Biosynthesis and Biological Activity of Carbasugars.

Silvia Roscales*[ϒ] and Joaquín Plumet*

Universidad Complutense. Facultad de Química. Departamento de Química Orgánica. Ciudad Universitaria, 28040, Madrid, Spain.

Publicado en *International Journal of Carbohydrate Chemistry*,
Volume **2016**, Article ID 4760548, 42 pages

Correspondence should be adressed to Joaquín Plumet; plumety@ucm.es and Silvia Roscales; s.roscales@hzdr.de

Abstract: The first synthesis of carbasugars, compounds in which the ring oxygen of a monosaccharide had been replaced by a methylene moiety, was described in 1966 by Prof. G.E. McCasland's group. Seven years later, the first true natural carbasugar (5a-carba-R-D-galactopyranose) was isolated from a fermentation broth of *Streptomyces* sp. MA-4145. In the following decades, the chemistry and biology of carbasugars have been extensively studied. Most of these compounds show interesting biological properties, especially enzymatic inhibitory activities and, in consequence, an important number of analogues have also been prepared in the search for improved biological activities. The aim of this review is to give coverage on the progress made in two important aspects of these compounds: the elucidation of their biosynthesis and the consideration of their biological properties, including the extensively studied carbapyranoses as well as the much less studied carbafuranoses.

1. Introduction.

In addition to their well-known role as chemical units for a) release of energy such as sucrose or glucose, b) energy storage such as starch or c) as responsible for structure and strength such as cellulose, carbohydrates are key elements in a variety of biological processes. In fact, the concept of *glycomic* has been defined as “the functional study of carbohydrates in living organism”.[1] Carbohydrates are key elements in a variety of processes such as signaling, cell-cell communication, and molecular and cellular targeting. Many biological processes involve carbohydrates and, in consequence, the biological implications of carbohydrates are strongly related with many diseases. In this context, it should be pointed out that the synthetic-carbohydrate vaccines show potential advantages over those based on carbohydrates from natural sources. Thus, medicinal chemistry techniques can potentially be used to derivatize and modify synthetic carbohydrates to make vaccines that are more immunogenic than those based on natural carbohydrates. For selected, general and recent reviews on these aspects of carbohydrate chemistry, see: (a) general teatrises: references [2-5]; (b) synthetic aspects: references [6-7]; (c) carbohydrates in biological and medicinal chemistry: references [8-11]; (d) glycobiology [12]; (d) signaling, cell-cell communication, and molecular and cellular

[ϒ] Present address: Helmholtz-Zentrum Dresden-Rossendorf. Radiopharmaceutical and Chemical Biology. Bautzner Landstraße 400, 01328, Dresden, Germany

targeting: references [13-18]; (e) therapeutic potential of glycoconjugates: references [19-20]; (f) carbohydrate-based vaccines: references [21-25].

On the other hand, novel carbohydrate structures whose biological functions were not always obvious have been discovered. For instance, intriguing compounds such as sialyl Lewis X (sLex) [26-28] or glycosylphosphatidylinositols (GPIs) are now known to play a pivotal role in numerous biological functions.[29-34] Moreover, carbohydrates constitute a very useful source of enantiomerically pure starting materials. They have been used for the synthesis of a wide range of compounds and have been found to be useful chiral auxiliaries which allowed the introduction of a range of functionalities in a highly enantioselective manner.[35-36]

On this basis, the search for new carbohydrate derivatives with analogous or even improved biological properties compared to those of the parent structures (the *carbohydrate mimetics*) [37-40] appears to be an attractive matter of research. The ***carbasugars*** (initially, the term *pseudosugars* was coined for this family of compounds, although they are currently known as carbasugars [41]), compounds in which the ring oxygen of a monosaccharide had been replaced by a methylene group (Figure 1), fall within this category [42-46]. The structural resemblance of carbasugars to the parent sugars may facilitate their recognition by enzymes or other biological systems in place of the related *true* sugars. On the other hand, these compounds could be more stable toward endogenous degradative enzymes.

The aim of this review is to give coverage on the progress made in the biosynthesis and biological activity of carbasugars until March 2016, including both carbapyranoses and carbafuranoses.

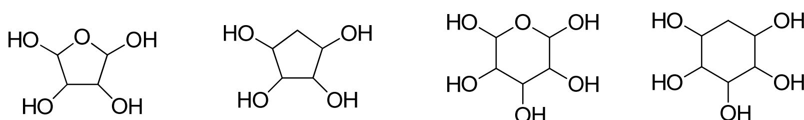


Figure 1. Monosaccharides and Carbamonosaccharides.

2. Natural Occurrence of Carbasugars.

2.1. Natural Carbafuranoses.

Carbafuranoses are scarcely encountered in Nature as free compound. Nevertheless, they are subunits of products isolated from natural sources, in particular carbanucleosides [47-48]. To the best of our knowledge, only two five-membered cyclitols derivatives have been isolated from natural sources (Figure 2): Caryose **1** [49-51], isolated from the lipopolysaccharide fraction of *Pseudomonas caryophylli* (a plant pathogenic bacteria), and calditol **2**, isolated from the thermoacidophilic archaebacterium *Sulfolobus acidocaldarius*, a thermoacidophilic archaeon belonging to *Sulfolobus* species. These species was found to grow optimally between 75-80º C, with pH optimum in the range of 2-3 [52-55]. The original proposed structure for calditol, an open-chain branched nonitol **3**, was soon questioned by various research groups. To unambiguously clarify this point, four isomeric cyclopentane-based structures were synthesized by Sinaÿ et *al*. Among them, compound **2** was found to be fully identical to the natural product present in several *Sulfolobus* species [56-57].

2.2. Natural Carbapyranoses

Carbapyranoses have been encountered in Nature rarely being carba-α-D-galactopyranose (4, Figure 3) the only "genuine" carbasugar isolated from natural sources (*Streptomyces* sp) [58].

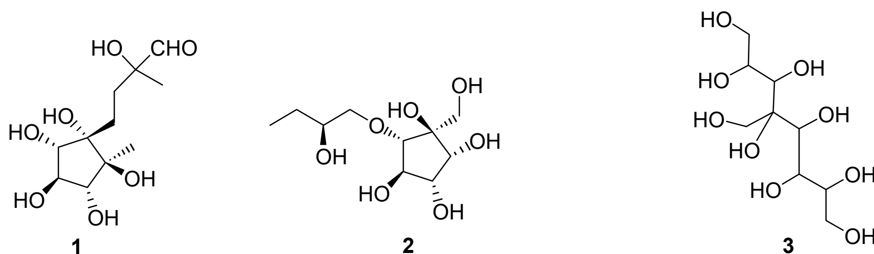


Figure 2. Structure of Caryose **1**, proposed structure of Calditol **3** and structure of Calditol **2**

However they are abundant as subunits of other natural products. On the other hand a large number of highly oxygenated cyclohexane and cyclohexene derivatives, closely related to carbasugars, have been isolated from Nature. Among them, epoxides [59-60] such as cyclophellitol (isolated from *Phellinus* sp)[61-65] (**5**, Figure 3), cyclohexene derivatives such as MK7607 (isolated from *Curvularia eragestrides*) [66], (**6**, Figure 3), streptol (isolated from *Streptomyces* sp) [67-68], (**7**, Figure 3), pericosines A-D (isolated from *Periconia byssoides*) (**8**-**13**, Figure 4) [69-70], carbonyl compounds such as the gabosine family (isolated from various *Streptomyces* strains) [71-73] (Figure 5, **15**-**28**), COTC (isolated from S*treptomyces griseosporeus*)[74] (Figure 5, **29**) and valienona (isolated from *Strptomyces lincolnensis*) [68] (Figure 5, **30**).

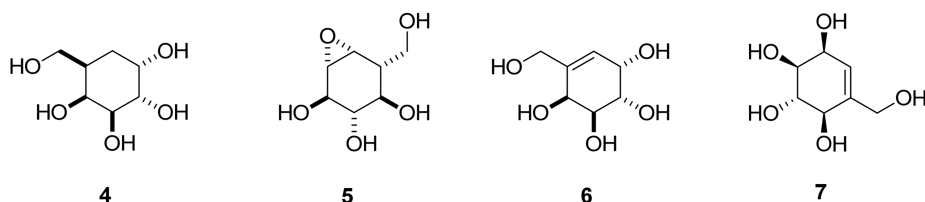


Figure 3. Some natural carbapyranoses: carba-α-D-galactopyranose, cyclophellitol, MK7607 and stretptol.

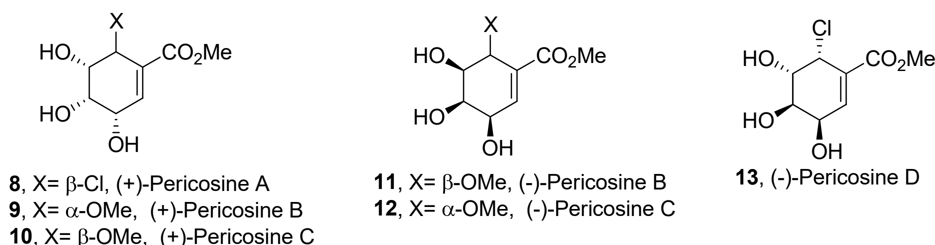


Figure 4. The pericosines.

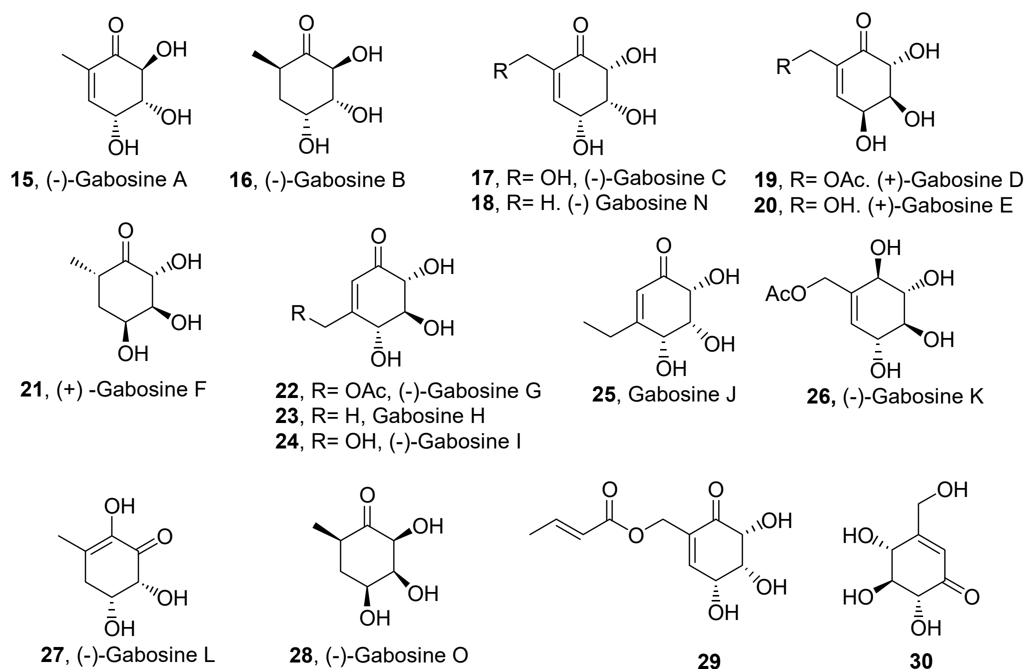


Figure 5. Gabosines, COTC and valienone. The absolute configuration of gabosines H (**23**) and J (**25**) remains, to the best of our knowledge, unknown.

Aminocarbasugars, such as valienamine (**31**) and validamine (**32**) (natural sources of validamine, include microbial degradation procedures [75-79], chemical degradation of validoxylamine-see below-) using NBS [80-81] and several biotechnological processes [82-84], hydroxyvalidamine [85] (**33**), and valiolamine [86-87] (**34**) (Figure 6), have been mainly found as subunits of more complex molecules (*Vide infra*). These derivatives are secondary metabolites exclusively produced by microorganisms. They have been detected only as minor components in the fermentation broth of *Streptomyces hygroscopicus* subsp. *Limoneus* [87]. Aminocarbasugars are mainly found in validamycins, acarbose, and related carbaoligosaccharides.

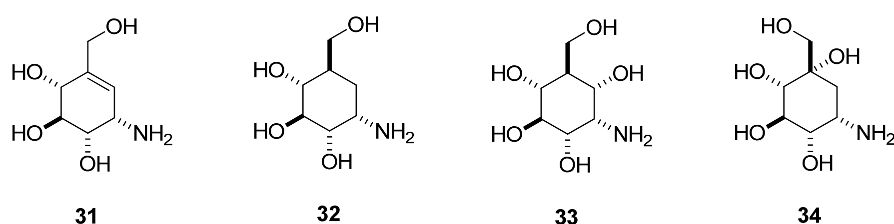


Figure 6. Aminocarbasugars valienamine, validamine, hydroxyvalidamine and valiolamine.

Validamycins (Figure 7) are a family of antibiotics discovered during the screening for new antibiotics from the fermentation culture of *Streptomyces hygroscopicus*.[88-91] The main component of the complex is Validamycin A (**35**), a pseudotrisaccharide consisting of a core moiety, validoxylamine A (**43**), and D-glucopyranose. The core consists of two aminocyclitols, valienamine (**31**), and validamine (**32**), which are connected through a single nitrogen atom. Validamycin B (**36**) differs from validamycin A in the second aminocyclitol unit which, in validamycin B (**36**), is hydroxyvalidamine (**33**). The minor components of the validamycins complex, validamycins C-F (**37-40**)

and validamycin H (**42**), contain validoxylamine A (**43**), as the core unit, but they differ in at least one of the following features: (a) the position of the glucosidic linkage, (b) the number of D-glucopyranose residues, or (c) the anomeric configuration of the D-glucopyranose unit [92-95]. Validamycin G (**41**) contains validoxylamine G (**45**) as its core unit.

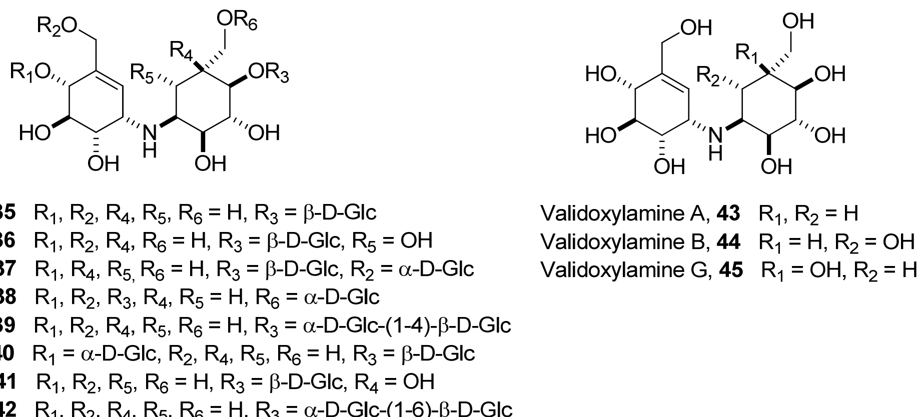


Figure 7. The Validamycins family.

Acarbose (Figure 8, **46**) [96-97] is one of the most clinically important compounds containing carbasugar units, since it is currently used for the treatment of type II insulin-independent diabetes. This disease is a metabolic disorder that is characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin [98-99]. In addition to acarbose, marketed by Bayer, there are two drugs, structurally related with acarbose, which belong to this class of α-glucosidase inhibitors: miglitol **47** –Sanofi- and voglibose **48** –Takeda- (Figure 8). Acarbose is a starch blocker, and inhibits α-amylase, an intestinal enzyme that releases glucose from larger carbohydrates [100-101]. Acarbose is a carbatrisaccharide which was found in a screening of strains of various *Actinomycete* genera and its structure was determined by degradation reactions, derivatization, and spectroscopic analysis. It is composed of valienamine (**31**), a deoxyhexose (4-amino-4,6-dideoxyglucose), and maltose. The carbadisaccharic core of acarbose, known as acarviosine (**49**), is postulated to be essential for its biological activity. The core unit, **49**, is also linked to a variable number of glucose residues, resulting in several other components of the complex mixture of acarbose. The formation of these components is highly dependent on the composition of the carbon source available in the culture medium. Media containing glucose and maltose will result in a specifically high yield of acarbose and the lower components, while media with high concentrations of starch will yield longer oligosaccharide species. The transglycosylation involved in this process was proposed to be catalyzed by an extracellular enzyme, acarviosyl transferase, found in the culture of the acarbose producer [102]. Acarbose has been the subject of interest and excellent reviews have been published, covering various specific aspects on the biochemistry and molecular biology of this compound [103-114].

The amylostatins, with general structure **50** (Figure 9), are related to acarbose analogues due to they contain the acarviosine core **49**. Amylostatins were isolated in the culture filtrate of *Streptomyces diastaticus* subsp. *Amilostaticus* [115-116].

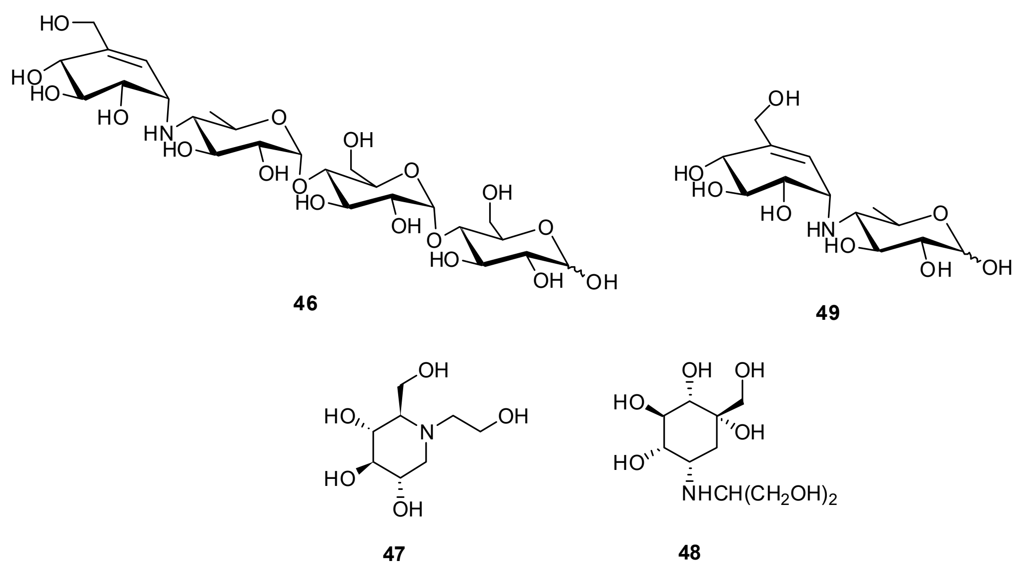


Figure 8. Structures of acarbose, acarviosine and marketed products **47** and **48**.

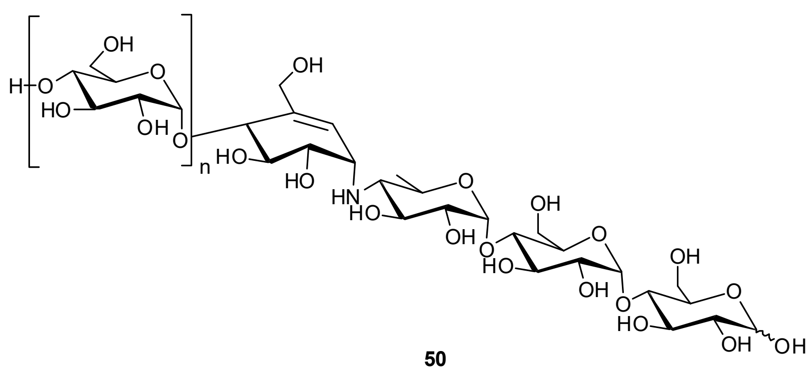


Figure 9. The amylostatins.

Adiposins (**51**, Figure 10) were isolated from *Streptomyces calvus* [117-124]. Structurally, adiposins are related to acarbose (**46**) and amylostatins (**50**). They are formed by an aminocarbasugar (valienamine, **31**)) and a deoxy sugar (4-amino-4-deoxyglucose).

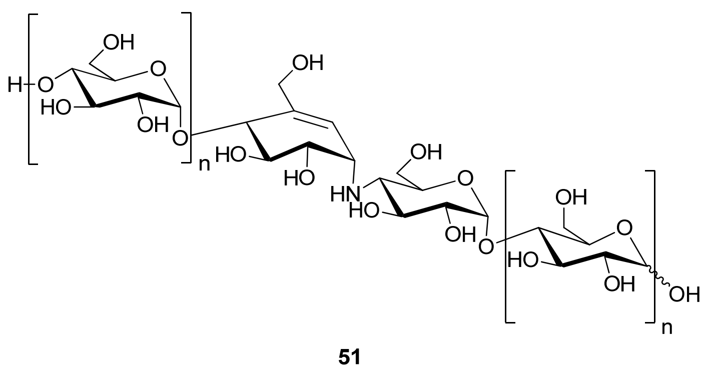


Figure 10. The adiposins.

Oligostatins (**52**, Figure 11) were obtained from culture broths of *Streptomyces myxogenes* [125-129]. They are carbaoligosaccharide antibiotics consisting of penta-, hexa-, and heptasaccharides containing hydroxyvalidamine rather than valienamine.

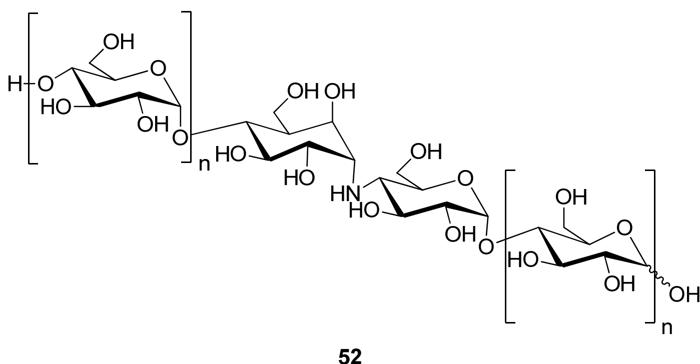


Figure 11. The oligostatins.

Trestatins (**53**, Figure 12) were isolated from fermentation cultures of *Streptomyces dimorphogenes* [130-131]. These carbaoligosaccharides contain one to three dehydro-oligobioamine units and terminate with one residue of α-D-glucopyranose linked 1,1- to the preceding glucose unit. Therefore, unlike the oligostatins **52** and the amylostatins **50**, the trestatins are nonreducing carbohydrates

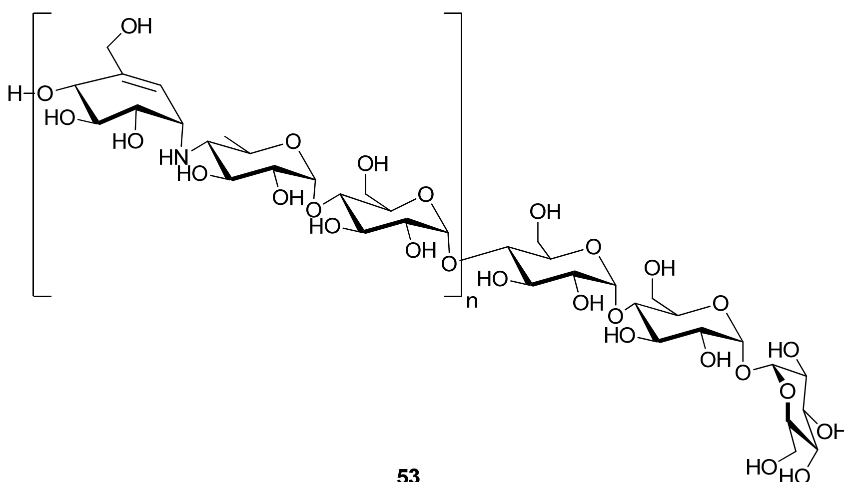


Figure 12. The trestatins.

