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Review

Heterologous expression facilitates the discovery and characterization of marine microbial natural products

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ABSTRACT

Microbial natural products and their derivatives have been developed as a considerable part of clinical drugs and agricultural chemicals. Marine microbial natural products exhibit diverse chemical structures and bioactivities with substantial potential for the development of novel pharmaceuticals. However, discovering compounds with new skeletons from marine microbes remains challenging. In recent decades, multiple approaches have been developed to discover novel marine microbial natural products, among which heterologous expression has proven to be an effective method. Facilitated by large DNA cloning and comparative metabolomic technologies, a few novel bioactive natural products from marine microorganisms have been identified by the expression of their biosynthetic gene clusters (BGCs) in heterologous hosts. Heterologous expression is advantageous for characterizing gene functions and elucidating the biosynthetic mechanisms of natural products. This review provides an overview of recent progress in heterologous expression-guided discovery, biosynthetic mechanism elucidation, and yield optimization of natural products from marine microorganisms and discusses the future directions of the heterologous expression strategy in facilitating novel natural product exploitation.

1. Introduction

Natural products are small organic compounds originating from animals, plants, and microorganisms. They often possess unique chemical structures and exhibit specific biological activities. Natural products are important sources of novel drugs and pesticides [1]. Natural products from microorganisms have made their most significant contribution to modern medicine in antibiotics, which have saved billions of lives in the clinical setting [2]. Since the discovery of penicillin in 1928, the seeking of bioactive microbial natural products, especially antibiotics, has attracted substantial attention and entered a short golden age [3]. However, the discovery of novel chemical skeletons has become difficult with the continuous bioactivity-guided screening of compounds. Moreover, the emergence and prevalence of multidrug-resistant pathogens have become prominent, conferring significant threats to human health. Therefore, the search for bioactive molecules and development of novel antibiotics are urgently necessary [4].

Oceans harbor the most abundant biological resources and possess great diversity of natural products. More than 40,000 compounds have been deposited in the marine natural product database (https://marinlit.rsc.org/, 2023), and 14 marine natural products and their derivatives have been marketed, including cytarabine, vidarabine, fludarabine, nelarabine, histochrome, eribulin mesylate, trabectedin, lurbinectedin, plitidepsin, ziconotide, Omega-3-acid ethyl esters, Omega-3-carboxylic acids, icosapent ethyl, and fish oil triglycerides [5]. In order to adapt to the special environment of high pressure, high salinity, low temperature, and insufficient light in the ecological niches in the ocean, marine microorganisms have evolved unique metabolic and biosynthetic pathways, enabling the synthesis of structurally novel and functionally distinctive compounds that cannot be produced by terrestrial microorganisms [6]. Since the beginning of the 21st century, the number of novel natural products discovered from marine microorganisms has increased rapidly. Compounds isolated from marine microorganisms include terpenoids, alkaloids, steroids, polyketones, peptides, glycosides, and halogenated compounds. Many of these compounds exhibit distinct bioactivities. Their antibacterial, antiviral, anticancer, anticardiovascular, antioxidant, anti-inflammatory, and other activities have substantial potential for drug discovery [7–9].

Genes involved in the synthesis of natural products are typically clustered in the genomes of microorganisms and are collectively referred to as biosynthetic gene clusters (BGCs). Secondary metabolite production involves multiple stages, including gene transcription, translation,

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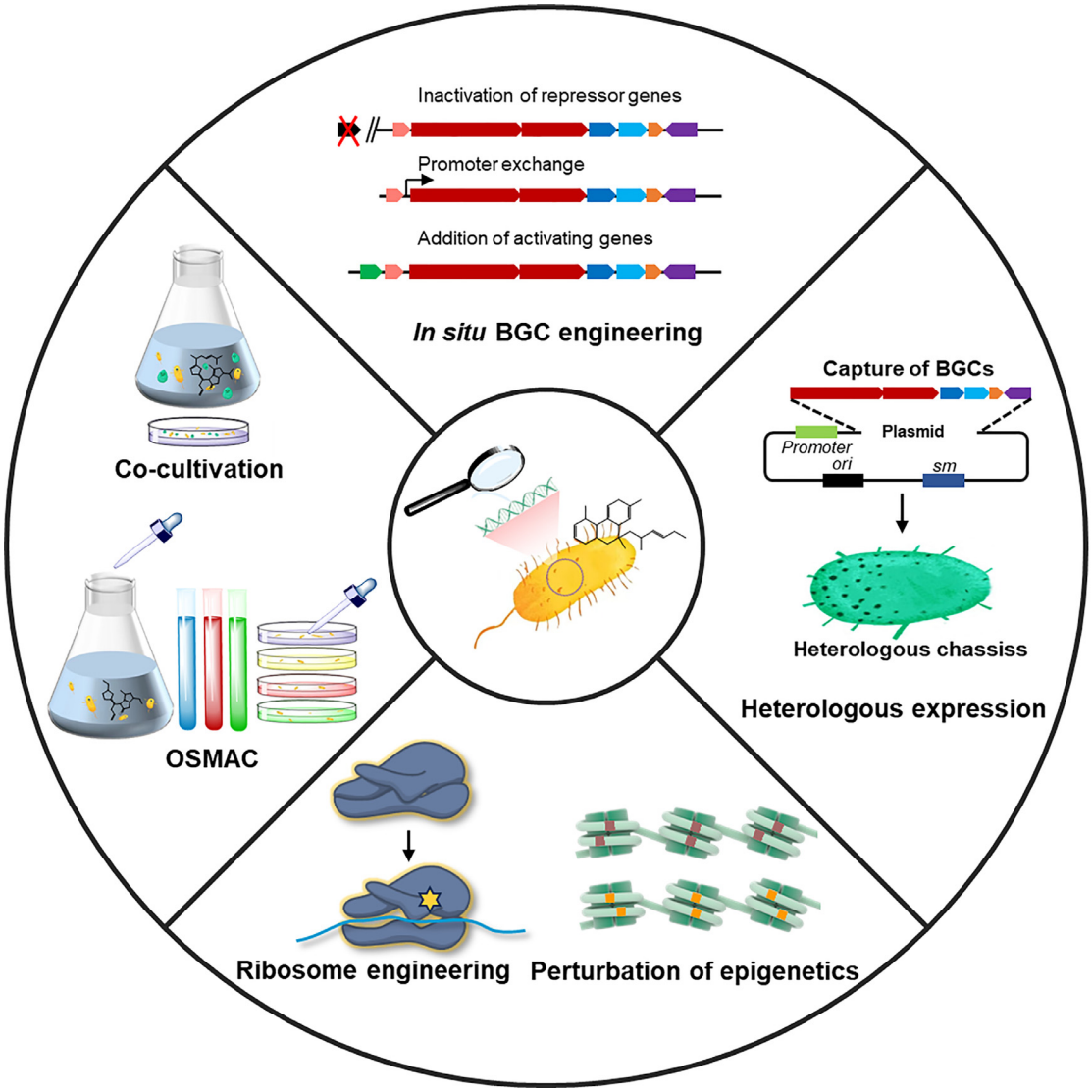

Fig. 1. Strategies for the discovery of new natural products from marine microorganisms.

and enzyme-catalyzed biosynthesis. This process is tightly controlled by various regulatory systems, and the BGCs are usually expressed under specific environmental conditions. The product yield is influenced by factors such as metabolic flux, codon preferences, and product stability. Therefore, most BGCs remain "silent" under laboratory conditions, restricting the identification of the corresponding products. Genome sequencing has uncovered many BGCs in the genomes of microorganisms; however, the products of most BGCs are unknown. Transforming unknown BGCs into natural product entities would contribute to the discovery of new chemicals and the development of novel drugs.

2. Strategies for the discovery of new natural products from marine microorganisms

In recent decades, multiple strategies have been developed to exploit hidden compounds from microorganisms. In this review, we provide an overview of the strategies for the discovery of natural products from marine microorganisms (Fig. 1). Specifically, the application of heterologous expression strategies in the research on natural products from marine bacteria and fungi is highlighted.

The combination of strain fermentation, bioactivity screening, and metabolomic analysis is a traditional route to identify natural products from marine microorganisms. This approach has led to the discovery of a variety of natural products, some of which have been applied in disease treatment. To elicit expression of biosynthetic pathways, 'one strain many compounds' strategy is developed by changing the composition of the media, aeration rate, cultivation conditions and supply of enzyme inhibitors [10]. Co-cultivation with other species is another route for maximizing chemical diversity [11,12]. Interspecies interactions between co-cultivated microorganisms may induce the expression of previously silent biosynthetic pathways.

DNA sequencing and bioinformatics analyses have uncovered a large number of BGCs in the genome of marine microbes. However, a large proportion of marine microorganisms are poorly cultivated or unculturable under laboratory conditions, and certain external or internal signals that elicit the expression of BGCs are unclear; thus, the discovery of marine natural products has been challenging. Therefore, although marine microorganisms possess unique metabolic and enzymatic mechanisms, most natural products are not produced or produced in trace amount under laboratory cultivation conditions, which are difficult to identify by bioactivity and metabolomic screening. Meanwhile, this approach has encountered problems in the rediscovery of known compounds [13,14].

BGCs can be activated by manipulating BGCs or regulatory networks *in situ* [15–17]. For example, Zhang *et al.* employed a successful CRISPR-Cas9 knock-in strategy to insert the *kasO**p promoter upstream of the first open reading frame in the native producer *Streptomyces roseosporus*, resulting in the successful production of photocyclized alteramide A and PTM (polycyclic tetramate macrolactam) [18]. Wang *et al.* intro-

duced a transcription factor decoy strategy to selectively activate large silent polyketide synthase (PKS) and non-ribosomal peptide synthetase (NRPS) genes, leading to the discovery of oxazolepoxidomycins, novel compounds belonging to the oxazole family [19]. In addition, epigenetic regulation and modification of DNA at the chromatin level has been observed to precisely control BGC expression by activating or blocking pathway-specific genes [20,21]. Ribosome engineering and the manipulation of protein-modifying genes can also assist in the production of natural products [22]. An example of the activation of silent biosynthetic pathways through ribosome engineering is the identification of the polyketide isoindolinomycin by screening rifampicin-resistant mutants [23]. Nevertheless, a premise for the aforementioned strategies is that the native host targeting the BGC can be genetically manipulated. Insufficient tools for the genetic manipulation of marine microbes restricts the exploitation of natural products in these routes.

In circumventing the challenges of operating native producers, an alternative approach is to transfer and express BGCs in genetically amenable heterologous hosts with clear metabolite backgrounds. Heterologous expression avoids the effects of the regulatory network and the requirement of signaling molecules for the transcriptional initiation of BGCs. In addition to facilitating the discovery of valuable new products, heterologous expression exhibits advantages in the characterization of biosynthetic mechanisms and generation of novel derivatives [24]. In a heterologous host, the genes of exogenous BGCs can be modified, and metabolome differences can be easily differentiated.

With the development of direct DNA cloning techniques, such as TAR [25], Red/ET recombineering [26,27], CAPTURE [28], and SIRA [29,30], natural product BGCs can be cloned from the genomes of marine microorganisms, and gene clusters from unculturable marine microorganisms or environmental samples can be obtained using *de novo* DNA synthesis and assembly. In order to choose an appropriate cloning method, the size of the BGC, G+C content, suitable enzyme cleavage sites, screening efficiency, and the host for DNA cloning should be considered [31]. After modification, for example, promoter engineering and supplementation of mobile elements, BGCs can be transferred into heterologous hosts, such as *S. coelicolor, Bacillus subtilis,* and *Escherichia coli*, through transformation or conjugative transfer. The gene cluster is then replicated in the host carried by a plasmid or integrated into the chromosome by integrase (*eg.* PhiC31 integrase), transposition, or homologous recombination, enabling the activation of BGCs and the production of compounds [32,33]. Several factors must be considered when selecting a suitable heterologous chassis. Generally, natural product-producing potential is an important factor to consider. Heterologous NRPS gene clusters can be easily expressed in heterologous hosts capable of producing multiple NRPS types [34]. Other factors include the type of BGC to be expressed, the existence of genes for precursor biosynthesis and post-assembly modifications, the genomic DNA G+C content of the heterologous host, and the phylogenetic relationship between the heterologous host and the native strain harboring the BGC. Furthermore, heterologous hosts can be optimized by deleting endogenous secondary metabolite BGCs, allowing more substrates and energy to participate in the synthesis of exogenous products [35]. The yield and diversity of products can be improved by introducing new metabolic pathways, adding synthetic precursors, or applying strong promoters to heterologous hosts. The heterologous hosts developed during the discovery and biosynthetic investigation of marine natural products are summarized in Table 1.

3. Discovery and characterization of marine natural products through heterologous expression

In recent decades, there has been substantial progress in the acquisition and characterization of natural products from marine microorganisms. In this section, we summarize natural products from marine bacteria (mainly Actinomyces and cyanobacteria) and fungi that investigated by using heterologous expression (Table 1).

3.1. Natural products from marine bacteria

3.1.1. Polyketides

3.1.1.1. Aromatic polyketides. Xu *et al.* isolated one new aromatic polyketide [36], prealnumycin B, and four known aromatic polyketides (K1115A, DHPA, phaeochromycin B, and (*R*)-7-acetyl-3,6-dihydroxy-8-propyl-3,4dihydronaphthalen-1(*2H*)-one) from the marine-derived *S. sundarbansensis* SCSIO NS01(Fig. 2). Genome analysis revealed a unique type II PKS gene cluster (*als*) in SCSIO NS01 associated with the biosynthesis of the isolated aromatic polyketides, which was confirmed by the expression of the *als* gene cluster in *S. coelicolor* M1152 and the production of the anticipated compounds. A novel aromatic polyketide, phaeochromycin L, and two known aromatic polyketides, phaeochromycins D and E, were produced.

3.1.1.2. Galbonolide. Galbonolide is a macrolactone with potent antifungal activity (Fig. 2). As an inositol phosphorylceramide (IPC) synthase inhibitor, it inhibits sphingolipid synthesis, exerting activity against pathogenic fungi [37,38]. Additionally, it effectively inhibits clinically important human pathogens, particularly the dangerous emerging pathogen *Candida auris* [39]. Liu *et al.* identified a putative BGC associated with galbonolide synthesis in the genome of a marine *Streptomyces* strain [40,41]. Heterologous expression of the *gbn* gene cluster in *S. coelicolor* ZM12 successfully generated galbonolide B [42].

