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Emerging Technologies for the Discovery and Characterization of Microbial Natural Products

Simon Sieber*

Abstract: The discovery of natural products has changed dramatically in recent years, and new technologies have been developed continuously to improve this process, including the integration of artificial intelligence tools. Herein, we summarize some emerging methodologies, including genome mining, activation of selected biosynthetic pathways, chemical probes, and mass spectrometry-based metabolomics. Selected examples are discussed in detail, highlighting and describing their discovery strategies.

Keywords: Drug discovery · Genome mining · Metabolomics · Natural products

Simon Sieber studied chemistry at EPFL, also conducting a research project at University College London with Prof. Deniz Tasdemir. He obtained his PhD from the University of Basel under the guidance of Prof. Karl Gademann, working on the discovery and total synthesis of natural products. He joined Prof. Shana Sturla's group as a Postdoctoral researcher at ETHZ, investigating the metabolic transformations carried out by the gut microbiota. Since 2016, he has held a senior scientist position with Prof. Karl Gademann at the University of Zurich. His research focuses on studying molecular communication among bacterial species, discovering novel natural product scaffolds, and developing novel methodologies to improve the efficacy of natural product discovery.

1. Introduction

Natural products have been the primary resource for treating infections and diseases for millennia. Even with the vast development of synthetic drugs, natural products remain an essential pillar of our health system today.[1,2] Their success is often linked to their extensive chemical diversity and complex structures, which have been refined and optimized through natural selection.[3] Traditionally, bioactive compounds are discovered through bioassay-guided fractionation of active crude extracts. The extract is separated into fractions, each tested in a specific bioassay, and the process is repeated until an active fraction yields a pure compound. This approach remains highly successful but faces several bottlenecks, including rediscovery of known compounds and limited biomass availability.[3] This review presents novel technologies that streamline natural product pipelines. Selected examples from the past five years are presented in detail, highlighting techniques developed in this research field.

2. Genome Mining

Natural product discovery has evolved rapidly over the last few decades with the development of sequencing and (meta)genome mining methodologies.[4–6] In 2025, it was estimated that public databases contain more than 1.5 million microbial genomes (reference sequences and metagenome-assembled genomes (MAGs)).[7] Furthermore, advances in understanding natural product biosynthesis led to the identification and characterization of several biosynthetic gene clusters (BGCs), which are publicly available in databases such as the manually curated minimum information for biosynthetic gene clusters (MIBiG).[8] Several bioinformatic tools have been developed to mine genomic and metagenomic data to detect and link BGCs to natural products. The most widely used platform is antiSMASH,[9,10] which incorporates several predictive tools, including ARTS,[11] GECCO,[12] BiG-SCAPE,[13] BiG-SLiCE,[13] NPLinker,[14] and DeepBGC.[15] Natural product discovery has strongly benefited from this quick and powerful development, and recent examples are highlighted in this section.

2.1 *Keanumycins*

One approach is to interrogate single strains by mining their genomes. This approach has been successfully applied in many cases and has already led us and others to the discovery of numerous natural products.[16–24] A recent example is the isolation of the amoebicidal and antifungal keanumycins A–C (**1**–**3**, Fig. 1).[25] The study initiated with the search for an amoebicidal compound produced by the strain *Pseudomonas sp*. QS1027, which has already been proven to be rich in active metabolites.[26,27] The genome of this organism, obtained by shotgun sequencing, was submitted to an in-depth analysis using the online platform antiSMASH.[9,10,28] The keanumycin BGC harboring nonribosomal peptide synthetase (NRPS) genes was particularly notable for its high sequence similarity with the previously characterized BGC responsible for the production of nunamycin, a known antifungal nonribosomal lipopeptide (NRLP).[29] This specific gene cluster was of interest because several antifungal compounds have already been shown to be active against amoebas. The keanumycin BGC was initially found to be split into two contigs, and further sequencing analyses enabled its full reconstruction. The functions of the enzymes encoded by this BGC guided the prediction of the keanumycin structures, which were subsequently identified using a comparative analysis between a deletion mutant and the wild type. The elucidation of the structure was performed using a combination of analytical and synthetic approaches, such as high-resolution mass spectrometry (HRMS), 1D and 2D nuclear magnetic resonance (NMR), and chemical derivatization and degradation experiments. Keanumycin C (**3**) was the most challenging compound due to the presence of a terminal imine moiety (Fig. 1), a functional group not yet observed in NRLP. Furthermore, keanumycin A (**1**) exhibited potent amoebicidal properties and antifungal activity against several fungal strains, most notably against

