1. MARINE CYANOBACTERIUM LYNGBYA

1.1 Introduction:

Oceans are now considered to be a great source of extremely potential drugs that have demonstrated significant activities as anti-inflammatory,\textsuperscript{1} anti-infective,\textsuperscript{2} anti-tuberculosis,\textsuperscript{3} antimicrobial,\textsuperscript{4} anticancer,\textsuperscript{5} antiviral,\textsuperscript{6} and antibiotic.\textsuperscript{7} Marine natural products are small- to medium- molecular weight compounds produced by marine plants, invertebrates and microbes (Bacteria and Fungi). In recent years, secondary metabolites isolated from the marine sponges, jelly fish, sea anemones, corals, bryozoans, molluscs, echinoderms, tunicates, crustaceans\textsuperscript{8} and others offer structurally unique and pharmacologically active compounds. As a result of the potential for new drug discovery, marine natural products have attracted scientists from different disciplines, such as organic chemistry, bioorganic chemistry, pharmacology, biology and ecology. Many of the medicines prescribed today are natural products obtained from terrestrial plants and microorganisms (Bacteria and Fungi). The bacteria and fungi from sea are also reported to produce substances, which affect central nervous system, respiratory system, cardiovascular system, neuromuscular system, and gastrointestinal system. Several marine bacteria exhibit antibiotic activity, among the many marine bacteria showing antimicrobial activity.\textsuperscript{9} Some of the substances are known to produce local effects, such as pain, necrosis, edema, parasthesias etc. Several marine bacteria produce toxins. Tetrodotoxin, one of the best known marine toxins, is frequently involved in fatal food poisoning.\textsuperscript{10} Saxitoxin and its derivatives are known for their involvement in highly fatal poisoning, called paralytic shellfish poisoning (PSP).\textsuperscript{11}

Microorganisms (Bacteria and Fungi) are an increasingly productive and successful focus for marine natural products research. Marine environment provides different biosynthetic conditions to organisms that live in it. Bacteria are a large domain of single-celled, prokaryote (single cells that do not contain nucleus) microorganisms. Bacteria have a wide range of shapes, ranging from spheres to rods and spirals.\textsuperscript{12} Bacteria are ubiquitous in every habitat on Earth, growing in soil, acidic hot springs, radioactive waste, water, and deep in the Earth's crust, as well as in
organic matter and the live bodies of plants and animals. Bacteria were first observed by Antonie van Leeuwenhoek in 1676, using a single-lens microscope. He called them as "animalcules". The name Bacterium was introduced later, by Christian Gottfried Ehrenberg in 1828. Bacteria exhibited an extremely wide variety of metabolic types.

**Bacteria metabolism:**

Bacterial metabolism is classified into nutritional groups on the basis of three major criteria, the kind of energy used for growth, the source of carbon, and the electron donors used for growth (Table 1).

**Table 1. Nutritional types in bacterial metabolism**

<table>
<thead>
<tr>
<th>Nutrition Type</th>
<th>Source of energy</th>
<th>Source of carbon</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototrophs</td>
<td>sunlight</td>
<td>Organic compounds (photoheterotrophs)</td>
<td><strong>Cyanobacteria</strong>, Green sulfur bacteria, Chloroflexi, or Purple bacteria</td>
</tr>
<tr>
<td>Lithotrophs</td>
<td>Inorganic</td>
<td>Organic compounds (lithoheterotrophs)</td>
<td>Thermodesulfbacteria, Hydrogenophilaceae, Nitrospirae</td>
</tr>
<tr>
<td>Organotrophs</td>
<td>Organic</td>
<td>Organic compounds (chemoheterotrophs)</td>
<td>Bacillus, Clostridium or Enterobacteriaceae</td>
</tr>
</tbody>
</table>

Carbon metabolism in bacteria is of two types; one is heterotrophic bacteria which include parasitic types, where organic carbon compounds are used as carbon sources and another one is autotrophic, where cellular carbon is obtained by fixing carbon dioxide. Typical examples of autotrophic bacteria are phototrophic **cyanobacteria**, green sulfur-bacteria and some purple bacteria. Some nitrifying or sulfur oxidizing bacteria are also reported as chemolithotrophic species. The kingdom of Bacteria was many phyla (sub division in classification) to accommodate all the variations. In this section we mainly discuss about **cyanobacteria**, one of the important classification in bacteria domain.
Cyanobacteria or Cyanophyceae:

Cyanobacteria, a phylum of Bacteria is also known as blue-green algae, blue-green bacteria, and Cyanophyta. The name "cyanobacteria" comes from the color of the bacteria (in Greek cyanos means blue). Cyanobacteria are aquatic and photosynthetic, that is, they live in the water, and can manufacture their own food through photosynthesis. Cyanobacteria have an elaborate and highly organized system of internal membranes which function in photosynthesis. Photosynthesis is their principal mode of energy metabolism. Majority of cyanobacteria are aerobic photoautotrophs. Their life processes require only water, carbon dioxide, inorganic substances and light. But these species can survive in both fresh water and marine environments and are able to produce secondary metabolites which possess powerful biological activities. Based on this they are classified into two types, fresh water cyanobacteria and marine cyanobacteria. In the natural environment, some species are able to survive long periods in complete darkness. Cyanobacteria can be found in almost every conceivable environment, from oceans to fresh water to bare rock to soil. They can occur as planktonic cells or can form phototrophic biofilms in fresh water and marine environments. They occur in damp soil or even on temporarily moistened rocks in deserts also. They are quite small and usually unicellular, though they often grow in colonies large enough to see (figure 1).

![Figure 1. Blue-green algae of Cyanobacterial colonies *](image_url)

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Cyanobacteria have the distinction of being the oldest known fossils, more than 3.5 billion years old. Cyanobacteria are still around; they are one of the largest
and most important groups of bacteria on earth. It is thought that bacteria were responsible for the first appearance of significant amounts of oxygen on earth about 2.3 billion years ago. The oxygen atmosphere that we depend on was generated by numerous cyanobacteria during the Archaean and Proterozoic Eras. Today, many different forms and shapes of Cyanobacteria are known. Cyanobacteria in environmental samples are easily recognized by light microscopy. If illuminated with green light, they will show bright red auto fluorescence. This is mainly due to the presence of phycobiliproteins and chlorophyll A.

**Importance of Cyanobacteria:**

Many cyanobacteria are able to reduce nitrogen and carbon dioxide under aerobic conditions; these factors are responsible for their evolutionary and ecological success. They have also been tremendously important in shaping the course of evolution and ecological change. The cyanobacteria are important providers of nitrogen fertilizer in the cultivation of rice and beans. The other great contribution of the cyanobacteria is the origin of plants. The chloroplast with which plants make food for themselves is actually a cyanobacterium living within the plant's cells. Cyanobacteria produce oxygen during photosynthesis. Due to the ability of cyanobacteria to perform oxygenic photosynthesis; it has the capacity to convert non-oxygenated area into oxygenated one. The presence of very small cells of cyanobacteria (in the size range 0.2-2 μm) has been recognized as a potentially significant source of primary reduction in various environments. Aquatic cyanobacteria are probably best known for the extensive and highly visible blooms that can form in both freshwater and the marine environment and can have the appearance of blue-green paint or scum. The association of toxicity with such blooms has frequently led to the closure of recreational waters when blooms are observed. Marine cyanobacteria are an extraordinarily rich source of bioactive and structurally diverse secondary metabolites, most of which derive biosynthetically from a combination of the non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) pathways. In particular cyanobacteria from marine and freshwater sources produce many metabolites which possess powerful biological activities.
variety of different cyanobacterial metabolites feature polyketide, alkaloid, peptides, glycoside macrolides and terpene fragments.

1.2 Classification of Cyanobacteria:

Cyanobacteria are further classified into Order and Species. Mainly six types of orders are present in the cyanobacteria phylum which is summarized in table 2. Cyanobacteria have a remarkable ability to store essential nutrients and metabolites within their cytoplasm. The structure, organization and prominent cytoplasmic inclusions of cyanobacteria can be studied with the help of light and electron microscopes. The basic morphology comprises unicellular, colonial and multicellular filamentous forms. Each order has some species and each species produce numerous biologically active and structurally diverse secondary metabolites.

