Published in final edited form as:

Nat Prod Rep. 2021 May 26; 38(5): 905–980. doi:10.1039/d0np00066c.

Bacterial Terpenome

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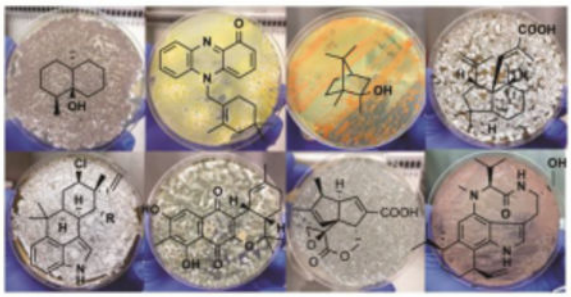
Abstract

Terpenoids, also called isoprenoids, are the largest and most structurally diverse family of natural products. Found in all domains of life, there are over 80,000 known compounds. The majority of characterized terpenoids, which include some of the most well known, pharmaceutically relevant, and commercially valuable natural products, are produced by plants and fungi. Comparatively, terpenoids of bacterial origin are rare. This is counter-intuitive to the fact that recent microbial genomics revealed that almost all bacteria have the biosynthetic potential to create the C_5 building blocks necessary for terpenoid biosynthesis. In this review, we catalogue terpenoids produced by bacteria. We collected 1062 natural products, consisting of both primary and secondary metabolites, and classified them into two major families and 55 distinct subfamilies. To highlight the structural and chemical space of bacterial terpenoids, we discuss their structures, biosynthesis, and biological activities. Although the bacterial terpenome is relatively small, it presents a fascinating dichotomy for future research. Similarities between bacterial and non-bacterial terpenoids and their biosynthetic pathways provides alternative model systems for detailed characterization while the abundance of novel skeletons, biosynthetic pathways, and bioactivies presents new opportunities for drug discovery, genome mining, and enzymology.

Graphical Abstract



We highlight the current state of the bacterial terpenome, emphasizing the discoveries, structures, biosynthetic pathways, and biological activities of these terpenoid natural products.

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/d0np00066c

[5]Conflicts of interest

There are no conflicts of interest to declare.

1 Introduction

Terpenoids, also called isoprenoids, are the largest family of natural products (NPs) with over 80,000 known compounds.[1] Found in all domains of life, but particularly prevalent in plants, fungi, and marine invertebrates,[1] terpenoids are essential constituents of both primary and secondary metabolism. They are some of the most studied and well-known NPs with steroids (e.g., cholesterol), vitamins (classes A, D, E, and K), flavors and fragrances (e.g., menthol, limonene, pinene), plant hormones and photosynthetic pigments (e.g., gibberellins and chlorophylls), and highly successful drugs (e.g., Taxol, artemisinin) all highlighting this superfamily.

This chemical library of compounds, coined the terpenome,[2] possesses an extraordinary amount of structural and stereochemical diversity. These diversities arise through an array of complex biosynthetic mechanisms including prenyltransfers, regio- and stereoselective cyclizations, skeleton rearrangements, attachments to a multitude of other scaffolds, and additional tailoring reactions. All terpenoids are built from two simple C_5 building blocks, the allylic dimethylallyl diphosphate (DMAPP) and the homoallylic isopentenyl diphosphate (IPP) (Scheme 1).[3] These activated isoprene units are either condensed to generate linear C_{5n} allylic diphosphates or used as prenyl donors to alkylate other chemical scaffolds (i.e., prenylation); in rare cases, two C_5 isoprene units are condensed to form branched or cyclic C_{10} diphosphates.[2] The nomenclature for terpenoid subfamilies is based on the number of isoprene units in the parent terpene: hemi- (C_5), mono- (C_{10}), sesqui- (C_{15}), di- (C_{20}), sester- (C_{25}), tri- (C_{30}), sesquar- (C_{35}), and tetraterpenoids (C_{40}). Hybrid natural products partially derived from terpenoid precursors are termed meroterpenoids; the prefix mero- means “part, partial, or fragment”.[4] Meroterpenoids may be the result of direct prenylation or the attachment of a terpenoid skeleton to another moiety via an alternative mechanism. Cyclization and rearrangement reactions occur on linear or cyclized prenyl diphosphates, linear prenyl chains lacking diphosphates, and meroterpenoids. As would be expected, the immensity of the terpenome and its vast structural and stereochemical diversity coincides with a wide range of biological activities.

Bacterial terpenoids remain a relatively small family of compounds. This reality is in spite of the fact that the origins of microbial terpenoids date back to the late 19th century with the study of the characteristic odor of soil.[5] This odor was later determined to be a combination of the degraded sesquiterpenoid geosmin (***121***) and the methylated monoterpenoid 2-methylisoborneol (2-MIB, ***23***).[6–8] Traditional NP programs utilizing structure- or activity-guided screening of bacterial extracts have been notably deficient in terpenoids.[9] The discrepancy in the number of total terpenoids versus those found in bacteria may suggest that bacteria (i) have not evolved terpenoid secondary metabolism on the same scale to that of other organisms and therefore do not have expansive biosynthetic machinery for terpenoid biosynthesis, (ii) have strict regulatory control of terpenoid biosynthetic pathways that does not translate well to traditional laboratory fermentation conditions, or (iii) that the NP community at large has not focused on or developed efficient means of bacterial terpenoid discovery.

Biochemical and genomics studies revealed that almost all bacteria biosynthesize terpenoids. Most bacteria solely employ the methylerythritol phosphate (MEP) pathway for terpenoid precursor biosynthesis, while some bacteria use the mevalonate (MVA) pathway, and some exploit both pathways.[10–13] For example, while all *Streptomyces*, well-known producers of NPs, use the MEP pathway for essential terpenoids, some strains also use the MVA pathway to supplement NP biosynthesis.[14,15] There are a few cases of bacteria, such as the parasitic *Mycoplasma*, that do not biosynthesize terpenoids de novo, instead relying on their host to supply any necessary terpenoids.[16]

Microbial genomics, in correlation with enzymatic studies, also indicate the enormous potential for terpenoid biosynthesis in bacteria. Well before the first genome sequences of actinomycetes were sequenced, it was clear that many actinomycetes, with *Streptomyces* in particular, produced volatile sesquiterpenoids.[17,18] Once the complete genomes of *Streptomyces coelicolor* and *Streptomyces avermitilis* were reported in the early 2000s,[19–21] a wealth of biosynthetic potential was revealed. Both known and novel terpene synthases (TSs), the enzymes responsible for the multitude of cyclization reactions,[22,23] as well as carotenoid biosynthetic enzymes were found in both species.[19–21,24] A decade later, bioinformatics analysis of 20 actinomycete genomes revealed over 120 candidate bacterial TSs; approximately six TSs per strain.[9] Three years later, in a seminal study confirming the prevalence of TSs in bacteria, 262 candidate TSs were identified from public genomic data.[25] It should be noted that while a significant portion of these TSs were from Gram-positive actinomycetes, likely reflecting their importance and dominance in the NP community, putative TSs were also identified in a variety of Gram-negative bacteria. Solidifying that these TSs were not all functionally redundant, heterologous expression of 29 selected TSs in *S. avermitilis* resulted in 13 novel cyclic sesqui- and diterpenes.[25] At the time of writing this introduction, there were ~2000 *Streptomyces* genome assemblies in the NCBI database. Assuming an average of six TSs per genome, there are over 12,000 TSs in *Streptomyces* alone (a search for “terpene synthase *Streptomyces*” in UniProt gave 3890)! To further underscore the biosynthetic potential for terpenoids in bacteria, this estimate does not include prenyltransferases (PTs)[26] or any of the 10 non-canonical TSs found in bacteria.[27]

In this review, we aim to describe the current state of the bacterial terpenome. We focus on the discoveries, structures, biosynthesis, and known biological activities of these unique NPs. This review does not address total synthetic efforts and does not emphasize the structural and mechanistic characterization of bacterial TSs. TSs will be described for certain classes of terpenoids for clarity when describing their discoveries or biosynthesis. For an in-depth examination of bacterial TSs and terpenoid biosynthesis in general, we direct readers to the excellent reviews cited here.[9,15,22,23,28–31]

To identify and collect terpenoids of bacterial origin, we initially utilized four main NP databases: (i) the Dictionary of Natural Products,[1] (ii) the Natural Products Atlas,[32] (iii) StreptomeDB,[33] and (iv) TeroKit.[34] This consolidated database was then checked for redundancy, structures were validated by examination of the primary literature, and terpenoids reported in the primary literature but not included in any of these NP databases were added. We included naturally occurring terpenoids, excluding biosynthetic intermediates or shunt pathway products that were only isolated through genetic mutation of

biosynthetic genes; however, NPs isolated through genetic manipulation of regulatory genes were included. Products of heterologous expression of full biosynthetic gene clusters (BGCs) were also included. We did not include terpenoids isolated only from in vitro enzyme reactions or biotransformations as these are either biosynthetic intermediates or not known to be produced in vivo. Our analysis resulted in a total of 1062 bacterial terpenoids (Fig. 1).[1]

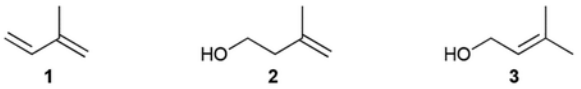
We organized these 1062 NPs into two major categories, Terpenoids and Meroterpenoids, further subdivided them into eight and 12 subfamilies, respectively. Those subfamilies were even further divided into 26 and 29 distinct categories, respectively. It should be noted that lines between these divisions are not always clear. The NPs found in the Terpenoids category (chapter 2) are mainly based on the condensation of multiple C_5 prenyl units to each other and in most cases, a single or multiple subsequent cyclization reactions. These foundational hydrocarbon skeletons are then extensively modified to produce the variety of structural, chemical, and functional diversities described below. The NPs found in the Meroterpenoids category (chapter 3) are hybrid molecules consisting of a terpenoid portion appended onto another structural motif. This addition provides an entirely different suite of chemical entities that can be structurally and functionally diversified through the addition of an electron-rich appendage. Prenyl groups can add hydrophobicity, provide an electron-rich alkyl chain for further modifications, or supply the framework for additional cyclization reactions. Prenylation is most commonly seen on aromatic rings and can naturally occur (on small molecules) on C, N, and O atoms.

In this review, only a selection of highlighted terpenoids are discussed in detail with their structures shown (compounds with in-text structures are italicized). Selected biosynthetic pathways of bacterial terpenoids are also depicted in schemes (in order to differentiate between isolated NPs discussed in this review and biosynthetic intermediates, known intermediates discussed in the text and shown in schemes are labelled with names and are not numbered). The full bacterial terpenoid database and all structures are available in ESI documents associated with this review. This database was also deposited in the Open Access Natural Products Atlas.[32]

2 Terpenoids

2.1 Hemiterpenoids

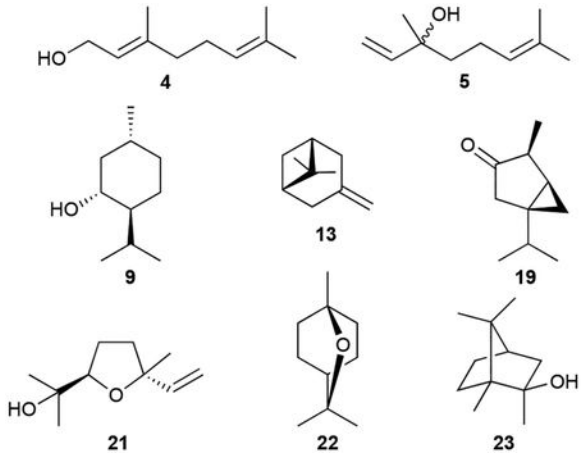
Hemiterpenoids are the smallest terpenoid NPs as they are generated directly from the C_5 building blocks IPP and DMAPP without the addition of any other chemical moieties. There are only three known hemiterpenoids that have been isolated from bacteria: isoprene (***1***), isoprenol (***2***), and prenol (***3***). Both Gram-positive and Gram-negative bacteria emit ***1***, or 2-methyl-1,3-butadiene, with *Bacilli* and actinobacteria particularly prevalent producers.[35–37] ***1***, the majority of which is produced by plants, is the most abundant natural volatile organic compound (VOC) on Earth and influences atmospheric chemistry.[38,39] Although the biosynthesis of ***1*** in plants is known to be the result of diphosphate elimination of DMAPP by isoprene synthase,[40] the biogenesis in bacteria remains unclear.[41,42] ***2*** (3-methyl-3-buten-1-ol or isopentenol) and ***3*** (3-methyl-2-buten-1-ol), which were initially detected in *Streptomyces*,[43] are the hydrolysis products of IPP and DMAPP, respectively.



2.2 Monoterpenoids

Bacteria also produce a significant number of terpenoid-based VOCs that can be categorized as monoterpenoids, sesquiterpenoids, diterpenoids, or various degradation products. Taxonomic and environmental differences in bacteria correspond to vast diversities in VOCs. Although VOCs are produced by most bacteria (it was estimated that 50–80% of bacteria produce VOCs in laboratory conditions[44]), each combination of emitted volatiles is different with some *Streptomyces* emitting up to 80 different volatile components.[37] The literature on VOCs is expansive and we direct readers to impressive reviews that focused solely on bacterial volatiles.[44,45]

Monoterpenoids are all derived from geranyl diphosphate (GPP) and can be in linear or cyclic form. Geraniol (***4***) and linalool (***5***) are linear hydrolysis products of GPP and its rearranged isomer linalyl diphosphate (LPP); β-myrcene (**6**) is the diphosphate elimination product of LPP. They have been found in *Streptomyces*.[37,43] Methyl geranate (**7**), was the only volatile terpenoid identified from *Salinispora tropica*.[46] Other bacterial monoterpenoid VOCs, most of which are also found in plants, include the monocyclic compounds limonene (**8**),[43] menthol (***9***), *p*-meth-1-en-4-ol (**10**), and α-terpineol (**11**),[47] the [2.2.1]bicyclic α- and β-pinenes (**12, *13***),[48] borneol (**14**) and *endo*-bornyl acetate (**15**),[49,50] camphor (**16**)[49,51] the [3.1.0]bicyclic thujene (**17**), thujanol (**18**), and isothujone (***19***)[37,52] and the tetrahydrofuran-containing *cis*- and *trans*-linalool oxides (**20, *21***).[53] The ether containing 1,8-cineole (***22***, eucalyptol) was initially found as a product of a type I TS in *Streptomyces clavuligerus* ATCC 27094 and later found as an emitted VOC.[54,55]



Due to its history, characteristic smell, and abundance in actinomycetes, 2-methylisoborneol (2-MIB, ***23***) is the most renowned (homo)monoterpenoid. Its structure was characterized after isolation from three different *Streptomyces* spp. but has also been found in myxobacteria and cyanobacteria.[7,56,57] Its [2.2.1]bicyclic structure only deviates from that of **14** with a C2 methyl group. Biosynthetic studies revealed that numerous linear and cyclic C2-methylated monoterpenoids (**24**–**32**) were also produced by various actinomycetes,

suggesting they were biosynthetically related to ***23***.[37,56,58] A highly oxidized derivative of ***23***, 2-methyl-2,5,6-bornantriol (**33**), was also found.[59]

Biosynthesis.—The biosynthesis of most of the bacterial monoterpenoids can be envisaged by a single type I TS acting on GPP. For the cyclic monoterpenoids, GPP must first be isomerized to LPP during catalysis (Scheme 2).[23,60] Cyclization of (*E*)-configured GPP after diphosphate abstraction would result in a highly strained (*E*)-cyclohexene intermediate. Instead, GPP is first converted into LPP, a prenyl diphosphate with a freely rotatable C2/C3 single bond.[23,60] The diphosphate of LPP is then abstracted and cyclization ensues. Until recently, only two bacterial mono-TSs were characterized: 1,8-cineole synthase (Scheme 2) and linalool synthase from *S. clavuligerus*;[54,61] another linalool synthase was also identified from *Chryseobacterium polytrichastri*.[62] A recent enzymological study screened 22 type I TSs from bacteria and revealed many of the NPs listed above.[63] The ability of several TSs to accept prenyl diphosphates of different lengths and therefore producing distinct products, some of which have not been seen in bacteria before, suggests that bacteria are likely a richer source of monoterpenoids than previously assumed.

The biosynthesis of ***23***, which possesses 11 carbons, has an added biosynthetic wrinkle. Early isotopically labeled precursor feeding experiments revealed that the extra carbon on ***23*** originated from *S*-adenosylmethionine (SAM) and that methyl incorporation likely happens prior to cyclization.[8,56] The 2-MIB BGC from *S. coelicolor* revealed a C-methyltransferase (MT) encoded adjacent to a type I TS.[64] In vitro studies confirmed that GPP is C2-methylated prior to cyclization by 2-MIB synthase; isomerization of 2-methyl-GPP into 2-methyl-LPP is also required for cyclization (Scheme 2). The mechanism of GPP methylation, i.e., alkene methylation resulting in a carbocation that is quenched by proton elimination, hinted at the future discovery of a family of SAM-dependent noncanonical TSs.[27]

It should also be mentioned that the cyclization of GPP or 2-methyl-GPP via LPP or 2-methyl-LPP, respectively, can occur with both enantiomers of LPP or 2-methyl-LPP.[60,65] This would result in enantiomeric intermediates and thus enantiomeric terpenoids. Some terpenoid-producing organisms biosynthesize just one set of enantiomers, but there are examples where both enantiomers are produced by the same organism.[65] The stereoselective binding of GPP, in either its right-handed or left-handed helical conformation, suggests that the TSs that control these reactions are structurally different.

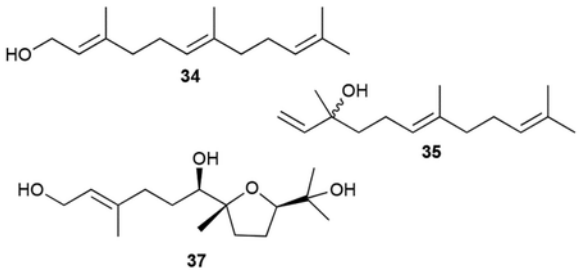
Biological activity.—The biological activities of monoterpenoids detected or isolated from bacteria are not commonly reported per se; however, as most of these NPs were originally isolated from plant source material and are constituents of essential oils, their bioactivities have been extensively studied. Many of these volatile monoterpenoids have anti-inflammatory properties, typically mediated by the reduction in levels of tumor necrosis factor (TNF)-α, interleukins, and nitric oxide.[66] Other bioactivities, too numerous to exhaustively list here, include antimicrobial and insecticidal, anticancer, analgesic and the antitussive and cooling properties synonymous with camphor and menthol.[67–72] The caveat

here is that it is not known if many of the monoterpenoids produced by bacteria are the same enantiomeric forms as those produced by plants.

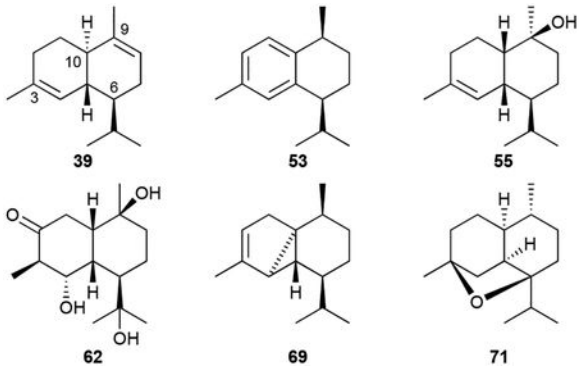
2.3 Sesquiterpenoids

Sesquiterpenoids are derived from farnesyl diphosphate (FPP) and are much more numerous in bacteria than their monoterpenoid counterparts. Given its C_{15} alkyl length is 50% longer than the monoterpene precursor GPP, as well as the fact that its additional C_5 unit possesses a third double bond, FPP can fold and cyclize into a myriad of skeletons creating significantly more structural diversity than monoterpenoids. As with monoterpenoids, some of the cyclization reactions for sesquiterpenoids require the isomerization of FPP into nerolidyl diphosphate (NPP), the C_{15} equivalent of LPP; both enantiomers of NPP are also possible. For simplicity, we consolidated several subclasses of sesquiterpenoids into larger families based on structural similarity. Most bacterial sesquiterpenoids are VOCs and their structures are in linear or cyclic form with the latter form more prevalent. We again point readers to reviews detailing bacterial VOCs.[44,45] As most of the biosynthesis of bacterial sesquiterpenoids is dependent solely on TSs, we will not discuss these in detail and direct readers to the cited reviews.[9,22,23]

2.3.1 Simple sesquiterpenoids—Although likely prevalent in many bacteria, the linear sesquiterpenoid volatiles farnesol (***34***), nerolidol (***35***), β-farnesene (**36**), hydrolysis and dehydration products of FPP and NPP, have been identified from myxobacteria.[47,73] Two monocyclic sesquiterpenoids, 7,10-epoxy-2-farnesene-1,6,11-triol (***37***) and its 6,10-epoxy analogue (**38**), were isolated from *Streptomyces scopuliridis*.[74] The tetrahydrofuran triol ***37*** is conspicuously similar to the terpenoid fragment of heronapyrrole (vide infra chapter 3.9).



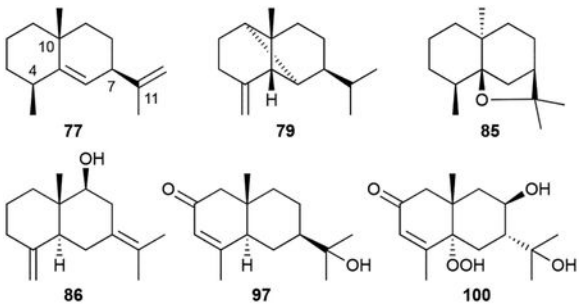
2.3.2 Cadinanes—The cadinene, muurolane, and amorphane skeletons all have 6/6 bicyclic frameworks with a 3,9-dimethyl-6-isopropyl substitution pattern; their skeletons only differ in their stereochemical configurations. About half of the bacterial cadinanes are purely hydrocarbons with 14 members being diene isomers. These VOCs, which are produced by various types bacteria, are cadinenes (***39***, **40**–**45**), muurolenes (**46**–**49**), zonarene (**50**), and bicyclosesquiphellandrene (**51**).[37,43,50,73] There are three aromatic 'trienes,' namely cadinatriene (**52**) and the *cis*- and *trans*-calamenenes (***53*, 54**).[37,47,73] There is the usual assortment of mono-, di-, and trihydroxylated diastereomeric terpenoids (***55***, **56**–**61**, ***62***) with hydroxyl groups commonly being positioned at C9 (i.e., muurolols, amorphenols, and cadinols) or C10 (i.e., cubenols).[17,37,50,73,75–77]



There are also three types of volatile tricyclic cadinene-like sesquiterpenoids. The cubebols (**63–67**) and cubebenes (**68**, ***69***) from *Sorangium cellulosum* So ce56 have a cyclopropane moiety constructed between C4–C5–C10;[73] α-copaene (**70**) has a cyclobutene ring between C4–C5–C10–C9;[48] and corvol ether A (***71***) is a tetrahydrofuran-containing 4,7-epoxy from *Kitasatospora setae* KM-6054.[78] Finally, although not detected as VOCs in *S. cellulosum*, T-cadinol (**72**), α-cadinol (**73**), 1,10-di-*epi*-cubenol (**74**), *epi*-zonarene (**75**) and cubebol (**76**) were all detected and/or isolated after the heterologous expression of a TS encoded by *sce6369*.[73]

Biological activity.: Most of the bacterial cadinane sesquiterpenoids do not have reported bioactivities. Only **57** was cytotoxic with a mean IC_{50} value of ~28 μM.[76]

2.3.3 Eudesmanes—Eudesmanes have a 6/6 bicyclic core motif with a 4,10-dimethyl-7-isopropyl substitution pattern. The basic hydrocarbon structures of eudesma-5,11-diene (***77***), selina-3,7(11)-diene (**78**), β-ylangene (***79***), and β-copaene (**80**) as well as the single oxygen-bearing α-eudesmol (**81**), β-eudesmol (**82**), rosifoliol (**83**), (+)-intermedeol (**84**), dihydroagarofuran (***85***), and selina-4(14),7(11)-diene-9-ol (***86***) are all VOCs.[18,37,43,47,50,79,80] Numerous diols and triols (**87–96**) have also been isolated from a variety of actinobacteria.[77,81–88]

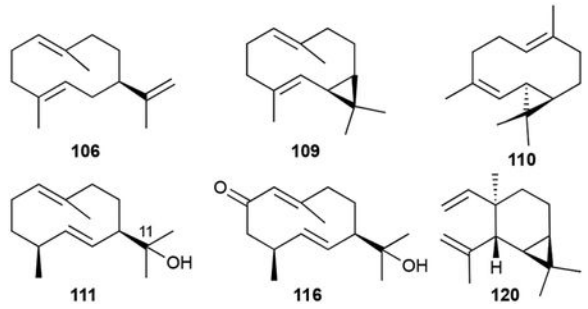


Although there are no congeners with hydroxy groups at C2 or C3, there are 2-oxo and 3-oxo eudesmane derivatives. The 2-oxo eudesmanes include isopterocarpolone (***97***), previously known as a plant metabolite,[89] and kandenols A–E (**98–102**).[90] Kandenols ***100*** and **101** possess hydroperoxides at C5. 6,12-Dihydroxy-1,4-eudesmadien-3-one (**103**), produced by the Gram-positive *Lentzea violacea* AS 08, is the only 3-oxo derivative, although its absolute configuration was not determined.[91] Hydroxyl or alkene functional

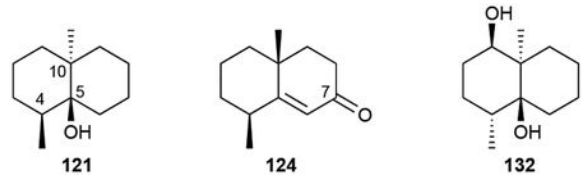
groups can also be modified with phenylacetate (**104**) and aminobenzoate (**105**) derivatives seen.[85,92]

Biological activity.: As with the cadinanes described above, most of the eudesmane bacterial sesquiterpenoids do not have reported bioactivities. Those that showed some activity, such as **98–104**, only have weak to moderate antibacterial or anticancer properties.[85,90,91]

2.3.4 Germacranes—The germacrene sesquiterpenoid skeleton is a cyclodecadiene monocycle. This skeleton is particularly relevant in sesquiterpenoid biosynthesis as the germacradienyl cation is an important intermediate in the formation of various hydrocarbon scaffolds including the geosmins and eudesmanes.[23] The bacterial germacrene VOCs, produced by a variety of *Streptomyces* and myxobacteria, include germacrene A (***106***), germacrene D (**107**), *iso*-germacrene D (**108**), and the bicyclo[8.1.0]undecane bicyclogermacrene (***109***) and lepidozene (***110***).[37,43,50] Oxygenated germacranes (***111***, **112–115**, ***116***), all possessing at least one hydroxyl group at C11, are common in actinobacteria.[43,93–95] The monocyclic elemene VOCs (**117–*120***) are commonly reported but may not be legitimate NPs as they are seen during routine GC analysis due to the thermal degradation of germacrenes.[43,50]



2.3.5 Geosmins—Geosmin (***121***), the volatile, earthy odor (literally!) present in actinomycetes and in some cyanobacteria, is a C_{12} 6/6 bicyclic norsesquiterpenoid.[6] Its *trans*-decalin ring is decorated as a 4*S*,10*R*-dimethyl-5*S*-alcohol. We categorized structurally similar C_{12} 4,10-dimethylbicycles as geosmin terpenoids. Volatile geosmins from the myxobacterium *Chondromyces crocatus* and *Streptomyces* sp. JMRC:ST027706 include the 3- (**122**) or 7-ketones (**123–126**, ***124***) and 7-alcohols (**127, 128**).[50,88] A panel of diols, triols, and tetrols (**128–136**, ***132***) have also been isolated from a variety of *Streptomyces* spp.[50,86,88,96,97] Octalins **137** and **138**, likely intermediates or shunt products in the cyclization cascade of ***121***, were detected in the headspace extracts of several myxobacteria and *Streptomyces* strains.[98]



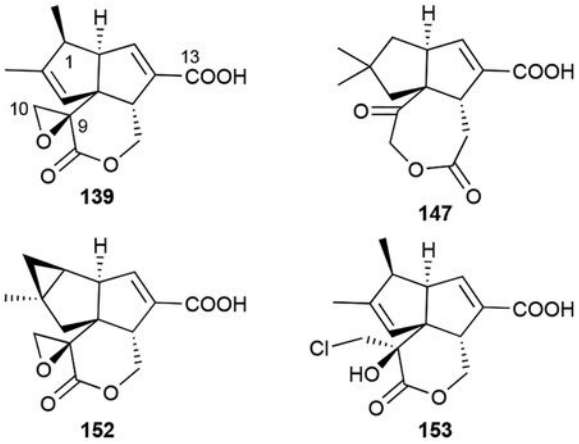
Biosynthesis.: The biosynthesis of geosmins has been extensively studied in *Streptomyces*, cyanobacteria, and plants.[9,23,99,100] Given the irregularity of the C_{12} scaffold, an isotopically-labeled precursor feeding study was required to determine that ***121*** is a degraded sesquiterpenoid.[8] Cloning and deletion of a single gene, *sco6073*, from *S. coelicolor* and subsequent biochemical studies revealed that a single protein is responsible for the totality of geosmin biosynthesis.[101–104] The didomain and multifunctional germacradienol-geosmin synthase synthesizes ***121*** from FPP via the intermediate germacradienol (***111***). Several mechanisms have been postulated including pathways consisting of only cationic and neutral intermediates[99] and pathways with additional oxidative[101] or both oxidative and reductive steps.[100] The currently valid model makes use of the cationic and neutral pathway with this unique TS catalyzing three distinct reactions: a type I cyclization of FPP into the germacradienyl cation via the neutral intermediate hedycaryol, a type II cyclization and subsequent retro-Prins fragmentation releasing acetone, and a final sequence of octalin ***137*** protonation, 1,2-hydride shift, and water quench to yield ***121*** (Scheme 3).[98,103,105] An alternative pathway through isolepidozene, a bicyclogermacrene isomeric intermediate, is also possible.[55,103]

Biological activity.: The multi-hydroxy geosmins show weak to moderate antimicrobial and cytotoxic activities with 11,12,13-trinor-1,5-eudesmanediol (***132***) having the most potent activity with a minimum inhibitory concentration (MIC) against *Candida* of 3.13 μg mL^{-1}.[77,86,88,96]

2.3.6 Pentalenolactones—

The pentalenolactone (PNT) family of tricyclic sesquiterpenoids is a structurally unique group of NPs produced by numerous *Streptomyces* spp. Known as an antibiotic since the mid 1950s,[106] the structure of PNT (***139***), also named arenaemycin after its reisolation,[107,108] was not fully elucidated until 1970.[109,110] The tricyclic scaffold of ***139*** is constructed from two fused cyclopentenes and a 6-membered lactone and functionalized with a C9–C10 epoxide and C13 carboxylic acid. Fifteen additional naturally produced PNT family members have been identified and can now be split into three categories: biosynthetic intermediates, shunt products (in regard to PNT biosynthesis), and proposed isolation artifacts.

The biosynthetic intermediates include pentalenene and PNTs D–F. Pentalenene (***140***), first isolated from *Streptomyces griseochromogenes*, is a 5/5/5 tricyclic hydrocarbon core with four methyl groups, two of which are found in the *gem*-dimethyl group on C2 that is absent in PNT.[111] PNTs D (**141**) and E (**142**) are carboxyl- and lactone-carrying congeners of ***140*** with PNT F (**143**) also possessing the epoxide.[112,113]



Shunt products include pentalenic acid (**144**),[114] the 9-epimer epi-PNT F (**145**), which was initially reported as PNT F prior to structural revision,[115–117] a glucuronidate of 1-deoxypentalenic acid (**146**),[118] and neopentalenoketolactone (***147***), an unusual 7-membered ketolactone.[119] ***147*** was produced through the heterologous expression of the entire *ptl* BGC in the engineered host *S. avermitilis* SUKA5.[120] The 1-hydroxylated and 1-keto congeners **144**, PNT G (**148**), and PNT H (**149**) were initially proposed as intermediates, but later found to be the result of adventitious oxidation.[114,121] Sesquiterpenoids with rearranged carbon skeletons, namely PNTs A, B, and P (**150–*152***),[113,122] were also found to be by-products of a unique rearrangement step.

Finally, the chlorohydrin PNT C/I (***153***, also named AA-57) and diol PNT O (**154**) are likely isolation artifacts due to the epoxide opening under acidic conditions.[107,122–124] We included these compounds in this review as they have distinct biological properties worth mentioning.

Biosynthesis.: Understanding PNT biosynthesis has been a focus of several research groups for 30 years and may be considered as one of the quintessential examples of the rationale for studying terpenoid biosynthetic pathways in bacteria.[9] Prior to the release of the full genome of *S. avermitilis*, which provided the *ptl* BGC,[120] PNT was known to be of mevalonate origin[125] and the sesqui-TS pentalenene synthase was found to form pentalenene.[126] The *ptl* BGC,[120] as well as the subsequently identified *pen* and *pnt* BGCs from *Streptomyces exfoliatus* and *Streptomyces arenae*, respectively,[127] provided the opportunity to use biochemical and genetic techniques to elucidate the full biosynthetic pathway (Scheme 4). After cyclization of FPP into ***140***, the cytochrome P450 PenI/PntI/PtlI first transforms the C13 methyl into a carboxylic acid by triple hydroxylation.[128] Then C11 hydroxylation and oxidation to ketone by the α-ketoglutarate (KG)-dependent dioxygenase PenH/PntH/PtlH and dehydrogenase PenF/PntF/PtlF prepare the scaffold for lactone formation.[129,130] ***141*** formation occurs via a Baeyer-Villiger reaction, catalyzed by the FAD-dependent PenE/PntE;[119] the homologous PtlE also is a Baeyer-Villiger monooxygenase but inserts its oxygen on the other side of the ketone, diverging its pathway towards ***147***.[131] Another α-KG-dependent dioxygenase, PenD/PntD/PtlD, performs sequential oxidation and epoxidation of the C9–C10 bond yielding the penultimate products ***143*** or the proposed neo-

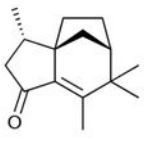
PNT F;[127,131] neo-PNT F is not stable and rearranges to ***147***.[131] The final step in ***139*** biosynthesis is a unique TS-like rearrangement catalyzed by the P450 PenM/PntM (Scheme 4).[132] This P450 performs an carbocation-based oxidative rearrangement of the sesquiterpenoid scaffold due to its innate steric hindrance precluding typical oxygen radical rebound.[133] The preclusion of oxygen rebound allows a typically kinetically silent electron transfer to occur, thus forming the C1 carbocation.[133] A 1,2-methyl shift and subsequent deprotonation yield **139**. The constitutional isomers **150–152** are proposed to be competing by-products of the generated carbocation intermediate.[132] Shunt pathway products with oxygens at C1 are the result of CYP105D7, a P450 that is encoded elsewhere in the genome.[134]

Biological activity.: The PNT antibiotics are active against both Gram-positive and Gram-negative bacteria as well as fungi.[135] ***139*** is quite potent with MICs approaching 100 ng mL^{-1}.[136] The mechanism of action was determined to be inhibition of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH).[107,108] PNTs are competitive, covalent inhibitors of GAPDH, specifically alkylating Cys149 via attack on the C9–C10 epoxide.[137,138] The inactivation of glucose metabolism is also evident in mammalian cells as ***139*** inhibits glycolysis of various cell types at 18–90 μM.[139]

139 and some variants also have antitumor properties.[118,140] ***139*** was seen to inhibit vascular smooth muscle cell proliferation mediated in part through its effect on the mitogen-activated protein kinase (MAPK) signalling pathway.[140] As ***139*** inhibited glycolysis at a concentration 10-fold higher (IC_{50} = 7.4 μM) than that of cell proliferation, the inhibition of GAPDH is likely not the mechanism for the inhibition of cell proliferation.

139 and the diol artifact **154**, which did not have antibiotic activity, were also found to be effective against DNA viruses including herpes simplex viruses-1 and −2, having EC_{50} values in the sub- to low μM range.[136] The chlorohydrin artifact **153**, which retained antibacterial activity (MICs as low as 2 μg mL^{-1}), also acted as an immunosuppressant by inhibiting interleukin (IL)-2 production at an IC_{50} of ~1.5 μM.[123,124]

2.3.7 Zizaanes—Zizaanes are a small family of [6.2.1.0^{1,5}] tricyclic undecanes. The first bacterial zizaane sesquiterpenoid found was albaflavenone (***155***), a 5/6/5 tricyclic antibiotic with an α,β-unsaturated ketone isolated from *Streptomyces albidoflavus* DSM 5415.[141,142] After the identification of the BGC for albaflavenone,[143] several additional zizaane sesquiterpenoids have been reported from both native strains and heterologous hosts harboring the albaflavenone BGC. These include the albaflavenols (***156–158***), albaflavenoid (***159***), 4β,5β-epoxy-2-*epi*-zizaan-6β-ol (**160**), and antartin (**161**), an anthrilinic acid derivative of albaflavenone.[144–147] Strepsesquitriol (***162***), identified in the deep-sea *Streptomyces* sp. SCSIO 10355, has a rearranged 5/6/5 tricycle.[148]



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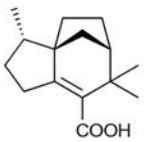

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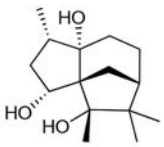


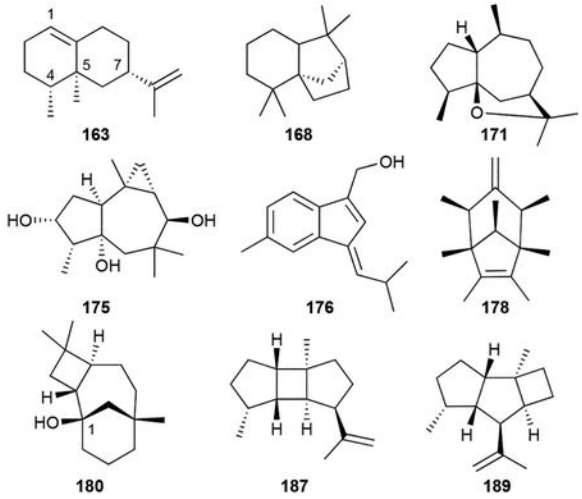
162

Biosynthesis.: Genome mining led to the discovery of *epi*-isozizaene synthase, a widespread type I TS in bacteria that is responsible for constructing the zizaane scaffold (Scheme 5).[143,149] The albaflavenone BGC from *S. coelicolor* is a two gene operon consisting of an *epi*-isozizaene synthase and a co-transcribed P450, CYP170A1.[150] CYP170A1 catalyzes two sequential allylic oxidations at C4 of *epi*-isozizaene, going through both stereoisomeric alcohols ***156*** and ***157***, to yield ***155*** (Scheme 5). Upon further investigation, CYP170A1 was seen to have moonlighting TS activity in vitro, converting FPP into several farnesene isomers including **36**.[151] This function was traced back to a secondary active site within the P450 structure that had an unusual TS-like α-helical barrel and signature TS sequence motifs.[151] It is unclear if this non-canonical TS activity is biologically relevant in vivo.[27]

Biological activity.: **155** was identified as an antibiotic against *Bacillus subtilis* with a modest MIC value of ~10 μg mL^{-1}.[141] Other zizaane sesquiterpenoids are not antimicrobials but affect eukaryotic cells. **162** inhibited lipopolysaccharide-induced tumor necrosis factor (TNF)-α production in macrophages.[148] Albaflavenol B (**158**), ***159***, and **161** were weakly cytotoxic with IC_{50} values of >20 μM, with the latter causing cell cycle arrest at the G1 phase.[146,147]

2.3.8 Miscellaneous Polycyclic Sesquiterpenoids—

There are many other polycyclic sesquiterpenoids produced by bacteria, many of which are VOCs and were originally discovered from plants. The volatile (+)-eremophilene (***163***), valerianol (**164**), and β-gurjunene (**165**) are similar to the eudesmanes but have a 4,5-dimethyl-7-isopropyl substitution pattern on their 6/6 cores.[37,47,50,152] β-Caryophyllene (**166**), clovene (**167**), and isolongifolene (***168***) were identified as volatiles in Flavobacteria.[49] Sesquiterpenoids with 5/7 hydrocarbon cores include α-gurjunene (**169**), γ-gurjunene (**170**), guaioxide (***171***), 8-daucen-11-ol (**172**), neomeranol B (**173**), isoafricanol (**174**), and africantriol (***175***).[37,80,153,154] **172** was initially named isodauc-8-en-11-ol,[80] but the position of its methyl group on the cycloheptene ring represents the daucane sesquiterpene skeleton and therefore **172** should be renamed 8-daucen-11-ol. Sesquiterpenoids with 5/6 hydrocarbon cores include the aromatic anmindenols (***176***, **177**),[155] sodorifen (***178***), an unusual symmetrical C_{16} volatile from *Serratia spp.*,[156] and the tetrahydrofuran-containing corvol ether B (**179**).[78]



The caryolanes, represented by (+)-caryolan-1-ol (***180***), caryolanediols (**181–183**), and bacaryolanes (**184**–**186**) are 6/7/4 tricyclic alcohols produced by *Streptomyces* spp.[84,157–159] Additional tricyclic sesquiterpenoids include the 5/4/5 bourbonenes (***187***, **188**), the 5/5/4 kelsoene (***189***), and the 5/5/5 triquinane isohirsutenes (**190, 191**).[37,4325,160]

Biosynthesis.: The biosynthesis of ***178*** revealed another example of a MT acting as a TS (see teleocidins in chapter 3.5.3 for first discovered example).[27] A genome mining and systematic genetic knockout approach was required to identify the *sod* BGC.[161,162] The simplicity of the BGC, only encoding two biosynthetic enzymes, a TS (SodD) and MT (SodC), contrasted with the complexity of the structure of ***178***, where every carbon has a methyl or methylidene substituent. However, FPP is methylated and cyclized by SodC into pre-sodorifen, a hexasubstituted cyclopentene diphosphate whose absolute configuration has not yet been solved, prior to an extraordinarily complex type I cyclization reaction catalyzed by SodD (Scheme 6).[163,164] The proposed cyclization cascade for ***178*** formation involves two highly unlikely primary cations and is thus an intriguing system for future mechanistic studies.[164]

The TS responsible for the formation of ***180*** was found in *Streptomyces griseus*.[157] The gene encoding this (+)-caryolan-1-ol synthase would serve as an excellent probe for the identification of the BGCs responsible for **181–186**; however, the genomes of these producing strains have not been reported. Similarly, related TSs in *Streptomyces violaceusniger* and *Streptomyces malaysiensis* were determined to be produce **174**,[153,165] the likely parent compound of ***175***, although the genome of the producing strain of ***175*** is not yet known.

