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MINI-REVIEW

Prenyltransferases as key enzymes in primary and secondary metabolism

Julia Winkelblech[1,2] · **Aili Fan**[1] · **Shu-Ming Li**[1,2]

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Abstract Attachment of isoprene units to various acceptors by prenylation plays an important role in primary and secondary metabolism of living organisms. Protein prenylation belongs to posttranslational modification and is involved in cellular regulation process. Prenylated secondary metabolites usually demonstrate promising biological and pharmacological activities. Prenyl transfer reactions catalyzed by prenyltransferases represent the key steps in the biosynthesis and contribute significantly to the structural and biological diversity of these compounds. In the last decade, remarkable progress has been achieved in the biochemical, molecular, and structural biological investigations of prenyltransferases, especially on those of the members of the dimethylallyltryptophan synthase (DMATS) superfamily. Until now, more than 40 of such soluble enzymes are identified and characterized biochemically. They catalyze usually regioselective and stereoselective prenylations of a series of aromatic substances including tryptophan, tryptophan-containing peptides, and other indole derivatives as well as tyrosine or even nitrogen-free substrates. Crystal structures of a number of prenyltransferases have been solved in the past 10 years and provide a solid basis for understanding the mechanism of prenyl transfer reactions.

✉ Shu-Ming Li
shuming.li@staff.uni-marburg.de

[1] Institut für Pharmazeutische Biologie und Biotechnologie, Philipps-Universität Marburg, Deutschhausstrasse 17A, D-35037 Marburg, Germany

[2] Zentrum für Synthetische Mikrobiologie, Philipps-Universität Marburg, D-35032 Marburg, Germany

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Introduction

Prenyltransferases catalyze the transfer reactions of prenyl moieties from different prenyl donors, e.g., dimethylallyl (DMAPP with a branched C_5-chain), geranyl (GPP, C_{10}), farnesyl (FPP, C_{15}), or geranylgeranyl (GGPP, C_{20}) diphosphate, to various aliphatic or aromatic acceptors of both low and high molecular substances including proteins and nucleic acids (Dumelin et al. 2012; Heide 2009a; Li 2009a; Oldfield and Lin 2012; Palsuledesai and Distefano 2015; Xie et al. 2007; Yazaki et al. 2009). The prenylation reactions can take place in regular manner (regular prenylation) by connection of the prenyl moieties via their C-1 to an acceptor or reverse manner (reverse prenylation) via their C-3 atoms (Heide 2009a; Yu and Li 2012).

Prenylated secondary metabolites including indole alkaloids, flavonoids, coumarins, xanthones, quinones, and naphthalenes are widely distributed in terrestrial and marine organisms (Fig. 1). They exhibit a wide range of biological activities such as cytotoxicity, antioxidant (Sunassee and Davies-Coleman 2012), and antimicrobial activities (Liu et al. 2013a; Oya et al. 2015), which are often distinct from their non-prenylated precursors. Prenyl transfer reactions usually represent the key steps in the biosynthesis of such compounds. Furthermore, the prenylated products can be further modified by cyclization, hydroxylation, oxidation, and so on (Raju et al. 2011; Tagami et al. 2013). Therefore, prenyltransferases

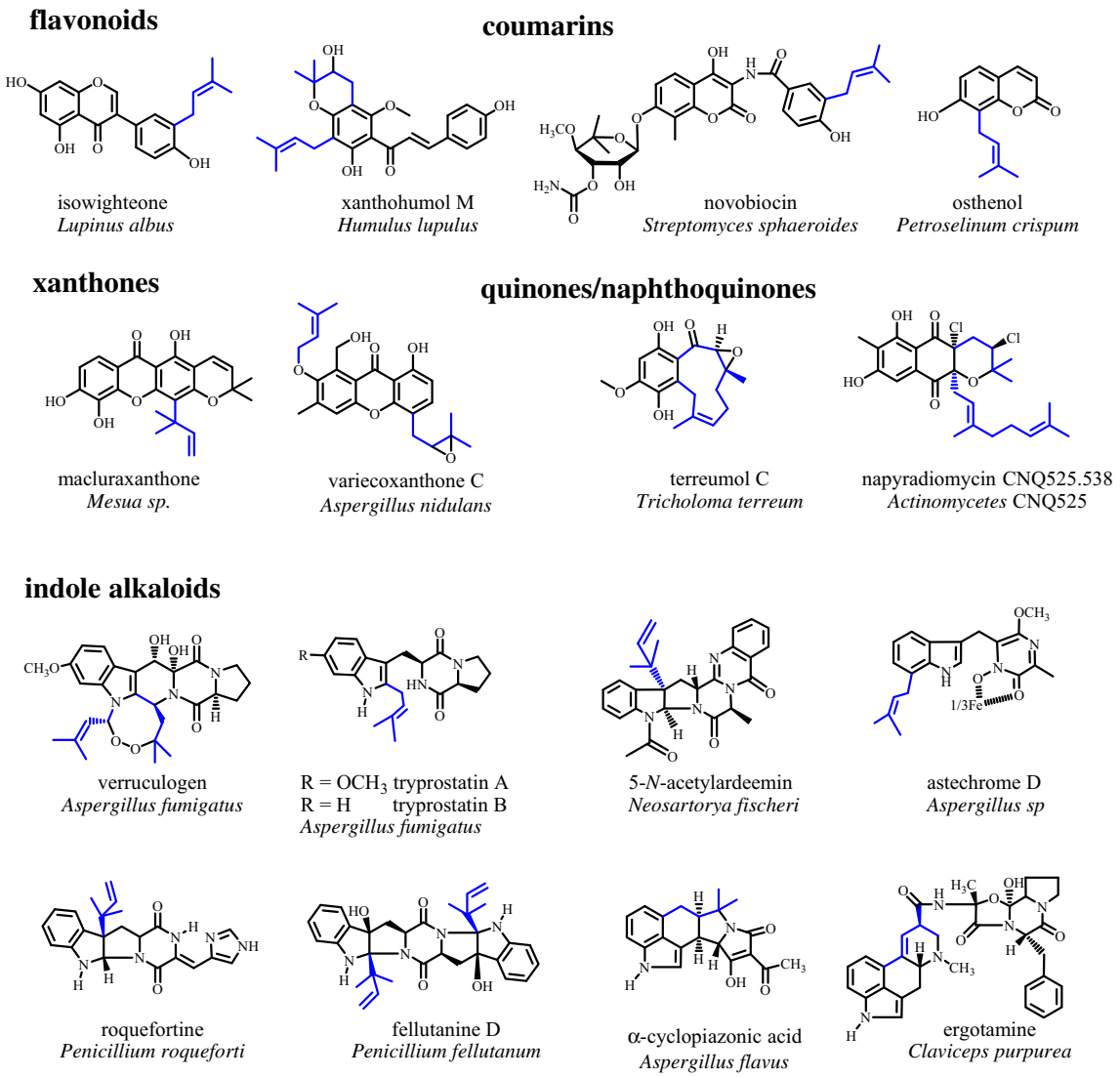


Fig. 1 Examples of prenylated natural products

contribute significantly to structural and biological diversity of natural products.

Based on their primary amino acid sequences, biochemical and structural characteristics, prenyltransferases are categorized into different subgroups (Table 1). Prenyl diphosphate synthases use prenyl diphosphate as donor and isopentenyl diphosphate (IPP) as acceptor (Oldfield and Lin 2012), while protein prenyltransferases catalyze the transfer reactions of C_{15} chain from FPP or C_{20} chain from GGPP to cysteine residues of proteins (Palsuledesai and Distefano 2015). Peptide prenyltransferases of the TruF family catalyze *O*-prenylations of tyrosyl residues of cyclic peptides in the presence of DMAPP. DMAPP and GPP serve as prenyl donors for tRNA prenyltransferases from bacteria (Dumelin et al. 2012; McIntosh et al. 2011, 2013; Xie et al. 2007). A large prenyltransferase group uses diverse nitrogen-containing and nitrogen-free aromatic compounds as substrates, and among them, the dimethylallyltryptophan synthase (DMATS) superfamily is one of the most investigated subgroup. The name of this superfamily was given due to their sequence similarity to DMATS involved in the biosynthesis of ergot alkaloids of *Claviceps* sp. (Tsai et al. 1995).