<table>
<thead>
<tr>
<th>Order</th>
<th>species</th>
<th>compounds</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chroococcales</td>
<td>11</td>
<td>36</td>
<td>Enzyme inhibitor, cytotoxic, cell-differentiation, tumour promoter, endotoxic, hepatotoxic</td>
</tr>
<tr>
<td>Pleurocapsales</td>
<td>1</td>
<td>2</td>
<td>Anti fungal activity</td>
</tr>
<tr>
<td>Oscillatoriales</td>
<td>15</td>
<td>300</td>
<td>Antialgal, anticancer, anti-HIV, antifeedant, antifungal, anti-inflammatory, antimicrobial, antiproliferative, antiviral, cytotoxicity, herbicidal, hepatotoxic, lethotoxic, neurotoxic, immunosuppressive, molluscidal, Pk activator, skin irritant, sunscreen pigment, toxin</td>
</tr>
<tr>
<td>Nostocales</td>
<td>41</td>
<td>126</td>
<td>Anticancer, anti-HIV, antifungal, anti-malarial, anti-inflammatory, antimicrobial, antimoitotic, antiviral, cytotoxicity, hepatotoxic, cytotoxic, toxin, neurotoxin, enzyme inhibitor</td>
</tr>
<tr>
<td>Stigonematales</td>
<td>6</td>
<td>16</td>
<td>Pigment, antibiotic, anticancer, antimitotic, cytotoxic, herbicidal</td>
</tr>
</tbody>
</table>

Basic morphology of Cyanobacteria:

Based on their shapes (morphologies), cyanobacteria have been classified into five groups: chroococcales, pleurocapsales, oscillatoriales, nostocales and stigonematales. The diversity of cyanobacteria can be seen in the multitude of structural and functional aspects of cell morphology and in variations in metabolic strategies, motility, cell division, developmental biology, etc.
Chroococcales:

In the order of Chroococcales, cells are in the form of Unicellular and isopolar. These have spherical, ovoid or in cylindrical shapes (figure 2). They occur singly when the daughter cells separate after reproduction by binary fission.

![Chroococcales](image)

**Figure 2**

The cells may aggregate in irregular colonies, being held together by the slimy matrix secreted during the growth of the colony. It can produce more ordered colonies by combining more or less regular series of cell divisions, with sheath secretions. In this order 11 variable species are identified till date and more than 36 secondary metabolites are isolated from them. Some of them are shown in table 3.

<table>
<thead>
<tr>
<th>Species</th>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Microsystis</em></td>
<td>Diarrhetic toxin</td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td><em>Microsystis aeruginosa</em></td>
<td>Microviridin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td><em>M.aeruginosa</em> and <em>M.wessenburgii</em></td>
<td>Cyclocliral</td>
<td>Anti cancer</td>
</tr>
<tr>
<td><em>Microcystis viridis</em></td>
<td>Cyanoviridin RR</td>
<td>Toxic</td>
</tr>
<tr>
<td><em>Synechococcus</em></td>
<td>Linolenic acid</td>
<td>Antibiotic</td>
</tr>
<tr>
<td><em>Synechocystis</em></td>
<td>Naktirul, Nakienone</td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td><em>Synechocystis tridemini</em></td>
<td>Didemnin</td>
<td>Anticancer, antiviral,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressive</td>
</tr>
</tbody>
</table>
Pleurocapsales:

These are also in unicellular, isopolar and pseudoparenchymatous (compactly interwoven short-celled filaments especially in fungi that resemble parenchyma of higher plants). The principal mode of replication in Pleurocapsales order is by a series of successive binary fissions converting a single mother cell into many minute daughter cells.

![Pleurocapsales](image1.png)

**Figure 3**

Only one species *Hyellocaspitose* was identified till date in this order and two secondary metabolites Carazostatin, Chlorohyellazole are isolated from this species. Carazostatin is an alkaloid based moiety and exhibited antifungal activity, whereas Chlorohyellazole has carbazole as basic structure and exhibited no biological activity.

Chamaesiphonales:

These are also unicellular, but heteropolar. The mode of reproduction in Chamaesiphonales order is by binary fission; particularly exospores are budded off from the upper ends of cells. No such important secondary metabolites having potent biological activity are isolated from this order.

