A Review Study on Macrolides Isolated from Cyanobacteria

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Abstract: Cyanobacteria are rich sources of structurally-diverse molecules with promising pharmacological activities. Marine cyanobacteria have been proven to be true producers of some significant bioactive metabolites from marine invertebrates. Macrolides are a class of bioactive compounds isolated from marine organisms, including marine microorganisms in particular. The structural characteristics of macrolides from cyanobacteria mainly manifest in the diversity of carbon skeletons, complexes of chlorinated thiazole-containing molecules and complex spatial configuration. In the present work, we systematically reviewed the structures and pharmacological activities of macrolides from cyanobacteria. Our data would help establish an effective support system for the discovery and development of cyanobacterium-derived macrolides.

Keywords: cyanobacteria; macrolides; secondary metabolites; bioactivity

1. Introduction

Cyanobacteria, also known as blue-green algae, including cyanobacteria from terrestrial, freshwater and marine ecosystems, are a group of ancient photosynthetic prokaryotes. As defensive chemicals, structurally-diverse secondary metabolites from cyanobacteria have been proven to greatly contribute to successful survival and reproduction of cyanobacteria in changing, complex and diverse environments during the long-lasting evolutionary process [1]. At present, hundreds of compounds with important bioactivities have been isolated from terrestrial or marine cyanobacteria [2]. Macrolides are a class of important bioactive compounds, which are commonly found in marine organisms, including cyanobacteria [3]. Some marine macrolides are promising candidates for future applications in medicine. For example, bryostatin-1 shows potent antitumor activity in phase I cancer clinical trials [4]. Macrolide antibiotics, such as erythromycin and polyene macrolides, have been employed for widespread application of severe bacterial infections [5]. Structurally-diverse macrolides from cyanobacteria often contain unique and unusual substituents, including chlorinated residues, thiazole residues [6] or pyran residues [7]. Macrolides usually exhibit potent antitumor or antibacterial activities [8]. In addition, cyanobacteria have great potentials as sustainable sources for production of bioactive macrolides because of their rapid growth, genetic tractability and cultivable property [2]. Although cyanobacteria possess cultivable properties similar to those of microorganisms, cyanobacteria have attracted far less attention than microorganisms.

In the present review paper, we systematically summarized the structures and bioactivities of macrolides isolated from cyanobacteria, and over 50 references were cited. Up to the end of 2016, a total of 64 macrolide compounds have been isolated from cyanobacteria, including 49 macrolides from marine cyanobacteria and 15 macrolides from terrestrial cyanobacteria, most of which are mainly from...
Lyngbya, Scytonema and Oscillatoria. It has been reported that most of these cyanobacterium-derived macrolides possess several noticeable bioactivities, including antitumor, antibacterial, antimalarial and toxicity to animals. This review summarizes new macrolides derived from cyanobacteria, providing useful information in the further discovery of novel cyanobacterial macrolides.

2. Anti-Neoplastic Property of Cyanobacterium-Derived Macrolides on Different Cell Lines

Nitrogen mustard has been used in the treatment of lymphoma cancer since 1940s, and more than 100 anti-cancer drugs are widely used in the world. Until now, natural products have largely contributed to cancer therapy and become an indispensable source for the development of innovative anti-cancer drugs [9]. Most macrolides from cyanobacteria display significant cytotoxicity to cancer cells. Cyanobacteria of the genera Symploca, Lyngbya, Scytonema and Oscillatoria are important sources of anti-cancer macrolides. Cyanobacterium-derived macrolides reported to have anti-neoplastic effects on different cell lines are given in Figure 1 and Table 1.

![Figure 1](image-url)  

**Figure 1.** Anti-neoplastic profiling results for cyanobacterium-derived macrolides on different cell lines. Data are represented as IC$_{50}$ [log(µM)].

**Table 1.** Anti-neoplastic property of cyanobacterium-derived macrolides on different cell lines.

| Metabolite          | Source            | Location                  | Target Cell Lines                        | Concentration/Effect          | Reference |
|---------------------|-------------------|---------------------------|------------------------------------------|------------------------------|-----------|
| Lyngbyabellin A (1) | *Lyngbya majuscula* | Guam                      | KB cells and LoVo cells                  | IC$_{50}$ value of 0.03 and 0.50 µg/mL respectively | [6]       |
| Lyngbyabellin B (2) | *Lyngbya majuscula* | Guam                      | KB cells and LoVo cells                  | IC$_{50}$ value of 0.10 and 0.83 µg/mL respectively | [10]      |
| Lyngbyabellin E (3) | *Lyngbya majuscula* | Papua New Guinea          | NCH-H460 human lung tumor and neuro-2a mouse neuroblastoma cells | LC$_{50}$ value of 0.4 and 1.2 µM respectively | [11]      |
| Lyngbyabellin F (4) | *Lyngbya majuscula* | Papua New Guinea          | NCH-H460 human lung tumor and neuro-2a mouse neuroblastoma cells | LC$_{50}$ value of 1.0 and 1.8 µM respectively | [11]      |
| Lyngbyabellin G (5) | *Lyngbya majuscula* | Papua New Guinea          | NCH-H460 human lung tumor and neuro-2a mouse neuroblastoma cells | LC$_{50}$ value of 2.2 and 4.8 µM respectively | [11]      |
| Lyngbyabellin H (6) | *Lyngbya majuscula* | Papua New Guinea          | NCH-H460 human lung tumor and neuro-2a mouse neuroblastoma cells | LC$_{50}$ value of 0.2 and 1.4 µM respectively | [11]      |
Table 1. Cont.