3.1.1.3. Neoabyssomicin/abyssomicin. This family of antimicrobials is generally composed of C19 spirotetronates, which often containing a four- or five-membered ring system within their architecture. They typically exhibit promising antibacterial activity. For example, in 2014, abyssomicin C isolated from the marine actinomycete strain *Verrucosispora* sp. AB-18032, showed promising antibacterial activity against several Gram-positive bacteria, including MRSA [43] and *M. tuberculosis* [44]. In 2017, neoabyssomicins A-B were isolated from marine-derived *S. koyangensis* SCSIO 5802, along with abyssomicins 2 and 4 [45]. Neoabyssomicin A augmented HIV-1 replication in a human lymphocyte model (Fig. 2). In 2018, Tu *et al.* cloned the BGC (*abm*) of neoabyssomicins and abyssomicins from *S. koyangensis* SCSIO 5802 and expressed them in the heterologous host *S. coelicolor* M1152 [46].

3.1.1.4. Shuangdaolides. Shuangdaolides and dumulmycin are polycyclic macrolides biosynthesized by the *trans*-AT PKS gene cluster. Some of these compounds contain rare internal five-membered carbocyclic moieties. Dumulmycin was first identified in *Streptomyces* spp. DM28 was obtained from a river in Republic of Korea [47]. Shuangdaolide BGC (*sdl*) was discovered in marine *Streptomyces* sp. B59, which was transferred into the heterologous host *S. albus* J1074, resulting in the production of shuangdaolides A-D and dumulmycin (Fig. 2). The production of the compounds was improved by exchanging the promoter of the *sdl* gene cluster [48]. Subsequent gene inactivations led to the accumulation of two biosynthetic intermediates, shuangdaolides E and F [47,48].

3.1.1.5. Streptoseomycin. Streptoseomycin is a novel macrodilactone isolated from marine *S. seoulensis* A01 [49] (Fig. 2). It exhibits significant activity against microaerophilic bacteria such as *Helicobacter pylori*. To gain insights into the biosynthetic mechanism of this compound, a type I PKS gene cluster was identified and confirmed as the BGC of streptoseomycin by using the expression in the heterologous host *S. chartreusis* 1018 [50].

3.1.1.6. Violapyrones. Violapyrones are a group of α-pyrone compounds that exhibit antimicrobial and anticancer activities. They were initially isolated by Zhang *et al.* from *S. violascens* YIM 100525 [51]. In 2016, Huang *et al.* activated violapyrone BGC by deleting the whiB-like (*wbl*) regulatory gene in deep sea-derived *S. somaliensis* SCSIO ZH66.

Table 1
Heterologous hosts applied in discovery and characterization of marine natural products.

Compound	Original producer	Heterologous host	Application
Prealnumycins	*S. sundarbansensis* SCSIO NS01	*S. coelicolor* M1152	compound discovery [36]
Ashimides A and B	*Streptomyces* sp. NA03103	*S. lividans* SBT18	compound discovery [54]
Berninamycins	*Streptomyces* sp. SCSIO 11878	*S. lividans SBT18; S. coelicolor* M1154; *S. albus* J1074	compound discovery [59]
Bonsecamin	*S. albus* subsp. *chlorinus* NRRL B-24108	*S. albus* Del14	compound discovery [60,61]
Chrodrimanins I and J	*Penicillium funiculosum* GWT2-24	*Aspergillus nidulans* A1145	biosynthetic investigation [122]
Desotamides	*S. scopuliridis* SCSIO ZJ46	*S. lividans* TK64; *S. coelicolor* M1152	compound discovery [63]
Diazaquinomycins	*Streptomyces* sp. strain F001	*S. coelicolor* M1152	biosynthetic investigation [102]
Galbonolide B	*Streptomyces* sp. LZ35	*S. coelicolor* ZM12	biosynthetic investigation [40,41]
Lasso peptides (RES-701-3, RES-701-4, Aborycin)	*S. caniferus* CA-271066; *Streptomyces* sp. SCSIO ZS0098	*S. coelicolor* M1152 / M1154	compound discovery [94]; yield optimization [95]
Neoabyssomicins / abyssomicins	*S. koyangensis* SCSIO 5802	*S. coelicolor* M1152	biosynthetic investigation [46]
Polycyclic tetramate macrolactams	*S. pactum* SCSIO 02999	*S. lividans* TK64	compound discovery [110]
Salinamides	*Streptomyces* sp. CNB-091	*S. coelicolor* M1146	biosynthetic investigation [78]
Streptoseomycin	*S. seoulensis* A01	*S.chartreusis* 1018	biosynthetic investigation [50]
Totopotensamide A	*S. pactum* SCSIO 02999	*S. lividans* TK64	yield optimization [80]
Violapyrones	*S. violascens* YIM 100525	*S. youssoufiensis* OUC6819	compound discovery [53]
Columbamides	*Moorena bouillonii* PNG5-198	*Anabaena* (*Nostoc*) PCC 7120	compound discovery [82]
Cryptomaldamide	*Moorea producens* JHB	*Synechococcus elongatus* PCC 7942	yield optimization [84]
4-*O*-demethylbarbamide	*M. producens* 19L	*S. venezuelae* DHS 2001	compound discovery [86]
Lyngbyatoxins	*M. producens*	*E. coli* GB05-MtaA; *Anabaena* sp. PCC 7120	yield optimization [71]; biosynthetic investigation [72]
Microginins	*Microcystis aeruginosa* LEGE 91341	*E. coli* BAP1	biosynthetic gene cluster characterizition [88]
Patellamides	*Prochloron didemni*	*E. coli* BL21(DE3) pLys	biosynthetic investigation [98]
Sphaerocyclamide	*Sphaerospermopsis* sp. LEGE 00249	*E. coli* TOP10	biosynthetic gene cluster characterizition [99]
Bromo-alterochromides	*Pseudoalteromonas piscicida* JCM 20779	*E. coli* BL21 (DE3)	biosynthetic investigation [91]
3-formyl-L-tyrosine-L-threonine dipeptide; 3-formyl-L-tyrosine	*P. tunicata* D2	*E. coli* BL21 (DE3)	biosynthetic investigation [104]
Polybrominated diphenyl ethers; Polybrominated bipyrroles	*P. luteoviolacea* 2ta16	*E. coli* BL21 (DE3)	biosynthetic investigation [109]
Violacein	*Pseudoalteromonas* sp. 520P1; *P. luteoviolacea* 2ta16	*E. coli* BL21 (DE3); *Pseudomonas putida* KT2440; *Agrobacterium tumefaciens* LBA4404	biosynthetic gene cluster characterizition [116]; yield optimization [117]
Penifulvins	*Penicillium griseofulvum* NRRL 35584	*Aspergillus nidulans* A1145	biosynthetic investigation [126]
Talaromyolides	*Talaromyces purpureogenus* CX11	*A. oryzae* NSAR1	biosynthetic investigation [132]
Phomoxanthones	*Diaporthe* sp. SYSU-MS4722	*A. oryzae* NSAR1	yield optimization; biosynthetic investigation [136,137]
Shimalactone A and B	*Emericella variecolor* GF10	*A. oryzae* M-2-3; *A. oryzae* NSAR1; *Saccharomyces cerevisiae* BJ5464	biosynthetic investigation [139]
Spiromaterpenes	*Spiromastix* sp. MCCC 3A00308	*S. cerevisiae; A. nidulans* LO8030	biosynthetic investigation [143]

The *wbl* plays a crucial role in morphological differentiation and secondary metabolism. The violapyrone BGC comprises the type III PKS gene *vioA* and the regulatory gene *vioB*, which are responsible for the synthesis of violapyrone B (VLP B). Inactivation *vioB* results in the production of violapyrones A, J, C, H [52]. Expressing *vioA* under the control of the constitutive promoter P_{gapDH} in marine-derived *S. youssoufiensis* OUC6819 led to the production of violapyrones B and I and the four novel compounds violapyrones Q–T (Fig. 2). These violapyrones were found to exhibit anti-influenza A [H1N1 (A/Virginia/ATCC1/2009) and H3N2 (A/Aichi/2/1968)] activities with IC_{50} values ranging from 30.6 to 132.4 μM and 45.3 to 150.0 μM, respectively. Also discovered was that the methylation at the 4-OH position of violapyrone enhanced antivirus activity but reduced anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activity [53].

3.1.2. Nonribosomal peptides

3.1.2.1. Ashimides. Using genome mining, Shi *et al.* discovered an NRPS-like BGC (*asm*) with a size of 32 kb in the marine *Streptomyces* strain NA03103, which was composed of single NRPS modules and with an absence of homologous counterparts in publicly available databases. Cloning of the complete *asm* gene cluster and its expression in the engineered host *Streptomyces* sp. SBT18 produced two novel cyclic peptide compounds, ashimides A and B (Fig. 3), with ashimide B exhibiting moderate cytotoxicity [54].

3.1.2.2. Berninamycin. Berninamycin are thiopeptides compounds [55–58]. In 2021, De *et al.* isolated berninamycins A and B from marine-derived *Streptomyces* spp. SCSIO 11878 and identified the 12.8 kb BGC of berninamycins from the genome [59]. This gene cluster contains 11 genes (*berA-J*). After transferring the gene cluster to *S. lividans* SBT18, *S. coelicolor* M1154, and *S. albus* J1074, berninamycins A and B were successfully detected in *S. lividans* SBT18 and *S. coelicolor* M1154, and two new thiopeptide antibiotics, berninamycin J and K, were produced in *S. albus* J1074, indicating the potential involvement of an unknown enzymatic function in *S. albus* J1074. Antimicrobial activity test showed potent inhibitory activity of berninamycins A, B, and K against Gram-positive bacteria (Fig. 3). No antibacterial activity was observed for berninamycin J, indicating that the hydroxyl group on the valine residue and the cyclized form of the thiopeptide are crucial for its antibacterial activity.

3.1.2.3. Bonsecamin. Lasch *et al.* discovered an uncharacterized NRPS gene cluster in *S. albus* subsp. *chlorinus* NRRL B-24108 [60,61]. The gene cluster is 35 kb in size and consists of 28 genes. After cloning the gene cluster into a BAC vector and introducing it into the heterologous host *S. albus* Del14, a novel cyclic pentapeptide, bonsecamin, was produced (Fig. 3).

3.1.2.4. Desotamides. Desotamides (DSAs) are a class of naturally occurring cyclic hexapeptides that exhibit strong inhibitory activity against *S. aureus, S. pneumoniae*, and methicillin-resistant *S. epidermidis*. Desotamides A-D were isolated from the deep-sea actinomycete *S. scopuliridis* SCSIO ZJ46 [62]. Li *et al.* identified a 39-kb NRPS gene cluster (*das*) from the genome of *S. scopuliridis* SCSIO ZJ46, which is putatively

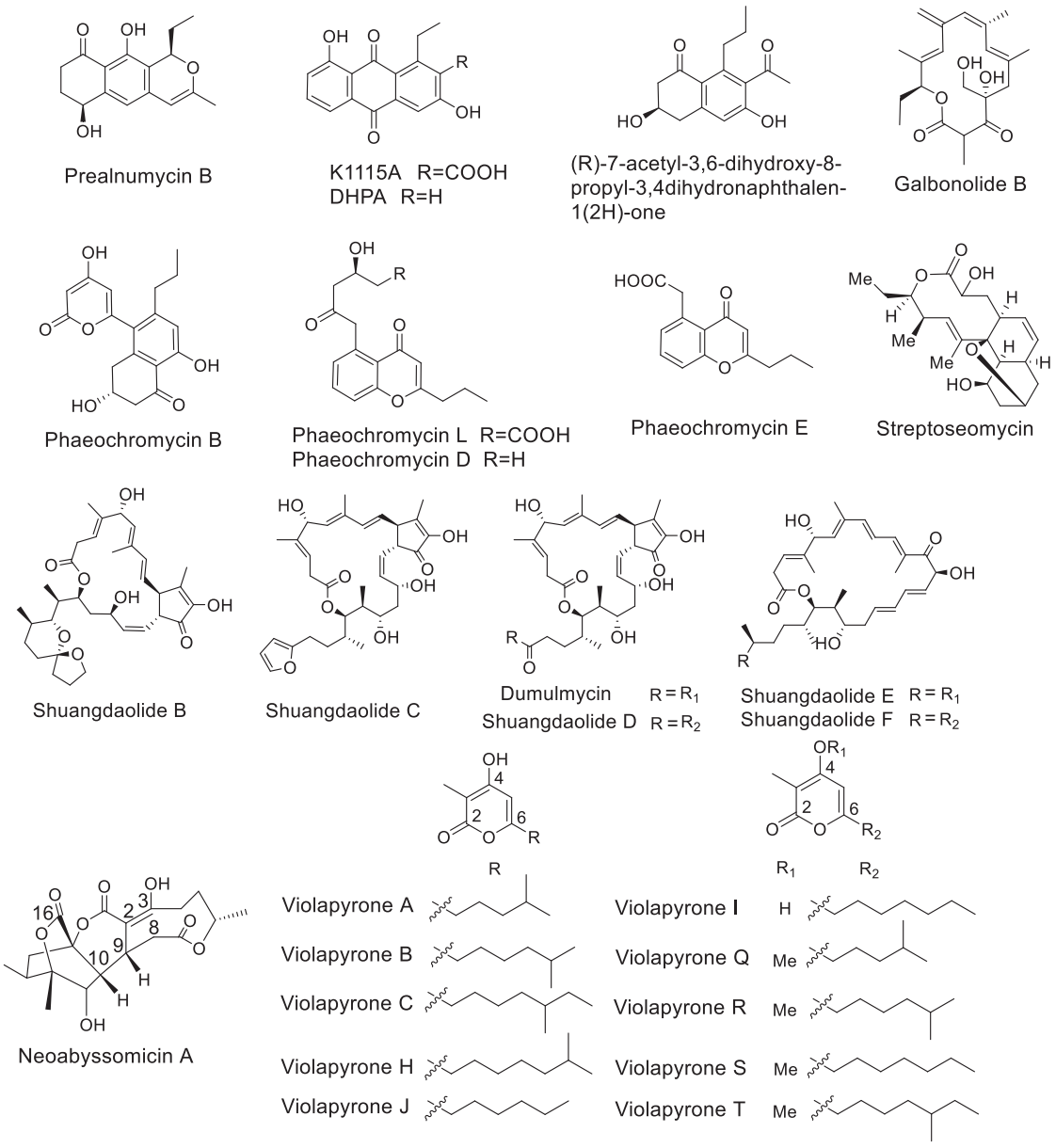

Fig. 2. Chemical structures of marine bacteria-derived polyketides investigated using heterologous expression.

responsible for desotamide biosynthesis [63]. For the validation of The desotamide biosynthetic pathway, the *das* gene cluster was cloned and integrated into the genomes of the heterologous hosts *S. lividans* TK64 and *S. coelicolor* strain M1152. A new compound, desotamide G (Fig. 3), was successfully produced in *S. coelicolor* M1152. Desotamide G is differentiated from desotamide A by an aspartic acid residue in its structure but exhibits lower antibacterial activity than that of desotamide A.