![Chamaesiphonales](image2.png)

**Figure 4**
**Stigonemetales and Nostocales:**

The orders Stigonemetales and Nostocales come under filamentous morphology (resulting from repeated cell divisions occurring in a single plane at right angles to the main axis of the filament). The multicellular structure consisting of a chain of cells is called a trichome.

The trichome may be straight or coiled. Filamentous organization are characterised with trichomes having a heterogeneous cellular composition. Vegetative cells can be differentiated into heterocysts and akinetes.

![Figure 5](image1.png)

**Table 4: Some of important Species , compounds and their biological activity of Order  Stigonemetales**

<table>
<thead>
<tr>
<th>Species</th>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fischerella muscacola</em></td>
<td>Fischerellin</td>
<td>Antifungal and herbicidal</td>
</tr>
<tr>
<td><em>Hapalosiphon fontinalis</em></td>
<td>Anhydrohapaloxindole</td>
<td>Antibiotic</td>
</tr>
<tr>
<td></td>
<td>Fontonamide</td>
<td>Antibiotic</td>
</tr>
<tr>
<td></td>
<td>Hapilindole</td>
<td>Antifungal</td>
</tr>
<tr>
<td><em>Hapalosiphon welwitschii</em></td>
<td>Hapalosin</td>
<td>Anticancer</td>
</tr>
<tr>
<td></td>
<td>Welwistatin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td></td>
<td>Welwitindolinone</td>
<td>Antimitotic</td>
</tr>
<tr>
<td><em>Stigonema dendroideum</em></td>
<td>Dendroamide</td>
<td>Cytotoxic and Antibiotic</td>
</tr>
<tr>
<td><em>Westiellopsis prolificans</em></td>
<td>Westiellamide</td>
<td>Cytotoxic</td>
</tr>
</tbody>
</table>

In the order Stigonemetales, filaments are often multiseriated, trichal with genuine branching (Figure 5). Both heterocysts and akinetes are present in this order.
Six major species are identified from this order and more than 16 compounds are isolated till date. Some of the important secondary metabolites isolated from this species and their biological activities are summarized in table 4. In Nostocales order, only heterocysts are present with no branching (Figure 5). In this order very huge no of species are identified till date. These species are prolific producers of structurally diverse and biologically potent metabolites. Some of the species, compounds isolated from this order and their biological activities are summarized in table 5.

**Table 5: Some of important Species, compounds and their biological activity of Order Nostocales**

<table>
<thead>
<tr>
<th>Species</th>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabesna basta</td>
<td>Micrystin</td>
<td>Cardioactive, hepatotoxin</td>
</tr>
<tr>
<td></td>
<td>Puwainaphycin</td>
<td>Antibiotic, cytotoxic, antiinflammatory</td>
</tr>
<tr>
<td></td>
<td>Bastadin</td>
<td></td>
</tr>
<tr>
<td>Aulosira fertilissima</td>
<td>Aulosirazole</td>
<td></td>
</tr>
<tr>
<td>Calothrix</td>
<td>Calothrixin</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Nodularia spumigena</td>
<td>ADDA Nodularin</td>
<td>Hepatotoxin, enzyme inhibition</td>
</tr>
<tr>
<td></td>
<td>Spumigan</td>
<td>cytotoxic, Anticancer, cytotoxic</td>
</tr>
<tr>
<td></td>
<td>Suomilide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryptophycins</td>
<td></td>
</tr>
<tr>
<td>Nostoc</td>
<td>Cyanovirin</td>
<td>Anti-HIV, antiviral</td>
</tr>
<tr>
<td>Nostoc ellipsosporum</td>
<td>Staurosporine</td>
<td>Antifungal</td>
</tr>
<tr>
<td></td>
<td>Indolecarbazole</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Nostoc sphaericum</td>
<td>Diodehydromirabazole</td>
<td>Antibiotic</td>
</tr>
<tr>
<td></td>
<td>Mirabazole</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Scytonema mirable</td>
<td>Halichondrin</td>
<td>Antifungal</td>
</tr>
<tr>
<td></td>
<td>Scytophycin</td>
<td>Antiviral</td>
</tr>
<tr>
<td></td>
<td>Swinholide</td>
<td>Antimitotic</td>
</tr>
<tr>
<td>Scytonema pseudohofmanni</td>
<td>Nonamethoxy-1-pentacosene</td>
<td></td>
</tr>
<tr>
<td>Tolypothrix conglutinata</td>
<td>Toyocamycin</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Tolypothrix tenuis</td>
<td>Tubercidin</td>
<td>cytotoxic</td>
</tr>
<tr>
<td>Rivularia firma</td>
<td>Polybrominated bisindoles</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td>Rivularin</td>
<td>Antibiotic</td>
</tr>
</tbody>
</table>
Oscillatoriales or Oscillatoriaceae:

Oscillatoriales are one of the important orders in Cyanobacteria family. These are also multicellular in form. The species present in the order Oscillatoriales exhibit uniseriated and unbranched trichomes composed of essentially identical cells. More than 15 species are present in Oscillatoriales order (*Lyngbya*, *lyngbyamajuscula*, *lyngbyabouillonii*, *scillatoria*, *Phormidium*, *Spirulina platensis* etc). Oscillatoriales species produce huge number of structurally interesting and biologically significant secondary metabolites (more than 300 compounds are reported) which cover almost all of the biological activities.

![Image of Oscillatoriales](Oscillatoriales.png)

**Figure 6**

Lyngbyabouillonii species:

*Lyngbya.bouillonii* is one of the important species in Oscillatoriales order. *L. bouillonii* is mainly found in coral reefs where it forms typical dark reddish, tenacious plant masses, strongly attached to madrepores in the infralittoral zone. It has rich source of new natural products including linear tetrapeptides (*lyngbyapeptin*), cyclic depsipeptide (*Alotamide A*), glycosidic macrolides (*lyngbyaloside and lyngbouilloside*). Lyngbouilloside\(^{26}\) and Alotamide\(^{27}\) were isolated by William H. Gerwick *et al.* from the marine cyanobacterium *Lyngbyabouillonii* collected from Papua New Guinea. Relative stereochemistry was deduced from homonuclear and heteronuclear coupling constants as well as NoE studies. Alotamide A (2, figure 7) features three contiguous peptidic residues and an unsaturated heptaketide. Lyngbouilloside (1, figure 7) was modestly cytotoxic to neuroblastomacells with IC\(_{50}\) value of 17 µM. Alotamide A shows an unusual calcium influx activation profile in murine cerebrocortical neurons with an EC\(_{50}\) of 4.18 µM. Desire Daloze *et al.* have isolated four novel metabolites Laingolide A (3), *lyngbyapeptin A* (4) *lyngbyaloside* (5) and Madangolide (6) in figure 7 from the same species *Lyngbyabouillonii*. 
collected from Papua New Guinea. Their structures have been established by Spectroscopic analysis including detailed high-field 1D and 2D NMR studies. Laingolide A\textsuperscript{28} and Madangolide\textsuperscript{29} exhibited cytotoxic activity. Lyngbyaloside\textsuperscript{30} (5, figure 7) a non-nitrogenous, brominated glycoside macrolide is structural analogue of lyngbouilloside (1). Lyngbyapeptin A\textsuperscript{31} (4, figure 7) is a novel tetrapeptide containing the rare 3-methoxy-2-butenooyl moiety. Some of the structures of important metabolites isolated from the species Lyngbyabouillonii are shown in figure 7.
Lyngbya Majuscula species:

Many species of cyanobacteria can adjust to a diversity of growth conditions and habitats. Lyngbya majuscula is one of the important species in Oscillatoriaceae order, which are able to grow in both fresh water and marine cyanobacteria environments. More than 200 chemical entities are reported in literature, in which majority of these compounds have been reported from collections of a single species, Lyngbya majuscula. The marine cyanobacteria Lyngbya majuscula produces an extraordinary variety of bioactive natural products including some toxins. Some of the metabolites of this species are responsible for sporadic outbreaks of a contact dermatitis popularly known as Swimmer’s itch. Most of the structures of these compounds are peptides and related molecules.