| Metabolite                  | Source          | Location                        | Target Cell Lines                                      | Concentration/Effect       | Reference  |
|-----------------------------|-----------------|---------------------------------|--------------------------------------------------------|-----------------------------|------------|
| lyngbyabellin I (7)         | Lyngbya majuscula | Papua New Guinea                 | NCI-H460 human lung tumor and neuro-2a mouse neuroblastoma cells | IC50 value of 1.0 and 0.7 μM respectively | [11]       |
| lyngbyabellin N (10)        | Moorea bouillonii | Palmyra Atoll, USA              | H460 human lung carcinoma and HCT116 colon cancer cell lines | IC50 value of 0.0048–1.8 μM and 15 μM respectively | [12]       |
| lyngbyaloside B (13)        | Lyngbya sp.      | Palau                           | KB cells and LoVo cells                                 | IC50 value of 4.3 and 15 μM respectively | [13]       |
| 2-oxo-lyngbyaloside (14)    | Lyngbya bouillonii | Apra Harbor, Guam               | HT29 colorectal adenocarcinoma and HeLa cells | IC50 value of 38 and 33 μM respectively | [14]       |
| 18E-lyngbyaloside C (15)    | Lyngbya bouillonii | Apra Harbor, Guam               | HT29 colorectal adenocarcinoma and HeLa cells | IC50 value of 13 and 9.3 μM respectively | [14]       |
| 18Z-lyngbyaloside C (16)    | Lyngbya bouillonii | Apra Harbor, Guam               | HT29 colorectal adenocarcinoma and HeLa cells | IC50 value of >100 μM and 53 μM respectively | [14]       |
| biselectyphasic acid (17)   | Lyngbya sp.      | Tokunoshima Island, Japan       | HeLa S3 cells                                          | IC50 value of 0.1 μg/mL      | [15]       |
| biselectyphasic acid B (18) | Lyngbya sp.      | Tokunoshima Island, Japan       | HeLa S3 cells and HL60 cells                           | IC50 value of 3.5 and 0.82 μM respectively | [16]       |
| biselectyphasic acid E (21) | Lyngbya sp.      | Ishigaki Island, Japan          | HeLa and HL60 cells                                    | IC50 value of 0.19 and 0.071 μM respectively | [17]       |
| biselectyphasic acid F (22) | Lyngbya sp.      | Ishigaki Island, Japan          | HeLa and HL60 cells                                    | IC50 value of 3.1 and 0.66 μM respectively | [17]       |
| biselectyphasic acid A (23) | Lyngbya sp.      | Tokunoshima Island, Japan       | HeLa S3 cells and HL60 cells                           | IC50 value of 0.22 and 0.027 μM respectively | [18]       |
| biselectyphasic acid B (24) | Lyngbya sp.      | Ishigaki Island, Japan          | HeLa S3 cells and HL60 cells                           | IC50 value of 0.028 and 0.0027 μM respectively | [19]       |
| caylobolide A (25)          | Lyngbya majuscula | Bahamian                        | human colon tumor cells HCT 116                        | IC50 values of 9.9 μM       | [20]       |
| caylobolide B (26)          | Phormidium spp.  | Florida USA                     | HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells | IC50 value of 4.5 and 12.2 μM respectively | [21]       |
| swinholide A (27)           | Symplocos sp.    | Fiji                            | several cancer cell lines                              | IC50 values of 0.37 nM–1.0 μM | [22]       |
| ankaraholide A (28)         | Geitlerinema sp.  | Madagascar                      | NCI-H460, Neuro-2a cells and MDA-MB-435 cells | IC50 value of 119, 262 and 8.9 nM respectively | [22]       |
| scytophyacin A (30)         | Scytonema pseudohofmanni | Oahu, Hawaii          | human carcinoma of nasopharynx Cell (KB cells) | IC50 value of 1 ng/mL       | [23]       |
| scytophyacin B (31)         | Scytonema pseudohofmanni | Oahu, Hawaii          | KB cells                                              | IC50 value of 1 ng/mL       | [23]       |
| scytophykins C-E (32–34)    | Scytonema pseudohofmanni | Oahu, Hawaii          | KB cells                                              | IC50 value of 10–100 ng/mL | [23]       |
| 6-hydroxyscytophyacin B (35)| Scytonema mirabile | cultured                  | KB cells and LoVo cells                                | MICs of 1–5 and 10–50 ng/mL respectively | [23]       |
| 19-O-demethylscytophyacin C (36)| Scytonema barmanicurn | cultured                 | KB cells and LoVo cells                                | MICs of 1–5 and 10–50 ng/mL respectively | [23]       |
| 6-hydroxy-7-O-methylscytophycin E (37)| Scytonema osellatum | cultured                 | KB cells and LoVo cells                                | MICs of 1–5 and 10–50 ng/mL respectively | [23]       |
| tolytoxin (38)              | Tolypothrix conglutinata var. colorata | Fanning Island     | KB cells and LoVo cells                                | IC50 value of 8.4 and 5.3 nM respectively | [24]       |
| debromoaplysiatoxin (39)    | Lyngbya majuscula | Marshall Islands                | P-388 lymphocytic mouse leukemia                       | weak                        | [25]       |
| lyngbouilloside (44)         | Lyngbya bouillonii | Papua New Guinea              | neuroblastoma cells                                    | IC50 value of 17 μM         | [26]       |
Table 1. Cont.