Trehalase inhibitor salbostatin (**54**, Figure 13) is a metabolite of *Streptomyces albus* species [132-134]. This basic nonreducing carbadisaccharide consisting of valienamine linked to 2-amino-1,5-anhydro-2-deoxyglucitol.

In 1995, the pyralomicins (**55-58**, Figure 14) were isolated from the strain of *Actinomadura spiralis* (which was later renamed *Microtetraspora spiralis*)[135-136]. Their chemical structures consist of benzopyranopyrrole chromophores containing a nitrogen atom which is also shared with 1-epi-valienamine.[137]. Pyralomicins are, thus far, the only examples of natural products having an aminocarbasugar unit, acting as the glycone, attached to a polyketide-derived core structure [138-140].

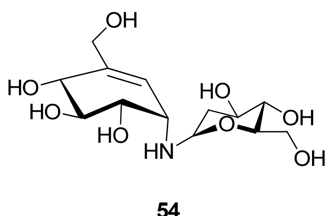
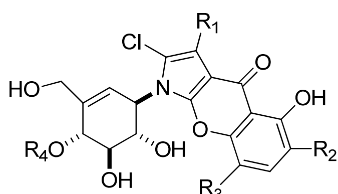


Figure 13. Structure of Salbostatin.



Pyralomicin 1a, **55** R_1 = H, R_2 = Cl, R_3, R_4 = CH_3
Pyralomicin 1b, **56** R_1 = H, R_2, R_4= CH_3, R_3 = Cl
Pyralomicin 1c, **57** R_1, R_4 = H, R_2 = Cl, R_3 = CH_3
Pyralomicin 1d, **58** R_1, R_2 = Cl, R_3 = CH_3, R_4= H

Figure 14. The pyralomicins.

3. Biosynthesis of carbasugars.

3.1. Carbafuranoses.

The biosynthesis of carbapentofuranoses has only been considered in the literature, to the best of our knowledge, in the context of the more biologically relevant carbocyclic nucleosides and in the case of the cyclitol calditol **2**.

3.1.1. Carbocyclic nucleosides.

Biosynthetic studies on aristeromycin (**59**) and neplanocin A (**60**) (Figure 15)[141-144] had established that the carbocyclic ribose ring was biosynthesize from D-glucose *via* the enone **61**, the first-formed carbocyclic intermediate. After reduction of the double bond in **61**, the reduction of ketone function of the resulting product **62** in an *anti* fashion and phosphorylation afford the carbocyclic analogue of 5-phosphoribosyl- 1-pyrophosphate **63** (Scheme 1). A detailed description of this sequence was described in Reference 42, p. 1923-1924.

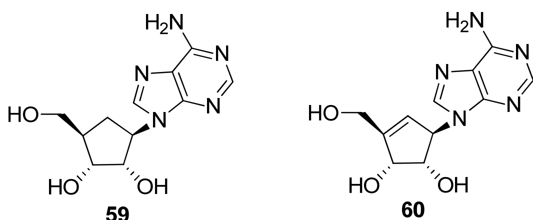
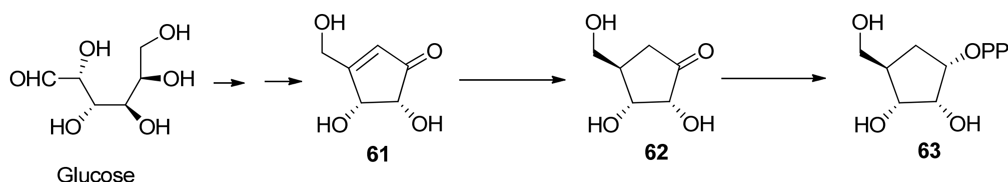


Figure 15. Structures of Aristeromycin **59** and neplanocin **60**.



Scheme 1. Proposed biosynthesis of carbaphosphorybosyl-1-phosphate from glucose.

3.1.2. Biosynthesis of Calditol.

Calditol **2** constitutes the cyclitol moiety of lipids such as **64** (Figure 16) and related compounds which are present in microorganisms belonging to the *Archaea* domain. As shows in Figure 16, the cyclitol fragment is linked to the rest of the molecule by ethereal bonding [145].

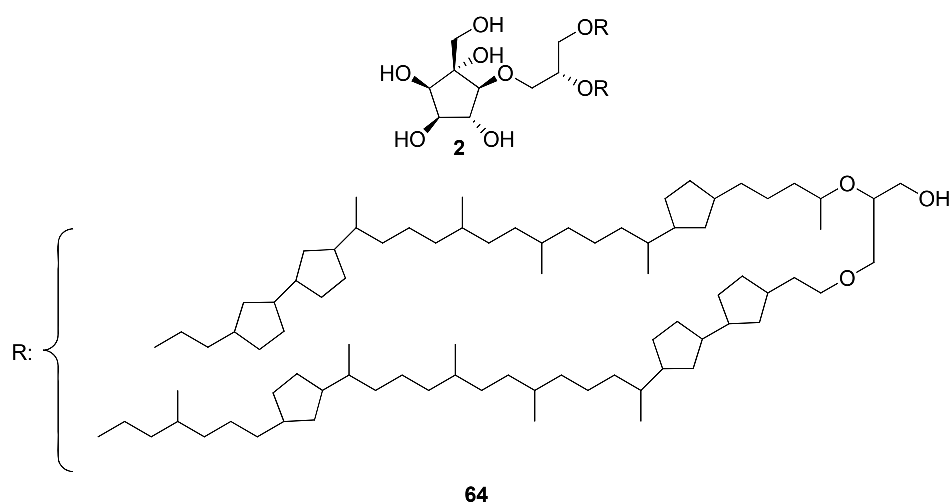


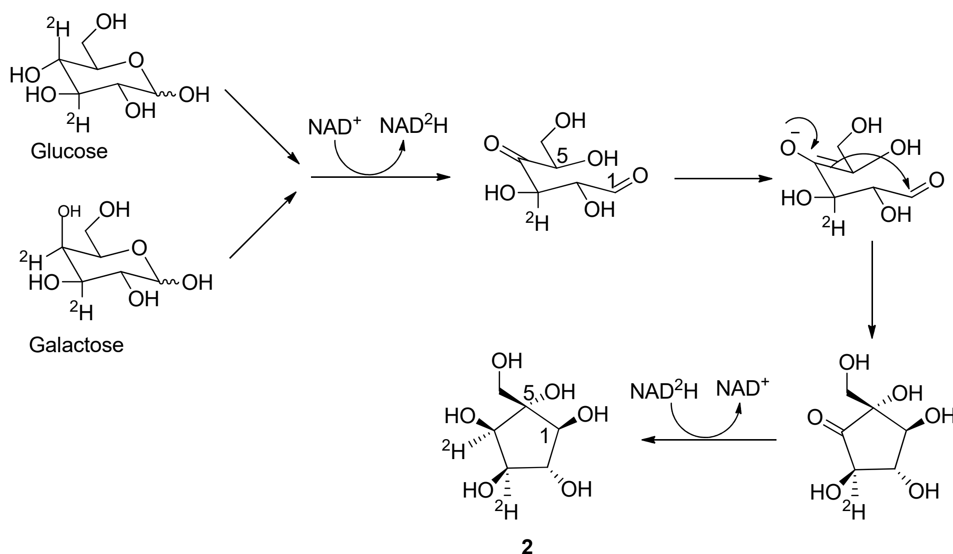
Figure 16. Structure of the lipids isolated from *Archae*.

From experiments using C-3 and C-4 deuterated glucose and galactose, a biosynthetic 'inositol like' pathway for the cyclopentanoid part of calditol has been proposed [146-149]. The sequence involves the formation of a 1,5 carbon bond mediated by a "cyclase" enzyme, followed by a stereospecific reduction at C-4 (Scheme 1). Regarding Caryose **1** no biogenetic proposal has been found in the literature.

3.2. Carbapyranoses.

3.2.1. Sedo-heptulose 7-phosphate.

Sedo-heptulose 7-phosphate (**75**), is a key intermediate in the biosynthetic pathway of valienamine and gabosines A, B, C and H. This compound derives from the pentose phosphate pathway [150-151]. The pentose phosphate pathway is the source of NADPH **68** used in reductive biosynthetic reactions and consists in two phases: the oxidative generation of NADPH (Scheme 3) and the nonoxidative interconversion of sugars (Scheme 4).



Scheme 1. Proposed biosynthesis of Calditol **2**.

In the oxidative phase, NADPH is generated from glucose 6-phosphate **65** and starts with the dehydrogenation **65** at C1 to give 6-phosphoglucono-δ-lactone **67** in a reaction catalyzed by glucose 6-phosphate dehydrogenase and mediated by $NADP^+$ (**66**). The next step is the hydrolysis of 6-phosphoglucono-δ-lactone **67** by a specific lactonase (6-phosphonogluconolactonase) to give 6-phosphogluconate **69**. This six-carbon sugar is then oxidatively decarboxylated by 6-phosphogluconate dehydrogenase to yield ribulose 5-phosphate **70**. In the non-oxidative phase, ribulose-5-phosphate **70** is transformed into xylulose-5-phosphate **71** and ribose-5-phosphate **72** via epimerization at C-3 and isomerization (through an enolate ion) respectively. Finally, a sequence of retroaldol-aldol reaction mediated by thyamine pyrophosphate **73** results in the formation of sedo-heptulose-5-phosphate **75** and glyceraldehyde-3-phosphate **74**.

3.2.2. Biosynthesis of gabosines.

The cyclization process of sedo-heptulose 7-phosphate (**75**) to a six membered carbocyclic intermediate, 2-epi-5-epi-valiolone **77** [152-155] is catalyzed by a sedoheptulose 7-phosphate cyclase (Scheme 5). These enzymes are phylogenetically related to the dehydroquinate synthases (DHQS) and use Co^{2+} as preferred cofactor. Dehydroquinate synthase (DHQS) is able to perform several consecutive chemical reactions in one active site. There has been considerable debate as to whether DHQS is actively involved in all these steps, or whether several steps occur spontaneously, making DHQS a spectator in its own mechanism. DHQS performs the second step in the shikimate pathway, the transformation of **78** (3-deoxy-D-arabino-heptalusonate-7-phosphate) into **79** (3-dehydroquinate), which is required for the synthesis of aromatic compounds in bacteria, microbial eukaryotes and plants (Scheme 5).[156-157].

The reaction is assumed to be initiated by transient dehydrogenation of C-5 to a ketone **76**, which sets the stage for the elimination of phosphate, followed by reduction of the C-5 ketone and ring-opening to produce the corresponding enolate. The latter then undergoes intramolecular aldol condensation to give 2-epi-5-epi-valiolone **77**. This compound is epimerized at C2 (compound **80**) and dehydrated via a *syn* elimination to

yield valienone **30** (Scheme 6). However, how exactly these final processes take place under the enzymatic point of view remain still obscure.

The transformation of 2-epi-5-epi-valionone **77** into gabosines requires a considerable number of steps such as dehydration, oxidation, reduction and epimerisation as depicted in Scheme 7 for the transformation of 2-epi-5-epi-valiolone **77** into gabosines A, B, C and N through the reduction product **81** (Scheme 7) [158]. It seems possible that the reduction at C-7 and the oxidation at C-1 (gabosines numeration) follow a similar mechanism, as described for the formation of 6-deoxy-4-keto sugars [159-160]. It can expect a considerably high number of specific involved enzymes working in a manner that is really not understood.

In this context a new hypothesis for the biosynthesis of gabosines from **77** has recently been proposed on the basis of an unexpected experimental observation [161]. When compound **82** (Scheme 8) was submitted to a simultaneous oxidation-elimination protocol by reaction with m-CPBA, a separable mixture of the expected α-hydroxymethyl enone **83** (10%) and β-hydroxymethyl enone **84** (68%) was obtained. The formation of **84** may be explained on the basis of a keto-enol equilibrium process followed by sulphide elimination. Considering that a similar keto-enol process had been observed [162] in a previous synthesis of gabosines N and O, a biosynthetic proposal starting from 2-epi-5-epi-valiolone **77** and involving keto-enol equilibrium cascade reactions has been formulated (Scheme 9). This kind of isomerizations has been observed in different biogenetic routes such as the transformation of ribulose-5-phosphate **70** into xilulose-5-phosphate **71** and ribose-5-phosphate **72** (see Scheme 4).

3.2.3. Biosynthesis of Validamycins.

Valienone **30** and they reduction product validone **87** are the more proximate precursor of validoxylamine A **43**, the aglycon moiety of validamycin A **35** (Scheme 10).[171-172] In the transformation of **30** into **87**, the stereochemistry of the reduction probably reflects the result of a nonenzymatic partial epimerization at C-6 of **87** due to enolization of the keto group at C-1.

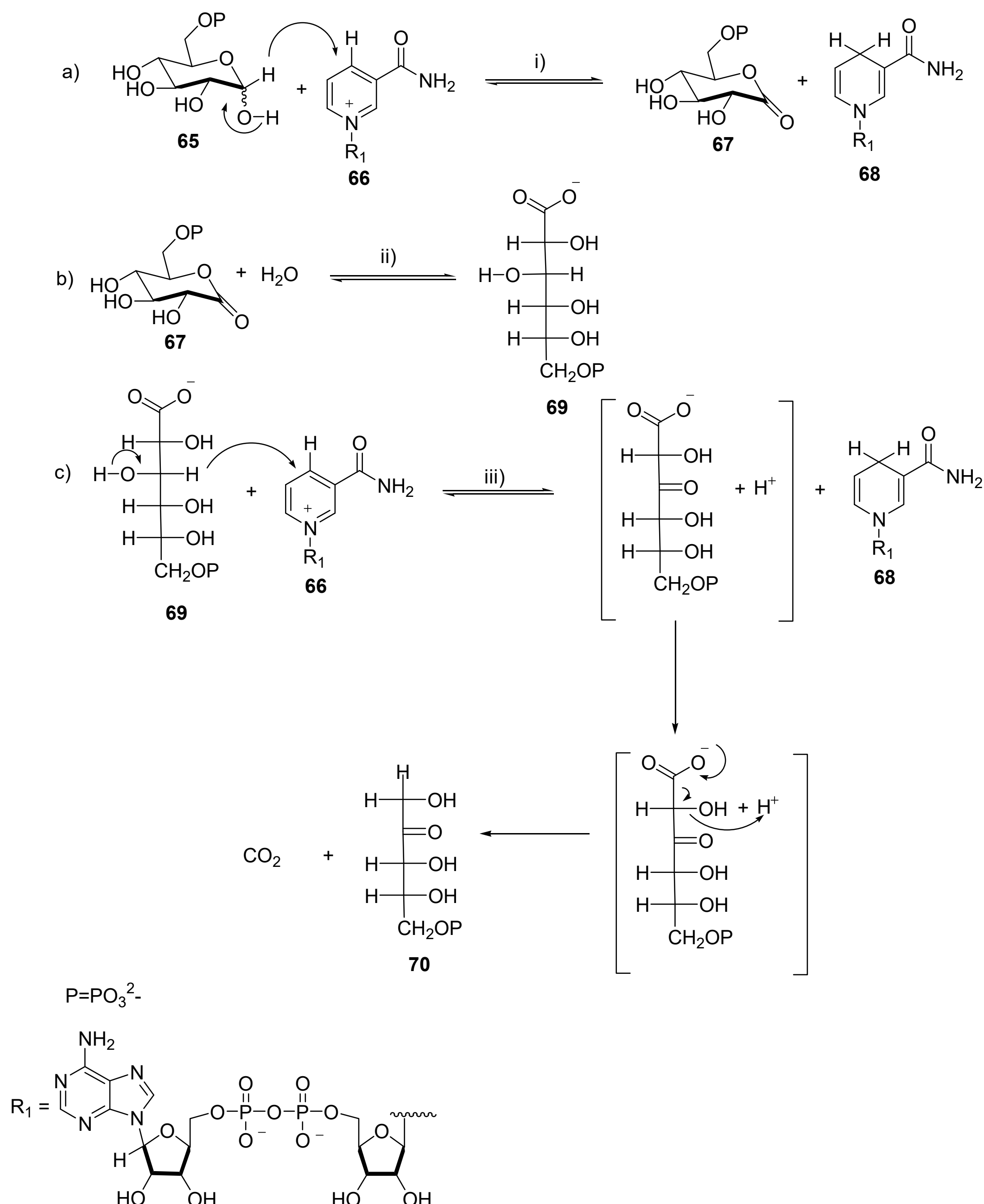
Two alternative possibilities can be envisaged for the formation of validoxylamine **43**, from **30** and **87** (Scheme 10). Either transamination of **30** would give valienamine **31**, which would then reductively couple with **87** or, alternatively, **87** would be transaminated to give validamine **32**, which would then couple with **30**. However, circumstantial evidence in favor of the second of these two scenarios comes from experimental observations using feeding experiments. Finally, incorporation of the glucose moiety should be mediated by a glucosyl transferase enzyme.

On the other hand, studies on *Actinoplanes* sp. have identified glutamate **88**, a typical substrate of transaminases, as the most efficient nitrogen donor. Also aspartate **89** and the α-nitrogens of asparagine **91** and glutamine **90** were also found to be good nitrogen sources in glutamate-depleted cultures [173]. It should be indicated that glutamate, aspartate, glutamine and asparagine are interconected in typycal reactions of the aminoacids metabolism as indicated in Scheme 11.

As we have previously indicated, the validamycin A fermentation also produces a number of minor components. Some of these, such as validamycins C (**37**), D (**38**), E

(**39**), and F (**40**), are derived from validamycin A **35**. The formation of the validamycin congeners which differ from **35** in the structure of the second cyclitol moiety would require the transamination of other ketocyclitols, such as 6-hydroxyvalidamine **33** for validamycin B (**36**) and valiolamine (**34**) for validamycin G (**41**) (Scheme 12).

Oxidative Phase.



Scheme 3. Oxidative phase. **Legend**: *a) Compounds*. **65**: Glucose-6-phosphate; **66**: $NADP^+$; **67**: 6-Phosphoglucono-δ-lactone; **68**: NADPH; **69**: 6-Phosphogluconate; **70**: Ribulose-5-phosphate; *b) Enzymes*: i) Glucose-6-phosphate dehydrogenase[163]; ii) 6-Phosphogluconolactonase [164]; iii) 6-Phosphogluconate dehydrogenase [165].

Non-oxidative phase.

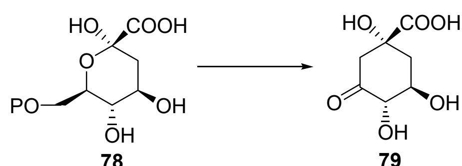
Scheme 4. Non-oxidative phase. **Legend***: a) Compounds*. **71**: Xylulose-5-phosphate; **72**: Ribose-5-phosphate; **73**: Thyamine pyrophosphate; **74**: Gliceraldehyde phosphate; **75**: Sedoheptulose-7-phosphate.; *b) Enzymes*: i) Ribulose-5-phosphate-3-epimerase [166-167]; ii) Ribulose-5-phosphate isomerase [166]; iii) Transketolase [168-170].

3.2.4. Biosynthesis of Acarbose. [176]

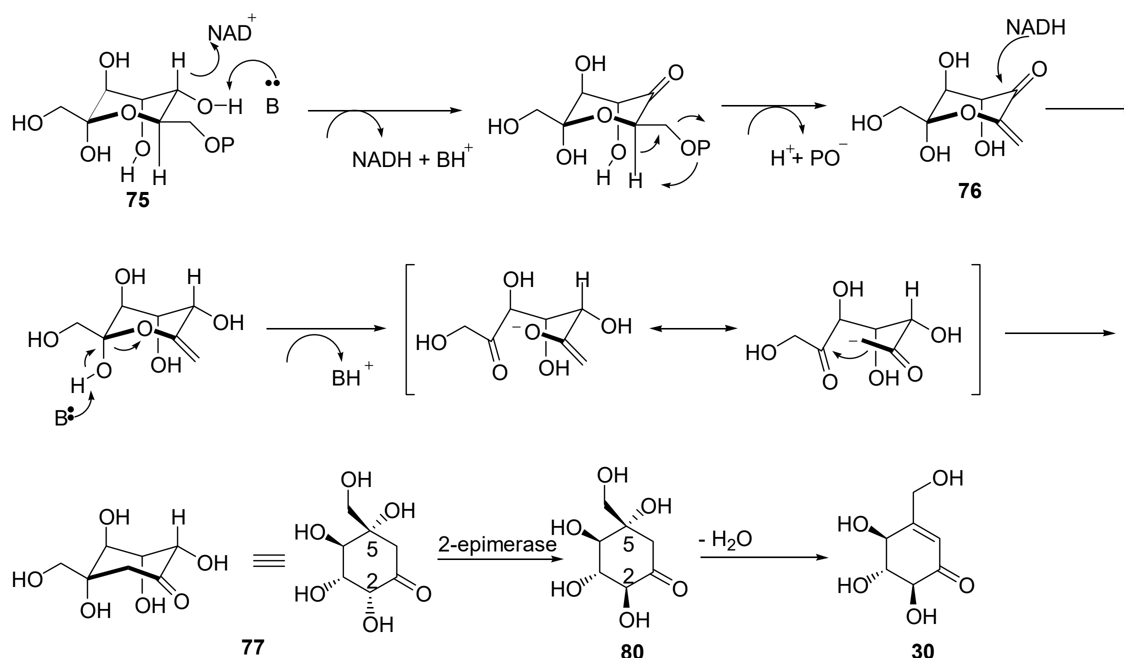
With the exception of 2-epi-5-epi-valiolone (**77**) none of the ketocyclitols 5-epi-valiolone (**80**), valienone (**30**), and validone (**87**) involved in the biosynthesis of the valienamine moiety of validamycins were incorporated (feeding experiments) into the valienamine moiety of acarbose. In consequence, the pathways in the formation of both metabolites seem to be substantially different. [177-178]

In a first approach to the biosynthesis of acarbose, it is assumed that the first generate intermediate is deoxythymidine diphosphate (dTDP) acarviose (93). It should be pointed out that Thymidine diphosphate dTDP (92, see Scheme 13) misnamed deoxythymidine diphosphate [179] consists of a pyrophosphate group attached to the

nucleoside thymidine.[180]. This intermediate is able to tranfer the acarviosyl moiety to C6' of maltose. It should be pointed out that acarbose is formed from maltotriose by two routes: (a) 60% of the acarbose is formed by attachment of maltose, produced by removing a glucose exclusively from the nonreducing end of maltotriose, to the pseudodisaccharide core unit. (b) The other 40% of acarbose is formed by direct attachment of maltotriose to the core unit followed by loss of the terminal glucose from the reducing end [181].



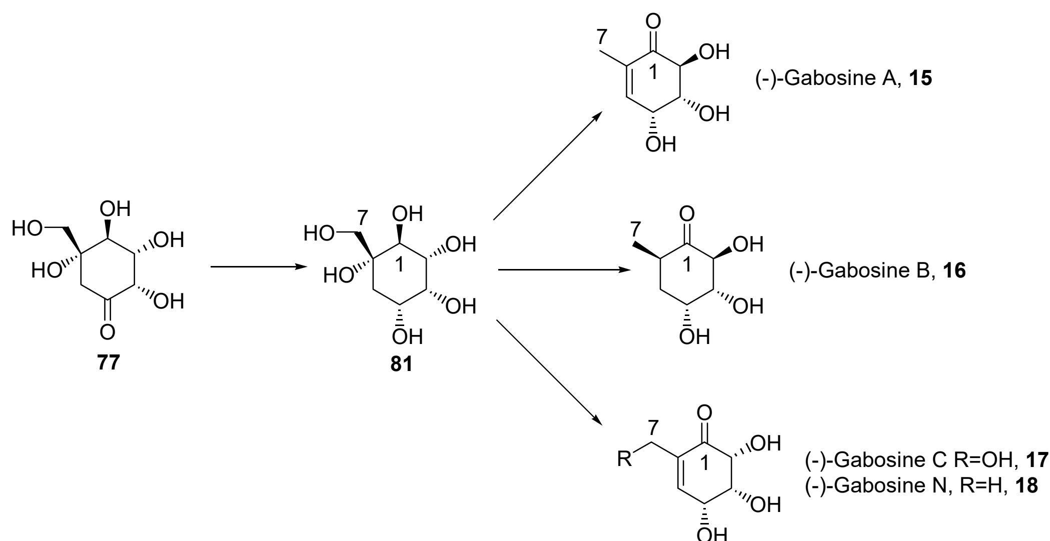
Scheme 5. Transformation of 3-deoxy-D-arabino-heptalusonate-7-phosphate into 3-dehydroquinate.



