md11093124
134. Asthana RK, Deepali, Tripathi MK, et al. Isolation and identification of a new antibacterial entity from the Antarctic cyanobacterium *Nostoc CCC 537*. *J Appl Phycol*. 2008;21(1):81-88.
doi: 10.1007/s10811-008-9328-2
135. Bajpai R, Sharma NK, Lawton LA, Edwards C, Rai AK. Microcystin producing cyanobacterium *Nostoc* sp. *BHU001* from a pond in India. *Toxicon*. 2009;53(5):587-590.
doi: 10.1016/j.toxicon.2009.01.023
136. Kaasalainen U, Jokela J, Fewer DP, Sivonen K, Rikkinen J. Microcystin production in the tripartite cyanolichen *Peltigera leucophlebia*. *Mol Plant Microbe Interact*. 2009;22(6):695-702.
doi: 10.1094/MPMI-22-6-0695
137. Takaichi S, Maoka T, Mochimaru M. Unique carotenoids in the terrestrial cyanobacterium *Nostoc commune* NIES-24: 2-hydroxymyxol 2'-fucoside, nostoxanthin and canthaxanthin. *Curr Microbiol*. 2009;59(4):413-419.
doi: 10.1007/s00284-009-9453-4
138. Vacek J, Hrbáč J, Kopecký J, Vostálová J. Cytotoxicity and Pro-Apoptotic Activity of 2,2'-Bis[4,5-bis(4-hydroxybenzyl)-2-(4-hydroxyphenyl)cyclopent-4-en-1,3-dione], a Phenolic Cyclopentenone Isolated from the Cyanobacterium Strain *Nostoc* sp. str. Lukešová 27/97. *Molecules*. 2011;16(5):4254-4263.
doi: 10.3390/molecules16054254
139. Genuário DB, Silva-Stenico ME, Welker M, Beraldo Moraes LA, Fiore ME. Characterization of a microcystin and detection of microcystin synthetase genes from a Brazilian isolate of *Nostoc*. *Toxicon*. 2010;55(4):846-854.
doi: 10.1016/j.toxicon.2009.12.001
140. Herfindal L, Myhren L, Kleppe R, et al. Nostocyclopeptide-M1: a potent, nontoxic inhibitor of the hepatocyte drug transporters OATP1B3 and OATP1B1. *Mol Pharm*. 2011;8(2):360-367.
doi: 10.1021/mp1002224
141. Ninomiya M, Satoh H, Yamaguchi Y, Takenaka H, Koketsu M. Antioxidative activity and chemical constituents of edible terrestrial alga *Nostoc commune* Vauch. *Biosci Biotechnol Biochem*. 2011;75(11):2175-2177.
doi: 10.1271/bbb.110466
142. Itoh T, Tsuchida A, Muramatsu Y, et al. Antimicrobial and anti-inflammatory properties of nostocionone isolated from *Nostoc commune* Vauch and its derivatives against *Propionibacterium acnes*. *Anaerobe*. 2014;27:56-63.
doi: 10.1016/j.anaerobe.2014.03.006
143. Matsui K, Nazifi E, Hirai Y, Wada N, Matsugo S, Sakamoto T. The cyanobacterial UV-absorbing pigment scytonemin displays radical-scavenging activity. *J Gen Appl Microbiol*. 2012;58(2):137-144.
doi: 10.2323/jgam.58.137
144. Itoh T, Tsuzuki R, Tanaka T, et al. Reduced scytonemin isolated from *Nostoc commune* induces autophagic cell

death in human T-lymphoid cell line Jurkat cells. *Food Chem Toxicol.* 2013;60:76-82.

doi: 10.1016/j.fct.2013.07.016

145. Jensen S, Petersen BO, Omarsdottir S, Paulsen BS, Duus JØ, Olafsdottir ES. Structural characterisation of a complex heteroglycan from the cyanobacterium *Nostoc commune*. *Carbohydrate Polymers.* 2012;91(1):370-376.

doi: 10.1016/j.carbpol.2012.08.063

146. Gehringer MM, Adler L, Roberts AA, *et al.* Nodularin, a cyanobacterial toxin, is synthesized in planta by symbiotic *Nostoc* sp. *ISME J.* 2012;6(10):1834-1847.

doi: 10.1038/ismej.2012.25

147. Hashtroudi MS, Shariatmadari Z, Riahi H, Ghassempour A.

Analysis of *Anabaena vaginicola* and *Nostoc calcicola* from Northern Iran, as rich sources of major carotenoids. *Food Chem.* 2013;136(3-4):1148-1153.

doi: 10.1016/j.foodchem.2012.09.055

148. Silva-Stenico M, Kaneno R, Zambuzi F, Vaz M, Alvarenga D, Fiore M. Natural Products from Cyanobacteria with Antimicrobial and Antitumor Activity. *Curr Pharm Biotechnol.* 2014;14(9):820-828.

doi: 10.2174/1389201014666131227114846

149. Humisto A, Jokela J, Liu L, *et al.* The Swinholide Biosynthesis Gene Cluster from a Terrestrial Cyanobacterium, *Nostoc* sp. Strain UHCC 0450. *Appl Environ Microbiol.* 2018;84(3):e02321-17.

doi: 10.1128/AEM.02321-17