*Correspondence: Dr. S. Sieber, E-mail: simon.sieber@uzh.ch
Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich

Botrytis cinerea SF011406, a broad host range phytopathogen responsible for significant crop losses worldwide.[30] Additionally, Stallforth and coworkers applied a similar genome-mining strategy to another *Pseudomonas* strain (*Pseudomonas nunensis* 4A2e), which led to the isolation and structure elucidation of another keanumycin family member, (keanumycin D).[31]

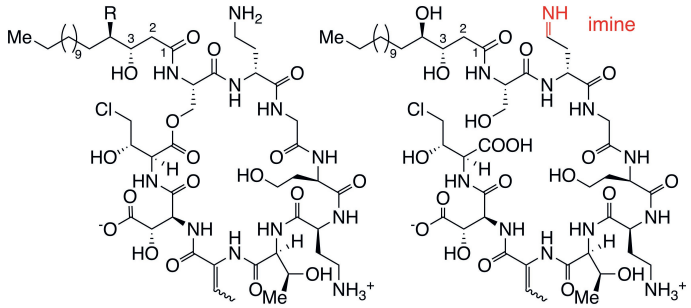

Fig. 1. Structures of keanumycin A–C, isolated from *Pseudomonas sp.* QS1027.[25]

2.2 *Origamins*

A productive strategy relies on defining a specific sequence tag based on a conserved biosynthetic domain or gene(s) within a molecular family and systematically searching databases for matching BGCs. The application of this methodology has led to the discovery of several novel natural products, spanning diverse biosynthetic classes, including ribosomally synthesized and post-translationally modified peptides (RiPPs),[32–40] NRPS-derived peptides,[41–43] polyketides (PKS[44–47] and PKS-NRPS hybrids),[18,48,49] alkaloids,[50] and terpenes.[51–54]

The discovery of the hypermodified RiPPs origamins (Fig. 2) is discussed below, highlighting the power of this methodology for unraveling a novel class of natural products.[34] The initial approach focused on the structurally unique polytheonamides, which are hypermodified RiPPs adopting a β-helical structure. These structural properties were found to be critical for their high cytotoxic activity and arise from the intercalation of D- and L-amino acids, as well as a recurring NX_5N sequence bearing Asn *N*-methylation. To target compounds with similar properties, databases (NCBI, mOTUs)[55] and computational search tools (EFI-GNT,[56] RODEO)[40] were used to identify and categorize BGCs possessing the NX_5N features, which were named *oxx*. A phylogenetic analysis revealed that *oxx* is present in numerous bacteria across 18 phyla and can be separated into four structural types (type I-IV). Further analyses focused on the production of origamins' BGCs of types I, II, and III from *Escherichia coli*, *Thermus scotoductus*, and *Polymorphum gilvum*, respectively. A successful strategy for the production of *N*-terminal tagged peptides involved heterologous expression of the tripartite precursor OpgA2 from *P. gilvum*, along with its posttranslational enzymes, using a two-plasmid system in *Microvirgula aerodenitrificans*. The fully modified untagged peptide bears 18 epimerizations, 13 *N*-methylations, and 13 *C*-methylations, and the predicted structure of this origamin is highlighted in Fig 2. The hypermodified peptide was expressed at a larger scale, and the purified fraction, containing a mixture of 11- and 12-fold *C*-methylated origamin, exhibited cytotoxicity in the nanomolar range (IC_{50} = 423.8 nM) against HT-29 human colorectal adenocarcinoma cells.

