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REVIEW

Macrolactins: biological activity and biosynthesis

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Abstract
Marine microorganisms have proven to be a rich source of natural products with unique structures and novel activities, due to their special living conditions. Macrolactins (MLNs), mostly produced by marine-derived microorganisms, are a group of 24-membered lactone natural products, which exhibit potent antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, anti-angiogenic and other activities. Their extensive biological activities make them potential compounds for drug development. MLNs are biosynthesized via a type I polyketide synthase (PKS) pathway with different tailoring steps, such as epoxidation, glycosylation and acylation. These modification steps provide opportunities to diversify their structures by combinatorial biosynthesis strategies. This review mainly focuses on the newly discovered MLNs in the past five years, including their biological activities and relevant biosynthetic studies.

Keywords Macrolactins · Biological activities · Biosynthesis · Structural diversity

Introduction

The ocean covers more than 70% of the earth's surface and hosts a considerable diversity of microorganisms, which could produce natural products with unique structures and novel activities (Jiménez 2018). Marine natural products play an important and promising role in biomedical research and drug development (Wang et al. 2017). Macrolactins (MLNs) represent a group of unique structural patterns containing a 24-membered lactone ring, which were mainly isolated from marine bacteria. Since macrolactins A-F (MLN A-F) were first isolated in 1989 (Gustafson et al. 1989), more than 33 MLNs have been reported (compounds **1–33**, Fig. 1). The main structural differences include the position and numbers of olefinic bonds in the lactone ring and the diverse types of post-modification groups. MLNs exhibit a wide range of pharmacological activities, including antibacterial (Nagao et al. 2001), antiviral (Gustafson et al. 1989), anticancer (Jin et al. 2017a), anti-inflammatory (Yan et al. 2016) and anti-angiogenic activities (Ji et al. 2012) (Table 1). Of note, MLN A (**1**) and 7-*O*-succinyl macrolactin A (SMA, **7**) are currently in preclinical evaluation as antimacular degeneration and antitumor agents (Ji et al. 2010, 2012; Jin et al. 2017a, b; Jung et al. 2014). Due to their various chemical structures and potent biological activities, MLNs are promising lead compounds for drug discovery (Wang et al. 2014). The backbone of MLNs is assembled by an AT-less polyketide synthase pathway, and the glycosylation tailoring step has been deciphered as well, which lead to the generation of 11 "unnatural" MLNs (Liu et al. 2016, 2018; Qin et al. 2014; Schneider et al. 2007). Herein, this review provides an overview of structures and biological activities of 17 new MLNs (discovered between 2014 and 2020), along with the biosynthesis of MLNs.

New natural MLNs since 2014 and their bioactivities

In the past five years, six new MLNs of natural origin have been reported, among which five are from *Bacillus* and one is from *Streptomyces*. With different modifications on the

