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Prenylated bacterial natural products: occurrence, chemical diversity, biosynthesis and bioactivity

Fan Zhang,† Di Zhao,† Yuzhu Wu† and Lei Li *

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Prenylated bacterial natural products (NPs), catalyzed by cluster-situated prenyltransferases (PTs), exhibit large structural diversity and broad biological activities and have received increasing attention for novel drug discovery and development. This review provides a comprehensive summary of the recent progress in the investigation of prenylated bacterial NPs. To highlight the structural and chemical space of prenylated bacterial NPs, we discuss their occurrence, structures, biosynthesis and bioactivities. Representative examples are summarized with illustrations of PT-catalyzed biosynthetic pathways of distinct NP classes, which present new opportunities for the discovery of novel prenylated bacterial NPs. The mechanistic study of PTs involved in bacterial NP biosynthesis has been outlined, and prenylated bacterial NPs hold great promise as novel biocatalysts for the synthesis of novel drug leads in modern medicine.

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1 Introduction

Bacterial natural products (NPs) have intrinsic chemical diversity, complexity and intriguing biological activities and play important roles in modern medicine, agriculture and

State Key Laboratory of Microbial Metabolism and School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai 200240, China. E-mail: lei.li@sjtu.edu.cn

† Fan Zhang, Di Zhao and Yuzhu Wu contributed equally to this work.

nutrition.[1] Historically, bacterial NPs have been widely developed as antibiotics, immunosuppressants and other pharmaceutical agents. With the advancement of high-throughput sequencing technologies and bioinformatic approaches, numerous bacterial NP-based biosynthetic gene clusters (BGCs) have been discovered, but most of them have not yet been identified.[2,3] These untapped BGCs have provided a rich source for the discovery and development of novel small-molecule drugs to combat global antimicrobial resistance and other health problems.[4–6]

The structural diversity and complexity of bacterial NPs arise from the use of different building blocks in their scaffolds and from tailoring enzyme-mediated distinct post-processing modifications of their scaffolds. These post-modifications mainly include methylation, oxidation, halogenation, glycosylation and prenylation.[7,8] In this review, we focus on prenylated bacterial NPs catalyzed by the prenyltransferase (PT) class of tailoring enzymes situated in bacterial NP BGCs. PTs are widely involved in bacterial primary and secondary metabolism by attaching diverse prenyl moieties to acceptor molecules, which are generally aromatic in nature.[9,10] As a major skeletal diversification approach, prenylation modification of bacterial NPs is generally capable of increasing their lipophilicity with higher affinity to bacterial membranes, thus improving their physiological and pharmacological activities.[8,11] Because of their biological benefits, bacterial prenylated NPs play important roles in cosmetics, food and medicine.[11,12] Moreover, bacterial PTs have been used as biocatalysts for the biosynthesis of novel drug leads and many clinically relevant NPs.[11,12]

Previous reviews reported in the literature have mainly focused on the enzymology and biotechnological applications of PTs in bacteria, fungi, animals and plants.[11–15] In this review, we aim to provide a comprehensive overview of prenylated bacterial NPs, including their cluster-situated PTs, occurrence, structures, biosynthesis and bioactivities. Representative examples are summarized herein with the illustration of PT-catalyzed biosynthetic pathways of different classes of bacterial NPs, such as non-ribosomal peptides (NRPs), ribosomally synthesized and post-translationally modified peptides (RiPPs), polyketides (PKs), diketopiperazines (DKPs) and

Fan Zhang

Fan Zhang is a PhD student at the School of Life Sciences and Biotechnology at the Shanghai Jiao Tong University. Fan earned his B.S. (2020) at the Northwest A&F University and his M.S. (2023) at the Zhejiang University. He is currently pursuing his PhD under the supervision of Prof. Lei Li. His research in the Li lab is aimed at the discovery of antimicrobial peptides with deep learning and bacterial prenylated natural products with bioinformatics tools.

Yuzhu Wu

Yuzhu Wu is a PhD student at the School of Life Sciences and Biotechnology at the Shanghai Jiao Tong University. Yuzhu earned her B.S. in Bioengineering (2021) and her M.S. in Biology (2024) at the Beijing Institute of Technology. She is currently pursuing her PhD under the supervision of Prof. Lei Li. Her research in the Li lab is aimed at the discovery of bacterial non-ribosomal peptides with global genome mining.

Di Zhao

Di Zhao is a PhD student at the School of Life Sciences and Biotechnology at the Shanghai Jiao Tong University. Di earned her B.S. (2020) at the Shandong Agricultural University and her M.S. (2023) at the Northwest A&F University. She is currently pursuing her PhD under the supervision of Prof. Lei Li. Her research in the Li lab is aimed at the discovery of bacterial prenylated natural products with global genome mining.

Lei Li

Lei Li is an associate professor at the School of Life Sciences and Biotechnology at the Shanghai Jiao Tong University. Before joining SJTU, he received his B.S (2011) in Biology at the Sichuan Agricultural University and his PhD (2017) in Microbiology with Prof. Weihong Jiang at the Center for Excellence in Molecular Plant Sciences, Chinese Academy of Sciences. He then carried out postdoctoral research with Prof. Weihong Jiang (2017–2019) and Prof. Sean Brady (2019–2022) at the Rockefeller University. Current research in the Li Lab includes the discovery, biosynthesis and bioengineering of bacterial natural products.

aminocoumarins. Furthermore, this article discusses the biotechnological applications of cluster-situated PTs to develop novel biocatalysts for synthetic biology and global genome mining of novel bacterial prenylated NPs for novel drug lead discovery.

2 Cluster-situated prenyltransferases involved in the biosynthesis of bacterial natural products

As a type of tailoring enzyme, PTs are capable of transferring prenyl units from a donor to an acceptor substrate, thus being involved in secondary bacterial metabolism.[13,14] The catalytic reactions can be divided into two categories: regular and reverse prenylation, in which the primary and tertiary carbons of the prenyl donor are added to the receptor, respectively.[13,14] Considering that the last review on cyanobactin PTs was published in 2023,[15] in this review, we focused on bacteria-derived cluster-situated PTs, with the exception of cyanobactin PTs. Based on structural features, evolutionary origins and solubility, PTs encoded by bacterial NP BGCs can be divided into three classes: (1) soluble DMATS (dimethylallyltryptophan synthase)-type PTs; (2) cytosolic ABBA (α-β-β-α) barrel PTs; (3) intramembrane UbiA-type PTs.[11–14] The sources and catalytic properties of the three bacterial PT types are summarized in Table 1.

DMATS, members of the ABBA-PT superfamily, are mainly responsible for the prenylation of indole derivatives, including Trp, diketopiperazines and Trp-containing peptides (Fig. 1A). Based on their natural substrate specificity, DMATS can be divided to four different groups, including (1) simple Trp derivative C-prenylating DMATS (*i.e.*, IptA and PriB); (2) NRP N-1-prenylating DMATS (*i.e.*, CymD and IlaO); (3) DKP C-prenylating DMATS (*i.e.*, DmtC1 and NozPT); 4) RiPP C-prenylating DMATS (*i.e.*, ComQ, PalQ and WygG)[16–25] (Table 1). Most C-prenylation reactions by DMATS involve regular prenylation, whereas the NRP N1-prenylating process catalyzed by DMATS involves reverse prenylation.[13–15] Interestingly, some DMATS-catalyzed prenylation reactions show large promiscuity when using diverse arrays of prenyl acceptors and donors. For instance, PriB prenylates large, complex small molecules such as daptomycin in addition to its natural small substrate L-tryptophan.[17]

ABBA, as another member of the ABBA-PT superfamily, mainly catalyzes the prenylation of 4-hydrophenylpyruvate (4-HPP), dihydroxynaphthalenes (DHNs), polyketides (PKs), indolactam V and dihydrophenazine (Fig. 1B).[26–32] Based on their natural substrate specificity, ABBA can be divided into three different groups, including (1) DHN ABBA-PTs (*i.e.*, ColQ, NovQ and NphB); (2) indolactam AABA-PTs (*i.e.*, MpnD and TleC); (3) Phenazine AABA-PTs (*i.e.*, EpzP) (Table 1).[26–32] Most ABBA PTs are permissive to diverse prenyl donors and acceptors. For instance, CloQ, NovQ and NphB have been shown to prenylate different receptor substrates, including 4-HPP, DHNs and PKs.[26–29] NphB could also catalyze the prenylation of DHNs at the C-2, C-4, and C-5 positions.[28,29] On the other side, MpnD and TleC display broad donor specificity with a large range of prenyl donors, including dimethylallyl pyrophosphate (DMAPP), geranyl pyrophosphate (GPP) and farnesyl diphosphate (FPP).[30,31]

Transmembrane UbiA-type PTs usually contain a conserved motif ((N/D)DXXD) that binds to diphosphate and Mg^{2+} ions (Fig. 1C).[34] They form an independent branch from soluble DMATS- or ABBA-type PTs and are widely involved in primary and secondary bacterial metabolism.[9,10] For instance, UbiA and MenA are responsible for ubiquinone and menaquinone biosynthesis in bacteria, respectively.[9] XimB is the only UbiA-type PT that is involved in bacterial NP biosynthesis (Table 1).[33] Interestingly, XimB, as a substrate-promiscuous PT, can catalyze prenylation reactions with several prenyl donors with different carbon chain lengths to both the natural substrate 4-hydroxybenzoate (4-HBA) and its derivatives at C-2 and C-3 positions.[33]

3 Prenylated bacterial natural products

3.1 Prenylated bacterial non-ribosomal peptides

Non-ribosomal peptides (NRPs) represent a diverse group of natural peptide compounds synthesized by non-ribosomal peptide synthetases (NRPSs).[35] Among the various chemical modifications of NRPs, prenylation contributes to the creation of novel molecular scaffolds with therapeutic potential.[36] In this article, prenylated bacterial NRPs are categorized into four distinct classes, each with unique structural scaffolds: (1) cyclomarins, ilamycins (also known as rufamycins) and metamarin, which feature a heptapeptide ring; (2) cyclomarazines and rufomyazines, distinguished by their cyclic dipeptide scaffold; (3) krisynomycins A–C, which feature an octapeptide ring; (4) teleocidins and analogs, which incorporate an indole ring.

3.1.1 Cyclomarins, ilamycins and metamarin. Prenylated cycloheptapeptides, such as cyclomarins, ilamycins, metamarin and M10709, are prenylated NRPs with significant biological activity that were discovered from *Streptomyces* species.[36] The four cycloheptapeptides are characterized by a common feature: their prenyl groups are attached to the nitrogen atom of tryptophan residues, followed by further modifications, such as oxidation and epoxidation. Moreover, prenylated cycloheptapeptides incorporate unique non-proteinogenic amino acids, such as β-methoxyphenylalanine and β-hydroxytryptophan.[20,37] Despite variations in the specific amino acid composition, the prenylated cycloheptapeptides exhibit certain shared characteristics. For instance, the tryptophan residues in the cyclomarin series are predominantly β-hydroxylated, while ilamycins contain nitrotyrosine and unsaturated amino acids.[20,37] M10709 and metamarin, discovered in 2010 and 2021, respectively, display subtle structural differences compared with cyclomarins (Fig. 2).[38,39]

For cyclomarins, prenylation modifications typically occur at the early stages of NRP backbone synthesis. Tryptophan residues are first catalyzed by the N1-prenylating DMATS-type PT CymD to accept a prenyl group, forming an *N*-prenylated

Table 1 Examples of characterized prenyltransferases encoded by bacterial natural product biosynthetic gene clusters and their substrate specificities

Enzyme	Gene ID	Organism	Natural products	Substrate	Donor	Region	Ref.
DMATS-type							
Simple Trp deriviate C-prenylating DMATS							
IptA	BAJ07990.1	*Actinacidiphila reveromycinica* SN-593	6-Dimethylallylindole (DMAI)-3-carbaldehyde	Trp derivatives	DMAPP	C-6	16
PriB	ANA09444.1	*Streptomyces* sp. RM-5-8	Prenylated Trp with the unsaturated hexuronic acid	Trp derivatives	DMAPP, GPP, FPP	C-6	17
Non-ribosomal peptide (NRP) N1-prenylating DMATS							
CymD	ABW00334.1	*Salinispora arenicola* CNS-205	Cyclomarins	Trp derivatives	DMAPP	N-1	18 and 19
IlaO	ASX95237.1	*Streptomyces atratus* SCSIO ZH16	Ilamycins	Trp derivatives	DMAPP	N-1	20
Diketopiperazine (DKP) C-prenylating DMATS							
DmtC1	AVP32202.1	*Streptomyces youssoufiensis* OUC6819	Drimentines	Indole DKPs	FPP	C-3	21
NozPT	UYF26245.1	*Nocardiopsis* sp. CMB-M0232	Nocardioazine B	Indole DKPs	DMAPP	C-3	22
Ribosomally synthesized and post-translationally modified peptide (RiPP) C-prenylating DMATS							
ComQ	BEH07154.1	*Bacillus subtilis* subsp. Natto	ComX	Trp derivatives	FPP	C-3	23
PalQ	EJW19250.1	*Paenibacillus alvei* DSM 29	PalX	Trp derivatives	DMAPP	C-3	24
WygG	WP_030301592.1	*Streptomyces katrae* B-16271	Wygwalassin A_1	Trp derivatives	DMAPP	C-5	25
ABBA-type PTs							
DHN AABA-PTs							
CloQ	AAN65239.1	*Streptomyces roseochromogenus*	Clorobiocin	4-HPP, DHNs	DMAPP	C-3	26
NovQ	AAF67510.2	*Streptomyces spheroides*	Novobiocin	4-HPP, DHNs	DMAPP	C-3	27
NphB	AWW43729.1	*Streptomyces* sp. CL190	Naphterpin	4-HPP, DHNs, PKs	DMAPP, GPP, FPP	C-2, C-5	28 and 29
Indolactam AABA-PTs							
MpnD	AFO85455.1	*Marinactinospora thermotolerans*	Pendolmycin	Indolactam V	DMAPP	C-7	30
TleC	BAP27943.1	*Streptomyces blastmyceticus*	Teleocidins	Indolactam V	DMAPP, GPP	C-7	31
Phenazine AABA-PTs							
EpzP	WP_414145683.1	*Acetobacter oryzifermentans*	5,10-Dihydroendophenazine A	Dihydrophenazine	DMAPP	C-9	32
UbiA-type PTs							
Hydroxybenzoate UbiA-PTs							
XimB	AGY49248.1	*Streptomyces xiamenensis* 318	Xiamenmycin	PHB, GBA	FPP, GPP, GGPP	C-2, C-3	33

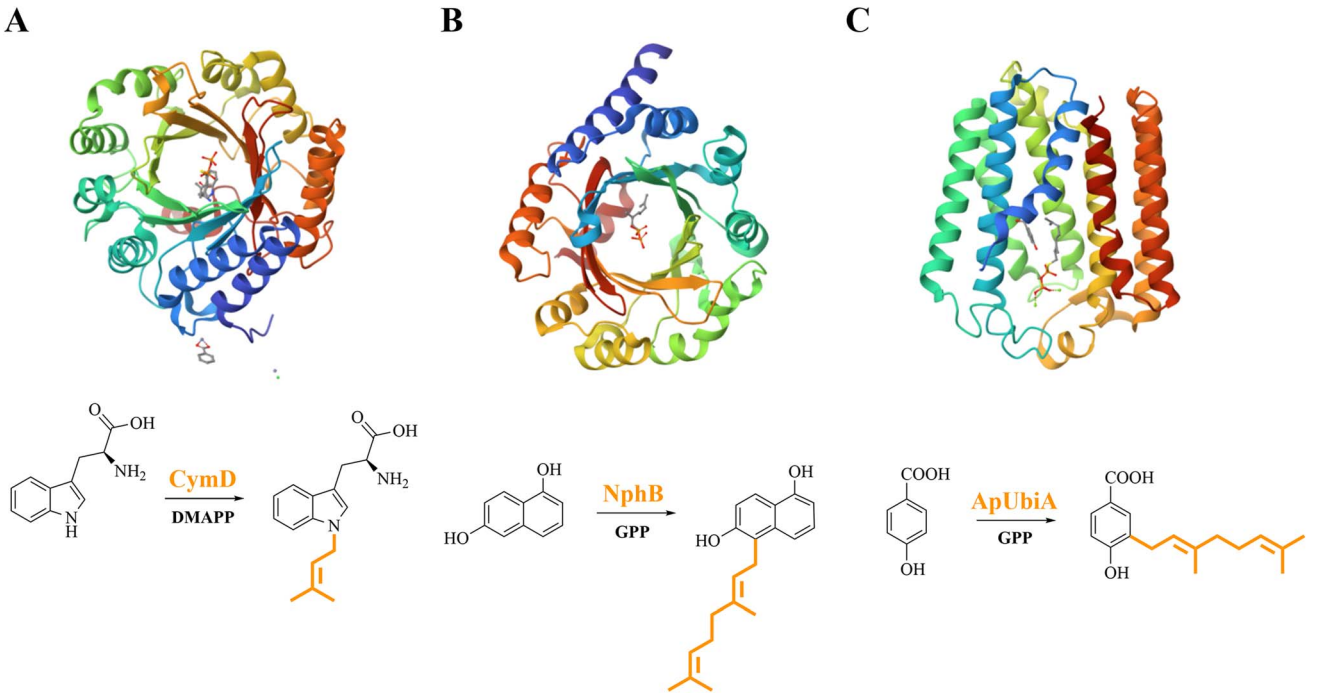

Fig. 1 Crystal structures and catalytic reactions of (A) DMATS-type PT CymD (PDB ID: 6OS6), (B) ABBA-type PT NphB (PDB ID: 7FHB) and (C) UbiA-type PT ApUbiA (PDB ID: 4OD5).

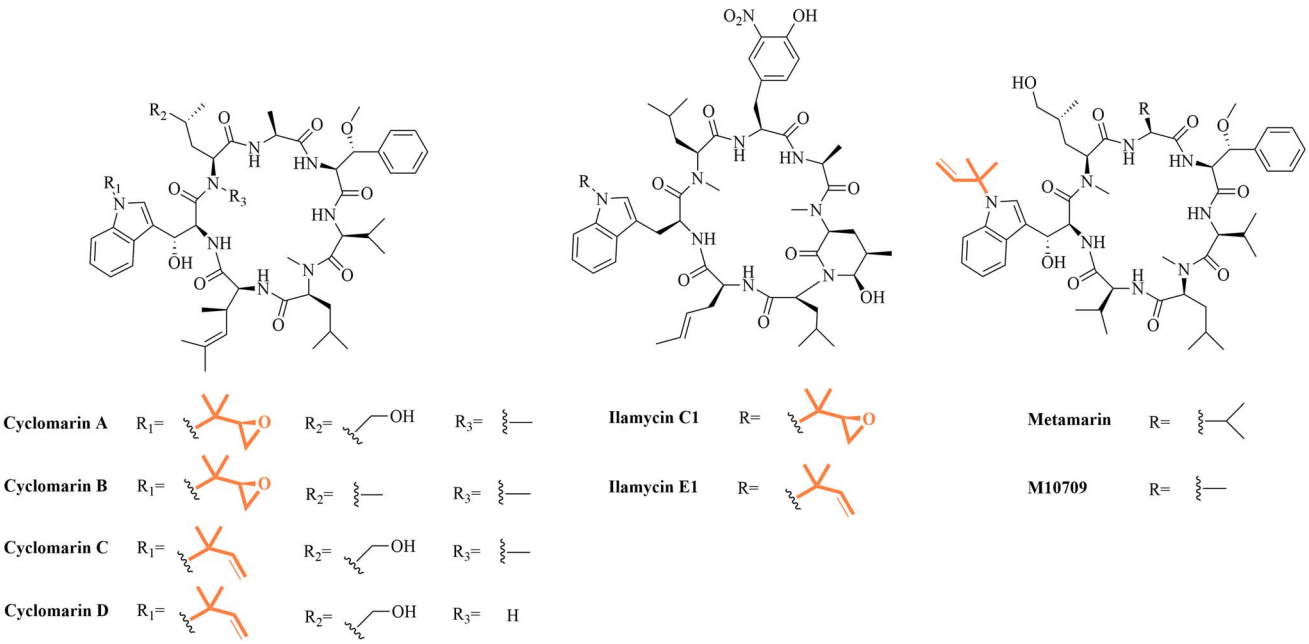

Fig. 2 Structures of cyclomarins, ilamycins, metamarin and M10709.

tryptophan residue.[18,37] The prenylated tryptophan residue serves as the starting unit for peptide chain elongation. Following the classic megasynthase assembly line mechanism, cyclomarin C was finally synthesized by NRPS CymA. In the post-assembly-line modification process, the elongated peptide chain undergoes an epoxidation reaction catalyzed by CymV, converting the prenylated tryptophan residue into epoxides in cyclomarin A (Fig. 3).[37]

Cyclomarins, ilamycins and metamarin exhibit potent antitubercular activity by binding to ClpC1 protein and inducing bacterial cell death.[39–41] Ilamycin E1/E2, with an MIC of 9.8 nM, is 30 times more potent than rifampin against *Mycobacterium tuberculosis*.[20] These compounds also show antimalarial activity

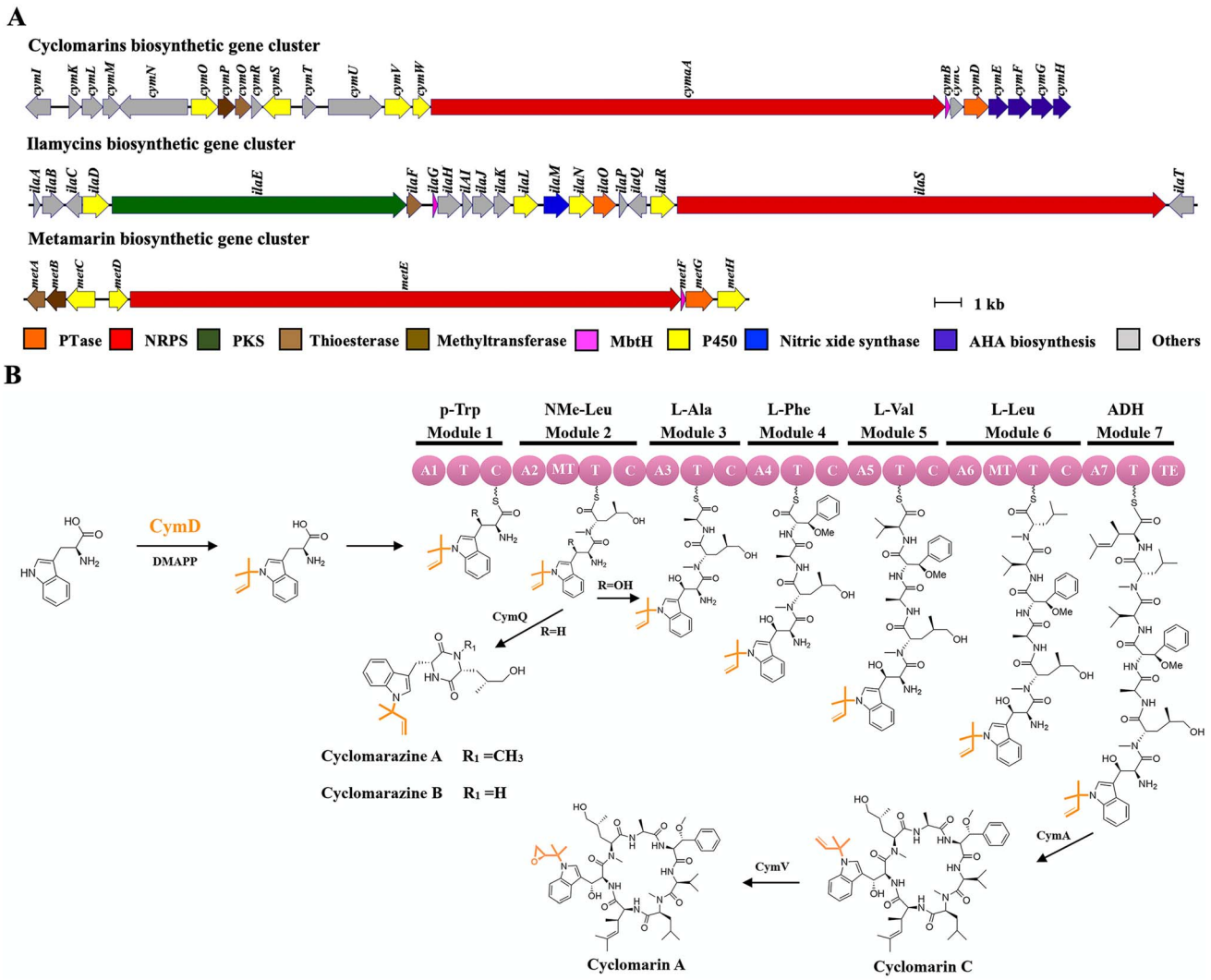

Fig. 3 Biosynthetic gene clusters and pathways of cyclomarin, ilamycin and metamarin. (A) Biosynthetic gene clusters of cyclomarin, ilamycin and metamarin; (B) biosynthetic pathways of cyclomarins and cyclomarazines.