3.1.2.5. Lyngbyatoxin. Lyngbyatoxin is a compound with the ability to activate protein kinase C and exhibit strong tumor-promoting activity [64,65]. Lyngbyatoxin A was initially isolated from the marine cyanobacterium *M. producens* (formerly *Lyngbya majuscula*) by Cardellina *et al.* in 1979 [66]. Subsequently, Aimi *et al.* isolated lyngbyatoxins B and C from *M. producens* in 1990 [67] (Fig. 3). Jiang *et al.* discovered several derivatives of lyngbyatoxin in *M. producens* collected from Hawaii [68,69]. The BGC of lyngbyatoxin consists of four genes: *ltxA-D* [70]. Because of the slow growth of marine cyanobacteria and low compound yields, obtaining sufficient compounds for further development is challenging. In 2013, Ongley *et al.* transferred the *ltx* gene cluster controlled by the *tetO* tetracycline-inducible promoter (P_{tetO}) into *E. coli* GB05-MtaA and achieved the high-level expression of lyngbyatoxin (25.6 mg L^{-1}) and the intermediate compounds NMVT and ILV [71]. In addition, Videau *et al.* introduced *ltxA-C* and *ltxA-D* into *Anabaena* PCC 7120 and successfully obtained lyngbyatoxin A [72].

3.1.3. Polyketide-nonribosomal peptide hybrids

3.1.3.1. Salinamide. Salinamides are a rare group of bicyclic depsipeptide antibiotics (Fig. 4). This group is characterized by the inclusion of a (4-methylhexa-2,4-dienoyl) glycine unit. Salinamides A and B have been isolated from the marine actinomycete *Streptomyces* sp. CNB-091 [73–75]. Subsequently, the series of salinamides has been expanded by the identification of various derivatives, including salinamides C, D, E, and F [76,77]. Ray *et al.* identified the BGC (*sln*) of salinamides from *Streptomyces* sp. CNB-091. Moreover, expression of the *sln* gene cluster in *S. coelicolor* M1146 led to the production of salinamides A-F [78].

3.1.3.2. Totopotensamide. Totopotensamide (TPM) is a polyketide peptide glycoside discovered by *in situ* activation of a cryptic gene cluster

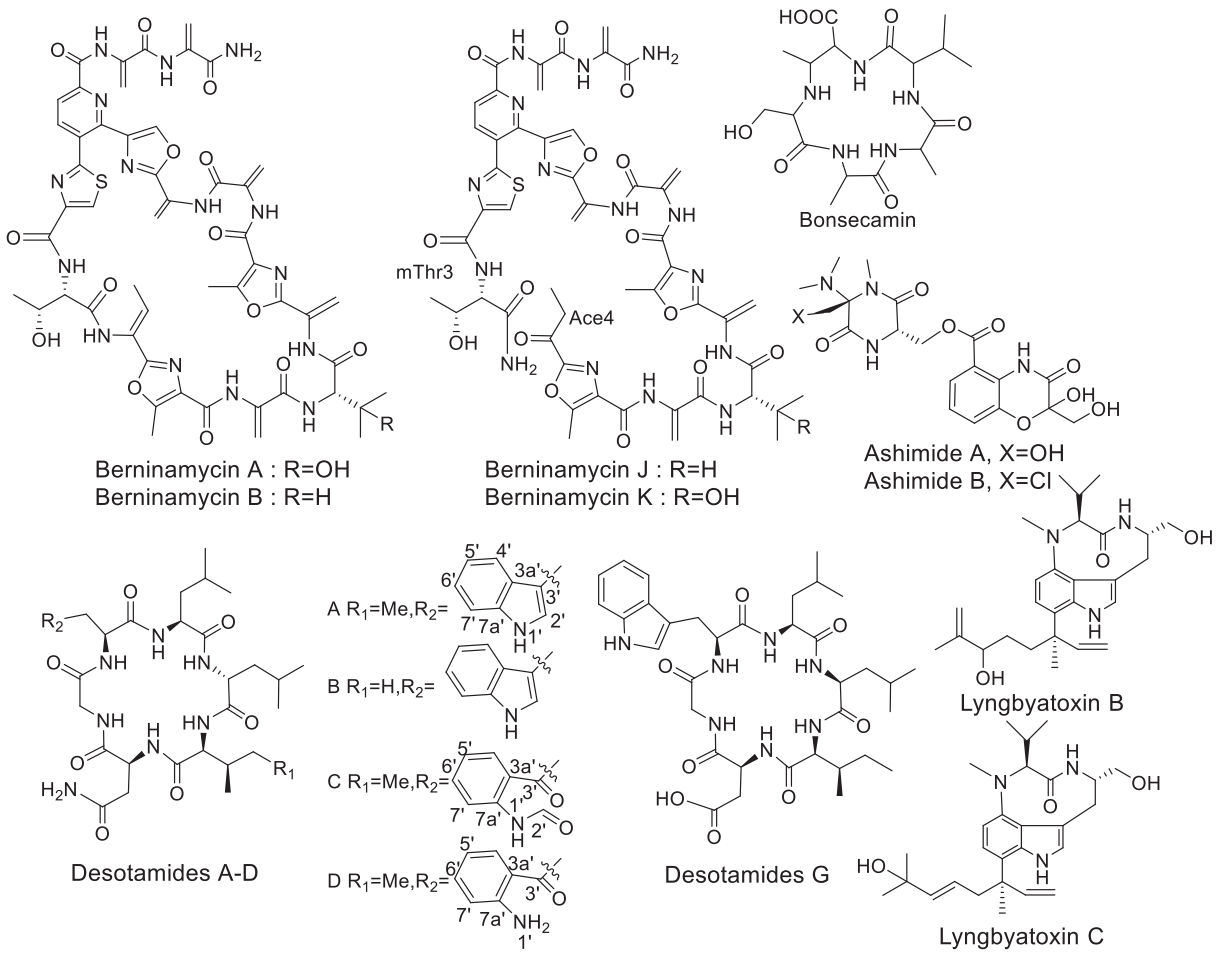

Fig. 3. Chemical structures of marine bacteria-derived nonribosomal peptides investigated by heterologous expression.

in marine-derived *S. pactum* SCSIO 02999 [79] (Fig. 4). However, the production of TPMs appeared unstable. Tan *et al.* cloned the *tot* gene cluster from *S. pactum* SCSIO 02999 and transferred it into *S. lividans* TK64, leading to the production of totopotensamide A. By knocking out two negative regulatory genes, *totR5* and *totR3*, totopotensamide A production increased six-fold [80].

3.1.3.3. Columbamide. Columbamides are chlorinated acyl amides initially isolated and identified from the filamentous marine cyanobacterium *Moorena bouillonii* PNG5-198 (Fig. 4) [81]; among them, columbamides A and B have been reported to be potent binders to the cannabinoid receptors CB1 and CB2. The biosynthetic pathway of columbamide was determined using a combination of mass spectrometry-based metabolomic and genomic analyses [82]. Expression of the 28.5 kb columbamide BGC in the heterologous host *Anabaena* (*Nostoc*) PCC 7120 led to the production of the previously characterized columbamides A-C and several new analogs, I-M [82]. A significant correlation was observed between columbamide production and NaCl concentration in the culture medium of *Anabaena*.

3.1.3.4. Cryptomaldamide. Cryptomaldamide was first isolated from the marine cyanobacterium *Moorea producens* (Fig. 4). This compound has a high nitrogen content and exhibits weak activity against H-460 human lung cancer cells [83]. Taton *et al.* cloned the 28.7 kb cryptomaldamide BGC from *Moorea producens* JHB and expressed it in the heterologous cyanobacterial strains *Synechococcus elongatus* PCC 7942 and *Anabaena (Nostoc)* PCC 7120, resulting in a high-titer production of cryptomaldamide in *Anabaena (Nostoc)* PCC 7120 [84].

3.1.3.5. 4-O-demethylbarbamide. Barbamide is a molluscicidal compound isolated from *Moorea producens*. A hybrid PKS/NRPS gene cluster was found to be responsible for the synthesis of barbamide [85]. Kim *et al.* cloned the barbamide BGC and expressed it in the engineered strain *S. venezuelae* DHS 2001, resulting in the production of 4-*O*-demethylbarbamide (Fig. 4), a new derivative of barbamide lacking an *O*-methyl group. Interestingly, this derivative exhibited significantly increased molluscicidal activity compared with barbamide, making it valuable for the development of insecticides [86].

3.1.3.6. Microginins. Microginins are lipopeptide protease inhibitors isolated from cyanobacteria. Their main characteristic is the presence of a 3-amino fatty acyl residue connected to the peptide (typically consisting of three or four amino acid residues). In 2009, Rounge *et al.* proposed that the NRPS/PKS hybrid gene cluster (*mic*) is responsible for the synthesis of microginin oscillaginins A and B in *Planktothrix prolifica* NIVA-CYA 98 but did not validate this hypothesis [87].

In 2022, Eusébio *et al.* isolated 12 new microginins and identified a *mic* gene cluster encoding a dimetallic carboxylate halogenase homolog in *M. aeruginosa* (LEGE 91341). The *mic* gene cluster was cloned from *M. aeruginosa* LEGE 91341 and expressed in *E. coli* BAP1, leading to the production of several known microginins and new variants (Fig. 4), confirming the involvement of the *mic* gene cluster in microginin synthesis [88].

3.1.3.7. Bromo-alterochromides. Alterochromides and their brominated derivatives, bromo-alterochromides, are lipopeptides produced by the marine bacteria *Pseudoalteromonas* species. Bromo-alterochromides isolated from *P. maricaloris* KMM 636T in 2005 possess potent antimicro-

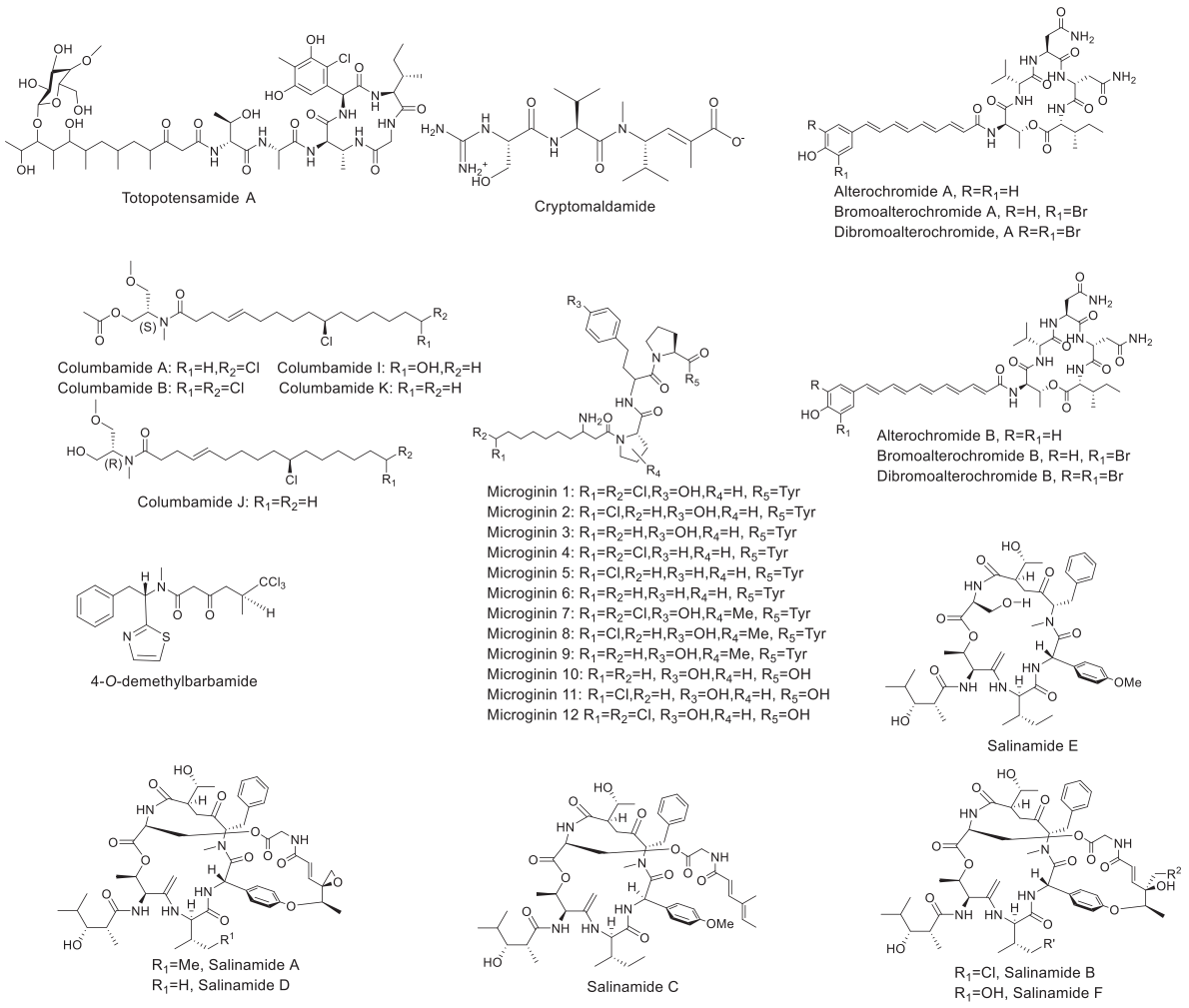

Fig. 4. Chemical structures of marine microbe-derived polyketide-nonribosomal peptide hybrids investigated by heterologous expression.

bial and cytotoxic activities [89]. In 2013, Nguyen *et al.* identified the BGC of bromo-alterochromides by using MS/MS networking and gene cluster analyses [90]. Ross *et al.* cloned the alterochromide BGC (*alt*) from the genome *P. piscicida* JCM 20779 and expressed it in the heterologous host *E. coli* BL21 (DE3) to decipher the biosynthetic pathway of (bromo-) alterochromides (Fig. 4) [91].