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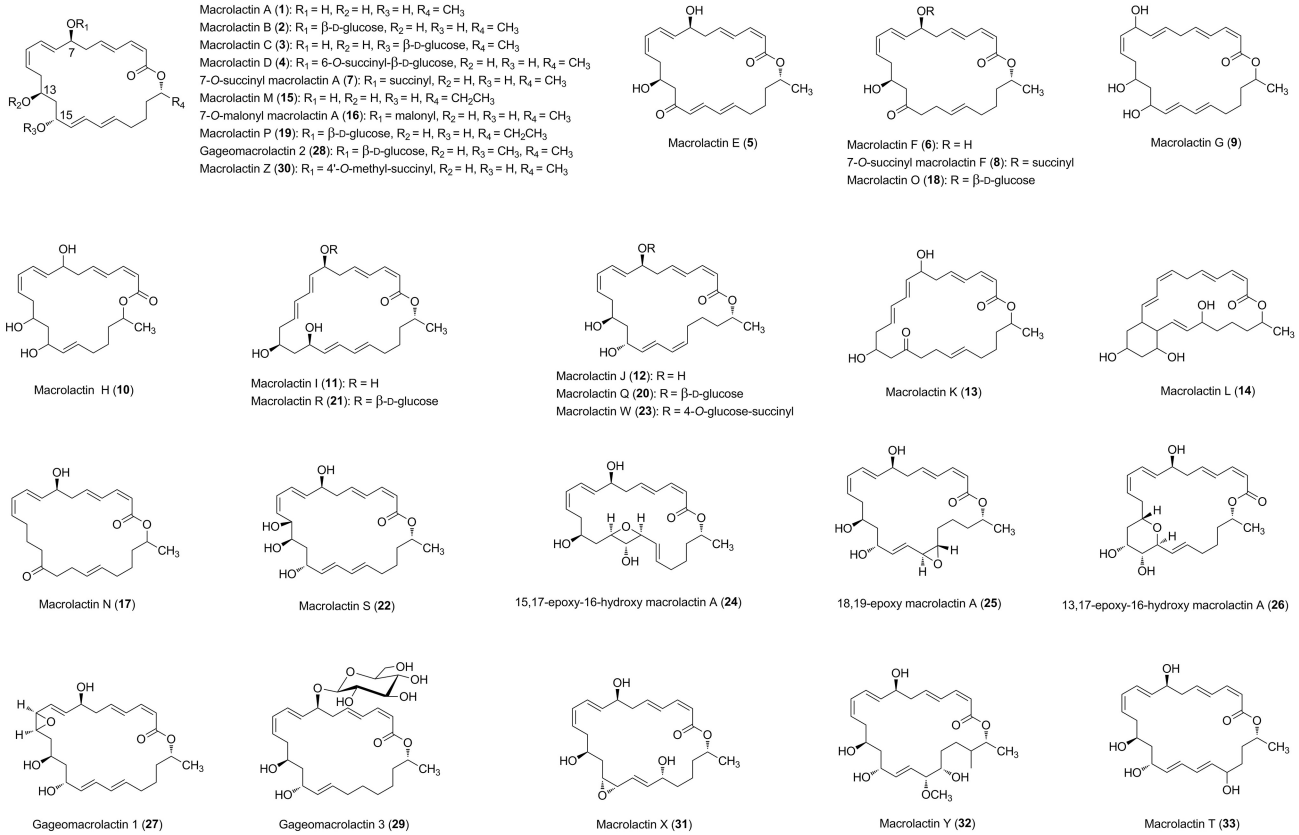

Fig. 1 Chemical structures of previously identified MLNs (**1–33**) (Chakraborty et al. 2014, 2017; Gustafson et al. 1989; Jaruchoktaweechai et al. 2000; Ji et al. 2010; Lu et al. 2008; Mohamad et al. 2012; Mondol et al. 2011b; Muhammad and Hee 2014; Nagao et al. 2001; Schneider et al. 2007; Tareq et al. 2013; Xue et al. 2008; Yan et al. 2016; Yoo et al. 2006; Zheng et al. 2007)

MLN backbone, including epoxidation, acylation and glycosylation, these new MLNs are endowed with various bioactivities (see Fig. 2).

7-*O*-methyl-5′-hydroxy-3′-heptenoate macrolactin (34) Chakraborty et al. (2014) isolated 7-*O*-methyl-5′-hydroxy-3′-heptenoate macrolactin (**34**) from *Bacillus subtilis* MTCC 10403. Compound **34** displays inhibitory activities toward a broad spectrum of food pathogenic bacteria, including *Aeromonas hydrophila*, *Vibrio parahemolyticus* ATCC 17802 and *Vibrio vulnificus.* The potent antibacterial activities of **34** can be inferred from the inductive (field/polar effect) and resonance effects of the 5-hydroxyhept-3-enoate side chain located in C-7 of the macrolactin ring. The 5-hydroxyhept-3-enoate moiety with an electronegative acetyl group could withdraw the electron cloud from the macrolactin ring by a combination of inductive and mesomeric effects, thus acting as the nucleophilic center of the molecule to result in broad-spectrum antibacterial activity.

7-*O*-glucosyl-13,17-epoxy-16-hydroxy macrolactin A (35) and 7-*O*-glucosyl-15,17-epoxy-16-hydroxy macrolactin A (36) In 2014, two new MLNs, 7-*O*-glucosyl-13,17-epoxy-16-hydroxy macrolactin A (**35**) and 7-*O*-glucosyl-15,17-epoxy-16-hydroxy macrolactin A (**36**) were isolated from *Streptomyces* sp. 06CH80. They could inhibit the growth of Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacteria with MICs ranging from 0.015 to 0.125 μg/ml. Both were less active than their parent compounds without the glycosyl group, which is probably due to the attachment of a sugar moiety at C-7 (Mondol et al. 2011a; Muhammad and Hee 2014). However, sugar moieties could increase the solubility of MLNs in polar solvents (Muhammad and Hee 2014).