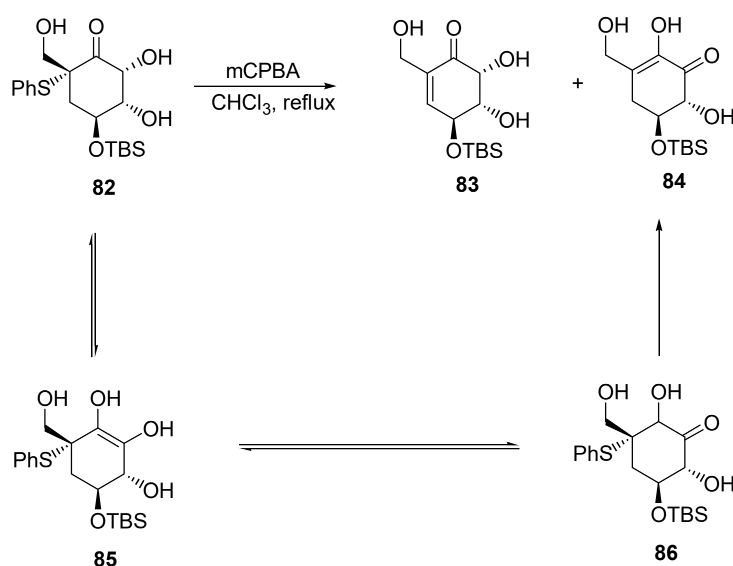
Scheme 6. Transformation of sedo-heptulose-7-phosphate **75** into valienone **30**.

A reasonable route for the formation of dTDP-acarviose (**93**) involves the introduction of the nitrogen atom into the deoxy sugar moiety via transamination of dTDP-4-keto-6-deoxy-D-glucose (**94**) to dTDP-4-amino-4,6-dideoxy-D-glucose (**95**). This compound then forms a Schiff's base with 2-epi-5-epi-valiolone (**77**) which undergoes 2-epimerization, 5,6-dehydration and final imine double bond reduction to **93** (Scheme 13).

An alternative hypothetical pathway involves the reduction of the keto-sugar **77** to 1-epi-valiol (**99**). Further activation of the C1 hydroxyl group as a phosphate (**100**) and subsequent nucleophilic displacement by the nitrogen of amino sugar **95** would afford pseudosaccharide **101**. This compound, after epimerization at C2 and 5,6-dehydration would give dTDP acarviose (**93**) (Scheme 14)[182].

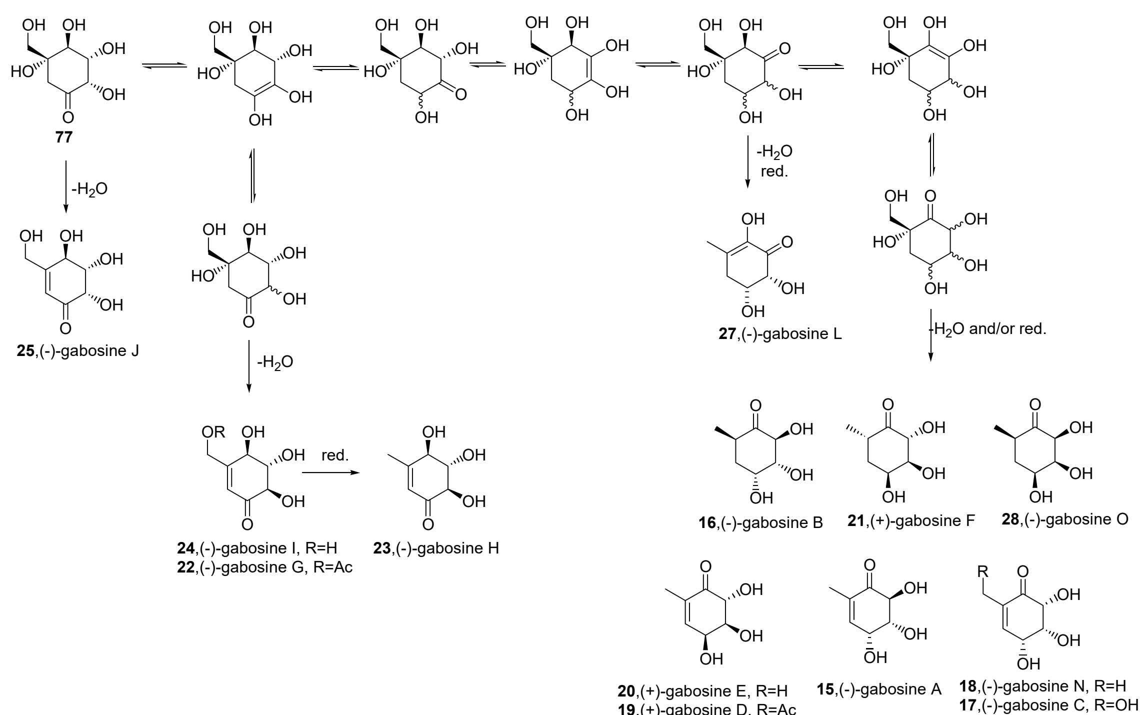


Scheme 7. Proposed transformation pathway of 2-epi-5-epi-valionone **77** into gabosines A, B, C and N.

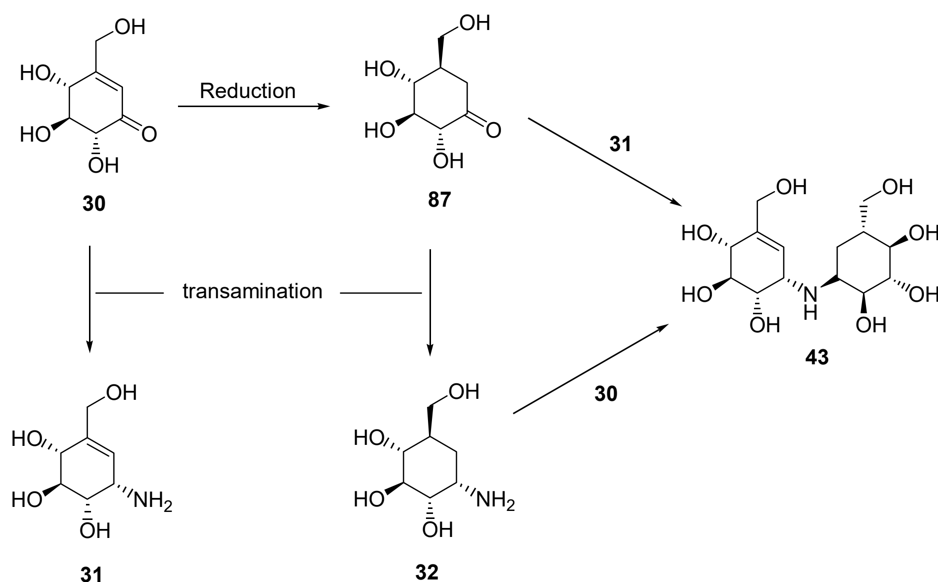


Scheme 8. Proposed mechanism for the formation of compound **84** from **82**.

More recently and on the basis of genetic and biochemical studies, a new mechanism for the biosynthesis of acarbose has been postulated. The Acarbose gene cluster (Acb) [183-186] gene cluster, involved or proposed in the sequence, are also indicated (Schem15). It should be indicated that a gene family is a set of homologous genes within one organism. A gene cluster is part of a gene family. The size of gene clusters can vary significantly from a few genes to several hundred genes. Regardless of the similarity of the DNA sequence of each gene within a gene cluster, the resulting protein of each gene is distinctive from the resulting protein of another gene within the cluster. The Acb corresponds to the 25 known gene cluster from *Actinoplanes* sp. SE50/110 identified and sequenced. Other Acb biosynthetic gene cluster from *Streptomyces glaucescens* has also been identified and sequenced.



Scheme 9. Biosynthesis of gabosines from 2-epi-5-epi-valiolone **77**.

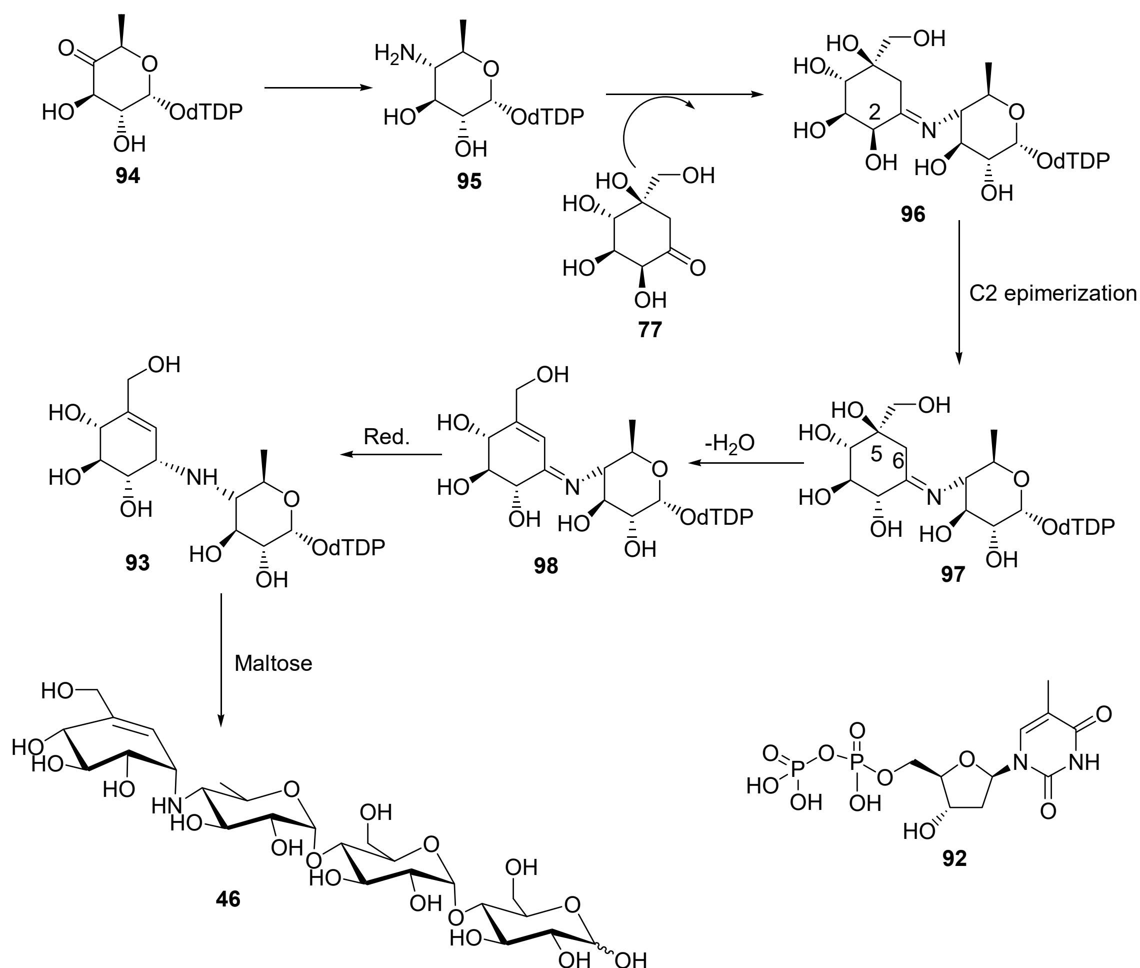


Scheme 10. Biosynthesis of validoxylamine **43** from valienone **30**.

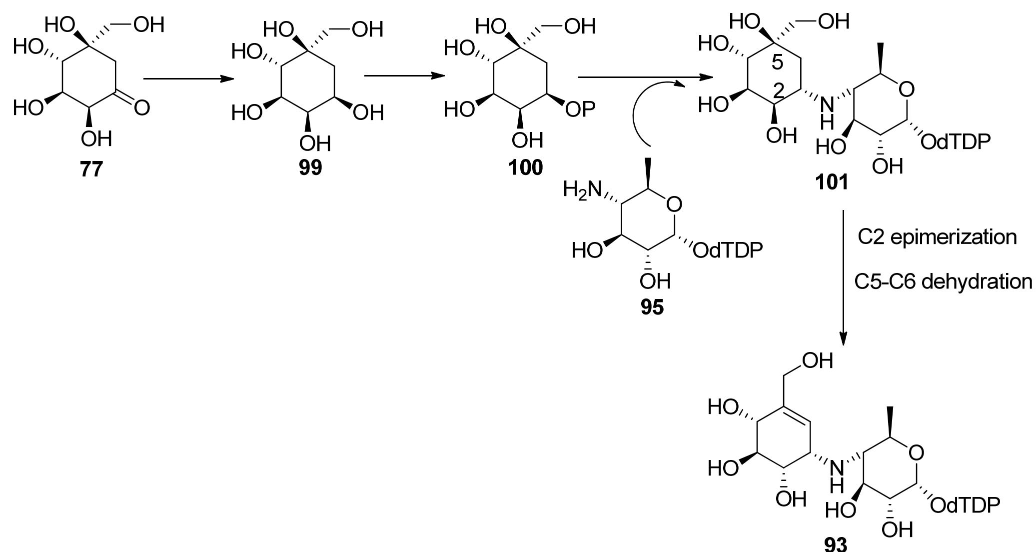
In this mechanism the cyclitol precursor, 2-epi-5-epi-valiolone (**77**), is phosphorylated to give 2-epi-5-epi-valiolone-7-phosphate (**102**) in a process mediated by the enzyme 2-epi-5-epi-valiolone 7-kinase. Compound **102** is then epimerized at C2 to give 5-epivalielone-7-phosphate (**103**). Further steps involving dehydration (**104**), carbonyl reduction and phosphorylations (**105**), nucleotidylation [187] (**106**) and final nucleophilic displacement by the nitrogen atom of **95**, would afford compound **93** [188-191]. In Scheme 15 The transformation **105-106** constitutes a nucleotidylation reaction: the transfer of an entire nucleotidyl unit, rather than just a phospho group [192].

Scheme 11. Biochemical interconversion of aminoacids glutamate, aspartate, glutamine and asparagine. Legend: i) Asparagine synthethase. [174-175]

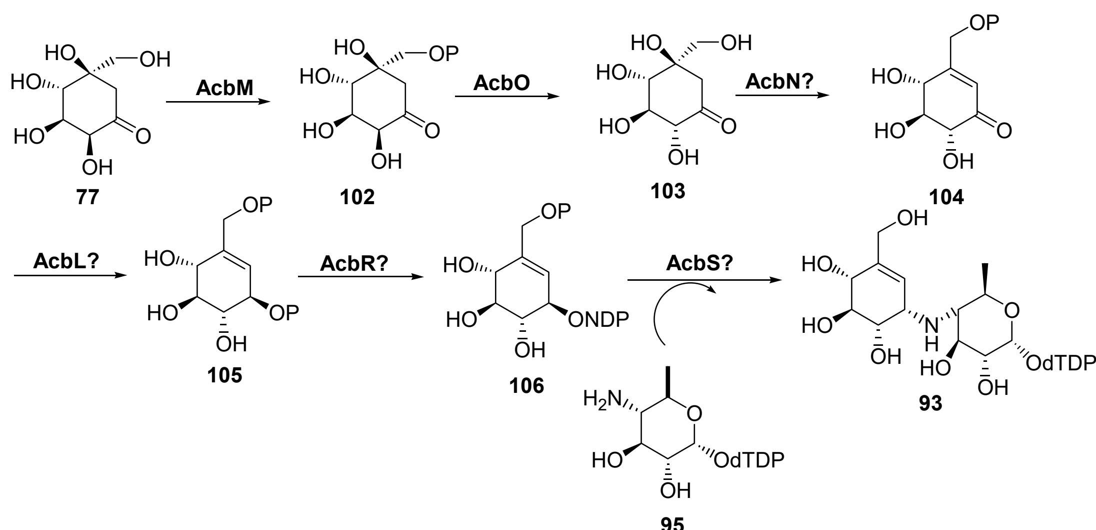
Scheme 12. Biosynthesis of Validamycins A (**35**), B (**36**), C (**37**), D (**38**), E (**39**), F (**40**) and G (**41**).



Scheme 13. Proposed biosynthetic pathway to acarbose **46** and structure of dTDP **92**.



Scheme 14. Alternative biosynthesis of dTDP-acarviose **93**.



Scheme 15. Revised proposal of the biosynthetic pathway to dTDP-acarbose **93**. NDP = nucleotidyl diphosphate.

3.2.5. Biosynthesis of Pyralomicins.

The biosynthetic gene cluster for the biosynthesis of pyralomicin antibiotics (PrI) has been isolated, cloned and sequenced from *Nonomuraea spiralis IMC* A-0156 [193]. The 41 kb (1000 base pairs) gene cluster contains 27 ORFs (the open reading frame –ORF- is the part of a reading frame that has the potential to code for a protein or peptide) [194-195] predicted to encode all of the functions for pyralomicin biosynthesis. This includes nonribosomal peptide synthetases (NRPS, Nonribosomal peptides (NRP) are a class of peptide secondary metabolites, usually produced by microorganisms. While there are a wide range of peptides that are not synthesized by ribosomes (the term *nonribosomal peptide* typically refers to a very specific set of these) and polyketide synthases (PKS) [196-197] required for the formation of the benzopyranopyrrole core unit. The PKS are a multi-domain enzyme complex involved in the biosynthesis of polyketides and fatty acids. The PKS genes for a certain polyketide are usually organized in one operon (an operon is a functioning unit of genomic DNA containing a cluster of genes under the control of a single promoter [198]) in bacteria and in gene clusters in eukaryotes. The biosynthesis of nonribosomal peptides shows several similarities with the polyketide and fatty acid biosynthesis. As consequence, some nonribosomal peptide synthetases contain polyketide synthase modules for the insertion of acetate or propionate-derived subunits into the peptide chain [199-201]. Others enzymes such as four halogenases [202] an O-methyltransferase [203-205] and an N-glycosyltransferase[206-207] necessary for further modifications of the core structure of pyralomicins have also been identified. In particular, the N-glycosyltransferase is involved in the transfer of either glucose or a pseudosugar (cyclitol) to the aglycone.

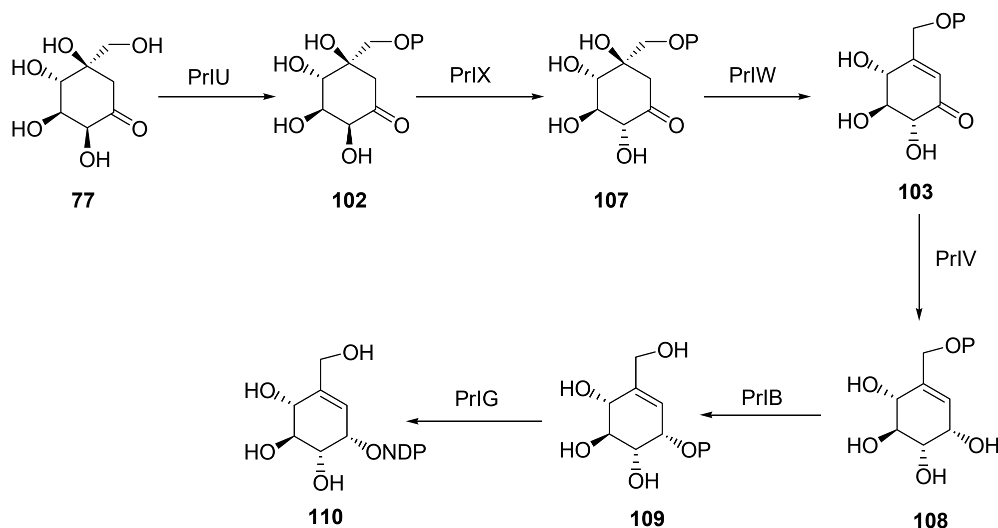
The formation of the cyclitol moiety of pyralomicyns is depicted in Scheme 16. This pathway appears to be mediated through the actions of several enzymes including the 2-epi-5-epi-valiolone synthase PrlA, a putative phosphomutase (PrlB), a cyclitol kinase (PrlU), two cyclitol dehydrogenases (PrlV and PrlW), and a 2-epi-5-epi-valiolone phosphate epimerase (PrlX). This cassette of genes shares high homology with the cyclitol biosynthetic genes from the salbostatin [208] and acarbose gene clusters.

On the other hand, the starting material for the biosynthesis of the aglycone portion of pyralomicin is the aminoacid L-proline and involves genes that share high identity with some related compounds.

3.2.6. Biosynthesis of Salbostatin.

In silico analysis of the putative biosynthetic gene cluster of salbostatin from *Streptomyces albus* ATCC 21838 revealed 20 open reading frames. The salbolstatins genes SalF, SalL, SalM, SalN, SalO, and SalR were found to be homologous to AcbR, AcbM, AcbL, AcbN, AcbO, and AcbP from the acarbose pathway, respectively (see above). That suggests that the biosynthesis of the aminocyclitol moiety of salbostatin may be very similar to that of acarbose (Scheme 17).

Thus, 2-epi-5-epi-valiolone **77** is first converted to its activated form, 2-epi-5-epi-valiolone 7-phosphate **102**, by the action of the 2- epi-5-epi-valiolone 7-kinase (AcbM), Epimerization at the C-2 position by AcbO gives 5-epi-valiolone 7- phosphate **107**. This compound is proposed to be converted to 5-epi-valiolol 7-phosphate **111** or valienone-7-phosphate **103** which were dehydrated (from **111**) or reduced (from **103**) to 1-epi-valienol 7-phosphate **112**. From **112**, 1-epi-valienol-l-phosphate **113**, and then NDP-1-epi-valienol **114** were successively formed. Condensation of NDP-1-epi-valienol **114** with deoxyglucosamine **115** (biosynthesized from N-acetylglucosamine) may finally result in the formation of salbostatin-6'-phosphate **116** which is then converted into salbostatin **54**.



Scheme 16. Proposed mode of formation of the cyclitol moiety of pyralomicins. Legend. **77**: 2-epi-5-epi-valiolone; **102**: 2-epi-5-epi-valiolone-7-phosphate; **107**: 5-epi-valiolone-7-phosphate; **103**: valienone-7-phosphate; **108**: valienol-7-phosphate; **109**: valienol-1-phosphate; **110**: NDP-valienol.

4. Biological Activity of Carbasugars.

As we have previously pointed out (see Introduction) and according to Prof. McCasland "pseudo-sugars may be found acceptable in place of corresponding true sugars to some but not all enzymes or biological systems, and thus might serve to inhibit growth of

malignant or pathogenic cells".[209] For instance, it, may be indicated that synthetic 6a-carba- β-DL-fructopyranose was found to be almost as sweet as D-fructose. [210-212]

In the context of enzymatic inhibition, [213] the structural similarity between true sugars and carbasugars can cause inhibition of enzymes involved in the digestion of carbohydrates which can lead to important consequences under medically point of view. For instance, the inhibition of carbohydrate digestive enzymes is considered a therapeutic tool for the treatment of type 2 diabetes.[214]. In the next paragraphs some applications of carbasugars and derivatives as enzymatic inhibitory agents wil be highlighted.