| Metabolite                              | Source                        | Location            | Target Cell Lines          | Concentration/Effect       | Reference |
|-----------------------------------------|-------------------------------|---------------------|-----------------------------|-----------------------------|-----------|
| koshikalide (45)                        | Lyngbya sp.                   | Mie Prefecture      | HeLa S<sub>2</sub> cells    | IC<sub>50</sub> value of 42 µg/mL | [27]      |
| sanctolide A (46)                       | Oscillatoria sancta           | cultured            | HT-29 and MDA-MB-435 cell lines | nd<sup>a</sup>           | [28]      |
| acutiphycin (47)                        | Oscillatoria acutissima       | Manoa Valley        | KB cells and NIH/3T3 cells  | ED<sub>50</sub> < 1 µg/mL  | [29]      |
| 20,21-didehydroacutiphycin (48)         | Oscillatoria acutissima       | Oahu, Hawaii        | KB cells and NIH/3T3 cells  | ED<sub>50</sub> < 1 µg/mL  | [29]      |
| polycavernoside D (49)                  | Okania sp.                    | Puerto Rican        | H-460 human lung cancer cell lines | EC<sub>50</sub> value of 2.5 µM | [30]      |
| bastimolide A (50)                      | Okania tirsuta                | Panama              | Vero cells                   | IC<sub>50</sub> value of 2.1 µM | [31]      |
| nuiapolide (51)                         | colonial cyanobacterium (071905-NII-01) | Hawaii | Jurkat cells and cancerous T lymphocytes | anti-chemotactic activity | [32]      |

<sup>a</sup> Not determined.

A series of cytotoxic marine cyanobacterial metabolites, named lyngbyabellins (1–11) possessing thiazole residues and chlorine substituents, have been isolated from the cyanobacterial genus Lyngbya (Figure 2). Isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Guam, lyngbyabellin A (1) exhibits potent in vitro cytotoxicity against human carcinoma of nasopharynx Cell (KB cells) and LoVo cells with IC<sub>50</sub> values of 0.03 and 0.50 µg/mL, respectively [6]. The analog of lyngbyabellin A (1), lyngbyabellin B (2), was isolated from the same strain of *Lyngbya majuscula*. Compared with lyngbyabellin A (1), lyngbyabellin B (2) is slightly less cytotoxic to KB and LoVo cells with IC<sub>50</sub> values of 0.10 and 0.83 µg/mL, respectively [10]. Five analogs of lyngbyabellin A (1), including lyngbyabellins E-I (3–7), are produced from the same strain of *Lyngbya majuscula* harvested in Papua New Guinea. To the best of our knowledge, lyngbyabellins E-I (3–7) have potent in vitro cytotoxicity against human lung tumor (NCI-H460) and mouse neuroblastoma (neuro-2a) cells. Lyngbyabellin E (3) and lyngbyabellin H (6) display significant cytotoxicity to NCI-H460 (LC<sub>50</sub> values of 0.4 and 0.2 µM, respectively) and neuro-2a cells (LC<sub>50</sub> values of 1.2 and 1.4 µM, respectively). Lyngbyabellins F-G (4–5) and lyngbyabellin I (7) are slightly less cytotoxic to NCI-H460 (LC<sub>50</sub> values of 1.0, 2.2 and 1.0 µM, respectively) and neuro-2a cells (LC<sub>50</sub> values of 1.8, 4.8 and 0.7 µM, respectively) [11]. The marine cyanobacterium *Moorea bouillonii* (formerly *Lyngbya bouillonii*) collected from Palmyra Atoll affords four analogs of lyngbyabellin A (1), lyngbyabellins K (8), L (9), N (10) and 7-epi-lyngbyabellin L (11). Lyngbyabellin N (10) shows variable cytotoxicity to H-460 human lung carcinoma (IC<sub>50</sub> = 0.0048–1.8 µM) and potent in vitro cytotoxicity against the HCT116 colon cancer cell line (IC<sub>50</sub> = 40.9 ± 3.3 nM). This result could perhaps be explained by the solubility problem of lyngbyabellin N (10). The nitrogen-containing side chain (leucine statine residue) of lyngbyabellin N (11) may be the basic structural feature for its cytotoxic activity [12].