3.1.4. Ribosomally synthesized and post-translationally modified peptides (RiPPs)

3.1.4.1. Lasso peptides. Lasso peptides are a class of RiPPs produced by bacteria. Lasso peptides possess a wide range of biological activities, including antibacterial, enzyme-inhibitory, and receptor-antagonistic activities. Because of their unusual topological structure and significant biological activity, lasso peptides have garnered increasing interest [92,93].

Oves-Costales *et al.* identified a 7.7 kb gene cluster consisting of seven genes in *S. caniferus* CA-271066. The cloning and expression of this gene cluster in *S. coelicolor* M1152 and M1154 generated two type II lasso peptides, RES-701-3 and RES-701-4 [94] (Fig. 5). Both lasso peptides exhibited activity against endothelin 1 with IC_{50} values of 5-10 mM, indicating their potential for the treatment of systemic hypertension, myocardial infarction, cardiac ischemia, diabetes, and other diseases.

Aborycin is a type I lasso peptide with strong antibacterial activity against *S. aureus* (Fig. 5), *Enterococcus faecalis* ATCC 29212, *B. subtilis*, and the poultry pathogen *Clostridium perfringens* 5F52C. It was isolated by Shao *et al.* from the deep-sea *Streptomyces* sp. SCSIO ZS 0098. The aborycin BGC (*abo*) was identified and expressed in *S. coelicolor* M1152, producing aborycin at a higher yield than in the original strain [95].

3.1.4.2. Patellamides. Patellamides are cyclic peptides that exhibit cytotoxicity against L1210 murine leukemia cells and the human ALL cell line CEM (Fig. 5). They were initially isolated from the patella of the didemnid ascidian *Lissoclinum patella* [96]. Further analysis revealed that patellamides were synthesized by the symbiotic cyanobacterium *Prochloron* [97]. However, the availability of these compounds is limited because of the difficulty in culturing *Prochloron*. Schmidt *et al.* identified the BGC of patellamides in *Prochloron* and validated it by successful expression in *E. coli* BL21(DE3) pLys [98].

3.1.4.3. Sphaerocyclamide. Sphaerocyclamide belongs to the cyanobactin family and has been isolated from *Sphaerospermopsis* spp. LEGE 00249 (Fig. 5). The bioactivity tests revealed a weak inhibitory effect on the growth of *Halomonas aquamarina*. A gene cluster encoding 10 proteins, including several proteases homologous to those involved in the synthesis of other cyanobactins, was identified and speculated to be involved in sphaerocyclamide biosynthesis. This speculation was confirmed by the heterologous expression of the gene cluster in *E. coli* TOP10 and the successful production of sphaerocyclamide [99].

3.1.5. Others

3.1.5.1. Diazaquinomycins. Diazaquinomycins are a class of neutral quinoid antibiotics that exhibit activity against drug-resistant *Mycobacterium tuberculosis* and other Gram-positive bacteria [100,101] (Fig. 5).

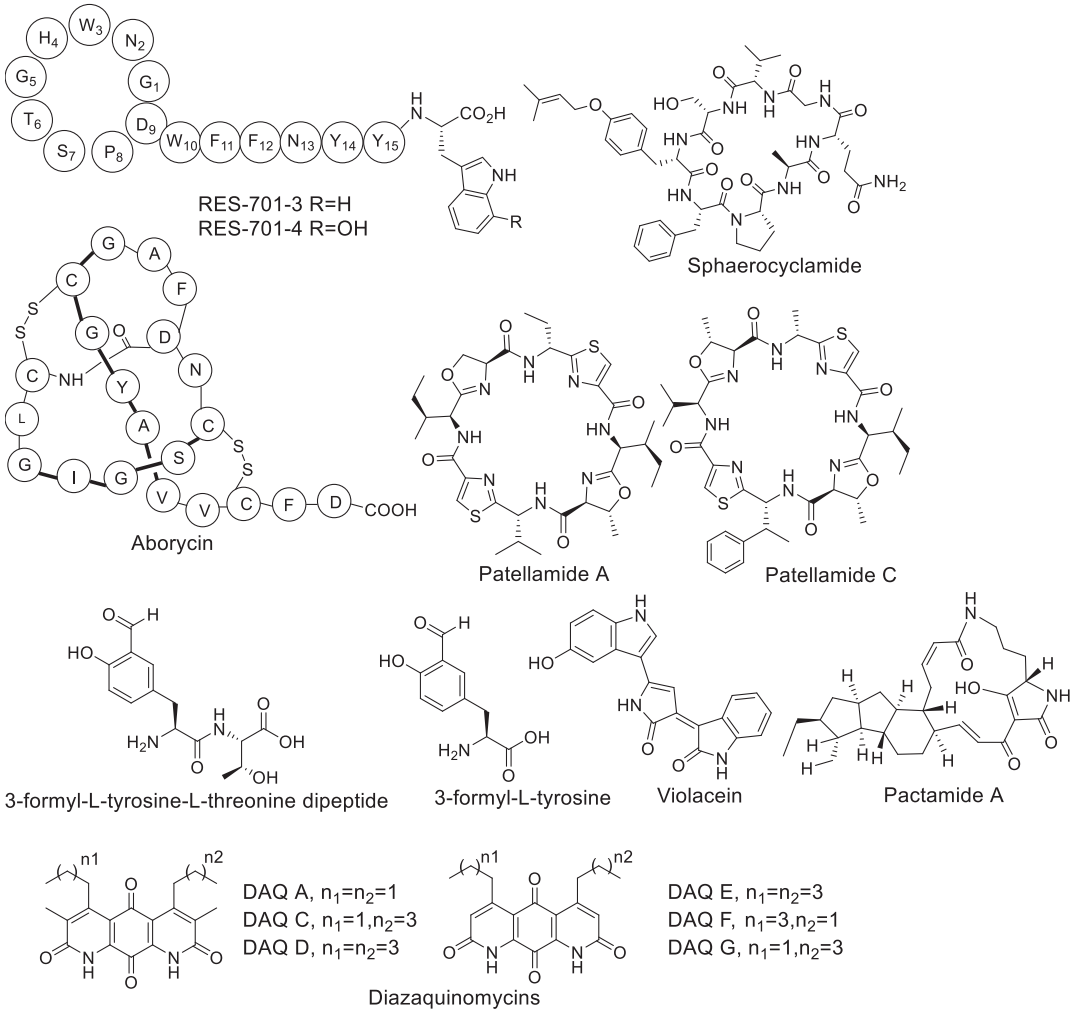

Fig. 5. Chemical structures of marine microbe-derived RiPPs and other types of compounds investigated by heterologous expression.

Further development of these compounds is restricted by their poor water solubility. Braesel *et al.* identified the *daq* gene cluster from the genome of the marine bacterium *Streptomyces* sp. F001, and the freshwater bacterium *Micromonospora* sp. B006. The *daq* gene cluster was 23.5 kb and comprised of 21 genes (*daqA-U*). The expression of the *daq* gene cluster in *S. coelicolor* M1152 led to the successful production of diazaquinomycins [102].

3.1.5.2. 3-formyl-L-tyrosine-L-threonine dipeptide and 3-formyl-L-tyrosine. Genome mining and the identification of natural products typically rely on the identification of BGCs or functional biosynthetic modules. However, studies have shown that other enzymes, such as ATP-grasp ligases, are important in natural product biosynthesis [103]. By identifying ATP-grasp enzymes, Blasiak *et al.* cloned a gene cluster (*fty*) from the marine gamma-proteobacterium *Pseudoalteromonas tunicate* D2 and expressed it in *E. coli*, which resulted in the production of 3-formyl-L-tyrosine-L-threonine dipeptide and 3-formyl-L-tyrosine (Fig. 5) [104].

3.1.5.3. PBDEs and polybrominated bipyrroles. Polybrominated diphenyl ethers (PBDEs) and polybrominated bipyrroles are a group of compounds with distinct halogenation properties that often provide protection against predators, parasites, and pathogens in symbiotic hosts of marine microorganisms. For example, tetrabromopyrrole can be used as an inducer of coral larval settlement and metamorphosis, and other types of polybromopyrroles were shown to inhibit Gram-positive bacteria. [105,106].

PBDEs have received substantial attention because of their persistence in the environment and potential toxicity to humans [107,108]. In 2014, Agarwal *et al.* identified a gene cluster (*bmp*) responsible for the biosynthesis of PBDEs and polybrominated bipyrroles in the strain *P. luteoviolacea* 2ta16 (Fig. 6). The *bmp1-8* is expressed in *E. coli*, leading to the production of PBDEs and polybrominated bipyrroles [109].

3.1.5.4. Polycyclic tetramate macrolactams. Polycyclic tetramate macrolactam (PTMs) compounds exhibit a broad spectrum of biological activities, including antifungal, antibacterial, antiprotozoal, antiulcer, antiviral, and cytotoxic activities. PTM BGCs are widely present in microbial genomes, but most are silent. Subhasish *et al.* performed a genomic analysis of the deep-sea bacterium *S. pactum* SCSIO 02999 and predicted a PTM synthesis-related gene cluster (*ptm*). Subsequent promoter exchange and heterologous expression of the *ptm* cluster in *Streptomyces. lividans* TK64 successfully generated five new PTMs. The newly generated compounds, pactamides A-E (Fig. 5), exhibited potent cytotoxicity against SF-268, MCF-7, NCI-H460, and Hep-G2 cell lines; among them, pactamide A demonstrated the highest cytotoxicity with IC_{50} values of 0.24-0.51 μM [110].

3.1.5.5. Violacein. Violacein is a purple pigment produced by a few Gram-negative bacteria (Fig. 5). It possesses various physiological activities such as antiprotozoal, antibacterial, antiviral, antimalarial, antifungal, and anticancer properties; thus, it of substantial interest in pharmacology [111]. Extensive studies have been performed on its biosyn-

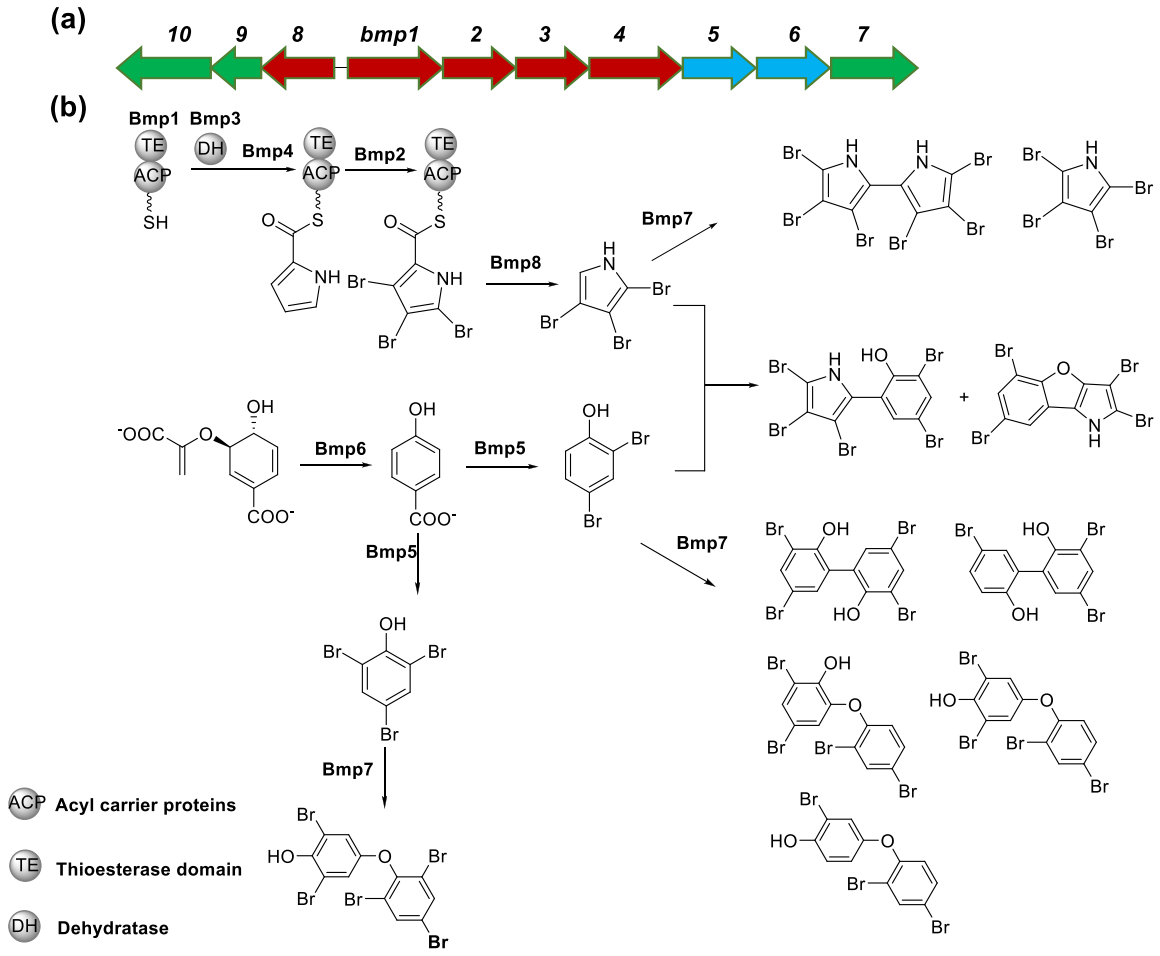

Fig. 6. Biosynthetic gene cluster (a) and assembly pathway of PBDEs and polybrominated bipyrroles (b). Bmp2, flavin-dependent halogenase; Bmp4, proline adenyltransferase; Bmp5, flavin-dependent oxygenase; Bmp6, chorismate lyase; Bmp7, cytochrome P450; Bmp8, carboxymuconolactone decarboxylase; Bmp9, ferredoxin; Bmp10, ferredoxin reductase.

thetic pathways and quorum-sensing mechanisms [112–115]. Zhang *et al.* cloned the 7.4 kb *vio* gene cluster from *Pseudoalteromonas* sp. 520P1 and achieved expression in *E. coli* after promoter engineering [116]. In addition, Zhang *et al.* cloned an *vio* gene cluster from *P. luteoviolacea* 2ta16 and successfully produced violacein in *Pseudomonas putida* KT2440 and *Agrobacterium tumefaciens* LBA4404 in high yields [117].