4.1. Biological activity of Carbafuranoses.

The carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP, Figure 17) is the only reported carbafuranose with significant biological activity.[215-217] This compound shows enzymatic inhibitory activity against the enzyme 5-phosphoribosyl R-1-pyrophosphate (PRPP) synthetase [218-220] with values [221] *K*i of 186 μM (human type PRPP synthetase) and a *K*i of 3811 mM (*Bacillus subtilis* PRPP synthetase). The enzyme PRPP-synthetase converts ribose 5-phosphate into phosphoribosyl pyrophosphate (PRPP) (Scheme 18). The resulting PRPP acts as an essential component of the purine salvage pathway (used to recover bases and nucleosides that are formed during degradation of RNA and DNA) and the *de novo* synthesis of purines. Mutations that lead to super-activity (increased enzyme activity or de-regulation of the enzyme) result in purine [222] overproduction. Super-activity symptoms include, among others, neurodevelopmental disorders [223]. On the other hand there is evidence that the activity of PRPP synthetase is elevated in tumors. Then, inhibitors of this enzyme show antineoplastic activity [224-225].

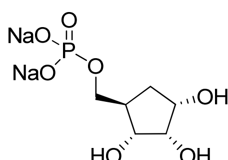
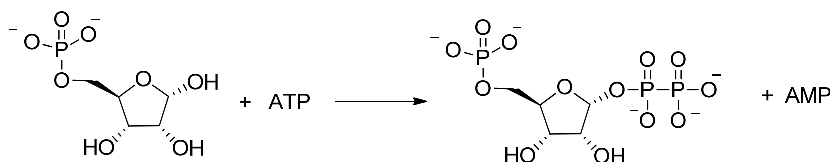
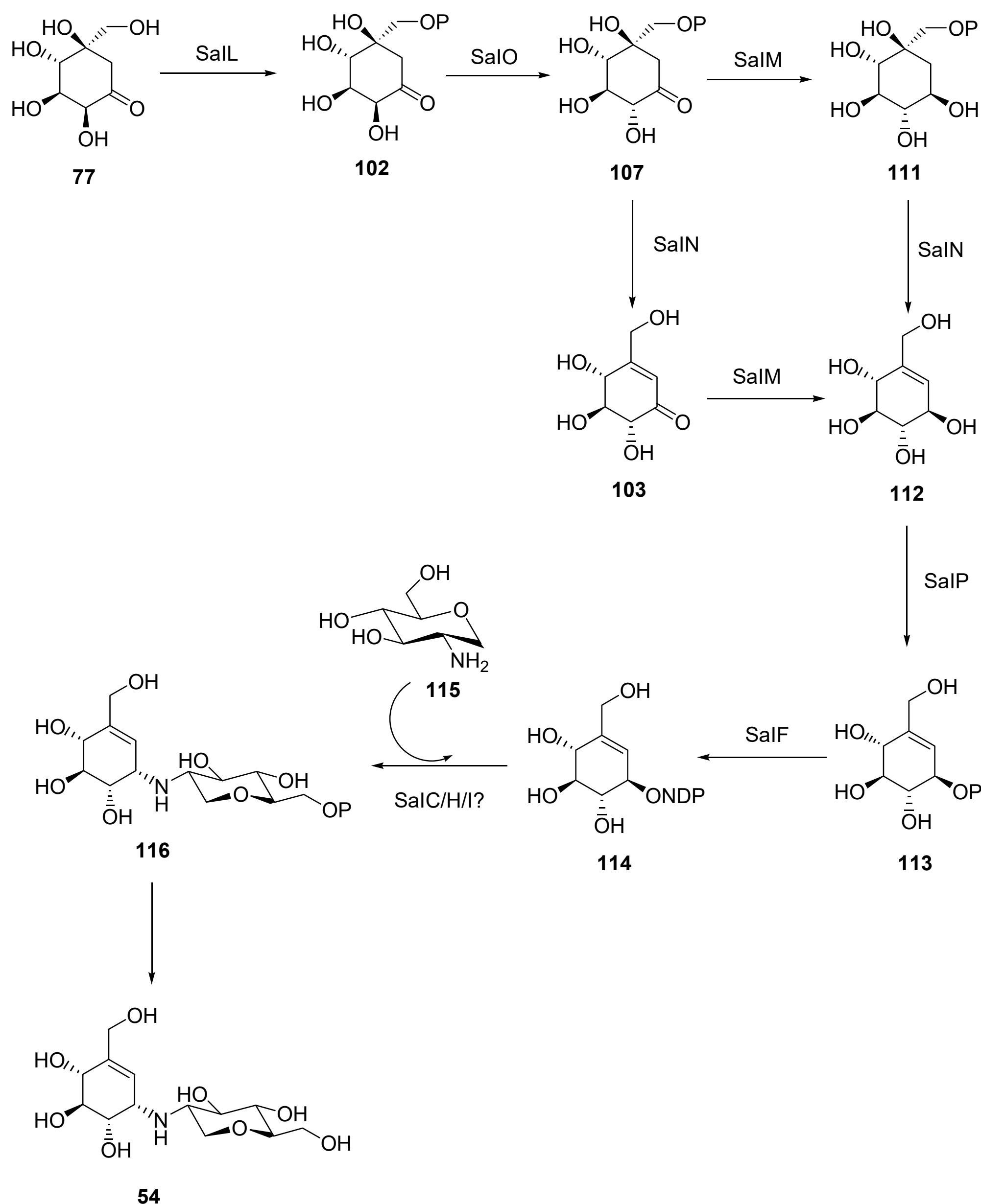


Figure 17



Scheme 18



Scheme 17. Proposed biosynthetic pathway for salbostatin.

4.2. Biological Activity of Carbapyranoses.

4.2.1. Cyclophellitol and derivatives.

(+)-Cyclophellitol (**5**) was found to be a specific inhibitor of β-glucosidases (enzymes that hydrolyze glycosidic bonds to release nonreducing terminal glucosyl residues from glycosides and oligosaccharides [226]) [227-228] with potential inhibition of the human immunodeficiency virus (HIV) and with possible antimetastatic therapeutic activity [229-231]. Several unnatural cyclophellitol derivatives also show interesting biological properties. [232-125]. For instance, (1*R*,6*S*)-cyclophellitol **120** –which is its unnatural diastereomer- inhibits α-glucosidases [236-237] and cyclophellitol aziridines [238-241] **121** are potent and selective irreversible inhibitors of retaining glycosidases (Figure 18).

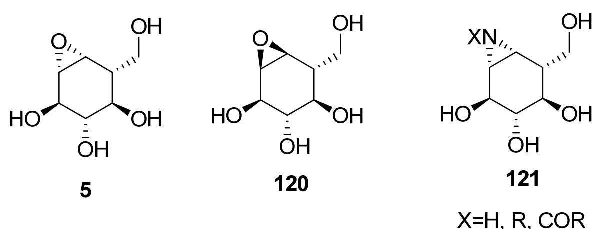


Figure 18. Structures of cyclophellitol **5**, (1*R*,6*S*)-cyclophellitol, **120**, and cyclophellitol aziridines, **121**.

Several natural and synthetic epoxyquinones and epoxyquinols with structures related to both cyclophellitol and gabosines (see below) also show interesting biological properties. The chemistry and biological activities of these compounds have been described in an autoritative reviews and will not be considered here [59].

4.2.2. MK-7067, carba-galactopyranose, carba-glucopyranose, streptol and COTC.

The unsaturated carbapyranose (+)-MK7067 **6** exhibited an effective herbicidal activity [242]. Carba-α-D-galactopyranose (**4**) was found to have a low antibiotic activity against *Klebsiella pneumonia* MB-1264, [243] whereas the L-enantiomer is inactive [244]. 5a-carba-α-DL-glucopyranose ((±)-**122**, Figure 19) is a glucokinase (a monomeric cytoplasmic enzyme found in the liver and pancreas. Its main function is regulation of glucose levels in these organs [245-246]) inhibitor. Carbasugar (±)-**122** and the *β*-anomer (±)-**121** were used as synthetic analogs of glucose anomers to study the mechanism of glucose-stimulated insulin release by pancreatic islets [247]. It was found that alpha isomer (±)-**122**, but not the beta-isomer (±)-**121**, inhibited both glucose-stimulated insulin release and islet glucokinase activity in a concentration-dependent manner. On the other hand, a cellobiose phosphorylase from *Cellvibrio gilvuse* recognizes only the beta-D-form of 5a-carba-glucopyranose (±)-**121** [248].

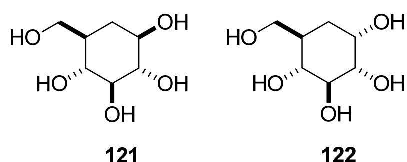
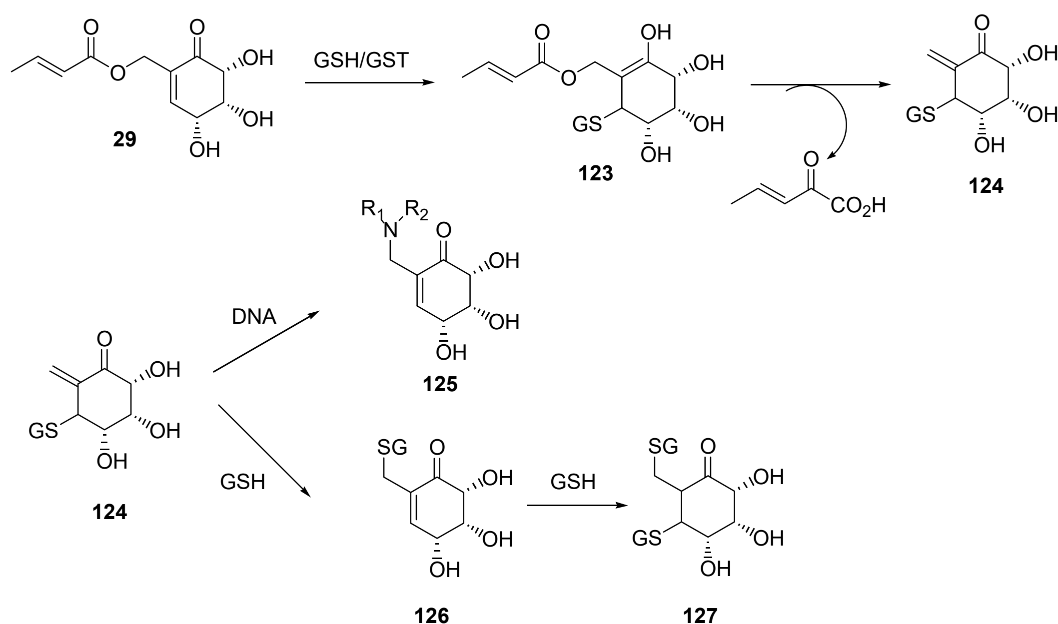


Figure 19. Structures of α-and β-glucopyranose (only D-enantiomers are shown).

Streptol (**7**) inhibited the root growth of lettuce seedlings at a concentration < 13 ppm.

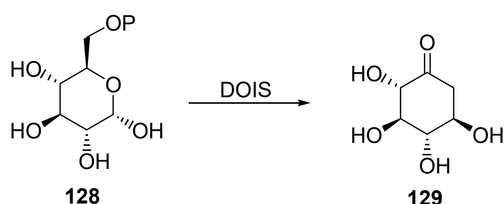
The 2-Crotonyloxy-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone, COTC (**29**) and derivatives have been shown to display notable toxicity towards a range of different cancer cell lines. The general mechanism for anti-cancer activity of COTC is depicted in Scheme 19 [249-253]. After conjugate addition of glutathione (γ-L-glutamyl-L-cysteinylglycine, GSH. Glutathione *S*-transferases (GSTs) comprise a family of isozymes -enzymes that differ in amino acid sequence but catalyze the same chemical reaction- known for their ability to catalyze the conjugation of the reduced form of glutathione (GSH) to xenobiotic -foreign chemical substance found within an organism that is not normally naturally- to the enone moiety of **29**, the resulting enol **123** undergoes expulsion of crotonic acid to generate exocyclic enone **124**. It should be

pointed out that the rate of formation of enol **123** is substantially increased by enzymatic catalysis *via* glutathione transferase (GST). Alkylation of intracellular proteins and/or nucleic acids by **124** then lead to cell death. Other processes may also contribute to the anti-cancer activity of this compound and derivatives. For instance, the GSH conjugate **126**, derived by trapping the exocyclic enone **124** with GSH, and bis-GSH adduct **127** are competitive inhibitor of human glyoxalase 1 (Glo1). This enzyme is vital for cell survival as part of a detoxification system for cytotoxic 2-oxoaldehydes or other toxic species and they inhibitors have previously been demonstrated to have anti-cancer properties [254-255]. On these bases, it seems logical to have carried out extensive efforts for the synthesis of new analogues COTC [256-264].



Scheme 19. Proposed mode of action of COTC and derivatives

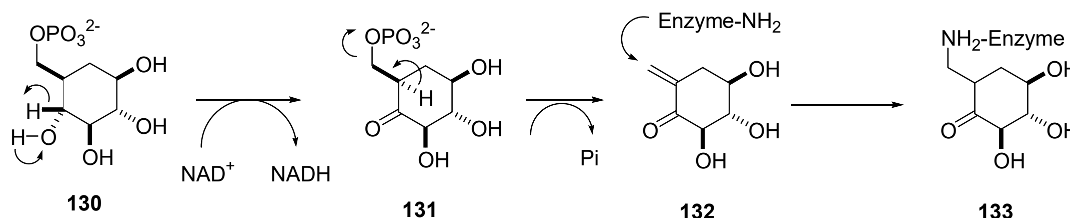
A key enzyme in the biosynthesis of clinically important aminoglycoside antibiotics such as neomycin, kanamycin and gentamicin, [265] among others, is 2-deoxy-scyllo-inosose synthase (DOIS), which catalyzes the carbocycle formation from D-glucose-6-phosphate **128** to 2-deoxy-scyllo-inosose (DOI, **129**, Scheme 20, [266]).



Scheme 20. Transformation of D-glucose-6-phosphate into 2-deoxy-scyllo-inosose.

5a-Carba-DL-glucose-6-phosphate (**130**) is an irreversible inhibitor of DOIS. The proposed reaction mechanism for this inhibitory action is shown in Scheme 21 [267]. Thus, after the initial oxidation at C4 and subsequent elimination of a phosphate, compound (±)-**130** was converted within the enzyme into an α,*β*-unsaturated methylene cyclohexanone (±)-**132**. This α,*β*-unsaturated carbonyl intermediate is attacked by a

specific nucleophilic residue in the active site (Lys-141) through a Michael-type 1,4-addition, resulting in the formation of compound **133**.



Scheme 21. Mechanism of irreversible inhibition of DOIS by 5a-Carba-DL-glucose-6-phosphate.

4.2.3. Pericosines and gabosines.

Pericosines A-C (**8**-**10**) exhibited significant growth inhibition against several tumor cell lines. In particular, pericosine A (**8**) shows significant *in vitro* cytotoxicity against P388 lymphocytic leukemia cells [268] also showing significant *in vivo* tumor inhibitory activity. In additionn, pericosine A inhibited [271] the protein kinase EGFR (the epidermal growth factor (EGF) stimulates cell growth, proliferation, and differentiation by binding to its receptor EGFR. Human EGF is a 6045-Da protein with 53 amino acid residues and three intramolecular disulfide bonds. Mutations that lead to EGFR overexpression or overactivity have been associated with a number of cancers. [269]) and topoisomerase II (topoisomerases are isomerise enzymes that act on the topology of DNA. Type II topoisomerases cut both strands of the DNA helix simultaneously in order to manage DNA. They use the hydrolysis of ATP, unlike Type I topoisomerases which are ATP-independent. [270]) Gabosine E (**20**) showed [273] a weak inhibitory effect on the cholesterol biosynthesis in cell line tests with HEP-G2 (This line has been found to express a wide variety of liver-specific metabolic functions. Among these functions are those related to cholesterol and triglyceride metabolism live cells [272]).

On the other hand, Gabosines A (**15**), B (**16**), F (**21**), N (**18**), and O (**28**) present DNA-binding properties [274-275]. Gabosine C (**17**) is the known antibiotic KD16-U [276] and its crotonyl ester is the previously considered carbasugar COTC. Gabosine J (**25**) inhibits α-mannosidase, an enzyme involved in the cleavage of the alpha form of mannose, [277] and some derivatives such as α-gabosinol **134** and β-gabosinol **135** inhibit β-galactosidase and β-glucosidase respectively (Figure 20) [278].

Some compounds structurally related with gabosines also show interesting biological properties. For instance, compound (+)-**136** has been reported [279] that is a cytotoxic and potential contraceptive agent. On the other hand, nigrospoxydon A (**137**) shows activity against *Staphylococcus aureus* ATCC 25923, a clinical isolate with the designation Seattle 1945 that is used as a standard laboratory testing control strain [280]. It has also been published that the closely related esters (−)-**138** and epoxydine B (**139**) display antibacterial, antifungal, and antialgal activities (Figure 20) [281]. The synthetic compound (+)-RKTS-33 (**140**) has inhibitory activity toward death receptor-mediated apoptosis [282-283]. The racemate of compound **141** is a nuclear factor-κB (NF-κB or nuclear factor kappa-light-chain-enhancer of activated B cells, is a protein complex that controls transcription of DNA, cytokine production and cell survival.[284-285])

inhibitor and therefore a suitable candidate as antiinflammatory and anticancer agent [286].

Finally, compound **142** shows [287] synergetic effect with cisplatin against lung cancer cell line A549 (adenocarcinomic human alveolar -terminal ends of the respiratorytree-basal epithelial cells [288], through the inhibition of GSTM1 (Glutathione S-transferase Mu 1 -gene name GSTM1- is a human glutathione S-transferase [289].

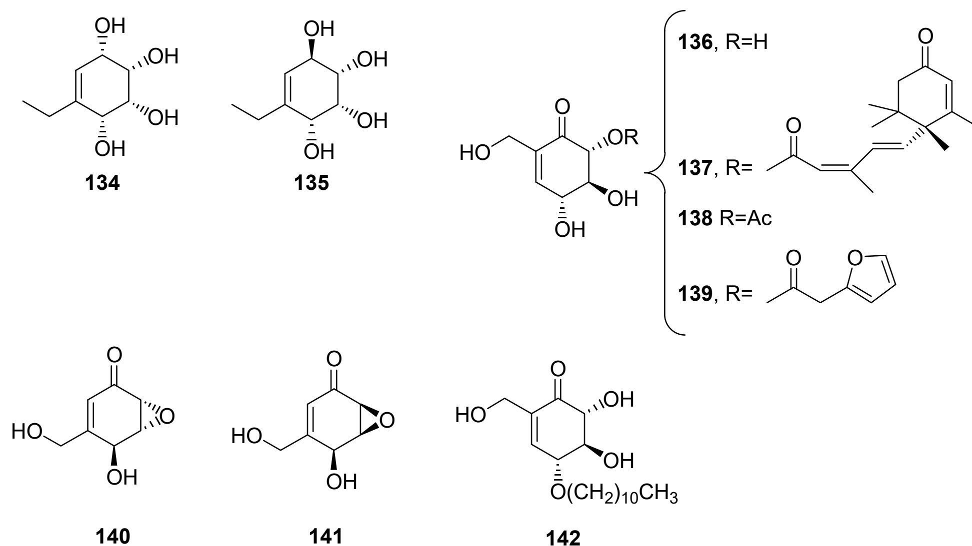


Figure 20. Some biologically active gabosine derivatives.

4.2.4. Carbaglycosides.

O-linked alkyl carba-β-D-glycosides **143** and **144** (Figure 21) have been shown [290] to be useful as primers for biocombinatorial glycosylation involving efficient uptake in B16 mouse melanoma cells, the most frequently used murine melanoma model [291].Uptake of the carbaglycosides resulted in β-galactosylation and subsequent sialylation of the galactose residues incorporated, to give rise to glycosylated products having a glycan similar to that in ganglioside GM3, a type of ganglioside, molecule composed of a glycosphingolipid with one or more sialic acids linked on the sugar chain. The letter G refers to ganglioside, and M is for monosialic acid as it has only one sialic acid residue. The numbering is based on its relative mobility in electrophoresis among other monosialic gangliosides. Recently, gangliosides have been found to be highly important molecules in immunology. Natural and semisynthetic gangliosides are considered possible therapeutics for neurodegenerative disorders [292-293]. This indicate that carbasugars can be stable and versatile building blocks for the biocombinatorial synthesis using a living cell. In addition, a strong and specific inhibition of β-galactosidase (bovine liver) was found for dodecyl 5a-carba-β-D-galactopyranoside (**144**).

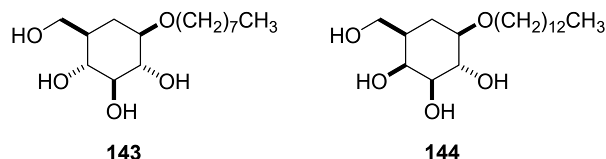


Figure 21. Structures of carba-*β*-D-glycosides **143** and **144**.

In addition, more complex carbaglycosides have interesting biological activities. Synthetic carbaxylosides of coumarins, i.e., (+)-**145** or (-)-**145**, have significant potential as oral antithrombotic agents [294], and a 5a-carba analogue of glucotropaeolin, (±)-**146**, was shown to display a good inhibition power [295] against myrosinase, the only known enzyme found in nature that can cleave a thio-linked glucose [296]. (Figure 22).

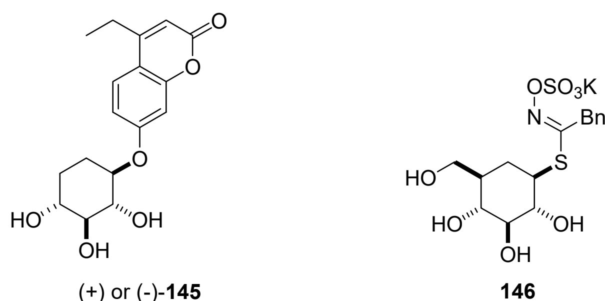


Figure 22. Structures of carba-glycosides **145** and **146**.

4.2.5. Carbanucleotides.

Some synthetic carbasugar-nucleotide displayed biological activity as glycosyltransferase inhibitors. For instance, uridine-5′-(5a-carba-α-D-galactopyranosyl diphosphate) **147** (Figure 23), the carbocyclic analog of UDP-galactose, exhibits inhibitory activity of *β*-(1→4) galactosyltransferase from bovine milk [297].

On the other hand, the carbocyclic analogue of GDP-fucose, consisting of 5a-carba-β-L-fucopyranose **148** [298]**,** was found to be a competitive inhibitor of fucosyltransferases, key enzymes in the biosynthesis of the Lewis-x determinant. Interestingly, the carba-fucose analogue **148** showed a *K*i value similar to that observed for the GDP-fucose indicating that the ring oxygen of fucose is not critical for the recognition of GDP-Fuc by the enzyme, albeit it is essential for the transfer to occur [299].

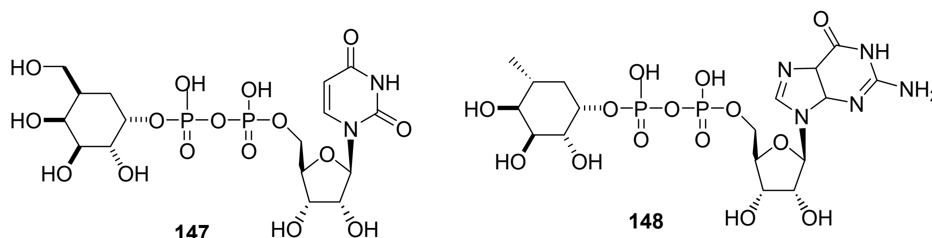


Figure 23. Structure of carbanucleotides **147** and **148**.

4.2.6. Aminocarbasugars.

Amino carbasugars [300] are the most important and appealing carbapyranose derivatives from a biological standpoint.