against *Plasmodium falciparum* by inhibiting PfAp3Aase and hindering parasite growth.[42] In addition, cyclomarins, particularly cyclomarin A, exert strong anti-inflammatory and cytotoxic effects.[37]

3.1.2 Cyclomarazines and rufomyazine. Cyclomarazines and rufomyazine are another class of dipeptides synthesized by NRPS with prenyl modifications and isolated from *Salinispora arenicola* CNS-205 and *Streptomyces* sp. MJU3502, respectively.[37,43] Compared with cycloheptapeptides such as cyclomarins and ilamycins, these dipeptides contain fewer amino acids and have simpler structures, but they still exhibit diverse biological activities, including antibacterial and anti-inflammatory effects.[37,43] Similar to the prenylated cycloheptapeptides, these prenylated dipeptides share the common feature of containing an *N*-(1,1-dimethyl-1-allyl)-tryptophan residue (Fig. 4). This prenyl modification structurally distinguished these compounds from typical tryptophan derivatives. Additionally, the tryptophan residues of prenylated dipeptides

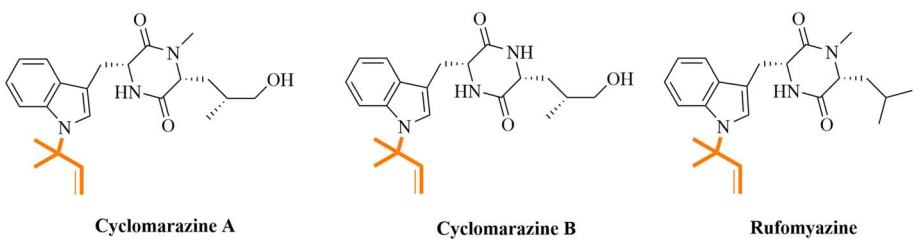

Fig. 4 Structures of cyclomarazines and rufomyazine.

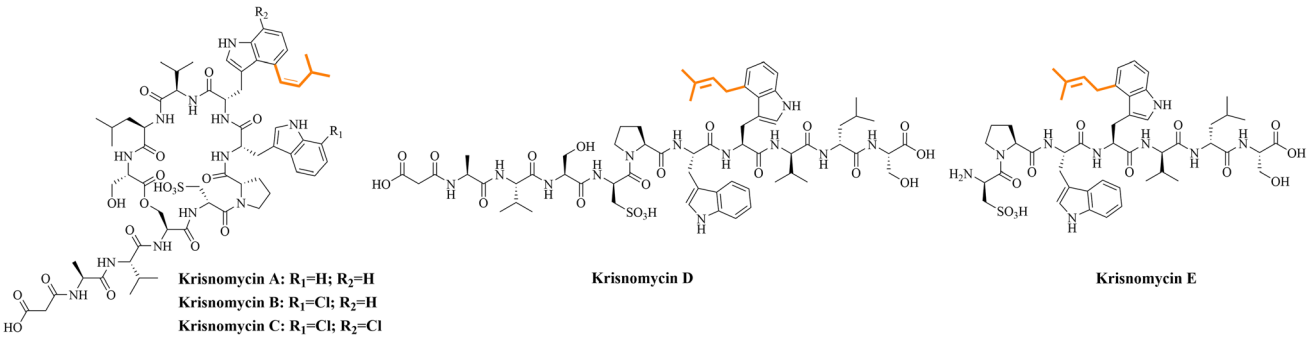

Fig. 5 Structures of krisynomycins A–E.

are usually not β-hydroxylated, and the isoprenyl groups lack certain oxidative modifications compared with prenylated cycloheptapeptides.[37,43,44]

Similar to the biosynthesis of cyclomarins, the prenylation of cyclomarazines typically occurs on the tryptophan residue of the precursor, forming *N*-(1,1-dimethyl-1-allyl)-tryptophan. This process is catalyzed by the N1-prenylating DMATS-type PT enzyme CymD.[37] Subsequently, CymQ facilitates the incorporation of the *N*-prenylated tryptophan residue with NMe-Leu, leading to the formation of cyclomarazines (Fig. 3).[37] Cyclomarazines A and B demonstrate moderate antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), with MIC values of 18 and 13 μg mL^{-1}, respectively.[37] Rufomyazine shows antitubercular activity with an MIC of approximately 5 μM.[43]

3.1.3 Krisynomycins. The cyclopeptide krisynomycins A, B and C were isolated from *Streptomyces fradiae* MA7310 and possess unique prenylation and chlorination modifications.[45] Two linear peptides krisynomycins D and E were later isolated from *Streptomyces tauricus* NA06920.[46] Unlike prenylated cycloheptapeptides such as cyclomarins and ilamycins, krisynomycins contain a unique 7-chloro-4-prenyltryptophan moiety,

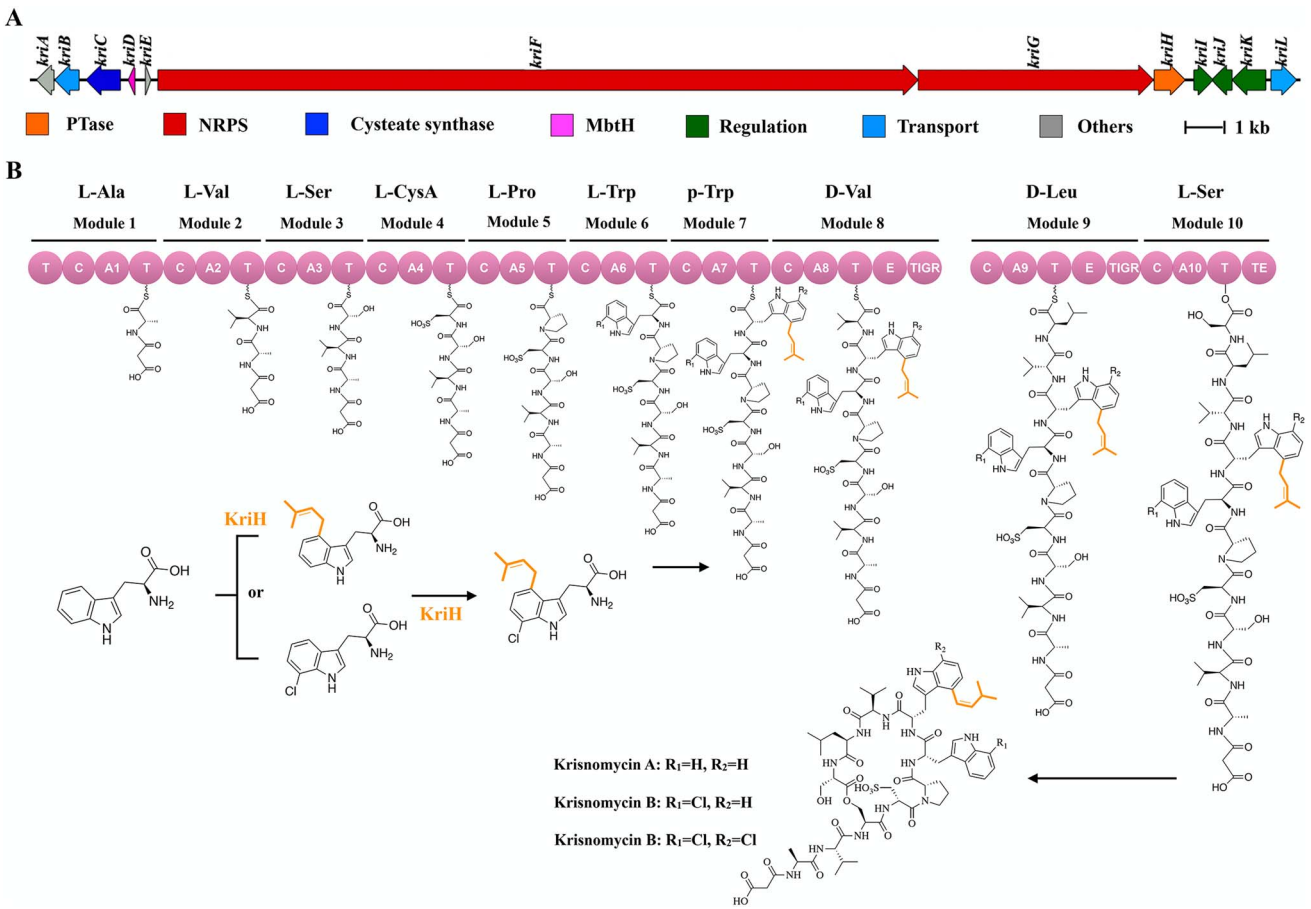

Fig. 6 Biosynthetic gene cluster (A) and pathway (B) of krisynomycins A–C.

a structural unit unprecedented in natural products, which is crucial for their bioactivity. Meanwhile, their prenylation modification occurs at the C-4 position of the tryptophan residue rather than at the N-1 position in the above prenylated cycloheptapeptides (Fig. 5).[45–47]

For krisynomycins, prenylation and chlorination modifications typically occur at the early stages of NRP backbone synthesis. In this process, the C-prenylating DMATS-type PT KriH is the key enzyme responsible for the prenylation at the C-4 position of the tryptophan residue.[47] The prenylated and/or chlorinated tryptophan residues are then used as building blocks for peptide chain elongation. Following the classic megasynthase assembly line mechanism, krisynomycins are finally synthesized by the NRPS KriF and KriG (Fig. 6).[47]

The primary bioactivity of krisynomycins lies in their ability to enhance the antibacterial efficacy of imipenem against MRSA. Although krisynomycins exhibit relatively weak antibacterial activity (with MIC values for krisynomycins B and C exceeding 128 μg mL^{-1}, and krisynomycin A having an MIC of 16–32 μg mL^{-1}), they significantly potentiate the effect of imipenem when used in combination, especially at lower doses.[45,47] This synergistic effect is achieved by affecting the synthesis of MRSA cell walls and increasing antibiotic penetration.[45,47] Furthermore, the chlorination pattern and prenylation modifications of krisynomycins play crucial roles in their bioactivity, with variations in the modification sites directly affecting their ability to enhance antibiotic efficacy.[47]

3.1.4 Teleocidins and analogs. Teleocidins were first isolated from *Streptomyces mediocidicus* and were initially identified as toxic substances with harmful effects on aquatic organisms.[48] Teleocidins feature a nine-membered lactam core derived from L-Trp and L-Val as well as prenyl groups and can be categorized into three subclasses based on their prenylation modifications: (1) teleocidins A-1, A-2 and their analog 7-geranylindolactam-V, which feature a linear C-10 group; (2) teleocidins B-1 to B-4, olivoretins A to E and blastmycetin E, which contain a cyclic C-11 group; (3) pendolmycins, which have dimethylallyl groups.[48–51] Compared with prenylated NRPs such as cyclomarins and cyclomarazines, teleocidins exhibit a more unique reverse geranyl modification at the C-7 position of the indole ring (Fig. 7).

The biosynthesis of teleocidins involves two primary steps. Initially, the process is initiated by NRPS, using NMe-Val and L-Trp as precursors to form the lactam backbone.[52,53] Subsequently, prenyl groups (such as geranyl and dimethylallyl groups) are attached to the lactam backbone by indolactam AABA-type PTs such as MpnD and TleC, thus generating pendolmycin, teleocidin A-1 or geranylindolactam V. Additionally, teleocidin A-1 undergoes further cyclization to form teleocidin B-4 (Fig. 8).[54,55]

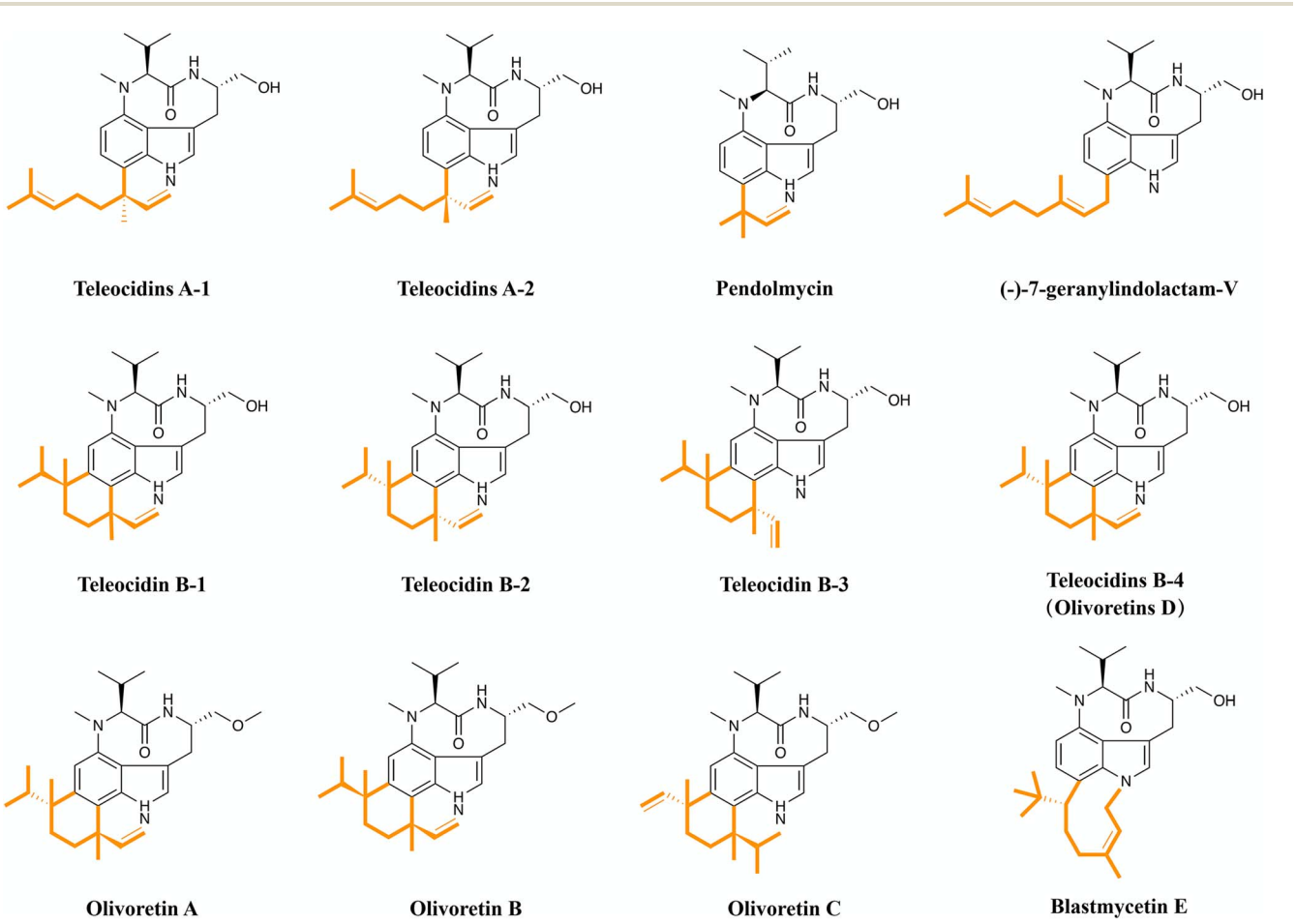

Fig. 7 Structures of teleocidin-family bacterial natural products.

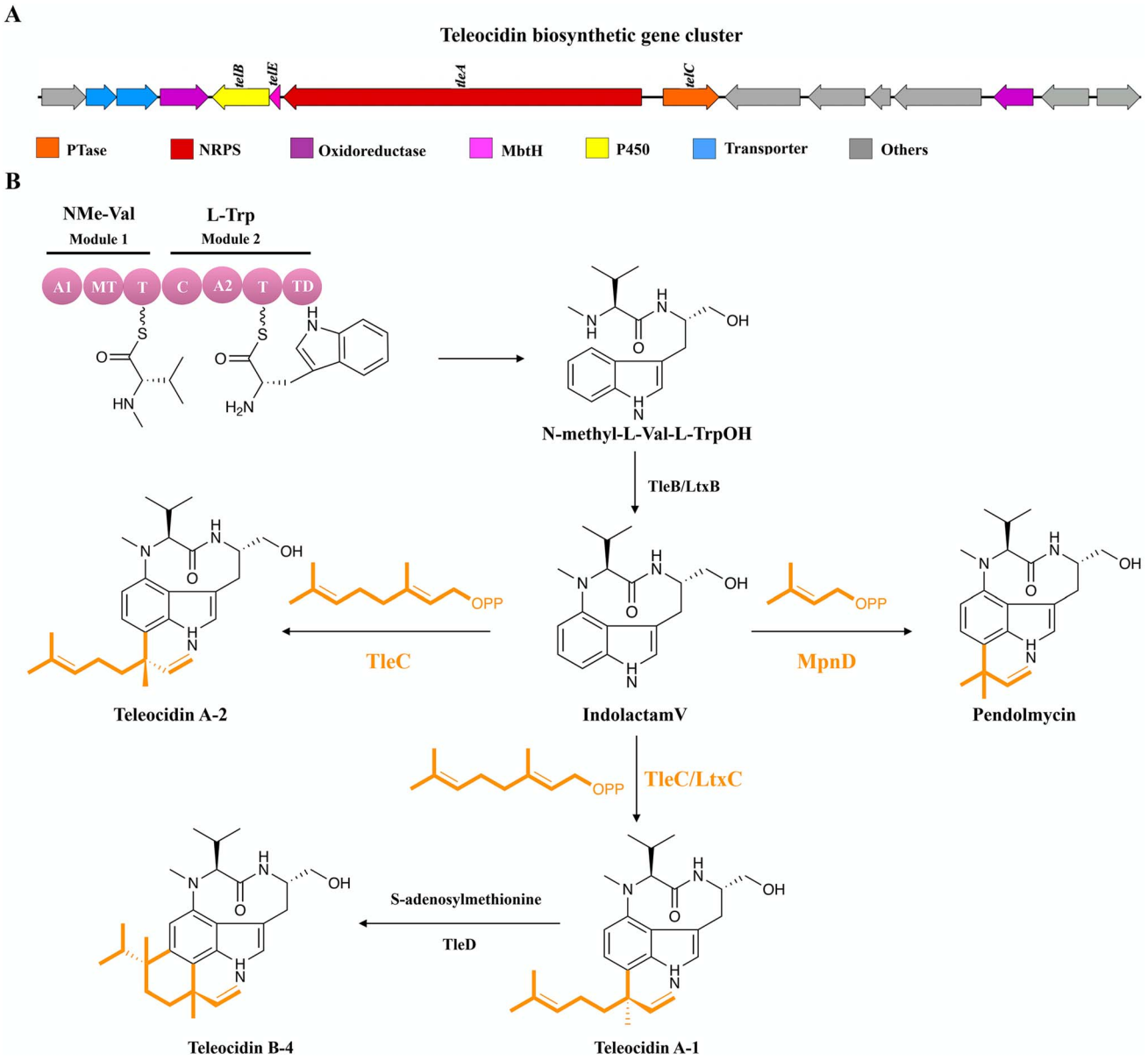

Fig. 8 Biosynthetic gene cluster (A) and pathway (B) of teleocidins.

Teleocidins, particularly teleocidin A-1 and teleocidin A-2, exhibit potent activation of protein kinase C (PKC), thereby promoting tumor cell proliferation and have been implicated in conditions such as skin inflammation, diabetes and cardiovascular diseases.[55,56] The prenyl modifications are crucial for enhancing their binding affinity to PKC, with longer isoprenyl chains significantly boosting their bioactivity.[57,58] This increase in bioactivity enhances their potential in cancer treatment and disease modulation.