![Lyngbyabellin A(1)](image1)
![Lyngbyabellin B(2)](image2)
![Lyngbyabellin G(5)](image3)

Figure 2. Cont.
Several 16-membered glycoside macrolides, termed lyngbyalosides, are produced from various species of the cyanobacterial genus *Lyngbya* (Figure 3). The marine *Lyngbya bouillonii*, collected from Laing Island, afford lyngbyaloside (12) [8]. Lyngbyaloside B (13), isolated from marine cyanobacterium *Lyngbya* sp., which was collected from Palaua, shows weak cytotoxicity against KB cells and LoVo cells with IC$_{50}$ values of 4.3 and 15 µM, respectively [13]. The total synthesis of lyngbyaloside B (13) has been reported by Fuwa et al. [33]. Three analogs of lyngbyaloside (12), including 2-epi-lyngbyaloside (14), 18E-lyngbyaloside C (15) and 18Z-lyngbyaloside C (16), were isolated from the marine cyanobacterium *Lyngbya bouillonii*, collected from Apra Harbor, Guam. Cytotoxicity assays revealed that these macrolides possess weak to moderate cytotoxicity against the human colorectal
adenocarcinoma cell line HT29 and HeLa cervical carcinoma cells. 18E-lyngbyaloside C (15) is more cytotoxic toward HT29 colorectal adenocarcinoma and HeLa cervical carcinoma cells (IC_{50} values of 13 and 9.3 μM, respectively) than 2-epi-lyngbyaloside (14) (IC_{50} values of 38 and 33 μM, respectively). 18E-Lyngbyaloside C (15) is approximately five-fold more cytotoxic than 18Z-lyngbyaloside C (16) (IC_{50} values of >100 μM and 53 μM, respectively) [14]. The total synthesis of lyngbyaloside C has also been accomplished [34].

Another distinct class of 18-membered ring glycoside macrolides has been isolated from the cyanobacterial genus Lyngbya (Figure 4). Biselyngbyaside (17) was discovered through a bioassay-guided screening for cytotoxic compounds from cyanobacterium Lyngbya sp. collected from Okinawa Prefecture, Japan. Biselyngbyaside (17) shows a broad spectrum of cytotoxicity against human solid tumor cell lines, especially for HeLa S3 cells with an IC_{50} value of 0.1 μg/mL [15], and its total synthesis was completed [35]. Extensive efforts toward finding cytotoxic natural products have resulted in the isolation of three analogs of biselyngbyaside (17), named biselyngbyasides B–D (18–20), from the marine cyanobacterium Lyngbya sp. Biselyngbyaside B (18) displays significant cytotoxicity against HeLa S3 and HL60 cells (IC_{50} values of 3.5 and 0.82 μM, respectively, using thapsigargin as a positive control drug). In addition, biselyngbyasides B–D (18–20) induced apoptosis of cancer cells by inhibiting calcium influx into the endoplasmic reticulum and increasing the concentration of intracellular calcium [16]. Two analogs of biselyngbyaside (17), biselyngbyasides E (21) and F (22), were isolated from the marine cyanobacterium Lyngbya sp. collected from Ishigaki Island, Japan. In vitro cell cytotoxicity assays showed that biselyngbyaside E (21) has higher cytotoxicity against HeLa and HL60 cells (IC_{50} values of 0.19 and 0.071 μM, respectively) than biselyngbyaside F (22) (IC_{50} values of 3.1 and 0.66 μM, respectively). Based on the trisubstituted olefin geometry, the presence and absence of the sugar moiety are crucial for the biological activities [17].

Like a cytotoxic biselyngbyaside-related macrolide, biselyngbyolide Α (23) was isolated from the marine cyanobacterium Lyngbya sp. harvested from Tokunoshima Island, Japan. Biselyngbyolide A (23) shows strong cytotoxicity against HeLa S3 cells and HL60 cells with IC_{50} values of 0.22 and 0.027 μM, respectively [18]. Biselyngbyolide B (24) was also isolated from the same strain of Lyngbya sp. and displays significant inhibitory effects on growth of HeLa S3 cells and HL60 cells (IC_{50} values of 0.028
and 0.0027 μM, respectively, using thapsigargin as a positive control drug). Moreover, biselyngbyolide B (24) has 3–100-fold more potent apoptosis-inducing activity than biselyngbyaside (17) [16,19].

A novel 36-membered macrolactone, caylobolide A (25), was isolated from Bahamian cyanobacterium Lyngbya majuscula, which contains an unprecedented repeating unit, an adjoining pentad of 1,5-diols and a 1,3,5-triol (Figure 5). In vitro cytotoxicity assay showed that caylobolide A (25) possesses potent cytotoxicity against human colon tumor cells HCT-116 with an IC50 value of 9.9 μM [20], and its total synthesis has been accomplished [36]. Caylobolide B (26) was isolated from the marine cyanobacterium Phormidium spp. collected from Key West, Florida, and it exhibits strong cytotoxicity against HT29 colorectal adenocarcinoma (IC50 value of 4.5 μM) and HeLa cervical carcinoma cells (IC50 value of 12.2 μM) [21].
Swinholide A (27), originally isolated from the marine sponge *Theonella swinhoei*, was isolated from the marine cyanobacterium *cf. Symploca* sp. collected from Fiji and was found to strongly inhibit the growth of several tumor cell lines with IC<sub>50</sub> values ranging from 0.37 nM to 1.0 μM [22]. Two swinholide-based glycosylated macrolides, named ankaraholides A, B (28, 29), were isolated from two field collections of marine cyanobacteria (Figure 6). Ankaraholide A (28) exhibits strong antiproliferative activity against NCI-H460, Neuro-2a and MDA-MB-435 cell lines with IC<sub>50</sub> values of 119, 262 and 8.9 nM, respectively. Ankaraholide A (28) inhibits proliferation of A-10 cells by inducing complete loss of the filamentous (F)-actin during the cell extending process when the concentration of ankaraholide A (28) reaches 30 nM [22].