Biological activity.: As with most of the other sesquiterpenoids, this group had either no or unreported biological properties, with the exception of several of the plant sesquiterpenoids that have been extensively studied.[66] Exceptions include the weak antibacterial activities of the bacaryolanes,[159] the moderate antifungal activity of ***180*** (IC_{50} = 26 μM for *Botrytis cinerea*,[166] and the ability of anmindenols ***176*** and **177** to inhibit nitric oxide (NO) production in macrophages (IC_{50} values of ~20 μM).[155]

2.4 Diterpenoids

Diterpenoids are derived from geranylgeranyl diphosphate (GGPP) and while they have been extensively studied in plants and fungi,[22,167–169] they are comparably rare in bacteria.[30] In terms of total numbers, bacterial diterpenoids rival that of bacterial sesquiterpenoids, although the number of structural families encompassed by the diterpenoid category is smaller. Given a total of four prenyl units in the C_{20} alkyl chain of GGPP, one biosynthetic advantage that diterpenoids possess is the ability to be cyclized solely by type I TSs or by a type II TS in combination with a type I TS or PT. This provides the potential for an extraordinary amount of structural diversity that has been seen in other organisms but not yet fully realized in bacteria.[30,169] Unlike the mono- and sesquiterpenoids, most isolated bacterial diterpenoids are functionalized and therefore are not VOCs, although there are a few volatile hydrocarbon skeletons that were identified from bacterial cultures. The TSs responsible for diterpenoid skeletal formation were recently reviewed and we direct readers to these excellent review articles.[23,28,30]

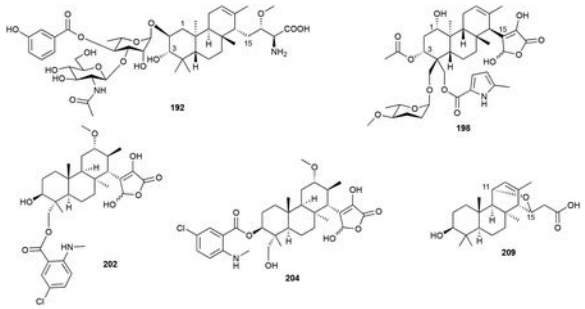
2.4.1 Brasilicardins, phenalinolactones, and tiancilactones—The brasilicardin, phenalinolactone, and tiancilactone family of diterpenoids contain perhydrophenanthrene scaffolds with various peripheral decorations. Brasilicardin A (***192***), the first member of this family to be discovered, was isolated from *Nocardia brasiliensis* IFM 0406 (later named *N. terpenica*).[170,171] Its *anti*/*syn*/*anti*-perhydrophenanthrene diterpenoid skeleton has an amino acid moiety appended to C15 and a tripartite structure on the C2 hydroxyl group. A 3-hydroxybenzoate and an *N*-acetylglucosamine are attached to the diterpenoid via a rhamnose linker. Other brasilicardins (**193–197**) have been isolated from both the native strain and by heterologous expression of the entire *bra* BGC in *Amycolatopsis japonicum*.[172,173]

Phenalinolactones (**198–201**), isolated from *Streptomyces* sp. Tü 6071, are also terpenoglycosides.[174] Their perhydrophenanthrene backbone is *anti/anti/syn*-configured (only its relative configuration is known) and in place of the amino acid moiety on C15 in the brasilicardins, the phenalinolactones have an uncommonly oxidized and unsaturated γ-butyrolactone. Its other peripheral decorations include L-amicetose and 5-methylpyrrole-2-carboxylic acid groups located on the *gem* dimethyls of the A-ring and a C3 acetyl unit.

The tiancilactones (**202–209**), structurally very similar to the phenalinolactones, were recently discovered by genome mining for atypical type II di-TSs in *Streptomyces*.[175] Tiancilactone A (***202***) had the same γ-butyrolactone, but a different oxygenation pattern on its *anti/anti/syn*-perhydrophenanthrene tricyclic core and a chloroanthranilate on C20. Other natural tiancilactones included a dechloro analogue (**203**), an isomerized chloroanthranilate ester (***204***), congeners with various γ-butyrolactone degradations (**205–208**), and a unique C11–C15 ether containing diterpenoid with a carboxylic acid tail (***209***). The concurrently discovered trinulactones A–D (**210**–**213**) from *Streptomyces* sp. S006 are also tiancilactones; trinulactones C and D are the methylated derivatives of tiancilactones A and C.[176]

Biosynthesis.—Early precursor feeding experiments confirmed that the terpenoid skeletons of the brasilicardins and phenalinolactones were derived from the MEP pathway;

[177,178] the exact building block for the additional three carbon atoms that end up as the amino acid or γ-butyrolactone moieties is unknown, although glucose is a definite precursor and pyruvate or phosphoenol pyruvate have both been suggested.[177,179]



The *pla* BGC, responsible for the production of ***198***, was identified by screening for genes encoding an NDP-glucose-4,6-dehydratase as it is involved in the formation of L-amicetose. [178] Bioinformatics, in vivo inactivation of select genes, extensive tandem MS detection, and a few in vitro experimental confirmations provided a biosynthetic proposal for the phenalinolactones.[178–180] GGPP is epoxidized at its terminal olefin leading to cyclization by the type II TS PlaT2 and subsequent prenylation onto an unknown C_3 unit is catalysed by the UbiA-like PT PlaT3. The next steps are isomerization of the C3 hydroxyl and oxidation of the C15-C16 bond into an olefin; however, the responsible enzymes are undetermined. Lactone formation, which is completed by the α-KG-dependent dioxygenase PlaO1, occurs prior to oxygenation of the terpene scaffold by various P450s at C1, C20, and C21 and the attachment of decorations at C3, C20, and C21 decorations (Scheme 7).[178,179] The biosynthetic proposal for the tiancilactones closely follows the above proposal and is supported by bioinformatics, in vivo knockouts, and isolated congeners.[175,176]

The brasilicardin BGC was later found after searching for GGPP synthases in the genome of *N. terpenica*.[170] After an initial biosynthetic proposal, the heterologous expression of the *bra* BGC produced four biosynthetic intermediates and prompted a revised pathway.[173] Hydroxylation at C2 by P450 Bra6 precedes C17 amination by Bra1. Although Bra0, a homologue of PlaO1, catalyzes C16 hydroxylation, the lack of the C15-C16 olefin precludes the rearrangement to the γ-butyrolactone of the phenalinolactones and tiancilactones. Ensuing methylation and glycosyltransfer reactions finalize the structure.[173]

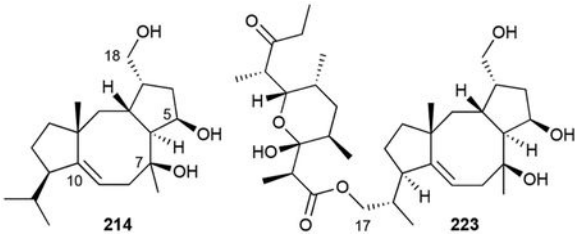
The proposed terpene epoxidation, cyclization, and prenylation reactions have not been experimentally confirmed. Their structural and BGC similarity to KS-505a (vide infra chapter 3.7) suggests that prenylation onto the C3 unit may occur prior to epoxidation and cyclization. In addition, the differences in the configurations of the tricyclic diterpenoid scaffolds of the brasilicardins and tiancilactones implies that these type II di-TSs do not all generate the same stereoisomers.[175]

Biological activity.: The phenalinolactones and tiancilactones are antibacterials with moderate levels of activity. Phenalinolactones ***198*** and **199** inhibited Gram-positive bacteria (MICs ≤10 μg mL^{-1}), but was inactive against Gram-negative bacteria, fungi, and human

cells.[174] The tiancilactones had MICs of 8–64 μg mL^{-1} for Gram-positive and some Gram-negative strains.[175]

Conversely, brasilicardins are unique and potent immunosuppressors with no antibacterial activity. ***192*** had an IC_{50} value of 67 nM in a mouse mixed lymphocyte assay and was cytotoxic against a variety of cancer cells; its most potent activity was an IC_{50} value of 87 nM against Adriamycin-resistant leukemia P388 cells.[181,182] By targeting the amino acid transport system L, inhibiting the uptake of amino acids, and arresting cells in the G1 phase, its mechanism of action is different from that of the well-known immunosuppressants cyclosporin A and FK-506.[183] Brasilicardins **193** and **194** were 50 times less potent than ***192*** asserting that the C2 decorations and C16 methoxy group are important for activity; brasilicardin **195** was inactive.[172]

2.4.2 Cyclooctatins—The cyclooctatins are named for their central 8-membered ring in their 5/8/5 fused tricyclic ring system. These bacterial diterpenoids are structurally very similar to the fusicoccin-type fungal toxins.[184] The namesake NP, cyclooctatin (***214***), was first identified as a lysophospholipase inhibitor from *Streptomyces melanosporofaciens* and is a 5,7,18-triol of the cyclooct-9(10)-ene carbon skeleton.[185,186] Seven analogues (**215–221**), all with varying combinations of hydroxyl groups, have since been discovered from various *Streptomyces* spp.[187–190] The hydroxyl groups at C17 and C18 are prone to esterification as evidenced by the isolation of 18-acetylcyclooctatin (**222**) and the fusicomycins (***223*–225**).[187,191]



Biosynthesis.: **214** is produced through the action of four enzymes, a GGPP synthase, TS, and two P450s, encoded within the *cot* BGC (Scheme 8).[192] CotB2, a type I di-TS, cyclizes GGPP into cyclooctat-9-en-7-ol, providing one of the three hydroxyl groups in cyclooctatin through a water quench of the carbocation at C7.[193] Successive P450 hydroxylations by CotB3 and CotB4 at C5 and C18, respectively, complete the biosynthesis.[192] Is it currently unknown what enzymes further modify cyclooctatin.

Biological activity.: **214** was first reported as a single digit μM inhibitor of lysophospholipase with no antimicrobial or cytotoxic activities;[185] it was later shown to be antiplasmodic with an IC_{50} value of 20 μM.[194] While some of the variants do have weak antibiotic activities against both Gram-positive and Gram-negative bacteria,[189,191] the fusicomycins showed cytotoxicities with low μM IC_{50} values.[187] The mode of action for fusicomycin cytotoxicity appears to be the inhibition of matrix metalloproteinases, resulting in the suppression of cell proliferation, cancer migration, and invasion.[187]

2.4.3 Cyslabdans—Cyslabdans, aptly named for their labdane diterpene skeleton and appended *N*-acetylcysteine moiety, are unique bacterial NPs. Cyslabdan A (***226***), the first representative isolated from *Streptomyces* sp. K04–0144, is a 7,8-dihydroxy-*trans*-decalin ring with the Cys unit attached via a thioether linkage at C17.[195,196] Cyslabdans B and C (**227**, **228**) and the 2-hydroxy (**229**) and 17-hydroxy (**230**) congeners of ***226*** were later isolated from the same strain and after the heterologous expression of the entire *cld* BGC in *S. avermitilis* SUKA22.[197,198] An 8,17-epoxy-labdadiene intermediate (***231***) was also isolated from this *cld*-expressing host.[198] Parallel heterologous expression of a highly homologous *rmn* BGC from *Streptomyces anulatus* GM95 only produced raimonol (***232***), a known plant NP.[198]

Biosynthesis.: Genome mining for the cyslabdan BGC was achieved by searching for genes encoding prenyl diphosphate synthases. The target gene, named *cldA*, was transcriptionally coupled with three other biosynthetic genes.[198] Heterologous expression of the *cld* BGC confirmed its role in cyslabdan biosynthesis and supported CldB and CldD as (+)-copalyl diphosphate (CPP) and labda-8(17),12*E*,14-triene synthases. CldC, a P450, is proposed to incorporate two oxygens, a hydroxyl and epoxide at C7 and C8/C17, respectively, forming ***231*** (Scheme 9). The *N*-acetylcysteine moiety is added by mycothiol-*S*-conjugation and subsequent hydrolysis. Mycothiol conjugation was proposed to occur non-enzymatically in vivo,[198] although it is feasible to consider an enzyme controls this crucial biosynthetic step. The divergence in ***232*** biosynthesis is due to the sole C7 hydroxylation of labda-8(17),12*E*,14-triene.[198]

Biological activity.: The cyslabdans do not have antibacterial activity themselves but are strong potentiators of imipenem activity against methicillin-resistant *Staphylococcus aureus* (MRSA). At 10 μg mL^{-1} of ***226***, a non-lethal concentration, the MIC of imipenem is 0.015 μg mL^{-1}; this corresponds to a >1000-fold decrease from its monotherapeutic MIC of 16 μg mL^{-1}.[199] **227** and **228** also enhanced imipenem activity, albeit at lower levels (123-fold and 533-fold, respectively) than ***226***.[197] The cellular target of cyslabdans is the binding and inhibition of FemA, an enzyme involved in the formation of the pentaglycine interpeptide bridge in peptidoglycan biosynthesis.[200] While the inhibition of FemA by the cyslabdans is apparently not detrimental enough to prevent cell wall synthesis and therefore cause cell death, it significantly improves the potency of β-lactam antibacterial activity.

2.4.4 Gibberellins—Gibberellins (GAs) are 6/5/6/5 tetracyclic diterpenoids that are well known plant and fungal NPs.[201,202] These phytohormones, at least the few that are bioactive (i.e., GA_1, GA_3, GA_4, and GA_7), are important in developmental and physiological processes of plants including seed germination and stem, leaf, flower, and fruit growth. The GA family, first identified in the fungal rice pathogen *Gibberella fujikuroi*, now includes over 100 different structural members.[1,202] These tetracyclic diterpenoids are derived from *ent*-kaurene, have rearranged B-rings, are highly oxidized, and are found as either C_{20} diterpenoids or C_{19} norditerpenoids.

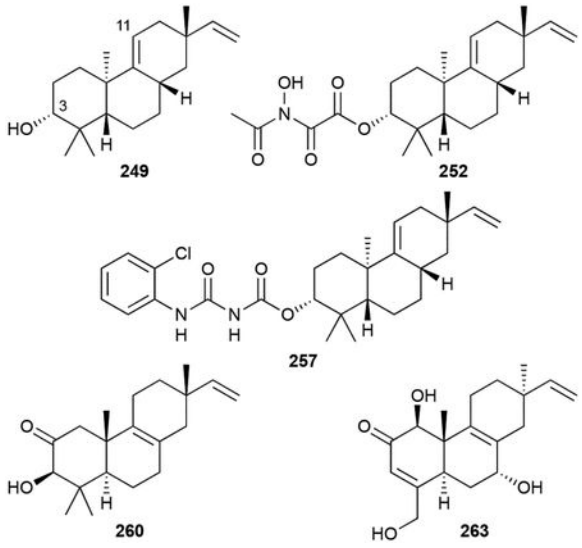
Over 30 years ago, bacteria were also found to produce gibberellins after GA_1 (**233**), GA_4 (***234***), GA_9 (***235***), and GA_{20} (**236**) were identified in the nitrogen-fixing Gram-negative

bacterium *Rhizobium phaseoli*.[203] Now there are a total of 16 known GAs in bacteria (**237–248**) produced by a variety of Gram-negative and Gram-positive genera including *Acinetobacter*, *Azospirillum*, *Bacillus*, *Bradyrhizobium*, *Burkholderia*, *Enterococcus*, *Pseudomonas*, *Rhizobium*, and *Sphingomonas*.[203–206] GAs in bacteria have been extensively reviewed.[168,201,202,206]

Biosynthesis.: The biosynthetic pathways of GAs in plants, fungi, and now bacteria are well understood.[206] Bacteria evolved their own pathway for GA biosynthesis, although it partially follows the pathway found in plants. The *ent*-kaurene skeleton is initially formed from GGPP by two distinct *ent*-CPP and *ent*-kaurene synthases (Scheme 10).[207] The GA operon was later identified in *Bradyrhizobium diazoefficiens* and functional characterization of five unknown genes led to a proposal for GA_9 biosynthesis.[208] Along with GGPP synthase and the two di-TSs, three P450s, a short chain dehydrogenase/reductase (SDR_{GA}), and a ferredoxin were encoded nearby. Using heterologous expression and in vivo knockouts, CYP117, CYP114, CYP112 and SDR_{GA} were all characterized as oxidases. CYP117 oxidizes *ent*-kaurene into *ent*-kauren-19-oic acid; CYP114 catalyzes C7 β-hydroxylation and B-ring contraction to form the aldehyde form of GA_{12}; SDR_{GA} completes C7 oxidation to the carboxylic acid ***239***; and finally, CYP112 catalyzes C20 oxidation and lactone ring closure with the C19 acid group via loss of C20 to yield ***235***.[208] A fourth P450 catalyzes C3 β-hydroxylation to yield the phytoactive ***234*** (Scheme 10).[209]

2.4.5 Oxaloterpins—Viguiepinol, or 3-hydroxypimara-9(11),15-diene (***249***), was first identified in bacteria after it was heterologously produced, along with (–)-pimara-9(11),15-diene (**250**), from the expression of a four gene operon from *Streptomyces* sp. KO-3988 in *Streptomyces lividans* TK23.[210] ***249*** was originally isolated from plants.[211] Re-fermentation of *Streptomyces* sp. KO-3988 not only yielded ***249***, but an additional six related diterpenoids, viguiepinone (**251**) and oxaloterpins A–E (***252*–256**).[212] Oxaloterpins are 3-acylated derivatives of viguiepinol with moieties including *N*-hydroxyoxalyl amides. The related chloroxaloterpins A and B (***257*, 258**), also from a *Streptomyces* sp., had unique 2-chloroaniline-containing side chains.[213]

Other isopimaradienols include **259**, ***260***, and **261**.[83,214,215] We also include here three C_{19} norditerpenoids, gifhorneolone A (**262**), actinomadurol (***263***), and JBIR-65 (**264**), that are proposed to originate from C20 decarboxylation of pimaradiene NPs.[83,216,217]



Biosynthesis.: Prior to the discovery of any oxaloterpin members from bacteria, a four gene operon containing a P450, two DTSs, and a GGPP synthase was found near MVA-encoding genes.[218] In vitro characterization of the type II di-TS, ORF2, revealed it to be a CPP synthase. Heterologous expression of the entire operon in *S. lividans* TK23 yielded both ***249*** and **250**.[210] Subsequent in vitro characterization of the type I di-TS ORF3, confirmed the pimaradiene scaffold is constructed prior to hydroxylation by the P450 ORF1.[219] With the exception of CYP1051A1-catalyzed C19 hydroxylation in isopimara-8,15-dien-19-ol (**259**) biosynthesis,[214] the other functionalities seen in the oxaloterpins, including the norditerpenoids, are biosynthetically uncharacterized.

Biological activity.: ***252*** and ***263*** are antibacterials with the latter effective against *S. aureus* and *Proteus hauseri* with MICs 0.39–0.78 μg mL^{-1};[212,216] **264** was not active and the other oxaloterpins were not tested.[212,217] Chloroxaloterpins ***257*** and **258** were found to inhibit spore germination in *Botrytis cinerea* with EC_{50} values of ~10 μM.[213]

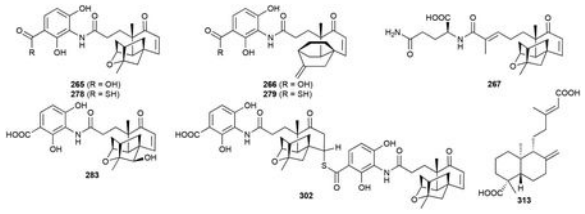
2.4.6 Platensimycin and platencin—

Platensimycin (PTM, ***265***) and platencin (PTN, ***266***) are unique hybrid natural products derived from labdane intermediates.[220] Discovered from *Streptomyces platensis* MA7327 and *S. platensis* MA7339 by Merck in 2006 and 2007, respectively, using an innovative antisense differential sensitivity whole-cell assay, ***265*** and ***266*** received worldwide attention due to their novel chemical structures and antibacterial mode of action.[221,222] Both ***265*** and ***266*** possess 3-amino-2,4-dihydroxybenzoic acid (ADHBA) moieties linked to diterpene-derived aliphatic cages via a flexible propionamide linker.[223,224] These polycyclic enone acids were initially called ketolides and while technically incorrect,[225] the term is still used in the literature. The ‘ketolides’ of ***265*** and ***266*** are 17-carbon polycyclic enones with differences in the polycyclic moieties. The polycyclic enone of ***265*** is a tetracyclic scaffold with a fused cyclohexyl-cyclopentyl-furan; the polycyclic enone of ***266*** is a tricyclic scaffold with an exocyclic methylene. Their structural similarities to *ent*-kaurene and *ent*-atiserene,[224] labeling studies,[225,226] the isolation of

homoplatensimide A (***267***),[227] a 20-carbon congener of ***265***, and subsequent biosynthetic studies confirmed their diterpenoid origins.[228–230]

An additional 54 naturally occurring PTM and PTN congeners have been isolated so far, mostly through the use of large-scale fermentations of the wild-type (WT) strains and the utilization of high-producing genetic mutants.[229,231] Given its hybrid nature, analogues have modified ADHBA moieties, polycyclic enones, or both. Variations in the ADHBA moiety include a carboxy amide (**268**), a cyclic carbamate (**269**), a decarboxyaniline (**270**), 5´-*O*-glucosides (**271–277**) and thiocarboxylic acids (***278***, ***279***) .[232–236] Biosynthetic studies support that the thiocarboxylic acids are the genuine, genetically encoded natural products.[236] Most congeners, like **280**, have also been isolated as their methyl benzoate derivatives. Although there is evidence that PTM and PTN congeners with methyl benzoates are artifacts of methanol-based isolations, a few congeners (**281**, **282**) were only isolated in their methyl benzoate forms and one glucosylated congener (**277**) was isolated as a methyl thiobenzoate.[234,237,238] Variations in the polycyclic enones mainly consisted of overoxidation products proposed to be generated from adventitious oxygenases (**275–277**, ***283*****–301**).[234,235,237–240] One unique variant, and the initial clue for the discovery of the thiocarboxylic acids ***278*** and ***279***, is the pseudo-dimer ***302***, which connects ***265*** and ***278*** via a thioester linkage at C7 of ***265***; this product was hypothesized to be the result of a non-enzymatic hetero-Michael addition.[241]

Shunt products of biosynthetic intermediates, both putative and confirmed, have also been isolated from native and overproducing strains. These include the C17 platensic or platencinic acids congeners (**281, 282, 303–307**) as well as the C20 enones, most of which are overoxidized and/or derivatized by amino acids (**267, 308**–**314**) or glycerol moieties (**315**).[227,234,237–239,242]



Heterologous expression of the entire *ptn* gene cluster in *S. lividans* K4–114 produced **266** and six other PTN congeners including both isomers of the C20 enones (**316**, **317**), *ent*-agathic acid (***313***), 12*R*-hydroxy-*ent*-atiseren-19-oic acid (**318**), an *N*-acetylcysteamine thioester of 7*R*-hydroxy-*ent*-atiseren-19-oic acid (**319**), and 14,15-dinor-13-oxo-8(17)-*ent*-labden-19-oic acid (**320**).[243] A glutaminylated *ent*-agathic acid derivative (**314**) was also isolated from a PTN overproducing strain.[234] Finally, 7-(3-butanonyl)-6,6-dimethyl-2-cyclohex-4-enone-2-carboxylic acid (**321**) appears to be either a diterpenoid-derived acid that was oxidatively cleaved in a manner similar to that of **320** or an apocarotenoid (vide infra chapter 2.8.3).[240]

Biosynthesis.: ***265*** and ***266*** are heavily modified diterpenoids and their biosynthesis has been expansively studied and recently reviewed.[220] The overall biosynthetic logic is a

divergent, but unified, model that requires construction of the diterpenoid skeleton, maturation of the C_{20} unit into a highly oxidized C_{17} coenzyme A (CoA) thioester, and condensation with the separately biosynthesized ADHBA moiety (Scheme 11). After GGPP is converted into *ent*-CPP by the type II TS PtmT2,[230] the two polycyclic diterpene scaffolds, *ent*-kaurenol and *ent*-atiserene, are formed from *ent*-CPP by two different type I TSs, PtmT3 and PtmT1, respectively.[228,244] A group of enzymes then processes both *ent*-kaurenol and *ent*-atiserene to the penultimate precursors platensicyl-CoA and platencinyl-CoA (Scheme 11). These enzymes, which perform reactions including oxygenations, epimerizations, CoA ligations, oxidations, and C–C bond cleavages,[229,245–247] must be flexible enough to accommodate both scaffolds; only one enzyme, a P450 that initiates ether formation in the ***265*** polycyclic enone, is specific to one pathway.[248] It was recently discovered that ADHBA is a precursor to the genetically encoded ADHBSH, a thiocarboxylic acid analogue of ADHBA, and that ADHBSH is likely the bona fide substrate for the final coupling reaction with platensicyl-CoA and platencinyl-CoA (Scheme 11).[236] There is one major question left to be answered in PTM and PTN biosynthesis: which enzyme controls the C4–C5 retro-aldol cleavage of the A ring?

PTM and PTN are truly a showcase for the importance of studying and understanding terpenoid biosynthesis in bacteria.

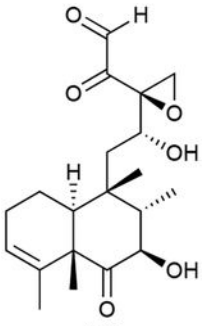
It was the discovery of PtmT1 that brought about the realization that noncanonical UbiA-like di-TSs from bacteria and fungi were an alternative to the canonical TSs and provided new opportunities for terpene enzymology and genome mining.[27,249] The identification and characterization of the thioacid cassette in the *ptm* and *ptn* BGCs led to the detection of 160 additional thioacid cassettes in bacteria, suggesting that thiocarboxlic acid-containing NPs are underrepresented in current NP databases.[236] PtmA1 and PtmA2, two acyl-CoA ligases, are the first example of a natural separation of the acyl-CoA ligation reaction[247] while PtmU3 is the first member of a triosephosphate isomerase (TIM)-barrel fold diiron monooxygenase.[246]

Biological activity.: ***265*** and ***266*** were originally discovered as potent bacteriostatics that targeted bacterial type II fatty acid synthesis.[221,222] ***265*** selectively inhibited *S. aureus* FabF (IC_{50} = 48 nM), an elongation condensing enzyme in the FASII cycle.[221] Conversely, ***265*** was a weak inhibitor of *S. aureus* FabH (IC_{50} = 67 μM), the initiation condensing enzyme. ***266*** was found to be a dual inhibitor of FabF (IC_{50} = 4.6 μM) and FabH (IC_{50} = 9.2 μM).[222] The MIC values for ***265*** and ***266*** were 0.1–1 μg mL^{-1} and <0.06–4 μg mL^{-1} against common drug-resistant Gram-positive pathogens including macrolide-, linezolid-, vancomycin- and MRSA, macrolide- and vancomycin-resistant enterococci (VRE), and *Streptococcus pneumoniae*.[221,222] ***265*** also showed moderate antibacterial activity against *Mycobacterium tuberculosis* (MIC = 12 μg mL^{-1}) due to its inhibition of mycolic acid biosynthesis.[250] ***265*** and ***266*** do not exhibit antibacterial activity against Gram-negative bacteria, except against the efflux-negative *Escherichia coli* (Δ*tolC*).[221,222] Although both ***265*** and ***266*** show efficacy in vivo when administering via continuous intravenous infusion,[221,222] they are limited by poor pharmacokinetics due to rapid renal clearance.[251] Recent studies aimed to address these limitations.[252–254]

Most PTM and PTN congeners have diminished or completely abolished antibacterial activity. While modest variations on the polycyclic enones can be tolerated with some loss of activity, minor modifications on the ADHBA moiety cause drastic negative effects on activity.[220] The exceptions are **278** (1–4 μg mL^{-1}), **279** (0.5–1 μg mL^{-1}), and, **302** (0.25–0.5 μg mL^{-1}), which retain the strong potencies of PTM and PTN.[236,241]

265 is also a promising drug lead for the treatment of diabetes in animal models. Studies in both mice and non-human primates support that ***265*** inhibits mammalian fatty acid synthase, selectively inhibits de novo lipogenesis, decreases glucose levels while reducing, or at least not significantly increasing, liver triglyceride levels, and leads to improved insulin sensitivity.[255,256] These studies substantiate that mammalian FAS is a viable target for a host of metabolic disorders.

2.4.7 Terpentecins—Terpentecin (***322***) is a highly functionalized clerodane antitumor antibiotic with a *trans*-decalin core.[257,258] Its heavily oxidized side chain consists of hydroxyl, epoxide, ketone, and aldehyde functional groups. Interestingly, a structurally very similar fungal antibiotic, clerocidin, was isolated the previous year from *Oidiodendron truncatum*.[259] Terpentecin are clerocidin are tautomeric in nature and can be found in their monomeric, hemiacetal, or dimeric forms depending on their solvent.[259] Other bacterial forms of terpentecin, which are all produced by actinomycetes, include the 18-hydroxy congener UCT4B (**323**) and the spirocardins (**324**, **325**), C14 and C15 reduced derivatives.[260–262]



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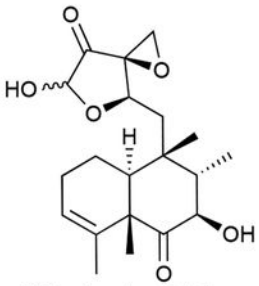


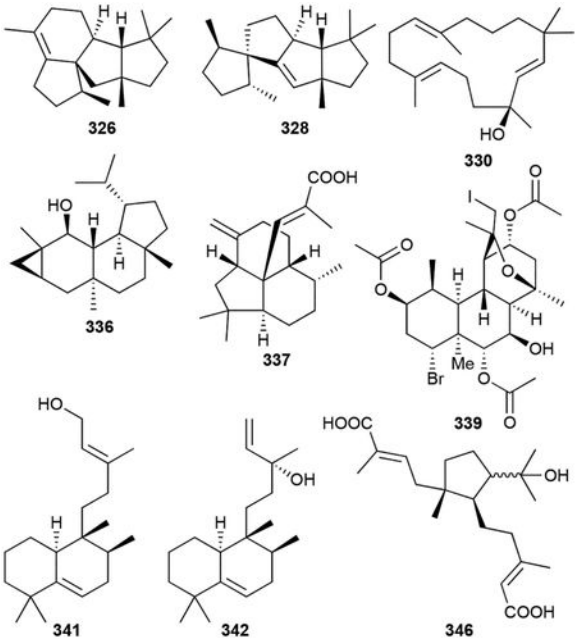
322 – hemiacetal form

Biosynthesis.: Early labelling studies supported that ***322*** is formed from MVA-derived isoprene units,[263] a finding that was reinforced after several MVA genes were found in its BGC.[264,265] The remaining biosynthetic enzymes included two TSs, two P450s and a ferredoxin.[265] In vitro studies confirmed that the type II di-TS Cyc1 converts GGPP into terpentedienyl diphosphate, a *trans-trans* clerodane, and the type I di-TS Cyc2 abstracts the diphosphate to yield terpentetriene.[266] The numerous oxygenation steps have yet to be revealed.

Biological activity.: The bacterial terpentecins, along with clerocidin, are potent antitumor antibiotics with the same mode of action. ***322*** was initially found to be a broad-spectrum antibiotic with MIC values as low as 0.05 μg mL^{-1};[257] the other analogues have similar potencies.[260,262] Investigation into its mode of action in bacteria showed that ***322*** inhibits

DNA synthesis and causes cell elongation at sub-MIC levels.[267] In mammals, ***322*** targets topoisomerase II, leading to DNA damage and cellular death. ***322***, along with clerocidin, induce the formation of a heat-stable complex and irreversibly inhibit the resealing of DNA.[268,269] The IC_{50} for ***322*** cytotoxicity is 82 nM, about 10 times more potent than that of clerocidin, suggesting the C6 and C7 functional groups contribute to its potency.[268]

2.4.8 Miscellaneous Diterpenoids—In this section, we combined 16 distinct diterpenoid scaffolds (23 total NPs) that do not fit into the categories above. Volatiles phomopsene (***326***), allokutznerene (**327**), spiroviolene (***328***), and cattleyene (**329**) are tetracyclic hydrocarbon ring systems and the volatile micromonocyclol (***330***) has a rare C_{15} monocyclic structure.[270–272] The neoverrucosanes (**331–335**) and (–)-verruconsan-2β-ol (***336***), well known constituents of plants, are 3/6/6/5 tetracycles; the neoverruconsanes were identified from marine gliding bacterium *Saprospira grandis* ATCC 23116 while ***336*** was found in the phototrophic *Chloroflexus aurantiacus*.[273,274] **331–336** were later found to be synthesized by UbiA-like TSs.[249]



Other tricyclic diterpenoids include enhygromic acid (***337***), a decahydroacenaphthylene fused 6/6/5 tricyclic skeleton with an acrylic acid on the central C atom;[275] isoagathenediol (**338**), which resembles the 6/6/6 tricyclic perhydrophenanthrene skeleton of the phenalinolactones, from the purple bacterium *Rhodospirillum rubrum*,[276] and the extensively functionalized cyanobacterial tasihalides A and B (***338***, **340**).[277] The tasihalides are extremely rare examples of natural iodinated diterpenoids and represent a new structural class of terpenoids with a *cis*-decalin core fused to an oxabicyclic system.

There are four known halimane diterpenoids in bacteria. Tuberculosinol (***341***) and isotuberculosinol (***342***, originally named edaxadiene), first identified from the in vitro characterization of the type II and type I DTSs, Rv3377c and Rv3378c, respectively, from

M. tuberculosis,[278–280] were later produced and detected in the membranes of *M. tuberculosis*.[281] These alcohols, although seen in vivo, appear to be shunt products in prenylated adenosine biosynthesis (vide infra chapter 3.4) via tuberculosinyl diphosphate hydrolysis.[282,283] Micromonohalimanes A and B (**343**, **344**) retain the halimane scaffold but have a significantly oxygenated prenyl chain at C9 of the decalin core, somewhat reminiscent of terpentecin.[284] (+)-*O*-Methylkolavelool (**345**), a diterpenoid with a clerodane scaffold yet similar to ***342*** and also proposed to be attached to adenosine, was first identified through in vitro experiments and later detected in vivo from *Herpetosiphon aurantiacus* ATCC 23779.[285]

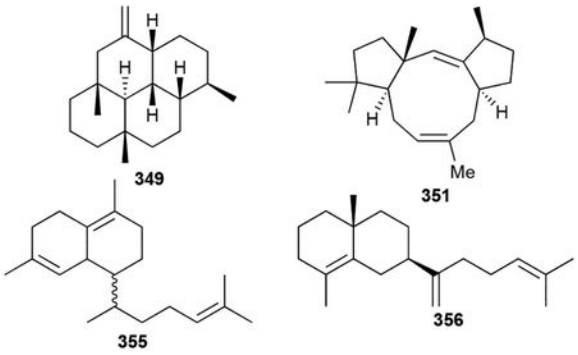
Finally, cystodienoic acid (***346***) is a unique monocyclic diacid from myxobacterium *Cystobacter* sp. Cbfe23 and two C_{19} abietadiene norditerpenoids with distinctive naphthalene cores (**347**, **348**) were reported from the cyanobacterium *Microcoleous lacustris*.[286,287]

Biological activity.: The abietadiene norditerpenoids are active against various Staphylococci with MICs of 14–20 μg mL^{-1} while micromonohalimanes **343** and **344** are weak (>40 μg mL^{-1}) bacteriostatic agents against MRSA.[284,287] ***337***, which enhances nerve growth factor-induced neurite outgrowth of rat adrenal cells, is an antitumor antibiotic with cytotoxicity against B16 melanoma cells (IC_{50} = 46 μM) and antibacterial against *B. subtilis* (MIC = 8 μg mL^{-1}).[275] ***346*** is cytostatic with a GI_{50} value of 1.33 μM against HCT-116.[286]

2.4.9 Heterologously expressed diterpenoids—

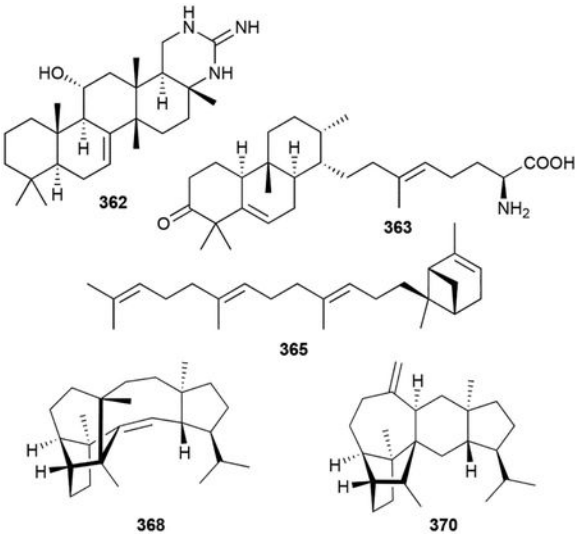
In this review, we elected not to include most terpenoids that were the result of heterologous expression of only the terpene synthase-encoding genes as they may not be genuine NPs. However, as we discussed the importance of the following study in the introduction, we feel it would be remiss to not include the novel skeletons identified from the heterologous expression of 29 TSs in *S. avermitilis*.[25]

Hydropyrene (***349***) and hydropyrenol (**350**) have novel 6/6/6/6 tetracyclic skeleton; the tricyclic tsukubadiene (***351***), odyverdienes A and B (**352**, **353**), and cyclooctat-7(8),10(14)-diene (**354**) have 5/9/5, 6/8/4, 6/7/5, and 5/8/5 ring systems, respectively; isoelisabethatriene B (***355***), and the clavulatrienes (***356***, **357**) are eudesmane-like 6/6 bicycles; and prenyl-β-elemene (**358**) and prenylgermacrene B (**359**) are the diterpenoid versions of ***118*** and ***106***, respectively.[160] It is highly likely that these TS products are precursors for further transformations given that many are encoded in genetic proximity to other putative NP biosynthetic enzymes.



2.5 Sesterterpenoids

Compared with the widespread mono-, sesqui-, di- and triterpenoids, the C_{25} sesterterpenoids are much more rare. Of the approximately 1000 known sesterterpenoids,[1] most of which have been discovered from plants and marine sponges,[288,289] there are only 15 of bacterial origin. Scytoscalarol (**360**), the first bacterial sesterterpenoid, was found in the cyanobacterium *Scytonema* sp. (UTEX 1163).[290] **360** has a tetracyclic scalarane skeleton, which is commonly found in marine sponges, with a guanidinium functional group attached to the methyl group on C18. Two additional guanidinium-containing sesterterpenoids were recently isolated from *Nostoc* sp. (BEA-0956).[291] The cybastacines A (**361**) and B (***362***) are pentacycles with a cyclic guanidino group composing the fifth six-membered ring.



Two additional sesterterpenoids, atolypenes A (***363***) and B (**364**), fall into the same family as the brasilicardin diterpenoids. Using a clever strategy of BGC disassembly and reassembly with inserted synthetic promoters, the *ato* BGC from *Amycolatopsis tolypomycina* NRRL B-24205 was heterologously expressed in *S. albus*.[292] The atolypene sesterterpenoids have the 6/6/6 tricyclic scaffold of their diterpenoid counterparts but are less oxidized, possess different methyl substitution patterns, and have an extended tail. The tails of atolypenes ***363*** and **364** resemble the γ-butyrolactone and amino acid moieties of the

phenalinolactones and brasilicardins, respectively. The *ato* BGC was initially identified as terpenoid given its inclusion of a type II TS.[292]

The somaliensenes A (***365***) and B (**366**) are bicyclo[3.1.1]heptene and cyclohexene terpenoids, respectively, with oligoprenyl linear chains.[293] These were discovered by heterologous expression of a TS gene from *Streptomyces somaliensis* in *E. coli*. Although we have not included most terpenoids that are the result of heterologous expression of only the TS gene, we included these two terpenoids given how few known members there are.

While genome mining for the TS responsible for the formation of the sesquarterpenoid tetraprenyl-β-curcumene (vide infra chapter 2.7), β-geranylfarnesene (**367**), a new linear sesterterpenoid, was identified.[294]

Very recently, novel sesterterpenoids were discovered from *Streptomyces mobaraensis*.[295] Sestermobaraenes A–C (***368***–***370***) are complex pentacycles that are released as VOCs from bacterial cultures on solid medium. A type I sester-TS (SmTS1) was identified in *S. mobaraensis* and shown to be responsible for the production of ***368***–***370***, as well as several other sestermobaraenes (**371**–**373**) and sestermobaraol (**374**) that were not detected in the headspace extracts of the bacterial culture.[295] A detailed mechanistic study was performed using extensive isotope labeling experiments revealing the plausible cationic intermediates leading to each of these sesterterpenoids.[295] SmTS1 is encoded next to a geranylfarnesyl diphosphate (GFPP) synthase, polyketide synthase (PKS), and glycosyltransferase. While the C_{25} polyprenyl synthase is the first characterized bacterial GFPP synthase, it is unclear if the other two enzymes are involved in the biosynthesis of a more complex NP.[295]

Biosynthesis.—The biosynthetic pathways of **360** and cybastacines **361** and ***362*** are unknown. The formation of somaliensenes ***365*** and **366** arises from the cyclization of GFPP by the UbiA-like TS StsC.[293] Given that a type II SHC-like TS is encoded only two genes away from *stsC*, it is likely that ***365*** and **366** are not the genetically encoded NP of the *sts* BGC. **367** is the result of diphosphate elimination of GFPP by the ‘large’ TS Bcl-TS.[27,294]

Biological activity.—The guanidinium-sesterterpenoids are antimicrobials. **360** was active against Gram-positive (MICs as low as 0.8 μg mL^{-1}) and Gram-negative bacteria (MIC against *E. coli* = ~12 μg mL^{-1}), as well as the fungus *Candida albicans* (MIC = 1.6 μg mL^{-1}).[290] ***362*** was most potent against Gram-positive bacteria with an MIC range of 2–4 μg mL^{-1}.[291] The atolypenes were moderately toxic to several human cell lines with ***363*** exhibiting IC_{50} values at ~15 μM.[292]

2.6 Triterpenoids

Triterpenoids are C_{30} NPs and include perhaps the most famous of all terpenoids, cholesterol. Unlike all of the terpenoids described above, which utilize precursors that are biosynthesized by adding successive C_5 units onto linear prenyl chains in a head-to-tail fashion, the common precursor for all triterpenoids is squalene (***375***), a linear isoprenoid created by a head-to-head fusion of two molecules of FPP. The lack of a diphosphate moiety on squalene necessitates that a type II TS catalyzes any ensuing cyclization reaction on squalene or its epoxidized derivative oxidosqualene. While the skeletal diversity of

triterpenoids is expansive, including linear carotenoids (vide infra chapter 2.8.1), mono-, bi-, tri-, tetra-, and pentacyclic systems,[296] triterpenoids in bacteria generally fall into three main categories: pentacyclic 6/6/6/6/5 and 6/6/6/6/6 hopanoids, and tetracyclic 6/6/6/5 sterols.[297–300]

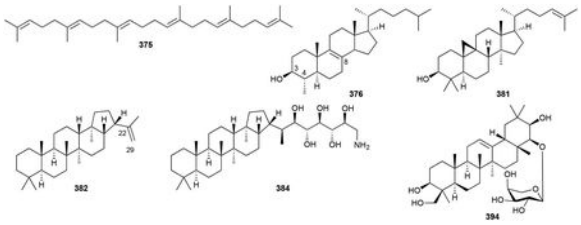
Triterpenoids are widely distributed in nature and have important roles in hormone signaling and membrane rigidity, stabilization, and organization.[301] Hopanoids, the most common triterpenoids in bacteria, structurally resemble the relatively planar tetracyclic sterols that are incorporated into eukaryotic membranes. Accordingly, hopanoids have long been proposed to be the functional equivalents of sterols in bacteria, although their differences in structure and chemical properties ensure that their functional abilities are not identical.[300,302–304] Other putative roles of hopanoids, and bacterial triterpenoids in general, such as lipid raft formation, stress tolerance, nitrogen fixation, and plant-bacteria communication should not be discounted[305]

In this section, we will not catalogue the multitude of tetracyclic and pentacyclic triterpenoids (our initial count of bacterial triterpenoids was ~200) or describe their well characterized biosynthesis or biological activities. This is for two main reasons: (i) triterpenoids and their biosynthesis are frequently and extensively reviewed[296,297,300,302,305–310] and (ii) there is still some debate whether many of the sterols isolated or detected from bacteria are biosynthesized de novo. While it is conclusive that certain types of bacteria do biosynthesize sterols,[311] very low quantities of reported sterols from some bacteria suggest that they were actually contaminants from media components, laboratory conditions, or other organisms.[312,313] Instead, we here introduce the triterpenoid skeletons most commonly found in bacteria by featuring some of the early discoveries as well as including some of the more exotic skeletons.