7-*O*-2′*E*-butenoyl macrolactin A (37) A new compound 7-*O*-2′*E*-butenoyl macrolactin A (**37**) was isolated from *Bacillus subtilis* B5. It exhibited antifungal activities against tea pathogenic fungi *Pestalotiopsis theae* and *Colletotrichum gloeosporioides* (Li et al. 2016).

7,13-epoxy macrolactin A (38) 7,13-epoxy macrolactin A (**38**) was isolated from a marine-derived bacteria *B. subtilis* B5 by Yan et al. (2016). Compared with **1**, **7**, **37** and 7-*O*-malonyl macrolactin A (MMA, **16**), **38** exhibited greater anti-inflammatory activity owing to the existence of the epoxy ring. Further analysis revealed that **38** could

Table 1 MLNs and their biological activities

Compounds	Biological activities	Source microorganism	References
Macrolactin A (**1**)	Antibacterial, anti-inflammatory, anti-angiogenic, anticancer, antiviral	Deep-sea bacterium unclassified	Gustafson et al. (1989)
Macrolactin B (**2**)	Antibacterial, antifungal	*Bacillus* sp. AH159-1	Zheng et al. (2007)
Macrolactin C (**3**)	Antibacterial	*Bacillus* sp. AH159-1	Zheng et al. (2007)
Macrolactin D (**4**)	–	*Bacillus amyloliquefaciens* FZB42	Schneider et al. (2007)
Macrolactins E–F (**5–6**)	Antibacterial	*Bacillus* sp. PP19-H3	Nagao et al. (2001
7-*O*-succinyl macrolactin A (**7**)	Antibacterial, anti-inflammatory, anti-angiogenic, anticancer	*Bacillus* sp. Sc026	Jaruchoktaweechai et al. (2000)
7-*O*-succinyl macrolactin F (**8**)	Antibacterial	*Bacillus* sp. Sc026	Jaruchoktaweechai et al. (2000)
Macrolactins G-M (**9–15**)	Antibacterial	*Bacillus* sp. PP19-H3	Nagao et al. (2001)
7-*O*-malonyl macrolactin A (**16**)	Anti-inflammatory, anti-angiogenic, anticancer	*Bacillus polyfermenticus* KJS-2	Ji et al. (2010)
Macrolactins N-R (**17–21**)	Antibacterial	*Bacillus* sp. AH159-1	Zheng et al. (2007)
Macrolactin S (**22**)	Antibacterial	*Bacillus* sp. 201721	Lu et al. (2008)
Macrolactin W (**23**)	Antibacterial	*Bacillus* sp. 09ID194	Mondol et al. (2011b)
15,17-epoxy-16-hydroxy macrolactin A, 18,19-epoxy macrolactin A, 13,17-epoxy-16-hydroxy macrolactin A (**24–26**)	Antibacterial	*Bacillus* sp. PP19-H3	Nagao et al. (2001)
Gageomacrolactins 1–3 (**27–29**)	Antibacterial, antifungal	*Bacillus subtilis* 109GGC020	Tareq et al. (2013)
Macrolactins X–Z (**30–32**)	Antibacterial	*Bacillus* sp. 09ID194	Mohamad et al. (2012)
Macrolactin T (**33**)	Antibacterial, antifungal	*Bacillus methylotrophicus* B-9987	Xue et al. (2008)
7-*O*-methyl-5′-hydroxy-3′-heptenoate macrolactin (**34**)	Antibacterial	*Bacillus subtilis* MTCC 10403	Chakraborty et al. (2014)
7-*O*-glucosyl-13,17-epoxy-16-hydroxy macrolactin A (**35**)	Antifungal	*Streptomyces* sp. 06CH80	Muhammad and Hee (2014)
7-*O*-glucosyl-15,17-epoxy-16-hydroxy macrolactin A (**36**)	Antibacterial, antifungal	*Streptomyces* sp. 06CH80	Muhammad and Hee (2014)
7-*O*-2′*E*-butenoyl macrolactin A (**37**)	Anti-inflammatory	*Bacillus subtilis* B5	Yan et al. (2016)
7,13-epoxy macrolactin A (**38**)	Anti-inflammatory	*Bacillus subtilis* B5	Yan et al. (2016)
7-*O*-6′-(2″-acetyl phenyl)-5′-hydroxyhexanoate macrolactin (**39**)	Antibacterial	*Bacillus subtilis* MTCC 10403	Chakraborty et al. (2017)

significantly inhibit the mRNA expression of inducible nitric oxide synthase (iNOS), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which are important targets in the treatment of inflammatory diseases.

