SECONDARY METABOLITES OF CYANOBACTERIA *NOSTOC* SP.

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Abstract Cyanobacteria attracted much attention recently because of their secondary metabolites with potent biological activities and unusual structures. This paper reviews some recent studies on the isolation, structural, elucidation and biological activities of the bioactive compounds from cyanobacteria *Nostoc* species.

Key words: cyanobacteria, antimitotic, antifungal, bioactive secondary metabolites, *Nostoc* sp.

INTRODUCTION

Cyanobacteria comprise the oldest group of oxygen-evolving photosynthetic organisms on earth, and have for long been known to possess unique protection mechanisms against UV-irradiation and desiccation stress.

Recently, the secondary metabolites of cyanobacteria have drawn attention because of their unique structural features and biological activities.

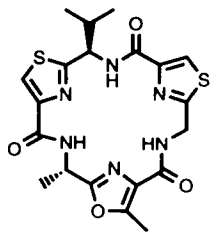
Nostoc species are filamentous cyanobacteria which are widely distributed in lakes, rivers, and soil surfaces throughout the world. This alga is often embedded within a dense glycan sheath and has desiccation tolerance. A field study of this alga enabled us to find several unique behaviors in its ecosystem, and the identification of unknown signaling factors for the cross talk with other organisms living in the habitat, and for establishing a desirable ecosystem, could be attractive research objectives.

A few researches on the protective mechanisms of this alga against abiotic environmental stresses such as drought (Potts et al., 1985, 1986, 1987, 1996; Angeloni et al., 1986, 1987; Olie et al., 1986; Xie et al., 1995), UV-irradiation (Scherer et al., 1988; Proteau et al., 1993; Sinha et al., 1996; Ehling-schulz et al., 1997) have been conducted, and a small number of reports on the secondary metabolites have been published. In this paper the authors introduce some recent studies of the bioactive compounds from cyanobacteria *Nostoc* species.

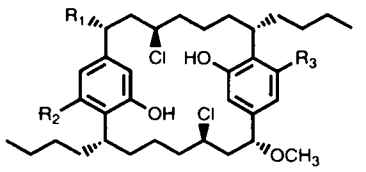
ANTIALGAL SECONDARY METABOLITE

Flores and Wolk tested 65 filamentous cyanobacteria for the prodution of antibiotics (Flores and Wolk, 1986). One of these strains, *Nostoc* sp. 31 had inhibitory activity against most cyanobacterial strains tested. In 1995, Todorova et al. purified a major active constituent, nostocyclamide [Fig. 1(1)] from this strain using a bioassay-guided isolation procedure (Todorova et al., 1995). The structure of nostocyclamide was elucidated by a ^{15}N-labeling experiment, chemical degradation, ^{1}H and ^{13}C NMR, and X-ray analysis. It was found to be a novel macrocyclic compound consisting of an 18-membered ring derived from one oxazole and two thiazole moieties alternating with amide

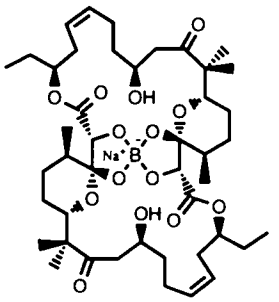
groups.



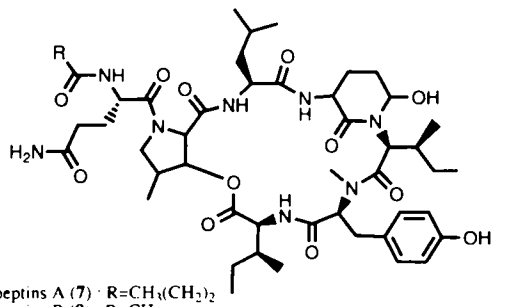
Nostocyclamide (1)



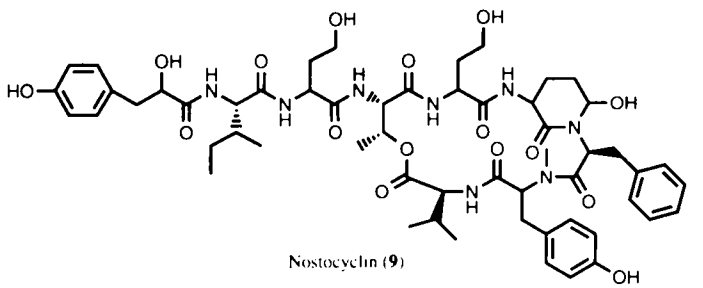
Nostocyclophane D (2) : R_1=OMe, R_2=OH, R_3=OH
Nostocyclophane A (3) : R_1=OMe, R_2=β-D-glucose, R_3=β-D-glucose
Nostocyclophane B (4) : R_1=OMe, R_2=OH, R_3=β-D-glucose
Nostocyclophane C (5) : R_1=OH, R_2=OH, R_3=OH