2.6.1 Hopanoids and sterols—The first hint of triterpenoid presence in bacteria came when squalene (***375***) and an unknown polycyclic derivative were identified in a few cyanobacteria.[314] Unequivocal data supporting the ability of bacteria to produce cyclic triterpenoids came a year later when *Methylococcus capsulatus* produced ***375***, 4-methyl-, and 4,4-dimethylcholesterol variants (***376***–**379**) on media only containing methane as its carbon source.[315,316] Myxobacteria were among the first type of bacteria found to produce true sterols; cholest-8(9)-en-3β-ol (**380**) was the main sterol of *Nannocystis exedens* and a later survey of other myxobacteria revealed several other sterols including cycloartenol (***381***).[317,318] A recent bioinformatics and lipid analysis study found that various bacteria including myxobacteria, methanotrophs, bacteriodetes, and α-proteobacteria all produce at least one sterol NP.[311]

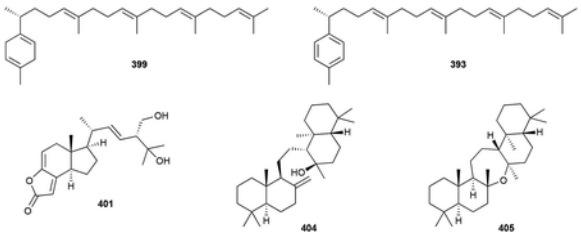
Hopanoids, which were first known as ubiquitous constituents in sedimentary rocks, are produced by many different types of bacteria including proteobacteria, actinobacteria, cyanobacteria, and acidobacteria.[298,305,319] The first bacterial hopanoid detected was diploptene [hop-22(29)-ene, ***382***].[320,321] The most common modification to hopanoids is the addition of a polyol alkyl side chain attached to C29. This C_5 addition, resulting in C_{35} hopanoids or homohopanoids, arises from the attachment and degradation of adenosine to the terminal olefin of ***382***.[305,309] The first bacterial homohopanoid, bacteriohopanetetrol

(**383**), was isolated from *Acetobacter xylinum*.[322,323] This family of triterpenoids, which can be diversified by core methylations or alkyl chain oxidations, aminations, esterifications, or glycosylations, is exemplified by members such as ***384*–389**.[324–327] The subclass of 6/6/6/6/6 pentacyclic hopanoids, including the tetrahymanols (**390–393**), MK800–62F1 (***394***), β-amyrin (**395**), and the soyasapogenols (**396, 397**) have core scaffolds that are much more highly oxidized than the 6/6/6/6/5 hopanoids.[328–331]



2.6.2 Miscellaneous triterpenoids—Other classes of triterpenoids are quite rare in bacteria. The linear β-hexaprene (**398**) and monocyclic triprenylcurcumenes (***399***, ***400***) are structurally related to the sesterterpenoids ***367*** and **366**, respectively.[294,332] The salimyxin antibiotics (***401***, **402**) are the first NPs found in the marine myxobacteria genus *Enhygromyxa*.[333] Their base structure, with a 6/5 hexhydroindane core fused to a 5-membered lactone, appears to be an unusually degraded sterol.

Onoceroids are a set of three unique triterpenoids first identified through heterologous expression of a TS, BmeTC, in *E. coli* and later identified from the hexane extracts of *Bacillus megaterium*.[334] All derived from squalene (***375***), the bicyclic 8α-hydroxypolypoda-13,17,21-triene (**403**) and tetracyclic 14β-hydroxyonocera-8(26)-ene (***404***) are on-pathway intermediates to the symmetrical and oxepane-containing pentacycle onoceranoxide (***405***). BmeTC is an unusual type II TS that appears to independently cyclize the two termini of squalene.[334]



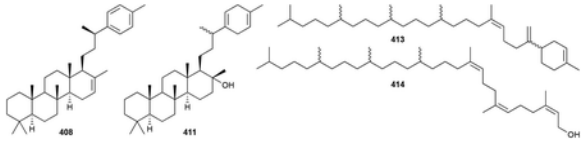
2.7 Sesquarterpenoids

Sesquarterpenoids, NPs derived from linear C_{35} precursors, are a recent addition to the superfamily of natural terpenoids with their name being coined about 10 years ago.[335] There are two types of bacterial sesquarterpenoids: the monocyclic and polycyclic curcumenes and sporulenes from *Bacillus* spp. and the monocyclic heptaprenylcyclines from *Mycobacterium* spp.[336]

Tetraprenyl-β-curcumene (**406**) and tetraprenyl-α-curcumene (**407**, originally named tetraprenyl-*ar*-curcumene for its aromaticity), were also isolated from various Gram-positive and Gram-negative bacteria, are the sesquarterpenoid versions of triprenyl-β-curcumene

(***399***) and triprenyl-*ar*-curcumene (***400***).[332] Subsequent studies exposed the seemingly related pentacyclic isoprenoids in the spores of *B. subtilis*;[337] these NPs, named sporulenes A–C (***408***–**410**), were structurally characterized after overproducing the putative TS responsible for cyclization.[338] After two C_{35} pentacyclic terpenols were discovered, it was proposed that the non-aromatic alcohol (***411***) was the legitimate NP and the aromatic analogue and dehydrated sporulenes were artifacts of autooxidation and thermal dehydration, respectively;[339] these alcohols were later named baciterpenols A (***411***) and B (**412**).[336]

Lipid analysis of various nonpathogenic *Mycobacterium* spp. revealed the presence of C_{35} terpenoids heptaprenylcycline (***413***) and octahydroheptaprenol (***414***).[340] ***414*** is proposed to be the hydrolysis product of heptaprenyl diphosphate analogue or the mycolic acids. Various heptaprenylcyclines have also been identified including congeners with additional *E* or *Z* olefins (**415**–**417**) or a C18 ketone (**418**).[341,342]



Biosynthesis.—The biosynthesis of the Bacilli sesquarterpenoids revealed a new class of ‘large’ TSs. Using a genome mining and systematic knockout approach to identify the TS responsible for initial cyclization reaction, YtpB was found to cyclize heptaprenyl diphosphate into the monocyclic **406**.[335] The type II TS SqhC then acts to yield the pentacyclic ***411***. Heptaprenyl diphosphate was later found to be formed by HepS/HepT, two (all-*E*)-prenyl diphosphate synthases.[343] At the time, YtpB was an unprecedented type I TS and had a primary sequence unlike any other characterized proteins.[335] Now, a new family of noncanonical ‘large’ TSs is beginning to be revealed and mechanistically characterized.[27]

The mycobacterial sesquarterpenoids rely on substrate flexible prenyltransferases and TSs. Synthetic preparation of octahydroheptaprenyl diphosphate and biotransformation in cell-free extracts of *Myobacterium chlorophenolicum* demonstrated it was the substrate of heptaprenylcycline formation.[340] Although the enzyme responsible for this transformation was unknown, this was the first example of a cyclization of a linear C_{35} terpenoid and suggested the presence of a natural *Z*-terpene cyclase. The discovery of numerous *E* and *Z* isomers of heptaprenylcyclines implied that linear *E* or *Z* precursors are distinctly formed by elongation of *E,E*-FPP or *E,E,E,*-GGPP and that the polyprenyl reductases can likely act on both substrate configurations.[336] Functional characterization of three *Z*-prenyl transferases supported this former proposal.[341] The heptaprenylcycline synthase has not been identified yet, but the ketone moiety on **418** is a plausible P450 functionalization.[344]

2.8 Tetraterpenoids

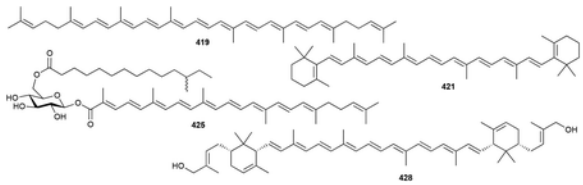
Tetraterpenoids are C_{40} NPs composed of two C_{20} units fused together in the same head-to-head manner as that of the triterpenoids. Although they are abundant in number, currently characterized tetraterpenoids are not very structurally diverse in comparison to the other terpenoids; tetraterpenoids are almost exclusively represented by C_{40} carotenoids.

Carotenoids contain extended conjugated polyene systems that are found in linear or 6-membered mono- or bicyclic form. The vast number of carotenoids arises from countless combinations of oxidation, oxygenation, cyclization, and glycosylation. Formation of polycyclic (not including the bicyclic carotenoids) tetraterpenoids is not yet known to occur, although given the capability of TSs to cyclize sesquarterpenoids, it would be reasonable to consider the possibility.

The polyenic nature of carotenoids imparts the ability to absorb light in the blue-green (450–570 nm) range of the visible spectrum, thus acting as accessory pigments that can absorb light in the absorption gap of chlorophyll.[345,346] The chemical properties of carotenoids also provide protection to the cell as scavengers of triplet chlorophyll and singlet oxygen.[345,347,348] In addition, these lipids may be incorporated into membranes to increase membrane rigidity.[349] Therefore, all photosynthetic organisms, including cyanobacteria and purple photosynthetic bacteria, as well as some non-photosynthetic bacteria, archaea, algae, and fungi, also produce C_{40} carotenoids. Animals require and utilize carotenoids, mainly as oxidatively degraded products (e.g., vitamin A), but they are not biosynthesized de novo and must be obtained from their diet.[350]

In this section, we will not describe the excessive numbers of carotenoids (our initial count of bacterial carotenoids was ~300) or describe their well characterized biosynthesis or biological activities. In fact, there is a database, ProCarDB, of 304 unique bacterial carotenoids available online.[351] Instead, we focus on introducing the most common scaffolds in bacteria and highlighting some of the tetraterpenoids and apocarotenoids that are not produced by other organisms. For comprehensive reviews on carotenoids, their biosynthesis, and biological activities, we highly recommend the reviews cited herein.[345,347,350,352]

2.8.1 Carotenoids—Common representatives of linear, monocyclic, and bicyclic C_{40} carotenoids include lycopene (***419***), γ-carotene (**420**), and β-carotene (***421***), respectively. The 6-membered rings are located terminally with the two rings in bicyclic carotenoids analogous to each other. These rings are most prevalent as cyclohexenes, but aromatic rings such as the benzoates seen in synechoxanthin (**422**) from *Syncechococcus* sp. PCC7002 have been identified.[353] Oxygens are typically incorporated at the termini with hydroxyl, ketone, and carboxylic acids commonly seen on the rings, as in canthaxanthin (**423**).[354] Carotenoids are also commonly modified as glucosides, as evidenced by the cyanobacterial myxol 2′-fucoside (**424**).[355]



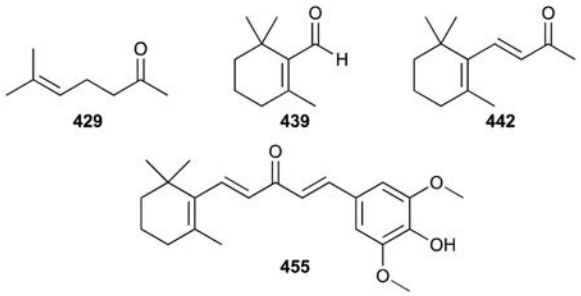
2.8.2 Other carotenoids—Although not technically tetraterpenoids, we thought it was logical to include here examples of C_{30} carotenoids and C_{45} and C_{50} homocarotenoids given their structural, biosynthetic (i.e., the head-to-head fusion of two isoprenoid precursors), and

functional similarities. Some bacteria, such as *S. aureus*, do not biosynthesize C_{40} carotenoids and instead utilize C_{30} carotenoids. Certainly, the most famous C_{30} carotenoid is the virulence factor staphyloxanthin (***425***), a linear and terminally oxidized C_{30} unit linked to an acylated glucose.[356] Other bacterial C_{45} and C_{50} homocarotenoids are elongated tetraterpenoids that have one or two dimethylallyl units appended onto the cyclohexene ring. Like the C_{40} carotenoids, these can be found as oxidized linear, monocyclic, or bicyclic variants exemplified by flavuxanthin (**426**), nonaprenoxanthin (**427**), and decaprenoxanthin (***428***), the first known natural C_{50} carotenoid.[357–360]

2.8.3 Norcarotenoids—Carotenoids are degraded into a variety of NPs and are commonly referred to as apocarotenoids;[345] vitamin A is the archetype apocarotenoid.[361] Carotenoid degradation, which may be the result of nonenzymatic or enzymatic oxidation, can occur at any of the numerous double bonds on linear, monocyclic, or bicyclic carotenoids yielding both linear and monocyclic apocarotenoids of various lengths.[345,362] Some apocarotenoids are pigments as they retain their polyene nature, but most of the detected apocarotenoids in bacteria are VOCs due to their small size and hydrophobic characteristics.[44]

Most bacterial apocarotenoids have been detected as VOCs from cyanobacteria,[44,363,364] but others have also been seen in *Streptomyces*, myxobacteria, and bacteroidetes.[37,44,47,49] Linear apocarotenoids, derived from oxidative cleavage from the uncyclized end of carotenoids or menaquinones, include C_8 (***429*, 430**), C_{13} (**431–433**), C_{18} (**434**), and C_{33} (**435**) alcohols and acetones;[37,47,49,365,366] the C_{11} homoterpenoid **436** was also identified in *Streptomyces* sp. GWS-BW-H5.[37]

Monocyclic apocarotenoids are much more common, or at least are more commonly identified, in cyanobacteria. Being derived from the terminal ring of carotenoids, these all have the trimethyl substituted 6-membered ring in common. Most structures are either simply oxidized 6-membered rings (**439–441, *439***) or derivatives of the β-ionone (***442*–449**) scaffold.[49,57,363,365,367,368] Variations lie in the position and type of added oxygen atoms on the ring and the level of olefin saturation. Recently, two abscisic acid sesquiterpenoids were reported from *Amycolatopsis alba* DSM 44262, but are likely just isophorones with extended acrylic acid tails (**450**, **451**).[369]



There are a couple of examples where the bacteria appear to utilize apocarotenoids as building blocks for additional modifications. A megastigmane diglycoside (**452**) from *Streptomyces* sp. YIM 6334 exhibits a trihydroxylated β-ionol core that has been adapted

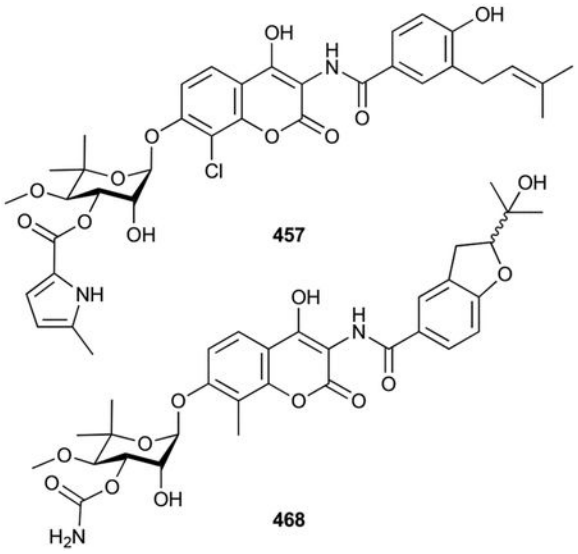
with a β-D-apiofuranosyl(1→2)-β-D-glucopyranoside.[370] There are two 2-hydroxymethylindole-3-carboxylic esters with linear apocarotenoid tails. Sphestrin (**453**) and the phytohormone rhodestrin (**454**) are metabolites from *Rhodobacter sphaeroides* produced when grown on media containing anthranilate.[371,372] The most exotic apocarotenoid is nostocionone (***455***).[373] This antioxidant from *Nostoc commune* is a formal aldol condensation product of **442** and syringic aldehyde.

3 Meroterpenoids

3.1 Aminocoumarins

Aminocoumarins are a family of antibiotics discovered during the Golden Age of Antibiotic Discovery.[374] They are categorized by the presence of a 3-amino-4,7-dihydroxycoumarin bicyclic nucleus and are all produced by *Streptomyces*. The three “classical” aminocoumarins, novobiocin, clorobiocin, and coumermycin A_1 have been thoroughly studied since their discoveries, revealing a wealth of knowledge on their biosynthesis and biology.[375] Not all aminocoumarins have isoprenoid moieties, but 18 family members have 3-prenyl-4-hydroxybenzoyl moieties linked to the aminocoumarin via an amide bond. Being the first antibiotic discovered with a side chain of terpenoid origin,[13] novobiocin, and the later discovered clorobiocin, have not only been used as probes to discover new modes of action for antibiotics and to understand the use of MVA and MEP pathways in NP biosynthesis, but biosynthetic studies revealed a novel family of PTs that opened up a new avenue for bacterial and fungal terpenoid enzymology and genome mining.

Novobiocin (***456***), also known early on as streptonivicin, cathomycin, and trademarked by Upjohn Company as Albamycin,[376–379] was discovered from *Streptomyces niveus* in 1955. Its structure is a composite of the aminocoumarin core, a 3-dimethylallyl-4-hydroxylbenzoyl moiety, and a 3-carbamoyl-4-*O*-methyl-5-*C*-methyl-L-rhamnose (L-noviose).[380,381] Clorobiocin (***457***), found in several *Streptomyces* species, differs from novobiocin only in its 8′-chloroaminocoumarin moiety and replacement of the acylated rhamnose with a 5-methyl-pyrrole-2-carboxyl moiety.[382] Most of the novobiocin analogues are either desmethyl (**458–460**) or descarbamoyl variations (**461**), or both (**462**); the C5 position of the benzoyl moiety is occasionally hydroxylated (**463–465**).[383–385] Clorobiocin (***457***) is the only aminocoumarin-terpenoid hybrid with a chlorine atom and novclobiocin 101 (**466**), the deschloro variant initially isolated from a halogenase mutant, was later found as a genuine NP.[386,387] Isonovobiocin (**467**), a 2′′-carbamoyl isomer of ***456***, was also isolated,[385] although it was previously shown to be a non-enzymatic isomerization product from novobiocin in the presence of dilute alkali.[388] Coumabiocin A–F (***468–473***) from *Streptomyces* sp. L-4–4 are the only analogues with modified prenylbenzoyl groups resulting in coumaran (A and B) or chromane (C and D) rings and/or hydroxylated units.[389]



Biosynthesis.—The biosynthesis of the aminocoumarins is comprehensive. A myriad of studies has detailed the construction of the aminocoumarin moiety, the noviose sugar, the 3-prenyl-4-hydroxybenzoyl group, the linkages of these three entities, as well as the regulatory and resistance mechanisms.[375] Studies of ***456*** and ***457*** prenylation led to the revelation of a new family of microbial soluble aromatic PTs. Prior to the report of any aminocoumarin BGCs, feeding studies using isotopically labeled precursors exposed that the dimethylallyl moiety of novobiocin originated via the MEP pathway, confirming its isoprenoid origin.[390,391] Almost simultaneously, a soluble protein fraction contained an unknown protein that catalyzed the prenylation of DMAPP onto 4-hydroxyphenylpyruvate, suggesting that prenylation occurred prior to the maturation of 4-hydroxybenzoic acid and its attachment to the nitrogen of the aminocoumarin scaffold (Scheme 12).[392] Bioinformatics analysis of the clorobiocin BGC revealed there were no gene candidates that had homology to known PTs.[393] CloQ, a soluble protein with no similarity to known PTs, no DDxxD motif, and no dependence on divalent cations, was later exposed as an aromatic PT.[394] The crystal structure of NphB, a CloQ homologue, revealed this unique family also had a novel structural fold, a β/α barrel with ten antiparallel β strands.[395] The five α-β-β-α secondary structure repeat elements led to the term ABBA PT.[396] The identification of CloQ led to a series of discoveries of homologous soluble aromatic PTs, including NovQ from the novobiocin BGC and a variety of fungal indole PTs.[394,396–399] These enzymes tend to have relaxed substrate specificities for both the prenyl donor and aromatic acceptor, making determination of its natural substrates via in vitro assays challenging while providing impressive chemoenzymatic tools.[26]

Biological activity.—The aminocoumarin family of antibiotics inhibit bacterial topoisomerase.[400] The fluoroquinolones are the quintessential antibiotic for topoisomerase inhibition, but novobiocin was discovered well before the quinolones and was licensed for a brief period as a commercial antibiotic for MRSA before being pulled due to its poor pharmacokinetic properties and toxicity.[375,401] Aminocoumarins, which bind to the ATP pocket of GyrB and ParE,[402] are potent inhibitors of DNA gyrase with IC_{50} values in the

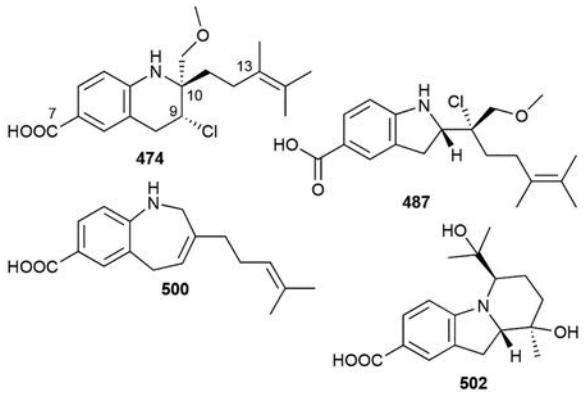
range of 10 nM.[400] Extensive SAR studies have been performed on the aminocoumarins and most modifications, including those on the prenyl group, have deleterious effects on antibacterial activity.[389] It was proposed that the prenylbenzoyl moiety may contribute to bacterial uptake and provide enhanced affinity to DNA gyrase.[403,404] In comparison with novobiocin, clorobiocin is 10-fold more active against DNA gyrase and 70-fold more active in the inhibition of topoisomerase IV;[405] even loss of just the chlorine atom results in 8-fold less activity.[386] Interestingly, the clorobiocin BGC possesses a resistant form of topoisomerase IV while the novobiocin BGC does not.[406] It is therefore expected, due to the targeting of two distinct essential enzymes, that clinical use of clorobiocin may be resilient to the development of antibiotic resistance.[375]

In accordance with the toxicity of aminocoumarins, ***456*** and ***465*** also have antiproliferative activities. These NPs, along with coumermycin A_1, bind to the C-terminal domain of 90 kDa heat shock protein (Hsp90) causing Hsp90 complex destabilization and client protein degradation.[407] Hsp90 plays crucial roles in stabilizing and folding proteins involved in oncogenic processes and is therefore an emerging target for anticancer treatments.[408] Some aminocoumarin analogues, such as **466**, also showed moderate antifungal activities.[387]

3.2 Benzastatins

Benzastatins are unique NPs derived from geranylated *p*-aminobenzoic acid (PABA) and produced by *Streptomyces*. Like the prenylated phenazines and pyrroles (vide infra chapters 3.6 and 3.9), they are radical scavengers with an assortment of other biological activities. The origin of the 29 benzastatins, in their four distinct forms, was expertly determined in a single biosynthetic study and led to the discovery of a novel nitrene transfer P450.[409]

Virantmycin (***474***), a unique chlorine-containing tetrahydroquinoline skeleton with a tetrasubstituted terminal olefin, was the first member of the benzastatin family to be discovered.[410,411] This bacterial alkaloid was initially discovered after screening for antiviral NPs from *Streptomyces nitrosporeus*.[412] Subsequent microbial screening programs led to the isolation of benzastatins A and B (**475, 476**), *p*-aminobenzamides with linear geranyl chains, and the tetrahydroquinoline benzastatins C (**477**) and D (**478**).[413] Benzastatin derivatives (**479–481**) with indoline, rather than tetrahydroquinoline scaffolds, were discovered soon after;[414] total synthesis of benzastatin E revealed the absolute configuration of the indolines is 9*S*,10*R*.[415] Other natural monocyclic, tetrahydroquinoline, and indoline benzastatins are modified with hydroxyl groups at various positions (**482–486**), chlorines at C9 or C10 (**477**, ***487***), an ergothioneine moiety at C9 (**488**), or a hydroxycyclopentenone moiety on the C7 amide group (**489**, **490**).[416–419] The unpublished ramthacins include didehydro (**491**) and hydroxyl variations (**492**, **493**) of ***465***.[420]



Heterologous expression of the entire *bez* gene cluster in *S. lividans* produced ***474***, **484**, **486**, and eight new benzastatin congeners.[409] Six of the eight new compounds were variants of monocyclic, tetrahydroquinoline, and indoline benzastatins (**494**–**499**); the other two had novel benz[*b*]azepine scaffolds (***500***, **501**). The production of new benzastatins was proposed to be the result of using inducible promoters rather than the native promoters found in the *bez* BGC.[409] One additional benzastatin-like NP, isolated from *Streptomyces* sp. SP301, is a 6/5/6 cyclized version of JBIR-67 (**484**) and was named aminobenzoate D (***502***).[421]

Biosynthesis.—The biosynthetic pathway of the benzastatins was recently revealed in an admirable study using heterologous expression, genetics, and in vitro biochemical experiments (Scheme 13).[409] The structural components of the benzastatin scaffold are created from modified PABA and geranyl units. GPP is C6 methylated and C10 hydroxylated; PABA is *N*-acetoxylated. Prenylation of the modified GPP onto the *meta* position of *N*-acetoxy-PABA is likely performed by a UbiA PT. The cyclization of this reactive intermediate into the tetrahydroquinoline or indoline bicycles is mediated by an unusual P450. BezE controls cyclization by successively forming iron nitrenoid and aziridine intermediates via acetic acid elimination and nitrene transfer to the nearby double bond of the geranyl moiety, respectively. The generation of tetrahydroquinoline and indoline is dependent on how the aziridine ring is opened, either at C9 by Cl^- or C10 by OH^- to give ***494*** or ***499***, respectively. BezE is expected to control the use of the chloride nucleophile in its active site. The biosynthesis of ***474*** is completed by *O*-methylation (Scheme 13).[409] The monocyclic benzastatins result from premature prenylation of PABA while the many hydroxyl and methyl variations stem from nonspecific use of prenyl donors. Given the innate reactivity of *N*-acetoxy-PABA, cyclization can also occur nonenzymatically resulting in the 5-, 6-, or 7-membered heterocycles. The ergothioneine moiety of **488** is also nonenzymatically formed as the C9 chlorine of ***474*** is a good leaving group.[409] The discovery of BezE as the first natural P450 nitrene transferase—mutants of the biotechnologically useful BM3 have previously been engineered for nitrene transfer[422]—supports the rationale for continued discovery of and biosynthetic studies on bacterial terpenoids.

Biological activity.—Benzastatins are known to have antibacterial, antifungal, antiviral, radical scavenging, and neuronal protection properties. The biological selectivities appear to

be highly dependent on the nature of the bicyclic moiety and the presence of the C9 chlorine atom. ***474*** is an antiviral antibiotic with potent inhibitory activities against both RNA and DNA viruses. The inhibition of viral plaque formation was seen at low concentrations (>0.01 μg mL^{-1}).[412] The tetrahydroquinoline structure, terpene chain, stereochemistry, and chorine atom of ***474*** and other benzastatins are all important for antiviral activity.[411,419,423]

Benzastatins have shown radical scavenging abilities by inhibiting lipid peroxidation in rat liver microsomes (IC_{50} values as low as 3.3 μM) and glutamate toxicity in neuronal cells (EC_{50} values as low as 1.7 μM).[413,414,416,424] Both ***474*** and ***487*** also potently activated hypoxia-induced factor (HIF) with EC_{50} values of 8 and 17 ng mL^{-1} (23 and 48 nM), respectively.[418] The dechlorinated analogues **485** and **486** lost this activity but retained their radical scavenging abilities suggesting that HIF induction requires the formation of a covalent bond. Later studies showed that ***487*** does not function as an iron chelator as most natural HIF activators do, but rather through interaction with an unidentified and likely metal-dependent target.[424]

3.3 Indoles

Indole is an electron-rich heteroatom-containing bicycle perhaps best known as part of the side chain of the proteinogenic amino acid Trp. It is a versatile nucleophile and functionalized indoles are prevalent throughout NPs. The nucleophilicity of indole is a perfect partner for the electrophilic prenyl diphosphates; in fact, prenylation of the indole core has been seen at each of the seven non-bridgehead atoms, N1 and C2–C7.[399,425] In this chapter, we separated prenylated indoles from peptides containing prenylated Trp residues (vide infra chapter 3.5).

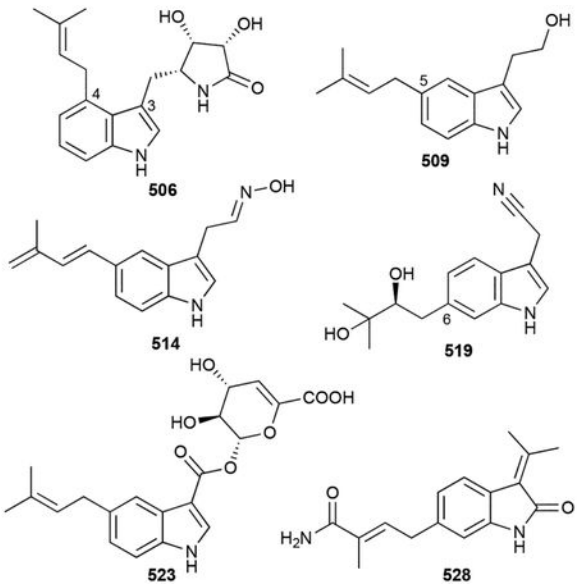
3.3.1 Simple indoles—There are 28 prenylated indoles that we categorized as ‘simple’ indoles, as opposed to the more complex polycyclic NPs below. The majority of these possess dimethylallyl moieties, or variants, appended to C4–C7 in a normal prenylation orientation. As would be expected given their origin from Trp, many of these simple indoles also have various functional groups at C3. The simplest prenylated indoles known in bacteria are 6-prenylindole (**503**, i.e., dimethylallylindole) and 6-dimethylallyltryptophan (**504**), first discovered from *Streptomyces* sp. TP-A0595 and *Actinoplanes missouriensis* NBRC 102363, respectively.[426,427]

Chloroindole, or 3-chloro-4-dimethylallylindole (**505**) from *Streptomyces* sp. SN0280 is the simplest C4 prenylated indole.[428] Other C4 prenylated indoles include amycolactam (***506***) from a sponge-associated *Amycolatopsis* sp. and indiacens A and B (**507**, **508**), C3-aldehydes with modified isoprenyl moieties from the myxobacterium *Sandaracinus amylolyticus* NOSO-4T.[429,430]

A family of related disubstituted indoles is differentiated by their prenylation pattern, being alkylated at either C5, C6, or C7, and their C3 functional groups. This family includes tryptophols (***509*–513**), indole acetaldoximes (***514*, 515**), indole acetonitriles (**516**–***519***), and indole carboxylic acids (**520–522**) or esters (***523***).[191,431–437] The dimethylallyl groups are mostly unmodified, but a few oxidized variations exist, including the uniquely modified

but-1*E*-en-3-one side chain (**511**).[433] Many of these NPs are from *Streptomyces* or myxobacteria.

Finally, there are also several 6- and 7-prenylated 2-oxindoles and isatins. These include 6-dimethylallylisatin (**524**) and its 3-hydroxyl congener (**525**), the 3-isopropylidene-2-oxindoles (**526**–***528***), 7-prenylisatin (**529**), and 3-acetonylidene-7-prenylindolin-2-one (**530**).[427,436,438–440]



Biosynthesis.: The full biosynthetic pathways of most of the simple indoles are unknown, although the prenylation reactions for many of them can be reasoned to be the result of prenylation of Trp by ABBA PTs. IptA, a 6-dimethylallyl-Trp synthase, was the first indole PT identified in bacteria.[441] Using *iptA* as a probe, multiple BGCs were identified containing nearby *iptA*-like genes next to tryptophanase-encoding genes.[427,440,442] PriB, from the BGC responsible for the production of ***523***, was shown to be a 6-dimethylallyl-Trp synthase and occurs prior to the action of tryptophanase. Although the *pri* BGC has two P450s, the conversion of 6-prenylindole into ***523*** is still not understood, as are most of the indole transformations in this family of NPs.[440,442]

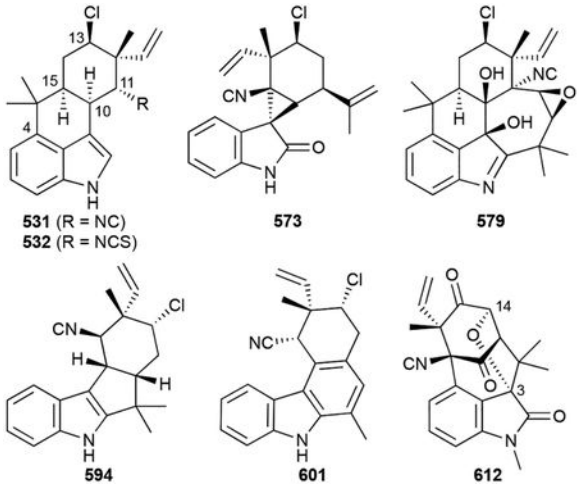
Biological activity.: Most of the simple prenylated indoles do not possess significant biological activities. Several (**503, 507, 508, *514*, 524, 526, 529**) had weak to moderate antimicrobial activities (MICs >20 μg mL^{-1}).[426,430,433,439,440] Only a few (***506*, 512, 515, 526, 530**) were moderately cytotoxic with IC_{50} values in the low to mid μM range, with 5-prenyltryptophol (***509***) also exhibiting bone morphogenetic protein-induced alkaline phosphatase inhibition (IC_{50} = 81 μM).[429,431,432,436,439]

3.3.2 Hapalindole-like indole alkaloids—

Over 80 natural members of the hapalindole family of cyanobacterial indole alkaloids are known. The structures, chemistry, biosynthesis, and biological activities of these prenylated indole alkaloids from the order Stigonematales have been extensively reviewed.[443,444]

There are four major classes of stigonematalean indole alkaloids: hapalindoles, fischerindoles, ambiguines, and welwitindolinones. These four classes can be further subdivided into nine structural groups.[444] Structural elements that are conserved amongst all nine groups include a polycyclic scaffold with an indole or oxindole core, a highly functionalized cyclohexane unit fused to the (ox)indole at C3, and a terminal vinyl group. Most members also possess isonitrile or isothiocyanate functional groups and a site-specific chlorine atom.

Hapalindoles are the largest class of these indole alkaloids. First isolated in 1984 from *Hapalosiphon fontinalis* while searching for the NP(s) responsible for its antialgal properties, hapalindoles A (***531***) and B (***532***) were identified as novel 10*R*,11*R*,12*R*,13*R*,15*S*-tetracyclic indole-containing scaffolds with 12-chloro and 11-isonitrile or -isothiocyanate functionalities, respectively.[445] Since then, 20 additional 'Group 1' tetracyclic hapalindoles, all possessing 3,4-fused indole cores, have been isolated from *Hapalosiphon* (**533–552,** ***538, 539, 541***). Most of these hapalindoles have variations in their stereochemical configurations at C10, C12, and C15, and are dechlorinated, hydroxylated, or epoxidized.[446–449] Hapalindoles T (**549**) and X (**550**) are unique with a cyclic thiocarbamate and a shifted allyl moiety, respectively.[446,449] Hapalindole formamides A (**536**) and J (**537**) were recently reported as NPs from *Hapalosiphon* sp. CBT1235, although a similar welwitindolinone formamide was earlier reported as an isolation artifact.[450,451] Hapaloxindoles (**553–555**), hapalonamides (**556–559**), and fontonamides (**560–562**) were also isolated as minor constituents and are likely oxidation products formed by singlet oxygen reactivity.[449,452,453]



The 'Group 2' tricyclic hapalindoles (**563–572,** ***567***) are very similar to the tetracyclic versions with the exception that the C4–C16 bond is not formed.[446,447,454] The 'Group 3' hapalindolinones, of which only two have been isolated from *Fischerella* ATCC 53558, are tetracyclic alkaloids with an unusual C3-spiro-fused cyclopropane connecting the 2-oxindole and cyclohexane rings (***573***, **574**).[455]

The ambiguine class of indole alkaloids, first isolated from *Fischerella ambigua* UTEX 1903, are categorized based on an additional dimethylallyl group that resides at C2 of the

indole ring.[456] 'Group 4' tetracyclic ambiguines (**575–577,** ***578***) are 2-reverse prenylated tetracyclic hapalindoles.[456,457] The 2-prenyl moieties of the 'Group 5' pentacyclic ambiguines are also attached to C11 to form a 7-membered ring (***579***–**590**, ***591***). Along with the expected isonitrile groups, these new rings have one, two, or three double bonds and are commonly substituted with oxygens.[456–460] Ambiguine G nitrile (**584**) was the first nitrile-containing analogue discovered.[458] Two 'Group 6' fischambiguines were later isolated from *Fischerella ambigua* UTEX 1903.[460] Fischambiguines A and B (**592, 593**) are also 2-prenylated pentacyclic alkaloids, but instead of a 7-membered ring, cyclization results in a new 6-membered ring.

Fischerindoles have similarity to the tetracyclic hapalindoles, but final cyclization onto the indole ring occurs at C2. These 'Group 7' tetracycles have been identified in both *Fischerella* and *Hapalosiphon* and have 6/5/5/6 (***594***–**600**) or 6/5/6/6 scaffolds (***601***, **602**).[454,461,462] The C rings in ***601*** and **602** are aromatic.[462]

The welwitindolinones combine to form the 'Group 8' and 'Group 9' tetracyclic indole alkaloids. 'Group 8' is a single unique molecule, welwitindolinone A (**603**), produced by *Hapalosiphon welwitschii* that displays a C3-spirocyclobutane ring on its 2-oxindole core.[454] The welwitindolinones in 'Group 9' have a cycloheptaenone connected to C3 and C4 of the 2-oxindole core and have differences in stereochemical configuration at C3, levels of oxidation, presence or absence of a methyl group on the indole *N*, and are either isonitriles or isothiocyanates (**604**–***612***).[451,454] Adding to the structural complexity of the welwitindolinones, is the C3–C14 cyclic ether-containing ***612***.

Biosynthesis.: Early biosynthetic proposals of the stigonematalean indole alkaloids, based on their structural similarities and the fact that most were isolated from the same strain, suggested a unified pathway that shared common intermediates.[454] A series of concurrent and successive genomic and biochemical studies revealed the *amb/fam* and *wel* BGCs from *F. ambigua* UTEX1903 and *H. welwitschii* UTEX B1830, respectively, and provided a new proposal with (3*R*)-3-geranyl-3-isocyanovinyl indolenine as a conserved and cryptic intermediate (Scheme 14);[463–465] additional BGCs were later identified.[466] This intermediate is generated by the Mg^{2+}-dependent C3-geranylation of *cis*-indolylvinyl isonitrile by the ABBA PT FamD2/AmbP1 or its homologues.[465,467] A family of Stig cyclases, a type of non-canonical TSs,[27] then catalyze regio- and stereoselective cyclization cascades to yield the tri- and tetracyclic scaffolds of the hapalindoles or fischerindoles. These fascinating terpene cyclization reactions follow a Cope rearrangement, stereoselective 6-*exo*-*trig* cyclization, and regioselective carbocation quench by electrophilic aromatic substitution (at C2 or C4 of indole) or deprotonation (Scheme 14).[465,466,468,469] Other characterized tailoring enzymes include a non-heme iron aliphatic halogenase, AmbO5, for C13 chlorination,[464,470] another ABBA PT, AmbP3, for ambiguine C2 prenylation,[463] and an *N*-MT for the welwitindolinones.[464] Other cyclization reactions, such as the C-3–C-11 fusion in 'Group 3' hapalindolinones, the unusual ring expansions in ***601*** and **602**, and the remaining tailoring steps including isothiocyanate formation and various oxidations are currently undetermined.