Since the first reviews on the DMATS enzymes in 2009 (Li 2009a, b; Steffan et al. 2009), significant progress has been achieved for this enzyme group. Thirty-two new enzymes have been characterized biochemically. The natural substrates of the DMATS enzymes were found to be much broader than just indole derivatives known at that time. Tyrosine, xanthones, tricyclic or tetracyclic aromatic or even nonaromatic compounds also serve as natural substrates of enzymes with sequence similarity to DMATS. In contrast, the spectrum of the natural prenyl donors of these enzymes is relatively narrow, and most of the members of the DMATS superfamily use DMAPP for prenylation. In addition, crystal structures of four DMATS enzymes were solved and used as basis for understanding

Table 1 Classification of prenyltransferases with their natural functions

Enzyme type	Donor	Acceptor (examples)	Function/biosynthesis
prenyl diphosphate synthases			
trans-prenyltransferases	prenyl diphosphate	isopentenyl diphosphate	all-*trans*-isoprenoids, terpenoids, steroids
cis-prenyltransferases	prenyl diphosphate	isopentenyl diphosphate	*trans*-/*cis*-isoprenoids, membrane components
peptide prenyltransferases	dimethylallyl, geranyl diphosphate	(cyclic) oligopeptides	pheromones/secondary metabolites
protein prenyltransferases	farnesyl or geranylgeranyl diphosphate	cysteine residue of proteins	posttranslational modification of proteins, cellular localization, protein-protein interaction
tRNA prenyltransferases	dimethylallyl and geranyl diphosphate	adenine or 5-methylaminomethyl-2-thiouridine	translational regulation
aromatic prenyltransferases			
membrane-bound prenyltransferases	prenyl diphosphate	benzoic & naphthoic acids, flavonoids	primary & secondary metabolites
soluble aromatic prenyltransferases			
NphB/CloQ group	dimethylallyl, geranyl and farnesyl diphosphate,	naphthalenes, quinones, phenols, phenazines	secondary metabolites
DMATS family	dimethylallyl, geranyl and farnesyl diphosphate	indole derivatives, tyrosine, naphthalenes, xanthones	secondary metabolites,

of the reaction mechanism. Since 2009, several reviews on different aspects of the DMATS superfamily, mainly on indole prenyltransferases, have appeared (Tanner 2014; Walsh 2014; Yu and Li 2012). A systematic summary covering classification, occurrence, natural function, biochemical properties, crystal structures, and reaction mechanism of this intriguing enzyme group is now necessary. For a better understanding of prenyltransferases as nxC_5 transferring enzymes onto diverse acceptors and their natural roles, we begin in this review with a brief overview on different classes of prenyltransferases and then focus on the members of the DMATS superfamily. In another mini-review in this issue, we will discuss the potential usage of DMATS prenyltransferases in biotechnology, which has been demonstrated by a large number of studies in the last years.

Classification of prenyltransferases

IPP and DMAPP, derived from the acetate-mevalonate or methylerythritol phosphate pathway (Boronat and Rodriguez-Concepcion 2015; Chang et al. 2013; Zhao et al. 2013), serve as precursors for prenyl diphosphate (nxC_5) biosynthesis (Oldfield and Lin 2012). The prenyl diphosphates can be used for the biosynthesis of different terpenoids by cyclization and oxidation or as prenyl donors for peptide, protein and tRNA prenyltransferases, or aromatic prenyltransferases. The donors, acceptors, products, and functions of different prenyltransferases are summarized in Table 1.

Prenyl diphosphate synthases

Over 63,000 isoprenoid natural products have been identified to date, which bear numerous important biological functions and show an enormous structural diversity based on their different carbon skeletons and substitutions (Liang et al. 2002; Ramamoorthy et al. 2015). In the biosynthesis of isoprenoids, prenyl diphosphate synthases catalyze the formation of the carbon backbone with defined chain length by sequential condensation of DMAPP or other prenyl diphosphates with a given number of IPP. According to the formed double bond configuration in the prenyl units, these chain elongating enzymes can be classified into two major groups, i.e., *trans*- and *cis*-prenyltransferases (Fig. 2).

FPP synthases (FPPase) belong to the first group and catalyze the formation of all-*trans* C_{15} precursor FPP by utilizing IPP as acceptor for the sequential condensations with DMAPP and GPP (Poulter 2006). FPP could serve as a precursor for a number of essential or important metabolites, e.g., sesquiterpenoids, triterpenoids, sterols, dolichols, and ubiquinones (Anderson et al. 1989).

GGPP synthases also belong to *trans*-prenyltransferases and catalyze, similar to FPPases, the formation of all-*trans* configured geranylgeranyl diphosphate. They are involved in the biosynthesis of plant secondary metabolites like diterpenoids or carotenoids (Liu et al. 2014b). Furthermore, octaprenyl diphosphate synthase (OPPS) catalyzes successive condensation reactions of FPP with five IPP to generate C_{40} products with *trans*-configured double bonds (Fig. 2). The resulted prenyl diphosphate can be used as donor for quinone

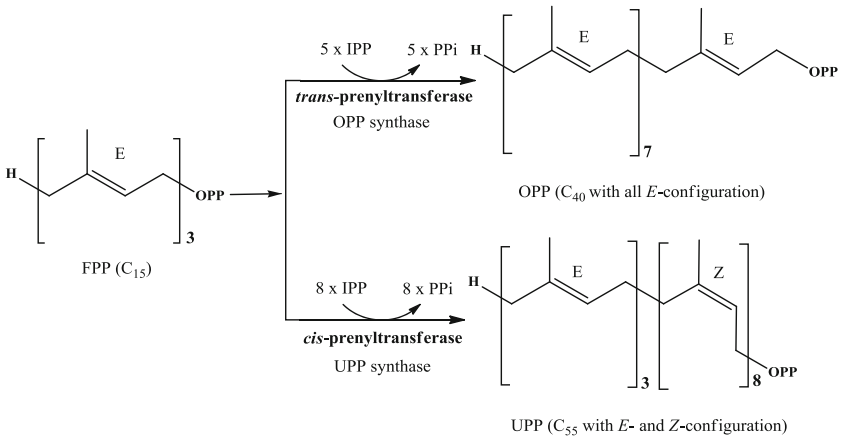


Fig. 2 Examples of prenyl diphosphate synthase reactions

prenylation in the biosynthesis of ubiquinone, menaquinone, or plastoquinones (Soballe and Poole 1999). The homodimeric enzymes of *trans*-prenyltransferases consist of α-helices with two conserved aspartate-rich DDxxD motifs, which allowed the binding of the substrates in complex with Mg^{2+} (Guo et al. 2004).

In contrast, *cis*-prenyltransferases produce prenyl diphosphates containing both *Z*- and *E*-configured double bonds, although they use the same substrates and their catalyzed reactions are Mg^{2+} dependent (Fig. 2). Their amino acid sequences and three-dimensional structures completely differ from those of *trans*-prenyltransferases. Instead of the DDxxD motif, an aspartate in the conserved P-loop of *cis*-prenyltransferases is involved in the chelating of Mg^{2+} (Guo et al. 2005). According to the length of their products, they are further classified into short- (C_{15}), medium- (C_{50}–C_{55}), and long-chain (C_{70}–C_{120}) *cis*-prenyltransferases (Lu et al. 2009; Takahashi and Koyama 2006). Undecaprenyl diphosphate synthase for example catalyzes the condensation of FPP with eight IPPs, resulting in the formation of a C_{55} product (Fig. 2). Undecaprenyl monophosphate acts as a lipid carrier in the peptidoglycan biosynthesis of bacterial cell wall and therefore serves as a target for antibacterial drugs (Danley et al. 2015).

Prenylated lipids are also found in membranes of archaeal bacteria. The geranylgeranylglyceryl phosphate synthase (GGGP synthase) from *Methanobacterium thermoautotrophicum*, which shows practically no homology to other prenyltransferases, catalyzes the alkylation of glyceryl phosphate in the presence of GGPP (Soderberg et al. 2001).

Peptide, protein, and tRNA prenyltransferases

The ComX pheromone identified in *Bacillus subtilis* is a hexapeptide containing a regularly *C3*-geranylated tryptophan residue. The responsible prenyltransferase ComQ was identified by overproduction in *Escherichia coli* (*E. coli*) and incubation with an oligopeptide comprising 58 amino acids in the presence of GPP. The C-terminal geranylated hexapeptide corresponding to the mature ComX pheromone was identified as a minor and a C-terminal geranylated heptapeptide as the main product (Tsuji et al. 2012).

Cyanobactins from *Lyngbya aestuarii* are cyclic heptapeptides containing regularly *C3*-prenylated tyrosyl residues. The prenyltransferase LynF uses cyclic heptapeptides as substrates and catalyzes regular and reverse *O*-prenylations of tyrosyl residues. The reversely prenylated enzyme products then undergo a Claisen rearrangement resulting in *C*-prenylated derivatives (McIntosh et al. 2011, 2013).

Protein prenyltransferases use polypeptides as substrates. They play an important role in the posttranslational modification of proteins in eukaryotes and represent interesting drug targets (Palsuledesai and Distefano 2015). They transfer either a farnesyl (C_{15}) or a geranylgeranyl (C_{20}) moiety to a conserved cysteine residue in a CaaX motif at the C-terminus of the targeted proteins or peptides (Palsuledesai and Distefano 2015; Perez-Sala 2007). These modifications are responsible for correct cellular localization and activity of several proteins including those from the Ras family. The primary sequences as well as the crystal structures of protein prenyltransferases clearly differ from that of the prenyl diphosphate synthases. For the Ras farnesyltransferase reaction, the formation of Zn^{2+}-activated thiolate by the cysteine residue of the CaaX box is necessary (Long et al. 2002). Due to the role of farnesylated proteins in oncogenic processes or several diseases including progeria, aging, parasitic diseases, and bacterial or viral infections, the underlying prenylation reaction and its inhibition by potential therapeutics have been extensively investigated (Abuhaie et al. 2013; Palsuledesai and Distefano 2015; Sousa et al. 2009; Zhu et al. 2014).