7-*O*-6′-(2″-acetylphenyl)-5′-hydroxyhexanoate macrolactin (39) In 2018, a group isolated an aryl-crowned macrolactin, 7-*O*-6′-(2″-acetylphenyl)-5′-hydroxyhexanoate-hexanoate macrolactin (**39**) from *B. subtilis* MTCC 10403. Compound **39** could inhibit *E. coli*, *Aeromonas hydrophilla*, *P. aeruginosa* and *Vibrio* sp. with MIC < 13 μg/ml, which is more active than tetracycline and ampicillin. The antimicrobial mode of **39** was found to be iron chelating similar to siderophores. It was proposed that the side chain 6-(2-acetylphenyl)-5-hydroxyhexanoate moiety and pentane-2,4-diol moiety of the lactone ring might potentially bind freely available Fe^{3+}, resulting in inadequacy of the essential elements required for multiplication of pathogens (Chakraborty et al. 2017).

Biosynthesis of MLNs

Macrolide backbone assembly of MLNs

The backbone of MLNs is assembled via an AT-less type I modular PKS pathway. By gene deletion experiments, Schneider et al. (2007) identified the *pks2* (*mln*) gene cluster and confirmed its involvement in the biosynthesis of MLN A in *Bacillus amyloliquefaciens* FZB42. Li's group also identified the *bmm* gene cluster in the genome of *Bacillus methylotrophicus* B-9987 is responsible for the biosynthesis of MLN A (Liu et al. 2014a). The *mln/bmm* gene cluster consists of

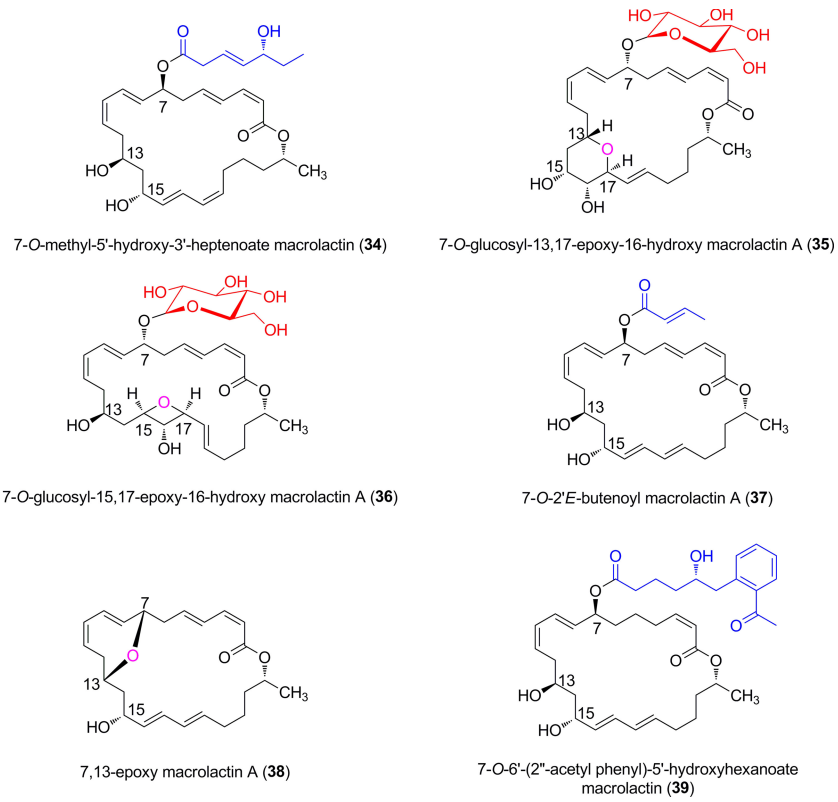

Fig. 2 Chemical structures of new natural MLNs since 2014 (**34**–**39**) (Chakraborty et al. 2014; Chakraborty et al. 2017; Li et al. 2016; Mondol et al. 2011a; Muhammad and Hee 2014; Yan et al. 2016)

nine genes (*mlnA-I/bmmA-I*), which are co-linear with the structure of MLN A (Fig. 3). *mlnA/bmmA* encodes a *trans*-acyltransferase, which is used iteratively for the translocation of malonyl-CoA in all extension units; *mlnB-H/bmmB-H* encode 11 PKS modules, which catalyze 11 successive Claisen condensations to form the polyketone chain; finally, the terminal hydroxyl group of the polyketone chain nucleophilically attacks the thioester-activated carbonyl group, generating MLN A (Liu et al. 2014a; Schneider et al. 2007).

