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A comprehensive review of glycosylated bacterial natural products

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Abstract

A systematic analysis of all naturally-occurring glycosylated bacterial secondary metabolites reported in the scientific literature up through early 2013 is presented. This comprehensive analysis of 15 940 bacterial natural products revealed 3426 glycosides containing 344 distinct appended carbohydrates and highlights a range of unique opportunities for future biosynthetic study and glycodiversification efforts.

1. Introduction

While it is well-established that the glycosylation of naturally-occurring and/or synthetic small molecule-based drugs can dramatically influence the pharmacological properties of the parent scaffold,[1–17] there remains a lack of accuracy regarding the prevalence and/or extent of glycosidic diversity in the context of naturally-occuring glycosides. The current review attempts to address this gap of knowledge by providing a systematic analysis of all naturally-occurring glycosylated bacterial secondary metabolites reported in the scientific literature. AntiBase 2012[18] served as a key resource for glycoside identification and all glycosides were structurally validated *via* an analysis of the primary literature and corrected where necessary prior to integration into this compilation. Based upon an analysis of 15 940 bacterial natural products, over one fifth (3426 compounds, 21.5%, Fig. 1) are glycosides wherein glycosylated macrolides and macrolactams represent the largest allocation (738 compounds, 21.5% of all bacterial glycosides, Fig. 2). Further analysis of the range of saccharides represented across all 3426 bacterial glycosides revealed 344 distinct carbohydrates (Fig. 3 and Table 1). For this latter consideration, carbohydrates were only designated as ‘distinct’ based upon differences within the fundamental monsaccharide core (specifically, notable stereochemical and/or functional group variation, including anomeric configuration) whereas simple modifications of a given common sugar core (*e.g.*, *O*/*N*/*S*-

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alkyl/acyl substitutions) were designated as identical to the parental core saccharide. The content of this comprehensive review has been organized based upon aglycon class/structure as indicated in Fig. 2 wherein each section provides additional relevant information pertaining to the glycosides represented within the selected metabolite classification. Illustrations throughout this review employ two standard conventions. First, regiospecificity of glycosylation is represented as a colored ball within the context of a representative aglycon, the latter of which are presented in many cases in generic form in an effort to emphasize glycosylation. Second, for simplicity, D-pyranoses are represented in the $^4C_1$ conformation while L-pyranoses are illustrated as $^1C_4$ conformers. For furanoses, and/or in cases where the chair conformation may obstruct field of view, a standard planar pentose or hexose ring is used. In addition, all pseudosugars found as part of the microbial glycosylated natural products discussed within this review are summarized in Fig. 4.

2. Aminoglycosides and related secondary metabolites

Aminoglycosides are structurally and functionally diverse and are noted for a range of biological activities including inhibition of bacterial protein synthesis (*e.g.*, anti-infectives such as gentamicin, kanamycin, streptomycin), glucosidase inhibition (*e.g.*, the antidiabetic acarbose), trehalase inhibition (*e.g.*, the crop protectant validamycin) and inhibition of bacterial/eukaryotic protein synthesis (*e.g.* the cytotoxin pactamycin).[19] The core sugar-derived carbocycle is the key structural signature of aminocylitols and this core is further diversified *via* variant functionalization (such as various degrees of deoxygenation and amination) where glycosylation at one or more positions is critical to the wide range of structural and functional diversity of this important natural product family.

2.1. Pactamycins

Members of this class include pactamycins, pactalactams, pactamycates, and cranomycin.[19–21] They all contain pseudosugars and are characterized by the presence of an acetophenone unit which is *N*-linked at the C-3 position to an aminocyclopentinol pseudosugar. Twenty compounds have been found to be produced naturally, through feeding studies, or through mutasynthesis.[22–27] Pseudosugar features common to all members include C-3′, C-4′ and C-5′-disubstitution (‘branching’) and conserved stereochemistry at all positions where pseudosugar divergence stems from variation of the C-2′ and C-3′-amine and/or C-9′-hydroxy substituents (Fig. 5). This family inhibits protein synthesis by binding the 30S subunit and displays broad activities including antibacterial, antiviral, antimalarial, and general cytotoxicity. This broad range of activities is due to the inhibition of protein synthesis in most organisms through binding with the 30S ribosomal subunit. The C-3′-1,3-dimethyl urea moiety of pactamycins at C-3′ (Fig. 5) has been noted to be important for activity while the C-9′ 6-methyl salicylic ester is considered dispensible.[25] Variation of the pseudosugar C-3′-branching (**P27a** and **P16a**) favored antimalarial acitivity with lowered overall mammalian cell line cytotoxicity.[26]

2.2. Other members

While a diverse array of carbocyles serves as the core aglycon of aminoglycosides, diamino carbocycles are among the most common. Metabolites that contain a 1,4-diamino carbocycle

core include both the 2-deoxy variants (**P1–P4**, Fig. 6) such as that found within the istamycins and related metabolites sporaricins and sannamycins,[28–31] as well as 2-hydroxy-containing cores found within metabolites like lysinomicin (**P6**)[32] and the fortimicins (**P6**, **P14**, **P15**, and **P18**).[33–36] The corresponding 2-deoxy-1,3-diamino carbocyclic aglycon 2-deoxystreptamine (2-DOS, **P7**) was found in majority of clinically used aminocyclitols including gentamicins,[37] kanamycins,[38] ribostamycin[39] and tobramycins while the related 2-hydroxy aglycon streptamine (**P8**) serves as the core of several aminoglycosides including streptomycins[40] and ashimycins.[41] In other aminoglycosides, including gentamicins and sagamycins,[42] a 1-deamino-1-hydroxy-2-DOS (**P9**) was reported as the aglycon. Aminoglycosides hygromycin A and *epi*-hygromycin contain the methylene-bridged aminocyclitol *neo*-inosamine (**P19**)[43] while a handful of secondary metabolites including acarbose,[44] amylostatins[45] and validamycins[46] utilize an unsaturated C7 cyclitol aglycon (**P13**). The D-*myo*-inositol (**P12**) and its aminated derivative **P24** were recently discovered in mycothiol and minosaminomycin, respectively.[47,48] The epimer of *myo*-inositol (**P25**) found as the aminocyclitol core of kasugamycin[49] and carbamoylated inositol (**P10**) anchors boholmycin.[50]

While a diverse range of aglycon glycosylation patterns exist among aminoglycosides, glycosylation at C-4 and C-6 are among the most prevalent. Sugars employed the context of C-4 glycosylation of core aglycons include: the highly deoxygenated diaminosugar **1** and its C-5′ branched **3** and **4** (gentamicins)[39,51] as well as the corresponding C-4′/C-5′-unsaturated variants **2** (sisomycin),[52] **15** and **16** (verdamicins);[53] 2′-amino-2′-deoxy-α-D-glucose (**5**), its C-5′-methyl branched analog **6** (gentamicins)[37] or its 2′-deoxy **14** (nebramycin);[54] 6′-amino-6′-deoxy-α-D-glucose (**7**, gentamicins and combimicins)[37,55] its corresponding 3′-deoxy **9** (combimicins)[56] or its C-5′-methyl branched **11** (gentamicins);[37] 2′,6′-diamino-2′,6′-dideoxy-α-D-glucose **10** (combimicins)[55] and its corresponding 3′-deoxy **8** (nebramine and tobramycin);[57] 3′-amino-3′-deoxy-α-D-glucose (**12**, nebramycins)[54] and 2′,6′-diamino-4′-deoxy **13** (seldomycins).[58] The novel 2′,4′-diamino-2′,3′,4′,6′-tetradeoxyhexose **41** comprised the C-4 attachment in minosaminomycin and C-1 in kasugamycin (Fig. 6). The bicyclic iminosugar **17** (gentamicins)[37] stands out as particularly unique among those found within the C4 glycoside series. Also noteworthy are the C-4′ octadiose moieties (**34** and **35**) observed among saccharomycins and apramycin.[59] The C-8′ of this unusual eight carbon carbohydrate was found to be further modified by 4′-amino-4′-deoxy-β-L-glucose (**36**) or α-D-glucose (**18**) in apramycin. C-4 glycosylation using select members of the sugars described above is also represented among other aminoglycosides including butirosins,[60] xylostatins and ribostamycins.[61]

In addition to a few sugars highlighted in the previous paragraph found appended at C-6 of aminoglycoside core aglycons (**2**, **4**, **8**, **10**, **12**),[54,62,63] additional sugar diversity has been found at C-6 including: α-D-glucose (**18**);[64] 3′-amino-3′-deoxy-α-D-xylose **21** (gentamicins and sisomicins)[37,65] and its C-4′-methyl branched **19** (prevalent in a range of aminoglycosides);[51,66,67] C-4′-methyl branched 3′-amino-3′-deoxy-α-D-galactose **20** (combimicins);[56] 3′-amino-3′-deoxy-β-L-arabinose (**22**, gentamicins and related compounds);[37,65] 2′-amino-2′-deoxy-α-D-xylose **24** and its corresponding 2′,3′-

diamino-2′,3′-dideoxy analog **23** (seldomycins);[58,68] as well as 3′-amino-3′-deoxy-β-D-mannose (**42**) and the diasaccharide **I** [comprised of the uniquely C-6′ oxidized mannose **43** and 2′-amino-2′-deoxy-α-D-xylose (**24**) in boholmycin].[50] Other C-6′-appended sugars include L-streptose (**28**), 5′-hydroxy-L-streptose (**30**) and the corresponding reduced forms **29** and **31** have been found among streptomycins[69–71] wherein further C-2′ glycosylation of the streptose moiety with 2′-amino-2′-deoxy-α-L-glucose (**32**) has been observed.

In addition to the previously noted **1** and **2**, D-xylose (**26**, xylostatin and butirosin A)[61] and D-ribose (**25**) are also found among the core C5 glycosides with the latter being most prevalent (as exemplified by butirosin B,[60] lividomycins,[72] paromomycins[72] and ribostamycin[61]). In addition, glycosides of the C-3 position of the appended ribose with **5** (neomycin),[73] **27** (neomycin B,[73] paromomycin and lividomycin A[74]) and **10** (neomycin C)[75] have been characterized. A C-4′/C-5′-diether bridged glycosidic connection to 3′-keto-sugar (**33**) and its enol form (**332**) has been observed in the context of spectinomycin and spenolimycin, respectively.

Additional glycosides that fall outside the scope of those described in the preceding paragraphs include the aromatic hexofuranose glycosides (**37** and **38**) of hygromycins,[43] various *N*-glycosides (4′,6′-dideoxy-α-D-glucose **39** in acarbose[44] and the unique 1′,2′-dideoxy-2′-aminohexose **40** in salbostatin[76]). It is important to note that minor modifications of functional groups such as *N*- and *O*-methylation, acetylation, carbamoylation, and formylation of sugar monomers, not specificied herein, are also prevalent.

3. Angucyclines

With more than 200 known bacterial-derived members,[18] angucyclines comprise one of the largest groups of polycyclic aromatic polyketides. Angucyclines are classified based upon their signature tetracyclic benz[*a*]anthracene system into five major classes: tetrangomycin-type (*e.g.*, landomycins); aquayamycin-type (*e.g.*, saquayamycins and urdamycins); benzanthrin-type (*e.g.*, benzanthrins); gilvocarcin-type and jadomycin-type (Fig. 7).[77–79] Despite their remarkable chemical diversity and divergent biological activties, angucyclines have failed to advance in clinical development due to off-target toxicities and/or poor drug-like properties.[79]

3.1. Tetrangomycin-type (landomycins)

The landomycins (Fig. 8) are one of the largest angucycline subclasses and all members contain a C-8 oligosaccharide of varying lengths.[77,79] Landomycins have been further subdivided based upon the polycyclic aromatic aglycon into three sub-types: landomycinone-based (sub-class I; landomycins A–L, S, V, X and Z); tetrangulol-based (sub-class II; landomycins M, O–R, T, U, W, and Y) and tetrangomycin-based (sub-class III; atramycins, brasiliquinones and TAN-1085). Despite their notable diversity, only three core sugars (β-D-olivose, **53**; β-D-amicetose, **48** and α-L-rhodinose, **44**) comprise the glycosyl components of landomycins.

Natural variants within sub-class I contain disaccharide to hexasaccharide glycosyl substitutions and include landomycins A–E, K, L and S–U and members of this group display potent *in vitro* cytotoxicity against cancer cell lines.[80–84] A common theme is the prevalence of the α-L-rhodinose-(1→3)-β-D-olivose and β-D-olivose-(1→4)-β-D-olivose repeat units within the oligosaccharide chains followed by chain termination with β-D-olivose (**53**). A notable distinction of landomycins K and L is the alternative termination of the saccharide chain with α-L-rhodinose (**44**). Additional members of sub-class I (landomycins F–J) have been generated *via* strain engineering where H and J stand out as among the only monosaccharide and trisaccharide-substituted members, respectively.[85–87]

For subclass II, landomycins M–Z have been isolated from a combination of native and engineered bacterial hosts.[88–90] Similar to sub-class I, a common glycosyl theme is the prevalence of β-D-olivose-3-1-α-L-rhodinose and β-D-olivose-4-1-β-D-olivose repeat units followed by chain termination with β-D-olivose (**53**). In contrast, in certain members of sub-class II (such as landomycins C, X–Z), β-D-olivose has been replaced with its corresponding 3-deoxy analog β-D-amicetose (**48**). A comparison of the *in vitro* cancer cell line cytotoxicities displayed by members within sub-class I and II revealed the aglycon C6 and C11 hydroxyls as important for activity and the saccharide length to also modulate potency. Specifically for the latter, the most active landomycins were those lacking sugars (*e.g.*, landomycinone, tetrangomycin, or tetrangulol) and those appended by penta- or hexasaccharide chains (*e.g.*, landomycins A and B). Based upon this comparison, it was proposed that the oligosaccharide-substituted landomycins and their sugar-free congeners may function *via* distinct mechanisms.[89,90]

Members of sub-class III also display notable *in vitro* cytotoxitity against representative cancer cell lines and include the atramycins,[91] brasiliquinones[92–94] and TAN-1085.[95–97] While the regiospecificity of glycosylation (aglycon C-8-glycosylation) of atramycins and brasiliquinones is reminiscent of that described for sub-classes I and II, the C-6 glycosylation of TAN-1085 stands out as an exception among tetrangomycin-type angucyclines. The brasiliquinones are unique among tetrangomycin-type angucyclines as they are the only members isolated from a non-*Streptomyces* strain (*Nocardia brasiliensis*) and the only members with glycosides reported to contain α-L-ristosamine-based sugars (**45**). These latter metabolites were active against Gram-positive bacteria (including Mycobacterium) and multiple drug-resistant P388/ADR tumor cell lines.

3.2. Aquayamycin-type (saquayamycin and urdamycin analogs)

C-9 *C*-glycosylation is a common signature among both the saquayamycin-type and urdamycin-type angucyclines and the main structural divergence stems from C-3 (saquayamycins) or C-12b (urdamycins) *O*-glycosylation. In addition to saquayamycins,[98–104] other structurally related saquayamycin-type bacterial metabolites include moromycins,[105] vieneomycins,[104,106,107] PI-080/083/085/087,[108,109] grincamycins,[110,111] Sch 47554/47555,[112,113] and amicenomycins (Fig. 9).[114] In addition to potent antibacterial activity and *in vitro* cytotoxicity against cancer cell lines, other activities noted among this broad group of metabolites include antifungal activity, and inhibition of platelet aggregation, UDP-GlcNAc enolpyruvyl transferase (EPTase) and inducible nitric

oxide synthase (iNOS). Many saquayamycin-type members have also been demonstrated to be efficacious in standard murine xenografts and, at least in some cases, to be reasonably well-tolerated (*e.g.*, the acute IP LD_{50} of the potent antibacterial amicenomycin *A* = 100.0 mg kg^{-1}).[114]

Only ten distinct monosaccharides (β-D-olivose, **53**; α-L-rhodinose, **44**; β-L-rhodinose, **169**; α-L-aculose, **54**; α-L-cinerulose, **51**; α-L-rednose, **50**; α-L-oliose, **49**; α-L-amicetose, **97**; β-D-amicetose, **48**; β-D-oliose, **47**; β-L-amicetose, **309**), have been observed among the saccharide constituents of saquayamycin-type bacterial natural products. Of these, only four (β-D-olivose, **53**; β-D-amicetose, **48**; α-L-rhodinose, **44** and β-L-rhodinose, **169**) have been found as *C*-glycosides where β-D-olivose (**53**), α-L-rhodinose, (**44**) and the β-D-amicetose (**48**) enantiomer α-L-amicetose (**97**) were also noted among *O*-glycosides. With respect to general trends, β-D-olivose (**53**), α-L-rhodinose, (**44**) and, to a lesser extent, α-L-amicetose (**97**) and α-L-oliose (**49**), predominate as the 'internal' sugars of appended oligosaccharides within this series wherein uniquely oxidized sugars (α-L-aculose, **54**; α-L-cinerulose, **51**; α-L-rednose, **50**) predominate among the terminal 'capping' sugars. Glycosidic bonds within the corresponding oligosaccharides extend from either C-3 or C-4 in β-D-olivose (**53**), C-4 of β-D-oliose (**49**), and the single C-4 hydroxyl group within rhodinose, (**44**/**169**) and amicetose (**48**/**97**/**309**). Among the 'capping' sugars, the terminal α-L-aculoside (**54**) was reported to convert to the corresponding α-L-cineruloside (**51**) during silica gel chromatography raising the question of whether this latter sugar is artifactual rather than a biosynthetic product. The aminated α-β-unsaturated ketosugar α-L-rednose (**50**) in saquayamycins H and I stands out as particularly unique and this sugar was found to contribute to enhanced *in vitro* cytotoxicity against certain cancer cell lines.[103]

Urdamycins differ from saquayamycins based upon their distinct regiospecificity of glycosylation (C-9 and C-12b of the angucycline core; Fig. 10). In addition to the numerous natural[115–119] and engineered urdamycins,[120–125] members of this subclass include the kerriamycins,[126] the N05WA963 series[127] and the urdamycin BA-12100 set of metabolites,[77,128] all of which derive from *Streptomyces*. Members of this sub-type are best known for their anti-proliferative properties against various cancers where C-9 C-trisaccharyl-substituted analogs are generally more potent. Six distinct monosaccharides (β-D-olivose, **53**; α-L-rhodinose, **44**; α-L-aculose, **54**; α-L-cinerulose, **51**; β-D-rhodinose, **56**; and β-D-kerriose, **55**) have been observed among the saccharides of urdamycin-type bacterial natural products with latter (β-D-kerriose, **55**) unique to this sub-type of aquayamycin-type angucyclines. Of these, only three (β-D-olivose, **53**; α-L-rhodinose, **44**; and β-D-rhodinose, **56**) have been found as C-9 *C*-glycosides where the predominant substitution at C-9 is comprised of α-L-rhodinosyl-(1→3)-β-D-olivose disaccharide (**III**, Fig. 10). In most members, this disaccharide is further capped by one of four monosaccharides (β-D-olivose, **53**; α-L-aculose, **54**; α-L-cinerulose, **51**; or β-D-kerriose, **55**). Urdamycins M, R, S and 12*b*,4′-di-urdaderhodinosyl-urdamycin S serve as the exception in this regard wherein each bear distinct C-9 *C*-rhodinosyl-based disaccharides.

3.3. Other related aquayamycin-type angucyclines

In addition to the above described angucyclines, a number of additional miscellaneous angucyclines have been reported and are organized herein based upon the regiospecificity of glycosylation. Angucyline C-1 or C-2 glycosylation is relatively rare with the benzanthrins from *Nocardia*,[129,130] pseudonocardones from *Pseudonocardia* (associated with the fungus-growing ant *Apterostigma dentigerum*)[131] and P371A1/A2 from *Streptomyces*[132,133] as the only representative bacterial metabolites within this subset. Members display variant activities including antibacterial, antiplasmodial, and/or cancer cell line cytotoxicity as well as inhibition of gastric acid secretion. Sugars employed in C-1-*O*-glycosides within this series include α-D-boivinose (**57**), β-L-rhodosamine (**67**), β-L-angolosamine (**66**), and a β-hexuronic acid moiety (**72**, absolute stereochemistry not determined). In contrast, glycosylation at C-2 is in the form of *C*-glycosylation with β-D-angolosamine (**59b**) as the sole sugar represented. P371A1/A2 also contain a C-9 *C*-trisaccharyl moiety (**V**, Fig. 11) initiating with the typical angucycline C-9 *C*-β-D-olivose (**53**) modified at C-3′ with a dideoxy branched β-D-mycarose (**64**) which is capped at C-4′ with a notably unique 4′-ureido tetradeoxysugar 4′-amino-4′-deoxy-β-D-amicetose (**63**).

Angucycline glycosylation at C-4a, C-5 or C-12b is also relatively rare. Bacterial metabolites representing C-4a-*O*-glycosides include the JBIR series of metabolites from *Streptomyces*,[134] and the rhodonocardins from *Nocardia*[135] where the sugars employed include α-D-glucose (**18**), α-L-rhodosamine (**70**) and α-L-oliose (**49**) and, in the case of the JBIR series, the C-4a-appended sugar is further substituted at C-4′ by α-D-oliose (**71**). This latter set of metabolites also contains the typical angucycline C-9 *C*-glycosidic β-D-olivose (**53**). The rhodonocardins, and the structurally-related BE-7585A from *Amycolatopsis*,[136] also carry the rare sugar 2′-thio-α-D-glucose (**61**) at C-5, connected as a typical *O*-glycoside in rhodonocardins or *via* an unsual thioether bond at C-2′ of the thiosugar (which is part of a ‘head-to-head’ α-D-glucose-containing disaccharide, **18**) in BE-7585A. In addition, rhodonocardin A and BE-7585A contain the C-12b-*O*-glycosidic α-D-rhodinose (**58**). Mayamycin from a marine *Streptomyces*[137] (unique among angucyclines as the only C-5 *C*-glycosyl member) contains *N*-desmethyl-β-D-angolosamine (**59a**) as the C-5 sugar. Grecocyclines from *Streptomyces*,[138] the other C-5-*O*-glycoside member within this subset, contains a C-5-appended *O*-4-*epi*-α-L-tolyposamine (**60a**) and a C-9 *C*-disaccharyl α-L-rhodinosyl-(1→4)-α-L-rhodinose moiety (disaccharide **I**, Fig. 11). The remaining C-12b-*O*-glycosides within this subset, sakyomicins from *Nocardia*,[139] contain α-D-rhodinose (**58**) at the C-12b-position reminiscent of rhodonocardin A and BE-7585A. Members within this cumulative subset have been reported as cytotoxic against representative cancer cell lines, to display antibacterial activity (including for antibiotic resistant strains) and as protein tyrosine phosphatase 1B and thymidylate synthase inhibitors.

Saccharothrixmicines A and B from a marine *Saccharothrix*,[140] represent the only angucycline C-8 and C-7 *O*-glycosides, respectively. Both metabolites contain the same sugar, α-L-6-deoxyaltrose (**62**), and were reported to display antifungal activities *in vitro*.

As with angucyclines discussed within preceding sections, C-9 *C*-glycosylation is a predominate modification among members described herein and include naturally-occurring

simocyclinones,[141–144] capoamycin,[145] dioxamycin,[146] MK844-mF10,[147] fradimycins,[148] frigocyclinone,[149] balmoralmycin,[150] and marmycins[151] as well as the engineered landomycin–urdamycin hybrid metabolite 9-*C*-D-olivosyl-tetrangulol.[152] With the exception of marmycin (produced by a marine actinomycete), all other metabolites within this grouping are *Streptomyces* metabolites. In addition to the the typical β-D-olivose (**53**), three additional sugars are represented as C-9-*C*-glycosides among members within this subgroup including β-D-amicetose (**48**), 3′/4′-*epi*-α-L-vancosamine (**65**) and the rare aminodeoxysugar α-L-ossamine (**60b**). In contrast to many previously discussed C-9-modified angucyclines (which contain C-9 *C*-oligosaccharyl modifications), the C-9 *C*-glycosylation patterns within this subgroup are limited to monosaccharides. Typically within this subgroup, β-D-olivose (**53**) and β-D-amicetose (**48**) is further acylated at C-3′/4′ with, in many cases, uniquely functionalized lipids which, in some cases (*e.g.*, simocyclinones), is further conjugated to an aminocoumarin. A notable standout within this series is the unique C-8/C-9 ring fusion that occurs from an additional bond between the angucycline C-8 and C-3′-amine 3′/4′-*epi*-α-L-vancosamine (**65**) within the marmycins. In addition to reported cancer cell line cytotoxicity and antibacterial activities, other reported activities of members of this subgroup include differentiation-inducing activity on myeloid leukemia cells (M1) and inhibition of protein kinase C-α (PKC-α).

3.4. Jadomycin- and gilvocarcin-types (jadomycins, ravidomycins, chrysomycins and gilvocarcins)

The gilvocarcin-type aryl-*C*-glycosides[79] contain a number of naturally-occurring (gilvocarcins,[153–162] polycarcins, BE-12406A/B,[163–165] ravidomycins[166–171] chrysomycins[172] and virenomycins[173,174]) and engineered (gilvocarcins and polycarcins)[172,175–177] *Streptomyces* metabolites wherein the signature *C*-glycosylation occurs at C-4 (Fig. 12). The monosaccharides found among naturally-occurring C-4-*C*-glycosides of this class include β-D-fucofuranose (**75**), α-L-rhamnose (**46**), β-D-ravidosamine (**78**), β-D-virenose (**77**), the 4′-keto analog of β-D-virenose (**79**) and a C-3′-branched analog of β-D-fucofuranose (**80**), wherein the presence of β-D-fucofuranose stands out as relatively rare among bacterial secondary metabolites. This set has been expanded to also include 4′-hydroxy-β-D-fucofuranose (**76**) and β-D-olivose (**53**) *via* metabolic engineering.[172,175,176] Some members of this subclass also contain a C-12-*O*-α-L-rhamnose (**46**) substituent. These metabolites are generally known as anticancer antibiotics where subtle differences within the appended sugar were found to improve the perceived therapeutic index (potency *versus* general toxicity).

The jadomycins from *Streptomyces* are angucyclines that contain a nitrogen at position 6 within ring B (Fig. 12).[79,178–181] Naturally-occurring jadomycins are C-8-*O*-glycosides of α-L-digitoxose (**68**) and an engineered variant that led to a replacement of this sugar with 6′-deoxy-α-L-altrose (**62**) has been reported.[180] The naturally-occurring B ring *Streptomyces* metabolite phenanthroviridin and is alternatively conjugated at C-1 to α-D-ristosamine (**69**).[182,183] Jadomycins display a range of bioactivities, including anticancer cytotoxicity, antimicrobial, anti-viral, and inhibition aurora-B kinase.

4. Anthracyclines, tetracyclines, quinones and tricyclines

4.1. Anthracyclines

According to 1963 Hans Brockman definition, anthracyclines are defined as red to orange natural/synthetic dyes with a skeleton of 7,8,9,10-tetrahydro-tetracene-5,12-quinone decorated with mono-, di-, tri-, tetra- and/or pentasaccharide side chains (Fig. 13, subclass **I**).[184] As exemplified by the early protypical members daunomycin (discovered in 1964)[185] and doxorubicin (adriamycin, discovered in 1969)[186,187] used to successfully treat cancer for nearly four decades, anthracyclines display a range of bioactivities of pharmaceutical utility.[188] To date,[18] 407 bacterial-derived anthracycline glycosides have been reported from a range of bacteria including, but not limited to *Streptomyces*, *Micromonospora*, *Actinomadura*, *Nomadura Actinosporangium, Chaetomium*, *Actinoplanes*, *Ampullariella* and *Nocardia*. For the scope of this discussion, members are classified into five sub-classes **I** (365 compounds), **II** (3 compounds), **III** (6 compounds), **IV** (9 compounds), and **V** (24 compounds), based upon aglycon structural divergence (Fig. 13). Cumulatively, anthracycline glycosides integrate 51 structurally distinct monosaccharide units (Fig. 14) incorporated within the anthracycline-appended mono-, di-(15 variations, **D1–D15**; Fig. 15), tri- (35 variations, trisccharides **I–XXXV**; Fig. 16), tetra- (eight variations, **T1–T8**; Fig. 17), and pentasaccharides (two variations, **P1** and **P2**; Fig. 18). While the predominant regiospecificity of anthracycline glycosylation occurs at C-7 and/or C-10, C-1-, C-3-, C-4-, and/or C-9-glycosylation (as well as C-4′-glycosylation in subclass V) has been observed (Fig. 13). Also, both *O*- and *C*-glycosides have been reported, the latter of which is less prevalent and mainly occurs at C-3 in sub-class **IV** (reminiscent of angucyclines and/or pluramycins).

Sub-class **I** contains 365 anthracycline *O*-glycosides (and a few *C*-glycosides) bearing variant carbohydrate substitution ranging from mono- to pentasaccharides. C7- and/or C10-*O*-glycosylation predominates (358 compounds) within sub-class **I** anthracyclines including D-788,[189–193] oxaunomycins,[193] doxorubicins,[194,195] spartanamicins,[196] daunorubicins,[194,195] daunomycins,[185,197,198] aclacinomycins (aklavins),[199–205] rhodomycins,[184,206–210] betaclamycins (and CG-21-C, CG1-C, CG21-B analogs),[211–213] auramycins,[214–219] MA-144-U and G analogs,[220–222] steffimycins,[223–226] baumycins,[227,228] pyrrocyclines,[222] rubeomycins,[229,230] pyrromycins,[231] oblemycins (cytorhodins),[232,233] sulfurmycins,[214–219] cinerubins,[188,234–236] mutactimycins,[237–239] alldimycins,[233,240] nocardicyclins,[241] violamycins,[242] ditrisarubicins,[243] aranciamycins,[244–247] A447A~D1,[248] ciclamycins,[249] isoquinocycline A,[188,250] kosinostatin (quinocycline B),[251,252] isoquinocycline B,[252,253] micromonomycin[254] and other representative anthracyclines.[100,188,201,202,211,229,255–263] Less common sub-class I *O*-glycoside regioselectivity was observed at C-1 (mutactimycin PR[237,238]), C-4 [histomodulin,[264] komodoquinone A[265,266] and 4-*O*-(β-D-glucopyranosyl)-ε-rhodomycinone[267]], and C-9 (cytorhodins X and Y).[188,268] In addition to the mono- to tetrasccharides observed, two pentasaccharide-containing members were reported [roseorubicin A (pentasaccharide **P1** at C-10; Fig. 18)[229] and β-rhodomycin-Roa2.deofuc.rod3 (pentasaccharide **P2** at C-7, and **70b** at C-10; Fig. 14 and 18)[269]] where roseorubicin SAR revealed improved potency to correlate

with increase oligosaccharide length.[229] Caeseorhodomycin[256] is distinguished among this series as a C-1-*C*-glycoside (**70c**; α-L-rhodosamine).

A reduced ring-C is the distinguishing feature of sub-class **II**. Only 3 metabolites (antibiotics W, Y and Z) fall within this sub-class, all of which are C-7-*O*-glycosides bearing α-L-daunosamine (**70a**; Fig. 14).[270] Sub-class **III** is unique by virtue of the C-10-keto ring D and contains only 6 metabolites, all of which are C-7-*O*-glycosides bearing α-L-sugars [2′-OMe-α-L-rhamnose (**46a**) or α-L-vancosamine (**118**)]. Sub-class **III** members include steffimycin A (**46a** at C-7),[223] 5-iminoaranciamycin (**46a** at C-7),[247] aranciamycin (**46a** at C-7),[244] aranciamycin anhydride (**46a**, R^3 = fragment **E**; at C-7),[245] and nocardicyclins A (**118** at C-7) and B (**118** at C-7).[241] The 7 glycosidic sub-class **IV** members contain a fully aromatized tetracycline backbone with, typically, C-3-*C*-glycosylation, and include galtamycin(one)s,[100,271,272] balmoralmycin (β-L-olivose, **100**; at C-3),[272] tetracenoquinocin (**46a** at C-7),[247] quanolirones I (trisaccharide **XXXII**, at C-3; Fig. 16) and II (disaccharide **D15**, at C-3; Fig. 15),[273] and the two D-ring-reduced metabolites N05WA963C[127] and grincamycin E[111] (both bearing the C-3-*C*-trisaccharide **XXXIII**). Finally, sub-class **V** members are differentiated by the presence of a fused ring A-sugar (connected 1-/1′-*O*- and 2/5′-*C*-) where the carbohydrate unit is comprised of α-L-mycaminose (**74a**) or 4′-*epi*-α-L-mycaminose (**312**). The 24 metabolites that fall within this sub-class include nogalamycin,[274–276] nogamycin,[229] nogalarol,[276,277] 7-*O*-methylnogalarol,[276] 7-con-*O*-methylnogarol,[229] arugorol,[277,278] arugomycin,[277–279] decilorubi-cin,[280–283] avidinorubicin,[284] respinomycins,[285–287] cororubicin,[288] and viriplanin and viriplanol analogs.[289,290] Additional C-4′ and/or C-7-*O*-glycosylation is observed with sugars **74a** and **312** and/or various lengths of mono- to tetra-saccharide side chains.

From a global perspective (Fig. 14), anthracyclines present several unique carbohydrates. For example, C-3′- and C-4′-branching is prevalent as exemplified by **101–103**, **105**, **107–110**, **112**, **118**, **120**, **122**, and **123**. Additionally, nitroso (**101**), hydroxylimino (**113**) and nitro (**102**, **105**, **107**, **120**, **121**) sugars are quite common. Unsaturated (**50**, **54**, **119**) and ketosugars (**50**, **51**, **54**, **98**, **117**, **119**) are also observed and the C-3′-*N*/C-4′-*O*-macrocylic substitution of **70d** is uncommon. The C-3′-disubstitution pattern of **120** 3′-methoxy-3′-nitro-2′,6′-dideoxy-α-L-talose in trisaccharide **XXXV** of 301-C[291] is of particular note as unprecedented carbohydrate functionality. In general, glycosylation is considered to be important to bioactivity in most cases studied. For example, Matsuzawa and Oki reported SAR on ~100 anthracyclines where they found the presence of an aminosugar (or amine-substituted aglycon) to be important and increased potency to also correlate with increased saccharide chain length.[229]

4.2. Hibarimicins

Hibarimicins are distinguished by their highly oxidized naphthyl-naphthoquinone aglycon which derives biosynthetically from dimerization of undecaketide-based precursors (Fig. 19).[292] To date, 11 herbimycin *O*-glycosides have been reported from *Microbiospora* where the regiospecificity of glycosylation is restricted to C-7/7′ and C-9/9′ (Fig. 19).[18,293–299] Glycosylation at these positions is composed of mono- and/or disaccharide side chains (Fig. 19) where five distinct sugar residues were observed including α-L-digitoxose (**129**), β-D-

amicetose (**48**), 4′-*C*-acetyl-2′,3′,6′-trideoxy-α-L-gulose (**123**), 4′-*C*-acetyl-2′,3′,6′-trideoxy-β-L-gulose (**130**) and α-L-4-*C*-acetyl-2,6-dideoxy-*xylo*-hexopyranosyl (**103**). In all cases, the C-7/C-7′-sugar was α-L-digitoxose (**129**) and C-9-/9′-sugar was β-D-amicetose (**48**), the latter of which in certain analogs was further 4′-*O*-glycosylated (**48**, **103**, **123** or **130** to present disaccharides **I–IV**, Fig. 19). HMP-P4 and HMB-Y6 are metabolites produced by *Microbiospora* engineered mutants.[295] Hibarimcins are selective *src* tyrosine kinase inhibitors and do not inhibit protein kinase C.[296] They display potent *in vitro* cytotoxicity against cancer cell lines and moderate Gram-positive antibacterial activity.[296]

4.3. Tetracycline-type antibiotics

Tetracyclines are tetracyclic polyketide-based broad spectrum antibiotics with a rich history that includes the discovery and implementation of a number of clinically important tetracycline-based drugs, extensive litigation beginning in the 1950's over tetracycline intellectual property and price fixing among major pharmaceutical companies of the time (Pfizer, American Cyanamid, Bristol-Myers) and a more recent discovery suggesting tetracycline 'use' dates back possibly to before 400–500 A.D. There are 26 glycosylated tetracyclines reported to date including the cervimycins,[300–302] HKI10311129[303] dutomycin,[304,305] polyketomycin,[306–308] elloramycins,[176,309,310] tetracenomycins,[176,311,312] TAN-1518 A, B and X (also known as SF-2575),[313–315] and dactylocyclines,[316–319] the latter of which being the only member of non-*Streptomyces* origin (*Dactylosporangium*). Regiospecificity of tetracycline glycosylation is limited to C-4, C-8, C-11 and C-12a where all members with the exception of one subgroup (the C-8-*C*-glycosidic TAN-1518 analogs) are *O*-glycosides.

Cervimycins A–D are glycosylated at C-4 and C-12a with tetra-[consisting of one β-D-amicetose (**48**) and three α-L-rhodinoses (**44**), tetrasaccharide **III**] and disaccharide (β-D-amicetosyl-(1→4)-β-D-amicetose, disaccharide **I**) moieties, respectively (Fig. 20).[300–302] The terminal rhodinose (**44**) of tetrasaccharide **III** is further modified with a 4′-*O*-dimethylmalonyl/or monomethylmalonyl ester. The structurally similar HKI10311129[303] displays an identical glycosylation pattern but lacks the terminal rhodinose ester modification while the related dutomycin and polyketomycin are C-4-*O*-glycosides bearing an a α-L-4′-*epi*-mycarosyl-(1′→4′)-β-D-amicetose (disaccharide **II**) but lacking C-12a glycosylation.[304–308] In these latter metabolites, the terminating mycarose is further modified *via* 4″-*O*-esterification and both have been noted as anticancer cytotoxins, antibiotics while dutomycin was also reported as a DNA methyltransferase inhibitor. Elloramycins are cytotoxic C-8-*O*-glycosides bearing *per*-methyl-α-L-rhamnose (**46**) where cytotoxicity, in this case, is attenuated *via* the presence of the sugar.[176,309,310,320] The corresponding tetracenomycin C-8-*O*-glycosides from strain engineering include substitution with α-L-digitoxose (**68**), β-D-glucose (**104**), 4′-keto-α-L-olivose (**126**), α-L-olivose (**184a**) and α-L-oleandrose (**184b**).[176,311,312] Dactylocyclines A and B from *Dactylosporangium* sp. (ATCC 53693)[316–319] are C-11-*O*-glycosides substituted with α-L-evernitrose (**127**) and its hydroxyl-amino congener **128** (monosaccharides more commonly associated with the orthosomycin everninomicin, Section 14.1).[321] Intriguingly, removal of the dactylocycline sugar improves Gram-negative antibacterial activity.[318] Finally, the naphthacenecarboxamides TAN-1518 A, B and X (also known as SF-2575) are C-8-*C*-

glycosides of β-D-olivose (*C*-**53**).[313–315] TAN-1518 A and B have been noted as topoismerase I inhibitors while TAN-1518 X displayed both Gram-positive antibacterial activity and *in vitro* and *in vivo* anticancer activity.[314] The structural elucidation of the TAN-X *C*-glycosyltransferase SsfS6 was recently reported as one among only a few *C*-glycosyltransferases to be structurally characterized to date.[322]

4.4. Aureolic acids and related tetracyclines

Mithramycin[314] is the prototypical member of the aureolic acid family of antitumor antibiotics that also includes chromomycins,[323] olivomycins,[324–326] durhamycins,[327] SR1768A,[328] UCH9,[329,330] chromocyclomycin,[325,331] 02-3D and 02-3G,[332] and variamycins[333,334] from *Streptomyces* and *Actinoplanes* as well as several other analogs (*e.g.*, ketopremithramycins and ketomithramycins)[335] generated by pathway engineering.[323–326,331,333,336–340] The defining structural feature of aureolic acids is their tricyclic polyketide architecture and, to date, 45 glycosylated analogs have been reported from bacteria. The predominant regiospecificity of glycosylation among naturally-occurring aureolic acids is C-2-and/or C-7-*O*-glycosylation with two family members [aureolic acid *C*-glycoside I (*C*-**47** at C-6) and aureolic acid *C*-glycoside II (*C*-**53** at C-6); Fig. 21] displaying atypical C-6-*C*-glycosylation. For the scope of this discussion, members have been divided into subclasses **I–III** based upon aglycon distinctions where the tetracyclic subclass **II** are primarily considered as biosynthetic precursors and subclass **III** (pillaromycin A)[341] also displays similarity to **II**.

Family members are glycosylated with mono-, di-, tri-, or tetrasaccharide side chains (Fig. 21). Sugars found as monosaccharide substitutions include the uncommon C-6-*C*-glycosidic β-D-oliose (*C*-**47**) and β-D-olivose (*C*-**53**)-substituted aureolic acid *C*-glycosides I and II[342] and the unusual C4′-branched sugar 4′-*C*-hydroxyethanone-2′,3′,6′-trideoxy-α-L-gulose (**132**, pillaromycin A).[341] Six different disaccharide (**D1–D6**) and trisccharide (**I–VI**) variations are represented among family members, which are comprised of 10 different distinct monosaccharide units where β-D-oliose (**47**) and β-D-olivose (**53**), are the most predominant. Other saccharides employed include β-D-amicetose (**48**), β-D-mycarose (**64**), α-D-oliose (**71**, R = H; α-D-chromose, R = CH_3), β-D-digitoxose (**131**), 4′-*C*-hydroxyethanone-2′,3′,6′-trideoxy-α-L-gulose (**132**), 4′-keto-β-D-mycarose (**133**), 4′-hydroxy-β-D-olivose (**134**), and 3′-*epi*-αL-mycarose (**195**, α-L-chromose B). Tetrasaccharide substitution is uncommon with UCH-9 and durhamycin A as the only C2-tetrasaccharide-bearing examples [β-D-olivosyl-(1→3)-β-D-olivosyl-(1→3)-β-D-oliosyl-(1→3)-β-D-olivose, tetrasaccharide **T1**].

Aureolic acids display potent Gram-positive antibacterial and anticancer activities. Mithramycin (plicamycin) was originally approved for the treatment of cancer however, off-target toxicities, potentially deriving from the ability of mithramycin to target the ubiquitous transcription factor Sp1, limited clinical use. Recent studies revealed mithramycin to selectively target the EWS/FLI1 transcription factor fusion found within Ewing's sarcoma, renewing interest in mithramycin and development of less toxic, more selective analogs.[343,344] Other activities noted among aureolic acids include inhibition of *mdr1* gene

expression and viral Tat transactivation inhibition. Intriguingly, pillaromycin A, a potent anticancer cytotoxin from this family, has been noted to display lower overall toxicity.[341,345]

4.5. Pyranonaphthoquinones

Pyranonaphthoquinones contain a naphtho[2,3-*c*]pyran-5,10-dione core where some members present an additional γ-lactone ring, or corresponding open ring carboxylic acid, fused to the dihydropyran ring (Fig. 22). Pyranonaphthoquinone antibiotics isolated from various bacterial strains (including *Streptomyces*, *Actinomycete*, and alkaphilic *Nocardiopsis*) exhibited antibacterial, antifungal, antiviral, as well as cytotoxic activities.[346] To date, 37 bacterial pyranonaphthoquinone glycosides have been reported, all of which contain single *C*-glycosidic sugars consisting of α-L-rhodinose (**44**), β-D-ribofuranose (**25**), β-D-angolosamine (**59**), α-D-forosamine (**81**), 3′-amino-*N*′,*N*′-dimethyl-*N*-oxido-2′,3′,6′-trideoxy-β-D-glucose (**82**), unusual cyclized sugars **I** (**83**) and **II** (**84**) or sugar mimetics **I** (**85**) and **II** (**86**) (Fig. 22). For the scope of this discussion, this family is further divided into subclasses **I–III** as further described below where the C6-C1′/C7-C5′ glycoside fusion found in Sch38519 from *Thermomonospora* is a notable outlier. This latter metabolite was reported to inhibit thrombin-induced aggregation of human platelets.[347,348]

Sub-class I is distinguished by a single C-8-*C*-glycosidic substitution and includes lactoquinomycins,[349–352] menoxymycins[353] exfoliamycins,[354,355] mederrhodins,[356] alnumycin (also known as K1115 B1 and K1115 A),[357,358] K 1115 B2,[355,356] and EI-2346.[359,360] Of the four sugars found among sub-class **I** members (**59** or **25** or **82** or **83**), *N*-oxide **82** (menoxymycin A) is unique.[353] The *C*-ribosyl **25** (exfoliamycins) was also observed to rearrange to unusual dioxane **83** (alnumycin,[361] K 1115 B2,[355,356] and EI-2346[331,332]).[362] Sub-class **II** members are distinguished by the 1,7-dioxaspiro-[5.5]undecane ring system (**85** or **86**), the C-1-spiroketal fused moiety of which, while likely polyketide-based, serves as a carbohydrate mimic.[363,364] Of the 12 griseusins mainly produced by *Nocardiopsis*,[337–343,365–371] the C-3′-*O*-α-D-forosaminyl-(+)-griseusin A is the only *O*-glycosylated member. Finally, sub-class **III** contains a C-7-*C*-glycosidic linkage where the corresponding sugar **84** is also fused to the pyranonapthoquinone core *via* a C-8-C-4′ bond to provide a bicyclic structure (Fig. 22). Eleven sub-class **III** members have been reported including granatomycins, granaticins, dihydrogranatirhodins, 4-deoxy-4-*S*-(*N*-acetylcysteinyl)granaticinic acid, MM 44785 and MM 447876.[256,346,372,373] Sugar **84** in three granaticin analogs [dihydrogranaticin B (MM 44325), MM 44785 and granaticin B (MM 44326)] is further C-3′-*O*-modified with α-L-rhodinose (**44**).

4.6. Benzoquinones related antibiotics

Napthoquinones represent a large class of bacterial natural products, the structural signature of which is a bicyclic aromatic-1,4-benzoquinone fused core structure 1,4-napthoquinone. Also included within this section are metabolites related to this core structure where the central benzoquinone has been reduced and/or further modified. The predominant regiospecificity of glycosylation across this series is glycosylation of the fused aromatic moiety either at the α- or β-carbon in relation to the ring junction or glycosylation of the quinone core (the precise numbering of which, in all cases, varies depending upon the specific aglycon, Fig. 23.

A series of α-aromatic *O*-glucuronides including julichrome Q_6 glucuronide[374] 671-C, genoketide A2, chrysophanol glucuronide and prechrysophanol glucuronide have been reported as metabolites of *Streptomyces*.[375] All share a common C-4-β-D-glucuronic acid (**72**) substitution. Julichrome Q_6 glucuronide was reported as the first monomeric member of the julimycin-B analogs, and displayed moderate unselective cytotoxicity against human tumor cell lines.[374] Genoketide A2 and prechrysophanol glucuronide were reported to inhibit the lymphoma cell proliferation *in vitro*.[375]

The β-aromatic glycosides include halawanones,[376] fridamycins/himalomycins,[77,377] adxanthromycins[378–382] and grecoketides[383] from various *Streptomyces*. Halawanones C and D, two tricyclic quinone-containing metabolites, are C-7-*O*-glycosides (β-D-olivose, **53**).[376] Fridamycins A (also known as vineomycinone B2), B, and D, and the structurally related himalomycins A and B,[377] are angucycline-related antitumor antibiotics that likely arise from a cleavage of the corresponding C-12b/C-l bond to afford the substituted tricyclic angucyclinone lacking ring-**A**.[77,377] Similar to the saquayamycins (Section 3.2), they are C-3- or C-9-*O*-glycosides bearing mono- or disaccharides (**IV–VI**) comprised of β-D-olivose (**53**), 2′,6′-dideoxy-β-D-altrose (**303**), α-L-rhodinose (**44**), α-L-cinerulose (**51**) and α-L-amicetose (**97**).[77,377,384] Himalomycins A and B along with fridamycin D exhibited strong antibacterial activity against Gram-positive and Gram-negative bacteria.[377] The two naphthoquinones grecoketides A and B are both disaccharyl-containing C-6-*C*-glycosides of the grecoketidone aglycon that differ in disaccharide composition.[383] Specifically, the C-6-*C*-glycosyl moiety of grecoketide A is α-L-rhodinose (**44**) while that in grecoketide B is β-D-rhodinose (**56**). In both, the rhodinose is further C-4′-*O*-glycosylated with α-L-rhodinose (**44**).[383] Finally, adxanthromycins A and B are unique dimeric peroxo-anthrone C-3-*O*-glycosides bearing α-D-galactose (**286**) and α-D-galactosyl-(1′→3′)-α-D-galactose (disaccharide **I**), respectively.[379–381] These compounds are reported as inhibitors of ICAM-1/LFA-1-mediated cell adhesion.[378–381]

Glycosides of the core quinone include halawanones A and B,[376] substituted naphthalene-1-ones,[382] lactonamycins[385,386] and lomaiviticins[387] from *Streptomyces* and *Micromonospora*. Halawanones A and B are structurally related to other isochromane quinone antibiotics from *Streptomyces* (including exfoliamycins, granaticins and griseusins; see the lactoquinomycins, Section 4.5) and, as C-8-*C*-glycosides (2′-keto-β-D-oliose, **325**) of the quinone core are unique among this class.[376] A product of a mutant *Streptomyces*, 4β, 8-dihydroxy-3α-*O*-(α-glucopyranosyl)hydroxymetyl-4α-methyl-1,2,3,4-tetrahydron-naphthalene-1-one is a simple side chain C-9-*O*-α-D-glucoside(**44**).[382] Lactonamycin, an antibiotic active against Gram-positive bacteria including MRSA and VRE, consists of a hexacyclic C-5a-*O*-glycoside bearing α-L-rhodinose (**44**).[385,386] In the related lactonamycin Z, rhodinose is replaced by α-L-digitoxose (**68a**).[388] This latter compound displayed potent antiproliferative activity against gastric adenocarcinoma cell lines. Finally, lomaiviticins A and B are two unique diazobenzofluorene *O*-glycosides produced by *Micromonospora*.[387] Both are C4/4′-*O*-glycosides of β-D-pyrrolosamine (**213**), a sugar previously identified in pyrrolosporin A.[389] Lomaiviticin A is further C-3/3′-*O*-glycosylated with an α-L-oleandrose (**184**), presumably preventing the tetrahydrofuran ring fusion observed in lomaiviticin B. Diazo-containing natural products like lomaiviticins and the structurally-

related kinamycins are rare.[390,391] Lomaiviticins function as DNA-damaging agents where lomaiviticin A cleaves double stranded DNA under reducing conditions.[387,392] Both were also reported as potent antibiotics against Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus faecium*.[387]

Two metabolites display unique glycosylation patterns that fall outside the scope of those described in the preceding paragraphs namely, lemonomycin[393] and heliquinomycin[394–396] from *Streptomyces*. Lemonomycin is C-18-*O*-glycoside (4′-amino-4′-deoxy-3′-*C*-methyl-6′-deoxy-α-L-fucose; **292**) of a uniquely fused pyrrolidine-tetrahydroisoquinoline aglycon while heliquinomycin is a C-3-*O*-glycosyl rubromycin member bearing α-L-cymarose (**68b**).[394–396] A glycoside of the rubromycins/griseorhodins,[395] this metabolite was found to selectively inhibit cellular DNA replication without affecting level of chromatin-bound MCM4 or activation of the DNA replication stress checkpoint system.[394–397]

5. Benanomicins and pradimicins

Benanomicin and pradimicin analogs consist of a benzo[*a*]-naphthacene quinone conjugated to various modified aminoacids at C-15. Glycosylation within this subclass consists of mono or disaccharide side chains at C-5 and, in some cases, also C-11 of the benzoquinone nucleus (rings B and E; Fig. 24).[398–404] These compounds have excellent *in vitro* and *in vivo* activities against a wide range of fungal strains including *Candida*, *Cryptococcus*, *Aspergillus* and *Trichophyton* and also are effective inhibitors of HIV syncytium formation.[405,406] The pradamicins uniquely function as small molecule ‘lectins’ wherein antifungal activity derives from specific binding to terminal D-mannosides of the fungal cell wall while specific interactions with the *N*-glycosylation patterns of HIV-1 gp120 contribute to antiviral activity *via* inhibition of viral entry. The monomers β-D-glucose (**104**), β-D-xylose (**136**), 3′-amino-β-D-fucose (**208**), and β-D-fucose (**270**), or modifications thereof, encompass the sugars represented and SAR studies to date point the importance of both the C-15 amino acid substitution and C-5 glycosylation for antifungal and anti-HIV activities.[357] C-5-glycosidic examples include pradimicins A–E,[400,406–409] FA-1,[410] FA-2,[410] FB,[411] FH, L, FL,[412] S,[413–415] FS[411] and other analogs.[17,18,399,416–419] C-11 glycosylation occurs less frequently and is restricted to β-D-xylose (**136**) as illustrated by pradimicin T2,[420,421] 11-*O*-L-xylosyl-pradimicin H[422] and 11-*O*-L-xylosyl-pradimicin FH,[422] all of which contain C-5 mono- or disaccharide substitutions.

6. Chartarin-analogs

Chartarin analogs are divided into two main classes distinguished by the B ring oxidation state and C-5 substitution of the fused pentacyclic ring aglycon (sub-classes **I** and **II**; Fig. 25). Sixteen naturally-occurring chartarin glycosides have been reported to date as bacterial metabolites (mainly from *Streptomyces*, Fig. 25) including the chartreusins (lambdamycins),[423–433] chrymutasins,[434–436] D329C,[437] elsamicins,[438–440] and hayumicins.[441] These compounds display notable antimicrobial and antitumor activities where glyco-sylation plays a key role in improving potency, formulation and *in vivo* properties wherein aminosugar-containing variants are among the most

advantagous.[423,438–440,442–445] In all cases reported to date, *O*-glycosylation is restricted to C-10 mono-, di- or trisaccharide substitution. Four different appended modified sugars are found among existing charterin analogs [β-D-fucose (**270**), β-D-elsarose (**266**), α-D-fucosamine (also known as α-D-elsaminose, **88**), and α-D-fucose (**319**)]. Of these four sugars, D-fucose (**270**) is the most predominant with a range of C-2′-, C-3′-, and/or C-4′-*O*-methyl/acetyl-substituted, as well as the C-3′-*C*-methyl-branched (β-D-elsarose, **266**) or the corresponding α-D-fucosamine (also known as α-D-elsaminose, **88**) analogs observed.

7. Coumarins

The aminocoumarin group of antibiotics are characterized by their 3-amino-4,7-dihydroxycoumarin moiety, the microbial source for which is currently restricted to *Streptomyces*. This family of antibiotics [which includes novobiocin, isonovobiocin,[446] 2562B, clorobiocin (2562A; RP 18 631),[447,448] coumermycin A1,[449,450] coumermycin A2,[451] vanillobiocin,[452] novenamine,[453,454] 11-hydroxynovobiocin,[455] isovanillobiocin,[455] declovanillobiocin,[455] biscarbamoylcoumermycin D,[456] 3-chlorocoumarobiocin,[457] and 8′-dechloro-3-chlorocoumarobiocin[457]] function as potent bacterial DNA gyrase inhibitors and were more recently discovered to inhibit Hsp90.[458–462] To date, 84 naturally-occurring aminocoumarins have been reported from bacteria, 65 of which are glycosylated representatives.[463–467] Importantly, the 3′-carbamoylation of the appended sugar in these metabolites is critical for DNA gyrase inhibitory activity but detrimental to Hsp90 inhibitory function.[460,468,469] The scope of glycosylated aminocoumarin derivatives has been notably expanded by Heide *et al. via* metabolic engineering, mutasynthesis and chemoenzymatic synthetic methods.[456,467,470–473] It is also important to note that there are currently no examples of native bacterial coumarin/isocoumarin glycoside production.

The glycosylated aminocoumarins are classified into subclasses **I–III** based upon subtle substitution/conjugation distinctions within the core aminocoumarin (Fig. 26). From the perspective of glycosylation, subclasses **I** and **II** are markedly similar in both the regiospecificity of glycosylation (C-6 of the aminocoumarin core) and the predominate sugar employed (4′-*O*-methyl-5′-*C*-methyl-L-rhamnose, more commonly referred to as α-L-noviose, **193**). In both subclasses **I** and **II**, the core sugar moiety is further modified *via* differential acylation of the 2′-OH and/or 3′-OH with a carbamoyl, 5-methyl-pyrrole-2-carboxyl or pyrrole-2-carboxyl moiety (Fig. 26, **193**). In addition, 4′-OH methylation was observed among some members. A notable departure from the structural/biosynthetic conservation among subclass **I** members is TPU-0031-B (5′-demethyl-novobiocin) which reportedly bears the distinct sugar α-D-5′-demethyl-noviose (**267**) and, given the glycosidic conservation among the metabolites in this family, may raise questions regarding the structural assignment in this case.[474]

Subclass **III** members are structurally distinguished by their conjugated system comprised of a novobiocin-type amino-coumarin connected to an ansamycin-like moiety *via* a 3,4-dihydroxydipioolinic acid central bridge, the latter of which serves as the site of glycosylation (specifically, C-4 of the 3,4-dihydroxydipioolinate). This subclass contains two antibiotics (rubradirin[475,476] and protorubradirin[477] from *Streptomyces*) distinguished by their corresponding uniquely functionalized appended sugars [the C-3′-nitro sugar β-D-

rubranitrose (**310**) and its C-3′-nitroso-analog (**284**), Fig. 26]. As in the case of the nitro sugar-containing orthosomycins (where aminosugars with differing levels of amine oxidation have been observed, Section 14), it is expected that NDP-rubranitrose biosynthesis proceeds *via* the C-3′-nitroso-analog. Interestingly, these two sugars have also been identified in anthracycline antibiotics (viriplanins A and D, Section 4).[289,290,477]

8. Enediynes

Enediynes are a group of antibiotic anticancer compounds characterized by the presence of bicyclo[7.3.0]dodecadienediyne or bicyclo[7.3.1]tridecenediyne and this structural distinction serves as a basis for classification of family members within 9- or 10-membered subclasses, respectively.[478] As an additional signature, 9-membered enediynes are commonly associated with a stabilizing apoprotein and 10-membered enediynes have been more recently been associdated with a novel self-sacrifice resistance mechansism.[479–481] Enediynes bind the minor groove of dsDNA in a sequence/context-specific fashion which is often mediated *via* their appended carbohydrates. Subsequent reductive/nucleophilic activation initiates a Bergman or Myers-Saito cyclization, the reactive diradical intermediate of which abstracts hydrogen from the DNA backbone to ultimately afford oxidative DNA strand cleavage.[482] Out of 46 enediynes and enediyne derived compounds isolated from bacteria, 38 glycosides have been characterized (Fig. 27). Members of this family are treated separately herein based upon enediyne ring size.

8.1. 9-Membered enediynes

The glycosylated 9-membered enediynes (Fig. 27) include C-1027,[483–485] neocarzinostatin,[486–488] maduropeptin,[489] kedar-cidin,[490–492] and two putative cycloaromatized analogs (NFκB inhibiting fijiolides[493] and cyanosporasides[494]) from *Streptomyces*, *Actinomadura*, *Streptoalloteichus*, *Salinospora*, and *Nocardiopsis*. Nine-membered enediyne glycosylation regiospecificity is restricted to C-9 or C-10 of the enediyne core. With one exception (cyanosporoside), all 9-membered enediyne glycosides contain an amino sugar (C-1027 and fijiolides, 4′-deoxy-4′-dimethylamino-5′,5′-dimethyl-β-D-ribose **87**; neocarzinostatin, *N*-methyl-α-D-fucosamine **88**; maduropeptin, 4′-amino-4′-deoxy-3′-methyl-β-D-ribose **89**; kedarcidin, α-L-kedarosamine **91**) where kedarcidin is the only member containing more than one carbohydrate (an additional α-L-mycarose **90**). Interestingly, the sugar appended to cyanosporoside is a rare oxo-β-D-fucose (**92**), reflecting a potential lack of a functional keto-sugar nucleotide aminotransferase common to members of this subclass. C-3′-, C-4′- or C-5′-branched sugars are also a predominate feature among 9-membered enediynes with *N*-methyl-α-D-fucosamine **88** (neocarzinostatin) and α-L-kedarosamine **91** (kedarcidin) as the only exceptions.

8.2. 10-Membered enediynes

Glycosylated 10-membered enediyne glycosides (Fig. 28) include the calicheamicins,[495–498] esperamicins,[499–505] shishijimicins,[506] and namenamicin[507] from *Micromonospora*, *Actinomadura* and potentially unidentified bacterial symbionts. With respect to the latter, shishijimicins and namenamicin were isolated from marine ascidians but based upon their structural resemblance to bacterial counterparts they are assumed to be of bacterial origin

and therefore included herein. Among the glycosylated 10-membered enediynes, C-8 and C-12 of the enediyne core are the primary points of glycosylation (Fig. 28). Both the calicheamicins and esperamicins contain a conserved C-8 trisaccharide moeity **I** comprised of 4′,6′-dideoxy-4′-hydroxyamino-β-D-glucose (**202**), 4′-thio-2′,4′,6′-trideoxy-β-D-altrose (**94**) and 4′-amino-2′,4′-dideoxy-α-L-xylose (**95**) where, in some calicheamicins (calicheamicin α_3^{I}, LL-E33288 B, and LL-E33288 α_3^{Br}), the aminopentose is lacking.[508–511] The corresponding terminal thiosugar is 4′-*S*-methylated (esperamicins) and 4′-*S*-acylated with a modified orsellinate (calicheamicins), the latter of which is typically *O*-glycosylated (3′-*O*-methyl-α-L-rhamnose, **46**; exceptions being calicheamicin α_2^{I}, LL-E33288 B and LL-E33288 α_2^{Br}). Esperamicin contains an additional C-12-*O*-glycoside (α-L-oliose, **49**) which is further esterified at C-3′ (esperamicin A_1 series, **49a**) or C-4′ (esperamicin A_2 series, **49b**) with a modified anthranilate (Fig. 28). Shishijimicins A and C contain an alternative C-8 disaccharide **III** comprised of a branched thiosugar (6′-deoxy-4′-pyridoindolylcarbonyl-4′-*S*-methyl-4′-thio-β-D-galactose, **96**) and 4′-amino-2′,4′-dideoxy-4′-*O*-methyl-α-L-xylose (**95**)[506] while shishijimicin B contains disaccharide **IV** where the branched thio sugar **96** present in A and C derivatives is replaced with a 4′,6′-dideoxy-4′-pyridoindolylcarbonyl-β-D-glucose (**93**). Namenamicin[507] contains the alternative C-8 trisaccharide **V** comprised of a non-branched thiosugar [6′-deoxy-4′-thio-4′-*S*-methyl-4′-*C*-(1,2-dihydroxyethyl)-β-D-galactose, **248**], and 4′-amino-2′,4′-dideoxy-4′-*O*-methyl-α-L-xylose (**95**), the thiosugar branch of which is C-7′-*O*-glycosylated with the esperamicin 4′-*S*-methylthiosugar **94** (Fig. 28).[506] It is also important to note that aminopentose **95** was also found appended to indolocarbazoles AT2433 (Section 10) and, as expected, common biosynthetic elements have been noted (Fig. 28).[512] In the calicheamicins and esperamicins, the C-8-saccharide substitution is known to be important for DNA binding. While there remains some controversy regarding whether the metabolite or DNA alters configuration upon complex formation,[513–515] the unique conformation of the calicheamicin/esperamicin hydroxyaminosugar glycoside bond is believed to be a key contributor. Interesting, this hydroxylaminoglycosidic bond also was recently demonstrated to serve as a chemo-selective handle for neoglycosylation.[10,516] It should also be noted that the biochemical study of the glycosyltransferases involved in calicheamicin biosynthesis revealed these reactions to be much more reversible, a phenomenon that has since to be found as relatively universal among glycosyltransferase-catalyzed reactions.[509]

9. Flavonoids and isoflavonoids

(Iso)flavonoids are a prevalent group of plant secondary metabolites that share a common three ring architecture with subtle ring regiospecificity distinctions as a defining feature. Specifically, the term ‘flavonoid’ generally encompasses scaffolds containing a 2-phenylchromen-4-one core while ‘isoflavonoid’ typically corresponds to compounds containing the corresponding 3-phenylchromen-4-one backbone. While the core scaffolds are not of bacterial origin, several novel analogs deriving from microbial bioconversion of soy-based media components have been reported in the context of bacterial natural products discovery.[517] Within this context, it is important to note recent strain engineering efforts to enable microbial (iso)flavonoid scaffold production[518,519] as well as engineered microbial strains recently developed to enable differential glycosylation of (iso)-flavonoids.[520–523]

Many diverse activities have been attributed to the vast repertoire of naturally-occurring (iso)flavonoids including antioxidative properties and/or inhibition of lytic/digestive enzymes as well as anticancer, antifungal and/or estrogenic action.[524] To date, 16 glycosylated (iso)flavonoid analogs have been reported from native bacterial media bioconversion by *Streptomyces*,[525–530] *Kitasatospora*,[531,532] and *Sorangium*[18,533] to afford the installation of five distinct sugars [α-L-rhamnose, **46**; α-D-ristosamine, **69**; 6′-deoxy-α-L-talose **125**; α-L-chinovose (6′-deoxy-4′-*epi*-α-L-glucose), **157**; and β-L-cymarose, **176**], the most predominate of which being α-L-rhamnose (**46**) (Fig. 29).

The dominate glycoside regiospecificity within this class is C-4a- and/or C7-*O*-glycosylation as exemplified by the various daidzein and genistein rhamnosides from *Streptomyces*,[525,526,530] the corresponding genistein-derived talosins A and B from *Kitasatospora kifunensis* MJM341 [which contain the unusual sugar 6′-deoxy-α-L-talose (**125**)[531,532] better known as a monosaccharide integrated within cell wall oligosaccharides of certain Gram negative bacteria][534–536] and the 4′,7-bis-(β-cymaropyranosyl)-genistein from *Streptomyces*.[528] In addition, the *Streptomyces*-derived actinoflavoside carries the rare 3′-amino-2′,3′,6′-trideoxy-ribopyranoside (α-D-ristosamine, **69**) at C-7.[527] Intriguingly, while genistein rhamnosides lack antifungal activity, the corresponding talosides (talosins A and B)[532] were reported as potent antifungals, implicating the inversion of a single stereo-center (C-3′) within the appended sugar as the distinguishing feature that invokes antifungal activity.

C-3a and C-6 represent less common points of *O*-glycosylation with N-99-596 A (7,4*a*-dihydroxyisoflavone-3*a*-*O*-α-L-rhamno-pyranoside) and N-99-596 B (5,7,4*a*-trihydroxyisoflavone-3*a*-*O*-αL-rhamnopyranoside)[529] from *Streptomyces* as the only examples of the former. For the latter, the α-L-chinovose (6′-deoxy-4′-*epi*-αL-glucose, **157**) containing luteolin-6-chinovoside from *Sorangium* represents the only C-6-glycoside within this series.[18,533]

10. Indoles and indolocarbazoles

For the scope of this discussion, indole-derived metabolites have been divided into two simple classes – those that contain a single indole as part of the aglycon core (indoles, kahakamides, neosidomycin, SF-2140, oxopropalines, pyridindolols, pyrroin-domycins and tryptamines), and aglycons comprised of fused bis-indole systems (indolocarbazoles, tjipanazoles, and akashins). Cumulatively, 79 glycosylated members are represented among these two classes where an intriguing bifurcation exists. Namely, with a few exceptions (kahakamides, neosidomycin, and SF-2140), indolocarbazole *N*-glycosylation is restricted to the fused bis-indole-containing members.

10.1. Fused indoles

Indolocarbazoles, the predominate metabolites within the fused indole series, are actinomycete-dervived alkaloids which inhibit topoisomerase I and kinases relevant to anticancer, antitubercular, antimalarial and antiviral lead development.[537–540] While many indolocarbazole analogs have been discovered or synthesized,[537,538] it is noteworthy that those that have advanced furthest clinically are either a known natural product (CT327, a

pegylated formulation of the natural product K252a currently in phase IIb for treating psoriasis)[541] or subtle variations thereof including *N*-acylated staurosporine [midostaurin/PKC412, which recently completed a successful phase II trial for acute myeloid leukemia (AML) and is currently in phase II evaluation for metastatic melanoma],[542] the *N*-alkylated rebeccamycin (becatecarin)[543,544] and a reduced K252a (lestauritinib/CEP-701 currently in clinical phase II/III evaluation for treating FLT3-ITD AML).[545]

Indolocarbazoles are characterized by their indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole core and generally divided into two separate sub-classes exemplified by rebeccamycin[546] and staurosporine[547] with 64 glycosides cumulatively reported to date (Fig. 30). The distinguishing features of the rebeccamycin-like indolocarbazoles (including both AT2433 and rebeccamycin analogs) include a 1*H*-pyrrole-2,5-dione, indole *N*-glycosylation and often indole halogenation. In contrast, staurosporine-like indolocarbazoles (including, indocarbazostatins, K-252, MLR-52, RK-286, RK-1409, staurosporine, UCN and ZHD-0501 variants) contain a reduced 1H-pyrrol-2(5*H*)-one, a signature fused *N*,*N*′-12,13-glycoside, and typically lack indole halogenation (Fig. 30). In general, mechanism of action coincides with these structural distinctions where staurosporine-like indolocarbazoles typically function as kinase inhibitors[548] while rebeccamycin-like indolocarbazoles inhibit topoisomerase I[549] and, in either case, glycosylation generally contributes to improved bioactivity.[549] Staurosporine-like indolocarbazoles have been reported from *Micromonospora*, *Nocardiopsis*, and *Streptomyces* while rebeccamycin-like analogs have been reported from *Saccharothrix* (later reclassified as *Lechevalieria*) and *Actinomadura*. In addition to the native natural products, indolocarbazole analogs have been generated *via* strain engineering,[540,548,549] feeding native producing strains with 6-fluoro-tryptophan,[550] bioconversion of aglycon mimetics by *E. coli* strains expressing genes encoding tailoring enzymes (*N*-glycosyltransferases and *N*-methyltransferases),[551] and exploiting the permissive nature of corresponding methyltransferases for differential alkylation.[552,553] In addition, the heterologous production of rebeccamycin in *E. coli* has been achieved.[554]

The staurosporine-like members can be further divided into *N*,*N*′-12,13-fused pyranosides and *N*,*N*′-12,13 furanosides. Of the former, a biosynthetic progression can be observed among isolates (suggesting notable sugar nucleotide tolerance within the corresponding *N*,*N*′-12,13 glycosyl-forming enzymes) beginning with the simple 6′-deoxy sugar α-L-rhamnose (**46b**) found in MLR-52 (Fig. 30).[555] Continuing, sugar C-2′-deoxygenation and C-3′-epimerization presents the methylated α-L-digitoxose **68b** of RK-286C[556,557] while corresponding sugar C-3′oxidation contributes to a staurosporine analog bearing the C-3′-keto sugar, 3′-keto-2′,3′,6′-trideoxy-α-L-glucose (**150**).[558] Subsequent C-3′ sugar transamination and C-3′ sugar amino modification provides a range of analogs including the flagship 3′-*N*-methyl-4′-*O*-methyl-α-L-ristosamine (**45b**, staurosporine,[547,559–561] TAN-999,[562] UCNs,[563,564] and RK-1409[565]) as well as *N*,*N*-dimethyl,[566] *N*-desmethyl,[567] and *N*-amide derivatives[568] in staurosporines; *N*-formyl and the corresponding C-3′/C-4′-cyclic carboxamide **45c** of ZHD-0501;[569] and *N*-oxidation to afford the hydroxyl-amino analog (**226**, associated with two *N*-hydroxystaurosporine derivatives and 4′-demethyl-*N*-formyl-*N*-hydroxystaurosporine) and hydroxylimino analog (**148**) of the TAN-1030A series (Fig. 30).[558] The same strain afforded metabolites containing the 3′-keto corresponding

sugars **150** and **151**.[558] Three divergent *N*,*N*′-12,13-pyranosides have also been observed including: 4′-*O*-methyl-α-L-olivose (**106**, RK-1409B);[570] 3′-nitro-2′,3′,6′-trideoxy-α-L-glucose (**143**, 4′-demethylamino-4′-nitro-staurosporine);[568] and 3′-amino-3′,6′-dideoxy-4′-*O*-methyl-α-L-altrose (**147**, 5′-hydroxystaurosporine and 4′-*N*-methyl-5′-hydroxystaurosporine from *Micromonospora*).[571] The corresponding *N*,*N*′-12,13-fused furanoside-containing members of this group include indocarbazostatins A–D,[572–574] all of which contain a novel branched α-L pentose **145** [differing *via* a C-3′-side chain ethyl (A/B) or methyl (C/D) ester], and K-252a-b.[566,575,576] K-252a and K-252b contain a novel branched α-L pentose **146** [differing *via* the presence of a C-3′-side chain free acid (b) or methyl ester (a)] while, in *N*-methyl-3′-amino-3′-deoxy K-252a, the **146** C-3′-hydroxyl has been replaced with a *N*-methyl-amino group to afford **149** (Fig. 30). From a biosynthetic perspective, general formation of the indole-*N*-sugar-C-5′ fusion, sugar branching (**145**, **146** and **149**), sugar *N*-oxidation (**143**, **148**, **335**) and formation of the C-3′/C-4′-cyclic carboxamide **45c** are expected to offer potential new chemistries.

In contrast to the *N*,*N*′-12,13-fused pyranosides and furanosides discussed in the preceding paragraph, rebeccamycins (from *Lechevalieria*),[546,577–579] AT2433 analogs (from *Actinomadura*),[580,581] holyrines (from a marine actinomycete strain N96C-47),[582] RK-286D (from *Streptomyces*),[557] tjipanazoles (from *Tolypothrix*),[583] akashins (from *Streptomyces*),[584,585] and K-252d (from a marine *Streptomyces* and *Nocardiopsis*)[566,575,576] represent related fused tryptophan ring-based systems that contain a single *N*-glycosidic attachment. A range of monosaccharides have been observed among the appended sugars within this subclass including: β-D-glucose (**104**) and its 4′-*O*-methyl-analog (rebeccamycins); α-L-digitoxose (**68a**) (RK-286D); α-L-ristosamine (**45a**) and the 2′,3′,6′-trideoxyaminohexose (**152**) (holyrines A and B, respectively); α-L-rhamnose **46a** (K-252d); 6′-deoxy-β-D-gulose (**135**), α-L-rhamnose (**46a**), β-D-glucose (**104**), or β-D-xylose (**136**) (tjipanazoles); 4′-amino-4′,6′-dideoxy-α-L-glucose (**137a**), 4′-acetamido-4′,6′-dideoxy-α-L-glucose (**137a**) and the corresponding C-3′/C-4′-oxazole sugar **137b** (akashins A, B and C, respectively), the latter of which is perhaps the most uniquely functionalized sugar among this series. The four AT2433 variants stand out as the only disaccharide-containing metabolites within the fused indole series where the deoxyaminopentose 4′-amino-2′,4′-dideoxy-α-L-xylose (**138**) or its 4′-*N*-methyl derivative is attached at 6′-position of indole 4′-*O*-methyl-β-D-*N*-glucoside (**104**) (reminiscent of rebeccamycin core structure) (Fig. 30). AT2433 and rebeccamycin share many common biosynthetic features and a biosynthetic relationship between AT2433 and the enediyne calicheamicin (Section 8.2, by virtue of their shared aminopentose) has also been noted.[512]

10.2. Simple indoles

Unlike members discussed in the previous subsection, indole *N*-glycosylation is uncommon among the simple indoles metabolites. Specifically, kahakamides (a marine *Nocardiopsis*),[586] neosidomycin (*Streptomyces*),[587] and SF-2140 (*Actinomadura*)[588] are the only members that contain indole *N*-glycosides, all of which contain either 4-deoxy-α-D-taluronamide (**314**; kahakamide A) or 4′-deoxy-α-D-taluronate (**139**; kahakamide B, neosidomycin, and SF-2140) (Fig. 31). Of these, SF-2140 displayed notable antiviral activity and a higher survival rate than amantadine in viral-challenged mice. Among other simple

indole/tryptophan analogs, two C-5-glycosylated *N*-acetyl tryptamine derivatives [β-D-quinovose (**140**) or α-L-rhamnose (**46**)], were discovered in the context of metabolic feeding studies using the staurosporine producer.[589] Sugar **46** was also present, as an unusual anomeric glycosyl ester, in an indolyl-3-carbonyl derivative isolated from *Streptomyces*.[590]

The pyrroindomycins from *Streptomyces* represent the only trisaccharyl-containing members of the simple indole group. Unlike the indolyl-glycosyl esters described above, the trisaccharide of pyrroindomycins is connected *via* an ester bond to the C-3′ terminus of a 4′-amino-2′,4′,6′-trideoxy-β-L-galactosyl-(1′→4′)-β-L-mycarosyl-(1′→4′)-β-D-rhodinosyl trisaccharide appended to a polyketide tetramic acid-containing macro-ring system (trisaccharide **I**, Fig. 31). These unique metabolites were noted for their antibacterial activity against the drug resistant pathogens including MRSA and VRSA.

The β-carbolines represent the last group of simple indole-containing metabolites and are signified by a fused pyridine-indole skeleton (Fig. 31). Members include the oxopropalines[591,592] and pyridindolols[593–596] from *Streptomyces* and have been noted for herbicidal and anti-fungal activities and as benzodiazepine-receptor ligands.[597,598] To date, only six glycosylated β-carbolines have been reported from bacteria. Variant side-chain regiospecificity of *O*-glycosylation was observed among this group with C-10, C-11, and C-12 mono-glycosylation [β-D-glucose (**104**)] observed in pyridindolols and C-11 and C-12 mono-glycosylation [α-L-rhamnose (**46**)] found among oxopropalines (Fig. 31). In the latter case, rhamnosylation was found to be detrimental to the observed anticancer activity of the parental aglycon.[592]

11. Lipids, polyenes and carotenoids

Microbial glycosylated lipids are ubiquitous and include both primary metabolites common to cell wall/membrane architecture as well as a range of bioactive secondary metabolites. As aglycon structure and glycosyl regioselectivity is highly diverse, this section simply highlights the diverse sugar structures observed among bacterial glycolipids.

Not surprisingly, *O*-β-D-glucosides (**104**) are among the most prevalent glycosyl substitutions represented as exemplified by fattiviracins,[599] moenomycins,[600] arthrobacillins,[601] glucolipsins,[602] and carotenoids.[603] The α-anomer **18** was also observed in a small set of glycosylated lipids[604,605] along with the corresponding common aminosugar variant (2′-amino-2′-deoxy-β-D-glucose, **153**), α-D-anomeric phosphate [2-amino-2-deoxy-α-D-glucose-1-phosphate (**5**) of lipid A][606] α-D-glucuronic acid (**154**), and C-5′ sulfonates (**155**).[607,608] The common 2′-epimer β-D-mannose (**156**) is also represented among many bacterial carotenoids[609] and *Flavobacterium* glycerolipids[610] while the corresponding C-2′, C-6′-disulfate (**160**),[611] as well as α-L-fucose (**157**),[612] β-D-arabinose (**158**),[613] α-L-rhamnose (**46**),[614] β-D-xylose (**136**),[615] β-D-glucofuranose (**159**),[604] β-D-galactose (**161**),[607] α-D-allose (**162**),[616] α-D-altrose (**163**),[617] Gram-negative phosphosphingolipid heptose sugar **166**,[618] and the unique 8-carbon thio sugar **167** (desalicetin 2′-butyrate)[619] are additional sugars represented among bacterial glycolipids, carotenoids and related metabolites. Di-saccharides **I** and **II** (Fig. 32), consisting of β-L-

hexanoic acid (**168**, β-L-iduronic acid) and β-D-glucosamine (**153**), or glucose-1-phosphate (**18**) and β-D-glucosamine (**153**), are also components of some glycolipids.[620,621]

Monosaccharides represented among secondary metabolites include the undefined 2′-amino-2′,6′-dideoxy hexose **164** (vancoresmycin),[622] β-L-xylose (**165**, malyngamide J),[623] β-L-rhodinose (**169**, streptolydigin)[624] β-D-digitoxose (**131**, α-lipomycin)[625] and α-D-altrose (**163**, moritoside).[617] While glucosamine (**153**) is commonly found as a lipid *O*-glycoside, it exists as an *N*-glycoside among racemomycins.[626] Alternatively, some secondary metabolites within this family contain *O*-oligosaccharyl substitutions as exemplified by moenomycin [Fig. 32; hexasaccharide chain **V** comprised of β-D-galacturonamide (**324**), 2′-*N*-acetyl-β-D-xylose (**173**), β-D-glucose (**104**), *N*-acetyl-β-D-2′-glucosamine (**153**) and phosphosugars **174** and **175**].[600]

Elfamycins and phenelfamycins represent a structurally unique group of metabolites from *Streptomyces*.[627–629] The polyene moieties found within these molecules are glycosylated with mono-, di-, or trisaccharides (Fig. 32) where α-L-oliose (**49a**/**49b**) serves as the predominate monomer and typically as the point of contact to the aglycon. Exceptions to this include disaccharide **III** of efrotomycin and *N*-demethylefrotomycin, comprised of the 6′-deoxy-β-D-allose (**170**) and α-L-rhamnose (**46**),[630–632] and the inclusion of β-L-digitoxose (**176**) in elfamycin analogs (disaccharide **VII** and trisaccharide **IV**). Aurantinin B from *Bacillus*, while also structurally related to elfamycins, is also unique by virtue of its rare 3′-keto-β-L-sugar (**171**).[633]

12. Macrolides and macrolactams

Macrolides and macrolactams are highly functionalized macro-cyclic polyketide-derived metabolites, the ring structures of which are formed *via* an intramolecular ester (macrolides) or amide (macrolactams) bond. This section summarizes the vast array of glycosylated macrolides (categorized by ring size and architecture in Sections 12.1–12.7), macrodiolides (Section 12.8), super macrolactones (Section 12.9), polyene macrolides Section 12.10), macrolactams (Section 12.11), spirotetronates (Section 12.12) and spinosyns (Section 12.13).

12.1. 12-Membered macrolides

Methymycin and pseudoerythromycin derivatives constitute the known 12-membered bacterial glycosylated macrolides from *Streptomyces*, where *O*-glycosylation is restricted to C-3 and/or C-5 of the macrolide core (Fig. 33). The most predominate sugar found appended to this class is β-D-desosamine (**177a**), at either C-3 or C-5,[634,635] but other sugars observed include the corresponding desosamine analogs *N*-desmethyl **177b** or *N*-oxide **178**. In addition, C-3-appended α-L-cladinose (**90b**) is present pseudo-erythromycins[634] while β-D-olivosyl (**53**) substituted methymycin has been generated *via* pathway engineering[636] and a range of non-native desosamine replacements (in the context of 12-, 14- and 16-membered macrolides) have been accomplished *via* chemoenzymatic methods.[637] Classical 12-, 14- and 16-membered macrolides function as antibacterials in a mechanistically similar manner as described in Section 12.3.

12.2. 14-Member macrolides

As exemplified by the naturally-occurring erythromycin or semi-synthetic clarithromycin, 14-membered macrolides are a mainstay in the clinical treatment of Gram-positive/negative infections.[638,639] There are 96 naturally-occurring 14-membered glycosylated macrolides reported to date from bacterial sources including *Streptomyces*, *Nocardia*, *Saccharopolyspora* and *Amycolatopsis*. C-3- and C-5-*O*-glycosylation is the most predominate among 14-membered macrolides, but C-6-, C-7-, C-9- and, in one case (CP 64537, containing either **140** or **170c**),[640] C15-*O*-glycosylation has also been observed. Reminiscent of classical 12- and 16-membered macrolides, 14-membered macrolides (including erythromycins,[634,641–643] megalomycin,[644,645] picromycin,[646] oleandomycins,[647] sporeamicins;[648–651] Sections 12.1 and 12.3) typically contain the common C-5 β-D-desosamine (**177a**). The corresponding *N*-desmethyl-β-D-desosamine (**177b**)[634] is also found at this position as exemplified by the cineromycins [which also contain a C7 α-D-glucose (**18**)][652] C-3-*O*-glycosylation is also prevalent, albeit less important for bioactivity, and includes 3-*O*-methyl-α-L-mycarose (also known as α-L-cladinose, **90b**),[634,648,653,654] α-L-mycarose (**90a**; as observed in CP64593,[640] sporeamicin-C[650] or the 2-norerythromycins deriving from pathway engineering),[655] or the C-3′/C-4′-modified form (**90c**/**90d**, Fig. 33) in megalomycin analogs.[656]

Additional C-3-appended sugars observed include 4′-*O*-acetyl-αL-arcanose (**122b**) [and corresponding engineered 2′,3′-anhydro-arcanose (**182**) and 3′-acetylated **180**[657,658]] of the lankamycins[659] and the kujimycins [which contain a C-3 α-L-arcanose (**122a**) or 4′-*O*-acetyl-α-L-arcanose (**122b**) and a C-5 β-D-lankavose (**181b**)][660] and α-L-oleandrose (**184**); found in oleandomycin[647,661] and the 3-*O*-oleandrosyl-5-*O*-desosaminyl-(8*S*)-8-hydroxyerythronolide B[662] from bioconversion. Additional sugars attached to C-5 include 3-keto-4,6-dideoxy-β-D-hexopyranose **179** (CP-63693[640]), β-D-chalcose (**181b**; lankamycins[659] and kujimycins[654]) and β-D-mycaminose (**185**; narbolide,[663] *via* biotransformation). C-6 substitution is restricted to α-L-megosamine (**45**; megalomycin[656] and SF2748[664]) while that of C-9 is limited to variants of α-L-rhamnose (**14–18**; lyngbyaloside and lyngbuilloside[665,666]). Arguably the most unique glycosylation among 14-membered macrolides is the α-L-cladinose (**90e**) orthoester of erythromycin E originally produced *via* bio-conversion[667] and later discovered as a metabolite of a pathogenic *Nocardia*.[668] Such orthoester glycosides are more typically associated with orthoester natural products (see Section 14). Classical 12-, 14- and 16-membered macrolides function as antibacterials in a mechanistically similar manner as described in Section 12.3.

12.3. 16-Membered macrolides

Bacterial 16-membered macrolide glycosides represent the largest subgroup with a total of 284 glycosylated members reported thus far primarly from actinomycetes. This group is further divided into two subgroups based upon macrolactone ring architecture of as depicted in Fig. 33, where the predominant subgroup **16-A** contains classical antibacterial macrolides reminiscent of their smaller counterparts described in the preceding sections. As with other classical macrolides, the prominent observed glycosyl regioselectivity within subgroup **16-A** is C-3 and/or C-5 where some members also display C-9 and/or 14-C *O*-glycosylation. A total of 21 sugar monomers are represented among 16-membered macrolides including β-D-

desosamine (**177a**, typically C-5), β-D-mycaminose (**185**, typically C-5) and α-L-mycarose (**90a**, typically C-5/C-3) commonly found in 12- and/or 14-membered counterparts as illustrated by rosamicins,[669] mycinamicins,[670–678] juvenimicins.[679] Similar to the 12-membered comparators, C-3 3′-*N*-oxo-β-D-desosamine (also called desosamine *N*-oxide, **178**) is observed among rosaramicins from *Micromonospora*[680] while the only pentose (α-D-arabinofuranose, **191**) is found at this position in epothilones.[681] C-5-*O*-glycosides of 4′,6′-dideoxy-β-D-glucose (**181a**), or subtle variations thereof (such as β-D-chalcose, **181b**, or 2-propionyl **181c**) are also observed as exemplified by chalcomycins,[682] GERI-155[683] and neutramycin A.[684] Angolamycins, in contrast, carry the 2′-deoxy-β-D-mycaminose (β-D-angolosamine, **59**)[685] while β-D-aldgarose (**190b**) and its acyclic precursor (**190a**) are found at the same position of aldgamycins[686–691] and swalpamycin.[692,693] C-4′-*O*-glycosylation of the C-5 β-D-mycaminose (**185**) is also a fairly common occurrence within this subgroup (disaccharides **I–IV**, Fig. 33)[694–696] where four L-sugars [α-L-amicetose (**97**), α-L-cinerulose (**51**), α-L-rhodinose (**44**) and α-L-mycarose (**90a**)], or subtle modifications thereof, make up the terminal sugar.[696–706] The angolamycins are distinguished within this context by their C-5-initiating sugar as described above (α-L-mycarose, **90**; disaccharide **V**). The highly deoxygenated sugar β-D-forosamine (**63**) is restricted to C-9-*O*-glycosylation as found in the spiramycins (also known as shengjimycins)[707–711] and chimeramycins.[699] Finally, C-14-*O*-glycosides have also been reported where the sugars utilized include: β-D-mycinose (**170c** in tylosin,[703] neutramycins,[684] mycinamycins[678] and GERI-155[683]); 6′-deoxy-β-D-allose, 6′-deoxy-2′-*O*-methyl-β-D-allose, or 4′-*O*-propionyl-β-D-mycinose (**170a**, **170b** or **170d**, respectively, in mycinamycin[677] and tylosin analogs[712]); β-D-boivinose and β-D-digitoxose variants (**187a/b** and **131a/b**, respectively in engineered tylosins[703]) as well as 3′,6′-dideoxy-4′-keto-2′-*O*-methyl-2′,3′-unsaturated-β-D-glucose (**188**) also *via* pathway engineering.[713]

A small set of 16-membered glycosylated macrolides are distinguished by the subgroup **16-B** branched macrocyclic lactone architecture, where *O*-glycosylation occurs at C-21 (Fig. 33). Examples include bafilomycin-A1-rhamnoside (α-L-rhamnose, **46a**)[714] leucanicidin (2′-methoxy-α-L-rhamnose, **46e**)[715] and formamicin (β-D-olivose, **53**).[716,717]

The final sub-group of the 16-membered macrolides are the avermectins (sub-class **16-C**, Fig. 33).[718–720] They are 16-membered macrolides produced by *Streptomyces*, *Amycolatopsis* and *Nocardia*. Avermectins typically contain a C-13 disaccharyl substitution (disaccharide **VI**). More recently, a variety of sugar analogs of this sub-class have been made *via* chemoenzymatic methods.[721]

Classical 12-, 14- and 16-membered macrolides inhibit bacterial protein synthesis by blocking the 50S ribosomal peptide exit tunnel.[722,723] Core contributions to the specific macrolide-ribosome interaction derive from the C-3 sugar (*e.g.*, desosamine, **177a**) 2′-hydroxyl and 3′-dimethylamino groups, the latter of which has been deemed most important, based upon both macrolide-ribosome complex structure elucidation[724] and bioactivity assessment of analogs.[725–727] Glucosylation of 2′-hydroxyl group of this aminosugar is an established mechanism of macrolide resistance,[728–730] where the corresponding *O*-glucosyltransferases have been recognized as highly permissive.[731,732]

C-5-disaccharyl-substituted macrolides further perturb the relative positioning of the 3′-end of P-site bound tRNA and 23 S rRNA in the ribosome where the terminal sugar of the disaccharide moiety extends into the peptidyl transferase center.[684,702,733–735] Some classical macrolides (*e.g.*, megalomicins) have been found to inhibit protein trafficking in the golgi and, while the megalomicin C-6 α-L-megosamine (**45**) has been put forth as a contributor to this activity,[736,737] this contention has not been experimentally validated. A number of 14-membered macrolides have also been noted for their immunomodulatory activities,[738–740] the mechanism for which remains poorly understood. Exceptions to the classical mode of action, the epothiolones are potent tubulin-targeted anticancer agents that advanced to clinical evaluation,[741,742] subgroup **16-B** members such as bafilomycins are potent inhibitors of vacuolar type H^+-ATPase,[743,744] and the avermectins are potent antihelmenthics.[745]

12.4. 18-Membered macrolides

There are only 23 reported bacterial 18-membered glycosylated macrolides the majority of which are tiacumycins and lipiarmycins[746,747] from *Micromonospora*, *Dactylosporangium*, *Actinoplanes* and *Catellatospora*. All analogs share a common macrolactone ring *O*-glycosylated at C-11 with variants of the branched 5′-*C*-methyl-β-L-rhamnose (**193a–f**) or at C-20 with variants of β-L-rhamnose (**322a**) (Fig. 34, **18-A**). TAN-1323 A-C (**18-B**)[748] and the recently isolated biselyngbyaside (**18-C**)[749] are distinguished from the tiacumicins by their C-17 side chains and corresponding glycosylation patterns. TAN-1323 A-C are C-23-*O*-glycosides of β-D-olivose (**53a**), 4-carbamyol-β-D-olivose (**53b**) and β-L-rhamnose (**322a**), respectively, while biselyngbyaside is a C-3-*O*-glucoside (2′-*O*-methyl-β-D-glucose, **104b**).

12.5. 20-Membered macrolides

Venturicidins, irumamycins, ammodicin and apoptolidins are the only known glycosylated 20-membered macrolides from *Nocardiopsis*, *Saccharotrix*, and *Streptomyces* (Fig. 34). Glycosylation regiospecificity is variant across this series with C-9-*O*-glycosides represented by ammocidin (6-deoxy-α-L-glucose, **194a**) and apoptolidin (4′-*O*-methyl-6-deoxy-α-L-glucose, **194b**). C-13-*O*-glycosides include the venturicidins (β-D-olivose, **53a**) and irumamycin (3′-carbamoyl-β-D-olivose, **53c**).[750–752] C-24-*O*-glycosides are disaccharide substitutions as exemplified by ammocidin [disaccharide **I** comprised of β-D-olivomicose (**192**) and β-D-digitoxose (**131**)].[753] In contrast, apoptolidin contains a C-27-*O*-disaccharide [disaccharide **II** comprised of 3′-*O*-methyl-β-D-olivose (**53d**) and α-L-chromose (**195**)].[754] Apoptolidin specifically induces apoptosis in E1A-transformed glial cells with little or no detectable normal cell toxicity and is believed to function *via* inhibition of mitochondrial F1F0-ATPase where the disaccharide appears to be dispensable.[754–756] Venturicidins and irumamycins are potent antifungals believed to inhibit ATP-driven proton transport and hydrolytic processes.[757,758] Interestingly, X-14952B which differs from irumamycin in the C-19 alkyl side chain possesses antibacterial activities.[759]

12.6. 22-Membered macrolactones

Pulvomycin from *Streptouerticillium* represents the only bacterial 22-membered macrolide (Fig. 34).[760] This metabolite is a C-33-*O*-glycoside of 2′,4′-di-*O*-methyl-β-D-fucose (**270**). Pulvomycin inhibits protein synthesis by preventing the formation of the elongation factor Tu (EF-Tu)/GTP/aa-tRNA ternary complex, the pulvomycin sugar contribution to which remains unknown.[761]

12.7. 24-Membered macrolactones

Macrolactins,[762] archazolids[763] and maduralides[764] represent 24-membered glycosylated macrolactones from *Bacillus*, *Cystobacter*, *Archangium* and *Maduramycetes* (Fig. 34). Macrolactins and archazolids are C-7 and/or C-15-*O*-β-D-glucosides (**104a**). Glycosylation in these molecules has been demonstrated to suppress their cytotoxic effects. Maduralide, a weak Gram-positive antibacterial, is a C-13-*O*-glycoside of 6-deoxy-3′-*O*-methyl-β-L-talose (**198**).

12.8. Macrodiolides

A small set of glycosylated macrocyclic dilactones have been reported from *Streptomyces* and *Microbiospora*. Elaiophylin, SNA-4606-1 and efomycins are C-13/13*a*-di-*O*-α-L-oliosides (**49a**),[765] where the sugars are 3′-*O*-methylated in (**49b**) efomycin A.[766] Bispolides from *Microbiospora* are comprised of larger dilactone rings containing 2′,6′-dideoxyhexose **196** at C15a and the same sugar or 6′-deoxyhexose **197** at C-15.[767] Axenomycins from *Streptomyces* are C-43-*O*-disaccharyl-substituted metabolites [disaccharide **III** comprised of β-D-amicetose (**48**) and L-axenose (**199**, anomeric stereocenter undefined)].[768] Liposidolide A encompasses a C-15-*O*-β-D-mannoside (**156**) and C-41-*O*-β-D-olivoside (**53e**), the latter of which is modified as depicted (Fig. 34).[769] Efomycins are non-toxic inhibitors of selectin-mediated leukocyte adhesion and have been considered as candidates for further development to treat autoimmune disorders.[770] Elaiophylin, efomycin G and SNA-4606 inhibit testosterone 5α-reductase and display growth-promoting, antiviral and antibacterial activities. Glycosylation does not impact upon efomycin activity and the glycosyl contribution to the latter metabolites has not been studied.

12.9. Super macrolactones (ring size 32–48)

There are 25 glycosylated super macrolactones (defined as macrolides with ≥32-membered ring systems) from bacterial sources including *Streptosporangium*, *Streptomyces* and *Nocardia* (Fig. 35). Brasilinolides are C-37-*O*-α-D-oliosyl (**71a**) bearing 32-membered macrolides where brasilinolide C contains unmodified α-D-oliose (**71a**),[771] brasilinolide A carries 3′-*O*-acyl-α-D-oliose (**71b**),[772] and bracilinolide B has the permethylated counterpart.[773] Liposidolide A has two appended sugars, a C-15-*O*-α-D-mannose (**160**) and a C-41-*O*-β-D-olivose (**53**) derivative modified at C-3′.[769] The 34-membered macrocyclic sporaviridins from *Streptosporangium* are glycosylated to a greater extent with a C-13-*O*-pentasaccharide (**III** and **IV**), a C-21-*O*-β-D-glucose (**104**) and a C-47-*O*-α-L-vancosamine (**118**).[774] The core of the sporaviridin pentasaccharide (**III** and **IV**) is a tri-substituted β-D-quinovose (**140**) which contains a C-2′-*O*-β-D-glucose (**104**) or 4′-amino-4,6-dideoxy-β-D-

glucose (**202**), a C-3′-*O*-3′-amino-3,6-dideoxy-β-D-glucose (**59**) and a C-4′-*O*-disccharide comprised of β-D-quinovose and 3-amino-3,6-dideoxy-β-D-glucose. The 32-membered macrolides notonesomycin[775] and A-77951[776] both possess C-37–*O*-glycosides. The former contains both 3-*O*-methyl-β-D-olivose (**53**) and β-L-rhodinose (**169**), connected *via* a modified para-aminobenzoic acid (fragment **II**) while the latter contains an undefined modified disaccharide (**205**, disaccharide **I**). The recently discovered 51-membered stambomycins represent the largest glycosylated bacterial macrolide and share a common C-5-*O*-*N*,*N*-dimethyl-3′,6′-dideoxy-β-D-glucoside (**185b**).[777] Primycins (C-18-*O*-α-D-arabinofuranose, **204**) and mathemycins (C-18-*O*-β-D-mannose, **156**) both carry an *O*-glycoside three carbons from the macro-cyclic ring forming oxygen. In addition, mathemycin contains a C-37-*O*-3′-amino-2,6-dideoxy-β-D-glucose (**185a**).[778] Finally, the 42-membered desertomycins and 48-membered monazomycins both share a C-22-*O*-α-D-mannose (**160**).[779–783]

In addition to antifungal activities, brasilinolide A and A-77951 were noted for their immunosuppressive effects.[772,776] Stambomycins, moderatively active against Gram-positive and Gram-negative bacteria, also were reportedly cytotoxic against a number of human cancer cell lines.[777] It should also be noted that acetylation of the sporaviridin aminosugar abolished antimicrobial activity.[774]

12.10. Polyene macrolide

A total of 49 glycosylated polyene macrolides have been reported from *Streptomyces*, *Actinoplanes*, and *Sorangium*. Members within this group share a common macrocyclic lactone of various sizes (26 to 38-membered rings) with 4–7 conjugated double bonds where the classical antifungals amphotericin and nystatin serve as prototypical examples. With the exception of chivosazoles[784–786] aglycons can be further distinguished by the presence or lack of an endocyclic pyran ring (core structures **A** and **B**, respectively; Fig. 36).

The aminosugar β-D-mycosamine (**206**) is the predominate *O*-glycoside among polyene macrolides as exemplified by amphotericins,[787] candicidins,[788] candihexins,[789] vacidin-A,[790] SCH 16656 complex (67–121 analogs)[791] and polyfungins.[792] With the exception of sorangiosides (glycosylated with β-D-glucose, **104**),[793] regioselectivity of glycosylation as β to the pyran ring is strictly conserved among prototypical polyene members (Fig. 36, position a, β-D-mycosamine **206**). Some polyfungins carry an additional C-35-*O*-α-L-digitoxose (**68**) and the mycosamine C-4′ is further modified with 6′-deoxy-β-D-mannose (**209**; disaccharide **I**) in 67-121C (Fig. 36). The 44-membered polyene antibiotic lienomycin is distinguished by its C-25-*O*-α-L-rhamnose (**46**),[794] while DJ-400-B and B2 are the only members with a C-5 β-D-mycosamine (**206**) (Fig. 36, position a).[795] The appended mycosamine is important to the antifungal activity of these metabolites where subtle changes dramatically influence potency.[796] While systemic toxicity presents a challenge to the clinical use of amphotericin, recent work with analogs bearing 2-deoxy mycosamine suggest a notable improvement of selectivity for ergosterol-containing fungal membranes.[797] As with other bacterial systems, reactions catalyzed by polyene glycosyltransferases have been found to be reversible and used to generate differentially-glycosylated polyene analogs.[798]

Distinct from the prototypical antifungal polyenes, chivosazoles are cytotoxins that contain an integrated aglycon oxazole ring and are C-11 glycosides (β-D-quinovose, **140**).[784,785]

12.11. Macrolactams and related glycosylated metabolites

Similar to the macrolactones discussed in the previous section, macrolactams, from *Streptomyces*, *Actinosynnema*, *Amicolatopsis*, *Actinomadura*, *Maduromycetes*, *Microtetraspora*, *Nonomuraea* and *Pseudonocardia* are large macrocyclic structures but are distinguished by a ring-closing amide bond. Compared to macrolactones, glycosylated macrolactams are fewer in number (53 total) and display variant glycosyl regiospecificity as summarized in Fig. 36.[18] Many members contain an integrated aromatic ring as part of the overall macrolactam aglycon, the exceptions being fluvirubicins, SCH 39185, SCH 38511, SCH 38516, SCH 42729, SCH 42282, cremimycins, vicenistatin, and incednine. Tolypomycins from *Streptomyces* stand out by virtue of their conjugation to the C-4′-amine of tolyposamine (**203a**) or *via* a corresponding C-4′-imine in tolypomycin-Y (**203b**).[18] Ansamitocinosides from *Actinosynnema* are unique as *N*-β-D-glucosides (**104**),[799] the sugar of which can be further modified as in ansacarbamitocins from *Amicolatopsis*.[800] In contrast, the phenolic hydroxyl is the glycosyl acceptor in the related C-22-*O*β-D-glucosyl-mycotrienin II.[801]

Fluvirucins,[802,803] SCH 39185, SCH 42729, and SCH 42282 are 14-membered macrolactams bearing either a C-3-*O*-3′,6′-dideoxy-3′-amino-α-L-talose (**73**) or C-9-O-glycoside comprised of the same sugar or α-L-mycosamine (**207**) (Fig. 36).[804] The C-2′-OH of α-L-mycosamine (**207**) is further glucosylated with α-L-glucose (**211**, disaccharide **II**, SCH-42729) which can also be C-4′-*O*-glucosylated with β-L-glucose (**210**, trisaccharide **III**, SCH-42282).[805] Modified macrolactams, ansaetherone,[806] and tetrapetalones (described in details in Section 23.5.3.),[806] Q-1047-A[807] and its hydroquinone analog Q-1047-R-A all are believed to contain C-9-*O*-β-D-rhodinose (**56**), although in some cases, the nature of the sugar has not been completely defined. The vicenistatins also contain a single C-7-*O*-glycoside comprised of β-D-vicenisamine (**212**), 3′-*epi*-β-D-vicenisamine (**213**), or β-D-mycarose (**64**)[808] while cremimycin contains a C-10-*O*-3′-*O*-methyl-β-D-digitoxose (**131**).[809] Finally, incedine from *Streptomyces* bears a C-11-*O*-disaccharyl moiety constructed from the two amino sugars 4′-*N*-methyl-β-D-forosamine (**63**) and 2′-deoxy-2′-methyl-amino-β-D-xylose (**173**).[810]

Glycosylated macrolactams are known to possess a variety of biological activities including antifungal, antibacterial, antihelmintic, antiviral, antitumor, radical scavenger and phospholipase C inhibition.[800,801,803,806,809–812] While the specific impact of the sugar upon bioactivity has not been delineated in most cases, recent studies in which the vicenistatin D-vicenisamine was replaced with the D-mycarose led to a complete loss of activity, implicating the aminosugar as important to metabolite cytotoxicity.[808] It should be noted that the glycosyltransferase involved in vicenistatin biosynthesis displays broad substrate tolerance and also was among the first to be studied in the context of glycosyltransferase reversibility.[813,814]

12.12. Spirotetronates

Spirotetronates are pentacyclic polyketides that contain a signature fused 6-membered/γ-butyrolactone spiro-bicyclic ring substructure and are produced by *Amycolatopsis*, *Streptomyces*, *Actinomadura* and *Micromonospora*. Several spirotetronate *O*-glycosides have been reported (Fig. 37) where dominant glycosyl regioselectivity observed is α- to the bicyclo[4.4.0]decene ring fusion (as exemplified by C-7 of chlorothricins or C-9 of tetrocarcins). Additional *O*-glycosylation is observed at C-17/19 of the largest macrocyclic ring in some members (as exemplified by tetrocarcins and versipelostatins, respectively) and, in one case, C-6 (PA-46101 B).

As noted above, C-7/C-9 *O*-glycosylation is a predominate feature. Examples of C-7 glycosylation include disaccharide **I** comprised of two β-D-olivose (**53**) units (chlorothricins,[815] MC-031 and MC-033[816]), disaccharide **II** comprised of a β-D-olivose (**53**) and β-D-quinovose (**140**) (hydroxychlorothricins,[815] K818,[817] MC-032, and MC-034),[816,817] or disaccharide **III** continaing 6′-deoxy-β-D-allose (**170**) and 5′-*O*-methyl-β-D-digitoxose (**131**) (PA-46101A and B).[818] The terminal olivose sugar (**53**) of these metabolites is often further modified as observed in chlorothricin and related analogs (Fig. 37, appendages **i–iii**) and, as previously noted, PA-46101 B also contains an additional C-6-appended 3′-C-methyl-α-L-rhamnose (**108**). C-9 glycosylation also predominates with monosaccharyl substitution observed on occasion (*e.g.*, the acylated trideoxy amino sugar **213** in BE-45722,[819] BMY-42448,[819] decatromicins,[820] pyrrolosporin A[389]) and oligosaccharyl substitutions units typically containing α- and/or β-L-digitoxose (**68** and **176**, respectively) and α-L-amicetose (**97**) as more prevalent (*e.g.*, oligosaccharides **IV–VII**, tetrocarcins[821] and AC6H);[822] disaccharide **VI**, arisostatins;[823] trisaccharide **VIII**, lobophorins;[824,825] tetrasaccharide **IX**, kijanimicin.[826,827] The α,β-unsaturated aldehyde-containing deoxysugar (**216**) of tetrocarcin K stands out as a unique glycoside among this series (Fig. 37, **VII**).[828]

C-17 and C-19 glycosylation is less common. Examples of C-17 glycosylation include the unique nitro sugar β-D-kijanose (also known as β-D-tetronitrose, **214**; tetrocarcins,[821,822] lobophorins B,[824,825] kijanimicin,[826,827] arisostatin A[823]), the corresponding amino analog **218** (AC6H, lobophorin A,[824,825] arisostatin B[823]), and variations of 3′,4′-diamino-2′,3′,4′,6′-tetradeoxy-β-D-galactose (**219**, MM 46115).[829] C-19 glycosylation is restricted to the larger versipelostatin aglycon and employs a series of oligosaccharides (**X–XVI**, Fig. 37) comprised of β–D-digitoxose (**131**), 3′-*O*-methyl-α-D-olivose (**183**) and/or α-L-oleandrose (**184**) monomers.[830–832]

Spirotetronates possess antitumor, antiviral and antimicrobial activities where metabolite glycosylation, in most cases, is critical to activity.[829] For example, a reduction in tetrocarcin glycosylation correlates to diminished antibacterial activity,[833] while the sugar variation among lobophorin analogs contributes to antibacterial activity modulation.[825] Sugar variation of MC-031 congeners also contributes to potency modulation in the context of cholesterol biosynthesis inhibition.[816] Versipelostatins were reported to down-regulate the GRP78 molecular chaperone which has potential application in cancer, Alzheimer's and Parkinson's.[832]

12.13. Spinosyns

Spinosyns are a structurally unique group of reduced polyketide macrolactams from *Saccharopolyspora*. A total of 23 spinosyn *O*-glycosides have been reported thus far.[18,834] Spinosyns contain two *O*-glycosides critical to their insecticidal activities, a C-9 α-L-rhamnose (**46**) and a C-17 β-D-forosamine (**63**) (Fig. 37). Spinosyn variation is based, in part, upon differential methylation of the corresponding glycosides and SAR studies revealed both sugars to contribute to bioactivity.[835]

13. Nucleosides and nucleoside-derived compounds

Compounds in this class are divided into pyrimidines (uracil- or cytosine-derived) and purines (adenine- or guanine- derived) metabolites. While metabolites with a modified ribose core are included herein, classical ribose-based nucleosides are considered outside the scope of this discussion. A total of 280 glycosylated bacterial metabolites are encompassed within this broad class where pyrimidine nucleoside antibiotics comprise the predominate group.[836]

13.1. Pyrimidine-derived nucleosides

13.1.1 Uracil-derived nucleosides—The first major subclass of uracil-derived nucleosides includes streptovirudins, tunicamycins, and corynetoxin isolated from *Streptomyces*, *Bacillus*, and *Coryne-bacterium*-infected *Lolium*.[837–840] This group includes 23 metabolites and structural signatures include a uracil or dihydrouracil (Fig. 38), an amide-linked fatty acid, a dialdose sugar attached to the N-1 of the uracil moeity, and *N*-acetylglucosamine (**5**). The corresponding dialdose sugar, a unique 11-carbon amino sugar (tunicamine, **222**) comprised of a carbon-carbon bond fusion between C-6 of galactosamine and the uridine ribose C-5, is connected head-to-head to *N*-acetyl-α-D-glucosamine (**5**) (Fig. 39).[841] While potent antibacterial cell wall inhibitors, these agents lack clinical utility due to their inhibition of *N*-linked protein glycosylation in mammalian cells.[842]

The next subclass, the uridylpeptide antibiotics, includes mureidomycins,[843,844] napsamycins,[845] pacidamycins,[846,847] and sansanmycins from *Streptomyces* and *Pseudomonas*.[848–850] The 25 members of this group share a common skeleton that consists of a uracil or dihydrouracil attached to a 4′,5′-unsaturated-3′,5′-dideoxyribose (**332**) at the uracil N-1. This modified ribose is connected to a 2,3-diaminobutyric acid (DABA) *via* a 4′,5′-enamide linkage to which are appended various amino acids (Fig. 39). The uridylpeptides selectively inhibit bacterial translocase (MraY) and, while both the modified ribose and uracil are critical to activity, analogs in which the enamide has been reduced retain activity.[851]

Twenty-two glycosylated muraymycins and related metabolites from *Streptomyces* comprise the next subclass.[852] The core structure is composed of a peptide, uracil, uronic acid (**330**), and a modified ribose which terminates with a hexahydro-2-imino-4-pyrimidylglycyl (epicapreomycidine)–urea–valine moiety (Fig. 39, X = **i**). Members of this family differ *via* either the terminal amino sugar [5′-amino-5′-deoxy-β-D-ribose (**221**), 2′-methoxy-**221**, or 5′-amino-2′,5′-dideoxy-β-D-ribose (**224**)] and/or the fatty acid (Fig. 39). Three related

epicapreomycidine-containing analogs [AA-896-A6, C5 and D4 (Fig. 39, X = **i**)] contain sugar **221** attached to C-5′ of the ribose moiety of uridine.[853] Muraymycins also effectively inhibit bacterial translocase (MraY). Interestingly, while removal of the aminoribose primary amine abolishes activity,[854] derivatives lacking aminoribose remain active.[855]

Eighteen glycosylated capuramycins (A-500359) and related metabolites produced by *Streptomyces* and *Amycolatopsis* comprise the next subclass. In addition to the structural aminocaprolactam signature (Fig. 39, X = **ii**), the capuramycin skeleton consists of a uracil nucleoside with a unique 4′,5′-unsaturated α-D-mannuronic acid (**225**) connected to the C-5′ of a modified ribose (**331** forming disaccharide **III**, Fig. 39). Exceptions include A-500359 D, which contains the 2′-deoxy analog of **225** (**333**), and A500359 J which bears the C-4′-C-5′-hydrated form of **225** (α-D-taluronic acid, **52**).[856] Inhibition of lysine biosynthesis, *via* feeding the capuramycin production strain 2-aminoethyl-L-cysteine, led to additional analogs where the signature aminocaprolactam moiety was lacking (A-500359 E, F, F-amide, H), or replaced with acetylcystamine (M-1) (Fig. 39, X = **iii**) or a thiazepanone moeity (M-2) (Fig. 39, X = **iv**).[857–859] A-503083 A, B, E, and F also contain disaccharide **III** composed of **225** and **331**.[860] A-102395, which has a benzene group in place of the caprolactam moiety, is the only analog isolated from a non-*Streptomyces* species.[861] Additional modifications of capuramycin-type metabolites include ribose 2′-*O*-acylation and 3′-*O*-methylation, the former of which has been noted to improve cell permeability.[862] Members of this class also function as translocase (MraY) inhibitors and display notable anti-tubercular activity but suffer from poor bioavailability. Based upon existing SAR, a core structure containing the modified ribose, an unsaturated hexuronic acid and an aminocaprolactam offers the best activity.

The liposidomycins and caprazamycins from *Streptomyces* comprise the next subclass and the 38 glycosylated members within this group share a common structural skeleton that is composed of uracil, a modified ribose (**330**), a corresponding ribose C-5′-appended aminoribose (5′-amino-5′-deoxy-β-D-ribose, **221**) and an acylated diazepanone (Fig. 39, X = **v**). Liposidomycins are subclassified into four types based on the presence or absence of the aminoribose (**221**) 2′-sulfate and/or the diazepanone side chain C-3 modifications (Fig. 39, X = **v**).[863–865] Type I contains both groups while type IV lacks both. Type II and III lack the diazepanone glutaryl modification and sulfation, respectively. Caprazamycins resemble type III, and to lesser extent type I, liposidomycins but contain an additional 2′,3′,4′-tri-*O*-methyl-α-L-rhamnose (**46**) attached to C-5 of diazepanone-appended methyl-glutaryl group (Fig. 39, appendage **v**). In A-90289 A and B, C-2′ sulfation of the modified ribose **330** rather than aminoribose **221** is observed.[866,867] Liposidomycins, caprazamycins, and A-90289 also inhibit translocase (MraY) where the type I analogs were found to be most active.[836,868] Synthetic derivatives modified at the ribose C-5′ display improved potency.[836]

Ezomycins are a group of pyrimidine-based *N*- and *C*- glycosidic antifungal compounds isolated from *Streptomyces*.[869–877] Glycosylation within this subclass occurs at either the N-1 (ezomycins A1 and A2), C-5 (ezomycins B1, B2, C1, C2), or C-8 (ezomycins D1/D2) (Fig. 38) where the predominate glycosylation signature is comprised of a *trans*-fused furopyranoside 3′,7′-anhydrooctose (**236**) which is further glycosylated at C-6′ with 3′-amino-3′,4′-dideoxy-β-D-glucuronic acid (**235**, also called ezoaminuroic acid).[875] This

octosyl nucleoside-ezoaminuroic acid (**235**) ezomycin core is sometimes referred to as ezomycin disaccharide (**VII**). Exceptions include ezomycins D_1 and D_2 which carry a 3′-amino-3′,4′-dideoxy-β-D-glucuronic acid-(1→4)-3′-deoxy-3′-ureal-β-D-guluronic acid disaccharide (**VIII**). Some ezomycins are further substituted *via* a hexuronic acid C-6′-L-cystathionine amide, a modification important to antifungal activity.

Nikkomycins (also referred to as neopolyoxins)[878–883] and polyoxins[884,885] are peptidyl nucleosides isolated from *Streptomyces* that contain a pyrimidine aglycon typically comprised of uracil, thymine or, in some cases, 4-formyl-4-imidazolin-2-one. For simplicity, all glycosylated nikkomycins and polyoxins regardless of the base are included herein. Nucleoside *N*-1-glycosylation with 5′-amino-5′-carboxy-5′-deoxy-β-D-ribose (**223**) is a predominate feature (Fig. 39) where this hexuronic acid is typically further modified in most nikkomycins by a rare amino acid hydroxypyridylhomo-threonine *via* a C-6′-amide linkage. Exceptions include nikkomycins S_x/S_z and So_x/So_z, which carry the bicyclic sugars **227** and **228**, respectively,[882] and the uracil C-5-*C*-glycosides nikkomycins pseudo J/Z. Octosyl acids are also structurally related to nikkomycins and polyoxins but lack the aminohexuronic acid.[886] Derivatives A and B contain modified pentose **227** while C contains the keto derivative **229**. While nikkomycins and polyoxins are potent inhibitors of chitin biosynthesis in fungi and display notable antifungal activity,[887] their unfavorable physicochemical properties has hampered their clinical development.

Other uracil-based metabolites include the C-5-*C*-nucleosides malayamycin A and de-*O*-methylmalayamycin A from *Streptomyces*, which are inhibitors of fungal sporulation and contain the bicyclic sugar **230** (Fig. 39).[888–890] A bacterial translocase inhibitor, A-94964A contains two unidentified sugars, 2′-deoxy-2′-aminohexosyl-1-phosphate (**234**) and a hexose (**334**), attached to a riboocturonic acid (**233**) appended to *N*-1 of uracil.[891,892]

13.1.2 Cytosine-derived nucleosides—The first main group in this subclass includes amicetins, cytosaminomycins, and SF-2457. This group is comprised of eleven metabolites from *Streptomyces*, *Arthrobacter*, and *Nocardia*,[893–899] most of which contain a *N*-1-β-disaccharide (**I** or **II**) and *p*-aminobenzamide-modification of the cytosine 4-NH_2. The dissaccharide is comprised of either β-D-amicetose (**48**) or β-D-olivose (**53**) attached α-(1′→4′) to either α-D-amosamine (**39**) or *N*-demethyl-α-D-amosamine (**39**). Amicetin inhibits the bacterial peptidyl transferase by binding 23S-like rRNA.[900] Amicetins were also found to be active against herpes virus 1 and poliovirus[901] cytosaminomycins have been noted for anticoccidial activity.[898,902]

Mildiomycins from *Streptoverticillium* are a group of cytosine *N*-1-glycosidic peptidyl nucleosides bearing C-2′-C-3′ unsaturated C-4′-*N*-acyl-β-D-hepturonic acid derivatives (**241** and **242**) (Fig. 40).[903–905] These molecules have activity against powdery mildews and function as protein synthesis inhibitors *via* binding the ribosomal large subunit.[906] The related sugar **240a** and corresponding esters are present in the antibacterial arginomycin and related 10381 series from *Streptomyces*,[907,908] while **240b** or its hydrated congener **243** exists as part of the antifungal blasticidins from *Streptomyces*. Cytosylglucuronic acid bearing a N1-2′-deoxy-β-D-glucuronic acid (**249**) was isolated from the same strain while cytosyl-*N*-1-glycosides bearing unique 4′-amino-, keto-, or oxime-functionality (**244a**,

244b, **245**, and **246**), were also isolated from bioconversion experiments with this same blasticidin producer.[909–913] Additional studies, in conjunction with enzyme inhibitors, yielded an even extended glycoside diversity to include β-D-glucose (**104**), **261–265**, **136**, **72** and **243** attached to pentopyranines.[910,913–915] Hikizimycin, also referred to as anthelmycin, from *Streptomyces* is a cytosyl-*N*-1-β-D-dissacharide (**III**), the latter of which is comprised of 3′-amino-3′-deoxy-β-D-glucose (kanosamine, **250**) linked β-(1′→6′) to an unusual 4′-amino-undecose (hikosamine, **256**) (Fig. 40).[916–918] Hikizimycin displays antiparasitic activities and inhibits protein synthesis.[919] The *Bacillus* metabolites bagougeramines A and B both contain modified cytosyl-*N*-1-4′-amino-4′-deoxy-β-D-glucuronamides (**251**, appendage **iv**) and function as antimicrobials.[920] Sugar **251** was also found to be present in mitaimeisu (appendage **v**),[921] gougerotin (appendage **vi**),[922] and possibly ningnanmycin;[923] although in the latter case the C-3′-stereochemistry remains undefined (**247**). Albomycins from *Streptomyces* are siderophore antibiotics similar to other sideromycins (Section 15.4) are composed of iron chelating portion in addition to a 6′-amino-6′-deoxy-4′-thio-heptofuranose (**315**) uronic acid moiety (Fig. 40).[924,925] Dapiramicins A and B from *Micromonospora* are *N*-glycosidic pyrrolopyrimidines bearing 6′-deoxy-α-D-glucose (**215**) or β-D-glucose (**104**), respectively, each capped (β1→4) with 4′-methyl-β-D-glucose (**104**).[926,927] The α-configured dapiramicin A with disaccharide **IV** possessed significantly higher activity against the plant disease, sheath blight than the analog bearing **V**.

13.2 Purine-derived nucleosides

13.2.1 Adenine-derived nucleosides—There are 32 adenine-based glycosides reported where *N*-glycosylation is restricted to the adenosyl N-9 and C-6-amine. The adenosyl *N*-9-amino-pentose 3′-amino-3′-deoxy-α-L-ribose (**253**) was found in puromycin[928] and A-201-A, C, D, and E,[929,930] from *Streptomyces* (Fig. 41) where the 3′-*N*-tyrosyl moiety contains additional glycosylation in the A-201 series (**335** in A, C, and D; **336** in E – capped with 3′, 4′-di-*O*-methylated α-L-rhamnose **46** in A, C, and E).

Sinefungins from *Streptomyces* are a group of adenosyl-*N*-9-glycosidic antileshmanial and antitrypanosomal metabolites signified by an unusual ribose-derived 10-carbon sugar, likely formed *via* a carbon–carbon bond-forming reaction between adenosine and an amino acid.[931–933] Sugar **337** and its amide derivative **339** are present in sinefungin and ureidosinefungin, respectively. Sugar **339** is also present in sinefungin VA with appendage **iii** attached to the terminal amino group (Fig. 41). Sugar **340** is a cyclic version of **339** and is present in cyclosinefungin. Sugars **252** and **338** are 4′,5′-unsaturated derivatives of **337** and **339**, respectively, and are present in other sinefungin derivatives. Dehydrosinefungin V and KSA-9432 contain the same sugar **338** with appendages **i** and **ii**, respectively (Fig. 41). These metabolites function as *S*-adenosylmethionine (AdoMet) mimetics and methyltransferase inhibitors where derivatives with unsaturated sugars were found to generally be less potent.[934]

Herbicidins are a group of herbicidal compounds isolated from *Streptomyces* that contain an interesting tricyclic furanopyranoside (**254**) attached to the adenosyl N-9 (Fig. 41).[935–939] The antitumor compound septacidin from *Streptomyces* contains a C-4′-amino-modified 4′-

amino-4′-deoxy-β-L-glucoheptose (**257**) connected to C-6 amino group of adenine (Fig. 41, appendage **vii**). Replacement of the natural sugar with 4′-amino-4′-deoxy- or 4′-amino-4′, 6′-dideoxy-L-glucose did not affect activity.[940] C-4′-amino-modified analogs of the C-2′-epimer (4′-amino-4′-deoxy-β-L-mannoheptose, **255**) are found in the antitumor compounds spicamycin and anicemycin from *Streptomyces*.[941,942] Agrocin 84 is a diglycoside structurally related to sugar phosphate opines used to control crown gall disease in plants.[943] Agrocin 84 contains a C-5′-modifed adenosyl-*N*-3′-deoxy-β-D-arabinofuranose (**259**) and a corresponding β-D-glucofuranoside (**258**) linked to the adenosyl C-6-amine *via* a phosphoramidate bond (Fig. 41 appendage **ix**). The β-L-gulosamine (**260**) in the pseudodisaccharide **III**, present in mitocides C-8030 C, D, and E from *Streptomyces*, is connected to the C-5′ of the ribose through a cyclohexane ring.[944] Anhydrothuriniensin isolated from *Bacillus* contains a disaccharide **IV** composed of α-D-glucose (**18**) linked to the β-D-ribose sugar of adenosine.[945,946] Griseolic acids isolated from a *Streptomyces* species, contain four unique nine carbon bicyclic sugars **341–344** (Fig. 41).[947,948] They were found to inhibit cyclic nucleotide phosphodiesterase.[949]

13.2.2. Guanine and other miscellaneous nucleosides—The sugar α-D-mannose (**160**) is present in the chitin synthase inhibitor guanofosfocin A from *Streptomyces*, the only guanine-based glycoside reported.[950] In this unique metabolite, the mannose serves to bridge the base C-8 and ribose C-5 of guanosine diphosphate (*via* connections at C-1′ and C-3′, respectively) (Fig. 41).

Miharamycins A and B,[951] amipurimycin[952,953] from *Streptomyces* belong to atypical purines. All are aminopurine *N*-9-glycosides where miharamycins contain modified bicyclic D-sugars (**238**) and amipurimycins the unusual modified D-sugar **239** (Fig. 41).

14. Orthoester glycosides

Orthoester glycosides are a group of metabolites that are characterized by the presence of one or more of acid sensitive orthoester glycosides. A total of 50 orthoester glycoside-containing bacterial metabolites have been reported, 47 of which fall within two major subclasses – orsellinic acids (subclass **I**) and aminocyclitols (subclass **II**). Three additional orthoester glycoside-containing outliers can be found within the macrolide (kanglemycin A and swalpamycin, Section 12) and the polyene (polyene SE-73, Section 11) sections.

14.1. Orsellinic acid derivatives

Members of the orsellinic acid subclass of the orthoester glycosides have attracted attention for both their exciting bioactivity and unprecedented oligosaccharide-based structural diversity. Members of this class possess potent activity against antibiotic-resistant *Staphylococcus* and *Enterococci* and include the everninomicins, avilamycins, and flambamycin.[954] These unique metabolites function *via* inhibiting bacterial protein synthesis through binding at a unique site of the bacterial 50S ribosomal subunit.[955,956] One member of this family, ziracin, advanced to phase III clinical studies but was ultimately discontinued due to side effects and poor pharmacokinetic properties.[957]

Sixteen avilamycins from *Streptomyces* contain a signature chloroisoeverninic C-4-heptasaccharide ester.[958–960] Additional avilamycin-derived gavibamycins were generated through pathway engineering.[961–964] The heptasaccharide moiety **I** of avilamycin A (Fig. 42), is composed of two units of β-D-olivose (A and B, **53**), 2′-deoxy-β-D-evalose (C, **192**), 4′-*O*-methyl-β-D-fucose (D1, **270**), 2′,6′-di-*O*-methyl-β-D-mannose (E, **156**), 2′-*O*-isobutyryl-α-L-lyxose (F, **111**), and the C-4′-branched sugar methyleurekanate (G1, **272**). Subtle variants where **272** has been substituted with **270** (β-D-fucose, avilamycin A1 and gavibamycin O), **273** (gavibamycins A3, B3, J3, K3, L3, E3, H3, I3) or **274** (avilamycin L) have also been reported. In addition, analogs where β-D-fucose (D1, **270**) has been replaced by 4′-*O*-methyl-β-D-arabinose (D2, **265**; avilamycin M) or β-D-galactose (D3, **161**; avilamycin K) are also known (Fig. 42).

The closely related everninomicins[965–968] from *Micromonospora* include both ziracin (evernimicin) and a series of SCH-compounds identified by Schering-Plough.[969–971] Everninomicins are distinguished by an additional sugar (C-3′-nitrosugar α-L-evernitrose, H1, **127** or aminosugar H2, **280**) attached to C-3′ of sugar A to provide octasaccharide **II**. Analogs that contain reduced nitro sugar such as the hydroxylamino (H3) or nitroso (H4) derivatives have also been obtained by reduction during structure elucidation or derivatization and have shown comparable antibacterial activity.[967] A second delineation stems from the replacement of the avilamycin sugar G (β-D-methyleurekanate) by β-D-eurekanate **265** (everninomicin C, ziracin, SCH49088, SCH58775) (Fig. 42) or the C-4′-branched sugar **271** (everninomicins B and D, 13385-1).[972] In some everninomicins, 2′-deoxy-β-D-evalose (C1, **192**) is replaced by 6′-deoxy-3′-*C*-methyl-β-D-mannose (C2, **268**). The hydrolytic products (sporacuracins and Sch-58777 which contain only sugars E, F, and G)[973] lack antibacterial activity[970] while removal of the nitro sugar has no major effect.[958,974]

14.2. Aminocyclitol derivatives

Members in this class are also considered aminoglycosides (Section 1) and include destomycins,[975–977] hygromycin B,[978] RH5012 C,[979] and SS-56-C[980] from different bacteria including *Streptomyces*, *Streptoverticillium*, and *Saccaropolyspora* (Fig. 43). The aglycon in this subclass contains an aminocyclitol moiety derived from D-streptamine (hyosamine, **P7**) bearing a C-5 glycoside comprised of either β-L-talose (**144**) or β-D-mannose (**156**). The signature orthoester glycoside linkage occurs between the C-2′/C-3′ and the anomeric carbon of the 7-membered amino sugar, destomic acid **275** (Fig. 43). It is worth noting that analogs which lack destomic acid (and thus, the orthoester linkage) are inactive.

15. Peptides

Glycosylated peptides represent a large and clinically-important group of bacterial metabolites and its members invoke a broad range of activities particularly relevant to anti-cancer and anti-infective development. For the scope of this discussion, glycosylated peptides have divided into distinct sections covering bleomycins, vancomycins,

mannopeptimycins, salmochelins and salmycins, linocosamides, thiazoles, lipoglycopeptides, miscellaneous antiinfective peptides and miscellaneous (other) members.

15.1. Bleomycins

Bleomycins are a group of cytotoxic glycopeptides from *Streptomyces* that bind both DNA and a metal [typically Cu(I) or Fe(II)] and invoke oxidative DNA strand cleavage.[981–986] While members of this family (Blenoxane®) have been used with great success clinically to treat malignant lymphomas,[478,986] dose-dependent pulmonary fibrosis and drug resistance restrict broader application. In conjunction with the structurally-related metabolites phleomycins,[987,988] tallysomycins,[989,990] zorbamycin,[991,992] cleomycins,[993,994] LL-BO 1208,[995] and platomycin,[996] the total number of glycopeptides in this class is 69.[985] Structure divergence among members derive primary from subtle variations within the peptide linker, oxidative state of the bithiazole (BTT), the terminal substituted amide[58,990,997,998] and, the presence (as in tallysomycins) or absence of a second point of glycosylation (Fig. 44). All members contain a conserved *O*-disaccharyl-substituted β-hydroxyhistidine, the disaccharide composition of which is 3′-*O*-carbamoyl-α-D-mannopyranosyl-(1′→2′)-α-L-gulose (**I**) in most [the exception being 3′-*O*-carbamoyl-α-D-mannopyranosyl-(1′→2′)-6′-deoxy-α-L-gulose in zorbamycin, **II**].[999] Tallysomycins differ from other members *via* an additional *O*-glycosylcarbinolamide bearing 4′-amino-4′, 6′-dideoxy-α-L-talose (**279**) at C-13 of the bithiazole moiety (Fig. 44). Zorbamycin-bleomycin disaccharyl hybrids have also been constructed *via* strain engineering.[1000] The precise role of the disaccharide remains controversial and hypotheses include improving DNA affinity and cleavage[985,1000,1001] as well as extracellular recognition and uptake.[1002,1003] In support of the latter, the disaccharide moiety was demonstrated to target tumor cells possibly by a specific ATP-dependent uptake mechanism.[1002,1003]

15.2. Vancomycins

Vancomycins are cyclic glycopeptides comprised of seven amino acids, the heptapeptide core of which presents two 16-membered and one 12-membered ring. Members are classified into four different subclasses based on the heptapeptide core and cumulatively, there are 133 corresponding bacterial glycopeptide members isolated from different bacteria including *Streptomyces*, *Nocardia*, *Pseudonocardia*, *Amycolatopsis*, *Actinoplanes*, *Kibdelosporangium*, *Micropolyspora*, *Saccharothrix*, *Actinomadura*.[1004] Type I glycopeptides contain two aliphatic (residues 1 and 3) and five aromatic amino acids, while types II–IV contain seven aromatic amino acids (Fig. 45). Type III differs from type II by an additional ether-bridged ring system between residues 1 and 3 while type IV (generally referred as lipoglycopeptides) differs from type III *via N*-acyl-substitution of appended sugars. Other compounds that are structurally related to vancomycins but lack the sugar include the complestatins,[1005–1007] chloropeptins,[1008] and A-47934.[1009] Each of the previous types, with a particular focus upon glycosylation, is further elaborated herein.

Vancomycin from *Amycolatopsis* is the prototypical member of the type I sublcass. First discovered in the mid-fifties, the structure of this metabolite was not elucidated until 30 years later.[1010–1012] Vancomycin is a potent antibiotic to treat life-threatening Gram-positive infections and inhibits bacterial cell wall biosynthesis by binding peptidoglycan L-Lys-D-

Ala-D-Ala.[1013–1015] In addition to vancomycin, there are 37 glycosylated type I metabolites. The predominate site of *O*-glycosylation within type I–IV members is the phenolic hydroxyl of residue 4 (hydroxyphenylglycine, HPG-4, Fig. 45). To a lesser extent, *O*-glycosylation of the substituted β-hydroxy-L-tyrosine (Tyr-6) is also observed among type I–IV members. HPG-4 *O*-glycosylation is comprised of a β-D-glucose (**104**, devancosamine vancomycin, M43C, most balhimycins, and chloro-orienticins B and E) or an α-L-sugar-(1′→2′)-β-D-glucose disaccharide (**I–IV**) where the L-sugar varies among members and includes: α-L-vancosamine (**118**, vancomycins)[1016–1018] 4′-oxo-α-L-vancosamine (**281**, balhimycin V, A-83850);[1019–1021] 4′-*epi*-α-L-vancosamine (**280**, eremomycin, orienticins, and chloro-orienticins A and D)[1022] and its *N*-carboxymethyl derivative (**280**, eremomycin B);[1023] or α-L-rhamnose (**46**, decaplanin, A-42867, MM 47761, and MM 49721) (Fig. 46).[1024] Sugars employed for residue 6 tyrosine (Tyr-6) β-hydroxy *O*-glycosylation within type I members include: ureido-α-L-vancosamine (**282**, ureidobalhimycin);[1019–1021] 4′-oxo-α-L-vancosamine (**281**, balhimycins);[1021] 4′-*epi*-α-L-vancosamine (**280**; eremomycin,[1022] orienticins, A, C, D, chloro-orienticins, decaplanin, MM 47761, MM 49721[1025]); α-L-olivose (**184**, orienticin B);[1026,1027] or α-L-vancosamine (**118**, MM 49727, A-42867) (Fig. 46).[1024] OA-7653[1028,1029] from *S. hygroscopicus* is unique among type I members as it contains α-D-glucose (**18**) attached to the residue 6 tyrosine-β-hydroxyl but, similar to chloro-orienticins C and F, lacks residue 4 phenolic hydroxyl glycosylation. Importantly, the broad substrate specificity of the residue 4 phenolic glucosyltransferase GtfE has been exploited to generate a wide range of differentially glycosylated analogs.[1030–1032]

There are 21 metabolites classified as type II including avoparcins,[1033,1034] galacardins,[1035] helvecardins,[1036] chloropolysporins,[1037] and actinoidins[1038–1041] from *Streptomyces*, *Nocardia*, *Pseudonocardia*, *Micropolyspora*, *Saccharothrix*, *and Nonomuraea*. Variant glycosylation is observed among type II metabolites with heavily glycosylated members containing maximally seven sugars at five glycosylation positions (galacardins) while sparsely glycosylated members contain just a single monosaccharide (demannosyl-A-40926). Of these, only avoparcins, galacardins, and actinoidins contain the residue 4 phenolic β-D-glucose (**104**, chloropolysporins and deristosaminyl-avoparcins) or α-L-sugar-(1′→2′)-β-D-glucose disaccharyl signature (**IV–VI**) typically observed among type I members where the terminating sugar can be α-L-rhamnose (**46**; actinoidin A2), α-L-ristosamine (**45**; avoparcins, galacardins and helvecardins), or α-L-actinosamine (**124**; actinoidins A and B, MM 47766, MM 47767, MM 55256, MM 55260) (Fig. 46). Like type I members, residue 6 tyrosine-β-hydroxyl *O*-glycosylation is also prevalent among type II members and includes α-L-ristosamine (**45**; avoparcins, galacardins, helvecardins, chloropolysporins) or 4′-*O*-methyl-α-L-actinosamine (**124**, actinoidins, MM 47766, MM 47767, MM 55256, MM 55260, MM 55261). Distinct from type I members, *O*-glycosylation of the residue 2 tyrosine-β-hydroxyl and/or phenolic hydroxyl of residues 1, 3 and/or 7 is also observed among type II members. Type II member residue 1 phenolic hydroxyl *O*-glycosylation employs two sugars α-L-rhamnose (**46**, chloropolysporins, helvecardin B, avoparcins) or a disaccharide α-L-rhamnosyl-(1′→4′)-α-D-galactose (**VII**, galacardins), while a single sugar, α-D-mannose (**160**), is observed for residue 2 tyrosine-β-hydroxyl *O*-glycosylation (avoparcins, galacardins, chloropolysporins, helvecardin A) (Fig. 46). An α-D-mannose (**160**) or β D-mannose (**156**) are observed at residue 7 phenolic *O*-glycosylation

(actinoidins, MM 47766, MM 47767, MM 55260). Finally, residue 3 phenolic *O*-glycosides are comprised of α-D-galactose (**286**, avoparcins and galacardin A). With respect to activity/use, the use of avoparcins as animal growth promoters was banned due to reports of increased vancomycin resistance[1042] while helvecardins were demonstrated to inhibit *Neisseria gonorrhoeae* in addition to Gram positive bacteria.[1036]

There are 23 metabolites classified as type III including ristocetins,[1043–1046] A41030 C, F, and G,[1047] actaplanins,[1048–1051] UK-69542, and UK-68,597[1052] from *Actinoplanes*, *Nocardia*, and *Streptomyces* species. Variant glycosylation is observed among type III metabolites with heavily glycosylated members containing maximally six sugars at three glycosylation positions (ristocetin A) and sparsely glycosylated members containing just single monosaccharides (A41030C). *O*-glycosylation of the residues 1, 3, 4, and/or 7 phenolic hydroxyls and/or the residue 6 tyrosine β-hydroxyl is observed among type II metabolites. Residue 1 phenolic hydroxyl *O*-glycosylation is only observed among A41030 metabolites with β-D-galactose (**161**) or a β-D-galactosyl-(1′→4′)-β-D-galactose disaccharide (**VIII**). Likewise, only a single sugar is observed [D-mannose, α-**160**, β-**156**] as residue 3 (actaplanins) and/or residue 7 (actaplanins, ristocetin A) phenolic hydroxyl *O*-glycosyl substituents. Wider variation is observed among the residue 4 phenolic hydroxyl *O*-glycosylation patterns. For example, actaplanins B2, C3, G, O, and brominated actaplanins contain the single sugar β-D-glucose (**104**) while other type III metabolites contain D-hexosyl-(1′→2′)-β-D-glucose (**IX**, **X**, **I**) disaccharyl substitution reminiscent of type I/II metabolites where the terminal sugar is either D-mannose (α-**160**, β-**156**) or α-L-vancosamine (**118**, UK-68597). Other observed disaccharides at this position include α-L-rhamnosyl-(1′→4′)-β-D-glucose (**XI**, actaplanins) and α-L-rhamnosyl-(1′→6′)-β-D-glucose (**XII**, actaplanins) (Fig. 46). Alternatively, in ristocetin A the α-D-mannosyl-(1′→2′)-β-D-glucose disaccharide is further modified at the glucose C-6′ by α-L-rhamnose (**46**) and at the mannose C-2′ by α-D-arabinose (**204**), forming tetrasaccharide **XIII**. Like type I/II metabolites, residue 6 tyrosine β-hydroxyl *O*-glycosylation in type III is observed to engage uniquely functionalized sugars including α-L-ristosamine (**45**; ristocetins and actaplanins) and the 2′,3′,6′-trideoxy-α-L-hexose **44** of UK-69542 (Fig. 46). Regarding activity/use, ristocetins were approved for clinical use but were subsequently removed due to thrombocytopenia and platelet agglutination.[1043–1045] While the corresponding mechanism remains unclear, ristocetin causes von Willebrand factor to bind the platelet receptor glycoprotein Ib (GpIb), and is now used solely in the context of *in vitro* assays for the diagnosis of conditions such as von Willebrand disease (vWD) and Bernard–Soulier syndrome. Semisynthetic analogs, including those deriving from differential glycosylation, have revealed derivatives with improved antibacterial/antiviral potency, and/or less toxicity.

Type IV is the largest subclass with 46 members including teicoplanins,[1053–1056] RS1-4,[1054] kibdelins (AAD-609),[1057] aridicins,[1058] A-40926 analogs, parvodicins,[1059–1061] and MM 49728, MM 55266, and MM 55268[1062] from *Actinoplanes*, *Actinomadura*, *Kibdelosporangium* and *Amycolatopsis*. CWI-785 A-C (symonicins) are comprised of a similar aglycon where methionine has replaced dihydroxyphenylglycine (residue 3).[1063] *O*-glycosylation of the residues 4, 5, and/or 7 phenolic hydroxyls and/or the residue 6 tyrosine

β-hydroxyl is observed among type IV metabolites. Residue 4 phenolic *O*-glycosylation has been observed with various monosaccharides including *N*-acyl-2′-amino-2′-deoxy-β-D-glucosamine (**153**; teicoplanins, RS1-4, kibdelins, AAD-609), *N*-acyl-2′-amino-2′-deoxy-β-D-glucuronic acid (**283**, aridicins, parvodicins, A-40926, A-84575A), β-D-mannose (**156**; MM 49728, MM 55266, MM 55268, MM 56597), or a disaccharide β-D-mannosyl-(1′→2′)-β-D-glucose (**X**, A-39893) (Fig. 46). It is noteworthy that teicoplanins (approved an an antibacterial, Targocid®) and RS1-4 isolated from the same strain differ mainly in their sugar 2′-*N*-acyl substitution and this served as inspiration for the clinically approved semi-synthetic analogs such as dalbavancin (Dalvance™). MM 49728, MM 56597, MM 56598, MM 55266 and MM 55268 are the only type IV members that contain residue 5 phenolic *O*-glycosylation (β-D-glucose, **104**) while some variation in the sugars employed for residue 6 tyrosine β-hydroxyl *O*-glycosylation is observed [*N*-acyl-β-D-glucosamine (**153**), teicoplanins; 2′-amino-2′-deoxy-α-D-glucuronic acid (**285**), MM 49728, MM 55266, and MM 55268; α-L-ristosamine (**45**), CWI-785 A-C (symonicins), A-39893]. Teicoplanins, kibdelins (with the exception of AAD-609D), and aridicins also carry an α-D-mannose (**160**) as a residue 7 phenolic hydroxyl modification. CWI-785 A-C (symonicins) also contain β-D-glucose (**104**), α and β-D-mannose (**160** and **156**, respectively), and α-L-rhamnose (**46**), the position of attachment for which has not been confirmed.[1063]

15.3. Mannopeptimycins

Mannopeptimycins α-ε are hexapeptides made from D-tyrosine(Tyr-1), β-methylphenylalanine (MePhe-2), glycine (Gly-3), L-serine (Ser-4), and 2 units of β-hydroxyenduracididines (HyEnd-5 and HyEnd-6) (Fig. 47).[1064] All members are *N*-glycosylated with α-D-mannose (**160**) at the *N*-5-terminus of HyEnd-5. In addition, all members except mannopeptimycin β contain a common α-D-mannosyl-(1′→4′)-α-D-mannose (disaccharide **I**) appended to Tyr-1 phenolic hydroxyl group (C-6). Analogs γ, δ, and ε contain a C-2′, C-3′, C-4′-isovaleryl (Fig. 47, appendage **i**) modification of the terminal mannose (**160**), respectively. Like vancomycins, mannopeptins inhibit bacterial cell wall biosynthesis and display potent Gram positive antibacterial activity. The presence of the isovaleryl moiety (**i**) is important for antibacterial potency possibly by virtue of improving cell membrane penetration.

15.4. Salmochelins and salmycins

Salmochelins are glycosides of the catecholate-type enterobactins from *Salmonella* which function as siderophores for metal sequestration.[1065,1066] Four salmochelins have been characterized including SX (monomer), S1 (dimer), S2 (linear trimer) and S4 (cyclic trimer) where each monomeric unit is comprised of a L-serine (Ser) attached to a dihydroxybenzamide (Bnz). Salmochelins exist as *C*-glucosides (β-D-glucose, **104**) of the dihydroxybenzamide core structure (Fig. 47). Salmycins, hydroxamate-containing siderophores from *Streptomyces violaceus*, are glycosylated danoxamins at the C-1 position with disaccharides **II** or **III**.[1067,1068] Disaccharide **II** present in salmycins A and D consists of a unique 6′-methylamino-D-heptopyranose (**288**) attached at the C-2′ position to the rare 2′-hydroxyimino-α-D-glucose (**289**). Disaccharide **III** present in salmycins B and C contains the α-D-keto sugar 2′-oxo-α-D-glucose (**287**) in place of the hydroxylimino sugar

(**289**) (Fig. 47). This disaccharide is attached to the aglycon *via* an ester bond to C-6′ of the modified glucosyl unit. Salmycins were found to be strong inhibitors of the growth of *Staphylococci* and *Streptococci* and are therefore considered siderophore antibiotics (sideromycins).

15.5. Lincosamides

Lincosamides from *Streptomyces* are a group of clinically important antibacterials that target Gram positive and anaerobic bacteria as well as some protozoa through inhibition of protein synthesis. Including the lincomycins first discovered in 1963 (which serve as the basis for the semi-synthetic drug clindamycin, Dalacin®), 29 naturally-occurring members have been reported from *Streptomyces* species including celesticetins and U-57930 analogs.[1069–1074] Their core structure is composed of a unique thioglycoside with variable substitution of the anomeric thioether and the 6′-prolylamide (Fig. 48). The anomeric stereochemistry of the central sugar, 6′-amino-6′,8′-dideoxy-1′-thio-D-*erythro*-α-D-galactose (methylthio-lincosamide, **290**) (Fig. 48) is critical for antibacterial activity and oxidation of the thioether (to a sulfoxide) is also detrimental to function.[1075,1076] Additional derivatives have been obtained *via* precursor-directed feeding[1077–1081] including ribonucleotide derivatives where the proline has been replaced with a 4-ethyl-piperidine moiety.[1082]

15.6. Thiazoles

Thiazolyl peptides contain one or more signature thiazoles embedded within their macrocyclic architecture. In spite of their potent antibacterial activity members of this family have not advanced to the clinic due to poor biodistribution and pharmacokinetic properties. Currently 21 thiazole glycosides have been reported from different Actinomycetes including *Micromonospora*, *Amycolatopsis*, *Nocardia, Actinoplanes*, and *Amycolata*. Regiospecificity of glycosylation among the thiazomycin-type members (which includes thiazomycins,[1083,1084] nocathiacins,[1085–1087] glycothiohexides,[1088,1089] philipimycins[1090] and S-54832-A series[1091]) is restricted to the hydroxyl group of a modified glutamate residue (Glu), the C-4 of a thiazole ring (Thz-3) or a C-3 phenolic substitution of the unique 2,5,6-trithiazolyl-3-hydroxypyridine (Pyr) (Fig. 48). In contrast, SCH 40832 glycosylation occurs at the Thr-1 side chain hydroxyl (disaccharide **II** composed of two units of β-D-olivose **53** connected 1′→3′)[1092] (Fig. 48). The sugars found within thiazomycins, nocathiacins, and glycothiohexides include 2′,4′-dideoxy-4′-dimethylamino-3′-*C*-methyl-α-L-fucose (**292a**), oxazolidine-substituted 2′,4′-dideoxy-4′-amino-3′-*C*-methyl-α-L-fucose (**292b**), β-L-chromose **186**, 4′-deoxy-2′,3′-di-*O*-methyl-β-D-glucose **291** or β-D-quinovose (**140**) (Fig. 48). The related philipimycin I contains a trisaccharide [trisaccharide **I** comprised of 2′,3′-dimethoxy-α-L-rhamnosyl-(1′→4′)-β-D-amicetosyl-(1′→4′)-2′,3′-dimethoxy-α-L-rhamnose].[1090] The degradation product of philipimycin I (philipimycin II) contains only the monosaccharide 2′,3′-dimethoxy-α-L-rhamnose (**46**). In general, thiazole glycosylation was found to improve both solubility and antibacterial potency.

15.7. Lipoglycopeptides

The lipoglycopeptides presented herein are macrocyclic peptides bearing one or more signature lipophilic side chains and are separated for discussion by glycosides of the peptide core backbone and glycosides of lipid side chains. While most members in this group display antifungal activity (hassillidins from *Hassallia*,[1093,1094] occidiofungins[1095] and burkholdine[1096] from *Burkholderia*, cepacidines from *Pseudomonas*,[1097,1098] herbicolins from *Erwinia*[1099,1100] and W-10β from *Aeromonas*[1101]), the ramoplanins from *Actinoplanes* stand out as agents recently approved by the FDA to treat *C. difficile* (Fig. 49).[1102,1103] Ramoplanins are phenolic *O*-disaccharyl-substituted metabolites, the disaccharide **I** of which is comprised of two α-D-mannose (**160**) monomers. Ramoplanins display broad antibacterial activity *via* inhibition of cell wall biosynthesis however; serum instability restricts current use to oral applications. The cyclic lipopeptide hassallidins are also peptide core *O*-mannosides, both containing *N*-methylthreonine (MeThr-9) C-3-*O*-β-D-mannose (**156**) and hassallidin B having an additional threonine (Thr-2) C-3-*O*-α-L-rhamnose (**46**) (Fig. 49).[1093,1094] Both the mono and diglycosylated analogs of hassallidins presented comparable antifungal activity against *Aspergillus* and *Candida*. Finally, W-10β isolated from *Aeromonas* is a threonine residue (Thr-1) C-3-*O*-β-D-glucoside (**104**) with antifungal activity (Fig. 49).[1101]

The octapeptides occidiofungins[1095] and burkholdine[1096] also possess broad antifungal properties and display both core peptide and side chain *O*-glycosylation. Occidiofungins are C-3-*O*-β-D-xylosides (**136**) of a deaminated lysyl monomer (Fig. 49) while burkholdines are C-7-*O*-D-xylosides (**136** or **293**, anomeric stereochemistry undetermined) of the appended lipid side chain. Importantly, the corresponding glycoside displayed 4–8 fold increased antifungal potency compared to the aglycon burkholdine.[1097] Lipid side chain *O*-D-xylosyl modification (**136** or **293**, anomeric stereochemistry undetermined) was also observed in the antifungal metabolites cepacidines A_1 and A_2 (Fig. 49), where glycosylation occurs at C-5 of the 5,7-dihydroxy-3,9-diaminooctadecanoic acid.[1097,1098] Finally, the antifungal lipodepsinonapeptide herbicolin A also displays lipid side chain *O*-glycosylation with α-D-glucose (**18**) found at the C-3 position of the hydroxytetradecanoic acid residue.[1099,1100]

15.8. Miscellaneous anti-infective peptides

Miscellaneous glycopeptides with reported antibacterial and antifungal activities that fall outside the scope of those previously discussed are combined within this subsection, the predominant representation of which are polyamine peptides. The first group of compounds are comprised of an acylated spermidine (glycocinnaspermicin D and cinodines from *Nocardia*)[1104,1105] or 3-aminopropanamidine (coumamidines from *Saccharopolyspora*)[846,1105] conjugated to a cinnamoic acid moiety, the latter of which is glycosylated at C-7 with unique di- or trisaccharides (Fig. 50). The corresponding disaccharide **I** and trisaccharides **II–IV** are comprised of the core sugars 2′,4′-diamino-2′, 4′,6′-trideoxy-α-D-glucose (**295**), 2′-amino-2′-deoxy-β-D-xylose (**173**), 2′-amino-2′-deoxy-α-D-xylose (**24**) and 2′,3′-diamino-2′,3′-dideoxy-α-L-pentose (**296a–296c**) (Fig. 50). Unique features among this series include the high degree of C-2′, C-3′ and/or C-4′ carbamidyl/guanidinyl modification of the corresponding sugar monomers and the carbamide-glycosyl linkage exclusive to this family of metabolites. These compounds

exhibited broad spectrum antibacterial activity. Other polyamine antibacterial compounds include the cyclitol antibiotics LL-BM-123α and LL-BM-782 series from *Nocardia* (Fig. 50). They are Gram negative bacterial growth inhibitors that contain a pseudotri- and pseudodisaccharide, respectively (**V** and **VI**).[1106,1107] The pseudotrisaccharide **V** in LL-BM-123α consists of an arginine *N*-linked to the C-2′ of α-D-glucosaminyl-(1′→4′)-β-D-mannose conjugated to a modified myoinosamine (**P20**). The corresponding sugar of pseudodisaccharide **VI** in LL-BM-782 series is 3′-guanidino-β-mannose (**42**) which is conjugated to the aglycon *via* a modified myoinosamine (**P12**). Both LL-BM-123α and LL-BM-782 compounds displayed *in vivo* efficacy against Gram negative bacteria where LL-BM-782 was more potent but also more cytotoxic.

Non-polyamine metabolites include SQ 28504 and SQ 28546 from *Chromobacterium*,[964,965] formadicins from *Flexibacter*,[1108,1109] and theopalauamide and theonegramide from bacterial symbionts of *Theonella*.[1110–1112] SQ 28504 and SQ 28546 are C-4 bulgecinine (Blg-1) and C-3 threonine (Thr-3) di-*O*-glycosides [*N*-acetyl-β-D-glucosamine (**153**)] where the Blg-1-appended sugar is C-4′-*O*-sulfated (Fig. 50). Both compounds potentiate the activity of β-lactam antibiotics. Formadicins are β-lactam antibiotics, two of which (formadicins A and B) are C-9-*O*-β-D-glucuronidates (**72**) (Fig. 50). Glycosylation is notably rare among naturally occurring β-lactams and these unique metabolites displayed antibacterial activity againts *Pseudomonas* and *Proteus* species where glyco-sylation contributed to reduced potency. Finally, the anti-fungals theopalauamide and theonegramide are histidine (His) N-3 *N*-glycosides of β-D-galactose (**161**) and a β-D-arabinose (**294**), respectively.[1110–1112]

15.9. Other peptides

Miscellaneous peptides that lack anti-infective related activity are summarized herein. These include aeruginosides,[1113] aeruginosins,[1114] muraceins,[1115] enkastines,[1116] banyasides,[1117] phosphoramidon,[1118] GlcNAc-TA,[1119] mycothiols,[47,1120] bacillithiols,[1121] and alanopine[1122] from *Streptomyces*, *Nostoc*, *Nocardia*, *Planktothrix*, *Bacillus*, *Staphylococcus Providencia*, *Proteus* and *Oscillatoria* (Fig. 51). Aeruginosides and aeruginosins share a common peptide skeleton [composed of 2-carboxy-6-hydroxyoctahydroindole (Choi), leucine (Leu) or hydroxyleucine (HLeu), phenyl lactic acid (Plac), and agmatin (Agm) or 1-amino-2-(*N*-amidino-Δ^3-pyrrolinyl)ethyl (Aeap)], a common sugar (α-D-xylose, **293**) but distinct regioselectivity of glycosylation (aeruginosides, Choi C-6; aeruginosins, HLeu C-3; Fig. 51).[1113,1114] Banyaside A and B are comprised of 1-amidino-3-(2-aminoethyl)-3-pyrroline (Aaep), an azabicyclononane (Abn) C-7-*O*-α-D-glucoside (**18**), D-leucine (Leu), and a 2-*O*-methylglyceric acid-3-*O*-sulfate (MGAS).[1117] They differ by subtle modifications of the appended glucose and, like aeruginosins, are potent inhibitors of trypsin and thrombin.

Muraceins are a group of *N*-acetylmuramyl peptides composed of alanine (Ala), glutamic acid (Glu), diaminopimelic acid (Dap), and, in the case of muracein C, serine (Ser).[1115] Glycosylation of muraceins is afforded *via* an amide bond between the *N*-terminus Ala α-amine and the C3′-side chain carboxylate of *N*-acetyl muramic acid (**153a**, Fig. 51). They

inhibit angiotensin-converting enzyme (ACE) and have been put forth as potential antihypertensives.

Enkastines I–IV are dipeptides composed of an *N*-terminal hydrophobic amino acid [isoleucine (Ile) or valine (Val)] and an acid amino acid [aspartic acid (Asp) or glutamic acid (Glu)]. All exist as *N*-terminal *N*-glycosides of 1′-deoxyfructopyranose (**201**) and inhibit enkephalinase endopeptidase.[1116] Phosphoramidon, another dipeptide endopeptidase inhibitor, consists of a *C*-terminal tryptophan (Trp) and and *N*-terminal leucine (Leu), the *N*-terminal amine of which is uniquely connected to α-L-rhamnose (**46**) *via* a phosphoramidate bridge.[1118] GlcNAc-TA is a prenylated indolactam C-14-*O*-glycoside (*N*-acetyl-β-D-glucosamine, **153**).[1119] This is the only naturally-occurring teleocidin glycoside and is a small molecule activator of protein kinase C and induces the release of excitatory neuropeptides.

Examples of amino acid glycosides include mycothiols,[47,1120] bacillithiol,[1121] and alanopine. Mycothiols are constructed of *N*-acetyl or *N*-propionyl cysteine (Cys) modified at C-1 with pseudodisaccharide **I** (composed of α-D-glucosamine **5** and D-myoinositol **P12**). In a similar manner, bacillithiol is a 1′-(2-butanedioic acid)-α-D-glucosamine (**5**)-conjugated L-cysteine. Both mycothiols and bacillithiol protect against oxidative stress.[1123] Alanopine, a component of bacterial lipopolysaccharide, is an *N*-carboxyethylalanine (CEAla) attached to 4′-amino-4′-deoxy-D-quinovose (α, **39**; β, **202**), the anomeric configuration for which was not established.[1122]

16. Phenazines

Phenazines comprise a large group of nitrogen-containing heterocyclic bacterial metabolites that display a range of activities including antibacterial, antitumor, antimalaria, and antiparasitic functions.[1124] Over 140 of different phenazine metabolites have been reported from bacteria, only 13 of which are glycosylated (Fig. 52).[18] Regiospecificity of *O*-glycosylation among these metabolites is restricted to the 4- and 6-positions of the phenazine ring as well as the less common glycosyl esters which occur at a phenazine 6-carboxylic acid. Only three sugars were observed among the corresponding glycosides where α-L-quinovose (**194**) and β-L-quinovose (**297**), a sugar common to saponin glycosides,[1125] were found as sugars with free reducing termini attached as sugar 2′/or 3′-esters of the phenazine C6-carboxylic acid [phenazine α-L-quinovose 2′-ester (**194**, C-6), phenazine α-L-quinovose 3′-ester (**194**, C-6), phenazine β-L-quinovose 2′-ester (**297**, C-6) and phenazine β-L-quinovose 3′-ester (**297**, C-6)] in metabolites of a marine *Streptomyces*.[1126] The remaining glycosylated phenazines (aestivophoenins A-C,[1127,1128] izuminosides A-C,[1129] and phenazoviridin[1130–1132] from *Streptomyces*) are mono-glycosylated with α-L-rhamnose (**46**) at the phenazine C-4- or C-6-position, or as anomeric glycosyl esters of the phenazine 6-carboxylic acid similar to that described above (Fig. 52). Izuminosides B and C were reported to have a synergistic activity in sensitizing tumor necrosis factor-related apoptosis-inducing ligand “TNF-RAIL”-resistance AGS cells.[1129]

17. Piericidins and pyranones

Piericidins are prenylated polyoxypyridines with variant functions that include general cytotoxicity and insecticidal activity. More than 38 naturally occurring piericidins and closely related pyranones have been reported from *Streptomyces*, 11 of which are piericidin C-3a or C-10 *O*-monoglycosides (Fig. 53).[18] Three different monosaccharides have been observed among glycoconjugates of this class including β-D-glucose (**104**), α-L-rhamnose (**46**) and 2′-*epi*-β-D-fucose (also known as 6′-deoxy-β-D-talose, **298**). Of these, β-D-glucose (**104**) is the most predominant, found in 6 of the 11 naturally-occurring members of this class including glucopiericidins A-C,[236,1133–1135] 13-hydroxyglucopiericidin A,[1136] and glucopiericidinols A_1 and A_2.[1134] In contrast, the C-3a-appended α-L-rhamnose (**46**) was only observed in 3*a*-rhamnopiericidin A1 (SN-198-C),[1137,1138] and 7-demethyl-3*a*-rhamnopiericidin A1 (SN-l98-B),[1139] while the C-3a attached 2′-*epi*-β-D-fucose (**298**) was observed only in 3-deoxytalopiericidin A1.[1140] Additionally, the two glucopyranone (PM-050511 and PM-060431) metabolites of a marine *Streptomyces* display C-10-*O*-β-D-glucosyl (**104**) regiospecificity reminiscent of corresponding glucopiericidin.[1141] Importantly, glycosylation generally correlates with improved antimicrobial properties and reduced general *in vivo* toxicity.[1133–1135,1137,1139–1141]

18. Pluramycins

The 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione core is a characteristic feature of the pluramycin antitumor antibiotics produced by *Streptomyces, Actinomyces*, *Actinomadura* and *Saccharotrix*.[1142,1143] To date, 45 pluramycin glycosides have been reported (Fig. 54) and a unique signature of most pluramycin members is the presence of C-8- and/or C-10-*C*-glycosides. C-2- and/or C-5-side chain *O*- and/or *C*-glycosylation has also been observed and two metabolites (clecarmycins)[1144] distinctly contain C-9-*C*-glycoside substitution. Those members that present the prototypical C-8-/C-10-*C*-glycosyl archetype include hedamycin,[1145–1148] DC92-B and DC92-D,[1149,1150] kidamycin and epoxy-kidamycin (largomycin FII chromophore component 4),[1151] PD 121222,[1152] ankinomycin,[1145,1146,1153–1155] altromycins,[1156–1159] saptomycins,[1160–1162] neopluramcin and pluramycin A,[1163–1165] pluraflavins,[1166] A51493A,[1167] rubiflavins[1168] and chromoxymycin,[1169–1171] the latter of which has a uniquely modified aglycon core at C-12. Eighteen monosaccharide units are represent among pluramycin glycosides where *N*-alkyl aminosugars are a predominate feature known to be critical for pluramycin metabolite DNA interaction and cytotoxicity.[940,1153,1168,1172–1177]

Among the sugars found as C-8-*C*-glycosides, β-D-anglosamine (**59**) is most common with 3′-*epi*-α-D-anglosamine (**69**; SS 21020B) and $\Delta^{1,2}$-D-anglosamine (**306**; DC92-D) also observed. Of these, the C-1′/C-2′-unsaturated $\Delta^{1,2}$-D-anglosamine (**306**; DC92-D) is perhaps the most unique. For C-10-*C*-glycosides, *N,N*-dimethyl-α-L vancosamine (**118c**) is the chief sugar where X-ray analyses revealed this sugar to adopt a boat confirmation.[1178–1180] Other monosaccharyl C-10-*C*-glycosides include *N,N*-dimethyl-β-L-vancosamine (**299**; SS 21020B, SS 21020C, isokidamycin), *N,N*-dimethyl-α-D-vancosamine (**304**; chromoxymycin), *N,N*-dimethyl-3′-*epi*-5′-hydroxy-β-D-vancosamine (**302**; DC-92B, DC-92D), α-L-vancosamine (**118a**; altromycin G) and *N,N*-dimethyl-β-D-

vancosamine (**301**; saptomycin B) and corresponding disaccharides have also been reported (altromycins, disaccharides **II**, **III**, **IV**; pluraflavins, disaccharide **I**). It is important to note that the C-10 *N*,*N*-dimethyl-α-D-vancosamine (**304**; chromoxymycin) was not observed in any other pluramycin member, potentially calling into question this assignment. Finally, altromycins A-G also present *C*-glycosylation of the C-5 side chain (2′,6′-didexoy-3′-methoxy-α-D-altrose, **129**; 3′-methoxy-6′-deoxy-α-D-altrose, **307**) while clecarmycins contain C9-*C*-glycosides of β-D-kerriose (**55**). While the genes encoding for the unique C-8-/C-10-*C*-glycosyltransferases have been identified,[1181] they remain resistant to biochemical study.

19. Polyethers

Polyether ionophores represent a large group of natural occurring biologically active compounds produced mainly by *Streptomyces*.[18,1182] This family of secondary metabolite contributes to the transport of metal cations across cell membranes and members also display a broad spectrum of activities including antibacterial, antifungal, antiviral, antiparasitic, and cancer cell line cytotoxicity. To date, 52 glycosylated bacterial polyethers have reported, subdivided herein into four sub-classes **I–IV** according to their aglycon core structural conservation (Fig. 55). Despite the rather large group of glycosylated analogs observed, the glycosides found are restricted to the use only eight distinct sugars (Fig. 55). The sugar 4′-*O*-methyl-β-D-amicetose (**48b**) represents the most predominant sugar, found in 34 of the 52 glycosylated bacterial polyethers. Exceptions to the use of **48b** are noted herein.

In sub-class **I**, 29 *O*-glycosylated polyethers were found with variant glycosyl regiospecificity (C5, C6, C15, C18, C22 and C27) including; antibiotics 6016,[1183–1186] A204-A [α-D-amicetose (**308**)],[1187] carriomycin,[1188,1189] K-41-A,[1190,1191] K-41-B,[1192] X-14868A (maduramicin α),[1193–1196] X-14868C~D,[1193] etheromycin,[1189,1197] >UK-58852, nanhumycin, RP-37454, A80789, CP-120509 [α-D-amicetose (**308**)],[1198] CP-91243,[1199] CP-91244,[1199] CP-96797,[1200] octacyclomycin,[1201] CP-82009,[1202] semduramicin [α-D-amicetose (**308**)],[1203] UK-58,852-methylketal,[1204] A-13001-C[1196] and SF-2361,[1205] along with the septamycin analogs.[1206,1207] Of these, β-D-amicetose (**48a**) was observed in CP-91243 and CP-91244.[1199] In addition, 4′-*O*-methyl-α-L-amicetose (**97**) was observed only in etheromycin (CP-38295) while X-14868A through D[1193] contain β-L-olivose (**100**) connected at the same position (C-22) of the aglycon. Sub-class **II**, contains the four glycosylated polyethers 26-*O*-β-D-glucopyranosylmonensin (β-D-glucose, **104**) and the α-D-amicetose (**308**)-bearing CP-47433 and CP-47434, and CP-82996.[1208] Alternatively, sub-class **III** members (16 compounds) contain 4′-*O*-methyl-β-D-amicetose (**48b**) connected at five different positions of the aglycon (C-11, C-15, 20-CH_2, and C-27) as exemplified by A-130-B,[1209] A-130-C,[1209] X-14934A, moyukamycin,[1210] lenoremycin (A-130),[1211,1212] leuseramycin,[1213] endusamycin,[1214] CP-60993,[1215] CP-80219,[1216] nangchangmycin[1217–1219] and dianemycin analogs.[1212,1220,1221] All subclass **VI** analogs are C-14-*O*-glycosides of 4′-*O*-methyl-β-D-amicetose (**48b**), including, 6270B,[1222] portmicin[1223] and CP-84657.[1224]

20. Pterins

Pterins are characterized by the presence of a pteridine or a tetrahydropterine ring and have been proposed to prevent the bleaching of photosynthetic pigments due to irradiation in bacteria.[1225] Fifteen glycosylated metabolites of this class were reported predominately from cyanobacteria, green sulfur bacteria or methanogens where, in all cases, regioselectivity of glycosylation was observed to occur at variable positions upon side chains appended at C-6 of the pterin ring structure (Fig. 56). Cyanopterin[1226,1227] and monapterin, representing members that display *O*-glycosylation closest to the ring, contains a C-9 4′-*O*-methyl-α-D-glucuronic acid-(1′→6′)-β-D-galactose disaccharide (**I**) and β-D-glucose (**104**), respectively. Limipterin, tetrahydrolimipterin, tepidopterin and biopterin glucoside represent C-10-*O*-glycosides, all which contain *N*-acetyl-β-D-glucosamine (**153**) with one exception (biopterin).[1225,1228,1229] The latter, incorrectly labeled 2′-*O*-(α-D-glucopyranosyl)biopterin, actually contains α-D-altrose (**163**). Solfapterin, the only C-11-*O*-glycoside within this series, contains α-D-glucosamine (**5**).[1230] Finally, tatiopterins, thermopterin, methanopterin, sarcinapterin, and tetrahydromethanopterin all contain uniquely functionalized anilines at C-9 that terminate with an *O*-glycosidic 5′-phospho-α-D-ribose (**231**) (Fig. 56).[1231–1233] In some cases, the corresponding 5′-phosphate is further modified with α-hydroxyglutaric moiety *via* a phosphodiester bond (Fig. 56, appendages **i**, **ii**, or **iii**).

21. Streptothricins

Streptothricins are *N*-glycosides composed of streptolidine or streptolidine lactam and a sugar (typically, β-D-gulosamine **320**) attached to the C-2 exocyclic amino group, the latter of which (**320**) is C-2′-amino modified *via* a β-lysine derived moiety (Fig. 57). The streptolidine lactam is typically *trans* but a few *cis* conformers were recently reported.[1234,1235] Including the first member discovered (streptothricin F in 1942),[1236–1238] 45 analogs have been reported as metabolites of *Streptomyces* and *Bacillus* including streptothricins, racemomycins, albothricin, glycinothricin, lavenothricins, boseimycin, and sclerothricin.[1234,1235,1239–1251] These metabolites act as broad spectrum antibiotics through inhibition of protein synthesis and lavendothricins B and C have also been reported as calcium channel blockers.[1252,1253] However, apparent renal toxicity has hampered further development.[1254,1255] As mentioned, the core sugar employed among these metabolites is β-D-gulosamine (**320**) where 43 out of the 45 derivatives contain subtle modifications of the C-2′ amino group and/or C-4′ and/or C-6′-carbamoylation and are contributors to activity modulation.[1246,1250,1251] The two exceptions include streptothricin F (which carries a corresponding C-2′, C-6′-modified α-D-gulosamine, **189**)[1235] and racemomycin O (which alternatively contains a corresponding C-2′,C-4′,C-5′-modifed β-D-glucosamine **153**).[1256] Sugar C-4′ carbomylation favors activity while cleavage of streptolidine lactam amide bond reduces activity and toxicity.[1251,1257]

22. Terpenes and sterols

While prominent among plant metabolites, terpenes are relatively rare in the context of bacterial natural products with only 41 glycosylated terpenoids reported from bacteria to date. These are discussed below in the context of standard terpene classification.

22.1. Sesquiterpenes and diterpenes

Sesquiterpenes are comprised of three isoprene units and only one, the mildly cytotoxic deoxypentalenylglucuron (containing an aglycon exocyclic C-6 acid anomeric ester of β-D-glucuronic acid **72**), has been reported from various *Streptomyces*.[1258]

Diterpenes are comprised of four isoprene units and 16 glycosylated diterpenoids have been reported as metabolites of *Strepomyces* and *Nocardia* including the phenalinolactones,[1259] lucensimycins,[1260] brasillicardins,[1261,1262] platensimycins,[1263] and platencins.[1264,1265] Phenalinolactones, C-4 glycosides of a methylated α-L-amicetose (**97**) (Fig. 58), display moderate activity against Gram positive bacteria.[1259] In contrast, brasillicardins are C-2 (α-L-rhamnose **46**) glycosides which, in brasillicardins A and B, are further modified at the rhamnose C-3′ with *N*-acetyl-β-D-glucosamine (**153**).[1261,1262] The latter sugar is believed to be essential for the immunosuppressive activity of brasillicardin A. Two of the seven lucensimycins from *Streptomyces* are glycosides,[1260] attached to the modified cysteine side chain *via* an amide bond between the cysteine C-1′ carboxylate and an aminosugar (2′-amino-2′-deoxy-α-L-idose, **316**) amine. The anomeric position of the latter forms a α-glycosidic bond with the C-1′ of *myo*-inositol (**P12**) to form pseudodisaccharide **II** (Fig. 58) and it is important to point out that some confusion exists in the literature regarding the structure of pseudodisaccharide **II**.[1131] Platensimycin B_4 and its methyl ester[1263] and platencins A9, A10 and A12–A15[1264,1265] are the known glycosylated derivatives of the platensimycins and platencins. Members of this class were found to be potent inhibitors of mammalian and bacterial fatty acid synthases with potential relevance for the treatment of metabolic disease and bacterial infections.[1266] All glycosylated analogs exist as 4′-β-D-glucosides (**104**) of the corresponding 3-amino-2,4-dihydroxybenzoic acid moiety (Fig. 58) and display attenuated inhibition of FAS.[1263]

22.2. Triterpenes

Triterpenes consist of six isoprene units and are hypothesized to function as cell membrane constituents in bacteria. Cholesteryl glucosides with hemolytic activity have been reported as metabolites of *Helicobacter* and *Streptomyces* (Fig. 59).[1267,1268] The former are C-3-α-glycosides bearing C-6′-modified α-D-glucose (**18**) while corresponding metabolites from *Streptomyces* are β-glucosides (**104**).[1268] Hopanoids are pentacyclic triterpenoids thought to function as membrane stabilizers in bacteria to enable adaptation to extreme environments and are occasionally used as biomarkers for bacterial chemical taxonomy.[1269–1276] Bacteriohopanepolyols are hopanes characterized by a signature C-21-polyol side chain where C-36-glycosylated members have been characterized from different bacterial species including *Zymomonas*, *Synechocystis*, *Synechococcus*, *Prochlorothrix*, *Acetobacter*, *Pseudomonas*, *Ralstonia*, and *Burkholderia*. Nine different monosaccharides have been observed among this group including 2′-*N*-methyl-β-D-glucosamine (**153**), 6′-amino-β-D-

glucose (**318**), β-D-glucose (**104**), 2′-amino-β-L-glucose (**260**), β-D-galacturonic acid (**172**), α-D-glucuronic acid (**154**), α-D-altropyranouronic acid (**317**), pseudosugar **P23**, and the unusual sugar 3,5-anhydrogalactouronic acid (**321**) (Fig. 59). MK800-62F1, a gammacerane and inhibitor of apotosis isolated from *Streptomyces*, is a C-22-glycoside of α-L-arabinose (**265**).[1277] It should also be noted that glycosylated bacterial carotenoids are briefly discussed in Section 11.

23. Miscellaneous

23.1. Trioxacarcin analogs

Trioxacarcins and LL-D49194 analogs are metabolites from *Streptomyces* that broadly inhibit the growth of cultured bacterial and eukaryotic cells.[1278–1281] To date, 16 glycosylated trioxacarcin metabolites have been reported, glycosylated at C-4-, C-13- and/or C-16 of the aglycon (Fig. 60). Three branched-chain sugar monomers are represented among this group including α-L-trioxacarcinose A (4′-*epi*-α-L-mycarose; **122**), α-L-trioxacarcinose B (**103**), and the corresponding keto-reduced trioxacarcinose B (**323**).[18] The C-4-*O*-α-L-trioxacarcinose A moiety (**122**) is common to all trioxacarcin glycosides, including the monoglycosidic trioxacarcins A1 (DC-45-A1) and E, the diglycosidic trioxacarcins (A, B, D, F), gutingimycin,[1282] and the triglycosidic LL-D49194 (α1, β1, β2, *e* and *w*1).[1283] Additional C16-*O*-glycosylation with a mono-(**122**) or disaccharide (fragment **I**) side chain was observed in the LL-D49194 analogs while additional C-13-*O*-glycosylation with α-L-trioxacarcinose B (**103**) or its corresponding keto-reduced trioxacarcinose B (**323**), was observed in trioxacarcins A–D, F and gutingimycin. Sugar **323** of trioxacarcin C and its keto-form **103** have also been found appended to the anthracycline antibiotics isoquinocycline A and kosinostatin (Section 4.1), respectively.[188,251]

23.2. Polycyclic xanthones and related analogs

Polycyclic xanthone natural products are a family of diverse polyketides characterized by highly oxygenated, angular hexacyclic frameworks, many of which are glycosylated. As described herein, C-11-*O*-glycosylation predominates but select members representing C-4-, C-6-, C-9- and C-10-*O*-glycosylation and C-11-*N*-glycosylation have also been characterized (Fig. 61). Among the C-11-glycosyl series, kibdelones A-C rhamnosides and isokibdelone A rhamnoside from *Kibdelosporangium* all exist as C-11-*O*-α-L-rhamnosides (**46**).[1284,1285] Interestingly, kibdelones display potent anticancer, antibacterial and nematocidal activity while isokibdelones lack activity.[1284,1285] Neocitreamicin II from *Nocardia* is a C-11-*O*-glycoside bearing 4′-acetylated-β-D-oliose (**47**).[1286] Both neocitreamicin II and its aglycon neocitreamicin I display equal *in vitro* potency against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*.[1286] FDA-594,[1287,1288] MSO 901809[1289] and BE-13793X,[1290] from *Streptomyces* are three *O*-trisaccharyl-appended antitumor antibiotics. MSO 901809 and FD-594 contain the same trisaccharide [β-D-oleandrosyl-(1′→4′)-*O*-β-D-olivosyl-(1′→4′)-*O*-β-D-olivose, trisaccharide **V**] connected at C-9 and C-11 of the xanthone backbone, respectively. A similar C-11-trisaccharide is found in BE-13793X which contains a distinct internal β-D-olivosyl-(1′→3′)-*O*-β-D-olivose connection [β-D-oleandrosyl-(1′→4′)-*O*-β-D-olivosyl-(1′→3′)-*O*-β-D-olivose,

trisaccharide **VI**]. Antibacterials/antimycoplasmodials SF2446A1, A2, B1 and B2 from *Streptomyces* along with the non-selective cytotoxin arenimycin from *Salinospora* also reflect C-11 glycosyl regiospecificity reminiscent of the kibdelones but are the only *N*-glycosidic members of this group, all bearing 2′,4′-di-*O*-methyl-β-L-rhamnose (**322**).[1291–1293]

Distinct from the C-11 glycosyl series, kigamicins A–E are antitumor antibiotics from *Amicolatopsis* that possess a fused octcyclic ring system comprised of seven six membered rings and an oxazolidine.[1294–1296] Kigamicins are C-10-*O*-glycosides bearing a mono- to tetrasaccharide comprised of β-D-amicetose (**48**) and β-D-oleandrose (**53b**).[1294–1296] The C-6-*O*-glycosyl regiospecificity of benaphthamycin-β-D-glucoside (**104**) from *Streptomyces* is unique from other members in this class. Likewise, the C4-*O*-glycosyl regiospecificity of IB-00208 (β-D-quinovose, **140**) from *Actinomadura* is unique from other members in this class.[236,1297,1298] IB-00208 displays both *in vitro* cytotoxicity against various tumor cell lines (P-388, A-549, HT-29 and SK-MEL-28) and activity against Gram-positive bacteria.[236,1297,1298]

23.3. Paulomycins related compounds

This class of compounds share a 2-amino-5-hydroxy-3,6-dioxocyclohex-1-enecarboxylate-based aglycon. Twenty analogs belong to this class and include ten paulomycins, two paldimycins, two $273a_2$ analogs, two paulomenols, U-77,802 and U-77,803, and two senfolomycins from *Streptomyces*.[1299–1303] These metabolites carry a C-5-*C*-glycoside which, in most cases, is α-L-paulomycosyl-(1′→3′)-α-D-allose (disaccharide **I**, Fig. 62). Exceptions to this include paulomycin E and senfolomycins which differ *via* subtle variations of the disaccharide C-4′-branched α-L-paulomycose (**328**) monomer (ketosugar **329** in disaccharide **II**, paulomycin E; ketosugar **103** in disaccharide **III**, senfolomycin A; epimer **323**, disaccharide **IV**, senfolomycin A). Modification of the disaccharide core [C-6′ of α-D-allose (**162**), C-3′ (**328** and **329**) and/or C-7′ (**328**) of the terminal branched sugar] further differentiates members as illustrated in Fig. 62. Members of this family display potent Gram positive antibacterial activity.

23.4. Phenyls and related compounds

Metabolites that contain a phenyl ring and do not belong to one of the previous classes are consolidated within this section which contains 10 structurally/functionally diverse glycosides. Myxotyrasoides, moderately cytotoxic *N*-acyl tyrosine derived metabolites from *Myxococcus*,[614] contain a phenolic-*O*-α-L-rhamnose (**46**) (Fig. 63). Myxotyrasoides, along with chivosazoles and sorangiosids (Section 12), are among the only glycosylated secondary metabolites reported from myxobacteria.

Sibiromycin and sibanomicin from *Streptosporangium* and *Micromonospora*, respectively, are C3-*O*-glycosides (α-L-sibirosamine, **327**) of modified pyrrolo[1,4]benzodiazepines.[1304–1306] Both are cytotoxic and sibiromycin binds the minor groove of DNA.[1307] Two C-6-*O*-2′,4′-di-*O*-methyl-β-D-xylosyl (**136**) quinoline alkaloids were isolated from the cyanobacterium *Lyngbya*[1308,1309] and the same sugar was also found

appended at C-4 of malyngamide J cyclohexanone core (a cytotoxin).[1310] Terfestatin A, a specific inhibitor of auxin signaling in *Arabidopsis*, is a C-3-*O*-β-D-glucoside (**104**).[1311]

Saccharomicins are *O*-heptadecaglycosides of *N*-(*m,p*-dihydroxycinnamoyl) taurine from *Saccharothrix*.[1312] Common monosaccharide units of the saccharomicin oligosaccharide include β-D-fucose (**270**), 2′-sulfate-β-D-fucose (**270**), the C-3′-branched β-D-saccharosamine (**269**), α-L-rhamnose (**46**), 4′-*epi*-α-L-vancosamine (**280**), and α-L-digitoxose (**68**). Saccharomicins A and B differ *via* a single tenth sugar residue (α-L-rhamnose **46** or α-L-digitoxose **68**, respectively). Both compounds display potent Gram-positive and Gram-negative antibacterial activity where the primary cellular target put forth was the bacterial membrane. While a new potential antibacterial class, their narrow therapeutic index has prohibited further development.

23.5. Heterocycles

23.5.1. Oxazoles—Fourteen oxazole glycosides have been reported from *Streptomyces*. Of these, seven are allosamidins (chitinase inhibitors) distinguished by the fused bicyclic pentanoidoxazolidine aglycon.[1313–1315] Members contain a C-5-*O*-β-D-*N*-acetyl-β-D-allosaminyl-β-(1′→4′)-*N*-acetyl-β-D-allosamine (disaccharide **I**, monomer **326**) or the C-6′-*O*-methyl variant (Fig. 64). Two related glucoallosamidins exist in which the proximal monomer (**326**) has been replaced by *N*-acetyl-β-D-glucosamine (**153**). *N*-glucosides trehazolin and trehalostatin share a similar bicyclic aglycon (trehazolamine) but carry a *N*-7-α-D-glucose (**18**).[1316,1317] Both function as specific irreversible inhibitors of trehalase, with trehazolin as the most potent.[1316,1318] One tricyclic streptazolin C-5-*O*-β-D-xyloside (**136**) was reported where the glycoside displayed notably higher *in vitro* anticancer cytotoxicity than non-glycosylated comparators.[1319] Finally, two glycosylated cyclocarbamides (SB-253514 and SB-315021 from *Pseudomonas*) both exist as C-14-*O*-α-L-rhamnosides (**46**).[1320] Both metabolites inhibit lipoprotein-associated phospholipase A_2 and exhibit anti-inflammatory properties.

23.5.2. Porphyrins—Porphyrins are heterocyclic tetrapyrrole-based macrocyclic metabolites (Fig. 65). Of the 27 porphyrins reported from bacteria, seven tolyporphins from *Tolypothrix* exist as C17-*C*-glycosides or C-7,C-17-di-*C*-glycosides. While 3′,6′-dideoxy-β-D-xylohexopyranose (**313**) was initially reported as the corresponding monosaccharide, a tolyporphin A structure revision by Moore and coworkers implicated 3′,6′-dideoxy-α-D-xylo-hexopyranose (**311**)[1321] and may call into question the anomeric configuration of other reported members. Tolyporphins inhibit P-glycoprotein[1321–1324] and can photosensitize tumor cells.[1325]

23.5.3. Other heterocycles—Eighteen other bacterial heterocyclic glycosides have been reported. Of these, the macrolactam tetracyclic tetrapetalones A-D from *Streptomyces* were discovered *via* a lipooxygenase inhibition guided-assay.[1326,1327] They are C-9-β-D-rhodinosides (**56**) (Fig. 66). The corresponding enantiomer, β-L-rhodinose (**169**), is appended to C12 of the C2-heptenylidene side chain in hatomamicin, a cytotoxic *Saccharopolyspora* metabolite.[1328] Gualaymycin from *Streptomyces* is a pyrrolidinyl butanoate metabolite bearing a C2-*C*-disaccharyl moiety [disaccharide **I**; 2′-deoxy-2′-

amino-β-D-gulosyl-(1′→4′)-α-D-galactose]. These metabolites are superior to dicofol as acaricidals.[1329] A phenoxazine *N*-β-D-glucosidic (**104**), questiomycin from *Microbispora*, was reported to have both antibacterial and cytotoxic activity where *N*-glucosylation was found to suppress bioactivity.[1330] Pyralomicins are chlorinated benzopyranopyrrole *N*-(pseudo)-glycosides produced by *Nonomuraea*.[1331–1333] Four derivatives 1a–d contain the pseudosugar 1′-*epi*-valienol (**P26**) proposed to arise from D-seduheptulose-7-phosphate[1334] while three others (2a–c) are *N*-β-D-glucosides (**104**). Pyralomicins display Gram-positive antibacterial activity where pseudosugar-based derivatives are superior to the corresponding glucosides.[1331] Pyrazomycins A and B from *Streptomyces* are pyrazole C-3-*C*-glycosides bearing β-D-ribose (**25**) and α-D-ribose (**231**), respectively. Two rings of the pentacyclic red pigment rubrolone from *Streptomyces* derive from a unique C-4-*O*-C1′/C-3-C-2′ fusion with β-D-fucose (**270**) (Fig. 66).[1335]

23.6. Additional simple aglycons

Compounds combined with this collection include 44 metabolites. While some are bacterial metabolites, most derive from precursor directed biosynthesis by feeding *Streptomyces* GT61150 a range of putative aglycons including benzoyls, pyrrolycarbonyls, furanylcarbonyls, phenylacetyls, thiophenylcarbonyls, indolylcarbonyls, pyridylcarbonyls, phenyls, and isovaleryls (Fig. 67) to afford the corresponding α-L-rhamnosides (**46**) or 6′-deoxy-α-L-talosides (**125**).[590,1336–1339] All corresponding products were monosaccharide-substituted with one exception, benzoyl dirhamnoside bearing both a phenolic hydroxyl- and ester-linked α-L-rhamnose (**46**) (Fig. 67). Rhamnosylated lactones analogs were found to inhibit the 3α-hydroxysteroid dehydrogenase.[590]

Additional metabolites include menisdaurin,[1340] byelyankacin,[1341] and two CKD-711 derivatives[1341–1343] from *Streptomyces* or *Enterobacter*. Menisdaurin is a C-3-β-D-glucoside (**104**) while byelyankacin is a C-1-α-L-rhamnoside (**46**) and potent tyrosinase inhibitor.[1341] CKD-711 and CKD-711a are epoxycyclohexanol C-1-*N*-glycosides bearing either a pentasaccharide **I** or a trisaccharide **II** (Fig. 67). Both oligosaccharides are comprised of one or two α-D-glucosyl-(1′→4′)-α-D-glucose units "**18**-(1′→4′)-**18**" terminating with a C-4-*O*-4′-deoxy-4′-amino-β-L-glucose (**36**) and inhibited α-glucosidase with the trisaccharyl derivative as the most potent. Both compounds also selectively inhibited the growth of the Gram negative bacteria *Comamonas terrigena* but displayed no other antibacterial/antifungal effects.[1342]

24. Conclusions

This cumulative analysis reveals a relatively high degree of natural product family-specific conservation in both glycosyl regiospecificity and the specific sugars employed as well as a moderate degree of crossover among natural product families in the use of less functionalized 'common' sugars (*e.g.*, standard metabolic sugars and simple corresponding deoxysugars). This likely parallels a higher prevalence (and therefore a higher likelihood of lateral gene transfer) of the core genes encoding some of the common sugar functionalization chemistry in both primary (cell wall) and secondary metabolism where the more complex natural product family-specific sugar functionalization may have derived *via*

divergent evolution. No clear overall general trends relating glycosylation to biological activity were observed (*i.e.*, glycosylation does not always improve or suppress biological activity) however, within a number of natural product subfamilies such trends were apparent. While this points to a lack of a predictive model to apply glycosylation as a medicinal chemistry tool for natural product optimization, it suggests efficient glycodiversification strategies (chemoenzymatic,[9,1344] chemoselective[10] and/or pathway engineering[1345]) to offer unique opportunities for improving and/or broadening natural product therapeutic potential. While notable advances have been made toward understanding the fundamental mechanisms and structural biology of enzymes involved in natural product glycosylation,[1346–1348] this review also exposes a number of uniquely functionalized sugars and glycosidic connections as a basis for the future discovery of unprecedented enzymatic chemistry.

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Biographies

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Sherif received his BS degree in Pharmaceutical Sciences (2000) from Cairo University, a Master’s degree in Pharmacognosy (2006) from the University of Mississippi and a PhD degree in Biochemistry and Molecular Biology (2012) from the School of Medicine at Oregon Health & Science University with Professor Margo Haygood. He is currently a postdoctoral scholar in the Center for Pharmaceutical Research and Innovation at University of Kentucky College of Pharmacy. Dr Elshahawi’s research interests include the isolation and phylogenetic analyses of microorganisms from unusual environments and the biosynthesis, isolation, bioassay and resistance of bioactive secondary metabolites.

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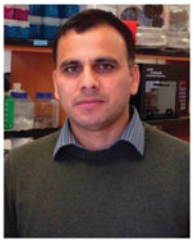


Madan K. Kharel

Dr Kharel obtained his BS (1998) and MS (2000) from the Tribhuvan University (Nepal), a PhD in biochemistry from the Sun Moon University (South Korea, 2007) and a PhD in pharmaceutical sciences from the University of Kentucky (2010, Professor Jürgen Rohr). Dr Kharel served as a research faculty in the University of Kentucky Center for Pharmaceutical Research and Innovation (2012–2013) and currently is an Assistant Professor of Medicinal Chemistry, Department of Pharmaceutical Sciences, University of Maryland Eastern Shore. His research interests include elucidation of function of novel enzymes, enzymatic synthesis of natural products, and isolation of new bioactive microbial natural products.

Jon S. Thorson

Jon received his BA from Augsburg College (1986), a PhD from the University of Minnesota (1993, Professor Hung-wen Liu) and was a Helen Hay Whitney postdoctoral fellow at the University of California, Berkeley (1993–1996, Professor Peter Schultz). He has served on the faculty of the Memorial Sloan-Kettering Cancer Center and the Sloan-Kettering Division, Joan and Sanford I. Weill Graduate School of Medical Sciences, Cornell University (1996–2001), the University of Wisconsin –Madison School of Pharmacy (2001–2011), and the University of Kentucky College of Pharmacy (2011–present) where he is also the director of the Center for Pharmaceutical Research and Innovation. His research interests include bioprospecting, biocatalysis and biosynthesis.

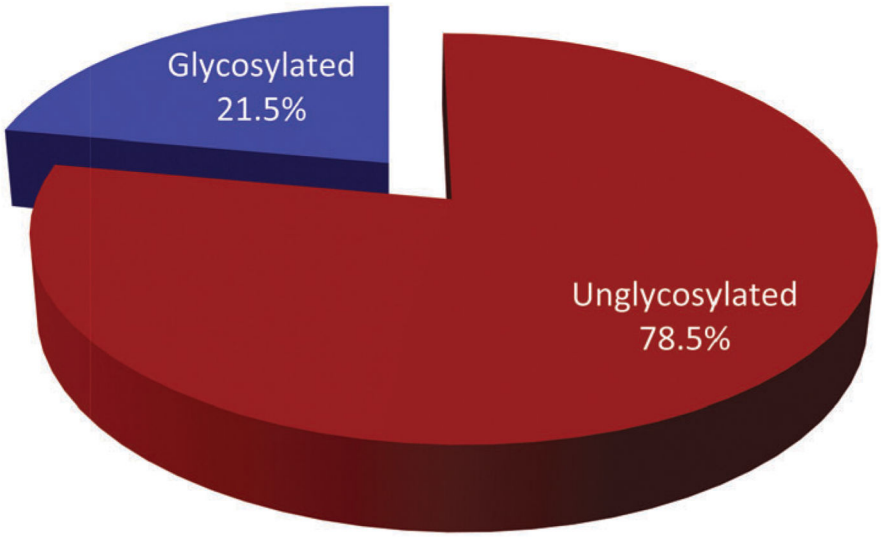


Fig. 1.
Bacterial glycosylated (21.5%; 3426 compounds) and unglycosylated (78.5%; 12 514 compounds) natural products.

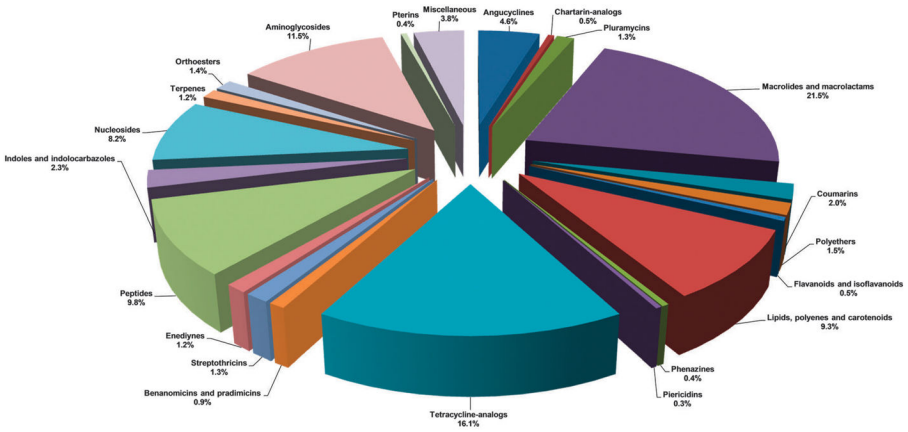
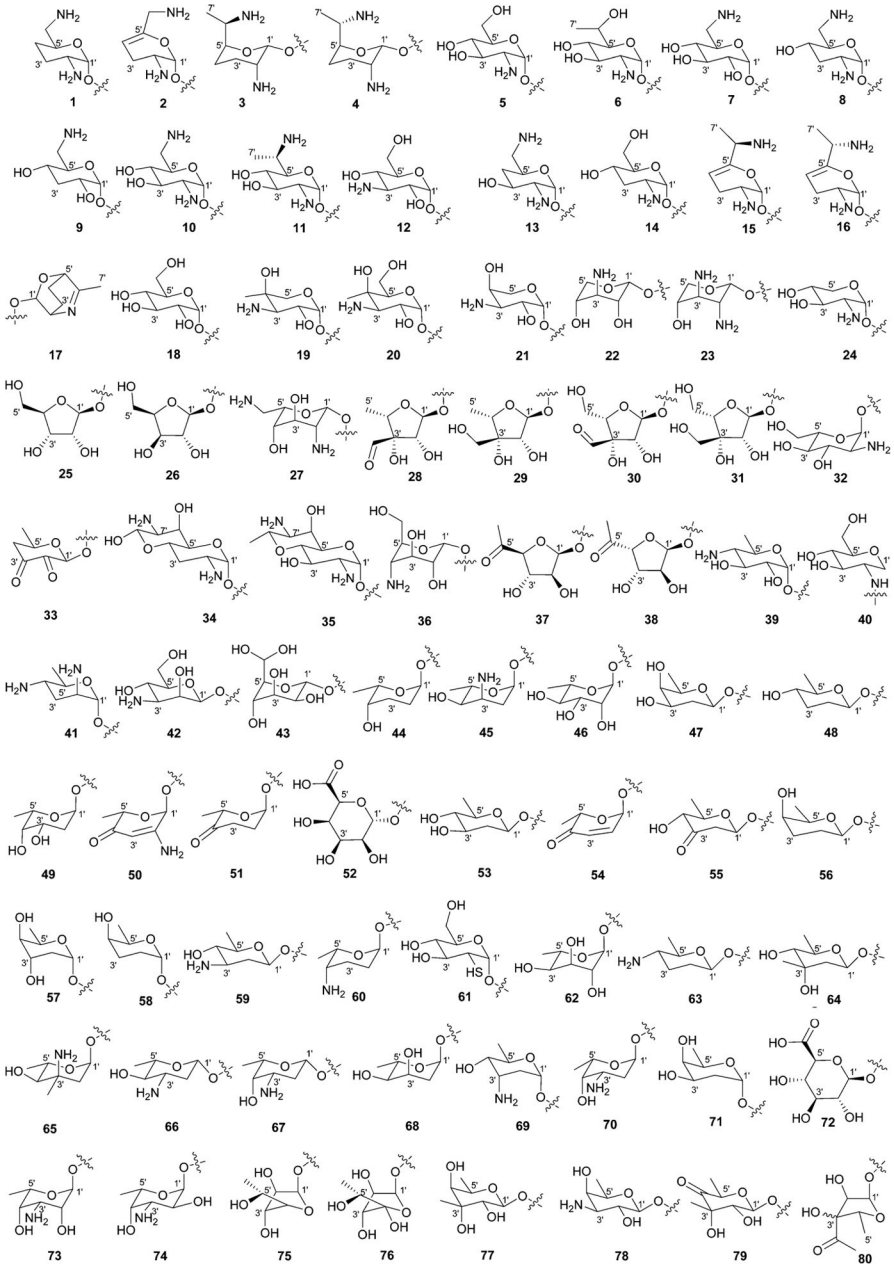
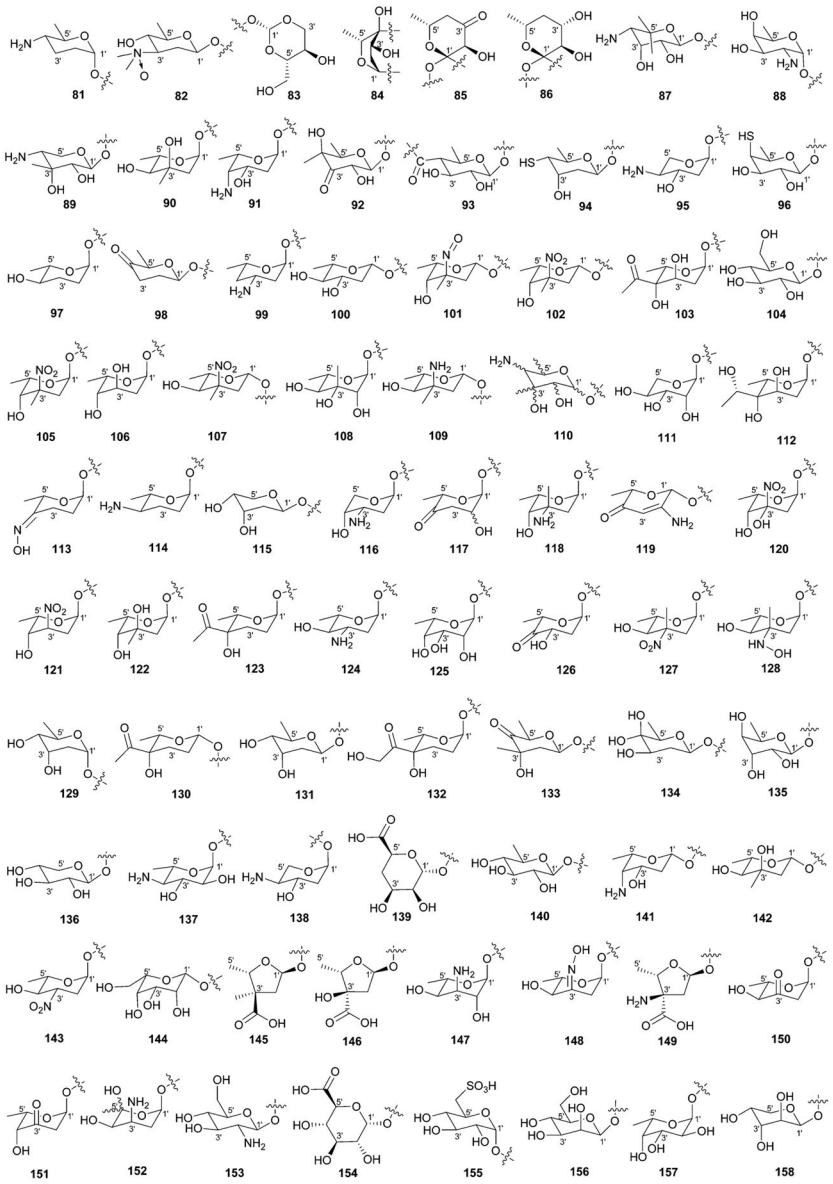
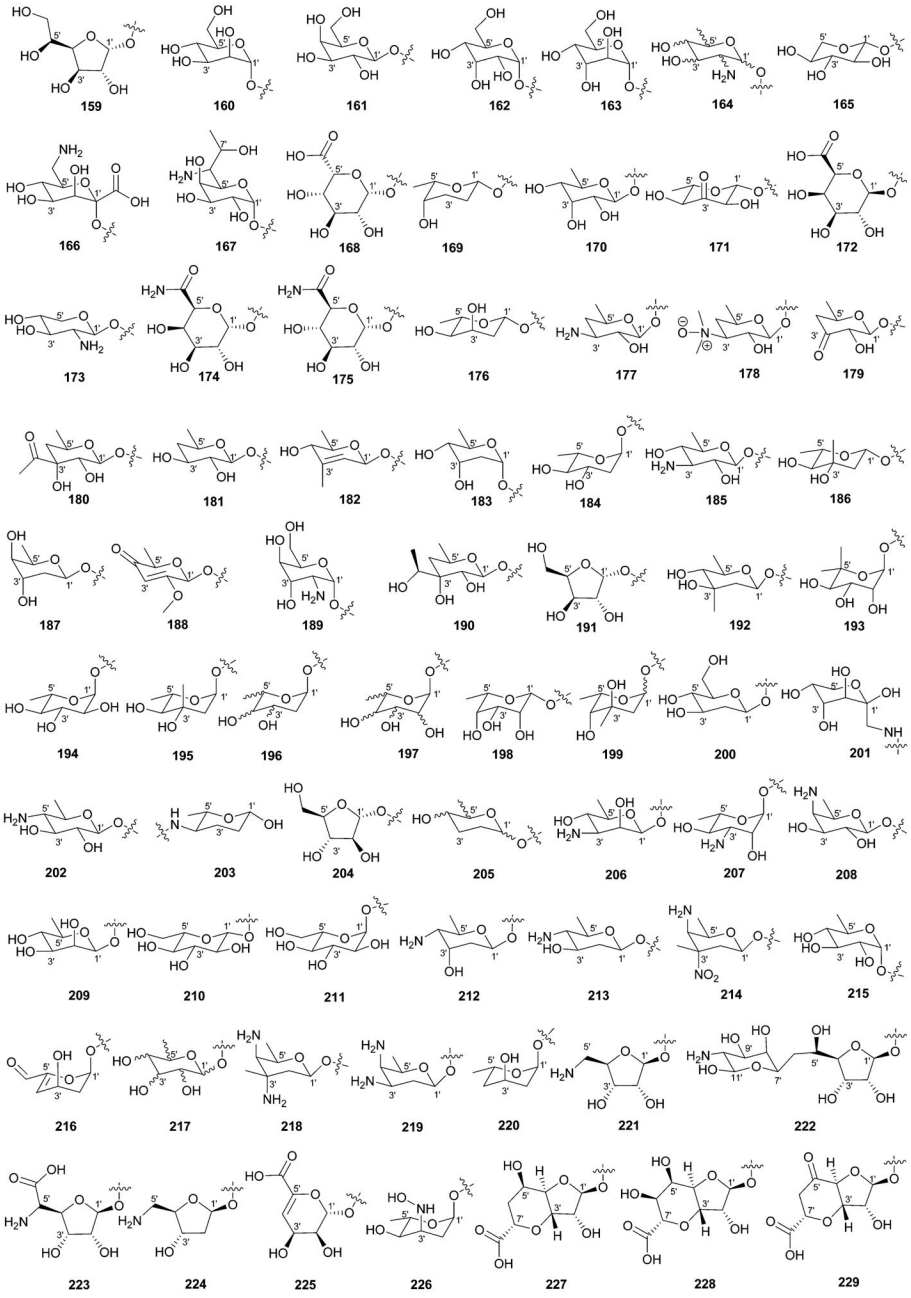


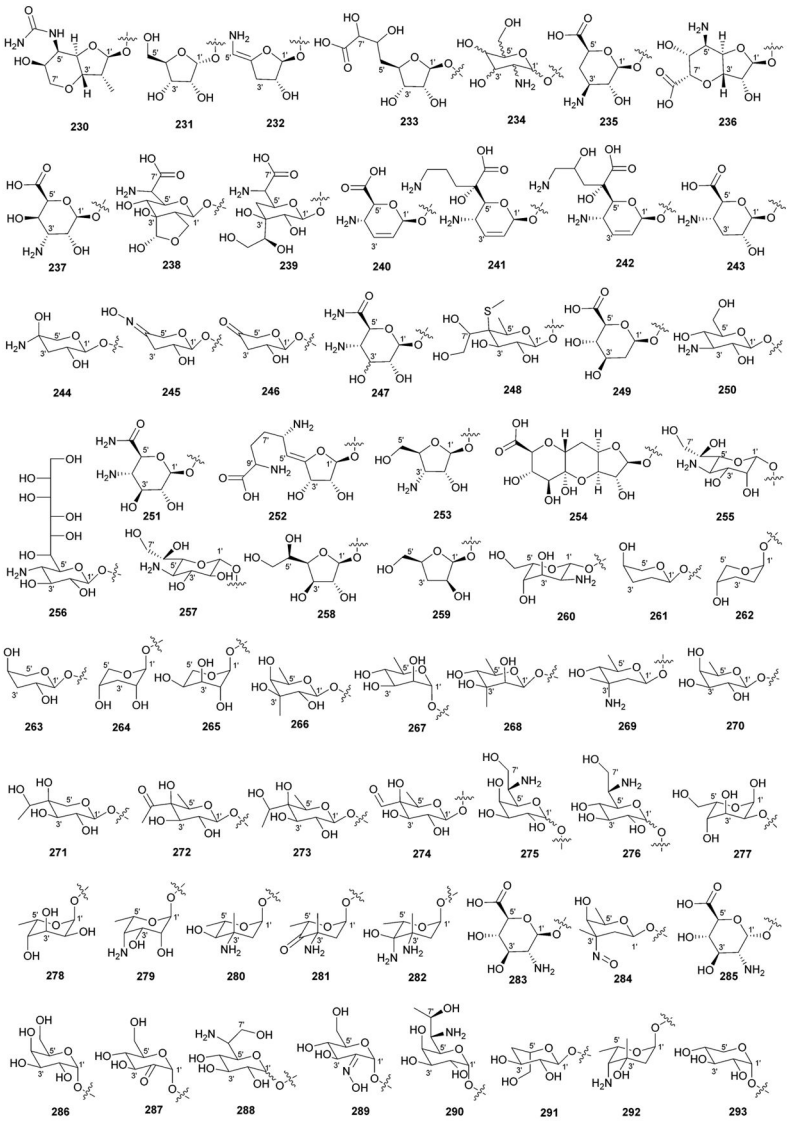
Fig. 2.

Chemical classes of glycosylated bacterial natural products (total 3426 compounds).









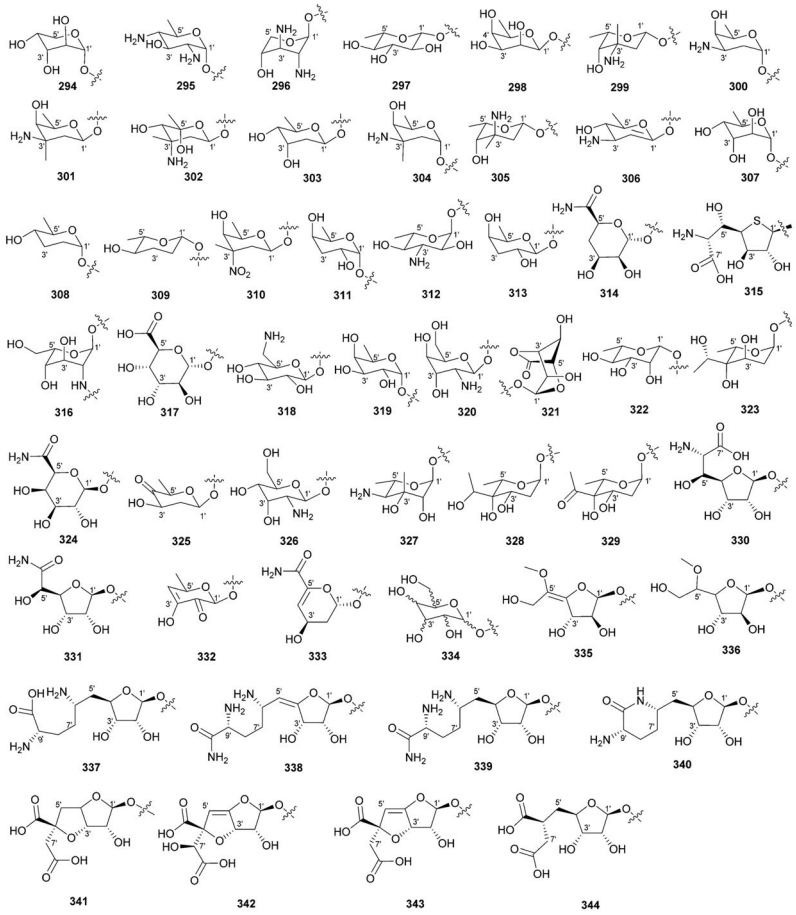


Fig. 3.

Summary of all sugars present in bacterial natural products (**1–344**). Only sugars that displayed differences within the fundamental monosaccharide core (specifically, notable stereochemical and/or functional group variation, including anomeric configuration) were considered as distinct. Modifications of a common sugar core (*e.g.*, *O*/*N*/*S*-alkyl/acyl substitutions) were designated as identical to the parental core saccharide.

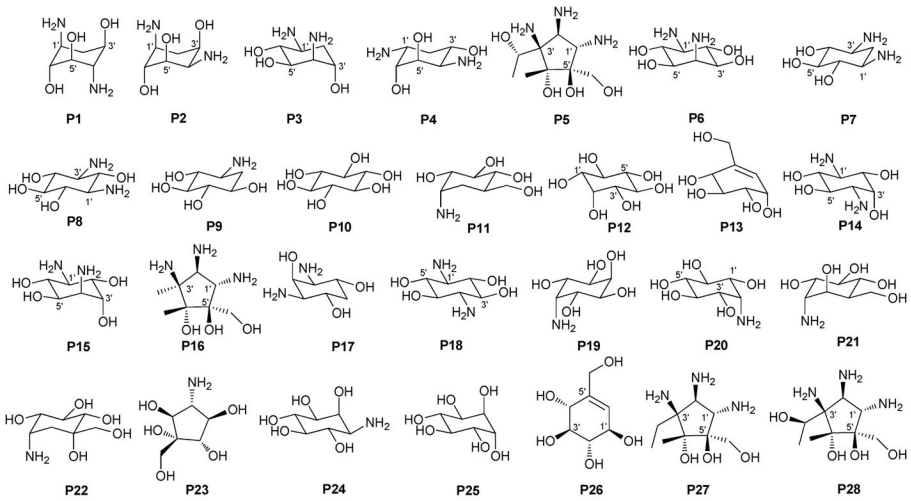


Fig. 4.

Summary of pseudosugars **P1–P28** present in bacterial natural products. This list represents only those pseudosugar found within the context of bacterial glycosides and does not reflect an exhaustive list of naturally-occurring pseudosugars.

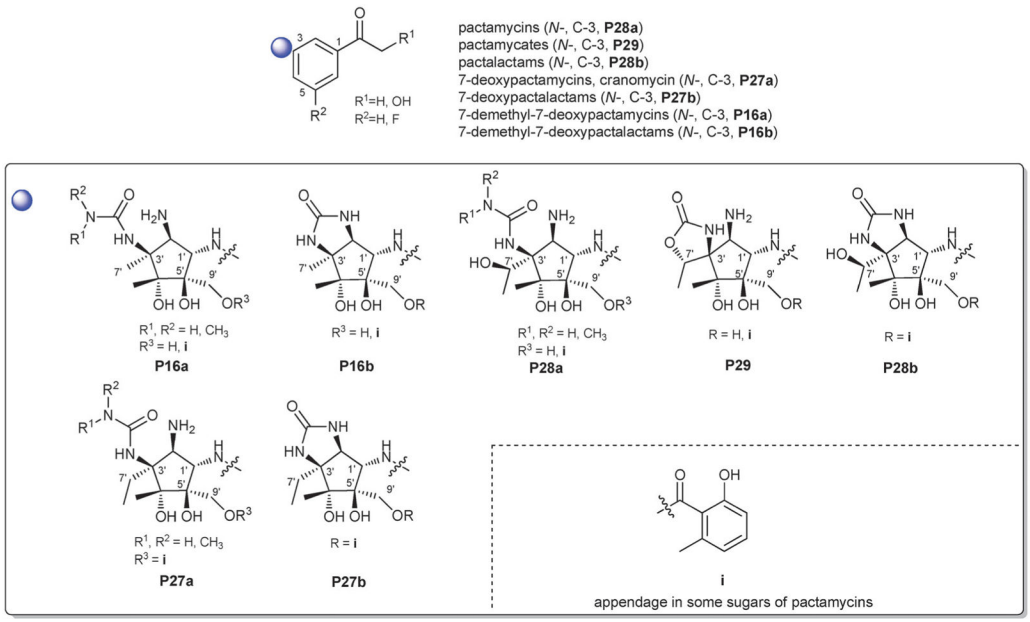


Fig. 5.
Pactamycin aglycons and associated pseudosugars.

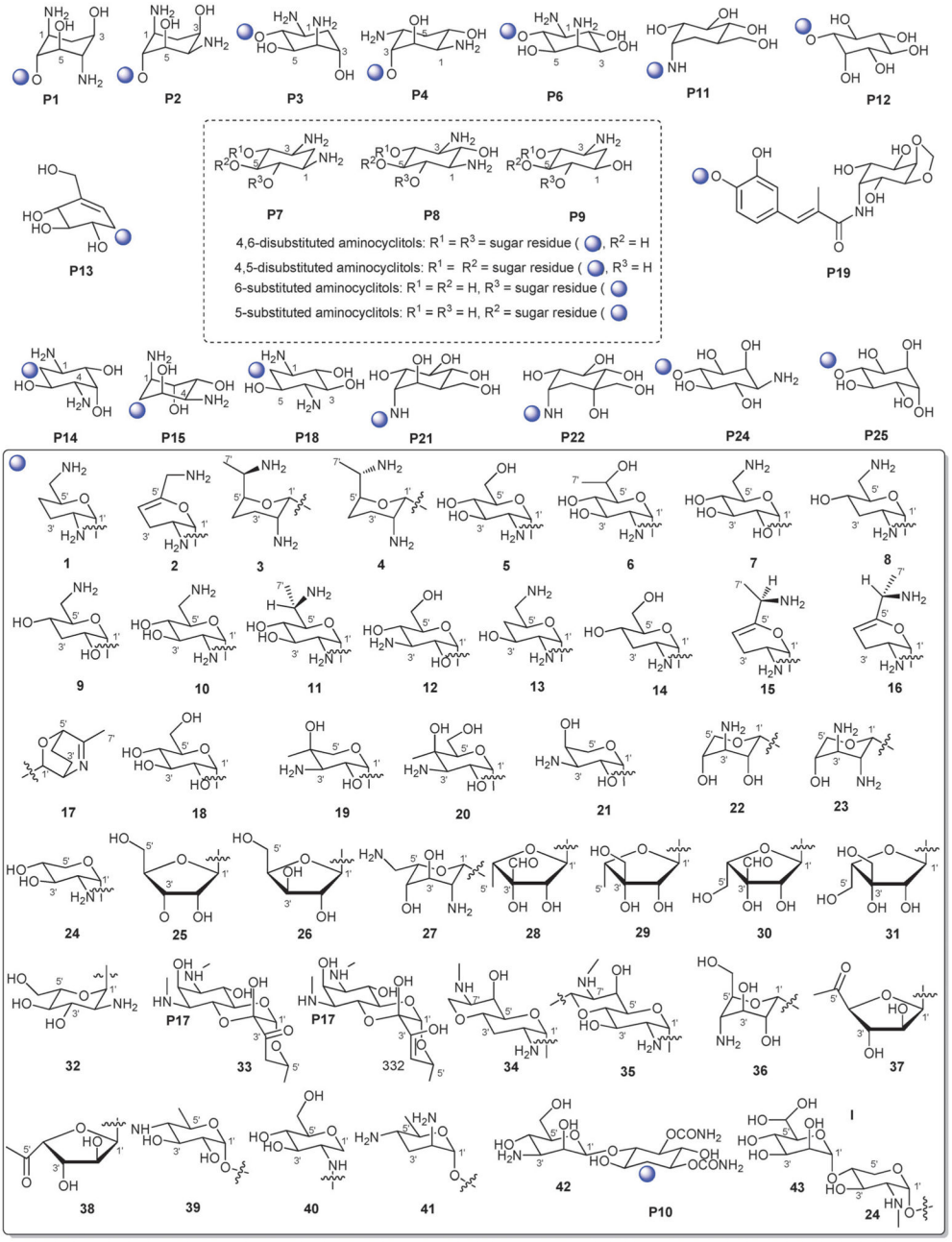


Fig. 6.

Aminoglycoside pseudosugars and associated sugars.

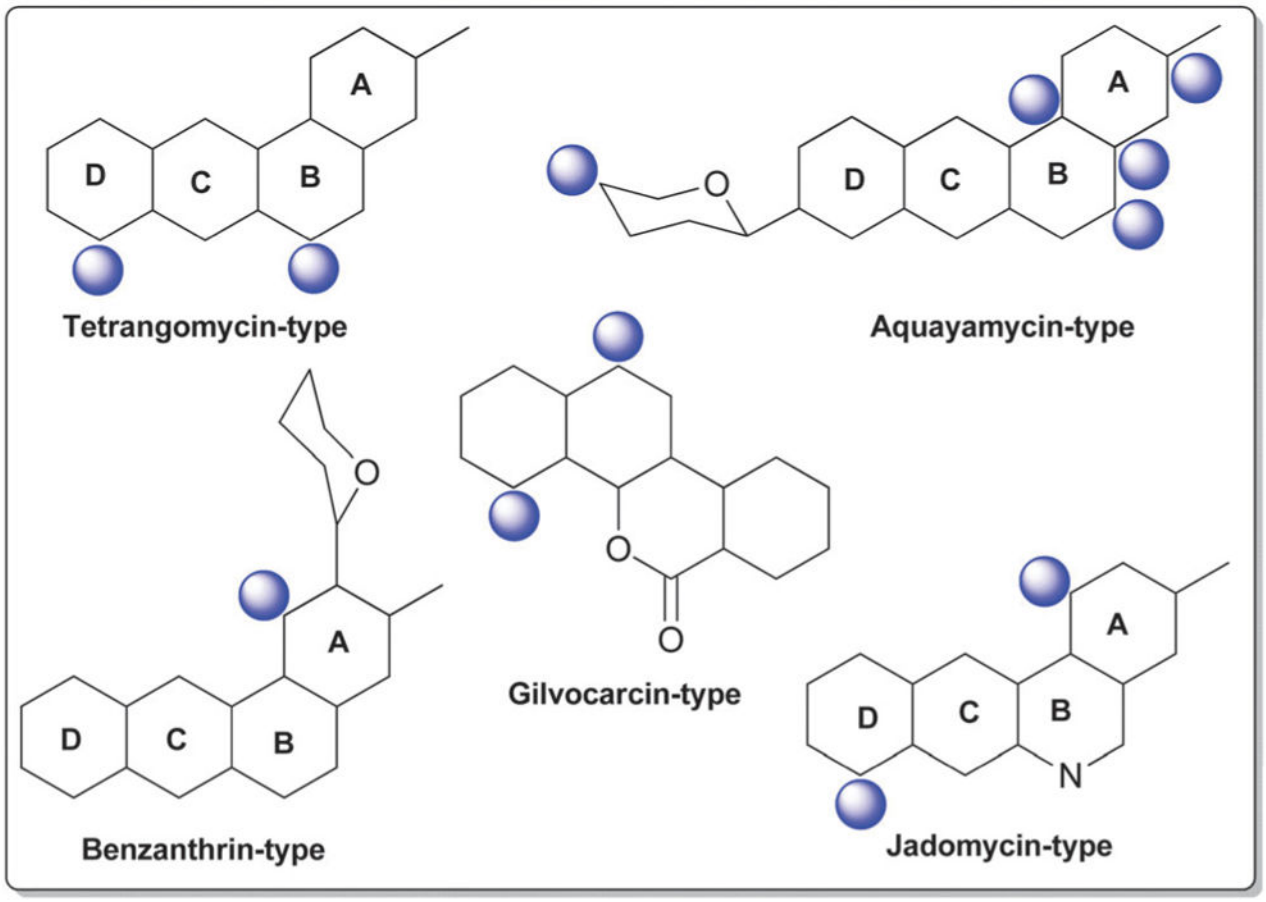


Fig. 7.
The five major types in angucyclines and glycosylation positions.

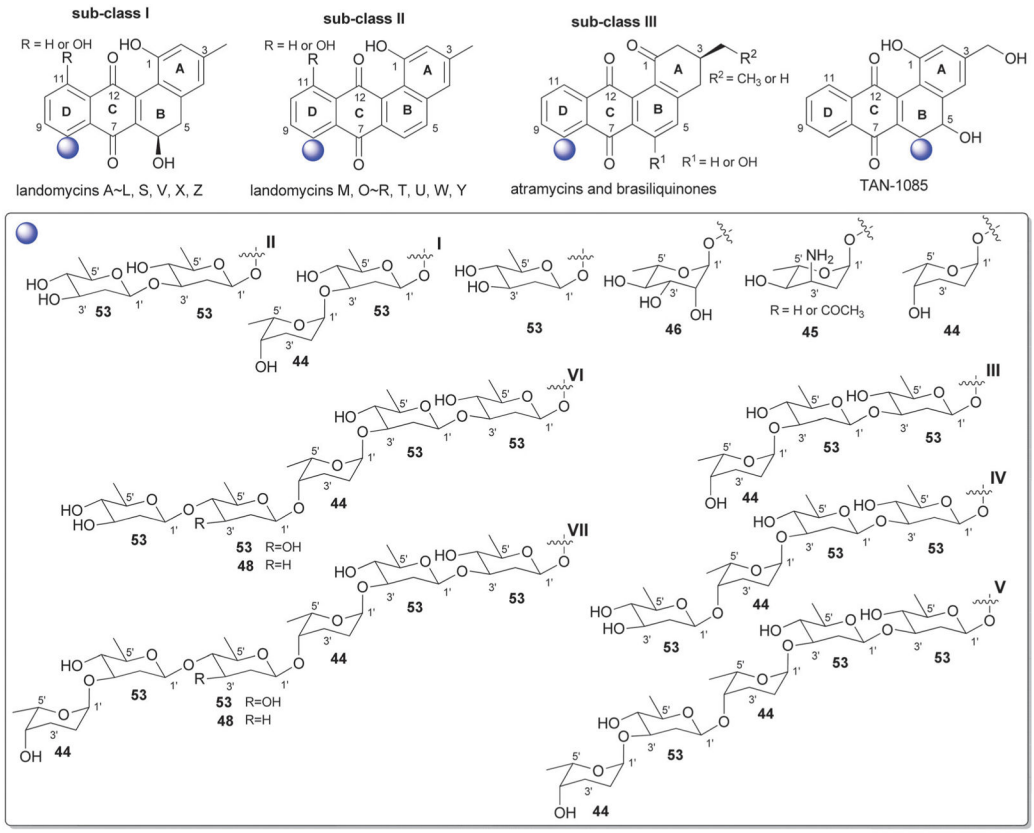


Fig. 8.
Landomycin aglycons and associated sugars.

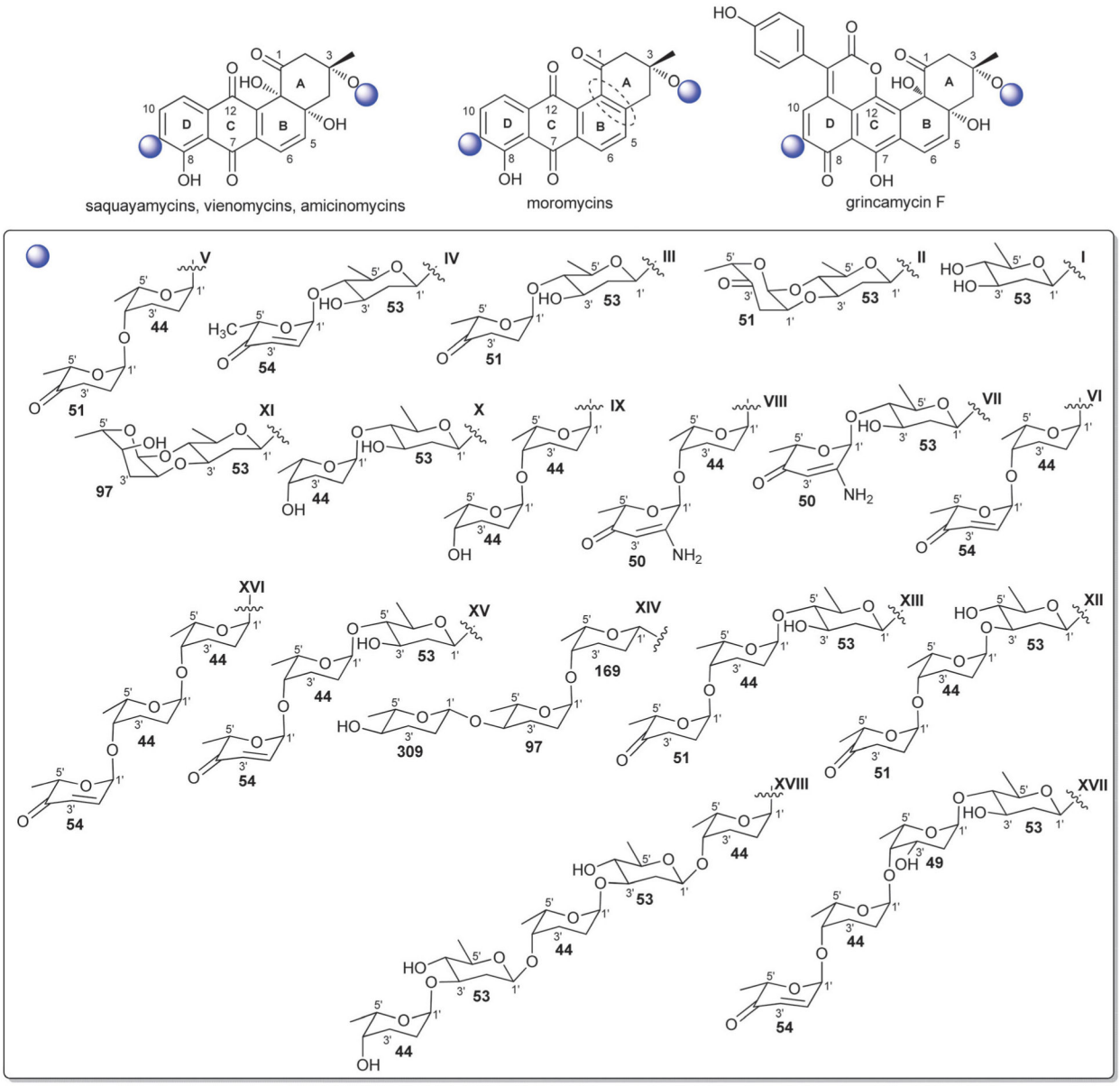


Fig. 9.
Saquayamycin aglycons and associated sugars.

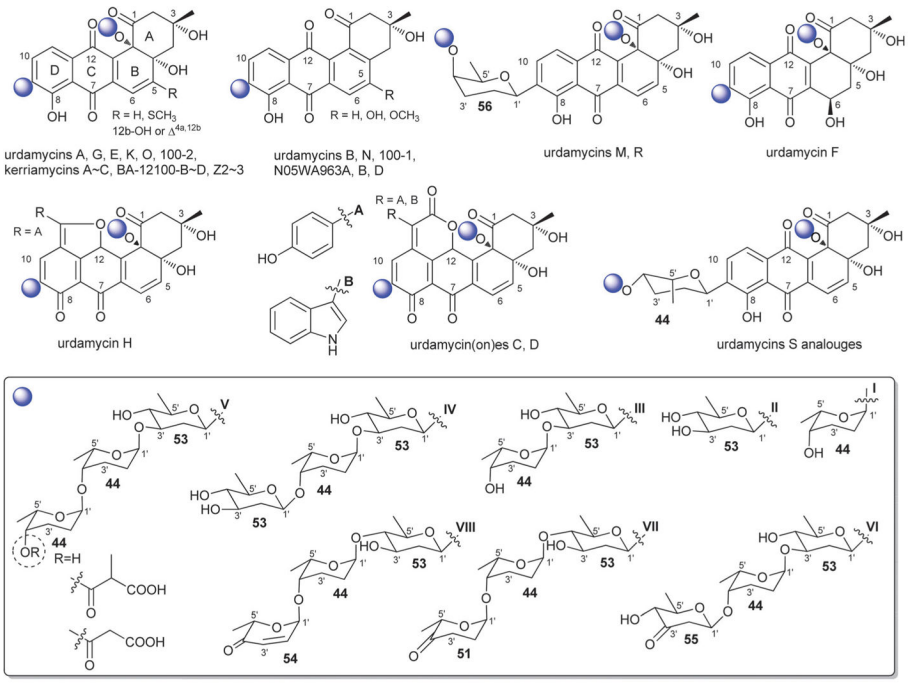


Fig. 10.

Urdamycin aglycons and associated sugars.

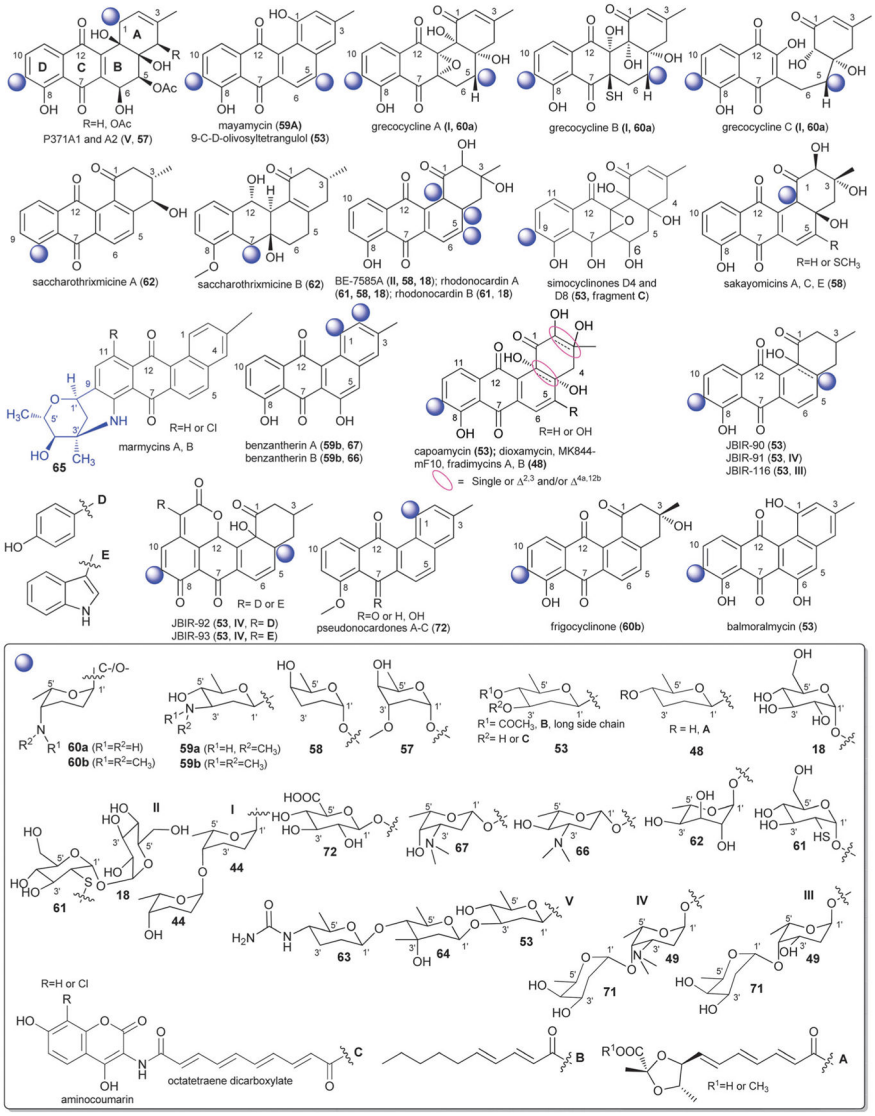


Fig. 11.

Other related angucycline aglycons and associated sugars.

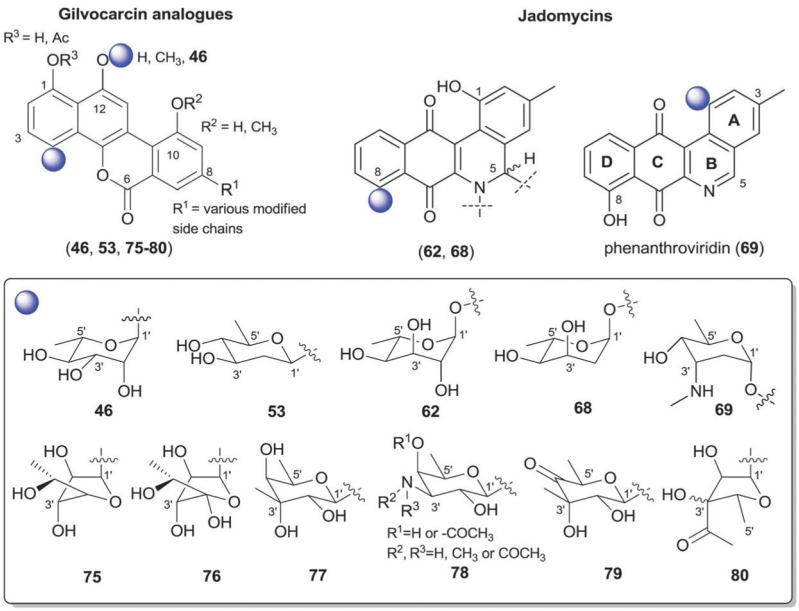


Fig. 12.

Gilvocarcin and jadomycin aglycons and associated sugars.

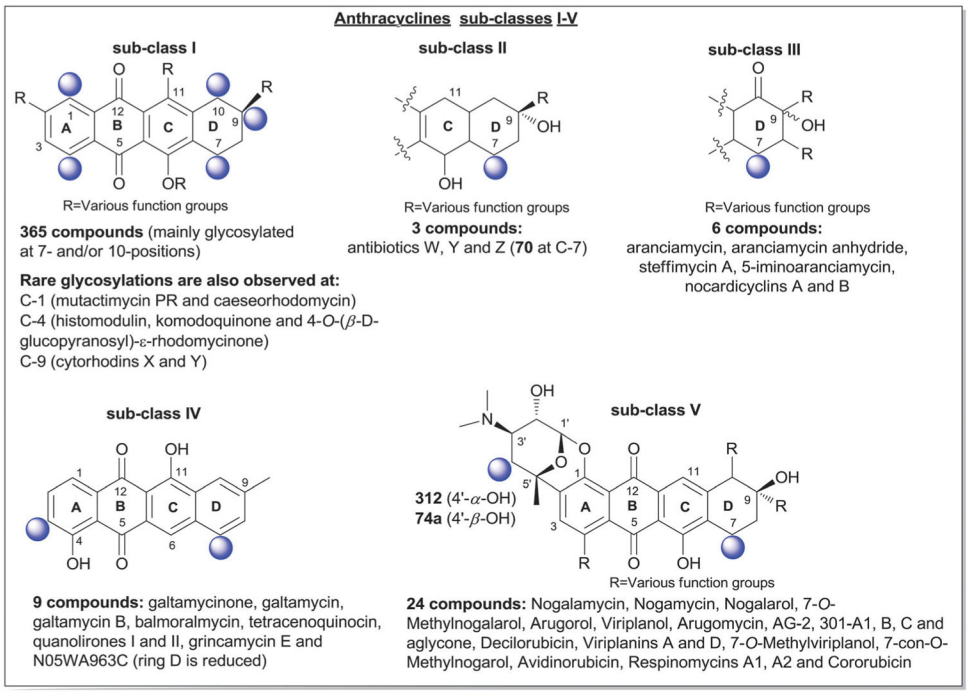


Fig. 13.

The five anthracycline sub-classes **I–V** and glycosylation positions.

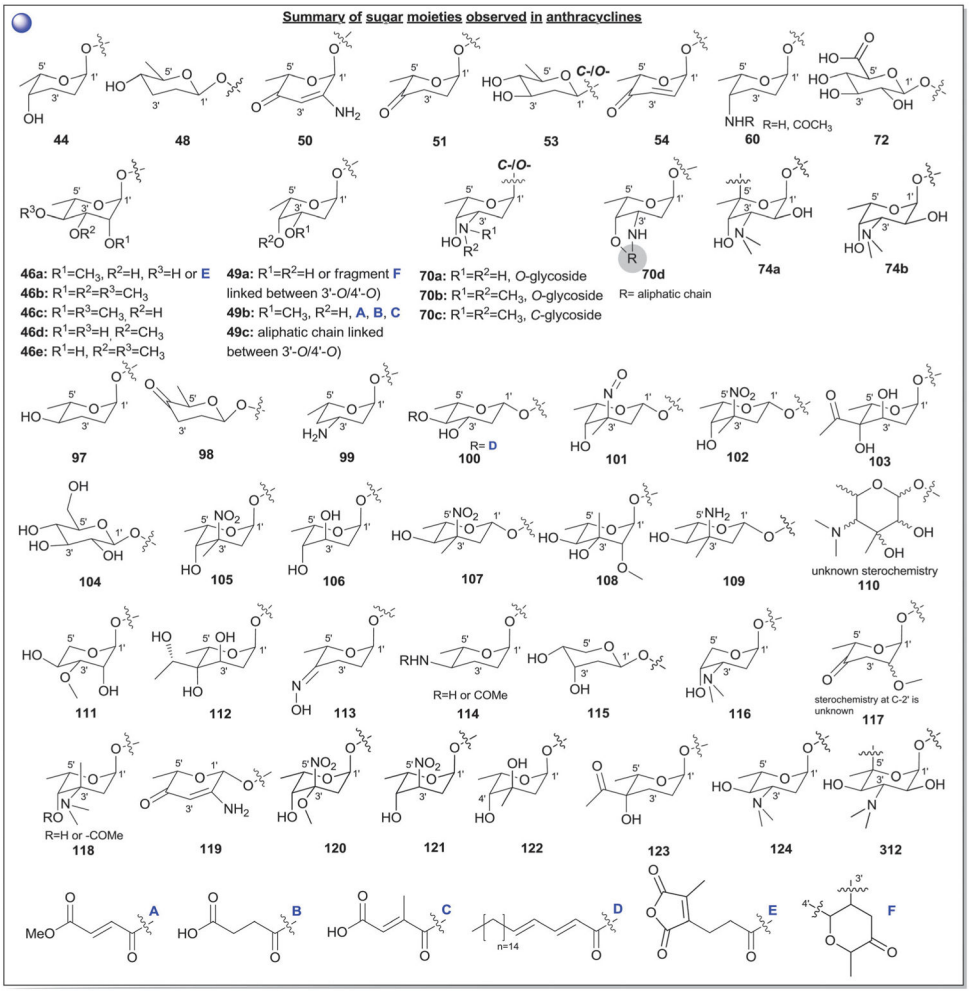


Fig. 14.
Sugars associated with anthracyclines.

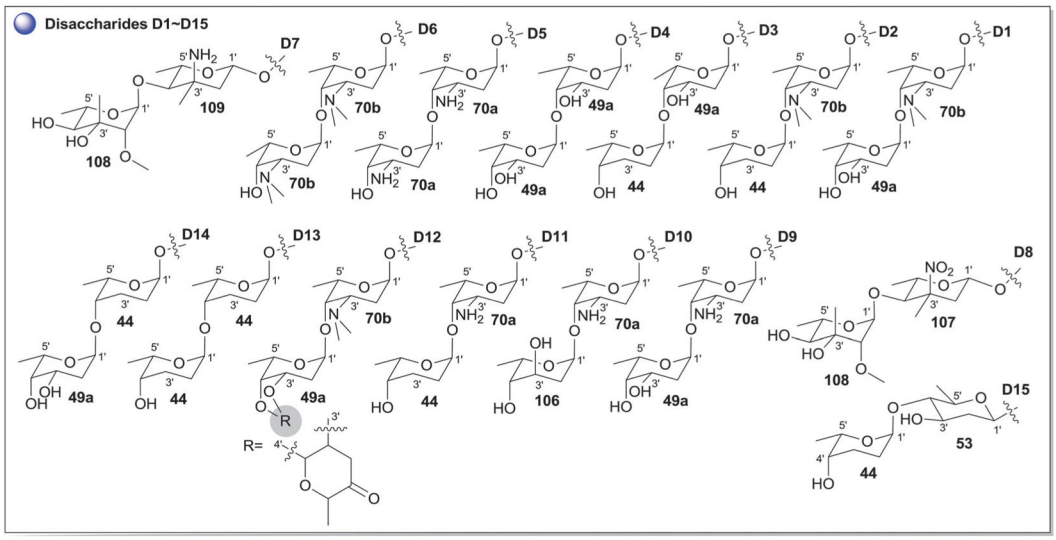


Fig. 15.

Disaccharide variations **D1–D15** observed in anthracyclines.

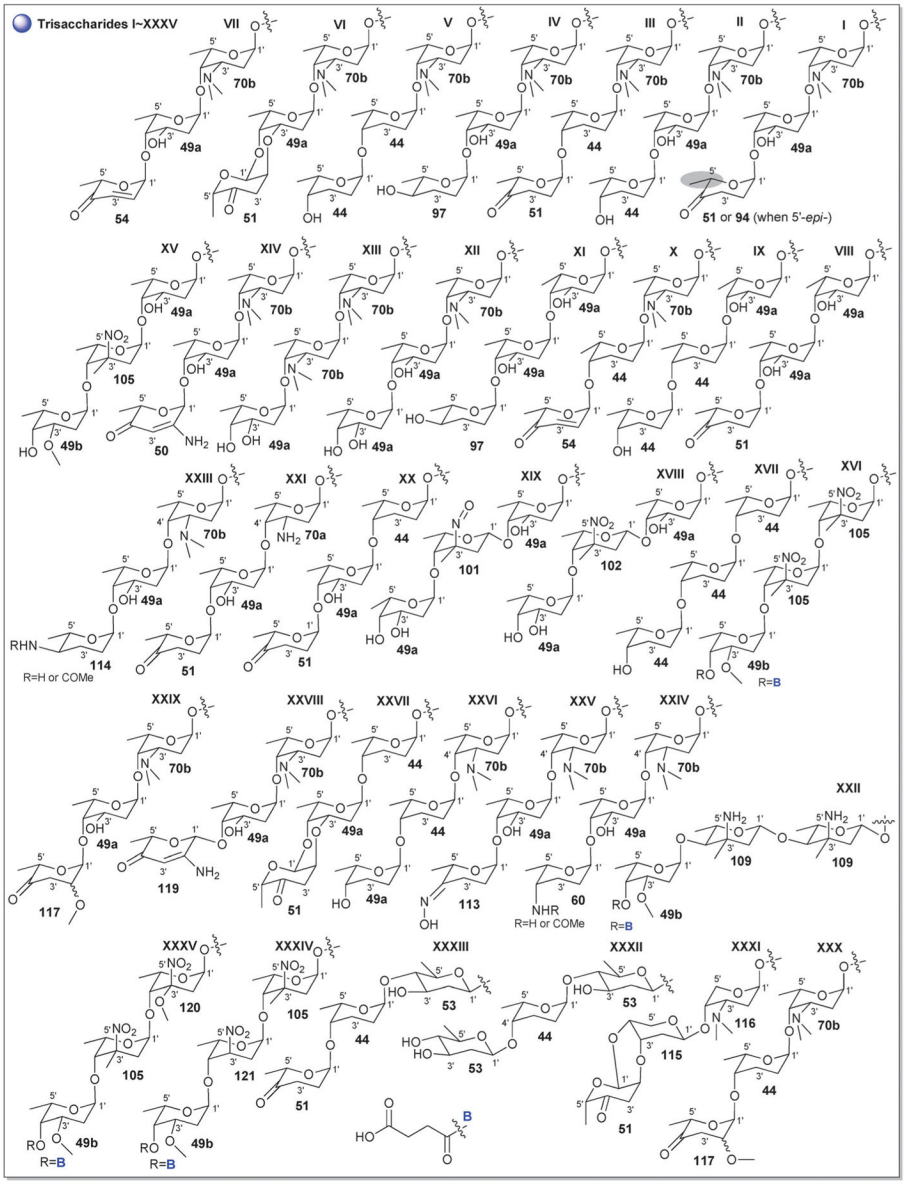


Fig. 16.

Trisaccharide variations (**I–XXXV**) observed in anthracyclines.

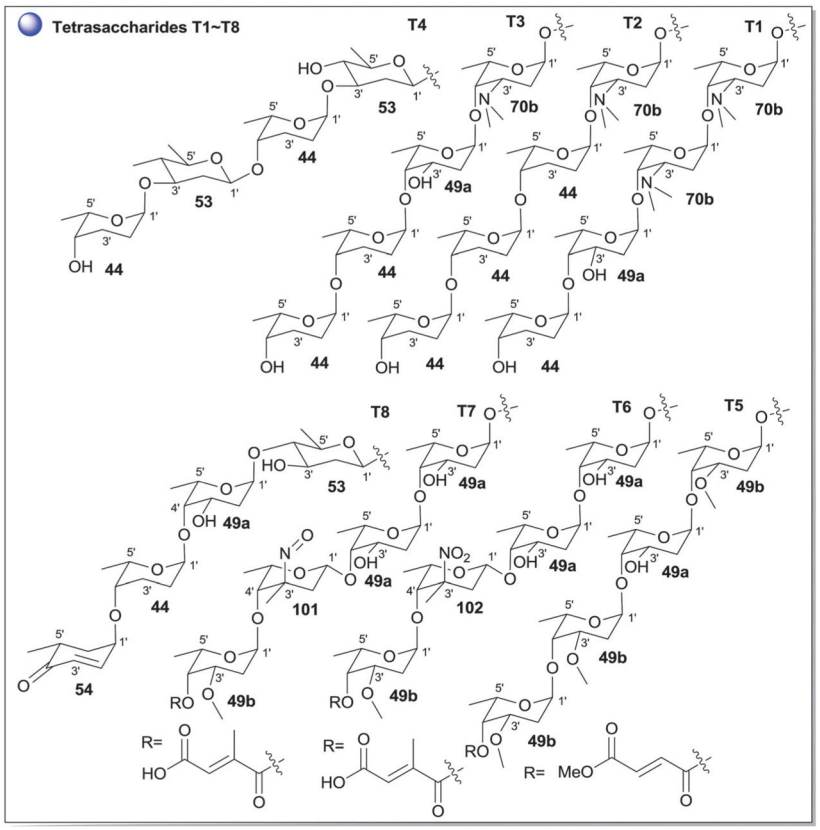


Fig. 17.

Tetrasaccharide variations (**T1–T8**) observed in anthracyclines.

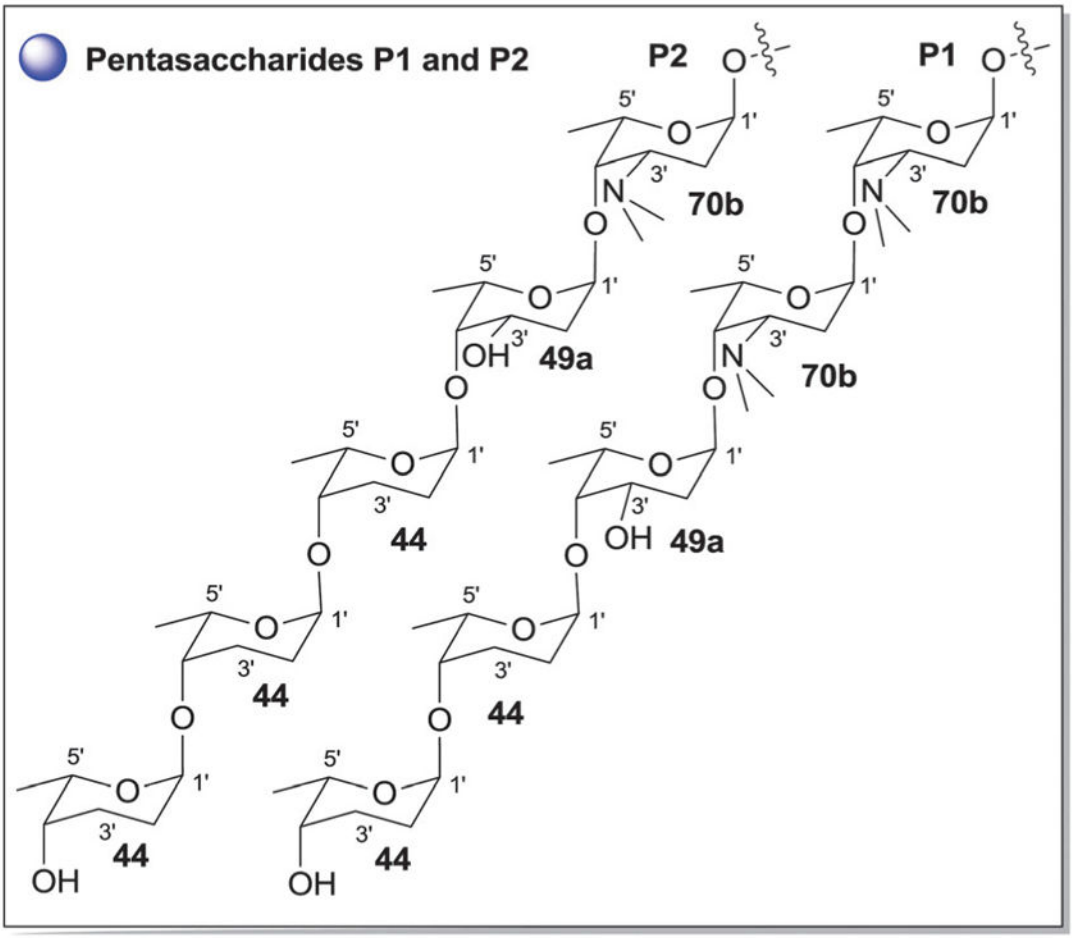


Fig. 18.
Pentasaccharide variations **P1–P2** observed in anthracyclines.

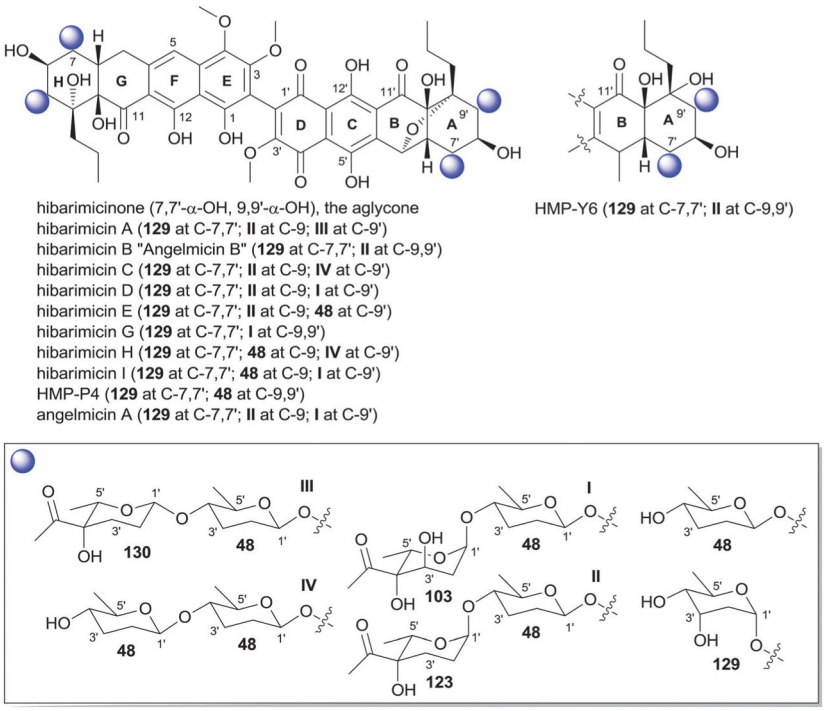


Fig. 19.
Hibarimicin aglycons and associated sugars.

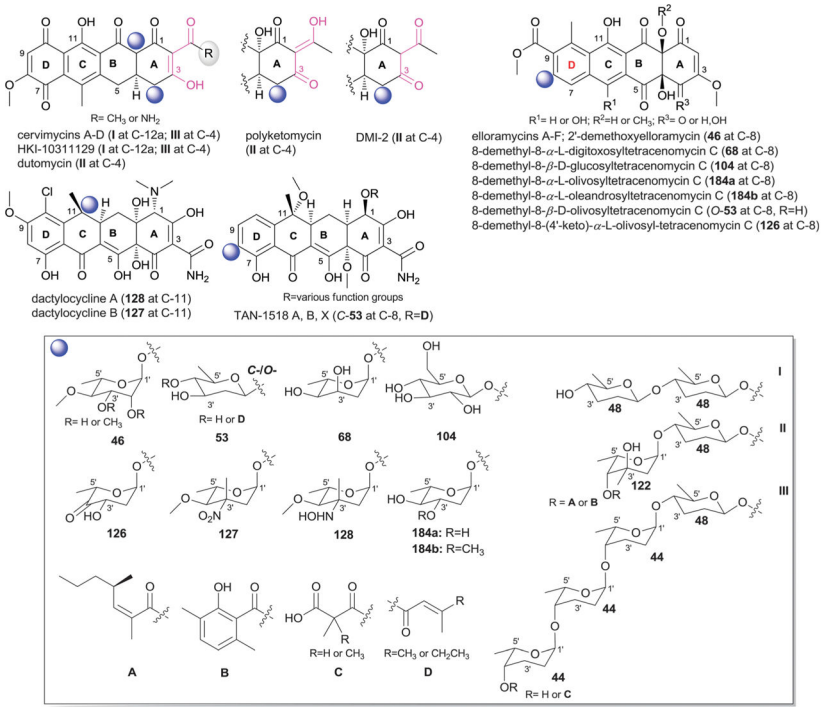


Fig. 20.
Tetracycline aglycons and associated sugars.

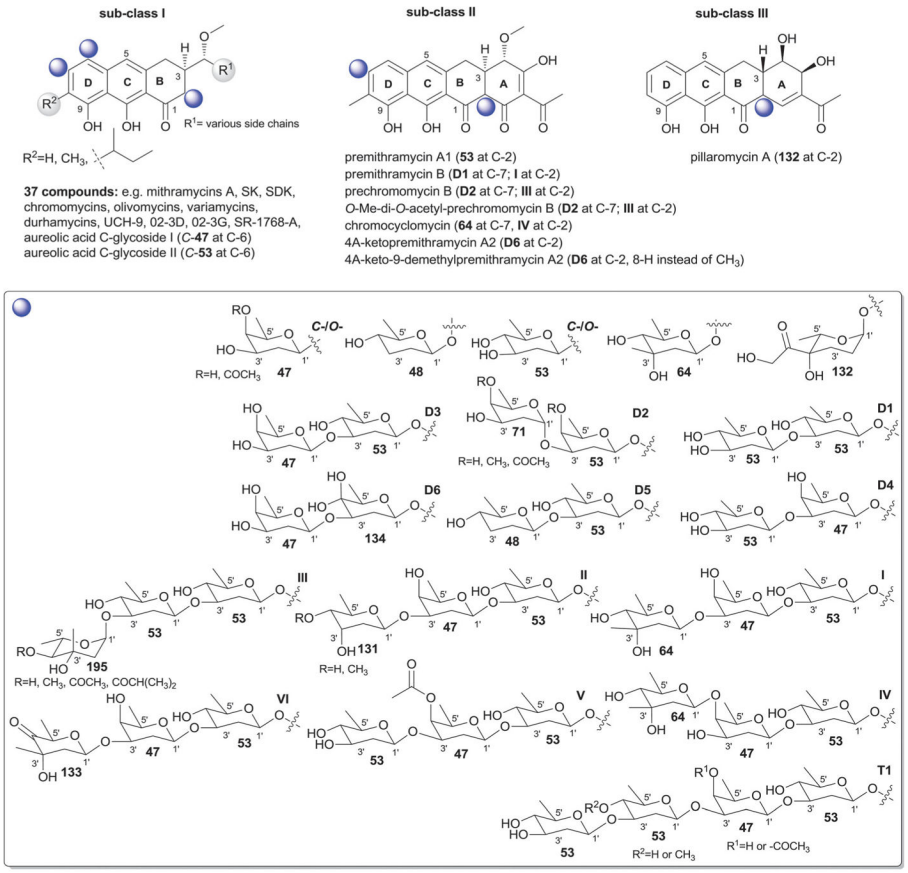


Fig. 21.
Aureolic acid analogs and associated sugars.

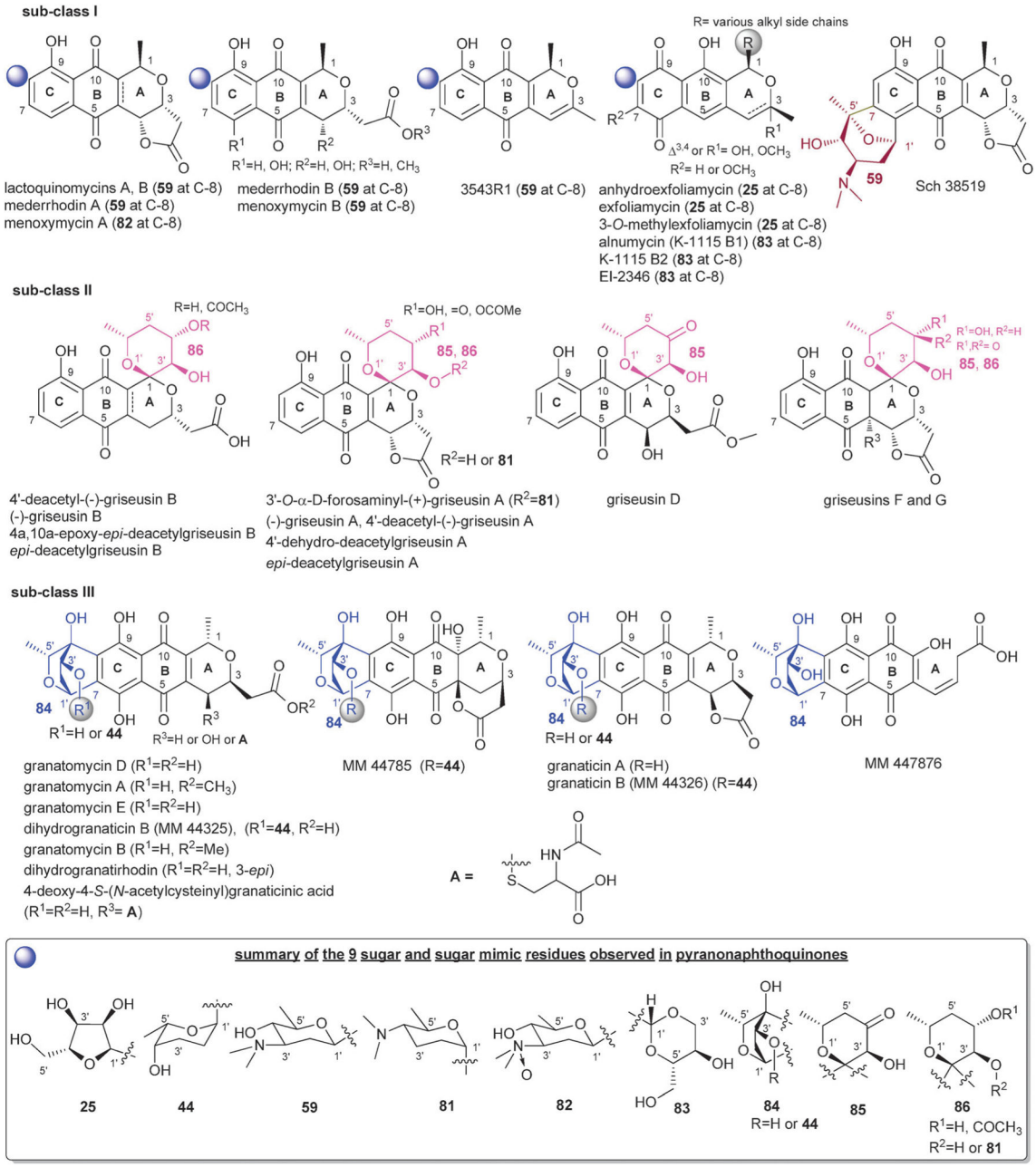


Fig. 22.

Pyranonaphthoquinone related aglycons and associated sugars.

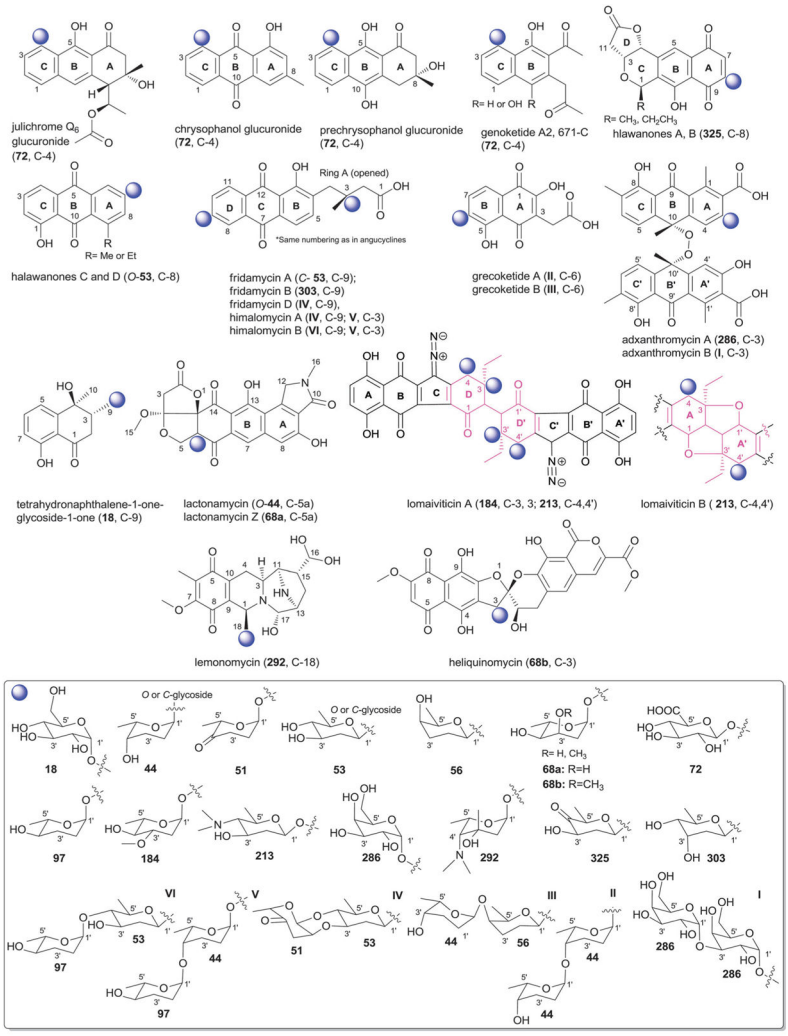


Fig. 23.

Benzoquinone-related aglycons and associated sugars.

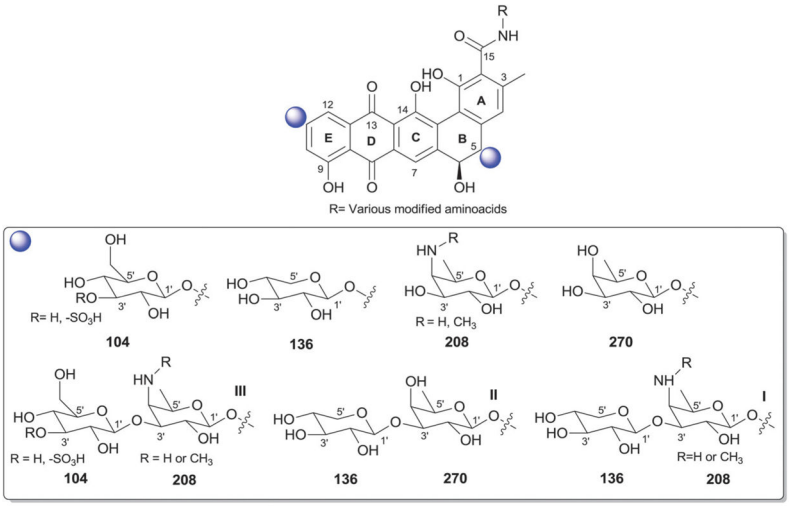


Fig. 24.

Benanomicin and pradimicin aglycons and associated sugars.

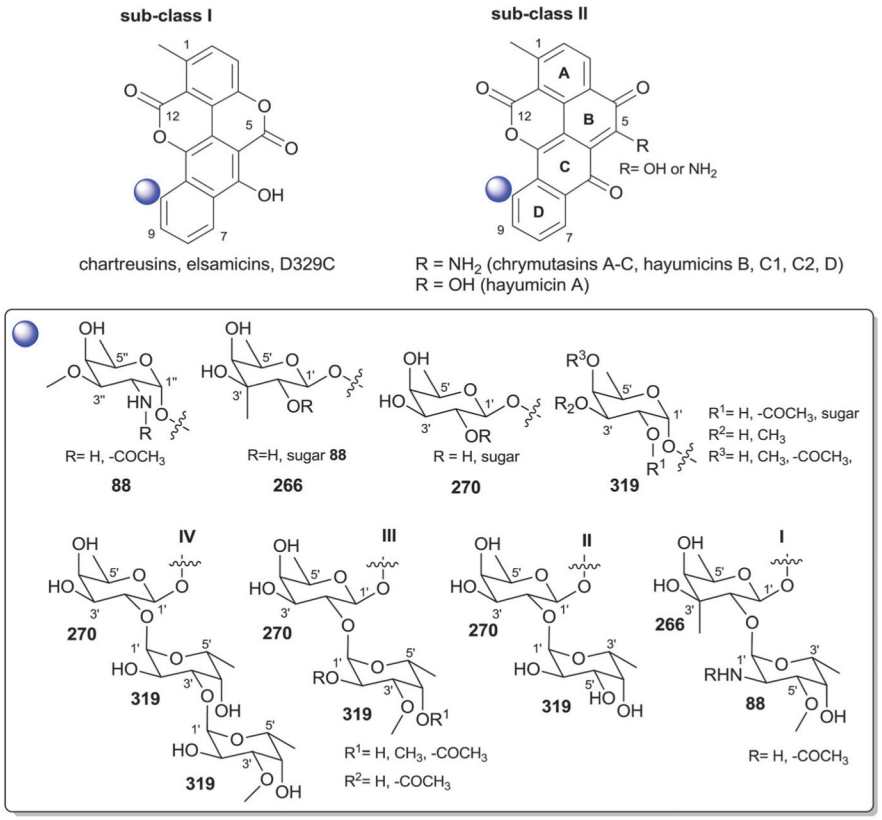


Fig. 25.
Chartarin aglycons and associated sugars.

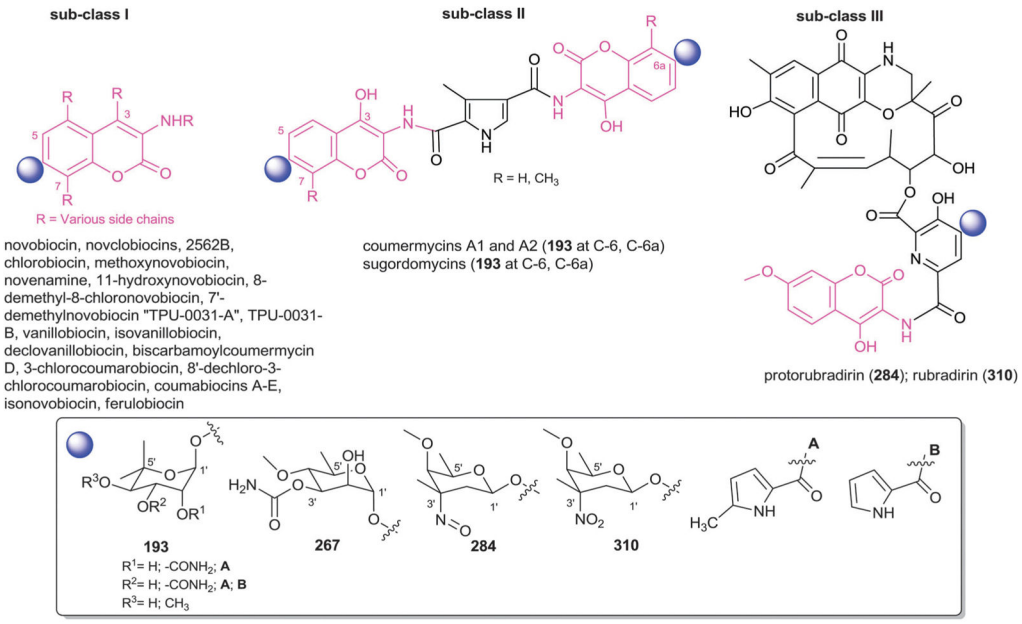


Fig. 26.
Coumarin aglycons and associated sugars.

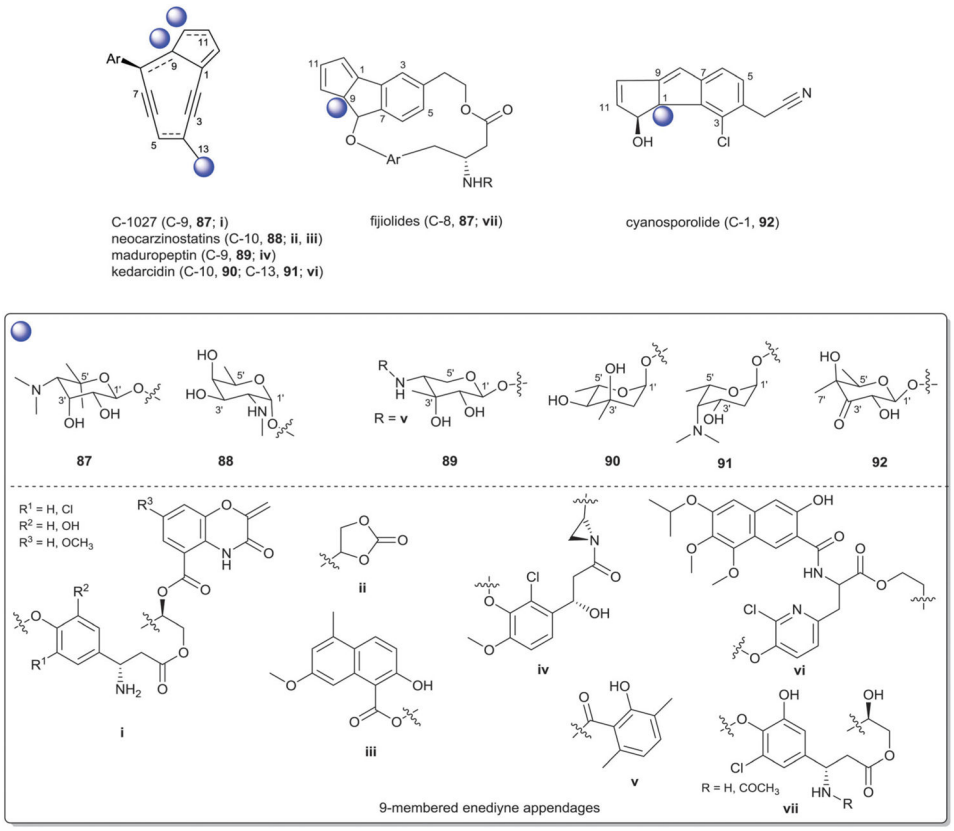


Fig. 27.

9-Membered enediyne aglycons and associated sugars. Ar, aromatic moiety.

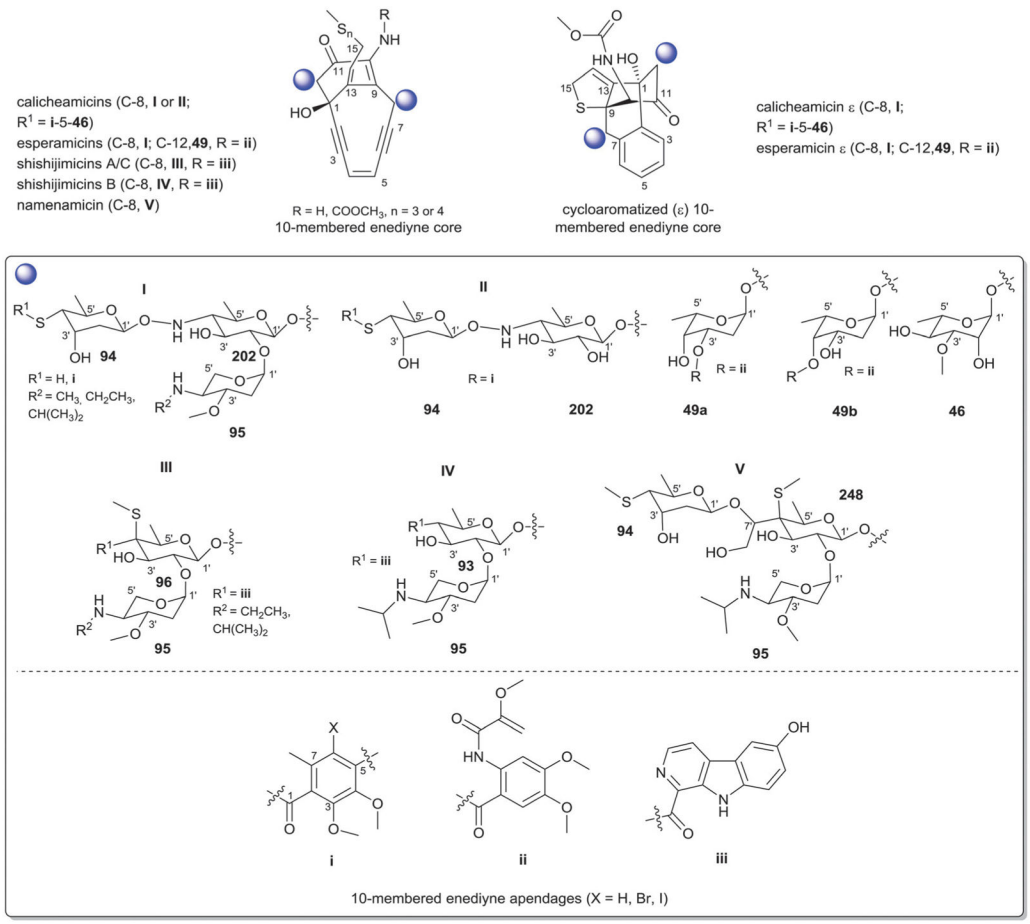


Fig. 28.

10-Membered enediyne aglycons and associated sugars. Ar, aromatic moiety.

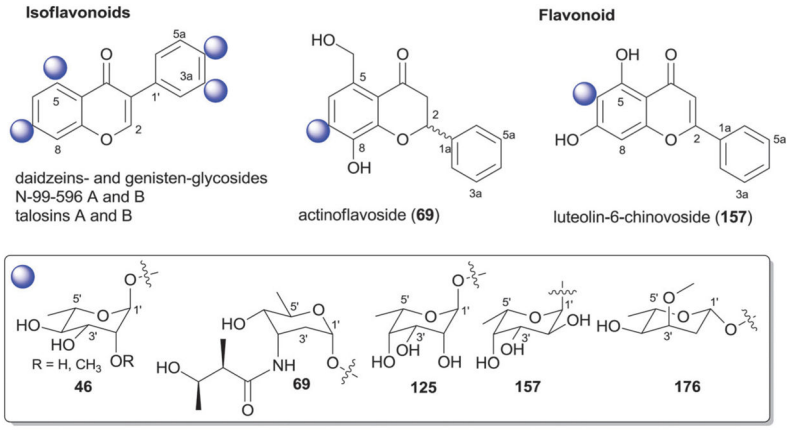


Fig. 29.
Flavonoid and isoflavonoid aglycons and associated sugars.

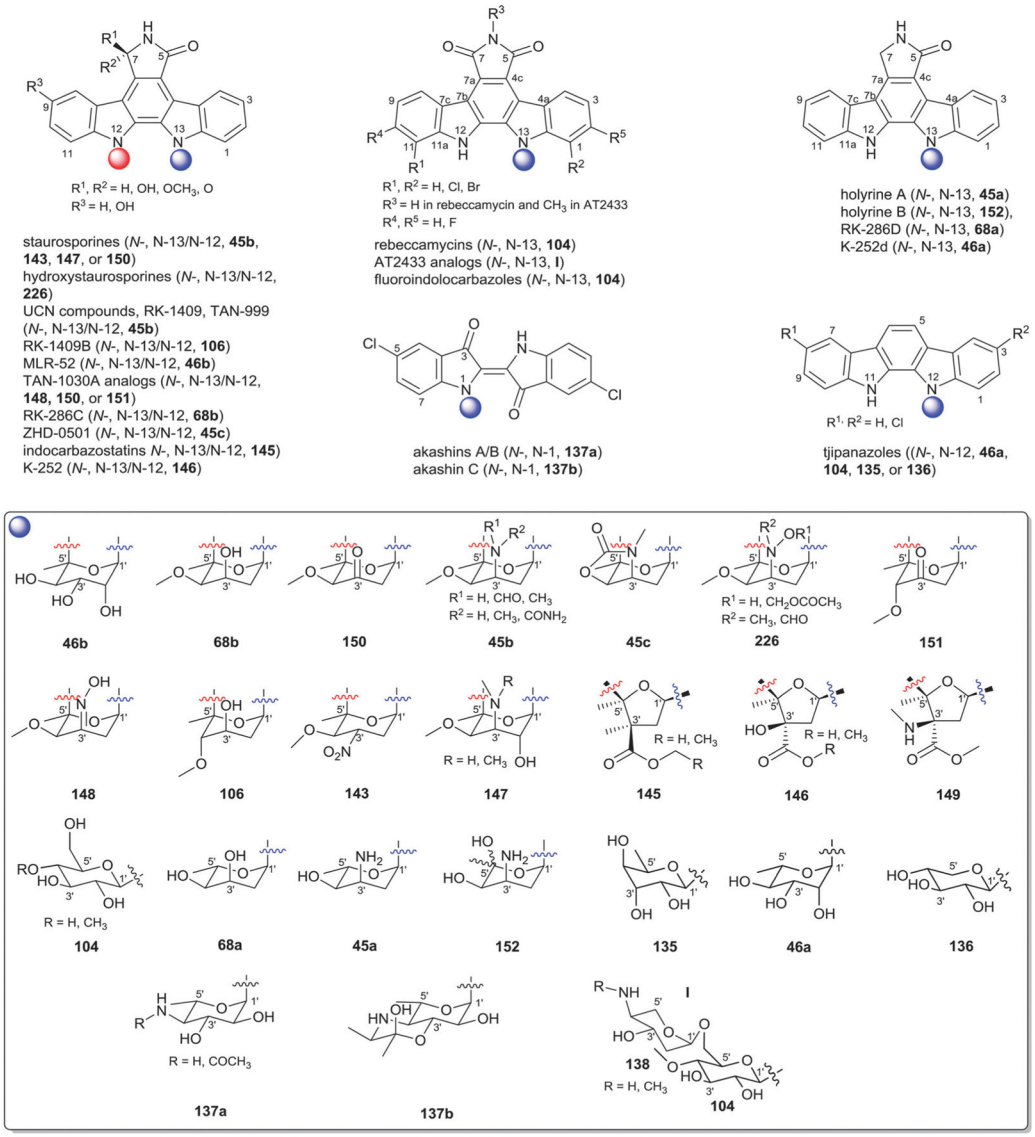


Fig. 30.

Fused indole-related aglycons and associated sugars where different colors distinguish multiple points of attachment.

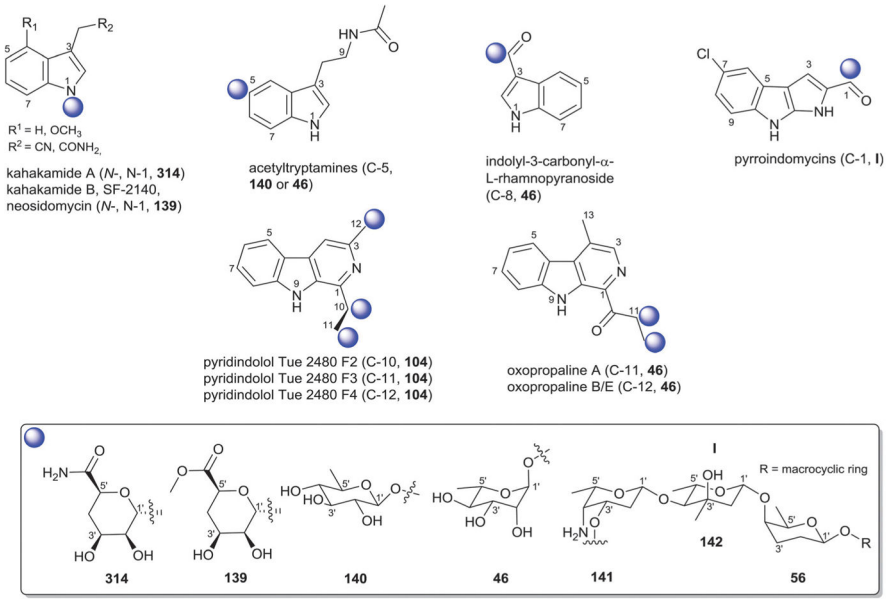


Fig. 31.
Simple indole-related aglycons and associated sugars.

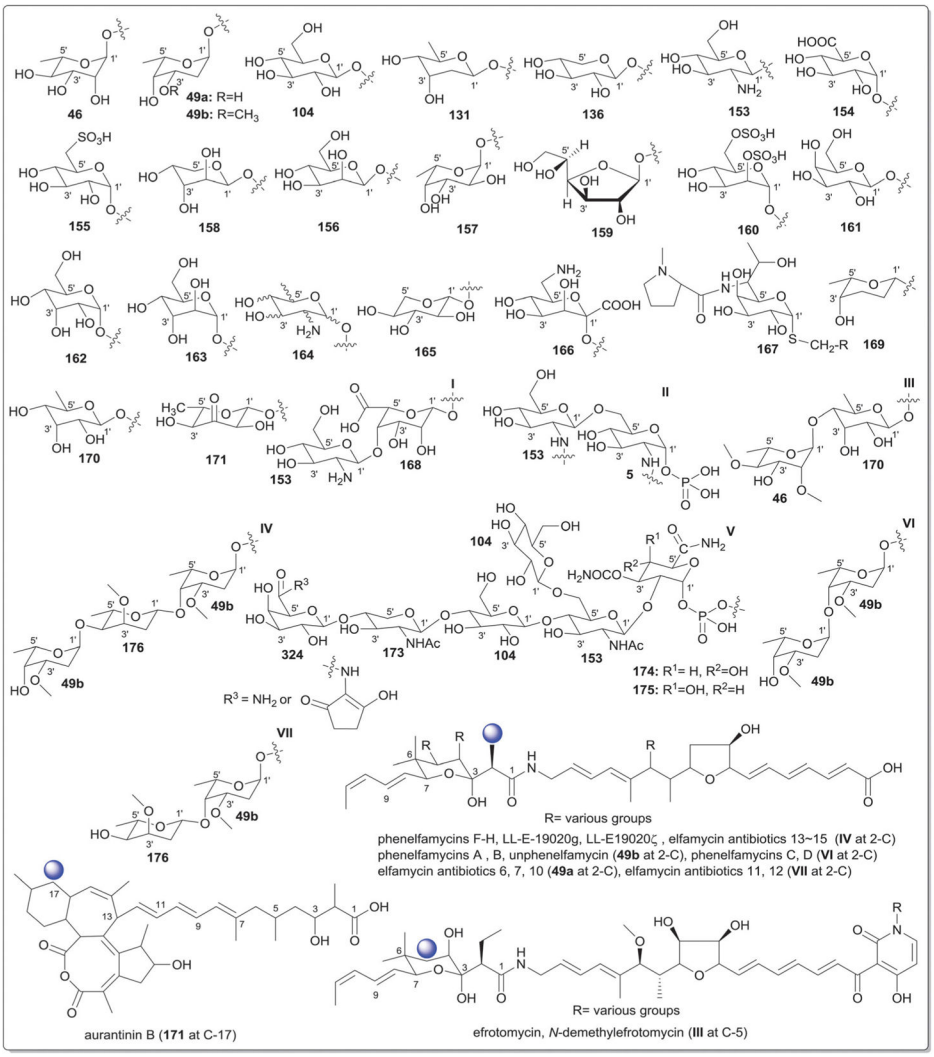


Fig. 32.

Glycolipids, polyenes and carotenoids and associated sugars.

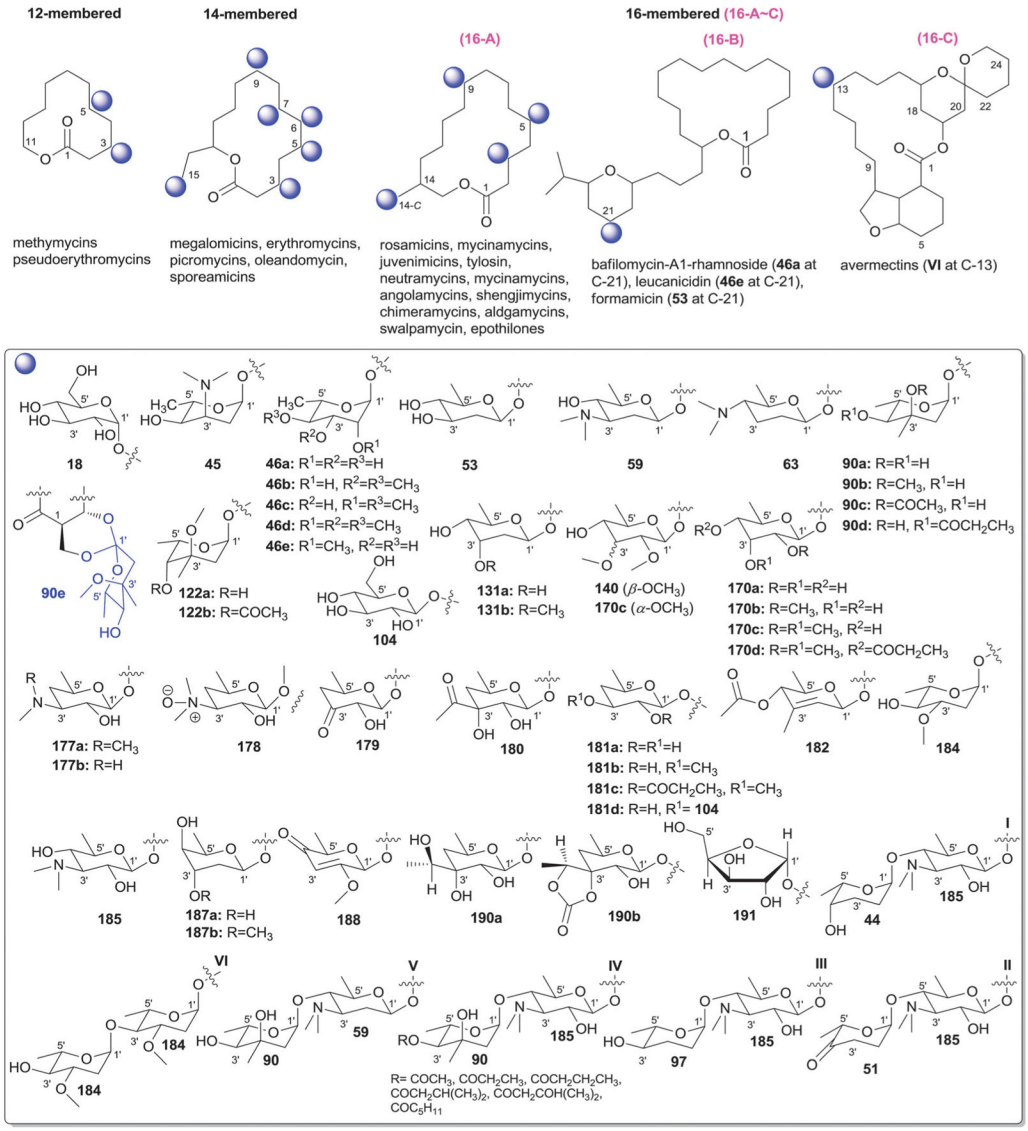


Fig. 33.

12-, 14- and 16-membered macrolactones and associated sugars.

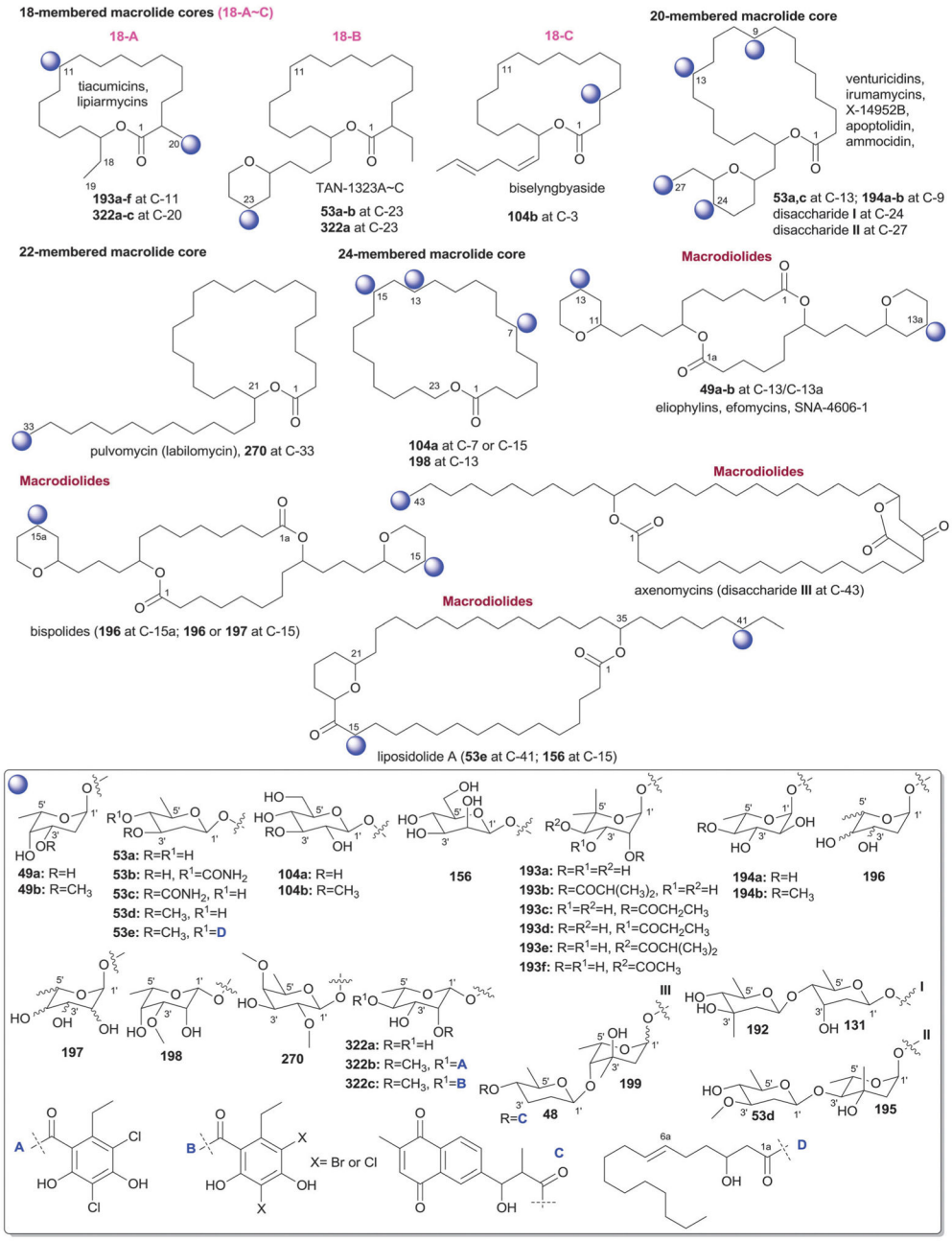


Fig. 34.

18-, 20-, 22-, 24-Membered macrolactones and macrodiolides and associated sugars.

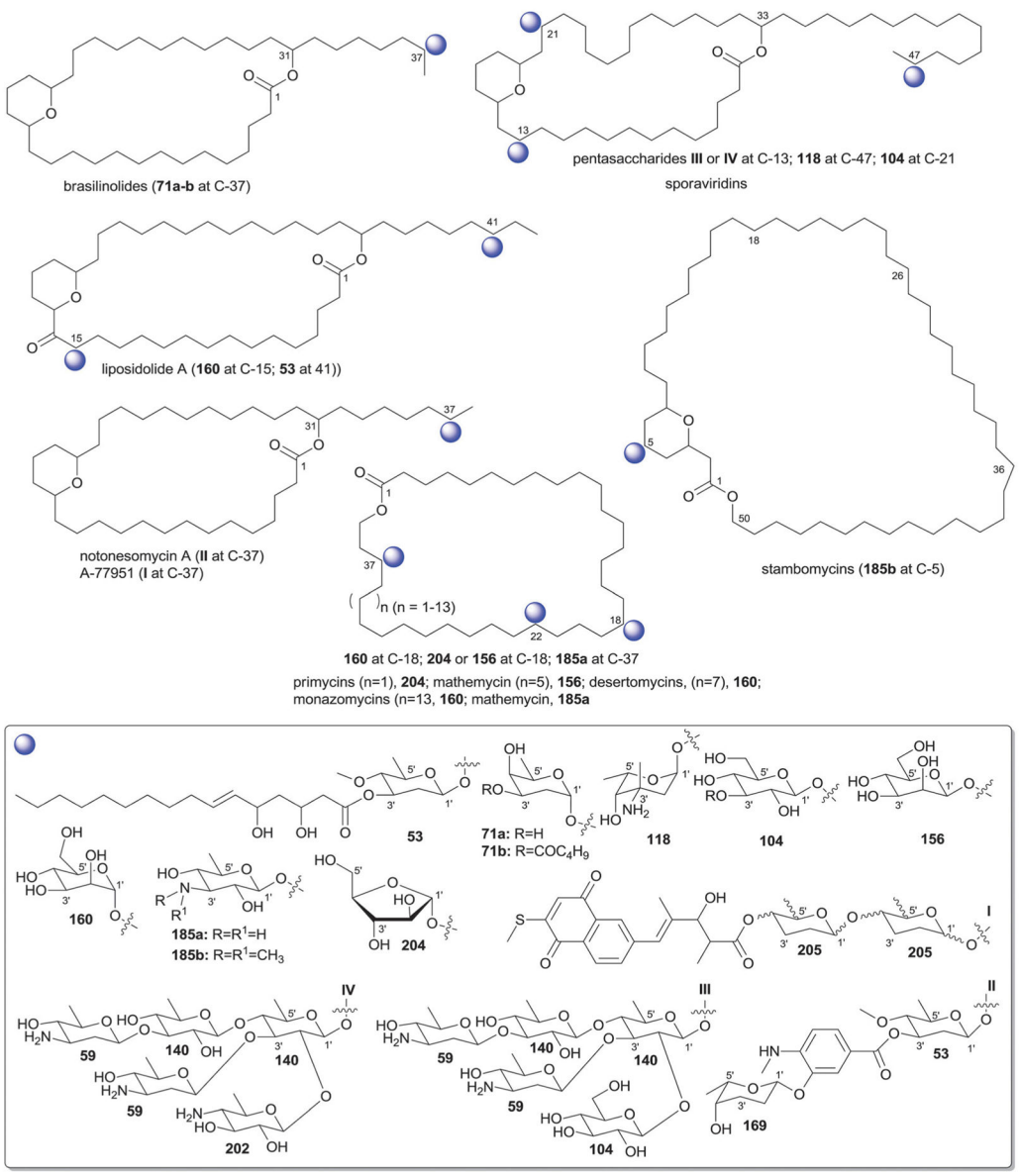


Fig. 35.

Super macrolactone (ring size 32–48) aglycons and associated sugars.

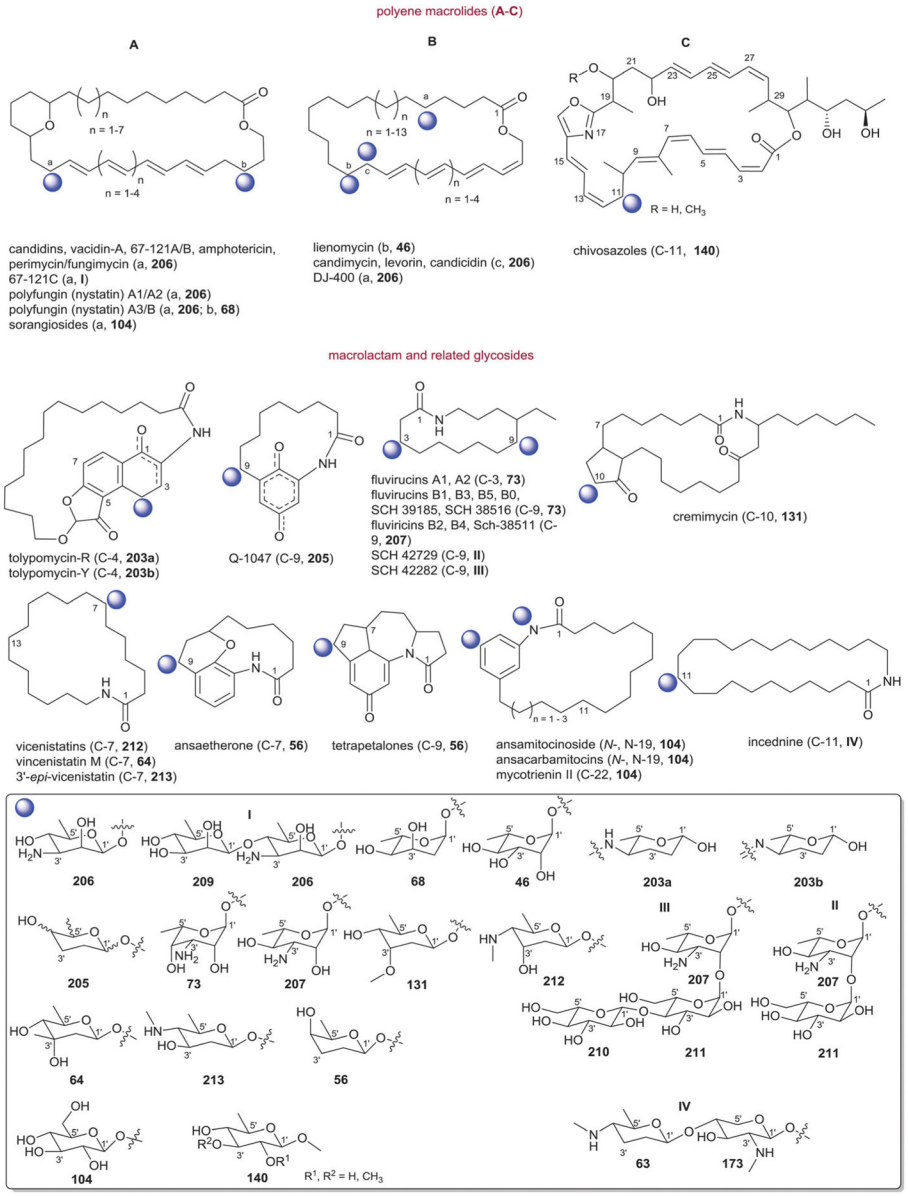


Fig. 36.

Polyene and macrolactam aglycons and associated sugars.

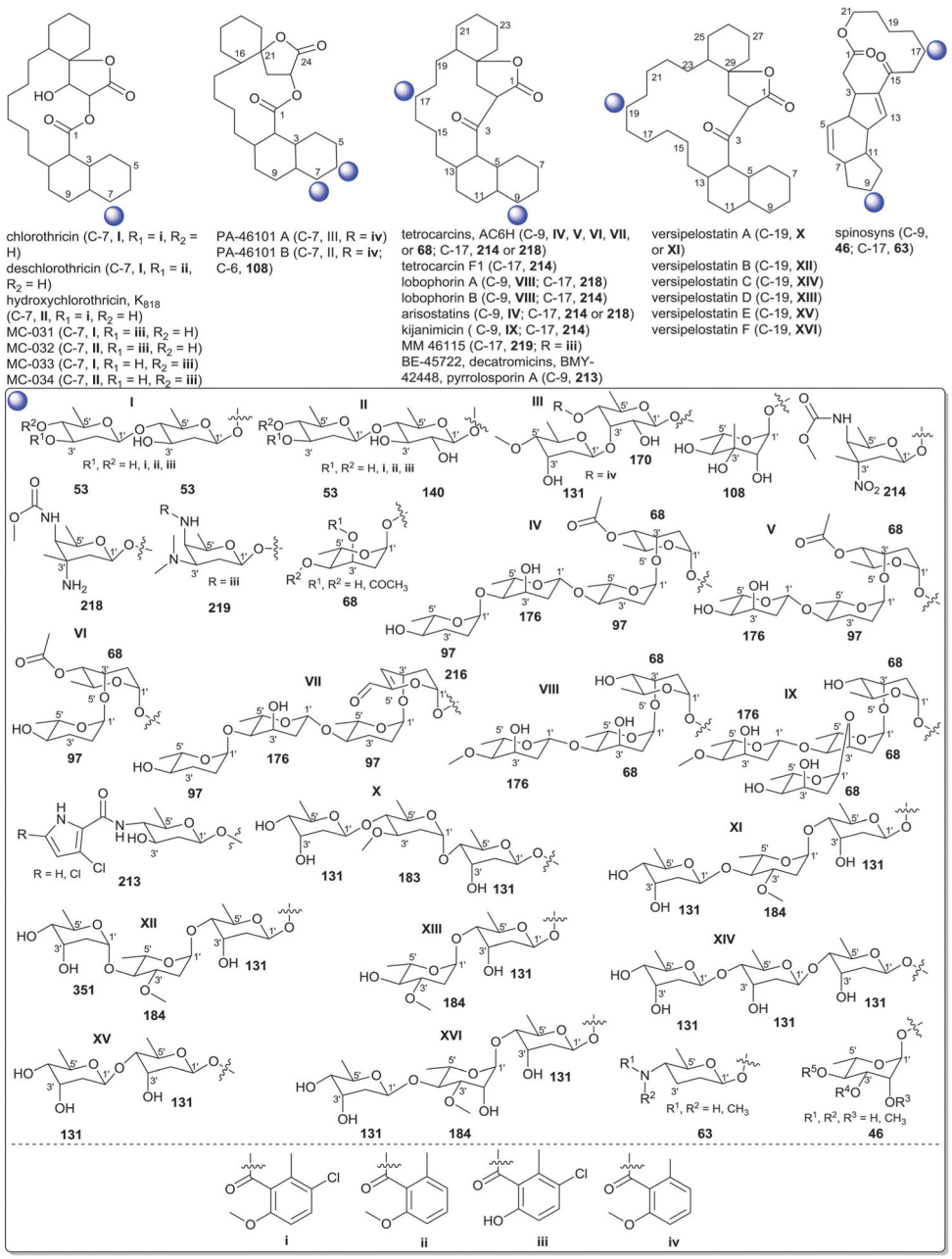


Fig. 37.
Spirotetronates and spinosyn aglycons and associated sugars.

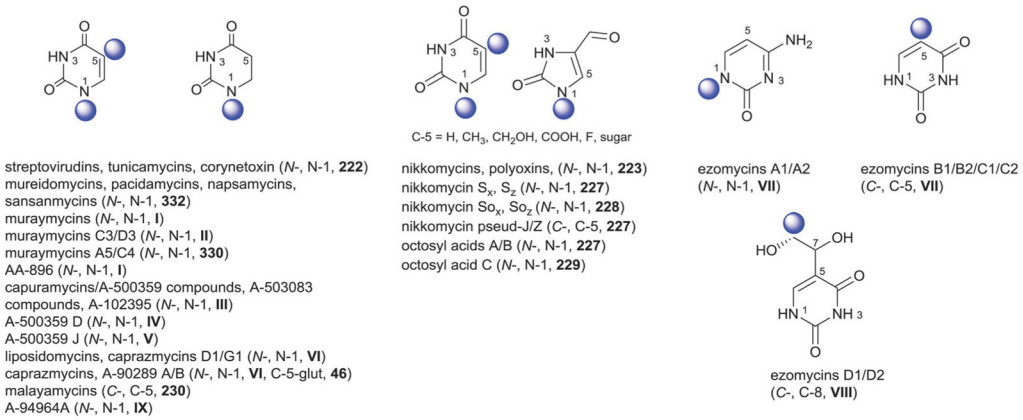


Fig. 38.
Uracil-derived aglycons.

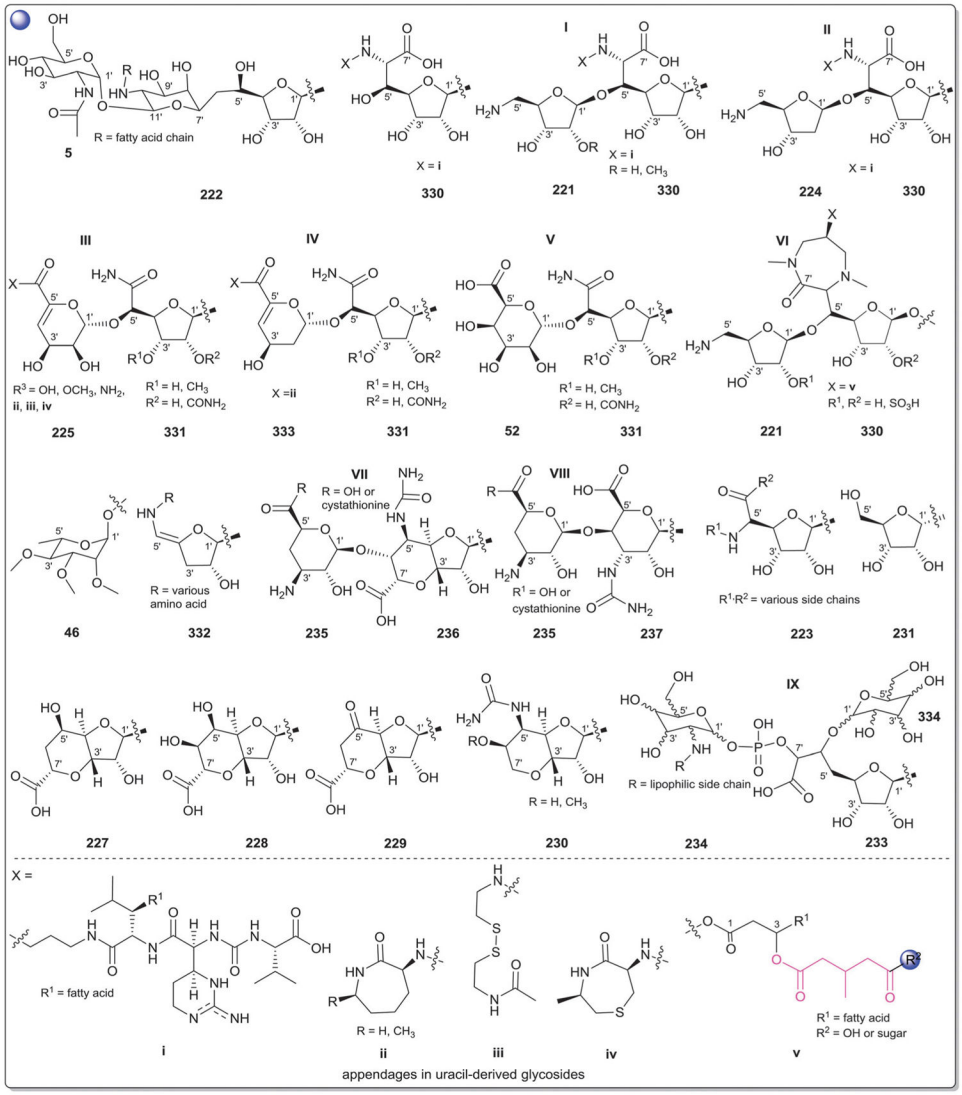


Fig. 39.