3.2 Prenylated ribosomally synthesized and post-translationally modified peptides from bacteria

Ribosomally synthesized and post-translationally modified peptides (RiPPs) were initially isolated from Gram-positive bacteria and later identified in other bacterial species.[59,60] RiPPs comprise a substantial group of peptides with broad bioactivities.[61] Prenylation modifications play a significant role in enhancing the structural diversity and biological activities of RiPPs.[62] The most distinctive feature of prenylated RiPPs is the prenylation of specific amino acids (*i.e.*, tryptophan). Upon prenylation, amino acid side chains may undergo cyclization or other stereochemical transformations, leading to significant alterations in the spatial structure and biological activity of RiPPs.[7,62]

For ComX RO-E-2 and ComX RO-C-2 isolated from *Bacillus subtilis*, the tryptophan C-3 positions were modified by the geranyl and farnesyl groups, respectively.[63,64] PalX, produced by *Paenibacillus alvei,* undergoes a simpler isoprenyl chain extension at the C-3 position, whereas wygwalassin A1, discovered in *Streptomyces katrae,* carries dimethylallyl modifications and exhibits tyrosine dehydrogenation (Fig. 9).[24,25]

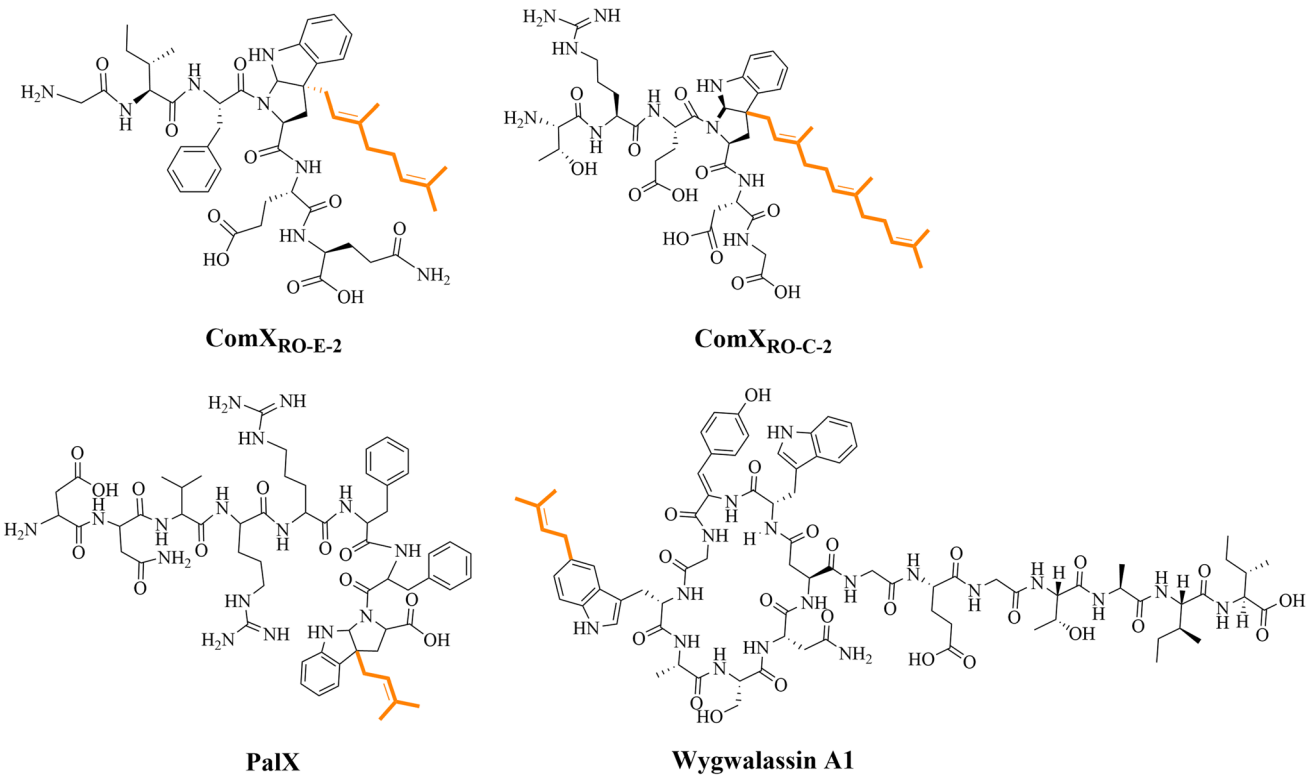

Fig. 9 Structures of ComX, PalX and wygwalassin A1.

The biosynthesis of ComX, PalX and Wygwalassin A1 involves two critical post-translational modification steps. For ComX, the process begins with prenylation of the tryptophan C-3 position catalyzed by the C-prenylating DMATS-type PT ComQ, followed by intramolecular cyclization to produce the compound.[23] Similarly, PalX undergoes prenylation at the C-3 position, mediated by the isoprenoid synthase-like enzyme PalQ, with subsequent cyclization or related modifications completing the structure.[24] The biosynthesis of wygwalassin A1 is more intricate, involving two sequential steps: dimethylallylation of the tryptophan C-5 position catalyzed by WygG, followed by dehydrogenation of tyrosine, potentially mediated by WygH or WygF, to form the rare α, β-dehydrotyrosine residue (Fig. 10).[25]

The primary biological activity of ComX lies in its role as a quorum-sensing signaling molecule that regulates bacterial gene expression. The isoprenylated side chain enhances ComX's specificity and binding affinity to its receptor.[63,64] Until now, no biological activities have been reported for PalQ and wygwalassin A1.[24,25]

3.3 Prenylated diketopiperazine derivatives from bacteria

Diketopiperazines (DKPs) are a class of bioactive cyclic dipeptides typically synthesized by cyclodipeptide synthases (CDPS) or NRPS.[65,66] These compounds are further modified by various tailoring enzymes, including PTs and cytochrome P450 s, which contribute to their structural complexity and diverse bioactivities. The core structure of DKP consists of cyclic dipeptides typically containing tryptophan (Trp) residues, with prenyl groups commonly attached at positions such as C3, C5 and N1.[67,68] These prenylated compounds are characterized by intricate prenyl modifications, including the prenyl, farnesyl and geranyl groups. Such modifications are typically found at C-3 or N-1 of the tryptophan residue, although they can also form more complex structural units *via* indirect bridging.

Nocardioazines A and B, derived from *Nocardiopsis* sp. CMB-M0232, displays a unique C3 prenyl modification in a tryptophan-based bis-amino structure.[67,68] Drimentines A, B, C and I are characterized by the presence of a sesquiterpene-derived drimane moiety and a C-3/N-1 double prenylation, which together form a seven-membered ring structure.[69,70] Indotertines A and B, similar to drimentines, consist of a Trp-Val dipeptide with a drimane group at C-2 and C-3, forming a pentacyclic 6/5/6/6/6 structure. Streptoazines A, griseocazines A1 and A3, from *Streptomyces leeuwenhoekii* and *Streptomyces griseocarneus*, respectively, feature prenyl modifications at C-3, enhancing anticancer activity.[69] Griseocazines B and C1 feature complex cyclic structures formed by farnesyl or geranyl modifications at C-3 and N-1. Griseocazine D2, with its farnesyl modification, shows notable neuroprotective effects (Fig. 11).[71] These prenyl modifications improve the molecular stability, target binding affinity, and introduce novel cyclic structures, significantly enhancing the structural diversity of DKPs and their potential for drug development.

The biosynthesis of prenylated DKP derivatives generally proceeds in two main stages: initial synthesis of the core cyclic

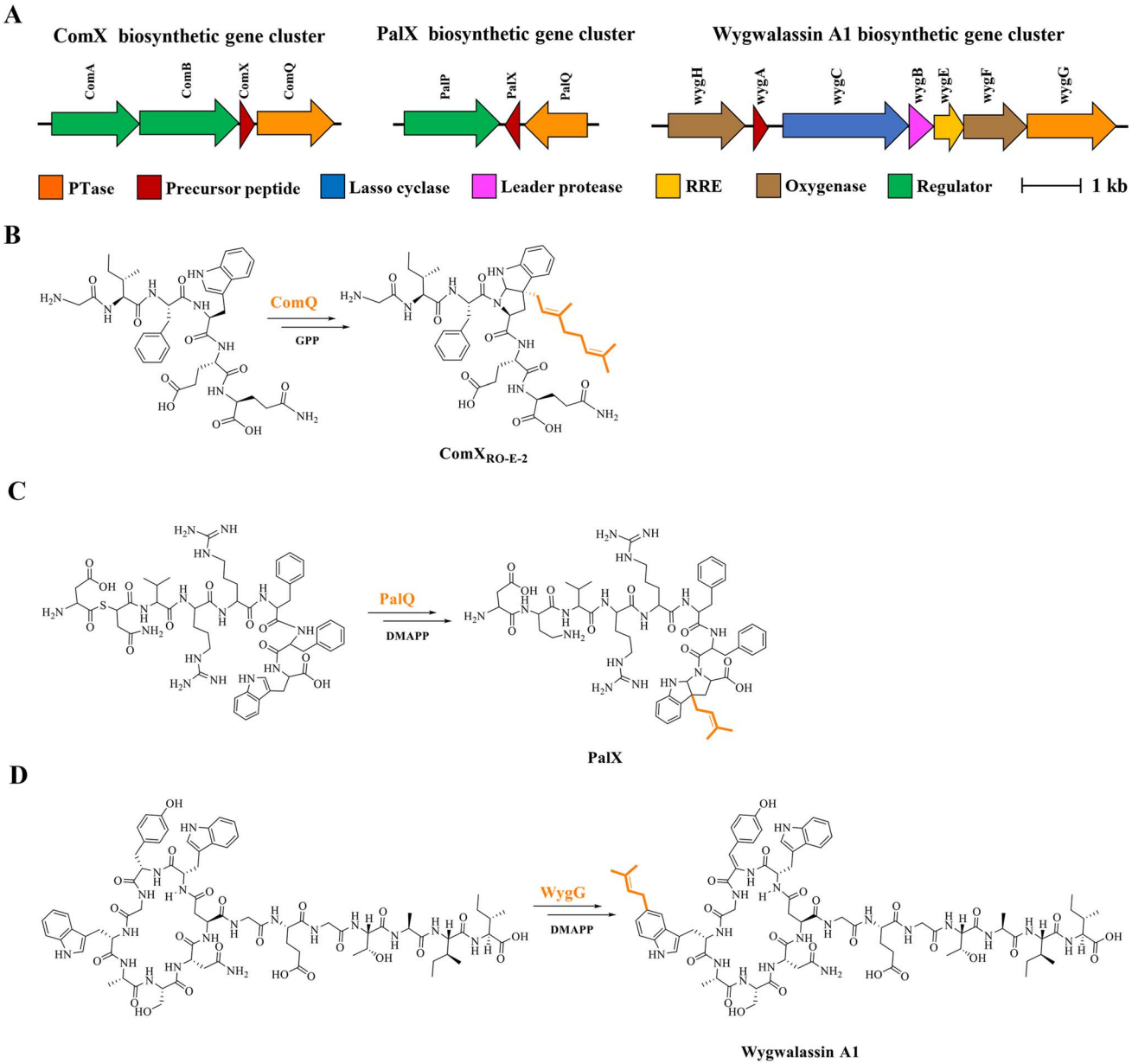

Fig. 10 Biosynthetic gene clusters and pathways of ComX, PalX and wygwalassin A1. (A) Biosynthetic gene clusters of ComX, PalX and wygwalassin A1; (B) biosynthetic pathway of ComX; (C) biosynthetic pathway of PalX; (D) biosynthetic pathway of wygwalassin A1.

dipeptide scaffold followed by prenylation. For compounds such as nocardioazines, streptoazine, and griseocazines, the cyclic dipeptide (*e.g.*, cyclo-L-Trp-L-Trp) is first synthesized by CDPS.[65,66] The dipeptide core is then further modified by the C-prenylating DMATS PTs, including NocZ, SasB, GczB and GczC.[66–73] These enzymes catalyze the attachment of prenyl groups, typically at the C-3 or N-1 positions of the cyclic dipeptide, resulting in the formation of bioactive compounds like nocardioazine B, streptoazine A and various griseocazines (*e.g.*, griseocazines A1, B, C1 and D1). For nocardioazines, the cyclic dipeptide is initially synthesized and then undergoes prenylation and methylation by PTs and P450, respectively, ultimately yielding bioactive nocardioazine A.[67] Notably, except for DMAPP, GPP or FPP is often incorporated in the biosynthesis of griseocazines, resulting in dual prenylation at distinct positions (Fig. 12).[71]

Although nocardioazines are not characterized by antimicrobial properties, they are known to inhibit P-glycoprotein, a key transporter protein implicated in multidrug resistance, thereby offering considerable potential for anticancer therapeutic applications.[67] In contrast, griseocazines and drimentines exert anticancer effects primarily through their effects on cell migration and inhibition of tumor cell proliferation.[69,71] Notably, griseocazines, particularly griseocazine D1, exhibit potent neuroprotective activity within a concentration range of 1.55–77.6 μM.[71]

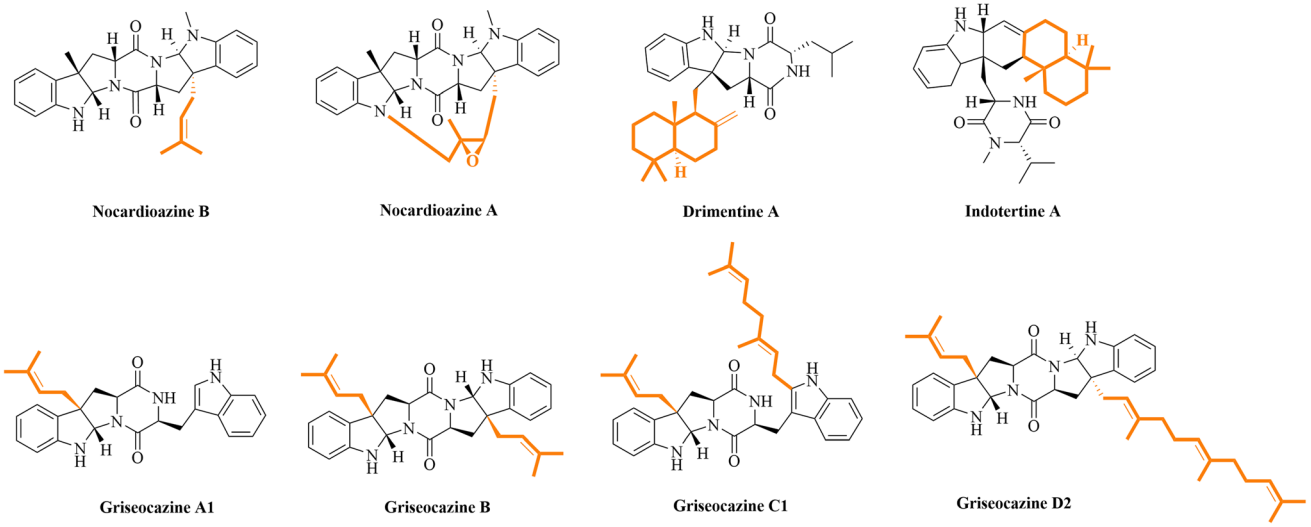

Fig. 11 Structures of prenylated diketopiperazine derivatives from bacteria.

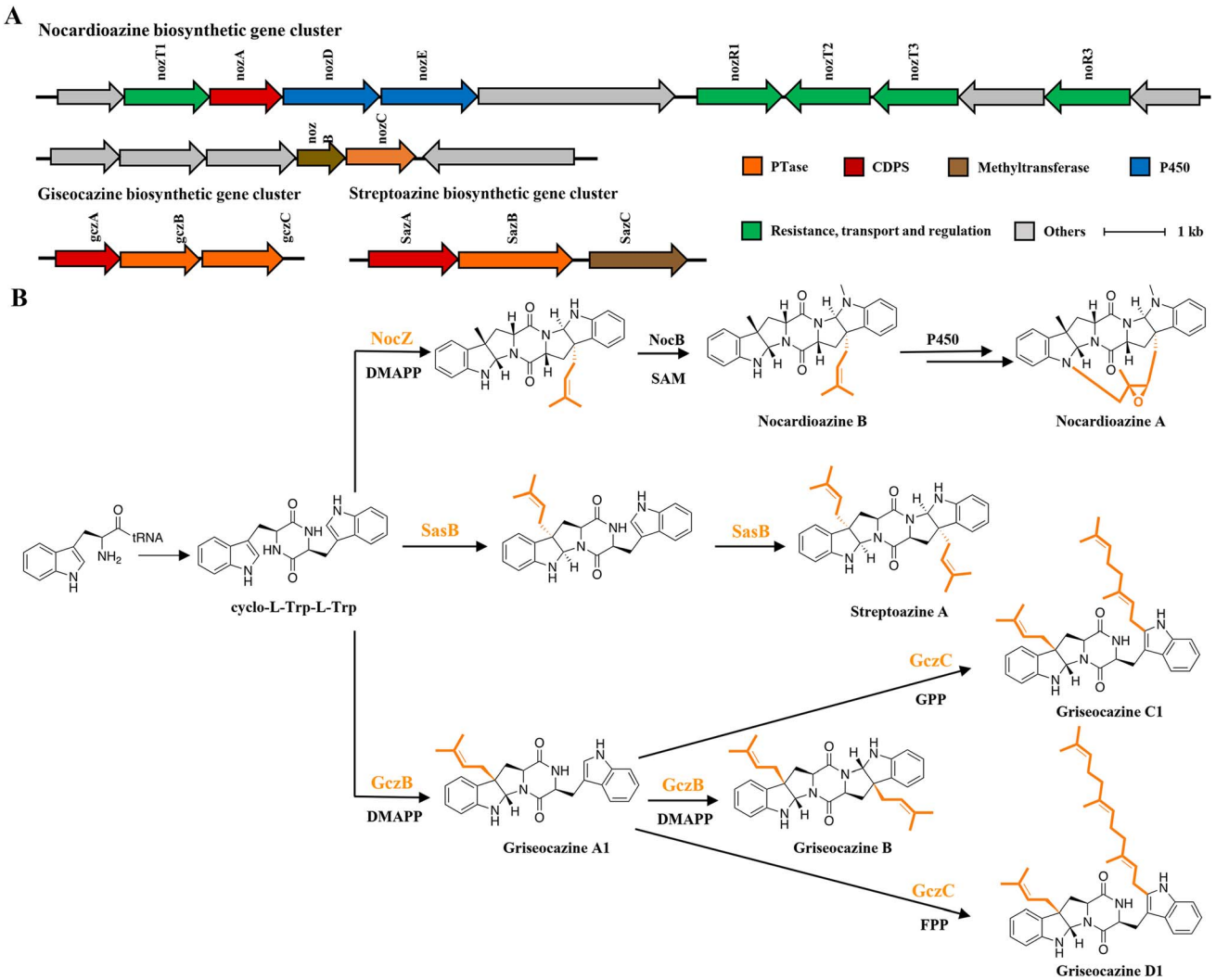

Fig. 12 Biosynthetic gene clusters (A) and pathways (B) of nocardioazines, griseocazines and streptoazines.

3.4 Prenylated bacterial polyketides

3.4.1 Prenylated flavonoids. Flavonoids represent a significant class of natural products that were initially studied in plants, such as isoflavones extracted from soybeans and other legumes.[74,75] In recent years, prenylated flavonoids derived from microbial sources, particularly actinomycetes, have gained increasing attention.[76–79] C-6-prenylated flavonoids typically introduce a prenyl group at the C-6 position, as seen in 6-prenyl-4′-methoxy-5,7-dihydroxyflavanone, which was first isolated from *Streptomyces* sp. G248 and exhibits notable anti-tuberculosis activity.[78] The distinct placement of the prenyl group leads to variations in biological effects, with C-8-prenylated compounds potentially exhibiting unique antibacterial and anticancer properties compared to their C-6 counterparts.[76–79] 7,3′-*O*-diprenylated flavonoids, which feature prenyl groups at both the 7 and 3′ positions, tend to show improved antimicrobial activity.[76] In addition, flavonoids modified with lavandulyl groups, such as lavandulyl-flavanones and lavandulyl-chalcones, typically feature a lavandulyl group at specific positions along the flavonoid backbone (Fig. 13).[79]

Prenylation significantly enhances the biological activity of flavonoid compounds, with its effects varying depending on the modification site and the type of prenyl group. C-6- and C-8-prenylated flavonoids exhibit prominent antibacterial activity, particularly against *Mycobacterium tuberculosis*, with IC_{90} values ranging from 6 to 11 μg mL^{-1}.[78] Flavonoids modified with lavandulyl groups exert remarkable broad-spectrum antimicrobial effects, effectively against both Gram-positive and Gram-negative bacteria, as well as certain fungi.[77–79]

3.4.2 Furaquinocins. Furaquinocins have attracted significant scientific interest because of their distinctive polycyclic structure and prenylation modifications.[80] Since their initial discovery, over ten prenylated furaquinocins have been identified, including furaquinocins, JBIR-136, PI-220, marfuraquinocins and fumaquinone.[81–90] The core structure of furaquinocins is a tricyclic naphthofuran-6,9-dione backbone characterized by modification of the prenylated side chain. The prenylation modifications commonly observed in these compounds include linear, cyclic, and oxygen-containing variants. Furaquinocins A–H exhibit various types of prenylation at the C-6 position, with further modifications such as hydroxylation or cyclization.[81–85] For example, furaquinocin A contains a linear prenyl group, whereas the prenyl side chain of furaquinocin E features a conjugated double bond structure.[81,82] Furaquinocin G, on the other hand, contains a cyclic hemiacetal.[82] Additionally, JBIR-136, isolated from *Streptomyces* sp. 4963H2 lacks a methyl group at C-3 compared with furaquinocin D and features a reduced scaffold.[86] In PI-220, the prenyl group is modified with a hydroxyl group at C-13 and a conjugated double bond.[87] Other compounds, such as neomarinone and marfuraquinocins A–D, display a cyclized C-15 prenyl side chain (Fig. 14).[88–90] These compounds exhibit a broad range of prenylation modifications, from simple linear structures to complex cyclic ones, highlighting their substantial structural diversity.

The biosynthesis of furaquinocins proceeds through a polyketide pathway, in which the core scaffold is first synthesized and subsequently coupled with a prenyl group.[91] For instance, in the case of furaquinocin A, its core structure, 1,3,6,8-tetrahydroxynaphthalene (THN), is initially constructed by the type III polyketide synthase Fur1. The THN skeleton is then oxidized to generate flaviolin by the monooxygenase Fur2 and further modified by methyltransferases Fur4 or Fur6. Then, a prenyl group is attached to the methoxy- and methoxyhydroxy-

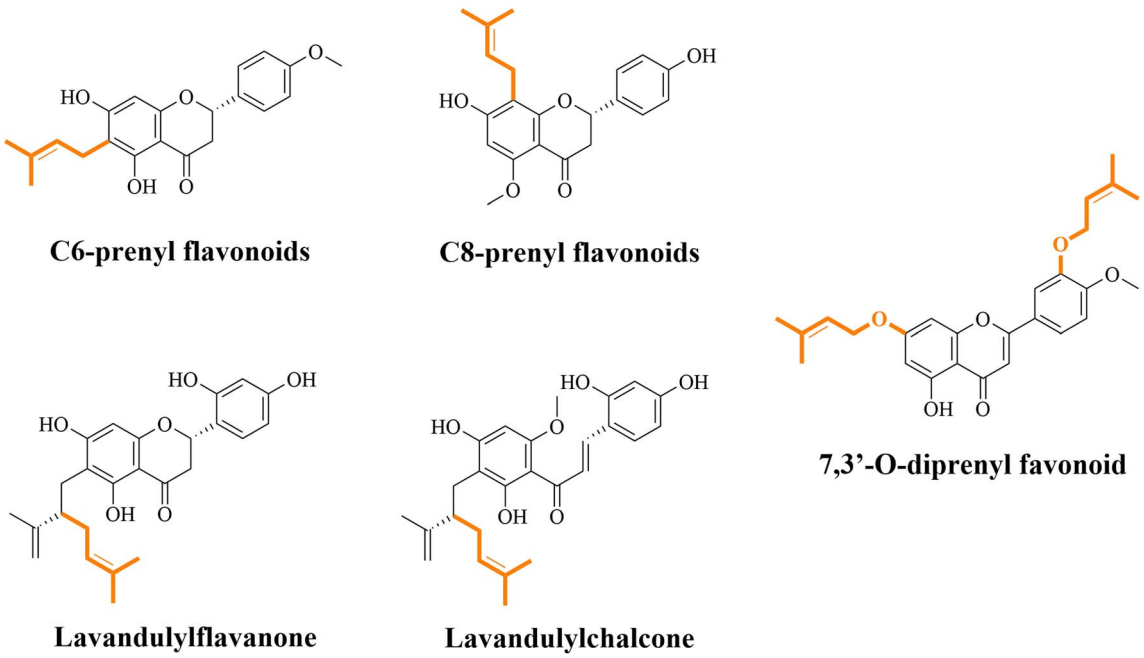

Fig. 13 Structures of prenylated flavonoids.