A family of potent cytotoxic natural products, scytophycins A–E (30–34), was isolated from the terrestrial cyanobacterium *Scytosclena pseudohofmannii* [37]. Scytophycins A (30) and B (31) display significant cytotoxicity against KB cells (IC<sub>50</sub> value of 1 ng/mL), while scytophycins C–E (32–34) are less cytotoxic to KB cells (IC<sub>50</sub> values ranging from 10 to 100 ng/mL) than scytophycin A (30) [23]. Total synthesis of scytophycin C (32) has been completed [38]. Screening of cyanobacteria leads to the discovery of three analogs of scytophycins, including 6-hydroxyscytophycin B (35), 19-O-demethylscytophycin C (36) and 6-hydroxy-7-O-methylscytophycin E (37) (Figure 7). These compounds (35–37) show strong inhibitory effect on the growth of KB (MIC values ranging from 1 to 5 ng/mL) and LoVo cells (MIC values ranging from 10 to 50 ng/mL) [23]. The cytotoxic tolytoxin (38) was isolated from terrestrial cyanobacterium *Toxoplophrix conglutinata*, collected from Fanning Island [39], and displays excellent cytotoxicity against LoVo and KB cells with IC<sub>50</sub> values of 8.4 and 5.3 nM, respectively [24].
Debromoaplysia toxin (39) was isolated from the marine cyanobacterium *Lyngya majuscula*, collected from Hawaii [40], and shows potent cytotoxicity against mouse lymphocytic leukemia P-388 [25]. Four analogs of debromoaplysia toxin (39), including oscillatoxin A (40), 19,21-dibromooscillatoxin A (41), 19-bromoaplysia toxin (42) and 21-bromooscillatoxin A (43), were isolated from a mixture of marine cyanobacteria *Oscillatoria nigroviroidis* and *Schizothrix calcicola* from Enewetak Island (Figure 8). These compounds (41–43) contain the same 14-membered macrocycle as debromoaplysia toxin (39), but they are bromine-containing macrolides [41]. A 14-membered glycosidic macrolide, lyngbouilloside (44), was isolated from the marine cyanobacterium *Lyngya bouillonii*, harvested from Papua New Guinea. It displays a modest cytotoxicity against neuroblastoma cells with an IC₅₀ value of 17 μM [26]. Another 14-membered macrolide, koshikalide (45), was isolated from the marine cyanobacterium *Lyngya* sp., collected from Mie Prefecture, Japan, and shows slight cytotoxicity against HeLa S₂₃ cells with an IC₅₀ value of 42 μg/mL [27]. In addition, the total synthesis of koshikalide (45) has been achieved by exploiting a novel convergent strategy [42]. A 14-membered
marine macrolide, sanctolide A (46), containing a rare $N$-methyl enamide and a 2-hydroxyisovaleric acid, was obtained from the culture of cyanobacterium Oscillatoria sancta. It is cytotoxic against HT-29 and MDA-MB-435 cell lines [28], and its total synthesis was achieved [43].

| Name                        | $R_1$ | $R_2$ | $R_3$ |
|-----------------------------|-------|-------|-------|
| debromoaplysiatoxin (39)    | Me    | H     | H     |
| oscillatoxin A (40)         | H     | H     | H     |
| 19,21-dibromooscillatoxin A (41) | H     | Br    | Br    |
| 19-bromoaplysiatoxin (42)   | Me    | Br    | Br    |
| 21-bromooscillatoxin A (43) | H     | Br    | H     |

![Chemical structures of Compounds 39–46](image)

**Figure 8.** Chemical structures of Compounds 39–46.

Two cytotoxic macrolides, acutiphycin (47) and 20,21-didehydroacutiphycin (48), were isolated from freshwater cyanobacterium Oscillatoria acutissima, collected from Manoa Valley, Oahu, and possess strong cytotoxicity against KB and NIH/3T3 cells ($ED_{50} < 1 \mu g/mL$), as well as Lewis lung carcinoma [29]. A rare marine toxin, polycavernoside D (49), was obtained from the marine Okeania sp. collected from the Caribbean (Figure 9). The discovery of polycavernoside D, for the first time, provides a conclusive proof that these lethal toxins (polycavernosides) have, in fact, a cyanobacterial origin rather than other marine organisms. Polycavernoside D (49) displays cytotoxicity against the H-460 human lung cancer cell line in a dose-dependent manner, with an $EC_{50}$ value of 2.5 $\mu$M [30]. Bastimolide A (50), isolated from the marine *Okeania hirsuta* from Bastimentos Park, Panama, is a rare 40-membered polyhydroxy macrolide consisting of one 1,3-diol, one 1,3,5-triol, six 1,5-diols and one tert-butyl group. Bastimolide A (50) exhibits strong cytotoxicity against Vero cells with an $IC_{50}$ value of 2.1 $\mu$M [31].