3.2. Natural products from marine fungi

3.2.1. Chrodrimanin-type meroterpenoids

Meroterpenoids derived from fungi have complex and diverse structures, and their skeletons are generally constructed by attaching terpenes to nonterpene parts, such as polyketides, nonribosomal peptides, and shikimates, by prenyltransferases (PTases) [118]. These compounds show a high practical value for clinical use, such as the first-line immunosuppressive drug mycophenolic acid [119] and the anti-angiogenic agent fumagillin [120]. Zhou *et al.* isolated seven meroterpenoids from the Antarctic moss-derived fungus *Penicillium funiculosum* GWT2-24, including the previously reported chrodrimannins A and B [121] and two structurally unique chrodrimannins I and J (Fig. 7). The specificities of chrodrimannins I and J are related to the cyclohexanone combination of a benzocyclohexanone moiety and a terpene moiety. Subsequently, heterologous production of chrodrimanins I and J was successfully achieved in *Aspergillus nidulans* A1145 by expressing the *cdn* and the *PKS47* gene clusters of GWT2-24, which may produce the precursor benzo-cyclohexanone [122].

3.2.2. Dioxafenestrane sesquiterpenes

Sesquiterpenes penifulvins A-E from the terrestrial fungus *Penicillium griseofulvum* and asperaculin A from the marine fungus *Aspergillus aculeatus* CRI323-04, both of which contain a unique [5.5.5.6] dioxafenestrane ring, are rare dioxafenestrane sesquiterpenes (Fig. 7); the former presented a specific killing activity against the crop pest *Spodoptera frugiperda* and has the potential for the development of innovative pesticide [123–125]. Zeng *et al.* elucidated the biosynthetic pathway of penifulvins and achieved their reconstitution in *A. nidulans* [126]. Subsequently, the same group identified an asperaculin BGC in the genome of *A. aculeatus*. Heterologous expression of biosynthetic genes in *A. nidulans* revealed that the penifulvin and asperaculin biosynthetic pathways share a similar mechanism for the generation of intermediate precursors but present significant differences in late-stage modifications [127].

3.2.3. Talaromyolides

Meroterpenoids are widely distributed in marine bacteria, fungi, and higher plants [128]. BGCs typically contain polyketide synthase genes, isoprene transferase genes, flavin monooxygenase genes, and terpene cyclase genes [129]. In 2019, Cao *et al.* isolated meroterpenoids talaromyolides A–D and talaromytin from the marine fungi *Talaromyces* sp. CX 11 [130]; subsequently, talaromyolides E–K were identified in the marine endophytic fungus *T. purpureogeneus*. Talaromyolides D and K showed good activity against pseudorabies virus [131]. Subsequently, Bai *et al.* identified the BGC of talaromylides (*tlx*) in *T. purpureogenus* based on a sequence alignment (Fig. 8) [121]. The talaromylide product was iden-

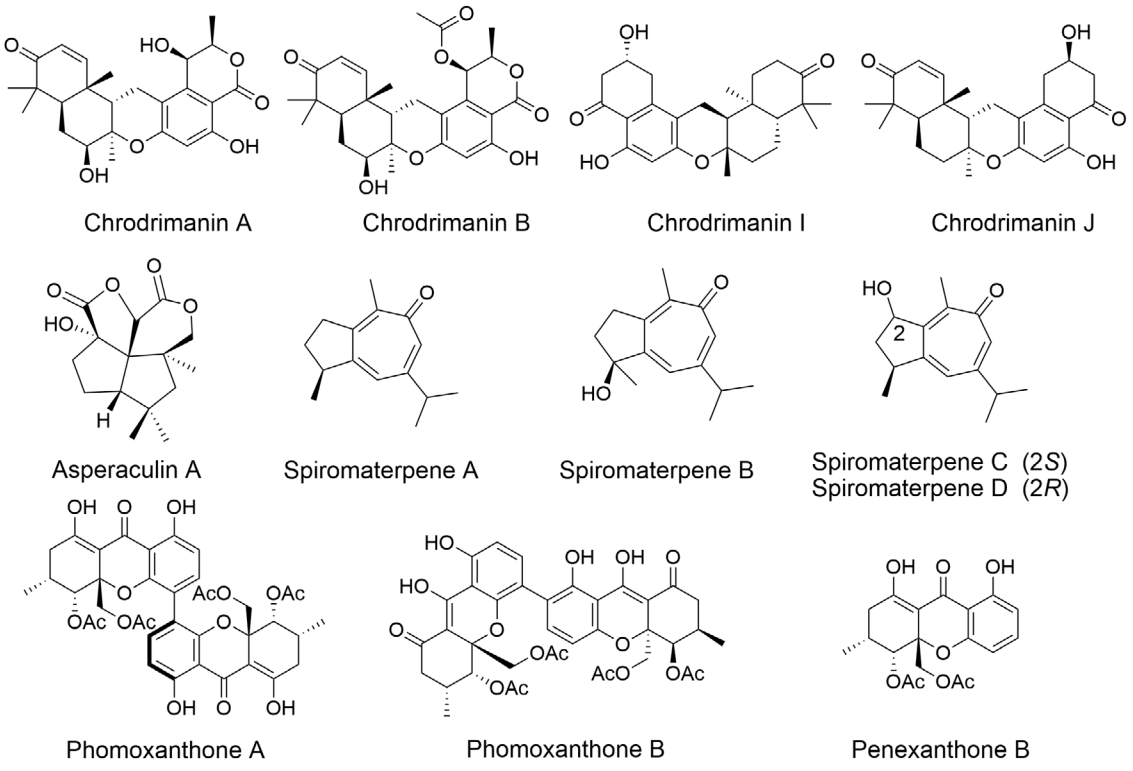

Fig. 7. Chemical structures of marine fungi-derived compounds investigated by heterologous expression.

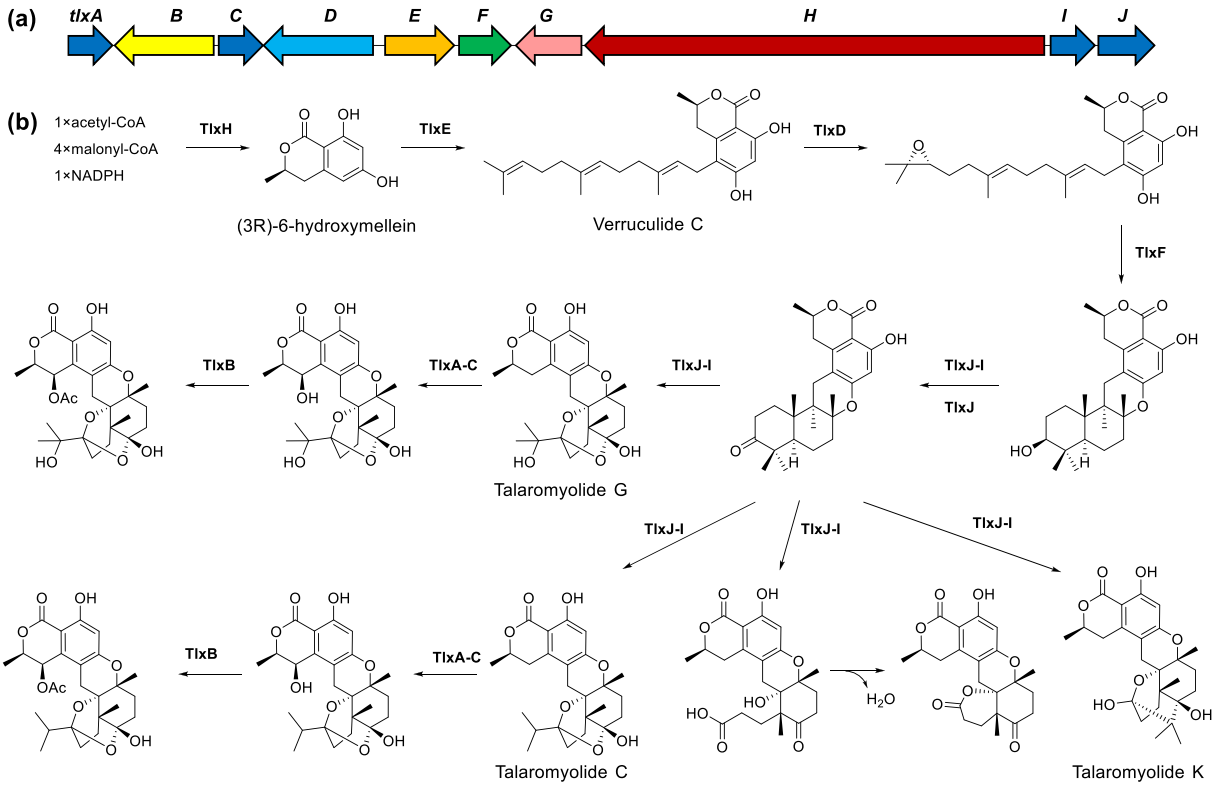

Fig. 8. Biosynthetic gene cluster (a) and assembly pathway of talaromyolides (b). TlxB, acetyltransferase; TlxD, flavin monooxygenase; TlxE, isoprene transferase; TlxF, terpene cyclase; TlxG, short-chain dehydrogenase/reductase (SDR); TlxH, non-heme PKS; TlxACIJ, four α- KG dependent non-heme iron oxygenase.

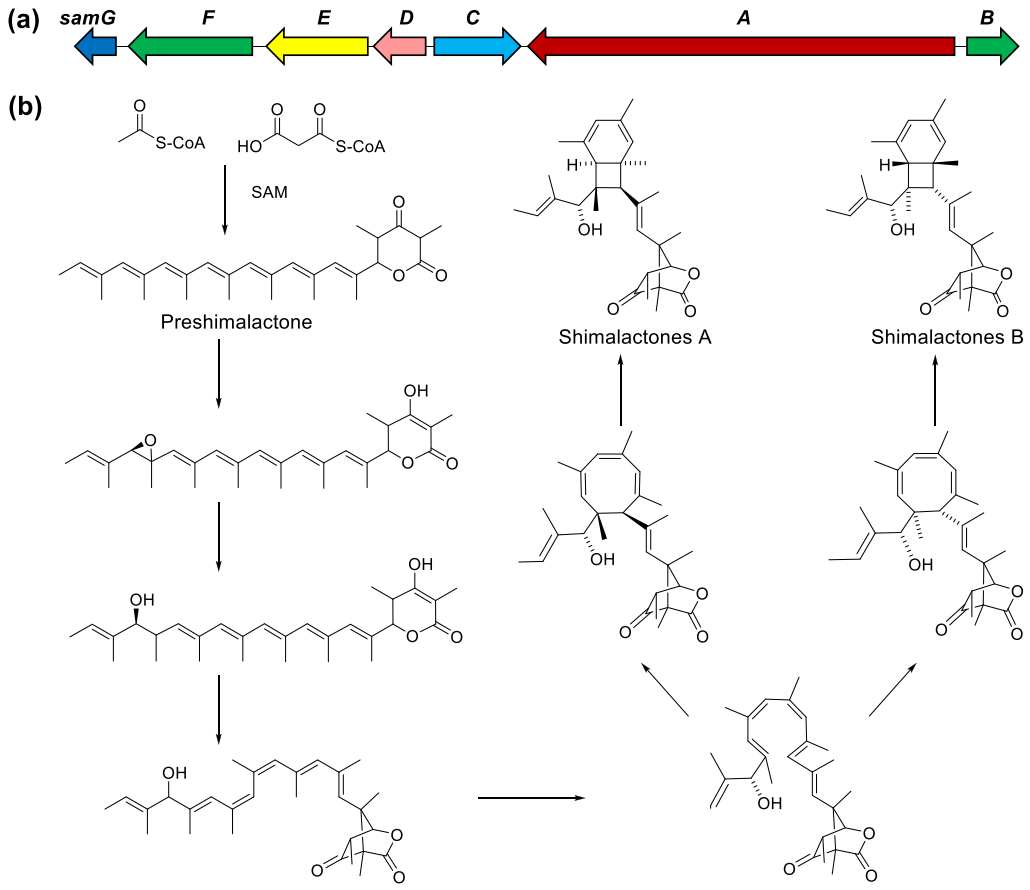

Fig. 9. Biosynthetic gene cluster (a) and assembly pathway of shimalactones A and B (b). ShmA, highly reducing iterative type I polyketide synthase (HR-PKS); ShmB, Flavin adenine dinucleotide (FAD)-dependent monooxygenase. ShmC, transporter; ShmD, iron-sulfur protein; ShmE, transcription factor; ShmF, FAD oxidoreductase; ShmG, integral membrane protein.

tified by the sequential transfer *tlxHEDFG* into *A. oryzae* NSAR1. Gene knockouts in the original strain revealed two pairs of heterodimeric NHI enzymes (TlxJ-TlxI and TlxA-TlxC) [132]. Expression of *tlxACIJ* in the prokaryotic host *E. coli* and *in vitro* biochemical analysis of recombinant proteins further confirmed that each monomer possesses specificity for heterodimer formation.

3.2.4. Phomoxanthones

Phomoxanthones A and B were discovered by Isaka *et al.* (Fig. 7) in the terrestrial fungus *Phomopsis* sp. BCC 1323 and revealed antimalarial and antitubercular activities [133]. Strong antibacterial, antifungal, and antineoplastic activities were later found for phomoxanthone A [134,135]. The BGC of phomoxanthones (*pho*) was identified and validated in the genome of the marine filamentous fungus *Dianporthe* sp. SYSU-MS4722 [136,137]. Owing to the low efficiency of gene editing in the original strain, the *pho* gene cluster was transferred to the heterologous host *Aspergillus oryzae* NSAR1, resulting in the production of penexanthone B and phomoxanthones. The biosynthetic mechanism of phomoxanthones was elucidated using gene knockout and metabolic analyses in *Aspergillus*.