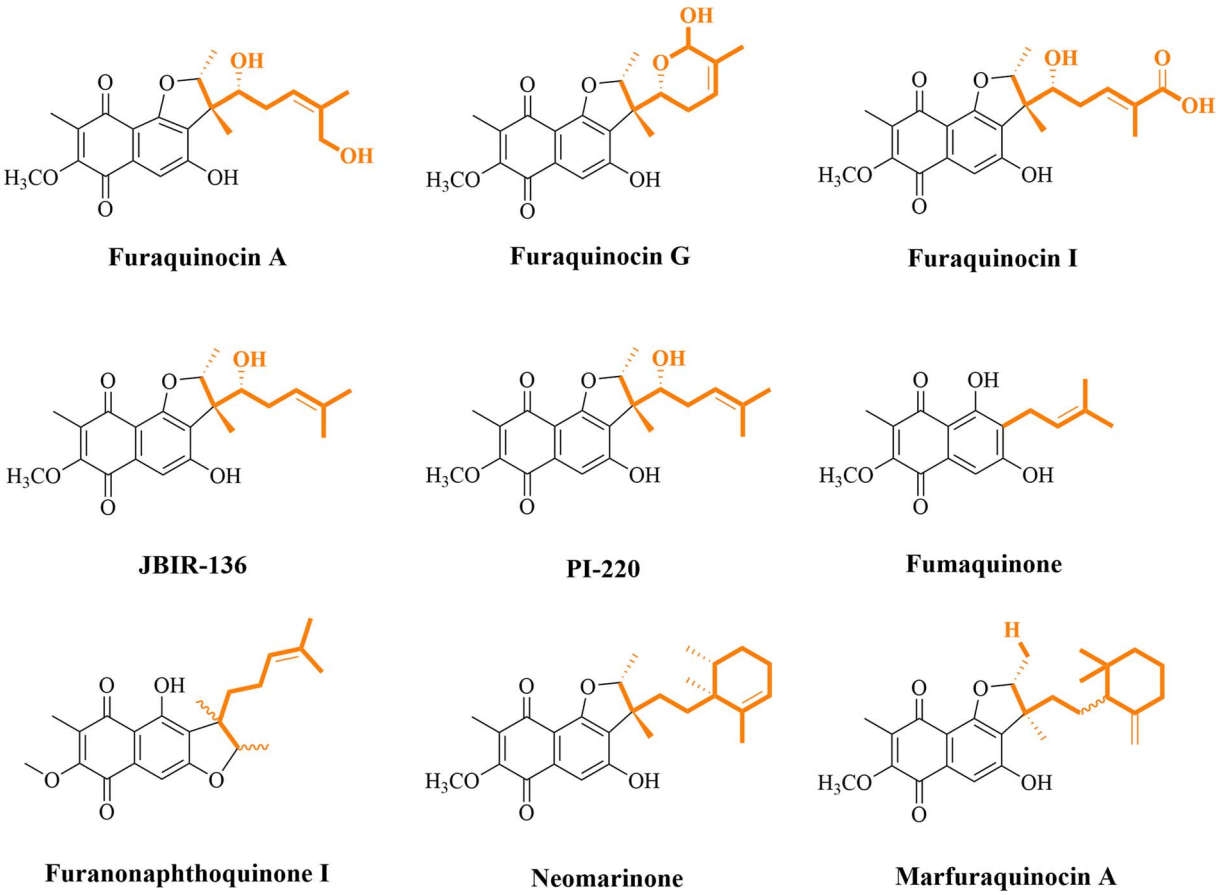

Fig. 14 Structures of furaquinocins.

modified core of 2-menthoxy-3-methylflaviolin by the C-6-trans-PT Fur7, resulting in the intermediate 6-prenyl-2-menthoxy-3-methylflaviolin.[92,93] This intermediate can undergo a series of steps to produce furaquinocins A.[91] For furaquinocin G and JBIR-136, the prenylation process involves more complex cyclization and oxidation reactions.[83,86] Unlike the linear prenylation observed in other compounds, the prenyl groups in neomarinone and marfuraquinocins are thought to originate from the sesquiterpene pathway before being incorporated into the core scaffold, suggesting potential flexibility in the sequence and pattern of prenylation modifications (Fig. 15).[88,94]

Furaquinocins A, B, C and H effectively inhibit the growth of HeLa and B16 melanoma cells, with furaquinocin H exhibiting IC_{50} values of 0.19 μM and 0.52 μM, respectively.[81,82,85] Marfuraquinocins A–D demonstrate significant inhibitory effects against *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis*, whereas furanonaphthoquinone I stands out for its potent inhibition of MRSA and *Helicobacter pylori*, with an MIC as low as 0.1 μg mL^{-1}.[88,95] The bioactivity of these compounds is primarily influenced by their prenylation modifications. For example, cyclic prenyl groups, as observed in neomarinone, enhance hydrophobicity, which in turn improves membrane permeability and target binding efficiency.[90,96] In contrast, prenyl groups with conjugated double bonds or hydroxylation, such as in furaquinocin E, significantly increase selective toxicity toward cancer cells by modulating electron transfer properties.[82]

3.4.3 Merochlorins. Merochlorins A–F are a class of polyketide natural products derived from *Streptomyces* sp. CNH-189.[97–99] Merochlorins feature a polyketide-terpene hybrid backbone, but the mode of prenylation and subsequent modifications result in significant structural variations. Merochlorins A and B differ in the connectivity of the prenyl group at the C-4 position, forming bicyclic octanedione and 6-5-5 tricyclic systems, respectively.[97,100] In detail, merochlorins A contains a benzo-bicyclo [3.2.1]-octadione ring system with a propan-2-ylidenecyclopentane moiety, whereas merochlorin B has a propan-2-ylidenecyclopentane-containing 6/5/5 fused tricycle with a chloroenone group.[100] In contrast, merochlorins C and D feature a sesquilavandulyl prenyl group attached at the C-3 position of the naphthoquinone backbone and further form a large 15-membered ring in the case of merochlorin C.[97] Merochlorins E and F are cyclic variants of merochlorin D, with the C-15 group exhibiting a complex three-dimensional configuration.[99] Intriguingly, meroindenon is significantly different from merochlorins because of its benzoin-dione core and is speculated to arise *via* a ring contraction reaction (Fig. 16).[99]

The biosynthesis of merochlorins is initiated by the independent synthesis of a polyketide backbone and a prenylated precursor, which are then condensed to form the common

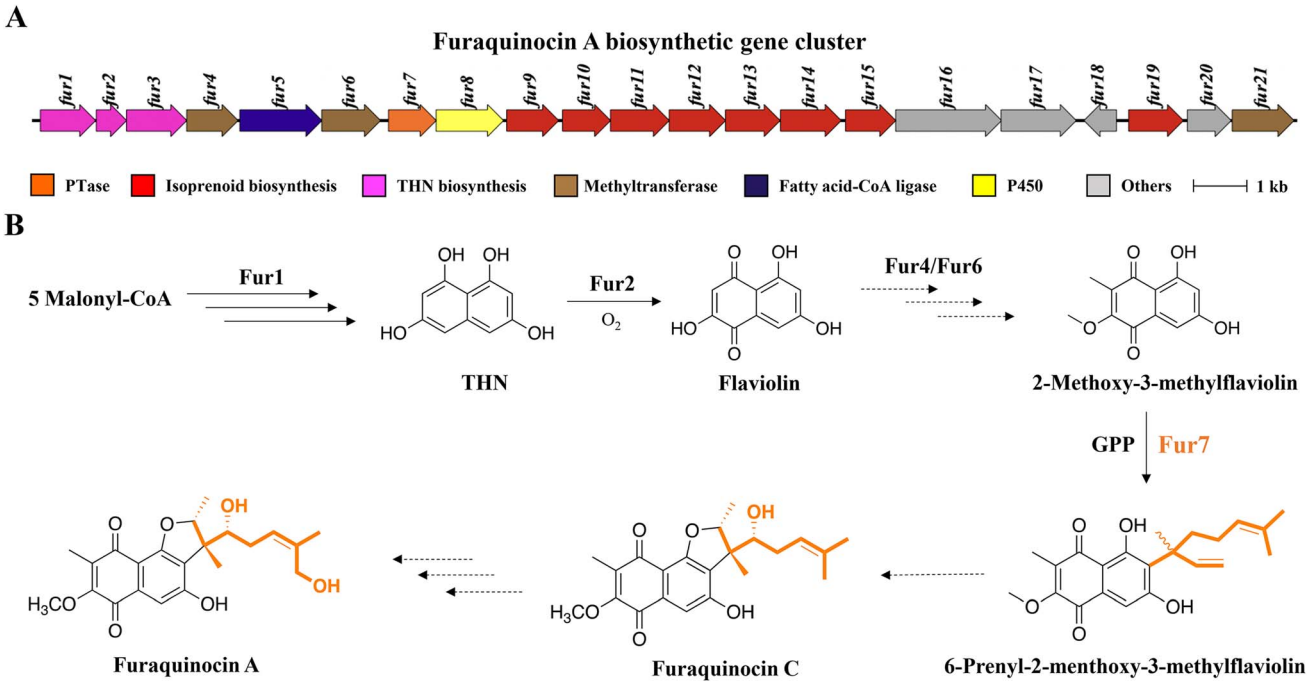

Fig. 15 Biosynthetic gene cluster (A) and pathway (B) of furaquinocin A.

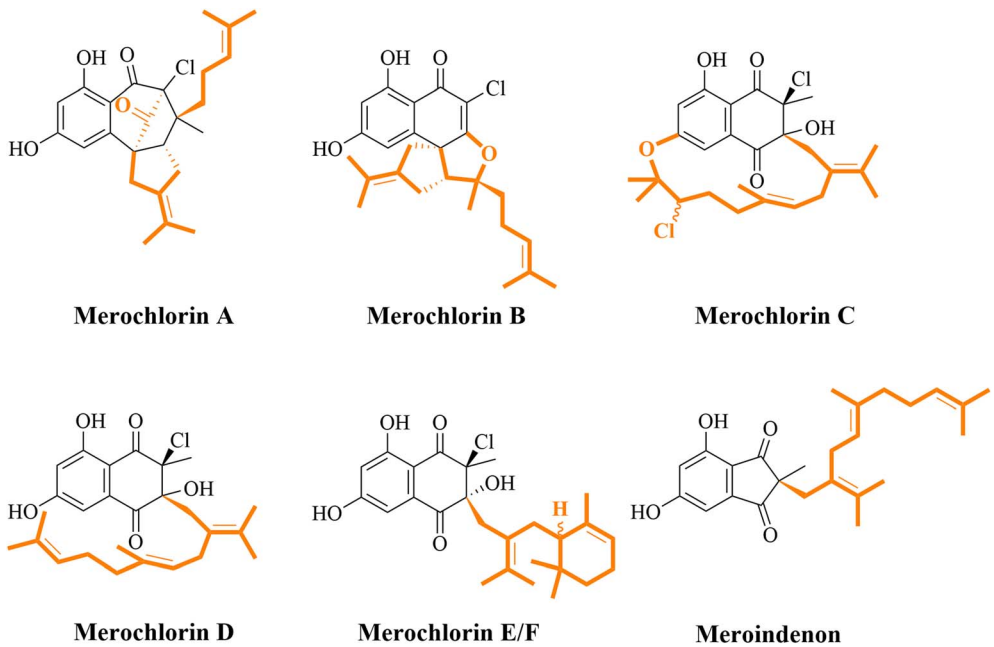

Fig. 16 Structures of merochlorins.

intermediate, premerochlorin.[100,101] The prenyl precursor is catalyzed by Mcl22, which uniquely combines DMAPP with GPP through a head-to-tail mechanism, resulting in the formation of the uncommon sesquilavandulyl pyrophosphate.[97,101] Then, Mcl23 introduces the sesquilavandulyl group at the C-4 position of the naphthoquinone backbone to generate premerochlorin. Mcl24 catalyzes the chlorination and cyclization of premerochlorin to generate merochlorins A and B.[97] Additionally, Mcl24 facilitates the hydroxy-keto rearrangement of premerochlorin, leading to the formation of the structural precursor of merochlorin D.[97] Finally, merochlorin D was converted to merochlorin C *via* a chloride-induced macrolactonization reaction (Fig. 17).[97]

Merochlorins exhibit potent inhibitory activity against multidrug-resistant Gram-positive pathogens, such as MRSA and VRE.[97–99] Merochlorins A and B may enhance the hydrophobicity and membrane permeability of the molecules

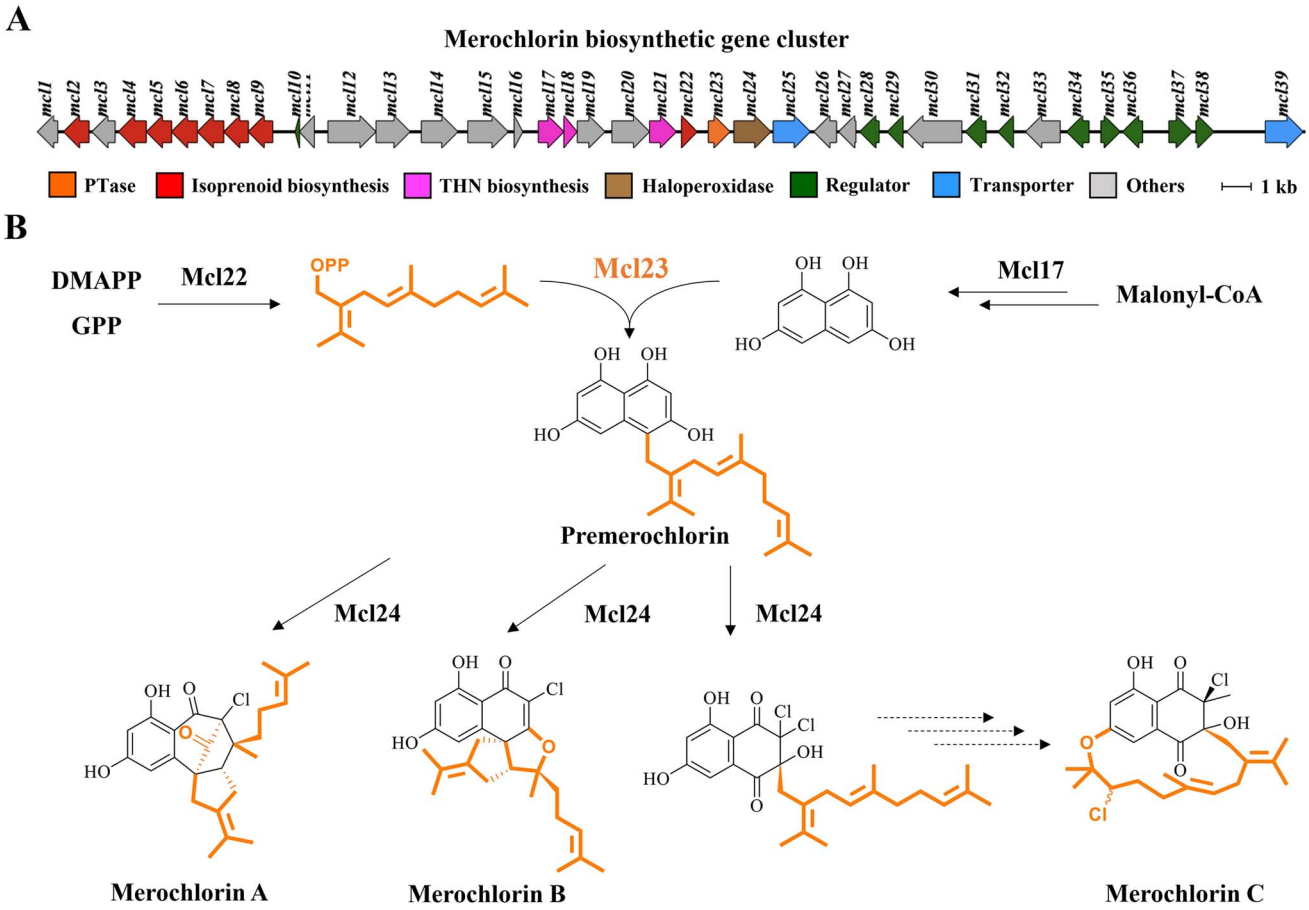

Fig. 17 Biosynthetic gene cluster (A) and pathway (B) of merochlorins.

through the cyclization of the prenyl group, thereby disrupting cell wall synthesis. In contrast, merochlorins C and D, due to their 15-membered macrolactone structure, improve target binding specificity, further augmenting their antibacterial efficacy.[97]

3.4.4 Miscellaneous polyketides. Miscellaneous polyketides represent a diverse class of natural products produced by bacteria, predominantly isolated from actinomycetes.[102–107] Miscellaneous polyketides exhibit diverse core scaffolds, including naphthoquinones, polyhydroxylated polycyclic

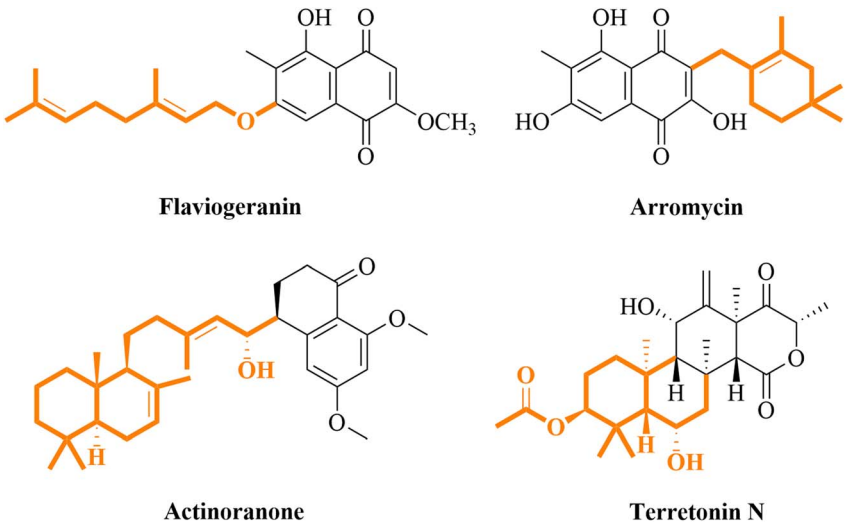

Fig. 18 Structures of miscellaneous polyketides.

structures and dihydronaphthones, with significantly enhanced structural diversity and complexity through prenylation modifications at the C or O positions. For example, flaviogeranin, isolated from *Streptomyces* sp. RAC226 features a naphthoquinone core with a 7-*O*-geranyl modification, in addition to oxidation, methylation and amine groups.[102] Similarly, arromycin, derived from *Streptomyces aculeolatus* MS1-6, contains a C3-cyclized lavandulyl modification, imparting strong hydrophobicity to the compound.[106] Actinoranone, isolated from the marine bacterium *Streptomyces* sp. CNQ-027 combines a dihydronaphthone core with a bicyclic labdane sesquiterpene unit, where prenylation modification is achieved through an intricate bicyclic formation.[104,105] Terretonin N is a highly oxidized tetracyclic system in which prenylation is accompanied by complex cyclization and stereospecific oxidation (Fig. 18).[107] Overall, the prenylation modifications of these compounds are highly varied, encompassing monomeric prenyl groups, cyclic prenyl groups and complex terpenoid structures. The various modes of prenylation attachment and cyclization patterns confer unique chemical and biological properties to miscellaneous polyketides.

The biosynthesis of various miscellaneous polyketides can be broadly inferred to begin with the formation of a polyketide backbone through the PKS pathway, followed by modification with prenyl groups derived from independently synthesized prenyl precursors. In the case of flaviogeranin, the geranyl group is directly transferred to the naphthoquinone scaffold *via* PT.[102] Arromycin undergoes stereoselective modification at the C-3 position of the core by a pre-assembled cyclic lavandulyl group. Actinoranone features a labdane diterpene unit that is enzymatically linked to the completed scaffold, followed by further oxidation.[103] Terretonin N, starting from 3,5-dimethylorsellinic acid, undergoes phenylation and membrane-associated cyclization catalyzed by a cyclase to form a complex cyclic structure.[108] These prenylation modifications exhibit diverse attachment modes and intricate enzymatic processes, significantly enhancing the chemical diversity and biological activity of these compounds. Although the biosyntheses of these meroterpenoids are not fully understood, reasonable proposals can be made based on related bacterial pathways.

Prenylation exerts a significant impact on the biological activity of miscellaneous polyketides, potentially enhancing their functional properties by modulating their molecular hydrophobicity, spatial configuration and target binding affinity. For instance, flaviogeranin exhibits nanomolar-level activity against glutamate toxicity inhibition without significant cytotoxicity.[102,103] Arromycin, with enhanced hydrophobicity due to prenylation, exhibits broad-spectrum antimicrobial activity with MIC values ranging from 3.13 to 6.25 μg mL^{-1}. Actinoranone exhibits cytotoxicity against HCT-116 cell lines with an LD_{50} of 4 μM.[104] The cyclized prenylation of terretonin N aids in molecular recognition, granting it moderate antimicrobial and anticancer activities.[108]

3.4.5 Naphterpins and marinones. Naphterpins and marinones are naphthoquinone derivatives with distinctive aromatic oxidation patterns that were first isolated from marine actinomycetes.[109] These compounds possess a core structure derived from 1,3,6,8-tetrahydroxynaphthalene (THN), which is further modified by unique prenylation.[109] Representative compounds, including naphterpin A, naphtegeranine E, JBIR-80 and marinones, display key structural traits such as trans or cis prenyl group linkages, the formation of polycyclic systems, and subsequent oxidation or methylation modifications.[109–113] For instance, the core structure of naphterpin A is derived from a naphthoquinone, with the formation of a 6/6/6/6 tetracyclic structure through prenyl group transfer.[109] JBIR-80, isolated from *Streptomyces* sp. RI24 is a distinctive tetracyclic compound that undergoes reverse prenylation at the C-7 position of the naphthoquinone core.[112] Marinones, exemplified by marinophenazine A, are derived from THN modified through farnesylation (Fig. 19).[113]

The biosynthesis of marinones begins with THN as the precursor, which is formed through the condensation and

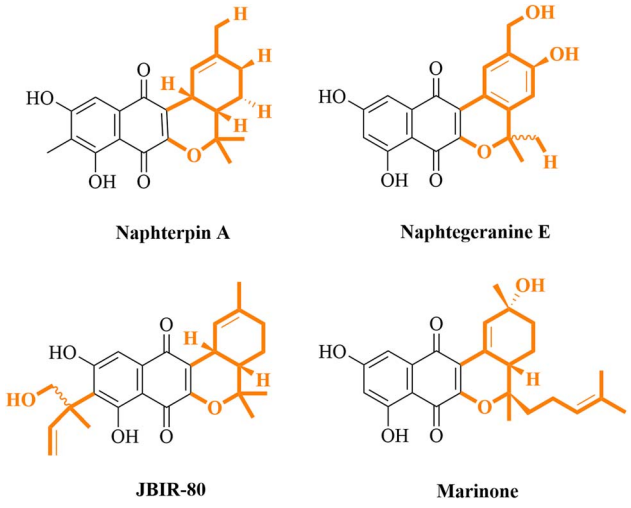

Fig. 19 Structures of naphterpins, JBIR-80 and marinones.