A rare 40-membered macrolactone, nuiapaside (51), was isolated from Niihau marine cyanobacterium. As a polyhydroxylated macrolide, nuiaposite (51) contains a rare tert-butyl carbinol residue, and it displays anti-chemotactic activity against Jurkat cells and cancerous T lymphocytes and can trigger a predominant G2/M phase shift in the cell cycle [32].
3. Antibacterial Activity

Some macrolides, such as erythromycin and azithromycin, have shown excellent antibacterial activity and are widely used in clinical practice of various types of bacterial infections [44]. Some macrolides from cyanobacteria also show good antibacterial activities. Cyanobacterium-derived macrolides with antimicrobial properties are listed in Table 2.

Scytophycins C–E (32–34) were isolated from the terrestrial cyanobacterium *Scytonema pseudohofmannii*, collected from Oahu, Hawaii, and were shown to exhibit weak antibacterial activity [37]. Three analogs of scytophycin C (32), including 6-hydroxyscytophycin B (35), 19-O-demethylscytophycin C (36) and 6-hydroxy-7-O-methylscytophycin E (37), were isolated from the cyanobacteria *S. mirabile*, *S. burmanicurn* and *S. ocellatum*, respectively. These macrolides (35–37) display antifungal activity against *Aspergillus oryzae*, *Candida albicans*, *Penicillium notatum* and *Saccharomyces cerevisiae* [23]. The cytotoxin, tolytoxin (38), was isolated from the terrestrial cyanobacterium *Tolypothrix conglutinata*, collected from Fanning Island [39], and was found to exhibit potent antifungal activity against various yeasts and filamentous fungi (MICS of 0.25–8 nM) [24].

![Chemical structures of Compounds 47–51.](image-url)
A bioactive marcolide, 7-OMe-scytophycin B (52), was identified from a culture of a marine cyanobacterium and was found to exhibit antifungal activity against Candida albicans HAMBl 484 and Candida guilliermondii HAMBI 257 with MIC values of 0.40 and 0.80 mM and IC_{50} values of 0.19 and 0.23 mM, respectively [45]. Two 40-membered macrolactones, amantelides A,B (53,54), are composed of a 1,3-diol and contiguous 1,5-diol units and a tert-butyl substituent. These compounds were isolated from a Guam cyanobacterium belonging to the family Oscillatoriales (Figure 10). Amantelide A (53) shows a broad spectrum of inhibitory effects on the growth of both eukaryotic and prokaryotic cells. The growth of the fungi Lindra thalassiae and Fusarium sp. is completely inhibited when the concentration of amantelide A (53) is 62.5 μg/mL. When the concentration of amantelide B (54) is 6.25 μg/mL, the growth of the fungus Dendryphiella salina is completely inhibited [46].

![Figure 10. Chemical structures of Compounds 52–54.](image-url)

### Table 2. Antibacterial and antifungal macrolides.

| Metabolite                      | Source          | Location   | Target                                      | Concentration/Effect | Reference |
|---------------------------------|-----------------|------------|---------------------------------------------|-----------------------|-----------|
| 6-hydroxy-scytophycin B (35)    | Scytonema mirabile | cultured | Fungus (1) Aspergillus oryzae (2) Candida albicans (3) Penicillium notatum (4) Saccharomyces cerevisiae | nd *                 | [23]      |
| 19-0-demethylscytophycin C (36) | Scytonema turmanicum | cultured | Fungus (1) Aspergillus oryzae (2) Candida albicans (3) Penicillium notatum (4) Saccharomyces cerevisiae | nd *                 | [23]      |
| 6-hydroxy-7-0-methylscytophycin E (37) | Scytonema ocellatum | cultured | Fungus (1) Aspergillus oryzae (2) Candida albicans (3) Penicillium notatum (4) Saccharomyces cerevisiae | nd *                 | [23]      |
| tolyxin (38)                    | Tolypothrix conglutinata var. colorata | Fanning Island | Fungi Penicillium notatum and Rhizoctonia solani 1165 | MIC value of 0.25 nM respectively | [24]      |
| 7-OMe-scytophycin B (52)        | Anabaena sp.    | cultured | Fungus Candida albicans HAMBl 484 and Candida guilliermondii HAMBI 257 | MIC values of 0.40 and 0.80 mM respectively; IC_{50} value of 0.19 and 0.23 μM respectively | [45]      |
| amantelide A (53)               | Oscillatoriales | Guam      | Fungi Lindra thalassiae and Fusarium sp. | totally inhibited of 62.5 μg/mL | [46]      |
| amantelide B (54)               | Oscillatoriales | Guam      | Fungus Dendryphiella salina | totally inhibited of 6.25 μg/mL | [46]      |

* Not determined.
4. Effects of Cyanobacterium-Derived Macrolides on Animals

Toxin-producing cyanobacterial blooms are a potential health risk for other living organisms, including humans [47]. Cyanobacterium-derived macrolides show toxicity to animals, such as brine shrimp and mice. The effects of cyanobacterium-derived macrolides on fauna are described in Table 3.