Modifications by prenylations are not only found in proteins, but also in nucleic acids, e.g., tRNAs. Two dimethylallyltransferases (DMATase) from *Pseudomonas aeruginosa* (*P. aeruginosa*) and *E. coli* were proven to prenylate the amino group of adenosine-37 (A37) of all tRNAs with uridine at the beginning (Xie et al. 2007).

Recently, SelU from *E. coli* was reported to catalyze *S*-geranylation of 5-methylaminomethyl-2-thiouridyl residue in tRNA in the presence of GPP (Dumelin et al. 2012).

Aromatic prenyltransferases

Aromatic prenyltransferases catalyze the transfer reactions of prenyl moieties onto aromatic acceptors such as phenols, phenolic acids, flavonoids, coumarins, naphthalenes, phenazines, or indole derivatives. These enzymes contribute substantially to the large diversity of prenylated secondary metabolites in plants, fungi, and bacteria (Heide 2009b; Li 2009b; Yazaki et al. 2009). They usually catalyze the formation of C–C, C–O, or C–N bonds between the carbon of the prenyl and carbon or functional groups of the aromatic substrates. Membrane-bound and soluble aromatic prenyltransferases were found to exhibit distinct characteristics such as structural fold, substrate binding motifs, or metal ion dependency.

Membrane-bound prenyltransferases for aromatic substrates

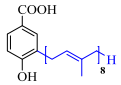
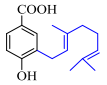
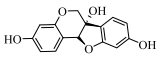
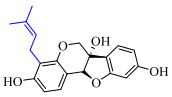
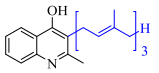
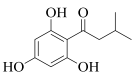
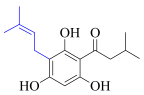
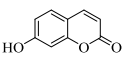
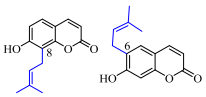
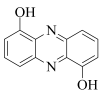
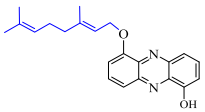
Members of this enzyme group are involved in the biosynthesis of both primary metabolites such as ubiquinones and menaquinones (Boronat and Rodriguez-Concepcion 2015; Meganathan and Kwon 2009) and secondary metabolites like microbial and plant natural products (Holm et al. 2014; Wang et al. 2014; Yazaki et al. 2009; Zeyhle et al. 2014a, b).

Ubiquinones and menaquinones function as electron and proton carrier in photosynthesis and cellular respiration and also as antioxidants for prevention of cell damage. Membrane-bound prenyltransferases contain, similar to the aforementioned FPPs, characteristic aspartate-rich motifs, e.g., NDxxDxxxD, and require metal ions such as Mg^{2+} for their catalytic activity. The underlying prenyl transfer reactions were observed for various aromatic substrates like 4-hydroxybenzoate (4HB), homogentisic acid, coumarines, flavonoids, 1,4-dihydroxy-2-naphthoate, or phenazines (Heide 2009a; Karamat et al. 2014; Yazaki et al. 2009; Zeyhle et al. 2014a, b). Several examples of membrane-bound prenyltransferases and their catalyzed reactions are summarized in Table 2. UbiA from *E. coli* as a prototype of this family plays an important role in the biosynthesis of ubiquinones and catalyzes the attachment of an all-*trans* octaprenyl moiety onto 4HB (Melzer and Heide 1994). UbiA shows a broad substrate specificity toward prenyl donors and is able to generate ubiquinones CoQ_6 to CoQ_{10} in different species (Cheng and Li 2014). Recently, the crystal structure of an archeal UbiA was reported (Cheng and Li 2014), which provides new insights into the substrate binding sites and mechanism of the enzyme catalysis. Very recently, a prenyltransferase UbiX from *P. aeruginosa* involved in the biosynthesis of ubiquinones was demonstrated to use flavin as a prenyl acceptor. In contrast to prenyl diphosphates for other known prenyltransferases, dimethylallyl monophosphate (DMAP) serves as prenyl donor for UbiX reaction (White et al. 2015).

In human cells, COQ2 is involved in the biosynthesis of ubiquinone for mitochondrial respiration, while UBIAD1 in the biosynthesis of vitamin K for maintaining vascular homeostasis (Hegarty et al. 2013; Nakagawa et al. 2010). UbiA homologs, e.g., AtPPT1 from *Arabidopsis thaliana* (*A. thaliana*) and OsPPT1 from *Oryza sativa*, were found to be involved in primary metabolism of plants (Okada et al. 2004; Ohara et al. 2006). In plants, membrane-bound aromatic prenyltransferases are also involved in the biosynthesis of secondary metabolites. The 4HB geranyltransferases LePGT-1 and LePGT-2 from *Lithospermum erythrorhizon* are involved in the biosynthesis of the naphthoquinone shikonin (Yazaki et al. 2002). In contrast to the 4HB prenyltransferases for ubiquinone biosynthesis, these enzymes are localized in the endoplasmatic reticulum rather than in mitochondria. They show strict substrate specificity for GPP as prenyl donor. Several members of the membrane-bound prenyltransferases are involved in the biosynthesis of prenylated flavonoids and isoflavonoids in plants. N8DT, G6DT, and SfiLDT from *Sophora flavescens* catalyze the prenylations of naringenin, genistein, and isoliquiritigenin, respectively (Chen et al. 2013; Sasaki et al. 2011). Furthermore, the formation of *C3′*-prenylated genistein was detected in vitro with LaPT1 from *Lupinus albus* (Shen et al. 2012). Pterocarpan 4-dimethylallytransferase (G4DT) catalyzes the transfer of a dimethylallyl moiety onto pterocarpan skeleton and is therefore responsible for the formation of the soybean phytoalexin glyceollin (Akashi et al. 2009). In plants, three kinds of homogentisic acid prenyltransferases use solanesyl (C_{45}), geranylgeranyl (C_{20}), and phytyl (C_{20}, partially saturated) diphosphate for their prenylation reactions in the biosynthesis of plastoquinones, tocotrienols, and tocopherols, respectively (Heide 2009a). The last two compounds are also known as vitamin E. Moreover, 1,4-dihydroxy-2-naphthoate serves as substrate for the octaprenyltransferase MenA in *E. coli* and for the phytyltransferase ABC4 in phylloquinone biosynthesis in *A. thaliana* (Shimada et al. 2005; Suvarna et al. 1998). In addition, chlorophyllide and protoheme IX were used by chlorophyll synthase ATG4 (Eckhardt et al. 2004) and protoheme IX farnesyltransferase COX10, both from *A. thaliana*, respectively (Saiki et al. 1993). Furthermore, two membrane-bound prenyltransferases were found to catalyze three sequential prenylation steps in the biosynthesis of bitter acid in hop (Li et al. 2015). PcPT from parsley was found to be a key enzyme in the biosynthesis of linear and angular furanocoumarins and to catalyze prenylations of umbelliferon at both C-6 and C-8 positions (Karamat et al. 2014).

Membrane-bound aromatic prenyltransferases were also identified for the secondary metabolism in bacteria. One

Table 2 Examples of membrane-bound prenyltransferases and their catalyzed reactions

Enzyme (accession number)	Organism	Substrate	Product	Biosynthetic pathway	Reference
UbiA (WP_000455227)	*E. coli*	 4-hydroxybenzoic acid	 3-octaprenyl-4-hydroxybenzoic acid	ubiquinones	(Melzer and Heide 1994)
LePGT-1 (BAB84122)	*L. erythrorhizon*	 4-hydroxybenzoic acid	 3-geranyl-4-hydroxybenzoic acid	shikonin	(Yazaki et al. 2002)
G4DT (BAH22520)	*Glycine max*	 (-)-glycinol	 4-dimethylallylglycinol	glyceollin	(Akashi et al. 2009)
AuaA (CCA65701)	*Stigmatella aurantiaca*	 2-methyl-4-hydroxy-quinoline	 aurachin D	aurachin A	(Stec et al. 2011)
HlPT-1 (BAJ61049)	*H. lupulus*	 phlorisovalerophenone	 prenyl phlorisovalerophenone	bitter acid	(Tsurumaru et al. 2012)
PcPT (BAO31627)	*P. crispum*	 umbelliferone	 osthenol + demethylsuberosin (DMS)	furanocoumarin	(Karamat et al. 2014)
CnqPT1 (AIT42139)	*Streptomyces sp. CNQ-509*	 1,6-dihydroxy phenazine	 marinophenazine B	marinophenazine	(Zeyhle et al. 2014b)

E. Escherichia, *L. Lithospermum*, *P. Petroselinum*, *H. Humulus*

example is the farnesyltransferase AuaA from the myxobacterium *Stigmatella aurantiaca* in the biosynthesis of aurachins, which catalyzes the farnesylation of 2-methyl-4-hydroxyquinoline (Stec et al. 2011). Very recently, two membrane-bound aromatic prenyltransferases were identified in *Streptomyces* and found to be responsible for phenazine prenylations (Zeyhle et al. 2014a, b).

