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Highlights of cyanobacterial metabolites reported between 2021–2024

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This review highlights cyanobacteria secondary metabolites reported between 2021 and 2024. Those compounds are categorised into major classes, including peptides, alkaloids, lipids, polyketides, terpenes/terpenoids, and natural products from other classes. For selected compounds, the review provides details of advanced methodologies employed in their discovery, isolation and structure elucidation. Particular attention is placed on techniques for determining the relative and absolute configurations of stereocentres, including computational approaches, chemical derivatisation, and total synthesis. Furthermore, the review outlines the biosynthetic pathway of several newly identified cyanobacterial natural products.

1. Introduction

Cyanobacteria are a well-recognised source of bioactive metabolites, and their chemical diversity and biological potential continue to attract substantial attention, as reflected by the numerous reports published each year.[1–14] In this review, we summarised novel natural products isolated from cyanobacteria over a recent time frame (2021 to 2024), allowing for a more in-depth discussion of a selected set of these compounds. Particular focus is placed on the methodologies employed for the structure elucidation, a process that is often complex and requires the integration of complementary techniques. In most cases, nuclear magnetic resonance (NMR) and mass spectrometry (MS) provide sufficient information to define the core structure and relative configuration of the natural products. However, assigning the absolute configuration is typically more challenging and frequently requires additional methodologies, such as computational approaches, chemical derivatisation, or total synthesis.[15–24] In some cases, biosynthetic insights derived from metagenomic analysis greatly facilitate both structural assignment and stereochemical determination. This review highlights representative examples illustrating the application of these methodologies to the structural characterisation of cyanobacterial metabolites.

Novel cyanobacterial metabolites are constantly being discovered, with 3162 entries (Fig. 1) as of the end of 2024, of which 3084 are listed in the open-access structural database CyanoMetDB (Version 03, 2024). This includes 110 compounds that have not been unequivocally associated with cyanobacteria, are of synthetic origin, or resemble degradation products.[25] In the years 2021 through 2024, a total of 335 metabolites have been newly reported, with 58, 99, 108, and 70 each respective year, highlighting the importance of these organisms as a source of novel natural products.

Herein, we report selected newly discovered structures and order them by compound class, including peptides, alkaloids, lipids, polyketides, terpenes/terpenoids, and natural products from other classes.

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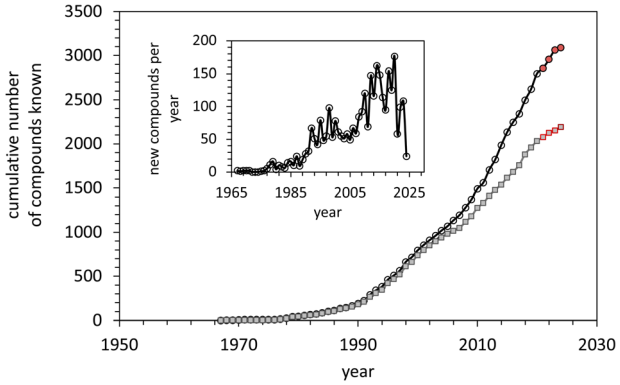

Fig. 1 Cumulative number of identified secondary metabolites from cyanobacteria between 1967–2024 for compounds identified using nuclear magnetic resonance (NMR) spectroscopy (grey diamonds), others mainly relying on mass spectrometry (black circles), with the years 2021, 2022, 2023, and 2024 marked in red. The inset shows the number of new compounds published each year.

2. Peptides

Peptides can have two different biosynthetic origins; they can be produced by ribosomes or by large non-ribosomal peptide synthetases (NRPS) complexes.[26] Structural diversity in ribosomally produced peptides is greatly increased by the action of tailoring enzymes, giving rise to the so-called ribosomally synthesised and post-translationally modified peptides (RiPPs).[27] Cyanobacteria are known to produce a great variety of peptides from NRPS and many families of RiPPs,[28] such as, for example, graspetides, cyanobactins, and proteusins.[29–32] The significance of these peptide classes is highlighted by the observation that more than 60 per cent of known cyanobacterial secondary metabolites contain at least one amide bond.[25] Between 2021 and 2024, a total of 253 new peptide-based metabolites were described, representing 75 per cent of all new metabolites in this time span. Many of these belong to familiar cyanopeptide classes, including 86 cyanopeptolins, 19 microginins, 8 anabaenopeptins, 8 microcystins, and 3 microviridins.

2.1. Ahp-cyclodepsipeptides

This class of cyclic peptides includes all compounds that possess the unusual 3-amino-6-hydroxy-2-piperidone (Ahp) moiety. Compounds from this class have recently been reviewed, covering 1989 to 2019.[33] Names vary significantly among members, including symplocamide, micropeptins, lyngbyastatins, and cyanopeptolins, which constitute most of the reported compounds. Between 2021 and 2024, 86 new cyanopeptolins have been identified, representing nearly 30% of the 291 known variants of the cyanopeptide class. Of those, 79 new cyanopeptolins alone were identified from *Nostoc edaphicum* CCNP1411 isolated from coastal waters in the Gulf of Gdańsk.[34] This *Nostoc* strain produces a total of 93 cyanopeptolins,[34–36] which is arguably the highest number of cyanopeptides ever recorded in a single strain. This high number is an impressive demonstration of how NRPS can lead to a wealth of structural modifications around a core scaffold of cyanopeptides. Mazur-Marzec and colleagues present an overview not only of the structural diversity of cyanopeptolins but also of the similarly diverse naming convention.[34] The characteristic features of cyanopeptolins are a cyclic structure of six amino acids, linked together through an ester bond (depsipeptide) and with the residue Ahp. The team detected 67 of the 79 cyanopeptolins from *Nostoc edaphicum* from liquid chromatography-high-resolution tandem mass spectrometry (LC-HRMS/MS) data while noting the limitations of structure elucidation based on MS/MS alone. Six cyanopeptides (CP999, CP990, CP983, CP949, CP941, and CP919) were isolated in sufficient quantities to confirm the structure assignments by 1D and 2D NMR analyses (500 MHz and 700 MHz, respectively). Additional NMR analysis of a previously published cyanopeptolin, CP999, led to a building block re-assignment to *N*,*O*-di-methyl tyrosine instead of methyl-homotyrosine formerly assigned by HRMS/MS,[37] emphasising the need to require a second line of spectroscopic evidence for structure elucidation. The bioactivity of 34 cyanopeptolins was further assessed, which allowed the proposal of a structure–activity relationship (SAR).[34] Inhibitory activity against trypsin was present when arginine is in position 2, while amino acids tyrosine, phenylalanine and leucine in position 2 inflicted inhibition of chymotrypsin, and elastase inhibition was present with leucine in position 2 and enhanced by 2-amino-2-butenoic acid at the N-terminus of the side chain (Fig. 2). The study also found that the viability of human cervical cancer (HeLa) cells was significantly decreased (at least 60%) by cyanopeptolins with arginine or leucine at position 2, making them potentially interesting compounds for pharmaceutical applications industries. Furthermore, additional Ahp-cyclodepsipeptides, named micropeptins LOF941, LOF925, and LOF953, have been isolated from a benthic mat dominated by a *Microcoleus autumnalis* strain.[38] The potent neurotoxin anatoxin-a was also detected in this extract, which resonates well with several recent studies reporting the production of anatoxin-a/dihydroanatoxin-a from *Microcoleus* strains around the world.[39–47]

In 2021, five novel cyclic peptides were identified by functional metabolomics using native mass spectrometry, which

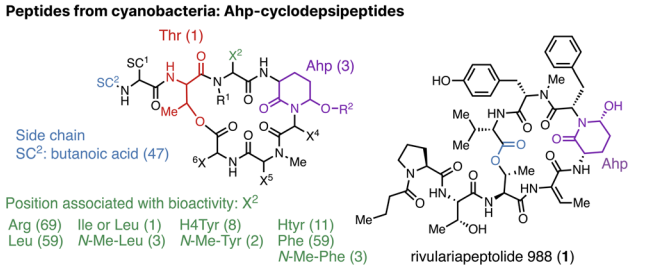

Fig. 2 General structure of cyanopeptolins listing common variants at position 2 (X^2) associated with bioactivity and butanoic acid (BA) at the terminus of the side chain (SC^2). The number of cyanopeptide variants with the respective variation is given in brackets based on CyanoMetDB (Version 03, 2024).[25] Potent protease inhibitor rivulariapeptolide 988 (**1**) isolated from *Rivularia* spp. PCC 7116.[48]

detected ligands, *i.e.* metabolites, directly bound to an enzyme.[48] To improve the identification of specific protein-metabolite interactions, Ultra-high performance liquid chromatography (UHPLC) separation was performed, followed by post-column pH and water content adjustment to make the conditions suitable for native MS, and the addition of a protein-binding partner, *i.e.*, chymotrypsin. By continuously infusing chymotrypsin post-column, a mass shift indicated when metabolites bind to this serine protease at a given retention time. Extracted metabolites from *Rivularia* spp. PCC 7116 were analysed by this technique, and a total of 30 chymotrypsin ligands were tentatively identified. Comparison with structural and spectral databases revealed that most were unknown at the time. Five such binding metabolites were isolated, their structures were elucidated by HRMS/MS, chemical derivatisation and NMR, and they were termed rivulariapeptolides, including rivulariapeptolide 988 (**1**, Fig. 2). Rivulariapeptolides can be considered a new group of cyanopeptides belonging to the class of Ahp-cyclodepsipeptides.[33]

2.2. Microginins

Those compounds are characterised by their linear peptidic scaffold terminating with 3-amino-2-hydroxydecanoic acid (Ahda) residue at the N-terminus.[49,50] Their structural diversity comprises variation in the number and identity of amino acids and in the modification of the aliphatic side chain by chlorination or deoxygenation, yielding the 3-aminodecanoic acid (Ada) moiety,[51] or further variation such as 2-amino-5-(4-hydroxyphenyl)pentanoic acid (Ahppa).[52] A wide variety of microginins have been newly reported, with 19 new members representing 15% of the total of variants identified to date.[51–53] Recent success relied on knowledge and characterisation of biosynthetic gene clusters (BGCs). For example, a metagenomic screen targeting homologues of the dimetal-carboxylate halogenase CylC[54] identified several microginin-producing strains.[55] The corresponding biosynthetic gene cluster, a hybrid polyketide synthase(PKS)/NRPS (PKS/NRPS) assembly, was designated *mic*.[51] The *mic* gene cluster from *Microcystis aeruginosa* LEGE 91341 was characterised in detail, and its heterologous expression in *Escherichia coli* using direct pathway cloning (DiPaC) technology led to the production of 12 new microginin congeners (Fig. 3).[51] As demonstrated, identification of the BGC

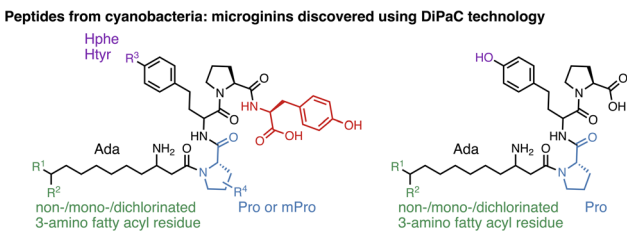

Fig. 3 General structure of 12 newly identified microginins based on the Ada, Pro/mPro, Hphe/Htyr, Pro, and Tyr residues containing non, mono or dichlorinated side chains with three variants missing the C-terminal Tyr.[51] Ada: 3-aminodecanoic acid; mPro: methyl proline; Hphe: homophenylalanine; Htyr: homotyrosine.

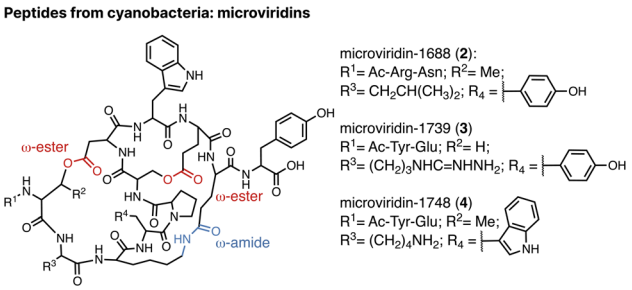

Fig. 4 Microviridins 1688 (**2**), 1739 (**3**), and 1748 (**4**) isolated from *Nostoc* sp. Th1SO1.[60]

for a natural product class and heterologous expression in model organisms can serve as a second line of evidence and allow for the production of larger quantities for novel compound identification.

2.3. Microviridins

The common scaffold of those RiPPs consists of a tricyclic peptide containing two ω-esters and one ω-amide bond (Fig. 4).[56,57] Most microviridins have been found to possess potent protease–inhibitory activity, with values reaching the nanomolar range.[58,59] The success of employing genome mining to identify novel metabolite variants was also demonstrated by the discovery of three new microviridins from the mat-forming cyanobacterium *Nostoc* sp. TH1SO1.[60] Genome mining of a single isolated filament of the cyanobacterium *Nostoc* sp. TH1SO1 led to the identification of three microviridin BGCs, which collectively encode five *mdnA* precursor peptide genes, within a high-quality metagenome-assembled genome (MAG). LC-HRMS/MS analysis of the extract enabled the identification of microviridin-1688 (**2**), microviridin-1739 (**3**) and microviridin-1748 (**4**) originating from the first of these BGCs (Fig. 4). No microviridins were predicted to be produced by the two other gene clusters, suggesting that these BGCs are not expressed under the culture conditions. Following the hypothesis that quorum-sensing molecules may trigger activation, the authors also investigated the BGCs of epibiont MAGs recovered from the same isolated *Nostoc* strain. One of the four autoinducer synthases (SGBI from *Sphingobium*) was heterologously expressed in *E. coli*, and the production of homoserine lactones (HSLs) was evident, previously associated with biofilm development of the cyanobacterium *Gloeothece*.[61] When *Nostoc* sp. TH1SO1 was cultured with HSLs, up to a two-fold increase in microviridin-1688 production was observed, suggesting HSL-mediated quorum sensing.

2.4. Anabaenopeptins and microcystins

Both are cyclic peptides produced by NRPS modules, with anabaenopeptins characterised by a conserved ureido group and microcystins by the unique 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda) residue.[62–65] In recent years, eight new anabaenopeptins were identified[52,66–68] and the most novel finding was a glutamic acid Cα ethyl ester.[66]

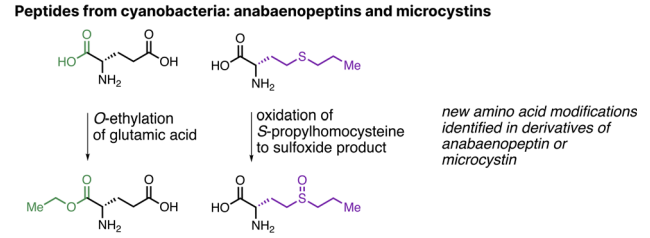

Fig. 5 *O*-Ethylation of glutamic acids and thioether oxidation to sulfoxide products are debated to be natural building blocks of secondary metabolites or artefacts formed during sample handling.[53,70]

This modified amino acid at this position had been proposed for only one variant before,[69] and none of the previously 126 known anabaenopeptin variants contained this residue at the C-terminus thus far, which is most often occupied by leucine, isoleucine, phenylalanine, arginine, or tyrosine.