2.3 *Macolacin Metagenomic Analysis*

Another discovery approach involves searching for similar BGCs associated with bioactive natural products. For example,

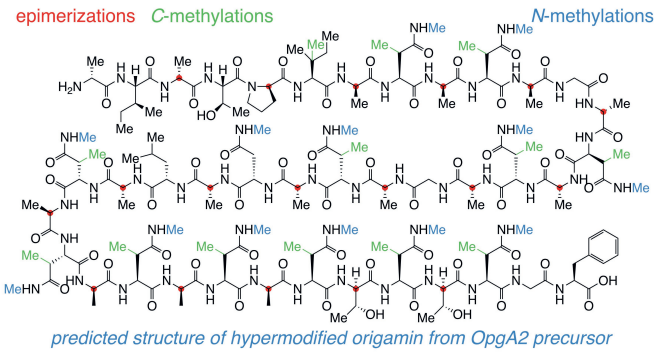

Fig. 2. Proposed structure of origamin produced by *Polymorphum gilvum* using the precursor peptide OpgA2. The posttranslational modifications are highlighted in red, blue, and green.[34]

colistin, a nonribosomal peptide (NRP) from the polymyxin family, is a last-resort antibiotic used against Gram-negative strains that have developed resistance to first-line antibiotics.[57,58] Unfortunately, colistin-resistant strains have increased in recent years, and novel treatments need to be developed. Searching for colistin analogs would help address resistant strains, and this approach was used to discover macolacin (**4**, Fig. 3).[59] A search of a library comprising 10,858 bacterial genomes identified 35 BGCs that encoded colistin-like compounds. The NRPS modules were analyzed, and the amino acid specificity of the adenylation domains was predicted using the Stachelhaus code. One of the 35 BGCs was particularly interesting because the predicted amino acid sequence showed variation at positions 3, 7, and 10, compared to colistin. Given the highly conserved structure of known colistin derivatives, the authors hypothesized that the structure of the putative compound could be directly deduced from its BGC. Therefore, the predicted compound, macolacin (**4**), was synthesized *via* solid-phase peptide synthesis (SPPS) and was proposed to be termed a synthetic bioinformatic natural product (*syn*-BNP). Macolacin (**4**) was tested against several wild-type and *mcr*-1-expressing colistin-resistant strains and was found to retain potent bioactivity. Furthermore, the compound's potency was increased by modifying its *N*-acyl side chain, as previously studied in polymyxins,[60,61] and the efficacy of the compound was evaluated in animal studies.

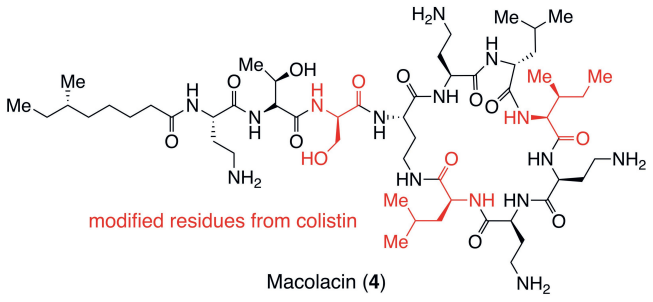

Fig. 3. Structure of the synthetic bioinformatic natural product macolacin (**4**).[59]

2.4 *Salinilactam, Muanlactam, and Concolactam (PCR)*

The microorganism's genome can also be searched using a direct experimental method such as the polymerase chain reaction (PCR). A characteristic biosynthetic gene, conserved in a specific compound family, is identified, and appropriate primers are constructed. A bacterial or metagenomic DNA library is then screened. This strategy has recently been applied to the discovery of novel macrolactams,[62] bartolosides,[63] and natu-

ral products bearing oxazole,[64] thiazole,[65] and thioamide[66] moieties.

In macrolactam biosynthesis, it is crucial to regulate the timing of lactam ring formation. Initially, the primary amino group is incorporated, then temporarily 'protected' by adding an amino acid residue *via* an adenylation enzyme. Right before cyclization, an aminohydrolase removes this 'protection residue'.[67] Primers for these two enzymes were designed, and in-house bacterial genomic DNA was screened.[62] A total of 43 double-hit strains were selected for evaluation of their ability to produce macrolactams using liquid chromatography-mass spectrometry (LC-MS)-based metabolomic analysis. Three strains (*Micromonospora sp*. JL29, *Streptomyces sp*. MA159 and *Streptomyces sp*. UTZ13) displayed promising metabolic profiles and were further investigated. A specific assay was developed to detect macrolactams by identifying characteristic correlations observed in $^{1}H–^{15}N$ heteronuclear single-quantum coherence–total correlation spectroscopy (HSQC-TOCSY) NMR experiments. The three selected strains were grown in ^{15}N-enriched medium and the NMR analysis of their crude extracts revealed the characteristic features of an α-methyl macrolactam for *Micromonospora sp*. JL29, an α-alkyl macrolactam for *Streptomyces sp*. MA159 and a β-methyl macrolactam for *Streptomyces sp*. UTZ13. The related compounds were isolated and purified, and their structures and biosynthetic pathways were elucidated. This resulted in the structure revision of salinilactam (**5**, Fig. 4) produced by *Micromonospora sp*. JL29, and the discovery of muanlactam (**6**) produced by *Streptomyces sp*. MA159 and concolactam (**7**) produced by *Streptomyces sp*. UTZ13. Notably, muanlactam (**6**) exhibited significant cytotoxicity with low micromolar IC_{50} values against several cancer cell lines (SK-HEP-1, MDA-MB-231, A549, HCT116, and SNU638).