Soluble prenyltransferases with PT barrel mostly for aromatic substrates

The large enzyme group for prenylation of aromatic substrates comprises the CloQ/NphB group and the extensively investigated DMATS superfamily, which are soluble proteins from bacteria and fungi. One common structural feature of these enzymes is their *aßßa*-fold (ABBA), termed PT-barrel and firstly observed for the naphthalene geranyltransferase NphB (Kumano et al. 2008; Kuzuyama et al. 2005).

Enzymes of the CloQ/NphB subgroup

Known prenyltransferases of the CloQ/NphB group use only aromatic compounds as substrates and catalyze prenylations of naphthalenes, phenazines, quinones, and phenolic compounds (Table 3) (Heide 2009a). They were found in both bacteria and fungi and differ strongly from the aforementioned membrane-bound prenyltransferases (Haug-Schifferdecker et al. 2010). They do not contain the aspartate-rich NDxxD motif, and their reactions are with the exception of that for NphB independent of divalent metal ions (Bonitz et al. 2011; Heide 2009a). The notation of the subgroup referred to the first identified enzyme CloQ from *Streptomyces roseochromogenes* and the 2 years later

reported NphB from *Streptomyces* sp. (Kuzuyama et al. 2005; Pojer et al. 2003). CloQ and its ortholog NovQ from *Streptomyces spheroides* catalyze the prenylation of 4-hydroxyphenylpyruvic acid in the biosynthesis of clorobiocin (Pojer et al. 2003) and novobiocin (Steffensky et al. 2000) (Fig. 1). NphB is involved in the biosynthesis of the geranylated derivative naphterpin (Kuzuyama et al. 2005). The crystal structures of NphB, CloQ, and EpzP share an ABBA barrel in common (Kuzuyama et al. 2005; Metzger et al. 2010; Wierenga et al. 2010; Zocher et al. 2012). These structures can serve as basis for molecular modeling studies and therefore provide valuable contributions to our knowledge on mechanisms of the prenyl transfer reactions (Bayse and Merz 2014; Yang et al. 2012). Furthermore, NphB shows a broad substrate specificity toward several phenolic compounds, e.g., resveratrol, flavonoids, and 4-HPP (Heide 2009a; Kumano et al. 2008; Kuzuyama et al. 2005). In the last years, several additional prenyltransferases of the CloQ/NphB group have been identified. SCO7190, a homolog of NphB from *Streptomyces coelicolor* A3(2), catalyzes the attachment of the dimethylallyl from DMAPP, but not geranyl moiety from GPP onto 1,6-dihydroxynaphthalene (Kumano et al. 2008; Kuzuyama et al. 2005). SCO7190 and NovQ were successfully used for production of novel prenylated polyphenols in transgenic plants (Sugiyama et al. 2011). Fnq26 from *Streptomyces cinnamonensis* DSM 1042 shares a sequence identity of 40 % with NphB and catalyzes reverse and regular *C*- as well as regular *O*-prenylations of several phenolic substrates (Haagen et al. 2007). Recently, McI23 from *Streptomyces* sp. CNH-189 was found to catalyze the formation of a prenylated precursor of merochlorin by utilizing a diphosphate of an unusual branched C_{15} unit as prenyl donor, which was formed by addition of a dimethylallyl moiety to GPP in a reverse manner catalyzed by Mcl22 (Teufel et al. 2014). In the secondary metabolism of *Streptomyces cinnamonensis* and *Streptomyces anulatus*, EpzP and PpzP catalyze the regiospecific *C9*-prenylation of 5,10-dihydrophenazine-1-carboxylic acid (Saleh et al. 2009; Seeger et al. 2011). As aforementioned, prenylation of phenazine derivatives can also be catalyzed by membrane-bound prenyltransferases (Table 3) (Zeyhle et al. 2014a, b). DzmP from *Micromonospora* sp. RV115 is the first member of this subgroup which utilize FPP instead of DMAPP and GPP as prenyl donor and catalyzes the unusual *N*-farnesylation of dibenzodiazepinone (Bonitz et al. 2013).

Enzymes of the DMATS superfamily

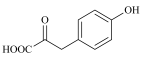
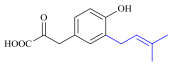
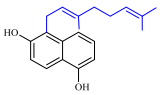
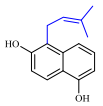
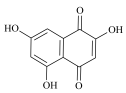
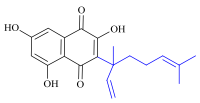
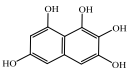
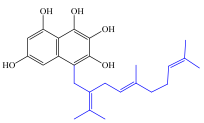
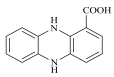
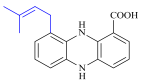
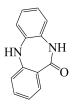
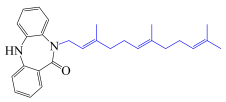
The DMATS superfamily is the most investigated subgroup among the prenyltransferases. In the last years, enormous advances have been achieved on the biochemical, molecular, and structural biological investigations of these soluble enzymes. So far, more than 40 such enzymes from fungi and bacteria have been identified mostly by genome mining and characterized biochemically by using the recombinant proteins (Fan et al. 2014; Pockrandt et al. 2014; Winkelblech and Li 2014; Wunsch et al. 2015; Yu et al. 2012; Yu and Li 2012). They mainly catalyze the prenylation of indole derivatives including tryptophan and tryptophan-containing cyclic dipeptides. DMATS prenyltransferases carry no aspartate-rich motifs and their catalysis is independent of the presence of metal ions, although Ca^{2+}, Mg^{2+}, or other metal ions strongly enhance their activities in several cases (Li 2009a; Pockrandt et al. 2012; Yu and Li 2012).

The first member of the DMATS superfamily was the tryptophan *C4*-prenyltransferase DmaW involved in the biosynthesis of ergot alkaloids in *Claviceps fusiformis*, reported as *Claviceps purpurea* (*C. purpurea*) (Gebler and Poulter 1992; Tsai et al. 1995). Its ortholog FgaPT2 from *Aspergillus fumigatus* (*A. fumigatus*) was identified in 2005 by genome mining using the DmaW sequence from *C. purpurea* (Tudzynski et al. 1999; Unsöld and Li 2005). Until now, 12 enzymes were identified, which catalyze different prenylations of tryptophan at N-1 and C-4 to C-7 (Table 4) (Li 2010; Yu and Li 2012). Cyclic (di)peptide or related prenyltransferases with 14 members build the largest group, which catalyze the prenylations at N-1, C-2, C-3, and C-7 of the indole ring (Table 5). In addition, a large number of indole derivatives were identified as substrates of these enzymes (Table 6). Two members of the DMATS superfamily, SirD and TyrPT, use tyrosine as substrate and catalyze *O*-prenylation (Table 6) (Fan et al. 2014; Kremer and Li 2010). Since 2010, nitrogen-free or nonaromatic compounds were identified as substrates of additional 16 prenyltransferases of the DMATS superfamily (Table 6). In total, 19 such enzymes have been characterized biochemically so far.

Tryptophan prenyltransferases

As summarized in Table 4, 12 tryptophan prenyltransferases, five from bacteria and seven from fungi, were identified and characterized biochemically. These enzymes catalyze the formation of dimethylallyltryptophan and therefore also termed DMATSs. As aforementioned, DmaW from *C. fusiformis* was identified as the first enzyme from the DMATS superfamily and catalyzes the first pathway-specific step in the biosynthesis of ergot alkaloids, i.e., the prenylation of tryptophan at C-4 of the indole ring (Gerhards et al. 2014; Tsai et al. 1995). With the identification and characterization of its ortholog, FgaPT2 from *A. fumigatus* in 2005 began the systematic study on the enzymes of the DMATS superfamily by genome mining and biochemical investigation (Unsöld and Li 2005).

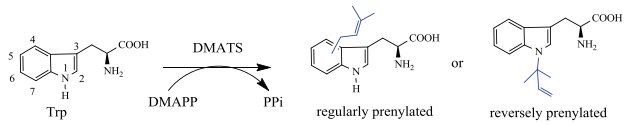
Table 3 Examples of prenyltransferases of the CloQ/NphB subgroup and their catalyzed reactions

Enzyme (accession number)	Organism	Substrate	Product	Biosynthetic pathway	References
CloQ/NovQ (AAN65239)/(AAF67510)	*Streptomyces roseochromogenes*/ *Streptomyces spheroids*	 4-hydroxyphenylpyruvic acid	 3-dimethylallyl-4-hydroxyphenylpyruvic acid	clorobiocin/ novobiocin	(Pojer et al. 2003)/(Ozaki et al. 2009)
NphB (1ZB6_A)	*Streptomyces sp.*	 1,6-dihydroxynaphthalene	 5-geranyl-1,6-dihydroxynaphthalene	naphterpin	(Kuzuyama et al. 2005)
SCO7190 (NP_631248)	*Streptomyces coelicolor* A3(2)	 1,6-dihydroxynaphthalene	 5-dimethylallyl-1,6-dihydroxynaphthalene	unknown	(Kumano et al. 2008)
Fnq26 (CAL34104)	*Streptomyces cinnamonensis*	 flaviolin	 3-geranyl-flaviolin	furano-naphthoquinone	(Haagen et al. 2007)
McI23 (AGH68908)	*Streptomyces sp* CNH-189	 1,3,6,8-tetrahydroxynaphthalene	 pre-merochlorin	merochlorin A & B	(Teufel et al. 2014)
EpzP/PpzP (ADQ43372)/(CAX48655)	*Streptomyces cinnamonensis*/ *Streptomyces anulatus*	 5,10-dihydrophenazine-1-carboxylic acid	 5,10-dihydrophenazine A	endophenazine	(Seeger et al. 2011)/(Saleh et al. 2009)
DzmP (AHG27152)	*Micromonospora sp.*	 dibenzodiazepinone	 *N10*-farnesyl-dibenzodiazepinone	diazepinomicin	(Bonitz et al. 2013).