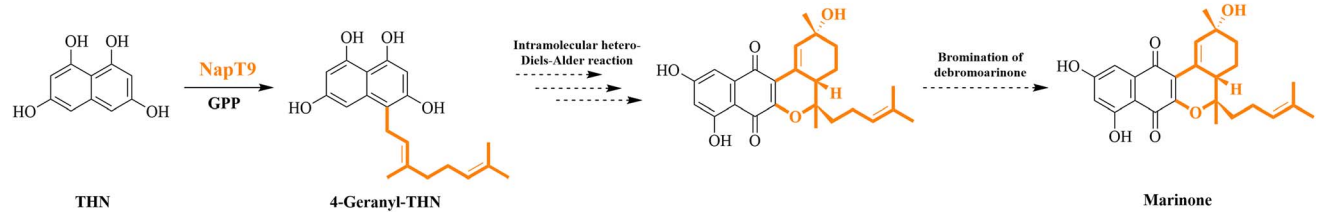

Fig. 20 Biosynthetic pathway of marinones.

aromatization of five malonyl-CoA units.[114] The key prenylation modification is catalyzed by the aromatic PT NapT9, which introduces a vanilloyl or other prenyl groups at the C-4 position.[115] These intermediates then undergo a series of complex reactions including oxidative dearomatization, isoprenyl site migration and Diels–Alder cyclization.[116] Prenylation cyclization with the naphthoquinone backbone forms debromomarinoquinones with a 6/6/6/6 tetracyclic structure.[116] The product is brominated at C-5 or C-7 by vanadium-dependent bromoperoxidase, to produce marinones (Fig. 20).[116]

Naphterpins and JBIR-80 exert neuroprotective effects that effectively mitigate glutamate toxicity.[109,112] Prenylation of naphterpin A enhances its antioxidant capacity, whereas the cyclization and bromination modifications of marinones increase their antibacterial potency.[109–111,116] Meanwhile, marinones exhibit potent activity against Gram-positive bacteria, with MIC values as low as 1–2 μg mL^{-1}.[113]

3.4.6 Prenylated napyradiomycin derivatives. Napyradiomycins represent another class of structurally diverse naphthoquinone compounds that were first discovered in *Streptomyces* species.[117] To date, more than 58 prenylated napyradiomycin derivatives have been characterized.[10] These compounds typically feature a naphthoquinone backbone with prenyl modifications, exhibiting significant structural diversity and biological activity. Prenylated napyradiomycins can be classified into three types based on the attachment patterns of isoprenoid groups: A-type with linear side chains, B-type featuring a 6/6/6 tricyclic structure and *C*-type with a 14-membered ring. A-type compounds, such as napyradiomycin A1, phosphatoquinone A and SF2415A1, contain linear vanilloyl side chains at the C3 position, with SF2415A1 also possessing a DMAPP group at the C-2 position.[117–119] B-type compounds are characterized by a 6/6/6 tricyclic structure in which the isoprenoid at the C-4 position undergoes cyclization to form a tetrahydrofuran ring. Representative compounds such as napyradiomycins B1 and B3 exhibit highly cyclized structures and can undergo further halogenation, such as chlorination and bromination.[120] C-type compounds, like napyradiomycin C1, form a 14-membered macrolactone spanning the C-3 and C-7 positions (Fig. 21).[121]

The precursor synthesis of napyradiomycins follows the same pathway as that of naphterpins, both of which originate from the core structure THN.[122] The biosynthesis of napyradiomycins is characterized by the coordinated action of multiple enzymes, with prenylation and scaffold construction as critical steps. Initially, the THN scaffold undergoes geranylation at the C-4 position, catalyzed by NapT9, an ABBA-type terpene synthase.[115] Subsequently, NapH1, a vanadium-dependent haloperoxidase (VHPO), catalyzes oxidative dearomatization and selective chlorination of the dihydroquinone ring.[123] During the secondary isoprenylation stage, NapT8 transfers an isoprenyl group to the C-2 position, followed by an α-hydroxyketone rearrangement mediated by NapH3, resulting in a naphthoquinone core featuring dual prenyl modifications, known as naphthomevalin.[114] Further structural stabilization is achieved through NapH1-catalyzed formation of

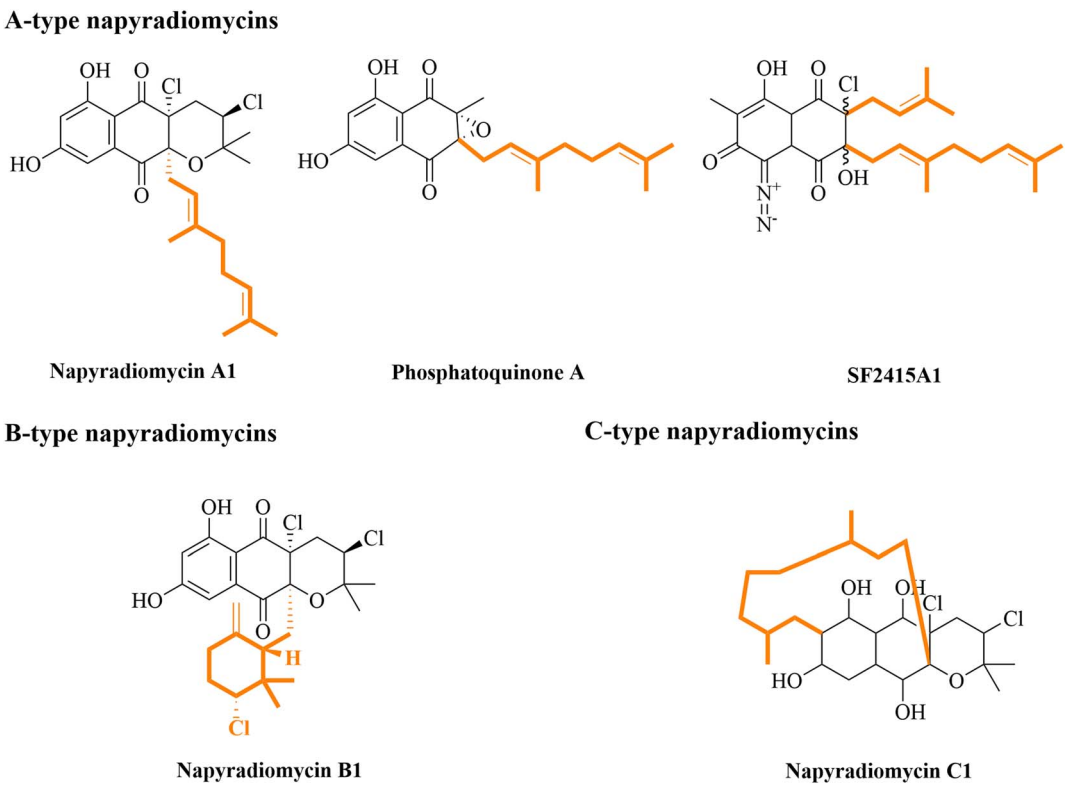

Fig. 21 Structures of A-type, B-type and C-type napyradiomycins.

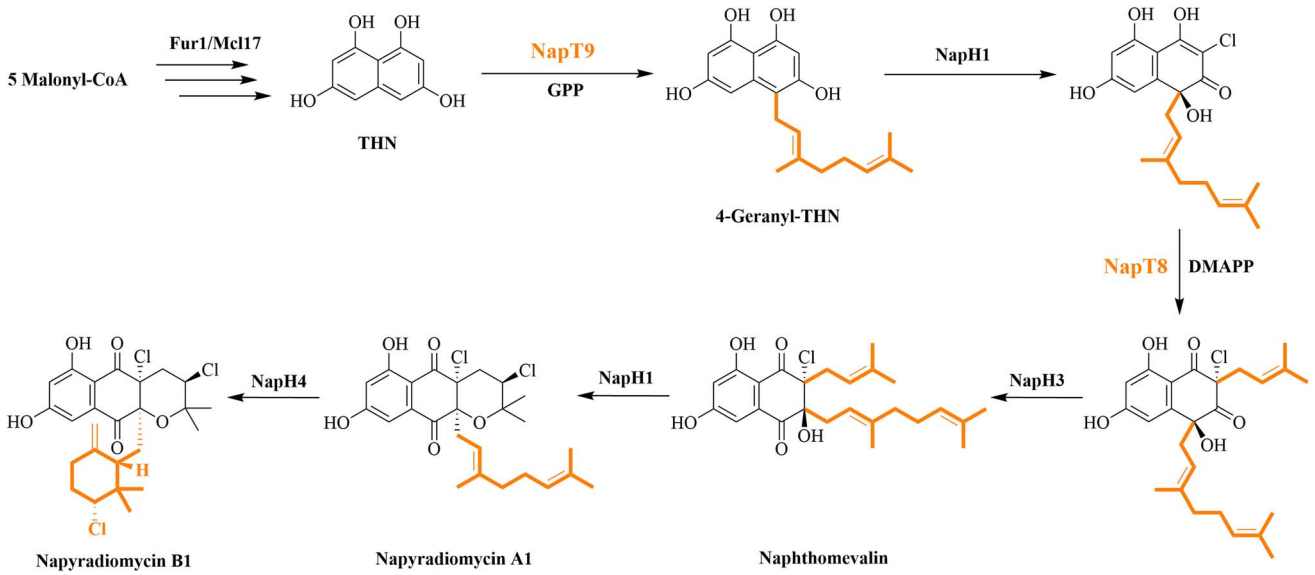

Fig. 22 Biosynthetic pathway of napyradiomycins.

a tetrahydropyran (THP) ring, leading to the generation of napyradiomycin A1.[114,115,124] The final step involves NapH4, which catalyzes the cyclization of the geranyl pyrophosphate (GPP) side chain *via* a chloronium ion-mediated intramolecular reaction, culminating in the formation of the six-membered ring structure characteristic of napyradiomycin B1 (Fig. 22).[122]

The biological activities of napyradiomycins are closely associated with their prenyl modifications, with distinct substitution patterns significantly influencing both their potency and mechanisms of action. A-type compounds, such as napyradiomycin A1, exhibit strong antibacterial activity, with an MIC as low as 1 μg mL^{-1}.[117] They also possess antitumor effects with IC_{50} values ranging from 2 to 20 μM and anti-angiogenic properties.[125] Among B-type compounds, napyradiomycin B3 displays the most pronounced antibacterial efficacy, achieving MIC values of 0.25 to 0.5 μg mL^{-1}, emphasizing the potential of structural optimization of cyclized isoprenoid moieties to enhance bioactivity[120] Conversely, C-type compounds, characterized by macrolactone structures arising from prenyl modifications, exhibit strong anti-biofilm activity but relatively lower antibacterial potency, with an MIC above 12.5 μg mL^{-1}.[121]

3.5 Prenylated aminocoumarin antibiotics from bacteria

Aminocoumarins, originally isolated from *Streptomyces* species, have unique antibacterial targets (DNA topoisomerases) and large structural diversity.[126] Typically, prenylated aminocoumarins, including novobiocin, clorobiocin and coumabiocins, feature a core bicyclic scaffold of 3-amino-4,7-dihydroxycoumarin, which forms the basis for various substituted structures.[126] Furthermore, the 3-prenyl-4-hydroxybenzoyl moiety is formed by combining the prenyl group with the hydroxybenzoyl group. Novobiocin, first discovered in *Streptomyces niveus*, and clorobiocin, identified across different *Streptomyces* strains, share a similar prenyl substitution. The main difference between these two species is the modification of the L-noviose sugar ring attached to the coumarin core. Unlike novobiocin and clorobiocin, the isoprenyl groups in coumabiocins A–F isolated from *Streptomyces* sp. L-4-4 undergoes hydroxylation and methylation, forming chromane rings with the hydroxybenzoyl moiety. Coumabiocins are unique analogs with modified isoprene-benzoyl groups, resulting in coumarins A/B or chromanes C/D rings and hydroxylated units (Fig. 23).[127]

The biosynthesis of aminocoumarins has been systematically elucidated through extensive biochemical and spectroscopic studies, revealing that they are assembled from three primary building blocks: the aminocoumarin core, noviose sugar, and the 3-isoprenyl-4-hydroxybenzoyl moiety. As illustrated, clorobiocin biosynthesis initiates with prephenate, followed by the formation of the 4-hydroxybenzoyl group.[128] The DMAPP unit, which originates from the MEP pathway, is subsequently appended at the 3-position of the 4-hydroxybenzoyl group, catalyzed by the DHN AABA-type PT CloQ.[26] The aminocoumarin core and noviose are then sequentially incorporated to yield the final product clorobiocin[128] (Fig. 24). The biosynthesis of other aminocoumarins, such as novobiocin, is similarly organized, with the DHN AABA-type PT NovQ serving as the crucial PT that facilitates the addition of the DMAPP unit to the aminocoumarin scaffold.[27,129]

Aminocoumarins specifically target bacterial topoisomerases like DNA gyrase and topoisomerase IV, thus showing potent activities against a panel of Gram-positive pathogens, including *Staphylococcus aureus* and *Enterococcus* species.[126] Novobiocin also exhibits antiproliferative activity by targeting heat shock protein Hsp90.[130] Intriguingly, clorobiocin shows 10-fold and 70-fold more potent inhibition of DNA gyrase and topoisomerase IV than novobiocin, respectively.[131,132] The enhanced inhibitory activity of clorobiocin is likely due to its prenylation, which induces a unique molecular conformation that better aligns with the active sites of topoisomerases. Conversely, altering or removing the prenyl group generally

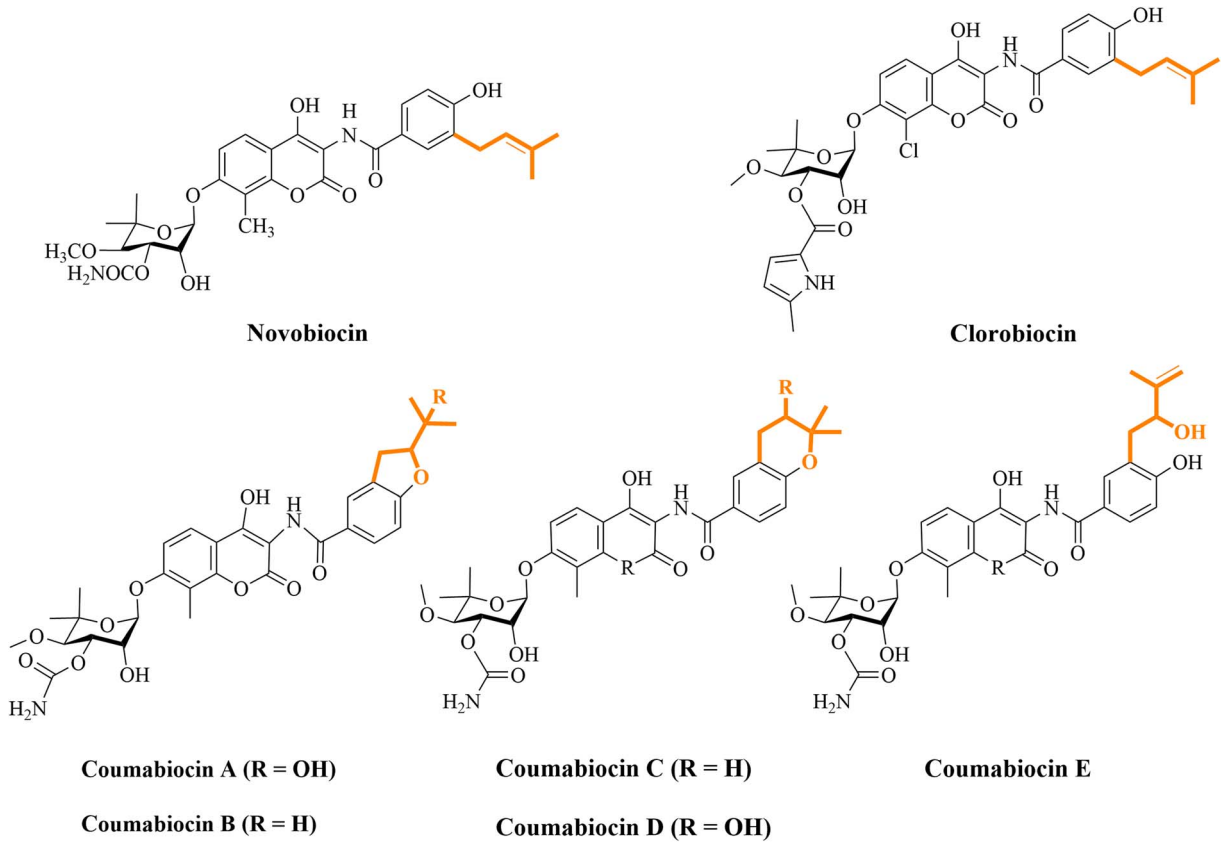

Fig. 23 Structures of prenylated aminocoumarin antibiotics.

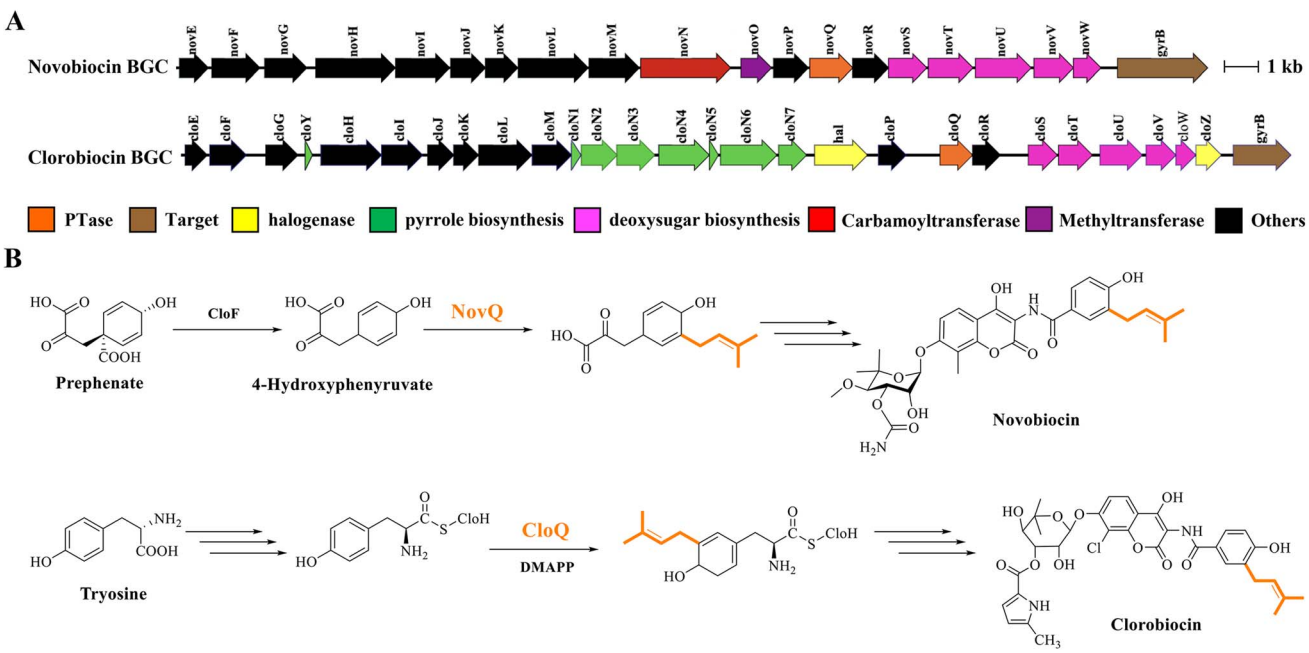

Fig. 24 Biosynthetic gene clusters (A) and pathways (B) of novobiocin and clorobiocin.

leads to reduced antibacterial potency of aminocoumarins, indicating that prenylation not only contributes to molecular stability but also enhances affinity with target proteins.[133]

3.6 Prenylated PABA-derived benzastatins from bacteria

Benzastatins, which are derived from geranylated *p*-amino benzoic acid (PABA), exhibit large structural diversity and broad

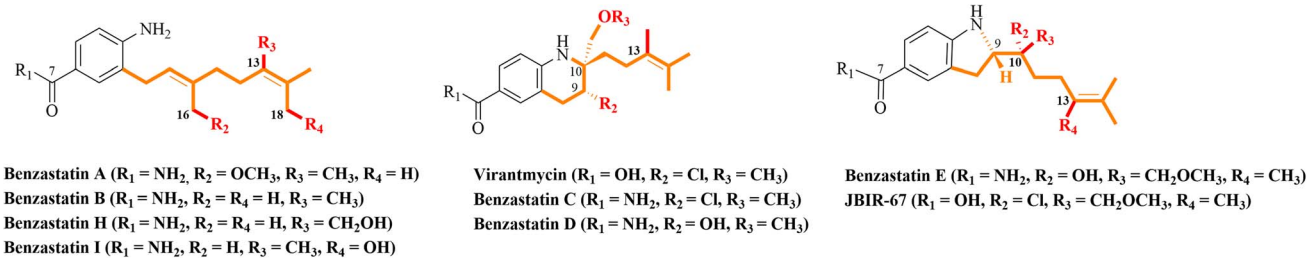

Fig. 25 Structures of prenylated PABA-derived benzastatins.

biological activity. Based on the structural variation arising from the involvement of the modified GPP moiety in the formation of indole ring, quinoline ring, or side chains during biosynthesis, benzastatins are divided into three distinct subclasses, including benzastatin A featuring an indole ring, virantmycin characterized by its quinoline skeleton and benzastatin E with a GPP side-chain group. The GPP moiety in benzastatins undergoes further substitution with chlorine atoms, hydroxyl, hydroxymethyl, methoxy or methyl groups, resulting in large structural diversity, as shown in compounds like benzastatins B, C, D and JBIR-67 (Fig. 25).[134–137]

The biosynthesis of benzastatins begins with a geranyl pyrophosphate (GPP) moiety in which a methyl group is sequentially added to the C-6 position by BezA using S-adenosylmethionine (SAM) as the methyl donor, followed by BezC catalyzing the formation of hydroxymethyl-GPP at the C-10 position. The GPP moiety, modified with methyl and hydroxymethyl groups, was attached to PABA by PT BezF. Then, virantmycin with a quinoline ring scaffold featuring a C-9 chlorine and C-10 methoxyl group, as well as 7-hydroxylbenzastatin F with an indole ring, are produced by BezE and BezB, respectively (Fig. 26).[138]

Benzastatins exhibit diverse bioactivities, including antibacterial, antiviral, antioxidant and neronal protection properties. For example, virantmycin A exhibits effective inhibitory effects against both RNA and DNA viruses, potentially by interfering with viral replication. Both benzastatins and virantmycin A can potently activate hypoxia-inducible factor (HIF), with an EC_{50} value of 23–48 nM. Benzastatins H and I exert protective effects against glutamate-induced toxicity in N18-RE-105 cells, with EC_{50} values of 30.3 μM and 21.6 μM, respectively.[135,137]

3.7 Prenylated bacterial quinolines

Quinoline is a class of nitrogen-containing heterocyclic compounds whose core structure is widely found in various natural products derived from microorganisms, plants and marine organisms. In recent years, some novel quinoline derivatives, including aurachins and marinoterpins, have been identified in diverse bacteria with unique prenyl modifications and notable pharmacological activities.[139,140]

3.7.1 Aurachins. Since the isolation of aurachins A and B from *Stigmatella aurantiaca* over 30 years ago, numerous

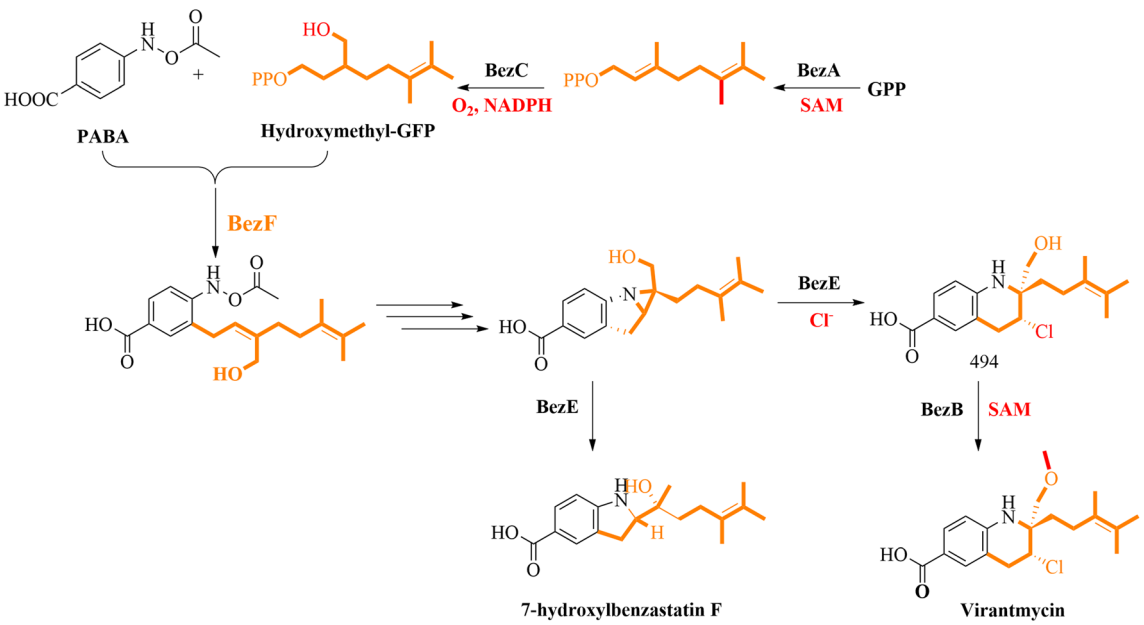

Fig. 26 Biosynthetic pathways of 7-hydroxylbenzastatin F and virantmycin.