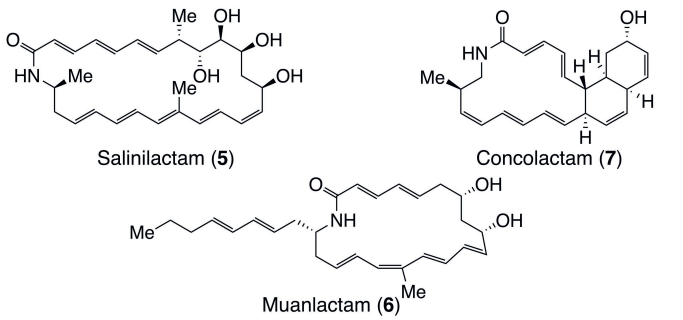

Fig. 4: Structures of salinilactam (**5**) produced by *Micromonospora sp*. JL29, muanlactam (**6**) by *Streptomyces sp*. MA159, and concolactam (**7**) by *Streptomyces sp*. UTZ13.[62]

2.5 *Natural Products in the Genomic Era*

The examples described in those sections illustrate the power of (meta)genomic analysis in the discovery of natural products. With the currently available tools and resources, natural products can be searched in a targeted approach by developing a specific tag or by searching for analogs of an active BGC. In parallel, a genome from an organism identified to produce bioactive compounds can be rapidly sequenced, allowing the determination of BGCs that may be linked to the production of active compounds. A targeted approach can likewise be applied to bacterial DNA by designing primers to screen for a specific gene of interest by PCR.

3. Activation of Biosynthetic Pathways

One strategy to target a specific class of natural products is to chemically or genetically manipulate their biosynthetic pathways. Recent examples have shown promising results for natural products with fatty acid residues,[68] halogenated biosynthetic precursors,[69] and polyketide scaffolds.[70] However, in some cases, producing certain natural products can be difficult. Various examples have shown that some BGCs are silent and are expressed only under specific conditions.[71,72] To overcome this problem, several technologies have been developed over the years. The most traditional approach is to modify the culture conditions using a one-strain many-compounds (OSMAC) strategy, which remains a very successful technique.[73–75] Expression of the desired BGC was also recently triggered by promoter exchange,[76] clustered regularly interspaced short palindromic repeats (CRISPR) interference and activation approaches,[77] deletion of the dominant antibiotic BGC,[78] and screening a chemical library of potential elicitors.[79–81] An example of the latter strategy is described below.

3.1 *Momomycin*

Some microorganisms' BGCs are not expressed under standard culture conditions, and it is hypothesized that the organisms produce those compounds in response to environmental stimuli.[82] A method was created to chemically stress the organisms using a high-throughput elicitor screening (HiTES) strategy.[82] Momomycin (**8**, Fig. 5) was discovered from *Streptomyces rimosus* ATCC 10970 using this activation strategy and matrix-assisted laser desorption/ionization (MALDI)-MS for metabolomic analysis.[80] The genome of *Streptomyces rimosus* ATCC 10970 exhibited significant discovery potential, as antiSMASH[9,10,28] analysis identified 45 BGCs, only a few of which were linked to known compounds. Initial results showed that the production of major metabolites, rimocidin and its derivatives, interfered with the production and detection of less abundant natural products. To mitigate this issue, a rimocidin BGC deletion mutant was created and tested with a natural product library of 502 potential elicitors. Three compounds, including momomycin (**8**), were selected for further analysis because they were produced abundantly in response to specific elicitors. Momomycin (**8**) was isolated and purified from large-scale culture, and its structure and biosynthetic pathway were determined. The natural product shows promising anticancer activity, with low-micromolar IC_{50} values of ~1.1 μM against HCT116 cells and 1.2 μM against MDA-MB-231 cells.