Later, two additional fungal 4-DMATS, i.e., DmaW-Cs from *Periglandula* (Markert et al. 2008; Steiner et al. 2011) and *Malbranchea* (Ding et al. 2008), were also identified. Identification of 7-DMATS from *A. fumigatus* as a tryptophan *C7*-prenylating enzyme obligated to donate the position of the prenyl moiety at the indole ring of tryptophan for prenyltransferase names. 7-DMATS was proven to be involved in the biosynthesis of hexadehydroastechrome (Yin et al. 2013c). Identification of 5-DMATS from *A. clavatus* filled the last gap of prenylation positions of fungal tryptophan and tryptophan-containing cyclic dipeptide prenyltransferases (Yu et al. 2012).

The first bacterial tryptophan prenyltransferase CymD was identified in *Salinispora arenicola* and catalyzes the *N1*-prenylation at the indole ring in the biosynthesis of the anti-inflammatory cyclomarin A and the antibacterial cyclomarazine A (Schultz et al. 2010). Later, four further bacterial DMATSs catalyzing the prenylations at *C-5* and *C-6* of the indole ring were identified from different *Streptomyces* strains (Subramanian et al. 2012; Takahashi et al. 2010; Winkelblech and Li 2014). Heterologous expression of the 5-DMATS gene *SCO7467* with the flavin-dependent monooxygenase gene *SCO7468* from *Streptomyces coelicolor* in *Streptomyces lividans* resulted in the formation of 5-dimethylallylindole-3-acetonitrile (Ozaki et al. 2013). IptA from *Streptomyces* sp. SN-593 was found to prenylate tryptophan at C-6 in the biosynthesis of 6-DMAI-3-carbaldehyde (Takahashi et al. 2010). 6-$DMATS_{Sa}$ from *Streptomyces ambofaciens* and 6-$DMATS_{Sv}$ from *Streptomyces violaceusniger* were identified as homologs of IptA. 6-$DMATS_{Sa}$ and 6-$DMATS_{Sv}$ can also utilize GPP as a prenyl donor and catalyze

Table 4 Tryptophan prenyltransferases and their catalyzed reactions



Enzyme (accession number)	Organism	Prenylation	Biosynthetic pathway	Reference
CymD (ABW00334)	*Sa. arenicola*	*N1*-reverse	cyclomarin/cyclomarazine	(Schultz et al. 2010)
DmaW (AAC18893)	*C. fusiformis*	*C4*-regular	ergot alkaloids	(Tsai et al. 1995)
FgaPT2 (AAX08549)	*A. fumigatus*	*C4*-regular	fumigaclavine C	(Unsöld and Li 2005)
DmaW-Cs (AAZ29613)	*Periglandula*	*C4*-regular	ergot alkaloids	(Markert et al. 2008; Steiner et al. 2011)
MaPT (EU4200091)	*M. aurantiaca*	*C4*-regular	unknown	(Ding et al. 2008)
5-DMATS (EAW08391)	*A. clavatus*	*C5*-regular	unknown	(Yu et al. 2012)
5-DMATS$_{Sc}$ (NP_631515)	*S. coelicolor*	*C5*-regular	5-DMAI-3-acetonitrile	(Subramanian et al. 2012)
IptA (BAJ07990)	*Streptomyces sp*	*C6*-regular	6-DMAI-3-carbaldehyde	(Takahashi et al. 2010)
6-DMATS$_{Sa}$ (CAJ89640)	*S. ambofaciens*	*C6*-regular	unknown	(Winkelblech and Li 2014)
6-DMATS$_{Sv}$ (AEM87819)	*S.violaceusniger*	*C6*-regular	unknown	(Winkelblech and Li 2014)
7-DMATS (ABS89001)	*A. fumigatus*	*C7*-regular	astechrome	(Kremer et al. 2007)
7-DMATS^{Neo} (not available)	*Neosartorya sp.*	*C7*-regular	unknown	(Miyamoto et al. 2014)

A. Aspergillus, *C. Claviceps*, *M. Malbranchea*, *S. Streptomyces*, *Sa. Salinispora*

prenylations at the same position as for DMAPP, which had not been reported for tryptophan prenyltransferases before (Winkelblech and Li 2014).

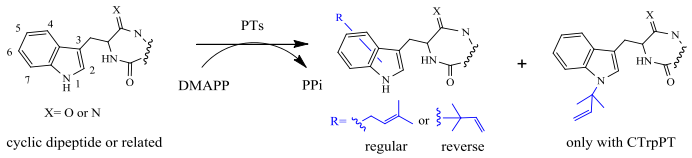
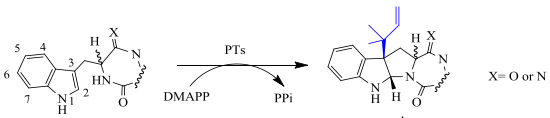
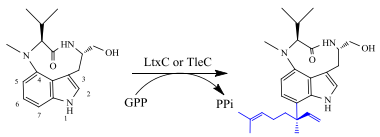
Tryptophan-containing cyclic dipeptide and related prenyltransferases

Tryptophan-containing cyclic dipeptide prenyltransferases catalyze regiospecific prenylations at different positions of the indole ring, especially at N-1, C-2, C-3, and C-7 (Grundmann and Li 2005; Wunsch et al. 2015; Yin et al. 2009, 2010, 2013a; Zou et al. 2010). Some peptide-related substances like *cyclo*-acetoacetyl-L-tryptophan (cAATrp) or ardeemin FQ, a derivative of the cyclic tripeptide of anthranilic acid, alanine, and tryptophan, were also identified as substrates of this subgroup (Haynes et al. 2013; Liu and Walsh 2009). Until now, 14 enzymes from this group have been characterized biochemically (Table 5). With the exception of the two geranyltransferases, LtxC from the cyanobacterium *Lyngbya majuscule* and TleC from the actinomycetes *Streptomyces blastmyceticus*, all other 12 enzymes are identified in fungi of *Aspergillus* and *Neosartorya* species.

The first identified cyclic dipeptide prenyltransferase was FtmPT1 from *A. fumigatus*, which catalyzes a regular *C2*-prenylation of brevianamide F (*cyclo*-L-Trp-L-Pro) in the biosynthesis of verruculogen/fumitremorgins (Grundmann and Li 2005; Li 2011). Three cyclic dipeptide reverse *C2*-prenyltransferases, NotF from an *Aspergillus* sp. and BrePT from *Aspergillus versicolor* involved in the biosynthesis of notoamides as well as CdpC2PT from *Neosartorya fischeri* (*N. fischeri*), were identified 5 years later (Table 5) (Ding et al. 2010; Mundt and Li 2013; Yin et al. 2013a). CdpC2PT was speculated to be involved in the biosynthesis of fellutanine (Mundt and Li 2013). Recently, a regular cyclic dipeptide *C7*-prenyltransferase CdpC7PT was identified in *Aspergillus terreus* (*A. terreus*) (Wunsch et al. 2015), with much higher regioselectivity and substrate flexibility toward cyclic dipeptides than CTrpPT, an *N1*- and *C7*-prenyltransferase from *Aspergillus oryzae* (*A. oryzae*) (Zou et al. 2010). CdpC7PT also accepted *cyclo*-L-Tyr-L-Tyr as substrate and catalyzed an *O*-prenylation at the tyrosyl residue, providing the first example from the DMATS superfamily with an *O*-prenyltransferase activity toward tyrosine-containing dipeptides (Wunsch et al. 2015). CdpNPT from *A. fumigatus* was reported to catalyze an *N1*-prenylation of cyclic dipeptides (Yin et al. 2007). The prenylation position was later revised to C-3 of the indoline ring (Schuller et al. 2012; Yu et al. 2013).