Among the eight newly discovered microcystins,[53,70–73] two contained *S*-propylhomocysteine and its sulfoxide variant at position 2 (comparable to the position of leucine in MC-LR), namely MC-PrhcysR and MC-Prhcys(O)R, respectively (Fig. 5).[53] Cysteines are rare in microcystins, as they are present in only 8 of the 332 reported microcystins.[25] Two additional microcystins contain a glutamic acid methyl ester, where it is possible that the esterification is also an artefact resulting from the extraction process.[70]

2.5. Prenylated cyanobactins

Prenylation, catalysed by prenyltransferases (PTases), is a post-translational modification found in several organisms, including cyanobacteria.[74–76] The modification can occur at two positions of the prenyl group; attachment at the C-1 position is termed forward prenylation, and attachment at the C-3 position is called reverse prenylation.[77] The identification of the novel cyanobactin tolypamide (**5**, Fig. 6) from the cyanobacterium *Tolypothrix* sp. PCC 7601 revealed forward *O*-prenylation of the threonine residue, a previously unknown modification in cyanobacterial metabolites.[78] The corresponding TolF PTase shared only low sequence coverage with known PTases, and further characterisation demonstrated its selectivity for serine and threonine forward prenylation.

Mono- and bis-prenylations of the guanidine moiety of arginine have also been reported in three new natural products called argicyclamides A–C (**6–8**, Fig. 6).[79] The argicyclamides were isolated from the cyanobacterium *Microcystis aeruginosa* NIES-88, and the authors demonstrated that prenylation occurred at either one or both N^{ω} atoms of the guanidinium group of arginine. The structures of the compounds were elucidated by HRMS and NMR analyses and further supported by the total synthesis and heterologous expression of the unprenylated argicyclamide C (**8**). Furthermore, biosynthetic studies revealed that the precursor peptide is matured by an enzyme encoded in the BGC of another RiPP (kawaguchipeptins) produced by the same strain.[81–83] Additionally, the predicted PTase AgcF was identified in the argicyclamide BGC

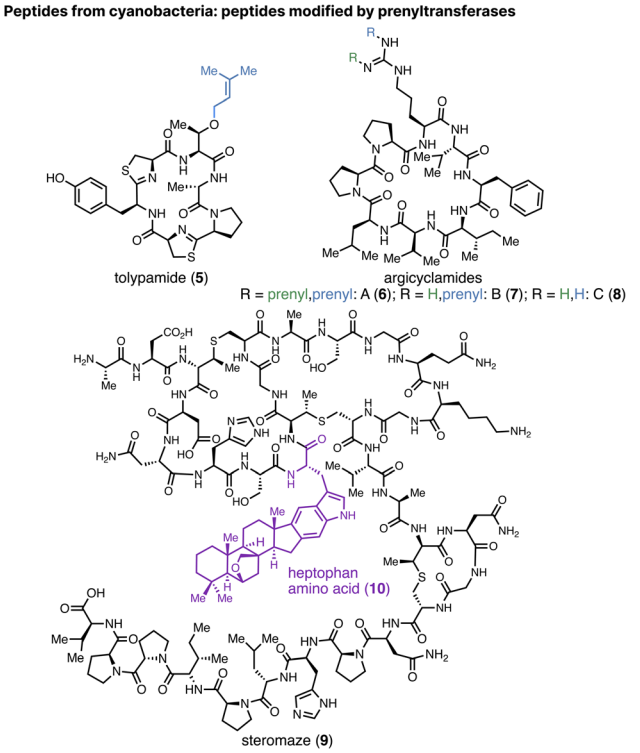

Fig. 6 Tolypamide (**5**) prenylated at threonine position isolated from *Tolypothrix* sp. PCC 7601 (ref. 78) and argicyclamides (**6–8**) mono- and diprenylated at the guanidine moieties of arginine from *Microcystis aeruginosa* NIES-88.[79] Steromaze (**9**) containing the post-translational modified heptophan amino acid (**10**) from *Nostoc calcicola* FACHB-389.[80]

and shows distinct sequence homology compared with previously identified guanidine PTases from cyanobacteria.

A more complex transformation was observed in the case of steromaze (**9**), with the formation of the heptophan amino acid (**10**) catalysed by a PTase-terpene cyclase (Fig. 6).[80] Metagenomic analysis targeting putative α-β-β-α architecture (ABBA-fold) PTases[84,85] led to the identification of a BGC named *nct* from *Nostoc calcicola* FACHB-389.This BGC contains two precursor peptides (NctA1 and NctA2), the predicted prenyltransferase-terpene cyclase (NctPC), a type II lanthionine synthetase (NctM) and an Fe^{II}/2-oxoglutarate-dependent oxygenase (NctI). Heterologous expression in *E. coli* was used to produce steromaze (**9**) from a modified NctA2 precursor peptide and the three maturation enzymes NctI, NctPC, and NctM. Its structure was elucidated using several analytical techniques, including NMR, MS, and chemical derivatisation. An extended version of steromaze, with five additional amino acids, was tested due to stability issues encountered during the final large-scale preparation step of **9**. This compound showed no cytotoxicity against HeLa cells at concentrations up to 125 μM, no antibacterial activity against several strains, including ESKAPE strains, at concentrations up to 134 μM, and exhibited anti-cyanobacterial activity against *Synechococcus elongatus* PCC 7942, with an IC_{50} of 61.2 μM. Interestingly, the non-prenylated analogue was also tested and found to be inactive against this cyanobacterium,

highlighting the importance of the heptophan amino acid for bioactivity.

2.6. Other lipopeptides

Lipopeptides constitute a diverse class of natural products characterised by fatty acid side chains. Between 2021 and 2024, 16 new linear lipopeptides have been described–caciqueamide,[86] cyanochelin A,[87] komesuamide,[88] odopenicillatamide,[88] phormidepistatin,[89] wenchangamide A,[90] amantamide B,[91] odookeanynes A and B,[92] pemuchiamides A and B,[93] amantamide C,[94] kavaratamides A-C,[95] *N*-desmethylmajusculamide B,[96] as well as 7 short-chain linear lipopeptides termed luquilloamides A-G.[97] The structural diversity and antifungal properties of cyclic lipopeptides have been presented in a recent review.[98] A group of eight new laxaphycins were discovered from *Nostoc* sp. UHCC 0702, adding to 28 previously published variants in this group of macrocyclic lipopeptides.[99] Among the 12 building blocks, a modified amino acid unusual among secondary metabolites in cyanobacteria was evident, 3-hydroxy-4-methylproline (OHMePro). The new compounds termed heinamides were shown to have antifungal properties identified by antimicrobial bioactivity screening against 19 strains of fungi and bacteria.[99] The complete genome (8.6 Mb) was assembled, harbouring the laxaphycin BGC (lxa, 93 kb) with 13 open reading frames and an unusual branch, as verified by heterologous expression. A review of microbial laxaphycins has also been published recently.[100] Six cyclic lipopeptides, each with a macrocycle of 10 or 12 amino acids, have been isolated from the cyanobacterium strain *Nodularia* sp. NIES-3585 and named noducyclamides A1-4 and B1-2.[101] Their bioactivity was evaluated, and noducyclamides A1, A2, and B1 were found to be active at low micromolar concentrations against the MCF7 breast cancer cell line. In addition, several novel aeruginosins (525,[102] KT688,[103] KT718,[103] and KT575) have recently been characterised and tested for protease-inhibitory activity.[103] Aeruginosin 525 is produced by the strain *Aphanizomenon* sp. KUCC C2, isolated from the Curonian Lagoon, Southeastern Baltic Sea.[102,104] The compound exhibits inhibitory activity against trypsin (IC_{50}: 71.7 μM), carboxypeptidase A (IC_{50}: 89.7 μM), and thrombin (IC_{50}: 0.59 μM). Aeruginosins KT688, KT718, and KT575 were isolated from *Microcystis* biomass collected in Lake Kinneret, Israel, during the 2016 spring bloom.[103] Aeruginosin KT688 inhibited trypsin with an IC_{50} value of 2.38 μM, and aeruginosin KT718 with an IC_{50} value of 1.43 μM. Furthermore, PM170453, which possesses a terminal alkyne functional group, was isolated from *Lyngbya* sp., and its structure features a depsipeptide macrocyclic core.[105]

2.7. Other peptides

In this section, natural products with peptidic scaffolds that do not fall into the preceding categories are described. Cyanobacterial blooms composed of *Lyngbya cf. confervoides* were collected during bloom seasons near the coast of Fort Lauderdale in Florida.[106] The cyclic peptide gatorbulin-1 (**11**, Fig. 7) was isolated *via* a bioassay-guided fractionation targeting anticancer compounds. The structure was elucidated by extensive

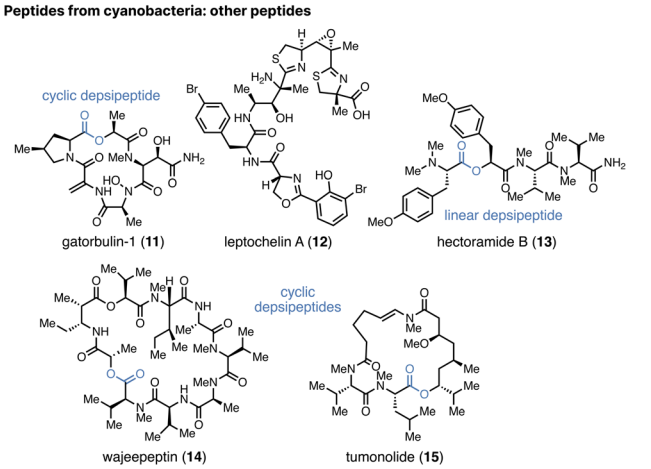

Fig. 7 Gatorbulin-1 (**11**), a highly modified tubulin binder, identified by activity-guided isolation,[106] the metallophore leptochelin A (**12**),[109] and three linear and cyclic depsipeptides: hectoramide B (**13**),[110] wajeepeptin (**14**),[111] and tumonolide (**15**).[112]

1D and 2D NMR analyses, together with Marfey's method[107] and chemical transformation to determine the absolute configuration. Gatorbulin-1 (**11**) is a cyclodepsipeptide containing unusual amino acid residues, including 4-methylproline, and featuring a hydroxamate group at the N terminus of alanine. To further evaluate the activity of the compound and confirm its structure, a total synthetic route was developed, providing **11** with an overall yield of 5.6% over 20 steps. The cytotoxic profile of gatorbulin-1 (**11**) was evaluated, and the results indicated a potential role as a tubulin polymerisation inhibitor. This hypothesis was confirmed by further experiments, and the precise mode of action was revealed through successful co-crystallisation of the compound with αβ-tubulin-DARPin complex.[108]

Cyanobacteria from the genus *Leptothoe* were isolated from three different locations (Indonesia in 1994, Egypt in 2007, and the Republic of Cape Verde in 2018), and all strains were found to produce novel metallophores leptochelin A-C (Fig. 7, leptochelin A (**12**)).[109] The metal-chelating properties were discovered during a detailed investigation of a minor metabolite, which was identified as the zinc complex of leptochelin A (**12**).

Finally, several linear and cyclic depsipeptides have been discovered in *Moorena* species[110,111] and in a cyanobacterium collected in Tumon Bay, Guam.[111,112] Hectoramide B (**13**) was isolated from a coculture composed of a cyanobacterium and the fungi *Candida albicans*.[110] The macrocycle wajeepeptin (**14**) was identified in a *Moorena* sp. and displayed cytotoxicity against HeLa cells and the parasite *Trypanosoma brucei rhodesiense*.[111] The enamide tumonolide (**15**) was isolated alongside its aldehyde derivative (tumonolide aldehyde), in which the enamide is converted to an aldehyde and a terminal amide.[112] Tumonolide (**15**) was screened against a selection of GPCRs and identified as a potent, selective antagonist of the tachykinin receptor TACR2.

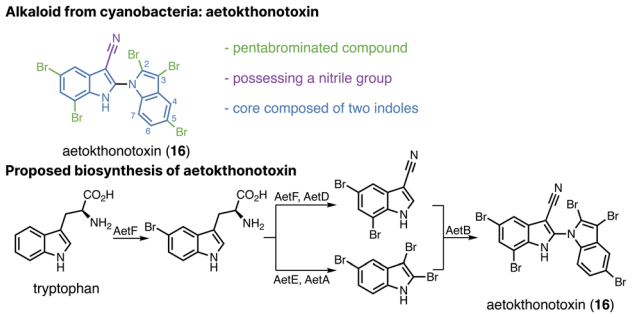

Fig. 8 Structure and proposed biosynthesis of the alkaloid aetokthonotoxin (**16**).[113,117] Figure adapted with permission from Adak *et al.*[117]

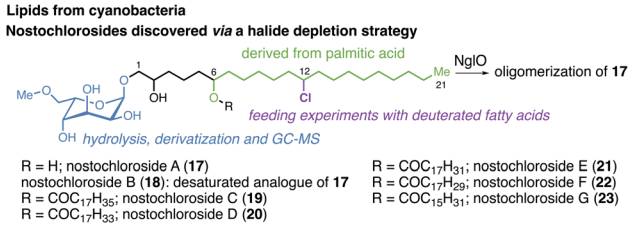

Fig. 9 Nostochloroside family class discovered in *Nostoc punctiforme* ATCC 29133 following a halide depletion strategy.[124]

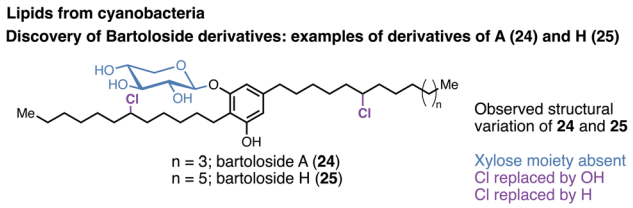

Fig. 10 Derivatives of the glycolipid bartolosides identified following a PCR screening and molecular network analysis. Bartoloside A (**24**) and H (**25**) are represented in this figure.[129]

3. Alkaloids

The primary alkaloid discovered in cyanobacteria in recent years is the neurotoxin aetokthonotoxin (AETX, **16**, Fig. 8), characterised by a pentabrominated biindole scaffold.[113] This study originated from investigations into the unexplained deaths of bald eagles suffering from a lethal neurological disease, vacuolar myelinopathy.[114] It was hypothesised that the cyanobacterium *Aetokthonos hydrillicola*,[115,116] growing on the invasive aquatic plant *Hydrilla verticillata*, was producing a potent toxin responsible for the bird deaths. The cyanobacterial strain was successfully isolated and cultured, and it was eventually found that bromine supplementation in the culture medium was necessary for toxin production.[113] After optimising culture conditions, AETX was isolated and its structure elucidated. Additionally, a metagenomic approach identified the AETX gene cluster, comprising six genes (*aetA* to *aetF*). AetF was predicted to function as a halogenase, and *in vitro* experiments confirmed its ability to brominate tryptophan at positions 5 and 7, corresponding to the left side of AETX.[113,117] Subsequently, the remaining enzymes from the gene cluster were expressed and purified.[117] *In vitro* experiments indicated that AetE is a tryptophanase that converts tryptophan to indole; AetA is a second halogenase that brominates indole at positions 2 and 3; AetD facilitates nitrile formation; and AetB, a cytochrome P450 enzyme, catalyses the C–N coupling (Fig. 8).[117] Crystallisation of AetF[118] and AetD[119,120] provided crucial insights into their enzymatic mechanisms.