Tailoring steps during MLN biosynthesis and "unnatural" new MLN compounds

While diverse modifications on the MLN backbone have been found, so far only the glycosylation step has been elucidated. Qin et al. (2014) and Liu et al. (2016) discovered three glycosyl transferase genes *bmmGT1-3* in the genome of *B. methylotrophicus* B-9987 by comparative genomics analysis. In vivo experiments demonstrated that *bmmGT1* is involved in the glycosylation of MLNs. In vitro studies showed that BmmGT1 could transfer a glucosyl group onto the 7-OH of MLN A (Fig. 3); BmmGT2 and BmmGT3 are also capable of transferring glucosyl groups onto 7-OH, 13-OH and 15-OH of MLN A, but interestingly with different regioselectivity (Liu et al. 2016; Qin et al. 2014). Through in vivo genetic experiments and in vitro biochemical reactions, 11 "unnatural" MLNs were obtained (Fig. 4).

7-*O*-acetylglucosamine macrolactin A (40), 7-*O*-succinyl-13-*O*-glucosyl macrolactin A (41), 7-*O*-succinyl macrolactin C (42), 7-*O*-malonyl-13-*O*-glucosyl macrolactin A (43) and 7-*O*-malonyl macrolactin C (44) Qin et al. (2014) explored the substrate promiscuity of BmmGT1 and found it could accept different sugar donors and acceptors. When using UDP-D-*N*-acetylglucosamine as the sugar donor, the acetylglucosamine group was transferred onto 7-OH of MLN A, generating 7-*O*-acetylglucosamine macrolactin A (**40**). They also probed the acceptor substrate specificity with different MLNs. When using SMA or MMA as the sugar acceptor, BmmGT1 could transfer the glucosyl group onto 13-OH of the substrates, generating 7-*O*-succinyl-13-*O*-glucosyl macrolactin A (**41**) or 7-*O*-malonyl-13-*O*-glucosyl macrolactin A (**43**); similarly, BmmGT1 could also transfer the glucosyl group onto the 15-OH of these substrates, generating 7-*O*-succinyl macrolactin C (**42**) or 7-*O*-malonyl macrolactin C (**44**) (Fig. 4a).

7-*O*-[glucosyl-(1 → 3)-glucosyl] macrolactin A (45) and 7-*O*-glucosyl-13-*O*-[glucosyl-(1 → 3)-glucosyl] macrolactin A (46) To further explore the application potential of BmmGT1, Liu et al. (2018) probed its regioselectivity on MLN A by optimization of the reaction time and working concentration of the enzyme. When the reaction time was extended to 1 h, BmmGT1 could transfer two glucosyl groups onto the 7-OH of MLN A, generating the di-*O*-glucosyl analog 7-*O*-[glucosyl-(1 → 3)-glucosyl]