3.2.5. Shimalactone

Wei *et al.* discovered shimalactone A, a novel neurogenic polyketone compound from the marine fungus *Emericella variecolor* GF10 [138]. Fujii *et al.* identified the BGC of shimalactone (*shm*) and elucidated its biosynthetic mechanism by expressing the *shm* gene cluster in *A. oryzae* and *Saccharomyces cerevisiae* (Fig. 9). Expression of the polyketide synthase gene *shmA* in *A. oryzae* M-2-3 generated a new compound, preshimalactone [139]. Subsequent gene transfer revealed that both *shmA and shmB* are necessary for the generation of shimalactone A and *shmDFG* did not affect the production of shimalactones, indicating that oxadiacyclization and 8π-6π electrocyclization were conducted spontaneously after the ring opening of preshimalactone epoxide without enzyme catalysis.

3.2.6. Spiromaterpenes

Guaiacane-type sesquiterpenes contain a 5/7 fusion ring skeleton with two methyl groups and an isopropyl group and are widely present in medicinal plants and marine organisms. They have been observed to exhibit excellent antitumor and anti-ulcer effects [140–142]. During the production of spirotarpenes by the difficult-to-cultivate marine fungus *Spiromastix* sp., Liu *et al.* identified two sesquiterpene synthases (SptA and SptB) that may be involved in the synthesis of the cycloheptadionene [143]. The co-expression of SptA and SptB in *Saccharomyces cerevisiae* and *Aspergillus nidulans* LO8030 successfully generated spiromaterpene A (Fig. 7).

4. Conclusion

Marine microbial natural products have been recognized as important sources of lead compounds for drug discovery. In marine microorganisms, many structurally and functionally unique compounds have been discovered, such as marine actinomycetes, fungi, cyanobacteria, and symbiotic bacteria. Heterologous expression plays an important role in the exploration and biosynthesis of marine natural products, providing a new method for large-scale production of valuable marine natural products. However, multiple limitations must be overcome for the heterologous expression of marine natural product biosynthetic pathways.

First, a suitable heterologous chassis is crucial for successful expression of gene clusters. Compared with the diverse heterologous platforms used for the expression of BGCs originating from terrestrial microorganisms, efficient heterologous hosts for marine biosynthetic pathways are relatively rare. Metagenomic analyses have uncovered a large number of BGCs in marine environments [144,145]. With the development of bioinformatics and synthetic biology technologies, the acquisition of solid BGC is no longer the main obstacle for genome-guided exploitation of marine microbial natural products. The screening and development of a versatile chassis suitable for the production of marine natural products are considerably important. Second, cutting-edge gene editing tools, *eg.* the CRISPR-Cas system, has been applied for the genetic modification of marine microbial genomes; however, the editing efficiency is considerably low, and most marine microorganisms remain genetically inaccessible. DNA transfer and genetic manipulation of marine microorganisms largely rely on conjugal transfer and homologous recombination, which restrict the genetic modification of marine microorganisms. Therefore, the development of efficient genetic systems for marine microbes is recommended in further research. Further investigations are also necessary to elucidate gene regulatory networks in marine microorganisms. In a special marine environment, marine microorganisms have most likely evolved gene regulatory mechanisms that differ from those of terrestrial microbes. Understanding the mode of BGC-related gene regulation will contribute to the activation of marine-derived BGC *in situ* and in heterologous hosts. A reasonable prediction is that heterologous expression strategies will play an important role in the exploration of additional marine natural products.

Declaration of AI in Scientific Writing

The authors declare no AI in scientific writing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT Authorship Contribution Statement

Shuang Zhao: Writing – review & editing, Writing – original draft, Conceptualization. **Ruiying Feng:** Writing – review & editing, Writing – original draft, Conceptualization. **Yuan Gu:** Writing – review & editing, Writing – original draft, Conceptualization. **Liyuan Han:** Writing – review & editing. **Xiaomei Cong:** Writing – review & editing. **Yang Liu:** Writing – review & editing. **Shuo Liu:** Writing – review & editing. **Qiyao Shen:** Writing – review & editing. **Liujie Huo:** Writing – review & editing. **Fu Yan:** Writing – review & editing, Supervision, Conceptualization.

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References

[1] D.J. Newman, G.M. Cragg, Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019, J Nat Prod 83 (3) (2020) 770–803.
[2] B.J.H.a.R.A. Shenvi, Natural products in the “Marketplace”: Interfacing synthesis and biology, J. Am. Chem. Soc 141 (8) (2019) 3332–3346.
[3] G.M. Cragg, D.J. Newman, Natural products: A continuing source of novel drug leads, Biochim Biophys Acta 1830 (6) (2013) 3670–3695.
[4] Z Q Xiong, J F Wang, Y Y Hao, Recent advances in the discovery and development of marine microbial natural products, Mar Drugs 11 (3) (2013) 700–717.
[5] N. Haque, S. Parveen, T. Tang, J. Wei, Z. Huang, Marine natural products in clinical use, Mar Drugs 20 (8) (2022) 528.
[6] J.A.M. A, T.J. A, M.A. B, C.B. A, Recent highlights of biosynthetic studies on marine natural products, Org Biomol Chem 19 (1) (2021) 123–140.
[7] P. Banerjee, A. Mandhare, V. Bagalkote, Marine natural products as source of new drugs: an updated patent review (July 2018-July 2021), Expert Opin Ther Pat 32 (3) (2021) 317–363.
[8] A. Carroll, B. Copp, R. Davis, R. Keyzers, M. Prinsep, Marine natural products, Nat Prod Rep 39 (6) (2022) 1122–1171.
[9] A.R. Carroll, B.R. Copp, R.A. Davis, R.A. Keyzers, M.R. Prinsep, Marine natural products, Nat Prod Rep 36 (1) (2019) 122–173.
[10] H.B. Bode, B. Bethe, R. Hofs, A. Zeeck, Big Effects from small changes: possible ways to explore nature’s chemical diversity, Chembiochem 3 (7) (2002) 619–627.
[11] A. Marmann, A. Aly, W. Lin, B. Wang, P. Proksch, Co-cultivation—a powerful emerging tool for enhancing the chemical diversity of microorganisms, Mar Drugs 12 (2) (2014) 1043–1065.
[12] D.M. Selegato, I. Castro-Gamboa, Enhancing chemical and biological diversity by co-cultivation, Front Microbiol 14 (2023) 1117559.
[13] M.N. Gwynn, A. Portnoy, S.F. Rittenhouse, D.J. Payne, Challenges of antibacterial discovery revisited, Ann N Y Acad Sci 1213 (2010) 5–19.
[14] M. Tulp, L. Bohlin, Rediscovery of known natural compounds: nuisance or goldmine? Bioorg Med Chem 13 (17) (2005) 5274–5282.
[15] X. Meng, Y. Fang, M. Ding, Y. Zhang, K. Jia, Z. Li, J. Collemare, W. Liu, Developing fungal heterologous expression platforms to explore and improve the production of natural products from fungal biodiversity, Biotechnol Adv 54 (2022) 107866.
[16] D. Montiel, H.S. Kang, F.Y. Chang, Z. Charlop-Powers, S.F. Brady, Yeast homologous recombination-based promoter engineering for the activation of silent natural product biosynthetic gene clusters, Proc Natl Acad Sci U S A 112 (29) (2015) 8953–8958.
[17] M. Myronovskyi, A. Luzhetskyy, Native and engineered promoters in natural product discovery, Nat Prod Rep 33 (8) (2016) 1006–1019.
[18] M.M. Zhang, F.T. Wong, Y. Wang, S. Luo, Y.H. Lim, E. Heng, W.L. Yeo, R.E. Cobb, B. Enghiad, E.L. Ang, CRISPR-Cas9 strategy for activation of silent *Streptomyces* biosynthetic gene clusters, Nat Chem Biol 10 (2017) 2341.
[19] B. Wang, F. Guo, S.H. Dong, H. Zhao, Activation of silent biosynthetic gene clusters using transcription factor decoys, Nat Chem Biol 15 (2) (2019) 111–114.
[20] S.S. Choi, Y. Katsuyama, L. Bai, Z. Deng, Y. Ohnishi, E.S. Kim, Genome engineering for microbial natural product discovery, Curr Opin Microbiol 45 (2018) 53–60.
[21] K. Scherlach, C. Hertweck, Mining and unearthing hidden biosynthetic potential, Nat Commun 12 (1) (2021) 3864.
[22] E. Kalkreuter, G. Pan, A.J. Cepeda, B. Shen, Targeting bacterial genomes for natural product discovery, Trends Pharmacol Sci 41 (1) (2020) 13–26.
[23] T.W. Li, S.Y. Kazuo, N. Makoto, K. Tomohisa, Discovery of an antibacterial isoindolinone-containing tetracyclic polyketide by cryptic gene activation and characterization of its biosynthetic gene cluster, ACS Chem Biol 13 (9) (2018) 2615–2622.
[24] l. Huo, J.J. Hug, C. Fu, X. Bian, Y. Zhang, R. Müller, Heterologous expression of bacterial natural product biosynthetic pathways, Nat Prod Rep 36 (10) (2019) 1412–1436.
[25] V. Larionov, N. Kouprina, J. Graves, X.N. Chen, J.R. Korenberg, M.A. Resnick, Specific cloning of human DNA as yeast artificial chromosomes by transformation-associated recombination, Proc Natl Acad Sci U S A 93 (1) (1996) 491–496.
[26] J. Wan, N. Ma, H. Yuan, Recent advances in the direct cloning of large natural product biosynthetic gene clusters, Engineering Microbiology 3 (2023) 100085.
[27] Y. Zhang, J.P.P. Muyrers, G. Testa, A.F. Stewart, DNA cloning by homologous recombination in Escherichia coli, Nat Biotechnol 18 (12) (2000) 1314–1317.
[28] B. Enghiad, C. Huang, F. Guo, G. Jiang, B. Wang, S.K. Tabatabaei, T.A. Martin, H. Zhao, Cas12a-assisted precise targeted cloning using *in vivo* Cre-lox recombination, Nat Commun 12 (1) (2021) 1171.
[29] Z.J. Jia, B.S. Moore, T. Xiaoyu, Engineering Salinispora tropica for heterologous expression of natural product biosynthetic gene clusters, Appl Microbiol Biotechnol 102 (19) (2018) 8437–8446.
[30] K. Yamanaka, K.A. Reynolds, R.D. Kersten, K.S. Ryan, D.J. Gonzalez, V. Nizet, P.C. Dorrestein, B.S. Moore, Direct cloning and refactoring of a silent lipopeptide biosynthetic gene cluster yields the antibiotic taromycin A, Proc Natl Acad Sci U S A 111 (5) (2014) 1957–1962.
[31] W. Wang, G. Zheng, Y. Lu, Recent Advances in Strategies for the Cloning of Natural Product Biosynthetic Gene Clusters, Front Bioeng Biotechnol (9) (2021) 692797.
[32] K. Alam, A. Mazumder, S. Sikdar, Y.-M. Zhao, J. Hao, C. Song, Y. Wang, R. Sarkar, S. Islam, Y. Zhang, A. Li, *Streptomyces*: The biofactory of secondary metabolites, Front Microbiol 13 (2022) 968053.
[33] J.J. Zhang, X. Tang, B.S. Moore, Genetic platforms for heterologous expression of microbial natural products, Nat Prod Rep 36 (9) (2019) 1313–1332.
[34] K. Alam, J. Hao, Y. Zhang, A. Li, Synthetic biology-inspired strategies and tools for engineering of microbial natural product biosynthetic pathways, Biotechnol Adv 49 (2021) 107759.
[35] Y. Luo, B.h. Li, D. Liu, L. Zhang, Y. Chen, B. Jia, B.u. Zeng, H. Zhao, Y.i. Yuan, Engineered biosynthesis of natural products in heterologous hosts, Chemical Society Reviews 46 (2015) 5265–5290.
[36] R. Xu, H. Zhu, H. Zhang, J. Ju, Q. Li, S. Fu, Six sets of aromatic polyketides differing in size and shape derive from a single biosynthetic gene cluster, Nat Prod Rep 86 (6) (2023) 1512–1519.
[37] U. Fauth, H.Z Hner, A. MüHLENFELD, H. Achenbach, Galbonolides A and B - two non-glycosidic antifungal macrolides, J Antibiot (Tokyo) 39 (12) (1986) 1760–1764.
[38] C. Zhen, H. Lu, Y. Jiang, Novel promising antifungal target proteins for conquering invasive fungal infections, Front Microbiol 13 (2022) 911322.

[39] M.A. Achenbach H, U Fauth, H. Zähner, The galbonolides. Novel, powerful antifungal macrolides from *Streptomyces galbus* ssp. eurythermus, Ann N Y Acad Sci 544 (1988) 128–140.

[40] C.H. Lu, Y.Y. Li, J.L. Zhang, Y.M. Shen, J. Zhu, *In vitro* reconstitution of a PKS pathway for the biosynthesis of galbonolides in *Streptomyces* sp LZ35, Chembiochem 16 (6) (2015) 998–1007.

[41] C.H. Lu, C. Liu, Y.M. Shen, J.L. Zhang, Heterologous expression of galbonolide biosynthetic genes in *Streptomyces coelicolor*, Antonie Van Leeuwenhoek 107 (5) (2015) 1359–1366.

[42] B. Wli, J. Paul, C. Sheldon, H. Richard, Purification and properties of the *Streptomyces peucetius* DpsC *β*ketoacyl:acyl carrier protein synthase III that specifies the propionate-starter unit for Type II polyketide biosynthesis, Biochemistry 38 (30)) (1999) 9752–9757.

[43] J. Riedlinger, A. Reicke, H. Z?Hner, B. Krismer, A.T. Bull, L.A. Maldonado, A.C. Ward, M. Goodfellow, B. Bister, D. Bischoff, Abyssomicins, inhibitors of the para-aminobenzoic acid pathway produced by the marine Verrucosispora strain AB-18-032, J Antibiot (Tokyo) 57 (4) (2004) 271–279.

[44] J.S. Freundlich, M. Lalgondar, J.R. Wei, S. Swanson, E.J. Sorensen, E.J. Rubin, J.C Sacchettini, The Abyssomicin C family as *in vitro* inhibitors of Mycobacterium tuberculosis, Tuberculosis (Edinb) 90 (5) (2010) 298–300.

[45] Y. Song, Q. Li, F. Qin, C. Sun, H. Liang, X. Wei, N.K. Wong, L. Ye, Y. Zhang, M. Shao, Neoabyssomicins A–C, polycyclic macrolactones from the deep-sea derived *Streptomyces koyangensis* SCSIO 5802, Tetrahedron (2017) 5366–5372.