The DMATS enzymes catalyze not only regiospecific, but also stereospecific prenylations. For example, AnaPT from *N. fischeri* is involved in the biosynthesis of acetylaszonalenin and catalyzes a reverse *C3α*-prenylation of (R)-benzodiazepinedinone, while CdpNPT from *A. fumigatus* and CdpC3PT from *N. fischeri* the reverse *C3ß*-prenylations of cyclic dipeptides (Schuller

Table 5 Tryptophan-containing peptide or peptide-related prenyltransferases and their catalyzed reactions

Enzyme (accession number, pdb code)	Organism	Aromatic substrate[a]	Prenylation	Biosynthetic pathway	Reference
					
CTrpPT (GU722589)	*A. oryzae*	c-L-Trp-L-Trp	*N1*-reverse, *C7*-regular	unknown	(Zou et al. 2010)
FtmPT1 (AAX56314/3O2K)	*A. fumigatus*	c-L-Trp-L-Pro	*C2*-regular	fumitremorgin/ verruculogen	(Grundmann and Li 2005)
NotF (ADM34132)	*Aspergillus* sp.	c-L-Trp-L-Pro	*C2*-reverse	notoamide	(Ding et al. 2010)
BrePT (AFM09725)	*A. versicolor*	c-L-Trp-L-Pro	*C2*-reverse	brevianamide	(Yin et al. 2013a)
CdpC2PT (EAW25546)	*N. fischeri*	c-L-Trp-L-Trp	*C2*-reverse	fellutanine	(Mundt and Li 2013)
CpaD-Af (EED51182)	*A. flavus*	c-AA-L-Trp	*C4*-regular	cyclopiazonic acid	(Liu and Walsh 2009)
CpaD-Ao (BAE59503)	*A. oryzae*	c-AA-L-Trp	*C4*-regular	cyclopiazonic acid	(Liu and Walsh 2009)
CdpC7PT (EAU36020)	*A. terreus*	c-D-Trp-Ant	*C7*-regular	unknown	(Wunsch et al. 2015)
					
AnaPT (EAW16181/4LD7)	*N. fischeri*	c-D-Trp-Ant	*anti-cis C3*-reverse	acetylaszo-nalenin	(Yin et al. 2009)
CdpNPT (ABR14712/4E0U)	*A. fumigatus*	c-L -Trp-Ant	*syn-cis -C3*-reverse	unknown	(Schuller et al. 2012)
CdpC3PT (EAW17508)	*N. fischeri*	c-L-Trp-L-Leu	*syn-cis-C3*-reverse	roquefortine (?)	(Yin et al. 2010)
ArdB (n.a.)	*A. fischeri*	ardeemin FQ	*syn-cis-C3*-reverse	ardeemin	(Haynes et al. 2013)
					
LtxC (AAT12285)	*L. majuscula*	(-)-indolactam V	*C7*-reverse	lyngbyatoxins	(Edwards and Gerwick 2004)
TleC (BAP27943)	*S. blastmyceticus*	(-)-indolactam V	*C7*-reverse	teleocidin B	(Awakawa et al. 2014)

A. Aspergillus, *N. Neosartorya*, *L. Lyngbya*, *Ant anthranilate*, *AA* acetoacetyl, *n.a.* not available

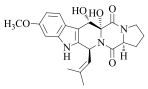
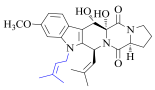
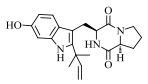
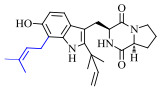
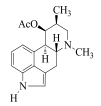
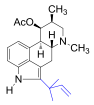
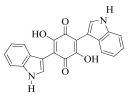
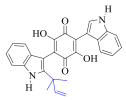
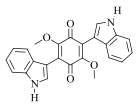
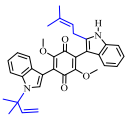
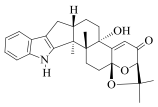
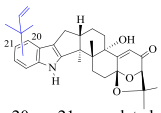
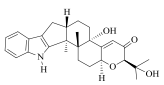
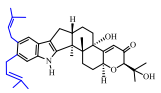
[a] Natural or if unknown the best accepted substrate was given

et al. 2012; Yin et al. 2009, 2010). ArdB from *Aspergillus fischeri* catalyzes *C3ß*-prenylation of ardeemin FQ at the indole ring (Haynes et al. 2013). Investigation with stereoisomers of cyclic dipeptides of tryptophan with proline or alanine revealed that AnaPT and CdpC3PT catalyze reverse *anti-cis* and *syn-cis C3*-prenylation, respectively. In contrast, CdpNPT produced both *anti-cis* and *syn-cis C3*-prenylated derivatives (Yu et al. 2013).

The product of a NRPS-PKS hybrid cAATrp was found to be the substrate of CpaD in the biosynthesis of the fungal neurotoxin α-cyclopiazonic acid in *Aspergillus flavus* (*A. flavus*) and *A. oryzae* (Liu and Walsh 2009). CpaD catalyzes the regiospecific *C4*-prenylation of cAATrp (Table 6) (Liu and Walsh 2009).

Several cyclic dipeptide prenyltransferases from bacteria use indolactams as substrates and catalyze prenylations at C-7 of the indole ring. In addition to LtxC mentioned above (Edwards and Gerwick 2004), the function of TleC in the biosynthetic pathway of teleocidin B in *Streptomyces blastmyceticus* was also characterized

Table 6 DMATS prenyltransferases of other substrates and their catalyzed reactions

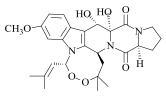
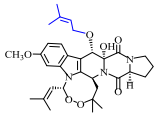
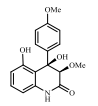
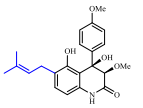
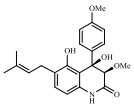
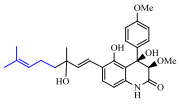
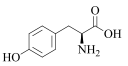
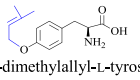
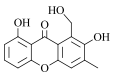
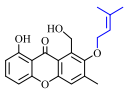
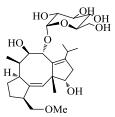
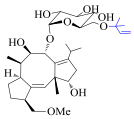
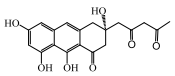
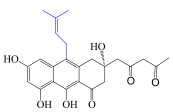
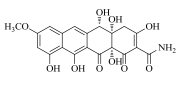
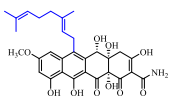
Enzyme (accession number)	Organism	Substrate	Product	Biosynthetic pathway	Reference
Prenyltransferases of other indole and quinolinone derivatives					
FtmPT2 (EU622826)	*A. fumigatus*	 12,13-dihydroxyfumtremorgin C	 fumitremorgin B	fumitremorgin/ verruculogen	(Grundmann et al. 2008)
NotC (BAH24002)	*Aspergillus* sp.	 6-hydroxy-deoxybrevianamide E	 notamide S	stephacidin/ notoamide	(Ding et al. 2010)
FgaPT1 (XP_756136)	*A. fumigatus*	 fumigaclavine A	 fumigaclavine C	fumigaclavine C	(Unsöld and Li 2006)
TdiB (ABU51603)	*A. nidulans*	 didemethylasterriquinone D	 asterriquinone C-1	terrequinone A	(Schneider et al. 2008)
AstPT (EAU29429)	*A. terreus*	 asterriquinone D	 *N1′*-reversely,*C2′′*-regularly diprenylated didemethyl-asterriqinnone D	unknown	(Tarcz et al. 2014)
AtmD (BAN67270)	*A. flavus*	 paspalinine	 20- or 21-prenylated aflatrem or *β*-aflatrem	(ß-)aflatrem	(Liu et al. 2013b)
PaxD (AAK11526)	*P. paxilli*	 paxilline	 21-,22- diprenylated paxillin	diprenylated paxillin, paspalitrem	(Liu et al. 2014a)

biochemically (Awakawa et al. 2014). Gene deletion experiments revealed the involvement of MpnD in the biosynthesis of methylpendolmycin in *Marinactinospora thermotolerans* (Ma et al. 2012).

Prenyltransferases utilizing other indole or quinolinone derivatives as prenyl acceptor

In addition to tryptophan and tryptophan-containing cyclic dipeptide prenyltransferases listed in Tables 4 and 5, eight members of the DMATS superfamily, which use other indole derivatives as prenylation substrates, are identified in different fungal strains (Table 6). These include FtmPT2 and FtmPT3 in the biosynthesis of verruculogen and fumitremorgin A in *A. fumigatus* and *N. fischeri* (Grundmann et al. 2008; Mundt et al. 2012). FgaPT1 from *A. fumigatus* catalyzes a reverse *C2*-prenylation, the last step in the biosynthesis of the ergot alkaloid fumigaclavine C (Unsöld and Li 2006). In addition to the cyclic dipeptide prenyltransferase NotF, NotC is also involved in the biosynthesis of stephacidin/notoamides (Ding et al. 2010). TdiB from *Aspergillus nidulans* (*A. nidulans*) and AstPT from *A. terreus* are involved in the biosynthesis of prenylated bisindolyl benzoquinones (Balibar et al. 2007; Schneider et al. 2008; Tarcz et al. 2014). AtmD from *A. flavus* and PaxD from *Penicillium paxilli* use indole diterpene derivatives as prenylation substrates (Liu et al. 2013b,

Table 6 (continued)