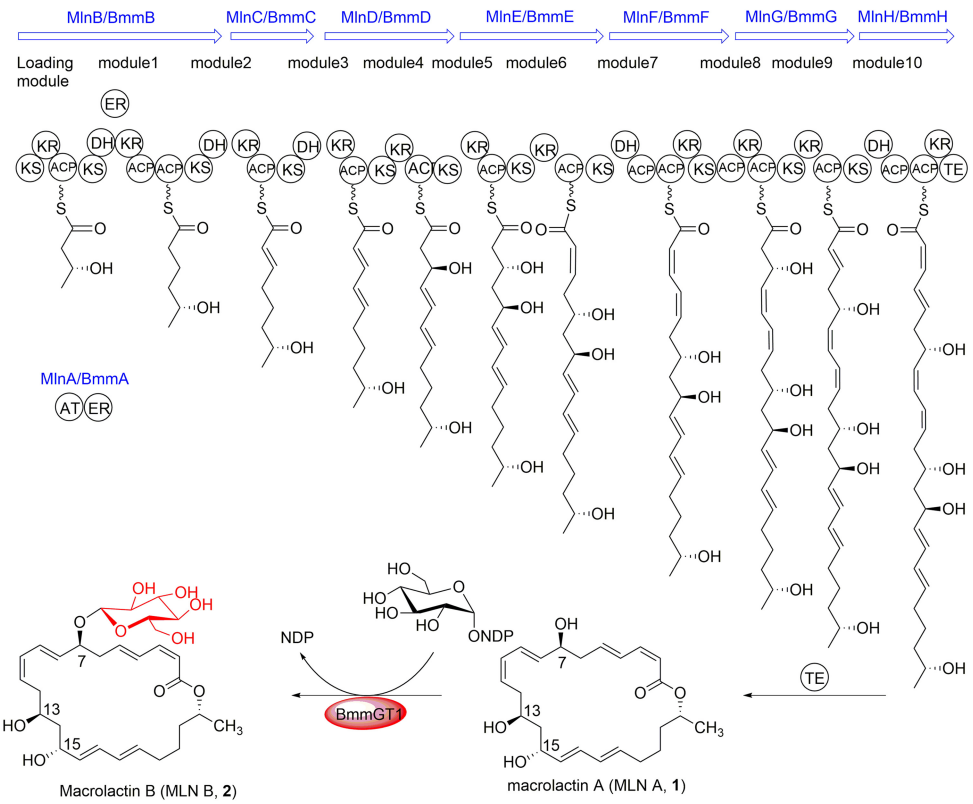

Fig. 3 The proposed biosynthetic pathway of MLNs. (Liu et al. 2014a; Qin et al. 2014; Schneider et al. 2007) *KS* ketosynthase, *ACP* acyl carrier protein, *AT* acyltransferase, *KR* ketoreductase, *DH* dehydratase, *ER* enoylreductase, *TE* thioesterase, *GT* glycosyltransferase. bmmGT1 is located outside of the MLN biosynthetic gene cluster

