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REVIEW

Isolation and identification of siderophores produced by cyanobacteria

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Abstract

Cyanobacteria are one of the most successful and oldest forms of life that are present on Earth. They are prokaryotic photoautotrophic microorganisms that colonize so diverse environments as soil, seawater, and freshwater, but also stones, plants, or extreme habitats such as snow and ice as well as hot springs. This diversity in the type of environment they live in requires a successful adaptation to completely different conditions. For this reason, cyanobacteria form a wide range of different secondary metabolites. In particular, the cyanobacteria living in both freshwater and sea produce many metabolites that have biological activity. In this review, we focus on metabolites called siderophores, which are low molecular weight chemical compounds specifically binding iron ions. They have a relatively low molecular weight and are produced by bacteria and also by fungi. The main role of siderophores is to obtain iron from the environment and to create a soluble complex available to microbial cells. Siderophores play an important role in microbial ecology; for example, in agriculture they support the growth of many plants and increase their production by increasing the availability of Fe in plants. The aim of this review is to demonstrate the modern use of physico-chemical methods for the detection of siderophores in cyanobacteria and the use of these methods for the detection and characterization of the siderophore-producing microorganisms. Using high-performance liquid chromatography-mass spectrometry (LC-MS), it is possible not only to discover new chemical structures but also to identify potential interactions between microorganisms. Based on tandem mass spectrometry (MS/MS) analyses, previous siderophore knowledge can be used to interpret MS/MS data to examine both known and new siderophores.

Introduction

Cyanobacteria are considered to be one of the oldest organisms found on Earth, with their age estimated at more than 2.5 billion years. Cyanobacteria consist of many species of Gram-negative bacteria and possess a characteristic oxygen-producing photosynthesis.

However, more than 2 billion years ago, there has been a change and oxygen-releasing microorganisms have emerged into the Earth's atmosphere. The medium thus gradually changed its properties from reducing to oxidizing (Blankenship and Hartman 1998; Summons et al. 1999). This change had dramatic consequences because almost all living forms were forced to adapt to these oxidation conditions or become extinct. The consequence of the change from the reductive to the oxidative atmosphere also had an effect on the water-soluble predominant salts of Fe^{2+}, which were oxidized to the corresponding iron oxide (Fe^{3+}) hydrates, e.g., $Fe(OH)^{2+}$, $Fe(OH)_3$ and $Fe(OH)^{4-}$. Unfortunately, these substances are almost insoluble in water (Crichton 2001). Photosynthetic picocyanobacteria and eukaryotic microorganisms that inhabit the open ocean need iron for their photosynthetic and respiratory needs. Physiological studies and recent sequencing of marine microorganism genomes and transcripts have revealed mechanisms of iron uptake and utilization that allow marine microorganisms to persist in a restricted iron environment. Most of these microorganisms get iron from strong chelates because most dissolved iron in sea water is complexed with organic ligands (Hopkinson and Morel 2009; Morrissey and Bowler 2012; Haque et al. 2017). The cyanobacteria that caused the whole change in the atmosphere had to develop new ways of obtaining Fe. This has resulted in the production of small organic ligands—siderophores (Raymond et al. 1984;

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Drechsel and Jung 1998). Siderophores are the strongest Fe^{3+} chelators secreted by microorganisms and plants. Siderophores are biosynthesized and in particular excreted under iron starvation, i.e., when intracellular iron concentrations drop below a certain threshold required for the functionality of biochemical processes in the cell. Siderophores is structurally possible to divide into four different structural types (Raymond et al. 1984; Drechsel and Jung 1998).

Cyanobacteria, unlike the algae, are prokaryotic organisms, which have a common way of obtaining organic matter with the algae—photosynthesis. In this review, we do not even address eukaryotic organisms, such as algae, even though they are a very important part of phytoplankton. Furthermore, we do not mention fungi (molds or yeasts) that normally produce siderophores. The same applies to "siderophores" of higher (flowering) plants, and, of course, we deliberately ignore organisms that can be taxonomically classified as unicellular protists, dinoflagellates, which often form a significant part of the plankton (red tide).

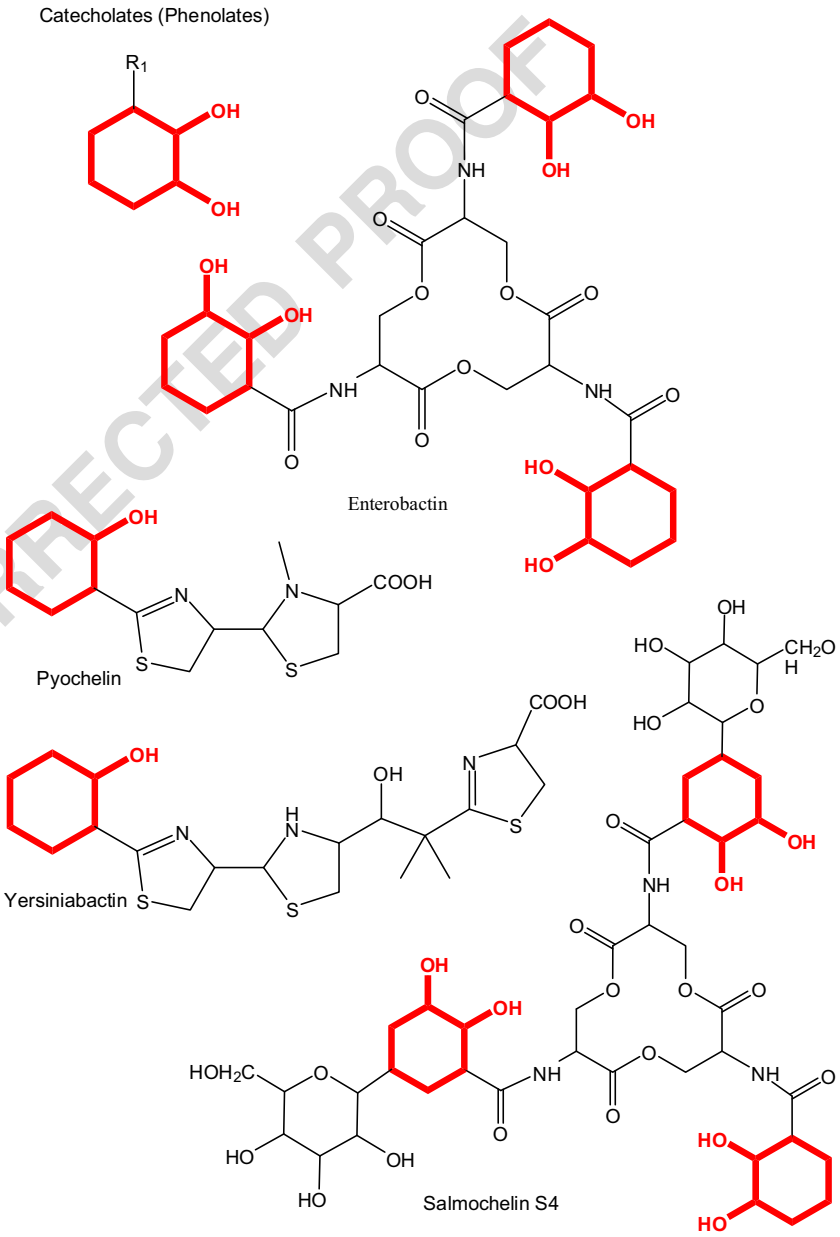


Fig. 1 The structures of catecholates (phenolates)