Since its discovery, research on AETX has expanded to include the development of a total synthetic route to the natural product in five steps with an overall yield of 29%,[121] and the creation of a PCR-based strategy for detecting AETX-producing cyanobacteria.[122] Furthermore, *Aetokthonos hydrillicola* was further investigated for bioactive metabolites and novel linear peptides, named aetokthonostatins, were discovered.[123]

4. Lipids

Glasser and coworkers developed a novel protocol to accelerate the discovery of such compounds using a halide depletion strategy.[124] This approach enabled the discovery of a new class of chlorinated glycolipids, nostochlorosides A–G (**17**–**23**, Fig. 9), from *Nostoc punctiforme* ATCC 29133. Those natural products consist of a hydroxylated lipid scaffold functionalised with a rare *O*-methylated gulose and chlorinated at the 12-position. The identity of the carbohydrate moiety was determined by GC-MS after hydrolysis and permethylation. In addition, the position of the chlorine atom was established *via* feeding experiments with D_2-labelled palmitic acid. Furthermore, the BGC *ngl* was identified as responsible for producing those compounds. One of the enzymes of interest is NglO, a homolog of CylK, which was found to catalyse a reaction at the halogenated carbon.[54,125,126] The biosynthetic role of NglO was elucidated as mediating the oligomerisation of nostochloroside A (**17**) *via* a nucleophilic chloride displacement by one of its hydroxyl groups. Evidence of this unique transformation was obtained by computational analysis and mutagenesis.

Another class of chlorinated glycolipids is the bartoloside family,[127,128] whose structural features include a dialkylresorcinol core bearing a xylose residue and chlorinated aliphatic side chains (Fig. 10; structures of bartoloside A (**24**) and H (**25**)). In 2024, Reis and coworkers reported a combined PCR- and metabolomics-based strategy to discover strains producing these compounds and to identify new derivatives.[129] This approach consisted of a PCR screening to detect the presence of *brtB* and *brtD*, which encode enzymes responsible for the *O*-alkylation of the side chain[130] and the formation of the dialkylresorcinol core, respectively. Selected cyanobacterial strains of the genus *Synechocystis* were cultured, their extracts analysed, and the data subjected to a molecular networking analysis. Using this strategy, derivatives of bartolosides A and H were identified that lacked the xylose unit or featured the replacement of the chlorine atom with hydrogen or hydroxyl groups (Fig. 10). Furthermore, additional derivatives of bartoloside B and bartoloside esters were also detected.

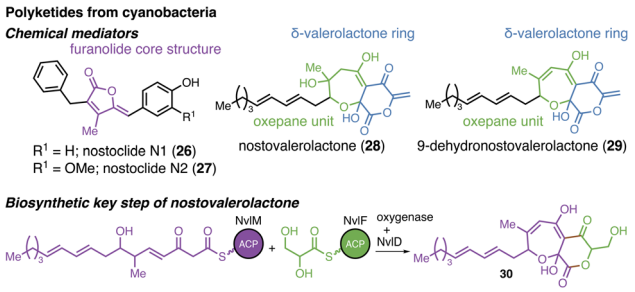

Fig. 11 (Top) nostoclides N1 (**26**) and N2 (**27**), nostovalerolactone (**28**) and 9-dehydronostovalerolactone (**29**) isolated from *Nostoc punctiforme* PCC 73102 and found as potential chemical mediators. (bottom) Key biosynthesis steps of nostovalerolactone (**28**).[132]

5. Polyketides

Some cyanobacteria have a significant capacity to produce secondary metabolites. For instance, it was reported in 2019 that *Nostoc punctiforme* PCC 73102 harbours 21 BGCs identified by antiSMASH, with a few reported to the production of a natural product.[131–133] Two of these BGCs, *pks*1 and *pks*2, were silent and *pks*1 was found to be significantly activated under high-density cultivation with high light intensity and CO_2 concentration.[131,132] It was hypothesised that *pks*1 produced quorum-sensing (QS) mediators as the gene cluster was highly transcribed at high cell density. An analysis of the *pks*1 BGC revealed that it is constituted of two subclusters, most likely positively regulated by an AraC-type transcription factor.[132] To identify those putative QS mediators, a mutant that over-expresses the AraC-type protein was constructed, and metabolite analysis led to the isolation of four novel polyketides named nostoclides N1 (**26**) and N2 (**27**), nostovalerolactone (**28**) and 9-dehydronostovalerolactone (**29**, Fig. 11). The nostoclides and nostovalerolactones were determined to be signalling messenger molecules, as they positively regulate seven BGCs from *Nostoc punctiforme* PCC 73102. The biosynthesis of nostovalerolactone (**28**) and its congener **29** was further investigated to elucidate the formation of the ∂-valerolactone ring fused to the oxepane-like unit (Fig. 11).[132] The bicyclic core structure **30** is proposed to be formed by NvlD, a FabH-like 3-oxoacyl-ACP synthase in concert with an oxygenase, which could be NvlQ or NvlH, two putative Baeyer-Villiger monooxygenases.

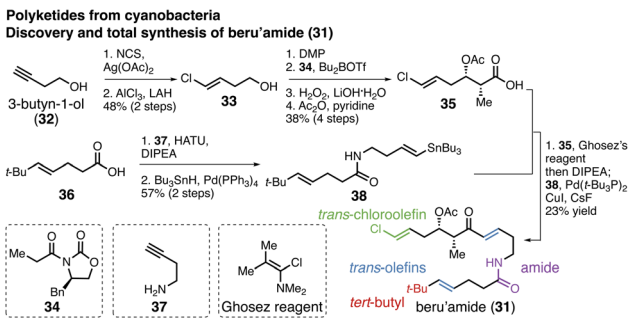

Fig. 12 Total synthesis of the polyketides beru'amide (**31**).[138]

Natural product discovery faces numerous challenges, with the limited material availability being particularly notable.[134] Fortunately, advances in instrumentation, such as high-performance NMR spectrometers, now enable characterisation of compounds at the nanomole scale.[135–137] The discovery of the polyketide beru'amide (**31**, Fig. 12) underscores the transformative potential of these technologies in uncovering and elucidating the structures of scarce natural products.[138] Beru'amide (**31**) was isolated from the marine cyanobacterium *Okeania* sp., collected along the Japanese coastline, using a ^{1}H-NMR-guided approach targeting the characteristic chemical shift of a *tert*-butyl group. Despite the small yield (68 μg), structure elucidation relied on HRMS and NMR spectra recorded on an 800 MHz spectrometer. This approach revealed that beru'amide contains two *trans*-olefins, a *trans*-chloroolefin, an amide group, and a *tert*-butyl group (Fig. 12). To further elucidate the structure, the authors employed computational methods[139,140] to calculate and compare chemical shifts using an optimised protocol developed by Hehre and coworkers[141] using DP4 probability.[142] The computational analysis suggested a *syn* relationship between the methyl and *O*-acetylated groups. A larger quantity of the compound was required to determine the absolute configuration of its stereocentres, and accordingly, a synthetic route to beru'amide (**31**, Fig. 12) was developed. This example highlights the importance of synthetic organic chemistry in the structural elucidation of natural products. The total synthesis began with the conversion of 3-butyn-1-ol (**32**) to the *trans*-chloroolefin **33** in two steps: chlorination of the terminal alkyne with *N*-chlorosuccinimide (NCS), followed by its reduction with lithium aluminium hydride (LAH) and $AlCl_3$. The intermediate alcohol **33** was oxidised with Dess-Martin periodinane (DMP), then subjected to an Evans-*syn* aldol reaction with **34**. The auxiliary was removed with H_2O_2, and the resulting hydroxy group was acetylated with acetic anhydride in pyridine, yielding the acetylated intermediate **35**. The second fragment was synthesised by coupling carboxylic acid **36** with 3-butyn-1-amine (**37**) to form an amide bond, followed by hydrostannylation to obtain the intermediate **38**. The final Stille coupling was performed by first activating the carboxylic acid **35** to its acyl chloride using Ghosez's reagent, then adding **38** and the catalyst Pd(*t*-$Bu_3P)_2$, which yielded beru'amide (**31**). The enantiomer was synthesised using the same strategy. Biological evaluation of beru'amide revealed activity in the low micromolar range, with IC_{50} values of 8.0 μM against HeLa cells and 1.2 μM against *Trypanosoma brucei rhodesiense (T. b. rhodesiense)*, a parasite causing life-threatening sleeping sickness.

In 2023, glycosylated macrolides named akunolides A–D (**39**–**42**, Fig. 13) were isolated from a species of *Okeania* sp. cyanobacterium collected at Akuna Beach, Okinawa, Japan.[143] Structural elucidation by HRMS and NMR revealed a 16-membered macrolide core glycosylated with either a mono- or dimethylated pyranose. For akunolide A (**39**), the structural features include a tetrahydropyran (THP) ring, a dimethylated pyranose, a terminal alkyne, two *gem*-dimethyl groups, and an s-*trans* diene (Fig. 13). The relative configuration of akunolide A was determined by analysing proton coupling constants and ^{1}H–^{1}H NOESY correlations. Akunolide B (**40**) differs from

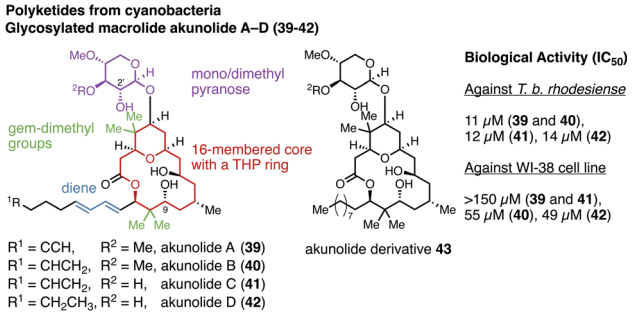

Fig. 13 Macrolide akunolide A–D (**39–42**) isolated from an *Okeania* sp. with their biological activities.[143] THP: tetrahydropyran, *T. b. rhodesiense*: *Trypanosoma brucei rhodesiense*.

akunolide A by the substitution of the terminal alkyne with an alkene. Both compounds (**39** and **40**) were subjected to catalytic hydrogenation, yielding the same saturated derivative **43**, thereby confirming the proposed structure of akunolide B (**40**). The absolute configuration of akunolide B was further investigated using a modified Mosher's method.[144] Mono- (C-9) and bis- (C-9 and C-2′) esterification were carried out using the *R*- and *S*- enantiomers of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA). Subsequent NMR analysis enabled the assignment of all stereocentres. The relative and absolute configurations of akunolides C (**41**) and D (**42**) were determined by comparing proton coupling constants and ^{13}C-NMR chemical shifts. The biological activity of akunolides A–D (**39–42**) was assessed against the parasite *T. b. rhodesiense*, and their cytotoxicities was evaluated using the normal human cell line WI-38. Akunolides A–D exhibited IC_{50} values of 11, 11, 12, and 14 μM, respectively, against *T. b. rhodesiense*, and >150, 55, >150, and 49 μM, respectively, against WI-38. Furthermore, the toxicity of akunolides A–C (**39–41**) was evaluated in mice *via* intraperitoneal injection, with no adverse effects observed at up to 200 μg per injection.[145] The therapeutic significance of this class of compounds is further highlighted by the discovery of a structurally related polyketide, moorenaside, reported in 2024.[146] This natural product exhibits notable anti-inflammatory properties by acting through the Keap1/Nrf2 oxidative stress pathway.

The polyketide caldorazole (**44**) was isolated from the cyanobacterium *Caldora* sp., found along the coastline of Ishigaki Island, Japan (Fig. 14).[147] Its structure was elucidated by HRMS and NMR spectroscopy. The individual components of the molecule were deduced from NMR correlations, in particular using the ^{1}H–^{1}H COSY and ^{1}H–^{1}H TOCSY spectra, and their connections were established *via* ^{1}H–^{13}C HMBC correlations. The configuration of the olefins was determined by ^{1}H–^{1}H NOESY, coupling constants analysis, and comparative ^{13}C-NMR analysis. Caldorazole (**44**) features notable structural elements, including two thiazole heterocycles, six *trans*-olefins, and an *O*-methylenolpyruvamide group. The biological activity of caldorazole was evaluated, revealing strong potency against several tumour cell lines, with IC_{50} values of 23 nM for HeLa, 68 nM for CaSki, and 74 nM for HT1080 cells. Initially, it was hypothesised that its activity was linked to the *O*-methylenolpyruvamide group and the connected conjugated diene, potentially acting as an alkylating agent. To test this hypothesis, a truncated mimic of caldorazole **45** was synthesised from pyruvic acid and 3-phenylpropanal. When tested against the HeLa cell line, this derivative exhibited at least 1000-fold lower potency than caldorazole (**44**), indicating that cytotoxicity is not solely dependent on those groups. Further investigations into the mode of action suggested that caldorazole induces apoptosis by depleting ATP. Tumour cells rely on two primary sources of ATP: glycolysis and mitochondrial oxidative phosphorylation (respiration). To explore these mechanisms, caldorazole was tested in the presence of a glycolysis inhibitor, and its cytotoxicity was found to be selective under glucose-restricted conditions. Moreover, it demonstrated potent inhibition of mitochondrial complex I, with an IC_{50} of 56 nM. A total synthesis of caldorazole was also achieved, employing a linear sequence of 15 steps.[148] Key transformations in the synthesis included a Stille cross-coupling, a sulfone coupling, and an amide coupling for the incorporation of the *O*-methylenolpyruvamide moiety.