Table 3. Effects of cyanobacterium-derived macrolides on animals.

| Metabolite       | Source                   | Location                | Target Fauna | Impacts              | Reference |
|------------------|--------------------------|-------------------------|--------------|----------------------|-----------|
| Lymbyabellin A (1) | Lyngbya majuscula        | Guam                    | mice         | LD50 value of 1.2-1.5 mg/kg | [6]       |
| tolytoxin (38)    | Sctonema pseudohofmannii | cultured               | mice         | LD50 value of 1.5 mg/kg | [24]      |
| sanctolide A (48) | Oscillatoria sancta      | cultured               | brine shrimp | LD50 value of 23.5 µM | [28]      |
| Gloeolactone (55) | Gloeotrichia sp.         | Clark Canyon Reservoir  | brine shrimp | 100% killed at 125 µg/mL | [48]      |
| Phormidolide (56) | Phormidium sp.           | Sulawesi, Indonesia    | brine shrimp | LD50 value of 1.5 µM | [49]      |
| Cyanolide A (57)  | Lyngbya bouillonii       | Papua New Guinea       | snail vector | LD50 value of 1.2 µM | [50]      |

The cytotoxic macrolactone, lymbyabellin A (1), exhibits potent toxicity to mice in vivo trials (lethal dose of 2.4 to 8.0 mg/kg; sublethal dose of 1.2 to 1.5 mg/kg) [6]. Tolytoxin (38) is highly toxic to mice with a sublethal dose (ip) of 1.5 mg /kg [24].

A 14-membered macrolide, sanctolide A (48), shows high toxicity toward the brine shrimp with an LC50 value of 23.5 µM [28]. A 10-membered ring macrolide, gloeolactone (55), was isolated from the cyanobacterium Gloeotrichia sp., harvested in Clark Canyon Reservoir (Figure 11). Gloeolactone (55) exhibits weak toxicity to brine shrimp. All brine shrimps are dead when the concentration of gloeolactone (55) is 125 µg/mL [48]. Phormidolide (56) was isolated from the marine cyanobacterium Phormidium sp. cultured in Indonesia and was found to exhibit very high toxicity (LC50 value of 1.5 µM) in the brine shrimp test [49].

![Figure 11. Chemical structures of Compounds 55–57.](image-url)
A symmetrical macrolide dimer, cyanolide A (57), was obtained from the marine cyanobacterium *Lyngbya bouillonii* collected from Papua New Guinea. Cyanolide A (57) displays potent molluscicidal activity against the snail vector *Biomphalaria glabrata* with an LC$_{50}$ value of 1.2 µM. Cyanolide A (57) can be used as a new, potent molluscicidal agent to effectively control the spread of schistosomiasis [50]. Its total synthesis has been accomplished [51].

5. Other Bioactivity

Cyanobacterium-derived macrolides with rich chemical diversity show various important bioactivities (Table 4). The macrolide biselyngbyaside (17), isolated from the marine cyanobacterium *Lyngbya* sp., has been investigated for its effects on osteoclast differentiation and function. Biselyngbyaside (17) inhibits RANKL-induced osteoclastogenesis by inhibiting the expression of c-Fos and NFATc1 in mouse monocytic RAW264 cells. Therefore, biselyngbyaside (17) is a potentially promising compound with therapeutic and preventive activities against bone-lytic diseases [52]. A toxic cyanobacterial macrolide, debromoaplysiatoxin (39), has been found to cause severe cutaneous inflammation in humans and other animals after topical application [25].

| Metabolite | Source | Location | Biological Activity | Reference |
|------------|--------|----------|---------------------|-----------|
| biselyngbyaside (17) | *Lyngbya* sp. | Okinawa Prefecture Japan | osteoclast differentiation and function | [52] |
| debromoaplysiatoxin (39) | *Lyngbya majuscula* | Enewetak Atoll, Marshall Islands | produce an irritant pustular folliculitis in humans and cause a severe cutaneous inflammatory reaction in the rabbit and in hairless mice | [25] |
| bastimolide A (50) | *Okeania hirsuta* | Caribbean coast of Panama | *Plasmodium falciparum* TM90-C2A, TM90-C2B, W2, TM91-C235 (IC$_{50}$ values of 80, 90, 140 and 270 nM respectively) | [31] |
| malyngolide dimer (58) | *Lyngbya majuscula* | Panama | *Plasmodium falciparum* (IC$_{50}$ values of 19 µM) | [53] |
| tanikolide dimer (59) | *Lyngbya majuscula* | Madagascar | SIRT2 (IC$_{50}$ = 176 nM to 2.4 µM) | [54] |
| palmyrolide A (60) | *Leptolyngbya cf. Oscillatoria* sp. | Palmyra Atoll | suppression of calcium influx in cerebrocortical neurons (IC$_{50}$ value of 3.70 µM) sodium channel blocking activity in neuro-2a cells (IC$_{50}$ value of 5.2 µM) | [55] |
| cocosolide (61) | *Symploca* sp. | Guam | inhibition of IL-2 production and T-cell proliferation | [7] |

A rare 40-membered polyhydroxy macrolide, bastimolide A (50), exhibits high selectivity and antimalarial activity against four drug-resistant malaria parasite strains, including TM90-C2A, TM90-C2B, W2 and TM91-C235, with IC$_{50}$ values of 80, 90, 140 and 270 nM, respectively. It has been proven that bastimolide A (50) is a potentially promising antimalarial lead compound with high selectivity and antimalarial activity against drug-resistant strains [31]. Malyngolide dimer (58) was isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Panama and was shown to exhibit moderate antimalarial activity against chloroquine-resistant *Plasmodium falciparum* (W2) with an IC$_{50}$ Value of 19 µM [53].