Borophycin (6)



Nostopeptins A (7) : R=$CH_3(CH_2)_2$
Nostopeptins B (8) : R=CH_3



Nostocyclin (9)

Fig.1 Chemical structures of bioactive compounds isolated from *Nostoc* sp. (I)

Nostocyclamide had very potent growth inhibitory activities against cyanobacteria (*Anabaena* P-9, *Anabaena* PCC 7120, *Synechococcus* PCC 6911 and *Synechocystis* PCC 6308) , diatoms (*Navicuia minima*) , and chlorophyceae (*Nannochloris coccoides* SAG 251 - 1) . In the overlayer test systems, it behaved as a cytotoxic rather than a cytostatic agent against the indicator strains. The compound did not show antifungal activity when tested against *Saccharomyces cerevisiae*. In liquid cultures, nostocyclamide inhibited the growth of *Anabaena* P-9 at a concentration of 0.1 μmol/L(1 week incubation in the light at 25℃) . Considerable toxicity (LC_{50} 12 μmol/L) to a freshwater rotifer (*Brachionus calyciflorus*) was observed.

The total synthesis of nostocyclamide was reported by Moody et al. (1996).

CYTOTOXIC METABOLITES

1. Nostocyclophanes

In 1990 Moore and his co-researchers reported the isolation and structure determination of the first naturally occurring [m.n] paracyclophane, nostocyclophane D [Fig.1(2)] from *Nostoc linckia* (Roth) Bornet ex Bornet & Flahault (UTEX B1932) (Moore et.al., 1990). Later they reported three minor paracyclophanes, nostocyclophane A – C [Fig.1(3 – 5)] as metabolites of the same strain (Chen et al.,1991).

The gross structures of these [7.7] paracyclophanes were elucidated by mass and NMR spectral analyses and the relative and absolute stereochemistry of nostocyclophane D was determined by X-ray crystallography. Since the CD spectra of the four compounds were essentially identical, nostocyclophanes A – D were proposed to have the same stereochemistry. The sugar unit in nostocyclophanes A and B was shown to be D-glucose by semisynthesis of nostocyclophanes B, 9-*O*-(2, 3,4, 6-tetra*O*-acetyl)β-D-glucopyranoside from nostocyclophanes B and D.

The major compound, nostocyclophane D showed cytotoxicity at 0.5 μg/ml (LC_{50}) against KB and LoVo tumor cell lines. The three minor compounds, nostocyclophane A-C, were cytotoxic at 1-2 μg/ml (LC_{50})

2. Borophycin

The lipophilic extract of a marine strain of *Nostoc linckia* (Roth), Bornet ex Bornet & Flahault (UH isolate GA-5-23) was found to have potent cytotoxicity against KB (MIC 3.3 μg/ml) and LoVo (MIC 0.066 μg/ml) tumor cell lines (Hemscheidt et.al., 1994). This extract, however, showed neither solid tumor selective nor tumor selective cytotoxicity. The active agent, borophycin [Fig.1(6)] was isolated and the total structure of this boron-containing compound was determined by spectral methods and X-ray crystallography.

Feeding experiment revealed that borophycin was acetate-derived polyketide that utilizes a C_3 precursor for the starter unit and methionine for the methyl branches on the polyketide chain. The C_3 starter was derived from acetate and methionine, but not from propionate.

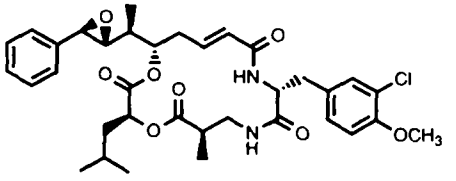
ELASTASE INHIBITORS

Elastase is suggested to be involved in pulmonary emphysema, rheumatoid arthritis, adult respiratory distress syndrome, and other inflammatory states (Groutas, 1987). Its inhibitors might be useful chemotherapeutic agents for these diseases.