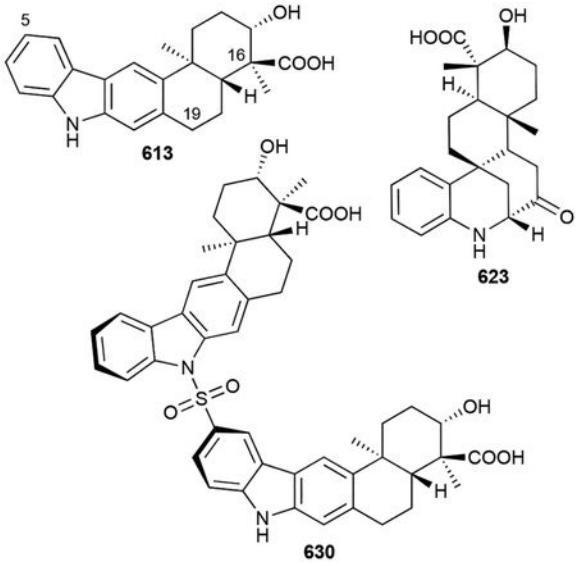
Biological activity.: The stigonematalean indole alkaloids have an amazing abundance of biological activities. They are known to have antimicrobial (antibacterial, antifungal, and antialgal) and anticancer properties, and have toxicity to plants, insects, and animals. The biological activities of these hapalindole-like alkaloids have been extensively reviewed.[443,444]

First isolated for their antialgal properties,[445] most of the hapalindoles and ambiguines have antimicrobial properties.[445,449,454,456,457,459,460,462] Active against mainly Gram-positive bacteria including *M. tuberculosis*, *Bacillus anthracis*, and *S. aureus*, as well as fungi *C. albicans* and *Saccharomyces cerevisiae*, most MIC values range from low to sub mM. It was later found that **569** competitively inhibits bacterial RNA polymerase, although given its lack of potency (K_i = ~1 mM) additional targets are expected.[471,472]

All four classes of indole alkaloids have members with weak to moderate levels (IC_{50} values of ~10–100 μM) of human cell cytotoxicity.[449,459,460] Several molecular targets and modes of action have been described for these activities. **582** inhibited NF-κB at an IC_{50} value of 30 nM, arrested cells in the G1 phase, and led to apoptosis in breast cancer cells.[473] Welwitindolinones inhibit P-glycoprotein-induced multi-drug resistance in human ovarian adenocarcinoma at concentrations as low as 100 nM and have antiproliferative effects associated with microtubule depolymerization.[474,475] Some hapalindoles are sodium channel-modulating neurotoxins with a recent report showing that hapalindoles also inhibit T cell proliferation, with ***531*** being the most potent (IC_{50} = 1.56 μM).[450,476]

Some alkaloids were also reported to be insecticides, phytotoxins, and teratogens. Hapalindoles killed fly and mosquito larvae at μM concentrations and **548** and **576** were toxic to developing zebrafish embryos.[444,448,477] ***579*** caused oxidative stress in lettuce via reactive oxygen species (ROS) generation, which led to lipid peroxidation and inhibited plant mitosis.[478]

3.3.3 Xiamycins—A structurally and biosynthetically unique family of indolosesquiterpenoids are the xiamycins. Carbazoles, tricyclic alkaloids with two benzenes flanking a pyrrole, are mainly found in plants, although they have also been isolated from algae, fungi, ascidians, and bacteria.[479] Most xiamycins have 6/5/6/6/6 pentacyclic skeletons and are found in either monomeric or dimeric form. Xiamycin A (***613***) and its methyl ester (**614**) from *Streptomyces* sp. GT2002/1503 and oridamycins A and B (**615, 616**) from *Streptomyces* sp. KS84, essentially discovered concurrently, were the first examples of this class of bacterial NPs.[480,481] Fused to the carbazole of ***613*** is a dimethyl decalin ring functionalized with hydroxyl and carboxylic acid groups. **615** is a C16 epimer of ***613***. Other monomeric xiamycins, all from *Streptomyces* spp., have added hydroxyl (**617–619**), keto (**620**), or chlorine (**621**) functionalities at positions C17 or C19.[482–484] Indosespene (***622***) sespenine (***623***), and oxiamycin (***624***) are all xiamycin variants, but do not possess the 6/5/6/6/6 pentacyclic scaffold.[482,483] ***622*** is a *seco* xiamycin intermediate with only a single connection between the indole and decalin ring systems; ***624*** has a seven-membered 2,3,4,5-tetrahydrooxepine ring fused to the carbazole; ***623*** has a rearranged skeleton with a tetrahydroquinoline-containing 6/6/6/6/6 pentacycle similar to the fungal NPs nominine and aspernomine.[485,486]



Numerous xiamycin dimers have also been isolated from both native strains and in heterologous hosts harboring the entire *xia* BGC. Dixiamycins A and B (***625***, **626**), N-N coupled dimers of ***613***, were originally discovered in the deep-sea *Streptomyces* sp. SCSIO 02999; this was the first example of a naturally occurring atropdiastereomeric N-N axis between carbazole nitrogens.[483,487] These two dimers were reisolated, along with N-C19 atropodiastereomers (**627, 628**) and a non-atropisomeric dimer bearing an N-C6 (C5 of indole ring) linkage (**629**), from *xia*-expressing *Streptomyces albus*.[488,489] Further MS analysis revealed the presence of three sulfonyl-containing dimers and ensuing full spectroscopic characterization confirmed the sulfonyl bridges of sulfadixiamycins A–C (***630***–**632**) were located between N-C6, C6-C6, and C6-C19, respectively.[490]

Biosynthesis.: The biosynthetic pathway of the xiamycins was systematically unveiled through a series of genetic and biochemical experiments, revealing several unique features. Two *xia* BGCs, simultaneously identified and independently named, were reported.[488,491] Initial bioinformatic analysis revealed the *xia* BGC did not encode canonical PT or TS genes. XiaM/P, which by protein sequence appears to be a polyprenyl synthase, is proposed to farnesylate indole or a related precursor. Terminal epoxidation sets up a type II TS cyclization reaction catalyzed by the integral membrane cyclase XiaE/H (Scheme 15).[488,491] Triple hydroxylation of the methyl on preindosespene by the P450 XiaJ/M yields ***622***[492] and suggests that a homologous reaction in oridamycin biosynthesis may occur on the methyl group on the opposite face of the decalin. A second cyclization reaction, catalyzed by the flavin-dependent oxidocyclase XiaF/I, another noncanonical TS,[27] occurs via cryptic hydroxylation at the C3 position of indole and nucleophilic attack by the exocyclic methylene.[493] Divergent phenyl migration or dehydration and spontaneous aromatization yield ***623*** or ***613***, respectively (Scheme 15).[488,491,493] Dimerization, for both the xiamycins and the sulfadixiamycins, occurs due to a suspected radical mechanism facilitated by the flavoenzyme XiaH/K; the role of XiaH/K was confirmed by gene knockout, genetic complementation, and biotransformation experiments.[489,490] Endogenous sulfur dioxide is suspected to react with the initial carbazole radical, forming a sulfonyl radical that can pair

with another carbazole radical.[490] ***624*** is also a product of XiaH/K acting on ***613***, perhaps occurring via a hydroperoxide radical rearrangement (Scheme 15).[489]

Biological activity.: Xiamycins are antibacterial antivirals. ***613*** and **614** were discovered as selective anti-HIV NPs (IC_{50} values >10 μM);[480] **619** and **620** were later seen to inhibit the replication of coronaviruses with EC_{50} values between 1 and 3 μM.[484] As this activity was reported prior to the severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) outbreak in 2019, it is unclear if xiamycins would be effective against SARS-CoV-2. The antibacterial properties of the monomeric xiamycins are fairly weak, although the dixiamycins and sulfadixiamycins were a little more effective (MIC range of 4–25 μg mL^{-1}) against *S. aureus*, *B. subtilis*, *E. coli*, and *Mycobacterium vaccae*.[482,483,490] **615** was also initially reported as an antifungal against the freshwater mold *Saprolegnia parasitica* with an MIC value of 3 μg mL^{-1}, although most xiamycins are not cytotoxic to other eukaryotes.[481]

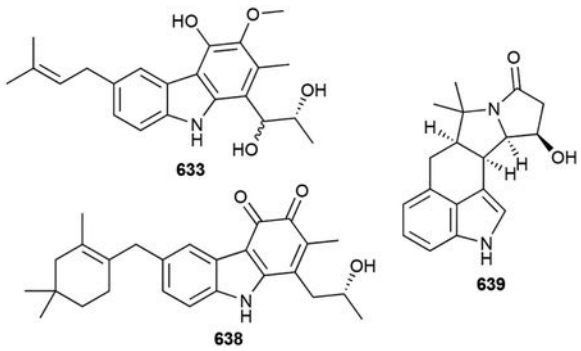
3.3.4 Miscellaneous polycyclic indoles—

Another family of terpenoid-carbazole NPs are the tricyclic neocarazostatins, carquinostatins, and lavanduquinocin. These carbazoles, however, are biosynthetically distinct from the xiamycins. Their carbazole skeleton does not include an isoprenoid component; instead, their prenyl units are located at C5 of the indole core.

Neocarazostatins A–C (***633*–635**), from *Streptomyces* sp. GP 38, were the first of this family to be discovered.[494] They are 5-dimethylallylcarbazoles with an alkylated *ortho*-hydroquinone unit. The carquinostatins A and B (**636**, **637**) were structurally identical to the neocarazostatins except for their *ortho* quinone functionality.[495,496] Lavanduquinocin (***638***), isolated from *S. viridochromogenes* 2942-SVS3, was **636** with cyclolavandulyl replacing the dimethylallyl group.[497]

An unusual bacterial indole alkaloid, amycocyclopiazonic acid (***639***) from the sponge-associated *Amycolatopsis* sp., is a 6/5/6/5/5 pentacycle with a C4-dimethylallyl moiety contributing to the polycyclic skeleton.[429] Prior to this discovery, cyclopiazonic acids were a class of indole alkaloids known in fungi, but not in bacteria.

Biosynthesis.: The neocarazostatin class of carbazoles are built from four building blocks: Trp, pyruvate, polyketide, and isoprenoid. Based on the C5-dimethylallyl group, the BGC was first identified after mining for IptA homologues.[498] However, after no homologues were found in the producing strain *Streptomyces* sp. MA37, a thiamine pyrophosphate-dependent enzyme responsible for C–C bond formation using pyruvate was used to identify the *nzs* BGC. Directly adjacent to this target gene was a gene bioinformatically predicted to encode a phytoene synthase, NzsG. NzsG is the C5-carbazole PT and suggested an emerging type of phytoene synthase-like PTs.[498] Later biosynthetic studies on the carquinostatin BGC completed the pathway by the realization of an unprecedented oxidative cyclization reaction catalyzed by a novel enzyme following the condensation of an indole-3-(α-hydroxyl-β-keto)-butanoic acid and 3-hydroxylbutyryl-ACP.[499] Prenylation and P450 hydroxylation both occur as late-stage tailoring reactions.[498]

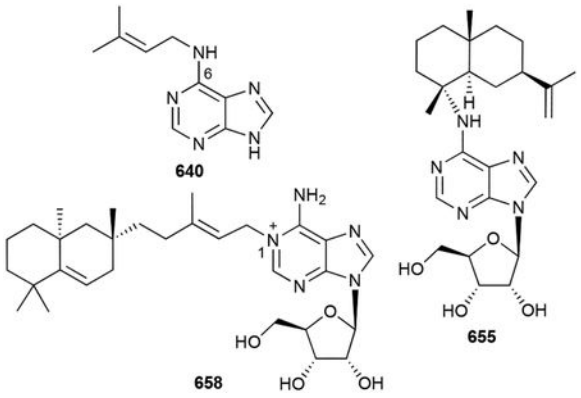


Biological activity.: Like the benzastatins, the neocarazostatin, carquinostatin, and lavanduquinocin family of carbazoles are potent radical scavengers. They showed strong sub-μM inhibitory activities against lipid peroxidation and prevented glutamate toxicity in neuronal cells (EC_{50} values as low as 3.1 nM).[494–497]

3.4 Nucleobases and nucleosides

Prenylated nucleobases and nucleosides are a relatively small family of NPs and can be classified into cytokinins, cyclic terpenoid adenosines, and uridine ethers. Cytokinins are important phytohormones that regulate plant growth, development, and reproductive competence.[500] Isoprenoid cytokinins, which all have a dimethylallyl moiety attached at N^6 of adenine or adenosine, are one of the most abundant classes of natural cytokinins and are ubiquitous in plants, but also produced in certain bacteria.[500] Isoprenoid cytokinins have had many names and abbreviations throughout the last 65 years; for naming simplicity, we chose to use the zeatin nomenclature in this review.

Bacterial zeatins were first found and structurally characterized in the Gram-positive phytopathogen *Corynebacterium fascians* (now named *Rhodococcus fascians*). Deoxyzeatin (***640***), the simplest zeatin with an unmodified dimethylallyl moiety attached to adenine, was the first zeatin identified in bacteria.[501] Numerous other zeatins, many of which were originally identified in plants, were later identified in species including *R. fascians*, *Pseudomonas amygdali*, and *Pseudomonas syringae*. The dimethylallyl moiety can be present in its hydroxylated, reduced, and/or methylated forms giving *cis*- or *trans*-zeatins (**641, 642**), dihydrozeatin (**643**), or 1′-methylzeatin (**644**).[502–504] The C2 position on adenine can also possess a 2-methylthio functional group (**645**).[505] These terpenoid-adenine hybrids are also commonly present in bacteria as terpenoid-adenosines, named here zeatin ribosides (**646–654**).[505–511]



There are three additional N^6-prenylated adenosines. Sorangiadenosine (***655***) and its 2-hydroxyl analogue (**656**), produced by the myxobacterium *S. cellulosum* KM 1003, have bicyclic eudesmane sesquiterpenoid moieties.[512,513] N^6-Tuberculosinyladenosine (**657**) has an appended tuberculosinyl skeleton (vide supra chapter 2.4.8) and is one of two diterpenoid-adenosine hybrids found in *M. tuberculosis*.[283] The other, 1-tuberculosinyladenosine (***658***), is found in significantly higher quantities and is likely the major biosynthetic product.[514]

Farnesides A and B, JBIR-68, and simamycin (**659**–**662**) compose the final class of 5′-*O*-prenylated nucleosides.[515–517] All found in *Streptomyces*, they have linear geranyl or oxidized farnesyl units on uridine or dihydrouridine nucleosides.

Biosynthesis.—Isoprenoid cytokinins can be biosynthesized de novo or from the degradation of prenylated tRNA molecules.[518] De novo biosynthesis in bacteria is only known to occur via the *N*-prenylation of AMP, catalyzed by isopentenyltransferases such as the isozymes Tmr and Tzs from *Agrobacterium tumefaciens*.[519–522] Interestingly, these enzymes can utilize DMAPP or its 5-hydroxyl variant to directly produce deoxy-or *trans*-zeatin glycosides.[521] The cytokinin BGC in *R. fascians* also encodes a P450 and phosphoribohydrolase that facilitate hydroxylation of deoxyzeatin and ribosyl hydrolysis, respectively, although the former has not been biochemically characterized.[523,524] Plant cytokinin biosynthesis is quite similar, although the PTs prefer ATP and ADP as prenyl acceptors.[525] This suggests that prenylation of ATP or ADP in bacteria is also a possibility.

Posttranscriptionally modified tRNA molecules can also be degraded into their respective monophosphate nucleotides.[518] The prenylation of preformed tRNA molecules, specifically the adenine adjacent to the 3′-end of the anticodon, is catalyzed by a tRNA dimethylallyltransferase.[526–528] This tRNA modification stabilizes the anticodon loop, enhances codon:anticodon recognition, and has been linked to the fidelity and speed of translation.[529] Other modifications on prenylated tRNA substrates, including isoprenyl hydroxylation and 2-methylthiolation, provide the precursors for the structural diversity seen in the zeatin family of NPs.[530,531]

The biosynthesis of the four cyclic terpenoid-adenosines follows a two-step process of initial terpene cyclization followed by prenylation. To account for the discovery of ***658***, after the

identification of the Rv3377c and Rv3378c TSs for the production of ***341***, the biosynthetic pathway was revised.[514] Rv3378c, which is required for the biosynthesis of ***658***, does not simply perform an elimination reaction after diphosphate abstraction as first reported;[280] Rv3378c is in fact a unique *cis*-PT with two substrate binding pockets that catalyzes the prenylation of adenosine at N1.[514] Sorangiadenosines ***655*** and **656** are proposed, based on bioinformatics, to be formed from the condensation of adenosine with a preformed 3,11-eudesmadiene, although in light of the activity of Rv3378c, it would be reasonable to consider that one enzyme catalyzes both terpene cyclization and prenylation of adenosine via attack on a cationic intermediate.[513] Supplementation of labeled acetate in *S. cellulosum*, which mainly utilizes the MVA pathway for terpene precursor biosynthesis, did not result in isotopically-labeled sorangiadenosines.[513] However, labeled dimethyl acrylic acid was incorporated into ***655*** and **656** supporting that their terpenoid moieties originate from the myxobacteria leucine degradation pathway, a pathway that branches off the MVA pathway; the genome of *S. cellulosum* was found to encode all proteins required for this alternative route.[513,532]

Biological activity.: The cytokinin phytohormones work in concert with the auxins to promote plant cell proliferation and development.[533,534] Cytokinins target a signal transduction pathway and are thus active at very low concentrations. In phytopathogenic bacteria, they act as virulence factors directing plant growth into a preferred infectious niche.[535]

658, a virulence factor from *M. tuberculosis*, has the unique ability to disrupt phagolysosomes.[283] Acting as an antacid because of its basic properties, ***658*** selectively accumulates in the acidic compartment, neutralizing the pH and causing swelling and structural remodeling of the lysosome. N^6-Tuberculosinyladenosine (**657**) is a weak base and thus not effective.[283]

The remaining terpenoid-nucleosides have weak to moderate activities against bacteria, influenzae plaque formation, and *Plasmodium falciparum*.[512,513,517,536]

3.5 Peptides—

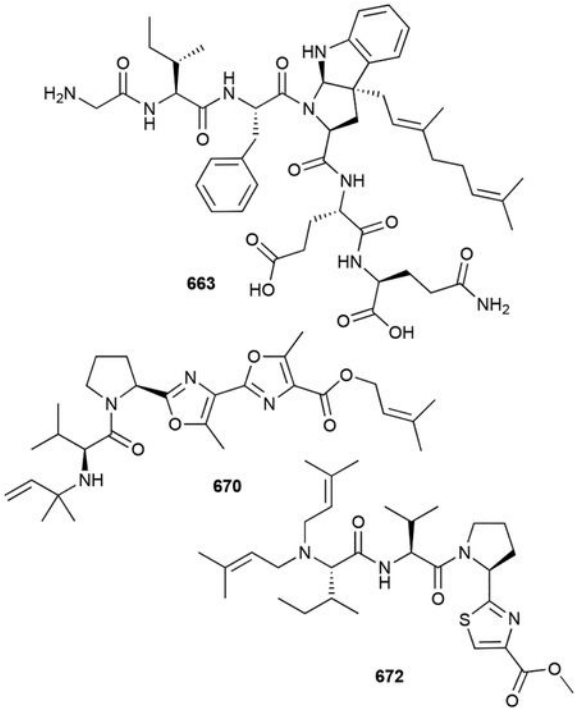
The posttranslational prenylation of proteins is a well understood and biologically important transformation[537] and therefore it is not surprising that there is a family of prenylated peptidyl NPs. There are at least three types of peptide NPs in bacteria: ribosomally synthesized and posttranslationally modified peptides (RiPPs), nonribosomal peptides, and cyclodipeptides constructed by tRNA-dependent cyclodipeptide synthases (CDPSs). Prenylation has been seen on all three types of peptides and can be the result of *C*, *N*, or *O*-prenylation in either normal or reverse fashion. The prenylation of peptides increases the lipophilicity of the compounds, provides additional structural aspects for further modifications and cyclizations, and impacts both biological and pharmacological properties.[538]

3.5.1 Ribosomal peptides—

The ComX pheromones are a group of quorum-sensing signals produced by *Bacillus subtilis* (***663*–669**).[539–542] These ribosomally synthesized peptide NPs stimulate natural competence in crowded microenvironments.[543,544] The structures of the ComX pheromones are divergent in their polypeptide sequences, but

typically range from six to twelve amino acids.[545] Conserved amongst all ComX pheromones is an internal Trp residue that is C3 prenylated and cyclized into a 6/5/5 tricyclic structure. The $ComX_{RO\text{-}E\text{-}2}$ pheromone (GIFW*EQ, ***663***) was the first to be structurally defined and had a normal geranyl moiety;[539] the Trp residue in $ComX_{RO\text{-}C\text{-}2}$ (TREW*DG, **666**) was farnesylated.[540]

Cyanobactins are ribosomally-derived peptides, either in macrocyclic or linear form, and are estimated to be produced by up to 30% of all cyanobacteria.[546] There are over 100 known cyanobactins, but only a handful of prenylated cyanobactins. Linear cyanobactins consist of the muscorides, aeruginosamides, and viridisamide. Discovered from *Nostoc muscorum*, muscoride A (***670***), a linear tetrapeptide containing two contiguous methyloxazoles, was the first reported linear cyanobactin.[547] Both its N- and C-termini were protected with reverse and normal dimethylallyl moieties, respectively. Later genome mining and heterologous expression of the *mus* BGC revealed muscoride B (**671**), an oxazole-containing pentapeptide with normal dimethylallyl moieties on both its termini.[548] The aeruginosamides (***672*–674**) from *Microcystis aeruginosa* and viridisamide A (**675**) from *Oscillatoria nigro-viridis* PCC 7112 are all prenylated peptides with a methyl thiazole-4-carboxylate moiety.[549,550] **674** has a unique diisoprenyl N-terminal amine.

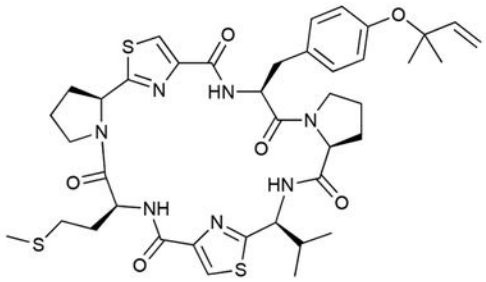


Macrocyclic cyanobactins have prenyl groups appended onto aromatic side chains. Kawaguchipeptin A (**676**) is a diprenylated cyclic undecapeptide from *M. aeruginosa* (NIES-88).[551] Like the ComQ pheromone, its two Trp residues have prenylated 6/5/5 tricyclic skeletons, although both Trps were modified with dimethylallyl units. Prenylagaramides A and B (**677, 678**), isolated from cyanobacteria *Oscillatoria agardhii* (NIES-205 and NIES-596), are cyclic nona- and heptapeptides that have the rarely seen *O*-

dimethylallyltyrosine side chain;[552] aestuaramide A (***679***) is a heptamer with a reverse prenyl unit on its Tyr.[553] Later genome mining afforded the related prenylagaramide C (**680**) and sphaerocyclamide (***681***).[554,555] Croissamide (**682**) and trikoramide A (**683**) from the *Symploca* genus are Pro-rich cyclic peptide with N1-reverse and C3-normal prenylated Trp units.[556,557] Unsurprisingly, the C3 prenylated Trp in **683** formed a 6/5/5 tricycle.

Biosynthesis.: The ComX pheromones require two posttranslational maturation steps. The *com* BGC consists of two key biosynthetic genes.[543,558] The precursor peptide, encoded by *comX*, is modified by ComQ.[558] ComQ is not homologous to ABBA PTs; instead it shows homology to polyprenyl diphosphate synthases. The internal Trp residue of the immature ComX peptide is prenylated at C3 attendant with a cyclization between the amide N and C2 forming a hexahydropyrrolloindole moiety (Scheme 16). The N–C2 cyclization is the result of an intramolecular capture of an imine tautomer created by the prenylation of C3.[425] A proteolysis reaction must occur to generate the mature ComX hexapeptide containing the geranylated hexahydropyrrolloindole, although the timing and responsible enzyme(s) for this posttranslational modification is unclear.

The related cyanobactin PT, KgpF, was found to catalyze a similar C3 normal prenylation reaction on two Trp residues of kawaguchipeptin B, yielding **676**.[559] KgpF can prenylate both linear and cyclic peptides, but only diprenylates kawaguichipeptin B. Although the reaction and subsequent cyclizations of the Trp residues are the same for KgpF and ComQ, the stereochemistry of the tricyclic structures differs.[560]



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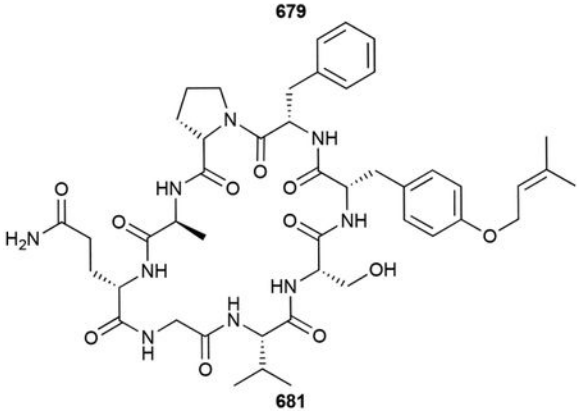

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The discovery of the prenylagaramide BGC (*pag*) led to the realization that cyanobactin BGCs can encode many different precursor peptides.[554] A later systematic survey of cyanobacteria expanded on the impressive biosynthetic potential of cyanobactin production.

[550] Regarding peptide prenylation, a majority of cyanobactin BGCs have at least one PT, which are phylogenetically related to the ABBA PTs, encoded within. LynF, a cyanobactin PT homologue from *Lyngbya aestuarii*, was the first ribosomal peptide prenyltransferase to be biochemically characterized.[561] At the time, there were no known cyanobactin NPs from the *lyn* pathway, yet LynF performed a reverse *O*-prenylation on a Tyr-containing substrate mimic. A spontaneous Claisen rearrangement then provided a C3-dimethylallyl-Tyr moiety. The later discovered ***679***, along with several other aestuaramides that were only tentatively identified by MS/MS, appear to support this initial reverse *O*-prenylation followed by Claisen rearrangement.[553] On a side note and perhaps biosynthetically related, 3-prenyl-L-tyrosine (**684**) and its acetylated derivative (**685**) were isolated as NPs from *Streptomyces* sp. IFM 10937.[562] A structural study of PagF, a LynF homologue from the *pag* BGC, revealed that the cyanobactin PTs are modified ABBA PTs with a truncated barrel fold, paving the way for the large peptide substrates to bind and help create a catalytically competent active site.[563]

This subfamily of ABBA PTs also *N*- and *O*-prenylates the termini of linear cyanobactins. Two PTs from the muscoride BGC (*mus*), MusF1 and MusF2, have substrate and reaction specificity.[548] MusF1 catalyzes normal prenylation on the C-terminus, while MusF2 catalyzes either normal or reverse prenylation on the N-terminus, depending on its peptide substrate. A unique bifunctional MT-PT protein, AgeMTPT, is responsible for the protection of both termini in aeruginosamide biosynthesis by catalyzing both N-terminal prenylation and C-terminal methylation reactions.[564]

Biological activity.: Cyanobactins have potential as drug leads based on their antimalarial and antitumor activities, as well as their ability to reverse multidrug resistance, although not all cyanobactins have known bioactive properties.[546,552] Aeruginosamides ***672*–674** and trikoramide **683** both have low μM IC_{50} values against various cancer cell lines.[549,557] Muscorides ***670*** and **671** are weak antibacterial agents against Gram-positive strains.[547] **685** had mild synergistic activity in sensitizing TNF-related apoptosis-inducing ligand (TRAIL)-resistant human gastric adenocarcinoma cells.[562]

3.5.2 Nonribosomal peptides—

Both macrocyclic and linear peptides are also formed by non-ribosomal peptide synthetases (NRPSs). These NPs commonly have non-proteinogenic amino acid components, including prenylated tryptophans. Cyclomarins A–D (***686*–689**) from *Streptomyces* sp. CNB-982 and *Salinispora arenicola* CNS-205 are cyclic heptapeptides with four unusual amino acids.[565,566] One of these residues is a *N*-reverse prenyl β-hydroxytryptophan, which is either epoxidized in A and B or left unmodified in C and D.

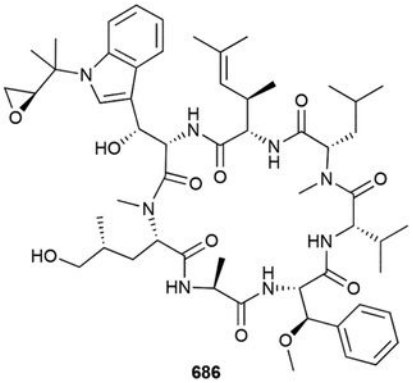
The ilamycins are cycloheptapeptides containing non-proteinogenic amino acids including 2-amino-4-hexenoic acid, 3-nitro-Tyr, and *N*-dimethyallyl-Trp. Several members of this family, including B1, B2, C1, C2, and D (**690–694**), were originally discovered as ilamycins from *Streptomyces islandicus and Streptomyces atratus* ATCC 14046 and later isolated as rufomycins from *Streptomyces macrosporeus* DSM-12818.[567–573] As with the cyclomarins, the reverse N-prenyl group was found in both unmodified (B1) or epoxidized forms (B2, C1, C2, D). The absolute configurations of the epoxidized ilamycins were not confirmed until

they were rediscovered, along with ilamycin E1 (**695**) from *S. atratus* SCSIO ZH16 in a genomic and biosynthetic study.[574] Eight new rufomycins, NBZ1–NBZ8 (**696–703**), and a chlorohydrin analogue (**704**) from *S. atratus* MJM3502 were found.[575]

The cyanobacterial aeruginoguanidines and microguanidines are exceptional NPs. They are linear peptides containing prenylated *N*-methyl-Arg residues and a trisubstituted phenyl trisulfate. Aeruginoguanidines 98-A–98-C (***705*–707**) from *M. aeruginosa* (NIES-98) have two Arg residues that have dimethylallyl, neryl, or modified neryl units attached to either one or both guanidium side chains.[576] The microguanidines, in either ester (**708, 709**) or amide (**710, 711**) form, only have one prenylated Arg with dimethylallyl, geranyl, or modified geranyl units.[577,578]

Biosynthesis.: The biosynthesis of prenylated nonribosomal peptides follows canonical megasynthetase assembly line biosynthesis. The reverse *N*-dimethylallyl-Trp residues are biosynthesized prior to incorporation into the growing polypeptide, or in the case of cyclomarins and ilamycins/rufomycins, prior to being used as the starter unit.[566,574] CymD, the ABBA PT from cyclomarin and cyclomarazine biosynthesis, confirmed its N1 prenylation of free L-Trp.[579] The epoxidation of the dimethylallyl moiety occurs late, if not last, in biosynthesis by associated P450s.[566,574]

Currently, the biosynthesis of aeruginoguanidines and microguanidines is only proposed based on bioinformatics analysis of the several homologous BGCs.[578] An NRPS condenses either one or two L-Arg residues with the unusual phenyl building block, which is proposed to be biosynthesized from isochorimate through a substituted phenylpyruvate intermediate.[578] Both prenylation, likely catalyzed by the undecaprenyl diphosphate synthase-like PT AgdJ, and sulfation are proposed to occur after the (depsi)peptide is formed.[578]



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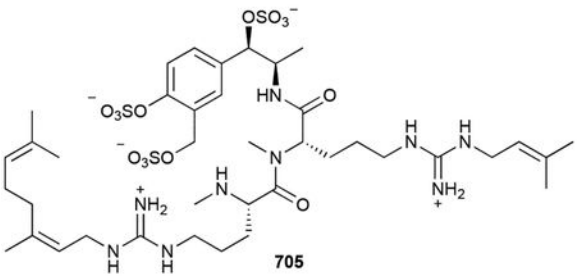

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Biological activity.: Prenylated nonribosomal peptides of bacterial origin are antitubercular and cytotoxic NPs. Cyclomarins ***686*–689**, whichh are cytotoxic to human cells with a mean IC_{50} of ~2 μM,[565,566] do not show antibacterial activity against any tested bacteria except *M. tuberculosis*. ***686*** kills Mtb persistor cells by targeting and activating the ClpC1 subunit of caseinolytic protease.[580,581] This activation leads to uncontrolled protein degradation and thus cell death;[582] it is bacteriocidal at 0.3 μM.[580] The ilamycin family of peptides are also potent antitubercular compounds, with MICs as low as 10 nM.[574,575,583] Ironically, their activity is due to inhibition of ClpC1.[584] The cytotoxicity of ilamycins, which is also in the low μM range, is at least partially controlled by the induction of apoptosis by the down-regulation of the anti-apoptotic protein Bcl-2; ilamycin C additionally suppresses the IL-6/STAT3 pathway leading to the inhibition of migration and invasion in triple-negative breast cancer cells.[585,586] Aeruginoguanidines ***705*–707** and microguanidines **708–711** have, at best, moderate cytotoxicities (IC_{50} = 25–50 μM).[576,577]

686 was also shown to have anti-inflammatory and quite potent antiplasmodial activity;[565,587] ***686*** prevents growth of *P. falciparum* (IC_{50} = 40 nM) by inhibiting the formation of the enzyme-substrate complex of diadenosine triphosphate hydrolase PfAp3Aase.[587]

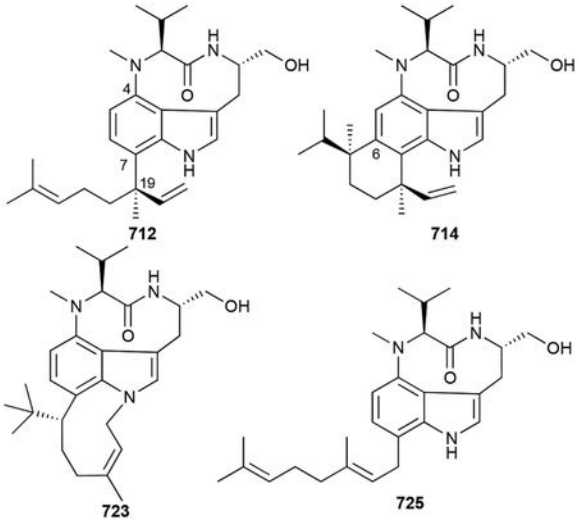
3.5.3 Teleocidins—

The teleocidins are indolactam-terpenoid hybrid NPs isolated from both cyanobacteria and actinobacteria. The overall structure of teleocidins consists of three components: an indole ring, an L-Trp-L-Val derived nine-membered lactam, and a terpenoid moiety appended to the indole. The teleocidins can be further divided into three major categories depending on its terpenoid moiety. Teleocidins A and lyngbyatoxins have linear geranyl (C_{10}) substituents at C7 of the indole ring, teleocidins B and olivoretins have cyclic C_{11} terpenoid units fused to C6 and C7, and pendolmycins have linear dimethylallyl (C_5) moieties at C7. Although the teleocidins are nonribosomal peptide meroterpenoids, we distinguish them in their own section to highlight their structures, biosynthesis, and activity.

‘Teleocidin’ was discovered from *Streptomyces mediocidicus* over 60 years ago as a toxic substance to fish.[588,589] The structural and stereochemical complexity of ‘teleocidin’ resulted in a series of reports culminating in an X-ray analysis of a hydrogenated bromoacetate derivative that provided full structural elucidation of ‘teleocidin B’.[590,591] Later chromatographic studies revealed that ‘teleocidin’ is a complex mixture of six distinct compounds.[592] Teleocidins A-1 (***712***), which was also isolated from the blue-green alga *Lyngbya majuscula*, named lyngbyatoxin A, and previously determined to have a reverse geranyl moiety at C7,[593] and teleocidin A-2 (**713**) are C19 epimers.[594] Teleocidins B-1–B-4 (***714–717***), which all contain 1,4-tetrasubstituted cyclohexanes fused to C6 and C7 of indole at its C2 and C3 positions, are diastereomers with the four possible stereochemical combinations at C19 and C25.[592] Olivoretins A–C (**718–720**) were concurrently reported as methyl ether variants from *Streptoverticillium olivoreticuli*; olivoretin D (***717***) is identical to teleocidin B-4.[595,596] **720**, its desmethyl analogue (**721**), and olivoretin E (**722**) were structurally distinct as their terpenoid connection patterns were reversed.[596–598] Blastmycetin E (***723***) from *Streptoverticillium blastmyceticum* NA34–17 is also structurally divergent.[599] Although it has a C_{11} group at C7, the other end is fused to N1 creating

another nine-membered ring; it also possesses a *Z* olefin and its C_{11} unit has an isobutyl functionality, similar to that of **722**.

Pendolmycin (**724**) and (–)-7-geranylindolactam-V (***725***) are teleocidin A analogues with reverse dimethylallyl and normal geranyl moieties, respectively.[600,601] There are only a few derivatives with variations in the peptidic core: methylpendolmycin (**726**) has an L-Ile in place of L-Val and 12-*epi*-lyngbyatoxin A (**727**) has a D-Val residue.[602,603] As would be expected, there are many other oxidized (**728–735**), *N*-desmethyl (**736–738**), *O*-methyl (**739**), *O*-acetyl (A2-**740**, B3-**741**), and *O*-glycosylated (**742**, **743**) teleocidins.[515,598,599,604–613]



Biosynthesis.: The biosynthesis of the teleocidins has been extensively studied and was recently reviewed, although some questions still remain.[614,615] Given the variety of prenyl groups (i.e., C_5 and C_{10}) attached at C7 of the indole core, it was evident that these moieties, even those with an additional carbon (C_{11}), were of terpenoid origin; these groups were later confirmed to be of MEP origin.[616] The lyngbyatoxin A BGC, *ltx*, from *L. majuscula* was found by probing a fosmid library for putative NRPS adenylation domains.[617] Three enzymes, an NRPS (LtxA), an MbtH/P450 (LtxB), and an ABBA PT (LtxC), were proposed to form the *N*-methyl-L-valine-L-tryptophanol dipeptide, catalyze macrocyclization to form indolactam V, and reverse geranylation at C7 yields ***712***, respectively (Scheme 17).[617] Follow-up biochemical experiments later confirmed that LtxA uses a four-electron reduction to release the dipeptide,[618] LtxB is a C–N bond forming P450,[619,620] and LtxC selectively forms ***712***.[617] When *ltx* was reported, LtxD, an oxidase/reductase was proposed to hydroxylate the geranyl moiety giving lyngbyatxins **729** and **730**, although this has not been confirmed.

With ***712*** proposed as the precursor to teleocidins B (i.e., ***714–717***),[617] the search for the MT and TS responsible for the modification of the C7 geranyl unit began. The *tle* BGC from *Streptomyces blastmyceticus* NBRC 12747 was identified, had the same three biosynthetic proteins from the *ltx* BGC, and heterologous expression of *tleABC* produced ***712***.[621] With no MTs or TSs encoded nearby, a genome-wide search for MTs resulted in the discovery of

TleD. Although located outside of the *tle* BGC, TleD catalyzed both C25 methylation and subsequent ring closure via fusion to C6 of indole (Scheme 17). This unusual mechanism of methylation-induced terpene cyclization is proposed to include a 1,2-hydride shift, C7 nucleophilic attack, and a final 1,2-alkyl shift to C6.[614,615,621] The various fusion patterns and diastereomers (e.g., ***714***, ***717***, ***721***) are formed depending on which carbon shifts and which face of the carbocation is attacked, although a post-methylation nonenzymatic cyclization has not been ruled out.[614]

During the search for TleD, another MT encoded outside of the *tle* BGC was found to be responsible for the methyl ether of olivoretins.[621] The (methyl)pendolmycin BGC, *mpn*, was also found to be highly homologous to the *ltx* and *tle* BGCs, with the major differences being that the NRPS can incorporate both L-Val and L-Ile and the ABBA PT MpnD is selective for C_5 prenylation; ***724*** is formed directly from indolactam V by MpnD (Scheme 15).[622] Enzymes responsible for other variations, whether in terpenoid attachment or teleocidin modification, remain enigmatic.

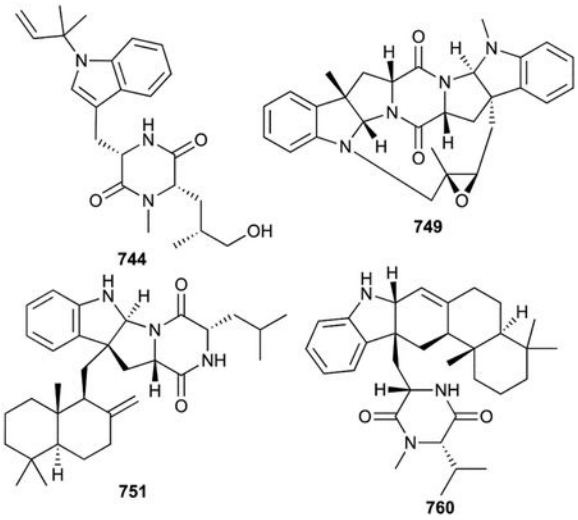
Biological activity.: Teleocidins are potent activators of protein kinase C (PKC). PKC isozymes play important roles in both normal and disease physiologies by controlling the phosphorylation states of protein within signal transduction cascades.[623] Overactivation of PKC leads to tumor cell proliferation as well as numerous other diseases including psoriasis, diabetes, heart disease, and autoimmune and neurological diseases.[624]

The original ‘teleocidin’ was initially found as a toxic substance to aquatic organisms, nematodes, and mice; it was also a mammalian skin irritant.[588,589] Teleocidins are not toxic to microorganisms,[588,589] although the methylpendolmycins are active against *P. falciparum* with IC_{50} values ranging from 5 to 20 μM.[613] The mammalian toxicities of ***712*** and ‘teleocidin B’ were later determined to be approximately equal with LD_{100} values in mice of ~0.3 mg kg^{-1}.[593] Soon after, the teleocidins were found to be potent tumor promoters with concentrations required for induction only 2–10 nM.[625,626] Tumor stimulation occurs via PKC activation at nM to μM concentrations.[627–629] While an intact indolactam ring is required for the activation of PKC,[603,610,611,628] longer terpenoid moieties improve potency, as evidenced by the various analogues.[601,606,628,630] **713** was also found to be a proteinase-activated receptor 2 antagonist in the low nM range, interfering with various cellular events including cancer cell migration.[629]

3.5.4 Diketopiperazines—

Another structural family of bioactive peptides produced by microorganisms are the 2,5-diketopiperazines (DKPs). These cyclic dipeptides are known to be synthesized by either NRPS or CDPS systems and commonly have associated tailoring enzymes such as PTs and P450s.[631] As of now, all bacterial prenylated DKPs have tryptophan residues. Cyclomarazines A and B (***744*, 745**), produced by *S. arenicola*, are likely premature NRPS truncation products of the cyclomarins.[566] Rufomyazine (**746**), found in *Streptomyces* sp. MJU3502, is also a likely truncation product of the ilamycin/rufomycin family.[632] The DKPs lansai A and B (**747, 748**) from *Streptomyces* sp. SUC1 are heptacyclic Trp dimers with a reverse dimethylallyl moiety on C5 of one indole ring.[633] Structurally similar, nocardioazines A and B (***749*, 750**) from *Nocardiopsis* sp. (CMB-M0232) also are heptacyclic Trp dimers, but their C_5 units are placed on C3 of one indole.

[634] The absolute configurations of ***749*** and **750** were revised after their total syntheses were completed,[635,636] revealing that both structures possessed two D-Trp units. In ***749***, this normal prenyl group, which is also epoxidized, forms a novel bridge with N1 of the other Trp forming an 11-membered ring.



Drimentines are a novel class of terpenylated DKPs as they have sesquiterpenoid-derived drimane units (***751*–759**). These NPs of actinomycete origin are unique as all other bacterial prenylated peptides have C_5 prenyl units, with the exception of the ComX pheromones (vide supra chapter 3.5.1). Natural drimentines are either Trp-Leu (***751*, 754–757**), Trp-Val (**758**), or Trp-Pro (**751, 753, 759**) DKPs and have been identified with drimane moieties singly attached to the C3 of indole (***751*–756**) or doubly attached to the C3 and N1 of indole (**757–759**).[637–640] The double fusion of drimane to the indole-containing DKP creates a unique heptacyclic skeleton. Two related compounds, named indotertines A and B (***760*, 761**) are drimane-possessing Trp-Val DKPs but a second fusion event between the C2 of indole and the exocyclic methylene of drimane creates a 6/5/6/6/6 indole-drimane pentacycle.[638,639]

Biosynthesis.: CDPSs, which employ amino-acyl-tRNAs as substrates to build dipeptide DKPs, are commonly associated with a variety of tailoring enzymes that act after the DKP core is built.[631] These enzymes create chemical diversity by the addition of structural units or functional groups or by modifying the amino acid components. The BGC responsible for the nocardioazines is located in two genetic loci where the MT NozB and PT NozC are not in genetic proximity to the associated CDPS, P450s, and regulatory genes.[641] Since ***749*** and **750** feature D-amino acids and CDPS are known to use charged aminoacyl-tRNA from primary metabolism (i.e., L-amino acids), an isomerase is expected to isomerize *cyclo*-L-Trp-L-Trp into *cyclo*-D-Trp-D-Trp.[641] Two methylation steps, at C3 and N1′, and prenylation at C3′ completes ***750*** biosynthesis (Scheme 18); alkylations at C3 and C3′ allow the formation of two pyrroloindoline moieties (as in ComX, vide supra Chapter 3.5.1). The timing of the C3′ prenylation and N1′ methylation steps is still unknown. In addition, it is unclear how the epoxidized dimethylallyl bridge is formed in ***749***, but two P450s are likely candidates.