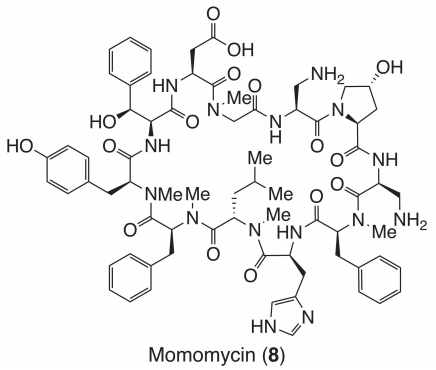

Fig. 5. Structure of momomycin (**8**) found from *Streptomyces rimosus* ATCC 10970.[80]

3.2 *Strategies to Awaken Silent BGCs*

Gene expression can be modulated by several strategies, with the OSMAC approach being widely used. Later developments in the field have included the creation of elicitor libraries to rapidly identify a compound that activates the desired BGC. Genetic engineering techniques have also been used, such as CRISPR-Cas9.[77]

Furthermore, tremendous progress has been made in the heterologous expression of BGCs, and these techniques have also been applied to express silent BGCs.

4. Chemical Probe for Natural Products Discovery

A group of natural products can be targeted by focusing on a common chemical characteristic shared by all its members using derivatization strategies.[83,84] This reactivity-based screening (RBS) method,[85] has recently been used for the profiling and discovery of, for example, isonitriles,[86–89] cyanopeptolins,[17] diazo-containing natural products,[90] amines,[91,92] carbonyls,[93] and azaphilic compounds.[94] Recent efforts have led to the development of reversible tagging techniques, such as a catch-enrich-and-release methodology, that enable recovery of the underivatized natural product at the end of the process. This approach was originally designed to target hydroxyl, carboxylic acid, and thiol functional groups[95–98] and was later extended to include natural products containing amine[99] and furan groups.[100]

4.1 *Rubriamides and Typhamides*

A workflow was created to identify new furan-containing natural products by integrating genomic and chemical probe methods.[100] The gene *rhzB* encodes a heme-dependent aromatic oxygenase that converts tyrosine (Tyr) to 3-furylalanine (Fua, Fig. 6),[101] serving as a specific sequence tag in genome-mining efforts. Fua synthases from different organisms were heterologously expressed, confirming Fua production in most cases. Five bacterial strains were chosen because they contain a BGC with a *rhzB* homolog and NRPS genes. A reversible derivatization method was developed to bind and release furan-containing natural products, involving a Diels-Alder (DA) reaction with the unsaturated heterocycle furyl, followed by a retro-DA (rDA) step to recover the natural products under mild thermal conditions. This method was applied to the five strains, yielding positive results in all. Bioactivity assays led to the selection of two strains, *Actinomadura rubrisoli* and *Streptomyces typhae*, for further study. The first strain was cultured under optimized conditions, and the main product was extracted and purified, resulting in the discovery and structure elucidation of rubriamide A (**9**, Fig. 6). Additional members of this family, rubriamides B-G, were identified through further extract analysis. Using a similar approach, typhamides A-G were identified from *Streptomyces typhae*. However, these were produced in small amounts, making the catch-and-release strategy crucial for purifying typhamide A (**10**). Certain members of the rubriamide and typhamide families exhibited cytotoxic effects, with rubriamide E being the most potent, showing IC_{50} values of 0.3 μM for HUVEC and 1.2 μM for K562 cancer cells, and 76 μM for *Caenorhabditis elegans*.