[46] J. Tu, S. Li, J. Chen, Y. Song, S. Fu, J. Ju, Q. Li, Characterization and heterologous expression of the neoabyssomicin/abyssomicin biosynthetic gene cluster from *Streptomyces koyangensis* SCSIO 5802, Microb Cell Fact 17 (1) (2018) 28.

[47] J.S. An, B. Shin, T.H. Kim, S. Hwang, Y.H. Shin, J. Cui, Y.E. Du, J. Yi, S.J. Nam, S. Hong, J. Shin, J. Jang, Y.J. Yoon, D.C. Oh, Dumulmycin, an antitubercular bicyclic macrolide from a riverine sediment-derived *Streptomyces* sp, Org Lett 23 (9) (2021) 3359–3363.

[48] Y. Liu, H. Zhou, Q. Shen, G. Dai, F. Yan, X. Li, X. Ren, Q. Sun, Y.J. Tang, Y. Zhang, Discovery of polycyclic macrolide shuangdaolides by heterologous expression of a Cryptic trans -AT PKS Gene Cluster, Org Lett 23 (17) (2021) 6967–6971.

[49] B. Zhang, K.B. Wang, W. Wang, S.F. Bi, Y.N. Mei, X.Z. Deng, R.H. Jiao, R.X. Tan, H.M. Ge, Discovery, biosynthesis, and heterologous production of streptoseomycin, an anti-microaerophilic bacteria macrodilactone, Org Lett 20 (10) (2018) 2967–2971.

[50] K.B. Wang, W. Wang, B. Zhang, X. Wang, H.M. Ge, A [6+4]-cycloaddition adduct is the biosynthetic intermediate in streptoseomycin biosynthesis, Nat Commun 12 (1) (2021) 2092.

[51] J. Zhang, Y. Jiang, Y. Cao, J. Liu, D. Zheng, X. Chen, L Han, C. Jiang, X. Huang, Violapyrones A-G, alpha-pyrone derivatives from *Streptomyces* violascens isolated from Hylobates hoolock feces, J Nat Prod 76 (11) (2013) 2126–2130.

[52] H. Huang, L. Hou, H. Li, Y. Qiu, J. Ju, W. Li, Activation of a plasmid-situated type III PKS gene cluster by deletion of a wbl gene in deepsea-derived *Streptomyces* somaliensis SCSIO ZH66, Microb Cell Fact 15 (1) (2016) 116.

[53] L. Hou, S.Y. Wang, H.M. Huang, H.Y. Li, W. Wang, W.L. Li, Generation of methylated violapyrones with improved anti-influenza A virus activity by heterologous expression of a type III PKS gene in a marine *Streptomyces* strain, Bioorg Med Chem Lett 28 (17) (2018) 2865–2868.

[54] J. Shi, Y.J. Zeng, B. Zhang, F.L. Shao, Y.C. Chen, X. Xu, Y. Sun, Q. Xu, R.X. Tan, H.M. Ge, Comparative genome mining and heterologous expression of an orphan NRPS gene cluster direct the production of ashimides, Chem Sci 10 (10) (2019) 3042–3048.

[55] R.C.M. Lau, K.L. Rinehart, Berninamycins B, C, and D, minor metabolites from *Streptomyces* bernensis, J Antibiot (Tokyo) 47 (12) (1994) 1466–1472.

[56] J.M. Liesch, D.S. Millington, R.C. Pandey, K.L. Rinehart, Berninamycin. 2. Products of acidic hydrolysis, methanolysis, and acetolysis of berninamycin A, J Am Chem Soc 98 (25) (1976) 8237–8249.

[57] J.M. Liesch, D.S. Millington, R.C. Pandey, K.L.J. Rinehart, ChemInform Abstract: Berninamycin. 2. Products of acidic hydrolysis, methanolysis, and acetolysis of berninamycin A, Chemischer Informationsdienst 8 (10) (1977).

[58] J.M. Liesch, K.L. Rinehart, Berninamycin. 3. Total structure of berninamycin A1,2, J Am Chem Soc 99 (5) (1977) 1645–1646.

[59] B.C. De, W. Zhang, G. Zhang, Z. Liu, B. Tan, Q. Zhang, L. Zhang, H. Zhang, Y. Zhu, C. Zhang, Host-dependent heterologous expression of berninamycin gene cluster leads to linear thiopeptide antibiotics, Org Biomol Chem 19 (41) (2021) 8940–8946.

[60] M.R. Estévez, M. Myronovskyi, N. Gummerlich, S. Nadmid, A. Luzhetskyy, Heterologous expression of the nybomycin gene cluster from the marine strain *streptomyces albus* subsp. chlorinus NRRL B-24108, Mar Drugs 16 (11) (2018) 435.

[61] C. Lasch, M. Stierhof, M.R. Estevez, A. Luzhetskyy, Bonsecamin: a new cyclic pentapeptide discovered through heterologous expression of a cryptic gene cluster, Microorganisms 9 (8) (2021) 1640.

[62] L.Q. Song Y, X Liu, Y Chen, Y Zhang, A Sun, W Zhang, J Zhang, J Ju, Cyclic Hexapeptides from the deep south china sea-derived *Streptomyces scopuliridis* SCSIO ZJ46 active against pathogenic Gram-positive bacteria, J Nat Prod 77 (8) (2014) 1937–1941.

[63] Q S.Y. Li, X Qin, X Zhang, A Sun, J. Ju, Identification of the biosynthetic gene cluster for the anti-infective desotamides and production of a new analogue in a heterologous host, J Nat Prod 78 (4) (2015) 944–948.

[64] H. Fujiki, M. Mori, M. Nakayasu, M. Terada, T. Sugimura, R.E. Moore, Indole alkaloids: dihydroteleocidin B, teleocidin, and lyngbyatoxin A as members of a new class of tumor promoters, Proceedings of the National Academy of Sciences 78 (1981) 3872–3876.

[65] H. Fujiki, Y. Tanaka, R. Miyake, U. Kikkawa, T. Sugimura, Activation of calcium-activated, phospholipid-dependent protein kinase (protein kinase C) by new classes of tumor promoters: Teleocidin and debromoaplysiatoxin, Biochem Biophys Res Commun 120 (1984) 339–343.

[66] J.H. Cardellina, F.-J. Marner, R.E. Moore, Seaweed dermatitis: structure of lyngbyatoxin A, Science 204 (1979) 193–195.

[67] N. Aimi, H. Odaka, S.-i. Sakai, H. Fujiki, M. Suganuma, R.E. Moore, G.M.L. Patterson, Lyngbyatoxins B and C, two new irritants from Lyngbya majuscula, J Nat Prod 53 (6) (1990) 1593–1596.

[68] W. Jiang, W. Zhou, H. Uchida, M. Kikumori, K. Irie, R. Watanabe, T. Suzuki, B. Sakamoto, M. Kamio, H. Nagai, A new lyngbyatoxin from the Hawaiian cyanobacterium Moorea producens, Mar Drugs 12 (5) (2014) 2748–2759.

[69] W. Jiang, S. Tan, Y. Hanaki, K. Irie, H. Uchida, R. Watanabe, T. Suzuki, B. Sakamoto, M. Kamio, H. Nagai, Two new lyngbyatoxin derivatives from the cyanobacterium, Moorea producens, Mar Drugs 12 (12) (2014) 5788–5800.

[70] D.J. Edwards, W.H. Gerwick, Lyngbyatoxin biosynthesis: sequence of biosynthetic gene cluster and identification of a novel aromatic prenyltransferase, J Am Chem Soc 126 (37) (2004) 11432–11433.

[71] S.E. Ongley, X. Bian, Y. Zhang, R. Chau, W.H. Gerwick, R. Müller, B.A. Neilan, High-titer heterologous production in E. coli of lyngbyatoxin, a protein kinase C activator from an uncultured marine cyanobacterium, ACS Chem Biol 8 (9) (2013) 1888-189.

[72] P. Videau, K. Wells, A.J. Singh, W.H. Gerwick, B. Philmus, Assessment of anabaena sp. Strain PCC 7120 as a Heterologous expression host for cyanobacterial natural products: production of Lyngbyatoxin A, ACS Synth Biol 5 (9) (2016) 978–988.

[73] D. Degen, Y. Feng, Y. Zhang, K.Y. Ebright, Y.W. Ebright, M. Gigliotti, H. Vahedianmovahed, S. Mandal, M. Talaue, N. Connell, Transcription inhibition by the depsipeptide antibiotic salinamide A, Elife 3 (2014) e02451.

[74] S. Miao, M.R. Anstee, K. Lamarco, J. Matthew, L.H.T. Huang, M.M. Brasseur, Inhibition of bacterial RNA polymerases. peptide metabolites from the cultures of *Streptomyces* sp, J Nat Prod 60 (8) (1997) 858–861.

[75] J.A. Trischman, D.M. Tapiolas, P.R. Jensen, R. Dwight, W. Fenical, T.C. Mckee, C.M. Ireland, T.J. Stout, J. Clardy, Salinamides A and B: anti-inflammatory depsipeptides from a marine streptomycete, J Am Chem Soc 116 (2) (1994) 757–758.

[76] J.A.T.B.S. Moore, D. Seng, D. Kho, P.R. Jensen, W. Fenical, Salinamides, antiinflammatory depsipeptides from a marine streptomycete, J. Org. Chem 64 (4) (1999) 1145–1150.

[77] H.M. Hassan, D. Degen, K.H. Jang, R.H. Ebright, W. Fenical, Salinamide F, new depsipeptide antibiotic and inhibitor of bacterial RNA polymerase from a marine-derived *Streptomyces* sp, J Antibiot 68 (3) (2015) 206–209.

[78] L. Ray, K. Yamanaka, B.S Moore, A peptidyl-transesterifying typeI thioesterase in salinamide biosynthesis, Angew Chem Int Ed Engl 55 (1) (2015) 364–367.

[79] R. Chen, Q. Zhang, B. Tan, L. Zheng, H. Li, Y. Zhu, C. Zhang, Genome mining and activation of a silent PKS/NRPS gene cluster direct the production of totopotensamides, Org Lett 19 (20) (2017) 5697–5700.

[80] B. Tan, Q. Zhang, Y. Zhu, H. Jin, C. Zhang, Deciphering biosynthetic enzymes leading to 4-Chloro-6-methyl-5,7-dihydroxyphenylglycine, a non-proteinogenic amino acid in totopotensamides, ACS Chem Biol 15 (3) (2020) 766–773.

[81] K. Kleigrewe, J. Almaliti, I.Y. Tian, R.B. Kinnel, A. Korobeynikov, E.A. Monroe, B.M. Duggan, V. Di Marzo, D.H. Sherman, P.C. Dorrestein, combining mass spectrometric metabolic profiling with genomic analysis: a powerful approach for discovering natural products from cyanobacteria, J Nat Prod 78 (7) (2015) 1671–1682.

[82] A. Taton, S.G. Rohrer, B. Diaz, R. Reher, A.M.C. Rodríguez, M.L. Pierce, P. Dorrestein, L. Gerwick, W. Gerwick, J.W. Golden, Heterologous expression in anabaena of the columbamide pathway from the cyanobacterium moorena bouillonii and production of new analogs, ACS Chem Biol 17 (7) (2022) 1910–1923.

[83] R.B. Kinnel, E. Esquenazi, T. Leao, N. Moss, E. Mevers, A.R. Pereira, E.A. Monroe, A maldiisotopic approach to discover natural products: cryptomaldamide, a hybrid tripeptide from the marine cyanobacterium moorea producens, J Nat Prod 80 (5) (2017) 1514–1521.

[84] A. Taton, A. Ecker, B. Diaz, N.A. Moss, J.W. Golden, Heterologous expression of cryptomaldamide in a cyanobacterial host, ACS Synth Biol 9 (12) (2020) 3364–3376.

[85] Z. Chang, P. Flatt, W.H. Gerwick, V.A. Nguyen, C.L. Willis, D.H. Sherman, The barbamide biosynthetic gene cluster: a novel marine cyanobacterial system of mixed polyketide synthase (PKS)-non-ribosomal peptide synthetase (NRPS) origin involving an unusual trichloroleucyl starter unit, Gene 296 (1-2) (2002) 235–247.

[86] E.J. Kim, J.H. Lee, H. Choi, A.R. Pereira, Y.H. Ban, Y.J. Yoo, E. Kim, J.W. Park, D.H. Sherman, W.H. Gerwick, Heterologous production of 4-*O*-Demethylbarbamide, a marine cyanobacterial natural Product, Org Lett 14 (23) (2012) 5824–5827.

[87] T.B. Rounge, T. Rohrlack, A.J. Nederbragt, T. Kristensen, K.S. Jakobsen, A genome-wide analysis of nonribosomal peptide synthetase gene clusters and their peptides in a Planktothrix rubescens strain, BMC Genomics 10 (2009) 396.

[88] R.Castelo-Branco Nádia.Eusébio, D. Sousa, M. Preto, P. D'Agostino, T.A.M. Gulder, P.N. Leo, Discovery and heterologous expression of microginins from, ACS Synth Biol 11 (10) (2022) 3493–3503.

[89] M.P. Sobolevskaya, O.F. Smetanina, M. Speitling, L.S. Shevchenko, G.B. Elyakov, Controlling production of brominated cyclic depsipeptides by Pseudoalteromonas maricaloris KMM 636T, Lett Appl Microbiol 40 (4) (2005) 243–248.

[90] D.D. Nguyen, C.H. Wu, W.J. Moree, A. Lamsa, M.H. Medema, X. Zhao, R.G. Gavilan, M. Aparicio, L. Atencio, C. Jackson, MS/MS networking guided analysis of molecule and gene cluster families, Proc Natl Acad Sci U S A 110 (28) (2013) E2611–E2620.

[91] A.C. Ross, L.E.S. Gulland, P.C. Dorrestein, B.S. Moore, Targeted capture and heterologous expression of the pseudoalteromonas alterochromide gene cluster in Escherichia coli represents a promising natural product exploratory platform, ACS Synth Biol 4 (4) (2014) 414–420.