Caylobolide A:

Caylobolide A (14, figure 11), a unique 36-membered poly hydroxyl macrolactone was isolated by Tadeusz F. Molinski et al. in 1999 from cyanobacterium Lyngbya majuscula at Bahamian. Structure of caylobolide contains an unprecedented repeated units of contiguous pentad of 1, 5 dioland a 1,3,5-triol. The relative steroechemistry of the 1, 3, 5-triol was determined using Kishi’s Universal NMR database, and absolute stereochemistry at C25, 27, 29 and C33 were determined by Mosher’s analysis and NMR techniques. Caylobolide A exhibited in vitro cytotoxicity against human colon tumor cell line HCT 116 with IC_{50} = 9.9 μM.
**Dolastatin and Kororamide:**

A collection of secondary metabolite peptides dolastatin (15), homodolastatin (16), kororamide (17) in figure 12 are isolated by D. John Faulkner *et al.* from the species *Lyngbyamajuscula* at Paula region.\(^\text{36}\) The structures of the new peptides homodolastatin and kororamide were determined by interpretation of spectroscopic data and chemical degradation. The \(^1\)H and \(^13\)C NMR spectra revealed signals characteristic of valine and isoleucine residues in dolastatin 15 and homodolastatin 16. The sequence of the amino acid residues was confirmed by HMBC experiment. The absolute configuration of the L-isoleucine, L-proline, and L-leucine residues was determined by hydrolysis followed by GC-MS analysis.

![Dolastatin and Kororamide](Figure 12)

These three compounds exhibited cytotoxic activity. Along with these three peptides Faulkne *et al.* has isolated another three spiro compounds aplysiatoxin (18), debromoaplysiatoxin (19) and oscillotoxin (20, figure 13) from the same species.
Aplysia toxins, popularly known as causative agent for swimmers itch, were originally isolated from *Stylocheilus longicauda*, a sea hare. It has been reported that *S. longicauda* preferentially feeds on *L. majuscula*, and chemical investigations of this cyanobacterium yielded aplysiatoxin and debromoaplysiatoxin, thus showing that the aplysiatoxins found in the sea hare were of dietary origin. This is the first report of the isolation of aplysiatoxin is from *L. majuscula* species. Aplysiatoxin (ATX) exhibited anticancer activity by growth inhibition assays against human cancer cell lines. Many of the aplysiatoxins have tumor-promoting activity through the activation of protein kinase C.\(^{37}\) whereas other metabolite Debromoaplysiatoxin has been reported to possess antiproliferative activity against a lymphocytic murine leukemia (P-388) cell line.\(^{38}\)

**Lyngbyabellin:**

Lyngbyabellin A (21, figure 14), a thiazole containing cyclic depsipeptide was isolated by Richard E. Moore *et al.* from a Guamanian strain of the marine cyanobacterium *Lyngbya majuscula*.\(^{39}\) This novel peptolide is structurally related to dolabellin in that both depsipeptides bear a dichlorinated \(\beta\)-hydroxy acid and two functionalized thiazole carboxylic acid units. The gross structure was elucidated by spectroscopy studies including 2D NMR techniques. The absolute stereochemistry was determined by chiral HPLC analysis of hydrolysis products and by

![Figure 13](image-url)
characterization of the degradation products. The total structure was further supported by molecular modeling studies.

Lyngbyabellin A 21

Figure 14

**Nhatrangins A and B:**

Two polyketide metabolites nhatrangins A and B (22 and 23, figure 15) were isolated by Jimmy Orjala *et al.* in 2010 from a Vietnamese collection of *Lyngbya majuscula* species. Thee compounds are related to the aplysiatoxin series of metabolites. The elucidation of 2D Structure was confirmed by NMR studies and LC-MS analysis. Conformational analysis was completed using J-based coupling constant analysis and selective NoE experiments. Synthetic and biological studies are going on this metabolite to evaluate the significant biological activity of Nhatrangins A and B.
Curacin A:

Curacin A, a novel lipid was isolated by William. Gerwick et al. from the organic extract of Curacao collection of *Lyngbyamajuscule* species. Curacin A (24, figure 16) is one of a family of related natural lipids found to inhibit microtubule formation and the binding of colchicine to tubulin dimers isolated in large yields (8–10% w/w) from the crude bacterial extract. curacin A 24 has an IC$_{50}$ of 1.8 pM in Chinese hamster Aux B1 cells. Curacin A has an unusual structure which features a novel cyclopropane substituted thiazoline as a key feature.