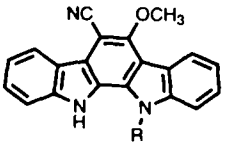
Okino et al. reported new elastase inhibitors designated as nostopeptins A [Fig.1(7)] and B [Fig.1(8)] from the cultured freshwater cyanobacterium *Nostoc minutum* (NIES-26) (Okino et al., 1997). These compounds are characterized by the unusual Ahp (3-amino-6-hydroxy-2-piperidone) component and esterified Hmp (3-hydroxy-4-methylproline). Hmp is present as a constituent of echinocandin B (Keller-Juslen et al., 1976) and pneumocandin A (Hensens et al., 1992) isolated from fermentation broth of fungi, but their Hmp is not esterified.

The effects of nostopeptins against elastase and the other proteolytic enzymes were investigated. Nostopeptins A and B inhibited elastase (IC_{50} 1.3 and 11.0 μg/ml) and chymotrypsin (LC_{50} 1.4 and 1.6 μg/ml), respectively, while neither compound inhibited papain, trypsin, thrombin, or plasmin even at 100 μg/ml.

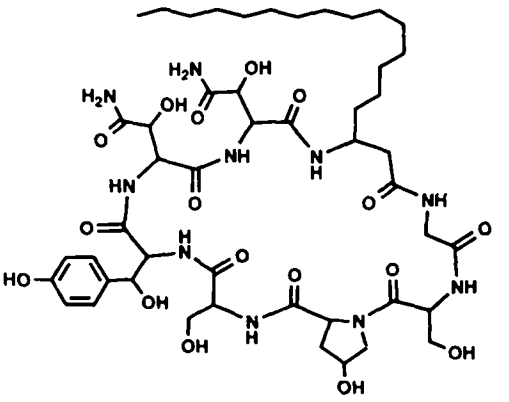
An Ahp containing compound, nostocylin [Fig.1(9)] was also isolated from *Nostoc* sp. (Kaya et al., 1996), though its biological activities were not mentioned.



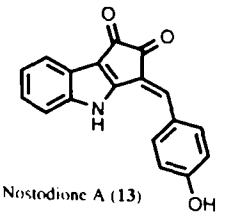
Cryptophycin A (10)



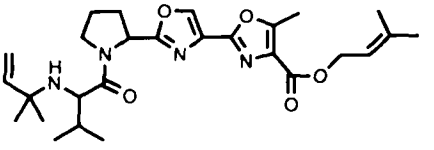
6-cyano-5 methoxy-12-methylindolo[2,3-a]carbazole (11) : R=Me
6-cyano-5 methoxy-indolo[2,3-a]carbazole (12) : R=H



Nostofungicidine (14) (tentative structure)



Nostodione A (13)



Muscoride A (15)

Fig.2 Chemical structures of bioactive compounds isolated from *Nostoc* sp. (Ⅱ)

ANTITUMOR DEPSIPEPTIDES

Cryptophycin 1 [Fig.2(10)] was isolated from *Nostoc* sp. ATCC 53789 as an antifungal agent (Schwartz et al., 1990). Trimurtulu et al. reported that cryptophycin 1 was also produced by another strain of *Nostoc* sp. GSV 224 and that this compound had strong tumor selective cytotoxicity against both drug-sensitive and drug-resistant tumor cells (Trimurtulu et al., 1994). Over 20 cryptophycin analogs were isolated from *Noctoc* sp. GSV 224 and their total structures have been estab-

lished using a combination of chemical and spectral techniques (Trimurtulu et al., 1995, Subbaraju et al., 1997).

Kerksiek et al. investigated the interaction of cryptophycin 1 with tubulin and microtubules (Kerksiek et al., 1995). Cryptophycin 1 was an effective inhibitor of tubulin polymerization, caused tubulin aggregation, and depolymerized microtubules to linear polymers somewhat similar to the spiral-like structures produced by the *Vinca* alkaloids. Cryptophycin 1 also interfered with vinblastine-binding to tubulin but not with colchicine-binding to tubulin. From these observations, they concluded that the cryptophycins might bind to the *Vinca* site in tubulin or to a site that overlaps with the *Vinca* site.

ANTIVIRAL INDOLOCARBAZOILES

Knübel et al. isolated a unique carbazole compound from the mass culture of *Nostoc shaerium* EX-5-1 (Knübel et al., 1990). They isolated this alga from a mud sample collected on the University of Hawaii campus grounds. Clonal cultures were prepared by repeated subculture on solidified media, and mass culture was performed. Cultures were illuminated continuously and aerated at a rate of 5 liters/min, with a mixture of 0.5% CO_2 in air, and incubated at 24℃.