FtmPT3 (EAW19377)	*N. fischeri*	 verruculogen	 fumitremorgin A	fumitremorgin	(Mundt et al. 2012)
PenI (n.a.)	*P. thymicola*	 quinolinone B	 7-dimethylallylquinolone	penigequinolones	(Zou et al. 2015)
PenG (n.a.)	*P. thymicola*	 7-dimethylallylquinolone	 styrenyl quinolone	penigequinolones	(Zou et al. 2015)
Tyrosine prenyltransferases					
SirD (AAS92554)	*L. maculans*	 L-tyrosine	 4-*O*-dimethylallyl-L-tyrosine	sirodesmin PL	(Kremer and Li 2010)
TyrPT (CAK41583)	*A. niger*			unknown	(Fan et al. 2014)
Prenyltransferases of miscellaneous substrates					
XptB (BN001302)	*A. nidulans*	 1,7-dihydroxy-6-methyl-8-hydroxymethylxanthone	 variecoxythone	shamixanthone/ epishamixanthone	(Pockrandt et al. 2012)
PAPT (BAL68129)	*Phomopsis amygdali*	 fusioccin P	 fusicoccin J	fusicoccin J	(Noike et al. 2012)
BAE61387 (AP007162)	*A. oryzae*	 R=H: 1-naphthol R=OH: 1,7-dihydroxy-naphthalene	 R=H: 4-dimethylallyl-1-naphthol R=OH: 4-dimethylallyl-1,7-dihydroxynaphthalene	unknown	(Pockrandt et al. 2014)
NscD (EAW20699)	*N. fischeri*				(Chooi et al. 2013)
Mc03599 (EEQ30780)	*Microsporum canis*			neosartoricins	(Chooi et al. 2012)
Tt06703 (EGD99349)	*T. tonsurans*				(Yin et al. 2013b)
VrtC (ADI24928)	*P. aethiopicum*	 naphtacenedione	 6-geranyl-naphtacenedione	viridicatumtoxin	(Chooi et al. 2012)

A. Aspergillus, *L. Leptosphaeria*, *N. Neosartorya*, *P. Penicillium*, *T. Trichophyton*, *n.a.* not available

2014a). With the exception of FtmPT3, which catalyzes an *O*-prenylation of a secondary alcohol, all other enzymes from this group carry out reverse or regular prenylations at the indole ring (Table 6).

Very recently, two members of the DMATS superfamily, PenI and PenG, have been identified in *Penicillium thymicola* and proven to be involved in the biosynthesis of penigequinolone I. Both enzymes use DMAPP as prenyl donor. PenI catalyzes the prenylation of the quinolinone core at C-7, whereas PenG transfers a C_5 unit to the dimethylallyl moiety of the product of PenI, i.e., the elongation of the prenyl moiety by addition of a second dimethylallyl unit (Zou et al. 2015).

Prenyltransferases of tyrosine and other aromatic or nonaromatic substrates

The tyrosine *O*-prenyltransferase SirD in the biosynthesis of sirodesmin PL in *Leptosphaeria maculans* was identified in 2010 as the first member of the DMATS superfamily, which use nonindole derivatives as prenylation substrates (Kremer and Li 2010). The second tyrosine *O*-prenyltransferase TyrPT of an unknown cluster was identified in *Aspergillus niger* (Fan et al. 2014). Both enzymes share relatively high sequence similarity with 7-DMATS from *A. fumigatus* and also catalyze the *C7*-prenylation of tryptophan (Fan et al. 2014; Kremer and Li 2010).

Since 2010, several enzymes of the DMATS superfamily were proven to use even polyketide products, e.g., xanthones by XptB from *A. nidulans* (Pockrandt et al. 2012), hydroxynaphthalenes by BAE61387 from *A. oryzae* (Pockrandt et al. 2014), or naphtacenedione by VrtC from *Penicillium aethiapicum* (Chooi et al. 2010). VrtC utilizes GPP instead of DMAPP as prenyl donor to generate a viridicatumtoxin precursor (Chooi et al. 2010). Interestingly, its homologs from *N. fischeri*, *Microsporum canis*, and *Trichophyton tonsurans* accepted DMAPP as prenyl donor and were proven to be involved in the biosynthesis of neosatoricin (Chooi et al. 2012, 2013; Yin et al. 2013b). More interestingly, PAPT from *Phomopsis amygdali* catalyzes an *O*-prenylation of the glucose moiety in the biosynthesis of fusicoccin A (Noike et al. 2012). It should be mentioned that all of the enzymes described here were identified in fungi.

Crystal structures of DMATS prenyltransferases providing basic knowledge for understanding the prenylation reactions

Determination of the crystal structure of the first indole prenyltransferase FgaPT2 was a fundamental step in the advanced understanding of prenyltransferases of the DMATS superfamily and their reaction mechanisms (Metzger et al. 2009). FgaPT2 revealed an unusual PT-barrel fold, formed by ten antiparallel *β*-strands surrounded by ten *α*-helices (Fig. 3). The active site is located in the center of the barrel, and the absence of any metal ion in this area is consistent with the independency of divalent metals for enzyme activity. Interestingly, this architecture has been already observed for the bacterial hydroxynaphthalene prenyltransferase NphB (Kuzuyama et al. 2005), although its primary amino acid sequence and active site differ substantially from that of FgaPT2. The structural information, gained from this work, allowed the first understanding of the enzymatic catalysis and also supported the hypothesis of a common evolutionary origin of the bacterial and the fungal prenyltransferases of the ABBA-family (Luk and Tanner 2009; Metzger et al. 2009). In 2010, the crystal structure of the cyclic dipeptide *C2*-prenyltransferase FtmPT1 was solved (Jost et al. 2010),

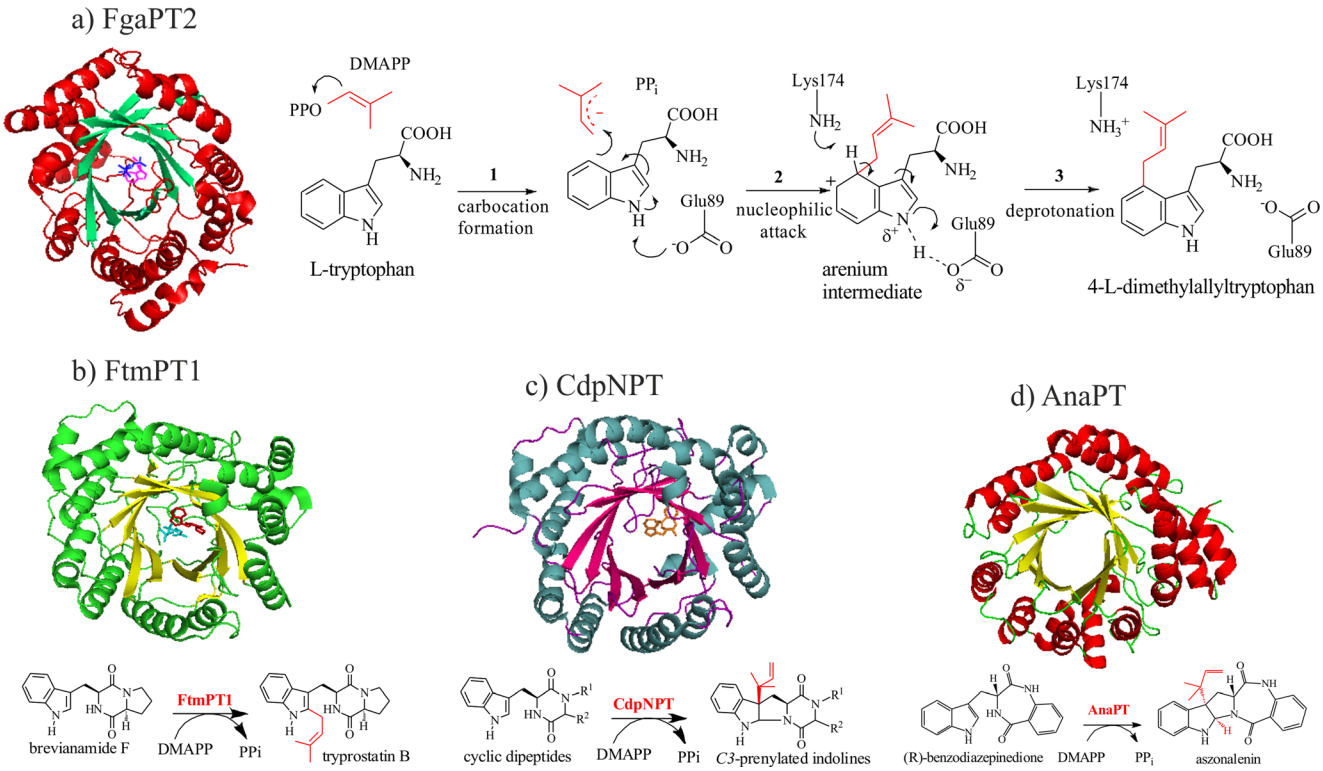


Fig. 3 Structures and enzyme reactions of FgaPT2 (**a**), FtmPT1 (**b**), CdpNPT (**c**), and AnaPT (**d**)

followed by the structures of two tryptophan-containing cyclic dipeptide *C3*-prenyltransferases CdpNPT and AnaPT in 2012 and 2013 (Schuller et al. 2012; Yu et al. 2013). Currently, the crystal structures of FgaPT2, FtmPT1, CdpNPT, and AnaPT are available in their unbound states. In addition, three of them (FgaPT2, FtmPT1, CdpNPT) were crystallized together with their aromatic substrates and an unreactive analog of DMAPP DMSPP (dimethylallyl S-thiolodiphosphate) or SPP (S-thiolodiphosphate). Comparison of the crystal structures revealed that they share a similar secondary core structure with the already described PT-barrel fold (Fig. 3). The amino acids in the DMAPP binding site seem to be strictly conserved in these four structures, whereas the binding sites of the aromatic substrates differ from each other. This feature makes molecular modeling with unknown structures more difficult. Therefore, additional enzyme structures from this superfamily are required. Nevertheless, the detailed structure analysis of the liganded and unliganded structures provides important insight into the catalyzed reaction mechanisms (Jost et al. 2010). Prenylations catalyzed by the enzymes of the DMATS superfamily were proposed as three-step reactions. They begin with the formation of a dimethylallyl cation by removal of the pyrophosphate group, which was proven by a positional isotope exchange with O^{18}-labeled DMAPP (Luk and Tanner