The terpenoid biosynthetic machinery responsible for the drimane unit of the drimentines consists of two unique enzymes. The *dmt* BGC from *Streptomyces* sp. CHQ-64, now named *Streptomyces youssoufiensis* OUC6819, consists of the CDPS DmtB1, a phytoene synthase-like PT DmtC1, and an integral membrane cyclase DmtA1.[642] The Trp-containing DKP is, as above, first prenylated at the C3 position of the indole ring, which leads to pyrroloindoline formation. The resultant farnesylated 6/5/5/6/5 pentacycle is the substrate for terpene cyclization by the noncanonical type II TS DmtA1.[27,642] The second fusion event between the drimane unit and the indole ring seen in drimentines **757**–**759** or indotertines ***760*** and **761** is less clear. Drimentines **757**–**759** may be isolation artifacts resulting from acidic conditions; in fact, **757** and **759** were converted into ***751*** and **752** in the presence of acid.[637] It is conceivable that ***760*** and **761** can be formed by the attachment of the drimenyl unit and subsequent attack by the drimenyl alkene at C3 and C2 of the indole ring, respectively. This would explain the lack of the pyrroloindoline moiety in ***760*** and **761** but require a different biosynthetic pathway where drimenyl diphosphate is formed prior to prenylation.

Biological activity.: Cyclomarazines ***744*** and **745** were moderately effective against MRSA and VRE with MIC values of <20 μg mL^{-1} while some of the drimane-containing drimentines and indotertines ***760*** and **761** showed anticancer activities ranging from 1–17 μM.[566,638–640] Conversely, the nocardioazines were not cytotoxic antibiotics, but ***749*** was shown to inhibit the membrane efflux pump P-glycoprotein responsible for some of the multidrug resistance in cancer cells.[634]

3.6 Phenazines

Phenazines are a well-known class of colorful and redox-active NPs. Their study dates back to the late 1850s when the blue pigment pyocyanin was observed in the discharged pus of patients infected by *Pseudomonas aeruginosa*.[643,644] Phenazines, or 9,10-diazaanthracenes (it should be noted that atom numbering for phenazines differ from that of anthracenes), are produced by Gram-positive and Gram-negative bacteria as well as some archaea.[644,645] The phenazine pigments are able to both donate and accept electrons and thereby act as free radical scavengers, generate reactive oxygen species, decrease intracellular glutathione, act as virulence factors by interfering with host cell functions, and regulate genes.[644,646] As discussed below, prenylated phenazines are typically produced by the Gram-positive actinomycetes.

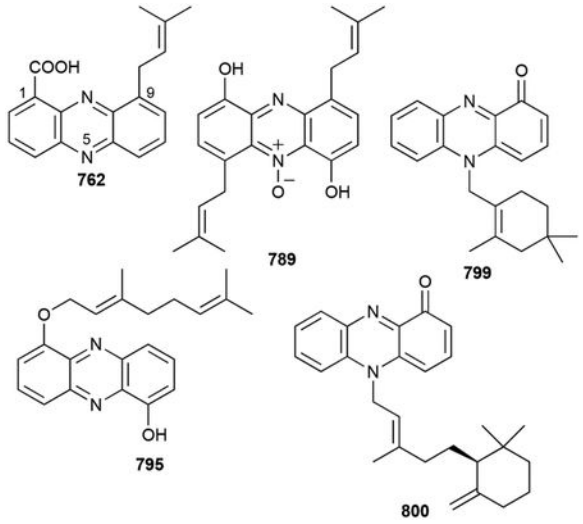
The first phenazine-terpenoid hybrid natural product was discovered from *Streptomyces cinnamonensis* ATCC 15413 and reported as 6-prenylphenazine-1-carboxylic acid.[647,648] The preponderance of C9-prenylated 1-phenazinecarboxylic acid (PCA) analogues subsequently discovered, however, including endophenazine A (***762***), which had NMR, MS, UV, and IR data identical to that of 6-prenylphenazine-1-carboxylic acid, suggests that the first prenylated phenazine was indeed 9-prenyl-1-PCA.[649] Other close relatives of ***762*** produced by various *Streptomyces* and *Kitasatospora* spp. include the 5,10-dihydrophenazine-N5-methylated endophenazine C (**763**),[649,650] the N5-alkylated phenazine-7-ones endophenazines B and F (**764, 765**), the hydroxylated endophenazines A1,

F1, and G (**766–768**), and the heterologously produced endophenazine E (**769**), an L-glutaminylated congener of ***762***.[649–653]

The benthocyanins, isolated from *Streptomyces prunicolor* 1884-SVT2, were early examples of prenylated phenazines with extended core structures and the first examples of geranylated phenazines. Benthocyanin A (**770**) is an N5-geranylated PCA with a fused phenyl-substituted γ-lactone.[654] Benthocyanin B (**771**) is a regioisomer of **770** with the carboxylic acid connected to C9 instead of C1 and benthocyanin C (**772**) displays a conjugated C8-keto-C7-phenylacetonitrile group.[655] Benthophoenin (**773**), also isolated from *S. prunicolor*, has benzoyl moieties at C3 and C7.[656] The chromophenazines (**774–779**), isolated 20 years later from *Streptomyces* sp. Ank315, revealed additional modifications to the phenazine core. While chromophenazine C (**776**) is an N5-prenyl-7-keto-phenazine-1-carboxamide and chromophenazines D–F (**777–779**) are dimethylallyl variations of benthophoenin, chromophenazines A and B (**774, 775**) have unique methylbenzene D rings.[657] Although the biosynthesis of this unique D ring is unknown, the planar structure suggests cyclization and aromatization of a C9-prenyl group.

Although glycosylated phenazines are rare, there are seven known structures encompassing both the endo- and chromophenazine scaffolds. Phenazoviridin (**780**) is a 6-deoxy-α-L-talopyranose ester of ***762*** although it was initially reported as a glycosylated analogue of 6-prenyl-PCA.[649,658] The endophenasides B and C (**781, 782**) are L-rhamnosyl esters of **766**; endophenaside D (**783**) is rhamnosylated **768**.[652] As the names suggest, aestivophoenins A and B (**784, 785**) have the same benthophoenin-like benzoyl additions to the phenazine core with additional decorations including L-rhamnosyl esters and in the case of B, a C9 prenyl group.[497] Aestivophoenin C (**786**) is debenzoyl **785**.[659]

Prenylated phenazines of bacterial origin have also been identified in their hydroxyphenazine and pyocyanin forms. JBIR-46, −47, and −48 (**787–789**) are C1,C6-dihydroxyphenainzes with either C9-prenyl or C4,C9-diprenyl groups, were isolated from *Streptomyces* spp. after using a PCR screen to identify potential terpenoid producers that possess 3-hydroxy-3-methylglutaryl-CoA reductase genes.[660,661] **787** and **789** are modified to the N5 oxide.[661] C4-Monoprenylated hydroxy- and methoxyphenazines (**790–793**) were also recently reported.[662] Other variants of hydroxyphenazines include the C9-alkylated geranylphenazinediol (**794**) and the *O*-geranylated phenaziterpenes (***795***, **796**) and phenazine SC (**797**).[662–664] An N-oxide form of ***795***, named marinophenazine A (**798**), was isolated from *Streptomyces* sp. CNQ-509.[665,666]



The pyocyanin-terpenoid hybrids were initially discovered after screening bacterial extracts for cytotoxicity. Lavanducyanin (***799***), named due to the presence of its rarely found in nature cyclolavandulyl moiety, and phenazinomycin (***800***), which exhibits an unusual (*S*)-*trans*-γ-monocyclofarnesol group, were both found in 1989 from *Streptomyces* sp. CL190 and *S.* sp. WK-2057, respectively.[667–669] Various halogenated (**801, 802**), hydroxylated (**803–805**), and esterified analogues (**806**) of ***799*** also exist.[670–672] One halogenated pyocyanin (**807**) has a simple dimethylallyl group on N5.[671] Overall, phenazines can be modified by *C*-, *N*-, and *O*-prenylation reactions at a variety of positions with hemi-, mono-, and sesquiterpene precursors that are in either their linear or cyclic forms.

Biosynthesis.—Phenazine biosynthesis is well documented.[644] Studies on the prenylation reactions catalyzed on phenazine NPs have revealed new enzymes in terpenoid biosynthesis. After the discovery of the ABBA PTs, PpzP and EpzP, ABBA PTs found within phenazine BGCs of *S. anulatus* and *S. cinnamonensis*, respectively, were determined to prenylate 5,10-dihydro-PCA.[673–675] Identification of EpzP was initially confounding given part of the *epz* BGC was found next to the *fnq* BGC (vide infra chapter 3.8.2), which contained the flaviolin ABBA PT Fnq26 and a seemingly nonfunctional ABBA PT Fnq28;[398,674] EpzP resided in a partial phenazine BGC found >40 kb away from *fnq* and *epz*.[675] Understandably, ABBA PTs were then used to genome mine for other phenazine PTs with mixed results.[665,676–678] Phm7, a putative ABBA *N*-PT found in the phenazinomycin BGC was identified next to the putative type II TS Phm1.[676] After no ABBA PTs were identified for the biosynthesis of **787–789** or ***795*** and **798**, the membrane-bound PTs Mpz10 and CnqPT1 were found to be responsible for the *C*-and *O*-prenylation reactions, respectively.[665,677] These proteins are more similar to UbiA-like PTs than the ABBA PTs. Finally, the *N*-prenylated ***799*** has a novel *cis*-PT-type cyclase that condenses two molecules of DMAPP in a “head-to-middle” fashion into cyclolavandulyl diphosphate (CLPP) prior to prenylation (Scheme 19).[27,679] The PT responsible for the attachment of CLPP to the phenazine core is still unknown.[679]

Biological activity.—In general, most biological activities of phenazines, which include antibacterial, antifungal, antitumor, insecticidal, and antiparasitic activities, stems from their

ability to negotiate redox systems, although there is no clear correlation between types of prenylated phenazines and their biological activities.[644,645]

Phenazines are well known as radical scavengers and some of their bioactive properties can be attributed to this ability.[644,646] **770** was initially reported to be an order of magnitude more potent than vitamin E.[654] **771** and **772**, along with **773**, inhibited lipid peroxidation in rat microsomes 30–70x stronger than vitamin E with IC_{50} values of 0.16, 0.29, and 0.15 μg mL^{-1}, respectively.[655,656] **780** inhibited lipid peroxidation in rat brain homogenate at IC_{50} = 6.6 μg mL^{-1}. This radical scavenging ability also translated to protective attributes with **780** and aestivophoenins **784–786** showing protective activities against KCN-induced hypoxia in mice and glutamate toxicity in the brain, respectively.[658,659,680]

Many of the prenylated phenazines possess weak to moderate antibacterial and antifungal activities. Endophenazines ***762***, **763**, and **767** all exhibited weak activity against Gram-positive bacteria with endophenazines **766** and **768** also showing activity against Mycobacteria.[648,650–652,681] Interestingly, the glycosylated endophenazines were active while the glutaminylated **769** was not.[652,653] Mode of action studies on **768** revealed that it is bacteriostatic against MRSA and that its interference on redox processes do not exclusively lead to its antibacterial activity.[681] **775** and **794** were also reported as weak antibacterials.[657,663] ***799***, its 2-chloro analogue **801**, and ***800*** are currently the most potent antibacterials with MIC values against Gram-positive strains as low as 1–2 μg mL^{-1}.[668,670] Several prenylated phenazines killed various fungal strains with **802** particularly potent with an MIC of 0.39 μg mL^{-1} against *C. albicans*.[650,657,672]

800 also exhibited a potent anti-*Trypanosoma brucei* IC_{50} value of 230 ng/mL with 23 times selectivity over cytotoxicity.[682] In an infection mouse model, ***800*** extended the mean survival days 2.7-fold, suggesting that it may be a lead candidate for new antitrypanosomal drugs.

Phenazines have been associated as potential anticancer agents since 1959 and prenylated phenazine-terpenoid hybrids continue that tradition. ***799*** was initially discovered during a cytotoxicity screen and was active against P388 and L1210 leukemia cells with IC_{50} values of 0.27 and 0.30 μM, respectively.[667,683] Likewise, marinocyanins **802–807**, brominated lavanducyanin analogues, were also potently cytotoxic with IC_{50} values ranging from 0.029–17.14 μM; compounds with modifications on the terpenoid ring had diminished potencies.[672] ***799*** and marinocyanins **802** and **807** induce apoptosis, possibly by their inhibition of TNF-α-induced NFκB (IC_{50} = 4.1–24.2 μM), COX-1 (IC_{50} = 5.6–30.0 μM), and COX-2 (IC_{50} = 4.0–34.0 μM) activities, and their reduction of PGE_2 (IC_{50} = 0.63–7.5 μM) and LPS-induced nitric oxide (IC_{50} = 8.0–>48.6 μM) production.[671] ***799***, at subinhibitory concentrations (0.01–10 ng mL^{-1}), also has been shown to stimulate cell proliferation.[684,685] The prenylated phenazine diols **787–789** also possessed cytotoxic activities, although they were >300-fold less active than ***799***.[660]

The inhibition of specific targets in humans have also been associated with prenylated phenazines. **794** and phenazines SA–SC possessed moderate inhibition (IC_{50} = ~2–3 μM) of human acetylcholinesterase.[662,663] The 1,6-phenazinediol core, but not the geranyl moiety,

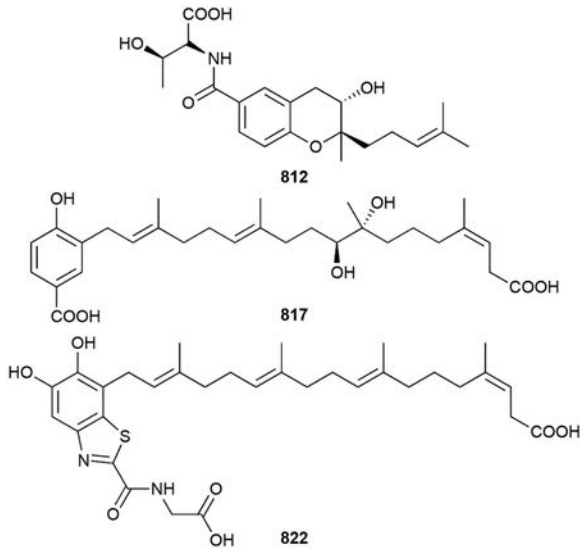
appears to be essential for this bioactivity. ***799*** inhibits testosterone 5α-reductase activity. Both ***799*** and **801** were reported to have IC_{50} values of 0.5 and 10 μM, respectively.[670]

3.7 Phenols

Phenols are common organic molecules found throughout NPs. Many of the prenylated phenolic NPs found in this review are described in other sections (e.g., aminocoumarins); however, a selection of phenolic meroterpenoids required a discrete section. During the biosynthesis of the universal benzoquinones (vide infra chapter 3.11.1), 4-hydroxybenzoate is prenylated and subsequently decarboxylated. This two-step process provides bacteria with 3-prenyl-4-hydroxybenzoates and 2-prenylphenols, which can be processed to benzoquinones or diverted to form other secondary metabolites.

The *ortho* prenylphenol substitution pattern is common in this group of terpenoids; hydroxyl groups are strong *ortho*/*para* directors in electrophilic aromatic substitution reactions (e.g., prenylations). Various 2-polyprenylphenols, direct precursors of benzoquinones, have been isolated from WT bacteria (**808**–**811**).[686,687] Xiamenmycins A, C, and D (***812***–**814**) from *Streptomyces xiamenensis* are benzopyrans generated by cyclization of a geranylated moiety onto the phenolic oxygen.[688–690] A related hemiterpenoid and aminocoumarin precursor, 3-dimethylallyl-4-hydroxybenzamide (**815**), as well as *p*-dimethylallylbenzamide (**816**), were also isolated from *Streptomyces*.[387,691]

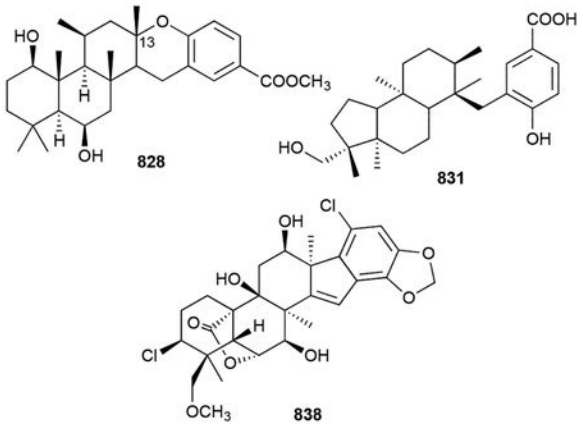
Erythrolic acids A–E (***817***–**821**) are unique prenylated NPs due to their unusual terpenoid lengths.[692] Produced by the *Erythrobacter*, a Gram-negative bacterium not known for producing NPs, the erythrolic acids are 4-hydroxybenzoate analogues with terminally oxidized prenyl moieties. Erythrolic acids ***817*** and **818**, **819**, and **820** have prenyl chain lengths of C_{22}, C_{17}, and C_{12}, respectively; erythrolic acids ***817***, **818**, and **820** also have terminal *Z* olefins.[692] Erythrazoles A and B (***822*****,** **823**), discovered prior to ***817***–**821**, are structurally related but contain rare tetrasubstituted benzothiazole core scaffolds.[693] Xanthomonic acid (**824**), produced by the plant pathogen *Xanthomonas citri* pv. *Mangiferaeindicae* and discovered using a differential isotope labeling experiment, has the extended and terminally oxidized prenyl moiety, which is appended to PABA at C3.[694] Pseudomonol (**825**), which was activated in *Pseudomonas* sp. SZ57 using a clever chimeric LuxR transcriptional activation system, is a C_{45} polyhydrated polyprenyl NP also at C3 of PABA.[695]



Another family of 3-prenylated 4-hydroxybenozates include the cyanobacterial noscomins, comnostins, and tolypodiols. These diterpenoid NPs are structurally, and likely biosynthetically, similar to the phenalinolactone-like diterpenoids. They are included in this section given that they are clearly the result of initial prenylation of 4-hydroxybenzoate. Noscomin (**826**) from *N. commune* Vaucher (EAWAG 122b) has a geranylgeranyl-derived dodecaphenanthrene 6/6/6 tricyclic scaffold.[696] The unnamed noscomin variant (**827**) has an additional tetrahydrobenzooxepane formed between the phenol oxygen and C7 of dodecaphenanthrene core.[697] The tolypodiols (***828*–830**), of which ***828*** was the first diterpenoid NP found in cyanobacteria, has a benzopyran fused to a perhydrophenanthrene core at C13.[698,699] Comnostins A–E (**831–835**) are similar but have a 5/6/6 dodecahydro-1H-benz[*e*]indene scaffold. The comnostins have different states of oxidation on C23; interestingly, **835** has an acetyl group on C3 and the acetal in **834** may be an artifact due to the use of methanol during extraction.[700]

KS-505a (***836***), also called longestin and produced by *Streptomyces argenteolus* A-2, is a unique decacyclic tetraterpenoid with unusually placed branched methyl groups, a 2-*O*-methylglucuronic acid, and a γ-hydroxy-γ-lactone that is in equilibrium with a ring-opened γ -ketocarboxylic acid.[701] The terpenoid octacycle is fused to succinylbenzoate in a similar manner to that of the tolypodiols.

The merosterols and habiterpenols are steroid-like phenol-diterpenoid hybrids. Habiterpenol (**837**), produced by *Phytohabitans suffuscus* 3787_5, has the familiar 6/6/6/5-tetracyclic scaffold fused to C3 and C4 of phenol.[702,703] Merosterols A and B (***838*** and **839**), which were found in cyanobacteria, share the same carbon skeleton and are highly functionalized.[704]



Nocarasin A (**840**) is simply 6-geranyl-3-hydroxymethylphenol; nocarasins B and C (**841, 842**), also produced by *N. brasiliensis* IFM 0667, are 3-hydroxybenzoate analogues.[705] Finally, farnesylbenzenediol (**843**), the reduced form of farnesylquinone (vide infra chapter 3.11.1), and the bicyclic nitrosporeunols E and F (**844, 845**) were isolated from *S. nitrosporeus* YBH10–5; geranylbenzenediol (**846**) was also identified.[706]

Biosynthesis.—The biosynthesis for most of these compounds is unknown, although UbiA and ABBA PTs are presumed culprits for the prenyltransfers. A five-gene BGC for xiamenmycins ***812*–814** was reported confirming the role of a UbiA-like 4-hydroxybenzoate PT (XimB).[707] Epoxidation of the 2′,3′-olefin leads to benzopyran formation by the SnoaL-like cyclase XimE with threonine derivatization by XimA concluding its biosynthesis.[708]

Currently, erythrolic acids ***817*–821** and erythrazoles ***822*** and **823** only have biosynthetic proposals.[692,693] A C_2 extension of prenyl chains may occur as the result of a Claisen condensation with acetyl-CoA and a terminally oxidized methyl group followed by dehydration and olefin isomerization. The isolation of **821** may support this proposal since its C_{15} chain is terminally oxidized.[692] Alternatively, oxidative cleavage of a longer prenyl chain at the terminal double bond could result in the loss of three carbons; olefin isomerization would be required in this case as well. If acetyl-CoA is used, the erythrazoles would be a rare case of a NP derived from four biosynthetic pathways: terpenoid, shikimate, nonribosomal peptide, and polyketide.[693]

The BGC for ***836*** was identified by PCR-guided gene discovery of its octaprenyl diphosphate synthase Lon12 and confirmed by gene inactivation of the putative TS Lon15.[709] Further studies revealed the unique methylation pattern of the cyclic tetraterpenoid skeleton.[710] Lon23 methylates the terminal vinyl carbon of IPP to form *Z*-homoIPP, which is elongated by two polyprenyl synthases, Lon22 and the aforementioned Lon12, with DMAPP and IPP to form dimethyloctaprenyl diphosphate (Scheme 20).[710] Although no other biosynthetic work has been reported, the structural similarity of ***836*** to the phenalinolactone diterpenoids suggests that the UbiA-like PT Lon13 first prenylates 4-hydroxy-2-succinylbenzoate at C3. Then, epoxidation at the terminal olefin and cyclization by the type II TS Lon15 is speculated to form the terpenoid octacyclic scaffold in one step. Oxygenations and glucuronidation at C3 completes the biosynthesis (Scheme 20). The

biosyntheses of noscomins **826** and **827**, comnostins **831–835**, and tolypodiols ***828*–830** are also unknown, however their pathways can be inferred based on their likely similarities to ***836*** and the phenalinolactone-like diterpenoids.

In merosterol (***838*** and **839**) biosynthesis, only prenylation and terpene cyclization is understood. First, the UbiA PT MstC catalyzes the geranylgeranylation of 3,4-dihydroxybenzoate at C5.[704] A subsequent type II TS, MstE, constructs the pentacyclic merosterol scaffold.

Biological activity.—The noscomins and nocarasins are antibacterial agents. Noscomins **826** and **827** are moderate to weak inhibitors of *Bacillus cereus*, *Staphylococcus epidermidis*, and *E. coli*.[696,697] Nocarasins **840** and **842** have MICs of 0.39–6.25 μg mL^{-1} against Gram-positive strains;[705] the 3-phenol is important for activity.

Comnostin B (**832**), which also has 47 μM molluscidial activity, **820**, **823**, and ***838*** and **839** all had low μM IC_{50} values against various cancer cell lines.[692,693,700,704] The lack of the terminal *Z* olefin or oxidation on the middle of the terpene chains of the *Erythrobacter* NPs appears to diminish their activities. The related xanthomonic acid (**824**) is also modestly cytotoxic and induces cell death via activation of autophagy.[694] While not cytotoxic, **837** selectively abrogates bleomycin-induced G2 arrest in Jurkat cells with an IC_{50} of 3.55 μM.[702]

Xiamenmycins ***812*–814**) showed anti-fibrotic activity with multiple effects including the inhibition of proliferation, cell adhesion, and contractile capacity of human lung fibroblasts.[688,689] The benzopyran, but not the affixed Thr is important for activity.

The tolypodiols are potential anti-inflammatory compounds with **830** inhibiting thromboxane B2 at an apparent IC_{50} of 100 nM.[698,699]

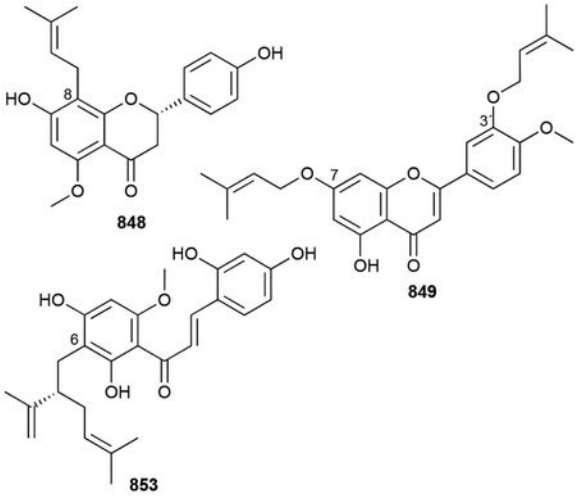
836, which was not antibacterial or antifungal, was a novel and selective in vitro and in vivo inhibitor of bovine brain calmodulin-dependent cyclic-nucleotide phosphodiesterase with an IC_{50} range of 65–170 nM.[701,711] ***836*** was also shown to have ~1 μM anti-trypansomal activity without cytotoxicity.[712]

3.8 Polyketides

Bacteria biosynthesize an immense diversity of polyketide NPs. Polyketides are built by megasynthethases, which are termed polyketide synthases (PKSs) and classified into three main types according to their protein makeup and how they utilize acyl-CoA precursors as building blocks.[713] Due to the modular biosynthetic logic of PKSs, polyketides have astonishing structural complexity and are commonly found in linear, macrocyclic, polycyclic, and aromatic forms.[713–715] Polyketide-derived meroterpenoids in bacteria are all the result of prenylation of an aromatic core. The most common aromatic polyketide that is used as the framework for initial prenylation is 1,3,6,8-tetrahydroxynaphthalene (THN). Chemical and biosynthetic studies of these unique bacterial meroterpenoids have revealed some of the most mechanistically intriguing enzymes involved in bacterial terpenoid biosynthesis. This family of meroterpenoids was recently reviewed.[716]

3.8.1 Flavonoids—The only prenylated flavonoids, which are very common type III polyketide NPs in plants,[717,718] of bacterial origin are the C6-prenyl (**847**), C8-prenyl (***848***), and 7,3´-*O*-diprenyl flavonoids (***849***) and the lavandulylflavanones (**850**, **851**, **852**) and lavandulylchalcones (***853*, 854**).[436,719–721] These are all produced by *Streptomyces* spp. and have not been biosynthetically studied as of yet.

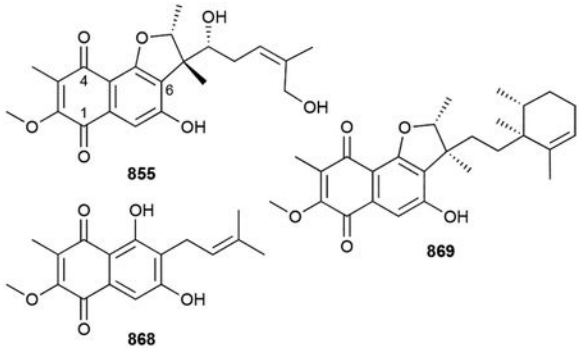
Biological activity.: The flavanones and chalcones with lavandulyl moieties are broad-spectrum antibiotics with activity against both Gram-positive and Gram-negative bacteria as well as fungi.[719–721] The lavadulyltetrahydroxyl analogue **850** is the most potent with IC_{90} values as low as 1 μg mL^{-1}. **847** and **851** and were effective against *M. tuberculosis* activity with IC_{90} values of 6 and 11 μg mL^{-1}.[720] These two flavonoids, along with isoxanthohumol (***848***), are also mildly cytotoxic.[720–722]



3.8.2 Furaquinocins—A screen for cytotoxic antibiotics resulted in the identification of furaquinocins A and B (***855***, **856**) from *Streptomyces* sp. KO-3988.[723] These NPs had a 6/6/5 tricyclic naphto[1,2-*b*]-furan-6,9-dione core that appeared to be a highly modified 1,4-naphthoquinone chromophore with a prenyl-like side chain consisting of ten carbons. At the time of discovery, these polyketide-derived meroterpenoids were quite unique, but have since become part of a larger family of meroterpenoids. In this subfamily, we included NPs with prenyl chains attached to C6 of the dihydroxybenzene ring.

Furaquinocins C, D, F, and H (**857–860**) are analogues of **855** with different hydroxylation patterns, E (**861**) has a conjugated *E,E*-diene on its prenyl chain, and the prenyl moiety on G (**862**) is a cyclic hemiacetal.[724] The absolute stereochemical configurations were later determined.[725] Furaquinocins I and J (**863, 864**) have C14 carboxyl and carboxamide functional groups at the end of the prenyl chain.[726] JBIR-136 (**865**) is a C3-demethyl and reduced form of furaquinocin D (**858**) and PI-220 (**866**) contains an 11*E* olefin and C13 hydroxyl group, although only its relative stereochemistry was determined.[727,728] Furanonaphthoquinone I (**867**), produced by *S. cinnamonensis* ATCC 15413, is very similar to **857**, although its 2,3-dihydrofuran ring is attached to the oxygen on C7.[729]

All of the meroterpenoids above are monoterpene-derived, but there are also known hemi- and sesquiterpene furaquinocin analogues. Fumaquinone (***868***) has a C6 noncyclized dimethylallyl moiety while neomarinone (***869***) and the marfuraquinocins A–D (**870–873**) have cyclized sesquiterpene chains.[664,730,731] ***869***, a product of the marine *Streptomyces* sp. MAR4 CNH-099, was initially reported to possess trisubstituted cyclopentane connected to the *cis* dihydrofuran ring by an 11*Z*-olefin.[731] Following biosynthetic studies and total synthesis, the prenyl moiety of ***869*** was later revised to a tetrasubstituted cyclohexene.[732,733] The tetrasubstituted cyclohexane rings in **870–873** likely originate from a different cyclization mechanism as that in ***869***.[664]



Biosynthesis.: The BGCs for furaquinocin A (***855***, *fur*) and furanonaphthoquinone (***867***, *fnq*) have been known for 15 years. Prior to any genetic studies, early precursor labeling studies confirmed that ***855*** and **856** were of mixed polyketide and MVA-derived terpenoid origin.[734] *fur*, the first reported hybrid polyketide-terpenoid BGC, was identified by genome mining for MVA pathway genes.[735] The structure of the furaquinocins and bioinformatics analysis supported a biosynthetic proposal of THN formation by a type III PKS, reverse prenylation of GPP by an ABBA PT (Fur7), an unknown cyclization reaction, and two methylation and multiple hydroxylation tailoring steps (Scheme 21). The *fnq* BGC, published in rapid succession, supported a similar biosynthetic proposal, with 2-*O* and C3 methylation being catalyzed by Fnq9 and Fnq27, respectively.[674]

Both in vivo knockouts and in vitro enzyme reactions support Fur7 as a C6-reverse PT that acts on 2-methoxy-3-methylflaviolin, a likely intermediate in both furaquinocin and ***867*** biosynthesis (Scheme 21).[736] It should be noted here that both Fur7 and the homologous Fnq26 catalyze C3-reverse prenylation of flaviolin.[674,736] Further biochemical studies revealed a cryptic 8-amino-flaviolin intermediate, synthesized by the aminotransferase Fur3 prior to demethylation, although its role and the fate of the amino group is unclear (Scheme 21).[737]

Two major terpene-related questions remain: (i) how is ether formation controlled in ***855*** and ***867*** biosynthesis and (ii) how and when does terminal cyclization of the sesquiterpene moiety occur in ***869*** and the marfuraquinocins (**870**–**873**) biosynthesis?

Biological activity.: Although furaquinocin meroterpenoids are considered as cytotoxic antibiotics, most of these NPs are cytotoxic without antibacterial or antifungal activities.

Only marfuraquinocins **870–873** had antibacterial activities (MIC values ≥8.0 μg mL^{-1}) against Gram-positive *S. aureus* and methicillin-resistant *S. epidermidis (*MRSE).[664]

Furaquinocins ***855*–858** and **860–862** were active against B16 melanoma and HeLa S3 cells with **860** being the most active (IC_{50} values of 0.19 and 0.52 μM, respectively).[724,738] Furaquinocins **859** and **863–865** were not cytotoxic,[724,726,727] but ***869***, **870**, **872** were active with IC_{50} values of ~19, 3.7, and 4.4 μM, respectively, against various cancer cell lines.[664,731] **866**, which was not cytotoxic, inhibited rabbit platelet aggregation with an IC_{50} value of 1.0–2.1 mM.[728] Furaquinocins ***855*–862** were also mentioned, but not published, to have antihypertensive, anticoagulative, and antiplatelet activities.[725]

3.8.3 Napyradiomycins—Napyradiomycins are unique halogenated polyketide-derived meroterpenoids with a naphthoquinone chromophore. The napyradiomycins are categorized into three types depending on how the prenyl groups are appended to the naphthoquinone core. Type A compounds have linear terpenoid side chains; type B have 6/6/6 tricyclic scaffolds where the C2-dimethylallyl group cyclizes onto 3-*O* to form a tetrahydropyran; type C members have monoterpenoid-derived 14-membered macrocycles between C3 and C7 (numbering based on naphthoquinone core).[739] There are 58 characterized napyradiomycin analogues, mostly produced by marine *Streptomyces* spp., with various regio- and stereoselective patterns of halogenation, oxygenations, and terpene cyclizations adding complexity.

The first napyradiomycins, A1 (originally named A), B1, B2, B3, C1, and C2 (***874–876*,** **877**–**879**) were reported in 1986 from the actinomycete *Chainia rubra* MG802-AF1 (now classified in the *Streptomyces* genus).[740] **874** was a dichloro-3-geranyl type B napyradiomycin; **875–877** were also type B, but their geranyl moieties were cyclized into chlorinated cyclohexanes; ***878*** and **879** also had the 6/6/6 core but the geranyl groups were found to also be connected to the naphthoquinone core at C7 thus erecting additional 14-membered rings. The first A-type napyradiomycins found were SF2415A1, A2, B1, and B2 (***880***–**883**) in *Streptomyces aculeolatus*, along with napyradiomycin A1 derivatives SF2415 A3 and B3 (***884*, 885**).[741] ***880***, **881**, and ***884*** had additional α-diazoketones on C5/C6 of their naphthoquinone cores.

There are seven additional type A napyradiomycins (**886–892**) including naphthomevalin (***888***) and the C2-deprenyl analogues phosphatoquinones A and B (***889*, 890**).[435,742–746] Other type B napyradiomycins with noncyclized geranyl moieties (**893–905**) and cyclohexyl geranyl moieties (**906–*922***) have been identified from native *Streptomyces* spp.[739,742,747–754] Heterologous expression of the *Streptomyces* sp. CNQ-525-based *nap* BGC produced at least seven B-type napyradiomycins including the new 2-deschloro-2-hydroxy-A80915C (**923**).[755]

The C-type napyradiomycins have garnered significant interest due to their unusual structures. Variations of C-type compounds include the “strained-ring” napyradiomcyin SR (***924***) that has a C3-, 6-*O*-, and C7 trifused geranyl moiety, the C16/17 *E* variant of ***924***, napyradiomycin D (***925***), and the 6-*O*-linked geranyl macrocycle napyradiomycin D1 (**926**).

[739,748,753] Other type C napyradiomycins include 16-dechloro-16-hydroxynapyradiomycin C2 (**927**), napyradiomycins A–C (**928–930**).[748,753]

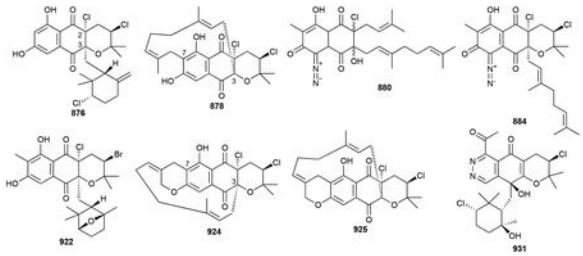
Azamerone (***931*)** from *Streptomyces* sp. CNQ-766 has a chloropyranophthalazinone core with a 3-chloro-6-hydroxy-2,2,6-trimethylcyclohexylmethyl side chain.[756] Its overall structure resembles that of the B-type napyradiomycins but with a conspicuous pyridazine ring.

Biosynthesis.: With early stable isotope feeding studies[757] and a large variety of natural A-, B-, and C-type napyradiomycins isolated prior to the discovery of the *nap* BGCs from *S. aculeolatus* NRRL 18422 and *Streptomyces* sp. CNQ-525,[755] it was clear that these hybrid polyketide-terpenoids originated from prenylated THN (Scheme 21).[758] Cloning of the *nap* BGCs revealed a type III PKS synthase, multiple PTs, and three vanadium-dependent haloperoxidases (VHPOs). It was clear that these VHPOs, typically known to introduce halides into NP scaffolds through either nonselective or enzyme-direct regio- and stereoselective halogenations,[759] were involved in both chlorination and terpene cyclization, [755] but their exact roles were not delineated for another decade.

An illuminating study, conceived by questioning how the electron poor C3 carbon of THN is geranylated in the napyradiomycins, as well as some of the merochlorins and naphterpins (vide infra chapter 3.8),[758] revealed a key non-chlorinating role for the VHPO NapH3. Naphthomevalin (***888***), the C2,C3-diprenylnaphthoquinone, is the result of an unprecedented enzyme-catalyzed α-hydroxyketone rearrangement and suggests that other related meroterpenoids arise through a similar VHPO-catalyzed mechanism.[760]

After the key finding of the activity of NapH3, the total enzyme syntheses of ***888***, ***874***, and ***875*** were conducted.[761] THN is first C4-geranylated by the ABBA PT NapT9, NapH1 then oxidatively dearomatizes and chlorinates the eventual dihydroquinone ring (Scheme 21). Another ABBA PT, NapT8, prenylates the chlorinated C2 position before the α-hydroxyketone rearrangement to form ***888***.[760] NapH1 then acts again to complete the cyclization of the tetrahydropyran ring forming ***874***.[761,762] NapH4 then mediates a chloronium-induced cyclization of the geranyl moiety to yield ***875*** (Scheme 21).[761] Given this biosynthetic pathway, one can appreciate that many of the napyradiomycin congeners are biosynthetic intermediates and by-products, or the result of non-enzymatic transformations; although differences in the associated BGCs may purposefully biosynthesize some variants. It is currently unclear how the diazo functional groups or the 14-membered macrocycles of the C-type napyradiomycins are installed.

Biosynthesis of ***931*** is proposed to occur through a diazonapyradiomycin intermediate that undergoes oxidative rearrangement, decarboxylation, and dehydration to form the aromatic pyridazine ring.[756] Labeling studies biosynthetically link ***931*** to the napyradiomycins as ***884*** was converted into ***931*** in a precursor feeding experiment.[763]



Biological activity.: The napyradiomycins were initially found as antibacterials but are now known for their broad spectrum antibacterial, anticancer, and antiogenic activities. Most A- and B-type napyradiomycins have respectable activities against both aerobic and anaerobic Gram-positive bacteria with potencies as low as 0.015 μg mL $^{-1}$.[435,739,742,743,748,749,752,754,764,765] **905** (0.78 μg mL^{-1}), **877** (0.25 μg mL^{-1}), and **908** (15 ng mL^{-1}) were particularly potent analogues.[742,749,765] **906** and **908** also had strong activities (MICs <8 ng mL^{-1}) against the Gram-negative *Haemophilus influenzae*.[742] C-type napyradiomycins are less potent with MICs >12.5 μg mL^{-1}.[740,753] The mode of action of antibiotic activity is uncertain, yet DNA, RNA, protein, and cell wall biosynthesis are all inhibited.[742]

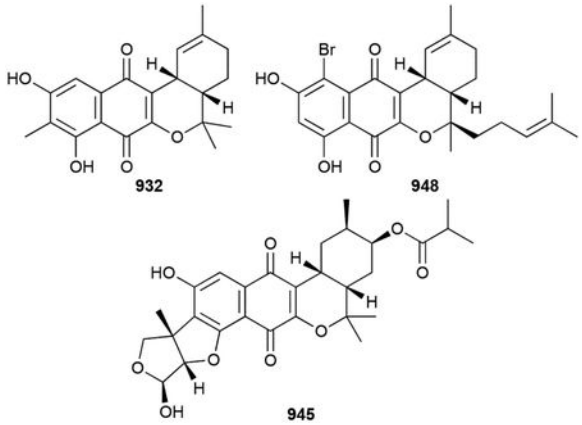
All three types of napyradiomycins also show moderate cytotoxicities against a variety of mammalian cells. Most antitumor IC_{50} values were in the low micromolar range (2–20 μM).[739,749,750,752,753,764] Type B napyradiomycins were shown to cause cell death via activation of apoptosis with **921** inducing apoptosis at 4 μM.[750] **921** and **907** localized in the ER of HCT-116 colon adenocarcinoma cells and targeted the human Hsp90 paralogue Grp97.[766]

Napyradiomycins hit a variety of targets in human cells. **906** was also found to be a noncovalent ~2 μM IC_{50} inhibitor of the gastric (H^+-K^+)-ATPase.[767] ***874*** and ***875*** act as estrogen receptor antagonists with IC_{50} values of 4.2 and 35 μM, respectively.[768] A1 also has various antiangiogenic effects including the suppression of blood vessel formation, endothelial cell proliferation and migration, and improved permeability of cell membranes.[769] The A-type phosphatoquinones **889** and **890** inhibited protein tyrosine phosphatase with IC_{50} values of 28 μM and 2.9 μM, respectively while **891** is an inhibitor of bovine aldolase reductase with an IC_{50} value of 0.2 μM.[744,745]

3.8.4 Naphterpins—We classified the naphterpin family of polyketide-derived meroterpenoids as those with 6/6/6/6 tetracyclic ring systems where geranyl or farnesyl prenylation at C3 of THN sets up formation of the additional two rings. Naphterpin A (***932***), isolated from *Streptomyces* sp. CL190 four years after the napyradiomycins, had a core similar to the 6/6/6 chromophore of B-type napyradiomycins but with an additional methylcyclohexene ring fused to the dihydropyran.[770] As with the napyradiomycins, various naphterpin analogues, naphterpins **933–936** and naphthgeranines A–F (**937–942**) were subsequently isolated with assorted functional group modifications, mostly on the terpenoid moiety.[771–775] Naphthgeranines **941** and **942** have aromatized D rings. The naphthoquinone core is sometimes reverse prenylated at C7, yielding naphthablins **943**–***945*** and JBIR-79 and −80 (**946, 947**).[776–778] Naphthablins **944** and ***945*** have extended 5/5/6/6/6/6 hexacyclic scaffolds after cyclization of the dimethylallyl moiety on C7.[777]

Prenylation with FPP and subsequent cyclization results in the marinones (***948***–**952**), sesquiterpenoid versions of naphterpins.[731,779] There is some ambiguity of the absolute configuration of these compounds in the literature as the relative stereochemistry was initially assigned, but a study on the total synthesis later depicted the enantiomeric forms.[780]

Biosynthesis.—Unsurprisingly, given their structural similarities to the napyradiomycins, the biosynthesis of naphterpins and marinones mirrors that of the napyradiomycins. An elegant biomimetic total synthesis led to the identification, through use of testing synthetic intermediates as substrates for biosynthetic enzymes, of two VHPOs that are responsible for formation of putative biosynthetic intermediates.[780] Initial geranylation (or farnesylation) of THN at C4 is likely and supported by early labelling studies.[781] MarH1 and MarH3, found in *Streptomyces* sp. CNQ-509,[782] successively catalyze the same reactions as NapH1 and NapH3, oxidative dearomatization and C2 chlorination and C4-to-C3 α-hydroxyketone rearrangement, respectively (vide supra Scheme 21).[780] The major difference being that MarH3 also adds an additional chlorine on C2 supporting that geminal disubstitution is required for alkyl migration.[760] The remaining biosynthetic steps have yet to be revealed; the current proposal includes 2,3-epoxidation, reductive dehalogenation, oxidation and alkene isomerization, and intramolecular hetero-Diels-Alder cyclization to form 7-demethylnaphterpin (or debromomarinone, **950**).[780] Bromination of **950** completes the biosynthesis of ***948*** or **949**.