4.2.6.1. Valienamine, validamine, hydroxyvalidamine, valiolamine and derivatives.

Simple aminocarbasugars such as valienamine (**31**), validamine (**32**), hydroxyvalidamine (**33**), and valiolamine (**34**) appeared to be active against several sugar hydrolases [301-302]. Valienamine, validamine and hydroxyvalidamine were reported as microbial oligosaccharide α-glucosidase inhibitors [303-306]. The α-galacto-, *β*-gluco-, and α-mannovalidamine analogues **149-151** (Figure 24) have been prepared and their glycosidase activity tested [307-309]. These compounds, however, displayed moderate activity as glycosidase inhibitors when compared with (α-gluco-validamine. Converselely, valiolamine (**34**) has more potent α-glucosidase inhibitory activity against porcine intestinal sucrase, maltase, and isomaltase than the rest of the aminocarbasugars [310]. That is why series of *N*-substituted valiolamines were synthesized, resulting in the preparation of the glycohydrolase inhibitor voglibose (**152**) [311-313]. Voglibose was launched as an antidiabetic agent in 1994 to improve postprandial hyperglycemia in diabetes mellitus [314-316]. Voglibose inhibits disaccharidases competitively, suppressing the elevation of the blood glucose concentration after oral sucrose, maltose, or starch administration, but not after oral glucose, fructose, or lactose intake.

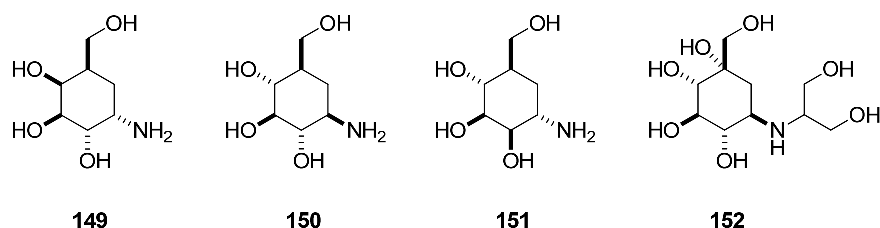


Figure 24. Structures of α-galacto-, *β*-gluco-, and α-mannovalidamine analogues (**149-151**) and Voglibose (**152**).

Moreover, carbocyclic analogues of glycosylamides [317], which contain the 5a-carba-D-hexopyranose residues (Figure 25), have also been synthesized. 5a-Carba-*β*-glucopyranosyl- and 5a-carba-*β*-galactopyranosyl-amides **153** and **154** have been shown to be potent immunomoduladors, comparable to the *true* sugars [318], suggesting that the glycolipid analogues may provide appropriate model compounds for biochemical studies in glycolipid chemistry. On the other hand, the glycosidase inhibitory effects of 1,2-bis-epi-valienamine **155** and 1-epi-2-acetamido-2-deoxy-valienamine **156** (Figure 25) have been investigated. 1,2-bis-epi-Valienamine **155** acts as a β-mannosidase [319] inhibitor whereas 2-acetamido-2-deoxy-1-epi-valienamine **156** has been shown [320] to inhibit various β-hexosaminidases, enzymes involved in the hydrolysis of terminal N-acetyl-D-hexosamine residues in N-acetyl-β-D-hexosaminides [321-323].

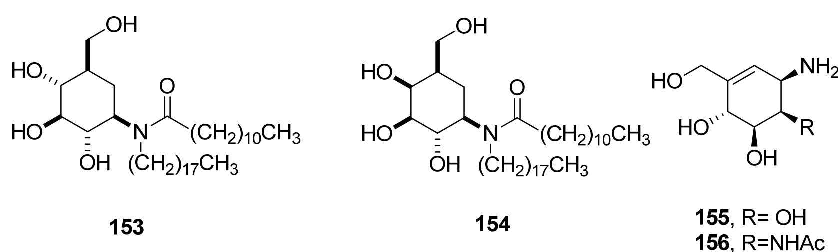


Figure 25. 5a-Carba-*β*-glucopyranosyl- and 5a-carba-*β*-galactopyranosyl-amides.

A serie of *N*-linked carbocyclic analogues of glycosylceramides, structurally related to glycosphingolipids and glycoglycerolipids, have also been synthesized by replacing the sugar residue with either saturated [324] (**157**, **158**, Figure 26) or unsaturated [325] (**159**, **160**, Figure 26) 5a-carba-D-gluco- or 5a-carba-D-galactopyranoses, respectively. Compounds **157** and **158** are mild immunomodulators and possess a mild inhibitory activity against gluco- and galactocerebrosidases, whereas the unsaturated gluco-**159** and galacto-**160** analogues were shown to be very potent and specific of gluco- and galactocerebrosidase inhibitors, respectively, thus showing the critical role played by the C4 configuration for specificity in inhibition.

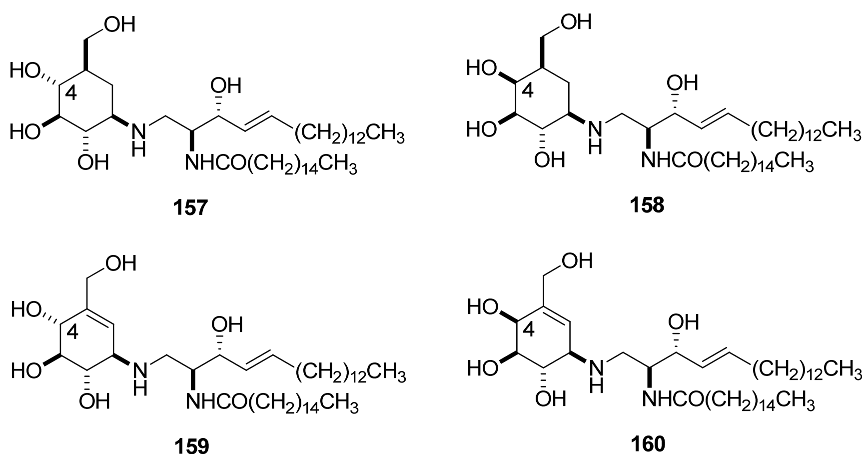


Figure 26. *N*-linked carbocyclic analogues of glycosylceramides **157**-**160**.

Various *N*-alkyl- and *N,N*-dialkyl-*β*-valienamines were synthesized and testing as glycosilases inhibitors [326-329]. For instance, N-benzylation of valienamine improves significantly they inhibitory activity toward α-glucosidases [330]. In this way, 91 pure N-alkylated valienamines **161** (Figure 27) prepared using solid-phase synthesis methodology are new β-glucosidase inhibitors, being most of them more potent than valienamine [331]. On the other hand, the spiroaziridines and spirodiaziridines **162** and **163** were prepared and evaluated as glycosidase inhibitors against β-glucosidases from almonds, β-glucosidase from *Caldocellum saccharolyticum*, and α-glucosidase from yeast with poor results compared with the cyclopentylamine **164** (Figure 27) [332].

Two isomeric bicyclo[4.1.0]heptane **165** and **166** (Figure 27) have been synthesized and evaluated against α-galactosidase enzymes from coffee bean and *E. coli* [333]. The activity of the glycosyl hydrolase family GH27 enzyme (coffee bean) was competitively inhibited by the 1R,6S-amine with a K_i value of 0.541 μM. The E. coli α-galactosidase exhibited a much weaker binding interaction with the 1R,6S-amine (IC_{50} = 80 μM). The diastereomeric 1S,6R-amine bound weakly to both galactosidases, (coffee bean, IC_{50} = 286 μM) and (E. coli, IC_{50} = 2.46 mM).

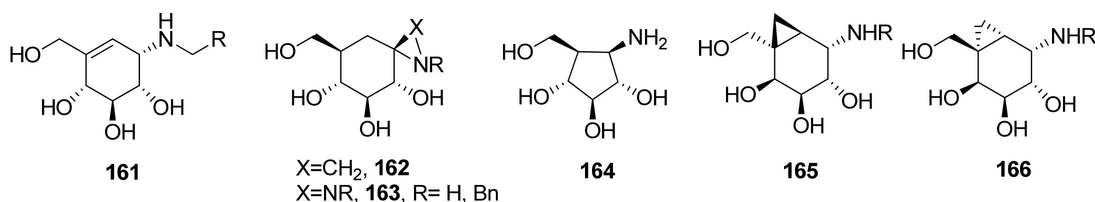


Figure 27. Alkylated valienamine derivatives, spiroaziridines **162**, spiroazirinas **163**, cyclopentylamine derivative **164** and bicyclo[4.1.0]heptane derivatives **165** and **166**.

N-Octyl-*β*-valienamine derivative **167** (Figure 28) is a potent and specific inhibitors of *β*-glucocerebrosidades (IC_{50} = 3 x 10^{-8} M). On the contrary, galacto derivative **168** did not show any improvement in potency. Additionally, it was later demonstrated that **167** and **168** are potent competitive inhibitors of human *β*-glucosidase and human *β*-galactosidase, respectively.

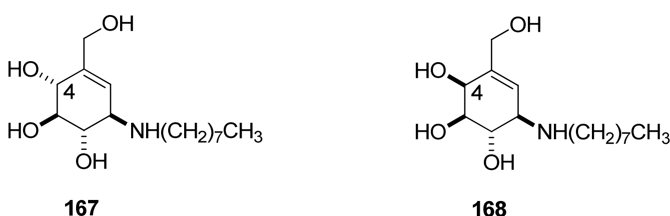


Figure 28. N-Octyl-β-valienamine derivatives.

These activities suggest that carbasugar derivatives **167** and **168** work as chemical chaperones,[334-337] to accelerate transport and maturation of mutant forms of enzyme proteins and therefore may be useful for certain patients with *β*-galactosidosis and potentially other lysosomal storage diseases [338-350]. It should be opportune at this point clarify the concept of chemical chaperone [351-353]. Pharmacological or molecular chaperone therapy is among the newest therapeutic ideas for lysosomal storage diseases. Lysosomes are enzymes within cells that digest large molecules and pass the fragments on to other parts of the cell for recycling. This process requires several critical enzymes. If one of these enzymes is defective, because of a mutation, the large molecules accumulate within the cell, eventually killing it. Pharmacological chaperones are small molecules that specifically bind to and stabilize the functional form or three-dimensional shape of a misfolded protein in the endoplasmic reticulum (ER) of a cell. When misfolded due to a genetic mutation, the enzyme is unable to adopt the correct functional shape and, in consequence, the enzyme activity is reduced. The binding of the chaperone molecule helps the protein fold into its correct three-dimensional shape. Pharmacological chaperone therapy is in early stage clinical trials for disease such as Fabry (a rare genetic lysosomal storage disease. Fabry disease can cause a wide range of systemic symptoms such as pain, kidney complications, high blood pressure, cardiomyopathy, fatigue, vertigue, nausea, diarrhea, etc) and Gaucher Type I (a genetic disorder in which glucocerebroside accumulates in cells and certain organs. The disorder is characterized by bruising, fatigue, anemia, low blood platelet count and enlargement of the liver and spleen. It is caused by a hereditary deficiency of the enzyme glucocerebrosidase which acts on glucocerebroside. When the enzyme is defective, glucocerebroside accumulates, particularly in white blood cells and especially in macrophages (mononuclear leukocytes).

In the search for different sugar hydrolase inhibitors, 5a-Carba-α-DL-fucopyranosyl amine [354-355] ((±)-**169**) and 5a-carba-*β*-L-fucopyranosylamine (**170**) [356] were prepared. These compounds have been shown to be strong inhibitors of α-L-fucosidase. α -Fucosidase inhibitors are interesting because they are potential candidates for cancer and HIV drugs, due to their inhibitory effect on the extracellular matrix secreted fucosidases [357]. Different N-substituted derivates of **(±)-169** were prepared. The

inhibitory activity was increased by incorporation of alkyl and phenylalkyl groups into the amino function of the parent (±)-**169**. The change of the *N*-alkyl substituents, from ethyl on **171a** to nonyl on **171e**, improved the inhibitory power. The *n*-octyl derivate (**171d**) was found to be the strongest inhibitor of α-L-fucosidase (bovine kidney) more potent (Ki = 0.016 μm) than deoxyfuconojirimicin (Ki = 0.031 μm), the most powerful mammalian α-L-fucosidase inhibitor identified [358]. In a similar manner, chemical modifications of **170** generated N-substituted derivatives (±)-**172a-g**, which were found to be very strong *β*-galactosidase as well as *β*-glucosidase inhibitors with no specificity associated with the 4-epimeric structures. This inhibitory activity appeared attributable to D-enantiomers exclusively, that is, *N*-alkyl-6-deoxy-5a-carba-*β*-D-galactopyranosylamines (D-**172**) [359]. (Figure 29).

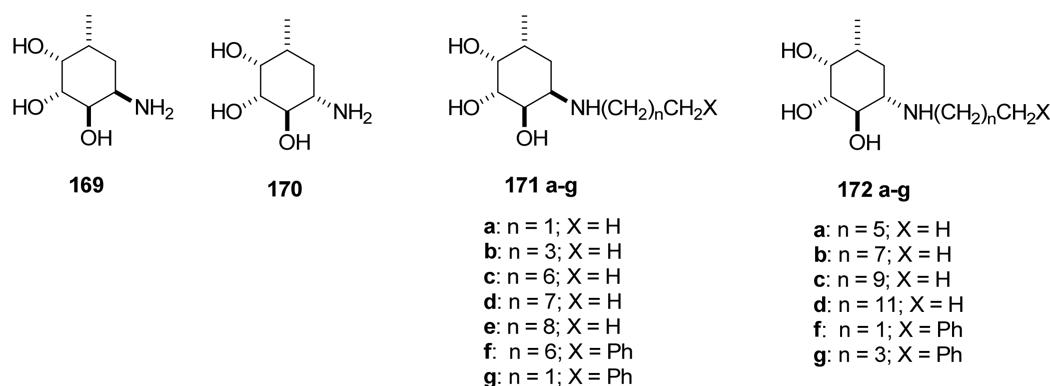


Figure 29. Carba-fucopyranosyl amines **169-172**.

Carbasugar derivatives have also been envisaged to play roles in elucidating and controlling other biological events that involve sugar moieties. This includes the synthesis of analogues of enzyme substrates, which were modified by replacing part of their structures with carbasugar units and which were expected to be used in the elucidation of the mode of action of sugar transferases [360]. These analogues have been recognized as good substrates, thus showing that the ring oxygen in the acceptor is not involved in the specific recognition by the enzyme. For instance, bovine *β*-(1→4)-galactosyltransferase was tested with α-galacto- (**173**), α- and *β*-manno- (**174** and **175**), and α- and *β*-gluco- (**176** and **177**) 2-acetamido-2-deoxy-5a-carba-DL-hexopyranoses [361]. Of these compounds, only **176** and **177** behave as galactosyl acceptors. The reactions afforded disaccharides **178** and **179**, but half of the material remained unreacted, suggesting that only the D-enantiomers behaved as acceptors. These results indicate that the ring oxygen atom is not used for specific recognition by bovine *β*-(1→4)-galactosyltransferase (Figure 30).

4.2.6.2. Validamycins, salbostatain, acarbose, amylostatins, adiposins, oligostatins, tetrastins and related compounds.

Validamycins **35-42** and salbostatin (**54**) have been reported to be mechanistically unique antifungal agents [362-366]. Validamycin A (**35**), the most active compound of the complex, is a fungicida that inhibits trehalases, enzymes that carry out the degradation of the non-reducing disaccharide trehalose [367-369] in plants, insects, and fungi as well as enhance trehalose accumulation in transgenic plants. It is widely used in rice-producing countries in Asia to control sheath blight disease of the rice plants caused by the fungus *Rhizoctonia solani* [370-384].

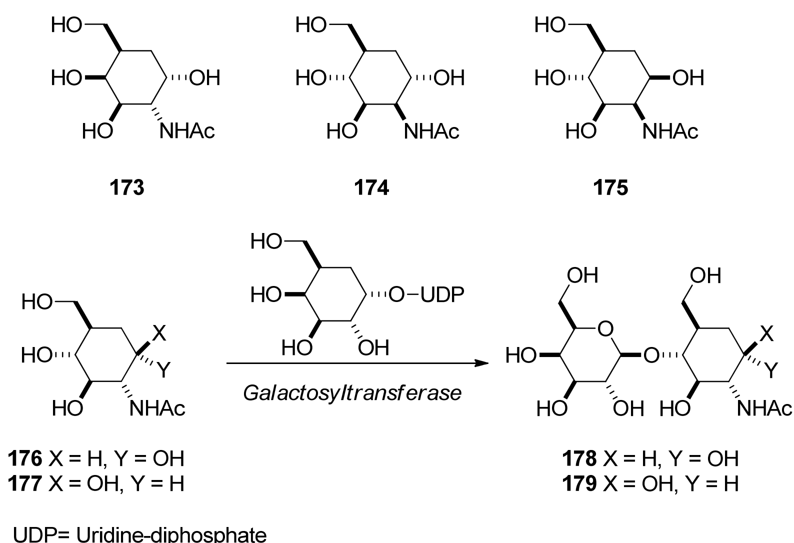


Figure 30. Carbasugars as sugar transferases.

Validamycin A is able to control the spread of the pathogen by inhibiting specifically the hyphal (a long, branching filamentous structure of a fungus, oomycete, or actinobacterium [385]) extension without affecting the specific growth rate. It means Validamycin A is effective against *Pellicularia sasakii* and *Rhizoctonia solani* in plants, but only decreases their virulence instead of exhibiting a fungicidal effect [386-389]. Further extensive studies on the mechanism of action of validamycin in controlling the hyphal extension have been carried out by several research groups, and it seems to be related to the anti trehalase activity [390-392] of the carba-disaccharide validoxylamine (**43**) [393]. For the purpose of developing more potent trehalase inhibitors, several pseudo-trehalosamines, such as **180** and **181**, as well as dicarba analogues of trehalose, **182**-**184**, composed of valienamine, validamine, and valiolamine moieties, were synthesized and they showed to possess strong inhibitory activity against trehalase (Figure 31) [394-396].

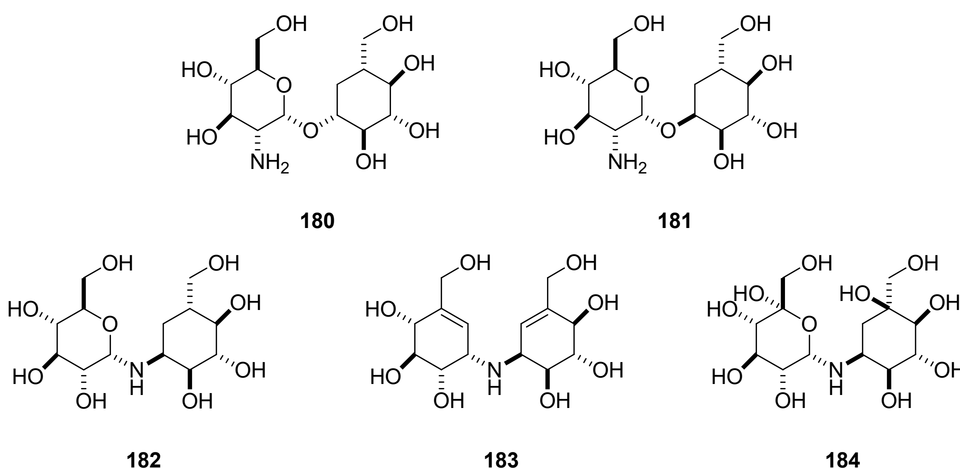


Figure 31. Carbasugars **180**-**184** with anti-tetrahalase activity

Many members of the carba-oligosaccharidic group, e.g., acarbose (**46**), amylostatins (**50**), adiposins (**51**), oligostatins (**52**), and trestatins (**53**), are known to display potent α-glucosidase inhibitory effects. Among these active metabolites, acarbose is of

considerable pharmacological interest. In addition to its α-glucosidase activity, acarbose also displays potent inhibitory activity against sucrase, maltase, dextrinase, and glucoamilase. This pronounced inhibitory effect has resulted in its use as a clinical drug for the treatment of type II non-insulin-dependent diabetes and, in some countries, prediabetes in order to enable patients to better control blood sugar contents while living with starch-containing diets. It is a starch blocker, and inhibits α-glucosidase, an intestinal enzyme that releases glucose from larger carbohydrates. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. Interestingly, individual members of different series of carba-oligosaccharides deactivate α-amylase and sucrase quite differently. Thus, whereas amylase inhibition is maximum with homologues of four and five glucose units, the greatest sucrase inhibition is caused by acarbose containing two glucose residues [397].

Adiposins (**51**) have exhibited potent inhibitory activities against α-glucoside hydrolases such as salivary and pancreatic α-amylases, and intestinal disaccharidases, such as sucrase, maltase, and isomaltase [398]. They have also showed antimicrobial activities against some Gram positive bacteria, Gram negative bacteria, some anaerobic bacteria, and some phytopathogenic fungi, and also showed a synergistic effect on the antibacterial activity with some maltooligosaccharides [399].

Oligostatins (**52**) exhibited not only strong α-amylase inhibitory activity but also they are active against Gram negative bacteria, while Gram positive bacteria are not affected [400].

The acarviosine, which is the core structure of acarbose and related carba-oligosaccharides α-amylase inhibitors, is the responsible of their glycosidase inhibitory activities due to the valienamine portion mimics the glucopyranosyl cation intermediate at the active site for hydrolysis of α-glucosides in the acarviosine moiety. Thereupon, several chemically modified acarviosin analogues, **185-190**, have been prepared and their glycosidase inhibitory activities were tested [401-404]. The results showed that the 4-amino-4,6-dideoxy moiety could be replaced by other simple structures, such as 1,6-anhydrohexoses, without losing its inhibitory power against α-glucosidase. However, modification of the valienamine portion, in order to mimic each substrate structure, did not result in any inhibitory activity against the targeted enzyme; see, for instance, compounds **189** and **190** for *β*-glucosidase and α-mannosidase activities, respectively (Figure 32).

Carbatrisaccharide **191**, an analogue of the “trimannosyl core” which frequently occurs in biologically important glycoconjugates [405-406], was found [407] to be fully active as an acceptor for *N*-acetylglucosaminyltransferase-V, both with the enzyme isolated from hamster kidney and with the one cloned from rat kidney. The kinetic parameters were functionally equivalent with those of the *true* trisaccharide. A preparative glycosylation reaction was performed using **191** as the acceptor with the cloned rat kidney enzyme. A tetrasaccharide formed by the addition of a Glc pNAc residue (**192**) was the sole product detected (Scheme 22).

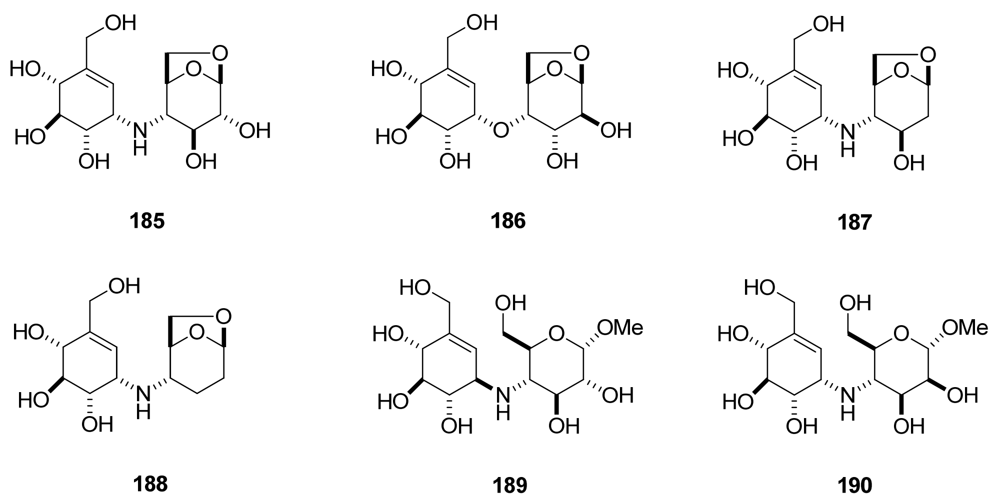
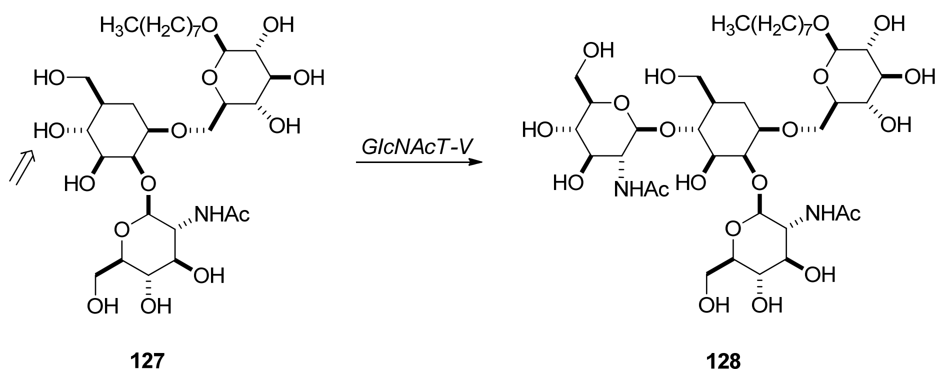


Figure 32. Acarviosine analogues **185-190**.