Structural types of siderophores

Catecholates

Examples of catecholate siderophores are shown in Fig. 1. Each catecholate group contains two oxygen atoms for iron chelation, which form a hexagonal octahedric complex where the ferric ion (Fe^{3+}) has a very high stability constant $K = 10^{52}$ mol/L. Such a high constant signifies that cyanobacteria can live in environments with very low iron concentrations. Some cyanobacteria can produce either catecholate siderophores, or mixed siderophores, in which catecholates are only one of the produced groups. A typical example is Gammaproteobacterium *Pseudomonas*, producing a mixed siderophores (pyoverdines), which contains both catecholates and hydroxamates (Gulledge et al. 2002).

The structure is characterized by a C3 symmetrical trilactone ring from which the exocyclic nitrogen atoms are acylated by the dihydroxybenzoic acid group. These ligands bind Fe with high binding constants of up to 10^{47} (Avdeef et al. 1978). Iron depletion in a cell can be achieved by protonation of catecholate by enzymatic hydrolysis of the lactone ring or by reduction of Fe^{3+} to Fe^{2+} (Stintzi et al. 2000).

The Neilands test is commonly used for detection; complexes exhibit absorbance at 495 nm. An O-CAS test, based on the utilization of chrome azurol S reagent using an overlay technique, may also be used for fast, non-toxic, and easy method for siderophore production on a solid medium. However, it should be noted that all these tests based on different color complexes provide minimal information about the structure of the siderophores. Modern instrumental methods are based on diode array detector and electrospray mass spectrometry (ESI-MS) analysis.

Hydroxamates

Hydroxamate siderophores contain one of the most common siderophore groups found in nature. These siderophores are produced by many cyanobacteria but also by bacteria and fungi (Fig. 2). Most hydroxamate siderophores contain a O=CR-N(OH)R′ group wherein R or R′ are either an amino acid or a derivative thereof. The two oxygens in the hydroxamate group form a divalent iron ligand, and the siderophore is thus able to form a hexavalent octahedral complex with Fe^{3+}. Hydroxamates bind ferric ion and have binding constants in the range of 10^{22} to 10^{32} mol/L. This strong connection of ferric iron

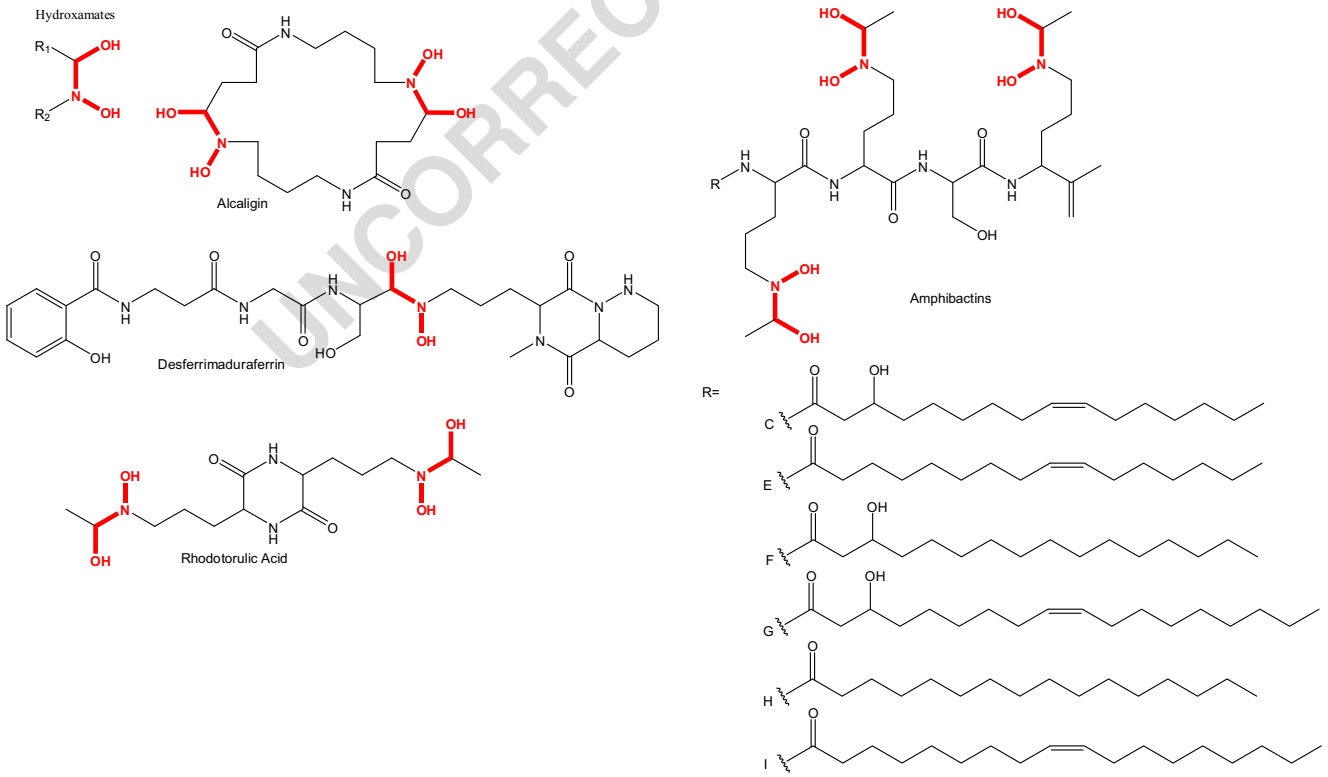
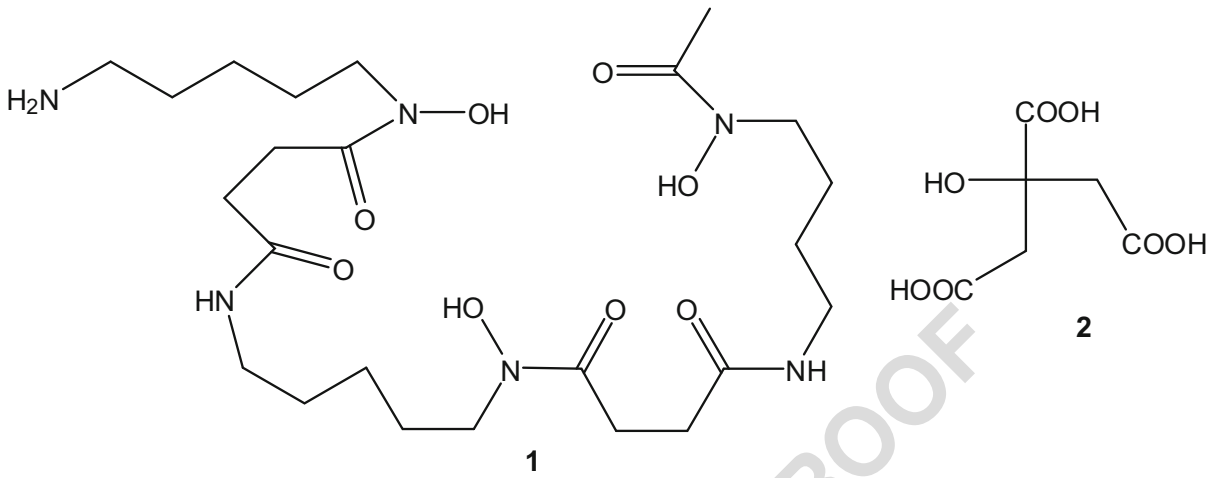