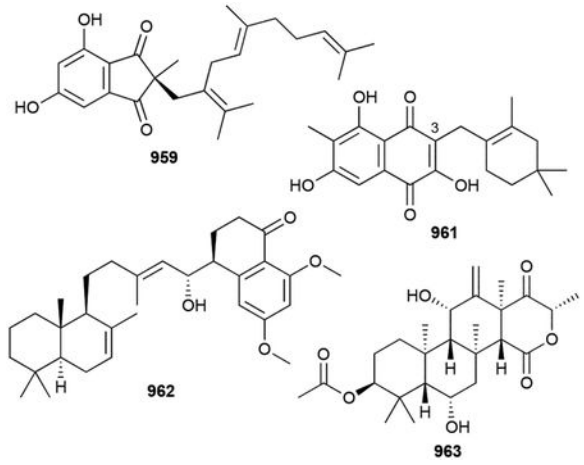


Biological activity.—Contrary to the napyradiomycins, most naphterpins did not show significant antibiotic activities;[770,773,775] only marinones ***948*** and **950** had MIC values as low as 1–2 μg mL^{-1} against Gram-positive pathogens.[779] A few analogues, including naphthgeranines **937** and **938**, marinones **950** and **951**, and naphthablins **944** and ***945***,[731,773,777] were cytotoxic at a level similar to that of the napyradiomycins. Naphthablin **943** was initially found in a screen for inhibitors of the tyrosine-protein kinase oncogene *abl*. **943** prevented Abl-induced morphological transformation in v-Abl-expressing NIH3T3 cells at 30 μg mL^{-1} and was shown to specifically inhibit RNA synthesis.[776]

The naphterpins also showed antioxidative properties with reported radical scavenging abilities.[770–772,774,778] **946** and **947** prevented glutamate toxicity in neuronal cells, but at a significantly decreased efficacy compared to the benzastatins.[778]

3.8.5 Merochlorins—Another family of structurally intriguing chlorinated naphthoquinone terpenoids are the merochlorins. Although the four members all have different molecular architectures, they share common features and a single BGC. Merochlorin A (***953***) has a unique benzo-bicyclo[3.2.1]-octadione ring system with a propan-2-ylidenecyclopentane moiety.[783] Merochlorin B (***954***) had the same molecular formula as that of A, but with a completely different carbon connectivity: a propan-2-ylidenecyclopentane-containing 6/5/5 fused tricycle with an α-chloroenone. Both ***953*** and ***954*** have their prenyl units attached at C4 of the naphthoquinone core.[784] Merochlorins C and D (***955*, 956**) had sesquilavandulyl moieties attached on the naphthyl unit at C3 with merochlorin C forming a 15-membered macrocycle by additional attachment at 6-O. The sesquilavandulyl moiety is a rearranged C15 unit that was unprecedented in bacteria at the time of discovery.

Merochlorins E and F (**957**, **958**) were recently identified as variants of merochlorin D with cyclized sesquilavandulyl groups.[785] Meroindenon (***959***) has an indanedione core, perhaps as the result of a pinacol-type ring contraction.[785]



Biosynthesis.: A single PKS-terpenoid hybrid BGC, similar to the BGCs described above, was found responsible for the production of merochlorins in *Streptomyces* sp. CNH-189. The differing prenylation patterns of ***953***/***954*** and ***955***/**956** initially hinted at two sites of direct prenylation.[784] Follow up studies confirmed the ABBA PT Mcl23 exclusively prenylates C4 of THN with sesquilavandulyl diphosphate, which is synthesized by Mcl22,[786] to give the oxygen-sensitive pre-merochlorin (Scheme 21).[787] Mcl24, a VHPO, performs tandem chloronium-induced dearomatization and terpene cyclization to yield both merochlorins ***953*** and ***954***.[788] Mcl24 can also catalyze α-hydroxyketone rearrangement on pre-merochlorin to an intermediate with a scaffold identical to **956**.[760] Mcl40 is proposed to then catalyze the chloronium-induced macrocyclization converting merochlorin **956** into ***955*** (Scheme 21).[758] It is fascinating that a single enzyme, Mcl24, is responsible for generating the vast structural diversities of the merochlorins.

Biological activity.: Merochlorins ***953***, ***954***, **957**, and **958** are effective Gram-positive antibacterials with an MIC range of 1–4 μg mL^{-1} against MRSA, VRE, and Streptococci.[783–785] *Clostridium difficile* is also inhibited by ***953*** (0.15–0.3 4 μg mL^{-1}).[783]

3.8.6 Miscellaneous Polyketides—A few other naphthoquinone meroterpenoids have been isolated. Flaviogeranin (**960**) is simply a 7-*O*-geranyl substituted naphthoquinone.[789] Arromycin (***961***) has a C3 cyclolavandulyl moiety and was identified after BioMAP antibiotic activity profile screening.[790] The menaquinone-type naphthoquinones are discussed in section 3.11.2 (vide infra).

Actinoranone (***962***), produced by the marine bacterium *Streptomyces* sp. CNQ-027, is an unusual polyketide meroterpenoid.[791,792] Although not a true prenylated naphthoquinone, ***962*** has a bicyclic labdane diterpenoid moiety attached to its substituted dihydronaphthalenone core.

Terretonins are polyketide meroterpenoid mycotoxins known in fungi for their structurally complex and highly functionalized ring systems.[793] Interestingly, the first bacterial member, terretonin N (***963***), was recently identified from a culture of *Nocardiopsis* sp. LGO5.[794] Its biosynthesis was not investigated but presumably follows biosynthesis in fungi with an initial farnesylation of the polyketide-based 3,5-dimethylorsellinic acid followed by a noncanonical TS cyclization by an integral membrane cyclase.[27,795,796]

Biosynthesis.—Nothing is known about the biosyntheses of these meroterpenoids, although reasonable proposals can be formed based on related bacterial, or fungal in the case of ***963***, meroterpenoids.

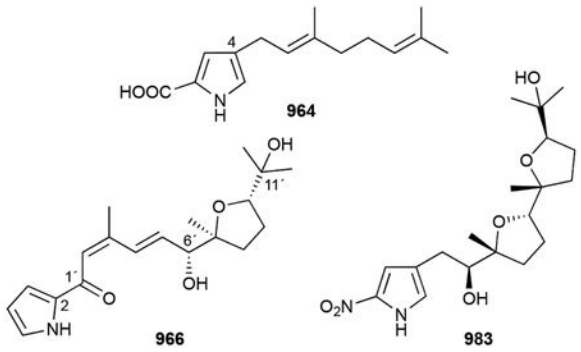
Biological activity.—*961* and ***963*** have antibacterial activities with only mild to no cytotoxic activity.[790,794] **960** shows nanomolar inhibition of glutamate toxicity in rat brain cancer cells with no cytotoxicity.[789] ***962*** was cytotoxic against HCT-116 with an LD_{50} value of 4 μM.[791]

3.9 Pyrroles

Pyrroles are five-membered nitrogen-containing heteroaromatic rings that are planar and electron rich. From a biological perspective, they are most renowned for their presence in the tetrapyrrole scaffolds of heme, chlorophyll, and vitamin B12.[797] The pyrrole ring, not including those contributing to the indole skeleton, is also found in many families of NPs, some of which are described in this review. The mixed pyrroloterpene class of NPs is small with only 21 known variants all produced by *Streptomyces*.

The first pyrrole-terpenoid hybrid NP discovered was also the simplest in structure. Pyrrolostatin (***964***) is a C4 geranylated pyrrole-2-carboxylic acid produced by *Streptomyces chrestomyceticus* EC50 and was identified in the same screen for free radical scavengers that resulted in the discovery of carazostatin and neocarazostatin.[798] Geranylpyrrol A (**965**), the only other pyrrolomonoterpenoid, is pyrrolostatin-3-acetamide methyl ester.[799]

The 19 other prenylated pyrroles are all farnesylated at either the *ortho* (i.e., C2 of pyrrole) or *meta* (i.e., C4 of 2-nitropyrrole) positions. The glaciapyrroles (***966*–968**), named after the Alaskan origin of their producer *Streptomyces* sp. NPS008187, and six unnamed analogues **969–974** are C2-farnesylated pyrroles with a 2′*Z*,4′*E*-dien-1-one modified sesquiterpene chain, each with a different state of oxidation. **966** contains a tetrahydrofuran (THF) ring and a 6′,11′-diol, **967** is a 6′,7′-diol, and **968** is a 6′,7′-epoxide.[800,801] The unnamed glaciapyrrole analogues **969–974** were all isolated from *Streptomyces* sp. Hd7–21. These terpenoid tails had different levels of oxidation at C9′–C12′.[802–805]



The nitropyrrolins and heronapyrroles both have the 2-nitro-4-prenyl pyrrole core. The nitropyrrolins A–E (**975**–**979**) all have linear farnesyl chains with various epoxy, hydroxyl, or chlorine modifications.[806] **978** was distinct with an additional *E* double bond between C3′–C4′. Chlorination at C3′ of **977** and **979** was unsurprising given the marine origin of their producer, *Streptomyces* sp. CNQ-509. 10′,11′-Epoxynitropyrrolin A (**980**) was initially reported in a perspective prior to the publication of **975**–**979** and later re-identified by UV, but its structural characterization, including stereochemistry, was never published.[807,808] The heronapyrroles (**981–984**), named for their isolation from a *Streptomyces* sp. collected off of Heron Island, Australia, are variations of the nitropyrrolins.[809] While **981** and **982** have oxidized linear terpenoid chains ***983*** is a cyclized version of A with two THF rings. In an interesting example of synthesis-guided NP discovery, the synthesis of a proposed biosynthetic alternative to heronapyrroles led to the identification of **984** as a genuine NP.[810] Although this monoether was produced in quantities too low for structural elucidation, comparison with synthetic **984** clearly confirmed its presence in *Streptomyces* sp. CMB-M0423.

Biosynthesis.—The biosynthesis of the pyrroloterpenoids is unknown. Their structures suggest that a relatively simple biosynthesis including the prenylation of pyrrole, oxidations and/or epoxidations on the terpene chain, and cyclization or epoxide hydrolysis via epoxide hydrolases. Acylation of pyrrol-2-carboxyl thioester with farnesol or farnesic acid followed by decarboxylation is an alternative proposal;[801] however, the pyrroloterpenoids without a ketone at C1′ suggests direct *m*-prenylation on pyrroles is likely. ABBA PTs are probable candidates for the prenylation of pyrroles, but no activity with pyrroles have been established.[678]

Biological activity.—Similar to the phenazines, ***964*** was initially discovered by searching for small molecule radical scavengers.[798] ***964*** inhibited lipid peroxidation in rat brain homogenate, showing an IC_{50} of 49 μM, and protected mice from KCN-induced acute hypoxia. It was speculated at the time that the mode of action of ***964*** is intrinsic Fe^{2+} chelation resulting in a reduction of hydroxyl radicals.[798]

The nitropyrrole-terpenoid heronapyrroles **981–984** were active against Gram-positive bacteria with MICs ranging from 0.7–6 μg mL^{-1}; they had no activity against Gram-negative bacteria and were not cytotoxic.[809,810] Conversely, the structurally related nitropyrrolins (**975**–**979**), which are moderately cytotoxic (vide infra), were not active against MRSA, although the synthesized 3-farnesylpyrrole had an MIC of 2.8 μg μL^{-1}.[806] It is unclear what leads to the difference in antibacterial activity for these two families of prenylated nitropyrroles.

The glaciapyrrole congeners and nitropyrrolins showed moderate to weak antitumor activity. **965** inhibited the cell growth of both colorectal adenocarcinoma HT-29 and melanoma B16-F10 with an IC_{50} value of 180 μM.[800] The oxidized analogues **970–973** were 5–22-fold more cytotoxic than ***966***.[803–805] The nonhydrolyzed **874** was inactive, suggesting that the presence of the oxirane precluded cytotoxicity.[805] Only the non-chlorinated nitropyrrolins **975**, **976**, and **978** showed activity against HCT-116 cells with **978** being the most potent (IC_{50} = 5.7 μM).[806]

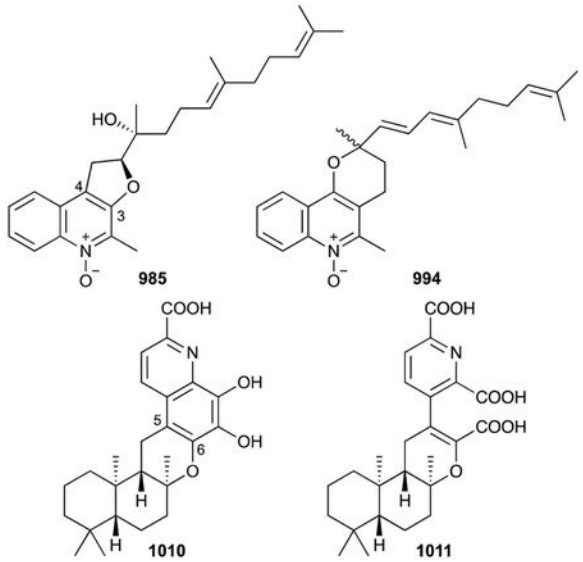
3.10 Quinolines—Quinolines, also known as 1-aza-naphthalenes, are heterocyclic and aromatic 6/6 scaffolds that have been established as pharmaceutically relevant drugs.[811,812] Most prenylated quinolines of bacterial origin fall into one family of compounds known as aurachins. They are unique isoprenoid alkaloids with farnesyl residues at C4 (A-type) or C3 of the quinoline nucleus (C-type); the position that does not have farnesyl attached is oxygenated. Aurachins have been isolated as quinolines, 4-quinolones, or quinoline *N*-oxides.

Aurachins were first identified from myxobacteria over 30 years ago.[813] Eleven aurachins, A–I, K, and L (***985*–995,** ***994***), were identified from *Stigmatella aurantiaca* SG a15 with aurachins ***985*–988** being the major constituents.[813–815] A-type aurachins include **987**, **986**, and **990** and C-type aurachins include **987**–**989** and **991**–**995**. Aurachins have non-modified farnesyl groups or farnesyl moieties that are cyclized onto the *ortho* oxygen substituent resulting 5- or 6-membered ether rings. **989** is a structural outlier with a cyclic urea functional group between N1 and C8.

Several other C-type aurachins (**996**–**998**) have been isolated from various *Rhodococcus*.[816,817] Aurachin SS (**999**), produced by *Streptomyces* sp. NA04227, is a 3-geranyl-4-methoxyquinoline *N*-oxide.[818] Aurachin P (**1000**), produced by *Stigmatella erecta* Pd e32, is the only other A-type reported.[819]

Another subfamily of aurachins are structurally related to aurachin C but have linear geranyl moieties at C2 of their 4-quinolone cores. Eight CJ-13 analogues (**1001–1008**) are produced by *Pseudonocardia* sp. CL38489.[820] Intervenolin (**1009**) from *Nocardia* sp. ML96–86F2 is

another 2-geranylquinolone with a dimethyl carbonimidodithioate moiety attached to the *N*-methyl of the quinolone.[821]



Saccharoquinoline (***1010***) and thallusin (***1011***), isolated from marine-derived *Saccharomonospora* sp. CNQ-490 and *Cytophaga* sp. YM2–23, respectively, appear to be related alkaloidal meroterpenoids.[822–824] Saccharoquinoline, which has a 6/6/6/6/6 pentacycle, is clearly a 2-carboxyquinoline with a drimane sesquiterpenoid moiety fused to C5 and 6-O. Thallusin (***1011***) has a sclareol-like structure linked to a 2,6-pyridinedicarboxylic acid,[823,824] although oxidative cleavage of the benzene ring of ***1010*** would yield ***1011***.[822]

An unnamed quinoline (**1012**) from *Streptomyces* sp. neau50 appears to be a prenylated quinoline as it has an 8-(3-methoxyisoprenyl) moiety on its 2-methylquinoline-4-carboxylic acid methyl ester scaffold, although no biosynthetic studies have confirmed its origin.[825]

Biosynthesis.: Based on early feeding studies and the aurachin BGC from *S. aurantiaca*, it was clear that the quinoline core is built from anthranilate and two polyketide units (Scheme 22).[826] In fact, anthranilate priming for PKS processing requires two adenylating enzymes, the CoA ligase AuaEII and acyltransferase AuaE.[827] A full biosynthetic pathway, including prenylation at C3 by a UbiA-like PT and a unique transposition of the farnesyl group from C3 to C4 (i.e., A-type aurachins are derived from C-type), was proposed based on feeding experiments[828] and was updated based on a combination of bioinformatics, in vitro, and in vivo studies. Farnesylation at C3 of 2-methyl-4-hydroxyquinoline by AuaA and N-hydroxylation by the Rieske[2Fe–2S] oxygenase AuaF yields ***988*** and ***987***, respectively; AuaG then catalyzes an FAD-dependent epoxidation of the 2,3-double bond (Scheme 22).[829,830] Reduction of the C4 keto group by AuaH forces a pinacol-type rearrangement after 4-*O* protonation to give ***986***. AuaJ epoxidation and cyclization catalysed by the epoxide hydrolase AuaI form the pyran of ***985***.[830] The genetic work in *S. aurantiaca* was complicated by the fact that the aurachin biosynthetic genes were located across three different genetic loci. *N*-hydroxylation in aurachin RE biosynthesis is catalysed by a

cytochrome P450, as opposed to a Rieske[2Fe–2S] oxygenase.[831] Divergent pathways to the other aurachins have been postulated, but no definitive steps have been characterized.[818,828]

Biological activity.: Aurachins ***985–988*** were potent Gram-positive antibacterials and antifungals with MICs as low as 0.05 μg mL^{-1}.[814] Aurachin RE (**996**) was also active against some Gram-negative bacteria, although not *E. coli* suggesting terpene hydroxylation may positively affect solubility or its ability to transverse the cell membrane.[816] The poor antibacterial activity of **999** hints that the shorter geranyl chain or 4-methoxy group negatively affects activity.[818] The CJ-13 analogues (**1001–1008**) and **1009** were selective and potent antibiotics against *Helicobacter pylori*.[820,821] For example, CJ-13,136 (**1001**) was bactericidal against *H. pylori* at 10 ng mL^{-1} and bacteriostatic at 0.1 ng mL^{-1}.

Being structurally similar to menaquinones, the aurachins are potent inhibitors of the electron transport chain. Aurachins ***985–988*** were initially found to block NADH oxidation in beef heart submitochondrial particles and later found to be excellent inhibitors of photosystem II and cytochrome b_6/f-complex (IC_{50} values of 63 and 100 nM, respectively, for ***987***).[814,832] ***987*** also inhibited the quinol oxidation sites of the terminal oxidases cytochrome *bo* and *bd* while ***988*** was selective for cytochrome *bd*.[833]

1009 and some of the CJ-13 analogues preferentially inhibited (~10-fold preference and IC_{50} = 0.4 μM) gastric and colorectal cancer cells when grown in the presence of their respective stromal cells compared to the cancer cells alone.[821]

Aurachin E (**989**), which had no antibacterial activity nor inhibited mitochondrial respiration, was a non-cytotoxic anti-plasmodial agent with IC_{50} values as low as 0.4 ng mL^{-1}.[815] Aurachins ***986–988*** also showed anti-plasmodial activity, but their antibacterial activities suggest a different mode of action. Aurachins ***987*** and **998** were also weak inhibitors of the glycogen synthase kinase 3β.[817]

1011 is an extremely potent algal morphogenesis inducer; in a cell differentiation assay, its minimum effective concentration was between 1 fg $mL^{-1}$and 1 ag mL^{-1}.[823] Its presumed precursor, ***1010***, was found to induce G1 arrest in HCT-116 cells resulting in mild cytotoxicity.[822]

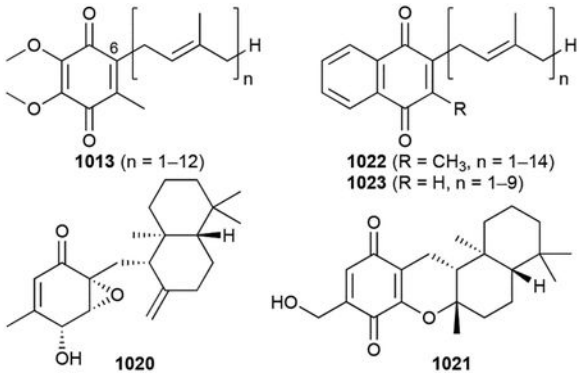
3.11 Quinones

Prenylated quinones are ubiquitous membrane-bound compounds that have essential physiological roles in electron transfer, energy generating processes, signaling, oxidative stress, antibiotic resistance, and virulence.[834] These hybrid natural products have polar aromatic head groups with hydrophobic polyprenyl side chains appended at C3 of the aromatic core. The quinone ring can undergo reversible two-step redox reactions yielding the oxidized 1,4-benzoquinone and the reduced hydroquinone (quinol, 1,4-dihydroxybenzene). This redox potential allows prenylated quinones to function as membrane-bound electron and proton shuttles in the electron transport chain. There are two major families of isoprenoid quinones: benzoquinones and the bicyclic naphthoquinones. Members of these families, separated into subfamilies based on their quinone ring substitution patterns, commonly have prenyl chains of various lengths and degrees of

saturation. The degree of prenyl saturation is organism and environment dependent.[835] Each organism produces its own quinone pool, consisting of quinones of both major and minor abundances; these have been used as chemotaxonomic markers.[835,836] In this section, we will not describe the numerous variants of isoprenoid quinones, but instead focus on introducing the most common scaffolds in bacteria and highlighting non-canonical linear and cyclized prenylated quinones. For a more in-depth look at isoprenoid quinones in bacteria, we direct readers to the excellent reviews cited herein.[834,835,837,838]

3.11.1 Benzoquinones—The most ubiquitous, and hence the name,[839] benzoquinones are the ubiquinones (UQs). UQ-8, possessing eight prenyl units, is the most well-known UQ, but UQs (***1013***) have been found with 1–12 prenyl units, various hydrogenation or epoxidation modifications, and are mainly found in aerobic Gram-negative bacteria.[835,837] Other commonly found benzoquinones are rhodoquinones (RQs), plastoquinones (PQs), and α-tocopherolquinone (α-TQ).[835,838] RQs (**1014**) are amino analogues of UQs and present in the purple bacterium *R. rubrum*. PQ (**1015**) and α-TQ, (**1016**) are key components of cyanobacteria (and plant) photosynthesis. PQs are nonaprenyl dimethylbenzoquinones and **1016** is a trimethylbenzoquinone with a saturated and hydroxylated geranyl side chain.

Pseudoalteromone A (**1017**), produced in *Pseudoalteromonas* sp. CGH2XX, is a UQ-2-like benzoquinone, but has a unique oxidized C_9 nor-monoterpenoid chain.[840]



Bioassay-guided NP discovery efforts using *Streptomyces nitrosporeus* YBH10–5 resulted in the isolation of unique prenylated benzoquinones.[706] Farnesylquinone (**1018**) is the oxidized form of 2-farnesyl-5-methyl-1,4-benzoquinone and appears to be the precursor to the 7-deacetoxyyanuthone (**1019**) and nitrosporeunol G (***1020***). ***1020*** is a drimane-type epoxyquinol and structurally very similar to the fungal macrophorin A.[841] Simple pyran formation of ***1020*** yielding a 6/6/6/6 tetracycle would give BE-40644 (***1021***), a compound isolated from *Actinoplanes* sp. A40644 almost 20 years earlier.[842,843]

Biosynthesis.—The bacterial biosynthesis of UQs is well understood while the pathways of RQs, PQs, and α-TQ are still incomplete.[834,838,844] *p*-Hydroxybenzoate, a product from chorismate via the shikimate pathway, is prenylated by the PT UbiA. The UbiA superfamily of PTs are membrane-bound aromatic PTs distinct from the ABBA PTs.[845] They typically have prenyl acceptor (i.e., quinone head group) specificity and prenyl donor flexibility. After prenylation, 3-polyprenol-4-hydroxybenzoic acid is decarboxylated by UbiD, a non-

oxidative decarboxylase that requires a novel prenylated-FMN (**1030**, vide infra chapter 3.12.2) cofactor made by UbiX.[846,847] The decarboxylation is facilitated via a 1,3-dipolar cycloaddition addition reaction with **1030**.[848] After decarboxylation, a series of hydroxylations and methylations are required to form UQ.[834,838]

No biosynthetic studies have ensued for **1017** or ***1020***, although their similarity to macrophorin A suggests cyclization occurs via a noncanonical integral membrane TS.[27]

Biological activity.—*1021* was originally found to be a selective thioredoxin (TRX) system inhibitor with IC_{50} values of 0.12 and 0.80 μg mL^{-1} for *E. coli* and human TRX, respectively.[842] The related, but non-cyclized, analogues **1018** and **1019** decreased lipid accumulation with **1018** comparable to lovastatin.[706] **1018** increased the production of PPAR-α controlled proteins by transcriptional upregulation.

1017 was cytotoxic against MOLT-4 human acute lymphoblastic leukemia cells (IC_{50} = 11.7 μM) and a possible anti-inflammatory agent as it inhibited the release of elastase by neutrophils.[840]

3.11.2 Naphthoquinones—

Menaquinones (MKs, vitamin K2) are the most ancient type of prenylated quinones and are solely found in most Gram-positive and anaerobic Gram-negative bacteria.[835,837] They have low redox potentials compared to ubiquinones and are highly reactive with molecular oxygen implying that their ancient use as respiratory quinones was due to the reducing character of the atmosphere at that time.[838] MKs (***1022***) are 2-methyl-3-polyprenyl-1,4-naphthoquinones with 1–14 prenyl units, although 6–10 units are most common.[835] Demethyl-MKs (DMKs, ***1023***) are also common in proteo- and Gram-positive bacteria.[835] Most identified MKs and DMKs have fully unsaturated polyprenyl chains, but partially (e.g., phylloquinone, **1024**) or fully saturated are possible. Naphthoquinone ring *C*- and *O*- methylations can also be present. Chlorobiumquinone (**1025**), is a uniquely 1′-oxidized MK found in the photosynthetic green sulfur bacterium *Chlorobium thiosulphatophilum*.[849,850] Other unique bacterial MKs include methionaquinone (**1026**) from *Hydrogenobacter thermophilus* TK-6,[851,852] the terminally sulfated sulfo-MK (**1027**) from *Mycobacterium tuberculosis*,[853] and a carotenoid-like cyclic MK (**1028**) from *Nocardia* spp.[854]

Biosynthesis.: There are two biosynthetic pathways for the biosynthesis of MKs and both are well characterized (Scheme 23).[838,855] Like the UQs, the precursor for MKs in both pathways is chorismate. In the classical pathway, deduced from studies in *E. coli*, chorismate is transformed into 1,4-dihydroxy-2-naphthoate via *o*-succinylbenzoyl-CoA by six enzymes from the *men* pathway. The UbiA-type PT, MenA, then catalyzes C2-decarboxylative prenylation before the biosynthesis is completed by methylation at C3.[838,845,856] The alternative pathway, found in *H. pylori*, *Campylobacter jejuni*, and *S. coelicolor*, generates 1,4-dihydroxy-6-naphthoate through futalosine.[855,857,858] The last two steps of the futalosine (*mqn*) pathway may parallel those in the *men* pathway,[838,855] but there are proposals of a distinct PT.[859] As opposed to the early prenylation in UQ biosynthesis, both MK pathways require a late prenylation reaction (Scheme 23). MK tailoring reactions, such

as methylations or sulfations are catalysed by radical SAM MTs or tandem P450–sulfate transferase reactions, respectively.[860,861]

Biological activity.: In vivo studies of **1027** revealed that it is a negative regulator of virulence in mouse infections indicating a possible role in human-pathogen interactions.[862]

3.12 Miscellaneous

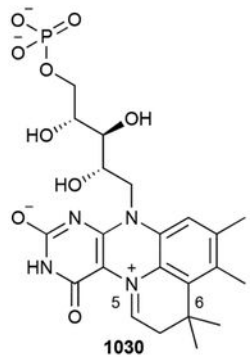
There are several other families of bacterial meroterpenoids that do not fit well into any of the categories mentioned above. These include the aromatic dibenzodiazepinones, flavins, and aminobenzoates and the nonaromatic phosphoglycolipids and saccharides. We also included the porpyrin-rich chlorophylls and hemes in this section. Although fairly scarce in number at the time of writing this review, it would be unwise to assume these NPs are not the beginning of expanding families of bacterial terpenoids.

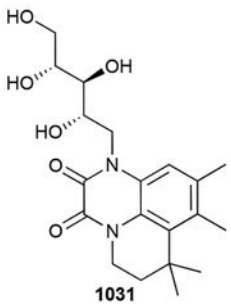
3.12.1 Dibenzodiazepinones—Diazepinomicin (***1029***) is a unique microbial metabolite produced by Micromonospora spp.[863] Its core is an exceptionally rare tricyclic dibenzodiazepinone alkaloid with the amide N carrying a farnesyl moiety.

Biosynthesis.: BGC analysis and labeled feeding experiments support that the dibenzodiazepinone core is built from the condensation of a 3-hydroxyanthranilic acid and 2-amino-6-hydroxy[1,4]benzoquinone (Scheme 24).[864] Feeding experiments also confirmed that the 3-hydroxyanthranilic acid precursor is obtained via the degradation of indole. The MVA-derived farnesyl unit[864] is fastened to the amide N by DzmP, an ABBA PT.[865]

Biological activity.: ***1029*** is an antitumor antibiotic. It has modest (8–32 μg mL^{-1}) antibacterial activity against Gram-positive bacteria and has low μM cytotoxic activity.[866,867] Its cytotoxicity is the result of its effect on the Ras-MAPK signaling pathway, specifically inhibiting the phosphorylation of downstream effector proteins.[867] Although it was an ineffective monotherapy in a glioblastoma clinical trial,[868] it is currently under evaluation as a therapeutic for the treatment of Phelan-McDermid Syndrome and co-morbid epilepsy.[869]

3.12.2 Flavins—Prenylated flavin mononucleotide (***1030***, prenyl-FMN) is a new cofactor that is utilized by the family of UbiD decarboxylases to catalyze α,β-unsaturated decarboxylation via 1,3-dipolar cycloaddition.[846,847] The UbiD family is most well-known for its role in ubiquinone biosynthesis, but recent studies show that this cofactor is also involved in microbial NP biosynthesis.[870,871] The isopentenyl adduct of prenyl-FMN, which is connected at N5 and C6 of FMN, forms a 6-membered ring.[846] In hindsight, the discovery of hunanamycin A (***1031***) from *Bacillus hunanensis*, a NP with a pyrido[1,2,3-de]quinoxaline-2,3-dione core, was a hint at the presence of ***1030***.[872] It is very likely an oxidative degradation product of ***1030***.





Biosynthesis.: One PT, UbiX or its homologues, acts as both a PT and TS to produce ***1030***.[847,873] *N*-prenylation sets up an ensuing TS-like mechanism, where protonation by the discarded inorganic pyrophosphate creates a prenyl carbocation that is quenched by the electron-rich C5 of FMN. Interestingly, some of these PTs are selective for dimethylallyl monophosphate or DMAPP as the prenyl donor, while some can utilize both.

Biological activity.: ***1031*** was a selective antibiotic active against *Salmonella enterica* with an MIC of 12.4 μM.[872]

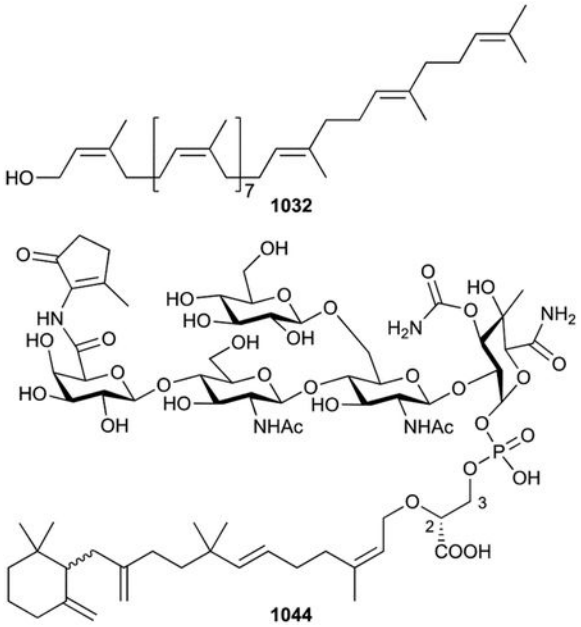
3.12.3 Phosphoglycolipids—

Phosphoglycolipds are important components of bacterial cell walls; the lipid portions are derived from fatty acids. However, a C_{55} isoprenoid lipid is used to shuttle the glycopeptide fragment of lipid II, the peptidoglycan building block, across the membrane; the C_{55} isoprenoid also serves as a membrane anchor for the growing peptidoglycan chain.[874] The C_{55} alcohol, bactoprenol (***1032***, undecaprenol), is found in high concentrations in Gram-positive bacteria and was structurally reported to be composed of eight *cis* and two *trans* double bonds.[875,876] As bactoprenol is utilized in its phosphorylated form, its concentration is regulated by an undecaprenol kinase/phosphatase.[877] Although bactoprenol is not typically seen in Gram-negative bacteria, an undecaprenyl phosphogalactosamine (**1033**) was isolated from the Gram-negative *Francisella novicida*.[878]

By far, the most structurally interesting and biologically relevant phosphoglycolipid NPs are the moenomycins. Members of the moenomycin class of antibiotics have three structural elements in common: a 3-phosphoglycerate (3-PG) backbone, an unusual C_{25} isoprenoid chain connected to 3-PG as an ether, and a tetrasaccharide tethered to 3-PG via a phosphodiester linkage. Most structural differences seen in the moenomycins reside in the tetrasaccharide component.

Moenomycin A (**1034**) was originally discovered in 1965 as an antibiotic and has been since produced from a variety of *Streptomyces* spp.[879–881] The complexity of its structure as well as its physicochemical properties delayed its complete structural determination for 25 years.[882,883] **1034** is a pentasaccharide with a 2-aminocyclopentane-1,3-dione unit (ring A) attached by an amide to the terminal sugar (ring B). Its isoprenoid chain was determined to be moenocinol, an irregularly linked C_{25} linear chain with a quaternary carbon at C8.[882,884]

There are several variants of **1034**, some of which have still not been fully structurally characterized.[884–887] Those that have been characterized include the moenomycins A_{12}, C_1, C_3, and C_4 (**1035–1038**), nosokomycins A–D (**1039–1042**), and pholipomycin (**1043**).[888–893] These phosphoglycolipids all have the moenocinol terpenoid unit and differ in the presence or absence of the 2-aminocyclopentane-1,3-dione (ring A) and the branching glucose (ring D) units, as well as the structure and functionalization of the sugar units C–F. AC326-α (***1044***), isolated from *Actinomyces* sp. AC326, is identical to that of moenomycin A with the exception that its terpenoid chain is the monocyclic diumycinol.[894] Nosokophic acid (**1045**), a predicted intermediate in nosokomycin biosynthesis bearing a *Z,E*-farnesyl moiety, was also isolated from *Streptomyces* sp. K04–0144.[895]



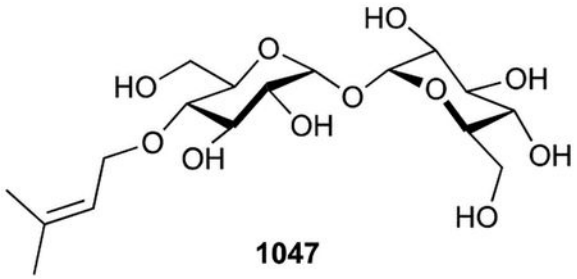
Biosynthesis.: The biogenic origins of moenomycins from *Streptomyces ghanaensis* has been extensively studied resulting in a proposed 17 step biosynthetic pathway.[896] Complicating the discovery of the *moe* BGC was the fact that all required precursors, except for the ring A chromophore, could be directly obtained from primary metabolism. In addition, not only was the BGC located across two genetic locations in the chromosome, the low sequence similarity of most of the *moe* genes to known NP biosynthetic genes at the time made for a challenging problem.[896]

The biosynthesis and attachment of the moenocinol moiety is of most relevance to this review (Scheme 25). Early tracer experiments supported that the unique C_{25} moenocinol moiety was of MEP origin and led to a mechanistic proposal of the joining and rearrangement of distinct farnesyl and geranyl units.[897] In vitro characterization of MoeO5, a TIM barrel PT of the geranylgeranylglycerol phosphate synthase family, revealed that the prenylation of 3-PG with *E,E*-FPP yielded 2-(*Z,E*)-farnesyl-3-PG as the first committed step in moenomycin biosynthesis.[896,898] The transformation of the C_{15} tail into the C_{25} moenocinol unit occurs at the trisaccharide stage and is catalyzed by MoeN5.[896,899] Detailed mechanistic experiments have not been performed but an unusual head-to-middle

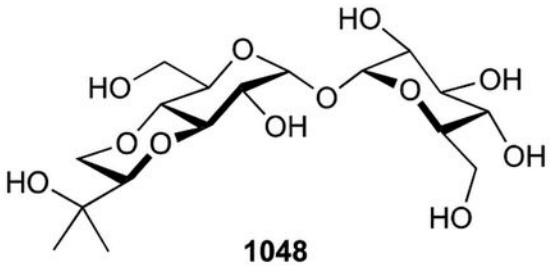
geranylation reaction must occur between the two terpenoid components followed by two rearrangements through cyclopentyl and cyclohexyl carbocations to produce the linear moenocinol sidechain-containing trisaccharide (Scheme 25).[881,897]

Biological activity.: The moenomycins are potent antibiotics. Their MICs range from 1–100 ng mL^{-1} for Gram-positive bacteria and 0.3–150 μg mL^{-1} against Gram-negative strains.[879,894,900,901] They are bacteriostatic at low concentrations (1 μg mL^{-1}) and bactericidal at high concentrations (10 μg mL^{-1}).[874] Being the only natural antibiotics that directly inhibit the transglycosylases responsible for the polymerization of the bacterial peptidoglycan layer, the moenomycins have been extensively studied and reviewed.[881,901] Unfortunately, these antibiotics suffer from poor pharmacokinetics and therefore are not clinically relevant in humans; they have, however, been successfully introduced as animal growth promoters. Interestingly, nosokophic acid, which does not have antibacterial activity, potentiates imipenem activity against MRSA 512-fold.[895]

3.12.4 Saccharides—While there are many NPs that contain both terpenoid and sugar moieties, there are only three bacterial NPs with prenyl groups attached directly onto sugars. Lentztrehaloses A–C (**1046,** ***1047, 1048***), isolated from the actinomycete *Lentzea* sp. ML457 mF8, are prenylated versions of the disaccharide trehalose.[902–904] ***1047*** retains an unmodified dimethylallyl group, while **1046** and ***1048*** appear to be the result of epoxide ring opening. The dimethylallyl moiety of ***1048*** was cyclized onto the trehalose forming an additional 1,4-dioxane ring. The biosynthesis of these terpenoid sugars has not been studied.



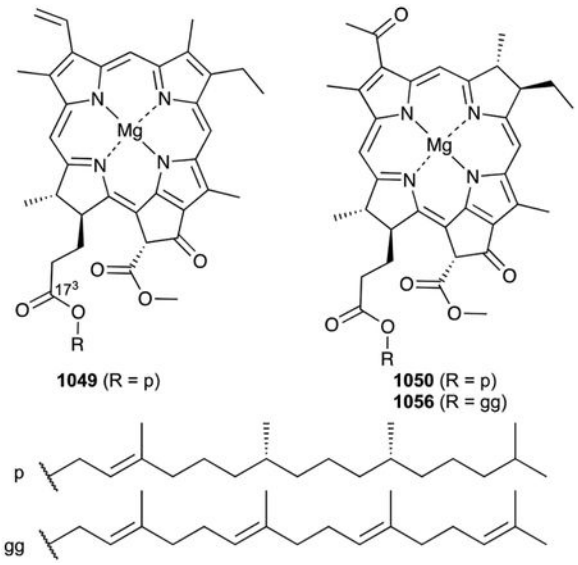
1047



1048

Biological activity.: Trehalose is used as a sweetener and is metabolized into glucose in vivo.[905] The lentztrehaloses are potential artificial sweetener substitutes for trehalose as they are nonhydrolyzable variants.[902,904] They do not appear to be toxic to microbes or mammalian cells, although they were shown to have antitumor activity in mice bearing S-180 sarcoma and induce autophagy in human cancer cells on a level comparable to that of trehalose.[902,904]

3.12.5 Chlorophylls—Chlorophylls (Chls) are pigments that are essential for photosynthesis and are widely distributed throughout nature, being present in plants, algae, photosynthetic bacteria, and even some animals.[906,907] While all Chls have a conserved central porphyrin core which coordinate a Mg^{2+} ion, there are over 100 characterized Chls with differences occurring in their ring structures, substituent patterns, and esterifying alcohols.[907,908] All photosynthetic Chls have a fifth isocyclic pentanone ring as exemplified by Chl a (***1049***), the most widely distributed Chl in nature;[907] bacteriochlorophylls (BChls), which is a misnomer considering they are in fact chlorins with two reduced pyrrole rings are particularly prevalent in bacteria.[909] The major functional difference between Chls and BChls is whether they partake in oxygenic photosynthesis (i.e., plants and cyanobacteria) or anoxygenic photosynthesis (e.g., green sulfur bacteria, purple bacteria), respectively.[908,909] We will not dwell on all the variations of Chls in this review as they have been exhaustively reviewed.[907–910] However, it should be noted here that many of the major Chls, including those found in bacteria, are esterified with terpenoid moieties making them de facto meroterpenoids.