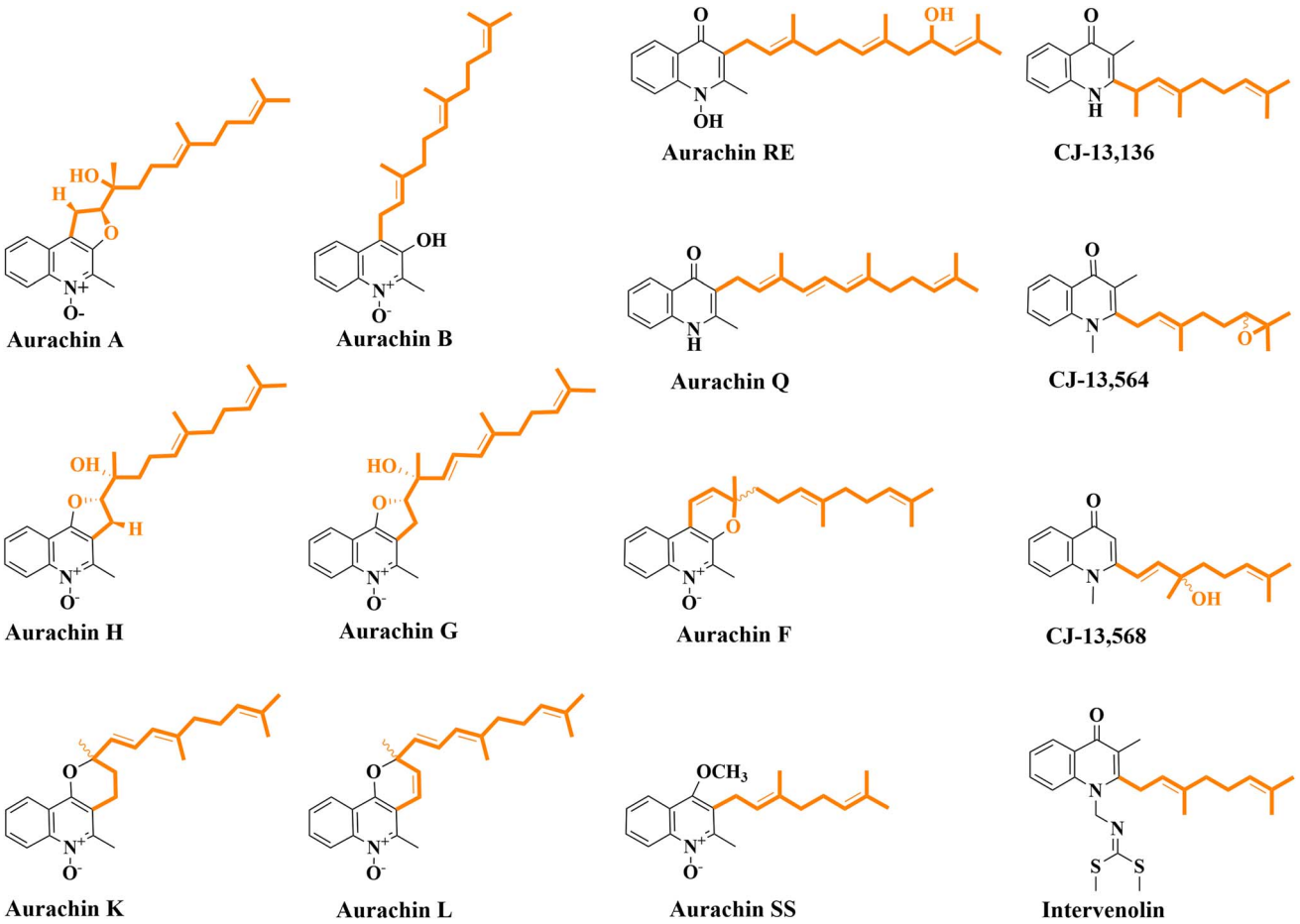

Fig. 27 Structures of aurachins-type natural products.

structurally diverse aurachins have been discovered.[139,140] These prenylated quinoline alkaloids exhibit potent biological activities, with particular pharmacological potentials in inhibiting the cellular respiratory chain and photosynthetic systems.[139,140] The prenyl groups of aurachins are typically attached to the C-3 or C-4 positions of the quinoline core in the form of farnesyl residues, followed by modifications such as hydroxylation or cyclization, which contribute to their unique chemical and biological properties. Based on the position of the prenyl attachment on the quinoline core, aurachins are mainly classified into type A and type C. In type A aurachins, such as aurachins A, B and C, the farnesyl group is attached at the C-4 position, whereas in type C aurachins, including aurachins F, G, H, K, L, Q, RE and SS, it is attached to the C-3 position. Some aurachins undergo further cyclization of the farnesyl group, leading to the formation of five- or six-membered ether rings, as seen in compounds like aurachins A, F, G, H, L and K.[139–143] Furthermore, another subset of quinoline derivatives features prenyl groups in the form of geranyl residues attached at the C-2 position, such as those found in the CJ-13 series and intervenolin (Fig. 27).[144,145]

The biosynthesis of aurachins begins with the assembly of a quinoline scaffold from aspartate and acetate units. Most aurachins are isoprenylated with farnesyl residues at the C-3 or C-4 position of the quinoline core, distinguishing between type A and type C aurachins. In type C aurachins, the farnesyl group is directly attached to the C-3 position by PTs such as UbiA.[146] In contrast, type A aurachins undergo farnesyl migration from C-3 to C-4, followed by *N*-hydroxylation, FAD-dependent epoxidation and C-4 reduction, ultimately producing aurachin B from aurachin D.[147] Further cyclization transforms aurachin B into aurachins A, F or P. On the other side, type C aurachins are derived from aurachin C *via* the cyclization of the farnesyl group, leading to unique five- or six-membered ring structures such as aurachin H, G, I, L and K (Fig. 28).[146,147]

Aurachins exhibit notable biological activities, including antibacterial, antifungal, antimalarial and anticancer effects. For instance, aurachins A-C and RE strongly inhibit the growth of Gram-positive bacteria and fungi with MICs as low as 0.05 mg mL^{-1}, and aurachin RE is also active against some Gram-negative bacteria.[139,148] Both the CJ-13 series and intervenolin show selective efficacy against gastric and colon cancer cells.[144,145]

3.7.2 Marinoterpins. Marinoterpins consist of a quinoline *N*-oxide core structure and a prenylated side chain with two five-membered ether rings.[149] The prenyl groups in these compounds are linked to the quinoline *N*-oxide core through a linear sesterterpenoid side chain, thus classifying them as structurally novel meroditerpenoids. Marinoterpin A was first

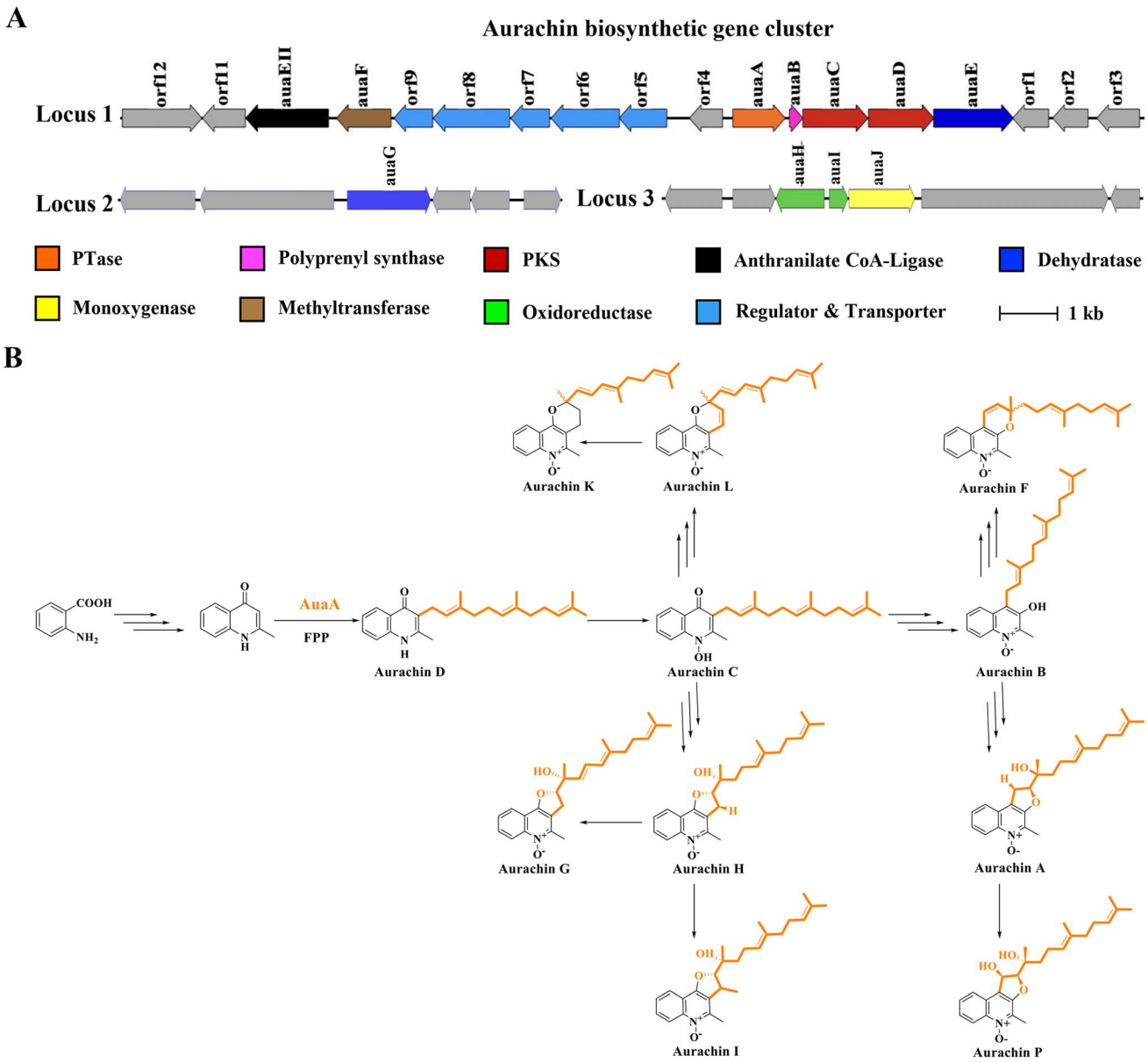

Fig. 28 Biosynthetic gene cluster (A) and pathway (B) of aurachins.

discovered in 2019, followed by the identification of marinoterpins B and C, all of which were isolated from marine actinomycetes *Streptomyces* sp. CNQ-253 or AJS-327.[149] These compounds share a highly similar structure, with the main differences being the hydroxylation modifications of the quinoline ring and prenyl side chain (Fig. 29).

In the biosynthesis of marinoterpins A, B and C, the GFPP side chain is transferred to the C3 position of the quinoline core under the action of the PT MrtA. Subsequently, the intermediate undergoes further modifications, including the introduction of an *N*-oxide group and the formation of two five-membered ether rings, which are mediated by the P450 enzymes MrtJ and MrtK, along with other tailoring enzymes (Fig. 30).[149]

To date, no study has confirmed whether marinoterpins exhibit biological activity. However, the incorporation and cyclization of isoprenyl groups in marinoterpins may alter their interaction mechanisms with cellular targets, enhancing their binding affinity and endowing them with potential biological activity.

3.8 Prenylated indole-type natural products from bacteria

Prenylated indole-type natural products undergo prenylation at various positions on the indole core (N-1, C-2 and C-7) and are a kind of widely distributed secondary metabolites prevalent across diverse natural sources, including bacteria, fungi and plants. In particular, bacteria, including *Bacillus*, *Streptomyces* and *Pseudomonas*, can produce diverse prenylated indole derivatives to adapt and inhibit rivals in competitive ecological niches.[150–155]

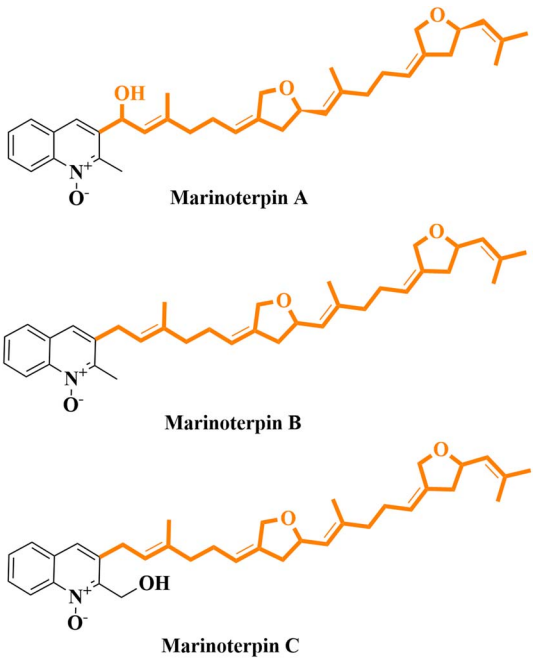

Fig. 29 Structures of marinoterpins A–C.

3.8.1 Simple prenylated indoles. Simple prenylated indoles refer to compounds modified by prenylation at different carbon atoms of a single indole ring (C-3, C-5, C-6, and C-7), which may significantly affect their bioactivities and physicochemical properties. 6-prenylindole and 6-dimethylallyl tryptophan, the structurally simplest prenylated indoles, were first identified in *Streptomyces* sp. TP-A0595 and *Nocardia missouriensis* NBRC 102363, respectively.[150,151] The prenyl moieties undergo further modifications, including chlorination, oxidation, hydroxylation and alkenylation, thus generating a variety of substituted prenylated indoles (Fig. 31).[152,153]

Generally, simple prenylated indoles are synthesized by attaching DMAPP to various positions on the indole ring *via* PTs. As illustrated in Fig. 32, 7-prenylinsatin, 3-hydroxy-6-dimethylallylindolein-2-one and 3-hydroxy-6-dimethylallylisatin are produced through multi-step catalytic reactions, in which DMAPP is added to the indole rings by the C-prenylating DMATS-type PTs IsaA, IptA, and PriB, respectively.[17,151,154]

Most prenylated indoles exhibit weak or moderate antimicrobial bioactivities. For instance, 6-prenylindole, 6-dimethylallylisatin and indole acetaldoximes have weak antimicrobial activities with MICs of >20 mg mL^{-1}.[77,150,153] Additionally, 5-prenyltryptophol showed bone morphogenetic protein-induced alkaline phosphatase inhibition activity with an IC_{50} value of 81 μM.[82,155]

3.8.2 Xiamycins. Xiamycins possess a pentacyclic scaffold composed of carbazole and dimethyl decahydronaphthalene formed through the cyclization of a farnesyl group. The structural diversity of xiamycins arises from variations in the number of carbon atoms in the rings, as well as the presence of different

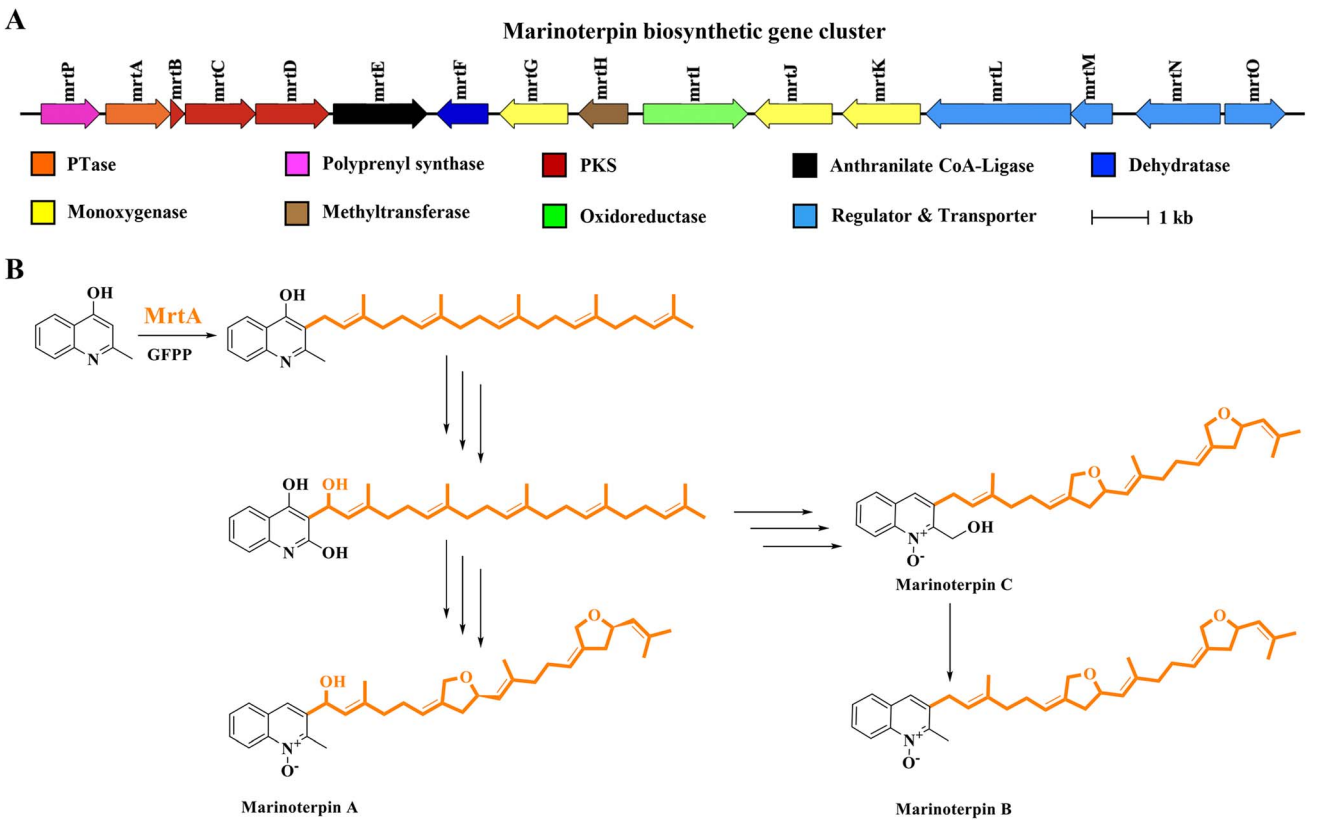

Fig. 30 Biosynthetic gene cluster (A) and pathway (B) of marinoterpins A–C.

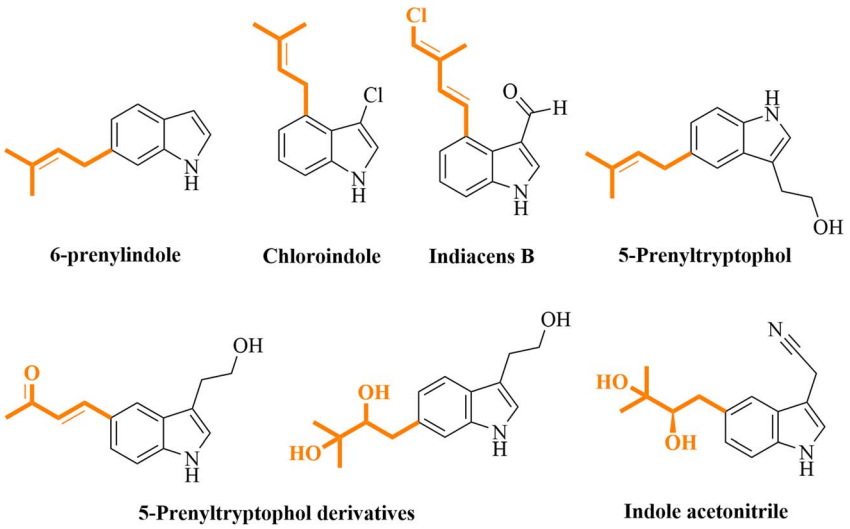

Fig. 31 Structures of simple prenylated indoles.