In 2021, Figueiredo and coworkers developed a targeted method to identify cyanobacterial metabolites containing a fatty acid unit.[149] They supplemented cyanobacterial cultures with stable isotopically labelled hexanoic acid (d_{11}-C_6, **46**, Fig. 15), hypothesising that the cyanobacteria would incorporate this precursor into secondary metabolites. This approach was applied to *Nodularia* sp. LEGE 06071 and nocuolactylates A–C (**47–49**) were identified through comparative metabolomic analysis (Fig. 15). The structures of these natural products were determined by NMR and HRMS/MS. A detailed analysis of the MS spectrum of nocuolactylate A (**47**) revealed an in-source fragment of the cytotoxic natural product nocuolin A (**50**, Fig. 15).[150] Additionally, the second part of the compound was found to derive from the chlorosphaerolactylate class of natural

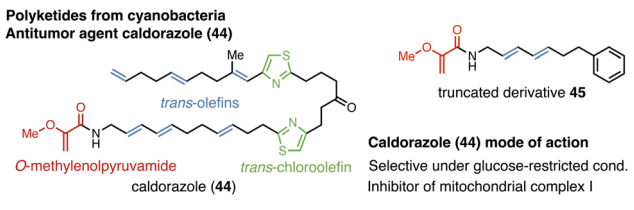

Fig. 14 Caldorazole (**44**) discovered from the cyanobacterium *Caldora* sp., its derivative **45** and its mode of action.[147]

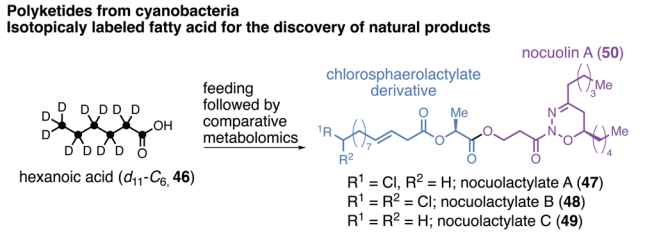

Fig. 15 Nocuolactylates (**47–49**): cyanobacterial polyketide metabolites isolated from *Nodularia* sp. LEGE 06071 following a stable isotopically labelling methodology.[149]

products.[151] The cytotoxic activity of nocuolactylates A (**47**) and B (**48**) was tested against multiple cell lines, showing lower potency than nocuolin A (**50**), suggesting a possible prodrug mode of action for this new class of compounds. Furthermore, other natural products, members of the hapalosin group, have been discovered using the same methodology by supplementing d_{11}-C_6 to the cyanobacterium *Fischerella* sp. PCC 9431.[149]

6. Terpenes/terpenoids

Two cyanobacteria strains, *Calothrix* sp. R-3-1 and *Scytonema* sp. U-3-3, were selected during a biological assay screening targeting the inhibition of the transient receptor potential melastatin 7 (TRPM7).[152] After approximately 45 days of culture, compounds present in the medium were extracted using the highly porous adsorbent Diaion™ HP20 resin. The analysis of the extract by HPLC-UV and MS led to the isolation of six novel terpenes, including spironostoic acid (**51**), 11,12-didehydrospironostoic acid (**52**), and 12-hydroxy-2-oxo-11-*epi*-hinesol (**53**) from the strain R-3-1, and stigolone (**54**), 11*R*,12-dihydroxystigolone (**55**), and 11*S*,12-dihydroxystigolone (**56**, Fig. 16) from the strain U-3-3. The core structures of these natural products were elucidated using a combination of HRMS, infrared (IR), and 1D and 2D NMR spectroscopy. The challenge was to assign the relative and absolute configurations given the number of possible conformers. A systematic methodology was developed to determine the structures of the spirovetivane-type compounds **51–53**. Initially, the strategy focused on determining the stereocentres at C-4 and C-5. Conformational analysis indicated the possibility of eight conformers for those four diastereomers (4*R*, 5*R*), (4*R*, 5*S*), (4*S*, 5*R*), and (4*S*, 5*S*). Analysis of the coupling constants indicated whether the methyl group attached to C-4 was in an axial or equatorial position, and ^{1}H–^{1}H NOESY key correlations indicated the relative configuration at position C-5, resulting in two possible conformers. Finally, electron circular dichroism (ECD) experiments could differentiate between the two. The configuration at C-7 was assigned through analysis of ^{1}H–^{1}H NOESY correlations, and computational analyses determined the configuration of the final stereocentre at C-11. A similar approach was used to determine the relative and absolute configurations of the eudesmane-type natural products isolated from strain U-3-3 **54–56**. The relative configuration was based on key ^{1}H–^{1}H NOESY correlations, coupling constants, and conformational analysis of the *trans*-decalin system. The absolute configuration was determined by comparative ECD analysis. The described compounds showed only slight activity at 50 μM against TRPM7, a transient receptor potential channel whose expression correlates with *in vitro* migration in cell lines, including tumour cell lines.

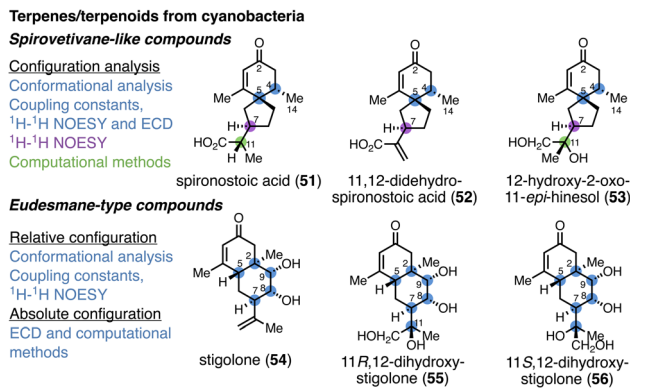

Fig. 16 Spirovetivate-like compounds isolated from *Calothrix* sp. R-3-1 and eudesmane-type compounds isolated from *Scytonema* sp. U-3-3.[152]

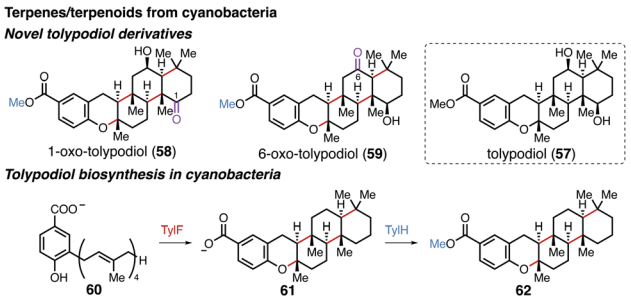

Fig. 17 Tolypodiol derivatives (**58** and **59**) from the cyanobacterium *Brasilonema* HT-58-2 and part of their biosynthesis.[164]

Research into natural products has undergone a significant transformation in recent years, driven by rapid advances in (meta)genomics and the availability of sophisticated tools for analysing BGCs.[153–161] However, the effective discovery of novel natural products using these tools critically depends on well-annotated and experimentally validated BGCs. In the case of cyanobacteria, terpene natural products are well-documented;[162] however, only a limited number of terpene gene clusters have been identified, *e.g.* the merosterol BGC in *Scytonema* sp. PCC 10023.[85] Recently, the cyanobacterium *Brasilonema* HT-58-2 was found to produce the terpenoid tolypodiol (**57**) along with some derivatives (Fig. 17).[163] In 2023, further investigation of this strain revealed two additional compounds, 1-oxo-tolypodiol (**58**) and 6-oxo-tolypodiol (**59**, Fig. 17).[164] The *tyl* BGC (tolypodiol) was identified through BLAST analysis of the *Brasilonema* HT-58-2 genome[165] and corroborated by previous literature.[166] To validate these findings, a heterologous expression approach was employed. The entire *tyl* BGC, comprising 13 enzymes with predicted functions, was expressed in the cyanobacterial host *Anabaena* sp. PCC 7120 (UTEX 2576). Tolypodiol and its derivatives were successfully produced and identified using NMR, MS, and computational analysis. Further analysis of the *tyl* gene cluster revealed that TylF is likely a member of a novel terpene cyclase family, predicted to recognise the carboxylate **60** as its substrate (Fig. 17). Additionally, TylH was identified as an *S*-adenosylmethionine (SAM)-dependent methyltransferase. To test its activity, the purified enzyme was assayed, and successful production of tolypodiol (**57**) from its desmethylated precursor was observed. This result supports the biosynthetic hypothesis that the carboxylate **61** is methylated by TylH to form the methyl ester **62**.

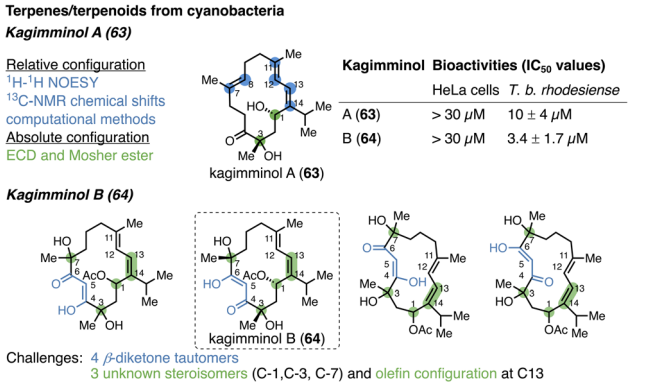

Fig. 18 Cembrene-type natural products isolated from cyanobacterium *Okeania* sp.[167]

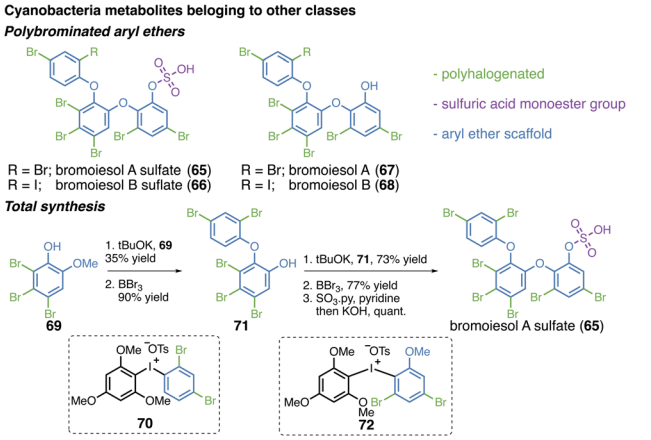

Fig. 19 Discovery of polyhalogenated aryl ethers from *Salileptolyngbya* sp.: bromoiesol A sulfate (**65**), bromoiesol B sulfate (**66**), bromoiesol A (**67**), and bromoiesol B (**68**).[169]

Kagimminols A (**63**) and B (**64**) are two novel cembrene-type natural products isolated from the cyanobacterium *Okeania* sp. collected near Kagimmi beach in Japan (Fig. 18).[167] The compounds were purified by preparative HPLC with trifluoroacetic acid (TFA) as an additive. However, kagimminol B (**64**) proved sensitive to the strongly acidic conditions generated during solvent evaporation of the HPLC fractions. To mitigate this effect, the HPLC fractions were neutralised with $NaHCO_3$ before concentration. The structure and relative configuration of kagimminol A (**63**) were elucidated by HRMS, and 1D and 2D NMR analyses. Key ^1H–^1H NOESY correlations and ^{13}C-NMR chemical shift comparisons were crucial for determining the configurations of the three olefins (C-7, C-11, and C-13). Moreover, a *syn* relationship between C-1 and C-3 was predicted from calculated NMR chemical shifts. The absolute configuration was determined by comparing theoretical and experimental ECD spectra and further confirmed by Mosher's ester analysis of the hydroxyl group at C-1. A similar approach was applied to the structure elucidation of kagimminol B (**64**). However, difficulties arose due to the β-diketone, which can exist in four tautomeric forms (Fig. 18), and an additional stereocentre at C-7. The relative configuration was determined by DP4 probability analysis,[142] allowing assignment of 1*S*, 3*S*, and 7*R*, and a *cis* configuration for the double bond between C-13 and C-14. The absolute configuration was established by comparing calculated and experimental ECD spectra. Both compounds were found inactive against HeLa cells at concentrations up to 30 μM but active at low micromolar concentrations against the parasite *T. b. rhodesiense*.

7. Natural products belonging to other classes

Artificial intelligence tools have also been employed to determine the structure of novel metabolites.[21,168] The cyanobacterium *Salileptolyngbya* sp. was collected from Ie Island, Okinawa, Japan.[169] Compounds exhibiting strong UV absorption were targeted first (bromoiesol A sulfate (**65**) and B sulfate (**66**)), and subsequent purification also revealed bromoiesol A (**67**) and B (**68**, Fig. 19). The low hydrogen atom content posed significant challenges for structural elucidation through standard NMR and HRMS techniques. To overcome this, an artificial intelligence tool, Small Molecule Accurate Recognition Technology (SMART),[170] was employed to propose a structural motif by analysing correlations observed in the ^1H–^{13}C HSQC spectrum. The analysis suggested the presence of aryl ethers, and the structure of bromoiesol A (**67**) and bromoiesol B (**68**) were unambiguously determined by single-crystal X-ray diffraction. Refined purification enabled the isolation of bromoiesol A and B sulfates (**65** and **66**). To confirm the structure of bromoiesol A sulfate, a total synthesis was undertaken (Fig. 19). The reported phenol **69** was [171] reacted with the iodonium salt **70**, and the resulting product was deprotected with BBr_3 to yield the phenol **71**. Repeating the same coupling/deprotection strategy with a different iodonium salt **72** facilitated the synthesis of bromoiesol A (**67**), and subsequent treatment with a sulphur trioxide-pyridine complex yielded bromoiesol A sulfate (**65**). The biological activity of these natural products was evaluated, revealing IC_{50} values in the low micromolar range against the parasite *T. b. rhodesiense*: 1.2 μM for **67**, 0.7 μM for **68**, 8.8 μM for **65**, and 7.9 μM for **66**.

In this section, we included new natural products with mixed scaffolds, such as iezoside (**73**, Fig. 20), which features peptide, polyketide, and glycosylated moieties.[172] During a screening for antitumor agents, the fractionated extract of the cyanobacterium *Leptochromothrix valpauliae* was selected for its potent cytotoxicity against HeLa cells, with an IC_{50} value of 79 ng mL^{-1}. The active compound, iezoside (**73**), was isolated and purified *via* a bioassay-guided fractionation approach. Its relative configuration was determined using a combination of HRMS, and 1D and 2D NMR analyses, with SMART[170] initially used to predict the structural core motif. The absolute configuration of iezoside was resolved using analytical techniques tailored to each moiety. For the peptide moiety, ozonolysis and hydrolysis were performed to release the amino acids, and chiral phase HPLC and Marfey's method were applied to assign the configurations at C-4 and C-10 [107] The stereocentres of the modified

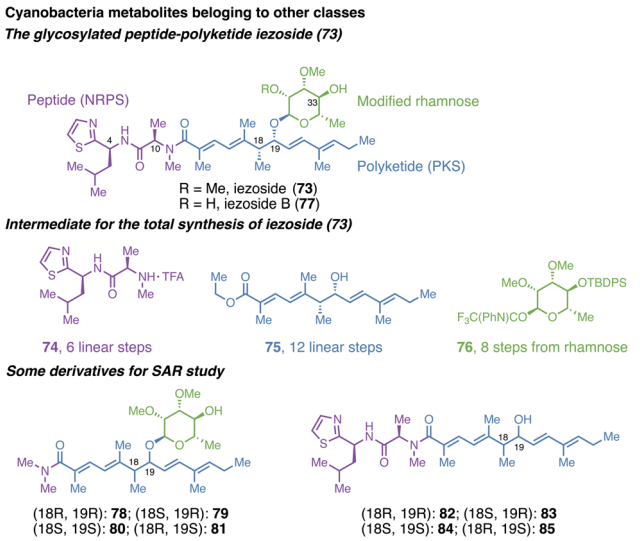

Fig. 20 The potent antiproliferative agents iezoside (**73**), iezoside B (**77**), the key intermediates for its total synthesis approach and some derivatives synthesised for the SAR study.[172,175,176]

rhamnose were elucidated by derivatising the hydroxy group at C-33 with Mosher's acid reagent, followed by NMR analysis.[144] Elucidation of the configurations of the remaining stereocentres at C-18 and C-19 posed a greater challenge. Conformational and computational studies were employed to calculate the proton and carbon chemical shifts of a truncated model system. A comparison of the predicted values indicated either a (18*R*, 19*R*) or (18*S*, 19*R*) configuration, with the former more probable. Additionally, calculated ECD spectra supported this assignment. A total synthesis was then developed to differentiate the two diastereomers and fully establish the absolute configuration of iezoside (**73**). This highly convergent synthetic strategy was based on coupling the peptide **74**, polyketide **75**, and glycoside **76** moieties (Fig. 20). The polyketide side chain was synthesised in 12 linear steps utilising the diastereoselective Evans aldol reaction.[173] The modified glycoside was prepared from rhamnose following a modified version of a previously reported route,[174] while the peptide moiety was synthesised in six steps starting from protected L-leucine. This strategy yielded both diastereomers, (18*R*, 19*R*)-iezoside and (18*S*, 19*R*)-iezoside, and comparison of the data enabled unambiguous assignment of the polyketide configuration as 18*R* and 19*R*.