[92] J.D. Hegemann, M. Zimmermann, X. Xie, M.A. Marahiel, Lasso peptides: an intriguing class of bacterial natural products, Acc Chem Res 48 (7) (2015) 1909–1919.
[93] C. Cheng, Z.-C. Hua, Lasso peptides: heterologous production and potential medical application, Front Bioeng Biotechnol 8 (2020) 571165.
[94] D. Ovescostales, O. Genilloud, Identification, Cloning and heterologous expression of the gene cluster directing RES-701-3, -4 Lasso peptides biosynthesis from a marine *Streptomyces* Strain, Mar Drugs 18 (5) (2020) 238.
[95] M. Shao, J. Ma, Q. Li, J. Ju, Identification of the anti-Infective aborycin biosynthetic gene cluster from deep-sea-derived *Streptomyces* sp. SCSIO ZS0098 enables production in a heterologous host, Mar Drugs 17 (2) (2019).
[96] C.M. Ireland, A.R. Durso, R.A. Newman, M.P. Hacker, Antineoplastic cyclic peptides from the marine tunicate Lissoclinum patella, J Org Chem 47 (10) (1982) 1807–1811.
[97] B.M. Degnan, C.J. Hawkins, M.F. Lavin, E.J. Mccaffrey, D.L. Parry, d.B. Van, L. Anna, D.J. Watters, New cyclic peptides with cytotoxic activity from the ascidian Lissoclinum patella, J Med Chem 32 (6) (1989) 1349–1354.
[98] E.W. Schmidt, J.T. Nelson, D.A. Rasko, S. Sudek, J.A. Eisen, M.G. Haygood, J. Ravel, Patellamide A and C biosynthesis by a microcin-like pathway in Prochloron didemni, the cyanobacterial symbiont of Lissoclinum patella, Proc Natl Acad Sci U S A 102 (20) (2005) 7315–7320.
[99] J. Martins, N. Leikoski, M. Wahlsten, J. Azevedo, J. Antunes, J. Jokela, K. Sivonen, V. Vasconcelos, D.P. Fewer, P.N. Leão, Sphaerocyclamide, a prenylated cyanobactin from the cyanobacterium Sphaerospermopsis sp. LEGE 00249, Sci Rep 8 (1) (2018) 14537.
[100] J. Braesel, J.-H. Lee, B. Arnould, B.T. Murphy, A.S. Eustáquio, Diazaquinomycin biosynthetic gene clusters from marine and freshwater actinomycetes, J Nat Prod 82 (4) (2019) 937–946.
[101] M. Murata, T. Miyasaka, H. Tanaka, S. Omura, Diazaquinomycin A, a new antifolate antibiotic, inhibits thymidylate synthase, Journal of Antibiotics 38 (1985) 1025–1033.
[102] J. Braesel, T.A. Tran, A.S. Eustáquio, Heterologous expression of the diazaquinomycin biosynthetic gene cluster, J Ind Microbiol Biotechnol 46 (9-10) (2019) 1359–1364.
[103] N. Ziemert, K. Ishida, A. Liaimer, C.Dr. Hertweck, E.Dr. Dittmann, Ribosomal synthesis of tricyclic depsipeptides in bloom-forming cyanobacteria, Angew Chem Int Ed Engl 47 (40) (2008) 7756–7759.
[104] L.C. Blasiak, J.C. Clardy, Discovery of 3-Formyl-Tyrosine Metabolites from pseudoalteromonas tunicata through heterologous expression, J Am Chem Soc 132 (3) (2010) 926–927.
[105] W. Shih-Wei, C. Chih-Ling, Y.C. Kao, R. Martin, C.L. Chen, Pentabromopseudilin: a myosin V inhibitor suppresses TGF- β activity by recruiting the type II TGF- β receptor to lysosomal degradation, J Enzyme Inhib Med Chem 33 (1) (2018) 920–935.
[106] J.M. Sneed, K.H. Sharp, K.B. Ritchie, V.J. Paul, The chemical cue tetrabromopyrrole from a biofilm bacterium induces settlement of multiple Caribbean corals, Proc Biol Sci 281 (1786) (2014) 130–143.
[107] K. Ni, Y. Lu, T. Wang, K. Kannan, J. Gosens, L. Xu, Q. Li, L. Wang, S. Liu, A review of human exposure to polybrominated diphenyl ethers (PBDEs) in China, Int J Hyg Environ Health 216 (6) (2013) 607–623.
[108] A.P. Vonderheide, K.E. Mueller, J. Meija, G.L. Welsh, Polybrominated diphenyl ethers: Causes for concern and knowledge gaps regarding environmental distribution, fate and toxicity, Sci Total Environ 400 (1-3) (2008) 425–436.
[109] V. Agarwal, A.A. El Gamal, K. Yamanaka, D. Poth, R.D. Kersten, M. Schorn, E.E. Allen, B.S. Moore, Biosynthesis of polybrominated aromatic organic compounds by marine bacteria, Nat Chem Biol 10 (8) (2014) 640–647.
[110] S. Saha, W. Zhang, G. Zhang, Y. Zhu, Y. Chen, W. Liu, C. Yuan, Q. Zhang, H. Zhang, L. Zhang, W. Zhang, C. Zhang, Activation and characterization of a cryptic gene cluster reveals a cyclization cascade for polycyclic tetramate macrolactams, Chem Sci 8 (2) (2017) 1607–1612.
[111] N. Durán, C.F.M. Menck, Chromobacterium violaceum: A review of pharmacological and industiral perspectives, Crit Rev Microbiol 27 (3) (2001) 201–222.
[112] J.M. Pemberton, K.M. Vincent, R.J. Penfold, Cloning and heterologous expression of the violacein biosynthesis gene cluster from Chromobacterium violaceum, Curr Microbiol 22 (1991) 355–358.
[113] C.J. Balibar, In vitro biosynthesis of violacein from L-tryptophan by the enzymes VioA-E from Chromobacterium violaceum, Biochemistry 45 (51) (2006) 15444–15457.
[114] P.R. August, T.H. Grossman, C. Minor, M.P. Draper, I.A. Macneil, J.M. Pemberton, K.M. Call, D. Holt, M.S. Osburne, Sequence analysis and functional characterization of the violacein biosynthetic pathway from Chromobacterium violaceum, J Mol Microbiol Biotechnol 2 (4) (2000) 513–519.
[115] Y. Wang, A. Ikawa, S. Okaue, S. Taniguchi, I. Osaka, A. Yoshimoto, Y. Kishida, R. Arakawa, K. Enomoto, Quorum sensing signaling molecules involved in the production of violacein by Pseudoalteromonas, Biosci Biotechnol Biochem 72 (7) (2008) 1958–1961.
[116] X. Zhang, K. Enomoto, Characterization of a gene cluster and its putative promoter region for violacein biosynthesis in Pseudoalteromonas sp. 520P1, Appl Microbiol Biotechnol 90 (6) (2011) 1963–1971.
[117] J.J. Zhang, X. Tang, M. Zhang, D. Nguyen, B.S. Moore, J.E. Davies, Broad--Host-Range expression reveals native and host regulatory elements that influence heterologous antibiotic production in Gram-negative bacteria, mBio 8 (5) (2017) e01291-01217.
[118] E. Goyer, C. Lavaud, G. Massiot, Meroterpenoids? A historical and critical review of this biogenetic determinant, Nat Prod Rep 40 (6) (2023) 1071–1077.
[119] W. Zhang, L. Du, Z. Qu, X. Zhang, F. Li, Z. Li, F. Qi, X. Wang, Y. Jiang, P. Men, Compartmentalized Biosynthesis of Mycophenolic Acid, Proc Natl Acad Sci U S A. 116 (27) (2019) 13305–13310.
[120] N. Sin, L. Meng, M.Q. Wang, J.J. Wen, W.G. Bornmann, C.M. Crews, The anti-angiogenic agent fumagillin covalently binds and inhibits the methionine aminopeptidase, MetAP-2, Proceedings of the National Academy of Sciences 94 (1997) 6099–6103.
[121] T. Bai, Z. Quan, R. Zhai, T. Awakawa, Y. Matsuda, I. Abe, Elucidation and heterologous reconstitution of chrodrimanin B biosynthesis, Org Lett 20 (23) (2018) 7504–7508.
[122] K. Zhang, G. Zhang, X. Hou, C. Ma, J. Liu, Q. Che, T. Zhu, D. Li, A Fungal Promiscuous UbiA Prenyltransferase Expands the Structural Diversity of Chrodrimanin-Type Meroterpenoids, Org Lett 24 (10) (2022) 2025–2029.
[123] D. Das, T.K. Chakraborty, An overview of the recent synthetic studies toward penifulvins and other fenestranes, Tetrahedron Lett 57 (33) (2016) 3665–3677.
[124] N. Ingavat, C. Mahidol, S. Ruchirawat, P. Kittakoop, Asperaculin A, a Sesquiterpenoid from a marine-derived fungus, aspergillus aculeatus, J Nat Prod 74 (7) (2011) 1650–1652.
[125] S.H. Shim, D.C. Swenson, J.B. Gloer, P.F. Dowd, D.T. Wicklow, Penifulvin A: A Sesquiterpenoid-derived metabolite containing a novel dioxa[5,5,5,6]fenestrane ring system from a fungicolous Isolate of penicillium griseofulvum, Org Lett 8 (6) (2006) 1225–1228.
[126] H. Zeng, G. Yin, Q. Wei, D. Li, Y. Wang, Y. Hu, C. Hu, Y. Zou, Unprecedented [5.5.5.6]dioxafenestrane ring construction in fungal insecticidal sesquiterpene biosynthesis, Angew Chem Int Ed Engl 58 (20) (2019) 6569–6573.
[127] Q. Wei, H.C. Zeng, Y. Zou, Divergent biosynthesis of fungal dioxafenestrane sesquiterpenes by the cooperation of distinctive baeyer–villiger monooxygenases and α-ketoglutarate-dependent dioxygenases, ACS Catalysis 11 (2) (2021) 948–957.
[128] R. Geris, T.J. Simpson, Meroterpenoids produced by fungi, Nat Prod Rep 26 (8) (2009) 1063–1094.
[129] Y. Matsuda, I. Abe, Biosynthesis of fungal meroterpenoids, Nat Prod Rep 33 (1) (2016) 26–53.
[130] X. Cao, Y. Shi, X. Wu, K. Wang, B. Wu, Talaromyolides A–D and talaromytin: polycyclic meroterpenoids from the fungus talaromyces sp. CX11, Org Lett 21 (16) (2019) 6539–6542.
[131] X. Cao, Y. Shi, S. Wu, X. Wu, B. Wu, Polycyclic meroterpenoids, talaromyolides E K for antiviral activity against pseudorabies virus from the endophytic fungus Talaromyces purpureogenus, Tetrahedron 76 (30) (2020) 131349.
[132] X. Li, T. Awakawa, T. Mori, M. Ling, D. Hu, B. Wu, I. Abe, Heterodimeric Non-heme Iron enzymes in fungal meroterpenoid biosynthesis, J Am Chem Soc 143 (50) (2021) 21425–21432.
[133] M. Isaka, A. Jaturapat, K. Rukseree, K. Danwisetkanjana, M. Tanticharoen, Y. Thebtaranonth, Phomoxanthones A and B, novel xanthone dimers from the endophytic fungus phomopsis species, J Nat Prod 64 (8) (2001) 1015–1018.
[134] B. Elssser, K. Krohn, U. Flörke, N. Root, H.-J. Aust, S. Draeger, B. Schulz, S. Antus, T. Kurtán, X-ray Structure Determination, Absolute configuration and biological activity of phomoxanthone A, Eur J Org Chem (2005) 4563–4570.
[135] C. Wang, L. Engelke, D. Bickel, A. Hamacher, M.U. Kassack, The tetrahydroxanthone-dimer phomoxanthone A is a strong inducer of apoptosis in cisplatin-resistant solid cancer cells, Bioorg Med Chem 27 (19) (2019) 115044.
[136] M. Frank, H. Niemann, P. Böhler, B. Stork, S. Wesselborg, W. Lin, Proksch, Phomoxanthone A - from mangrove forests to anticancer therapy, Curr Med Chem 22 (30) (2015) 3523–3532.
[137] S.W. Yuan, S.H. Chen, H. Guo, L.T. Chen, H.J. Shen, L. Liu, Z.Z. Gao, Elucidation of the complete biosynthetic pathway of phomoxanthone A and Identification of a Para-Para selective phenol coupling dimerase, Org Lett 24 (16) (2022) 3069–3074.
[138] H. Wei, T. Itoh, M. Kinoshita, N. Kotoku, S. Aoki, M. Kobayashi, Shimalactone A, a novel polyketide, from marine-derived fungus Emericella variecolor GF10, Tetrahedron 61 (33) (2005) 8054–8058.
[139] I. Fujii, M. Hashimoto, K. Konishi, A. Unezawa, H. Sakuraba, K. Suzuki, H. Tsushima, M. Iwasaki, S. Yoshida, A. Kudo, Shimalactone biosynthesis involves spontaneous double bicyclo-ring formation with 8π-6π electrocyclization, Angew Chem Int Ed Engl 59 (22) (2020).
[140] T. Abu-Izneid, A. Rauf, M.A. Shariati, A.A. Khalil, M. Imran, M. Rebezov, M.S. Uddin, M.F. Mahomoodally, K.R.R. Rengasamy, Sesquiterpenes and their derivatives–natural anticancer compounds: An update, Pharmacol Res (2020) 161.
[141] X. Guo, Q. Meng, S. Niu, J. Liu, W. Lin, Epigenetic manipulation to trigger production of guaiane-type sesquiterpenes from a marine-derived spiromastix sp. fungus with antineuroin flammatory effects, J Nat Prod 84 (7) (2021).
[142] Z. Yin, J.S. Dickschat, Engineering fungal terpene biosynthesis, Nat Prod Rep 40 (1) (2023) 28–45.
[143] J. Liu, X. Guo, X. Guo, B. Zhong, T. Wang, D. Liu, H. Jin, J. Ren, Z. Liu, J. Gao, Concise biosynthesis of tropone-containing spiromaterpenes by a sesquiterpene cyclase and a multifunctional P450 from a deep-Sea-derived, J Nat Prod 85 (12) (2022) 2723–2730.
[144] A. Rego, A. Fernandez-Guerra, P. Duarte, P. Assmy, P.N. Leão, C. Magalhães, Secondary metabolite biosynthetic diversity in Arctic Ocean metagenomes, Microb Genom 7 (12) (2021).
[145] C. Loureiro, A. Galani, A. Gavriilidou, M. Chaib de Mares, J. van der Oost, M.H. Medema, D. Sipkema, Comparative metagenomic analysis of biosynthetic diversity across sponge microbiomes highlights metabolic novelty, Conservation, and diversification, MSystems 7 (4) (2022) e00357-00322.