Scheme 22. Carbatrisaccharides **191** and **192**.

Fucosyl and sialyl transferasas are involved in the synthesis of Sialyl Lewis-x, one of the most important blood group antigens, which is a tumor-associated tetrasaccharide, and ligand of *E*-selectin-mediated inflammatory extravasation of granulocytes and monocytes [408]. Fucosyl and sialyl transferases are involved in the last steps of the biosynthesis of Lewis oligosaccharide antigens by transferring α-fucopyranosyl residues [409-411]. Therefore, an area of interest is the design of potential inhibitors of these enzymes involved in the assembly of the Sialyl Lewis-x structure. In the search for inhibitors of the biosynthesis of Lewis oligosaccharide antigens, the synthesis of carbasugar analogues of the disaccharide fragment highlighted in Figure 33 was carried out by Ogawa *et al* [412-413]. They prepared ether- and imino-linked *N*-acetyl-5a′-carba-*β*-lactosaminides and -isolactiminides, and tested them against fucosyltransferases. Biological assays showed that compounds **193a** and **193b** (Figure 33) are acceptor substrate for human-milk α-(1 → 3/4)-fucosyltransferase with kinetic parameters comparable to those observed for standard *true* disaccharides. Small-scale enzymatic synthesis was carried out by treatment of **193a** and **193b** with GDPfucose and milk fucosyltransferase which resulted in the conversion into the corresponding trisaccharides (by fucosylation at O3). Interestingly, compounds **194a** and **194b** were neither acceptors nor inhibitors for milk fucosyltransferase, suggesting that α-(1→4) transfer is not possible. The milk preparation contains a mixture of two different [α-(1→3/4)- and α-(1→3)-] fucosyl transferase enzymes. These enzymes were separated, and it was shown that both forms utilized compounds **193a** and **193b** as acceptor

substrates, whereas **194a** and **194b** were not. This was the first demonstration of a specific substrate for a α-(1→3)-fucosyltransferase.

In contrast with these results, screening carried out on isomeric octyl 5a-carba-*β*-lactosaminide (**195b**) and isolactosaminide (**196b**) (where the carbasugar unit is at the reducing end) showed that both compounds were good substrates for α-(1→3)-fucosyltransferase V (human recombinant, *Spodoptera frugiperda*) as well as α-(2→3)-(N) sialyltransferase (rat, recombinant, *Spodoptera frugiperda*) when compared to the parent compounds **195a** and **196a** [414].

The inhibitory activity of four new carbadisaccharides (ether-linked methyl 5a'-carba-*β*-lactoside (**197a**) and imino-linked methyl 5a'-carba-*β*-lactoside (**197b**), methyl *N*-acetyl-5a'-carba-*β*-lactosaminide (**197c**), and methyl *N*-acetyl-5a'-carba-*β*-isolactosaminide (**198**)) toward rat recombinant α-(2→3)-sialyl and rat liver α-(2→6)-sialyl transferases with the presence of 4-methylumbellipheryl-labeled Lac-NAc as an acceptor substrate was evaluated [415]. Compounds **197a**, **197b**, and **198** showed more inhibition for α-(2→3)-sialyltransferase than for α-(2→6)-sialyltransferase. In addition, the enzyme-inhibition assays showed that compound **197b** possess potent and specific inhibitory activity toward rat recombinant α-(2→3)-sialyltransferase. Moreover, compounds **197b** (K_m) = 185 μM) and **198** (K_m = 245 μM) presented IC_{50} values similar to that for the acceptor (K_m = 264 μM) toward α-(2→3)-sialyltransferases, whereas compound **133c** displayed less inhibition (K_m = 419 μM). Surprisingly, compound **197c**, which was expected to inhibit both enzymes, did not show any appreciable inhibition toward any of them. The authors concluded from this study that the imino function enhances affinity for sialyltransferases but that when two nitrogen atoms exist, the enzymes maintain an equilibrium of interaction between them. They also established that a carbagalactose residue in carbadisaccharides may bind to sialyltransferases, but without the transfer of sialic acid.

4.2.6.3. Pyralomicins.

The pyralomicins **55-58** show activity against various bacteria, particularly strains of *Micrococcus luteus*, an opportunistic Gram-positive bacterium. The antibacterial activity of the pyralomicins appears to be dependent upon the number and the position of chlorine atoms within the molecules and the nature and methylation of the glycone [416]. That suggests a role for the cyclitol moiety in the antimicrobial activity.

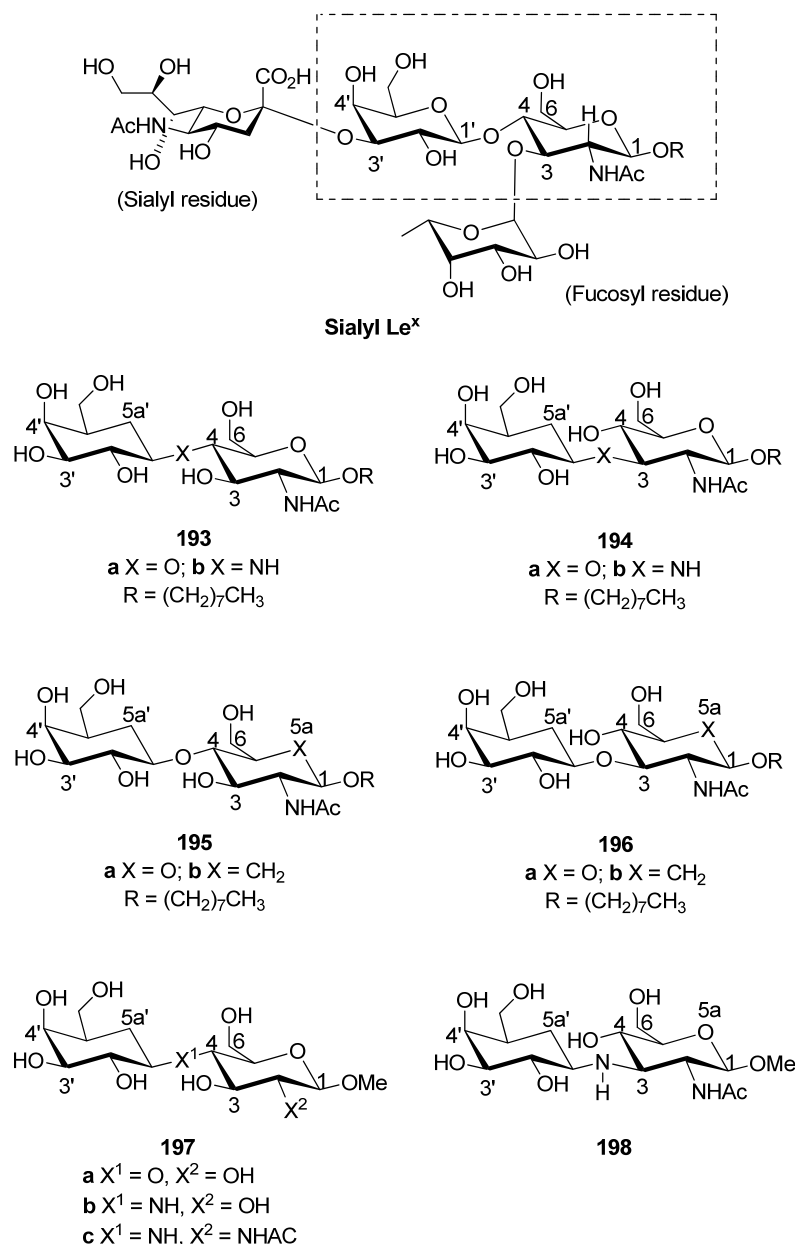


Figure 33. Carbasugars disaccharide analogues as inhibitors of fucosyl- and sialyl transferases.

5. Conclusions.

More than four decades have already elapsed since the first synthesis of a carbocyclic analogue of a carbohydrate: a *carbasugar*. Because these compounds enjoy enhanced chemical stability, the prediction was that these new compounds could replace carbohydrates in their interaction with enzymes thus showing important biological properties. This prediction has been amply confirmed and several biologically active natural products containing *carbasugars* moieties have been discovered and their biosynthesis, synthesis and biological properties were objective of different authoritative research. In addition, many synthetic analogues of these natural products have been synthesized in the search for improved biological properties. It seems fair to predict that the future holds considerable promise for advances in this area.

6. Acknowledgments.

One of us (S.R.) thanks Fundación Ramón Areces (Spain) for a post-doctoral fellowship.

Conflict of Interest.

The authors declare that there is not conflict of interests regarding the publication of this paper.

---

7. References.

1. de Paz, J. L.; Seeberger, P. H. Recent advances in carbohydrate microarrays. *QSAR Comb. Sci*. **2006**, *25*, 1027-1032.
2 Miljkovic, M. in *Carbohydrates. Synthesis, Mechanism and Stereoelectronic Effects.* Springer, **2010**.
3. Stick, R. V.; Williams, S. J. in *Carbohydrates: The Essential Molecules of Life.* Second Edition. Elsevier, **2009**.
4. *Carbohydrate Chemistry and Biochemistry: Structure and Mechanism.* RSC. First Edition: Sinnott, M. ed., 2007. Second Edition: Sinnott, M. ed., **2013**.
5. *Carbohydrate Chemistry. Chem. Rev*. **2000**, *100*, Issue 12. Bashkin, J.K. ed
6. *Modern Synthetic Methods in Carbohydrate Chemistry. From Monosaccharides to Complex Glycoconjugates*. Werz, D.B.; Vidal, S. eds., Wiley, **2013**
7. *Carbohydrate Chemistry. Proven Synthetic Methods.* CRC Press. Taylor & Francis Group. Vol. 1: Kovac, P. ed., **2011**. Vol. 2, van der Mare, G; Coreen, J. eds., **2014**. Vol. 3: Roy, R.; Vidal, S. eds., **2015**.
8 *Recognition of Carbohydrates in Biological Systems. Part A: General Procedures*. Lee, Y.C.; Lee, R.T. eds. *Methods in Enzymology*. Vol. 362. Academic Press, **2003**. *Part B. Specific Applications*. Lee, Y. C.; Lee, R. T. eds. *Methods in Enzymology.* Vol. 363. Academic Press, **2003**.
9. *Carbohydrate Recognition. Biological Problems, Methods and Applications.* Wang; B.; Boons, G. J. eds., Wiley, **2011**.
10. *Carbohydrates as Drugs. Topics in Med. Chem., Vol. 12;* Seeberger, P.H.; Rademacher, Ch. eds., Springer, **2014**.
11. *Carbohydrates in Drug Design and Discovery,* Jiménez-Barbero, J.; Cañada, J.; Martín-Santamaría, S. eds. RSC: Drug Discovery Series. Vol. 43, **2015**.
12. *Chem. Rev*. **2002**, *102*, Issue 2. Dwek, R.A.; Bothers, T.D. eds.
13. Lis, H.; Sharm, N. Lectins: Carbohydrate-Specific Proteins that Mediate Cellular Recognition. *Chem. Rev*. **1998**, *98*, 637-674.
14. Campo, V. L.; Aragón-Leoneti, V.; Teixeira, M. B. M.; Carvalho, I. Carbohydrates and glycoproteins: cellular recognition and drug design. *New. Develop. Med. Chem*., **2010**, *1*, 133-151.
15. Kiessling, L. L.; Grim, J. C. Glycopolymer probes of signal transduction. *Chem. Soc. Rev.* **2013**, *42*, 4476-4491.
16. Ruan, Y. L. Sucrose metabolism: gateway to diverse carbon use and sugar signalling. *Annu. Rev. Plant Biol*. **2014**, *65*, 33-67.
17. Liung, K.; Nembauser, J. L.; Perata, P. New mechanistic links between sugar and hormone signalling networks. *Curr.Opp. Plalnt Biol*. **2015**, *25*, 130-137.
18. Rini, J. M.; Leffer, H.: *Carbohydrate Recognition and Signaling* in Functioning of Transmembrane receptors in Signaling Mechanism. Cell Signaling Collection. Bradshaw, R.; Dennis, E. A. eds., Academic Press, **2011**. Chapter 13, p. 341-347.
19. The therapeutic potential of glycoconjugates has been described in: Doores, K. J.; Gamblin, D. P.; Davis, B. G. Exploring and exploiting the therapeutic potential of glycoconjugates *Chem. Eur. J*., **2006**, *12*, 656-665.
20. The concept of “Medicinal Glycoscience” was developed in: Koeeler, K. M.; Wong, C. H. Emerging themes in medicinal glycoscience. *Nat. Biotech*. **2000**, *18*, 835-841.

21. Keding, S. J.; Danishefsky, S. J.: *Synthetic Carbohydrate-Based Vaccines* in Carbohydrate-Based Drug Discovery. Wong, C. H. ed., Wiley, **2003**, p. 381-406.
22. Hecht, M. L.; Stallforth, F.; Silva, D. V.; Adibekian, A.; Seeberger, P. H. Recent advances in carbohydrate-based vaccines. *Curr. Opinion Chem. Biol*. **2009**, *13*, 354-359.
23. Morelli, L.; Poletti, L.; Lay, L. Carbohydrates and Immunology: Synthetic Oligosaccharide Antigens for Vaccine Formulation. *Eur. J. Org. Chem*. **2011**, 5723-5777.
24. Bathia, S.; Dimde, M.; Hazg, R. Multivalent glycoconjugates as vaccines and potential drug candidates. *Med.Chem.Med. Comm.* **2014**, *5*, 862-878.
25. Danishefsky, S. J.; Allen, J. R. From the laboratory to the clinic: a retrospective on fully synthetic carbohydrate-based anticancer vaccines. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 836-863.
26. Sialyl Lewis X is a tetrasaccharide that is usually attached to O-glycans on the surface of cells. It is known to play a vital role in cell-to-cell recognition processes. See: *Syalo Glyco Chemistry and Biology*. Part I: Biosynthesis, Structural Diversity and Sialoglycopathologies. Part II: Tools and Technique to Identify and Capture Sialoglycans. Gerardy-Schahn, R.; Delamoy, P.; von Itzsein M. eds. *Topics in Current Chem.,* Vols. 366 and 367. Springer, **2015**.
27. Pudelko, M.; Bull, J.; Kunz, H. Chemical and chemo-enzymatic synthesis of glycopeptide selectin ligands containing sialyl Lewis X structures. *ChemBioChem* **2010**, *11*, 904-930.
28. Kaila, N.; Thomas IV, B. E. Design and synthesis of sialyl Lewisx mimics as E- and P-selectin inhibitors. *Med. Res. Rev*. **2002**, *22*, 566-601.
29. *Biology of Inositols and Phosphoinositides*. Subcellular Biochemistry. Vol. 39; Majunder, A. L.; Biswass, B. B. eds. Springer, **2006**.
30. Kukisis, A. in *Inositol Phospholipid Metabolism and Phosphatidyl Inositol Kimases*. Laboratory Techniques in Biochemistry and Molecular Biology. Vol 30. Pillai, S.; Van der Viet, P. C. Editors Series. Elsevier **2003**. See in particular Chapter 5, p. 253-334.
31. *Glycosylphosphatidylinositols (GPI) Anchoring of Proteins.* The Enzimes. Vol. XXVI Menon, A. K.; Orlean, P.; Kinoshita, T.; Tamanoi, F. eds. Elsevier, **2009**.
32. GPI *Membrane Anchors. The much needed link.* Dangerfield, J. A. ed. Metamer, Ch. co-ed. Bentham, **2010**.
33. Vilotijevic, I.; Gutze, S.; Seeberger, P. H.; Silva, D. V.: *Chemical Synthesis of GPI Anchors and GPI Anchored Molecules.* Modern Synthetic Methods in Carbohydrate Chemistry. Werz, D. B.; Vidal, S. eds.; Wiley, **2014**; p. 335-372.
34. Zurzolo, Ch.; Simons, K. Glycosylphosphatidylinositol-anchored proteins. Membrane, organization and transport. *Biochim. Biophys. Acta*, **2015**. In press. DOI 10.1016/j.bbamem.2015.12.018. Reference BBAMEM 82077.
35. Boons, G. H.; Hale, K. J. in *Organic Synthesis with Carbohydrates*.. Wiley-Blackwell, **2000**.
36. *Carbohydrates Tools for Stereoselective Synthesis*. Boysen, M. M. K. ed., Wiley, **2013**.
37. Sears, P.; Wong, C. H. Carbohydrate mimetics: a new strategy for tackling the problem of carbohydrate-mediated biological recognition. *Angew. Chem. Int. Ed*. **1999**, *38*, 2301-2324.
38. Gruper, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. Carbohydrate-Based Mimetics in Drug Design: Sugar Amino Acids and Carbohydrate Scaffolds. *Chem. Rev*. **2002**, *102*, 491-514.
39. Koester, D. C.; Holkerbrink, A.; Werz, D. B. Recent advances in the synthesis of carbohydrate mimetics. *Synthesis* **2010**, 3217-3242.
40. Cipolla, L.; Peri, F. Carbohydrate-based bioactive compounds for medicinal chemistry applications. *Mini-Rev. Med. Chem.* **2011**, *11*, 39-54.
41. *Joint Commission on Biochemical Nomenclature* (A. D. McNaught) *Pure Appl. Chem.* **1996**, *68*, 1919-2008.
42. Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. Synthesis and Conformational and Biological Aspects of Carbasugars. *Chem. Rev*. **2007**, *107*, 1919-2036.
43. Plumet, J.; Gómez, A. M.; López, J. C. Synthesis of carbasugars based on ring closing metathesis: 2000-2006. *Mini-Rev. Org. Chem*. **2007**, *4*, 201-216.
44. Jarosa, S.; Nowogrodzki, M.; Magdyca, M.; Potopnyk, M. Carbobicyclic sugar mimics. *Carbohydr. Chem*. **2012**, *37*, 303-325.
45. Soengas, R. G.; Otero, J. M.; Estevez, A. M.; Praster, A. P.; Cachatra, V.; Estevez, J. C.; Estevez, R. J. An overview of key routes for the transformation of sugars into carbasugars and related compounds. *Carbohydr. Chem,* **2012**, *38*, 263-302.
46. Lahiri, R.; Ansari, A. A.; Vankar, Y. D. Recent developments in design and synthesis of bicyclic azasugars, carbasugars and related molecules as glycosidase inhibitors. *Chem. Soc. Rev*. **2013**, *42*, 5102-5118.

47. Bessieres, M.; Chevrier, F.; Roy, V.; Agrofoglio, L. Recent progress for the synthesis of selected carbocyclic nucleosides. *Future Med. Chem.* **2015**, *7*, 1809-1828.
48. *Chemical Synthesis of Nucleoside Analogues*. P. Merino, ed. Wiley, **2013**.
49. Adinolfi, M.; Corsaro, M. M.; De Castro, C.; Evidente, A.; Lanzetta, R.; Molinaro, A.; Parrilli, M. Caryose: a carbocyclic monosaccharide from *Pseudomonas caryophylli*. *Carbohydr. Res.* **1996**, *284*, 111-118.
50. Adinolfi, M.; Corsaro, M. M.; DeCastro, C.; Evidente, A.; Lanzetta, R.; Lavermicocca, M.; Parrilli, M. Analysis of the polysaccharide components of the lipopolysaccharide fraction *of Pseudomonas caryophylli*. *Carbohydr. Res*. **1996**, *284*, 119-133.
51. Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Manna, R. Synthesis of caryose, the carbocyclic monosaccharide component of the lipopolysaccharide from *Pseudomonas caryophylli*. *Tetrahedron* **1997**, *53*, 11767-11780.
52. Brock, T. D.; Brock, K. M.; Belly, R. T.; Weiss, R. L. *Sulfolobus*: a new genus of sulphur-oxidizing bacteria living at low pH and high temperature. *Archiv fur Mikrobiol.* **1972**, *84*, 54–68.
53. De Rosa, M.; De Rosa, S.; Gambacorta, A.; Minale, L.; Bullock, J. D. Chemical structure of the ether lipids of thermophilic acidophilic bacteria of the *Caldariella* group. *Phytochemistry* **1977,** *16*, 1961-1965.
54. De Rosa, M.; De Rosa, S.; Gambacorta, A.; Bullock, J. D. Structure of calditol, a new branched-chain nonitol, and of the derived tetraether lipids in thermoacidophile archaebacteria of the *Caldariella* group. *Phytochemistry* **1980**, *19*, 249-254.
55. Bode, M. L.; Buddoo, S. A.; Minnaar, S. H.; du Plessis, C. A. Extraction, isolation and NMR data of the tetraether lipid calditol glycerocaldarchaeol (GDNT) from *Sulfolobus metallicus* harvested from a bioleaching reactor. *Chem.Phys.Lipids* **2008**, *154*, 94-104.
56. Untersteller, E.; Fritz, B.; Bliériot, Y.; Sinaÿ, P. The structure of calditol isolated from the thermoacidophilic archaebacterium *Sulfolobus acidocaldarius*. *Compt. Rend. Acad. Sci (IIC-Chem.)* **1999**, 429-433.
57. Bleriot, Y.; Untersteller, E.; Fritz;, B.; Sinaÿ, P. Total synthesis of calditol: structural clarification of this typical component of archaea order *Sulfolobales*. *Chem. Eur. J.* **2002**, *8*, 240-246.
58. Miller, T. W.; Arison, B. H.; Albers-Schonberg, G. Isolation of a cyclitol antibiotic: 2,3,4,5-tetrahydroxycyclohexanemethanol. *Biotechnol. Bioeng*. **1973**, *15*, 1075-1080.
59. Marco-Contelles, J.; Molina, M. T.; Anjum, S. Naturally occurring cyclohexane epoxides: sources, biological activities, and synthesis. *Chem. Re*v. **2004**, *104*, 2857-2899.
60. Thebtaranonth, Ch.; Thebtaranonth, Y. Naturally occurring cyclohexene oxides *Acc. Chem. Res.* **1986**, *19*, 84-90.
61. Marco-Contelles, J. Cyclohexane Epoxides − Chemistry and Biochemistry of (+)-Cyclophellitol. *Eur. J. Org. Chem*. **2001**, 1607-1618.
62. Kobayashi, Y. Glycoscience, Chemistry and Chemical Biology; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, **2001**; Chapter 10.3, Vol. III.
63. Tatsuta, K. Total synthesis and chemical design of useful glycosidase inhibitors. *Pure Appl. Chem*. **1996**, *68*, 1341-1346.
64. Ogawa, S.; Kanto, M. Synthesis of bio-active compounds from cyclitol derivatives provided by bioconversion of myo-inositol. *Curr. Trends Med. Chem.* **2008**, *5*, 1-13.
65. Fraser-Reid, B.; Lopez, J. C. Unsaturated sugars: a rich platform for methodological and synthetic studies. *Curr. Org. Chem*. **2009**, *13*, 532-553.
66. Nobuji, Y.; Noriko, C.; Takashi, M.; Shigeru, U.; Kenzon, A.; Michaki, I. *Jpn. Kokai Tokkyo Koho, JP*, *06306000*, **1994**.
67. Isogai, A.; Sakuda, S.; Nakayama, J.; Watanabe, S.; Suzuki, A. Isolation and structural elucidation of a new cyclitol derivative, streptol, as a plant growth regulator. *Agricultural Biol. Chem.* **1987**, *51*, 2277-2279.
68. Sedmera, P.; Halada, P.; Pospisil, S. New carbasugars from *Streptomyces lincolnensis. Magn. Res. Chem*. **2009**, *47*, 519-522..
69. Yamada, T.; Iritani, M.; Ohishi, H.; Tanaka, K.; Minoura, K.; Doi, M.; Numata, A. Pericosines, antitumor metabolites from the sea hare-derived fungus *Periconia byssoides*. Structures and biological activities. *Org. Biomol. Chem*. **2007**. *5*, 3979-3986.
70. For a review, see: Usami, V. Synthesis of marine-derived carbasugar pericosines. *Studies Nat. Prod. Chem*. **2014**, *41*, 287-319.
71. Bayon, P.; Figueredo, M. The Gabosine and Anhydrogabosine Family of Secondary Metabolites. *Chem. Rev*. **2013**, *113*, 4680-4707.