With the structure elucidated, the cytotoxicity of iezoside (**73**) against HeLa cells was evaluated, revealing a high potency with an IC_{50} value of 6.8 nM. The mode of action was investigated using the anticancer drug screening platform of the Japanese Foundation for Cancer Research 39 (JFCR39).[177] Comparative growth inhibition profiling across multiple cancer cell lines suggested that iezoside (**73**) targets a Ca^{2+} transporter. Subsequent experiments identified the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) as the target. Furthermore, iezoside (**73**) and its desmethylated analogue, iezoside B (**77** Fig. 20), have also been isolated from the cyanobacterium *Dichothrix* sp., and iezoside B exhibited lower activity than iezoside.[175]

A structure–activity relationship (SAR) study was initiated to assess the significance of various structural features for biological activity.[176] First, the two remaining diastereomers of the polyketide side chain, (18*S*, 19*S*)-iezoside and (18*R*, 19*S*)-iezoside, were synthesised and evaluated for antiproliferative activity against HeLa cells and for SERCA inhibitory activity. Both showed reduced potency compared with the natural product (18*R*, 19*R*)-iezoside (**73**). (18*S*, 19*S*)-Iezoside, which features a *syn*-configuration at C-18 and C-19 was the most active analogue, underscoring the importance of this configuration. The role of the peptide moiety was further examined by synthesising dimethylamine analogues of all diastereomers ((18*R*, 19*R*)-**78**, (18*S*, 19*R*)-**79**, (18*S*, 19*S*)-**80**, and (18*R*, 19*S*)-**81**, Fig. 20). These derivatives showed a complete loss of activity, highlighting the necessity of the peptide moiety for biological function. Finally, the aglycone derivatives (18*R*, 19*R*)-**82**, (18*S*, 19*R*)-**83**, (18*S*, 19*S*)-**84**, and (18*R*, 19*S*)-**85** were synthesised, and (18*R*, 19*R*)-**82** was the most potent among them. This derivative showed a twofold decrease in activity in the SERCA bioassay and over a 100-fold decrease against HeLa cells, potentially due to the relative instability of the aglycone in solution. In addition to these exciting results, the discovery of iezoside (**73**) has garnered significant interest within the scientific community, which was summarised in two recent publications.[178,179]

The next natural product provides another example of how cyanobacteria isolated from Japan are a valuable resource for drug discovery. *Rivularia* sp. was collected from Higashi-Hennazaki on Miyakojima Island, and purification of an ethanolic extract yielded two pyrrolinone-containing natural products, hennaminal (**86**) and hennamide (**87**) (Fig. 21).[180] Their structures and relative configurations were determined by HRMS, and 1D and 2D NMR analyses. The absolute configuration of hennaminal (**86**) was established by comparing its experimental ECD spectrum with that obtained using computational chemistry. To further confirm this result, hennaminal (**86**) was subjected to ozonolysis followed by oxidative workup

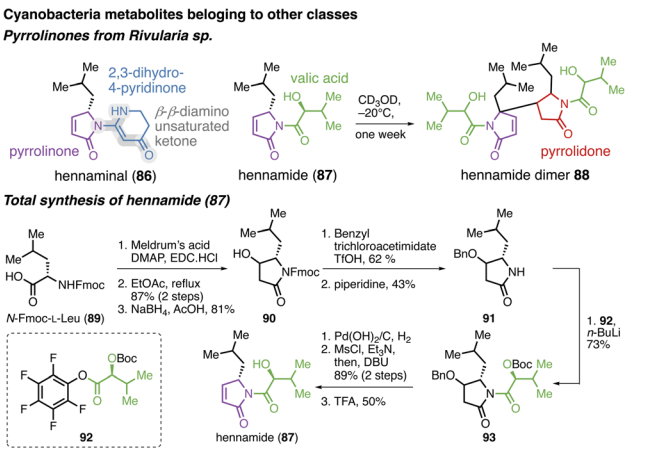

Fig. 21 Pyrrolinones isolated from *Rivularia* sp. and total synthesis of hennamide (**87**).[180]

and hydrolysis (4M HCl), yielding L-leucine. The configuration of the isolated amino acid was determined using a chiral column and analytical standards. An unexpected transformation was observed when hennamide (**87**) was stored in CD_3OD at −20 °C for one week. During this period, the compound converted completely into its dimeric form, hennamide dimer (**88**) (Fig. 21). Consequently, a total synthesis of hennamide (**87**) was undertaken to confirm its absolute configuration. The synthetic route began with the condensation of protected L-leucine **89** with Meldrum's acid, followed by cyclisation under reflux conditions. The resulting ketone was reduced with $NaBH_4$ to give the pyrrolidone **90**. The key intermediate **91** was obtained *via* a protection–deprotection sequence using benzyl trichloroacetimidate and piperidine. Subsequently, pyrrolidone **91** was coupled with the pentafluorophenol ester **92** to form **93**, which was then converted into hennamide (**87**) *via* benzyl group deprotection, elimination, and removal of the Boc protecting group. Using the same strategy, (4*S*,10*R*)-*epi*-hennamide was synthesised, and a comparison of the optical rotations between the natural and synthetic compounds allowed the stereochemical assignment of C-4 and C-10 as *S*-configured. Furthermore, the bioactivity of hennaminal (**86**) and hennamide (**87**) was evaluated. Both compounds exhibited cytotoxicity against HeLa cells, with IC_{50} values exceeding 20 μM, and against the parasite *T. b. rhodesiense*, with IC_{50} values of 11 μM for hennaminal (**86**) and 9.7 μM for hennamide (**87**).

8. Conclusions

Recent discoveries of cyanobacterial metabolites reported between 2021 and 2024 have revealed remarkable structural diversity across multiple compound classes. Many of the challenges associated with their structural elucidation have been addressed through modern analytical and computational technologies. High-performance NMR, together with artificial intelligence-assisted data analysis, has enabled structural elucidation from small sample quantities and complex spectra. Furthermore, significant advances in (meta)genomic approaches, including direct pathway cloning and heterologous expression, have facilitated the identification of numerous new compounds. Extensive efforts have been made to integrate spectrometry, spectroscopy, synthetic chemistry and (meta) genomic analyses for the structural elucidation of novel natural products. Overall, this review underscores the importance of cyanobacteria as a rich source of structurally diverse and innovative molecular scaffolds.

9. Author contributions

Simon Sieber: conceptualisation, writing original draft and editing, visualisations. Elisabeth Janssen: conceptualisation, writing original draft and editing, data curation.

10. Conflicts of interest

There are no conflicts to declare.

11. Data availability

The review highlights the natural products isolated from cyanobacteria from 2021 to 2024. No new data were generated during this work. Furthermore, this manuscript does not include primary research results, software, or code. No new data were generated or analysed as part of this review.

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13. References

1 A. H. Banday, N. ul Azha, R. Farooq, S. A. Sheikh, M. A. Ganie, M. N. Parray, H. Mushtaq, I. Hameed and M. A. Lone, *Phytochem. Lett.*, 2024, **59**, 124–135.
2 A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers and M. R. Prinsep, *Nat. Prod. Rep.*, 2019, **36**, 122–173.
3 A. R. Carroll, B. R. Copp, T. Grkovic, R. A. Keyzers and M. R. Prinsep, *Nat. Prod. Rep.*, 2025, **42**, 257–297.
4 M. B. Weiss, R. M. Borges, P. Sullivan, J. P. B. Domingues, F. H. S. da Silva, V. G. S. Trindade, S. Luo, J. Orjala and C. M. Crnkovic, *Nat. Prod. Rep.*, 2025, **42**, 6–49.
5 S. Ferrinho, H. Connaris, N. J. Mouncey and R. J. M. Goss, *Water Res.*, 2024, **256**, 121492.
6 P. N. N. de Freitas, F. R. Jacinavicius, L. S. Passos, A. O. de Souza, R. B. Dextro and E. Pinto, *Algal Res.*, 2024, **82**, 103617.
7 M. A. Haffar, Z. Fajloun, S. Azar, J.-M. Sabatier and Z. A. Khattar, *Toxins*, 2024, **16**, 551.
8 L. T. Tan and N. F. Salleh, *Molecules*, 2024, **29**, 5307.
9 H. Luesch, E. K. Ellis, Q.-Y. Chen and R. Ratnayake, *Nat. Prod. Rep.*, 2024, **42**, 208–256.
10 Y. He, Y. Chen, H. Tao, X. Zhou, J. Liu, Y. Liu and B. Yang, *Phytochem. Rev.*, 2025, **24**, 483–525.
11 N. Barzkar, S. Sukhikh and O. Babich, *Front. Microbiol.*, 2024, **14**, 1285902.
12 J. J. Huang, W. Xu, S. Lin and P. C. K. Cheung, *Crit. Rev. Biotechnol.*, 2025, **45**, 276–304.
13 R. Carpine and S. Sieber, *Curr. Res. Biotechnol.*, 2021, **3**, 65–81.
14 M. Gugger, A. Boullié and T. Laurent, *Toxins*, 2023, **15**, 388.
15 M. Meunier, A. Schinkovitz and S. Derbré, *Nat. Prod. Rep.*, 2024, **41**, 1766–1786.
16 M. DiBello, A. R. Healy, H. Nikolayevskiy, Z. Xu and S. B. Herzon, *Acc. Chem. Res.*, 2023, **56**, 1656–1668.
17 B. B. Basnet, Z.-Y. Zhou, B. Wei and H. Wang, *Crit. Rev. Biotechnol.*, 2025, **45**, 1527–1558.
18 B. E. Hetzler, D. Trauner and A. L. Lawrence, *Nat. Rev. Chem.*, 2022, **6**, 170–181.
19 G. Hu and M. Qiu, *Nat. Prod. Rep.*, 2023, **40**, 1735–1753.

20 A. Najmi, S. A. Javed, M. A. Bratty and H. A. Alhazmi, *Molecules*, 2022, **27**, 349.
21 M. W. Mullowney, K. R. Duncan, S. S. Elsayed, N. Garg, J. J. J. van der Hooft, N. I. Martin, D. Meijer, B. R. Terlouw, F. Biermann, K. Blin, J. Durairaj, M. G. González, E. J. N. Helfrich, F. Huber, S. Leopold-Messer, K. Rajan, T. de Rond, J. A. van Santen, M. Sorokina, M. J. Balunas, M. A. Beniddir, D. A. van Bergeijk, L. M. Carroll, C. M. Clark, D.-A. Clevert, C. A. Dejong, C. Du, S. Ferrinho, F. Grisoni, A. Hofstetter, W. Jespers, O. V. Kalinina, S. A. Kautsar, H. Kim, T. F. Leao, J. Masschelein, E. R. Rees, R. Reher, D. Reker, P. Schwaller, M. Segler, M. A. Skinnider, A. S. Walker, E. L. Willighagen, B. Zdrazil, N. Ziemert, R. J. M. Goss, P. Guyomard, A. Volkamer, W. H. Gerwick, H. U. Kim, R. Müller, G. P. van Wezel, G. J. P. van Westen, A. K. H. Hirsch, R. G. Linington, S. L. Robinson and M. H. Medema, *Nat. Rev. Drug Discovery*, 2023, **22**, 895–916.
22 M. Grigalunas, S. Brakmann and H. Waldmann, *J. Am. Chem. Soc.*, 2022, **144**, 3314–3329.
23 S. P. Gaudêncio, E. Bayram, L. L. Bilela, M. Cueto, A. R. Díaz-Marrero, B. Z. Haznedaroglu, C. Jimenez, M. Mandalakis, F. Pereira, F. Reyes and D. Tasdemir, *Mar. Drugs*, 2023, **21**, 308.
24 Z. Huang, T. Bi, H. Jiang and H. Liu, *Phytochem. Anal.*, 2024, **35**, 5–16.
25 E. M.-L. Janssen, M. R. Jones, E. Pinto, F. Dörr, M. A. Torres, F. R. Jacinavicius, H. Mazur-Marzec, K. Szubert, R. Konkel, L. Tartaglione, C. Dell'Aversano, A. Miglione, P. McCarron, D. G. Beach, C. O. Miles, D. P. Fewer, K. Sivonen, J. Jokela, M. Wahlsten, T. H. J. Niedermeyer, F. Schanbacher, P. Leão, M. Preto, P. M. D'Agostino, M. Baunach, E. Dittmann, M. Miguel-Gordo, R. Reher, S. Sieber and E. Schymanski, *Zenodo*, 2024, DOI: 10.5281/zenodo.13854577.
26 R. D. Süssmuth and A. Mainz, *Angew. Chem., Int. Ed.*, 2017, **56**, 3770–3821.
27 P. G. Arnison, M. J. Bibb, G. Bierbaum, A. A. Bowers, T. S. Bugni, G. Bulaj, J. A. Camarero, D. J. Campopiano, G. L. Challis, J. Clardy, P. D. Cotter, D. J. Craik, M. Dawson, E. Dittmann, S. Donadio, P. C. Dorrestein, K.-D. Entian, M. A. Fischbach, J. S. Garavelli, U. Göransson, C. W. Gruber, D. H. Haft, T. K. Hemscheidt, C. Hertweck, C. Hill, A. R. Horswill, M. Jaspars, W. L. Kelly, J. P. Klinman, O. P. Kuipers, A. J. Link, W. Liu, M. A. Marahiel, D. A. Mitchell, G. N. Moll, B. S. Moore, R. Müller, S. K. Nair, I. F. Nes, G. E. Norris, B. M. Olivera, H. Onaka, M. L. Patchett, J. Piel, M. J. T. Reaney, S. Rebuffat, R. P. Ross, H.-G. Sahl, E. W. Schmidt, M. E. Selsted, K. Severinov, B. Shen, K. Sivonen, L. Smith, T. Stein, R. D. Süssmuth, J. R. Tagg, G.-L. Tang, A. W. Truman, J. C. Vederas, C. T. Walsh, J. D. Walton, S. C. Wenzel, J. M. Willey and W. A. van der Donk, *Nat. Prod. Rep.*, 2013, **30**, 108–160.
28 M. Montalbán-López, T. A. Scott, S. Ramesh, I. R. Rahman, A. J. van Heel, J. H. Viel, V. Bandarian, E. Dittmann, O. Genilloud, Y. Goto, M. J. G. Burgos, C. Hill, S. Kim, J. Koehnke, J. A. Latham, A. J. Link, B. Martínez, S. K. Nair, Y. Nicolet, S. Rebuffat, H.-G. Sahl, D. Sareen, E. W. Schmidt, L. Schmitt, K. Severinov, R. D. Süssmuth, A. W. Truman, H. Wang, J.-K. Weng, G. P. van Wezel, Q. Zhang, J. Zhong, J. Piel, D. A. Mitchell, O. P. Kuipers and W. A. van der Donk, *Nat. Prod. Rep.*, 2020, **38**, 130–239.
29 M. N. Ahmed, E. Reyna-González, B. Schmid, V. Wiebach, R. D. Süssmuth, E. Dittmann and D. P. Fewer, *ACS Chem. Biol.*, 2017, **12**, 1538–1546.
30 N. M. Bösch, M. Borsa, U. Greczmiel, B. I. Morinaka, M. Gugger, A. Oxenius, A. L. Vagstad and J. Piel, *Angew. Chem., Int. Ed.*, 2020, **59**, 11763–11768.
31 K. Sivonen, N. Leikoski, D. P. Fewer and J. Jokela, *Appl. Microbiol. Biotechnol.*, 2010, **86**, 1213–1225.
32 A. H. Khan and C.-S. Phan, *Front. Nat. Prod.*, 2025, **4**, 1616031.
33 S. Köcher, S. Resch, T. Kessenbrock, L. Schrapp, M. Ehrmann and M. Kaiser, *Nat. Prod. Rep.*, 2019, **37**, 163–174.
34 R. Konkel, M. Cegłowska, K. Szubert, E. Wieczerzak, S. Iliakopoulou, T. Kaloudis and H. Mazur-Marzec, *Mar. Drugs*, 2023, **21**, 508.
35 H. Mazur-Marzec, A. Fidor, M. Cegłowska, E. Wieczerzak, M. Kropidłowska, M. Goua, J. Macaskill and C. Edwards, *Mar. Drugs*, 2018, **16**, 220.
36 M. Welker, M. Brunke, K. Preussel, I. Lippert and H. V. Döhren, *Microbiology*, 2004, **150**, 1785–1796.
37 T. Okino, S. Qi, H. Matsuda, M. Murakami and K. Yamaguchi, *J. Nat. Prod.*, 1997, **60**, 158–161.
38 S. O'Brien, R. Alvariño, B. Kennedy, L. M. Botana and O. P. Thomas, *Phytochemistry*, 2024, **223**, 114137.
39 P. Junier, G. Cailleau, M. Fatton, P. Udriet, I. Hashmi, D. Bregnard, A. Corona-Ramirez, E. di Francesco, T. Kuhn, N. Mangia, S. Zhioua, D. Hunkeler, S. Bindschedler, S. Sieber and D. Gonzalez, *Water Res.:X*, 2024, **24**, 100252.
40 M. J. Müller, A. Dorst, C. Paulus, I. Khan and S. Sieber, *Chem. Commun.*, 2022, **58**, 12560–12563.
41 S. M. Brown, J. R. Blaszczak, R. K. Shriver, R. C. Jones, A. Sohrab, R. Goel, G. L. Boyer, B. Wei, K. M. Manoylov, T. R. Nelson, J. M. Zabrecky and R. Stancheva, *Harmful Algae*, 2025, **144**, 102834.
42 C. Valadez-Cano, A. Reyes-Prieto, L. Johnston, Y. Huang, H. Morris, L. Zamlynny, A. M. Comeau, D. G. Beach, R. C. Jamieson and J. Lawrence, *Toxicon*, 2025, **264**, 108461.
43 A. Diez-Chiappe, M. Á. Muñoz-Martín, S. Cirés, A. Quesada and E. Perona, *Harmful Algae*, 2025, **149**, 102942.
44 A. Sohrab, S. Kaiser, B. Bhattarai, R. Stancheva and R. Goel, *Sci. Total Environ.*, 2025, **997**, 180194.
45 C. Valadez-Cano, N. Tromas, A. Reyes-Prieto, L. Johnston, Y. Huang, H. Morris, L. Zamlynny, D. G. Beach, R. C. Jamieson and J. Lawrence, *Environ. Microbiol.*, 2025, **27**, e70067.
46 S. A. Wood, L. Biessy and J. Puddick, *Harmful Algae*, 2018, **80**, 88–95.
47 S. A. Wood, L. T. Kelly, K. Bouma-Gregson, J. Humbert, H. D. Laughinghouse, J. Lazorchak, T. G. McAllister, A. McQueen, K. Pokrzywinski, J. Puddick, C. Quiblier,