Fig. 2 The structures of hydroxamates

and siderophore protects complexes from hydrolysis and enzymatic degradation. An example is the hydroxamate siderophore desferrioxamine (*1*). The key building blocks are hydroxamic acid units that can chelate Fe^{3+}.



Carboxylates and hydroxycarboxylates

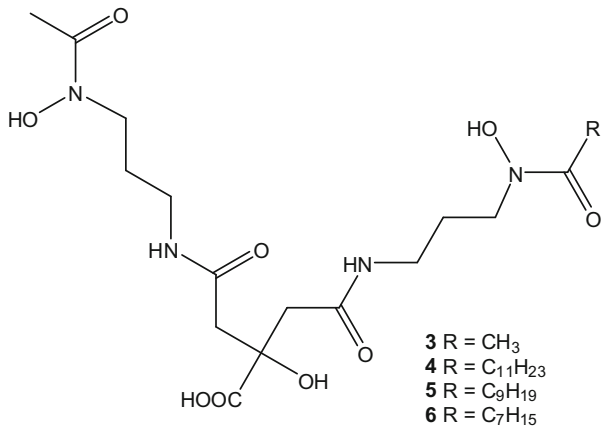
Siderophores containing the carboxylate group are often produced by cyanobacteria, (see Fig. 3). This type of siderophores binds to iron through carboxyl and hydroxyl groups. As a model compound, the basic building unit is citric acid (*2*). As described above, they can be detected by spectrophotometric assays, e.g., O-CAS or copper complex, and subsequent detection in the UV spectrum (190–280 nm). The LC-MS method has been used to determine the structure (Rao et al. 2002).

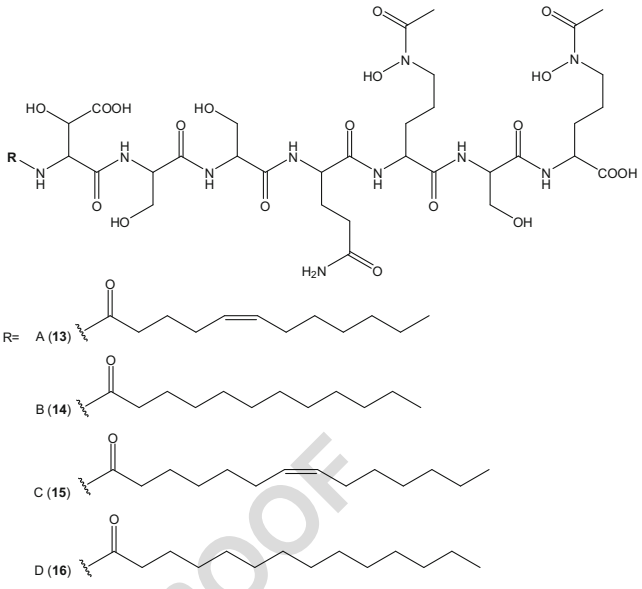
Cyanobacterial siderophores

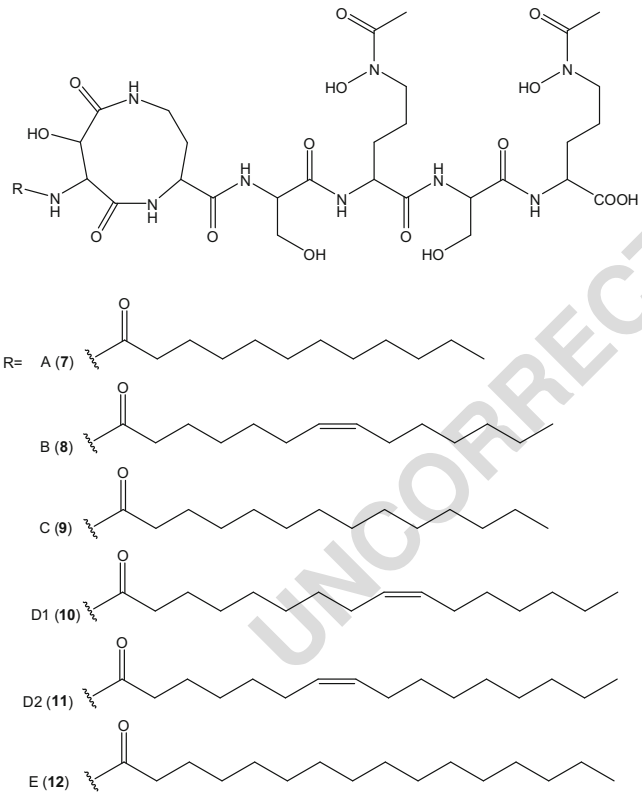
While bacterial siderophores have been actively investigated for decades, siderophores of cyanobacteria have been largely neglected. As an example, the number of citations in the Web of Science includes more than 9000 citations for the keywords "bacteria and siderophores," but only 208 papers are cited for the keywords "cyanobacteria and siderophores." There may be several causes of this. Based on our experience, we see them above all in the lower availability of cyanobacteria, especially cultivation of cyanobacteria under autotrophic conditions that requires specialized equipment. Long ago, the predominance of cyanobacteria as a microorganism living in water (whether fresh or sea water) produce only basic siderophores of the simple hydroxamic (Armstrong and van Baalen 1979) or citric acid type (Simpson and Neilands 1976). It was the assumption that the formation of complex organic molecules is too energy-consuming and complex, because these compounds are highly diluted by excretion into the environment.