72. Mac, D. H.; Chandrasekhar, S.; Gree, R. Total Synthesis of Gabosines. *Eur. J. Org. Chem*. **2012**, 5881-5895.
73. Das, M.; Manna, K. Bioactive Cyclohexenones: A Mini Review. *Curr. Bioactiv. Comp*. **2015**, *11*, 239-248.
74. Chimura, H.; Nakamura, T.; Takita, T.; Takeuchi, H.; Umezawa, K.; Kato, S.; Saito, T.; Tomisawa, Y.; Iitaka,Y. The structure of a glyoxalase I inhibitor and its chemical reactivity with SH-compounds. *J. Antibiot*. **1975**, *28*, 743-748.
75. Kameda, Y.; Horii, S. The unsaturated cyclitol part of the new antibiotics, the validamycins. *J. Chem. Soc., Chem. Commun*. **1972**, 746-747.
76. Kameda, Y.; Horii, S. Microbial transformation of validamycins. *J. Antibiot*. **1975**, *28*, 298-306.
77. Kameda, Y.; Asano, N.; Teranishi, M.; Matsui, K. New cyclitols, degradation of validamycin A by *Flavobacterium saccharophilum*. *J. Antibiot*. **1980**, *33*, 1573-1574..
78. Kameda, Y.; Asano, N.; Teranishi, M.; Yoshikawa, M.; Matsui, K. Cefmetazole in the treatment of bacterial infections in the newborn. *J. Antibiot.* **1981**, *34*, 1237-1246.
79. Asano, N.; Takeuchi, M.; Ninomiya, K.; Kameda, Y.; Matsui, K. Microbial degradation of validamycin A by *Flavobacterium saccharophilum*. Enzymatic cleavage of C-N linkage in validoxylamine A. *J. Antibiot*. **1984**, *37*, 859-867.
80. Ogawa, S.; Miyamoto, Y.; Nakajima, A. Cleavage of the Imino Bonds of Validoxylamine A Derivatives with N-Bromosuccinimide. *Chem. Lett.* **1989**, 725-728.
81. Ogawa, S.; Nakajima, A.; Miyamoto, Y. Cleavage of validoxylamine A derivatives with N-bromosuccinimide: preparation of blocked synthons useful for the construction of carba-oligosaccharides composed of imino linkages. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3287-3290.
82. Xu, H.; Yang, J.; Bai, L.; Deng, Z.; Mahmud, T. Genetically engineered production of 1,1'-bis-valienamine and validienamycin in *Streptomyces hygroscopicus* and their conversion to valienamine. *Applied Microbiol.* **2009**, *81*, 895-902.
83. Xue, Y.-P.; Zheng, Y.-G.; Shen, Y.-Ch. Enhanced production of valienamine by *Stenotrophomonas maltrophilia* with fed-batch culture in a stirred tank bioreactor. *Process Biochem*. **2007**, *42*, 1033-1038.
84. Wang, Y.-S.; Zheng, Y.-G.; Shen, Y.-C, J. Isolation and identification of a novel_valienamine-producing bacterium. *Applied Microbiol*. **2007**, *102*, 838-844.
85. Horii, S.; Iwasa, T.; Kameda, Y. Validamycins, new antibiotics. V. Degradation studies. *J. Antibiot.* **1971**, *24*, 57-58.
86. Horii, S.; Iwasa, T.; Kameda, Y. Studies on validamycins, new antibiotics. VI. Validamine, hydroxyvalidamine and validatol, new cyclictols. *J. Antibiot*. **1971**, *24*, 59-63.
87. Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. Valiolamine, a new α-glucosidase inhibiting aminocyclitol produced by *Streptomyces hygroscopicus*. *J. Antibiot* **1984**, *37*, 1301-1307.
88. Mahmud T., The C7N aminocyclitol family of natural products. *Nat. Prod. Reports* **2003**, *20*, 137-166.
89. Suami, T. Synthesis of biologically active pseudo-oligosaccharides. Carbohydrates. Ogura, H.; Hasegawa, A.; Suami, T. eds., Verlag (VCH), **1992**, p. 136-173.
90. Iwasa, T.; Yamamoto, H.; Shibata, M. J. Studies on validamycins, new antibiotics. I. *Streptomyces hygroscopicus* var. limoneus., validamycin-producing organism. *J. Antibiot.* **1970**, *23*, 595-602.
91. Iwasa, T.; Higashide, E.; Yamamoto, H.; Shibata, M. J. Studies on validamycins, new antibiotics. II. Production and biological properties of validamycins A and B. *J. Antibiot*. **1971**, *24*, 107-113.
92. Horii, S.; Kameda, Y.; Kawahara, K. Validamycins, new antibiotics. 8. Isolation and characterization of validamycins C,D,E and F. *J. Antibiot*. **1972**, *25*, 48-53.
93. Kameda, Y.; Asano, N.; Matsui, K.; Horii, H.; Fukase, H. Structures of minor components of the Validamycin complex. *J. Antibiot*. **1989**, *41*, 1488-1492.
94. Kameda, Y.; Asano, N.; Yamaguchi, T.; Matsui, K.; Horii, H.; Fukase, H. Validamycin G and validoxylamine G, new members of the validamycins. *J. Antibiot*. **1986**, *39*, 1491-1494.
95. Asano, N.; Kameda, Y.; Matsui, K.; Horii, H.; Fukase, H. Validamycin H, a new pseudo-tetrasaccharide antibiotic. *J. Antibiot*. **1990**, *43*, 1039-1041.
96. Schmidt, D. D.; Frommer, W.; Junge, B.; Muller, L.; Wingender, W.; Truscheit, E.; Schafer, D. α-glucosidase inhibitors. New complex oligosaccharides of microbial origin *Naturwissenschaften* **1977**, *64*, 535-536.
97. Junge, B.; Heiken, R.-R.; Kurz, J.; Muller, L.; Schmidt, D. D.; Wunsche, C. Untersuchungen zur struktur des α-d-glucosidaseinhibitors acarbose. *Carbohydr. Res*. **1984**, *128*, 235-268.

98. Masharani, U.; German, M. S. *Pancreatic Hormones and Diabetes Mellitus.* Greenspan's basic & clinical endocrinology (9th ed.). Gardner, D. G.; Shoback, D. eds. McGraw-Hill Medical, **2011**, Chapter 17
99. Buse, J. B.; Polonsky, K. S.; Burant, Ch. F. *Type 2 Diabetes Mellitus*. Melmed, S.; Polonsky, K. S.; Larsen, P. R.; Kronenberg, H. M. eds. Williams textbook of endocrinology (12th ed.) Elsevier, **2012**, Section 7, Chapter 31.
100. Kadziola, A.; Abe, J.; Svensson, B.; Haser, R. Crystal and molecular structure of barley alpha-amylase. *J. Mol. Biol*. **1994**, *239*, 104–121.
101. Machius, M.; Wiegand, G.; Huber, R. Crystal structure of calcium-depleted *Bacillus licheniformis* alpha-amylase at 2.2 A resolution. *J. Mol. Biol*. **1995**, *246*, 545–559.
102. Hemker, M.; Stratmann, A.; Goeke, K.; Schroder, W.; Lenz, J.; Piepersberg, W.; Pape, H. Identification, Cloning, Expression, and Characterization of the Extracellular Acarbose-Modifying Glycosyltransferase, AcbD, from *Actinoplanes sp*. Strain SE50. *J. Bacteriol*. **2001**, *183*, 4484-4492.
103. Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D.; Wingeder, W. Chemistry and Biochemistry of Microbial α-Glucosidase Inhibitors. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 744-761.
104. Wehmeier, U. F.; Piepersberg, W. Biotechnology and molecular biology of the α-glucosidase inhibitor acarbose *Appl. Microbiol. Biotechnol*. **2004**, *63*, 613-625.
105. Wehmeier, U. F. The Biosynthesis and Metabolism of Acarbose in Actinoplanes species SE 50/110. *Progress Report. Biocatal. Biotransf.* **2003**, *21*, 279-284.
106. Laube, H. Acarbose. An Update of Its Therapeutic Use in Diabetes Treatment *Clin. Drug. Invest*. **2002**, *22*, 141-156.
107. Scheen, A. J. Clinical efficacy of acarbose in diabetes mellitus: A critical review of controlled trials. *Diabetes Metabol*. **1998**, *24*, 311-320.
108. Breuer, H.-W. M. Review of acarbose therapeutic strategies in the long-term treatment and in the prevention of type 2 diabetes. *Int. J. Clin. Pharmacol. Therapeut*. **2003**, *41*, 421-440.
109. Ogawa, S.; Kanto, M.; Suzuki, Y. Development and medical application of unsaturated carbaglycosylamine glycosidase inhibitors. *Mini-Rev. Med. Chem*. **2007**, *7*, 679-691.
110. Bedekar, A.; Shah, K.; Koffas, M. Natural products for type II diabetes treatment. *Adv. Appl. Microbiol*. **2010**, *71*, 21-73.
111. Rios, J. L.; Francini, F.; Schinella, G. R. Natural Products for the Treatment of Type 2 Diabetes Mellitus. *Planta Medica* **2015**, *81*, 975-994.
112. Harvey, A. L. Plant natural products in anti-diabetic drug discovery. *Curr. Org. Chem*. **2010**, *14*, 1670-1677.
113. Moorthy, N. S. H. N.; Ramos, M. J.; Fernandes, P. A. Studies on α-glucosidase inhibitors development: magic molecules for the treatment of carbohydrate mediated diseases. *Mini-Rev. Med. Chem*. **2012**, *12*, 713-720.
114. Ghani, U. Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: Finding needle in the haystack. *Eur. J. Med. Chem*. **2015**, *103*, 133-162.
115. Fukuhara, K.-i.; Murai, H.; Murao, S. Amylostatins, other amylase inhibitors produced by *Streptomyces diastaticus* subsp. *Amylostaticus* No 2476. *Agric. Biol. Chem*. **1982**, *46*, 2021-2030.
116. Fukuhara, K.-i.; Murai, H.; Murao, S. Isolation and Structure-activity Relationship of Some Amylostatins (F-1b Fraction) Produced by *Streptomyces diastaticus* subsp. *Amylostaticus* No 9410. *Agric. Biol. Chem*. **1982**, *46*, 1941-1945.
117. Namiki, S.; Kangouri, K.; Nagate, T.; Hara, H.; Sugita, K.; Omura, S. Studies on the α-glucoside hydrolase inhibitor, Adiposin I. Isolation and physicochemical properties. *J. Antibiot*. **1982**, *35*, 1234-1236.
118. Namiki, S.; Kangouri, K.; Nagate, T.; Hara, H.; Sugita, K.; Omura, S. Studies on the α.-glucoside hydrolase inhibitor, adiposin. II. Taxonomic studies on the producing microorganism. *J. Antibiot*. **1982**, *35*, 1156-1159.
119. Kangouri, K.; Namiki, S.; Nagate, T.; Hara, H.; Sugita, K.; Omura, S. Studies on the α-glucoside hydrolase inhibitor, adiposin. III. α-Glucoside hydrolase inhibitory activity and antibacterial activity *in vitro*. *J. Antibiot.* **1982**, *35*, 1160-1166.
120. Namiki, S.; Kangouri, K.; Nagate, T.; Hara, H.; Sugita, K.; Noda, K.; Tarumoto, Y.; Omura, S. Studies on the α-glucoside hydrolase inhibitor,_adiposin. IV. Effect of adiposin on intestinal digestion of carbohydrates in experimental animals. *J. Antibiot.* **1982**, *35*, 1167-1173.
121. Ogawa, S.; Iwasawa, Y.; Toyokuni, T.; Suami, T. Synthesis of adiposin-1, α-glucoside hydrolase inhibitor. *Chem. Lett*. **1983**, 337-340.

122. Ogawa, S.; Iwasawa, Y.; Toyokuni, T.; Suami, T. Synthesis of pseudooligosaccharidic glycosidase inhibitors. Part 1. Synthesis of adiposin-1 and related compounds. *Carbohydr. Res*. **1985**, *141*, 29-40.
123. Ogawa, S.; Shibata, Y. Total synthesis of acarbose and adiposin-2. *J. Chem. Soc. Chem.. Comm*. **1988**, 605-606.
124. Shibata, Y.; Ogawa, S. Synthesis of pseudo-oligosaccharide glycosidase inhibitors. Part VII. Total synthesis of acarbose and adiposin-2. *Carbohydr. Res*, **1989**, *189*, 309-322.
125. Itoh, J.; Omoto, S.; Shomura, T.; Ogino, H.; Iwamatsu, K.; Inouye, S.; Hidaka, H. Oligostatins, new antibiotics with amylase inhibitory activity. I. Production, isolation and characterization. *J. Antibiot.* **1981**, *34*, 1424-1428.
126. Omoto, S.; Itoh, J.; Ogino, H.; Iwamatsu, K.; Nishizawa, N.; Inouye, S. Oligostatins, new antibiotics with amylase inhibitory activity. II. Structures of oligostatins C, D and E. *J. Antibiot.* **1981**, *34*, 1429-1433.
127. Ogawa, S.; Iwasawa, Y.; Toyokuni, T.; Suami, T. Synthesis of a common structural unit of the antibiotic Oligostatins. *Chem. Lett.* **1982**, 1729-1732.
128. Ogawa, S.; Iwasawa, Y.; Toyokuni, T.; Suami, T. Synthesis of pseudo-oligosaccharide glycosidase inhibitors. Part IV. Synthesis of a core structure of the antibiotic oligostatin. *Carbohydr. Res*. **1985**, *144*, 155-162.
129. Shibata, Y.; Kosuge, Y.; Ogawa, S. Synthesis of pseudooligosaccharide glycosidase inhibitors. VII. Synthesis and biological activities of methyl oligobiosaminide and some deoxy isomers thereof. *Carbohydr. Res*. **1990**, *199*, 37-54.
130. Watanabe, K.; Furumai, T.; Sudoh, M.; Yokose, K.; Muruyama, H. B. New α.-amylase inhibitor, trestatins. IV. Taxonomy of the producing strains and fermentation of trestatin A. *J. Antibiot.* **1984**, *37*, 479-486.
131. Yokose, K.; Ogawa, K.; Sano, T.; Watanabe, K.; Maruyama, H.-B.; Suhara, Y. New α-amylase inhibitor, trestatins. I. Isolation, characterization and biological activities of trestatins A, B and C. *J. Antibiot.* **1983**, *36*, 1157-1165.
132. Vértesy, L.; Fehlhaber, H.-W.; Schulz, A. The trehalase inhibitor salbostatin, a novel metabolite from *Streptomyces albus*, ATCC21838. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1844-1846.
133. Yamagishi, T.; Uchida, Ch.; Ogawa, S. Total synthesis of the trehalase inhibitor salbostatin. *Chem. Eur. J.* **1996**, *1*, 634-636.
134. Yamagishi, T.; Uchida, Ch.; Ogawa, S. Total synthesis of trehalase inhibitor salbostatin. *Biorg. Med. Chem. Lett.* **1995**, *5*, 487-490.
135. Kawamura, N.; Kinoshita, N.; Sawa, R.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. Pyralomicins, novel antibiotics from *Microtetraspora spiralis*. I. Taxonomy and production. *J. Antibiot*. **1996**, *49*, 706-709.
136. Kawamura, N.; Sawa, R.; Takahashi, Y.; Issiki, K.; Sawa, T.; Kinoshita, N.; Naganawa, H.; Hamada, M.; Takeuchi, T. Pyralomicins, new antibiotics from *Actinomadura spiralis*. *J. Antibiot*. **1995**, *48*, 435-437.
137. Kawamura, N.; Sawa, R.; Takahashi, Y.; Issiki, K.; Sawa, T.; Kinoshita, N.; Naganawa, H.; Takeuchi, T. Pyralomicins, novel antibiotics from *Microtetraspora spiralis*. II. Structure determination. *J. Antibiot.* **1996**, *49*, 651-656.
138. Kelly, T. R.; Moiseyeva, R. L. Total Synthesis of the Pyralomicinones. *J. Org. Chem.* **1998**, *63*, 3147-3150.
139. Tatsuta, K.; Takahashi, M.; Tanaka, N. The first total synthesis of pyralomicin 2c. *Tetrahedron Lett*. **1999**, *40*, 1929-1932.
140. Tatsuta, K.; Takahashi, M.; Tanaka, N. The first total synthesis of pyralomicin 1c. *J. Antibiot*. **2000**, *53*, 88-91.
141. Jenkins, G. N.; Turner, N, The biosynthesis of carbocyclic nucleosides. *Chem. Soc. Re*v. **1995**, *24*, 169-176.
142. Parry, R. J., Investigations of the biosynthesis of aristeromycin. *Environ. Sci. Research* **1992**, *44*, 89-104.
143. Hill, J. M.; Jenkins, G. N.; Rush, C. P.; Turner, N. J.; Willetts, A. J.; Buss, A. D.; Dawson, M. J.; Rudd, B. A. M., Revised pathway for the biosynthesis of aristeromycin and neplanocin A from D-glucose in *Streptomyces citricolor*. *J .Am.Chem.Soc.* **1995**, *117*, 5391-5392.
144. Parry, R. J.; Jian, Y., The biosynthesis of aristeromycin. Conversion of neplanocin A to aristeromycin by a novel enzymic reduction. *Tetrahedron Lett.* **1994**, *35*, 9665-9668.
145. Review: Gambacorta, A.; Gliozzi, A.; De Rosa, M. World, J. Archeal lipids and their biotechnological applications. *Microbiol. Biotechnol*. **1995**, *11*, 115-131.

146. Gambacorta, A; Caracciolo, G.; Trabasso, D.; Izzo, I.; Spinella, A.; Sodano, G. Biosynthesis of calditol, the cyclopentanoid containing moiety of the membrane lipids of the archaeon *Sulfolobus solfataricus. Tetrahedron Lett*. **2002**, *43*, 451-453.
147. Yamauchi, N.; Ueoka, H.; Kamada, N.; Murae, T. Resemblance of carbocycle formation from carbohydrates between archaea and eucarya/eubacteria. Biosynthesis of calditol, the characteristic lipid-content molecule in *Sulfolobus acidocaldarius*. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 771-778.
148. Yamauchi, N.; Kamada, N.; Ueoka, H., The possibility of involvement of "cyclase" enzyme of the calditol carbocycle with broad substrate specificity in *Sulfolobus acidcaldarius*, a typical thermophilic archaea. *Chem. Lett*. **2006**, *35*, 1230-1231.
149. For the biosynthesis of the lipid moiety, see: Nicolau, B.; Trincone, A.; Esposito, E.; Vaccaro, M. R.; Gambacorta, A.; De Rosa, M., Calditol tetraether lipids of the archaebacterium *Sulfolobus solfataricus*. Biosynthetic studies. *Biochem. J*. **1990**, *266*, 785-791.
150. Voet, D.; Voet, J. G. in Biochemistry, 3nd.. Edition, Wiley, **2004**. Chapter 21.
151. Berg, J. M.; Tymoczko, J. L.; Stryer, L. Biochemistry, 5th. Edition. W.H. Freeman, **2002**, Chapter 20.
152. Widlanski, T.; Bender, S. L.; Knowles, J. R. Dehydroquinate synthase: a sheep in wolf's clothing?. *J. Am. Chem. Soc.* **1989**, *111*, 2299-2300.
153. Stratmann, A.; Mahmud, T.; Lee, S.; Distler, J.; Floss, H. G.; Piepersberg, W. The AcbC protein from *Actinoplanes* species is a C7-cyclitol synthase related to 3-dehydroquinate synthases and is involved in the biosynthesis of the α-glucosidase inhibitor acarbose. *J. Biol. Chem*. **1999**, *274*, 10889-10896.
154. Asamizu, S.; Xie, P.; Brumsted, C. J.; Flatt, P. M.; Mahmud, T. Evolutionary Divergence of Sedoheptulose 7-Phosphate Cyclases Leads to Several Distinct Cyclic Products, *J. Am. Chem. Soc*. **2012**, *134*, 12219−12229.
155. Kean, K. M.; Codding, S. J.; Asamizu, S.; Mahmud, T.; Karplus, P. A. Structure of a sedoheptulose 7-phosphate cyclase: ValA from *Streptomyces hygroscopicus*. *Biochem*. **2014**, *53*, 4250-4260.
156. Carpenter, E. P.; Hawkins, A. R.; Frost J. W.; Brown, K. A. Structure of dehydroquinate synthase reveals an active site capable of multistep catalysis. *Nature* **1998**, *394*, 299-302.
157. Herrmann, K. M., The Shikimate Pathway: Early Steps in the Biosynthesis of Aromatic Compounds. *Plant Cell* **1995**, *7*, 907-919.
158. Höfs, R.; Schoppe, S.; Thiericke, R.; Zeeck, Biosynthesis of Gabosines A, B, and C, Carba Sugars from *Streptomyces cellulosae*. *Eur. J. Org. Chem*. **2000**, 1883-1887.
159. Liu, S.-Y.; Rosazza, J. P. N. Enzymatic Conversion of Glucose to UDP-4-Keto-6-Deoxyglucose in *Streptomyces* spp. *Appl. Environ. Microbiol*. **1998**, *64*, 103972-103976.
160. Thibodeaux, Ch. J., Melangon, Ch. E.; Liu, H. Unusual sugar biosynthesis and natural product glycodiversification. *Nature* **2007**, *446*, 1008-1016.
161. Fresneda, M. A.; Alibés, R.; Font, J.; Bayón, P.; Figueredo, M. How a diversity.oriented approach has inspired a new hypothesis for the gabosine byosynthetic pathway. A new synthesis of (+)-gabosine C. *Org. Biomol. Chem*. **2013**, *11*, 6562-6568.
162. Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. Enantioselective Synthesis and Absolute Configuration Assignment of Gabosine O. Stnthesis of (+)- and (-)-Gabosine N and (+)-and (-)-Epigabosines N and O. *Org. Lett.* **2006**, *8*, 1617-1620.
163. Review: Singh, S.; Anand, A.; Srivastava, P. K. Regulation and properties of glucose- 6-phosphate dehydrogenase: a review. *Int. J. Plant Physiol. Biochem*. **2012**, *4*, 1-19 and references therein.
164. For a short review, see: Hofer, H. W.; Bauer, H. P. 6-Phosphogluconolactonase. *Cell Biochem. Funct*. **1987**, *5,* 97-99.
165. Rippa, M.; Hanau, S.; Cervellati, C.; Dallocchio, F. 6-Phosphogluconate dehydrogenase: structural symmetry and functional asymmetry. *Protein Pept. Lett,* **2000**, *7*, 341-348.
166. Williamson, W. T.; Wood, W. A. D-Ribulose-5-phosphate 3-epimerase. *Methods Enzymol.* **1966**, *9*, 605-608.
167. Wood, T. Assay for D-ribose-5-phosphate ketol isomerase and D-ribulose-5-phosphate 3-epimerase, *Methods Enzymol*. **1975**, *41*, 63-66.
168. Kochetov, G. A.; Solovjeva, O. N. Structure and functioning mechanism of transketolase. *Biochim. Biophys. Acta,* **2014**, *1844*, 1608-1618.
169. Ranoux, A.; Hanefeld, U. Improving Transketolase. *Topics Catalys*. **2013**, *56*, 750-764.