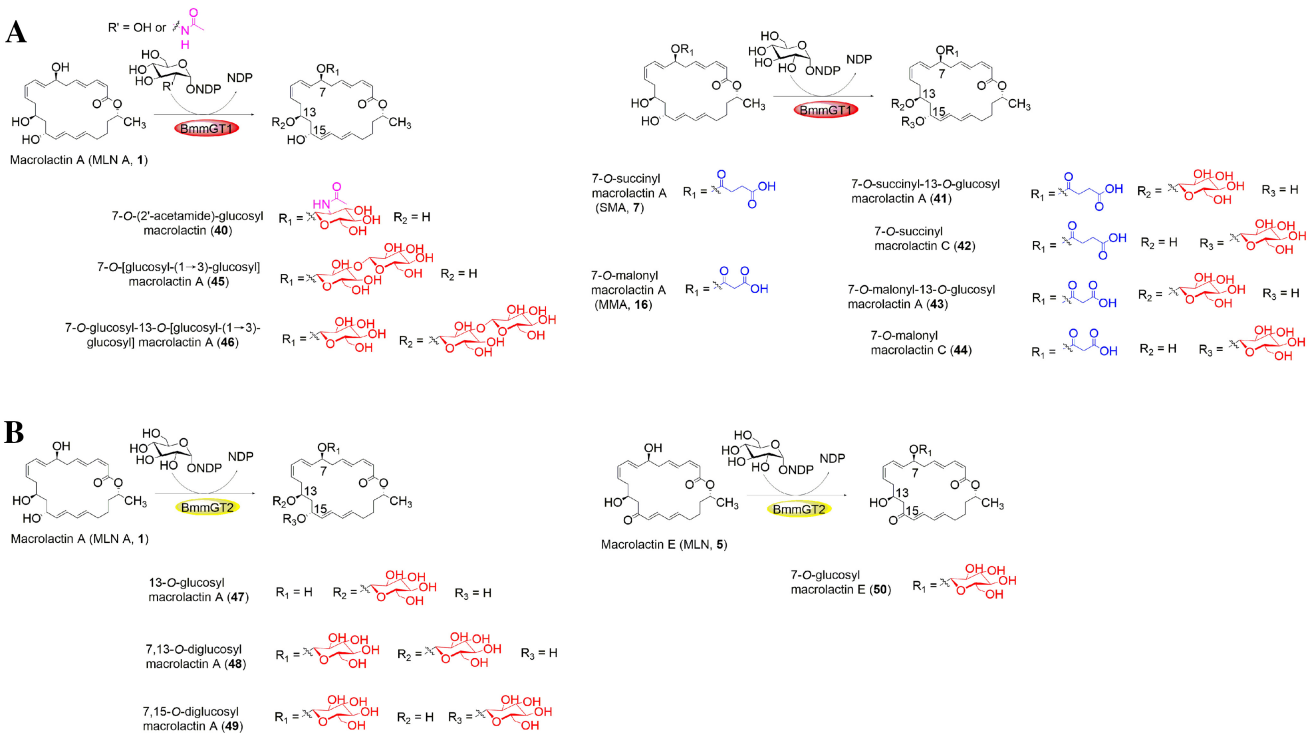

Fig. 4 Generation of "unnatural" new MLNs (**40–50**). **a** Generation of compounds **40–46** by BmmGT1; **b** generation of compounds **47–50** by BmmGT2 (Liu et al. 2018; Liu et al. 2016; Qin et al. 2014)

macrolactin A (**45**). On the other hand, as the enzyme concentration was increased to 4 μmol/L, two glucosyl groups were transferred onto the 13-OH of MLN A and one glucosyl group was transferred onto the 7-OH of MLN A, generating the tri-*O*-glucosyl analog 7-*O*-glucosyl-13-*O*-[glucosyl-(1 → 3)-glucosyl] macrolactin A (**46**) (Fig. 4a).

13-*O*-glucosyl macrolactin A (47), 7,13-*O*-diglucosyl macrolactin A (48), 7,15-*O*-diglucosyl macrolactin A (49) and 7-*O*-glucosyl macrolactin E (50) BmmGT2 also has a broad substrate selectivity, recognizing MLN A, MMA and macrolactin E (MLN E, **5**). When MLN A was used as sugar acceptor, UDP-D-glucose as sugar donor, BmmGT2 could transfer the glucosyl group onto 15-OH of MLN A, generating macrolactin C (MLN C, **3**), or onto 13-OH, generating a new compound 13-*O*-glucosyl macrolactin A (**47**). With the increase in enzyme concentration to 10 μmol/L, two di-*O*-glucosyl analogs 7,13-*O*-diglucosyl macrolactin A (**48**) and 7,15-*O*-diglucosyl macrolactin A (**49**) were generated. When MLN E was used as sugar acceptor, a new compound 7-*O*-glucosyl macrolactin E (**50**) was obtained (Fig. 4b) (Liu et al. 2016).

In addition, Liu et al. (2018) found BmmGT1 was also able to catalyze the glycosylation of thiol (*S*-) or amine (*N*-) sites of 3,4-dichloroaniline and 3,4-dichlorothiophenol, generating *N*- or *S*-glycosides. The broad substrate spectrum of BmmGT1 makes it a potential enzyme tool for structural diversification of active compounds.

Yield improvement of MLN A

The source scarcity has precluded further pharmacological investigation of MLNs. Chemical synthesis of MLNs has been accomplished, but with multiple steps and unsatisfying yields (Kim et al. 1998; Marino et al. 2002; Smith and Ott 1998). To efficiently improve the production of MLNs, He et al. (2013) used response surface methodology to optimize the fermentation conditions of *Bacillus amyloliquefaciens* ESB-2. The yield of MLN A was improved to 21.63 mg/L, which increased 2.4-fold compared to that in the original conditions. By overexpression of the *trans*-acyltransferase gene *mlnA* homolog *bmmA* in *B. methylotrophicus* B-9987, the production of MLN A was enhanced by about 0.6-fold (Liu et al. 2014b). Similarly, overexpression of *sfp* encoding phosphopantetheinyl transferase in *B. methylotrophicus* B-9987 also led to the production improvement of MLN A by 1.6-fold (Liu et al. 2014a; Nakano et al. 1992). In the *bmmGT1* inactivation mutant *ΔbmmGT1*, the production of MLN A reached 105 mg/L, which was about 6-fold higher than that of the wild-type strain (Qin et al. 2014).

Concluding remarks/Perspective

Most naturally isolated MLNs are from marine-derived *Bacillus* strains. While MLNs possess a wide range of bioactivities, their modes of action are still not very clear. With the amendable genetic manipulation system of their producer, as well as the disclosed tailoring biocatalysts, more MLNs derivatives with novel structures and improved bioactivities would be generated, which would contribute to structural diversification for drug development as well as elucidation of the action mechanism of MLNs.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interests.

Animal and human rights statement No animal and human rights are involved in this article.

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