Siderophores from sea water cyanobacteria

The first mention of siderophore from cyanobacteria dates back to 1976 and concerned hydroxamate siderophores (Murphy et al. 1976) and siderophore schizokinen (*3*) isolated from freshwater *Anabaena* (Simpson and Neilands 1976; Lammers and Sanders-Loehr 1982; Goldman et al. 1983). This compound, originally isolated from the soil bacterium *Bacillus megaterium* (Lankford et al. 1966; Arceneaux and Lankford 1966), is a derivative of citric acid in which two carboxylate groups form an amide with an acetylhydroxamine. In 2005, synechobactins (*4*, *5*, *6*) were isolated from *Synechococcus* strain living in coastal seawater, and were shown to be siderophores (Ito and Butler 2005). A citrate group from synechobactin (*23*) was also found in petrobactin (*24*) (Barbeau et al. 2002). These compounds form schizoquinone derivatives, where one of the hydroxamic acids is replaced by long chain fatty acid. The authors assume that this amphiphilic structure helps to anchor siderophore into the membrane of the cyanobacteria and thus prevents its loss of dilution in the marine cyanobacteria. This is supported by data on several other amphiphilic siderophores isolated from the marine cyanobacteria, such as marinobactins (*7*–*12*), aquachelins A, B, C, and D (*13*–*16*) and amfibactins C, E, F, G, H, and I (*17*–*22*), all carrying a long hydrophobic chain (Martinez et al. 2003).







A mixture of complex siderophores called anachelins, i.e., H (*25*), 1 (*26*), and 2 (*27*) and anachelin esters (*28*, *29*) is produced by the cyanobacterium *Anabaena cylindrica*. These anachelins contain terminal salicylamide and

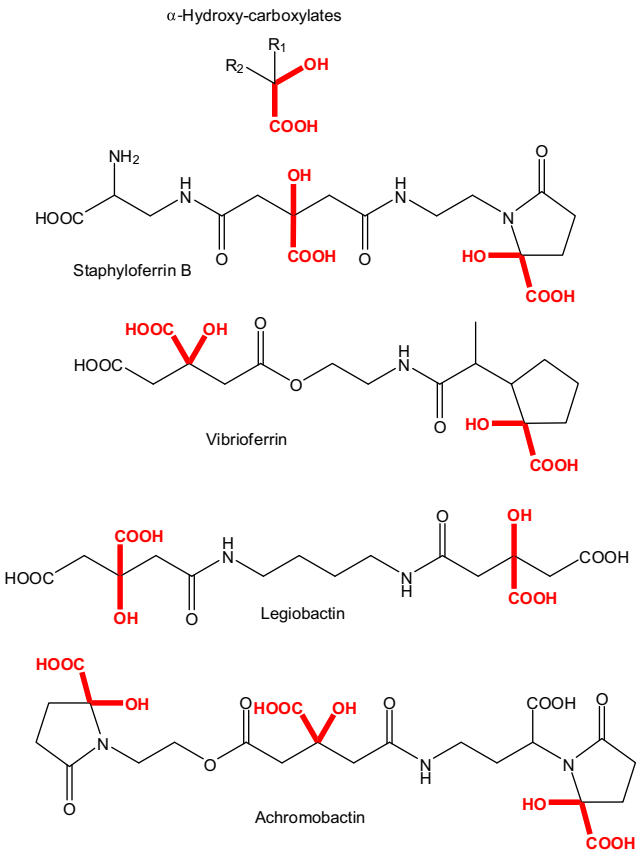
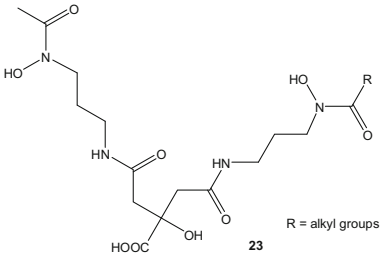


Fig. 3 The structures of α-hydroxy-carboxylates

Transfer of iron in the form of siderophores through the outer and inner membrane of the cyanobacteria is an energy-intensive process associated with hydrolysis of ATP (Armstrong et al. 2004; Martinez and Butler 2007). The biosynthesis of both siderophores and their protein receptor on the outside of the membrane is suppressed when the amount of iron in the intracellular space reaches the physiological boundary.

oxazoline ring (Beiderbeck et al. 2000). This indicates that these compounds are structurally complex metabolites that contain fragments of different biosynthetic origins. The salicylate unit can originate from a polyketide pathway or from chorismic acid; furthermore, anachelin contains a mixed fragment of polyketide and amino acid in the tripeptide moiety and an unusual fragment resembling the tetrahydroquinoline skeleton. Its structure, including determination of stereochemistry (absolute and relative configuration), was determined by Ito et al. (2001). Unfortunately, the complete determination of the structure is complicated by the formation of artifacts, i.e., by the formation of similar structures, for example due to hydrolysis upon standing in aqueous solution or by dehydration during lyophilization. Anachelin chromophore has been found to recognize metal oxide surfaces found in minerals. This postulated first step in iron uptake has a great effect on the molecular understanding of iron extraction in marine and freshwater organisms (Zürcher et al. 2006).



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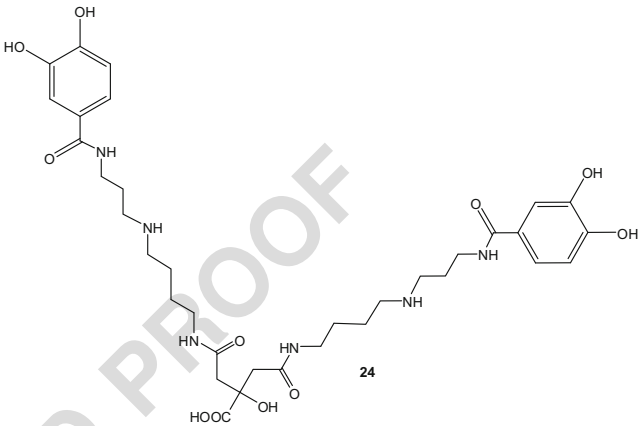

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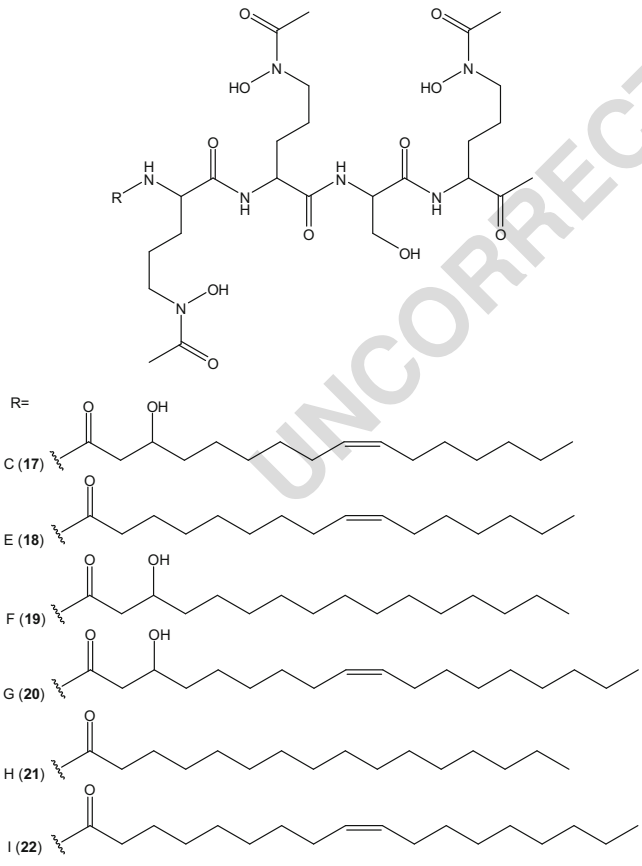
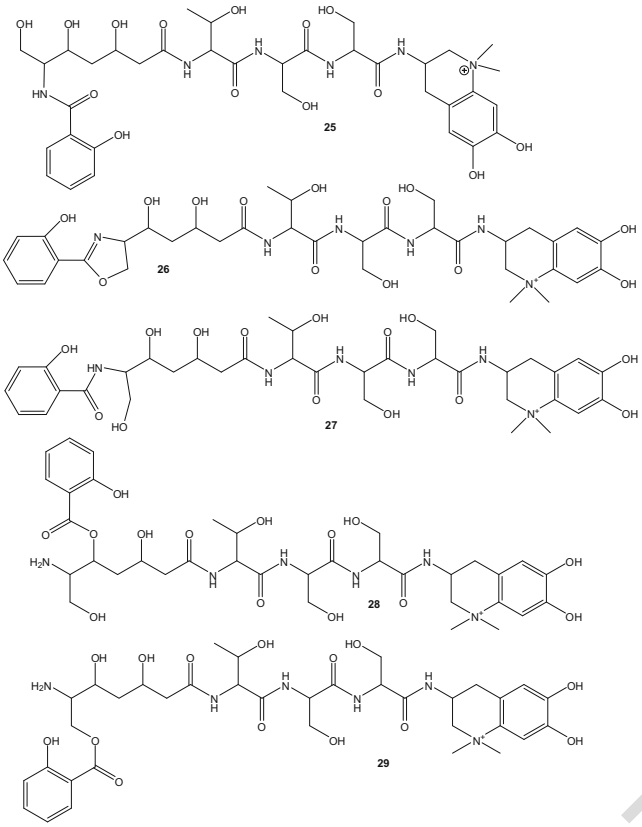
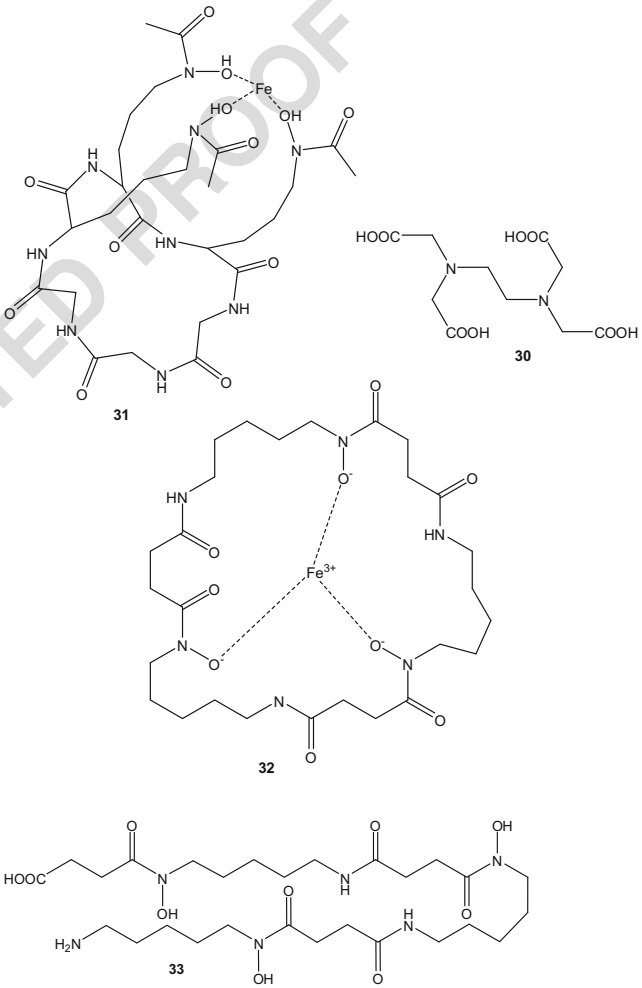


Four marine cyanobacteria belonging to the species *Nostoc calcicola*, *Oscillatoria boryana*, *Phormidium valderianum*, and *Synechococcus elongatus* were tested for the production of siderophores in a medium with low iron concentration (Rashmi et al. 2013). They were found to produce siderophores of the hydroxamate type. Uranium, a radionuclide, caused siderophore production in all four marine cyanobacteria, was tested. All the tested organisms in uranium-dosed media irrespective of the presence of iron showed siderophore production. The production of siderophore in the presence of uranium can be explained by the fact that uranium in the medium acts as a competitive agent and iron becomes unavailable to the organism. Furthermore, complexation of uranium and siderophore has been confirmed, which means that marine cyanobacteria can be used as organisms sequestering uranium as well as other actinides.



The use of modern physico-chemical methods, which were and are common in the identification of siderophores in bacteria (Pluháček et al. 2016), slowly gain a place also in the analysis of cyanobacteria. Boiteau and Repeta (2015) used high-performance liquid chromatography (HPLC), induced coupled plasma mass spectrometry (ICP/MS), and high-resolution electrospray ionization mass spectrometry (ESI/MS) to identify siderophores in *Synechococcus* sp. Three hydroxamate siderophores, synechobactins A-C (*4*–*6*) have previously been isolated and characterized in this cyanobacterium. Their structure is based on citric acid backbone and two hydroxamates linked to the side chains, which form variable length chain fatty acids from C8 to C12 (R is even numbered, i.e., C7, C9, and C11). In total, six complex organic compounds were identified by LC-ICP/MS and LC-ESI/MS further identified synechobactins A, B, and C based on the tandem mass spectra. In addition, new synechobactins having homologous fatty acid moieties, i.e., C11, C13, and C14 were identified. These results show the potential of combined LC/MS techniques for the identification of novel iron organic complexes.

Siderophores in marine bacterium *Vibrio cyclitrophicus* and marine cyanobacterium *Synechococcus* sp. were characterized using 21 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FTICR/MS) with injection electrospray ionization. Thanks to this technique, synechobactins A (*4*), B (*5*), C (*6*), C11, C13, and C14 were identified based on high mass accuracy and resolution for observation of specific Fe isotopes and high-resolution mass spectra (Walker et al. 2017). The use of a highly sophisticated method such as the high-resolution FTICR/MS will enable researchers to quickly discover and identify new siderophores in the environment.



Imaging mass spectrometry (IMS) using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) was applied to determine metabolic products of the genes of three

cyanobacteria of genera *Microcystis*, *Anabaena*, and *Nodularia* (Sandonato et al. 2017). Among others, siderophore anachelins, e.g., *25*, etc., were also identified and displayed. The examples show the great potential of IMS for spatial monitoring of biochemical processes in cyanobacteria.

Siderophores from marine-ocean plankton

The RP-HPLC/ESI tandem MS method using ICP/MS for detecting low concentrations of organic Fe ligands was used to determine siderophores in sea water and marine phytoplankton. The detection limit was less than 1 pmol of Fe, and the effect of the $^{40}Ar^{16}O^{+}$ adduct which could interfere with ^{56}Fe (Boiteau et al. 2013) was eliminated due to the ICP-MS multicollector. The analysis was performed on both standards (e.g., Fe-EDTA (*30*), ferrichrome (*31*), ferrioxamine E (*32*)) as well as Fe ligand complexes extracted from South Pacific surface water and *Synechococcus* spp. The method allows for fast and especially sensitive determination of Fe ligand complexes, while the popular chrome azurol sulfonate (CAS) assay is three orders of magnitude less sensitive (1 μmol/L by this method versus the detection limit of 2 nmol/L of free ligand by CAS) (Schwyn and Neilands 1987; Hasegawa et al. 2004). This assay is based on the transfer of ferric iron complexed with CAS to siderophores, which is accompanied by a shift from blue to yellow.

The siderophores ferrioxamine E (*32*) and desferrioxamine G (*33*) from the Atlantic Ocean were identified by HPLC-ESI/MS using electrospray ionization, ranging from 0.1 to 11.6 μmol/L (Mawji et al. 2008). Surprisingly, the concentrations of both ferrioxamines were low, in units of pmol/L as compared to dissolved iron, around 0.58 nmol/L. Unfortunately, the authors analyzed only a small part of the known siderophores present in ocean waters. If the sum of all siderophores were taken into account, the ratio of 1:1000 will change significantly.

Velasquez et al. (2011) detected the hydroxamate siderophores in the coastal and sub-Antarctic waters off the South East Coast of New Zealand and determined them using chrome azurol S assay, competing ligand equilibration-cathodic stripping voltammetry and liquid chromatography-tandem mass spectrometry using the natural iron-isotope pattern. Unfortunately, the authors did not take advantage of the excellent possibility of comparing the results of all three methods, as they themselves wrote "No quantification of siderophorous type compounds by LC-MS was pursued".

Identification and quantification of siderophores (ferrioxamines B, E, and G) from the water collected in the lower latitudes in the Atlantic Ocean was carried out by LC-ICP/MS and LC-ESI/MS) (Mohamed and Gledhill 2015). It has been found that the concentration of the above mentioned siderophores is only a dozen attomol (10^{-18} mol).

HPLC-ESI/MS was used for separation and detection of siderophores produced by marine bacterioplankton (McCormack et al. 2003). The Fe^{3+} complexes of the hydroxamate siderophores rhodotoluric acid, deferrioxamine B, and deferrichrome were identified with detection limits for the 26 nmol/L for Fe^{3+} rhodotoluate, 0.23 nmol/L for ferrioxamine, and 0.40 nmol/L for ferrichrome. Although the tandem MS method was used, the main peak B from seawater was not identified after HPLC-ESI/MS^2.

Photochemical reactions of siderophores

One of the many ways to reduce the efficiency of siderophores released into the environment is their photoreactivity, which includes photochemical reactions involving reactive oxygen species, but also direct photolysis of Fe^{3+}-siderophore complexes. It has been reported (Barbeau et al. 2003) that photoreactivity of siderophores is primarily determined by the structure of the linking groups which they form—hydroxamate, catecholate, or

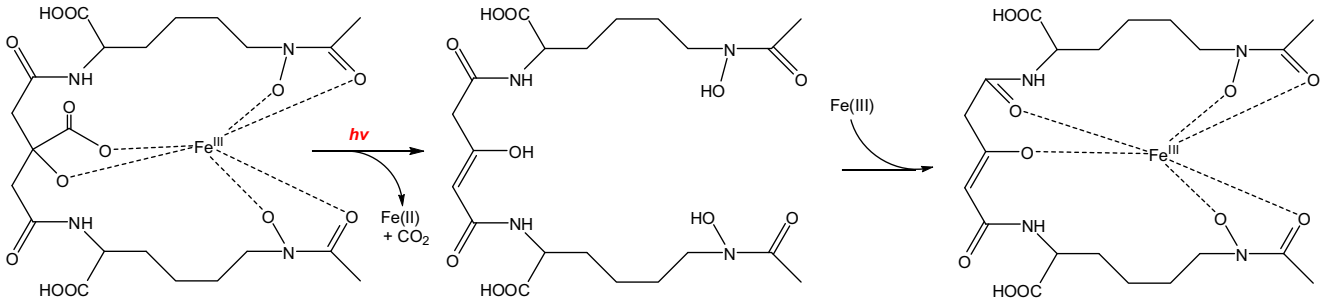
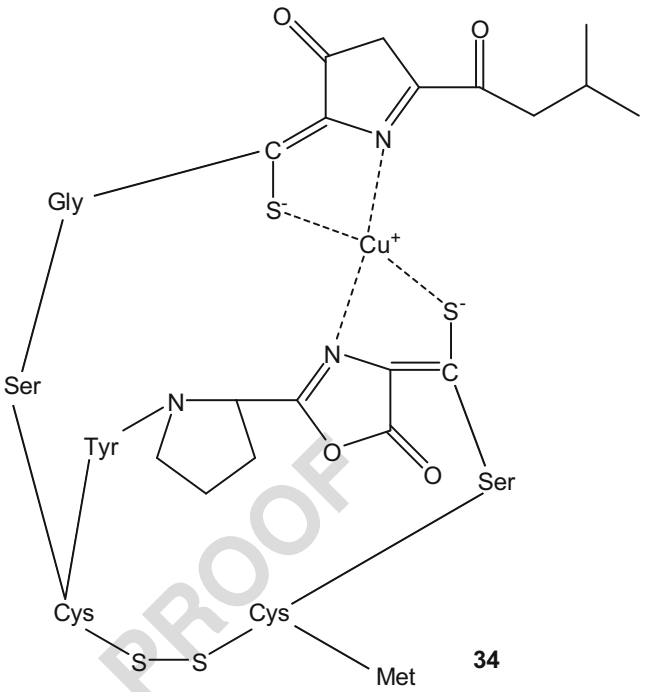


Fig. 4 Photolysis of Fe^{3+}-aerobactin by ultraviolet light

t1.1 **Table 1** The examples of trace metals solution used for cultivation of cyanobacteria

Salt
$Cd(NO_3)_2.4H_2O$
$CoSO_4.7H_2O$
$Cr(NO_3)_3.9H_2O$
$CuSO_4.5H_2O$
$MnSO_4.4H_2O$
$(NH_4)_6Mo_7O_{24}.4H_2O$
$NiSO_4(NH_4)_2SO_4.6H_2O$
$V_2O_4(SO_4)_3.16H_2O$
$Na_2WO_4.2H_2O$
$ZnSO_4.7H_2O$



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α-hydroxycarboxylate moieties. Catecholates are prone to photooxidation in a noncomplex form, i.e., without Fe complex, but are stabilized against light-induced oxidation when combined or mixed with ferrate or other iron compounds. Alpha-hydroxycarboxylate groups, on the other hand, are stable in uncomplexed form. In the form of a complex with Fe, they oxidize after light induction to form Fe^{2+} and, on the other hand, the hydroxamate siderophores are photochemically resistant irrespective of the complexation of Fe.