The preliminary experiment showed that the ethanolic extract of this alga possessed antiviral activity and weak, non-selective cytotoxicity against several cell lines. This alga produced two carbazole compounds (6-cyano-5-methoxy-12-methyl-indolo[2,3-a] carbazole [Fig.2(11)], 6-cyano-5-methoxy indolo[2,3-a] carbazole [Fig.2(12)] and their structures were elucidated by spectroscopic analyses, especially HMQC, HMBC and NOE experiments in NMR. The location of the cyano group was rigorously established by one-dimensional $^{13}C-^{13}C$ decoupling experiments with a uniformly ^{13}C-enriched compound.

6-Cyano-5-methoxy-12-methyl-indolo[2,3-a] carbazole isolated as a major component gave two peaks in HPLC, indicating that this compound occurred in a 4:1 mixture with its regioisomer.

6-Cyano-5-methoxy-12-methyl-indolo[2,3-a]carbazole was responsible for most of the antiviral activity and cytotoxicity associated with the extract of the alga. This carbazole was moderately active against herpes simplex type 2; i.e., in infected mink lung cells the virus titer was reduced 95% at 1 μg/ml. The virus population, however, was not totally eliminated at any concentration below the MIC for cytotoxicity (100 μg/ml). It was weakly cytotoxic (MIC 5 μg/ml) against KB and LoVo human carcinoma cell lines, but the crude extract of this alga showed no tumor selective cytotoxicity in Corbett assay (Corbett et al., 1988) The minor compound, 6-cyano-5-methoxyindo[2,3-a] carbazole, showed similar antiviral activity and cytotoxicity.

ANTIMITOTIC COMPOUND

The authors reported a novel antimitotic compound nostodione A in 1994 (Kobayashi et al., 1994). The methanolic extract of field-grown *Nostoc commune* collected on the campus of Okayama University showed pronounced antifungal, cytotoxic and seed germination inhibitory activities. One of the active principles, nostodione A [Fig.2(12)], was isolated using the sea urchin embryo assay.

The structure of nostodione A was elucidated by various spectroscopic analyses and chemical degradation.

Nostodione A arrested the first cleavage of sea urchin eggs (*Hemicentrotus pulcherrimus*) completely at the concentration of 2.5 μg/ml. At lower concentration, 1.25 μg/ml, the embryonic development was blocked in the morula stage, *ca*. 12 h after fertilization. It is known that most respiratory inhibitors block the motility of the sperm of sea urchin, and that the decrease of the fertility rate primarily parallels the sperm motility. However, the sperm treated with nostodione A (20 μg/ml) still possesed fertility. These findings suggested that nostodione A could act on the mitotic spindle. Therefore, the mitotic spindle formation of the nostodione A-treated eggs was followed under a polarization microscope as well as a fluorescence microscope. When 20 μg of nostodione A was administered, the normal spindles were not seen at the metaphase, but small spindles with low birefringence density appeared, and the following egg division was completely suppressed. Moreover, quantitative fluorescence microscope analysis of DAPI (4',6-diamidino-2-phenylindole-dihydrochloride) stained sea urchin eggs revealed that nostodione A did not inhibit the DNA synthesis. This mode of operation was almost identical to that of a typical spindle poison, colcemid (Kobayashi et al., 1989). Nostodione A is not only the first compound found in blue-green algae but also possesses a very unique carbon skeleton, close to that of scytonemin (Proteau et al., 1993).

Recently, the authors isolated another minor cytotoxic compound named nostolide A from the lipophilic extract of field-grown *Nostoc commune*. Nostolide A (M.W. m/z 603) had stronger cytotoxicity against fertilized sea urchin eggs (MIC 0.8 μg/ml) than nostodione A. The structural elucidation is almost completed and the tentative planer structure was disclosed in the annual meeting of the Japan Society for Bioscience, Biotechnology, and Agrochemistry in 1995. The total structure and antimitotic activity of nostolide A will be reported soon.