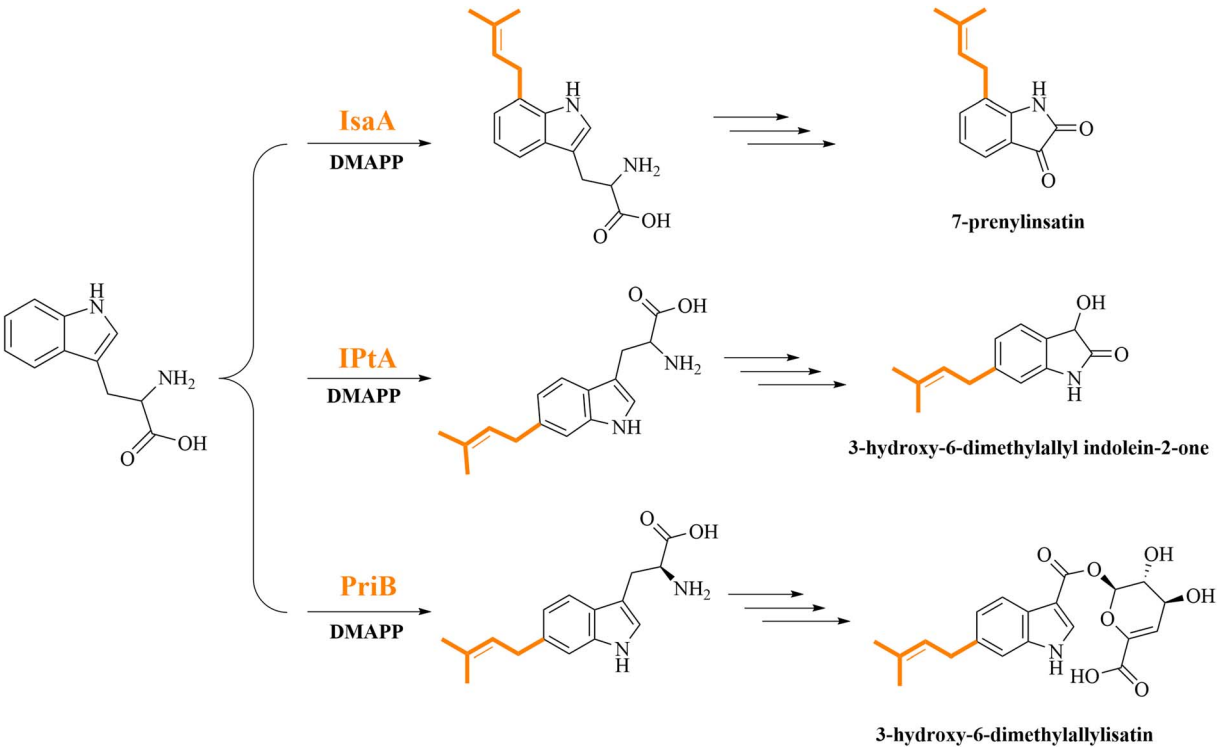

Fig. 32 Biosynthetic pathways of 7-prenylinsatin, 3-hydroxy-6-dimethylallyl indolein-2-one and 3-hydroxy-6-dimethylallylisatin

substituents on the rings, such as a hydroxyl group, a ketone group and a chlorine atom.[156,157] For instance, xiamycin A isolated from *Streptomyces* sp. GT2002/1503 features a fused scaffold of dimethyl decalin and farnesylated carbazole, along with hydroxyl and carboxylic acid groups (Fig. 33).[156]

The synthesis of xiamycins begins with indole as the substrate. Then, the addition of a farnesyl group to the carbon atom at the 3rd position of the indole ring is catalyzed by the polyprenyl synthase XiaM/P to generate 3-farnesylindole.[158] This farnesyl group is subsequently subjected to multiple oxidation or cyclization reactions, resulting in the formation of pentacyclic compounds such as sespenine, oxiamycin and xiamycin A, all of which are modified with hydroxyl and carboxylic acid groups. Finally, xiamycin A is dimerized through an N–N linkage to form dixiamycin A (Fig. 34).[159,160]

As a versatile class of indole-derived antibiotics, xiamycins exhibit diverse bioactivities, including antibacterial, antiviral and anticancer effects. For example, xiamycin A and its methyl

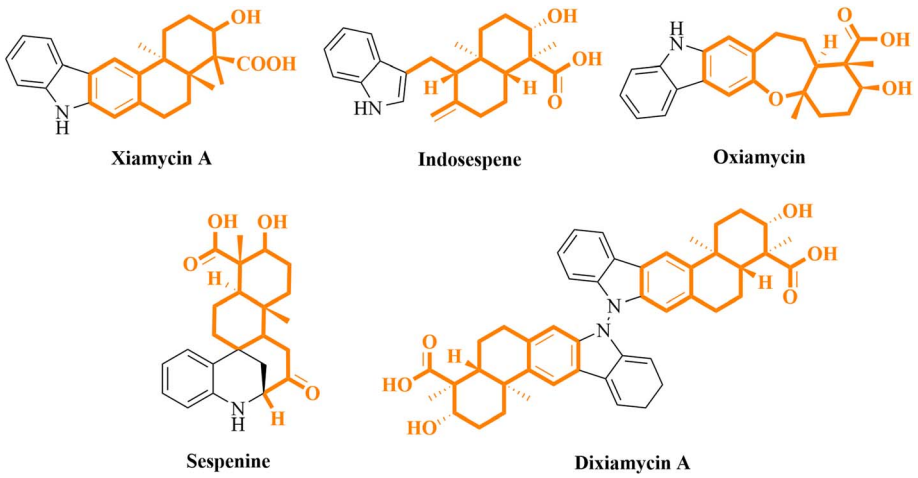

Fig. 33 Structures of xiamycins.

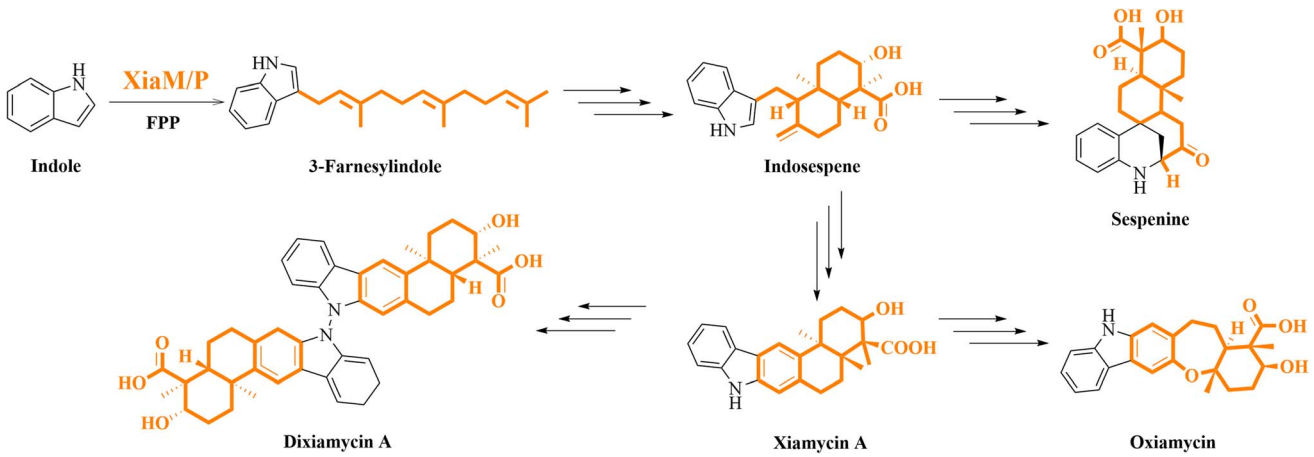

Fig. 34 Biosynthetic pathways of xiamycins.

ester act as selective HIV inhibitors with an IC_{50} value over 10 μM, likely by blocking reverse transcriptase and thereby preventing viral genome replication in host cells.[156] Xiamycin C, D and E have also been demonstrated to have promising inhibitory activity against the Nsp10 protein of SARS-CoV-2.[161–163] Although monomeric xiamycins exhibit limited antibacterial efficacy, dimeric and sulfonyl-dimeric forms exhibit stronger activities against different Gram-positive bacteria, including *Mycobacterium tuberculosis* and *S. aureus*.[161–164]

3.8.3 Miscellaneous polycyclic indoles. Unlike xiamycins, the polycyclic skeletons of miscellaneous polycyclic indoles are not generally formed by prenyl groups. Instead, these prenyl moieties are attached to the C5 position of the indole core *via* side-chain modification. Neocarazostatin A, derived from *Streptomyces* sp. GP38, was the first known representative of miscellaneous polycyclic indoles.[165] Carquinostatin A, which resembles neocarazostatin A in terms of structural modifications, has a distinct ortho-quinone functionality. Lavanducyanin features a prenyl group that integrates into a cyclic lavandulyl moiety.[166,167] A unique example of a polycyclic indole compound is amycocyclopiazonic acid, which is characterized by a prenyl side chain at the C4 position of the indole that contributes to the formation of a polycyclic skeleton (Fig. 35).

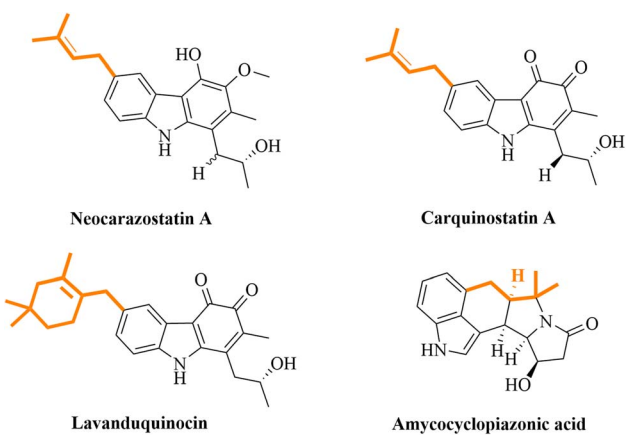

Fig. 35 Structures of miscellaneous polycyclic indoles.

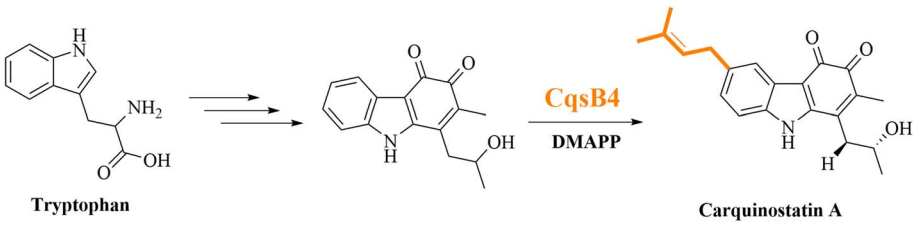

Fig. 36 Biosynthetic pathway of carquinostatin A.

Neocarazostatins are composed of four components: tryptophan, pyruvate, polyketones and isoprene. The biosynthesis of carquinostatin A begins with tryptophan and involves multiple steps to form a common precursor. Subsequently, the addition of DMAPP to the carbon atom at the 4th position of the indole ring is catalyzed by the C-prenylating DMATS-type PT CsqsB4 in carquinostatin A (Fig. 36).[168]

Neocarazostatins, carquinostatin A and lavanducyanin have demonstrated potential in diverse bioactivities, including anticancer, antibacterial, antioxidant and anti-inflammatory effects.[169,170] For example, by inhibiting lipid peroxidation, neocarazostatins can prevent glutamate-induced neurotoxicity in nerve cells with EC_{50} values as low as 3.1 nM.[165]

3.9 Prenylated bacterial phenazines

Phenazines are redox-active polycyclic aromatic compounds, of which the blue pigment pyocyanin produced by *Pseudomonas aeruginosa* was the first identified member.[171] Prenylated phenazines are characterized by the introduction of one or more prenyl groups at carbon, nitrogen or hydroxyl positions on the phenazine ring. This modification typically occurs at C-3, N-5 or C-9 of the phenazine ring, and in some cases, involves complex chain-like or cyclic alterations as well as the addition of multifunctional groups. These diverse prenylation patterns highlight the structural complexity of the type of natural products. For example, endophenazine A and endophenazine F, isolated from *Streptomyces cinnamonensis* ATCC 15413, are characterized by prenylation at C-9 and N-5, respectively.[172,173] JBIR-46 and JBIR-47, isolated from *Streptomyces* sp. SpC080624SC-11, possess one or two prenyl modifications at C-3 and C-9, respectively, with additional hydroxylation at C-1 and C-6.[174,175] Chromophenazine A, isolated from *Streptomyces* sp. Ank315, contains a unique methylphenyl D-ring fused to the phenazine core, possibly formed by the cyclization and aromaticity of C-9-prenylated intermediates.[176] Benthocyanin A, isolated from *Streptomyces prunicolor* 1884-SVT2, exhibits geranylation at N-5 and its extended phenyl-γ-lactone structure further enhances its complexity.[177] Geranylphenazinediol and marinophenazine B introduce geranyl groups at different hydroxyl or methoxy positions on the phenazine ring, forming unique heterocyclic derivatives.[178] Lavanducyanin and phenazinomycin have particularly distinctive structures: lavanducyanin is named for its rare cyclopentanoyl group, whereas phenazinomycin contains a rare (S)-trans-monocyclic farnesyl group.[179,180] Additionally, ester derivatives of lavanducyanin expand the chemical space with further functional group diversity (Fig. 37).[181]

The biosynthetic pathway of prenylated phenazines involves two key steps, including the generation of the prenyl group and its modification on the phenazine. The prenyl group is mainly derived from isopentenyl pyrophosphate (IPP) and DMAPP. In some cases, these two precursors further form GPP, as observed for marinophenazine A.[177] For phenazine synthesis, the phenazine backbone is formed *via* phenazine synthase using chorismic acid as the precursor. The transfer of the prenyl group to specific positions on phenazine is catalyzed by different phenazine AABA-type PTs, such as CnqPT1, Mpz10 and PpzP, resulting in mono- or diprenylated products like marinophenazine A/B, JBIR-46/47/48 and endophenazine A/F.[174–177] The prenyl groups may then undergo further modifications, such as oxidation, cyclization or side-chain alterations, which contribute to the diversification of these molecules. In some cases, the prenyl group may first undergo cyclization before being transferred to specific positions on phenazine, as observed in the synthesis of lavanducyanin (Fig. 38).[179,180,182] Overall, the coordination of these different biosynthetic pathways leads to a rich diversity of structures and functional properties in prenylated phenazines.

Prenylated phenazines exhibit broad biological activities, including antimicrobial, anticancer, antioxidant and antiparasitic properties. The aromatic conjugated system of phenazines acts as a free radical scavenger to generate reactive oxygen species, resulting in strong antioxidant activity. For example, benthocyanin A shows more than 30 times than vitamin E in inhibiting lipid peroxidation.[183] Furthermore, prenylation in the kind of natural products can enhance their hydrophobicity and membrane permeability, thus boosting their antimicrobial and anticancer activities. For instance, lavnducyanin exhibits potent activity against MRSA, with an MIC as low as 1–2 μg mL^{-1}.[184] Prenylated phenazines can also induce apoptosis in tumor cells by inhibiting both NF-κB and COX-2 signaling pathways, resulting in potent anticancer activity.[185]

3.10 Prenylated bacterial phenols

Bacteria-derived prenylated phenols were initially identified in *Streptomyces* and *Pseudomonas* genera. These microorganisms employ PTs to catalyze the regio- and stereospecific attachment of prenyl groups or their derivatives to phenolic scaffolds, resulting in structurally distinct molecules. Both xiamenmycins and KS-505a feature prenylation at the ortho-position of the phenol ring. This regioselectivity is attributed to the strong

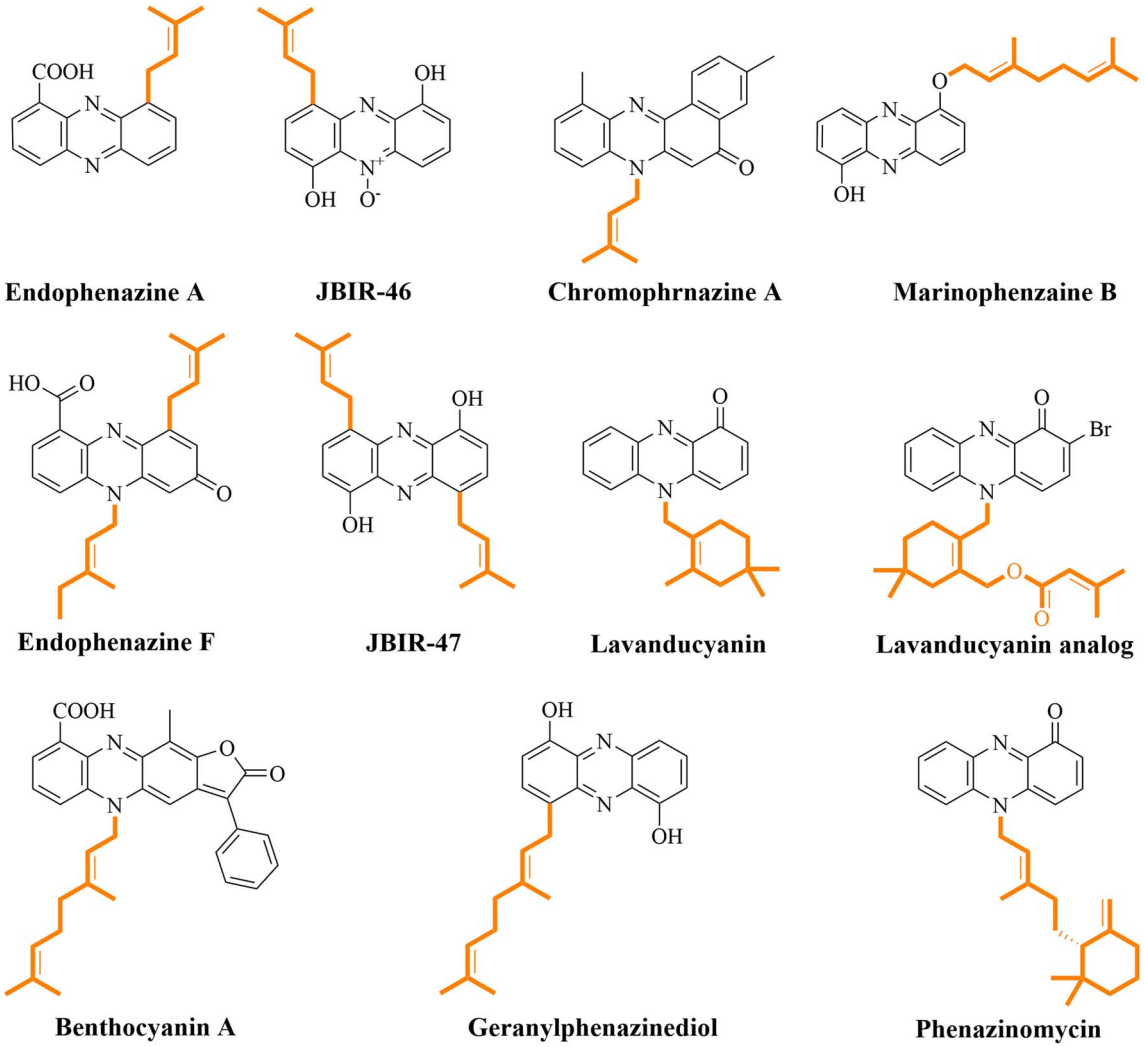

Fig. 37 Structures of prenylated bacterial phenazines.

electron-donating effect of the hydroxyl group on the phenol ring. Xiamenmycin A and D, isolated from *Streptomyces,* are formed *via* prenylation, oxidation, and subsequent cyclization of the phenol.[186] The prenylated moiety in KS-505a consists of a side chain formed by multiple IPP and GPP units, which undergo further cyclization. Due to the unique nature of its prenylated group, KS-505a is also classified as a decacyclic diterpene compound (Fig. 39).[187]

The biosynthesis of xiamenmycin A is catalyzed by the UbiA-type PT XimB, which transfers a GPP group onto the phenol ring, followed by cyclization, hydroxylation and methylation, resulting in the formation of a benzopyran structure.[188,189] The biosynthesis of KS-505a involves two key steps. First, dimethylgeranylgeranyl pyrophosphate (dimethyl-GGPP) containing four molecules of IPP is catalyzed by the polyprenyl synthase Lon12, resulting in the formation of long-chain dimethyloctaprenylgeranyl pyrophosphate (dimethyloctaprenyl-GGPP). Subsequently, this prenylation is transferred by Lon13 to the ortho-position of a phenol ring, which is then modified through cyclization and glycosylation to yield the final compound (Fig. 40).[190,191]

By increasing lipophilicity and enhancing binding affinity to biological targets, prenylation enhances the antimicrobial activity of prenylated phenols and improves their effectiveness in metabolic pathways such as antifibrosis, autophagy and apoptosis. Xiamenmycin A exhibits potent antifibrotic activity by reducing intercellular tension and adhesion for treating pulmonary fibrosis.[186] KS-505a exhibits good activity against Gram-positive pathogens with MICs of 6.25–12.5 μg mL^{-1} against *Bacillus cereus* and *S. epidermidis*.[187]

3.11 Prenylated phosphonated natural products from bacteria

Prenylated phosphorylated NPs are a unique class of phosphoglycerides, first discovered in Streptomycetes.[190] A common characteristic of these compounds is the combination of prenylation modifications with phosphoryl groups, which play crucial roles in cell membrane stability and cell wall synthesis (Fig. 40). The number of bacteria-derived prenylated phosphorylated NPs is relatively small, but they play significant roles in bacterial cell wall biosynthesis. Moenomycin A is

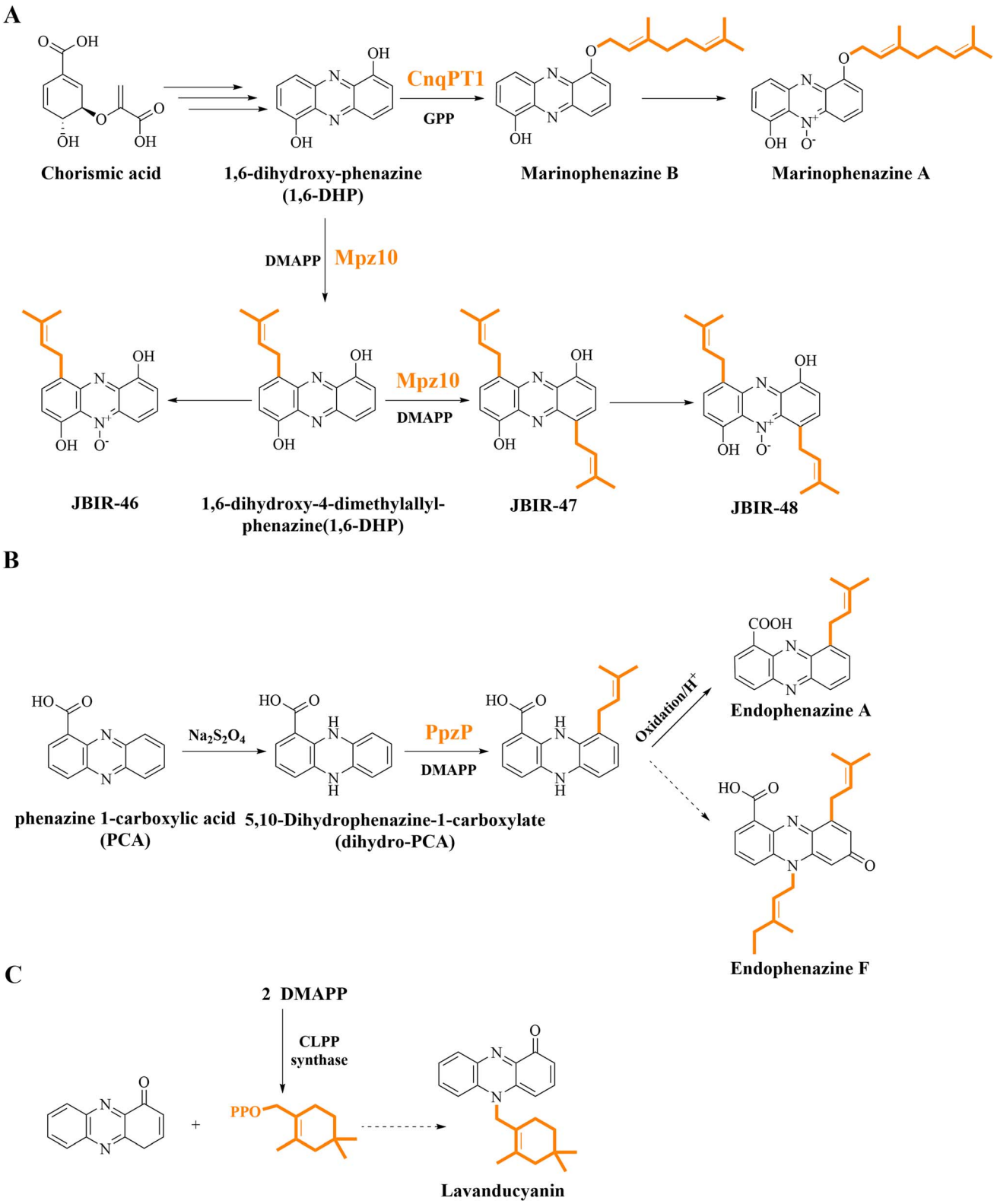

Fig. 38 Biosynthetic pathways of marinophenazines, JBIR-46/47/48, endophenazines and lavanducyanin. (A) Biosynthetic pathways of marinophenazines and JBIR-46/47/48; (B) biosynthetic pathways of endophenazine A and F; (C) biosynthetic pathway of lavanducyanin.