These photochemical properties determine the reactivity of siderophores in the complex with Fe^{3+} in surface waters, which can significantly affect the biogeochemical cycle of iron. In photolysis of Fe^{3+}-aerobactin by ultraviolet light (~300 nm), Fe^{3+} is reduced to Fe^{2+} and the ligand is oxidized to produce a photoproduct (Fig. 4) which can also coordinate Fe^{3+} through the remaining hydroxamate groups (Barbeau et al. 2001).

Conclusion

Furthermore, it is surprising that although dozens of articles are written in which the importance of other metals for the growth of cyanobacteria such as Cu, Zn, Co, and Cd, as well as others, e.g. Co, Ni, V, Mo, Mn, including the addition of a mixture of their salts to the culture medium, see Table 1, their presence in the metal complexes with organic ligands present in marine water is totally unexplored (Leão et al. 2007) and so the knowledge of the structure of these complexes is at the very beginning.

By way of example, the complex organic methanobactin compound (*34*), in which copper is bound, has been isolated from an obligatory aerobic and methane-oxidizing α-proteobacterium *Methylosinus trichosporium*, not from a cyanobacterium (Kim et al. 2004).

Further developments in gaining more information on the siderophores in cyanobacteria are seen primarily in the following areas. With today's instrumentation, especially LC-ICP/MS, LC high-resolution ESI tandem MS, possibly in conjunction with LC-NMR, etc., it is possible to determine the structure from about 1 mg of an organocomplex. However, considerable problems that it is necessary first to get enough starting substances (mixtures of substances). This is especially possible by cultivating cyanobacteria in a medium containing no iron. Based on our experience and supported by ICP/MS (unpublished data), the iron in the culture medium is always contained, mostly in the chemicals used, or in the water used for cultivation. Another option, especially for marine cyanobacteria, is to filter and extract siderophores from this water, which comes from seawater. After determining the structure, it is also possible to collect water in areas with a naturally low concentration of iron, which is about 20% of the total area of the oceans (Vraspir and Butler 2009).

Boiteau et al. (2016) describes that siderophores as an important active component of the microbial iron cycling in the ocean. The report shows that horizontal transfer of the amphibactin NRPS biosynthetic gene cluster across Gammaproteobacteria could give some microorganisms the ability to produce of siderophore and iron uptake abilities, which gives them a competitive advantage in iron-poor oceans.

High sensitivity molecular technology (qPCR) to search for siderophore biosynthesis genes related to the

production of photoactive siderophores (Gärdes et al. 2013) or using degenerate PCR and the sequencing of cloned products demonstrated that NRPSs and PKSs genes have remarkable diversity and likely novelty within the cyanobacteria (Ehrenreich et al. 2005).

On this basis, further experiments on physiology, biochemistry, and genetics of cyanobacteria can be developed.

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References

Arceneaux JL, Lankford CE (1966) A schizokinen (siderochrome) auxotroph of *Bacillus megaterium* induced with N-methyl-N'-nitro-N-nitrosoguanidine. Biochem Biophys Res Commun 24(3):370–375

Armstrong JE, van Baalen C (1979) Iron transport in microalgae: the isolation and biological activity of a hydroxamate siderophore from the blue- green alga Agmenellum quadruplicatum. J Gen Microbiol 111:253–262

Armstrong E, Granger J, Mann EL, Price NM (2004) Outer-membrane siderophore receptors of heterotrophic oceanic bacteria. Limnol Oceanogr 49(2):579–587

Avdeef A, Sofen SR, Bregante TL, Raymond KN (1978) Coordination chemistry of microbial iron transport compounds. 9. Stability constants for catechol models of enterobactin. J Am Chem Soc 100(17): 5362–5370

Barbeau K, Rue EL, Bruland KW, Butler A (2001) Photochemical cycling of iron in the surface ocean mediated by microbial iron(III)-binding ligands. Nature 413:409–413

Barbeau K, Zhang G, Live DH, Butler A (2002) Petrobactin, a photoreactive siderophore produced by the oil-degrading marine bacterium *Marinobacter hydrocarbonoclasticus*. J Am Chem Soc 124(3):378–379

Barbeau K, Rue EL, Trick CG, Bruland KW, Butler A (2003) Photochemical reactivity of siderophores produced by marine heterotrophic bacteria and cyanobacteria based on characteristic Fe(III) binding groups. Limnol Oceanogr 48(3):1069–1078

Beiderbeck H, Taraz K, Budzikiewicz H, Walsby AE (2000) Anachelin, the siderophore of the cyanobacterium *Anabaena cylindrica* CCAP 1403/2A. Z Naturforsch C 55(9–10):681–687

Blankenship RE, Hartman H (1998) The origin and evolution of oxygenic photosynthesis. Trends Biochem Sci 23(3):94–97

Boiteau RM, Repeta DJ (2015) An extended siderophore suite from *Synechococcus* sp. PCC 7002 revealed by LC-ICPMS-ESIMS. Metallomics 7(5):877–884

Boiteau RM, Fitzsimmons JN, Repeta DJ, Boyle EA (2013) Detection of iron ligands in seawater and marine cyanobacteria cultures by high-performance liquid chromatography-inductively coupled plasma-mass spectrometry. Anal Chem 85(9):4357–4362

Boiteau RM, Mende DR, Hawco NJ, McIlvin MR, Fitzsimmons JN, Saito MA, Sedwick PN, DeLong EF, Repeta DJ (2016) Siderophore-based microbial adaptations to iron scarcity across the eastern Pacific Ocean. PNAS 113(50):14237–14242

Crichton RR (2001) Inorganic biochemistry of iron metabolism: from molecular mechanisms to clinical consequences, 2nd edn. Wiley, New York

Drechsel H, Jung G (1998) Peptide siderophores. J Pept Sci 4(3):147–181

Ehrenreich IM, Waterbury JB, Webb EA (2005) Distribution and diversity of natural product genes in marine and freshwater cyanobacterial cultures and genomes. Appl Environ Microbiol 71(11):7401–7413