A novel SIRT2-selective inhibitor, tanikolide dimer (59), was isolated from marine cyanobacterium *Lyngbya majuscula* collected from Madagascar, and it possesses a symmetrical dimer, which has been elucidated by comparison of the natural and synthetic stereoisomers using chiral GC-MS (Figure 12). The tanikolide dimer (59) is a potent and selective SIRT2 inhibitor with an IC$_{50}$ value of 176 nM [54].
The above intriguing experimental results suggest that palmyrolide A (isolated from cyanobacteria, including 49 macrolides from marine cyanobacteria and 15 macrolides harvested in Laing Island, Papua-New Guinea (Figure 12). The structures of these macrolides (62–64) have been identified from the marine cyanobacterium Symploca sp. harvested in Palmyra Atoll. Palmyrolide A (60) contains a rare N-methyl enamide and an intriguing tert-butyl group, and it can potently inhibit Ca\(^{2+}\) oscillations in murine cerebrocortical neuronal cells with an IC\(_{50}\) value of 3.70 µM. Moreover, palmyrolide A (60) can significantly block the sodium channel activity of neuro-2a cells (IC\(_{50}\) value of 5.2 µM) without appreciable cytotoxicity. The above intriguing experimental results suggest that palmyrolide A (60) could be a promising drug candidate for further pharmacological exploration [55], and its total synthesis has been completed [56].

A dimeric macrolide, cocosolide (61), was isolated from the marine cyanobacterium *Symploca* sp. from Guam, and it strongly inhibits IL-2 production in both T-cell receptor-dependent and independent manners. Both the presence of the sugar moiety and the integrity of the dimeric structure ensure the functionality of cocosolide (61). In addition, the total synthesis of cocosolide (61) has been accomplished [7].

Three novel nitrogen-containing macrolides, laigolide (62) [57], laigolide A (63) and madangolide (64) [58], have been identified from the marine cyanobacterium *Lyngbya bouillonii* harvested in Laing Island, Papua-New Guinea (Figure 12). The structures of these macrolides (62–64) contain a lactone ring of 15, 15 and 17 members, respectively [58].

**6. Conclusions**

Cyanobacteria are rich sources of various natural products with unprecedented pharmacological and biological activities. Up to the end of 2016, a total of 64 macrolide compounds have been isolated from cyanobacteria, including 49 macrolides from marine cyanobacteria and 15 macrolides...
from terrestrial cyanobacteria. More than half of the cyanobacterium-derived macrolides, a total of 36 compounds, were isolated from the cyanobacterial genus *Lyngbya* species, particularly from *Lyngbya majuscula*. Most of these cyanobacterium-derived macrolides possess several noticeable bioactivities, including antitumor, antibacterial and antimalarial. The overwhelming majority of cyanobacteria derived macrolides (1–51) display in vitro antitumor activity. Secondary metabolites of cyanobacteria are widely evaluated for their antitumor effects since many metabolites of cyanobacteria have exhibited potent antitumor activities. Some of these macrolides, including tolytoxin (38), bastimolide A (50) and tanikolide dimer (59), exhibited surprisingly strong bioactivity, thus representing potential new drug lead compounds, which are worthy of further research on synthesis and pharmacological activity. The total synthesis of 10 bioactive macrolides, such as cocosolide, has been achieved with a great deal of efforts. The research on the total synthesis of macrolides will promote pharmacologic research and create new opportunities to undertake research in drug discovery, medicine design and large-scale manufacturing. At present, three scholars, including Luesch, Moore and Gerwick, have greatly contributed to the discovery of new macrolides from cyanobacteria. Cyanobacteria have great potentials as sustainable sources for the production of bioactive metabolites because of their rapid growth, genetic tractability and cultivable property. Although cyanobacteria possess the cultivable properties similar to those of microorganisms, cyanobacteria have attracted far less attention than microorganisms. More efforts should be devoted to improving the production of bioactive metabolites in cyanobacteria via cultivation design, metabolic engineering together with efficient isolation. In addition, the programs for drug discovery from cyanobacteria, including the Panama International Cooperative Biodiversity Group (ICGB) program, might facilitate and enhance drug discovery from cyanobacteria. A systematic review on macrolides from cyanobacteria would help establish an effective support system for the discovery and development of cyanobacterium-derived macrolides, and such a support system could also facilitate collection, purification and identification of bioactive macrolides, leading to improve bioactivity assay, synthesis, data analysis and information technology.

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