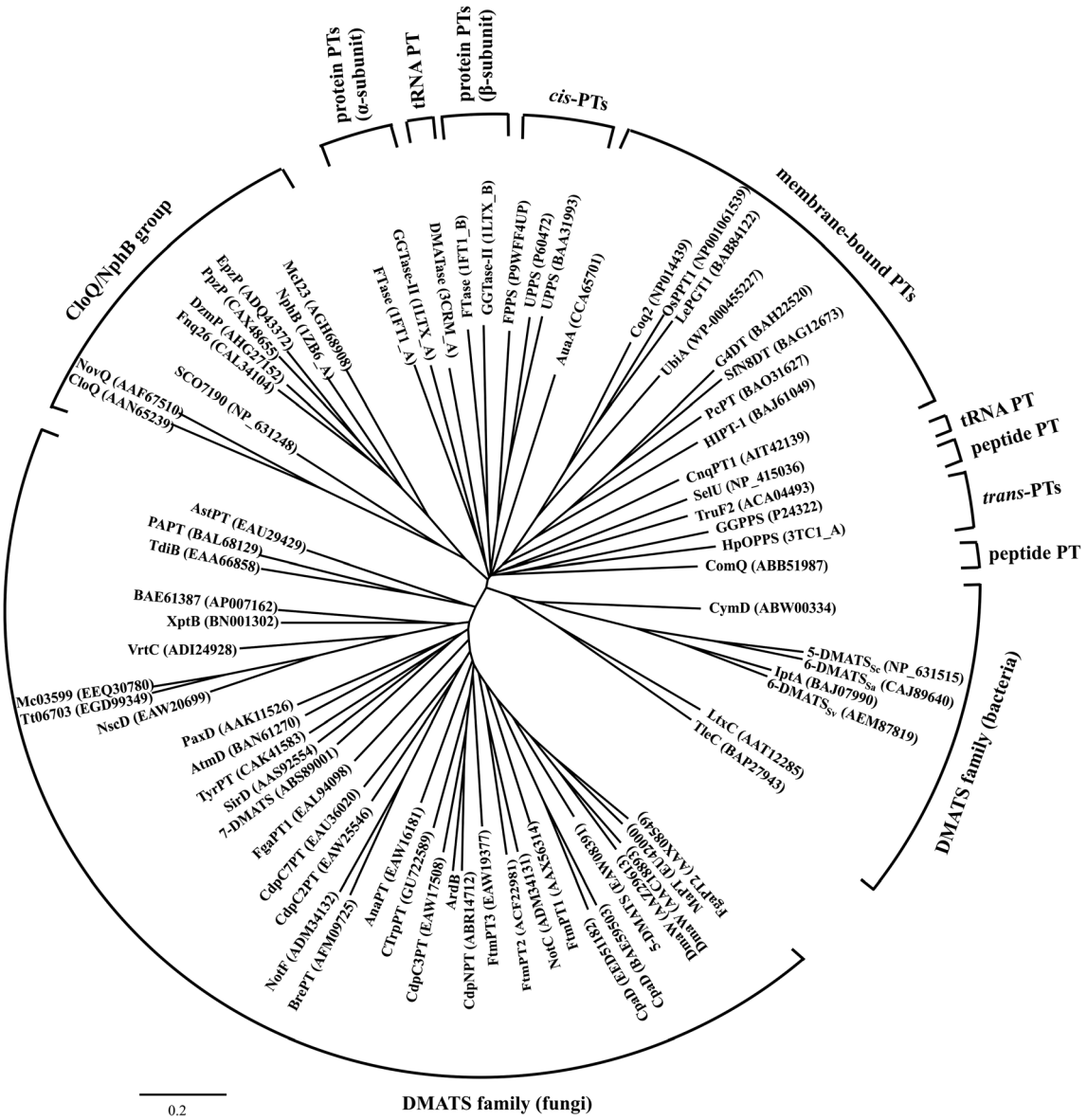


Fig. 4 Phylogenetic relationships of different prenyltransferases (PTs). The phylogenetic tree was created by using the programs ClustalX2 (http://www.clustal.org/) and Treedyn (www.phylogeny.fr). In addition to enzymes listed in Tables 2, 3, 4, 5 and 6, *cis*- and *trans*-PTs, peptide and tRNA PTs as well as α- and β-subunits of protein PTs are also included. The accession numbers or pdb codes of the enzymes are given in *parenthesis*

2009). The subsequent nucleophilic attack of this cation by the indole nucleus or other electron-rich atoms to form the σ-complex defined the second step. Then, the resulting arenium intermediate was deprotonated to generate the final product (Fig. 3a). The most controversial issue of this mechanism focused on the second step, whether an electrophilic aromatic substitution mechanism occurs directly at the site of substitution or as results of rearrangements after initial prenylation at C-3 of the indole ring to generate the final product (Luk et al. 2011; Mahmoodi et al. 2013; Mahmoodi and Tanner 2013; Tanner 2014). Furthermore, these results could be applied for generation of modified prenyltransferases by modeling and site-directed mutagenesis experiments. For example, the enzymatic reaction of FtmPT1 was modified by a single point mutation to perform a reverse prenylation at C-3 of the indole nucleus instead of a regular *C2*-prenylation.

Phylogenic relationships of different prenyltransferases

To get insights into the phylogenetic relationships of prenyltransferases, enzymes listed in Tables 2, 3, 4, 5, and 6 and examples of prenyl diphosphate synthases as well as peptide, protein, and tRNA prenyltransferases were analyzed and illustrated as a phylogenetic tree in Fig. 4. The phylogenetic analysis confirmed the diversity of prenyltransferases, which are located in different clades. The membrane-bound prenyltransferases from different sources are grouped together, while the enzymes of the CloQ/NphB group build a defined clade. The members of the DMATS family are found in two clades, one with fungal and another with bacterial origin. The *cis*- and *trans*-prenyltransferases of prenyl diphosphate synthases are clearly separated from each other. The relationships among peptide prenyltransferases appear to be very far. This is also observed for tRNA prenyltransferases.

Conclusion and outlook

In this review, we demonstrated the sequence, biochemical, and structural diversities of prenyltransferases, which catalyze the transfer of nxC_5 units to different acceptors such as prenyl moieties, peptides, proteins, tRNAs, and aliphatic or aromatic small molecules (Dumelin et al. 2012; McIntosh et al. 2013; Palsuledesai and Distefano 2015). As given in Fig. 4, enzyme groups mentioned in this review can be found in different clades.

Prenyltransferases play important roles in primary and secondary metabolism as well as in the cellular regulation (Heide 2009a; Palsuledesai and Distefano 2015; Yazaki et al. 2009; Yu and Li 2012). The most intensively studied prenyltransferases belong to the DMATS superfamily, which are mainly identified in fungi, but also in bacteria. They are of great importance for the biosynthesis of secondary metabolites in microorganisms. Until now, no example from this group was known from plants and animals. To date, over 40 members of the DMATS superfamily have been identified and characterized biochemically, and crystal structures of four members are available. Members of this family do not require metal ions for their transfer reactions. Most of these enzymes utilize DMAPP as prenyl donor and an aromatic scaffold as prenyl acceptor, e.g., tryptophan, tyrosine, tryptophan-containing cyclic dipeptides, or other indole derivatives. With the first solved crystal structure of the 4-DMATS and its unexpected PT-barrel, new insights into reaction mechanism, substrate binding, and evolutionary origin were gained.

As demonstrated in the last years, mining of available genome sequences has proven to be a convenient approach for identification of putative prenyltransferase genes. It can be expected that additional prenyltransferases with new features will be identified in the next years. Prenyltransferases, especially the members of the DMATS superfamily, show a high potential for production of biologically active low molecular weight compounds by in vitro catalysis or by synthetic biology. This has already been demonstrated by a large number of studies on their substrate and catalytic promiscuity in the last years. This aspect will be discussed in another mini-review in the same issue in detail. Moreover, elucidation of further prenyltransferase structures would provide new chance and challenge for a better understanding of their functionality. This in turn will enable us to create modified enzymes with special features, e.g., changes in substrate specificity, regioselectivity, and stereoselectivity.

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Conflict of interest The authors declare that there are no conflicts of interest.

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