a representative compound of this class, first isolated from *Streptomyces ghanaensis* ATCC14672. It features a 25-carbon modification group formed by farnesyl and geranyl units, which is attached to a 3-phosphoglyceric acid (3-PG) backbone, with five sugar moieties linked to the 3-PG core *via* phosphodiester bonds.[192] AC326-alpha, isolated from *Actinomyces* sp. AC326,

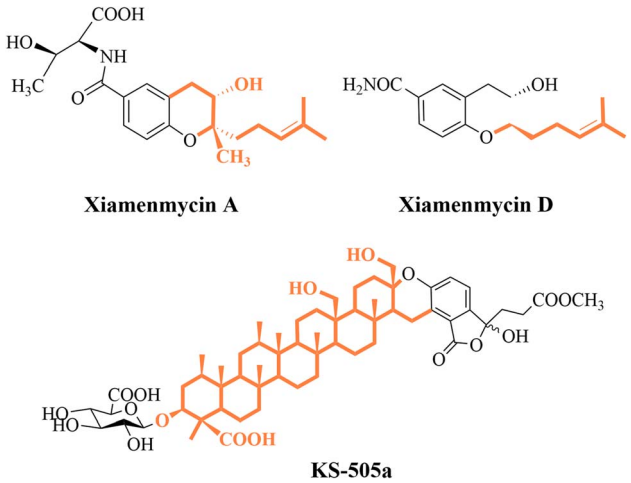

Fig. 39 Structures of xiamenmycins and KS-505a.

shares a similar structure with moenomycin A, but differs in that the GPP group on the isoprenyl side chain is replaced by a monocyclic dihydromyceroic unit.[193] Another representative compound isolated from *Streptomyces* sp. K04-0144 was nosokophic acid. Compared with moenomycin A, nosokophic acid has a simpler structure with a farnesyl modification group, a single sugar unit and 3-phosphoglyceric acid, which is therefore predicted to be an intermediate in the biosynthesis of nosokomycin (Fig. 41).[194]

The biosynthetic pathway of moenomycin A has been extensively studied. First, the transfer of a farnesyl group to 3-phosphoglyceric acid is catalyzed by MoeO5, resulting in the formation of 2-*Z*, *E*-farnesyl-3-phosphoglyceric acid.[195,196] Next, the attachment of a GPP moiety to an intermediate, which has undergone rearrangement of the farnesyl group and the addition of three sugar moieties, is catalyzed by MoeN5. Finally, two additional sugar units are further incorporated, leading to the formation of moenomycin A (Fig. 42).[195,197]

Prenylated phosphorylated NPs exhibit distinctive bioactivities, particularly antibacterial effects and drug potentiation. Moenomycin A, the only known natural antibiotic that directly inhibits bacterial peptidoglycan polymerization, demonstrates potent activity with MICs ranging from 1 to 100 ng mL^{-1} against Gram-positive bacteria.[192] AC326-alpha also exhibits significant antibiotic activity against Gram-positive bacteria with low MIC values, but shows limited efficacy against Gram-negative

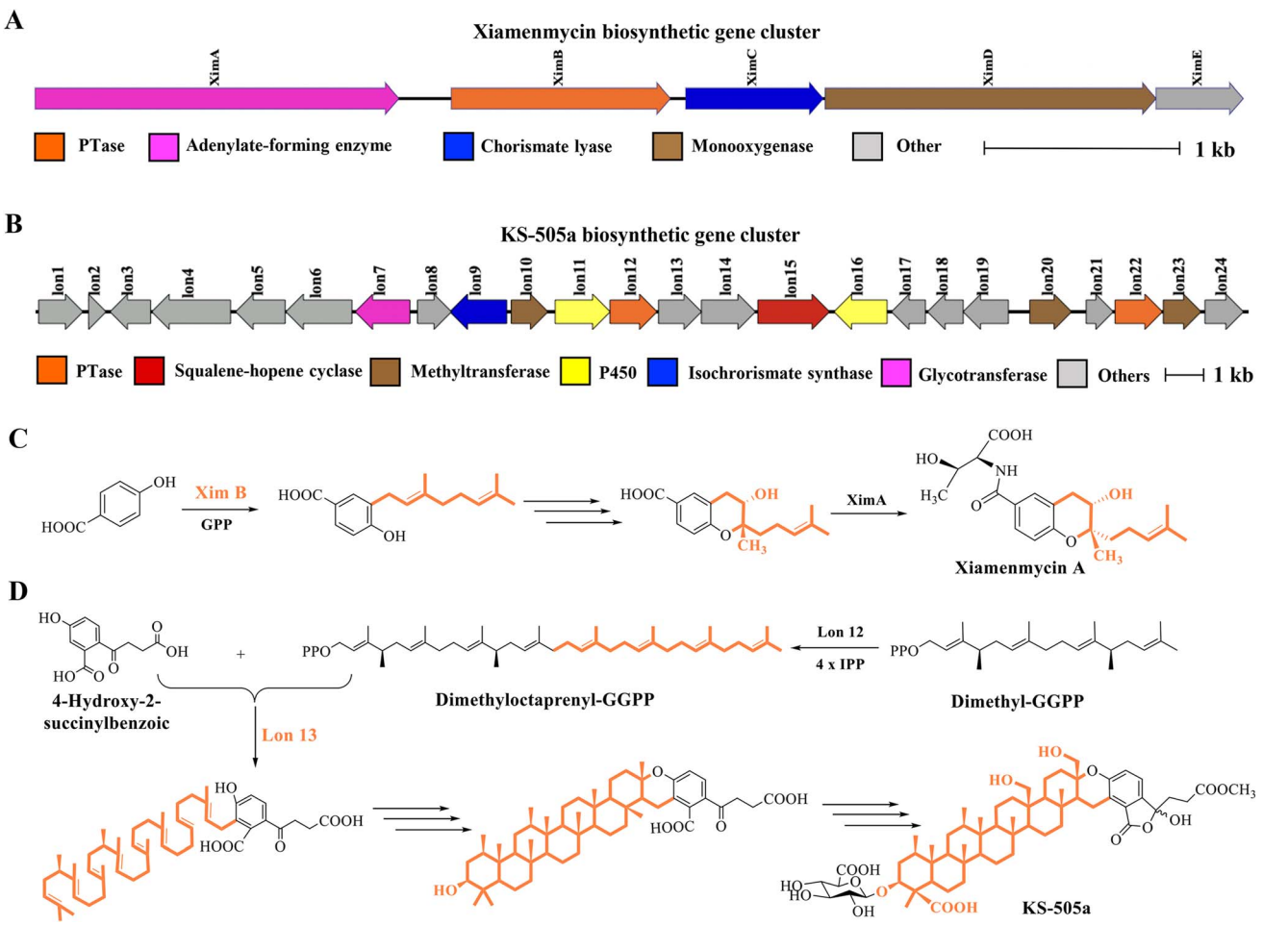

Fig. 40 Biosynthetic gene clusters and pathways of xiamenmycins and KS-505a. (A) Biosynthetic gene cluster of xiamenmycins; (B) biosynthetic gene cluster of KS-505a; (C) biosynthetic pathway of xiamenmycin A; (D) biosynthetic pathway of KS-505a.

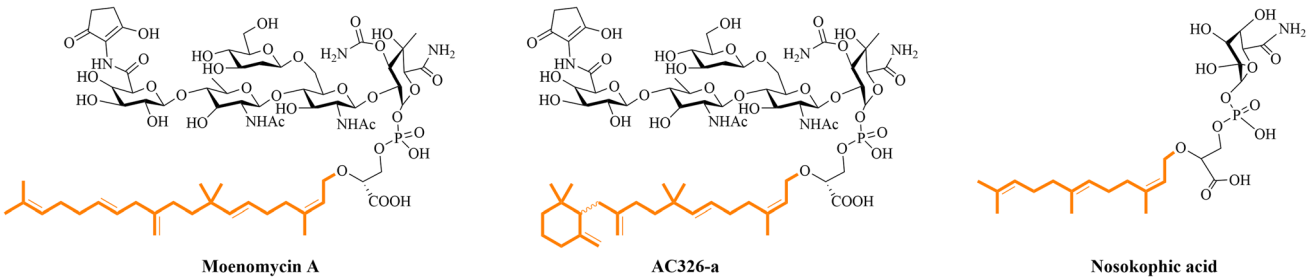

Fig. 41 Structures of moenomycin A, AC326-a and nosokophic acid.

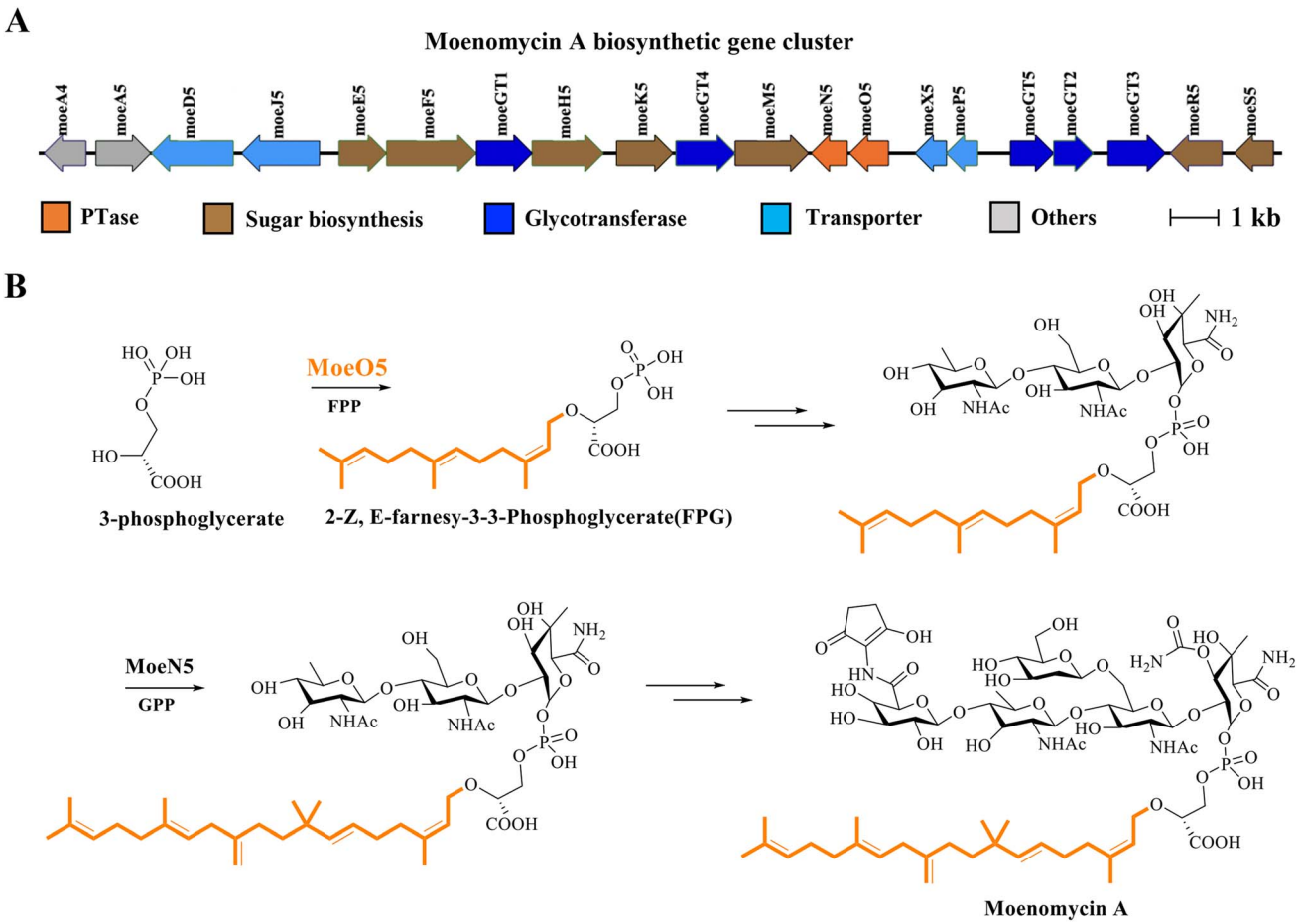

Fig. 42 Biosynthetic gene cluster (A) and pathway (B) of moenomycin A.

bacteria and fungi.[193] Nosokophic acid lacks direct antibacterial activity but significantly enhances the potency of imipenem up to 512-fold against MRSA, highlighting its potential as an antibiotic adjuvant.[194]

4 Conclusion and perspectives

4.1 Biotechnological applications of PTs as novel biocatalysts

Bacterial prenylated NPs have various applications in medicine, cosmetics and food.[8,9,11] The regio- and stereospecific attachments of prenyl groups on bacterial NPs not only augment biological activities by enhancing lipophilicity and membrane affinity but also provide a handle for further chemical modifications (*i.e.*, cyclization and oxidation), thus generating complex compounds with diverse structures and functions.[8] Therefore, bacterial PTs have been increasingly used as robust biocatalytic tools to produce various prenylated NPs recently.[11]

4.1.1 PrenDB: a PT substrate prediction database. To predict the substrate specificity of PTs, Jakub *et al.* used 32 PTs and 167 substrates to create possible prenylation reaction

matrices, thus developing a substrate prediction database, PrenDB (www.kolblab.org/prendb.php).[198] By systematic detection of reactions between potential substrates and known PTs, the database could determine which PTs' substrates and reactions are worth testing. Therefore, the database enables the biocatalytic use of PTs by predicting the potential substrates for chemoenzymatic synthesis of complex scaffolds (*i.e.*, bacterial NPs and synthetic small molecule drugs) based on substructure similarity and virtual chemical transformation approaches.[11,12] In the future, the database could provide bioinformatic guidance for collectively predicting substrates and aiding in the creation of novel chemical entities, thus highly efficiently using PTs as biocatalytic tools to synthesize a large variety of prenylated NPs.

4.1.2 Prenylated daptomycins with improved antibacterial activity by PriB. As an L-tryptophan C-6 C-prenylating DMATS, PriB is highly permissive to several prenyl donors and acceptors and can therefore be used as a biocatalyst for non-native modification of complex bacterial NP core scaffolds.[17] Daptomycin, a natural cyclic lipopeptide, has been developed as a clinically used antibiotic to treat multidrug-resistant Gram-positive bacterial infections. Elshahawi *et al.* found that three known PTs, PriB, CdpNPT (an indole reverse C-3 *C*-PT) and FgaPT2 (an indole C-4 *C*-PT), could prenylate daptomycin, thus generating 6-C-prenyl-Trp or *N*-prenyl-Trp daptomycin. In particular, the two prenylated forms of daptomycin showed significantly improved antibacterial activity compared with daptomycin, possibly due to their increased lipophilicity to the bacterial membranes.[17] PriB and other permissive PTs provide a series of efficient biocatalytic tools for the exploration of native or non-native peptide or protein-based targets.

4.1.3 Engineering TelC and MpnD to generate unnatural indolactams. TleC and MpnD, as a kind of ABBA-type PTs, can catalyze reverse prenylation reactions and are involved in the biosynthesis of lyngbyatoxin and pendolmycin from actinobacteria, respectively. Both proteins recognize various prenyl donors and exhibit relaxed substrate specificity.[30,31] Mori *et al.* successfully changed the preference of the two PTs for the chain lengths of prenyl donors using structure-guided enzyme engineering. Meanwhile, the regio- and stereo-selectivities of the two engineered PTs-mediated prenylation reactions have been altered, thus producing a panel of unnatural novel indolactams.[31] The study expands PTs'catalytic repertoire of the enzymes by enzyme engineering to design novel scaffolds for drug discovery and development.

4.2 Targeted genome mining of novel prenylated bacterial natural products

4.2.1 Global genome mining of novel prenylated bacterial natural products. Prenylated bacterial NPs have received increasing attention owing to their large structural diversity and broad bioactivities. The mining of novel prenylated bacterial NPs can provide numerous chemical entities for drug discovery. In this study, we proposed a global genome mining approach for the large-scale discovery of novel prenylated bacterial NP BGCs based on the co-occurrence analysis of PT genes and core NP biosynthetic genes. Considering that most of the prenylated bacterial NPs are from actinobacteria, we therefore tried to

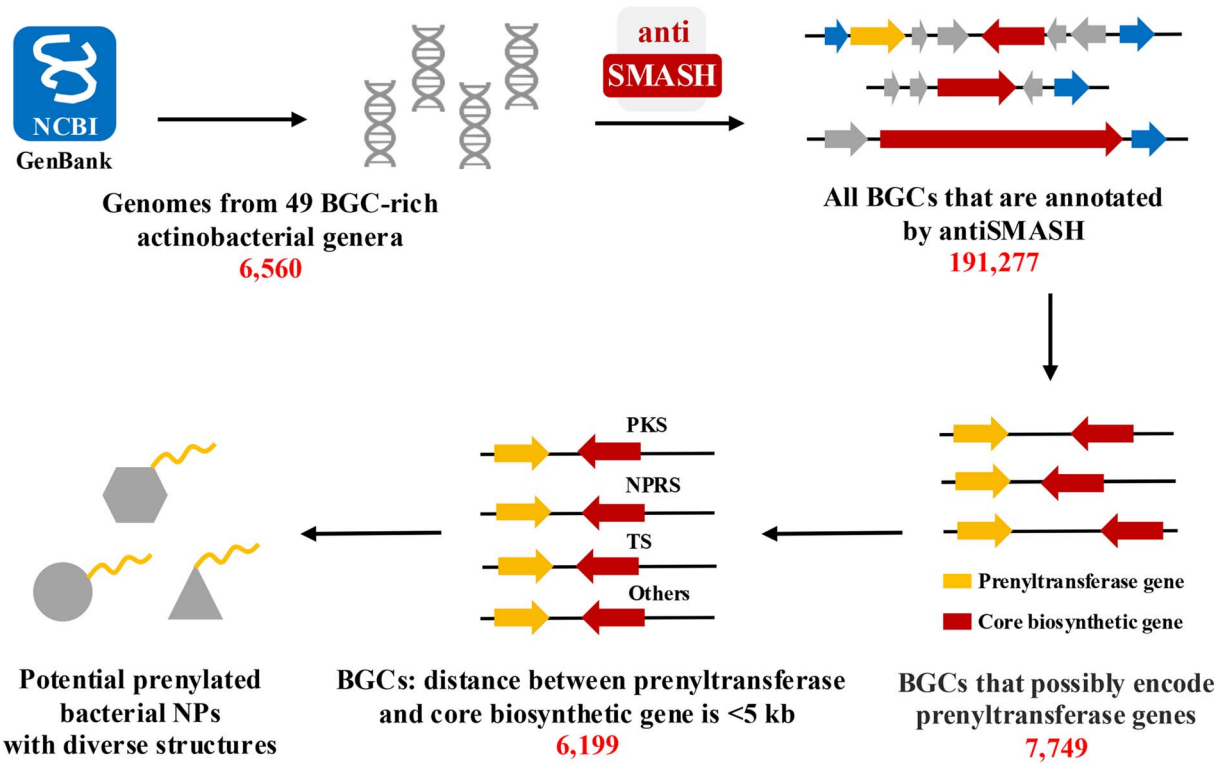

Fig. 43 Global genome mining of potential prenylated natural products from actinobacteria.

verify our approach using sequenced actinobacterial genomic data. First, 6560 genomes from 49 BGC-rich actinobacterial genera were downloaded from GenBank and analyzed for BGC detection using antiSMASH 7.0.0. Then, bioinformatic analysis showed that 7749 antiSMASH-annotated genomic regions encoding at least one NP BGC contain a PT gene. Notably, there were fewer than five kb between the PT gene and core biosynthetic genes in the 6199 annotated BGCs, indicating that they can encode prenylated small molecules with high possibility (Fig. 43). Using the BigSCAPE algorithm,[199] we found that the 6199 BGCs potentially encoding prenylated NPs belong to 930 gene cluster families (GCFs) and that only 15% of GCFs are related to known BGCs from the MIBiG database. Collectively, our results indicate that actinobacteria may produce novel prenylated NPs, which could be unearthed by emerging synthetic biology approaches and modern analytical techniques in the near future.

4.2.2 Discovery of prenylated bacterial natural products catalyzed by diterpene synthases. Bacterial terpene biosynthesis starts with a prenylation or carbocation-based cyclization reaction, which is catalyzed by PTs and terpene synthases (TSs). In 2021, Xu *et al.* reported a novel type of TSs that can catalyze both prenylation and diterpene cyclization in small molecules.[200] The prenylated positions on compounds by TSs showed large diversity, including C-, N-, O-, and S-prenylation. Although the cryptic function of TSs was only confirmed *in vitro* or as a heterologous expression artifact, previous studies indicated that some TSs may instead be PTs involved in the biosynthesis of known meroterpenoids, indicating that TS-mediated prenylation may be physiologically relevant.[200] Therefore, for future genome mining of prenylated bacterial NPs, a PT-dominant TS may be used as another search tool for naturally annotated PTs.

Prenylated bacterial NPs, catalyzed by cluster-situated PTs, exhibit large structural diversity and broad biological activities, which play an important role in the fields of medicine, nutraceuticals and cosmetics. In this review, we briefly discuss the mechanistic study of PTs involved in bacterial NP biosynthesis and then systematically summarize the structural diversity, biosynthetic pathways and biological functions of prenylated bacterial NPs. The comprehensive and comparative review will guide future efforts in the biological applications of PTs in metabolic engineering and synthetic biology, as well as in the discovery of novel prenylated bacterial NPs for drug development.

5 Conflicts of interest

The authors declare no conflicts of interest.

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