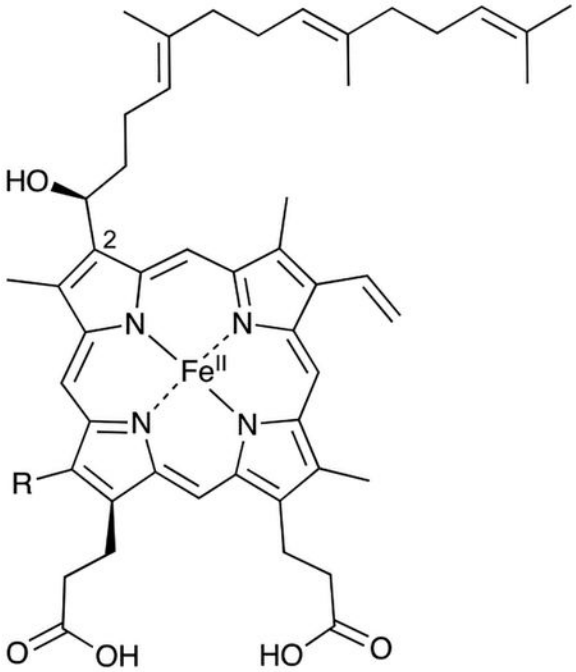
Most chlorophylls, such as ***1049***, have a C_{20} phytanyl moiety attached to their $C17^3$ carboxylic acid.[907,910] BChls, on the other hand, have one of six prenyl chain variations; this prenyl preference appears to be species specific. The predominant esterifying alcohol of the archetypal BChls a and b (***1050*, 1051**) is phytol while that of BChls c, d, e, and g (**1052–1055**) is farnesol.[911–917] Some BChls have been isolated with geranylgeranyl, dihydrogeranylgeranyl, tetrahydrogeranylgeranyl, or Δ2,6-phytadienyl moieties (***1056*–1060**).[911,914,918–921]

Biosynthesis.—We will leave discussion regarding the biosynthesis of the porphyrin core to the numerous reviews currently in the literature.[907,908,910,922–924] We will note, however, that the final steps in (B)Chl biosynthesis is the esterification of the $C17^3$ carboxylic acid and any reduction of the poly-olefin side chain. Attachment of the C_{15} or C_{20} isoprenoid moiety occurs via a subfamily of UbiA PTs, named chlorophyll or bacteriochlorophyll

synthases. ChlG and BchG from *Synechocystis* and *Rhodobacter* spp., respectively, are Chl a and BChl a synthases; based on total conversion in vitro, they both appear to minorly (~2-fold) prefer phytyl diphosphate over GGPP.[925] Other (B)Chl PTs responsible for geranylgeranylation and farnesylation have been identified and characterized.[922,926,927] Reduction of GGPP to phytyl diphosphate, or geranylgeranylated (B)Chls to the various reduced counterparts is catalyzed by the NADPH-dependent reductase BchP and its homologues.[922,928] It is unclear whether reduction occurs prior to or after prenylation as in vitro experiments with various PTs can accept diverse prenyl diphosphate substrates, although the range of isolated reduced C_{20} esters on Chls suggests reduction occurs after prenylation.[907,924]

3.12.6 Hemes—Hemes are another biological scaffold that contains a metallated porphyrin core. These redox active prosthetic groups play essential roles as cofactors for a variety of essential cellular functions in most living organisms.[929–931] In bacteria, heme plays an important role in respiration as the prosthetic group in cytochrome oxidases, membrane-bound heme-copper oxidative proton pumps in the electron transport chain that catalyze electron transfer from quinols or cytochrome *c* to molecular oxygen.[932] While there are several types of hemes, there are two prenylated hemes, heme A (***1061***) and heme O (***1062***).[933] Structurally, hemes A and O only differ in the presence of a formyl group on one of the pyrrole rings; both possess a hydroxyethylfarnesyl chain on C2 of pyrrole ring A.[933,934] Heme A has long been known, in both eukaryotic mitochondria and bacteria (e.g., *Paracoccus* and *Rhodobacter*), to be present in aa_3-type cytochrome *c* oxidase.[935,936] Heme O was extracted from cytochrome *o*, one of two terminal ubiquinol oxidases in *E. coli*.[934]

Biosynthesis.: The biosynthesis of the porphyrin ring is similar to that in the Chls and is reviewed elsewhere.[923,937] The farnesyl group on hemes A and O originate from the prenylation of farnesylation of the exocyclic vinyl group of pyrrole ring A in heme B (protoporphyrin IX). This PT reaction is catalyzed by heme O synthase,[938] a UbiA PT that this phylogenetically divergent from those seen in Chl biosynthesis.[845] This was confirmed by both in vivo knockout and complementation experiments as well as in vitro biochemical characterization.[938,939] ***1062*** is a direct precursor of ***1061***, only requiring two successive oxidations on a methyl group to provide the aldehyde functionality.[940] Interestingly, heme O and heme A synthases directly interact, likely providing a direct route of formation from heme B to ***1061***.[941]



1061 (R = CHO)
1062 (R = CH_3)

4 Conclusion

In this review, we described the current state of the bacterial terpenome. Our goal was to showcase the diversity of structures, biosynthetic enzymes, and biological activities of these natural products while providing access to this collection of compounds, structures, and references (all entries included in the ESI documents and were deposited into the open-access Natural Products Atlas).[32]

It is clear that bacteria are a major resource for novel terpenoids and terpenoid biosynthetic pathways and enzymes. Terpene cyclization and prenylation, fundamental steps in terpenoid biosynthesis, are known to be catalyzed by TSs and PTs. However, bacteria, as a whole, have more than one family of enzymes to perform these essential chemical reactions. Both canonical and non-canonical TSs cyclize linear prenyl diphosphates, multiple types of PTs can append prenyl groups onto a diverse array of scaffolds, and some families of enzymes (e.g., UbiA PTs) can perform both PT and TS reactions. With every new discovery and enzyme characterization, new opportunities for novel NP discovery will be presented.

Currently, genome mining for bacterial terpenoids is particularly appealing. Over the last two decades, genome mining-based NP discovery programs have mainly utilized the most recognizable TSs and PTs to target and quickly identify new terpenoids. These efforts clearly led to an overall improvement in bacterial terpenoid discovery and characterization (Fig. 1) and provide optimism for the future of bacterial terpenoid discovery. Imagine all of the exciting new avenues to pursue and NPs that will be discovered by using these new TSs, PT, and other functionalization enzymes as probes in future genome mining efforts!

NP research in bacteria has dramatically changed since advances in DNA sequencing technologies have provided the ability to easily obtain microbial genomes. Genome mining allows the simultaneous discovery of NPs and their BGCs and enzymes. Even if research groups continue to use traditional NP discovery methods, it is quick and fairly straightforward to sequence the producing organisms genome and identify an associated BGC. These types of multidisciplinary studies not only facilitate future NP discovery efforts and provide opportunities for NP biosynthetic studies, they also inspire and accelerate orthogonal research directions. These may include the discovery of enzymes with novel functions,[846,847] understanding new biological modes of action,[221,222] and the exploitation of bacterial terpenoid oxygenases for the chemoenzymatic synthesis of non-bacterial NPs.[942]

Finally, while it is clear that bacteria have evolved their own systems to create terpenoid diversity, bacteria also biosynthesize some of the same classes of terpenoids, even some of the same compounds, found in plants, fungi, and other organisms. These relationships provide accessible and renewable prokaryotic systems for eukaryotic natural products biosynthesis and enzymology. Consider the phytohormone gibberellins or the sponge-associated sesterterpenoids. The discovery and characterization of gibberellins in bacteria provided an evolutionary perspective on gibberellin biosynthesis. Identification of a NP from a non-renewable resource precludes the ability to further its development, isolated congeners, or study its biosynthesis. Isolating similar NPs from a culturable bacterium provides opportunities that would otherwise be incredibly difficult.

In conclusion, we hope it is evident from this review that (i) novel terpenoids can and should still be targeted for discovery efforts, (ii) the biosynthetic pathways of bacterial terpenoids are far from complete, (iii) the pathways that have been extensively studied have revealed a fascinating array of cyclization, prenylation, and functionalization enzymes, (iv) and most of these NPs are biologically active with a few key scaffolds paving a path towards potential drug development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Studies on natural products discovery, biosynthesis, and enzymology in the Rudolf laboratory are currently supported in part by a National Institutes of Health grant R00 GM124461 and the University of Florida.

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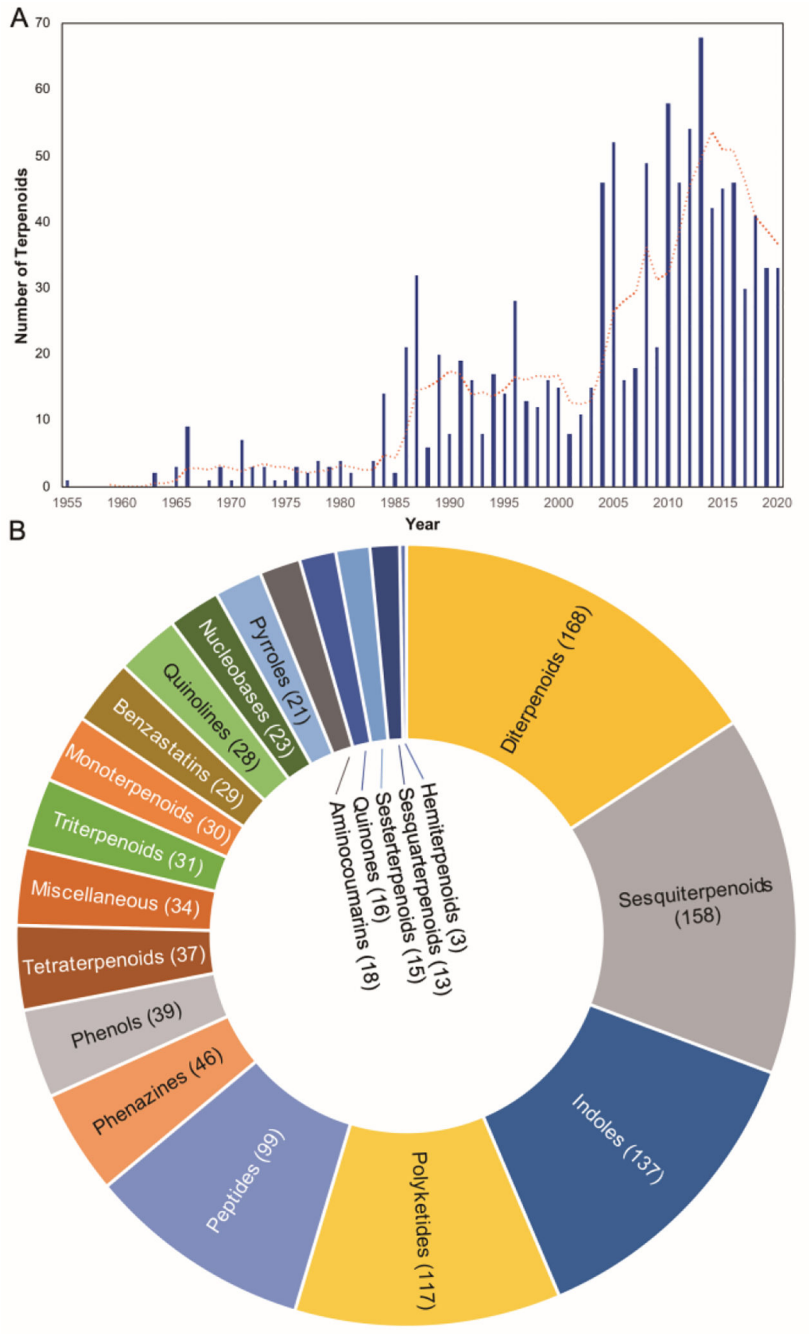
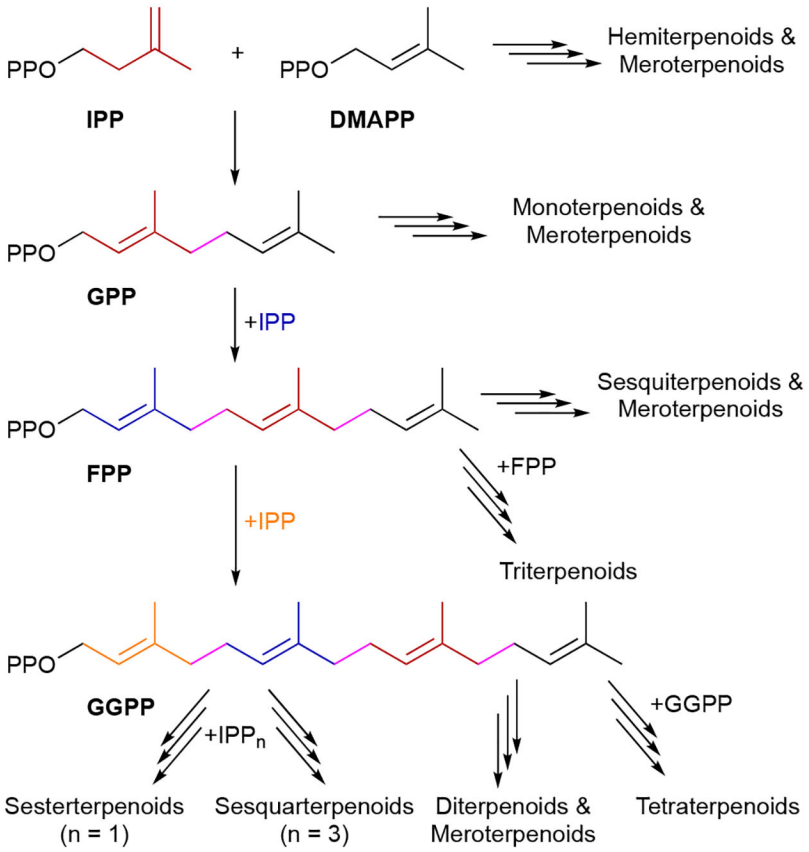
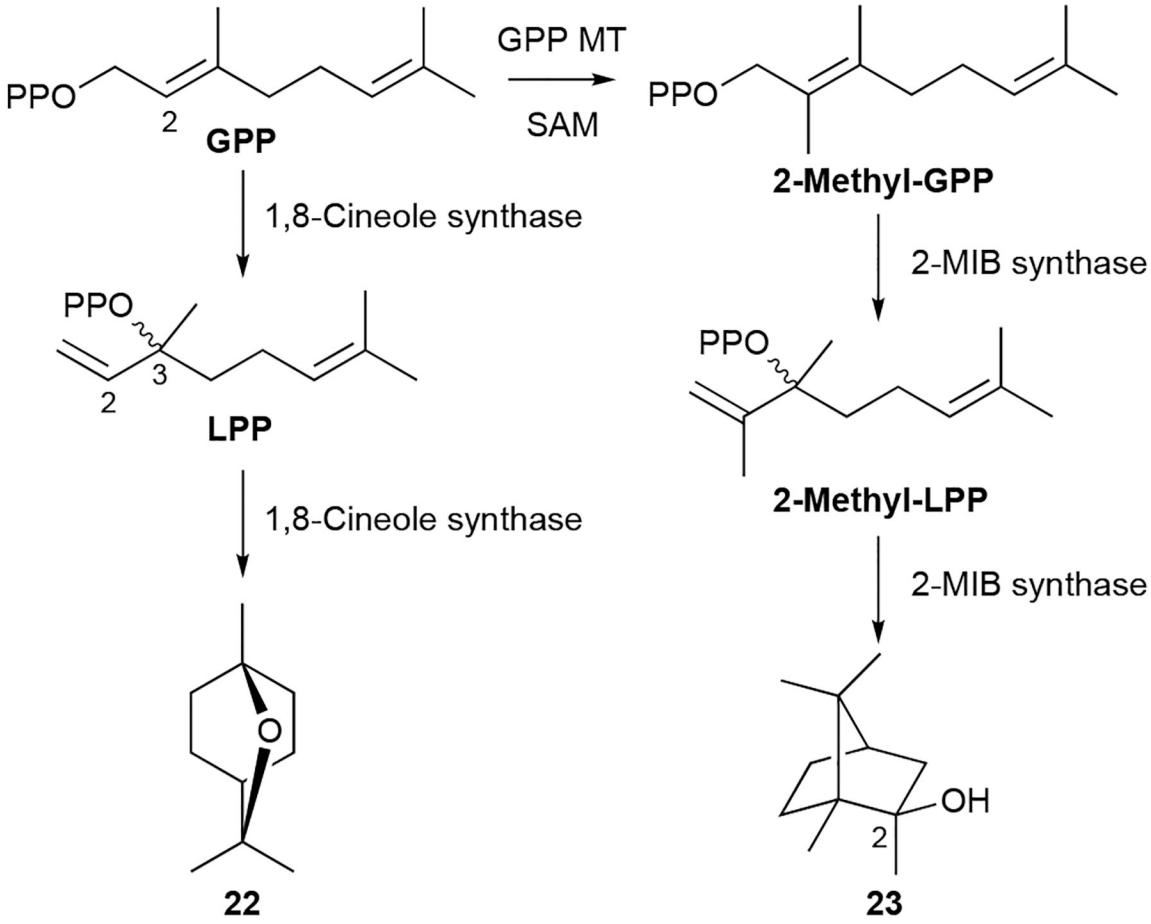


Fig. 1.

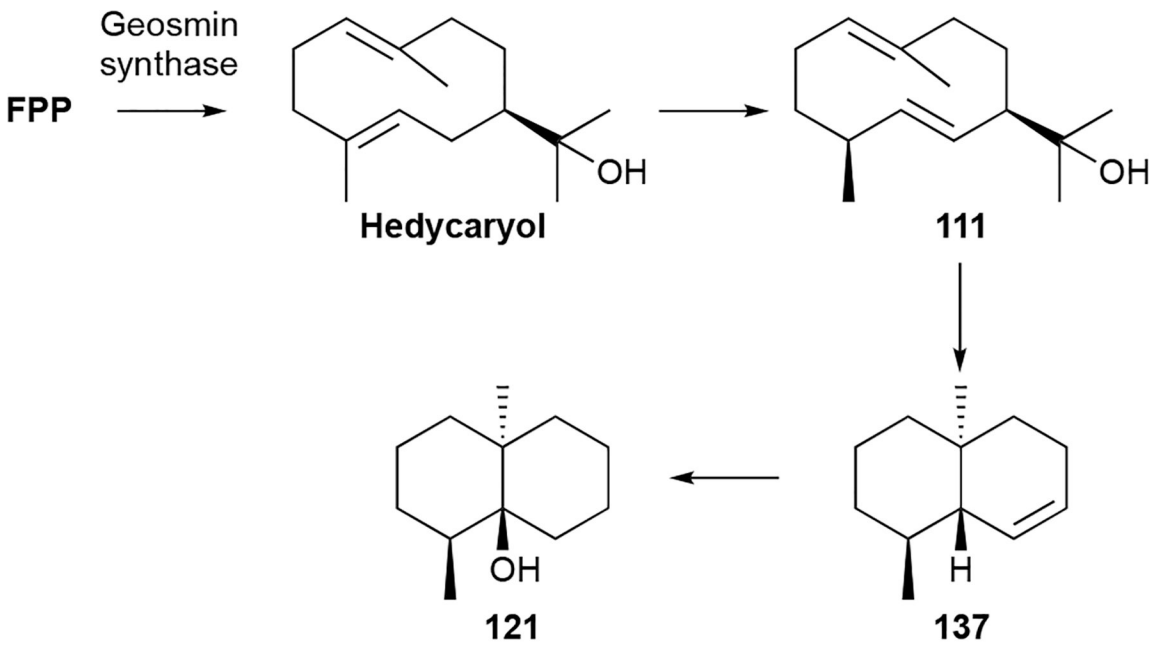
Summary of bacterial terpenoids in the literature. (A) Number of terpenoids discovered in bacteria per year. The orange line is a moving average of five years. Count for 2020 only includes up to mid-2020. (B) Distribution of terpenoids. The parenthetical numbers represent the number of bacterial terpenoids compiled in this review.



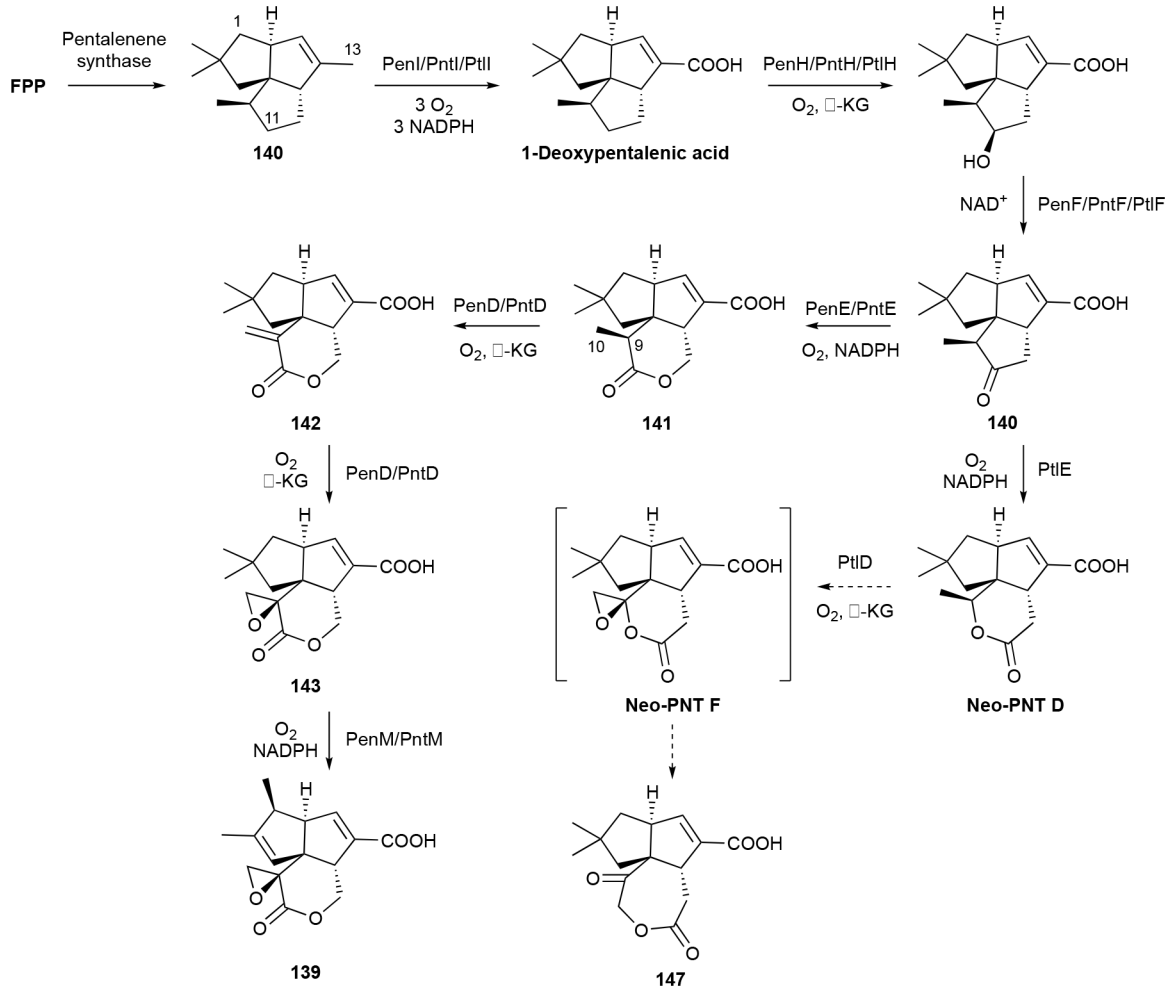
Scheme 1.
The biosynthesis of terpenoids.



Scheme 2.
Biosynthesis of 1,8-cineole (**22**) and 2-MIB (**23**).

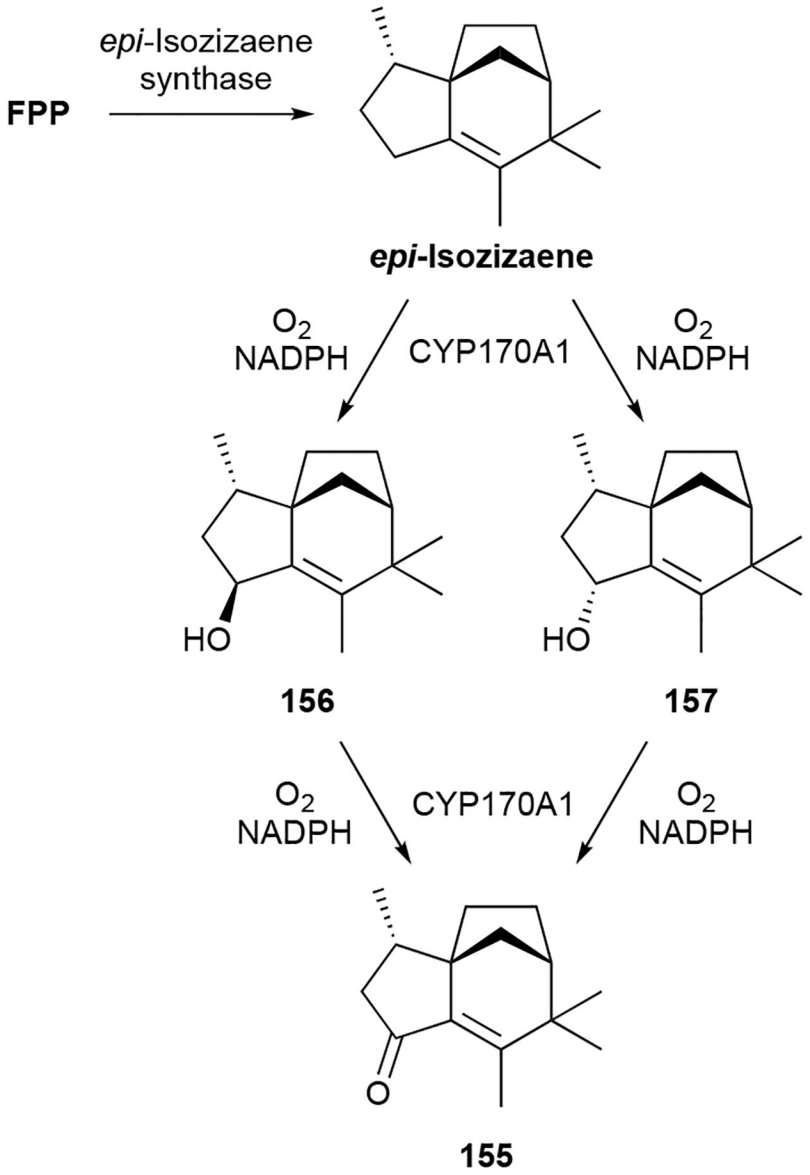


Scheme 3.
Biosynthesis of geosmin (**121**).

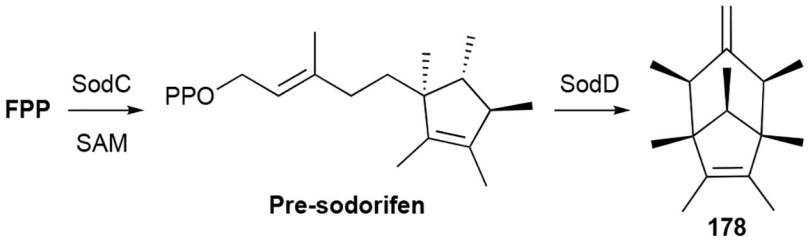


Scheme 4.

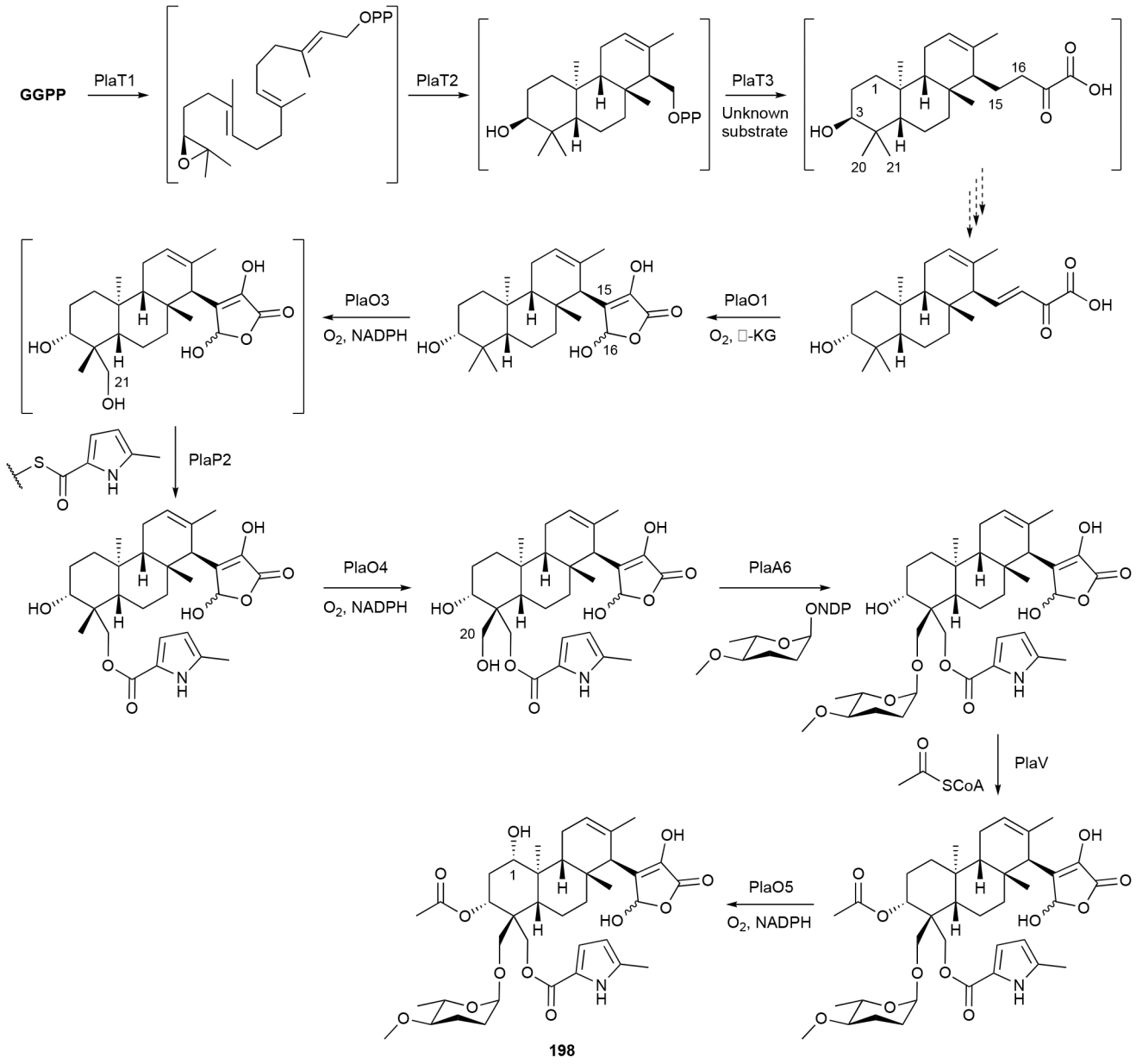
Biosynthesis of PNT (**139**) and neopentalenoketolactone (**147**).



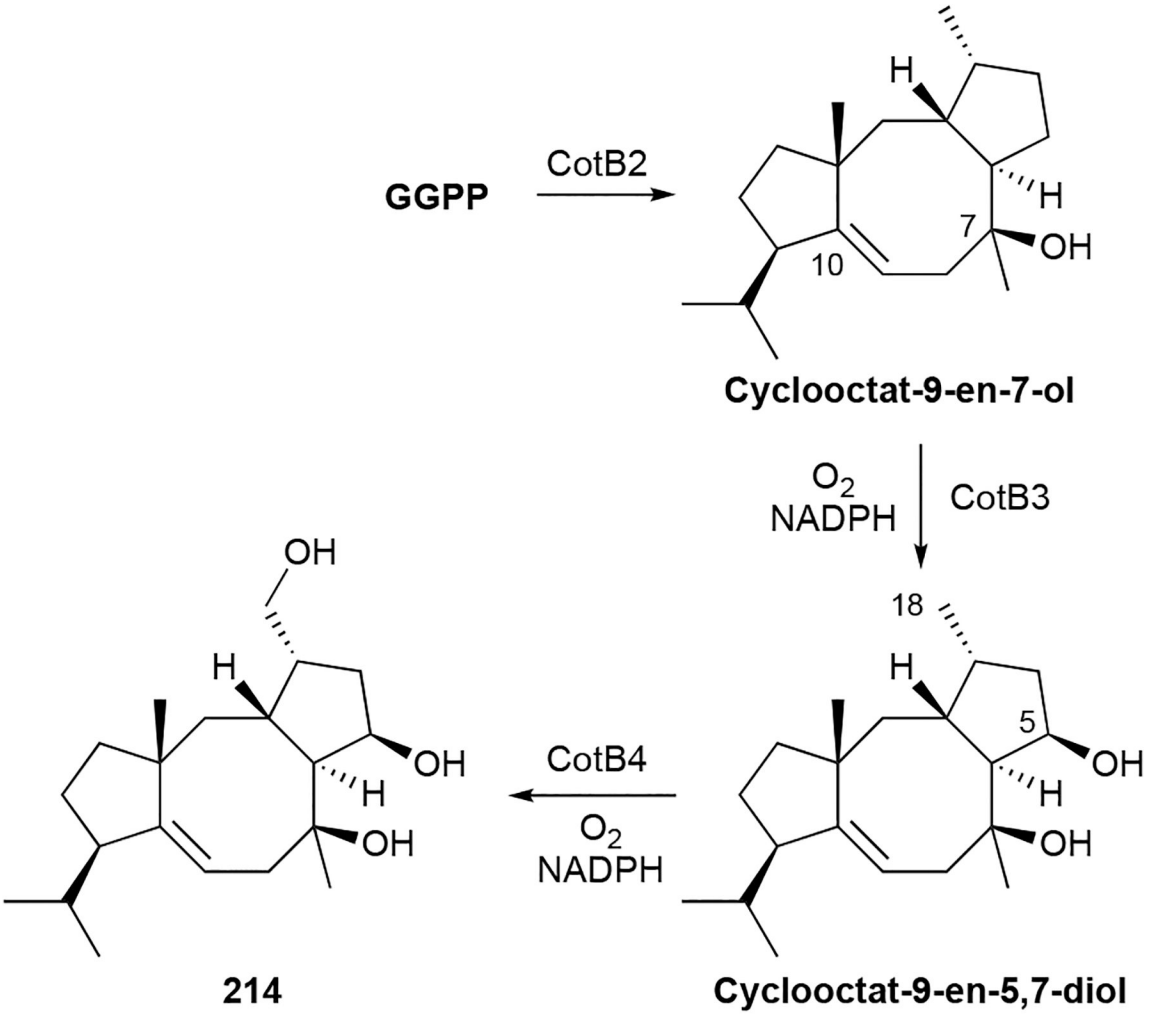
Scheme 5.
Biosynthesis of albaflavenone (**155**).



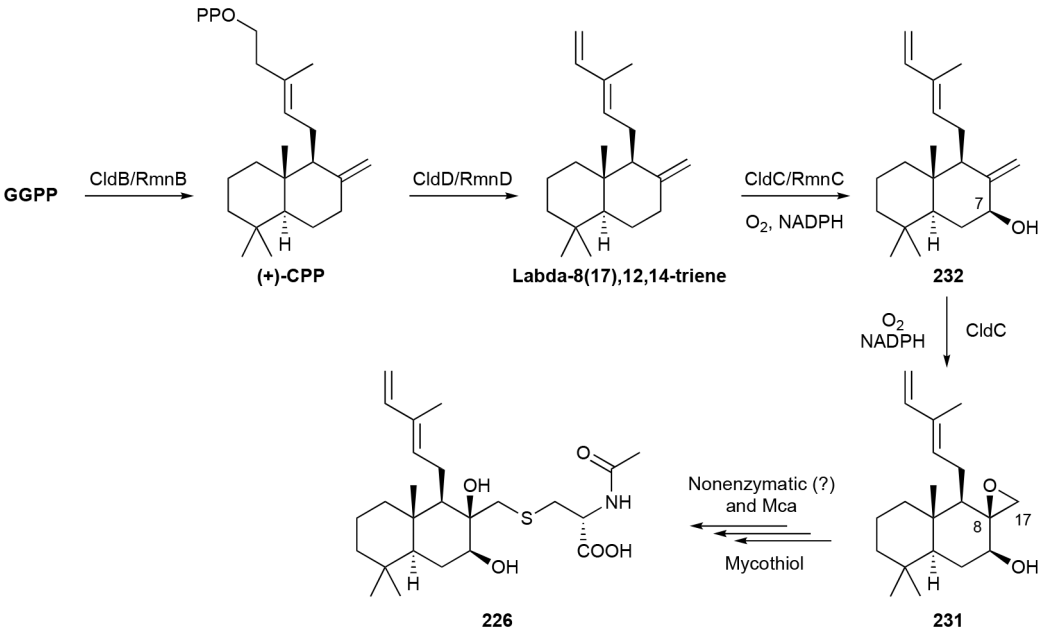
Scheme 6.
Biosynthesis of sodorifen (**178**).



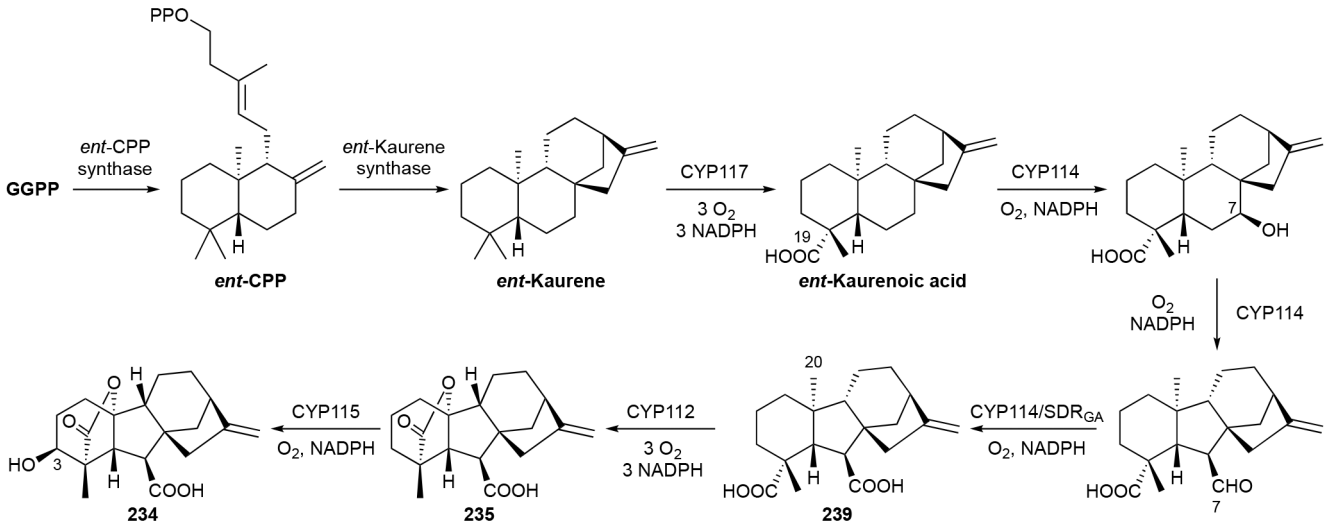
Scheme 7.
Biosynthesis of phenalinolactone A (**198**).



Scheme 8.
Biosynthesis of cyclooctatin (**214**).

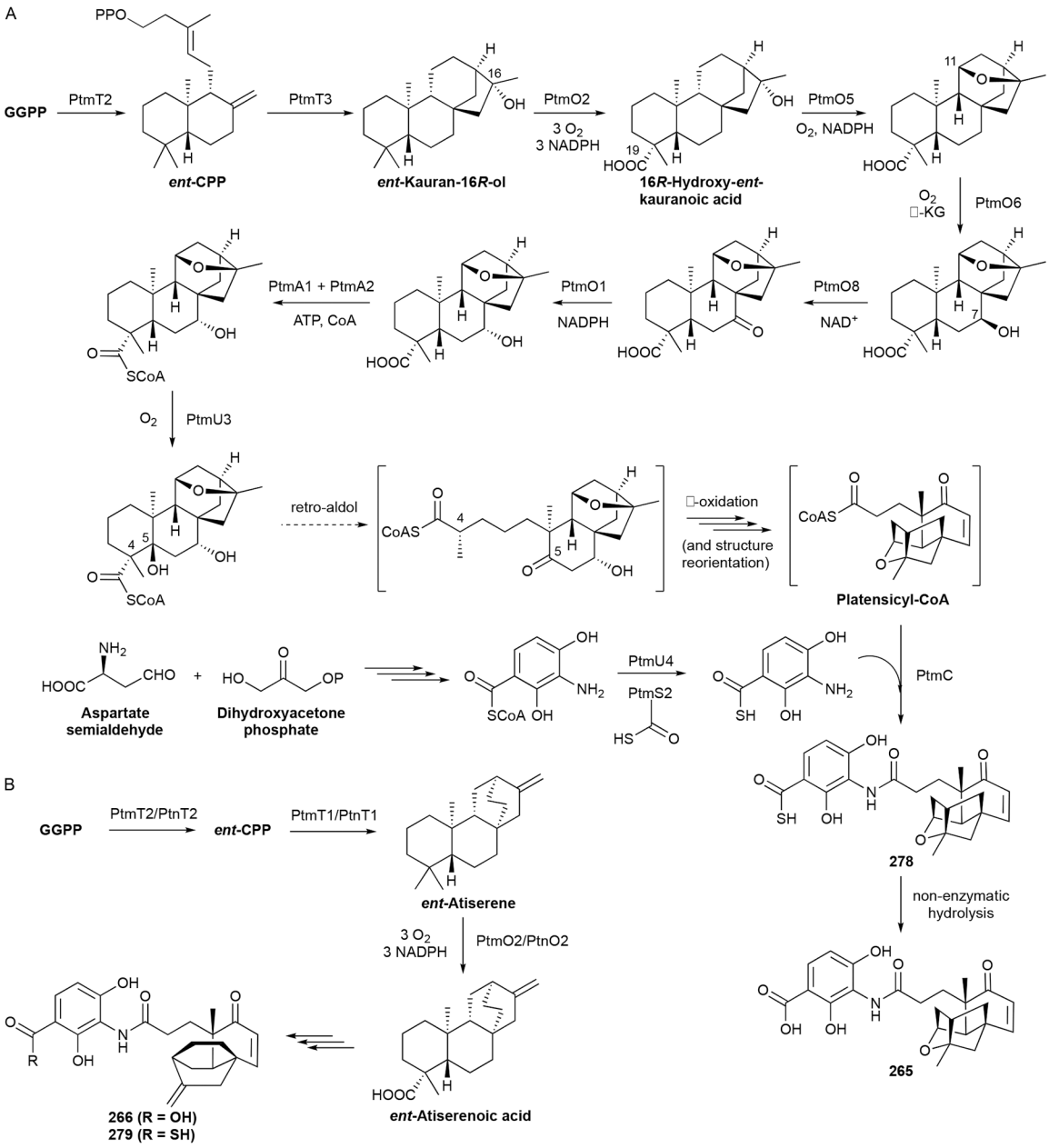


Scheme 9.
Biosynthesis of cyslabdan (**226**).