![Curacin A](Figure 16)

Lynghyalargerheimii species:

*Largerheimii* is also one of the important species from this order, but very few secondary metabolites are known in the literature till date. Tetrazolium based microculture assay was used to screen the extracts of cultured cyanobacteria of *Largerheimii* species for inhibition of the cytopathic effects of the human immunodeficiency virus (HIV-1) and found to be active towards this virus.

Sulfolipid:

Sulfolipid, a sulfonic acid-containing glycolipid was isolated by Michael R. Boyd et al. from the species of *Lyngbya largerheimii*. The pure compound of Sulfolipid was found to be remarkably active against HIV-1 in cultured human lymphoblastoid CEM, MT-2, LDV-7, and C3-44 cell lines in the tetrazolium assay as well as in p24 viral protein and syncytium formation assays.
**Lyngbya** species:

Filamentous cyanobacteria of the genus *Lyngbya* are the most frequently encountered cyanobacteria in tropical areas and have the ability to fix nitrogen through heterocysts. Most of the secondary metabolites produced by *Lyngbya sp.* arise by the incorporation of nitrogen into a combination of polyketide and peptide biosynthetic pathways. *Lyngbya* sp. are prolific producers of secondary metabolites, many of which possess a wide range of biological activities. Some of those novel metabolites and their biological activities are discussed below.

**Koshikalide and Bisebromoamide:**

Suenega and co-workers have been isolated another two biologically active secondary metabolites koshikalide\(^4^5\) and bisebromoamide\(^4^6\) from cyanobacterium *Lyngbya* sp. Koshikalide (10, figure 9), a 14 membered macrolide was isolated from Mie prefecture, whereas Bisebromoamide (11, figure 9), a novel cytotoxic peptide was isolated from Okinawa prefecture. The absolute stereostructure of bisebromoamide was determined by chemical degradation followed by chiral HPLC analysis. Bisebromoamide exhibited antiproliferative activity at nanomolar levels and is a potent protein kinase inhibition. The phosphorylation of ERK in NRK cells by PDGF stimulation was selectively inhibited by treatment with 10-0.1 μM. The planar structure of Koshikalide was elucidated by spectroscopic analysis.
The relative stereochemistry of C11 and C13 was elucidated by NOESY experiments and by $^1$H NMR analysis. Koshikalide also exhibited weak cytotoxicity against HeLa S3 tumour cells.

**Ulongapeptin and Palauamide:**

Nitrogen containing cyclic depsipeptides, ulongapeptin$^{47}$ (12, figure 10) and palauamide$^{48}$ (13, figure 10) was reported by Richard E. Moore *et al.* isolated from cyanobacterium *Lyngbya* sp. in 2000 at Ulong channel, near Palau. Both of these secondary metabolites are almost similar in structural motif and biological activity.

The gross structure, relative and absolute stereochemistry of these two cyclic depsipeptides are elucidated by COSY, HMBC and one dimensional TOCSY experiments. Both exhibited cytotoxicity against KB (human nasopharyngeal
carcinoma) cells. Palauamide (IC$_{50} = 13$ nM) shows better activity when compared with ulongapeptin (IC$_{50} = 0.63$ μm) against KB cell line.

**Biselyngbyaside:**

Biselyngbyaside (9, figure 8), a densely olefinated 18 membered macrolide glycoside was isolated by Kiyotake Suenaga *et al.* in 2009 from marine cyanobacterium *Lyngbya* sp. collected in Okinawa Prefecture and extracted with methanol. The structure and stereochemistry was confirmed by spectroscopic analysis including 2D-NMR techniques, HMBC correlations and degradation experiments. Biselyngbyaside$^{49}$ exhibited broad-spectrum cytotoxicity against HeLaS$_3$ cells in human tumor cell line with IC$_{50}$ 0.1 μg/mL.

![Biselyngbyaside 9](image)

**Figure 8**

Biselyngbyaside is one of the novel and structurally interesting marine cyanobacterial metabolite with antitumor activity in *Lyngbya* species. The absolute stereochemistries of C3, C17, and the 3-O-methylglucoside moiety were determined by the modified Mosher’s method$^{50}$ and synthetic studies.
1.3 References:


