



A comprehensive review of glycosylated bacterial natural products

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A comprehensive review of glycosylated bacterial natural productsSherif I. Elshahawi,^{*ab} Khaled A. Shaaban,^{*ab} Madan K. Kharel^c and Jon S. Thorson^{†ab}

^a Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY, USA; ^b Center for Pharmaceutical Research and Innovation, College of Pharmacy, University of Kentucky, Lexington, KY, USA; ^c School of Pharmacy, University of Maryland Eastern Shore, Princess Anne, Maryland, USA

* Sherif I. Elshahawi and Khaled A. Shaaban have contributed equally to this work.

† Corresponding Author, Email: jsthorson@uky.edu.

Covering all the glycosylated bacterial natural products through 2012 and some of 2013

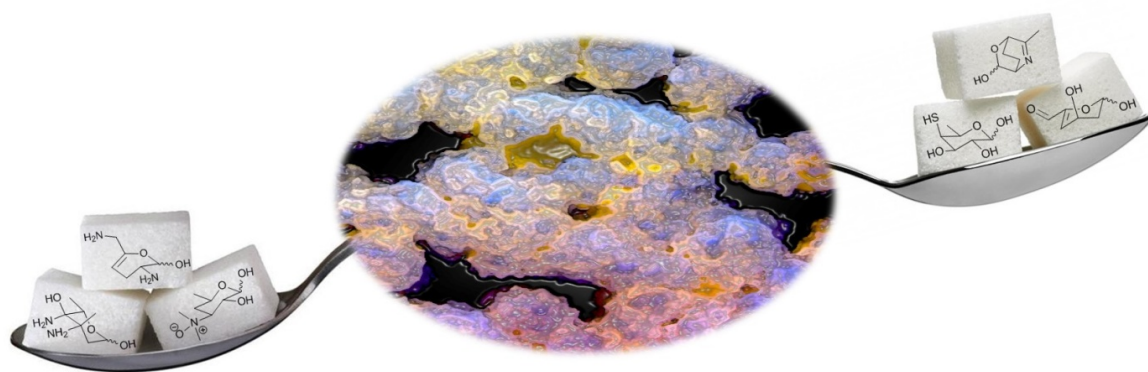
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Abstract

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 3,426 glycosides containing 344 distinct appended carbohydrates and highlights a range of unique opportunities for future biosynthetic study and glycodiversification efforts.

TOC GRAPHIC: A compilation of the rich diversity of bacterial secondary metabolite glycosides.



Keywords

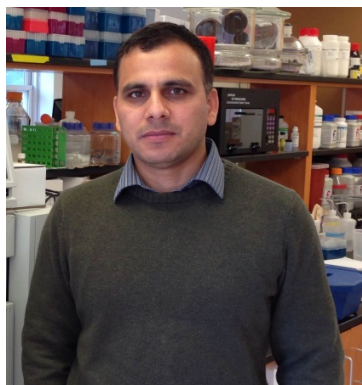
aminoglycosides, angucyclines, anthracyclines, benanomycins, carbohydrates, chartarins, coumarins, enediynes, flavonoids, glycosyltransferases, indoles, indolocarbazoles, lipids, macrolactams, macrolides, nucleosides, orthoesters, paulomycins, peptides, phenazines, piericidins, pluramycins, polyenes, polyethers, polyketides, porphyrins, pradimicins, pterins, saccharides, secondary metabolites, streptothricins, sugars, terpenes, tetracyclines, trioxacarcins, xanthenes

Biosketch

Sherif Elshahawi received his B.S. degree in Pharmaceutical Sciences (2000) from Cairo University, a Master's degree in Pharmacognosy (2006) from the University of Mississippi and a Ph.D. 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.



Dr. Khaled A. Shaaban obtained his B.S. degree in Chemistry (2000) from Mansoura University (Egypt) and M.S. (2005) and PhD. degrees in Organic Chemistry (2009) from the University of Göttingen (Germany) with Professor Hartmut Laatsch. He subsequently held postdoctoral appointments at the University of Kentucky (Professor Jürgen Rohr, 2009-2011) and The Scripps Research Institute (TSRI Florida, Professor Ben Shen, 2011-2012) prior to joining the Center for Pharmaceutical Research and Innovation at University of Kentucky College of Pharmacy as a Research Scientist. His major research interests include isolation of bacterial strains, screening, scale-up fermentation, isolation and structure elucidation of novel bioactive microbial natural products.



Dr. Kharel obtained his B.S. (1998) and M.S. (2000) from the Tribhuvan University (Nepal), a Ph.D. in biochemistry from the Sun Moon University (South Korea, 2007) and a Ph.D. 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 received his B.A. from Augsburg College (1986), a Ph.D. 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.

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-occurring 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 2012¹⁸ 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 (3,426 compounds, 21.5%, Figure 1A) are glycosides wherein glycosylated macrolides and macrolactams represent the largest allocation (738 compounds, 21.5% of all bacterial glycosides, Figure 1B). Further analysis of the range of saccharides represented across all 3,426 bacterial glycosides revealed 344 distinct carbohydrates (Figure 1C and Table 1). For this latter consideration, carbohydrates were only designated as 'distinct' based upon differences within the fundamental monosaccharide 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*-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 Figure 1B 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 ⁴C₁ conformation while L-pyranoses are illustrated as ¹C₄ 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.

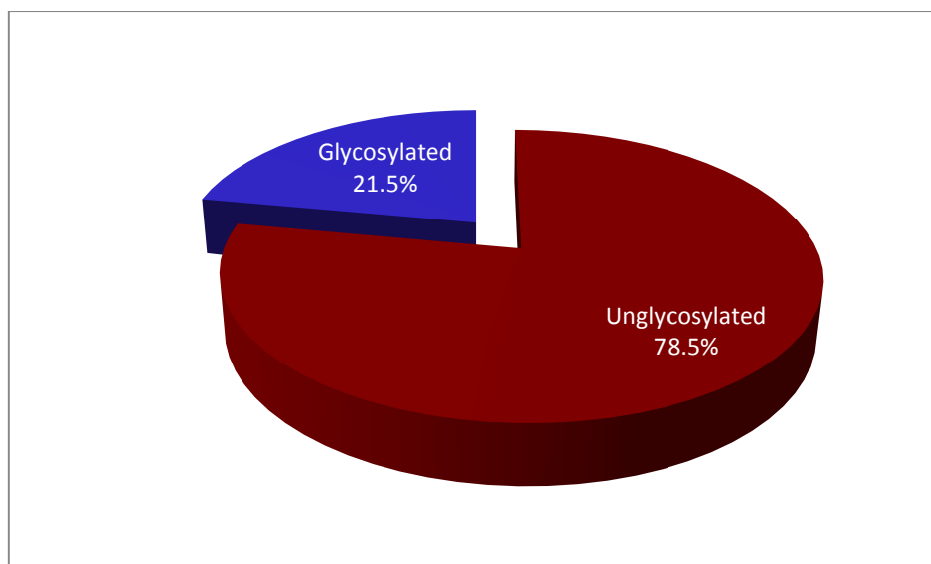


Figure 1A. Bacterial glycosylated (21.5%; 3,426 compounds) and unglycosylated (78.5 %; 12,514 compounds) natural products

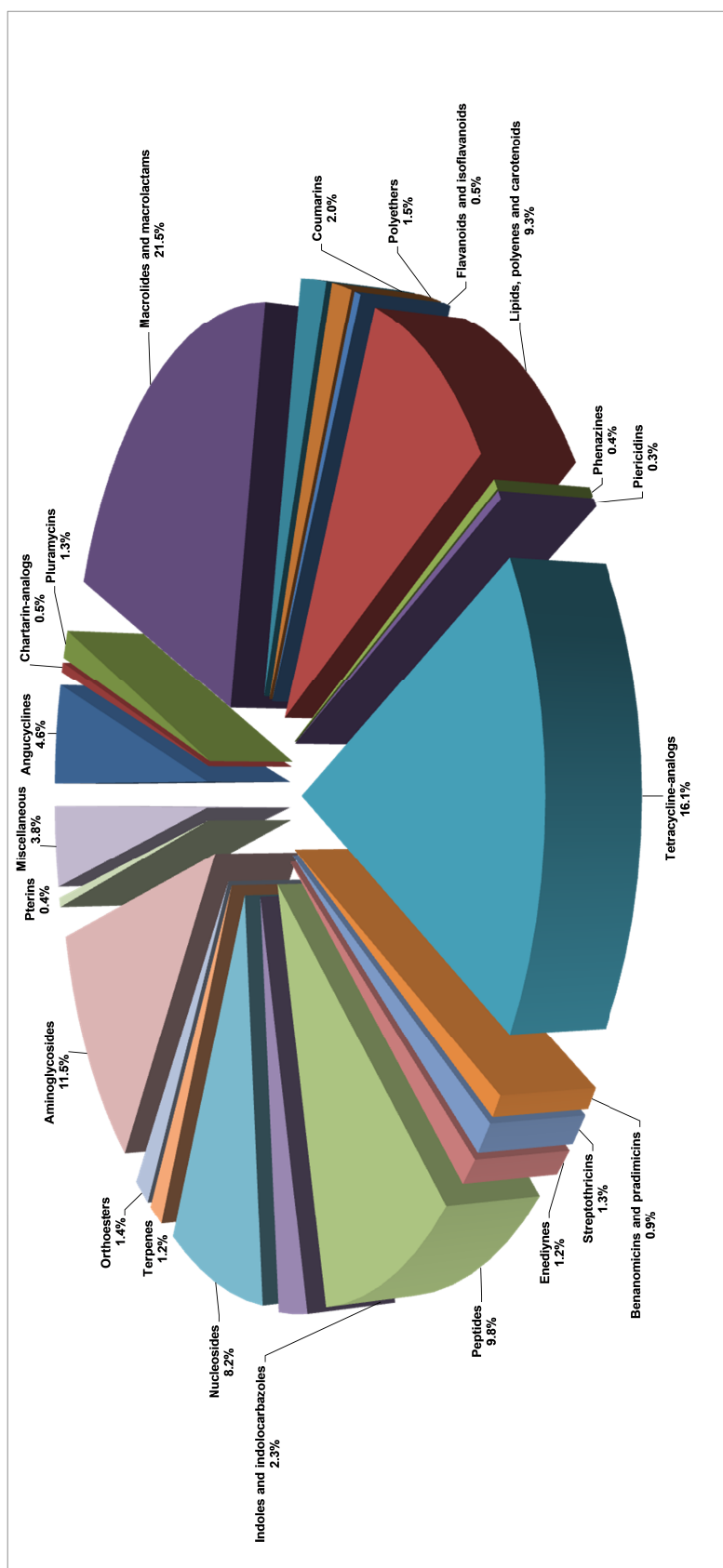
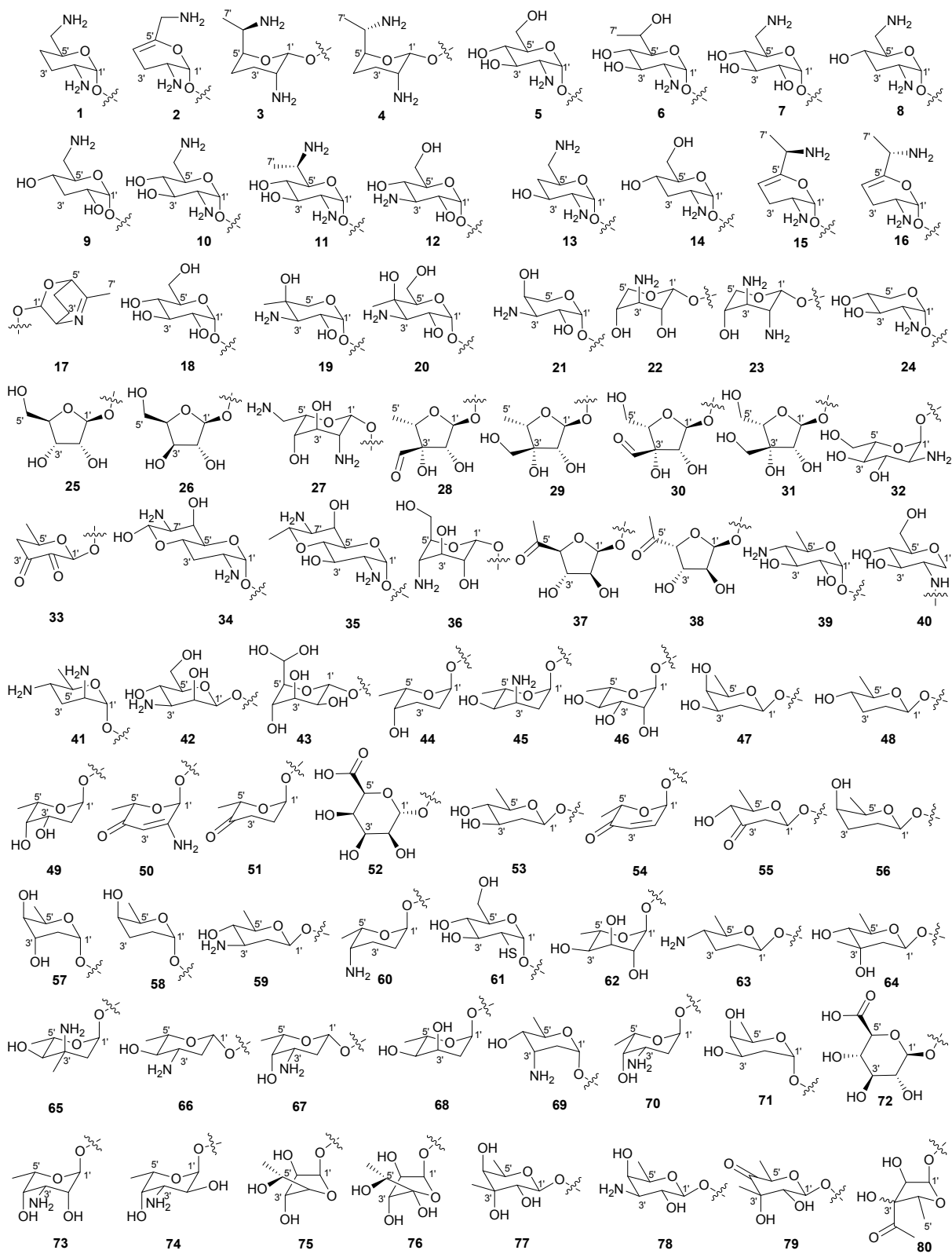
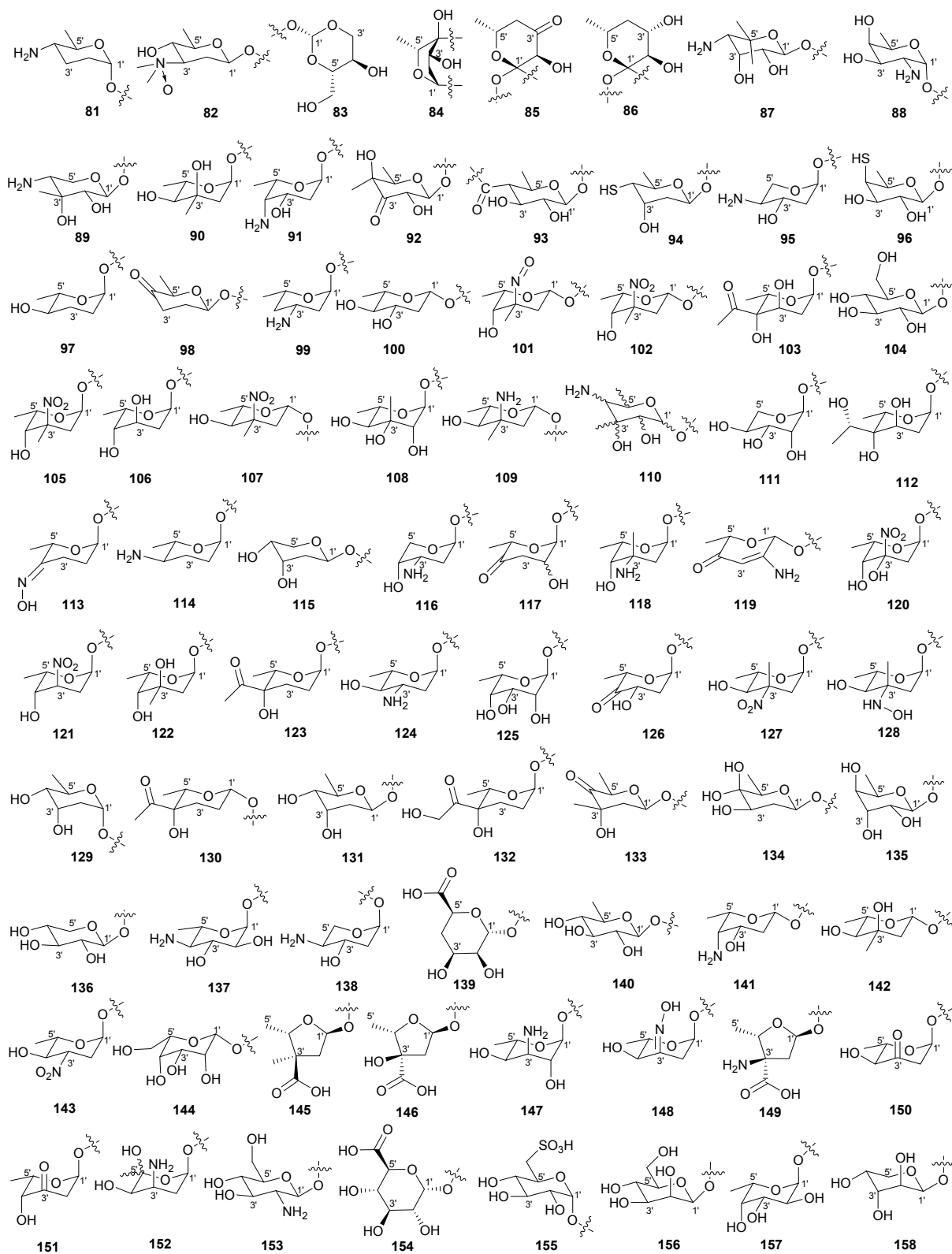
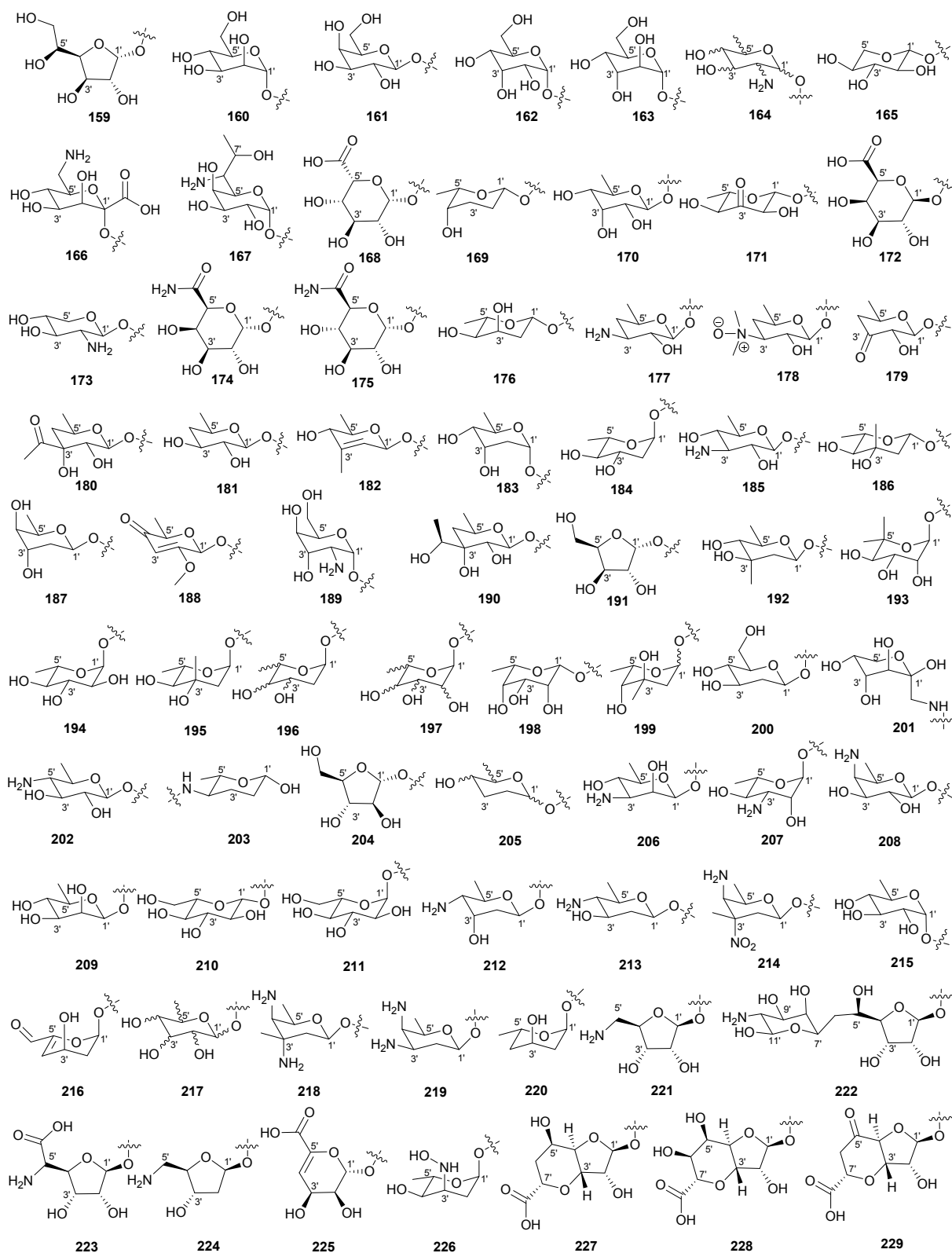
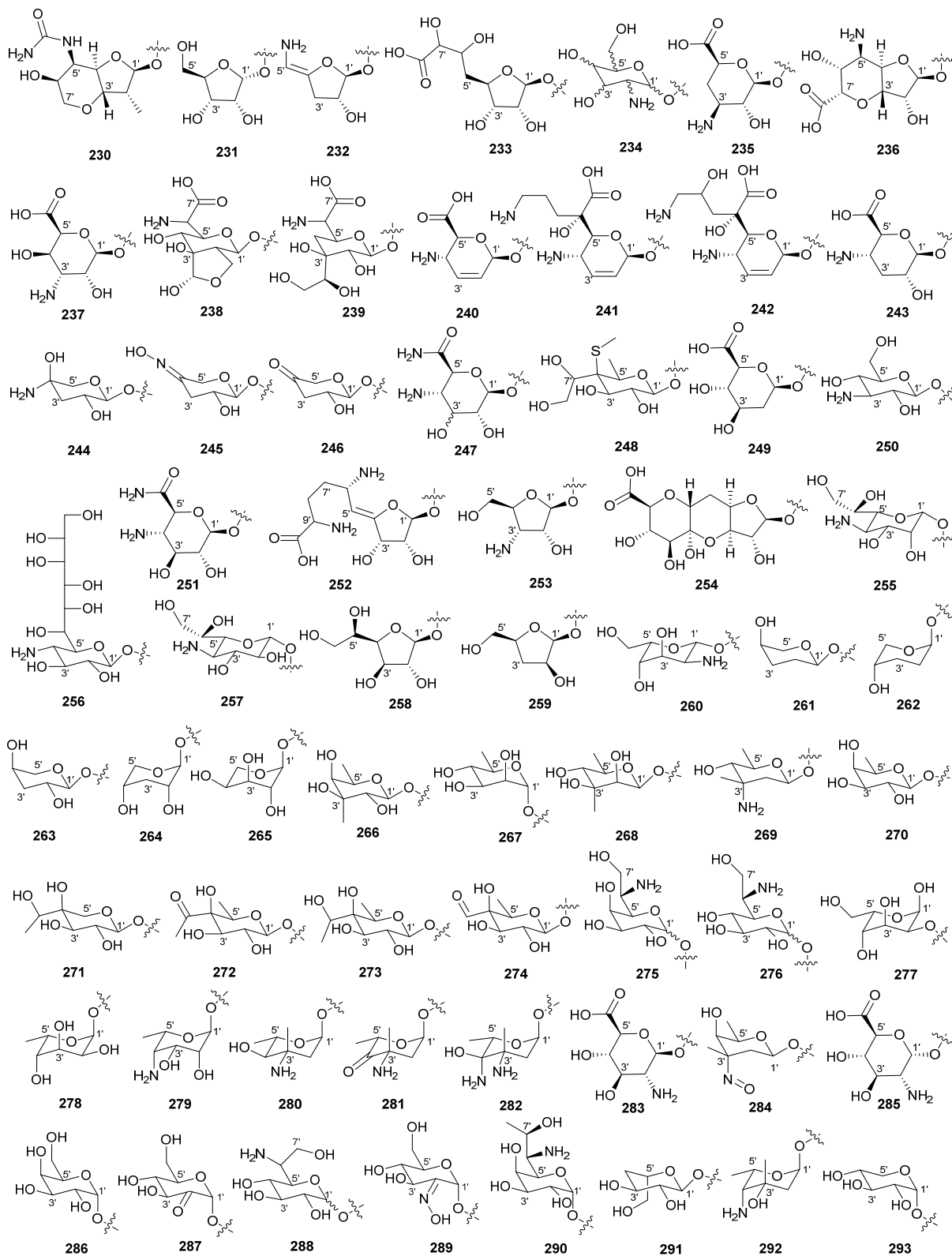


Figure 1B. Chemical classes of glycosylated bacterial natural products (total 3,426 compounds)









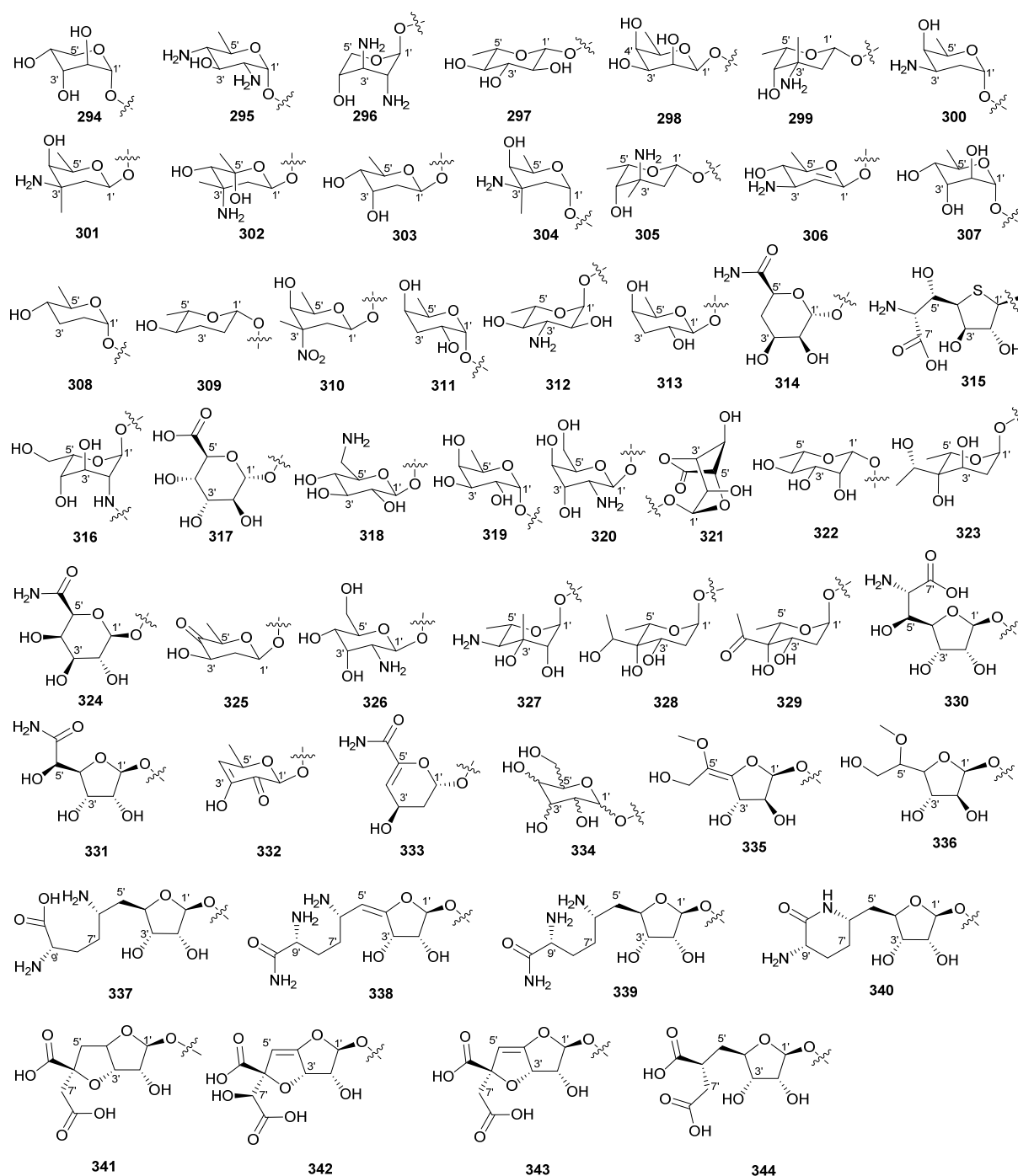


Figure 1C. Summary of all sugars present in bacterial natural products (1-344). Only sugars that displayed differences within the fundamental monosaccharide core (specifically, notable stereochemical and/or functional group variation, including anomeric configuration) were considered as distinct. Modifications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

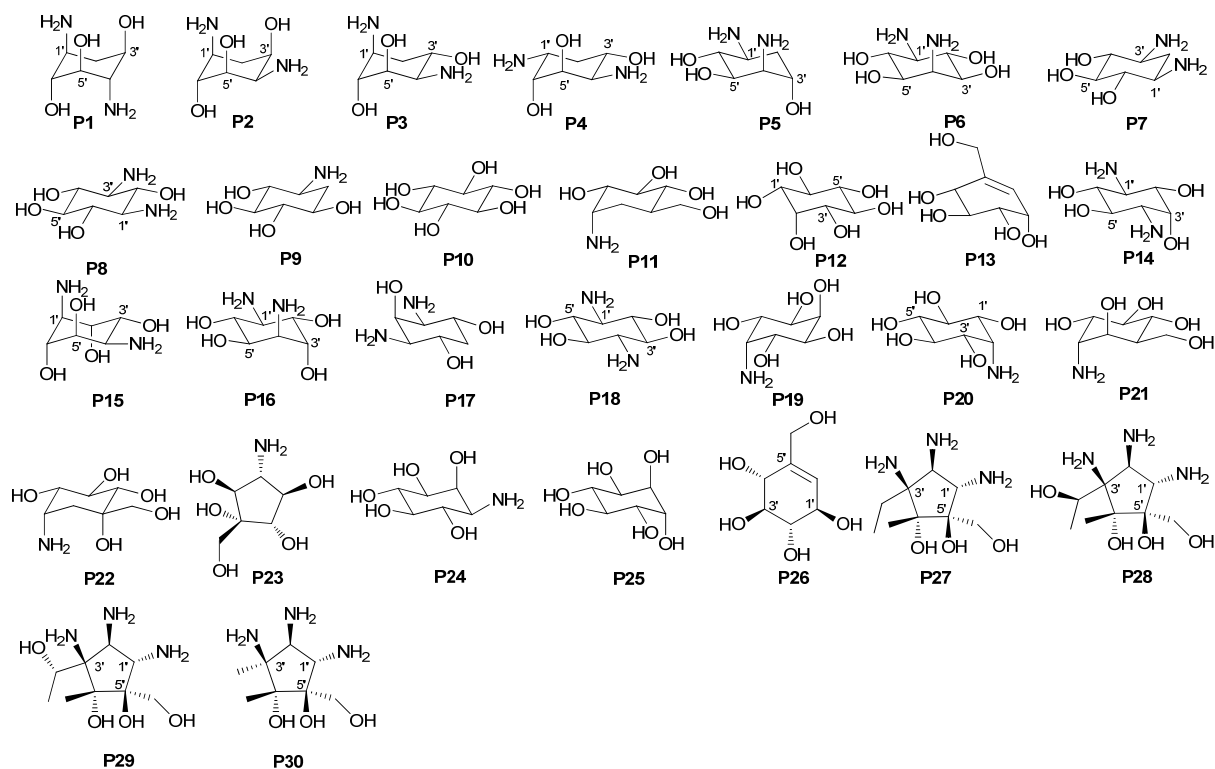


Figure 1D. Summary of pseudosugars **P1-P30** present in bacterial natural products. This list represents only those pseudosugar found within the context of bacterial glycosides and does not reflect an exhaustive list of naturally-occurring pseudosugars.

Table 1. Names of sugars present in bacterial natural products. Numbers correspond to sugars in Figure 1C. For simplicity and convenience for the readers, common names were preferred than IUPAC nomenclature.

Sugar No.	Sugar Name	Sugar No.	Sugar Name
1	2',6' diamino-2',3',4',6'-tetra-deoxy- α -D-glucose	173	2'-amino-2'-deoxy- β -D-xylose
2	2',6' diamino-2',3',4',6'-tetra-deoxy-4',5'-unsaturated- α -D-glucose	174	α -D-galacturonamide
3	(6'R)-2',6'-diamino-2',3',4',6',7'-pentadeoxy- β -L-glucoheptose	175	α -D-glucuronamide
4	(6'S)-2',6'-diamino-2',3',4',6',7'-pentadeoxy- β -L-glucoheptose	176	β -L-digitoxose
5	2'-amino-2'-deoxy- α -D-glucose	177	3'-amino-3',4'-dideoxy- β -D-fucose
6	2'-amino-2',7'-dideoxy- α -D-glucoheptose	178	3'-N-oxido- β -D-desosamine
7	6'-amino-6'-deoxy- α -D-glucose	179	4',6'-dideoxy-3'-keto- β -D-fucose
8	2',6'-diamino-2',3',6'-trideoxy- α -D-glucose	180	3'-C-acetyl-4',6'-dideoxy- β -D-allose
9	6'-amino-3',6'-dideoxy- α -D-glucose	181	4'-deoxy- β -D-fucose
10	2',6'-diamino-2',6'-dideoxy- α -D-glucose	182	3'-C-methyl-2',3',6'-trideoxy-2',3'-unsaturated- β -D-glucose
11	2',6'-diamino-2',6',7'-trideoxy- α -D-glucoheptose	183	2',6'-dideoxy- α -D-altrose
12	3'-amino-3'-deoxy- α -D-glucose	184	α -L-olivose
13	2',6'-diamino-2',4',6'-trideoxy- α -D-glucose	185	3'-amino-3',6'-dideoxy- β -D-glucose
14	2'-amino-2',3'-dideoxy- α -D-glucose	186	β -L-chromose
15	(6'R)-2',6'-diamino-2',3',4',6',7'-pentadeoxy-4',5'-unsaturated- α -D-glucoheptose	187	β -D-boivinose
16	(6'S)-2',6'-diamino-2',3',4',6',7'-pentadeoxy-4',5'-unsaturated- α -D-glucoheptose	188	3',6'-dideoxy-4'-keto-2'-O-methyl-2',3'-unsaturated- β -D-glucose
17	cyclic unsaturated analog of 3/4	189	α -D-gulosamine
18	α -D-glucose	190	4',6'-dideoxy-3'-C-hydroxyethyl- β -D-allose
19	3'-amino-3'-deoxy-4'-C-methyl-4'- <i>epi</i> - α -D-xylose	191	α -D-xylofuranose
20	3'-amino-3'-deoxy-4'-C-methyl- α -D-galactose	192	β -D-olivomucose
21	3'-amino-3'-deoxy-4'- <i>epi</i> - α -D-xylose	193	5'-C-methyl- α -L-rhamnose (4'-O-desmethyl- α -L-noviose)
22	3'-amino-3'-deoxy- β -L-xylose	194	α -L-quinovose
23	2',3'-diamino-2',3'-dideoxy- β -L-xylose	195	α -L-chromose
24	2'-amino-2'-deoxy- α -D-xylose	196	2',6'-dideoxyhexose
25	β -D-ribofuranose	197	6'-deoxyhexose
26	β -D-xylofuranose	198	6'-deoxy- β -L-talose
27	2',6'-diamino-2',6'-dideoxy- β -L-idose	199	L-axenose
28	3'-C-carbaldehyde-5'-deoxy- α -L-lyxofuranose	200	2'-deoxy- β -D-glucose
29	5'-deoxy-3'-C-hydroxymethyl- α -L-lyxofuranose	201	1'-C-methylamine- β -D-arabinose
30	3'-C-carbaldehyde- α -L-lyxofuranose	202	4'-amino-4',6'-dideoxy- β -D-glucose
31	3'-C-hydroxymethyl- α -L-lyxofuranose	203	4'-amino-2',3',4',6'-tetra-deoxyhexose
32	α -L-glucosamine	204	α -D-arabinofuranose
33	α -D-spectinose	205	2',3',6'-trideoxyhexose
34	unusual cyclized analog of 3'-deoxyglucosamine	206	β -D-mycosamine
35	unusual cyclized analog of glucosamine	207	α -L-mycosamine
36	4'-deoxy-4'-amino- β -L-glucose	208	4'-amino-4'-deoxy- β -D-fucose
37	5'-keto-5'-C-methyl- β -D-arabinofuranose	209	6'-deoxy- β -D-mannose
38	5'-keto-5'-C-methyl- α -L-xylofuranose	210	β -L-glucose
39	4'-amino-4',6'-dideoxy- α -D-glucose	211	α -L-glucose
40	2'-amino-1',2'-dideoxy- α -D-glucose	212	N-desmethyl- β -D-vicenisamine
41	2',4'-diamino-2',3',4',6'-tetra-deoxy- α -D-mannose	213	β -D-pyrrolosamine
42	3'-amino-3'-deoxy- β -D-mannose	214	N-desmethylcarbamate- β -D-tetronitrose
43	6'-hydroxy- β -L-mannose	215	α -D-quinovose
44	α -L-rhodinose	216	5'-C-carbaldehyde-4',5'-unsaturated- β -D-digitoxose
45	α -L-ristosamine	217	6'-deoxyhexose
46	α -L-rhamnose	218	3',4'-diamino-3'-C-methyl-2',3',4',6'-tetra-deoxy- β -D-gulose
47	β -D-oliose	219	3',4'-diamino-2',3',4',6'-tetra-deoxy- β -D-galactose
48	β -D-amicetose	220	4'-deoxy- α -L-digitoxose
49	α -L-oliose	221	5'-amino-5'-deoxy- β -D-ribofuranose
50	α -L-rednose	222	tunicamine
51	α -L-cinerulose	223	5'-amino-5'-C-carboxy-5'-deoxy- β -D-ribofuranose
52	α -D-taluronic acid	224	2',5'-dideoxy-5'-amino- β -D-ribofuranose

53	β -D-olivose	225	4',5'-unsaturated- α -D-mannuronic acid
54	α -L-aculose	226	3'-hydroxylamine-2',3',6'-trideoxy- α -L-allose
55	β -D-kerriose	227	unusual bicyclic sugar I
56	β -D-rhodinose	228	unusual bicyclic sugar II
57	α -D-boivinose	229	unusual bicyclic sugar III
58	α -D-rhodinose	230	unusual bicyclic sugar IV
59	3'-amino-2',3',6'-trideoxy- β -D-glucose	231	α -D-ribofuranose
60	4'- <i>epi</i> - α -L-tolyposamine	232	5'-amino-5'-deoxy-4',5'-unsaturated- β -D-ribofuranose
61	2'-thio- α -D-glucose	233	5'-deoxy- β -D-ribo-octofuranuronic acid
62	6'-deoxy- α -L-altrose	234	2'-deoxy-2'-aminohexose
63	4'-amino-4'-deoxy- β -D-amicetose	235	3'-amino-3',4'-dideoxy- β -D-glucuronic acid
64	β -D-mycarose	236	unusual dicyclic sugar
65	3'- <i>epi</i> -4'- <i>epi</i> - α -L-vancosamine	237	2'-amino-2'-deoxy- β -D-guluronic acid
66	3'-amino-2',3',6'-trideoxy- β -L-glucose	238	unusual β -D-sugar
67	3'-amino-2',3'-dideoxy- β -L-fucose	239	unusual β -D-sugar analog of 238
68	α -L-digitoxose	240	4'-amino-4'-deoxy-2',3'-unsaturated- β -D-glucuronic acid
69	α -D-ristosamine	241	4'-amino-6'-C-carboxy-4'-deoxy-6'-C-propylamine-2',3'-unsaturated- β -D-glucose
70	3'-amino-2',3'-dideoxy- α -L-fucose	242	hydroxy analog of 241
71	α -D-oliose	243	4'-amino-3'-4'-dideoxy- β -D-glucuronic acid
72	β -D-glucuronic acid	244	4'-C-amino-3'-deoxypentose
73	3'-amino-3',6'-dideoxy- α -L-talose	245	4'-oximo-3',4',5'-trideoxy- β -D-xylose
74	3'-amino-3',6'-dideoxy- α -L-galactose	246	4'-keto-3',4',5'-trideoxy- β -D-xylose
75	β -D-fucofuranose	247	4'-amino-4'-deoxy- β -D-hexuronamide
76	4'-hydroxy- β -D-fucofuranose	248	6'-deoxy-4'-thio-4'-S-methyl-4'-C-(1,2-dihydroxyethyl)- β -D-galactose
77	β -D-virenose	249	2'-deoxy- β -D-glucuronic acid
78	3'-deoxy-3'-amino- β -D-fucose (β -D-ravidosamine)	250	3'-amino-3'-deoxy- β -D-glucose
79	4'-keto- β -D-virenose	251	4'-amino-4'-deoxy- β -D-glucuronamide
80	3'-C-acetylpentofuranose	252	6',9'-diamino-5',6',7',8',9'-pentadexoy-4',5'-unsaturated- α -L-ribo-decofuranuronic acid
81	4'-amino-4'-deoxy- α -D-amicetose (α -D-forasmine)	253	3'-amino-3'-deoxy- β -D-ribofuranose
82	3'-amino-N,N'-dimethyl-N-oxido-2',3',6'-trideoxy- β -D-glucose	254	unusual tricyclic sugar
83	unusual cyclized sugar I	255	4'-amino-4'-deoxy- β -L-mannoheptose
84	unusual cyclized sugar II	256	unusual C-C sugar
85	potential sugar I	257	4'-amino-4'-deoxy- β -L-glucoheptose
86	potential sugar II	258	β -D-glucofuranose
87	4'-amino-4',6'-dideoxy- β -D-allose	259	3'-deoxy- β -D-arabinofuranose
88	α -D-fucosamine; α -D-elsaminose	260	β -L-gulosamine
89	4'-amino-4'-deoxy-3'-C-methyl- β -D-ribose	261	2',3',dideoxy-4'- <i>epi</i> - β -D-xylose
90	α -L-mycarose	262	2',3'-dideoxy-4'- <i>epi</i> - α -L-xylose
91	4'-amino-2',4'-dideoxy- β -L-fucose	263	3'-deoxy-4'- <i>epi</i> - β -D-xylose
92	3'-keto-4'-C-methyl- β -D-fucose	264	3'-deoxy-4'- <i>epi</i> - α -L-arabinose
93	4',6'-dideoxy-4'-carbonyl- β -D-glucose	265	4'- α -L-arabinose
94	4'-thio-2',4',6'-trideoxy- β -D-altrose	266	β -D-elsarose
95	4'-amino-2',4'-dideoxy- α -L-xylose	267	6'-deoxy- α -D-mannose
96	4'-deoxy-4'-thio- β -D-fucose	268	6'-deoxy-3'-C-methyl- β -D-mannose
97	α -L-amicetose	269	β -D-saccharosamine
98	β -D-cinerulose	270	β -D-fucose
99	4'-deoxy- α -L-daunosamine	271	β -D-eurekanate I
100	β -L-olivose	272	β -D-eurekanate II
101	3'-C-methyl-3'-nitroso-2',3',6'-trideoxy- β -L-gulose	273	β -D-eurekanate III
102	β -L-decilonitrose	274	β -D-eurekanate IV
103	4'-C-acetyl-2',6'-dideoxy- α -L-gulose (α -L-trioxacarinose B)	275	D-destomic acid
104	β -D-glucose	276	4'- <i>epi</i> -destomic acid
105	α -L-decilonitrose	277	α -L-gulose
106	2',6'-dideoxy- α -L-gulose	278	6'-deoxy- α -L-gulose
107	4'- <i>epi</i> - β -L-decilonitrose	279	4'-amino-4',6'-dideoxy- α -L-talose
108	3'-C-methyl- α -L-rhamnose	280	4'- <i>epi</i> - α -L-vancosamine
109	β -L-avidinosamine	281	4'-keto- α -L-vancosamine
110	4'-amino-4',6'-dideoxy-3'-C-methylhexose	282	4'-C-amino-4'- <i>epi</i> - α -L-vancosamine
111	α -L-lyxose	283	2'-amino-2'-deoxy- β -D-glucuronic acid
112	2',6'-dideoxy-4'-C-hydroxyethyl- α -L-gulose	284	3'-C-methyl-3'-nitroso-2',3',6'-trideoxy- β -D-gulose
113	4'-oximo-2',3',4'-trideoxy- α -L-fucose	285	2'-amino-2'-deoxy- α -D-glucuronic acid
114	4'-amino-2',3',4',6'-tetraideoxy- α -L-glucose	286	α -D-galactose

115	2'-deoxy- β -D-ribose	287	2'-keto- α -D-glucose
116	3'-amino-2',3'-dideoxy-4'- <i>epi</i> - α -L-xylose	288	6'-amino-6'-deoxy-D-glucoheptose
117	3',6'-dideoxy-4'-keto- α -L-hexose	289	2'-oximo- α -D-glucose
118	α -L-vancosamine	290	7'-C-methyl-destomic acid
119	β -L-rednose	291	4'-deoxy- β -D-glucose
120	3'-hydroxy-3'-C-nitro-2',6'-dideoxy- α -L-talose	292	4'-amino-4'-deoxy-3'-C-methyl- α -L-fucose
121	3'-nitro-2',3',6'-trideoxy- α -L-gulose (3'-desmethyl- α -L-decilonitrose)	293	α -D-xylose
122	4'- <i>epi</i> - α -L-mycarose	294	α -D-arabinose
123	4'-C-acetyl-2',3',6'-trideoxy- α -L-gulose	295	2',4'-diamino-2',4',6'-trideoxy- α -D-glucose
124	α -L-actinosamine	296	2',3'-diamino-2',3'-dideoxy- α -L-pentose
125	6'-deoxy- α -L-talose	297	β -L-quinovose
126	4'-keto- α -L-olivose	298	6'-deoxy- β -D-talose
127	3'- <i>epi</i> -4'- <i>epi</i> - α -L-decilonitrose (4'-desmethyl- α -L-evernitrose)	299	β -L-vancosamine
128	3'-denitro-3'-hydroxylamine-3'- <i>epi</i> -4'- <i>epi</i> - α -L-decilonitrose	300	3'-amino-2',3'-dideoxy- α -D-fucose
129	α -D-digitoxose	301	β -D-vancosamine
130	4'-C-acetyl-2',3',6'-trideoxy- β -L-gulose	302	3'- <i>epi</i> -4'- <i>epi</i> -5'-hydroxy- β -D-vancosamine
131	β -D-digitoxose	303	2',6'-dideoxy- β -D-altrose
132	4'-C-hydroxyethanone-2',3',6'-trideoxy- α -L-gulose	304	α -D-vancosamine
133	4'-keto- β -D-mycarose	305	3'- <i>epi</i> - β -L-vancosamine
134	4'-hydroxy- β -D-olivose	306	$\Delta^{1,2}$ -D-anglosamine
135	6'-deoxy- β -D-gulose	307	6'-deoxy- α -D-altrose
136	β -D-xylose	308	α -D-amicetose
137	4'-amino-4',6'-dideoxy- α -L-glucose	309	β -L-amicetose
138	4'-amino-2',4'-dideoxy- α -L-xylose	310	3'-O-desmethyl- β -D-rubranitrose
139	4'-deoxy- α -D-taluronic acid	311	3'-deoxy- α -D-fucose
140	β -D-quinovose	312	3'-amino-3',6'-dideoxy- α -L-glucose
141	4'-amino-2',4',6'-trideoxy- β -L-galactose	313	3'-deoxy- β -D-fucose
142	β -L-mycarose	314	4'-deoxy- α -D-taluronamide
143	3'-nitro-2',3',6'-trideoxy- α -L-glucose	315	6'-amino-6'-deoxy-4'-thio-heptofuranuronic acid
144	β -L-talose	316	2'-amino-2'-deoxy- α -L-idose
145	3'-C-carboxy-3'-C-methyl-2',3',5'-trideoxy- α -L-xylofuranose	317	α -D-altruronic acid
146	3'-C-carboxy-2',5'-dideoxy- α -L-ribofuranose	318	6'-amino-6'-deoxy- β -D-glucose
147	3'-amino-3',6'-dideoxy- α -L-altrose	319	α -D-fucose; 3-O-desmethyl- α -D-digitalose
148	2',3',6'-trideoxy-3'-oximo- α -L-altrose	320	2'-deoxy-2'-amino- β -D-gulose
149	3'-amino-3'-C-carboxy-2',3',5'-trideoxy- α -L-ribofuranose	321	3',5'-unsaturated galactouronic acid
150	3'-keto-2',3',6'-trideoxy- α -L-glucose	322	β -L-rhamnose
151	2'-deoxy-3'-keto- α -L-fucose	323	2',6'-dideoxy-3'-hydroxyethyl- α -L-gulose (analog of 324)
152	3'-amino-5'-hydroxy-2',3',6'-trideoxyhexose	324	β -D-galacturonamide
153	β -D-glucosamine	325	4'-keto- β -D-olivose
154	α -D-glucuronic acid	326	β -D-allosamine
155	α -D-quinovose-6'-sulfonic acid	327	α -L-sibirosamine
156	β -D-mannose	328	α -L-paulomyose
157	α -L-fucose	329	α -L-keto analog of 328
158	β -D-arabinose	330	6'-amino-6'-deoxy- β -D-ribofuranhepturonic acid
159	α -D-glucofuranose	331	β -D-ribofuranhexuronamide
160	α -D-mannose	332	enol form of spectinose (33)
161	β -D-galactose	333	2',4'-dideoxy-4',5'-unsaturated- α -D-galacturonamide
162	α -D-allose	334	hexose
163	α -D-altrose	335	5'-O-methyl-4',5'-unsaturated- β -D-arabinofuranohexose
164	6'-deoxyhexosamine	336	5'-O-methyl- β -D-arabinofuranohexose
165	β -L-xylose	337	6',9'-diamino-5',6',7',8',9'-pentadeoxy- β -D-ribofuranodecuronic acid
166	6'-amino-1'-carboxy-6'-deoxy- β -D-mannose	338	6',9'-diamino-5',6',7',8',9'-pentadeoxy-4',5'-unsaturated- β -D-ribofuranodecuronamide
167	6'-amino-6',8'-dideoxy- α -D-galactose	339	6',9'-diamino-5',6',7',8',9'-pentadeoxy- β -D-ribofuranodecuronamide
168	β -L-iduronic acid	340	cyclic analog of 339
169	β -L-rhodinose	341	unusual nine carbon bicyclic sugar I (cyclic form of 344)
170	6'-deoxy- β -D-allose	342	unusual nine carbon bicyclic sugar II
171	6'-deoxy-3'-keto- β -L-glucose	343	unusual nine carbon bicyclic sugar III
172	β -D-galacturonic acid	344	6'-C-carboxy-5',6',7'-trideoxy- β -D-ribofuranoocturonic acid

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 anti-diabetic 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 aminocyclitols 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 aminocyclopentanol 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 (Figure 2A). 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' (Figure 2A) has been noted to be important for activity while the C-9' 6-methyl salicylic ester is considered dispensable.²⁵ Variation of the pseudosugar C-3'-branching (**P27a** and **P30a**) favored antimalarial activity with lowered overall mammalian cell line cytotoxicity.²⁶

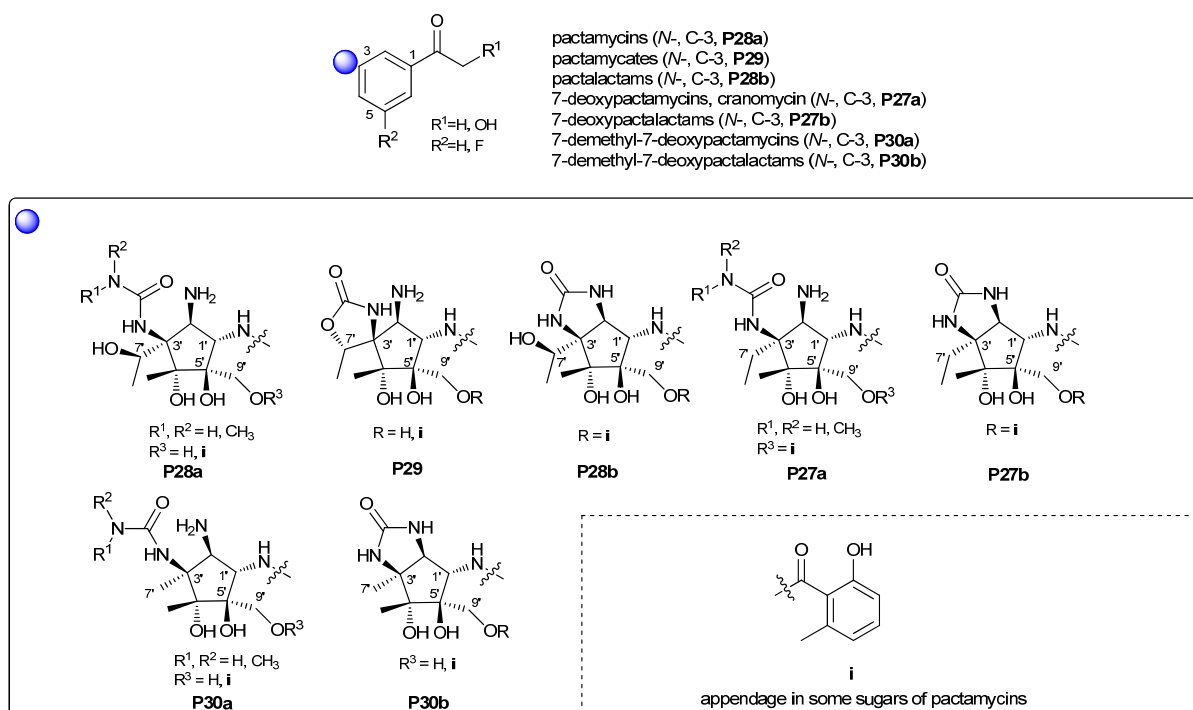


Figure 2A. Pactamycin aglycons and associated pseudosugars

2.2. Other members

While a diverse array of carbocycles 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-P5**, Figure 2B) 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 lysinomycin (**P6**)³² and the fortimycins (**P6**, **P14**, **P15**, **P16**, 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 ribostamycin³⁹ and tobramycins while the related 2-hydroxy aglycon streptamine (**P8**) serves as the core of several aminoglycosides including streptomycins⁴⁰ 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 amylostatin⁴⁵ and

validamycins⁴⁶ 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 kasugamycin⁴⁹ 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'-tetra-deoxyhexose **41** comprised the C-4 attachment in minosaminomycin and C-1 in kasugamycin (Figure 2B). 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 disaccharide **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 streptomycins⁶⁹⁻⁷¹ 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 paromomycins⁷² and ribostamycin⁶¹). In addition, glycosides of the C-3 position of the appended ribose with **5** (neomycin),⁷³ **27** (neomycin B,⁷³ paromomycin and lividomycin A⁷⁴) 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 acarbose⁴⁴ and the unique 1'-2'-dideoxy-2'-aminohexose **40** in salbostatin⁷⁶). 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 specified herein, are also prevalent.

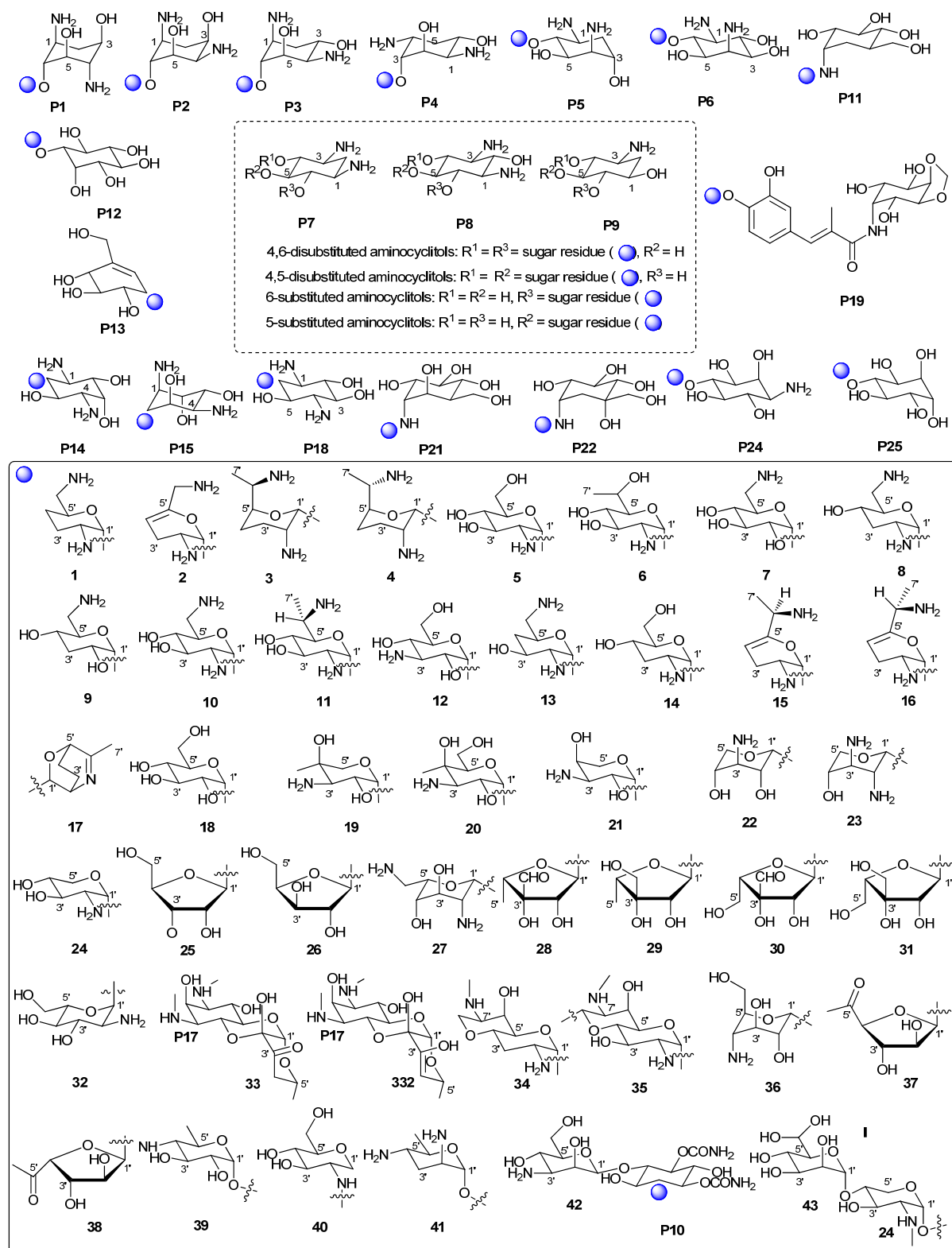


Figure 2B. Aminoglycoside pseudosugars and associated sugars

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); benzanthrins-type (*e.g.*, benzanthrins); gilvocarcin-type and jadomycin-type (Figure 3A).⁷⁷⁻⁷⁹ Despite their remarkable chemical diversity and divergent biological activities, angucyclines have failed to advance in clinical development due to off-target toxicities and/or poor drug-like properties.⁷⁹

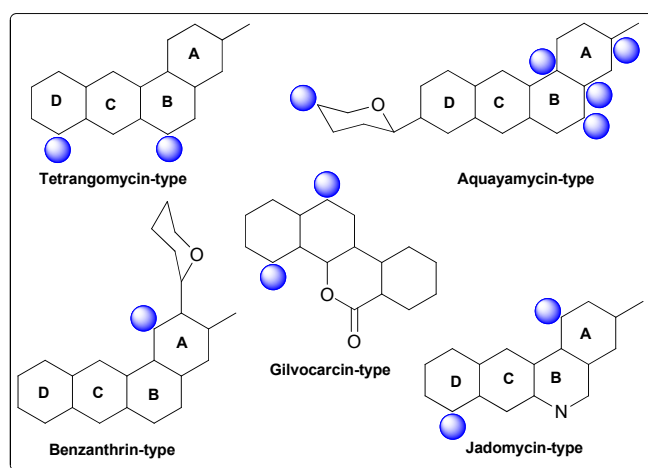


Figure 3A. The five major types in angucyclines and glycosylation positions

3.1. Tetrangomycin-Type (Landomycins)

The landomycins (Figure 3B) are one of the largest angucycline sub-classes 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 β -D-olivose-3-1- α -L-rhodinose and β -D-olivose-4-1- 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 cytotoxicity against representative cancer cell lines and include the atramycins,⁹¹ brasiliquinones⁹²⁻⁹⁴ 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.

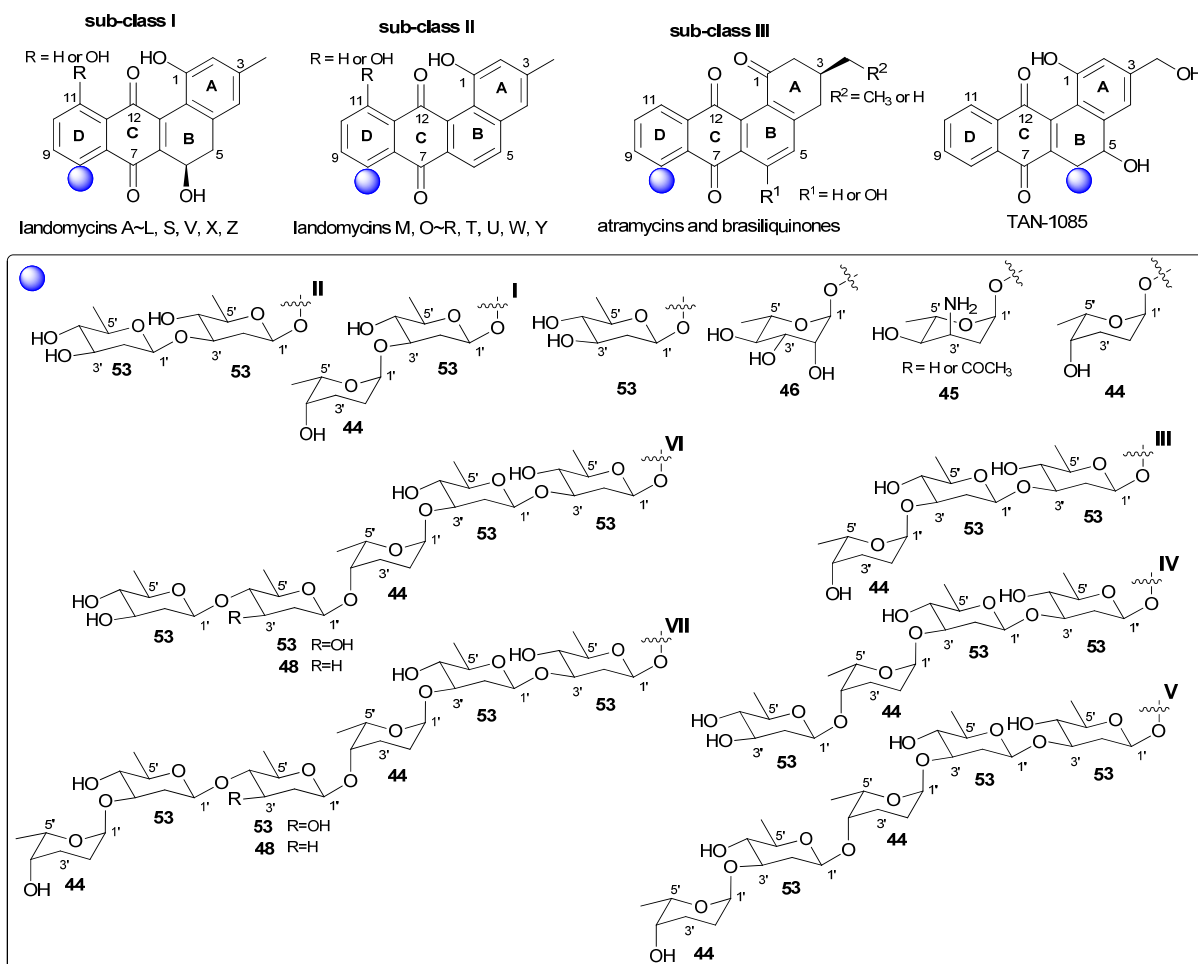


Figure 3B. Landomycin aglycons and associated sugars

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 (Figure 3C).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 LD₅₀ of the potent antibacterial amicenomycin A = 100.0 mg/kg).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

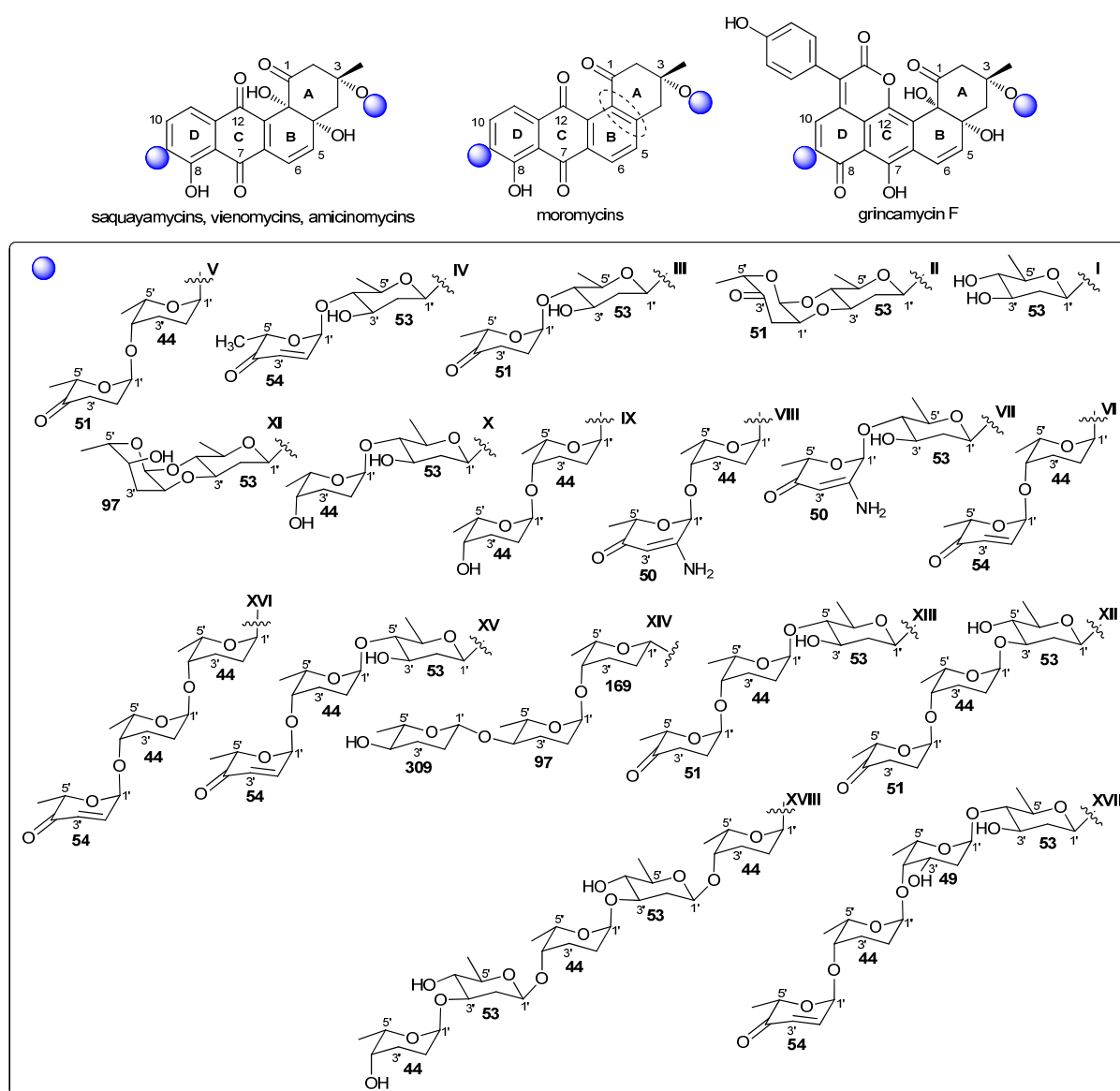


Figure 3C. Saquayamycin aglycons and associated sugars

Urdamycins differ from saquayamycins based upon their distinct regiospecificity of glycosylation (C-9 and C-12b of the angucycline core; Figure 3D). In addition to the numerous natural¹¹⁵⁻¹¹⁹ and engineered urdamycins,¹²⁰⁻¹²⁵ members of this subclass include the kerriamycins,¹²⁶ the N05WA963 series¹²⁷ 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 \rightarrow 3)- β -D-olivose disaccharide (**III**, Figure 3D). In most members, this disaccharide is further capped by one of four monosaccharides (β -D-olivose, **SG4**; α -L-aculose, **SG7**; α -L-cinerulose, **SG8**; or β -D-kerriose, **SG14**). Urdamycins M, R, S and 12b,4'-di-urdaderhodinosyl-urdamycin S serve as the exception in this regard wherein each bear distinct C-9 C-rhodinosyl-based disaccharides.

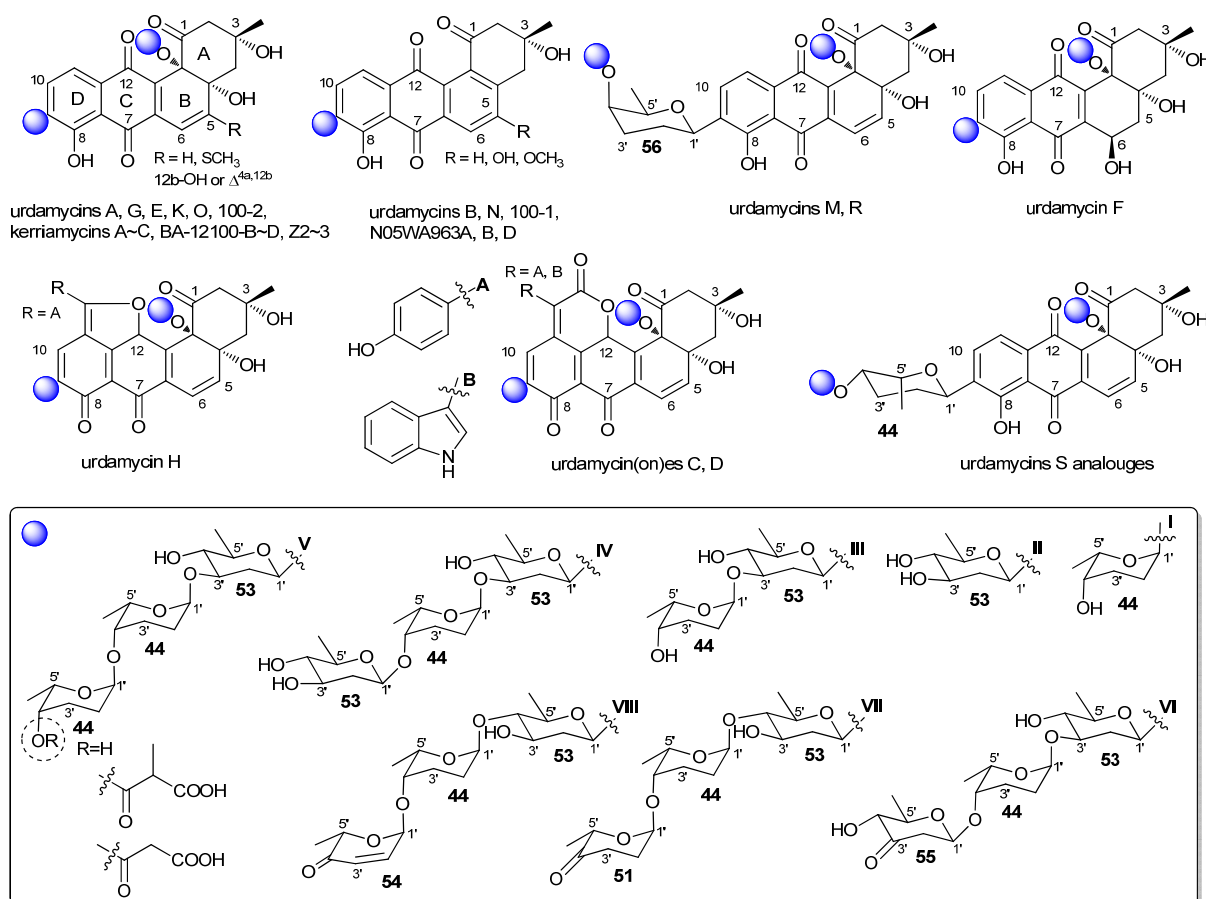


Figure 3D. Urdamycin aglycons and associated sugars

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-rhodamine (**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**, Figure 3E) 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 tetra-deoxysugar 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-rhodamine (**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 unusual 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 \rightarrow 4)- α -L-rhodinose moiety (disaccharide **I**, Figure 3E). 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 marmycins¹⁵¹ as well as the engineered landomycin/urdamycin hybrid metabolite 9-*C*-*D*-olivoyl-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).

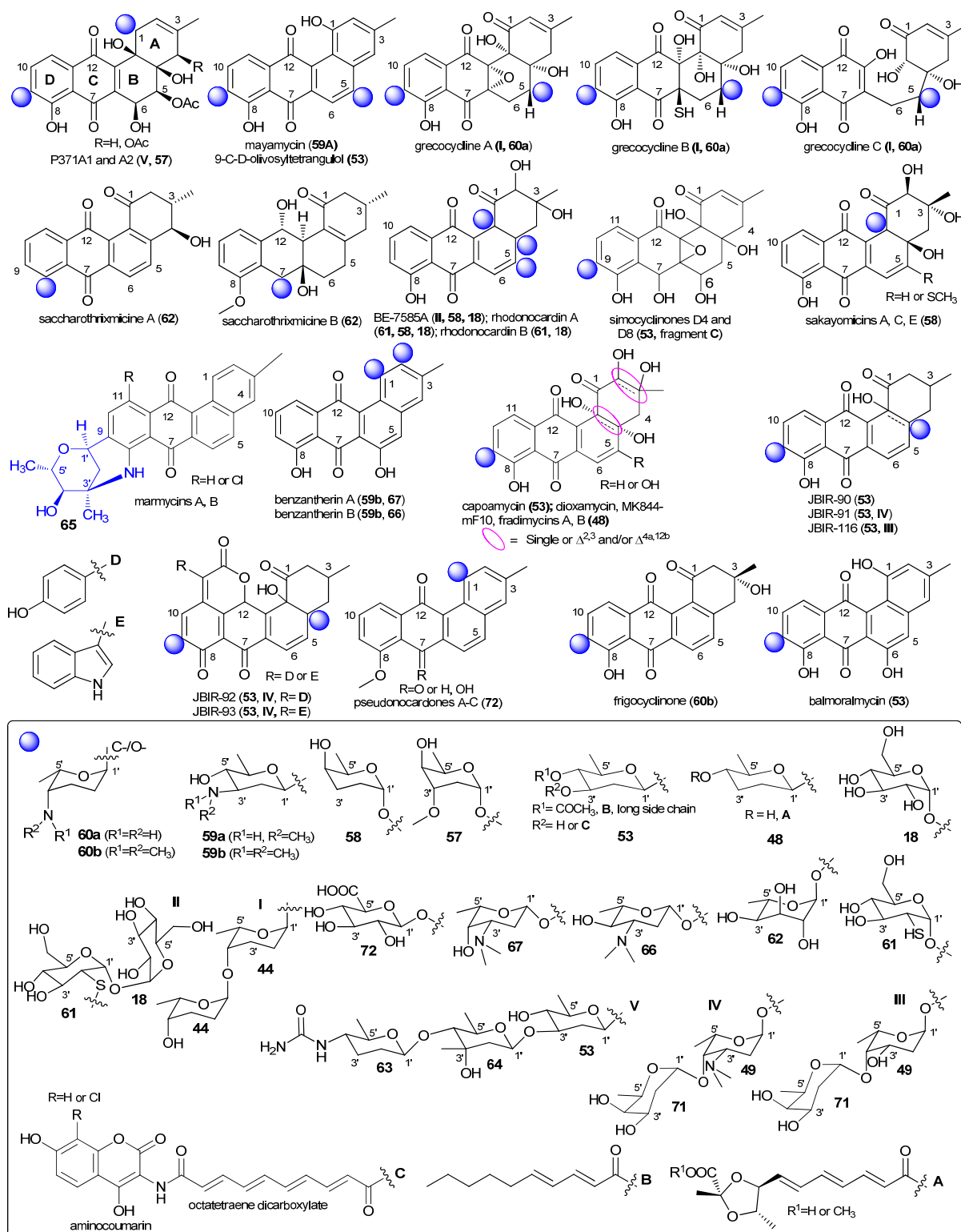


Figure 3E. Other related angucycline aglycons and associated sugars

3.4. Jadomycin- and Gilvocarcin-Types (Jadomycons, Ravidomycons, Chrysoomycons and Gilvocarcins)

The gilvocarcin-type aryl-*C*-glycosides⁷⁹ contain a number of naturally-occurring (gilvocarcins,¹⁵³⁻¹⁶² polycarcins, BE-12406A/B,¹⁶³⁻¹⁶⁵ ravidomycons¹⁶⁶⁻¹⁷¹ chrysoomycons¹⁷² and virenoomycons^{173, 174}) and engineered (gilvocarcins and polycarcins)^{172, 175-177} *Streptomyces* metabolites wherein the signature *C*-glycosylation occurs at C-4 (Figure 3F). 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 jadomycons from *Streptomyces* are angucyclines that contain a nitrogen at position 6 within ring B (Figure 3F).^{79, 178-181} Naturally-occurring jadomycons 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} Jadomycons display a range of bioactivities, including anticancer cytotoxicity, antimicrobial, anti-viral, and inhibition aurora-B kinase.

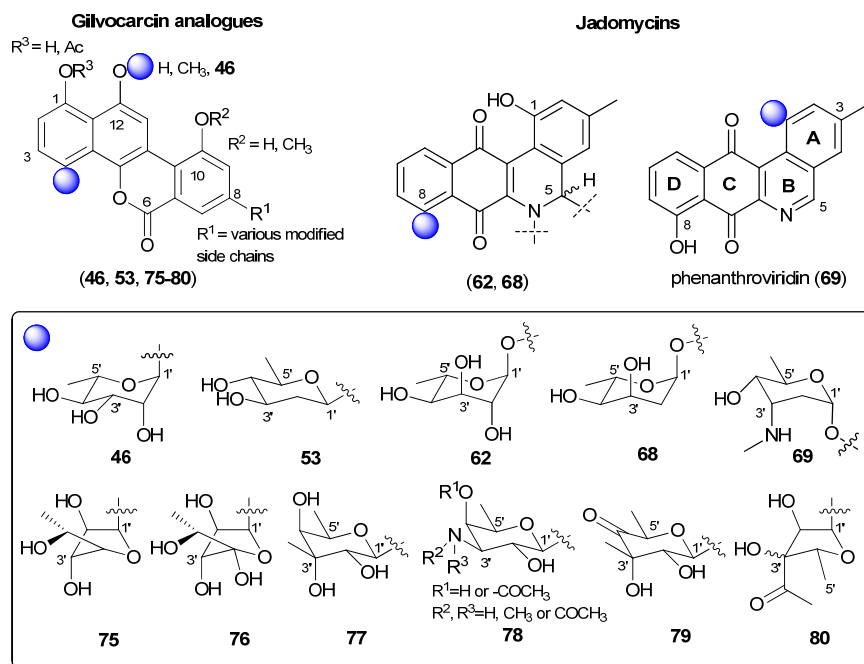


Figure 3F. Gilvocarcin and jadomycin aglycons and associated sugars

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 (Figure 4A, sub-class I).¹⁸⁴ As exemplified by the early prototypical 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 (Figure 4A). Cumulatively, anthracycline glycosides integrate

51 structurally distinct monosaccharide units (Figure 4B) incorporated within the anthracycline-appended mono-, di- (15 variations, **D1-D15**; Figure 4C), tri- (35 variations, trischarides **I-XXXV**; Figure 4D), tetra- (eight variations, **T1-T8**; Figure 4E), and pentasaccharides (two variations, **P1** and **P2**; Figure 4F). While the predominant regioselectivity 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 (Figure 4A). 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).

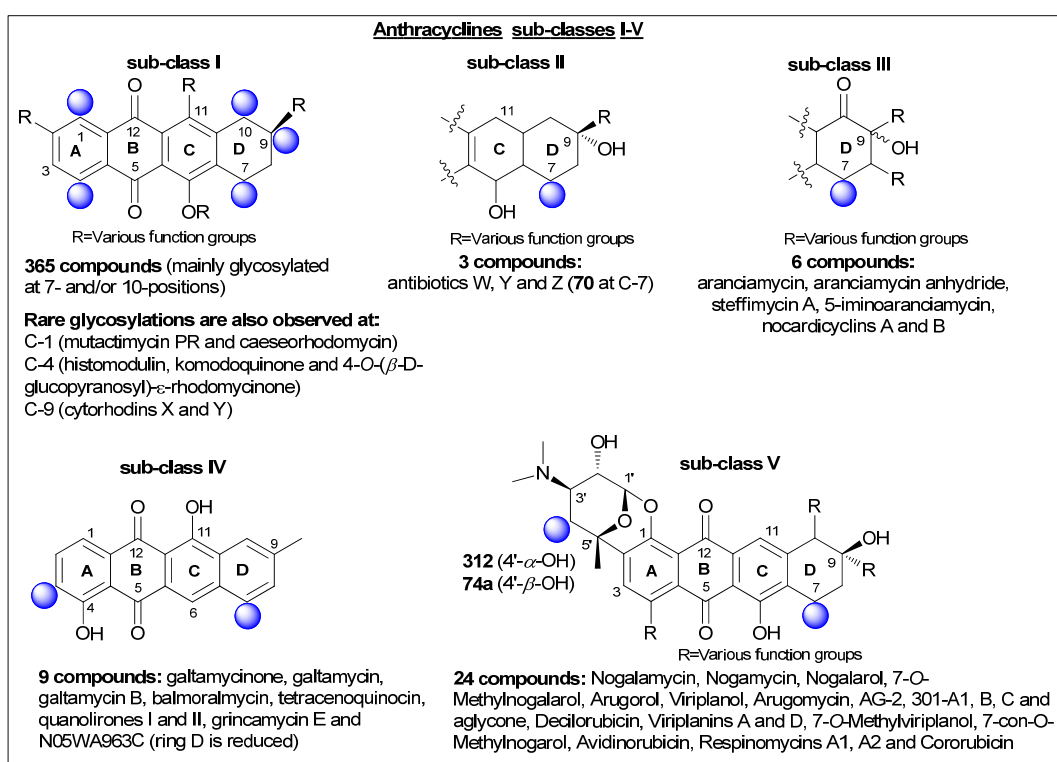


Figure 4A. The five anthracycline sub-classes **I-V** and glycosylation positions

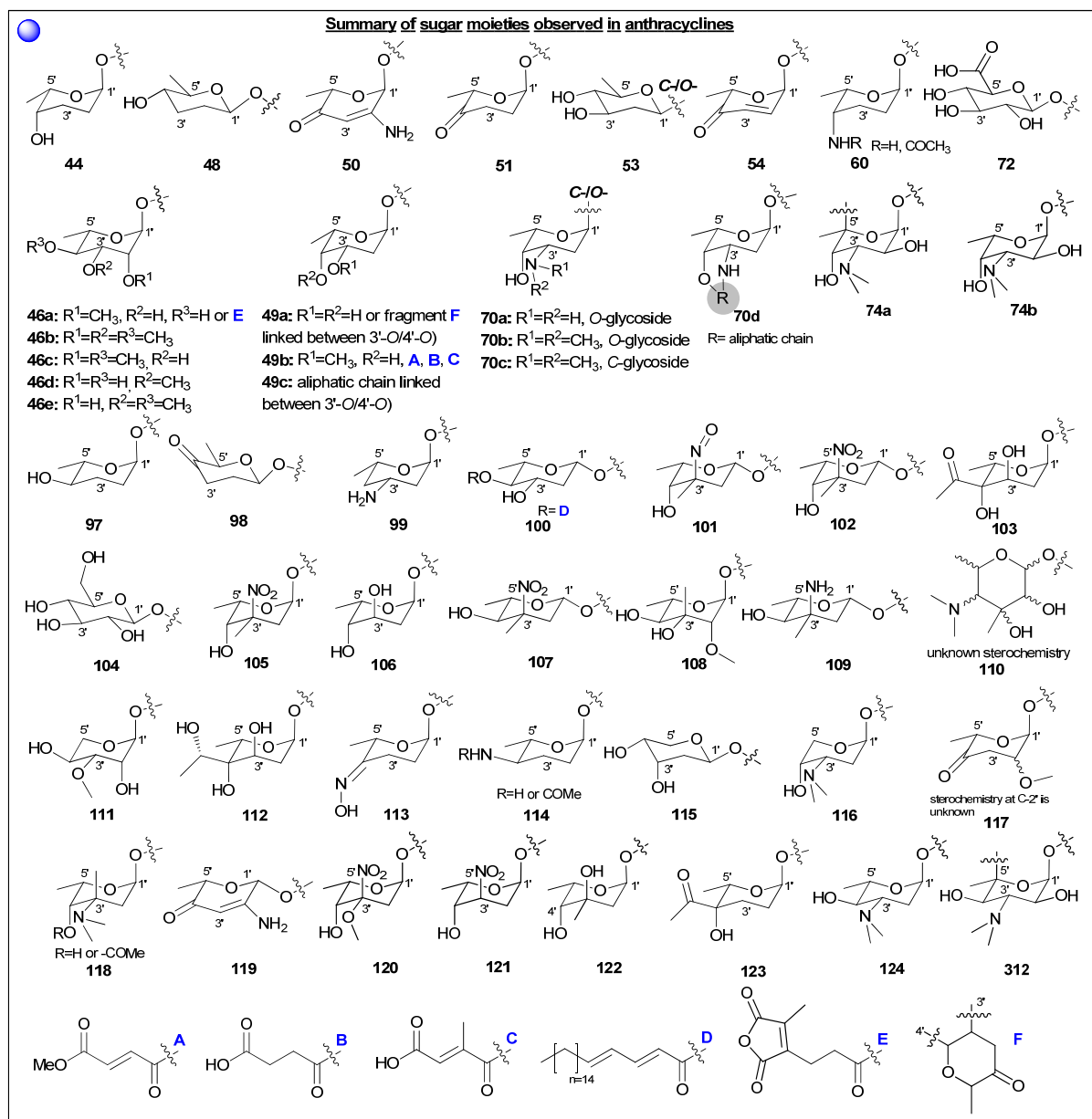


Figure 4B. Sugars associated with anthracyclines

Sub-class **I** contains 365 anthracycline *O*-glycosides (and a few *C*-glycosides) bearing variant carbohydrate substitution ranging from mono- to pentasaccharides. *C*7- and/or *C*10-*O*-glycosylation predominates (358 compounds) within sub-class **I** anthracyclines including D-788,¹⁸⁹⁻¹⁹³ oxauranomyins,¹⁹³ doxorubicins,^{194, 195} spartanamicins,¹⁹⁶ daunorubicins,^{194, 195} daunomyins,^{185, 197, 198} aclacinomyins

(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 aranciamycins²⁴⁴⁻²⁴⁷, A447A~D1,²⁴⁸ ciclamycins,²⁴⁹ isoquinocycline A,^{188, 250} kosinostatin (quinocycline B),^{251, 252} isoquinocycline B,^{252, 253} micromonomycin²⁵⁴ 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 -rhodomycinone²⁶⁷], and C9 (cytorhodins X and Y).^{188, 268} In addition to the mono- to tetrasaccharides observed, two pentasaccharide-containing members were reported [roseorubicin A (pentasaccharide **P1** at C-10; Figure 4F)²²⁹ and β -rhodomycin-Roa2.deofuc.rod3 (pentasaccharide **P2** at C-7, and **70b** at C-10; Figures 4B and 4F)²⁶⁹] where roseorubicin SAR revealed improved potency to correlate with increase oligosaccharide length.²²⁹ Caeseorhodomycin²⁵⁶ 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**; Figure 4B).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**, R³= 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} balmormalmycin (β -L-olivose, **100**; at C-3),²⁷² tetracenoquinocin (**46a** at C-7),²⁴⁷ quanolirones I (trisaccharide **XXXII**, at C-3; Figure 4D) and II (disaccharide **D15**, at C-3; Figure 4C),²⁷³ and the two D-ring-reduced metabolites N05WA963C¹²⁷ and grincamycin E¹¹¹ (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 decilorubicin,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 (Figure 4B), anthracyclines present several unique carbohydrates. For example, C-3'- and C-4'-branching is prevalent as exemplified by **101-103**, **105-110**, **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-C²⁹¹) 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

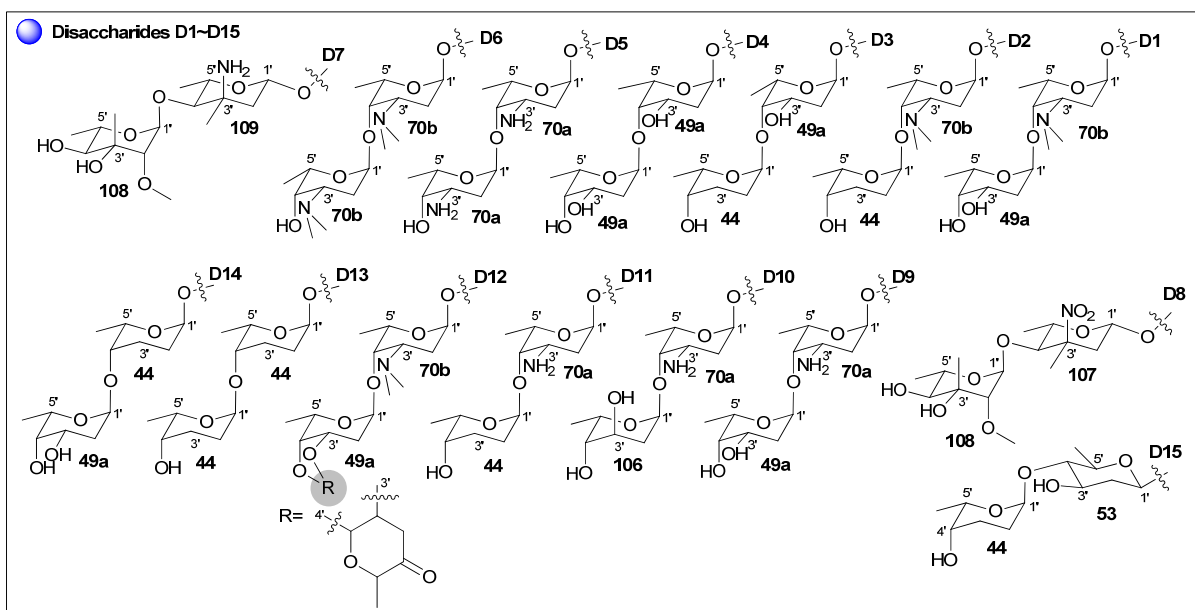


Figure 4C. Disaccharide variations D1-D15 observed in anthracyclines.

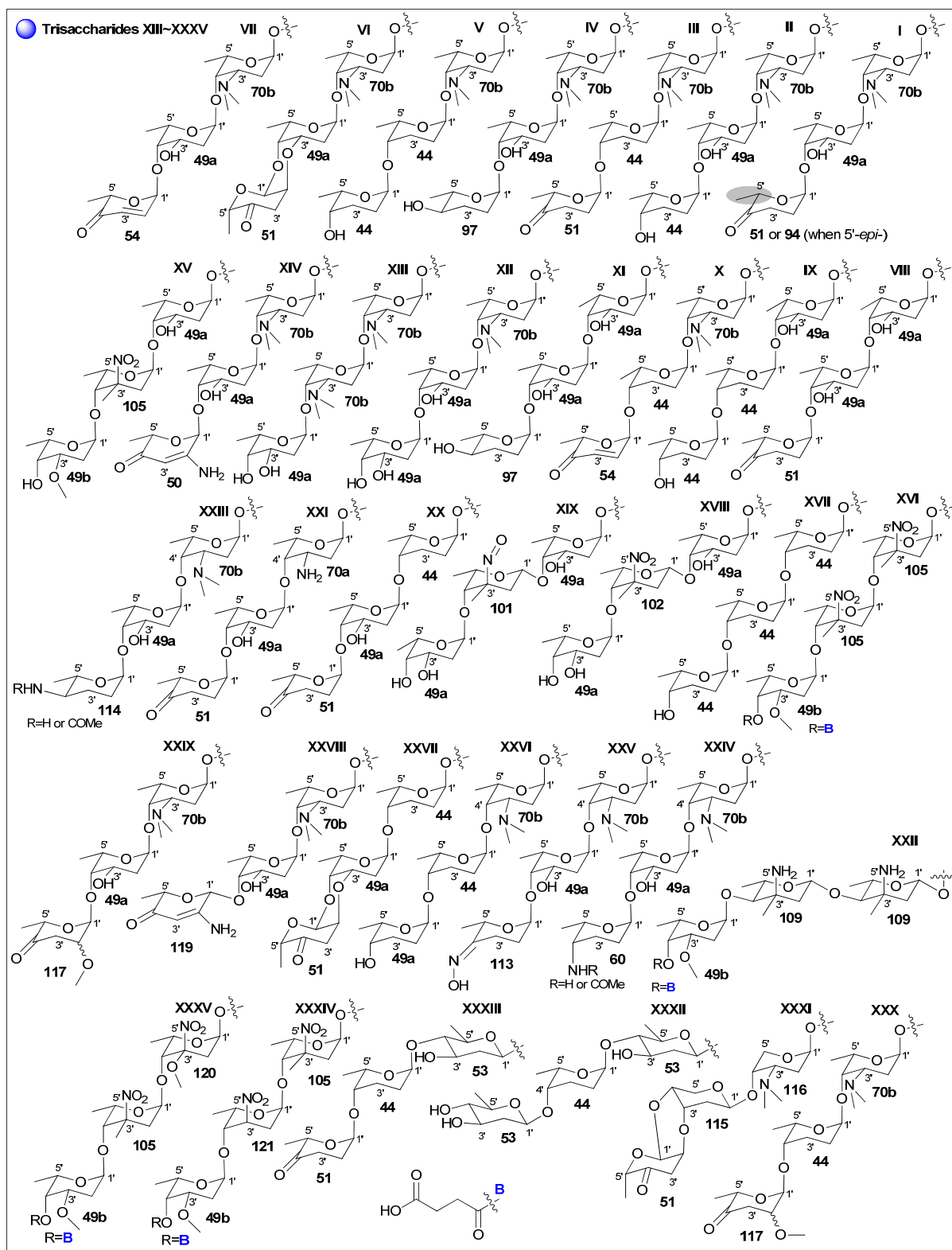


Figure 4D. Trisaccharide variations (I-XXXV) observed in anthracyclines.

4.2. Hibarimicins

Hibarimicins are distinguished by their highly oxidized naphthyl-naphthoquinone aglycon which derives biosynthetically from dimerization of undecaketide-based precursors (Figure 4G).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' (Figure 4G).^{18, 293-299} Glycosylation at these positions is composed of mono- and/or disaccharide side chains (Figure 4G) 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**, Figure 4G). HMP-P4 and HMB-Y6 are metabolites produced by *Microbiospora* engineered mutants.²⁹⁵ Hibarimicins 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

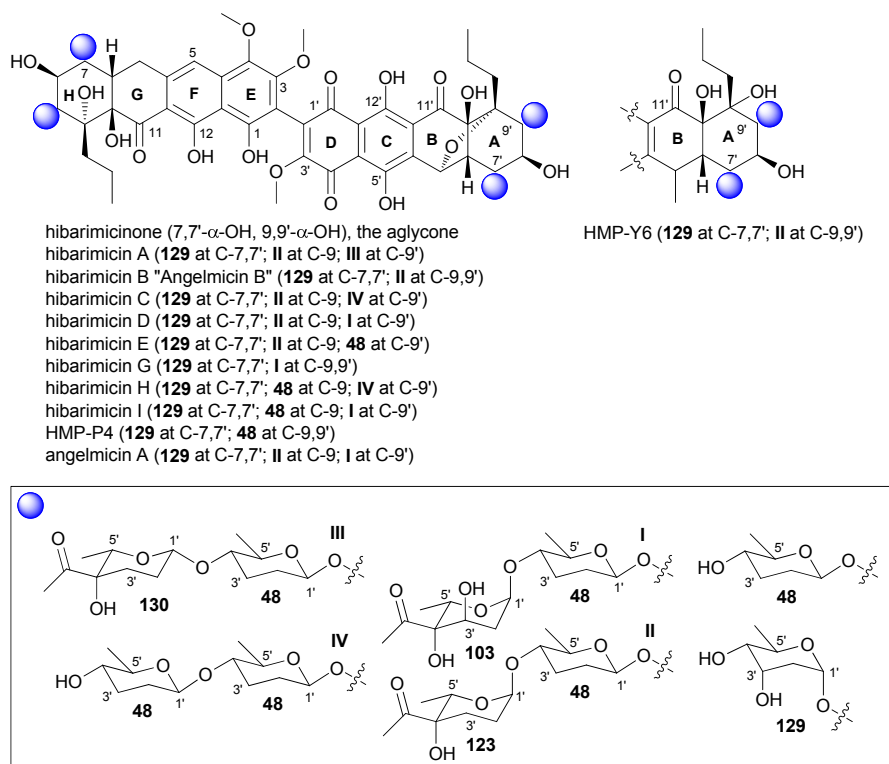


Figure 4G. Hibarimicin aglycons and associated sugars

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 HKI10311129³⁰³ dutomycin,^{304, 305} polyketomycin,³⁰⁶⁻³⁰⁸ elloramycins,^{176, 309, 310} tetraenomycins,^{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 \rightarrow 4)- β -D-amicetose, disaccharide **I**) moieties, respectively (Figure 4H).³⁰⁰⁻³⁰² The terminal rhodnose (**44**) of tetrasaccharide **III** is further modified with a 4'-*O*-dimethylmalonyl/or monomethylmalonyl ester. The structurally similar HKI10311129³⁰³ displays an identical glycosylation pattern but lacks the terminal rhodnose ester modification while the related dutomycin and polyketomycin are C-4-*O*-glycosides bearing an α -L-4'-*epi*-mycarosyl-(1' \rightarrow 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 hydroxylamino 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 topoisomerase 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

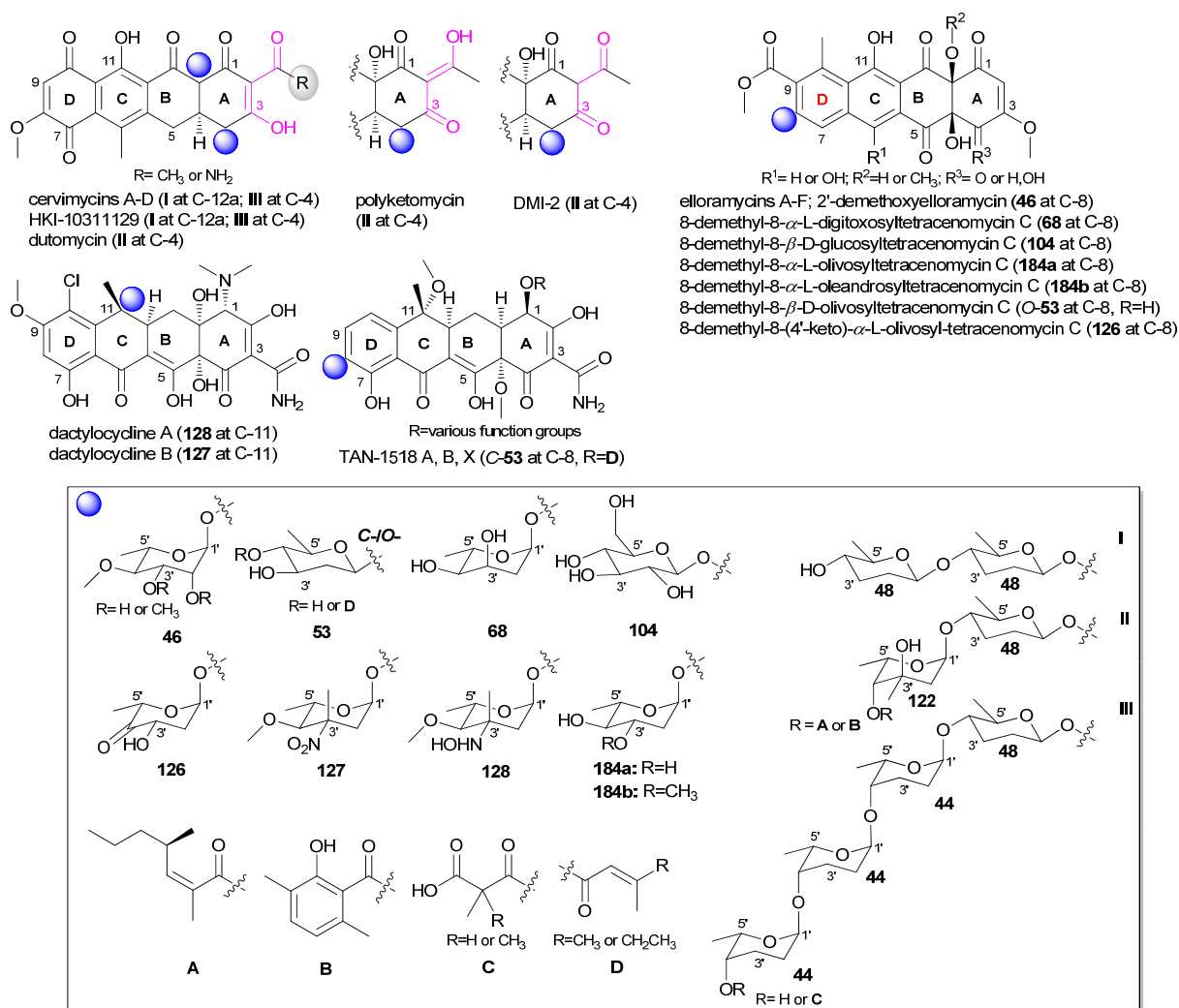


Figure 4H. Tetracycline aglycons and associated sugars

4.4. Aureolic Acids and Related Tetracyclines

Mithramycin³¹⁴ 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 regioselectivity 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); Figure 4I] 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 (Figure 4I). 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 II³⁴² 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 trisaccharide (**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=CH₃), 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*- α -L-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 \rightarrow 3)- β -D-olivosyl-(1 \rightarrow 3)- β -D-oliosyl-(1 \rightarrow 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}

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**) (Figure 4J). For the scope of this discussion, this family is further divided into sub-classes **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 menoxymycins³⁵³ 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 *Nocardiosis*,³⁶⁵⁻³⁷¹ 337-343 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 pyranonaphthoquinone core via a C-8-C-4' bond to provide a bicyclic structure (Figure 4J). Eleven sub-class **III** members have been reported including granatomyocins, 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**).

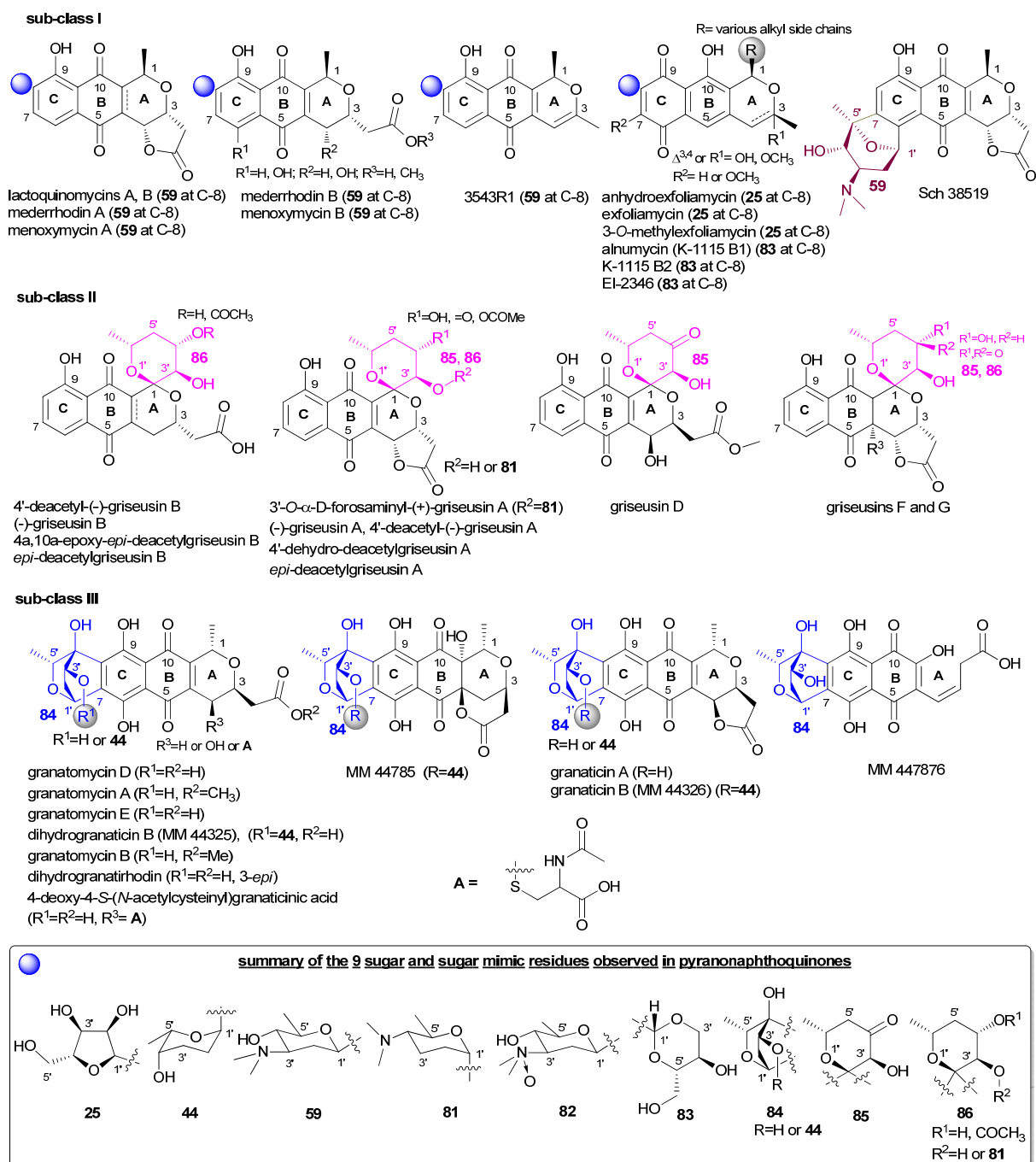


Figure 4J. Naphthoquinone aglycons and associated sugars

4.6. Benzoquinones Related Antibiotics

Naphthoquinones 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-naphthoquinone. 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, Figure 4K).

A series of α -aromatic *O*-glucuronides including julichrome Q₆ glucuronide³⁷⁴ 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 Q₆ 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} adxanthromycins³⁷⁸⁻³⁸² and grecocketides³⁸³ 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-1 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 grecocketides A and B are both disaccharyl-containing C-6-*C*-glycosides of the grecocketidone aglycon that differ in disaccharide composition.³⁸³ Specifically, the C-6-*C*-glycosyl moiety of grecocketide A is α -L-rhodinose (**44**) while that in grecocketide 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 peroxy-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 lomaiviticins³⁸⁷ 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*, 4 β ,8-dihydroxy-3 α -O-(α -glucopyranosyl)hydroxymethyl-4 α -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, lemomycin³⁹³ and heliquinomycin³⁹⁴⁻³⁹⁶ from *Streptomyces*. Lemomycin 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

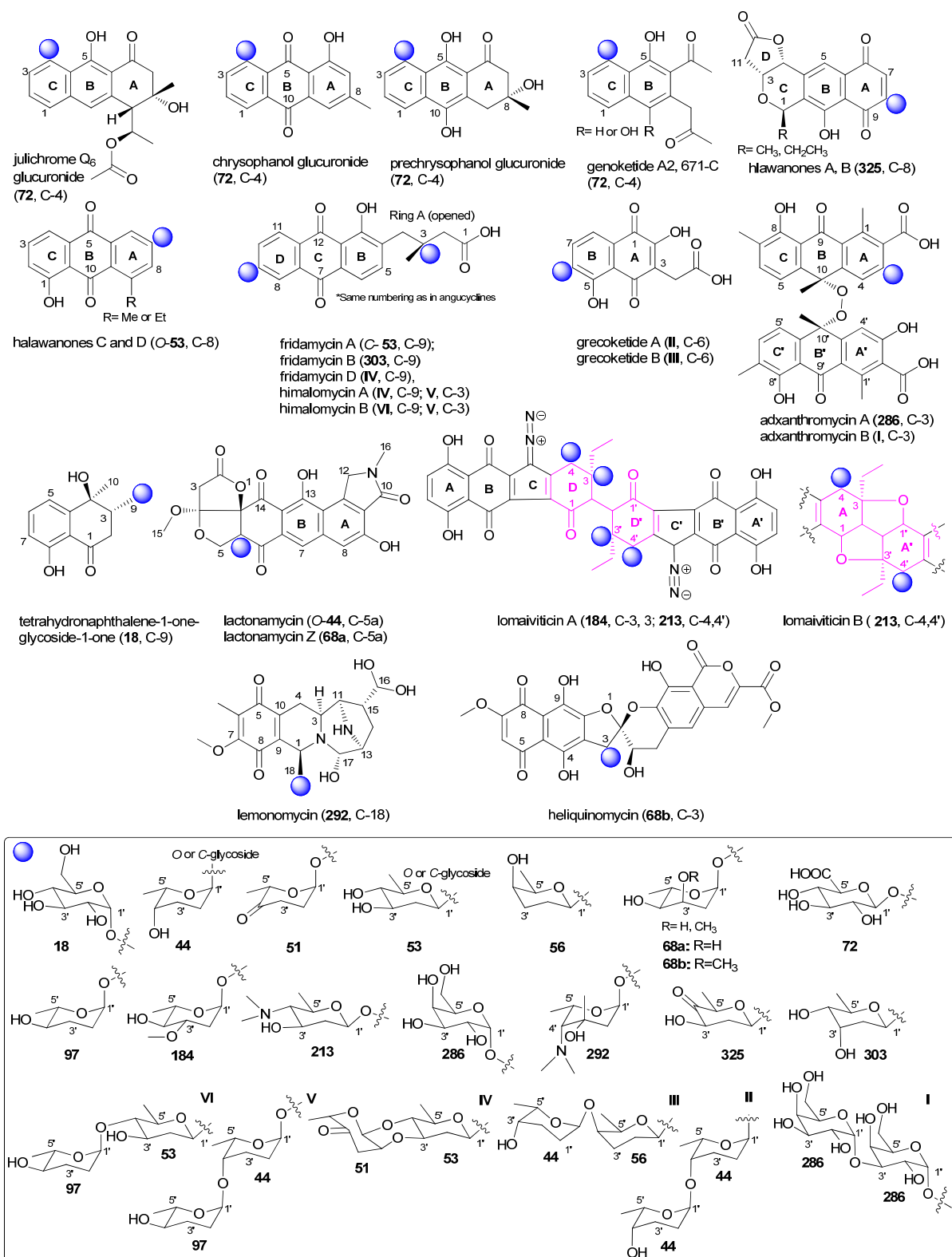


Figure 4K. Benzoquinone aglycons and associated sugars

5. Benanomicins and Pradimicins

Benanomicin and pradimicin analogs consist of a benzo[a]naphthacene quinone conjugated to various modified amino-acids 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; Figure 5A).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 pradimicins 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**), β -D-3'-amino-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^{2,400, 406-409}, FA-1⁴¹⁰, FA-2⁴¹⁰, FB⁴¹¹, FH, L, FL⁴¹², S⁴¹³⁻⁴¹⁵, FS⁴¹¹ and other analogs.^{399,17,18,416-419} 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 H⁴²² and 11-*O*-L-xylosyl-pradimicin FH,⁴²² all which are also contain C-5 mono- or disaccharide substitutions.

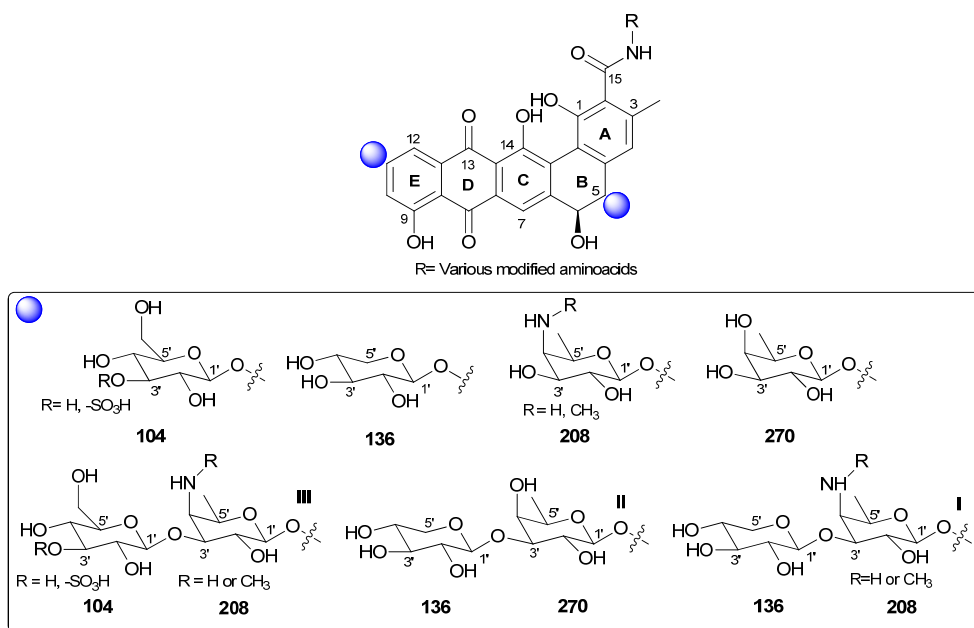


Figure 5A. Benanomycin and pradimicin aglycons and associated sugars

6. Chartarin-analogs

Charterin 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**; Figure 6A). Sixteen naturally-occurring charterin glycosides have been reported to date as bacterial metabolites (mainly from *Streptomyces*, Figure 6A) including the chartreusins (lambdamycins),⁴²³⁻⁴³³ chrymutasins,⁴³⁴⁻⁴³⁶ D329C,⁴³⁷ elsamicins,⁴³⁸⁻⁴⁴⁰ and hayumicins.⁴⁴¹ These compounds display notable antimicrobial and antitumor-activity where glycosylation plays a key role in improving potency, formulation and in vivo properties wherein aminosugar-containing variants are among the most advantageous.^{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.

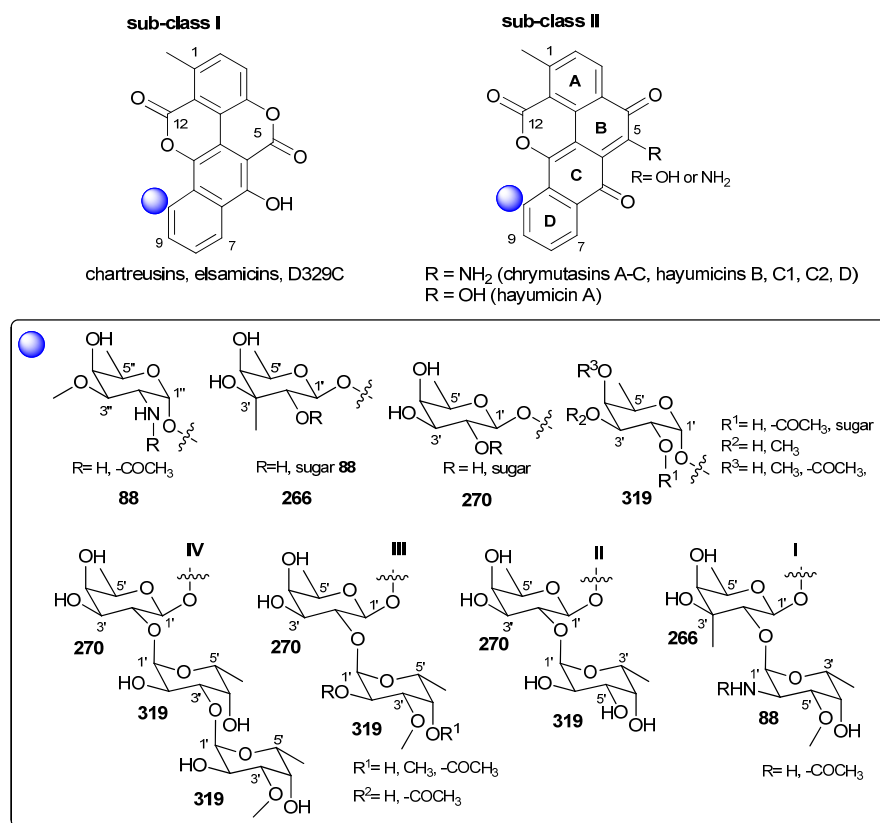


Figure 6A. Chartarin aglycons and associated sugars

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-chlorocoumarobiocin⁴⁵⁷) 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'-carbamylation 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 (Figure 7A). 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 (Figure 7A, **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'-demethylnovobiocin) 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 aminocoumarin 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 protorubradirin⁴⁷⁷ 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**), Figure 7A]. 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}

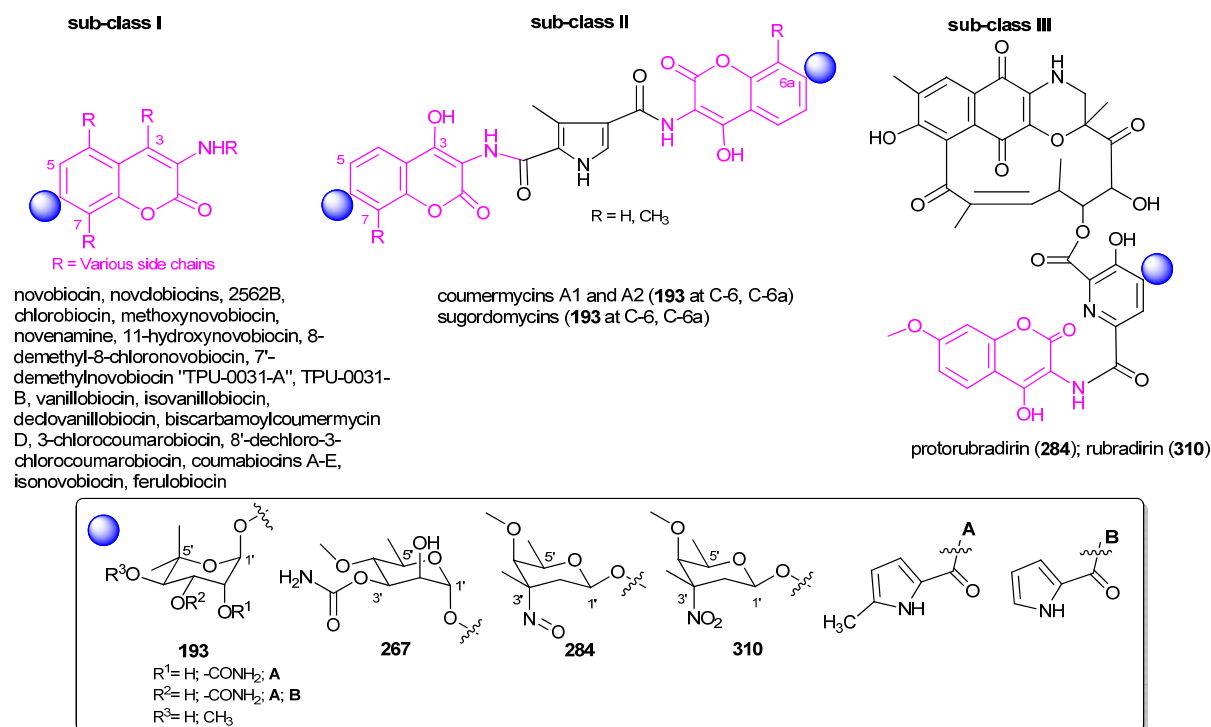


Figure 7A. Coumarin aglycons and associated sugars

8. Enediynes

Enediynes are a group of antibiotic anticancer compounds characterized by the presence of bicyclo[7.3.0]dodecenediyne 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 associated with a novel self-sacrifice resistance mechanism.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 (Figure 8A). Members of this family are treated separately herein based upon enediyne ring size.

8.1. 9-Membered Enediynes

The glycosylated 9-membered enediynes (Figure 8A) include C-1027,⁴⁸³⁻⁴⁸⁵ neocarzinostatin,⁴⁸⁶⁻⁴⁸⁸ maduropeptin,⁴⁸⁹ kedarcidin,⁴⁹⁰⁻⁴⁹² and two putative cycloaromatized analogs (NFκB inhibiting fijiolides⁴⁹³ and cyanosporasides⁴⁹⁴) from *Streptomyces*, *Actinomadura*, *Streptoalloteichus*, *Salinospora*, and *Nocardioopsis*. Nine-membered enediyne glycosylation regioselectivity 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-kedarasamine **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-kedarasamine **91** (kedarcidin) as the only exceptions.

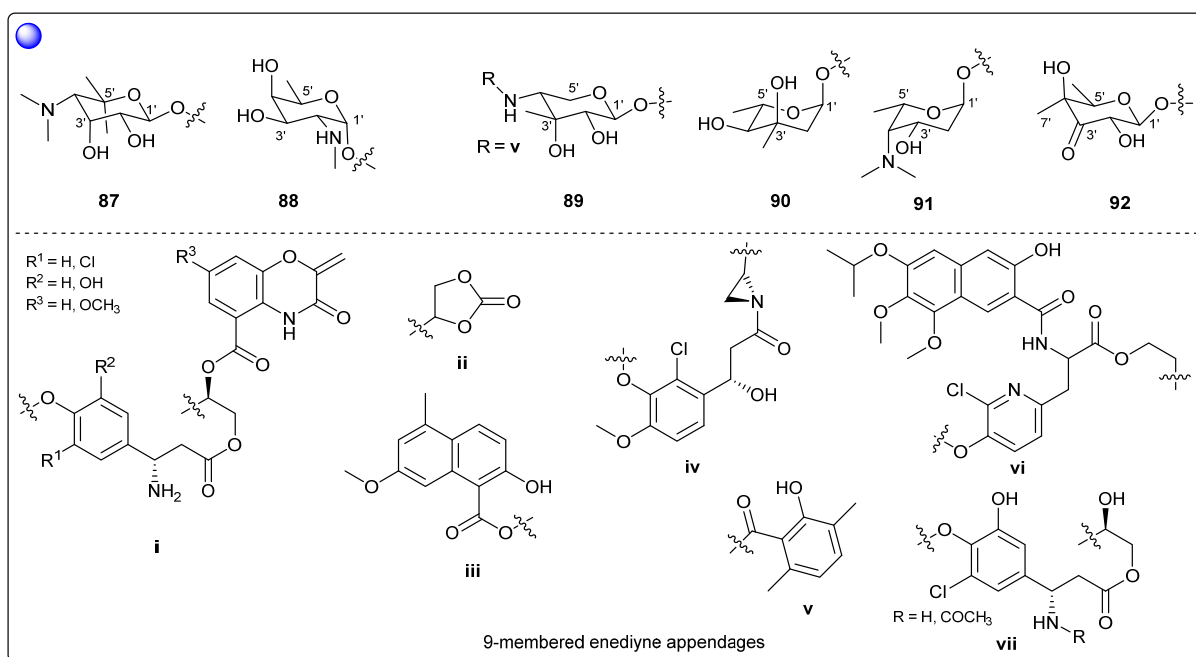
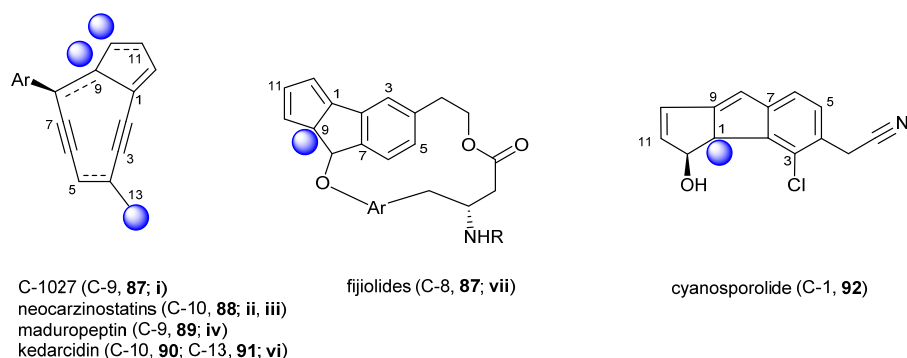


Figure 8A. 9-Membered enediyne aglycons and associated sugars. Ar, aromatic moiety.

8.2. 10-Membered Enediynes

Glycosylated 10-membered enediyne glycosides (Figure 8B) include the calicheamicins,⁴⁹⁵⁻⁴⁹⁸ esperamicins,⁴⁹⁹⁻⁵⁰⁵ shishijimicins,⁵⁰⁶ and namenamicin⁵⁰⁷ 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 (Figure 8B). Both the calicheamicins and esperamicins contain a conserved C-8 trisaccharide moiety **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 A₁ series, **49a**) or C-4' (esperamicin A₂ series, **49b**) with a modified anthranilate (Figure 8B). 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**). Namenamicin⁵⁰⁷ 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*-methyl-thiosugar **94** (Figure 8B).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 (Figure 8B).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 chemoselective 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

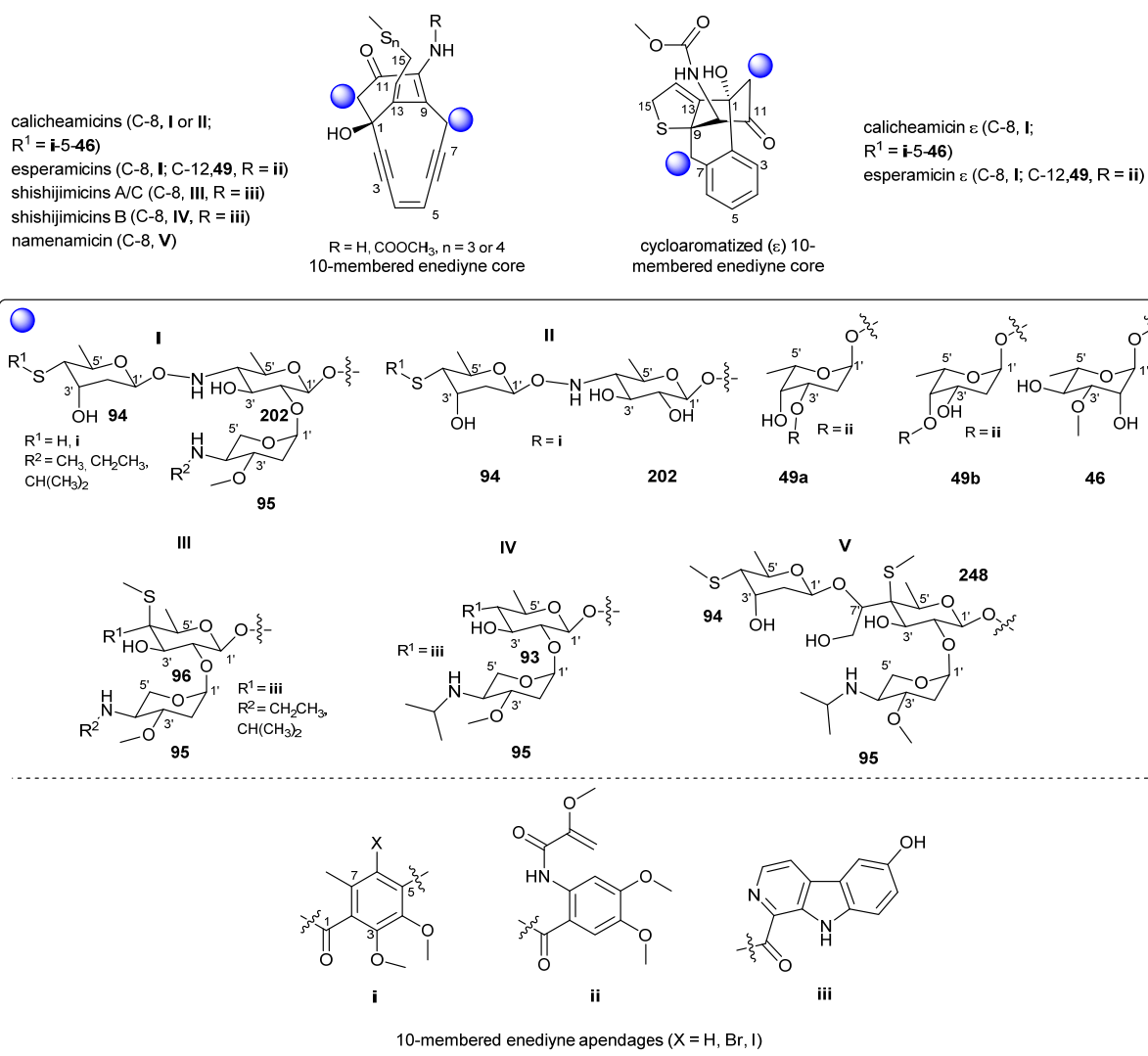


Figure 8B. 10-Membered enediyne aglycons and associated sugars; Ar, aromatic moiety

9. Flavonoids and Isoflavonoids

(Iso)flavonoids are a prevalent group of plant secondary metabolites that share a common three ring architecture with subtle ring regioselectivity 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**) (Figure 9A).

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-ribose (6'-deoxy- α -L-rhamnose, **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 stereocenter (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 (7,4a-dihydroxyisoflavone-3a-*O*- α -L-rhamnopyranoside) and N-99-596 B (5,7,4a-trihydroxyisoflavone-3a-*O*- α -L-rhamnopyranoside)⁵²⁹ from *Streptomyces* as the only examples of the former. For the latter, the α -L-chinovose (6'-deoxy-4'-*epi*- α -L-glucose, **157**) containing luteolin-6-chinovoside from *Sorangium* represents the only C-6-glycoside within this series.^{18, 533}

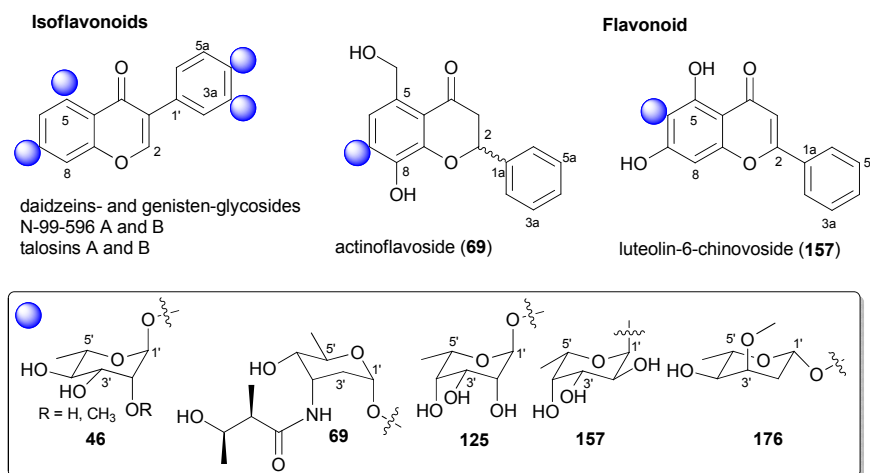


Figure 9A. Flavonoid and isoflavonoid aglycons and associated sugars

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, pyrroindomycins 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-derived 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 rebeccamycin⁵⁴⁶ and staurosporine⁵⁴⁷ with 64 glycosides cumulatively reported to date (Figure 10A). The distinguishing features of the rebeccamycin-like indolocarbazoles (including both AT2433 and rebeccamycin analogs) include a 1H-pyrrole-2,5-dione, indole *N*-glycosylation and often indole halogenation. In contrast, staurosporine-like indolocarbazoles (including, indocarbazostatsins, K-252, MLR-52, RK-286, RK-1409, staurosporine, UCN and ZHD-0501 variants) contain a reduced 1H-pyrrol-2(5H)-one, a signature fused *N,N'*-12,13-glycoside, and typically lack indole halogenation (Figure 10A). In general, mechanism of action coincides with these structural distinctions where staurosporine-like indolocarbazoles typically function as kinase inhibitors⁵⁴⁸ while rebeccamycin-like indolocarbazoles inhibit topoisomerase I⁵⁴⁹ 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 (Figure 10A).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-1409⁵⁶⁵) as well as *N,N*-dimethyl,⁵⁶⁶ *N*-desmethyl,⁵⁶⁷ and *N*-amide derivatives⁵⁶⁸ in staurosporines; *N*-formyl and the corresponding C-3'/C-4'-cyclic carboxamide **45c** of ZHD-0501,⁵⁶⁹ and *N*-oxidation to afford the hydroxylamino analog (**226**, associated with two *N*-hydroxystaurosporine derivatives and 4'-demethyl-*N*-formyl-*N*-hydroxystaurosporine) and hydroxylimino analog (**148**) of the TAN-1030A series (Figure 10A).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** (Figure 10A). 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

Nocardiosis)^{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) (Figure 10A). 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

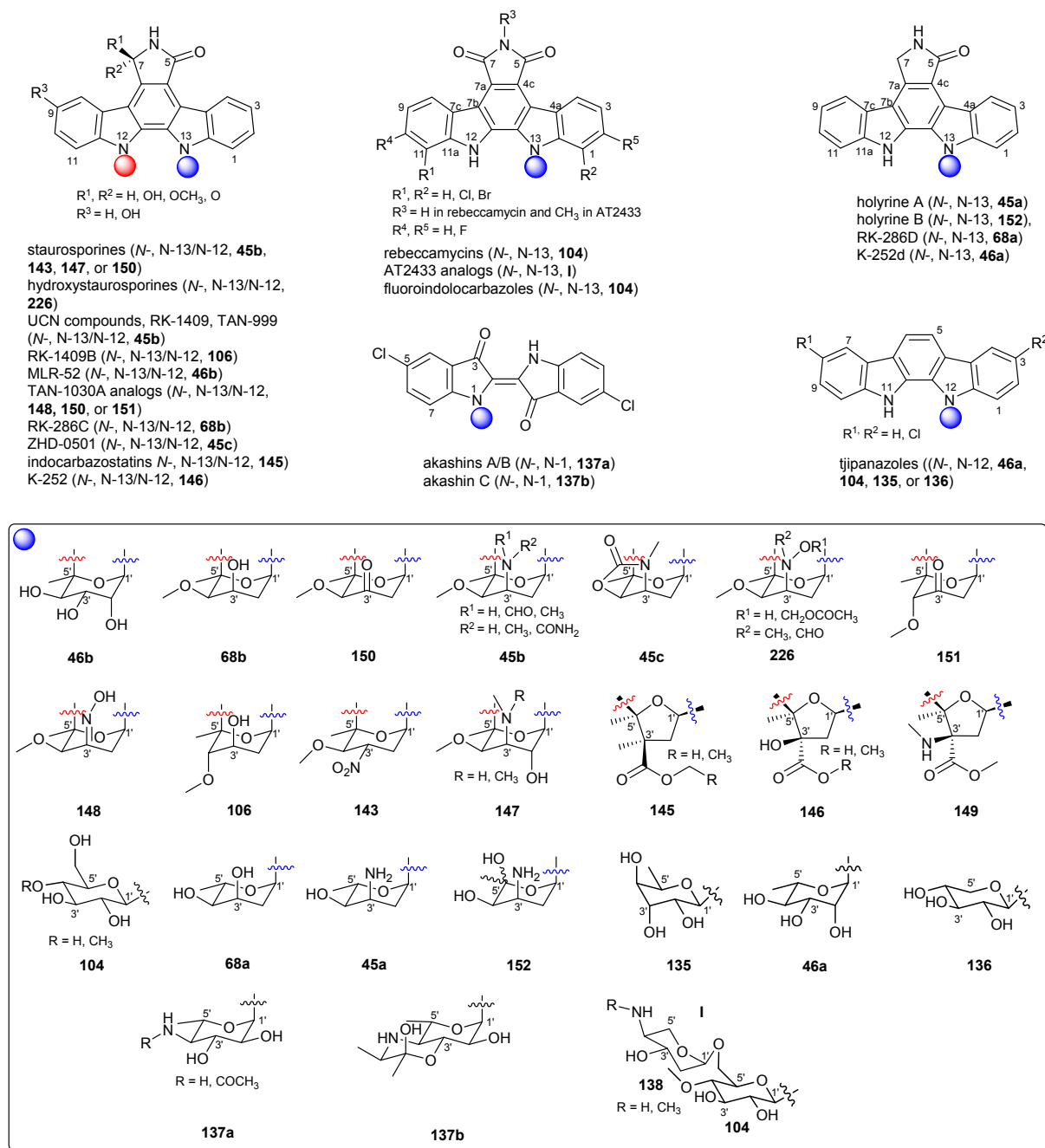


Figure 10A. Fused indole-related aglycons and associated sugars where different colors distinguish multiple points of attachment.

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 *Nocardioopsis*),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) (Figure 10B). 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-rhodosyl trisaccharide appended to a polyketide tetramic acid-containing macro-ring system (Trisaccharide **I**, Figure 10B). 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 (Figure 10B). Members include the oxopropalines^{591, 592} and pyridindolols⁵⁹³⁻⁵⁹⁶ 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 (Figure 10B). In the latter case, rhamnosylation was found to be detrimental to the observed anticancer activity of the parental aglycon.⁵⁹²

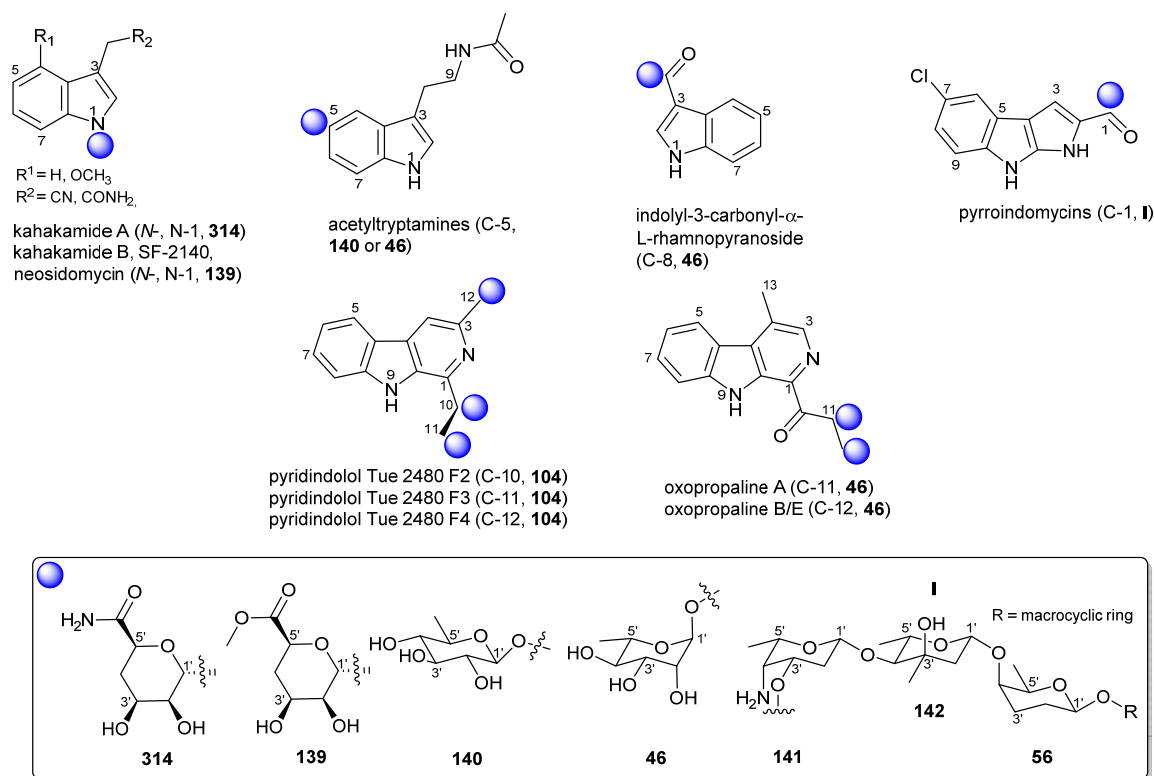


Figure 10B. Simple indole-related aglycons and associated sugars.

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 arthrobaicillins,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 carotenoids⁶⁰⁹ and *Flavobacterium* glycerolipids⁶¹⁰ 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** (desalicytin 2'-butyrate)⁶¹⁹ are additional sugars represented among bacterial glycolipids, carotenoids and related metabolites. Disaccharides **I** and **II** (Figure 11A), 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 [Figure 11A; 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 (Figure 11A) 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

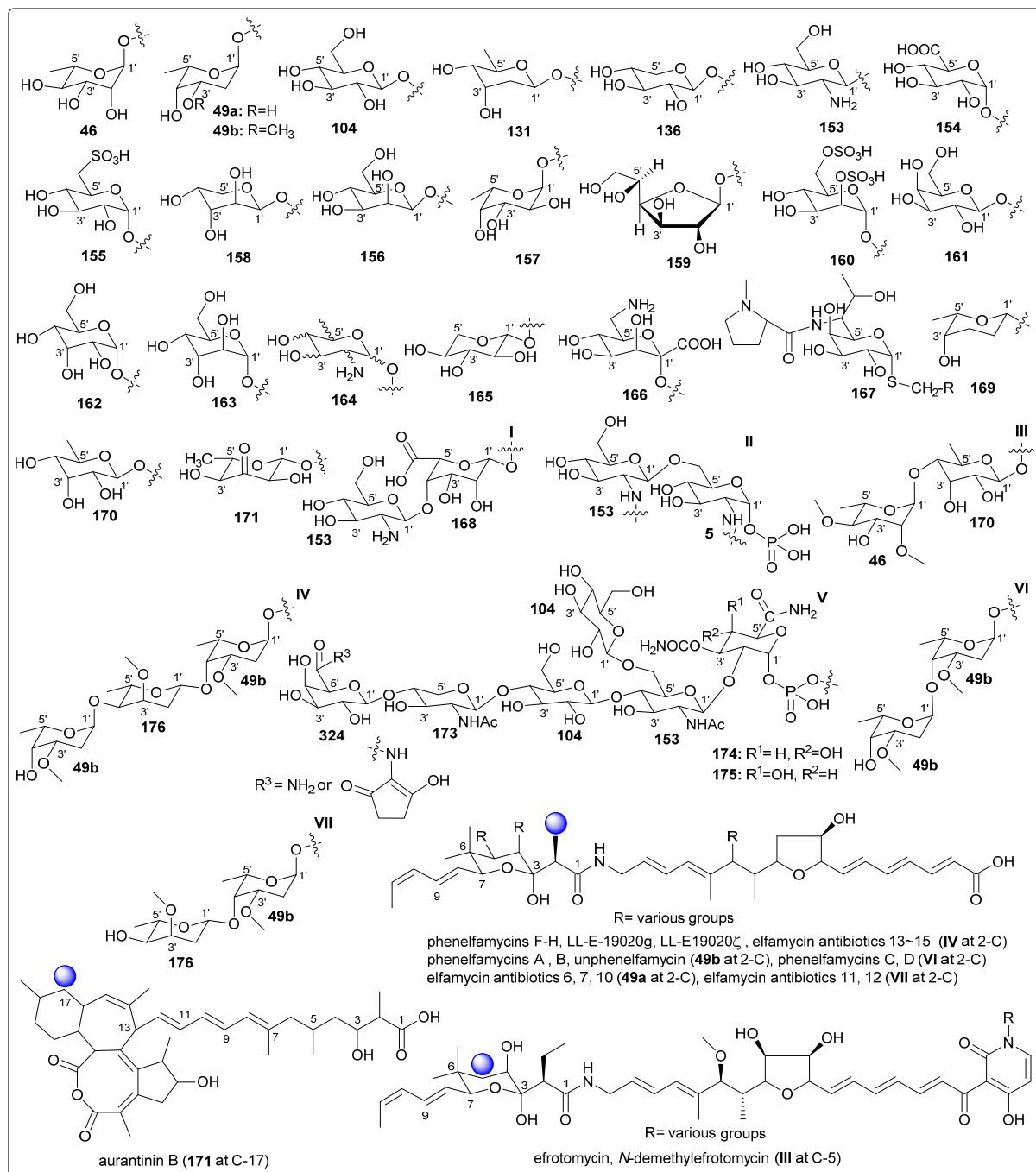


Figure 11A. Glycolipids, polyenes and carotenoids and associated sugars

12. Macrolides and Macrolactams

Macrolides and macrolactams are highly functionalized macrocyclic 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 subsections 12.1-12.7), macrodiolides (subsection 12.8), super macrolactones (subsection 12.9), polyene macrolides (subsection 12.10), macrolactams (subsection 12.11), spirotetronates (subsection 12.12) and spinosyns (subsection 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 (Figure 12A). 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 pseudoerythromycins⁶³⁴ while β -D-oliviosyl (**53**) substituted methymycin has been generated via pathway engineering⁶³⁶ 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-C⁶⁵⁰ or the 2-norerythromycins deriving from pathway engineering),⁶⁵⁵ or the or C-3'/C-4'-modified form (**90c/90d**, Figure 12A) in megalomycin analogs.⁶⁵⁶

Additional C-3-appended sugars observed include 4'-*O*-acetyl- α -L-arcanose (**122b**) [and corresponding engineered 2',3'-anhydro-arcanose (**182**) and 3'-acetylated **180**^{657, 658}] of the lankamycins⁶⁵⁹ and the kujimycins [which contain a C-3 α -L-arcanose (**122a**) or 4'-*O*-acetyl- α -L-arcanose (**122b**) and a C5 β -D-lankavose (**181b**)]⁶⁶⁰ and α -L-oleandrose (**184**; found in oleandomycin^{647, 661} and the 3-*O*-oleandrosyl-5-*O*-desosaminy-(8*S*)-8-hydroxyerythronolide B⁶⁶² from bioconversion]. Additional sugars attached to C-5 include 3-keto-4,6-dideoxy- β -D-hexopyranose **179** (CP-63693⁶⁴⁰), β -D-chalcose (**181b**; lankamycins⁶⁵⁹ and kujimycins⁶⁵⁴) and β -D-mycaminose (**185**; narbolide,⁶⁶³ via biotransformation). C-6 substitution is restricted to α -L-megosamine (**45**; megalomycin⁶⁵⁶ and SF2748⁶⁶⁴) 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 bioconversion⁶⁶⁷ 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 primarily from actinomycetes. This group is further divided into two subgroups based upon macrolactone ring architecture of as depicted in figure 12A, 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-chalchose, **181b**, or 2-propionyl **181c**) are also observed as exemplified by chalcomycins,⁶⁸² GERI-155⁶⁸³ 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 aldgamycins⁶⁸⁶⁻⁶⁹¹ 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**, figure 12A)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 mycinamycins⁶⁷⁸ and GERI-155⁶⁸³); 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 mycinamycin⁶⁷⁷ and tylosin analogs⁷¹²); β -D-boivinose and β -D-digitoxose variants (**187a/b** and **131a/b**, respectively in engineered tylosins⁷⁰³) 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 (Figure 12A). 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**, Figure 12 A).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 elucidation⁷²⁴ 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 epothilones 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

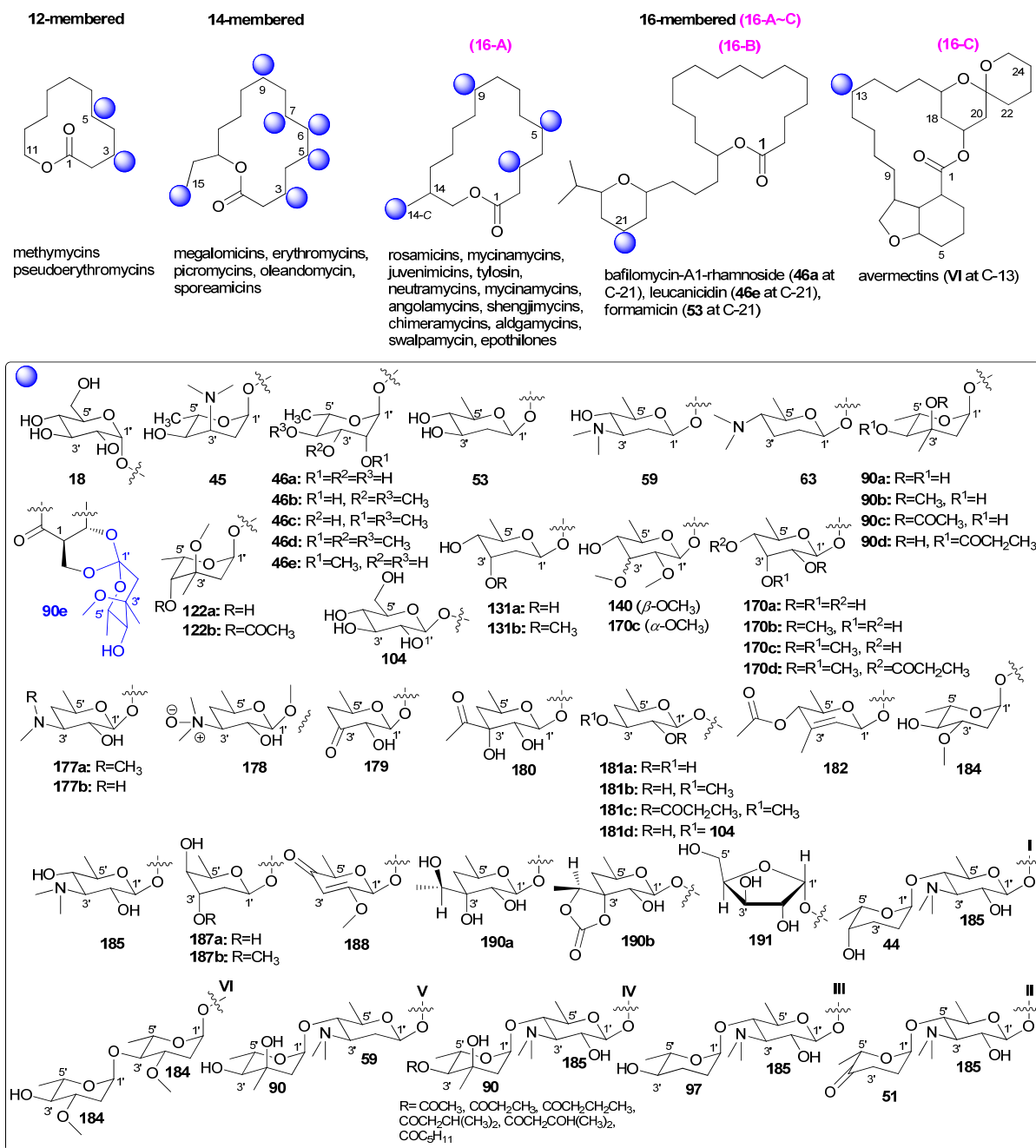


Figure 12A. 12-, 14- and 16-Membered macrolactones and associated sugars

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**) (Figure 12B, **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 *Nocardioopsis*, *Saccharotrix*, and *Streptomyces* (Figure 12B). Glycosylation regiospecificity is variant across this series with C-9-*O*-glycosides represented by ammodicin (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 ammodicin [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 (Figure 12B).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 archazolids⁷⁶³ and maduralides⁷⁶⁴ represent 24-membered glycosylated macrolactones from *Bacillus*, *Cystobacter*, *Archangium* and *Maduramycetes* (Figure 12B). 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-13/13a-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-olivaside (**53e**), the latter of which is modified as depicted (Figure 12B).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 5 α -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.

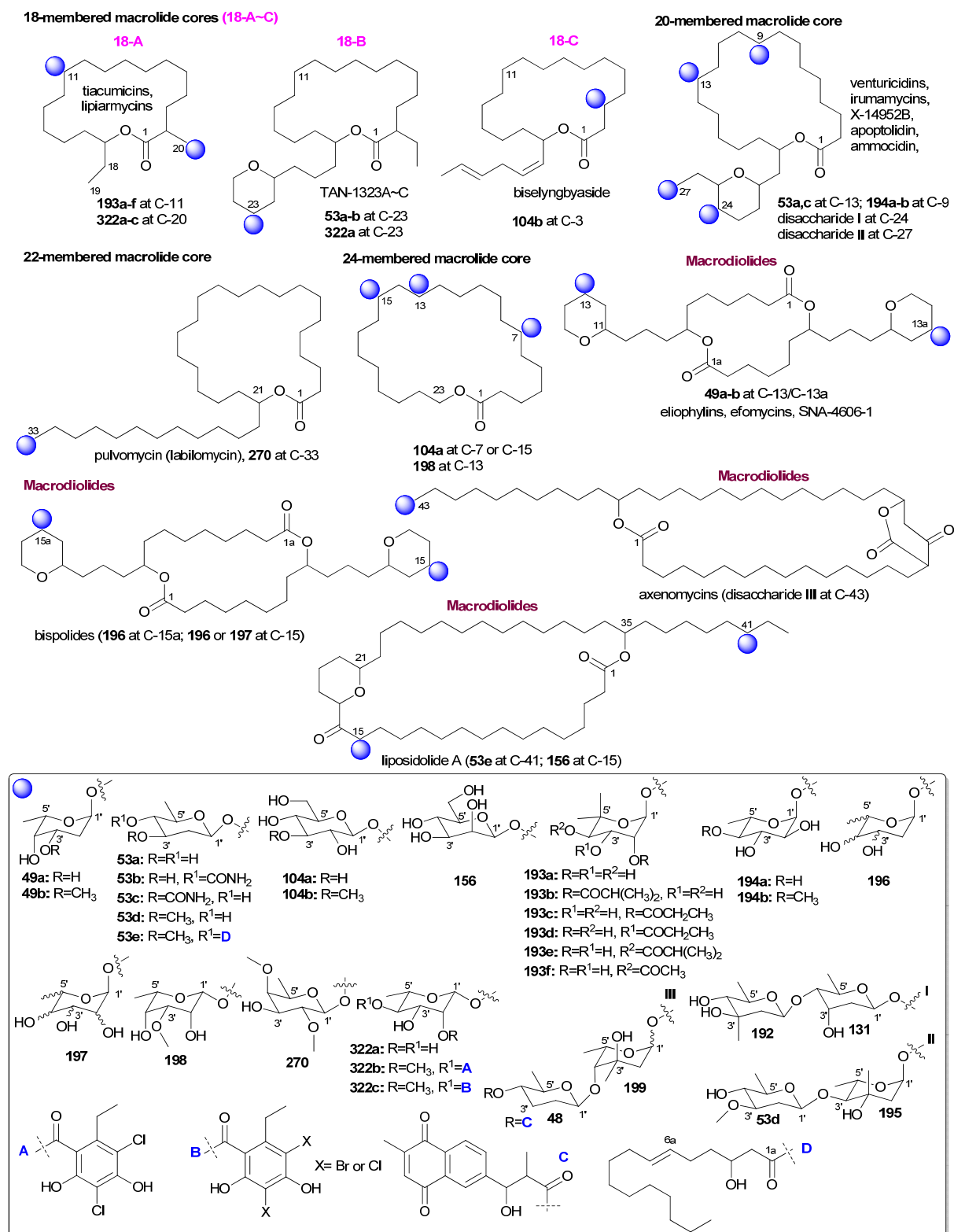


Figure 12B. 18-, 20-, 22-, 24-Membered macrolactones and macrodiolides and associated sugars

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* (Figure 12C). 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 brasilinolide 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*-disaccharide comprised of β -D-quinovose and 3-amino-3,6-dideoxy- β -D-glucose. The 32-membered macrolides notonesomycin⁷⁷⁵ and A-77951⁷⁷⁶ 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 macrocyclic 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, moderately 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 sporavidin aminosugar abolished antimicrobial activity.⁷⁷⁴

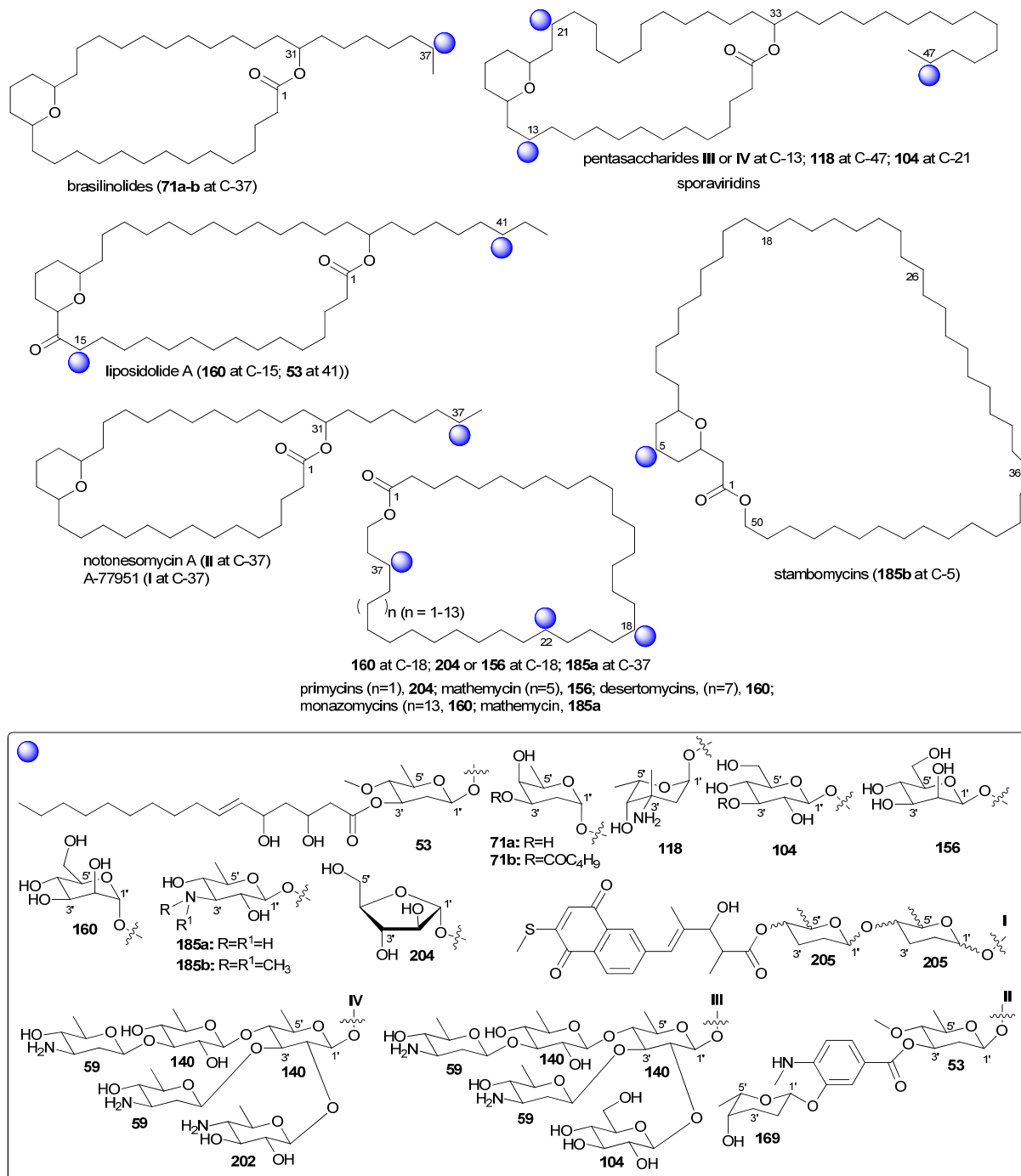


Figure 12C. Super macrolactone (ring size 32-48) aglycons and associated sugars

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 chivosazoles⁷⁸⁴⁻⁷⁸⁶ aglycons can be further distinguished by the presence or lack of an endocyclic pyran ring (core structures **A** and **B**, respectively; Figure 12D).

The aminosugar β -D-mycosamine (**206**) is the predominate *O*-glycoside among polyene macrolides as exemplified by amphotericins,⁷⁸⁷ candidins,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 (Figure 12D, 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 (Figure 12D). 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**) (Figure 12D, 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*, *Amicولاتopsis*, *Actinomadura*, *Maduromyces*, *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 regioselectivity as summarized in Figure 12D.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, vicienistatin, and incedine. 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 *Amicولاتopsis*.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**) (Figure 12D).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-A⁸⁰⁷ 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 vicienistatins 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'-methylamino- 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}

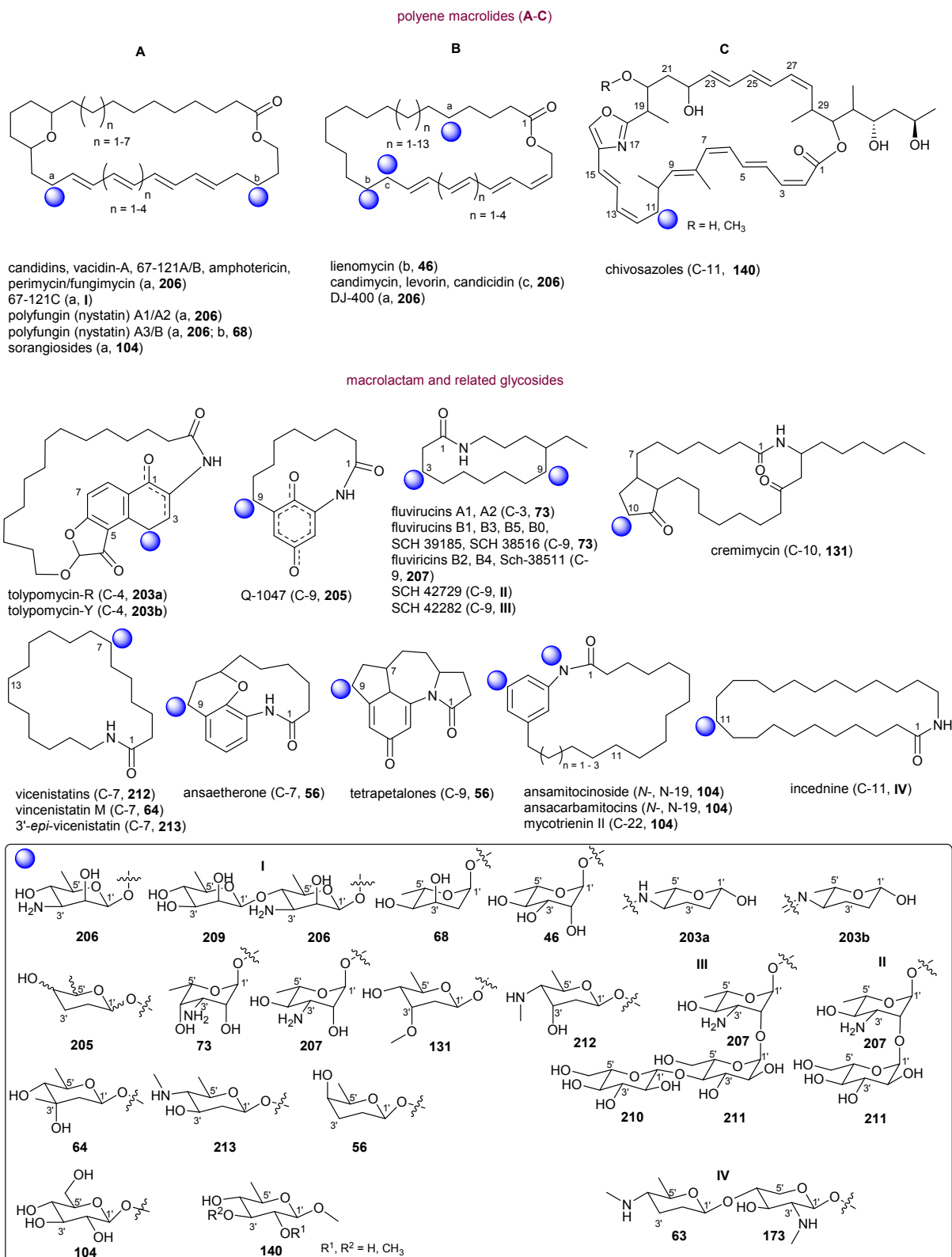


Figure 12D. Polyene and macrolactam aglycons and associated sugars

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 spiro-tetronate *O*-glycosides have been reported (Figure 12E) 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-033⁸¹⁶), 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** containing 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 (Figure 12E, 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 A³⁸⁹) 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**, tetrocarcins⁸²¹ 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 (Figure 12E, **VII**).⁸²⁸

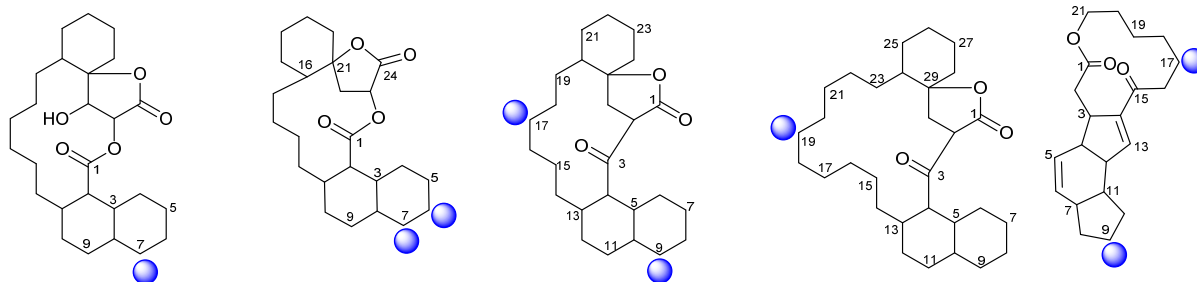
C-17 and C-19 glycosylation is less common. Examples of C-17 glycosylation include the unique nitro sugar β -D-kijanose (also known as β -D-tetronitrose, **214**; tetrocarcins,^{821, 822} lobophorins B,^{824, 825} kijanimicin,^{826, 827} arisostatin A⁸²³), the corresponding amino analog **218** (AC6H, lobophorin A,^{824, 825}

arisostatin B⁸²³), and variations of 3',4'-diamino-2',3',4',6'-tetra-deoxy- 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**, Figure 12E) 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**) (Figure 12E). Spinosyn variation is based, in part, upon differential methylation of the corresponding glycosides and SAR studies revealed both sugars to contribute to bioactivity.⁸³⁵



chlorothricin (C-7, I, $R_1 = \text{i}$, $R_2 = \text{H}$)
 deschlorothricin (C-7, I, $R_1 = \text{ii}$, $R_2 = \text{H}$)
 hydroxychlorothricin, K_{818} (C-7, II, $R_1 = \text{i}$, $R_2 = \text{H}$)
 MC-031 (C-7, I, $R_1 = \text{iii}$, $R_2 = \text{H}$)
 MC-032 (C-7, II, $R_1 = \text{iii}$, $R_2 = \text{H}$)
 MC-033 (C-7, I, $R_1 = \text{H}$, $R_2 = \text{iii}$)
 MC-034 (C-7, II, $R_1 = \text{H}$, $R_2 = \text{iii}$)

PA-46101 A (C-7, III, $R = \text{iv}$)
 PA-46101 B (C-7, II, $R = \text{iv}$; C-6, **108**)

tetrocarcins, AC6H (C-9, IV, V, VI, VII, or **68**; C-17, **214** or **218**)
 tetrocarkin F1 (C-17, **214**)
 lobophorin A (C-9, VIII; C-17, **218**)
 lobophorin B (C-9, VIII; C-17, **214**)
 arisostatsins (C-9, IV; C-17, **214** or **218**)
 kijanimicin (C-9, IX; C-17, **214**)
 MM 46115 (C-17, **219**; $R = \text{iii}$)
 BE-45722, decatromicins, BMY-42448, pyrrolosporin A (C-9, **213**)

versipelostatins A (C-19, X or XI)
 versipelostatins B (C-19, XII)
 versipelostatins C (C-19, XIV)
 versipelostatins D (C-19, XIII)
 versipelostatins E (C-19, XV)
 versipelostatins F (C-19, XVI)

spinosyns (C-9, **46**; C-17, **63**)

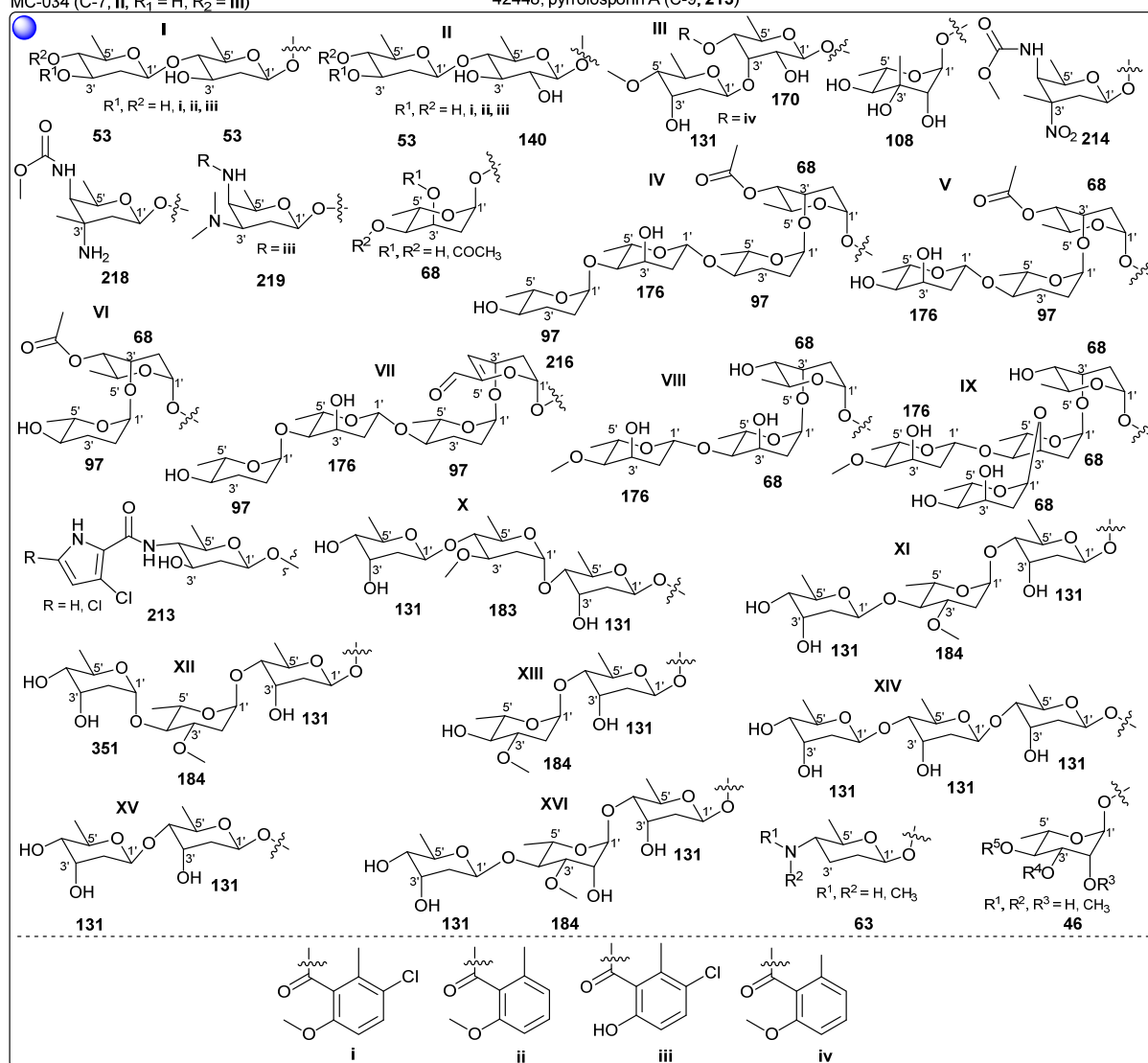


Figure 12E. Spirotetrone aglycons and spinosyn aglycons and associated sugars

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 *Corynebacterium*-infected *Lolium*.⁸³⁷⁻⁸⁴⁰ This group includes 23 metabolites and structural signatures include a uracil or dihydrouracil (Figure 13A), an amide-linked fatty acid, a dialdose sugar attached to the N-1 of the uracil moiety, 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**) (Figure 13B).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 (Figure 13B). 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 (epicapreomycin)-urea-valine moiety (Figure 13B, 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 (Figure 13B). Three related epicapreomycin-containing analogs [AA-896-A6, C5 and D4 (Figure 13B, 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 (Figure 13B, 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**, Figure 13B). 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) (Figure 13B, X = **iii**) or a thiazepanone moiety (M-2) (Figure 13B, 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 (Figure 13B, 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 (Figure 13B, 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 methylglutaryl group (Figure 13B, 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) (Figure 13A) 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 D₁ and D₂ which carry a 3'-amino-3',4'-dideoxy- β -D-glucuronic acid-(1 \rightarrow 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 (Figure 13B) where this hexuronic acid is typically further modified in most nikkomycins by a rare amino acid hydroxypyridylhomothreonine 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** (Figure 13B).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}

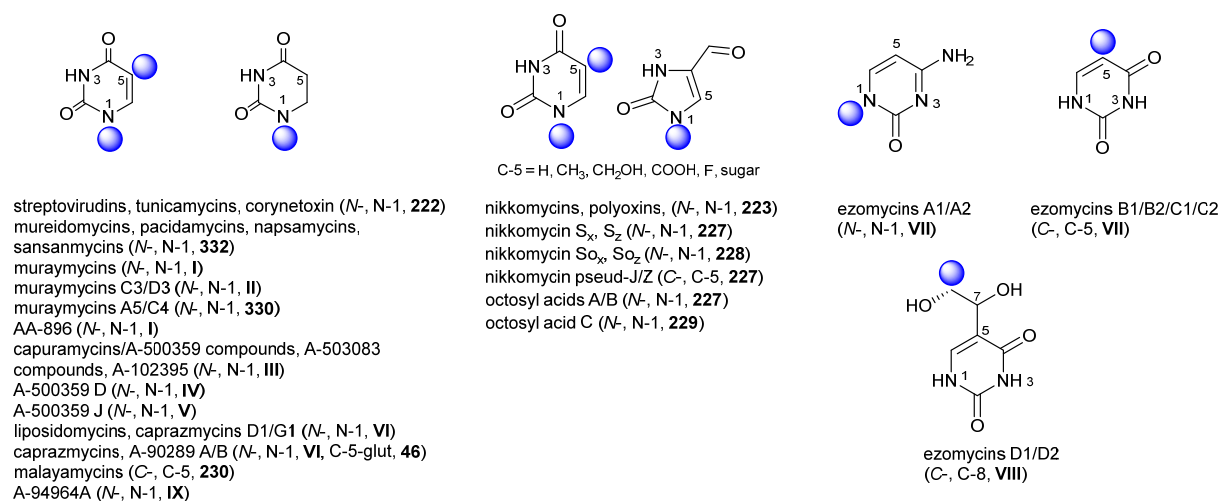


Figure 13A. Uracil-derived aglycons

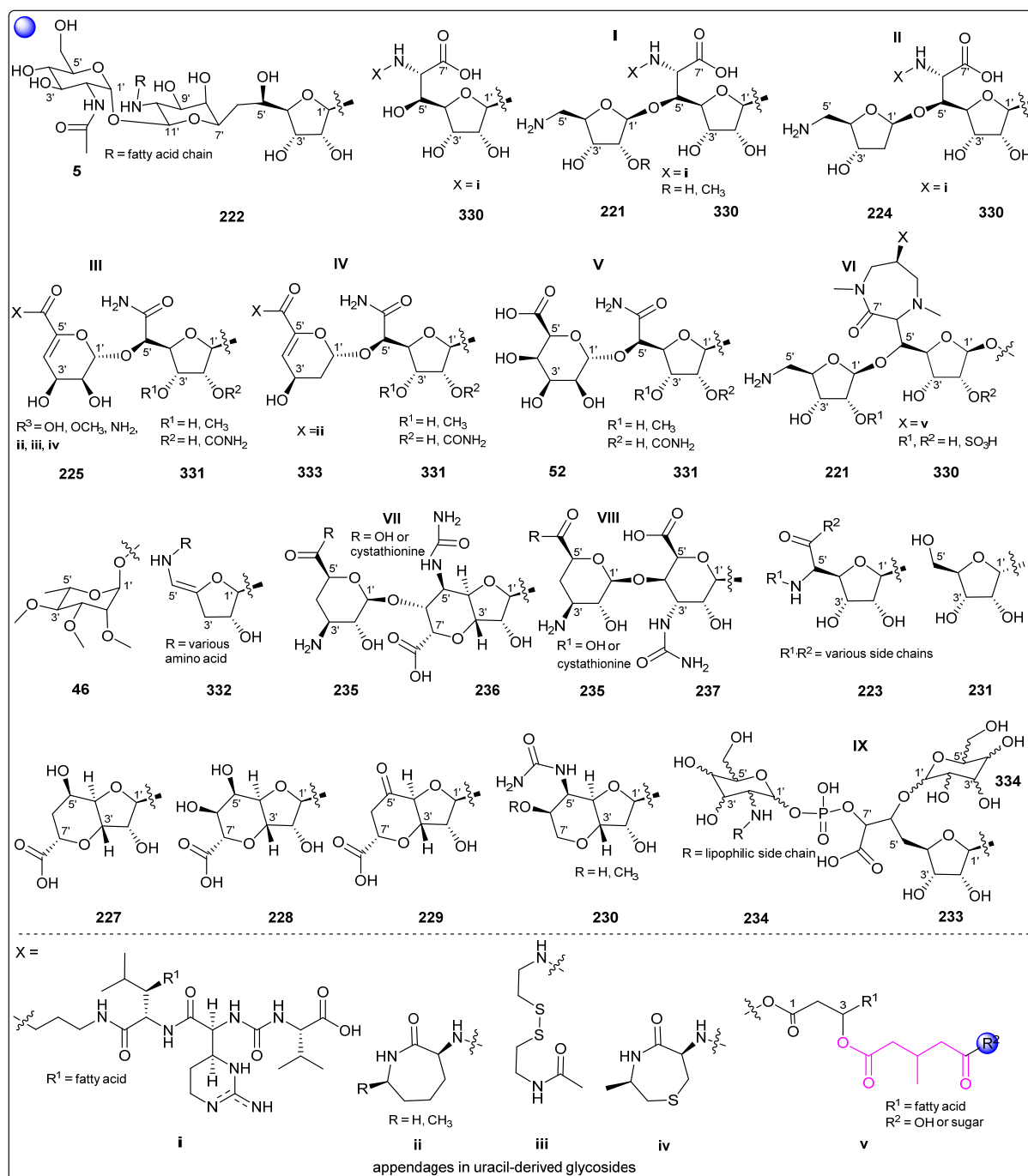


Figure 13B. Sugars associated with uracil-derived aglycons. Pink fragment is absent in some derivatives.

13.1.2 Cytosine-Derived Nucleosides

The first main group in this subclass includes amicitins, 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-NH₂. The disaccharide is comprised of either β -D-amicetose (**48**) or β -D-olivose (**53**) attached α -(1' \rightarrow 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 poliovirus⁹⁰¹ cytosaminomycins have been noted for anticoccidial activity.^{898, 902}

Mildiomyces 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**) (Figure 13C).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 the antifungal blasticidins from *Streptomyces*. Cytosylglucuronic acid bearing a *N*1-2'-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 anthelmicycin, from *Streptomyces* is a cytosyl-*N*-1- β -D-dissaccharide (**III**), the latter of which is comprised of 3'-amino-3'-deoxy- β -D-glucose (kanosamine, **250**) linked β -(1' \rightarrow 6') to an unusual 4'-aminoundecose (hikosamine, **256**) (Figure 13C).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**). Albomyces from *Streptomyces* are siderophore antibiotics similar to other sideropmycins (section 15.4) are composed of iron chelating portion in addition to a 6'-amino-6'-deoxy-4'-thio-heptofuranose (**315**) uronic acid moiety (Figure 13C).^{924, 925} Dapiramycins A and B from

Micromonospora are *N*-glycosidic pyrrolopyrimidines bearing 6'-deoxy- α -D-glucose (**215**) or β -D-glucose (**104**), respectively, each capped (β 1 \rightarrow 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**.

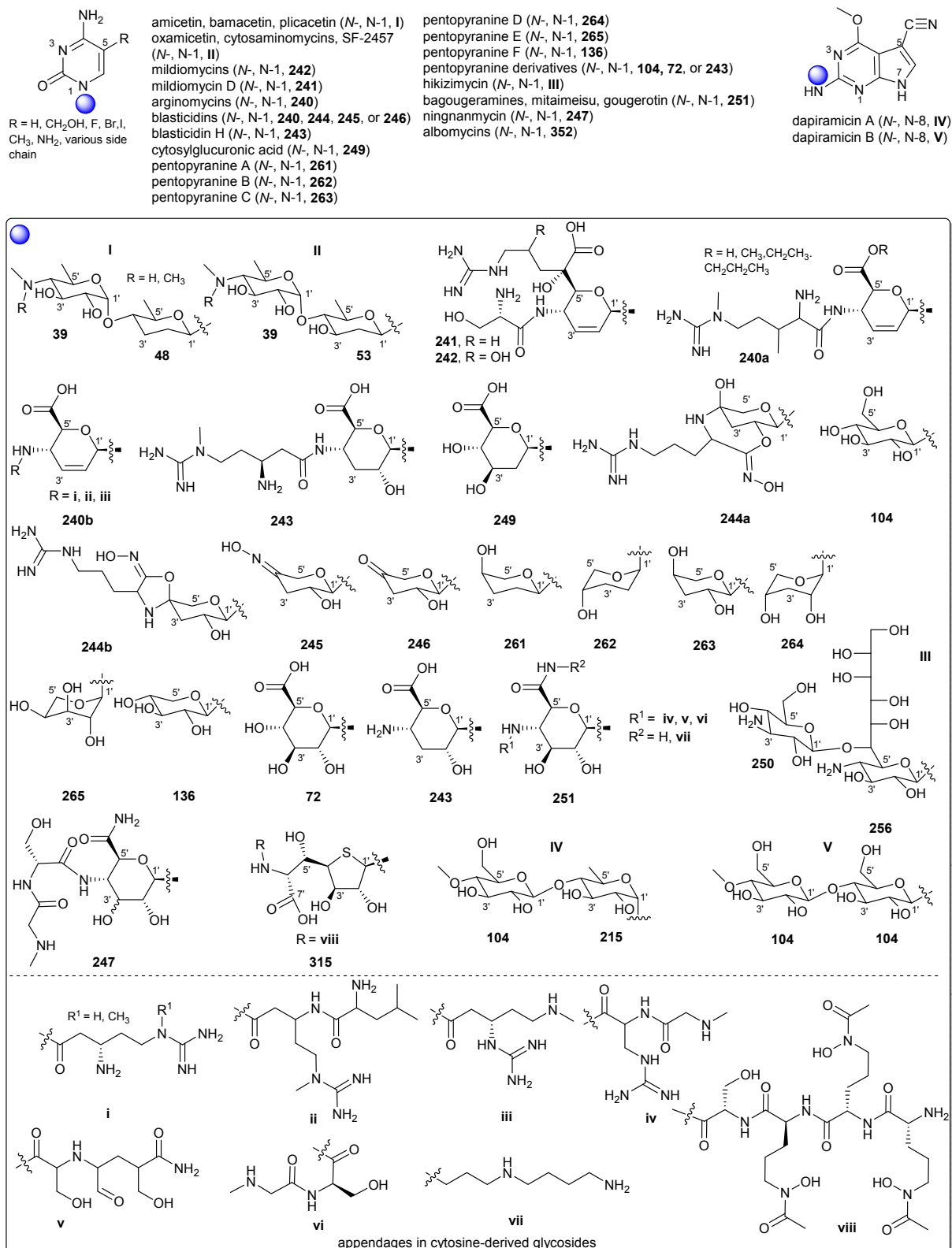


Figure 13C. Cytosine-derived aglycons and associated sugars

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-aminopentose 3'-amino-3'-deoxy- α -L-ribose (**253**) was found in puromycin⁹²⁸ and A-201-A, C, D, and E,^{929, 930} from *Streptomyces* (Figure 13D) 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 antileishmanial 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 (Figure 13D). 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 (Figure 13D). 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 (Figure 13D).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 (Figure 13D, 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'-modified 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 (Figure 13D 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** (Figure 13D).^{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) (Figure 13D).

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** (Figure 13D).

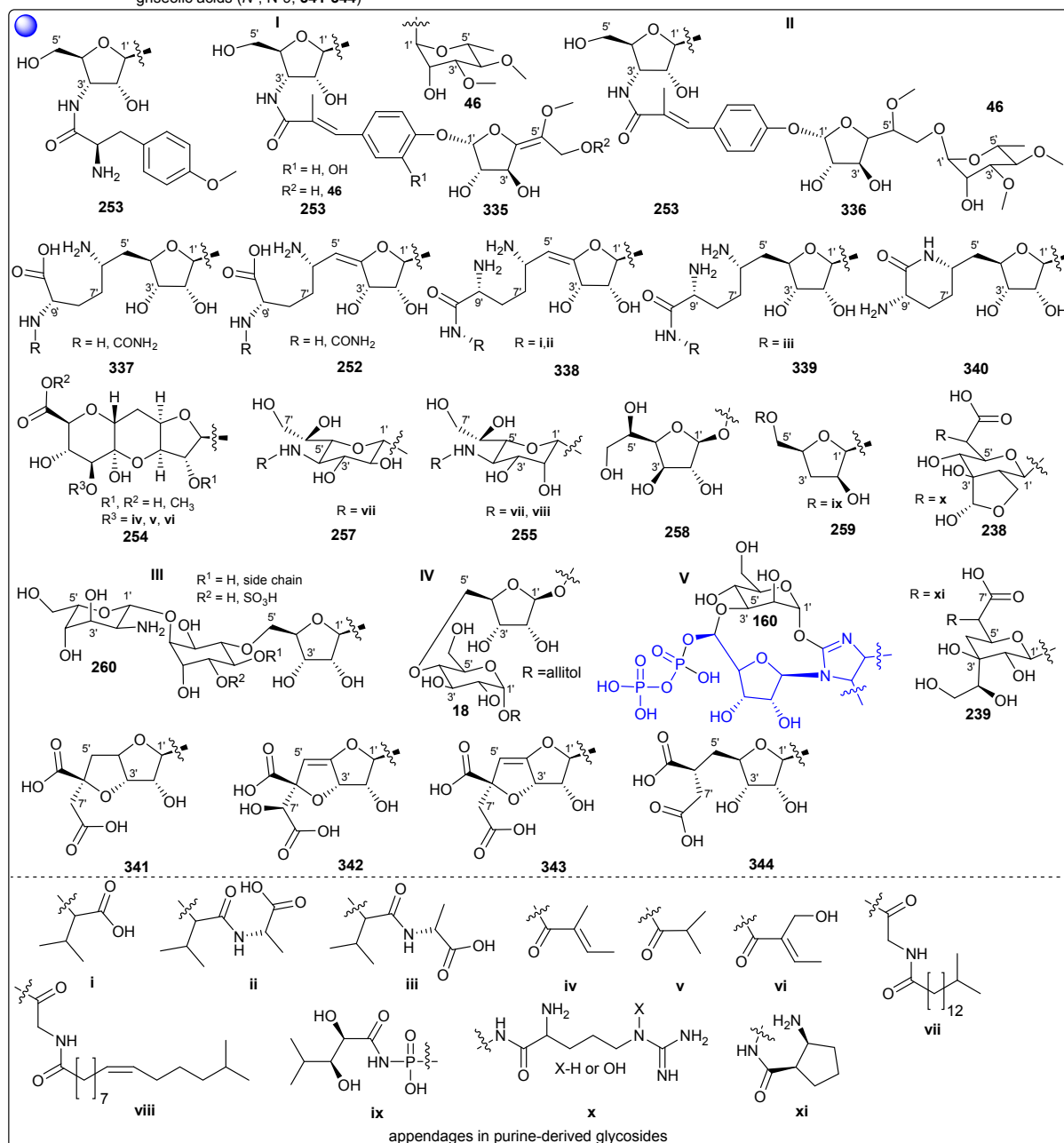
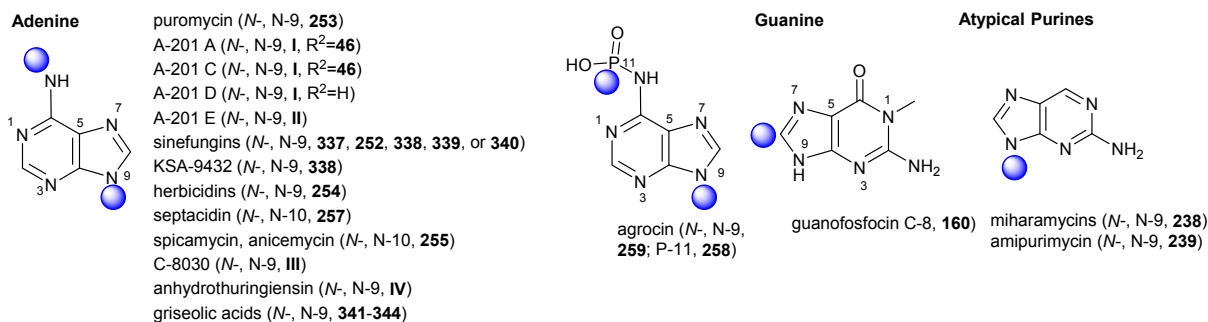


Figure 13D. Purine-derived aglycons and associated sugars

14. Orthoesters 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 chloroisoverninic C-4-heptasaccharide ester.⁹⁵⁸⁻⁹⁶⁰ Additional avilamycin-derived gavibamycins were generated through pathway engineering.⁹⁶¹⁻⁹⁶⁴ The heptasaccharide moiety **I** of avilamycin A (Figure 14A), 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 (Figure 14A).

The closely related everninomicins⁹⁶⁵⁻⁹⁶⁸ 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) (Figure 14A) 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 activity⁹⁷⁰ while removal of the nitro sugar has no major effect.^{958, 974}

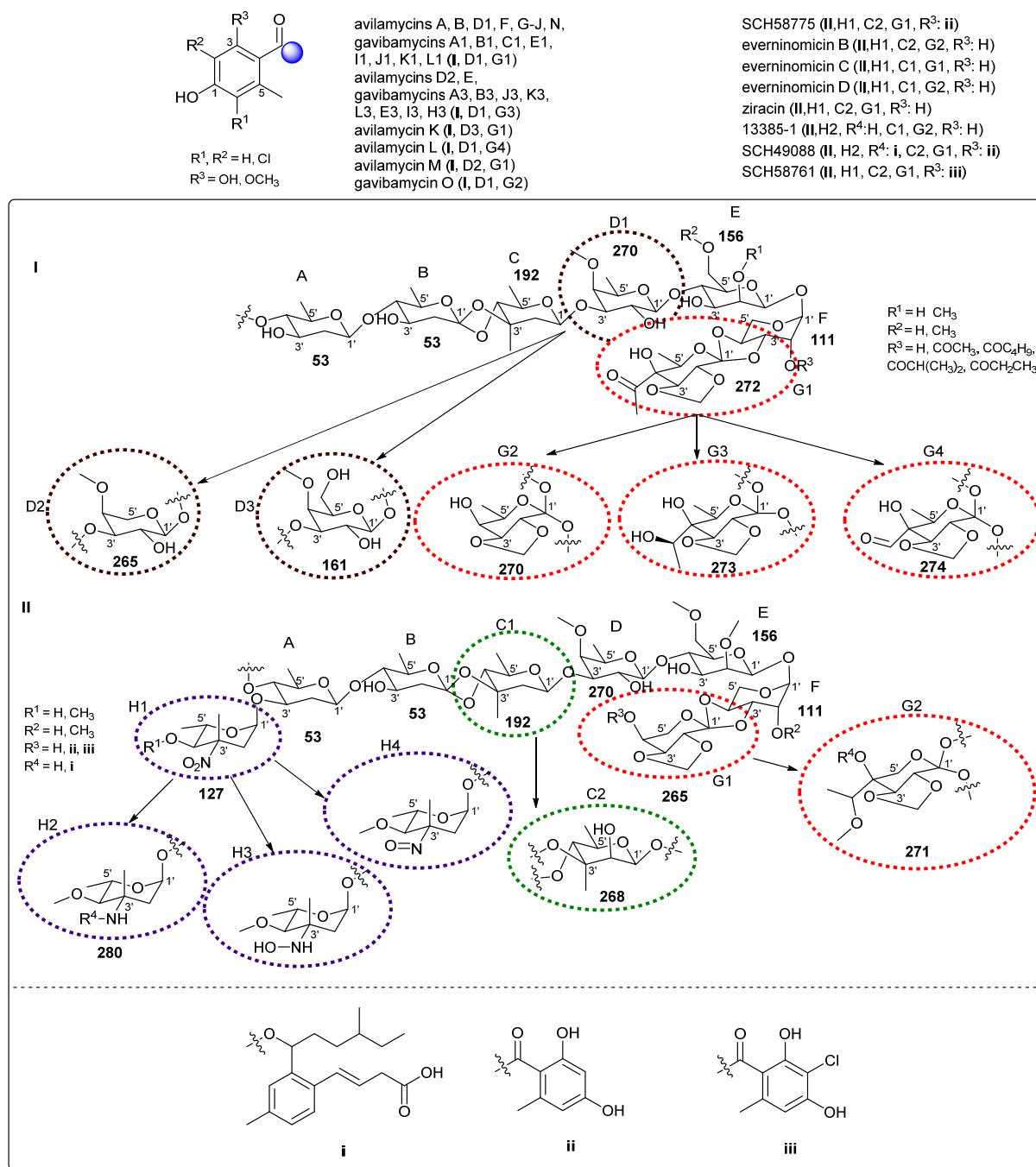


Figure 14A. Orsellinic acid aglycons and associated sugars

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-C⁹⁸⁰ from different bacteria including *Streptomyces*,

Streptovercillium, and *Saccaropolyspora* (Figure 14B). 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** (Figure 14B). It is worth noting that analogs which lack destomic acid (and thus, the orthoester linkage) are inactive.

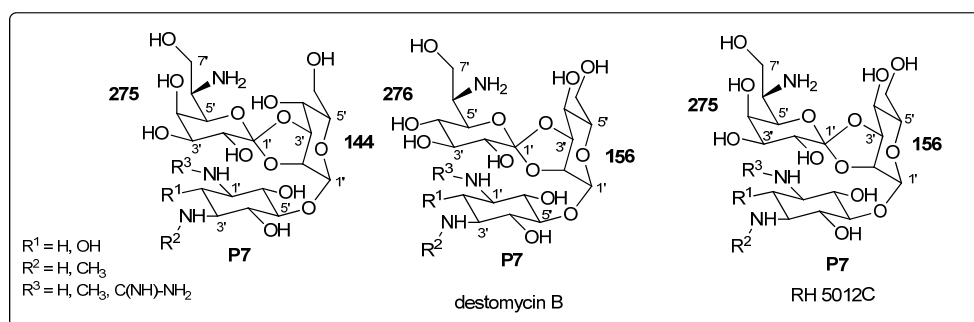


Figure 14B. Sugars associated with orthoester aminocyclitols

15. Peptides

Glycosylated peptides represent 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 (Figure 15A). 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 (Figure 15A). 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 has been demonstrated to target tumor cells possibly by a specific ATP-dependent uptake mechanism.^{1002, 1003}

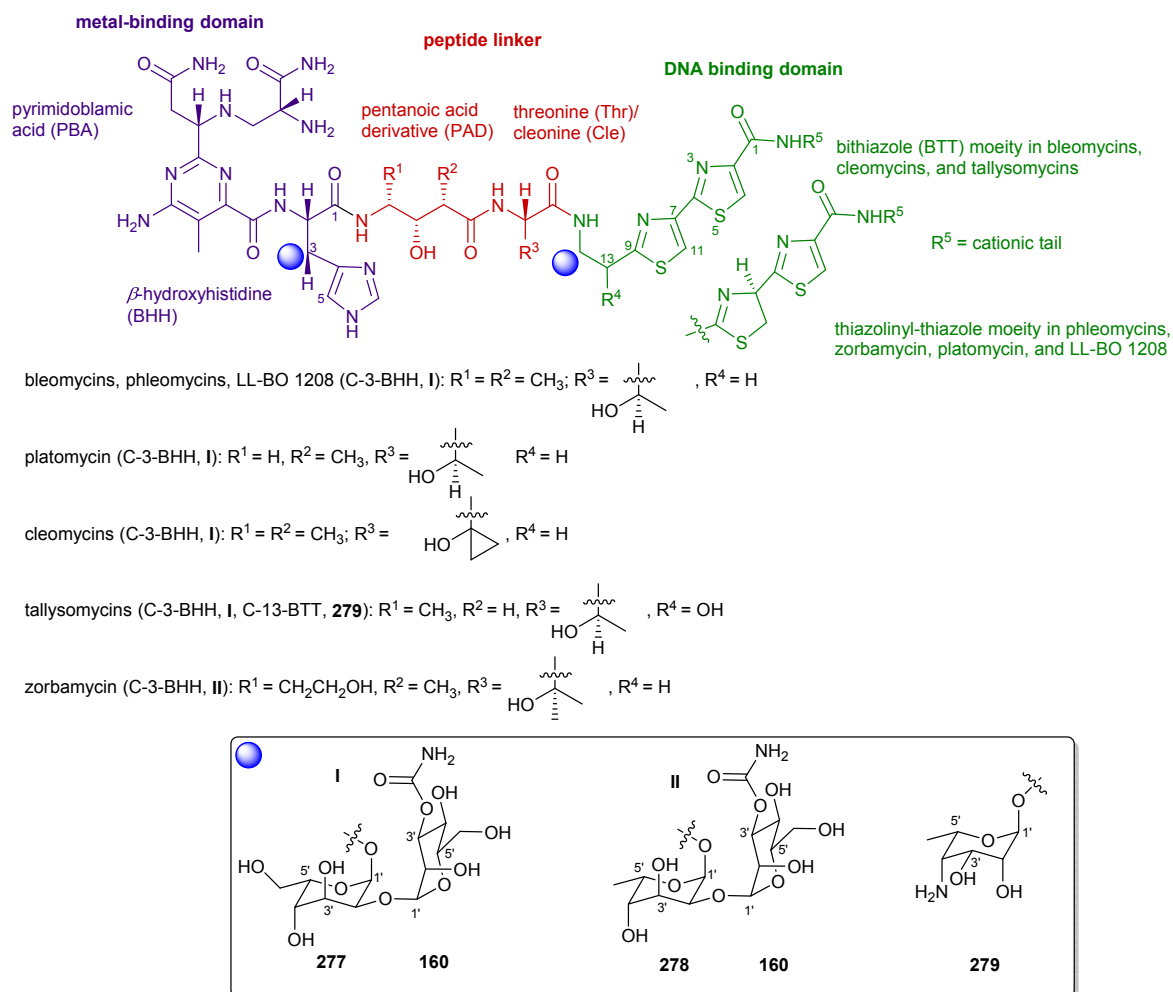


Figure 15A. Bleomycin aglycons and associated sugars. Platomycin structure is based on partial structure reported.

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 (Figure 15B). 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 chloro-peptins,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 subclass. 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, Figure 15B). 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) (Figure 15C).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 49721¹⁰²⁵); α -L-olivose (**184**, orienticin B);^{1026, 1027} or α -L-vancosamine (**118**, MM 49727, A-42867) (Figure 15C).¹⁰²⁴ OA-7653^{1028, 1029} from *S. hygrosopicusis* 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 actinoidins¹⁰³⁸⁻¹⁰⁴¹ 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 \rightarrow 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) (Figure 15C). 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 employed 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**), was observed for residue 2 tyrosine- β -hydroxyl *O*-glycosylation (avoparcins, galacardins, chloropolysporins, helvecardin A) (Figure 15C). An α -D-mannose (**160**) or β -D-mannose (**156**) were observed at residue 7 phenolic *O*-glycosylation (actinoidins, MM 47766, MM 47767, MM 55260). Finally, residue 3 phenolic *O*-glycosides were 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 resistance¹⁰⁴² 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-68,597¹⁰⁵² 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 was 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 was observed [β -D-mannose, α -**160**, β -**156**] as residue 3 (actaplanins) and/or residue 7 (actaplanins, ristocetin A) phenolic hydroxyl *O*-glycosyl substituents. Wider variation was 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 was either D-mannose (α -**160**, β -**156**) or α -L-vancosamine (**118**, UK-68,597). 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) (Figure 15C). 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 was also 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 (Figure 15C). 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, parvodocins,¹⁰⁵⁹⁻¹⁰⁶¹ and MM 49728, MM 55266, and MM 55268¹⁰⁶² 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, parvodocins, 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) (Figure 15C). It is noteworthy that teicoplanins (approved as 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 (DalvanceTM). 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 was 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

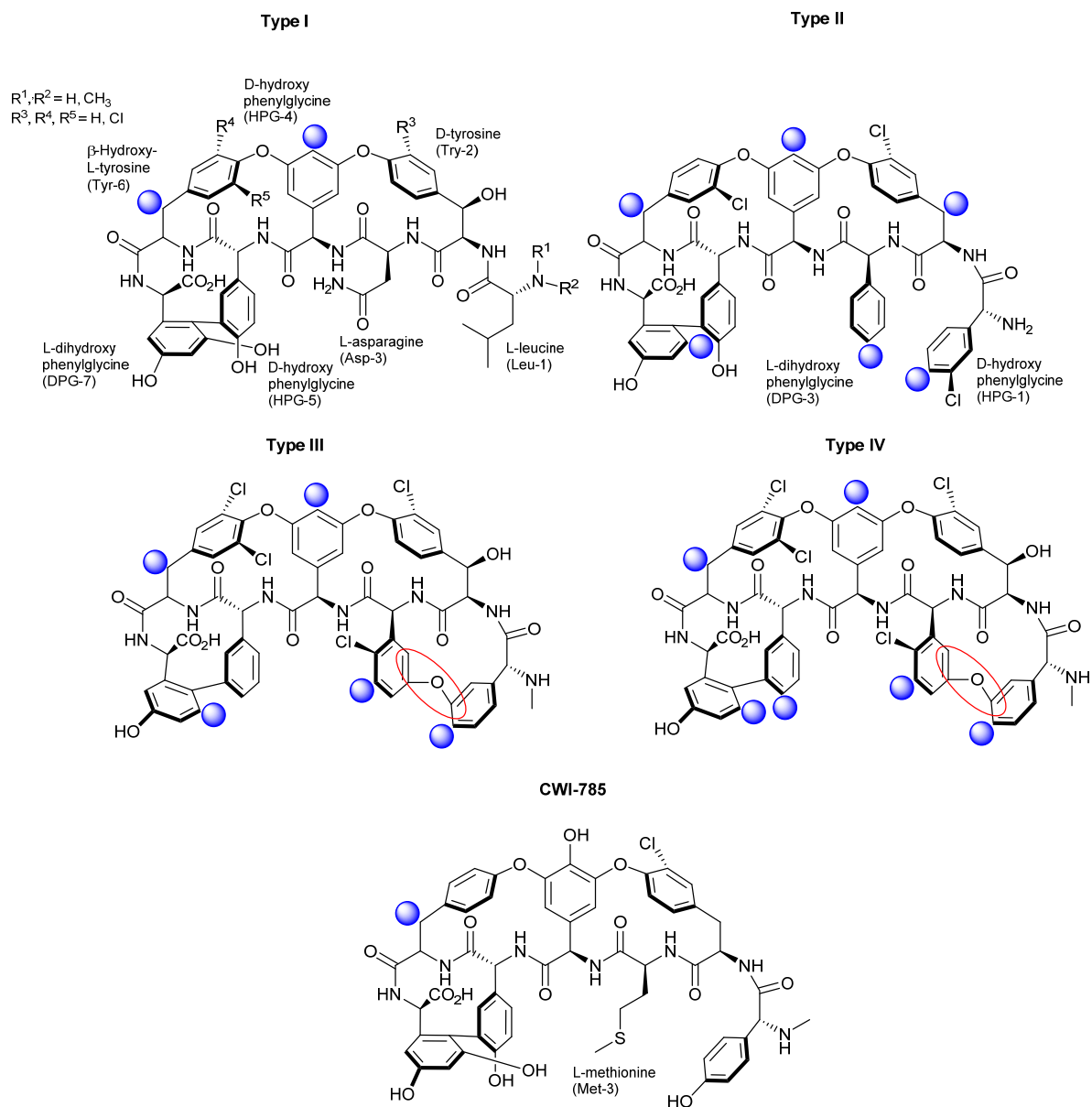


Figure 15B. Aglycons of the five types of vancomycin. The ether bridge in types III and IV is highlighted in red. Locations of attachment to most sugars in CWI-785 series is not determined.

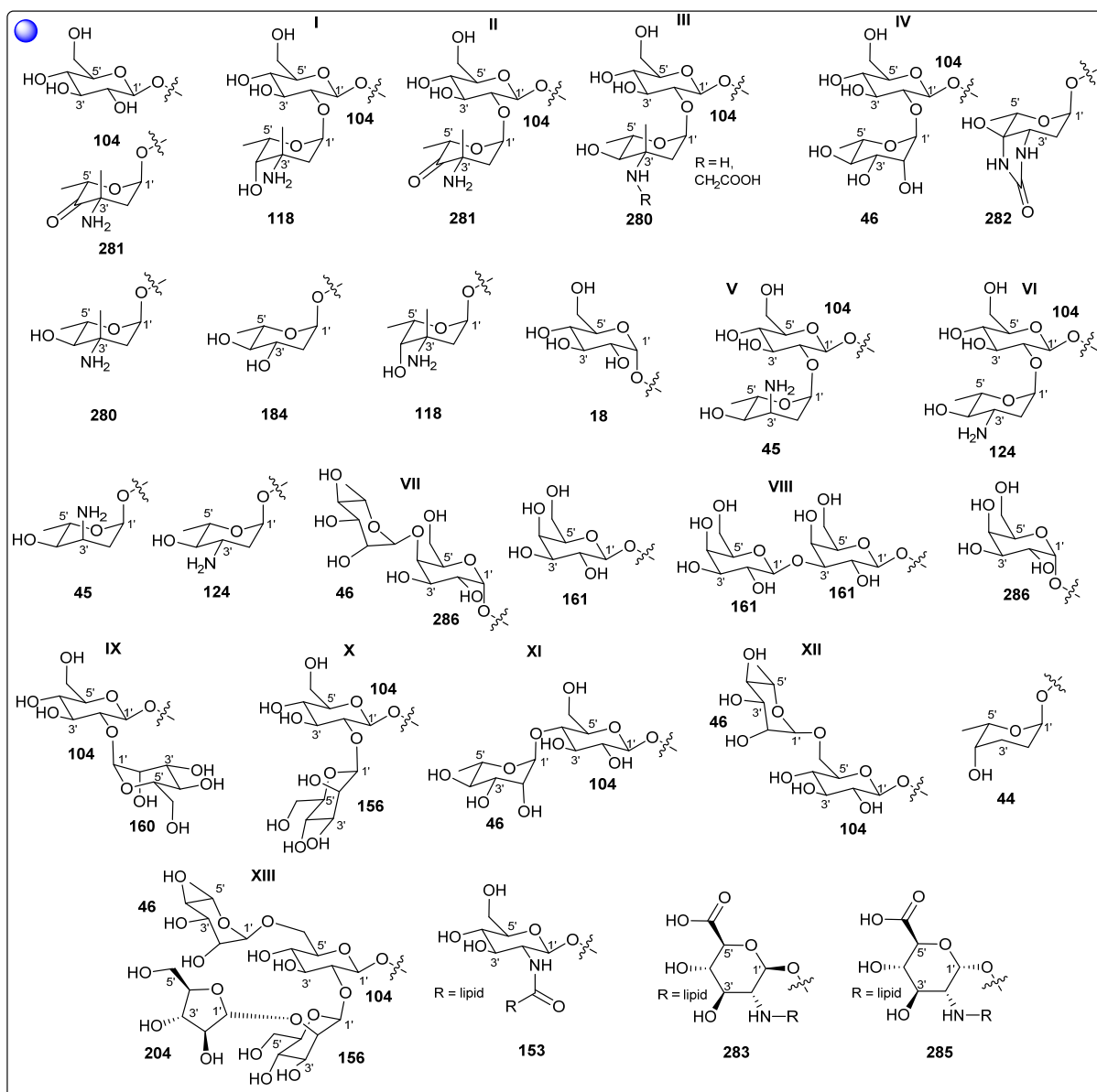


Figure 15C. Sugars associated with vancomycins.

15.3. Mannopectimycins

Mannopectimycins 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) (Figure 15D).¹⁰⁶⁴ All members are *N*-glycosylated with α -D-mannose (**160**) at the *N*-5-terminus of HyEnd-5. In addition, all members except mannopectimycin 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 (Figure 15D, 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 (Figure 15D). 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 hydroxyimino sugar (**289**) (Figure 15D). 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).

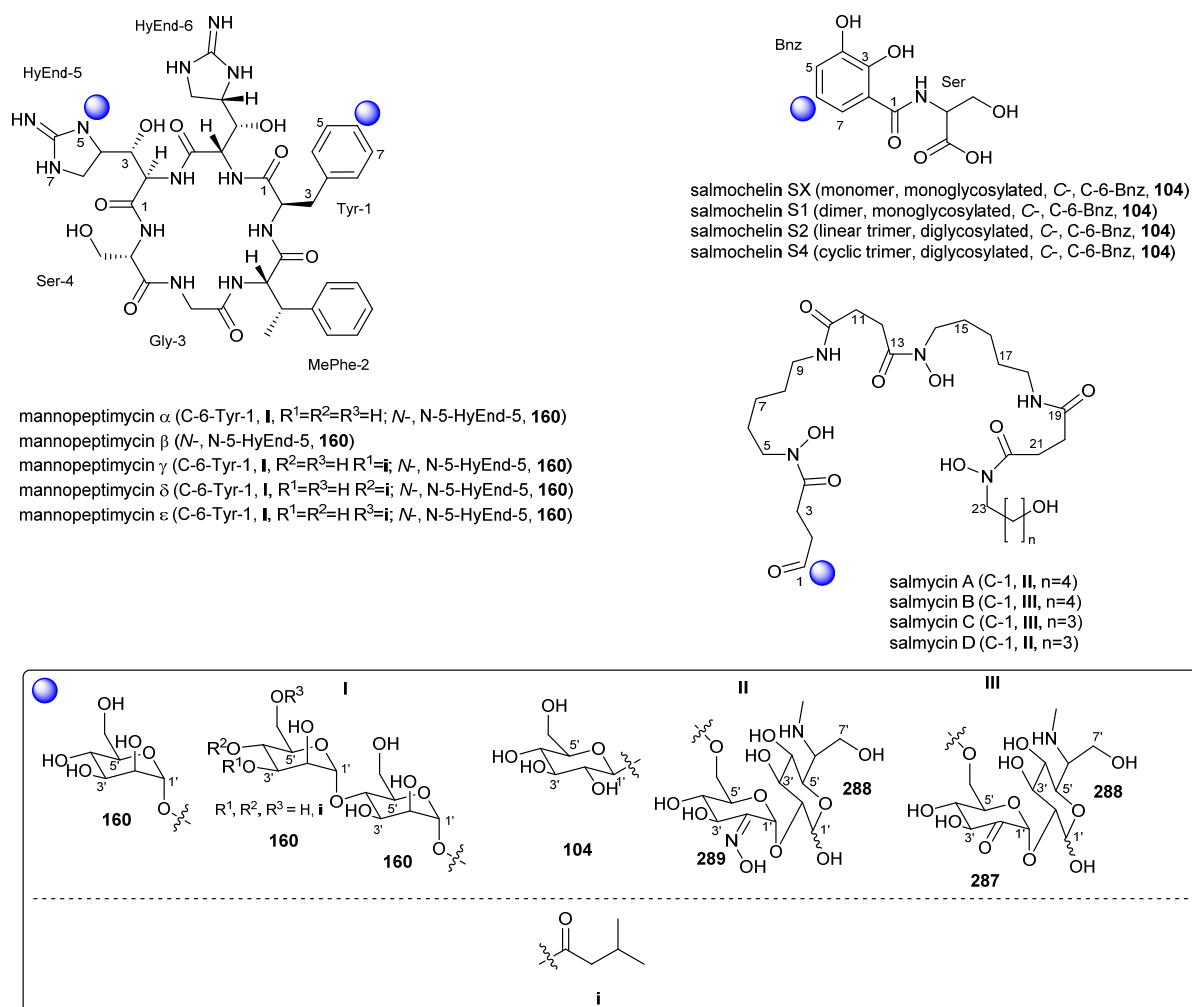


Figure 15D. Mannopeptimycin, salmochelin, and salmomycin aglycons and associated sugars.

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 (Figure 15E). The anomeric stereochemistry of the central sugar, 6'-amino-6',8'-dideoxy-1'-thio-D-erythro- α -D-

galactose (methylthiolincosamide, **290**) (Figure 15E) 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 feeding¹⁰⁷⁷⁻¹⁰⁸¹ 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} philipimycins¹⁰⁹⁰ and S-54832-A series¹⁰⁹¹) 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) (Figure 15E). 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 (Figure 15E). 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**) (Figure 15E). 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.

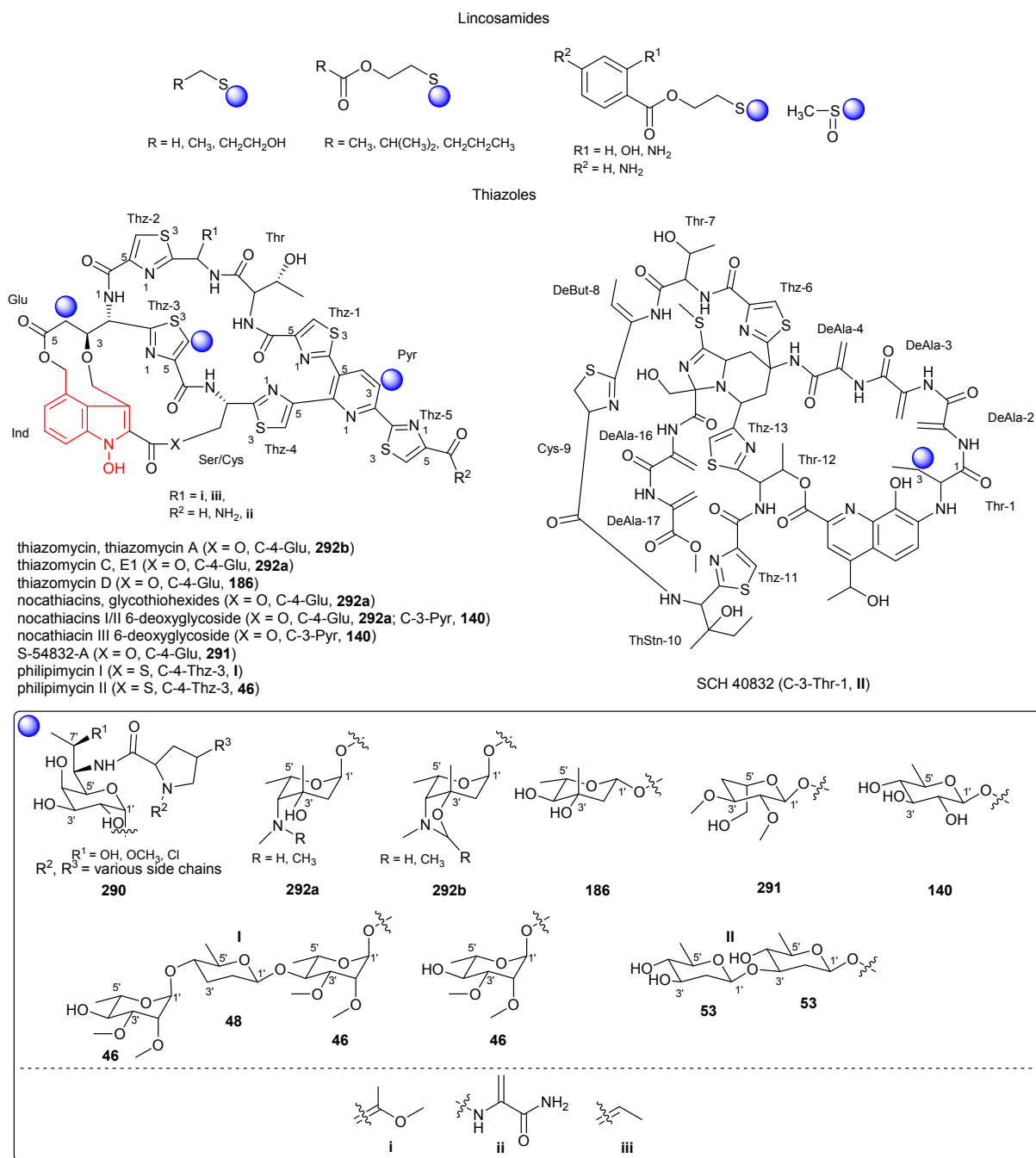


Figure 15E. Lincosamide and thiazolyl peptide sglycons and associated sugars. Indole moiety in red is absent or replaced by quinoline in different members.

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} occidiofungins¹⁰⁹⁵ and burkholdine¹⁰⁹⁶ from *Burkholderia*, cepacidines from *Pseudomonas*,^{1097, 1098} herbicolins from *Erwinia*^{1099, 1100} and W-10 β from *Aeromonas*¹¹⁰¹), the ramoplanins from *Actinoplanes* stand out as agents recently approved by the FDA to treat *C. difficile* (Figure 15F).^{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**) (Figure 15F).^{1093, 1094} Both the mono and diglycosylated analogs of hassallidins presented comparable antifungal activity against *Aspergillus* and *Candida*. Finally, W-10 β isolated from *Aeromonas* is a threonine residue (Thr-1) C-3-*O*- β -D-glucoside (**104**) with antifungal activity (Figure 15F).¹¹⁰¹

The octapeptides occidiofungins¹⁰⁹⁵ and burkholdine¹⁰⁹⁶ 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 (Figure 15F) 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 A₁ and A₂ (Figure 15F), 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}

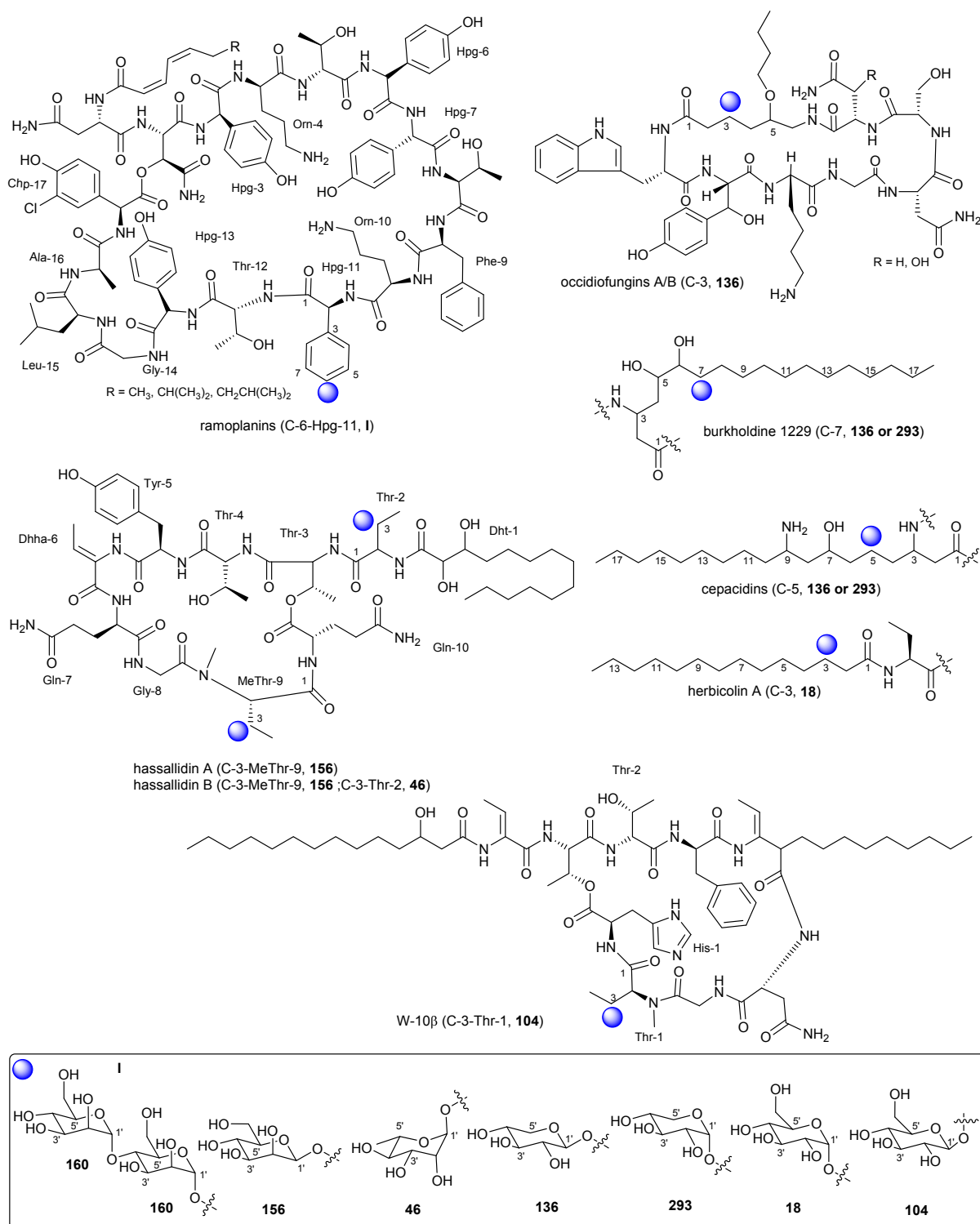


Figure 15F. Lipoglycopeptide aglycons and associated sugars. Only partial structures of burkholdine, cepacidins, and herbicolin are shown.

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-aminopropanamide (coumamidines from *Saccharopolyspora*)^{846, 1105} conjugated to a cinnamic acid moiety, the latter of which is glycosylated at C-7 with unique di- or trisaccharides (Figure 15G). 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**) (Figure 15G). 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-123 α and LL-BM-782 series from *Nocardia* (Figure 15G). They are Gram negative bacterial growth inhibitors that contain a pseudotri- and pseudodi-saccharide, respectively (**V** and **VI**).^{1106, 1107} The pseudotrisaccharide **V** in LL-BM-123 α 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 conjugate to the aglycon via a modified myoinosamine (**P12**). Both LL-BM-123 α 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 (Figure

15G). 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**) (Figure 15G). Glycosylation is notably rare among naturally occurring β -lactams and these unique metabolites displayed antibacterial activity against *Pseudomonas* and *Proteus* species where glycosylation contributed to reduced potency. Finally, the antifungals theopalauamide and theonegramide are histidine (His) N-3 *N*-glycosides of β -D-galactose (**161**) and a β -D-arabinose (**294**), respectively.¹¹¹⁰⁻¹¹¹²

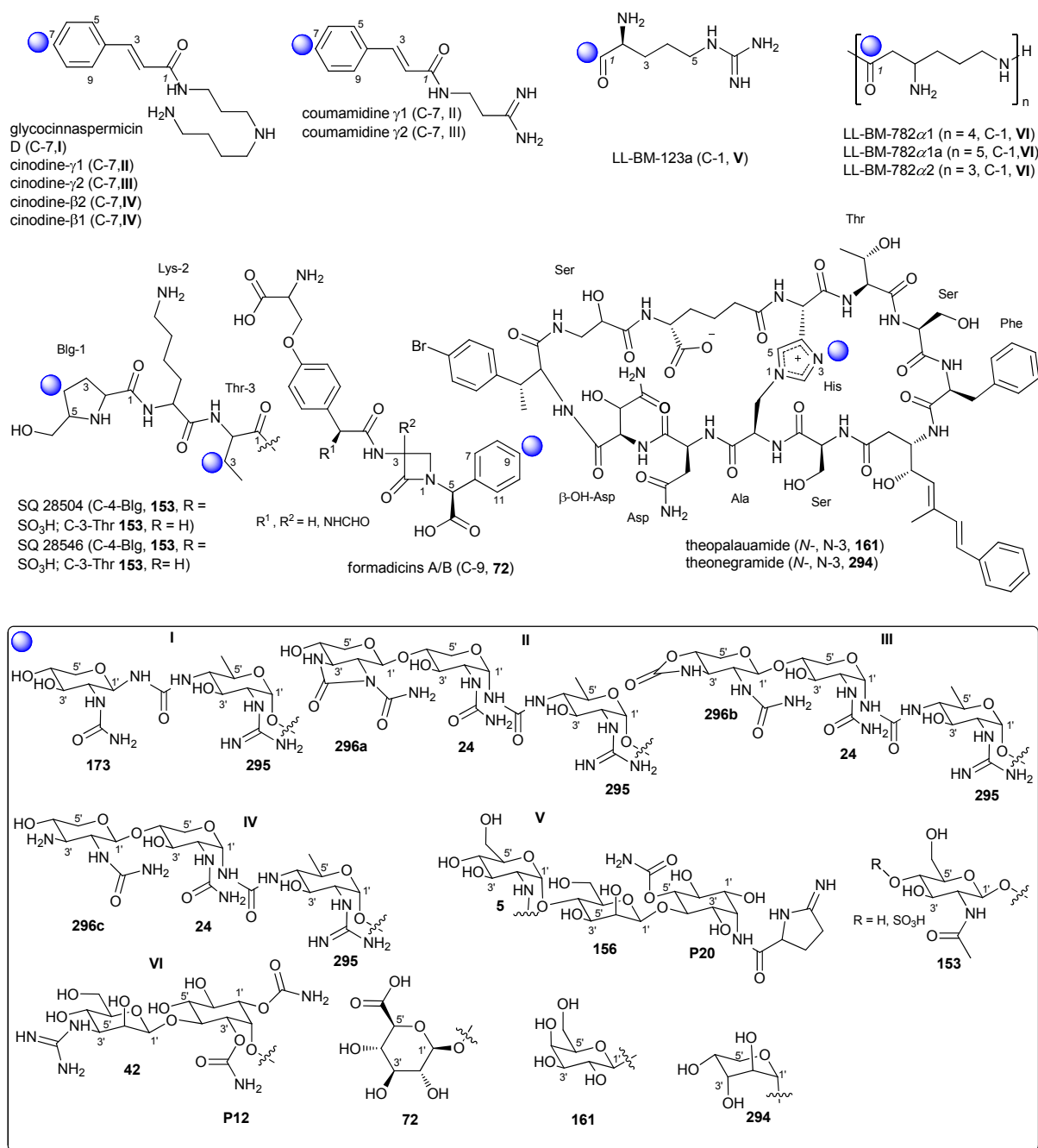


Figure 15G. Miscellaneous anti-infective peptide aglycons and associated sugars

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 alanopine¹¹²² from *Streptomyces*, *Nostoc*, *Nocardia*, *Planktothrix*, *Bacillus*, *Staphylococcus* *Providencia*, *Proteus* and *Oscillatoria* (Figure 15H). 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; Figure 15H).^{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**, Figure 15H). 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 *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

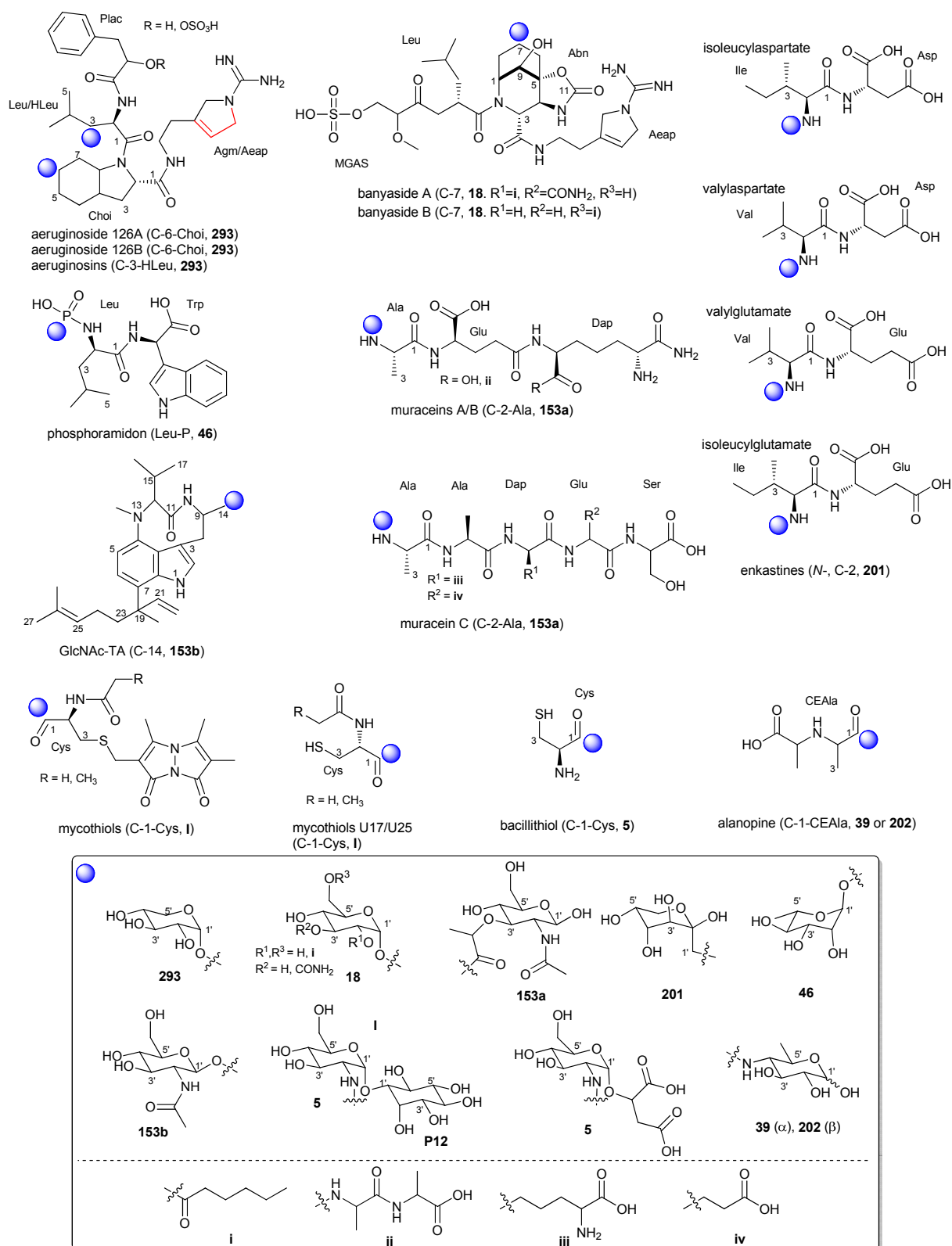


Figure 15H. Miscellaneous peptide aglycons and associated sugars

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 (Figure 16A).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 (aestivopheonins A-C,^{1127, 1128} izuminosides A-C,¹¹²⁹ and phenazoviridin¹¹³⁰⁻¹¹³² 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 (Figure 16A). 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

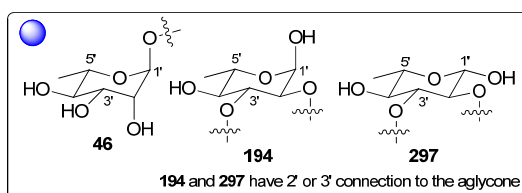
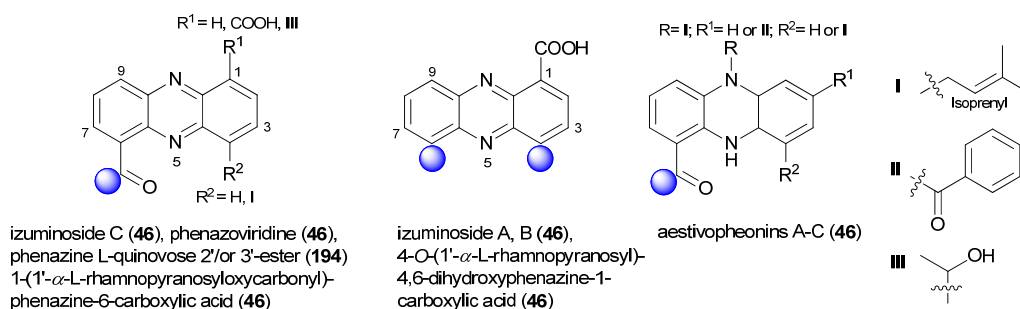


Figure 16A. Phenazine aglycons and associated sugars

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-10 or C-17 *O*-monoglycosides (Figure 17A).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 A₁ and A₂.¹¹³⁴ In contrast, the C-3a-appended α -L-rhamnose (**46**) was only observed in 3a-rhamnopericidin A1 (SN-198-C),^{1137, 1138} and 7-demethyl-3a-rhamnopericidin A1 (SN-198-B),¹¹³⁹ while the C-3a attached 2'-*epi*- β -D-fucose (**298**) was observed only in 3-deoxytalopericidin A1.¹¹⁴⁰ Additionally, the two glucopyranone (PM-050511 and PM-060431) metabolites of a marine *Streptomyces* display C-10-*O*- β -D-glucosyl (**104**) regioselectivity reminiscent of corresponding glucopiericidin.¹¹⁴¹ Importantly, glycosylation generally correlates with improved antimicrobial properties and reduced general in vivo toxicity.^{1133-1135, 1137, 1139-1141}

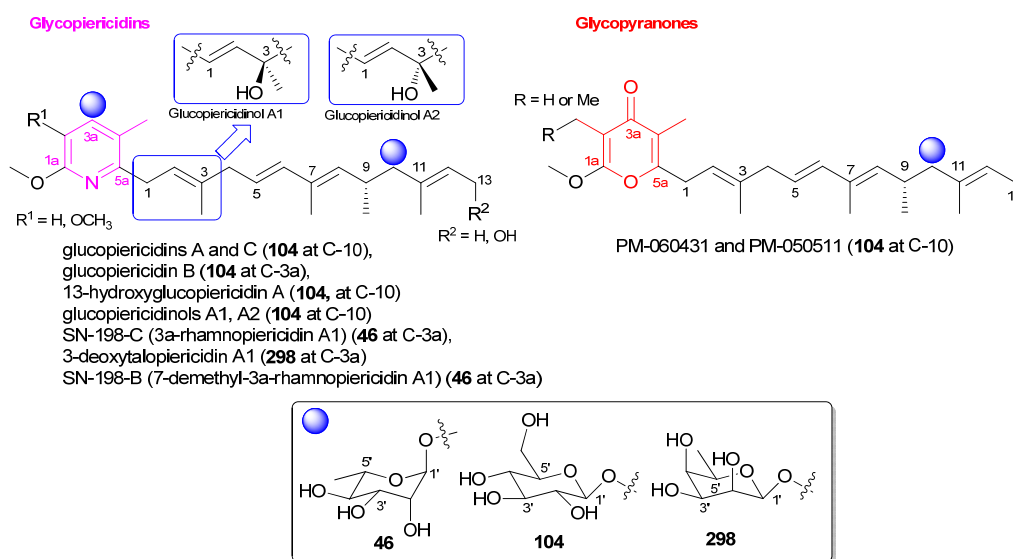


Figure 17A. Piericidin and pyranone aglycons and associated sugars

18. Pluramycins

The *4H*-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 (Figure 18A) 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 121222¹¹⁵², ankinomycin,^{1145, 1146, 1153-1155} altromycins,¹¹⁵⁶⁻¹¹⁵⁹ saptomycins,¹¹⁶⁰⁻¹¹⁶² neopluramcin and pluramycin A,¹¹⁶³⁻¹¹⁶⁵ pluraflavins,¹¹⁶⁶ A51493A,¹¹⁶⁷ rubiflavins¹¹⁶⁸ 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.

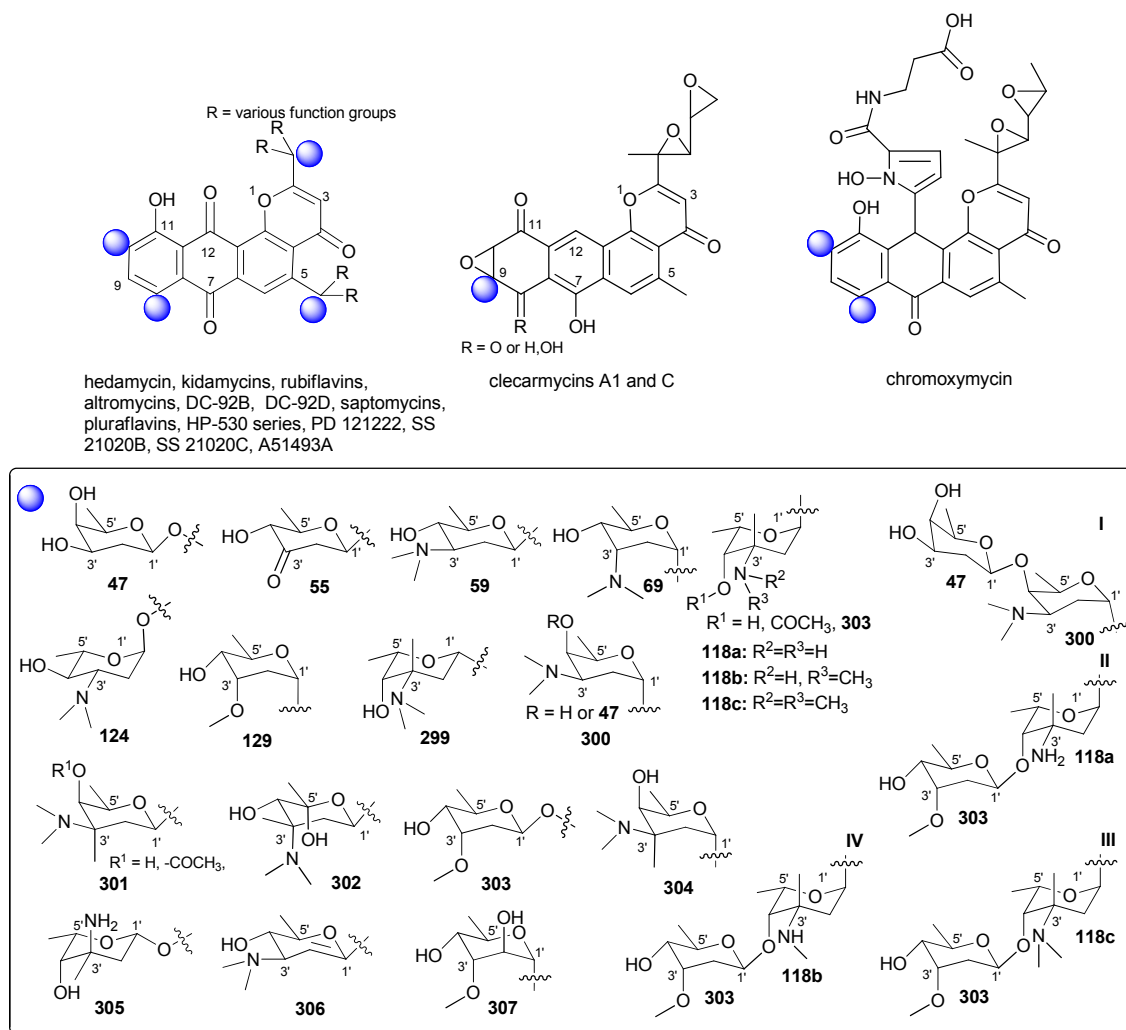


Figure 18A. Pluramycin aglycons and associated sugars

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 (Figure 19A). Despite the rather large group of glycosylated analogs observed, the glycosides found are restricted to the use only eight distinct sugars (Figure 19A). 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 regioselectivity (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-C¹¹⁹⁶ 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 D¹¹⁹³ 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**), 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-CH₂, and C-27) as exemplified by A-130-B,¹²⁰⁹ A-130-C,¹²⁰⁹ X-14934A, moyukamycin,¹²¹⁰ lenoremicin (A-130),^{1211, 1212} leuseramicin,¹²¹³ endusamicin,¹²¹⁴ CP-60993,¹²¹⁵ CP-80219,¹²¹⁶ nangchangmycin¹²¹⁷⁻¹²¹⁹ and dianemycin analogs.^{1212, 1220, 1221} All sub-class **VI** analogs are C-14-*O*-glycosides of 4'-*O*-methyl- β -D-amicetose (**48b**), including, 6270B,¹²²² portmicin¹²²³ and CP-84657.¹²²⁴

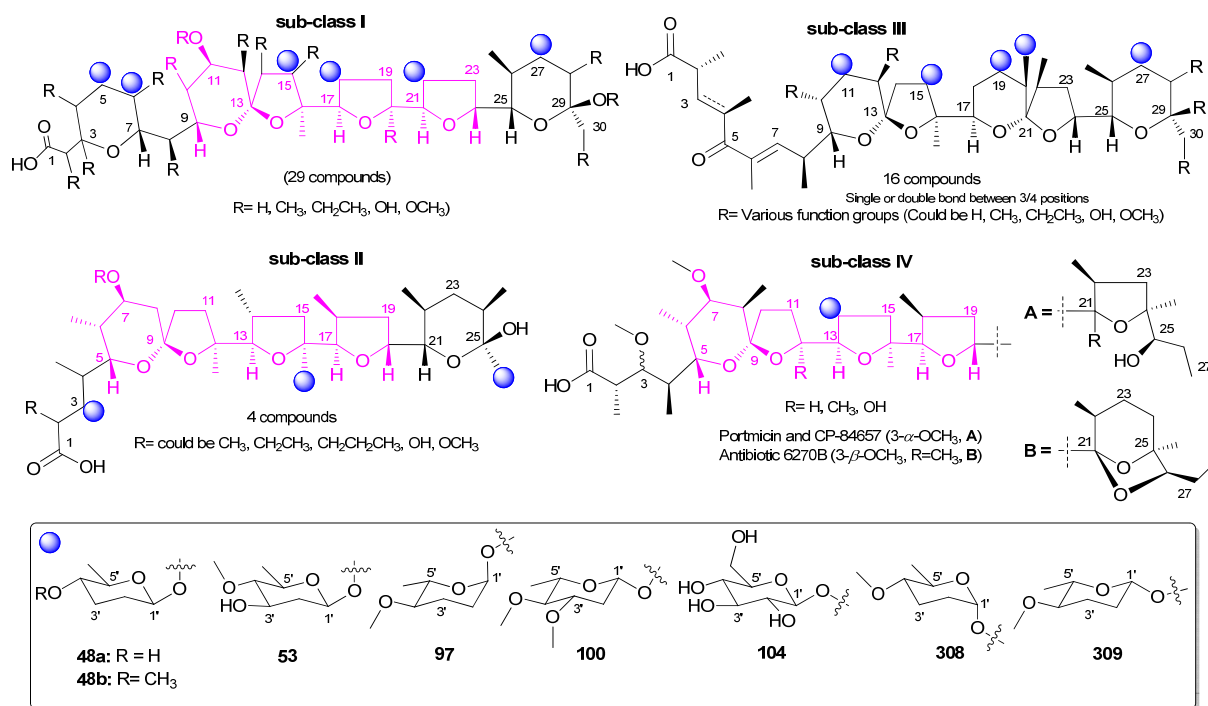


Figure 19A. Polyethers aglycons and associated sugars

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 (Figure 20A). 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**) (Figure 20A).¹²³¹⁻¹²³³ In some cases, the corresponding 5'-phosphate is further modified with α -hydroxyglutaric moiety via a phosphodiester bond (Figure 20A, appendages **i**, **ii**, or **iii**).

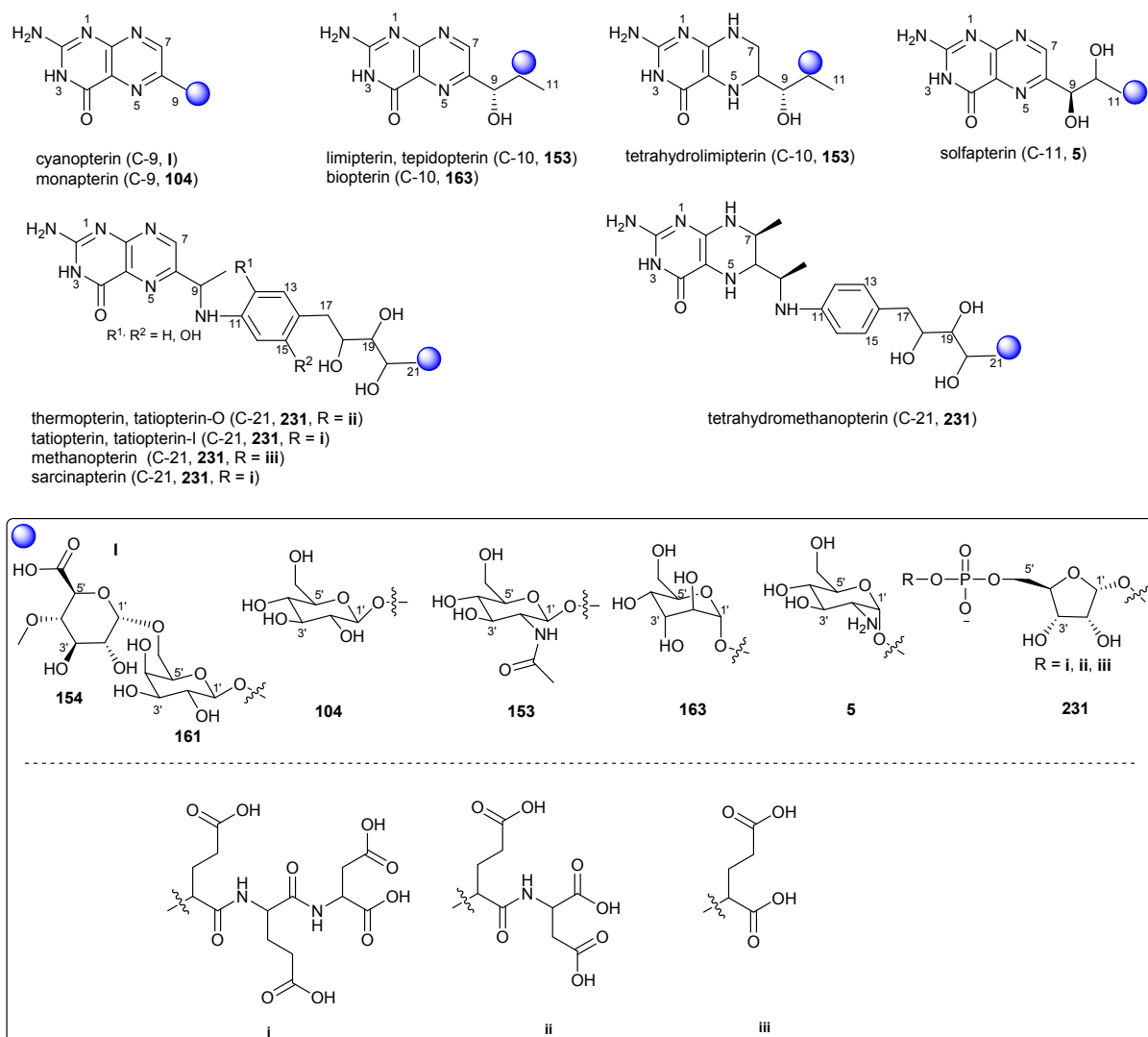


Figure 20A. Pterin aglycons and associated sugars

21. Streptothricins

Streptothricins are *N*-glycosides composed of streptolidine or streptolidine lactam, 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 (Figure 21A). 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'-carbamylation 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'-modified β -D-glucosamine **153**).¹²⁵⁶ Sugar C-4' carbamylation favors activity while cleavage of streptolidine lactam amide bond reduces activity and toxicity.^{1251, 1257}

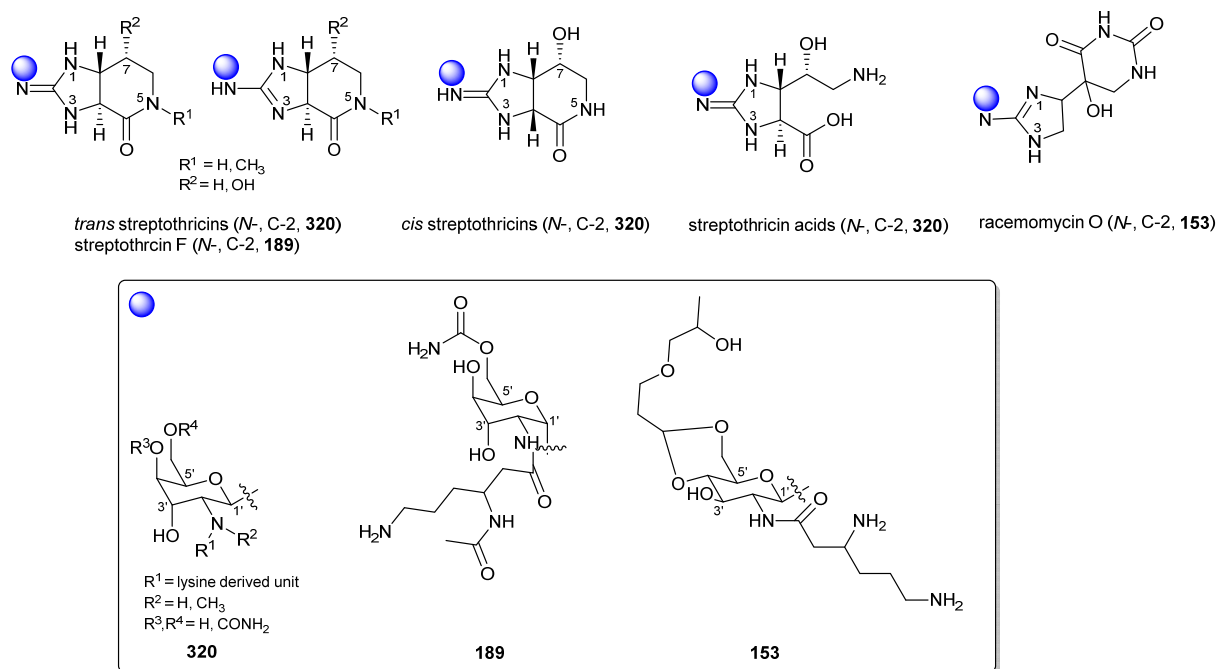


Figure 21A. Streptothricin aglycons and associated sugars

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 *Streptomyces* 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**) (Figure 22A), 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** (Figure 22A) and it is important to point out that some confusion exists in the literature regarding the structure of pseudodisaccharide **II**.¹¹³¹ Platensimycin B₄ 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 (Figure 22A) and display attenuated inhibition of FAS.¹²⁶³

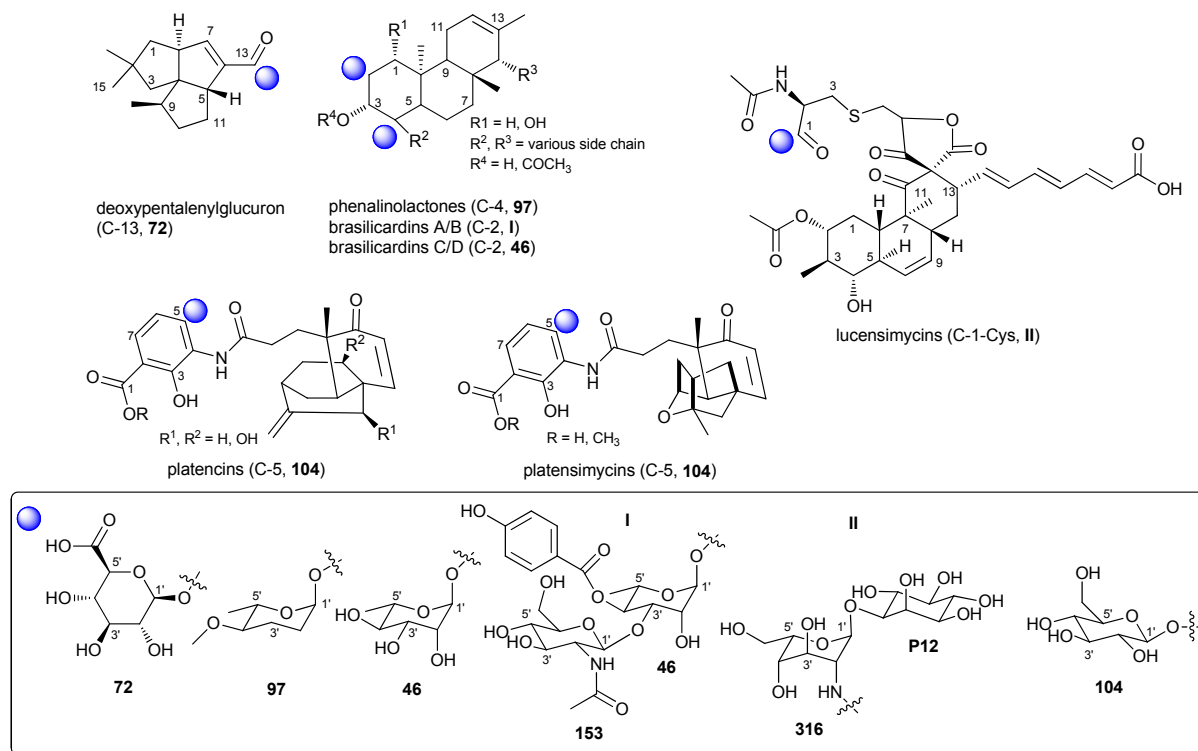


Figure 22A. Sesquiterpene and diterpene aglycons and associated sugars

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* (Figure 22B).^{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-gulose (**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**) (Figure 22B). MK800-62F1, a gammacerane and inhibitor of apoptosis 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.

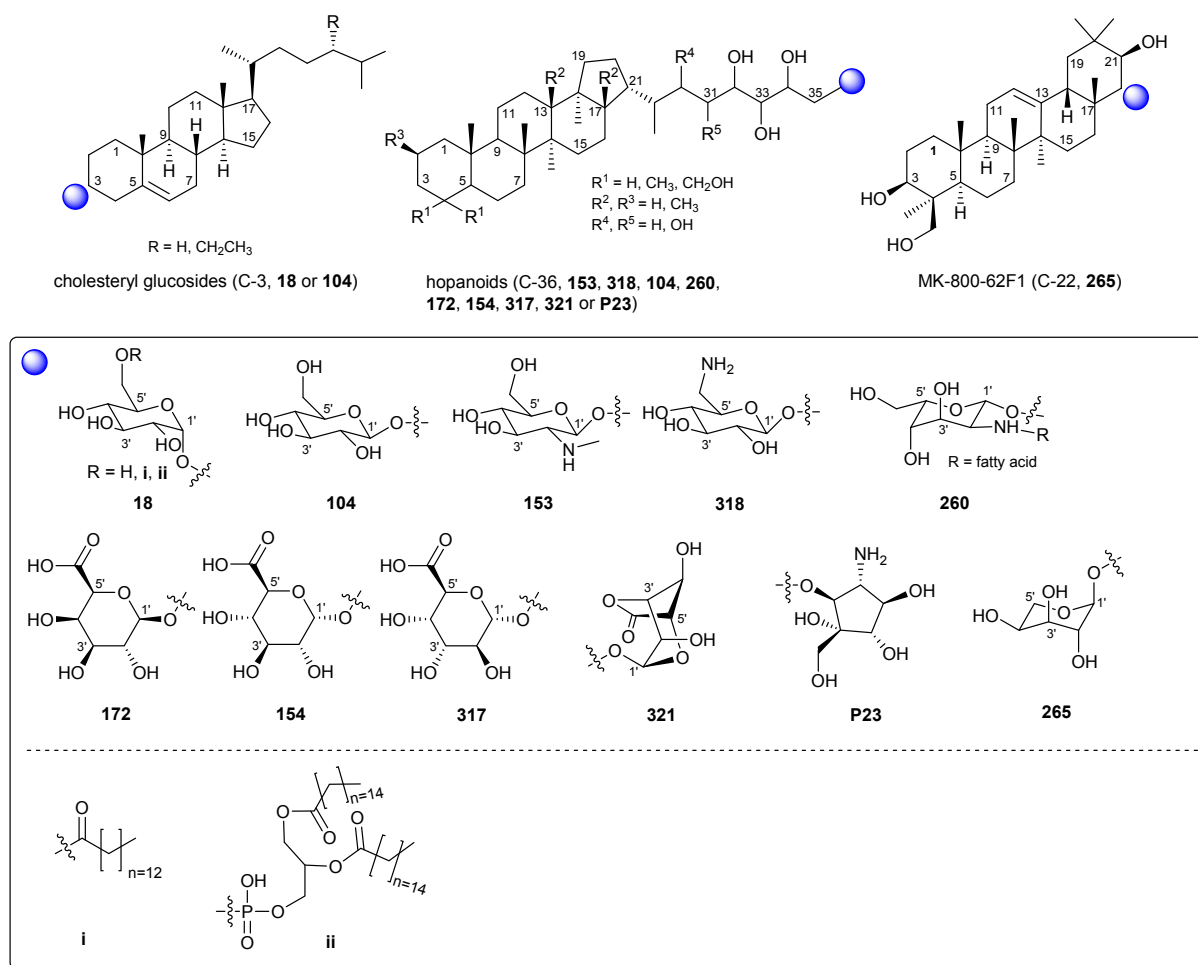


Figure 22B. Triterpenes aglycons and associated sugars

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 (Figure 23A). 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 ($\alpha 1$, $\beta 1$, $\beta 2$, e and $w1$).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}

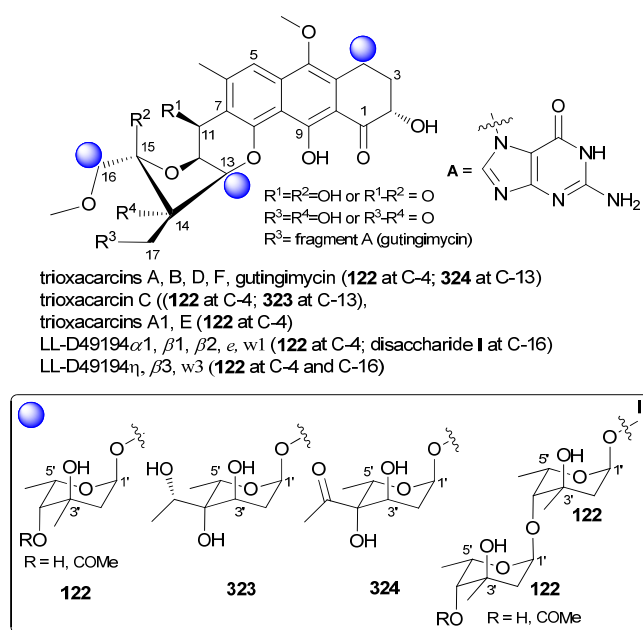


Figure 23A. Trioxacarcins and LL-D49194 aglycons and associated sugars

23.2. Polycyclic Xanthenes 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 (Figure 23B). 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-oliiose (**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 901809¹²⁸⁹ 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-oliviosyl-(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-oliviosyl-(1'→3')-*O*- β -D-olivose connection (β -D-oleandrosyl-(1'→4')-*O*- β -D-oliviosyl-(1'→3')-*O*- β -D-olivose, trisaccharide **VI**). Antibacterials/antimycoplasmidials 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 *Amiclatopsis* that possess a fused octacyclic 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}

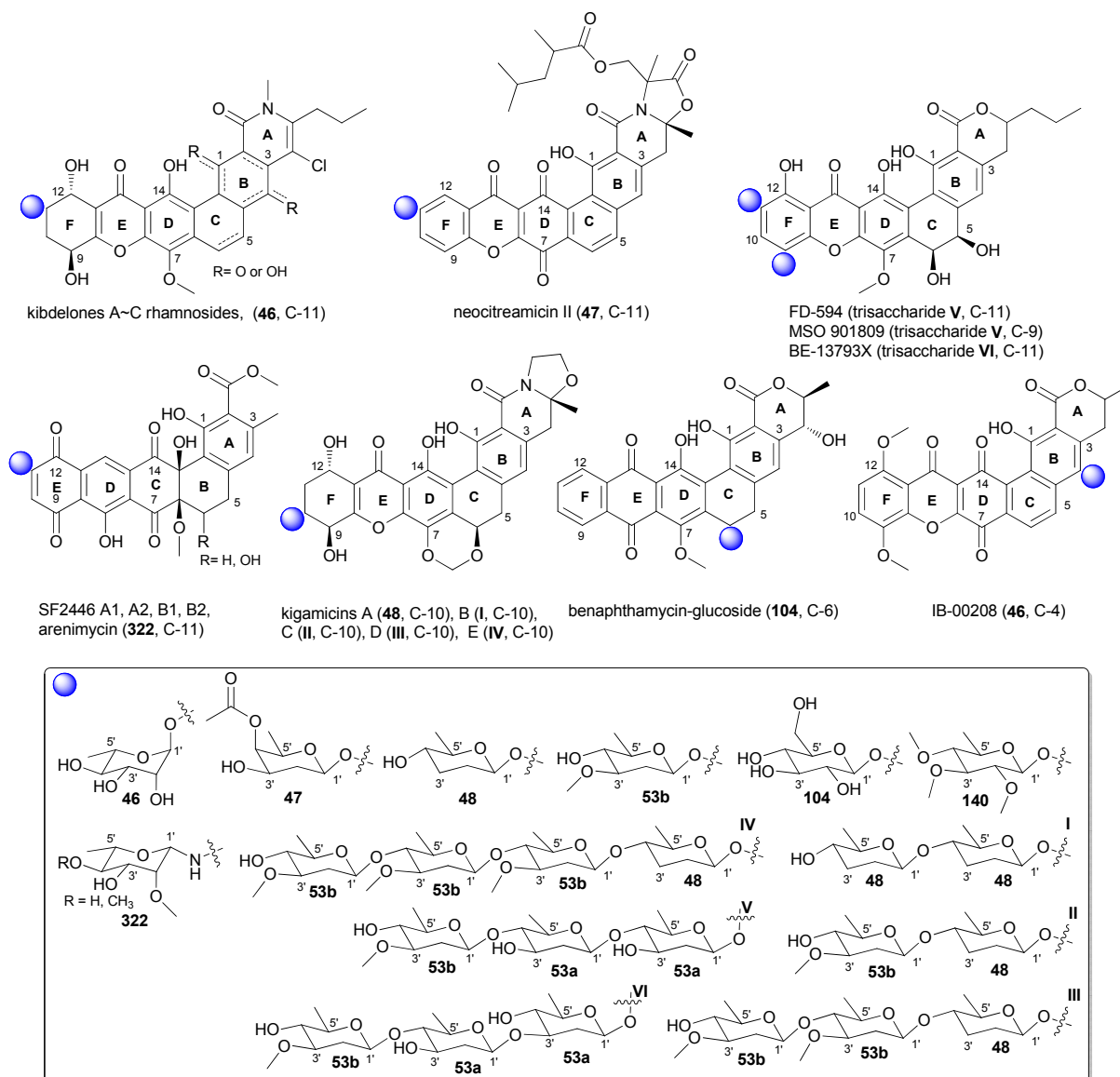


Figure 23B. Polycyclic xanthone aglycons and associated sugars

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 273a₂ 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**, Figure 23C). 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 Figure 23C. Members of this family display potent Gram positive antibacterial activity.

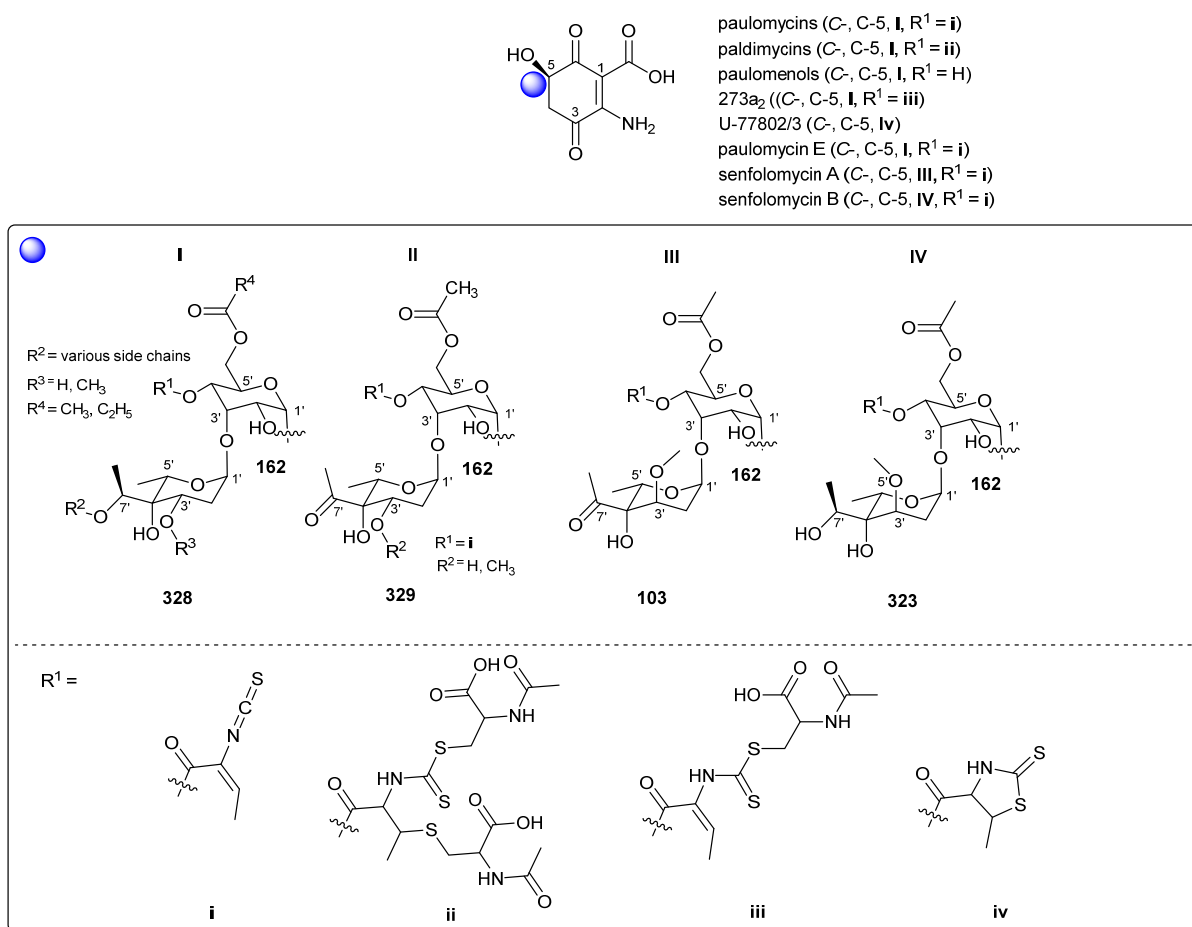


Figure 23C. Paulomycins and associated sugars

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**) (Figure 23D). 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 monosaccharides 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.

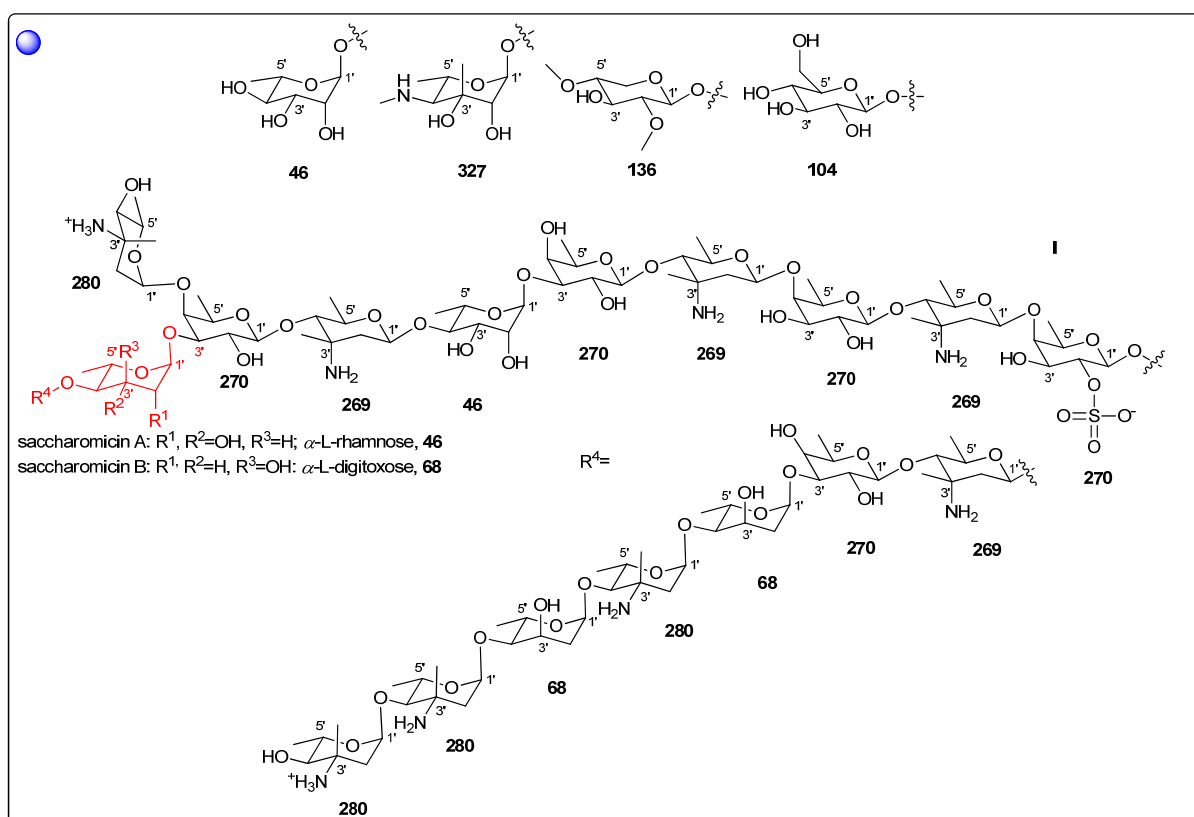
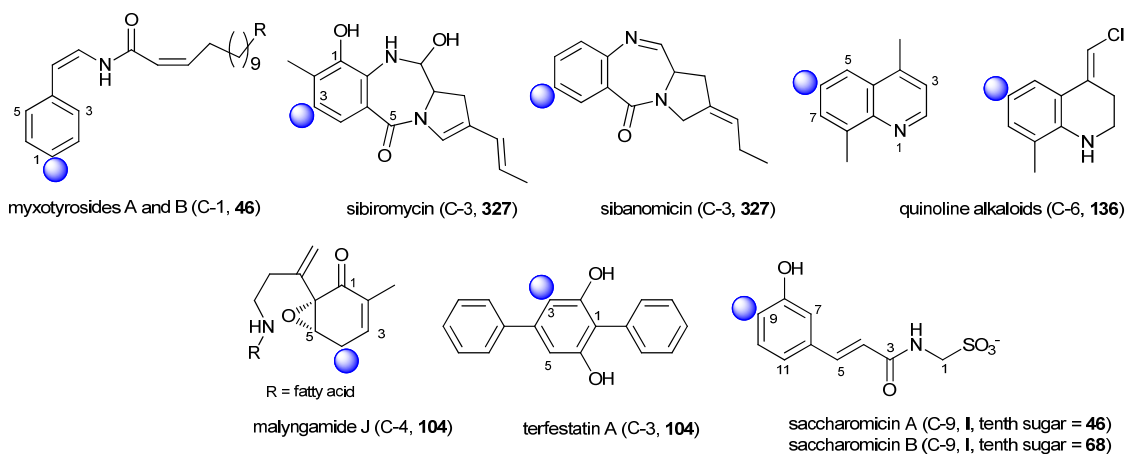


Figure 23D. Phenyl glycosides and associated sugars

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 pentanoid-oxazolidine aglycon.¹³¹³⁻¹³¹⁵ Members

contain a C-5-*O*- β -D-*N*-acetyl- β -D-allosaminy- β -(1'→4')-*N*-acetyl- β -D-allosamine (disaccharide **I**, monomer **326**) or the C-6'-*O*-methyl variant (Figure 23E). 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 A₂ and exhibit anti-inflammatory properties.

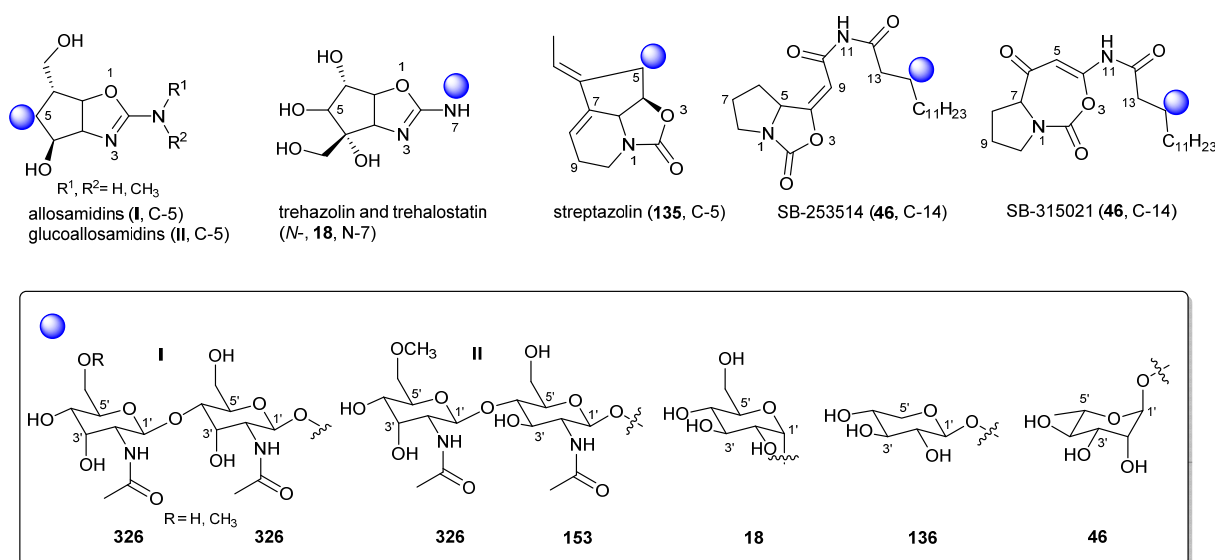


Figure 23E. Oxazole aglycons and associated sugars

23.5.2. Porphyrins

Porphyrins are heterocyclic tetrapyrrole-based macrocyclic metabolites (Figure 23F). Of the 27 porphyrins reported from bacteria, seven tolyporphyrins from *Tolypothrix* exist as C17-*C*-glycosides or C-7,*C*-17-di-*C*-glycosides. While 3',6'-dideoxy- β -D-xylo-hexopyranose (**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-glycoprotein¹³²¹⁻¹³²⁴ and can photosensitize tumor cells.¹³²⁵

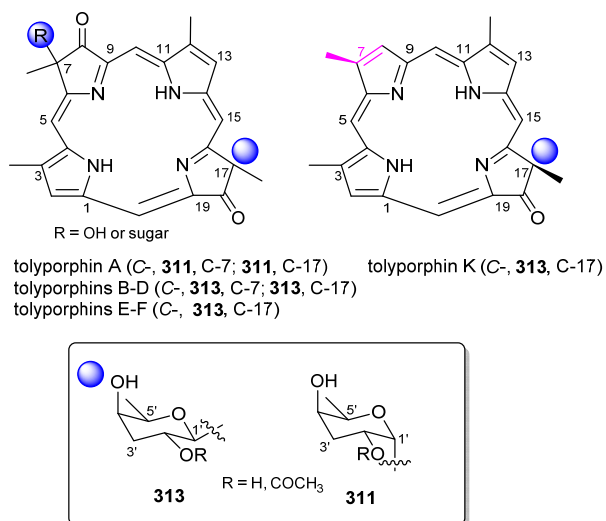


Figure 23F. Porphyrin aglycons and associated sugars

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 lipoxygenase inhibition guided-assay.^{1326, 1327} They are C-9- β -D-rhodosides (**56**) (Figure 23G). The corresponding enantiomer, β -L-rhodoside (**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 acaricidal.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-phosphate¹³³⁴ 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**) (Figure 23G).¹³³⁵

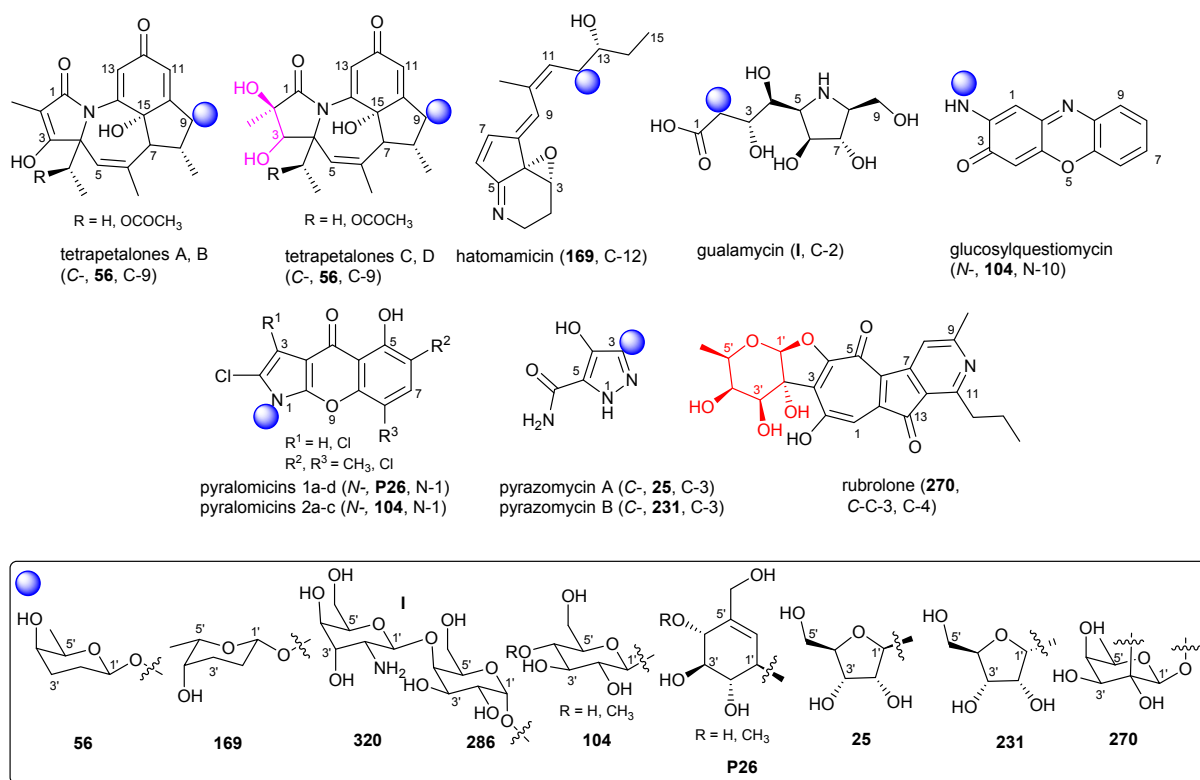


Figure 23G. Other heterocycle aglycons and associated sugars. Pink fragment highlights differences between tetrapetalones. Red fragment highlights sugar in rubrolone.

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 (Figure 23H) 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**) (Figure 23H). Rhamnosylated lactones analogs were found to inhibit the 3 α -hydroxysteroid dehydrogenase.⁵⁹⁰

Additional metabolites include menisdaurin,¹³⁴⁰ byelyankacin,¹³⁴¹ and two CKD-711 derivatives¹³⁴¹⁻¹³⁴³ 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 epoxy-cyclohexanol C-1-*N*-glycosides bearing either a pentasaccharide **I** or a trisaccharide **II** (Figure 23H). 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

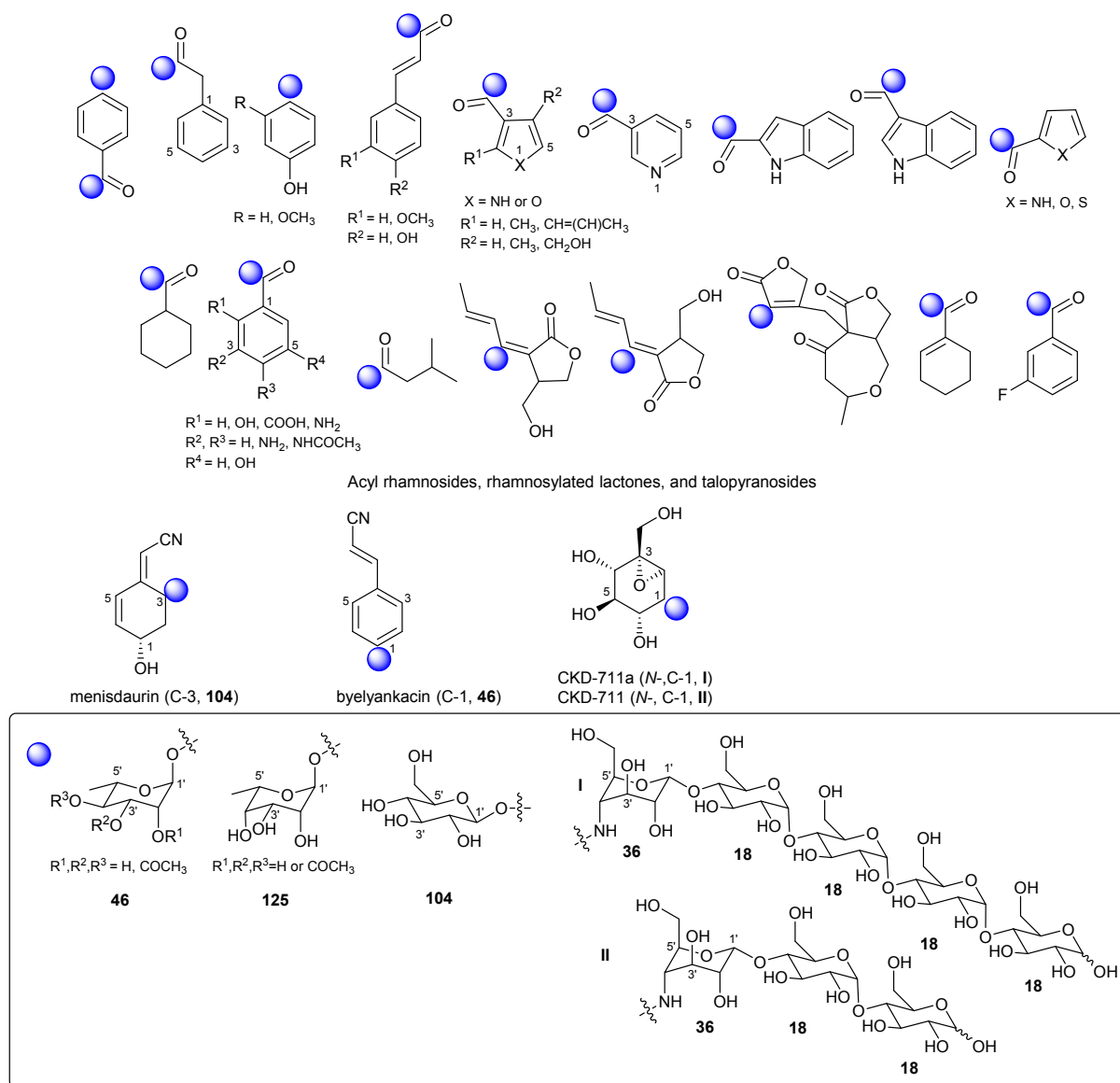


Figure 23H. Aglycons with simple moieties and associated sugars

24. Conclusions

This cumulative analysis reveals a relatively high degree of natural product family-specific conservation in both regioselectivity and the sugars employed and a moderate degree of natural product crossover 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 tool for natural product lead medicinal chemistry, it suggests efficient glycodiversification strategies (chemoenzymatic,^{9, 1344} chemoselective¹⁰ and/or pathway engineering¹³⁴⁵) 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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