L. A. Reitz, K. G. Ryan, Y. Vadeboncoeur, A. Zastepa and T. W. Davis, *Freshw. Biol.*, 2020, **65**, 1824–1842.
48 R. Reher, A. T. Aron, P. Fajtová, P. Stincone, B. Wagner, A. I. Pérez-Lorente, C. Liu, I. Y. B. Shalom, W. Bittremieux, M. Wang, K. Jeong, M. L. Matos-Hernandez, K. L. Alexander, E. J. Caro-Diaz, C. B. Naman, J. H. W. Scanlan, P. M. M. Hochban, W. E. Diederich, C. Molina-Santiago, D. Romero, K. A. Selim, P. Sass, H. Brötz-Oesterhelt, C. C. Hughes, P. C. Dorrestein, A. J. O'Donoghue, W. H. Gerwick and D. Petras, *Nat. Commun.*, 2022, **13**, 4619.
49 T. Okino, H. Matsuda, M. Murakami and K. Yamaguchi, *Tetrahedron Lett.*, 1993, **34**, 501–504.
50 J. da S. P. Neto, G. M. Serra, L. P. Xavier and A. V. Santos, *Int. J. Mol. Sci.*, 2025, **26**, 6117.
51 N. Eusébio, R. Castelo-Branco, D. Sousa, M. Preto, P. D'Agostino, T. A. M. Gulder and P. N. Leão, *ACS Synth. Biol.*, 2022, **11**, 3493–3503.
52 C.-S. Phan, Z. Ling, J. J. Mehjabin, K. Matsuda, N. I. Prakoso, T. Umezawa, T. Wakimoto and T. Okino, *J. Nat. Prod.*, 2024, **87**, 2629–2639.
53 F. Varriale, L. Tartaglione, S.-K. Zervou, C. O. Miles, H. Mazur-Marzec, T. M. Triantis, T. Kaloudis, A. Hiskia and C. Dell'Aversano, *Chemosphere*, 2023, **311**, 137012.
54 H. Nakamura, E. E. Schultz and E. P. Balskus, *Nat. Chem. Biol.*, 2017, **13**, 916–921.
55 N. Eusebio, A. Rego, N. R. Glasser, R. Castelo-Branco, E. P. Balskus and P. N. Leão, *BMC Genom.*, 2021, **22**, 633.
56 S. C. do Amaral, P. R. Monteiro, J. da S. P. Neto, G. M. Serra, E. C. Gonçalves, L. P. Xavier and A. V. Santos, *Mar. Drugs*, 2021, **19**, 17.
57 T. K. Hemscheidt, *Methods Enzymol.*, 2012, **516**, 25–35.
58 S. Sieber, S. M. Grendelmeier, L. A. Harris, D. A. Mitchell and K. Gademann, *J. Nat. Prod.*, 2020, **83**, 438–446.
59 T. Okino, H. Matsuda, M. Murakami and K. Yamaguchi, *Tetrahedron*, 1995, **51**, 10679–10686.
60 S. Saha, P.-A. Bulzu, P. Urajová, J. Mareš, G. Konert, J. C. Manoel, M. Macho, D. Ewe, P. Hrouzek, J. Masojídek, R. Ghai and K. Saurav, *mSphere*, 2021, **6**, e00562.
61 D. I. Sharif, J. Gallon, C. J. Smith and E. Dudley, *ISME J.*, 2008, **2**, 1171–1182.
62 P. R. Monteiro, S. C. do Amaral, A. S. Siqueira, L. P. Xavier and A. V. Santos, *Toxins*, 2021, **13**, 522.
63 N. Bouaïcha, C. O. Miles, D. G. Beach, Z. Labidi, A. Djabri, N. Y. Benayache and T. Nguyen-Quang, *Toxins*, 2019, **11**, 714.
64 L. Rouhiainen, J. Jokela, D. P. Fewer, M. Urmann and K. Sivonen, *Chem. Biol.*, 2010, **17**, 265–273.
65 D. Tillett, E. Dittmann, M. Erhard, H. von Döhren, T. Börner and B. A. Neilan, *Chem. Biol.*, 2000, **7**, 753–764.
66 S.-K. Zervou, T. Kaloudis, S. Gkelis, A. Hiskia and H. Mazur-Marzec, *Toxins*, 2021, **14**, 4.
67 R. Konkel, M. Grabski, M. Cegłowska, E. Wieczerzak, G. Węgrzyn and H. Mazur-Marzec, *Int. J. Environ. Res. Public Health*, 2022, **19**, 12346.
68 B. Bober, E. Chrapusta-Srebrny and J. Bialczyk, *Eur. J. Phycol.*, 2020, **56**, 244–254.
69 E. Zafrir-Ilan and S. Carmeli, *Tetrahedron*, 2010, **66**, 9194–9202.
70 D. Baliu-Rodriguez, N. J. Peraino, S. H. Premathilaka, J. A. Birbeck, T. Baliu-Rodriguez, J. A. Westrick and D. Isailovic, *Environ. Sci. Technol.*, 2022, **56**, 1652–1663.
71 K. Thomas, R. A. Perez Calderon, S. D. Giddings, I. Rajotte, C. O. Miles and P. McCarron, in *Biotoxin Metrology Certificate of Analysis CRM-MCLA-20210128*, National Research Council Canada, Halifax, 2022.
72 S. H. Premathilaka, J. A. Westrick and D. Isailovic, *Anal. Chem.*, 2024, **96**, 775–786.
73 K. A. Cottrill, C. O. Miles, L. C. Krajewski, B. R. Cunningham, W. Bragg, N. R. Boise, K. D. Victry, D. S. Wunschel, K. L. Wahl and E. I. Hamelin, *Harmful Algae*, 2024, **139**, 102739.
74 Y. Zhang, Y. Goto and H. Suga, *Trends Biochem. Sci.*, 2023, **48**, 360–374.
75 F. Zhang, D. Zhao, Y. Wu and L. Li, *Nat. Prod. Rep.*, 2025, **42**, 1303–1343.
76 F. Hubrich, *Nat. Prod. Rep.*, 2026, DOI: 10.1039/d5np00075k.
77 Y. Hao, E. Pierce, D. Roe, M. Morita, J. A. McIntosh, V. Agarwal, T. E. Cheatham, E. W. Schmidt and S. K. Nair, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, 14037–14042.
78 M. Purushothaman, S. Sarkar, M. Morita, M. Gugger, E. W. Schmidt and B. I. Morinaka, *Angew. Chem.*, 2021, **133**, 8541–8546.
79 C.-S. Phan, K. Matsuda, N. Balloo, K. Fujita, T. Wakimoto and T. Okino, *J. Am. Chem. Soc.*, 2021, **143**, 10083–10087.
80 F. Hubrich, S. K. Kandy, C. Chepkirui, C. Padhi, S. Mordhorst, P. Moosmann, T. Zhu, M. Gugger, J. R. Chekan and J. Piel, *Chem*, 2024, **10**, 3224–3242.
81 K. Ishida, H. Matsuda, M. Murakami and K. Yamaguchi, *Tetrahedron*, 1996, **52**, 9025–9030.
82 K. Ishida, H. Matsuda, M. Murakami and K. Yamaguchi, *J. Nat. Prod.*, 1997, **60**, 724–726.
83 A. Parajuli, D. H. Kwak, L. Dalponte, N. Leikoski, T. Galica, U. Umeobika, L. Trembleau, A. Bent, K. Sivonen, M. Wahlsten, H. Wang, E. Rizzi, G. D. Bellis, J. Naismith, M. Jaspars, X. Liu, W. Houssen and D. P. Fewer, *Angew. Chem., Int. Ed.*, 2016, **55**, 3596–3599.
84 P. Moosmann, F. Ecker, S. Leopold-Messer, J. K. B. Cahn, C. L. Dieterich, M. Groll and J. Piel, *Nat. Chem.*, 2020, **12**, 968–972.
85 P. Moosmann, R. Ueoka, L. Grauso, A. Mangoni, B. I. Morinaka, M. Gugger and J. Piel, *Angew. Chem., Int. Ed.*, 2017, **56**, 4987–4990.
86 O. Demirkiran, J. Almaliti, T. Leão, G. Navarro, T. Byrum, F. A. Valeriote, L. Gerwick and W. H. Gerwick, *J. Nat. Prod.*, 2021, **84**, 2081–2093.
87 T. Galica, N. Borbone, J. Mareš, A. Kust, A. Caso, G. Esposito, K. Saurav, J. Hájek, K. Řeháková, P. Urajová, V. Costantino and P. Hrouzek, *Appl. Environ. Microbiol.*, 2021, **87**, e03128–20.
88 K. Ozaki, A. Jinno, N. Natsume, S. Sumimoto, A. Iwasaki, K. Suenaga and T. Teruya, *Tetrahedron*, 2021, **85**, 131969.