ANTIFUNGAL COMPOUND

The methanolic extract of field-grown *Nostoc commune* collected on the campus of Okayama University showed antifungal activity together with cytotoxicity as described above. Nostodione A and nostolide A, however, showed no antifungal activity against *Cladosporium herbarum*, suggesting that the methanolic extract should contain other bioactive components. This observation encouraged us to isolate an antifungal principle. The isolation of an active constituent was achieved by repeated column chromatography and preparative HPLC guided by an antifungal assay using *Cladosporium herbarum* as a test fungus (Kobayashi et al., 1993). The active compound, named nostofungicidine was obtained as the white amorphous solid (0.003% yield based on the crude extract). The spectral analyses including UV, IR, and NMR suggested that nostofungicidine was a lipopeptide. Amino acid analysis of the acid hydrolysate of nostofungicidine (6 mol/L HCl, 12 h) indicated the presence of Ser and Gly (2:1) and one immino acid ascribable to hydroxyproline. The tentative structure of nostofungicidine [Fig. 2(14)] elucidated from analyses of $^{1}H-^{1}H$ COSY and HMQC experiments. The complete structural elucidation will be reported elsewhere.

Nostofungicidine showed strong antifungal activities against four test fungi, *Aspergillus candidus* (MIC 1.6 μg/ml), *Cladosporium herbarum* (MIC 3.1 μg/ml), *Botrytis fabae* (MIC 0.8μg/ml), *Cercospora beticala* (MIC 1.6 μg/ml), and moderate activities against *Glomerella cingulata* (50 μg/ml), *Sclerotium rolfsii* (25 μg/ml), *Rhizoctonia solani* (100 μg/ml) but no activity against bacteria. Nostofungicidine also had considerable cytotoxicity against NFS-60 murine myeloid leukemic cell line (LC_{50} 1.5 μg/ml).

ANTIBACTERIAL COMPOUND

An unusual oxazole peptide alkaloid, muscoride A [Fig.2(15)], which had moderate antibacterial activity against *Bacillus subtilis* was isolated from *Nostoc muscorum* IAM M-14 (Nagatsu et al., 1995) The planer structure was elucidated by NMR measurements including phase-sensitive ^{13}C decoupled HMBC method. Muscoride A was the first compound possessing N-(2-methyl-3-buten-2-yl) valine and two contiguous methyloxazoles.

DISCUSSION

Nostoc species are often found in the tropical, subtropical, and temperate zones in Asia. A variety of bioactive compounds has been isolated from *Nostoc* growing in aquatic and terrestrial habitats. These compounds often have unique structural features in which unusual amino acids and heterocyclic compounds are built in as key components.

Nostopeptins, nostocylin, cryptophycins, nostofungicidine, and nostocyclamide are cyclic peptides with unusual amino acids. Muscoride A and nostocyclamide have thiazole and/or oxazole rings in their structures. Nostocyclophane D is a unique symmetric compound and the first naturally occurring [m.n.] paracyclophane. Nostodione A and 6-cyano-5-methoxy-12-methylindolo[2,3-a]carbazole are planar compounds with indole ring(s) and high unsaturation. Borophycin is a boron-containing compound reminiscent of the ionophoric antibiotics boromycin (Lee et al., 1985) and aplasmomycin (Stout et al.,1991).

The algal biosynthesis of these structurally unique metabolites is not thoroughly understood since establishment of axenic cultures is difficult. *Nostoc* species are often embedded within a dense glycan sheath where many microbes are residing, and it is difficult to verify complete sterilization of microorganisms from the jelly when we study biosynthesis of axenic cultures of the algae. Axenic cultures do not always produce the targeted compounds, and the co-residing microbes may affect the secondary metabolism of the algae.

After massive efforts at establishing a pure culture from a wild *Nostoc* sample we succeeded in obtaining an axenic strain of *Nostoc commune*. However, the *Nostoc* pure culture has not so far produced a detectable level of nostodione A, nostolide A and nostofungicidine.

We recently found that a strain of actinomycete, isolated from the jelly sheath produced a quinoxaline antibiotic, echinomycin (Dell et al., 1975) which had a broad inhibitory spectrum to gram-positive bacteria, suggesting that these several unique metabolites of the field-grown *Nostoc* species might control the ecolgical condition of the glycan sheath coating algal cells.

We are now trying to analyze the interactions involved in arbitrary dual culture systems with the axenic strain and the microorganisms from the field-grown *Nostoc commune* sample. Such a new culture method can be considered as a new source of bioactive compounds and can also be used for drug discovery and development.

ACKNOWLEDGMENT

The authors are grateful to Dr. Hiroyuki Kojima (Osaka National Research Institute) for giving us an opportunity to submit this review.

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