Sugars associated with uracil-derived aglycons. Pink fragment is absent in some derivatives.

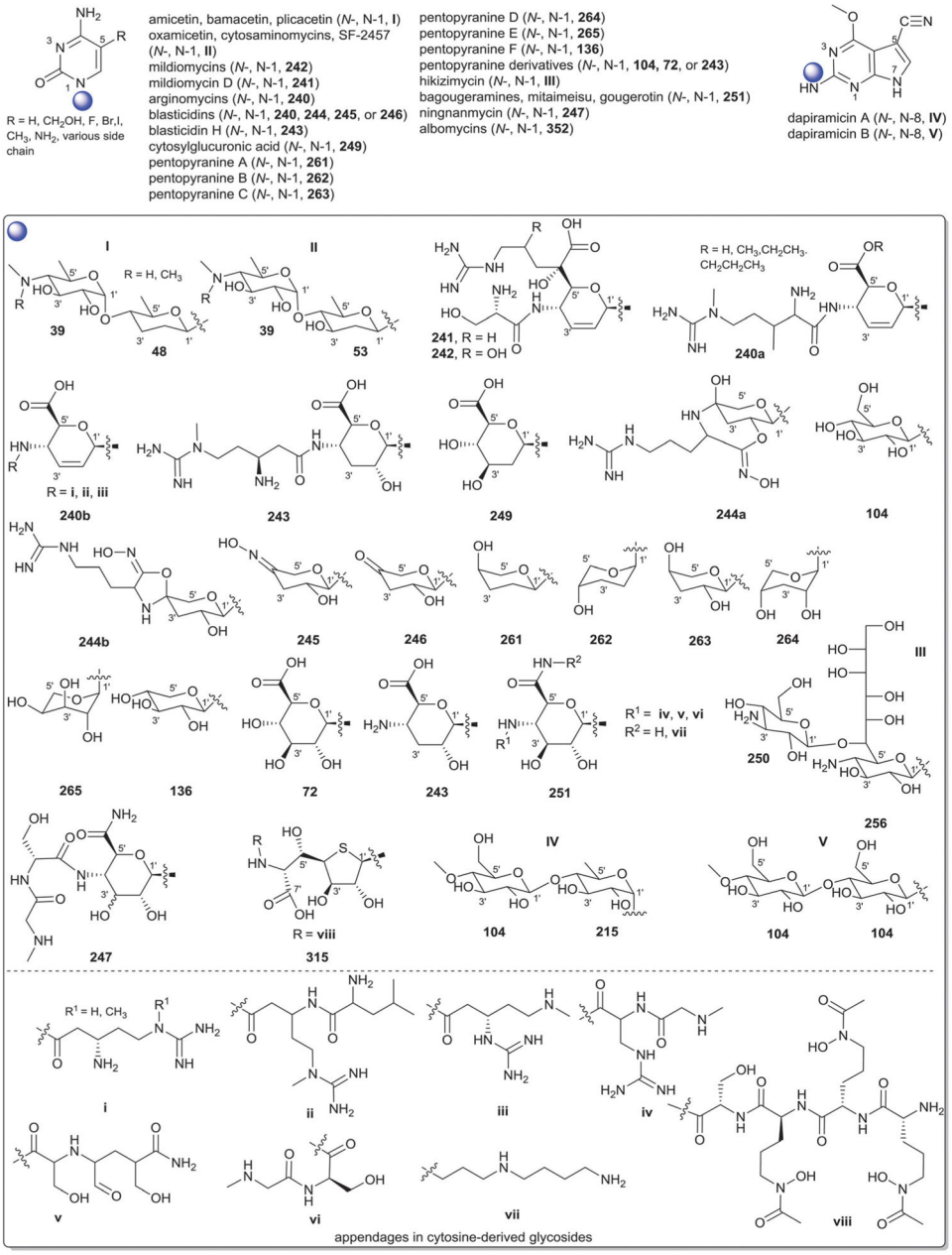


Fig. 40.
Cytosine-derived aglycons and associated sugars.

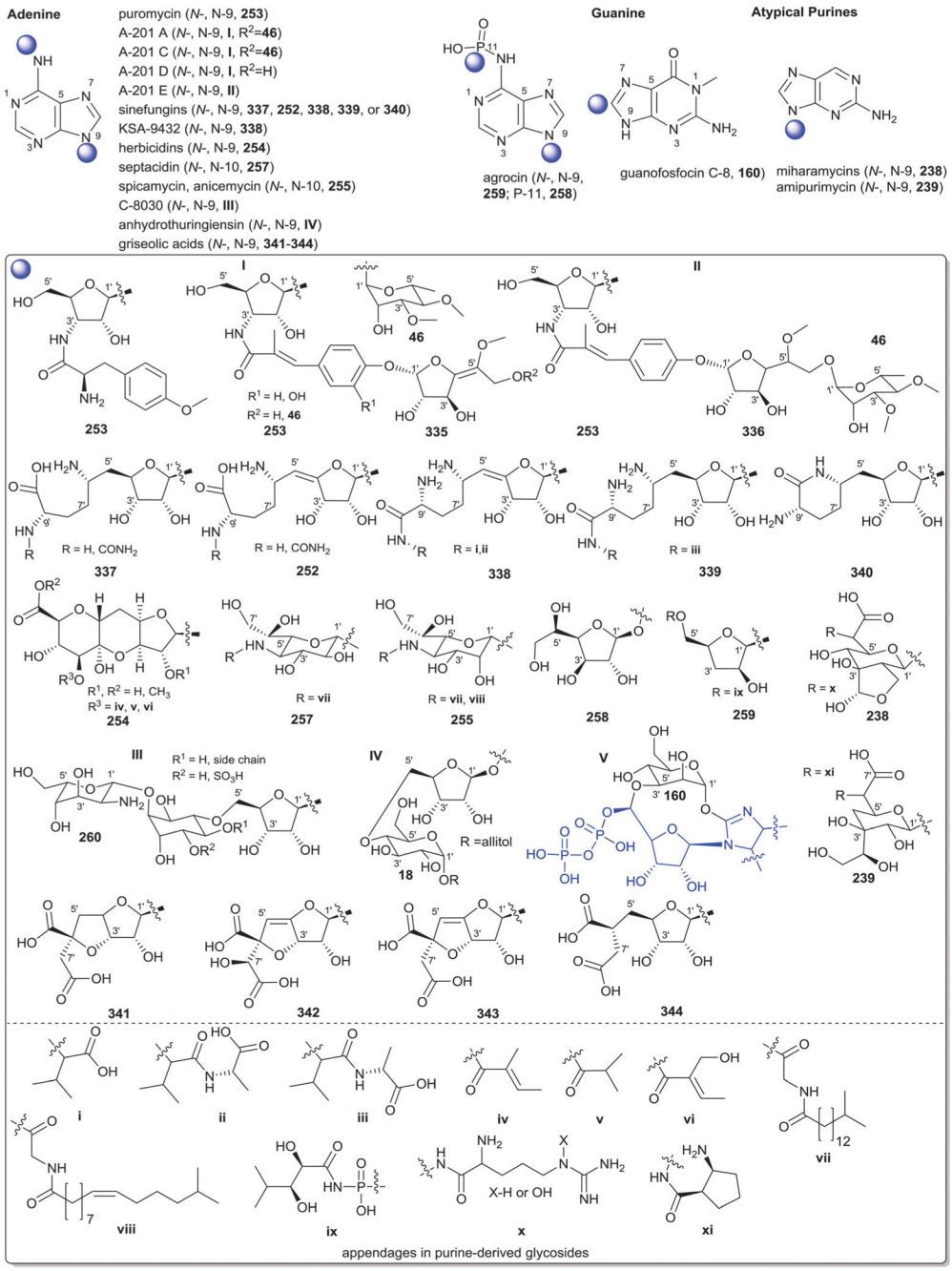


Fig. 41.
Purine-derived aglycons and associated sugars.

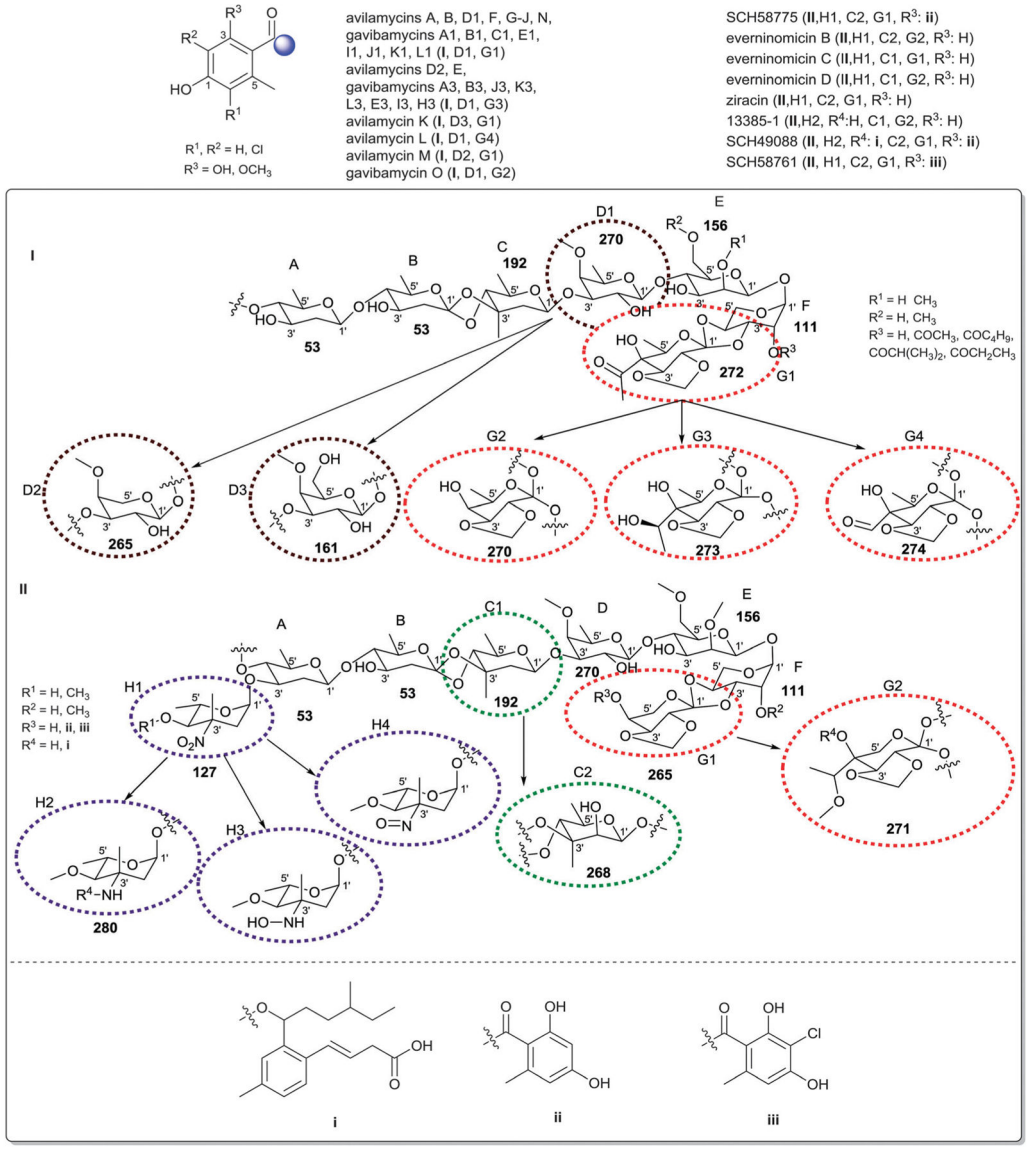


Fig. 42.
Orsellinic acid aglycons and associated sugars.

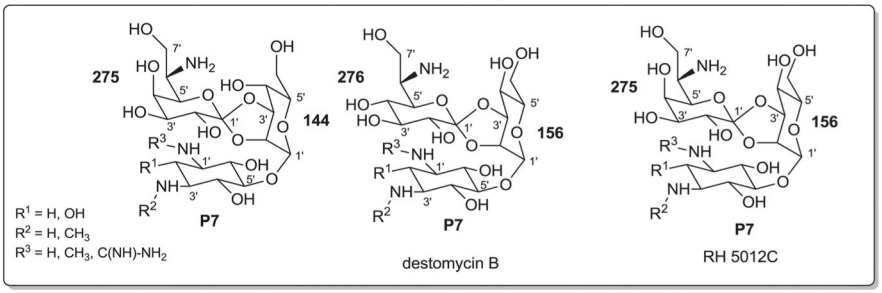


Fig. 43.
Sugars associated with orthoester aminocyclitols.

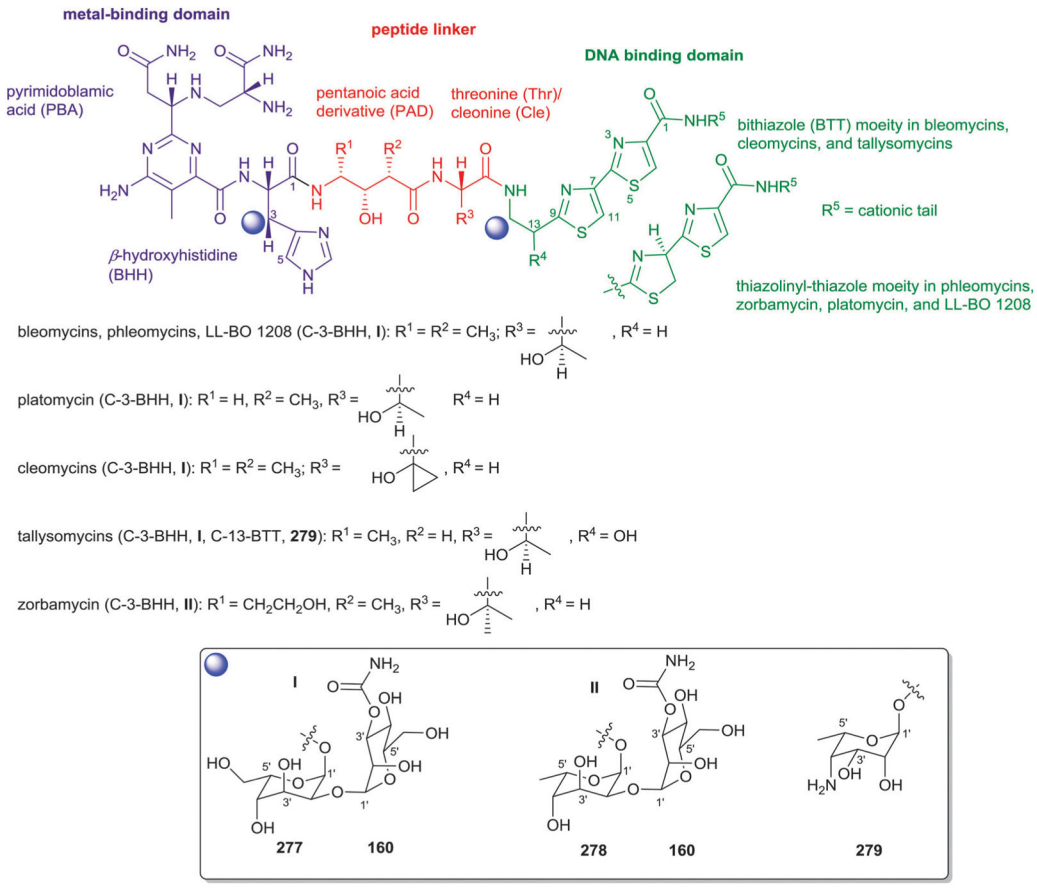


Fig. 44.

Bleomycin aglycons and associated sugars. Platomycin structure is based on partial structure reported.

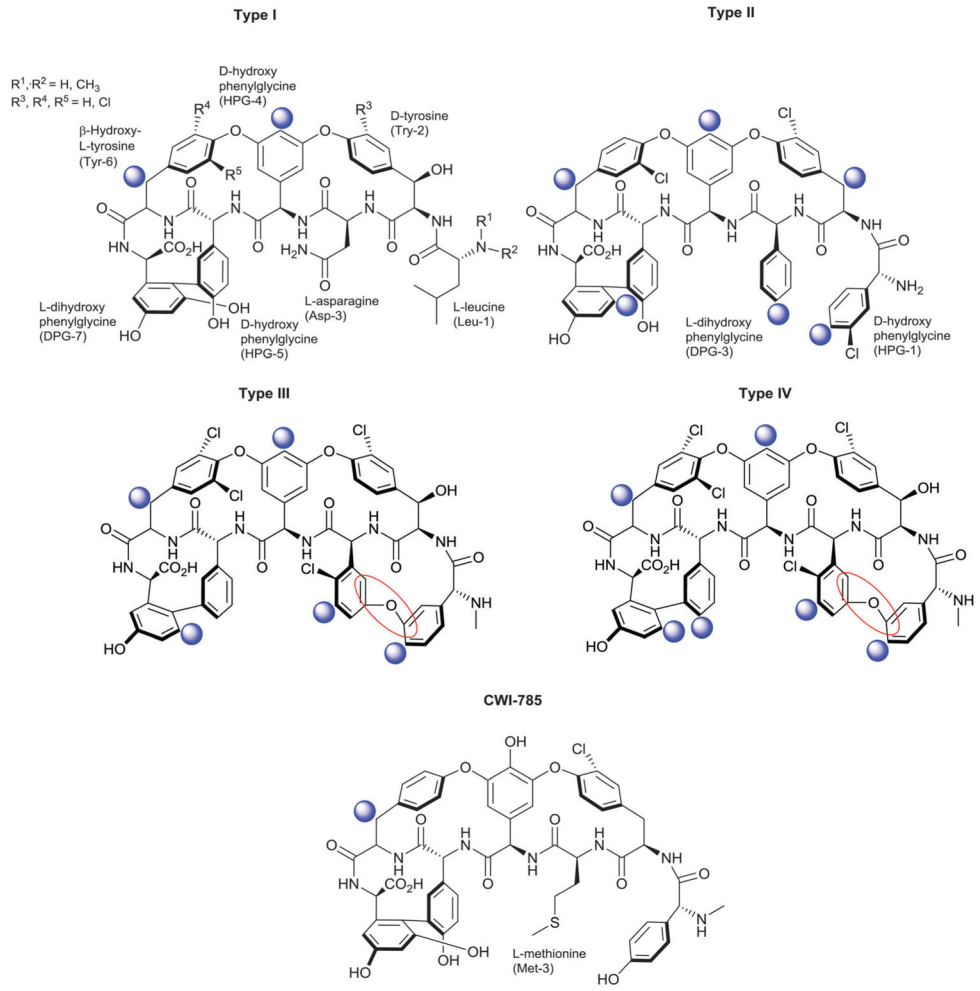


Fig. 45.

Aglycons of the five types of vancomycin. The ether bridge in types III and IV is highlighted in red. Locataions of attachment to most sugars in CWI-785 series is not determined.

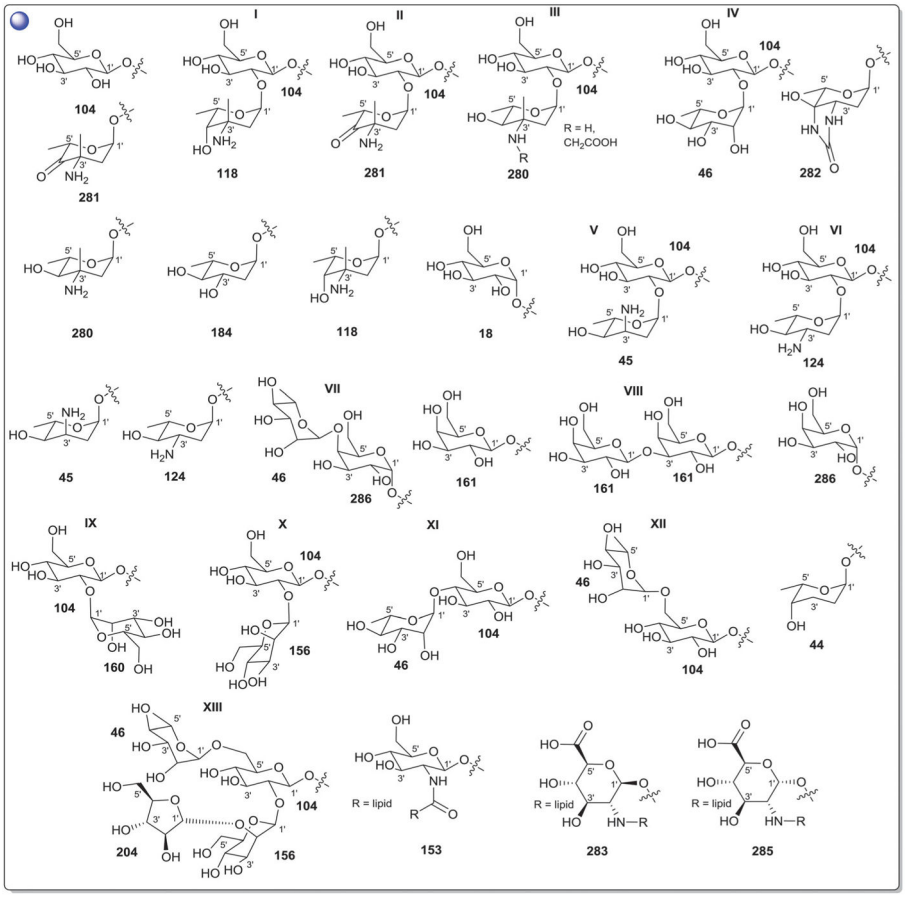
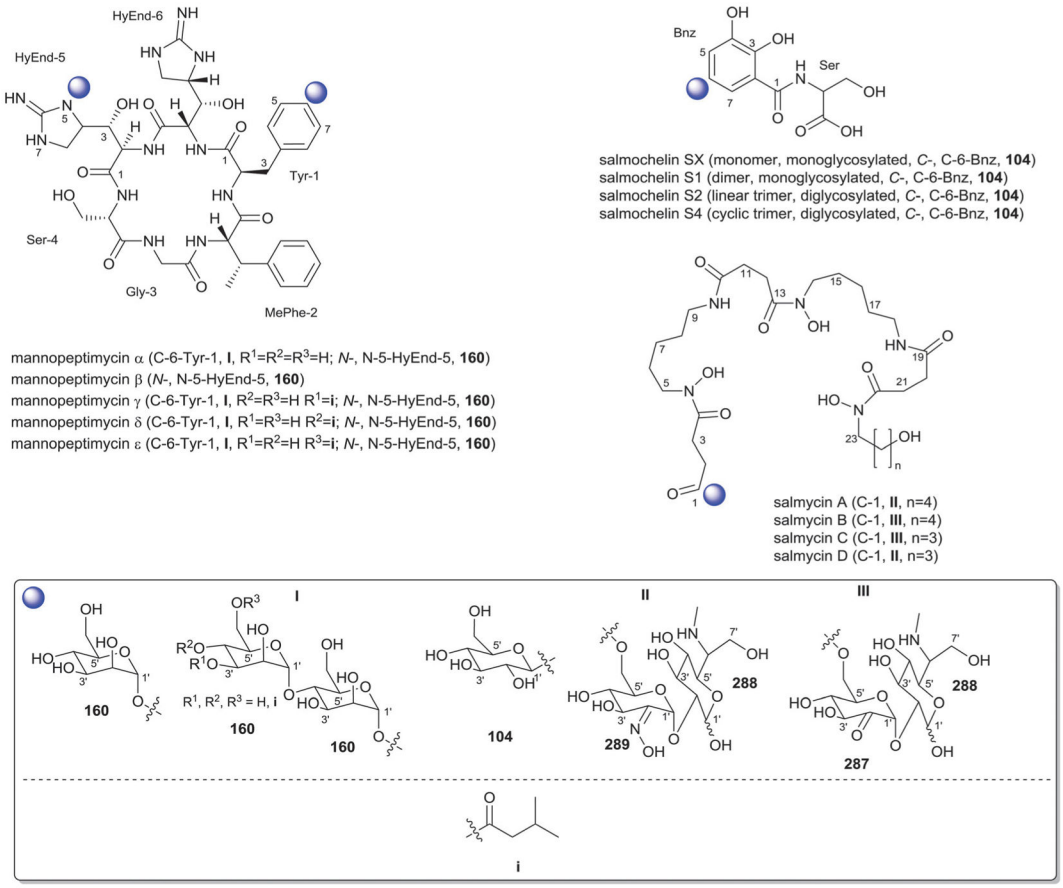


Fig. 46.
Sugars associated with vancomycins.



mannopeptimycin α (C-6-Tyr-1, **I**, R^1=R^2=R^3=H; *N*-, N-5-HyEnd-5, **160**)
mannopeptimycin β (*N*-, N-5-HyEnd-5, **160**)
mannopeptimycin γ (C-6-Tyr-1, **I**, R^2=R^3=H R^1=i; *N*-, N-5-HyEnd-5, **160**)
mannopeptimycin δ (C-6-Tyr-1, **I**, R^1=R^3=H R^2=i; *N*-, N-5-HyEnd-5, **160**)
mannopeptimycin ε (C-6-Tyr-1, **I**, R^1=R^2=H R^3=i; *N*-, N-5-HyEnd-5, **160**)

salmochelin SX (monomer, monoglycosylated, *C*-, C-6-Bnz, **104**)
salmochelin S1 (dimer, monoglycosylated, *C*-, C-6-Bnz, **104**)
salmochelin S2 (linear trimer, diglycosylated, *C*-, C-6-Bnz, **104**)
salmochelin S4 (cyclic trimer, diglycosylated, *C*-, C-6-Bnz, **104**)

salmycin A (C-1, **II**, n=4)
salmycin B (C-1, **III**, n=4)
salmycin C (C-1, **III**, n=3)
salmycin D (C-1, **II**, n=3)

Fig. 47.
Mannopeptimycin, salmochelin, and salmomycin aglycons and associated sugars.

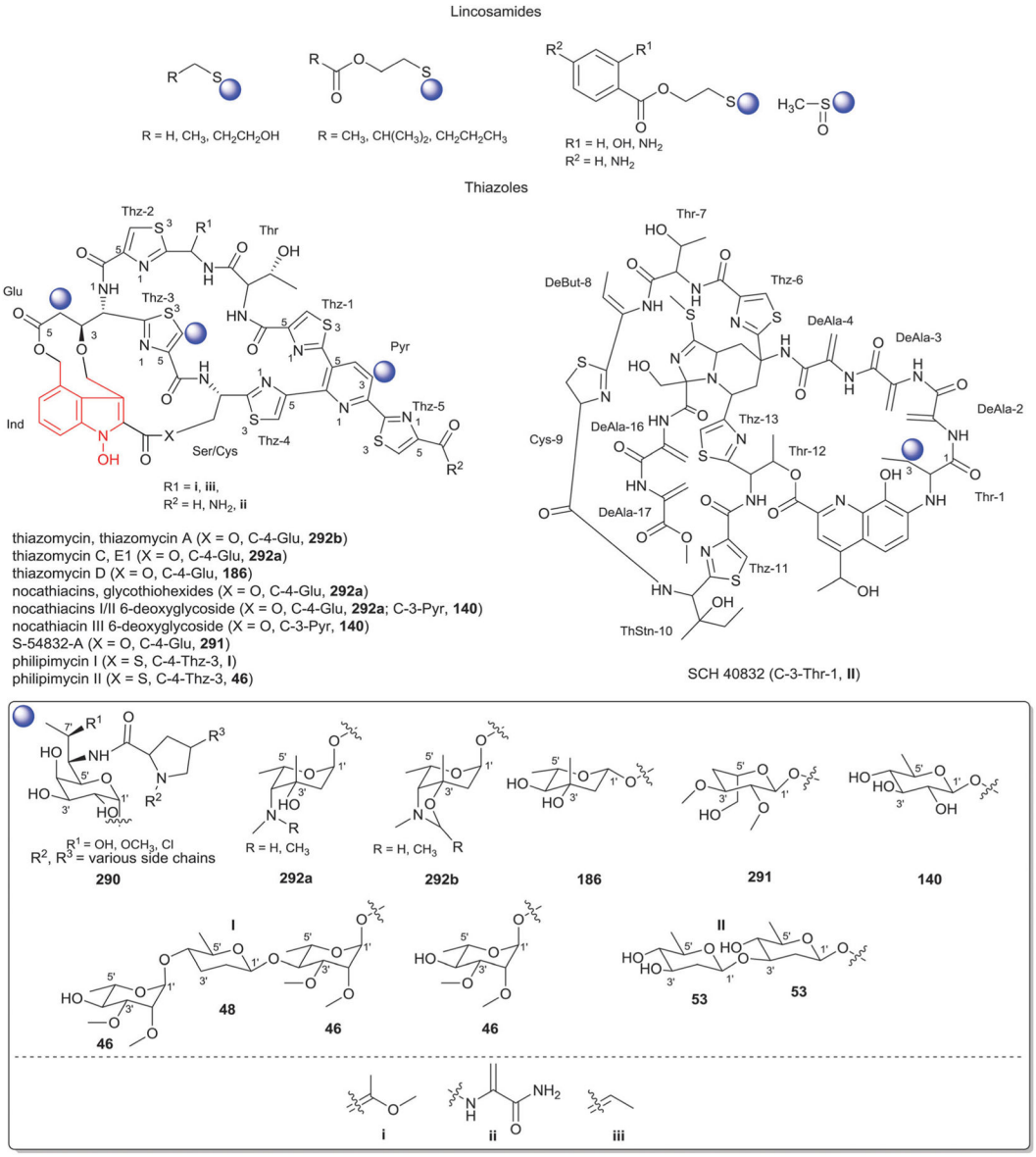


Fig. 48.

Lincosamide and thiazolyl peptide aglycons and associated sugars. Indole moiety in red is absent or replaced by quinoline in different members.

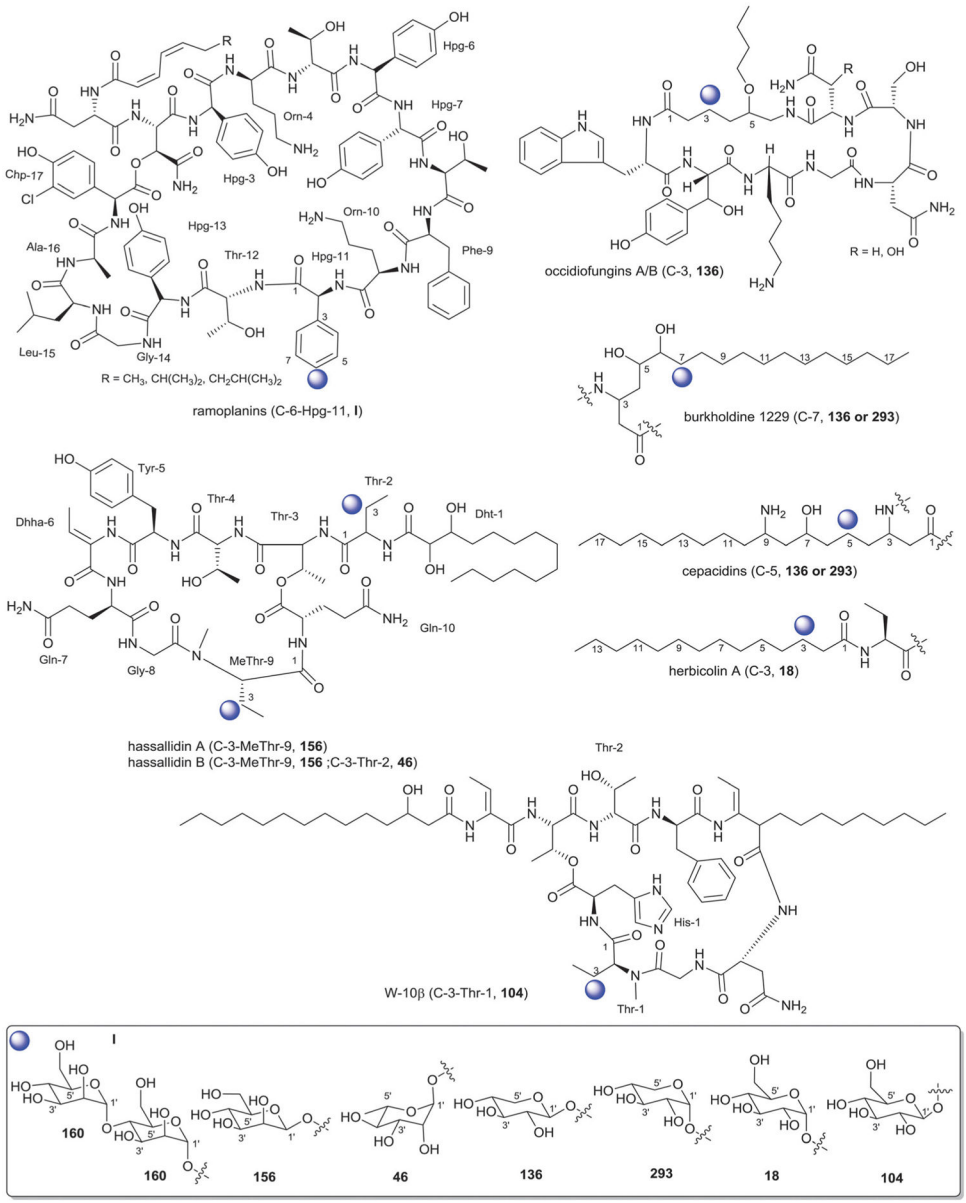


Fig. 49.

Lipoglycopeptide aglycons and associated sugars. Only partial structures of burkholdine, cepacidins, and herbicolin are shown.

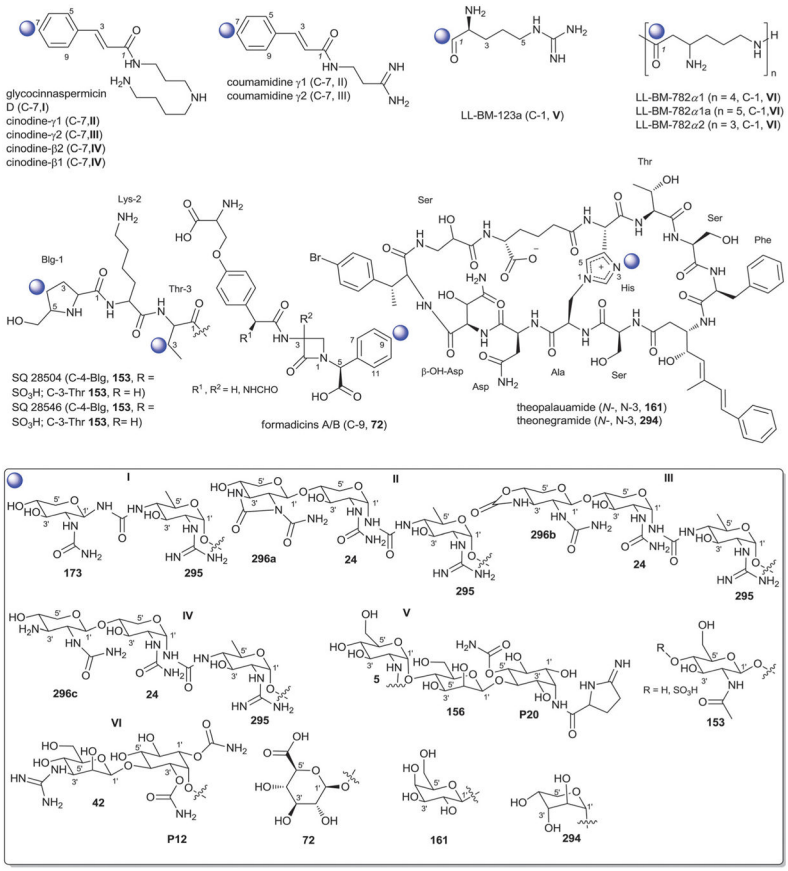


Fig. 50.
Miscellaneous antiinfective peptide aglycons and associated sugars.

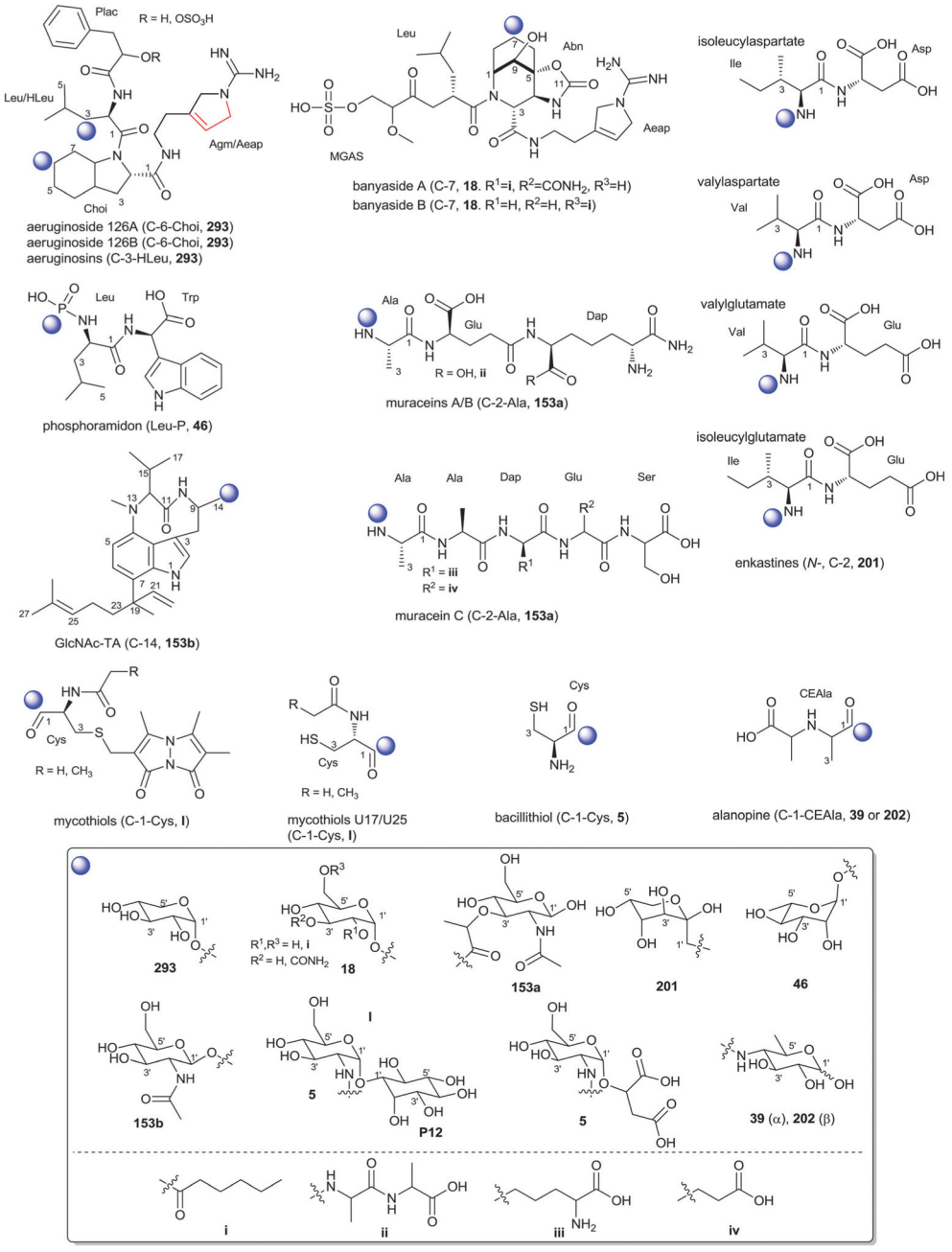


Fig. 51.

Miscellaneous peptide aglycons and associated sugars.

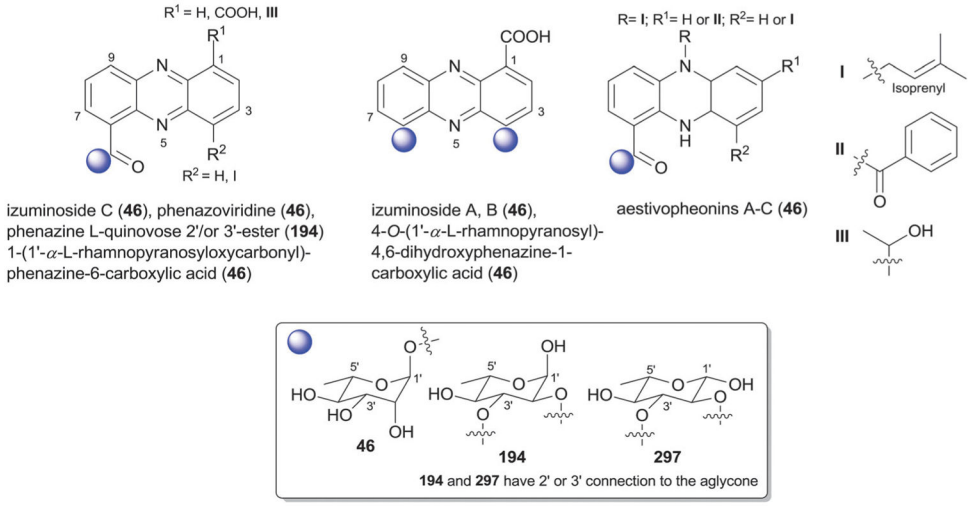


Fig. 52.
Phenazine aglycons and associated sugars.

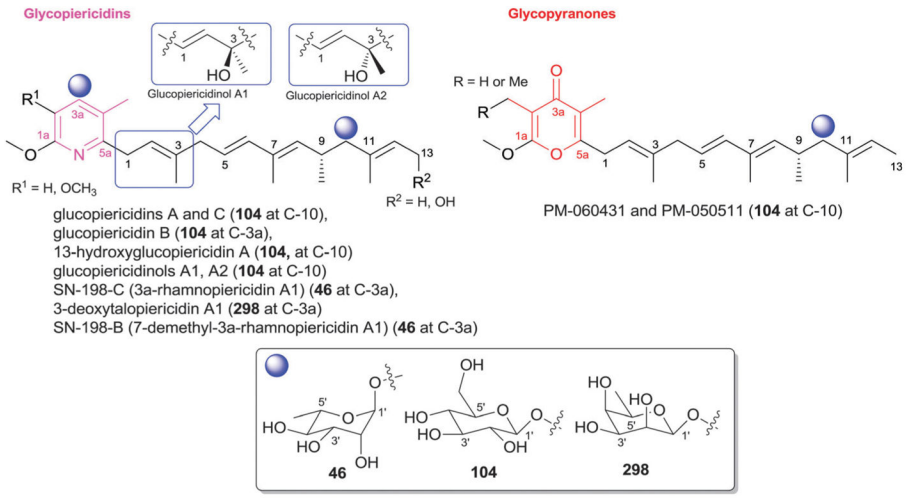


Fig. 53.
Piericidin and pyranone aglycons and associated sugars.

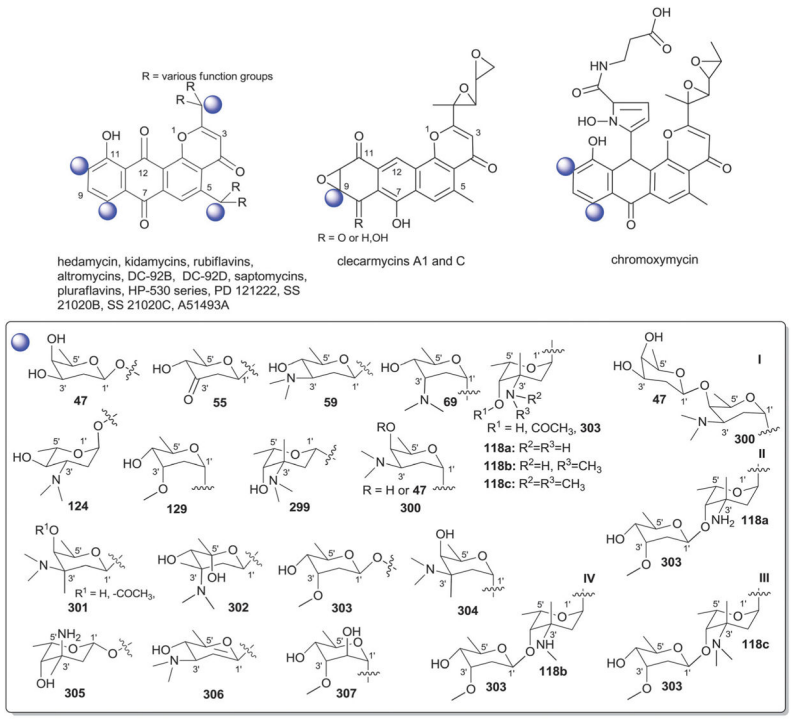


Fig. 54.
Pluramycin aglycons and associated sugars.

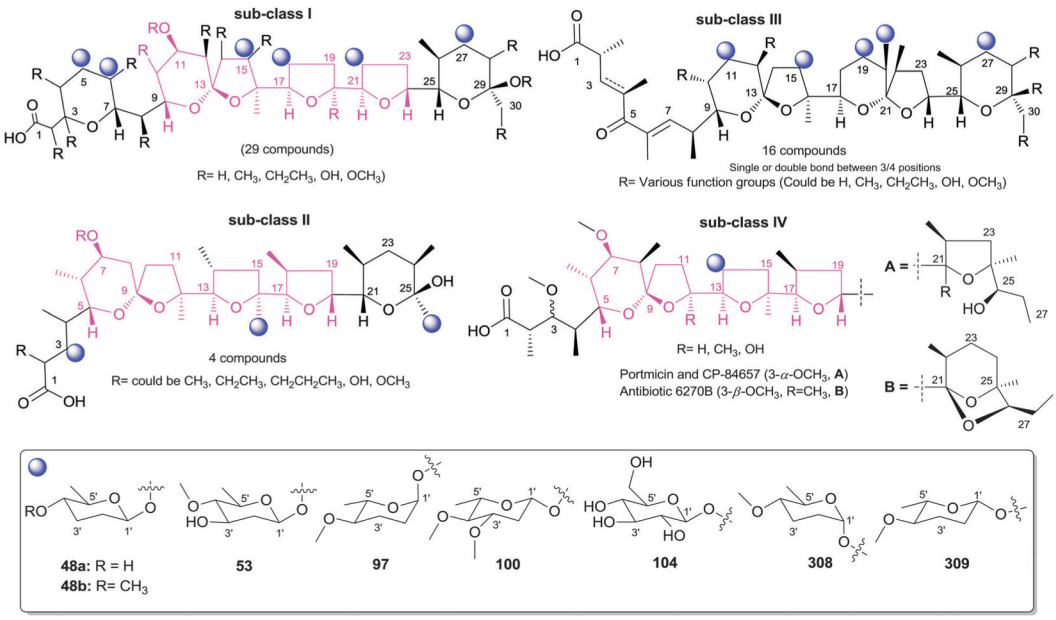


Fig. 55.
Polyethers aglycons and associated sugars.

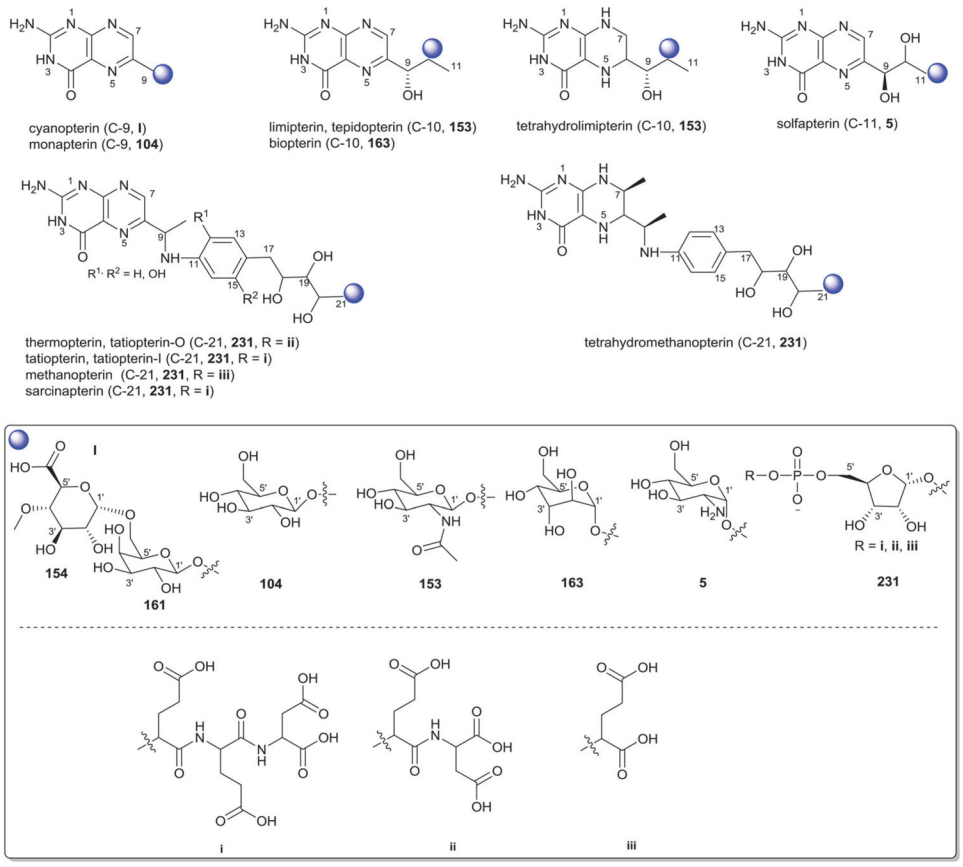


Fig. 56.

Pterin aglycons and associated sugars.

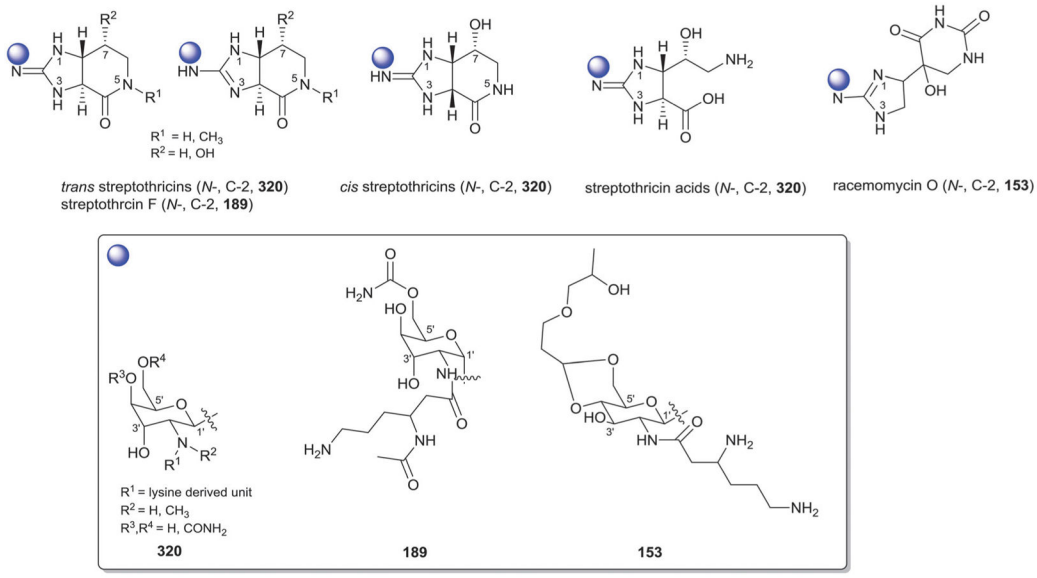


Fig. 57.
Streptothricin aglycons and associated sugars.

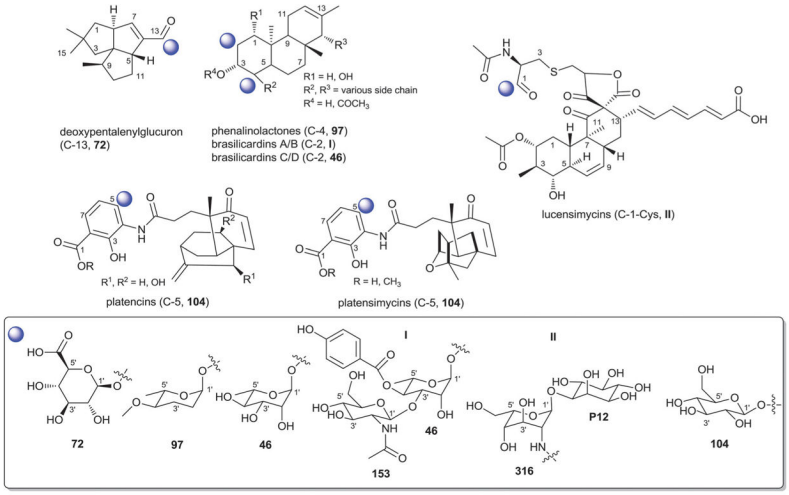


Fig. 58.

Sesquiterpene and diterpene aglycons and associated sugars.

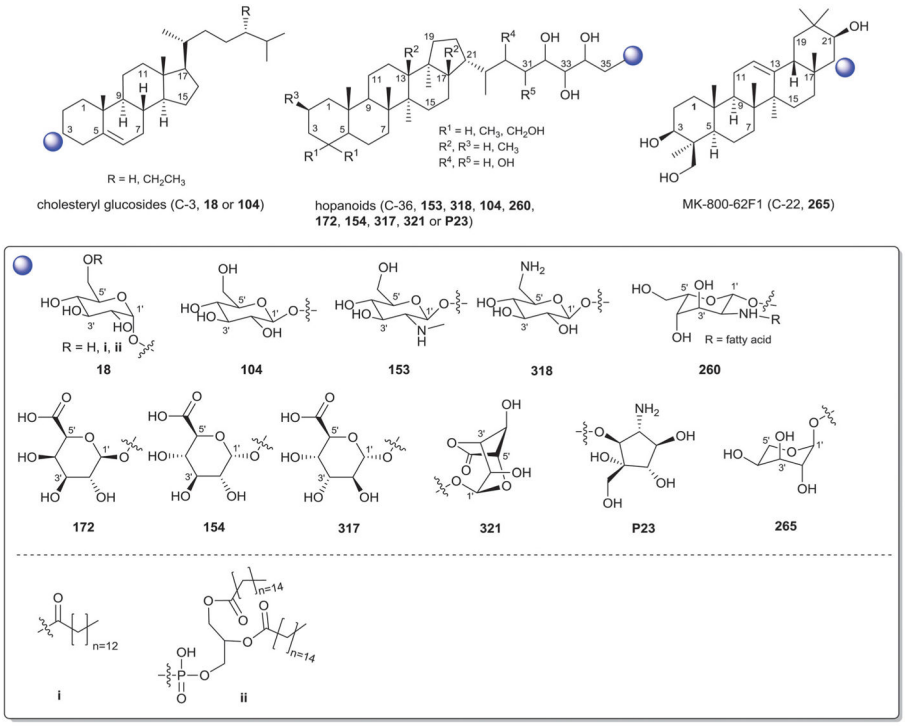


Fig. 59.
Triterpenes aglycons and associated sugars.

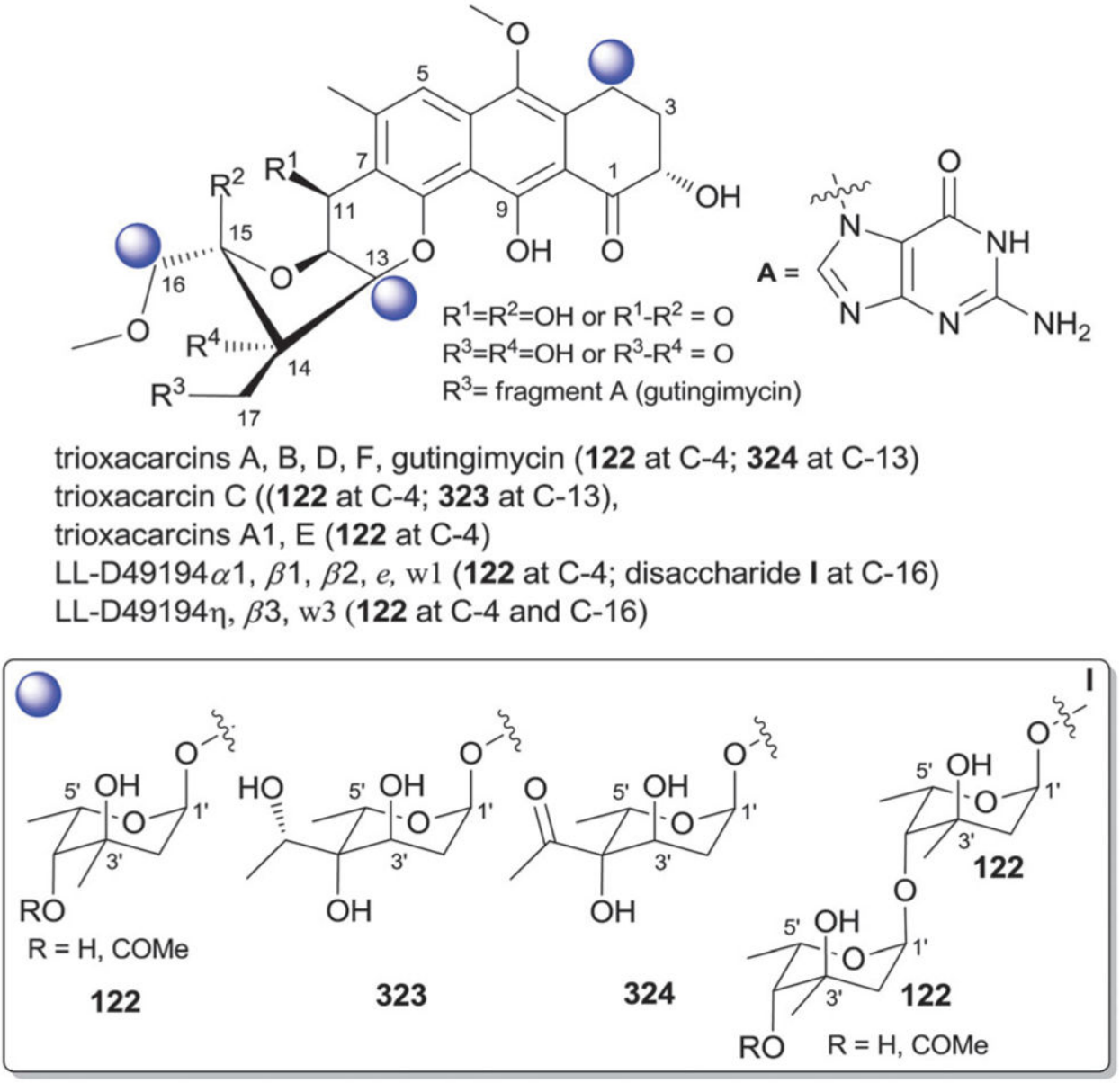


Fig. 60.
Trioxacarcins and LL-D49194 aglycons and associated sugars.

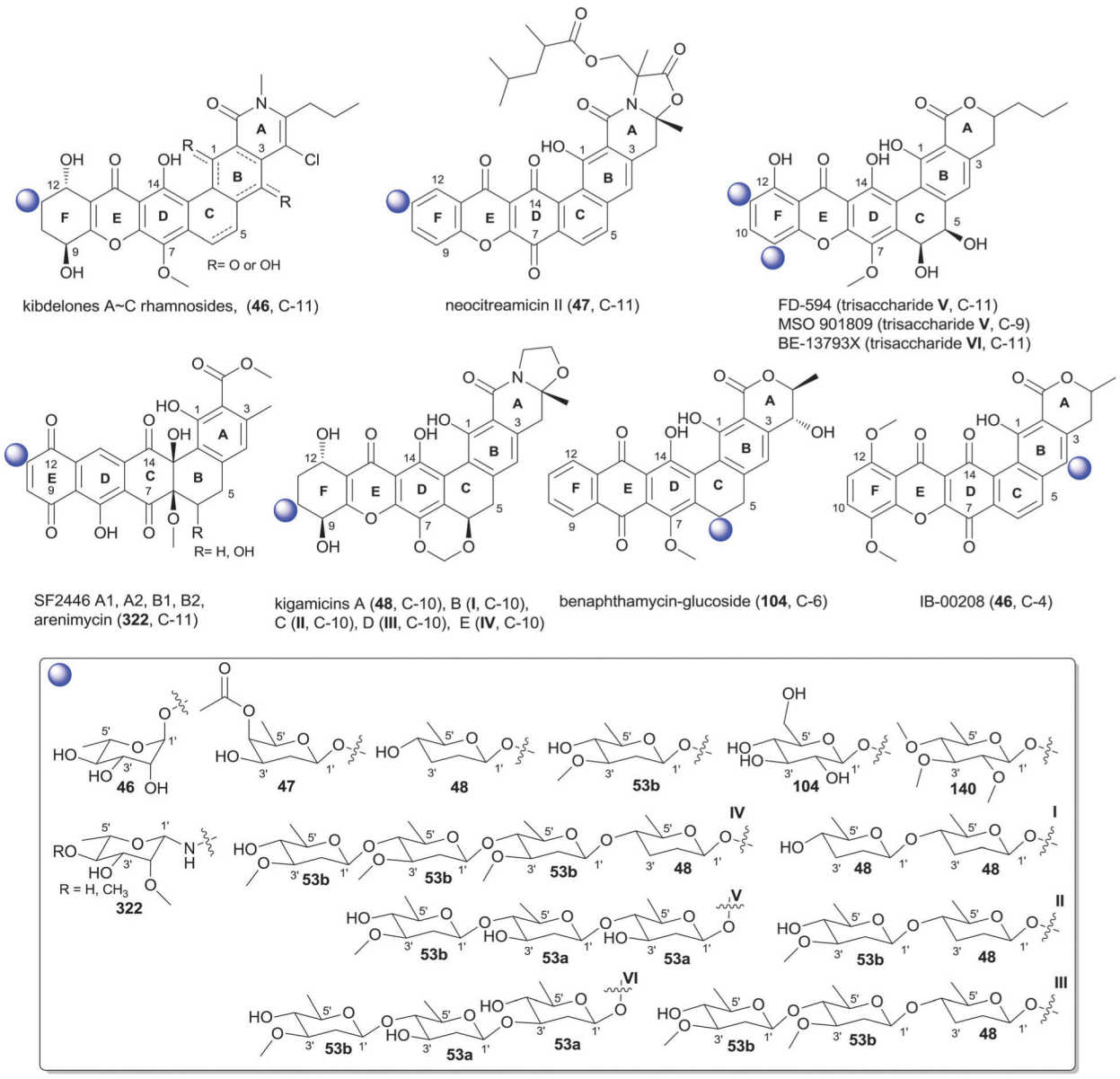


Fig. 61.
Polycyclic xanthone aglycons and associated sugars.

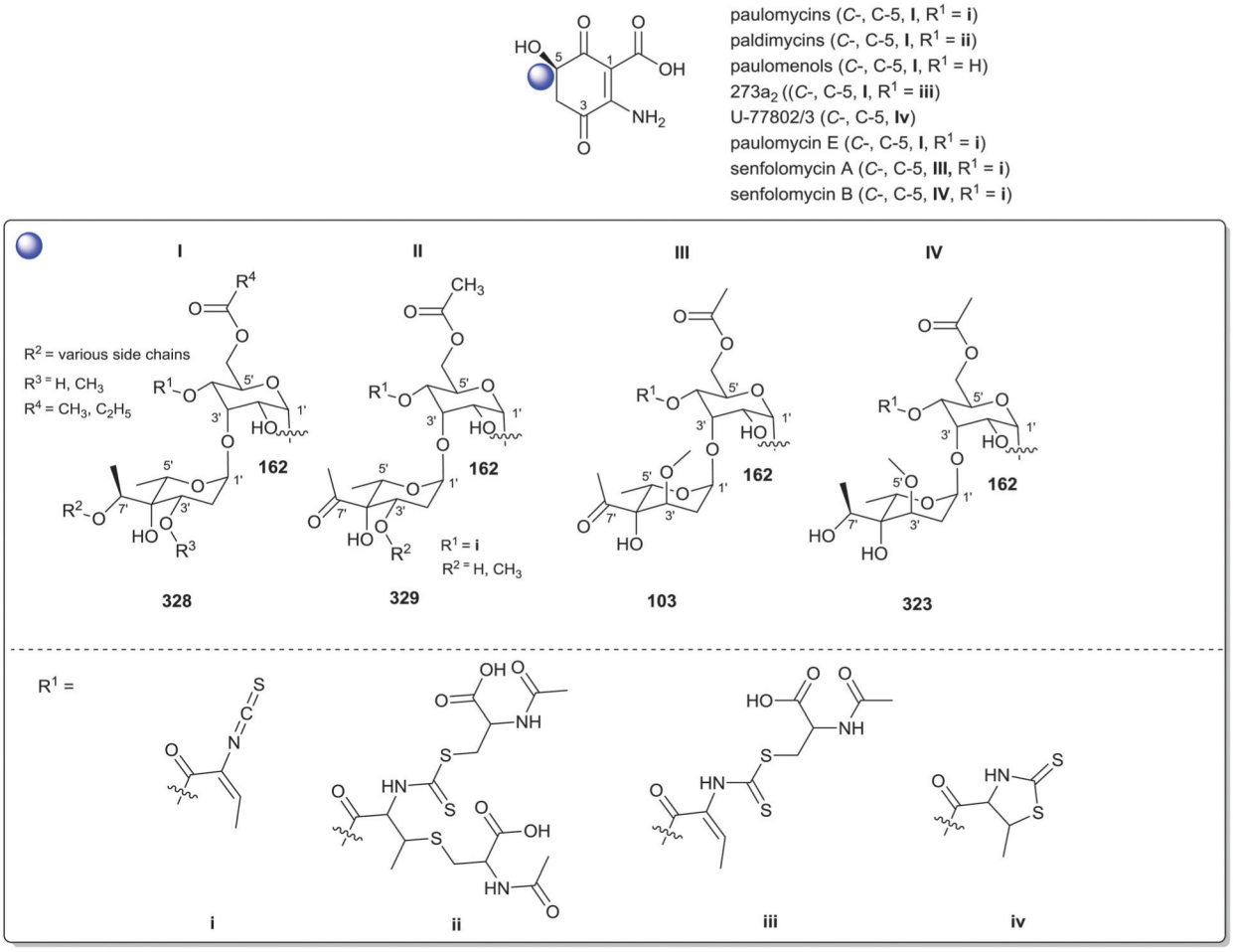


Fig. 62.
Paulomycins and associated sugars.

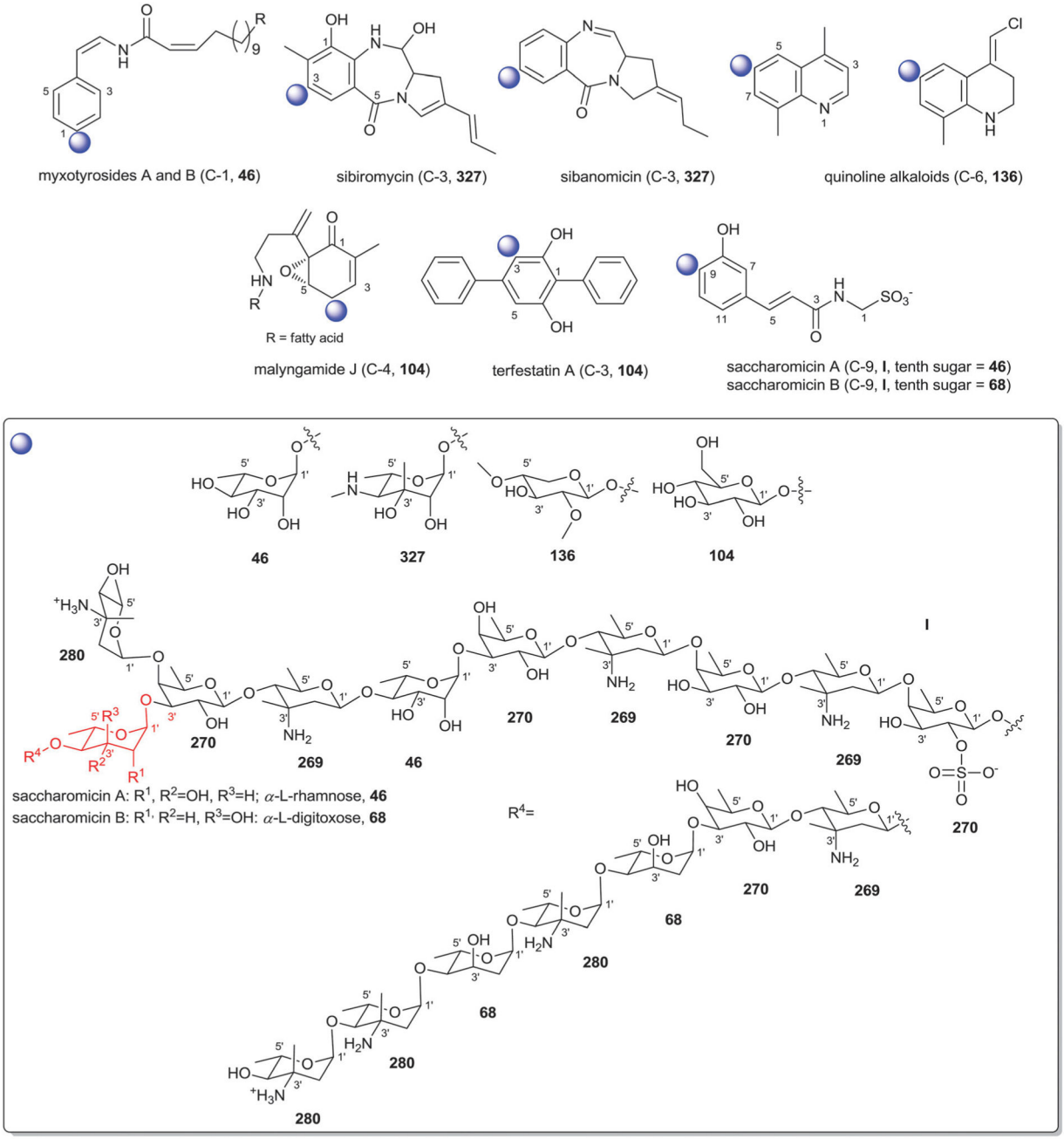


Fig. 63.
Phenyl glycosides and associated sugars.

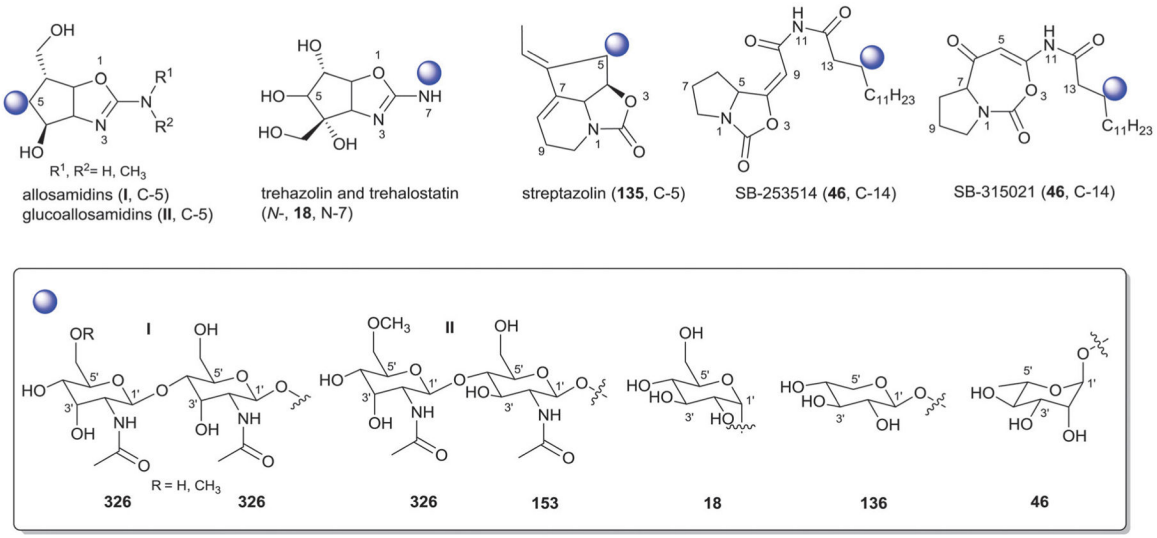


Fig. 64.
Oxazole aglycons and associated sugars.

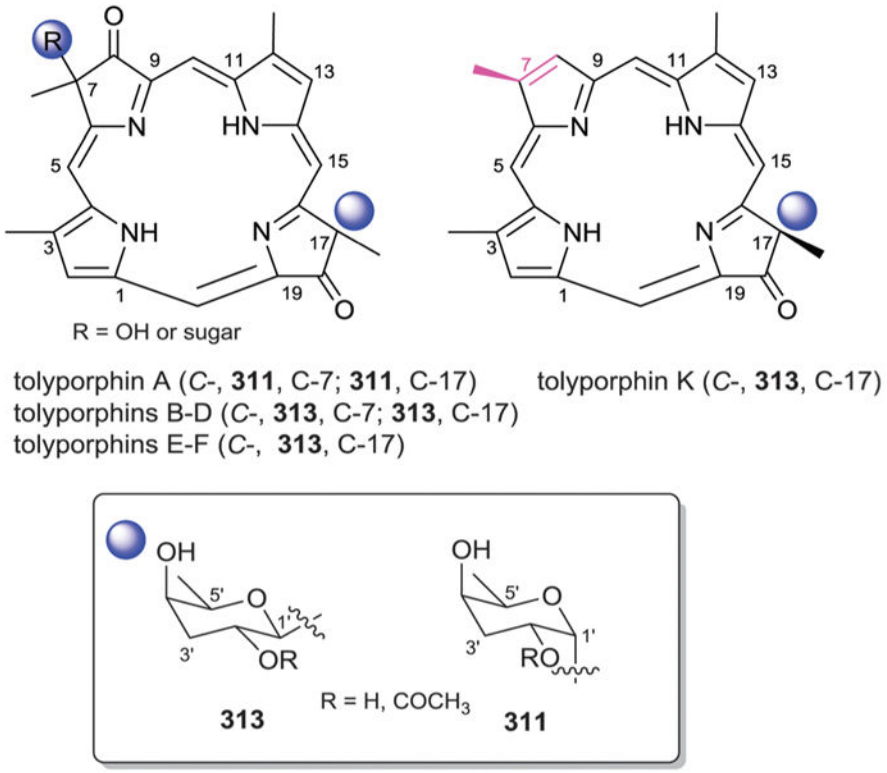


Fig. 65.
Porphyrin aglycons and associated sugars.

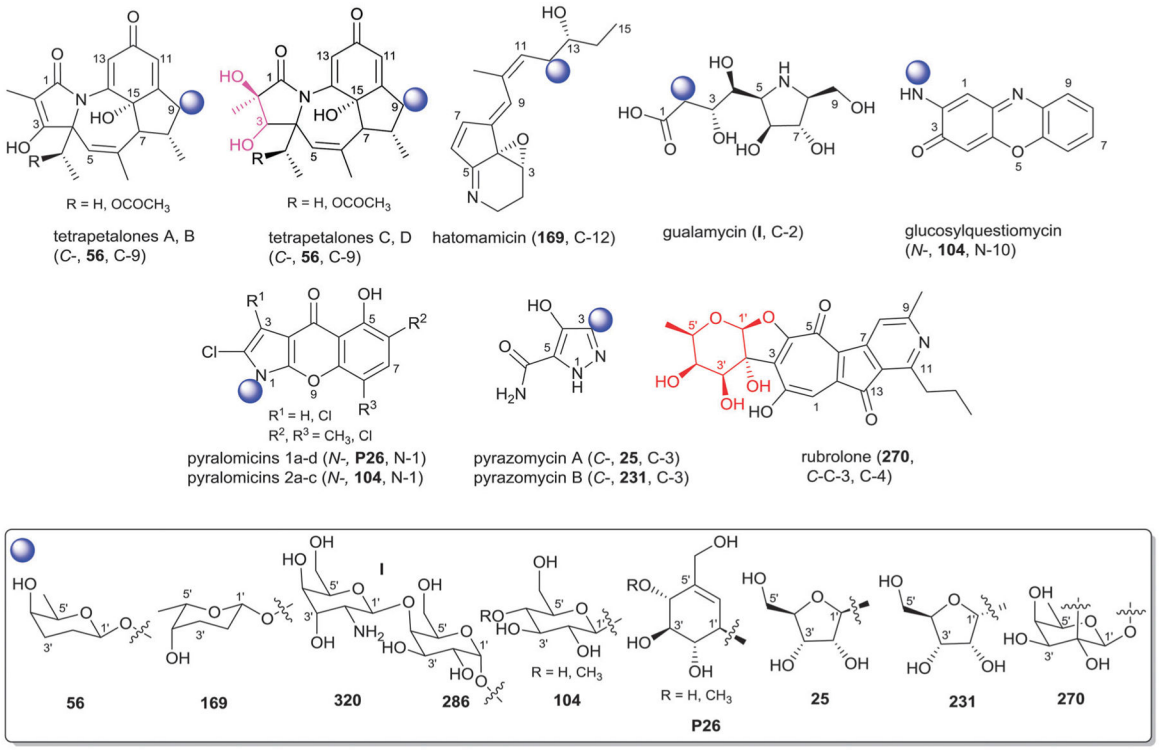


Fig. 66.

Other heterocycle aglycons and associated sugars. Pink fragment highlights differences between tetrapetalones. Red fragment highlights sugar in rubrolone.

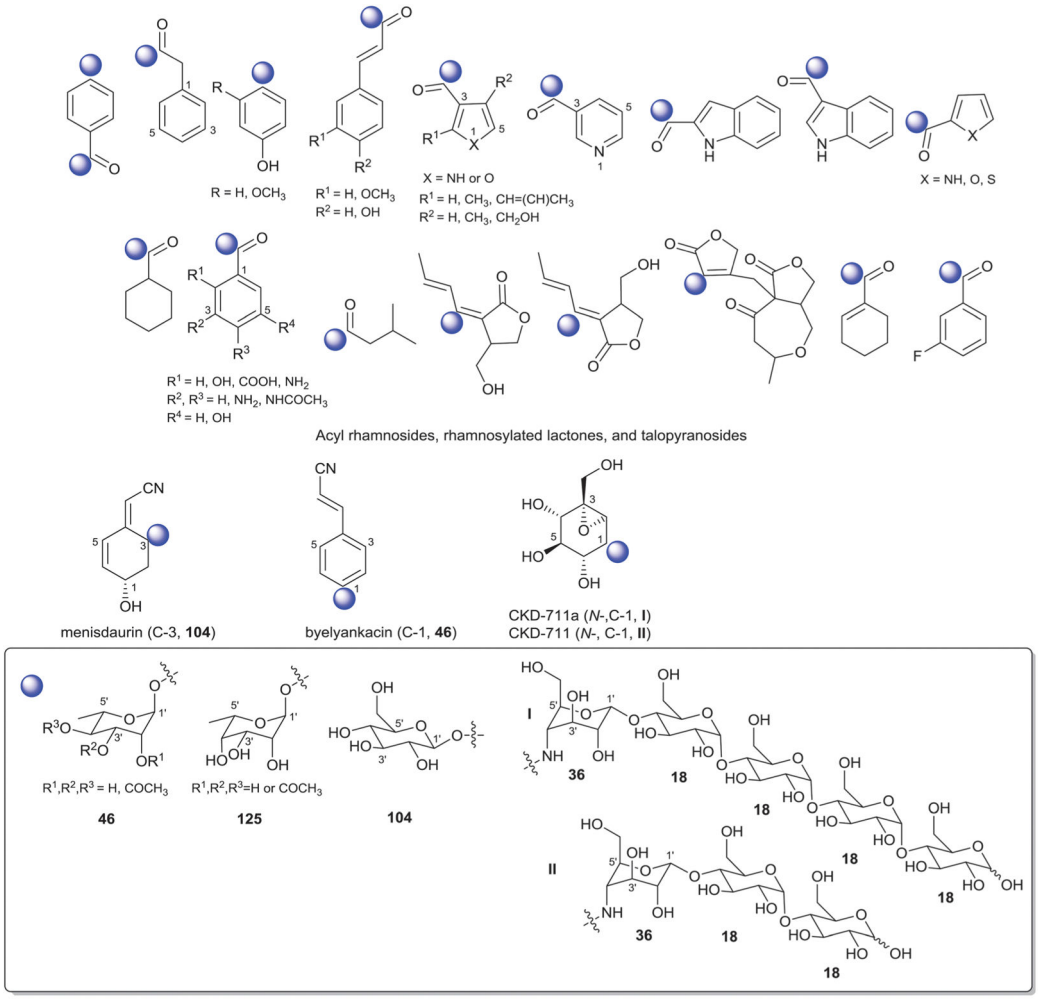


Fig. 67.
Aglycons with simple moieties and associated sugars.

Table 1

Names of sugars present in bacterial natural products. Numbers correspond to sugars in Fig. 3. For simplicity and convenience for the readers, common names were preferred than IUPAC nomenclature

Sugar no.	Sugar name
1	2′,6′-Diamino-2′,3′,4′,6′-tetradeoxy-α-D-glucose
2	2′,6′-Diamino-2′,3′,4′,6′-tetradeoxy-4′,5′-unsaturated-α-D-glucose
3	(6′*R*)-2′,6′-Diamino-2′,3′,4′,6′,7′-pentadeoxy-β-L-glucoheptose
4	(6′*S*)-2′,6′-Diamino-2′,3′,4′,6′,7′-pentadeoxy-β-L-glucoheptose
5	2′-Amino-2′-deoxy-α-D-glucose
6	2′-Amino-2′,7′-dideoxy-α-D-glucoheptose
7	6′-Amino-6′-deoxy-α-D-glucose
8	2′,6′-Diamino-2′,3′,6′-trideoxy-α-D-glucose
9	6′-Amino-3′,6′-dideoxy-α-D-glucose
10	2′,6′-Diamino-2′,6′-dideoxy-α-D-glucose
11	2′,6′-Diamino-2′,6′,7′-trideoxy-α-D-glucoheptose
12	3′-Amino-3′-deoxy-α-D-glucose
13	2′,6′-Diamino-2′,4′,6′-trideoxy-α-D-glucose
14	2′-Amino-2′,3′-dideoxy-α-D-glucose
15	(6′*R*)-2′,6′-Diamino-2′,3′,4′,6′,7′-pentadeoxy-4′,5′-unsaturated-α-D-glucoheptose
16	(6′*S*)-2′,6′-Diamino-2′,3′,4′,6′,7′-pentadeoxy-4′,5′-unsaturated-α-D-glucoheptose
17	Cyclic unsaturated analog of **3**/**4**
18	α-D-Glucose
19	3′-Amino-3′-deoxy-4′-*C*-methyl-4′-*epi*-α-D-xylose
20	3′-Amino-3′-deoxy-4′-*C*-methyl-α-D-galactose
21	3′-Amino-3′-deoxy-4′-*epi*-α-D-xylose
22	3′-Amino-3′-deoxy-β-L-xylose
23	2′,3′-Diamino-2′,3′-dideoxy-β-L-xylose
24	2′-Amino-2′-deoxy-α-D-xylose
25	β-D-Ribofuranose
26	β-D-Xylofuranose
27	2′,6′-Diamino-2′,6′-dideoxy-β-L-idose
28	3′-*C*-Carbaldehyde-5′-deoxy-α-L-lyxofuranose
29	5′-Deoxy-3′-*C*-hydroxymethyl-α-L-lyxofuranose
30	3′-*C*-Carbaldehyde-α-L-lyxofuranose
31	3′-*C*-Hydroxymethyl-α-L-lyxofuranose
32	α-L-Glucosamine
33	α-D-Spectinose
34	Unusual cyclized analog of 3′-deoxyglucosamine
35	Unusual cyclized analog of glucosamine
36	4′-Deoxy-4′-amino-β-L-glucose
37	5′-Keto-5′-*C*-methyl-β-D-arabinofuranose
38	5′-Keto-5′-*C*-methyl-α-L-xylofuranose

Sugar no.	Sugar name
39	4′-Amino-4′,6′-dideoxy-α-D-glucose
40	2′-Amino-1′,2′-dideoxy-α-D-glucose
41	2′,4′-Diamino-2′,3′,4′,6′-tetradeoxy-α-D-mannose
42	3′-Amino-3′-deoxy-β-D-mannose
43	6′-Hydroxy-β-L-mannose
44	α-L-Rhodinose
45	α-L-Ristosamine
46	α-L-Rhamnose
47	β-D-Oliose
48	β-D-Amicetose
49	α-L-Oliose
50	α-L-Rednose
51	α-L-Cinerulose
52	α-D-Taluronic acid
53	β-D-Olivose
54	α-L-Aculose
55	β-D-Kerriose
56	β-D-Rhodinose
57	α-D-Boivinose
58	α-D-Rhodinose
59	3′-Amino-2′,3′,6′-trideoxy-β-D-glucose
60	4′-*epi*-α-L-Tolyposamine
61	2′-Thio-α-D-glucose
62	6′-Deoxy-α-L-altrose
63	4′-Amino-4′-deoxy-β-D-amicetose
64	β-D-Mycarose
65	3′-*epi*-4′-*epi*-α-L-Vancosamine
66	3′-Amino-2′,3′,6′-trideoxy-β-L-glucose
67	3′-Amino-2′,3′-dideoxy-β-L-fucose
68	α-L-Digitoxose
69	α-D-Ristosamine
70	3′-Amino-2′,3′-dideoxy-α-L-fucose
71	α-D-Oliose
72	β-D-Glucuronic acid
73	3′-Amino-3′,6′-dideoxy-α-L-talose
74	3′-Amino-3′,6′-dideoxy-α-L-galactose
75	β-D-Fucofuranose
76	4′-Hydroxy-β-D-fucofuranose
77	β-D-Virenose
78	3′-Deoxy-3′-amino-β-D-fucose (β-D-ravidosamine)
79	4′-Keto-β-D-virenose
80	3′-*C*-Acetylpentofuranose

Sugar no.	Sugar name
81	4′-Amino-4′-deoxy-α-D-amicetose (α-D-forasmine)
82	3′-Amino-*N*′,*N*′-dimethyl-*N*-oxido-2′,3′,6′-trideoxy-β-D-glucose
83	Unusual cyclized sugar I
84	Unusual cyclized sugar II
85	Potential sugar I
86	Potential sugar II
87	4′-Amino-4′,6′-dideoxy-β-D-allose
88	α-D-Fucosamine; α-D-elsaminose
89	4′-Amino-4′-deoxy-3′-*C*-methyl-β-D-ribose
90	α-L-Mycarose
91	4′-Amino-2′,4′-dideoxy-β-L-fucose
92	3′-Keto-4′-*C*-methyl-β-D-fucose
93	4′,6′-Dideoxy-4′-carbonyl-β-D-glucose
94	4′-Thio-2′,4′,6′-trideoxy-β-D-altrose
95	4′-Amino-2′,4′-dideoxy-α-L-xylose
96	4′-Deoxy-4′-thio-β-D-fucose
97	α-L-Amicetose
98	β-D-Cinerulose
99	4′-Deoxy-α-L-daunosamine
100	β-L-Olivose
101	3′-*C*-Methyl-3′-nitrose-2′,3′,6′-trideoxy-β-L-gulose
102	β-L-Decilonitrose
103	4′-*C*-Acetyl-2′,6′-dideoxy-α-L-gulose (α-L-trioxacarcinose B)
104	β-D-Glucose
105	α-L-Decilonitrose
106	2′,6′-Dideoxy-α-L-gulose
107	4′-*epi*-β-L-Decilonitrose
108	3′-*C*-Methyl-α-L-rhamnose
109	β-L-Avidinosamine
110	4′-Amino-4′,6′-dideoxy-3′-*C*-methylhexose
111	α-L-Lyxose
112	2′,6′-Dideoxy-4′-*C*-hydroxyethyl-α-L-gulose
113	4′-Oximo-2′,3′,4′-trideoxy-α-L-fucose
114	4′-Amino-2′,3′,4′,6′-tetradeoxy-α-L-glucose
115	2′-Deoxy-β-D-ribose
116	3′-Amino-2′,3′-dideoxy-4′-*epi*-α-L-xylose
117	3′,6′-Dideoxy-4′-keto-α-L-hexose
118	α-L-Vancosamine
119	β-L-Rednose
120	3′-Hydroxy-3′-*C*-nitro-2′,6′-dideoxy-α-L-talose
121	3′-Nitro-2′,3′,6′-trideoxy-α-L-gulose (3′-desmethyl-α-L-decilonitrose)
122	4′-*epi*-α-L-Mycarose

Sugar no.	Sugar name
123	4′-*C*-Acetyl-2′,3′,6′-trideoxy-α-L-gulose
124	α-L-Actinosamine
125	6′-Deoxy-α-L-talose
126	4′-Keto-α-L-olivose
127	3′-*epi*-4′-*epi*-α-L-Decilonitrose (4′-desmethyl-α-L-evernitrose)
128	3′-Denitro-3′-hydroxylamine-3′-*epi*-4′-*epi*-α-L-decilonitrose
129	α-D-Digitoxose
130	4′-*C*-Acetyl-2′,3′,6′-trideoxy-β-L-gulose
131	β-D-Digitoxose
132	4′-*C*-Hydroxyethanone-2′,3′,6′-trideoxy-α-L-gulose
133	4′-Keto-β-D-mycarose
134	4′-Hydroxy-β-D-olivose
135	6′-Deoxy-β-D-gulose
136	β-D-Xylose
137	4′-Amino-4′,6′-dideoxy-α-L-glucose
138	4′-Amino-2′,4′-dideoxy-α-L-xylose
139	4′-Deoxy-α-D-taluronic acid
140	β-D-Quinovose
141	4′-Amino-2′,4′,6′-trideoxy-β-L-galactose
142	β-L-Mycarose
143	3′-Nitro-2′,3′,6′-trideoxy-α-L-glucose
144	β-L-Talose
145	3′-*C*-Carboxy-3′-*C*-methyl-2′,3′,5′-trideoxy-α-L-xylofuranose
146	3′-*C*-Carboxy-2′,5′-dideoxy-α-L-ribofuranose
147	3′-Amino-3′,6′-dideoxy-α-L-altrose
148	2′,3′,6′-Trideoxy-3′-oximo-α-L-altrose
149	3′-Amino-3′-*C*-carboxy-2′,3′,5′-trideoxy-α-L-ribofuranose
150	3′-Keto-2′,3′,6′-trideoxy-α-L-glucose
151	2′-Deoxy-3′-keto-α-L-fucose
152	3′-Amino-5′-hydroxy-2′,3′,6′-trideoxyhexose
153	β-D-Glucosamine
154	α-D-Glucuronic acid
155	α-D-Quinovose-6′-sulfonic acid
156	β-D-Mannose
157	α-L-Fucose
158	β-D-Arabinose
159	α-D-Glucofuranose
160	α-D-Mannose
161	β-D-Galactose
162	α-D-Allose
163	α-D-Altrose
164	6′-Deoxyhexosamine

Sugar no.	Sugar name
165	β-L-Xylose
166	6′-Amino-1′-carboxy-6′-deoxy-β-D-mannose
167	6′-Amino-6′,8′-dideoxy-α-D-galactoctose
168	β-L-Iduronic acid
169	β-L-Rhodinose
170	6′-Deoxy-β-D-allose
171	6′-Deoxy-3′-keto-β-L-glucose
172	β-D-Galacturonic acid
173	2′-Amino-2′-deoxy-β-D-xylose
174	α-D-Galacturonamide
175	α-D-Glucuronamide
176	β-L-Digitoxose
177	3′-Amino-3′,4′-dideoxy-β-D-fucose
178	3′-*N*-Oxido-β-D-desosamine
179	4′,6′-Dideoxy-3′-keto-β-D-fucose
180	3′-*C*-Acetyl-4′,6′-dideoxy-β-D-allose
181	4′-Deoxy-β-D-fucose
182	3′-*C*-Methyl-2′,3′,6′-trideoxy-2′,3′-unsaturated-β-D-glucose
183	2′,6′-Dideoxy-α-D-altrose
184	α-L-Olivose
185	3′-Amino-3′,6′-dideoxy-β-D-glucose
186	β-L-Chromose
187	β-D-Boivinose
188	3′,6′-Dideoxy-4′-keto-2′-*O*-methyl-2′,3′-unsaturated-β-D-glucose
189	α-D-Gulosamine
190	4′,6′-Dideoxy-3′-*C*-hydroxyethyl-β-D-allose
191	α-D-Xylofuranose
192	β-D-Olivomicose
193	5′-*C*-Methyl-α-L-rhamnose (4′-*O*-desmethyl-α-L-noviose)
194	α-L-Quinovose
195	α-L-Chromose
196	2′,6′-Dideoxyhexose
197	6′-Deoxyhexose
198	6′-Deoxy-β-L-talose
199	L-Axenose
200	2′-Deoxy-β-D-glucose
201	1′-*C*-Methylamine-β-D-arabinose
202	4′-Amino-4′,6′-dideoxy-β-D-glucose
203	4′-Amino-2′,3′,4′,6′-tetradeoxyhexose
204	α-D-Arabinofuranose
205	2′,3′,6′-Trideoxyhexose
206	β-D-Mycosamine

Sugar no.	Sugar name
207	α-L-Mycosamine
208	4′-Amino-4′-deoxy-β-D-fucose
209	6′-Deoxy-β-D-mannose
210	β-L-Glucose
211	α-L-Glucose
212	*N*-Desmethyl-β-D-vicenisamine
213	β-D-Pyrrolosamine
214	*N*-Desmethylcarbamate-β-D-tetronitrose
215	α-D-Quinovose
216	5′-*C*-Carbaldehyde-4′,5′-unsaturated-β-D-digitoxose
217	6′-Deoxyhexose
218	3′,4′-Diamino-3′-*C*-methyl-2′,3′,4′,6′-tetradeoxy-β-D-gulose
219	3′,4′-Diamino-2′,3′,4′,6′-tetradeoxy-β-D-galactose
220	4′-Deoxy-α-L-digitoxose
221	5′-Amino-5′-deoxy-β-D-ribofuranose
222	Tunicamine
223	5′-Amino-5′-*C*-carboxy-5′-deoxy-β-D-ribofuranose
224	2′,5′-Dideoxy-5′-amino-β-D-ribofuranose
225	4′,5′-Unsaturated-α-D-mannuronic acid
226	3′-Hydroxylamine-2′,3′,6′-trideoxy-α-L-allose
227	Unusual bicyclic sugar I
228	Unusual bicyclic sugar II
229	Unusual bicyclic sugar III
230	Unusual bicyclic sugar IV
231	α-D-Ribofuranose
232	5′-Amino-5′-deoxy-4′,5′-unsaturated-β-D-ribofuranose
233	5′-Deoxy-β-D-ribo-octofuranuronic acid
234	2′-Deoxy-2′-aminohexose
235	3′-Amino-3′,4′-dideoxy-β-D-glucuronic acid
236	Unusual dicyclic sugar
237	2′-Amino-2′-deoxy-β-D-guluronic acid
238	Unusual β-D-sugar
239	Unusual β-D-sugar analog of **238**
240	4′-Amino-4′-deoxy-2′,3′-unsaturated-β-D-glucuronic acid
241	4′-Amino-6′-*C*-carboxy-4′-deoxy-6′-*C*-propylamine-2′,3′-unsaturated-β-D-glucose
242	Hydroxy analog of **241**
243	4′-Amino-3′-4′-dideoxy-β-D-glucuronic acid
244	4′-*C*-Amino-3′-deoxypentose
245	4′-Oximo-3′,4′,5′-trideoxy-β-D-xylose
246	4′-Keto-3′,4′,5′-trideoxy-β-D-xylose
247	4′-Amino-4′-deoxy-β-D-hexuronamide
248	6′-Deoxy-4′-thio-4′-*S*-methyl-4′-*C*-(1,2-dihydroxyethyl)-β-D-galactose

Sugar no.	Sugar name
249	2′-Deoxy-β-D-glucuronic acid
250	3′-Amino-3′-deoxy-β-D-glucose
251	4′-Amino-4′-deoxy-β-D-glucuronamide
252	6′,9′-Diamino-5′,6′,7′,8′,9′-pentadexoy-4′,5′-unsaturated-α-L-ribo-decofuranuronic acid
253	3′-Amino-3′-deoxy-β-D-ribofuranose
254	Unusual tricyclic sugar
255	4′-Amino-4′-deoxy-β-L-mannoheptose
256	Unusual C–C sugar
257	4′-Amino-4′-deoxy-β-L-glucoheptose
258	β-D-Glucofuranose
259	3′-Deoxy-β-D-arabinofuranose
260	β-L-Gulosamine
261	2′,3′-Dideoxy-4′-*epi*-β-D-xylose
262	2′,3′-Dideoxy-4′-*epi*-α-L-xylose
263	3′-Deoxy-4′-*epi*-β-D-xylose
264	3′-Deoxy-4′-*epi*-α-L-arabinose
265	4′-α-L-Arabinose
266	β-D-Elsarose
267	6′-Deoxy-α-D-mannose
268	6′-Deoxy-3′-*C*-methyl-β-D-mannose
269	β-D-Saccharosamine
270	β-D-Fucose
271	β-D-Eurekanate I
272	β-D-Eurekanate II
273	β-D-Eurekanate III
274	β-D-Eurekanate IV
275	D-Destomic acid
276	4′-*epi*-Destomic acid
277	α-L-Gulose
278	6′-Deoxy-α-L-gulose
279	4′-Amino-4′,6′-dideoxy-α-L-talose
280	4′-*epi*-α-L-Vancosamine
281	4′-Keto-α-L-vancosamine
282	4′-*C*-Amino-4′-*epi*-α-L-vancosamine
283	2′-Amino-2′-deoxy-β-D-glucuronic acid
284	3′-*C*-Methyl-3′-nitroso-2′,3′,6′-trideoxy-β-D-gulose
285	2′-Amino-2′-deoxy-α-D-glucuronic acid
286	α-D-galactose
287	2′-Keto-α-D-glucose
288	6′-Amino-6′-deoxy-D-glucoheptose
289	2′-Oximo-α-D-glucose
290	7′-*C*-Methyl-destomic acid

Sugar no.	Sugar name
291	4′-Deoxy-β-D-glucose
292	4′-Amino-4′-deoxy-3′-*C*-methyl-α-L-fucose
293	α-D-Xylose
294	α-D-Arabinose
295	2′,4′-Diamino-2′,4′,6′-trideoxy-α-D-glucose
296	2′,3′-Diamino-2′,3′-dideoxy-α-L-pentose
297	β-L-Quinovose
298	6′-Deoxy-β-D-talose
299	β-L-Vancosamine
300	3′-Amino-2′,3′-dideoxy-α-D-fucose
301	β-D-Vancosamine
302	3′-*epi*-4′-*epi*-5′-Hydroxy-β-D-vancosamine
303	2′,6′-Dideoxy-β-D-altrose
304	α-D-Vancosamine
305	3′-*epi*-β-L-Vancosamine
306	$\Delta^{1,2}$-D-Anglosamine
307	6′-Deoxy-α-D-altrose
308	α-D-Amicetose
309	β-L-Amicetose
310	3′-*O*-desmethyl-β-D-rubranitrose
311	3′-Deoxy-α-D-fucose
312	3′-Amino-3′,6′-dideoxy-α-L-glucose
313	3′-Deoxy-β-D-fucose
314	4′-Deoxy-α-D-taluronamide
315	6′-Amino-6′-deoxy-4′-thio-heptofuranuronic acid
316	2′-Amino-2′-deoxy-α-L-idose
317	α-D-Altruronic acid
318	6′-Amino-6′-deoxy-β-D-glucose
319	α-D-Fucose; 3-*O*-desmthyl-α-D-digitalose
320	2′-Deoxy-2′-amino-β-D-gulose
321	3′,5′-Unsaturated galactouronic acid
322	β-L-Rhamnose
323	2′,6′-Dideoxy-3′-hydroxyethyl-α-L-gulose (analog of **324**)
324	β-D-Galacturonamide
325	4′-Keto-β-D-olivose
326	β-D-Allosamine
327	α-L-Sibirosamine
328	α-L-Paulomycose
329	α-L-Keto analog of **328**
330	6′-Amino-6′-deoxy-β-D-ribofuranhepturonic acid
331	β-D-Ribofuranhexuronamide
332	enol form of spectinose (**33**)

Sugar no.	Sugar name
333	2′,4′-Dideoxy-4′,5′-unsaturated-α-D-glucuronamide
334	Hexose
335	5′-*O*-Methyl-4′,5′-unsaturated-β-D-arabinofuranohexose
336	5′-*O*-Methyl-β-D-arabinofuranohexose
337	6′,9′-Diamino-5′,6′,7′,8′,9′-pentadeoxy-β-D-ribofuranodecuronic acid
338	6′,9′-Diamino-5′,6′,7′,8′,9′-pentadeoxy-4′,5′-unsaturated-β-D-ribofuranodecuronamide
339	6′,9′-Diamino-5′,6′,7′,8′,9′-pentadeoxy-β-D-ribofuranodecuronamide
340	Cyclic analog of **339**
341	Unusual nine carbon bicyclic sugar I (cyclic form of **344**)
342	Unusual nine carbon bicyclic sugar II
343	Unusual nine carbon bicyclic sugar III
344	6′-*C*-Carboxy-5′,6′,7′-trideoxy-β-D-ribofuranoocturonic acid