89 P. Sullivan, A. Krunic, L. J. Davis, H. S. Kim, J. E. Burdette and J. Orjala, *J. Nat. Prod.*, 2021, **84**, 2256–2264.
90 L. Ding, R. Bar-Shalom, D. Aharonovich, N. Kurisawa, G. Patial, S. Li, S. He, X. Yan, A. Iwasaki, K. Suenaga, C. Zhu, H. Luo, F. Tian, F. Fares, C. B. Naman and T. Luzzatto-Knaan, *Mar. Drugs*, 2021, **19**, 397.
91 T. Li, C. Xi, Y. Yu, N. Wang, X. Wang, A. Iwasaki, F. Fang, L. Ding, S. Li, W. Zhang, Y. Yuan, T. Wang, X. Yan, S. He, Z. Cao and C. B. Naman, *J. Nat. Prod.*, 2022, **85**, 493–500.
92 A. Yamano, Y. Asato, N. Natsume, A. Iwasaki, K. Suenaga and T. Teruya, *J. Nat. Prod.*, 2022, **85**, 169–175.
93 K. Irie, G. Jeelani, T. Nozaki and A. Iwasaki, *J. Nat. Prod.*, 2024, **87**, 2292–2301.
94 N. Watanabe, G. Jeelani, T. Nozaki and A. Iwasaki, *ACS Omega*, 2024, **9**, 36795–36801.
95 B. Ryu, E. Glukhov, T. R. Teixeira, C. R. Caffrey, S. Madiyan, V. Joseph, N. E. Avalon, C. A. Leber, C. B. Naman and W. H. Gerwick, *J. Nat. Prod.*, 2024, **87**, 1601–1610.
96 B.-T. Zhang, H. Nishino, R. Kawabe, M. Kamio, R. Watanabe, H. Uchida, M. Satake and H. Nagai, *Biosci., Biotechnol., Biochem.*, 2024, **88**, 517–521.
97 G. J. Kim, S. J. Mascuch, E. Mevers, P. D. Boudreau, W. H. Gerwick and H. Choi, *J. Org. Chem.*, 2022, **87**, 1043–1055.
98 D. P. Fewer, J. Jokela, L. Heinilä, R. Aesoy, K. Sivonen, T. Galica, P. Hrouzek and L. Herfindal, *Physiol. Plant.*, 2021, **173**, 639–650.
99 L. M. P. Heinilä, D. P. Fewer, J. K. Jokela, M. Wahlsten, X. Ouyang, P. Permi, A. Jortikka and K. Sivonen, *Org. Biomol. Chem.*, 2021, **19**, 5577–5588.
100 L. Darcel, S. Das, I. Bonnard, B. Banaigs and N. Inguimbert, *Mar. Drugs*, 2021, **19**, 473.
101 J. J. Mehjabin, C.-S. Phan and T. Okino, *J. Nat. Prod.*, 2024, **87**, 984–993.
102 D. Overlingė, M. Cegłowska, R. Konkel and H. Mazur-Marzec, *Mar. Drugs*, 2024, **22**, 506.
103 S. W. Algor, A. Sukenik and S. Carmeli, *Mar. Drugs*, 2024, **22**, 389.
104 D. Overlingė, A. Toruńska-Sitarz, M. Cegłowska, K. Szubert and H. Mazur-Marzec, *Sci. Rep.*, 2024, **14**, 24686.
105 R. Fernández, M. Pérez, A. Losada, S. Reboredo, A. G.-S. Juan, M. J. Martín, A. Francesch, S. Munt and C. Cuevas, *Mar. Drugs*, 2024, **22**, 303.
106 S. Matthew, Q.-Y. Chen, R. Ratnayake, C. S. Fermaintt, D. Lucena-Agell, F. Bonato, A. E. Prota, S. T. Lim, X. Wang, J. F. Díaz, A. L. Risinger, V. J. Paul, M. Á. Oliva and H. Luesch, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2021847118.
107 P. Marfey, *Carlsberg Res. Commun.*, 1984, **49**, 591–596.
108 T. Weinert, N. Olieric, R. Cheng, S. Brünle, D. James, D. Ozerov, D. Gashi, L. Vera, M. Marsh, K. Jaeger, F. Dworkowski, E. Panepucci, S. Basu, P. Skopintsev, A. S. Doré, T. Geng, R. M. Cooke, M. Liang, A. E. Prota, V. Panneels, P. Nogly, U. Ermler, G. Schertler, M. Hennig, M. O. Steinmetz, M. Wang and J. Standfuss, *Nat. Commun.*, 2017, **8**, 542.
109 N. E. Avalon, M. A. Reis, C. C. Thornburg, R. T. Williamson, D. Petras, A. T. Aron, G. F. Neuhaus, M. Al-Hindy, J. Mitrevska, L. Ferreira, J. Morais, Y. E. Abiead, E. Glukhov, K. L. Alexander, F. A. Vulpanovici, M. J. Bertin, S. Whitner, H. Choi, G. Spengler, K. Blinov, A. M. Almohammadi, L. A. Shaala, W. R. Kew, L. Paša-Tolić, D. T. A. Youssef, P. C. Dorrestein, V. Vasconcelos, L. Gerwick, K. L. McPhail and W. H. Gerwick, *J. Am. Chem. Soc.*, 2024, **146**, 18626–18638.
110 T.-E. Ngo, A. Ecker, B. Ryu, A. Guild, A. Remmel, P. D. Boudreau, K. L. Alexander, C. B. Naman, E. Glukhov, N. E. Avalon, V. V. Shende, L. Thomas, S. Dahesh, V. Nizet, L. Gerwick and W. H. Gerwick, *ACS Chem. Biol.*, 2024, **19**, 619–628.
111 N. Kurisawa, G. Jeelani, T. Nozaki, A. L. Agusta, K. Suenaga and A. Iwasaki, *J. Nat. Prod.*, 2024, **87**, 1838–1843.
112 S. Kokkaliari, L. Grauso, A. Mangoni, G. Seabra, V. J. Paul and H. Luesch, *Chem. – Eur. J.*, 2024, **30**, e202401393.
113 S. Breinlinger, T. J. Phillips, B. N. Haram, J. Mareš, J. A. M. Yerena, P. Hrouzek, R. Sobotka, W. M. Henderson, P. Schmieder, S. M. Williams, J. D. Lauderdale, H. D. Wilde, W. Gerrin, A. Kust, J. W. Washington, C. Wagner, B. Geier, M. Liebeke, H. Enke, T. H. J. Niedermeyer and S. B. Wilde, *Science*, 2021, **371**, eaax9050.
114 N. J. Thomas, C. U. Meteyer and L. Sileo, *Vet. Pathol.*, 1998, **35**, 479–487.
115 S. K. Williams, J. Kempton, S. B. Wilde and A. Lewitus, *Harmful Algae*, 2007, **6**, 343–353.
116 S. B. Wilde, T. M. Murphy, C. P. Hope, S. K. Habrun, J. Kempton, A. Birrenkott, F. Wiley, W. W. Bowerman and A. J. Lewitus, *Environ. Toxicol.*, 2005, **20**, 348–353.
117 S. Adak, A. L. Lukowski, R. J. B. Schäfer and B. S. Moore, *J. Am. Chem. Soc.*, 2022, **144**, 2861–2866.
118 S. Gäfe and H. H. Niemann, *Acta Crystallogr., Sect. D:Biol. Crystallogr.*, 2023, **79**, 596–609.
119 H. Li, J.-W. Huang, L. Dai, H. Zheng, S. Dai, Q. Zhang, L. Yao, Y. Yang, Y. Yang, J. Min, R.-T. Guo and C.-C. Chen, *Nat. Commun.*, 2023, **14**, 7425.
120 S. Adak, N. Ye, L. A. Calderone, M. Duan, W. Lubeck, R. J. B. Schäfer, A. L. Lukowski, K. N. Houk, M.-E. Pandelia, C. L. Drennan and B. S. Moore, *Nat. Chem.*, 2024, **16**, 1989–1998.
121 M. G. Ricardo, M. Schwark, D. Llanes, T. H. J. Niedermeyer and B. Westermann, *Chem. – Eur. J.*, 2021, **27**, 12032–12035.
122 L. Štenclová, S. B. Wilde, M. Schwark, J. L. Cullen, S. A. McWhorter, T. H. J. Niedermeyer, W. M. Henderson and J. Mareš, *Harmful Algae*, 2023, **125**, 102425.
123 M. Schwark, J. A. M. Yerena, K. Röhrborn, P. Hrouzek, P. Divoká, L. Štenclová, K. Delawská, H. Enke, C. Vorreiter, F. Wiley, W. Sippl, R. Sobotka, S. Saha, S. B. Wilde, J. Mareš and T. H. J. Niedermeyer, *Proc. Natl. Acad. Sci. U. S. A.*, 2023, **120**, e2219230120.
124 N. R. Glasser, D. Cui, D. D. Risser, C. D. Okafor and E. P. Balskus, *Nat. Chem.*, 2024, **16**, 173–182.
125 H. Nakamura, H. A. Hamer, G. Sirasani and E. P. Balskus, *J. Am. Chem. Soc.*, 2012, **134**, 18518–18521.

126 E. E. Schultz, N. R. Braffman, M. U. Luescher, H. H. Hager and E. P. Balskus, *Angew. Chem., Int. Ed.*, 2019, **58**, 3151–3155.
127 P. N. Leão, H. Nakamura, M. Costa, A. R. Pereira, R. Martins, V. Vasconcelos, W. H. Gerwick and E. P. Balskus, *Angew. Chem., Int. Ed.*, 2015, **54**, 11063–11067.
128 T. B. Afonso, M. S. Costa, R. R. de Castro, S. Freitas, A. Silva, M. P. C. Schneider, R. Martins and P. N. Leão, *J. Nat. Prod.*, 2016, **79**, 2504–2513.
129 J. P. A. Reis, S. Freitas, T. Procházková and P. N. Leão, *J. Nat. Prod.*, 2024, **87**, 2709–2715.
130 J. P. A. Reis, S. A. C. Figueiredo, M. L. Sousa and P. N. Leão, *Nat. Commun.*, 2020, **11**, 1458.
131 D. Dehm, J. Krumbholz, M. Baunach, V. Wiebach, K. Hinrichs, A. Guljamow, T. Tabuchi, H. Jenke-Kodama, R. D. Süssmuth and E. Dittmann, *ACS Chem. Biol.*, 2019, **14**, 1271–1279.
132 J. Krumbholz, K. Ishida, M. Baunach, J. E. Teikari, M. M. Rose, S. Sasso, C. Hertweck and E. Dittmann, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204545.
133 A. Guljamow, M. Kreische, K. Ishida, A. Liaimer, B. Altermark, L. Bähr, C. Hertweck, R. Ehwald and E. Dittmann, *Appl. Environ. Microbiol.*, 2017, **83**, e01510–e01517.
134 A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, I. E. Orhan, M. Banach, J. M. Rollinger, D. Barreca, W. Weckwerth, R. Bauer, E. A. Bayer, M. Majeed, A. Bishayee, V. Bochkov, G. K. Bonn, N. Braidy, F. Bucar, A. Cifuentes, G. D'Onofrio, M. Bodkin, M. Diederich, A. T. Dinkova-Kostova, T. Efferth, K. E. Bairi, N. Arkells, T.-P. Fan, B. L. Fiebich, M. Freissmuth, M. I. Georgiev, S. Gibbons, K. M. Godfrey, C. W. Gruber, J. Heer, L. A. Huber, E. Ibanez, A. Kijjoa, A. K. Kiss, A. Lu, F. A. Macias, M. J. S. Miller, A. Mocan, R. Müller, F. Nicoletti, G. Perry, V. Pittalà, L. Rastrelli, M. Ristow, G. L. Russo, A. S. Silva, D. Schuster, H. Sheridan, K. Skalicka-Woźniak, L. Skaltsounis, E. Sobarzo-Sánchez, D. S. Bredt, H. Stuppner, A. Sureda, N. T. Tzvetkov, R. A. Vacca, B. B. Aggarwal, M. Battino, F. Giampieri, M. Wink, J.-L. Wolfender, J. Xiao, A. W. K. Yeung, G. Lizard, M. A. Popp, M. Heinrich, I. Berindan-Neagoe, M. Stadler, M. Daglia, R. Verpoorte and C. T. Supuran, *Nat. Rev. Drug Discovery*, 2021, **20**, 200–216.
135 T. F. Molinski, *Nat. Prod. Rep.*, 2010, **27**, 321–329.
136 D. S. Wishart, *J. Magn. Reson.*, 2019, **306**, 155–161.
137 S. Sieber, A. Carlier, M. Neuburger, G. Grabenweger, L. Eberl and K. Gademann, *Angew. Chem., Int. Ed.*, 2015, **54**, 7968–7970.
138 R. Taguchi, A. Iwasaki, A. Ebihara, G. Jeelani, T. Nozaki and K. Suenaga, *Org. Lett.*, 2022, **24**, 4710–4714.
139 N. Grimblat, M. M. Zanardi and A. M. Sarotti, *J. Org. Chem.*, 2015, **80**, 12526–12534.
140 N. Grimblat, J. A. Gavín, A. H. Daranas and A. M. Sarotti, *Org. Lett.*, 2019, **21**, 4003–4007.
141 W. Hehre, P. Klunzinger, B. Deppmeier, A. Driessen, N. Uchida, M. Hashimoto, E. Fukushi and Y. Takata, *J. Nat. Prod.*, 2019, **82**, 2299–2306.
142 S. G. Smith and J. M. Goodman, *J. Am. Chem. Soc.*, 2010, **132**, 12946–12959.
143 K. Umeda, A. Iwasaki, R. Taguchi, N. Kurisawa, G. Jeelani, T. Nozaki and K. Suenaga, *J. Nat. Prod.*, 2023, **86**, 2529–2538.
144 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092–4096.
145 M. Yotsu-Yamashita, K. Umeda, A. Iwasaki and K. Suenaga, *Toxicon*, 2024, **250**, 108122.
146 F. H. Al-Awadhi, S. Kokkaliari, R. Ratnayake, V. J. Paul and H. Luesch, *J. Nat. Prod.*, 2024, **87**, 2355–2365.
147 O. Ohno, A. Iwasaki, K. Same, C. Kudo, E. Aida, K. Sugiura, S. Sumimoto, T. Teruya, E. Tashiro, S. Simizu, K. Matsuno, M. Imoto and K. Suenaga, *Org. Lett.*, 2022, **24**, 4547–4551.
148 Y. Miyamoto, A. Iwasaki, H. Fujimura, C. Kudo, N. Kurisawa, O. Ohno and K. Suenaga, *J. Org. Chem.*, 2023, **88**, 3208–3216.
149 S. A. C. Figueiredo, M. Preto, G. Moreira, T. P. Martins, K. Abt, A. Melo, V. M. Vasconcelos and P. N. Leão, *Angew. Chem., Int. Ed.*, 2021, **60**, 10064–10072.
150 K. Voráčová, J. Hájek, J. Mareš, P. Urajová, M. Kuzma, J. Cheel, A. Villunger, A. Kapuscik, M. Bally, P. Novák, M. Kabeláč, G. Krumschnabel, M. Lukeš, L. Voloshko, J. Kopecký and P. Hrouzek, *PLoS One*, 2017, **12**, e0172850.
151 I. Gutiérrez-del-Río, N. B. de Fraissinette, R. Castelo-Branco, F. Oliveira, J. Morais, S. Redondo-Blanco, C. J. Villar, M. J. Iglesias, R. Soengas, V. Cepas, Y. L. Cubillos, G. Sampietro, L. Rodolfi, F. Lombó, S. M. S. González, F. L. Ortiz, V. Vasconcelos and M. A. Reis, *J. Nat. Prod.*, 2020, **83**, 1885–1890.
152 T. J. O'Donnell, Y. Luo, W. Y. Yoshida, S. Suzuki, R. Sun and P. G. Williams, *J. Nat. Prod.*, 2022, **85**, 415–425.
153 M. H. Medema, R. Kottmann, P. Yilmaz, M. Cummings, J. B. Biggins, K. Blin, I. de Bruijn, Y. H. Chooi, J. Claesen, R. C. Coates, P. Cruz-Morales, S. Duddela, S. Düsterhus, D. J. Edwards, D. P. Fewer, N. Garg, C. Geiger, J. P. Gomez-Escribano, A. Greule, M. Hadjithomas, A. S. Haines, E. J. N. Helfrich, M. L. Hillwig, K. Ishida, A. C. Jones, C. S. Jones, K. Jungmann, C. Kegler, H. U. Kim, P. Kötter, D. Krug, J. Masschelein, A. V. Melnik, S. M. Mantovani, E. A. Monroe, M. Moore, N. Moss, H.-W. Nützmann, G. Pan, A. Pati, D. Petras, F. J. Reen, F. Rosconi, Z. Rui, Z. Tian, N. J. Tobias, Y. Tsunematsu, P. Wiemann, E. Wyckoff, X. Yan, G. Yim, F. Yu, Y. Xie, B. Aigle, A. K. Apel, C. J. Balibar, E. P. Balskus, F. Barona-Gómez, A. Bechthold, H. B. Bode, R. Borriss, S. F. Brady, A. A. Brakhage, P. Caffrey, Y.-Q. Cheng, J. Clardy, R. J. Cox, R. D. Mot, S. Donadio, M. S. Donia, W. A. van der Donk, P. C. Dorrestein, S. Doyle, A. J. M. Driessen, M. Ehling-Schulz, K.-D. Entian, M. A. Fischbach, L. Gerwick, W. H. Gerwick, H. Gross, B. Gust, C. Hertweck, M. Höfte, S. E. Jensen, J. Ju, L. Katz, L. Kaysser, J. L. Klassen, N. P. Keller, J. Kormanec, O. P. Kuipers, T. Kuzuyama, N. C. Kyrpides, H.-J. Kwon, S. Lautru, R. Lavigne, C. Y. Lee, B. Linquan, X. Liu, W. Liu, A. Luzhetskyy, T. Mahmud, Y. Mast, C. Méndez, M. Metsä-Ketelä, J. Micklefield, D. A. Mitchell,

B. S. Moore, L. M. Moreira, R. Müller, B. A. Neilan, M. Nett, J. Nielsen, F. O'Gara, H. Oikawa, A. Osbourn, M. S. Osburne, B. Ostash, S. M. Payne, J.-L. Pernodet, M. Petricek, J. Piel, O. Ploux, J. M. Raaijmakers, J. A. Salas, E. K. Schmitt, B. Scott, R. F. Seipke, B. Shen, D. H. Sherman, K. Sivonen, M. J. Smanski, M. Sosio, E. Stegmann, R. D. Süssmuth, K. Tahlan, C. M. Thomas, Y. Tang, A. W. Truman, M. Viaud, J. D. Walton, C. T. Walsh, T. Weber, G. P. van Wezel, B. Wilkinson, J. M. Willey, W. Wohlleben, G. D. Wright, N. Ziemert, C. Zhang, S. B. Zotchev, R. Breitling, E. Takano and F. O. Glöckner, *Nat. Chem. Biol.*, 2015, **11**, 625–631.