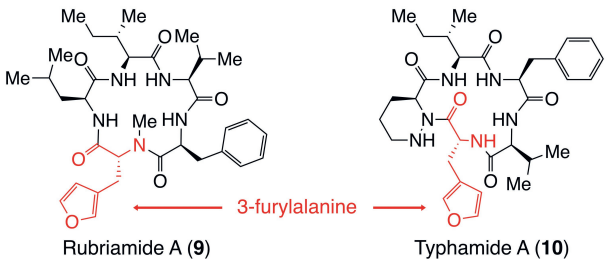

Fig. 6. Rubriamide A (**9**) and typhamide A (**10**) isolated from *Actinomadura rubrisoli* and *Streptomyces typhae*, respectively.[100]

4.2 *Chemical Targeting of Natural Products*

Natural products can also be targeted based on their structural features. Recent developments have demonstrated chemoselective strategies reacting with a functional group representative of a specific class of compounds. These strategies offer a complementary approach to genome mining and metabolomics.

5. Mass-spectrometry-based Metabolomics

In recent years, the discovery of natural products has benefited tremendously from advances in analytical instruments, bioinformatics software, and databases. This section will focus primarily on a selection of recent MS-based metabolomics strategies. Among the major developments in this area is the creation of a growing range of platforms and software for analyzing MS and MS/MS data, enabling the prioritization of novel natural products and reducing the re-isolation of known compounds by quickly identifying them (dereplication process).[102] In parallel, specialized MS methods have recently been developed for natural product discovery, such as the IDBac protocol, which is based on matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS analysis analysis of bacterial colonies,[103,104] and the mass defect filtering (MDF) workflows used to profile specific classes of natural products.[105] Additionally, advances in mass spectrometry technology now enable routine analysis of intact proteins and protein complexes, and native mass spectrometry has recently been used for the rapid screening of natural product ligands against protein targets, contributing to the field of native metabolomics.[106–108]

5.1 *Pteridines*

Native metabolomics is a powerful approach for identifying protein-binding natural products. This strategy was used to identify natural substrates that bind to an enigmatic protein named CutA, which was suspected to participate in bacterial copper tolerance.[107] The CutA protein was heterologously expressed and purified. Crude extracts were screened against CutA by post-column infusion of the protein in a buffer at a pH that mimics physiological conditions. This method resulted in the identification of the novel natural product 2'-deoxyxanthopterin B2 (**11**) from the *Synechococcus elongatus* extract as a CutA ligand based on HRMS analysis of the protein-ligand complex and subsequent dereplication of the extract. The structure of 2'-deoxyxanthopterin B2 (**11**) was elucidated, and three related derivatives (isosepiapterin (**12**), 6-propionyllumazine (**13**), and 6-propionylpterin (**14**)) were also identified by molecular networking analysis. Further native MS and nano differential scanning fluorimetry (NanoDSF) experiments suggested that **11**-**14** bind to CutA. Additionally, the results suggest that copper also acts as a ligand for CutA and that these compounds might function as cofactors (Fig. 7).

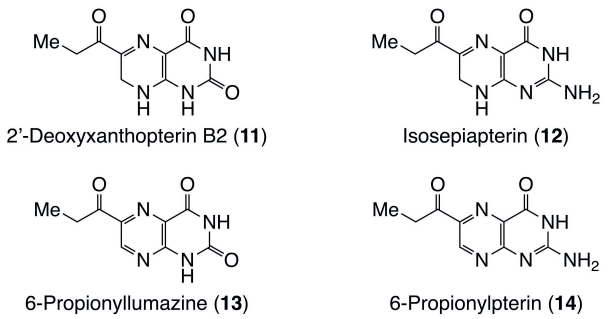

Fig. 7. Structures of pteridines (**11**-**14**) produced by *Synechococcus elongatus*.[107]

5.2 *Mass Spectrometry Advances for Natural Products Discovery*

MS-based metabolomics has benefited from tremendous progress in databases and search tools, combined with advances in

instrument sensitivity. Routine analysis enabled rapid identification of known natural products and structure prediction of analogs of known compounds. Furthermore, native metabolomics enabled direct identification of the target ligand.

6. Conclusions

Natural product discovery has progressed rapidly in recent years. These advances may be explained by major developments in sequencing, genomic analysis, and MS-based metabolomics. Furthermore, an exciting range of software and online resources has boosted the field by making information accessible and searchable. Together, these approaches offer powerful tools for discovering and characterizing novel natural products. Furthermore, publicly available databases are constantly increasing in size, and software is increasing in analytical capacity, and both will certainly be major drivers of future discovery.

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