Gärdes A, Triana C, Amin SA, Green DH, Romano A, Trimble L (2013) Detection of photoactive siderophore biosynthetic genes in the marine environment. Biometals 26(3):507–516

Goldman SJ, Lammers PJ, Berman MS, Sanders-Loehr J (1983) Siderophore-mediated iron uptake in different strains of *Anabaena* sp. J Bacteriol 156(3):1144–1150

Gulledge BM, Aggen JB, Huang HB, Nairn AC, Chamberlin AR (2002) The microcystins and nodularins: cyclic polypeptide inhibitors of PP1 and PP2A. Curr Med Chem 9(22):1991–2003

Haque F, Banayan S, Yee J, Chiang YW (2017) Extraction and applications of cyanotoxins and other cyanobacterial secondary metabolites. Chemosphere 183:164–175. https://doi.org/10.1016/j.chemosphere.2017.05.106

Hasegawa H, Maki T, Asano K, Ueda K, Ueda K (2004) Detection of iron(III)-binding ligands originating from marine phytoplankton using cathodic stripping voltammetry. Anal Sci 20(1):89–93

Hopkinson BM, Morel FM (2009) The role of siderophores in iron acquisition by photosynthetic marine microorganisms. Biometals 22(4):659–669. https://doi.org/10.1007/s10534-009-9235-2

Ito Y, Butler A (2005) Structure of synechobactins, new siderophores of the marine cyanobacterium *Synechococcus* sp. PCC 7002. Limnol Oceanogr 50(6):1918–1923

Ito Y, Okada S, Murakami M (2001) Two structural isomeric siderophores from the freshwater cyanobacterium *Anabaena cylindrica* (NIES-19). Tetrahedron 57:9093–9099

Kim HJ, Graham DW, DiSpirito AA, Alterman MA, Galeva N, Larive CK, Asunskis D, Sherwood PM (2004) Methanobactin, a copper-acquisition compound from methane-oxidizing bacteria. Science 305(5690):1612–1615

Lammers PJ, Sanders-Loehr J (1982) Active transport of ferric schizokinen in *Anabaena* sp. J Bacteriol 151(1):288–294

Lankford CE, Walker JR, Reeves JB, Nabbut NH, Byers BR, Jones RJ (1966) Inoculum-dependent division lag of *Bacillus* cultures and its relation to an endogenous factor(s) ("schizokinen"). J Bacteriol 91(3):1070–1079

Leão PN, Vasconcelos MT, Vasconcelos VM (2007) Role of marine cyanobacteria in trace metal bioavailability in seawater. Microb Ecol 53(1):104–109

Martinez JS, Butler A (2007) Marine amphiphilic siderophores: marinobactin structure, uptake, and microbial partitioning. J Inorg Biochem 101(11–12):1692–1698

Martinez J, Carter-Franklin J, Mann E, Martin J, Haygood M, Butler A (2003) Structure and membrane affinity of a suite of amphiphilic siderophores produced by a marine bacterium. Proc Natl Acad Sci U S A 100:3754–3759

Mawji E, Gledhill M, Milton JA, Tarran GA, Ussher S, Thompson A, Wolff GA, Worsfold PJ, Achterberg EP (2008) Hydroxamate siderophores: occurrence and importance in the Atlantic Ocean. Environ Sci Technol 42(23):8675–8680

McCormack P, Worsfold PJ, Gledhill M (2003) Separation and detection of siderophores produced by marine bacterioplankton using high-performance liquid chromatography with electrospray ionization mass spectrometry. Anal Chem 75(11):2647–2652

Mohamed KN, Gledhill M (2015) Determination of specific iron chelator by using LC-ICP-MS and LC-ESI-MS. Procedia Environ Sci 30: 256–261

Morrissey J, Bowler C (2012) Iron utilization in marine cyanobacteria and eukaryotic algae. Front Microbiol 3:43. https://doi.org/10.3389/fmicb.2012.00043

Murphy TP, Lean DR, Nalewajko C (1976) Blue-green algae: their excretion of iron-selective chelators enables them to dominate other algae. Science 192(4242):900–902

Pluháček T, Lemr K, Ghosh D, Milde D, Novák J, Havlíček V (2016) Characterization of microbial siderophores by mass spectrometry. Mass Spectrom Rev 35(1):35–47

Rao PV, Gupta N, Bhaskar AS, Jayaraj R (2002) Toxins and bioactive compounds from cyanobacteria and their implications on human health. J Environ Biol 23(3):215–224

Rashmi V, Shylajanaciyar M, Rajalakshmi R, D'Souza SF, Prabaharan D, Uma L (2013) Siderophore mediated uranium sequestration by marine cyanobacterium *Synechococcus elongatus* BDU 130911. Bioresour Technol 130:204–210

Raymond KN, Muller G, Matzanke BF (1984) Complexation of iron by siderophores—a review of their solution and structural chemistry and biological function. Top Curr Chem 123:49–102

Sandonato BB, Santos VG, Luizete MF, Bronzel JL Jr, Eberlinb MN, Milagre HMS (2017) MALDI imaging mass spectrometry of fresh water cyanobacteria: spatial distribution of toxins and other metabolites. J Braz Chem Soc 28(4):521–528

Schwyn B, Neilands JB (1987) Universal chemical-assay for the detection and determination of siderophores. Anal Biochem 160(1):47–56

Simpson FB, Neilands JB (1976) Siderochromes in cyanophyceae: isolation and characterization of schizokinen from *Anabaena* sp. J Phycol 12:44–48

Stintzi A, Barnes C, Xu J, Raymond KN (2000) Microbial iron transport via a siderophore shuttle: a membrane ion transport paradigm. Proc Natl Acad Sci U S A 97(20):10691–10696

Summons RE, Jahnke LL, Hope JM, Logan GA (1999) 2-Methylhopanoids as biomarkers for cyanobacterial oxygenic photosynthesis. Nature 400(6744):554–557

Velasquez I, Nunn BL, Ibisanmi E, Goodlett DR, Hunter KA, Sander SG (2011) Detection of hydroxamate siderophores in coastal and sub-Antarctic waters off the South Eastern Coast of New Zealand. Mar Chem 126(1–4):97–107

Vraspir JM, Butler A (2009) Chemistry of marine ligands and siderophores. Annu Rev Mar Sci 1:43–63

Walker LR, Tfaily MM, Shaw JB, Hess NJ, Paša-Tolić L, Koppenaal DW (2017) Unambiguous identification and discovery of bacterial siderophores by direct injection 21 Tesla Fourier transform ion cyclotron resonance mass spectrometry. Metallomics 9(1):82–92

Zürcher S, Wäckerlin D, Bethuel Y, Malisova B, Textor M, Tosatti S, Gademann K (2006) Biomimetic surface modifications based on the cyanobacterial iron chelator anachelin. J Am Chem Soc 128(4): 1064–1065