154 S. A. Kautsar, K. Blin, S. Shaw, J. C. Navarro-Muñoz, B. R. Terlouw, J. J. J. van der Hooft, J. A. van Santen, V. Tracanna, H. G. Suarez Duran, V. Pascal Andreu, N. Selem-Mojica, M. Alanjary, S. L. Robinson, G. Lund, S. C. Epstein, A. C. Sisto, L. K. Charkoudian, J. Collemare, R. G. Linington, T. Weber and M. H. Medema, *Nucleic Acids Res.*, 2019, **48**, D454–D458.

155 B. R. Terlouw, K. Blin, J. C. Navarro-Muñoz, N. E. Avalon, M. G. Chevrette, S. Egbert, S. Lee, D. Meijer, M. J. J. Recchia, Z. L. Reitz, J. A. van Santen, N. Selem-Mojica, T. Tørring, L. Zaroubi, M. Alanjary, G. Aleti, C. Aguilar, S. A. A. Al-Salihi, H. E. Augustijn, J. A. Avelar-Rivas, L. A. Avitia-Domínguez, F. Barona-Gómez, J. Bernaldo-Agüero, V. A. Bielinski, F. Biermann, T. J. Booth, V. J. C. Bravo, R. Castelo-Branco, F. O. Chagas, P. Cruz-Morales, C. Du, K. R. Duncan, A. Gavriilidou, D. Gayrard, K. Gutiérrez-García, K. Haslinger, E. J. N. Helfrich, J. J. J. van der Hooft, A. P. Jati, E. Kalkreuter, N. Kalyvas, K. B. Kang, S. Kautsar, W. Kim, A. M. Kunjapur, Y.-X. Li, G.-M. Lin, C. Loureiro, J. J. R. Louwen, N. L. L. Louwen, G. Lund, J. Parra, B. Philmus, B. Pourmohsenin, L. J. U. Pronk, A. Rego, D. A. B. Rex, S. Robinson, L. R. Rosas-Becerra, E. T. Roxborough, M. A. Schorn, D. J. Scobie, K. S. Singh, N. Sokolova, X. Tang, D. Udwary, A. Vigneshwari, K. Vind, S. P. J. M. Vromans, V. Waschulin, S. E. Williams, J. M. Winter, T. E. Witte, H. Xie, D. Yang, J. Yu, M. Zdouc, Z. Zhong, J. Collemare, R. G. Linington, T. Weber and M. H. Medema, *Nucleic Acids Res.*, 2022, **51**, D603–D610.

156 M. M. Zdouc, K. Blin, N. L. L. Louwen, J. Navarro, C. Loureiro, C. D. Bader, C. B. Bailey, L. Barra, T. J. Booth, K. A. J. Bozhüyük, J. D. D. Cediel-Becerra, Z. Charlop-Powers, M. G. Chevrette, Y. H. Chooi, P. M. D'Agostino, T. de Rond, E. D. Pup, K. R. Duncan, W. Gu, N. Hanif, E. J. N. Helfrich, M. Jenner, Y. Katsuyama, A. Korenskaia, D. Krug, V. Libis, G. A. Lund, S. Mantri, K. D. Morgan, C. Owen, C.-S. Phan, B. Philmus, Z. L. Reitz, S. L. Robinson, K. S. Singh, R. Teufel, Y. Tong, F. Tugizimana, D. Ulanova, J. M. Winter, C. Aguilar, D. Y. Akiyama, S. A. A. Al-Salihi, M. Alanjary, F. Alberti, G. Aleti, S. A. Alharthi, M. Y. A. Rojo, A. A. Arishi, H. E. Augustijn, N. E. Avalon, J. A. Avelar-Rivas, K. K. Axt, H. B. Barbieri, J. C. J. Barbosa, L. G. B. Segato, S. E. Barrett, M. Baunach, C. Beemelmanns, D. Beqaj, T. Berger, J. Bernaldo-Agüero, S. M. Bettenbühl, V. A. Bielinski, F. Biermann, R. M. Borges, R. Borriss, M. Breitenbach, K. M. Bretscher, M. W. Brigham, L. Buedenbender, B. W. Bulcock, C. Cano-Prieto, J. Capela, V. J. Carrion, R. S. Carter, R. Castelo-Branco, G. Castro-Falcón, F. O. Chagas, E. Charria-Girón, A. A. Chaudhri, V. Chaudhry, H. Choi, Y. Choi, R. Choupannejad, J. Chromy, M. S. C. Donahey, J. Collemare, J. A. Connolly, K. E. Creamer, M. Crüsemann, A. A. Cruz, A. Cumsille, J.-F. Dallery, L. C. Damas-Ramos, T. Damiani, M. de Kruijff, B. D. Martín, G. D. Sala, J. Dillen, D. T. Doering, S. R. Dommaraju, S. Durusu, S. Egbert, M. Ellerhorst, B. Faussurier, A. Fetter, M. Feuermann, D. P. Fewer, J. Foldi, A. Frediansyah, E. A. Garza, A. Gavriilidou, A. Gentile, J. Gerke, H. Gerstmans, J. P. Gomez-Escribano, L. A. González-Salazar, N. E. Grayson, C. Greco, J. E. G. Gomez, S. Guerra, S. G. Flores, A. Gurevich, K. Gutiérrez-García, L. Hart, K. Haslinger, B. He, T. Hebra, J. L. Hemmann, H. Hindra, L. Höing, D. C. Holland, J. E. Holme, T. Horch, P. Hrab, J. Hu, T.-H. Huynh, J.-Y. Hwang, R. Iacovelli, D. Iftime, M. Iorio, S. Jayachandran, E. Jeong, J. Jing, J. J. Jung, Y. Kakumu, E. Kalkreuter, K. B. Kang, S. Kang, W. Kim, G. J. Kim, H. Kim, H. U. Kim, M. Klapper, R. A. Koetsier, C. Kollten, Á. T. Kovács, Y. Kriukova, N. Kubach, A. M. Kunjapur, A. K. Kushnareva, A. Kust, J. Lamber, M. Larralde, N. J. Larsen, A. P. Launay, N.-T.-H. Le, S. Lebeer, B. T. Lee, K. Lee, K. L. Lev, S.-M. Li, Y.-X. Li, C. Licona-Cassani, A. Lien, J. Liu, J. A. V. Lopez, N. V. Machushynets, M. I. Macias, T. Mahmud, M. Maleckis, A. M. Martinez-Martinez, Y. Mast, M. F. Maximo, C. M. McBride, R. M. McLellan, K. M. Bhatt, C. Melkonian, A. Merrild, M. Metsä-Ketelä, D. A. Mitchell, A. V. Müller, G.-S. Nguyen, H. T. Nguyen, T. H. J. Niedermeyer, J. H. O'Hare, A. Ossowicki, B. O. Ostash, H. Otani, L. Padva, S. Paliyal, X. Pan, M. Panghal, D. S. Parade, J. Park, J. Parra, M. P. Rubio, H. T. Pham, S. J. Pidot, J. Piel, B. Pourmohsenin, M. Rakhmanov, S. Ramesh, M. H. Rasmussen, A. Rego, R. Reher, A. J. Rice, A. Rigolet, A. Romero-Otero, L. R. Rosas-Becerra, P. Y. Rosiles, A. Rutz, B. Ryu, L.-A. Sahadeo, M. Saldanha, L. Salvi, E. Sánchez-Carvajal, C. Santos-Medellin, N. Sbaraini, S. M. Schoellhorn, C. Schumm, L. Sehnal, N. Selem, A. D. Shah, T. K. Shishido, S. Sieber, V. Silviani, G. Singh, H. Singh, N. Sokolova, E. C. Sonnenschein, M. Sosio, S. T. Sowa, K. Steffen, E. Stegmann, A. B. Streiff, A. Strüder, F. Surup, T. Svenningsen, D. Sweeney, J. Szenei, A. Tagirdzhanov, B. Tan, M. J. Tarnowski, B. R. Terlouw, T. Rey, N. U. Thome, L. R. T. Ortega, T. Tørring, M. Trindade, A. W. Truman, M. Tvilum, D. W. Udwary, C. Ulbricht, L. Vader, G. P. van Wezel, M. Walmsley, R. Warnasinghe, H. G. Weddeling, A. N. M. Weir, K. Williams, S. E. Williams, T. E. Witte, S. M. W. Rocca, K. Yamada, D. Yang, D. Yang, J. Yu, Z. Zhou, N. Ziemert, L. Zimmer, A. Zimmermann, C. Zimmermann, J. J. J. van der Hooft,

R. G. Linington, T. Weber and M. H. Medema, *Nucleic Acids Res.*, 2024, **53**, D678–D690.
157 K. Palaniappan, I.-M. A. Chen, K. Chu, A. Ratner, R. Seshadri, N. C. Kyrpides, N. N. Ivanova and N. J. Mouncey, *Nucleic Acids Res.*, 2019, **48**, D422–D430.
158 S. A. Kautsar, K. Blin, S. Shaw, T. Weber and M. H. Medema, *Nucleic Acids Res.*, 2020, **49**, D490–D497.
159 K. Blin, M. H. Medema, R. Kottmann, S. Y. Lee and T. Weber, *Nucleic Acids Res.*, 2017, **45**, D555–D559.
160 K. Blin, S. Shaw, A. M. Kloosterman, Z. Charlop-Powers, G. P. van Wezel, M. H. Medema and T. Weber, *Nucleic Acids Res.*, 2021, **49**, W29–W35.
161 A. Rutz, D. Probst, C. Aguilar, D. Y. Akiyama, F. Alberti, H. E. Augustijn, N. E. Avalon, C. Beemelmanns, H. B. Barbieri, F. Biermann, A. J. Bridge, E. C. Girón, R. Cox, M. Crüsemann, P. M. D'Agostino, M. Feuermann, J. Gerke, K. G. García, J. E. Holme, J.-Y. Hwang, R. Iacovelli, J. C. J. Barbosa, N. Kaur, M. Klapper, A. M. Köhler, A. Korenskaia, N. Kubach, B. T. Lee, C. Loureiro, S. Mantri, S. Narula, D. Meijer, J. C. Navarro-Muñoz, G.-S. Nguyen, S. Paliyal, M. Panghal, L. Rao, S. Sieber, N. Sokolova, S. T. Sowa, J. Szenei, B. R. Terlouw, H. G. Weddeling, J. Yu, N. Ziemert, T. Weber, K. Blin, J. J. J. van der Hooft, M. H. Medema and M. M. Zdouc, *Nucleic Acids Res.*, 2025, gkaf969.
162 J. D. Rudolf, T. A. Alsup, B. Xu and Z. Li, *Nat. Prod. Rep.*, 2020, **38**, 905–980.
163 J. R. Gurr, T. J. O'Donnell, Y. Luo, W. Y. Yoshida, M. L. Hall, A. M. S. Mayer, R. Sun and P. G. Williams, *J. Nat. Prod.*, 2020, **83**, 1691–1695.
164 D. Back, T. J. O'Donnell, K. K. Axt, J. R. Gurr, J. M. Vanegas, P. G. Williams and B. Philmus, *ACS Chem. Biol.*, 2023, **18**, 1797–1807.
165 R.-A. Hughes, Y. Zhang, R. Zhang, P. G. Williams, J. S. Lindsey and E. S. Miller, *Appl. Environ. Microbiol.*, 2017, **83**, e01068–17.
166 X. Jin, E. S. Miller and J. S. Lindsey, *Life*, 2021, **11**, 356.
167 A. Ebihara, R. Taguchi, G. Jeelani, T. Nozaki, K. Suenaga and A. Iwasaki, *J. Nat. Prod.*, 2024, **87**, 1116–1123.
168 F. I. Saldívar-González, V. D. Aldas-Bulos, J. L. Medina-Franco and F. Plisson, *Chem. Sci.*, 2021, **13**, 1526–1546.
169 A. Ebihara, A. Iwasaki, Y. Miura, G. Jeelani, T. Nozaki and K. Suenaga, *J. Org. Chem.*, 2021, **86**, 11763–11770.
170 R. Reher, H. W. Kim, C. Zhang, H. H. Mao, M. Wang, L.-F. Nothias, A. M. Caraballo-Rodriguez, E. Glukhov, B. Teke, T. Leao, K. L. Alexander, B. M. Duggan, E. L. V. Everbroeck, P. C. Dorrestein, G. W. Cottrell and W. H. Gerwick, *J. Am. Chem. Soc.*, 2020, **142**, 4114–4120.
171 N. L. Drake, H. C. Harris and C. B. Jaeger, *J. Am. Chem. Soc.*, 1948, **70**, 168–171.
172 N. Kurisawa, A. Iwasaki, K. Teranuma, S. Dan, C. Toyoshima, M. Hashimoto and K. Suenaga, *J. Am. Chem. Soc.*, 2022, **144**, 11019–11032.
173 D. A. Evans, D. L. Rieger, M. T. Bilodeau and F. Urpi, *J. Am. Chem. Soc.*, 1991, **113**, 1047–1049.
174 Y. K. Zhang, M. A. Sanchez-Ayala, P. W. Sternberg, J. Srinivasan and F. C. Schroeder, *Org. Lett.*, 2017, **19**, 2837–2840.
175 S. Kokkaliari, D. Luo, V. J. Paul and H. Luesch, *Mar. Drugs*, 2023, **21**, 378.
176 N. Kurisawa, K. Teranuma, A. Noto, A. Iwasaki, Y. Kabashima, R. Nakajima, C. Toyoshima and K. Suenaga, *Bull. Chem. Soc. Jpn.*, 2024, **97**, uoae070.
177 D. Kong and T. Yamori, *Bioorg. Med. Chem.*, 2012, **20**, 1947–1951.
178 D. Trauner and K.-P. Ruehmann, *Synfacts*, 2022, **18**, 1028.
179 N. Kurisawa, A. Iwasaki and K. Suenaga, *J. Synth. Org. Chem., Jpn.*, 2024, **82**, 1107–1116.
180 H. Takahashi, A. Iwasaki, A. Ebihara, R. Taguchi, G. Jeelani, T. Nozaki and K. Suenaga, *Org. Lett.*, 2023, **25**, 2400–2404.