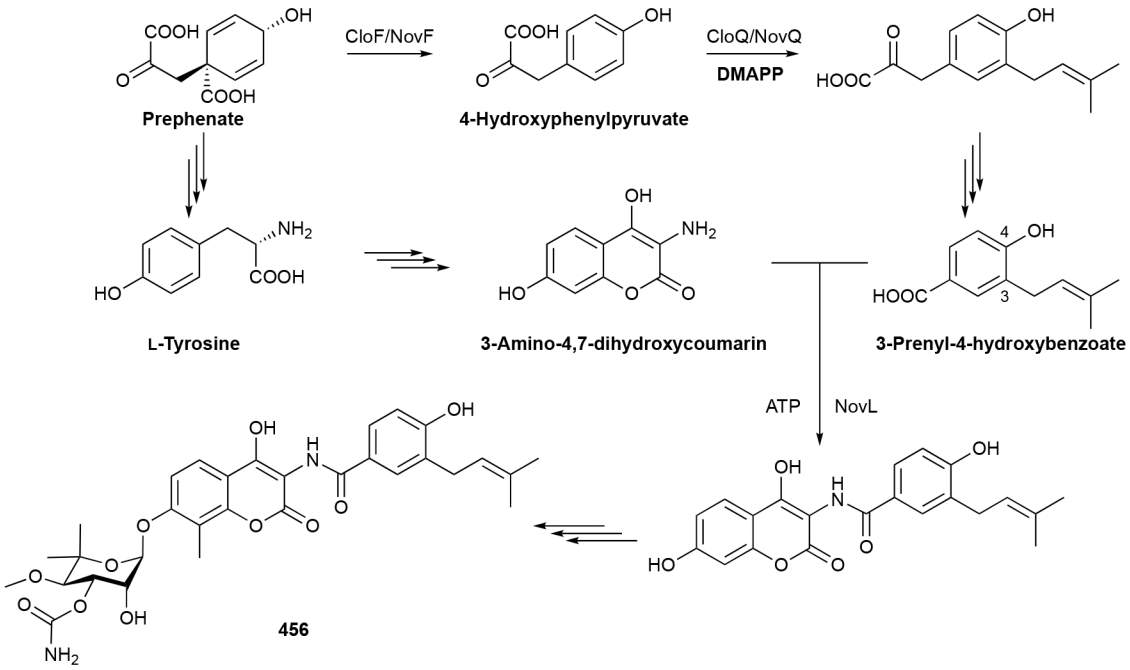
Scheme 10.

Biosynthesis of GA_9 (**235**) and GA_4 (**234**).

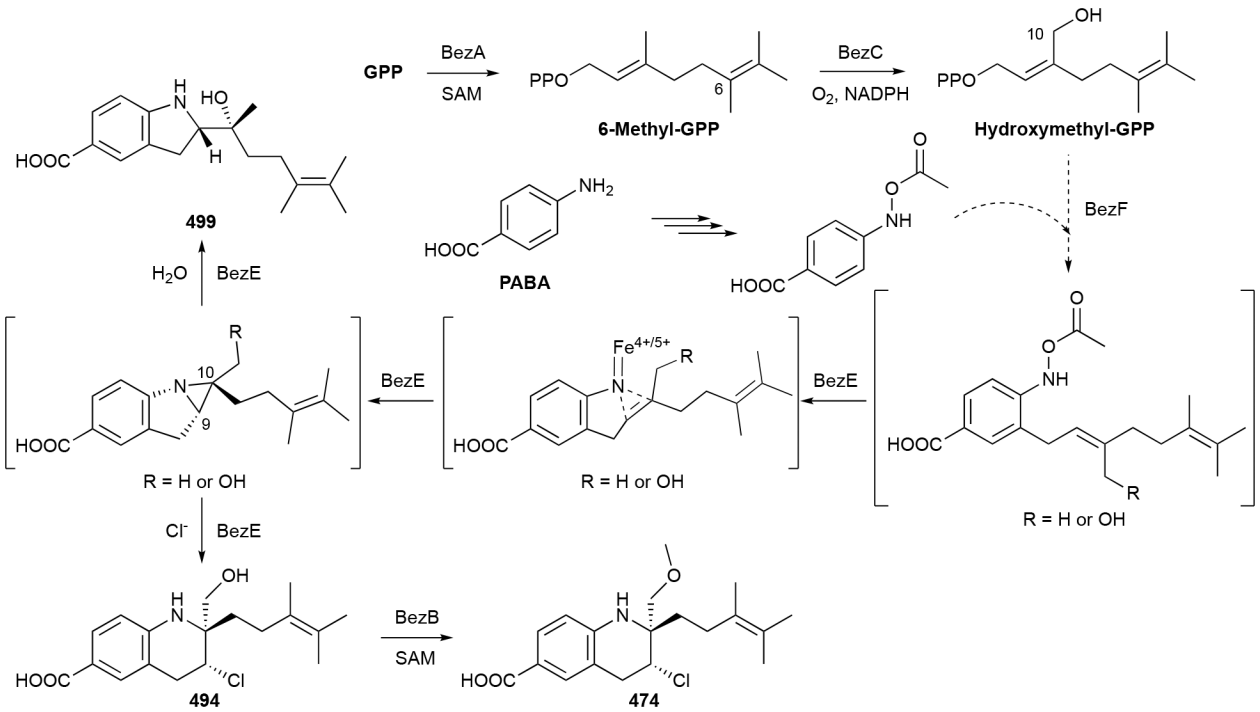


Scheme 11.

Biosynthesis of PTM (**265**), PTN (**266**), and their thioacid analogues (**278** and **279**).

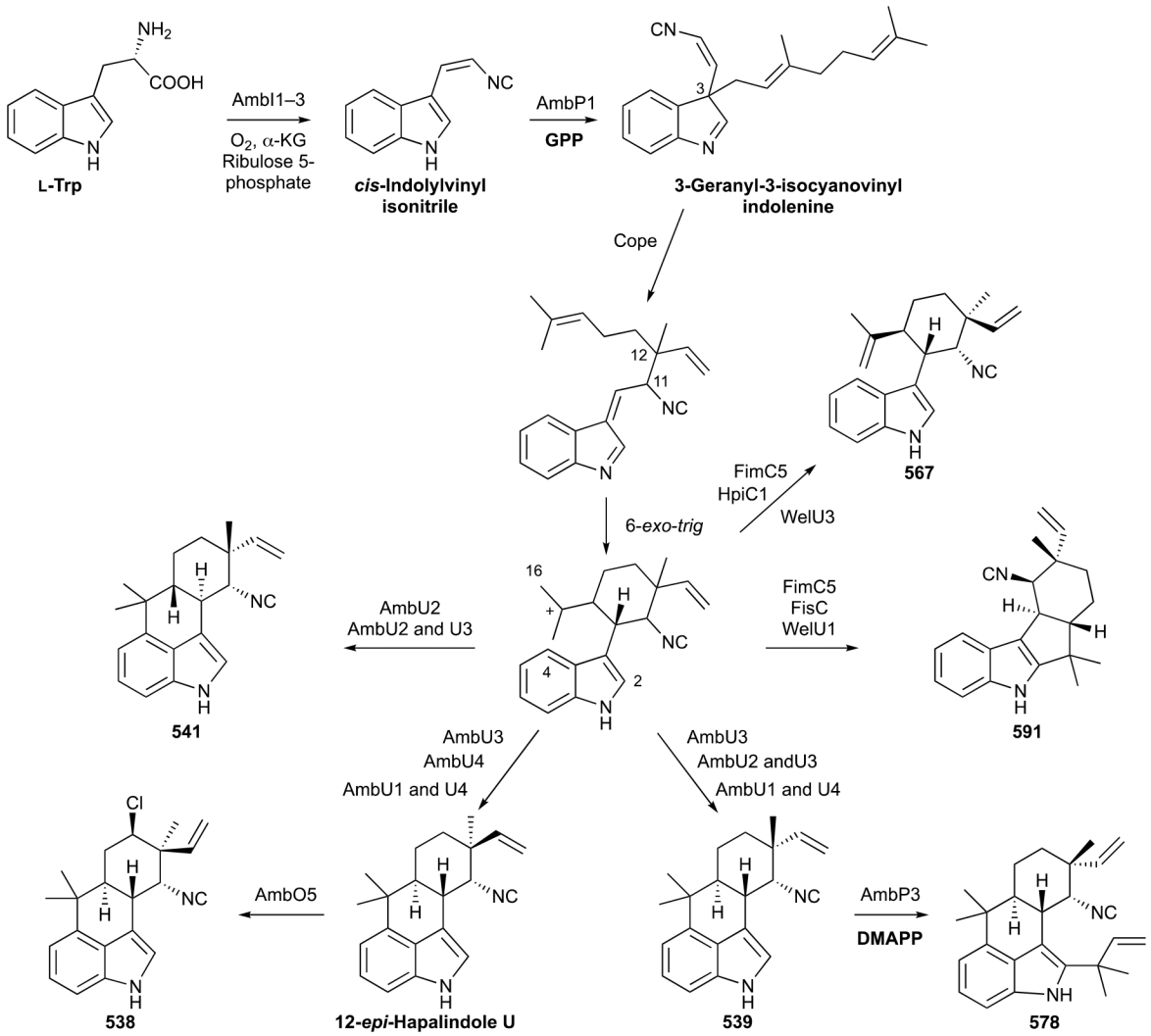


Scheme 12.
Biosynthesis of novobiocin (**456**).



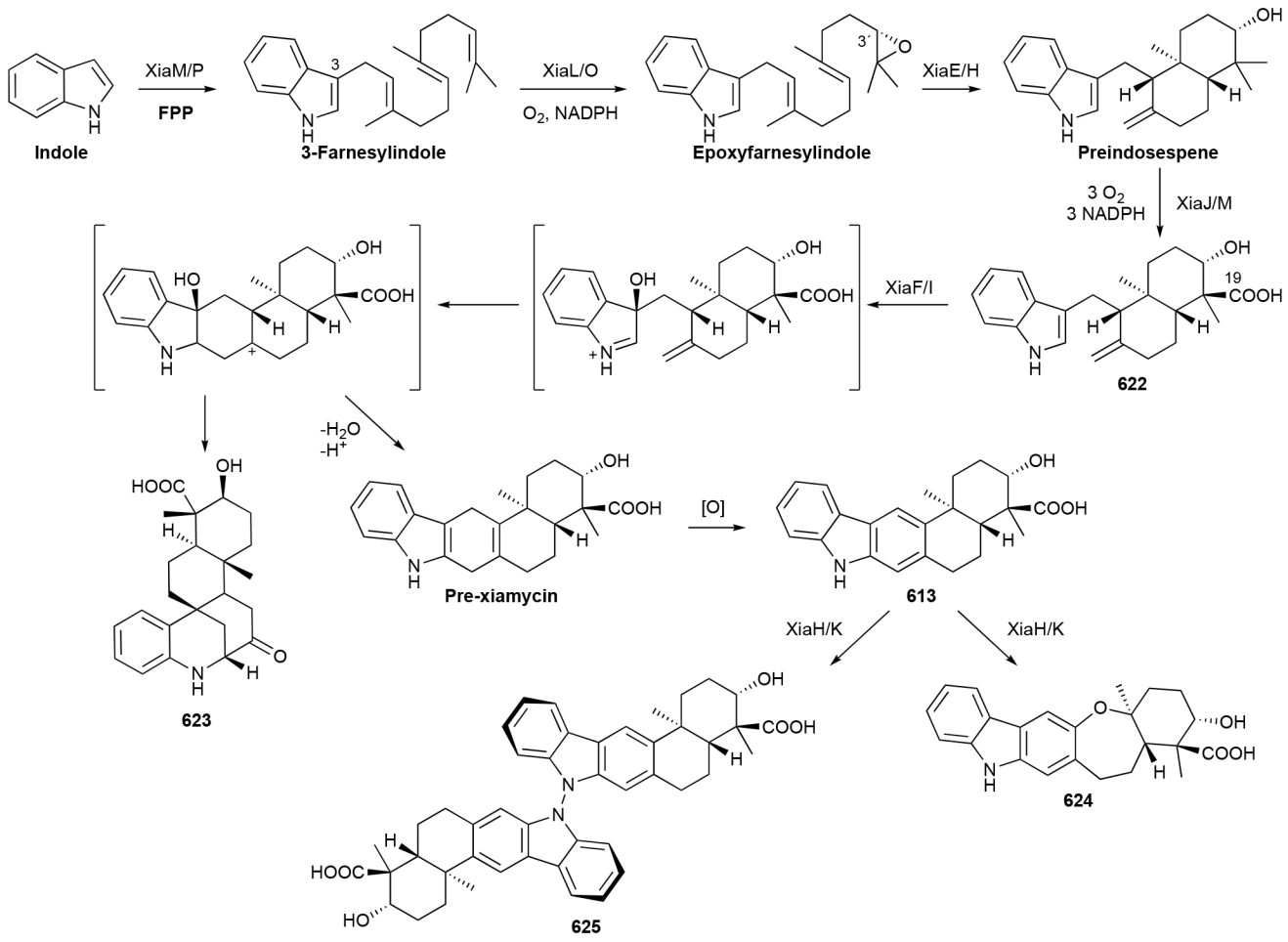
Scheme 13.

Biosynthesis of virantmycin (**474**) and 7-hydroxylbenzastatin F (**499**).



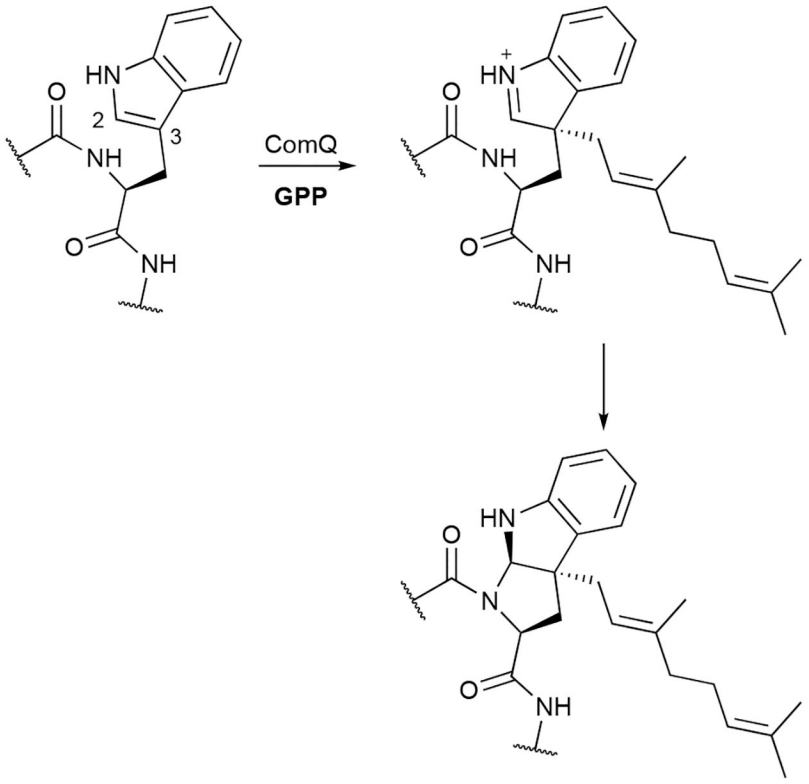
Scheme 14.

Biosynthesis of hapalindoles **538**, **539**, **541**, and **567** and ambiguines **578** and **591**.

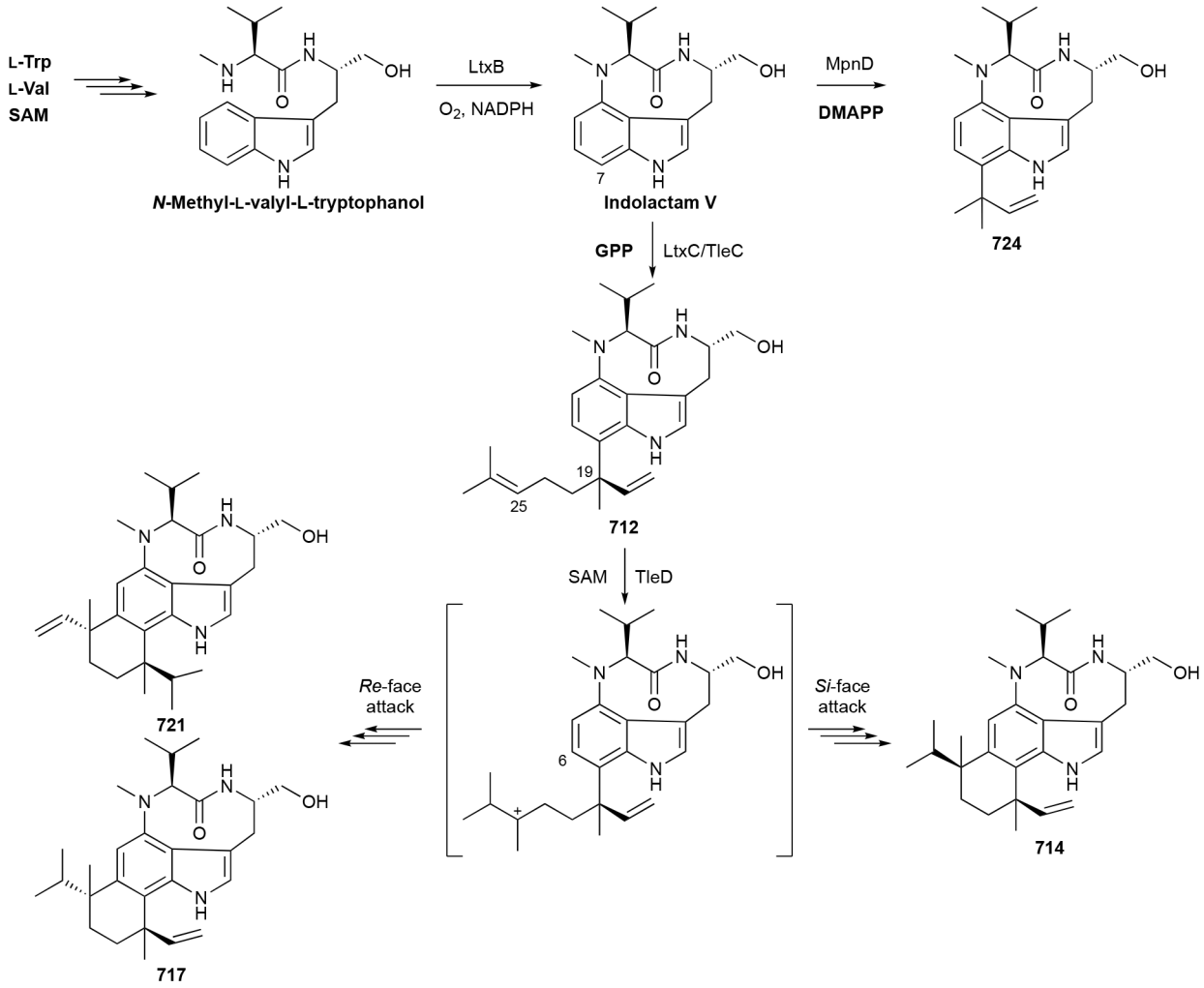


Scheme 15.

Biosynthesis of xiamycin A (**613**), oxiamycin (**624**), dixiamycin A (**625**), and sespenine (**623**).

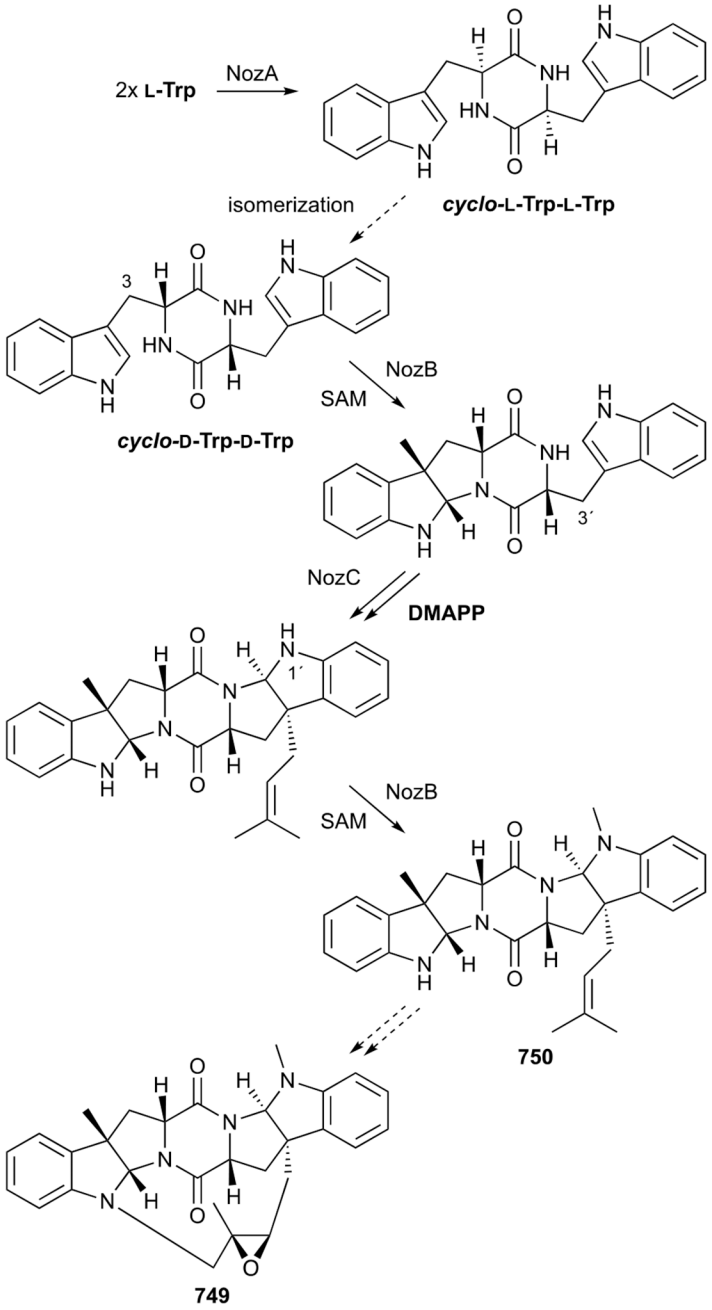


Scheme 16.
Prenylation and cyclization of ComX pheromones.

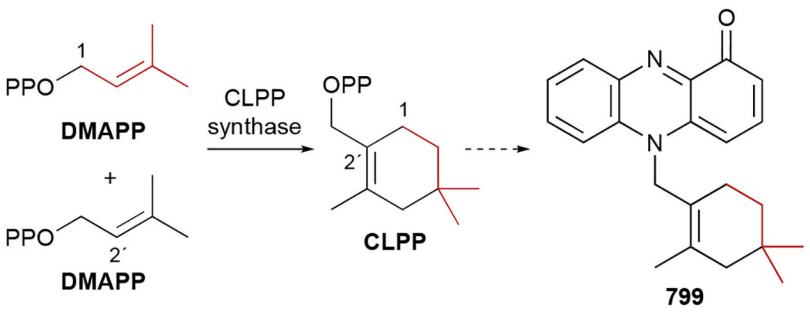


Scheme 17.

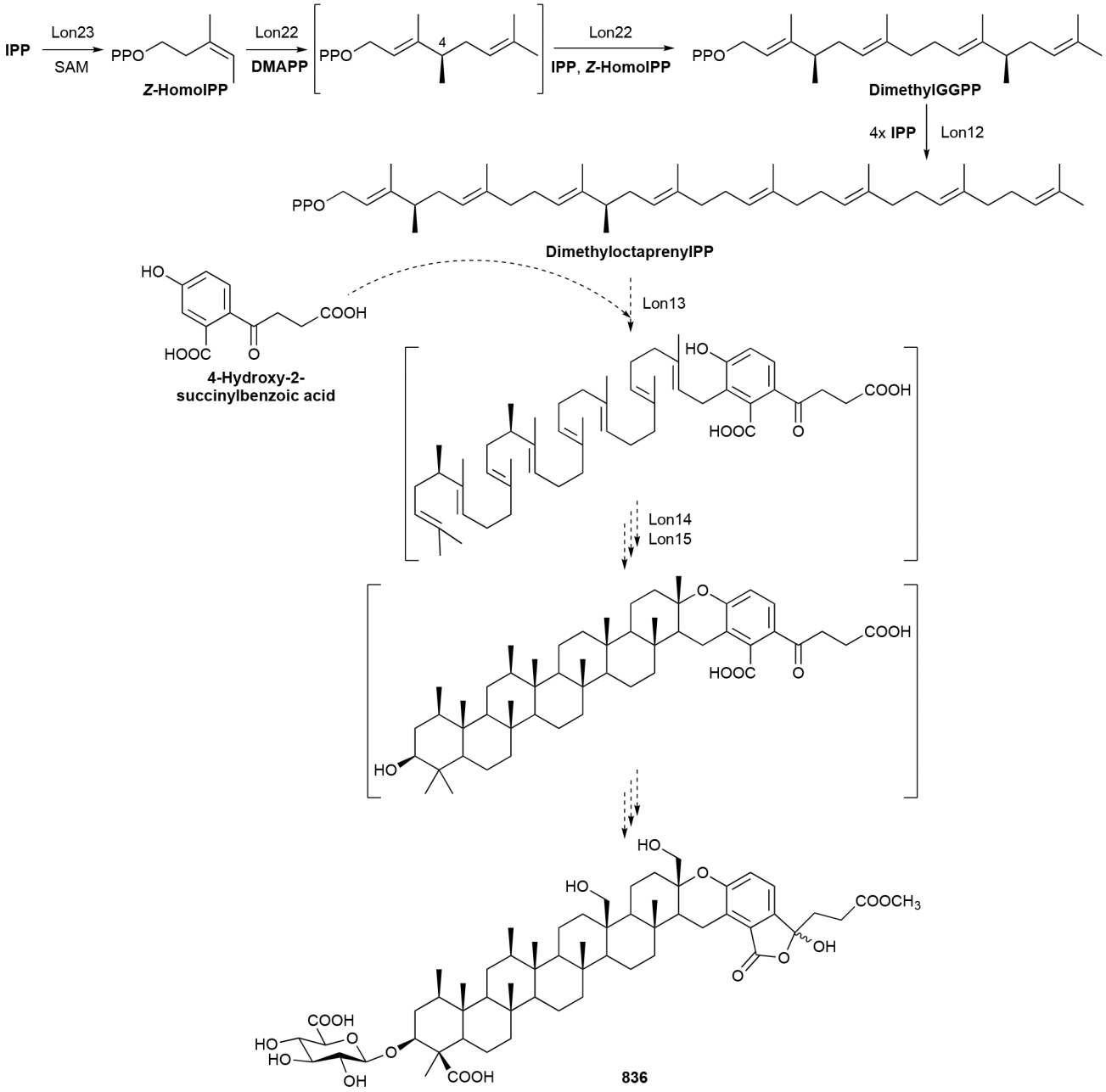
Biosynthesis of lyngbyatoxin A (**712**), teleocidin B-1 (**714**), teleocidin B-4 (**717**), des-*O*-methylolivoretin C (**721**), and pendolmycin (**724**).



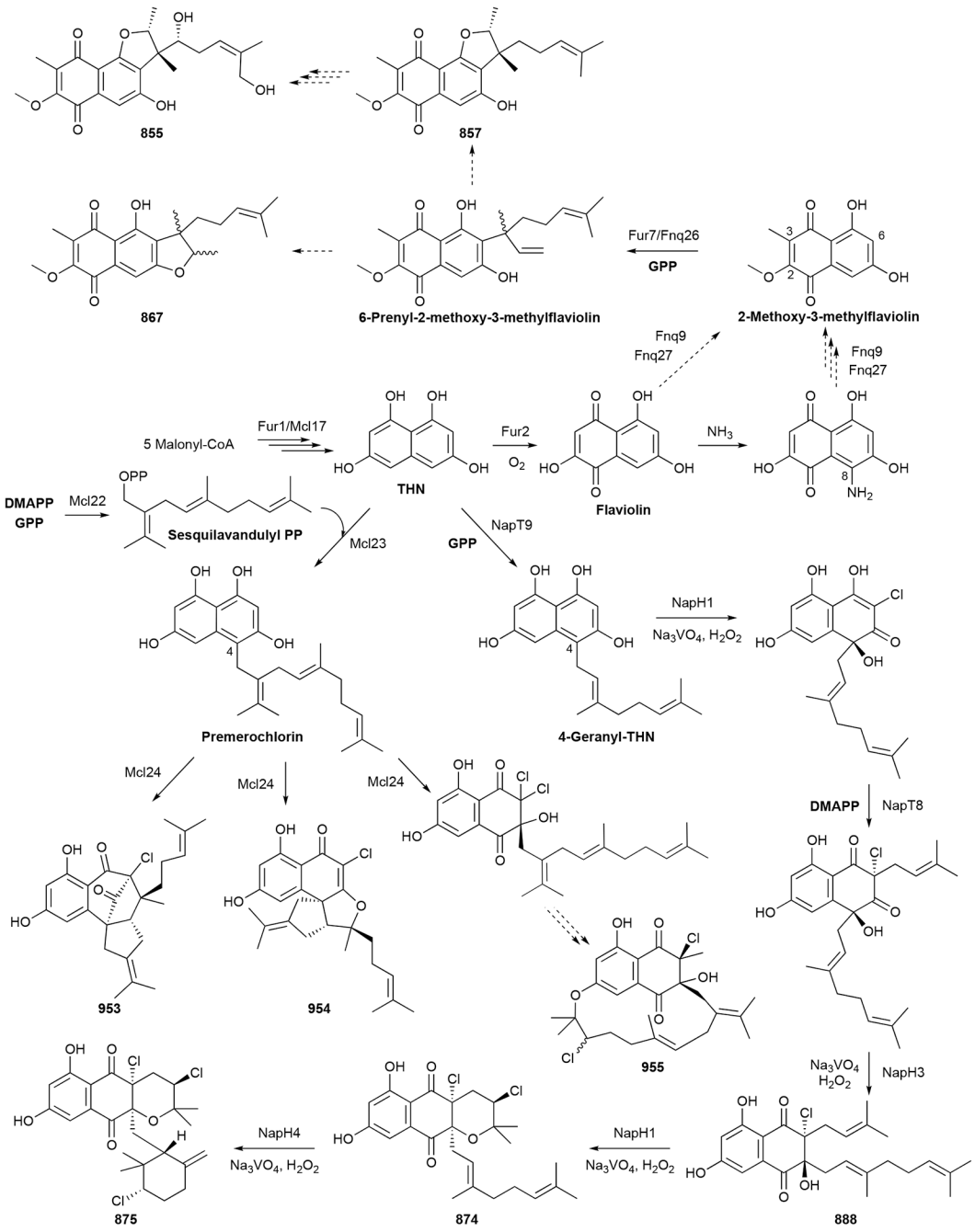
Scheme 18.
Biosynthesis of nocardioazine A (**749**).



Scheme 19.
Biosynthesis of lavanducyanin (**799**).

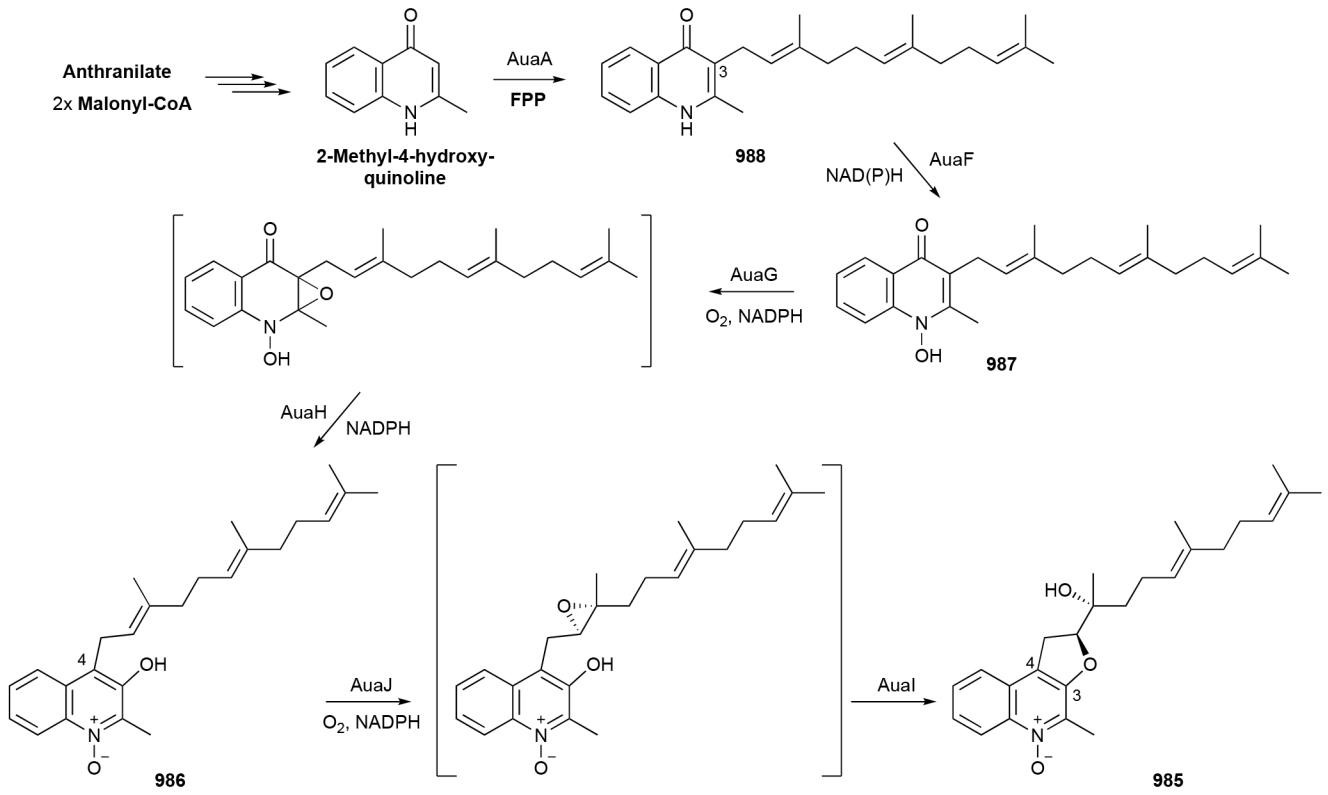


Scheme 20.
Biosynthesis of KS-505a (**836**).



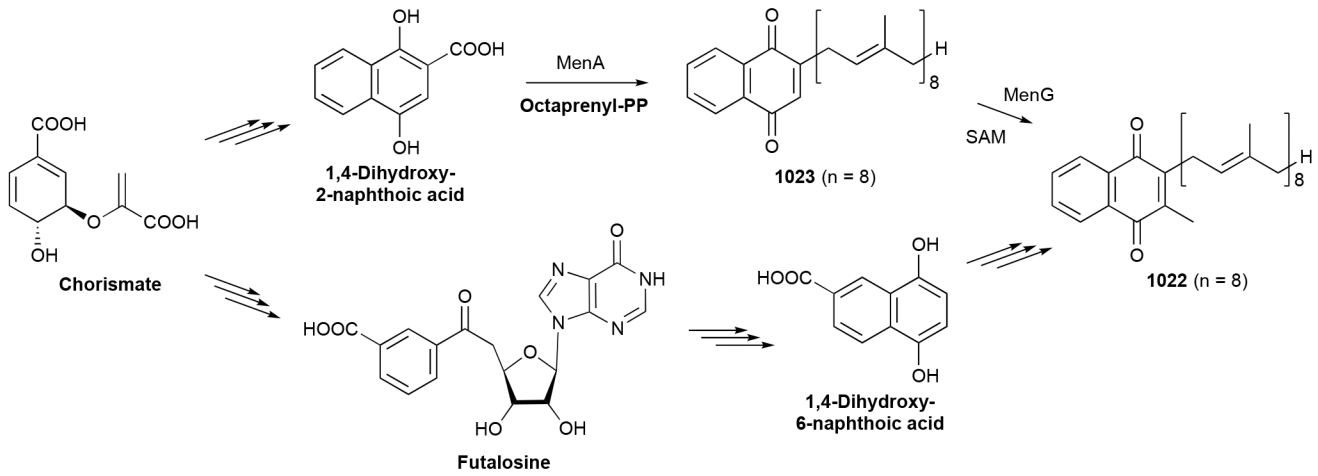
Scheme 21.

Biosynthesis of furaquinocin A (**855**), furanonaphthoquinone I (**867**), napyradiomycin B1 (**875**), and merochlorins A–C (**953–955**).



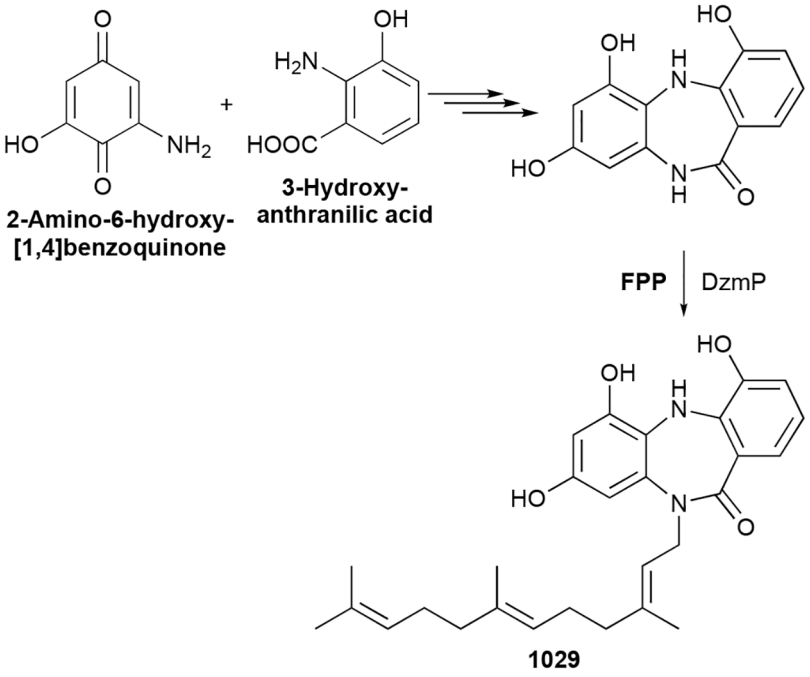
Scheme 22.

Biosynthesis of aurachins A (**985**), B (**986**), C (**987**), and D (**988**).

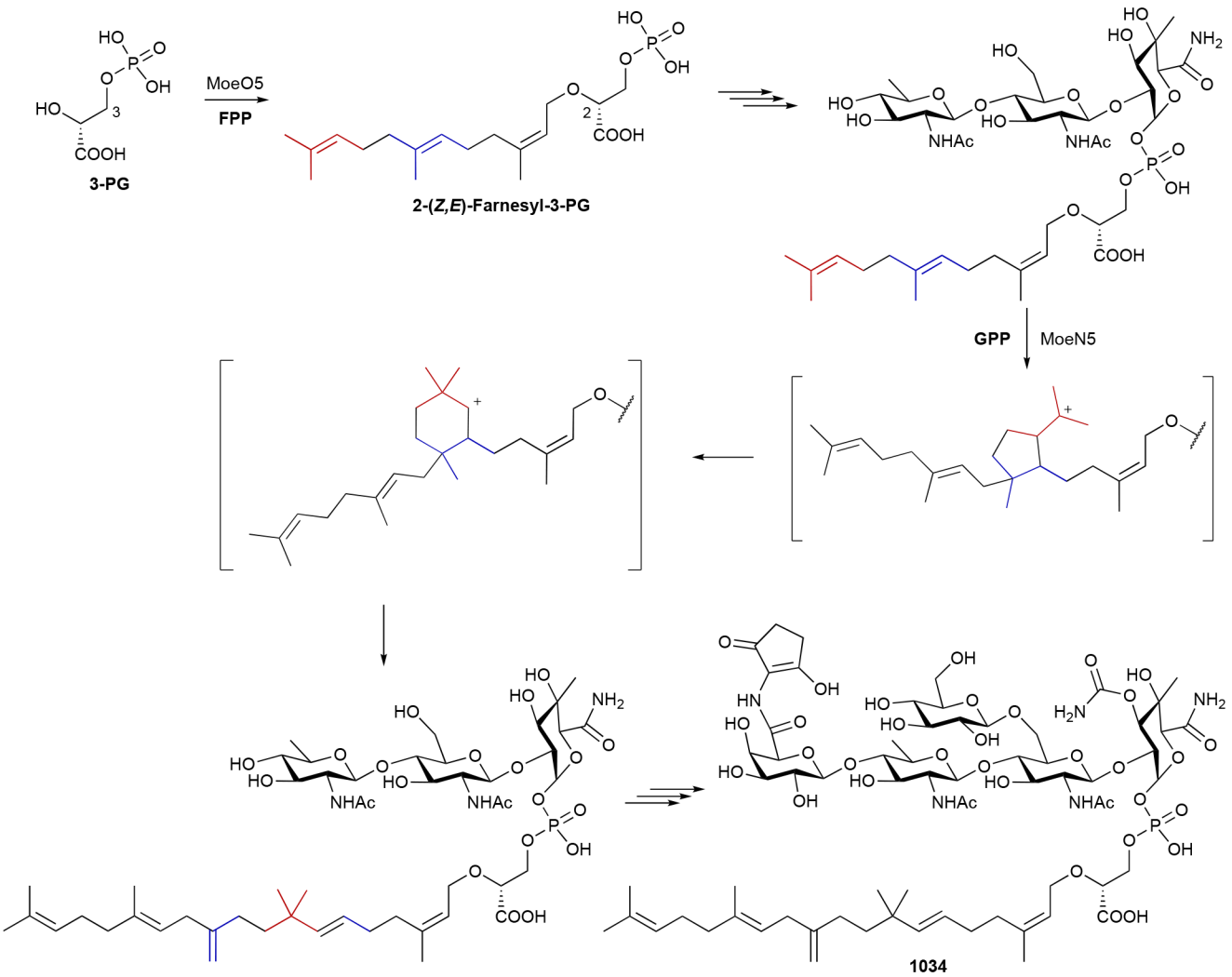


Scheme 23.

Biosynthesis of menaquinones (**1022**).



Scheme 24.
Biosynthesis of diazepinomicin (**1029**).



Scheme 25.
Biosynthesis of moenomycin A (**1034**).