170. For a review considering the use of transketolases in various organic synthesis, see: (c) Wohlgemuth, R.; Smith, M. E. B.; Dalby, P. A.; Woodley, J. M. Transketolases. Encyclopedia of Industrial Biotechnology. Flickinger, M. C. ed., Wiley, **2010**, Vol. 7, p. 4746-4752.
171. Dong, H.; Mahmud, T.; Tornus, I.; Lee, S.; G. Floss, H.G. Biosynthesis of the Validamycins: Identification of Intermediates in the Biosynthesis of Validamycin A by *Streptomyces hygroscopicus* var. *limoneus*. *J. Am. Chem. Soc*. **2001**, *123*, 2733-2742.
172. Lee, S.-H.; Choe, H.; Bae, K. S.; Park, D.-S.; Nasir, A.; Kim, K. M. Complete genome of *Streptomyces hygroscopicus* subsp. limoneus KCTC 1717 (=KCCM 11405), a soil bacterium producing validamycin and diverse secondary metabolites. *J. Biotech.* **2016**, *219*, 1-2.
173. Lee, S.; Egelkrout, E. Biosynthetic studies on the α-glucosidase inhibitor acarbose in *Actinoplanes* sp.: glutamate is the primary source of the nitrogen in acarbose. *J. Antibiot.* **1998**, *51*, 225-227.
174. Patterson, M. K., Jr.; Orr, G. R. Asparagine biosynthesis by the Novikoff hepatoma. Isolation, purification, property, and mechanism studies of the enzyme system. *J. Biol. Chem.* **1968**, *243*, 376–380.
175. Tesson, A. R.; Soper, T. S.; Ciustea, M.; Richards, N. G. Revisiting the steady state kinetic mechanism of glutamine-dependent asparagine synthetase from *Escherichia coli*. *Arch. Biochem. Biophys.* **2003**, *413*, 23–31.
176. Mahmud, T.; Lee, S.; Floss, H. G. The biosynthesis of acarbose and validamycin. *Chem. Rec.* **2001**, *1*, 300-310.
177. Arakawa, K.; Bowers, S. G.; Michels, B.; Trin, V.; Mahmud, T. Biosynthetic studies on the α-glucosidase inhibitor of acarbose: the chemicals synthesis of isotopically labeled 2-epi-5-epi valiolone analogs. *Carbohydr. Res*. **2003**, *338*, 2075- 2082.
178. Mahmud, T.; Tornus, I.; Egelkrout, E.; Wolf, E.; Uy, C.; Floss, H. G.; Lee, S. Biosynthetic studies on the α-glucosidase inhibitor acarbose in *Actinoplate*s sp.: 2-epi-5-epi-valiolones is the direct precursor of the valienamine moiety. *J. Am. Chem. Soc*. **1999**, *121*, 6973-6983.
179. See *The ACS style guide: effective communication of scientific diphosphates information*, 3rd ed. Coghill, A. M.; Garson, L. R. ed. American Chemical Society. Washington, D.C. **2006**, p. 244.
180. Selected review: Cui, Q.; Shin, W. S.; Luo, Y.; Tian, J.; Cui, H.; Yin, D. Thymidylate kinase: an old topic brings new perspectives *Curr. Med. Chem*. **2013**, *20*, 1286-1305.
181. Lee, S.; Sauerbrei, B.; Niggemann, J.; Egelkrout, E. Biosynthetic studies on the α-glucosidase inhibitor acarbose in *Actinoplanes* sp.: source of the maltose unit. *J. Antibiot*. **1997**, *50*, 954-960.
182. Bowers, S. G.; Mahmud, T.; Floss, H. G. Biosynthetic studies on the alpha-glucosidase inhibitor acarbose: the chemical synthesis of dTDP-4-amino-4,6-dideoxy-alpha-glucose. *Carbohydr. Res.* **2002**, *337*, 297-304.
183. Wehmeier, U. F.; Piepersberg, W. Enzymology of Aminoglycoside Biosynthesis-Deduction from Gene Cluster. *Methods in Enzymology*. Vol 459. Complex Enzymes in Microbial Natural Products Biosynthesis. Part B.: Polyketides, Aminocoumarins and Carbohydrates. Howood, D. A. ed.. Elsevier, **2009**. Chapter 19, p. 479.
184. Lodish, H.; Berk, A.; Kaiser, Ch.; Krieger, M.; Bretscher, A.; Ploegh, H.; Amon, A.; Mathew, S. Genes, Genomics and Chromosomes. Molecular Cell Biology. 7 ed., Freeman, **2013**. p 227-230.
185. Gangman, Y.; Sze, S.-H.; Thon, M. Identifying clusters in functionally related genes in genomes. *Bioinformatics* **2007**, *23*, 1053–1060.
186. Overbeek, R.; Fonstein, M.; D'Souza, M.; Pusch, G.; Maitsev, D. The Use of Gene Clusters to Infer Functional Coupling. *Proceed. Nat. Acad. Sci. USA* **1999**, *96*, 2896–2901.
187. J. Yang; H. Xu; Y. Zhang; L. Bai; Z. Deng; T. Mahmud. Nucleotidylation of Unsaturated Carbasugars in Validamycin Biosynthesis. *Org. Biomol. Chem.* **2011**, *9*, 438-439.
188. Zhang, Ch.-S.; Podeschwa, M.; Altenbach, H.-J.; Piepersberg, W.; Wehmeier, U. F. Identification of a 1-epi-vañienol 7-kinase activity in the producer of acarbose, *Actinoplates* sp. SE50/110. *FEBS Lett.* **2003**, *540*, 53-57.
189. Zhang, Ch.-S.; Stratmann, A.; Block, O.; Bruckner, R.; Podeschwa, M.; Altenbach, H.-J.; Wehmeier, U. F.; Piepersberg, W. Biosynthesis of the C7-ciclytol moiety of acarbose in *Actinoplates* species SE50/110: 7-O-phosphorylation of the initial cyclitol precursors lead to proposeed a new biosynthetic pathway. *J. Biol. Chem*. **2002**, *277*, 22853-22862.
190. Stratmann, A.; Mahmud, T.; Lee, S.; Distler, J.; Floss, H. G.; Piepersberg, W. The AcbC protein from *Actinoplanes* species is a C7-cyclitol synthase related to 3-dehydroquinate synthases and is involved in the biosynthesis of the α-glucosidase inhibitor acarbose. *J. Biol. Chem*. **1999**, *274*, 10889-10896.

191. Wendler, S.; Ortseifen, V.; Persicke, M.; Klein, A.; Neshat, A.; Niehaus, K.; Schneiker-Bekel, S.; Walter, F.; Wehmeier, Udo F.; Kalinowski, J.; Puehler, A. Carbon source-dependent biosynthesis of acarviose metabolites in *Actinoplanes* sp. SE50/110. *J. Biotech.* **2014**, *191*, 113-120.
192. See D. E. Metzler. Biochemistry. The Chemical reactions of Living Cells. 2nd Edition. Elsevier, **2003**. Vol. 1, p. 545.
193. Flatt, P. M.; Wu, X.; Perry, S.; Mahmud, T. Genetic Insights into Pyralomicin Biosynthesis in *Nonomuraeae spiralis* IMC A-0156. *J. Nat. Prod*. **2013**, *76*, 939-946.
194. Schwarzer, D.; Finking, R., Mohamed A.; Marahiel, M. A. Nonribosomal peptides: from genes to products. *Nat. Prod. Rep.* **2003**, *20*, 275-287
195. Marahiel, M. A.; Stachelhaus, T.; Mootz , H. D. Modular Peptide Synthetases Involved in Nonribosomal Peptide Synthesis, *Chem. Rev.* **1997**, *97*, 2651–2674.
196. Khosla, C.; Gokhale, R. S.; Jacobsen, J. R.; Cane, D. E. Tolerance and Specificity of Polyketide Synthases. *Ann. Rev. Biochem.* **1999**, *68*, 219–253.
197. Jenke-Kodama, H.; Sandmann, A.; Müller, R.; Dittmann, E. Evolutionary Implications of Bacterial Polyketide Synthases. *Mol. Biol.& Evol*. **2005**, *22*, 2027–2039.
198. Lodish, H.; Zipursky, L.; Matsudaira, P. B., David, D.; Darnel, J. Molecular Definition of a Gene *Molecular Cell Biology*. Freeman, **2000**, Chapter 9.
199. Williams, G. J. Engineering polyketide synthases and nonribosomal peptide synthetases. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 3010-3012.
200. Hutchinson, C. R. Polyketide and non-ribosomal peptide synthases: Falling together by coming apart. *Nat. Prod. Reports* **2007**, *24*, 1073-1090.
201. Horsman, M.E.; Taylor P. A.; Hari, T.P.A.; Boddy, Ch.N. Polyketide synthase and non-ribosomal peptide synthetase thioesterase selectivity: logic gate or a victim of fate?. *Nat. Prod. Rep.* **2016**, *33*, 183-202.
202. Smith, D. M. R.; Grüschow, S.; Goss, R. J. M. Scope and potential of halogenases in biosynthetic applications. *Curr. Op. Chem. Biol*. **2013**, *17*, 276-283.
203. Lam, K. C.; Ibrahim, R. K.; Behdad, B.; Dayanandan, S. Structure, function, and evolution of plant O-methyltransferases. *Genome* **2007**, *50*, 1001-1013.
204. Singh, S.; Phillips, G. N., Jr; Thorson, J. S. The structural biology of enzymes involved in natural product glycosylation. *Nat. Prod. Report*s **2012**, *29*, 1201–1237.
205. Chang, A.; Singh, S.; Phillips, G. N., Jr.; Thorson, J. S. Glycosyltransferase structural biology and its role in the design of catalysts for glycosylation. *Curr.Opinion Biotech*. **2012**, *22*, 800–808.
206. Nothaft, H.; Szymanski, C. M. Protein glycosylation in bacteria: sweeter than ever. *Nat. Rev. Microbiol*. **2010**, *8*, 765–778.
207. Calo, D.; Kaminski, L.; Eichler, J. Protein glycosylation in Archaea: sweet and extreme. *Glycobiology* **2010**, *20*, 1065–1076.
208. Choi, W. S.; Wu, X.; Choeng, Y. H.; Mahmud, T.; Jeong, B. C.; Lee, S. H.; Chang, Y. K.; Kim, C. J.; Hong, S. K Genetic organization of the putative biosynthetic gene cluster including the 2-epi-5-epi valiolone synthase gene in *Streptomyces albus* ATCC 21838. *Appl. Microbiol. Biotechnol*. **2008**, *80*, 637−645.
209. McCasland, G. E.; Furuta, S.; Durham, L. J. Alicyclic carbohydrates. XXIX. Synthesis of pseudohexose (2,3,4,5-tetrahydroxycyclohexanemethanol). *J. Org. Chem*. **1966**, *31*, 1516-1521.
210. Suami, T.; Ogawa, S.; Takata, M.; Yasuda, K.; Suga, A.; Takei, K.; Uematsu, Y. Synthesis and sweet tasting pseudo-β-fructopyranose. *Chem. Lett*. **1985**, 719-722
211. Suami, T.; Ogawa, S.; Takata, M.; Yasuda, K.; Takei, K.; Suga, A. Pseudo-sugars. XIV. Synthesis of sweet-tasting pseudo-β-DL-fructopyranose. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 819-821.
212. Ogawa, S.; Uematsu, Y.; Yoshida, S.; Sasaki, N.; Suami, T.J. Pseudo sugars. Part XVIII. Synthesis and sweetness of pseudo-β-D- and L-fructopyranose. J. *Carbohydr. Chem.* **1987**, *6*, 471-478.
213. Berg, J. M.; Tymoczko, J. L.; Stryer, L. Biochemistry. 5th edition. Freeman, **2002**. Chapter 8. Section 8.5.
214. Etxeberria, U.; de la Garza, A. L.; Canapión, J.; Martínez, J. A.; Milagro, F. I. Antidiabetic effects of natural plant extracts via inhibition of carbohydrate hydrolysis enzymes with emphasis on pancreatic alpha amylase. *Expert Opin. Ther. Targets* **2012**, *16*, 1-29.
215. Parry, R. J.; Burns, M. R.; Skae, P. N.; Hoyt, J. C.; Pal, B. Carbocyclic analogs of D-ribose-5-phosphate: synthesis and behavior with 5-phosphoribosyl α-1-pyrophosphate synthetases *Bioorg. Med. Chem*. **1996**, *4*, 1077-1088.

216. Kim, J. H.; Wolle, D.; Haridas, K.; Parry, R. J.; Smith, J. L.; Zalkin, H. A stable carbocyclic analog of 5-phosphoribosyl-1-pyrophosphate to probe the mechanism of catalysis and regulation of glutamine phosphoribosylpyrophosphate amidotransferase. *J. Biol. Chem*. **1995**, *270*, 17394-17399.
217. Parry, R. J.; Haridas, K., Synthesis of 1α-pyrophosphoryl-2α,3α-dihydroxy-4β-cyclopentanemethanol 5-phosphate, a carbocyclic analog of 5-phosphoribosyl-1-pyrophosphate (PRPP). *Tetrahedron Lett*. **1993**, *34*, 7013-7016.
218. Duley, J. A.; Christodoulou, J.; de Brouwer, A. P. M., The PRPP Synthetase Spectrum: What Does it Demonstrate About Nucleotide Syndromes?. *Nucleosides, Nucleotides & Nucleic Acids* **2011**, *30*, 1129-1139.
219. Tatibana, M.; Kita, K.; Taira, M.; Ishijima, S. Sonoda, T.; Ishizuka, T.; Iizasa, T.; Ahmad, I. Mammalian phosphoribosyl-pyrophosphate synthetase *Adv. Enz. Regulation* **1995**, *35*, 29-249.
220. Fujimori, S. in *Genetic bases of gout and hyperuricemia*. *I. PRPP synthetase superactivity*. Genetic Errors Associated with Purine and Pyrimidine Metabolism in Humans: Diagnosis and Treatment. Moriwaki, Y.; Yamamoto, T. eds. Research Signpost, Trivandrum, India, **2006**, p. 6-14.
221. United States Food and Drug Administration. Guidance for Industry. Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling. September **2006**. Clinical Pharmacology.
222. Fujimori, S. in *Genetic bases of gout and hyperuricemia*. *I. PRPP synthetase superactivity*. Genetic Errors Associated with Purine and Pyrimidine Metabolism in Humans: Diagnosis and Treatment. Moriwaki, Y.; Yamamoto, T. eds. Research Signpost, Trivandrum, India, **2006**, p. 6-14.
223. Becker, M. A.; Smith, P. R.; Taylor, W.; Mustafi. R.; Switzer, R. L, The genetic and functional basis of purine nucleotide feedback-resistant phosphoribosylpyrophosphate synthetase superactivity. *J. Clin. Invest.* **1995**, *96*, 2133–2141.
224. Mazurek, S.; Boschek, C. B.; Eigenbrodt, E. The role of phosphometabolites in cell proliferation, energy metabolism, and tumor therapy. *J. Bioenerg. and Biomemb*. **1997**, *29*, 315-330.
225. Sunamura, M.; Oonuma, M.; Motoi, F.; Abe, H.; Saitoh, Y.; Hoshida, T.; Ottomo S.; Horii, A.; Matsuno, S. Gene therapy for pancreatic cancer targeting the genomic alterations of tumor suppressor genes using replication-selective oncolytic adenovirus. *Human Cell*, **2002**, *15*, 138-150.
226. Ketudat Cairns, J. R.; Esen, A. β-Glucosidases. *Cell Mol. Life Sci*. **2010**, *67*, 3389–3405.
227. Tatsuta, K. Total synthesis and chemical design of useful glycosidase inhibitors. Carbohydrate Mimics. Chapleur, Y. ed, Wiley, **1998**, p. 283-305.
228. Kallemeijn, W. W.; Aerts, J. M. F. G.; Witte, M. D.; Waennekes, T. Mechanism-based inhibitors of glycosidases: design and applications. *Adv. Carbohydr. Chem. Biochem.* **2014**, *71*, 297-308.
229. Atsumi, S.; Iinuma, H.; Nosaka, C.; Umezawa, K. Biological activities of cyclophellitol. *J. Antibiot.* **1990**, *43*, 1579-1585.
230. Pengthaisong, S.; Chen, C.-F.; Withers, S. G.; Kuaprasert, B.; Ketudat C. J. R. Rice. BGlu1 glycosynthase and wild type transglycosylation activities distinguished by cyclophellitol inhibition. *Carbohydr. Res*. **2012**, *352*, 51-59.
231. Gloster, T. M.; Madsen, R.; Davies, G. J. Structural basis for cyclophellitol inhibition of a β-glucosidase. *Org. Biomol. Chem*. **2007**, *5*, 444-446.
232. Nakata, M.; Chong, C.; Niwata, Y.; Toshima, K.; Tatsuta, K. A family of cyclophellitol analogs: synthesis and evaluation. *J. Antibiot*. **1993**, *46*, 1919-1922.
233. Tai, V. W.-F.; Fung, P.-H.; Wong, Y.-S.; Shing, T. K. M. Synthesis and glycosidase-inhibitory activity of cyclophellitol analogs. *Tetrahedron: Asymm*. **1994**, *5*, 1353-1362.
234. Tai, V. W.-F.; Fung, P.-H.; Wong, Y.-S.; Shing, T. K. M. Kinetic studies on cyclophellitol analogs-mechanism-based inactivators. *Biochem. Biophys. Res. Comm*. **1995**, *213*, 175-180.
235. Li, K.-Y-; Jiang, J.; Witte, M. D.; Kallemeijn, W. W.; Donker-Koopman, W. E.; Boot, R. G.; Aerts, J. M. F. G.; Codee, J. D. C.; van der Marel, G. A.; Overkleeft, H. S. Exploring functional cyclophellitol analogues as human retaining beta-glucosidase inhibitors. *Org. Biomol. Chem*. **2014**, *12*, 7786-7791.
236. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. Enantiospecific synthesis and biological evaluation of 1,6-epi-cyclophellitol. *J. Antibiot*. **1991**, *44*, 456-458.
237. Atsumi, S.; Nosaka, Ch.; Ochi, Y.; Iinuma, H.; Umezawa, K. Inhibition of experimental metastasis by an α-glucosidase inhibitor, 1,6-epi-cyclophellitol. *Cancer Res*. **1993**, *53*, 4896-4899.

238. See for instance: (a) Kallemeijn, W. W.; Li, K.-Y.; Witte, M. D.; Marques, A. R. A.; Aten, J.; Scheij, S.; Jiang, J.; Willems, L. I.; Voorn-Brouwer, T. M.; van Roomen, C. P. A. A.; Ottenhoff, R.; Boot, R. G.; van den Elst, H.; Walvoort, M. T. C.; Florea, B. I.; Codee, J. D. C.; van der Marel, G. A.; Aerts, J. M. F. G.; Overkleeft, H. S. Novel Activity-Based Probes for Broad-Spectrum Profiling of Retaining β-Exoglucosidases In Situ and In Vivo. *Angew. Chem. Int. Ed.* **2012**, *51*, 12529-12533.
239. Li, K.-Y.; Jiang, Ji.; Witte, M. D.; Kallemeijn, W. W.; van den Elst, H.; Wong, Ch.-S.; Chander, S. D.; Hoogendoorn, S.; Beenakker, T. J. M.; Codee, J. D. C.; Aerts, J. M. F. G.; van der Marel, G. A.; Overkleeft, H. S. Synthesis of Cyclophellitol, Cyclophellitol Aziridine, and Their Tagged Derivatives. *Eur. J. Org. Chem*. **2014**, 6030-6043.
240. Willems, L. I.; Beenakker, T. J. M.; Murray, B.; Gagestein, B.; van den Elst, H.; van Rijssel, E. R.; Codee, J. D. C.; Kallemeijn, W. W.; Aerts, J. M. F. G.; van der Marel, G A.; Overkleeft, H. S. Synthesis of α- and β-Galactopyranose-Configured Isomers of Cyclophellitol and Cyclophellitol Aziridine. *Eur. J. Org. Chem*. **2014**, 6044-6056.
241. Jiang, J.; Beenakker, T. J. M.; Kallemeijn, W. W.; van der Marel, G. A.; van den Elst, H.; Codee, J. D. C.; Aerts, J. M. F. G.; Overkleeft, H. S. Comparing Cyclophellitol N-Alkyl and N-Acyl Cyclophellitol Aziridines as Activity-Based Glycosidase Probes. *Chem. Eur. J.* **2015**, *21*, 10861-10869.
242. Nobuji, Y.; Noriko, C.; Takashi, M.; Shigern, U.; Kenzou, H.; Michiaki, I. Jpn. Kokai Tokkyo Koho JP06306000, **1994**.
243. Miller, T. W.; Arison, B. H.; Albers-Schonberg, G. Isolation of a cyclitol antibiotic: 2,3,4,5-tetrahydroxycyclohexanemethanol. *Biotechnol. Bioeng*. **1973**, *15*, 1075-1080.
244. Suami, T.; Ogawa, S. Chemistry of carba-sugars (pseudo-sugars) and their derivatives. *Adv. Carbohydr. Chem. Biochem*. **1990**, *48*, 21-90.
245. Kamata, K.; Mitsuya, M.; Nishimura, T.; Eiki, J.; Nagata Y. Structural Basis for allosteric Regulation of the monomeric allosteric enzyme human Glucokinase. *Structure* **2004**, *12*, 429-438.
246. Postic, C.; Shiota, M.; Magnuson, M. A. Cell-specific roles of glucokinase in glucose homeostasis. *Recent Progress in Hormone Research* **2001**, *56*, 195-218.
247. Miwa, I.; Hara, H.; Okuda, J.; Suami, T.; Ogawa, S. Inhibition of glucose-stimulated insulin release by pseudo-alpha-DL-glucose as a glucokinase inhibitor. *Biochem. Int.* **1985**, *11*, 809-816.
248. Kitaoka, M.; Ogawa, S.; Taniguchi, H. A cellobiose phosphorylase from *Cellvibrio gilvus* recognizes only the beta-D-form of 5a-carba-glucopyranose. *Carbohydr. Res*. **1993**, *247*, 355-359.
249. Sugimoto, Y.; Suzuki, H.; Yamaki, H.; Nishimura, T.; Tanaka, N. Mechanism of action of 2-crotonyloxymethyl-4,5,6-trihydroxycyclohex-2-enone, a sulfhydryl inhibitory antitumor antibiotic, and its effect on drug-resistant neoplastic cells. *J. Antibiot.* **1982**, *35*, 1222-1230.
250. Huntley, C. F. M.; Hamilton, D. S.; Creighton, D. J.; Ganem, B. Reaction of COTC with Glutathione: Structure of the Putative Glyoxalase I Inhibitor. *Org. Lett.* **2000**, *2*, 3143-3144.
251. Kamiya, D.; Uchihata, Y.; Ichikawa, E.; Kato, K.; Umezawa, K. Reversal of anticancer drug resistance by COTC based on intracellular glutathione and glyoxalase I. *Biorg. Med. Chem. Lett.* **2005**, *15*, 111-1114.
252. Collu, F.; Bonsignore, L.; Casu, M.; Floris, C.; Gertsch, J.; Cottiglia, F. New cytotoxic saturated and unsaturated cyclohexanones from *Anthemis maritima*. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1559-1562.
253. Joseph, E.; Eiseman, J. L.; Hamilton, D. S.; Wang, H.; Tak, H.; Ding, Z.; Ganem, B.; Creighton, D. J. Molecular Basis of the Antitumos Activities of 2-Croyonyloxymethyl-2-cycloalkenones. *J. Med. Chem*. **2003**, *46*, 194-196.
254. Thornlley, P. J. Glyoxalase I-structure, function and a critical role in the enzymatic defence against glycation. *Biochem. Soc. Trans.* **2003**, *31*, 1343–1348.
255. Creighton, D. J.; Hamilton, D. S. Brief history of glyoxalase I and what we have learned about metal ion-dependent, enzyme-catalyzed isomerizations. *Arch. Biochem. Biophys,* **2001**, *387,* 1–10.
256. Mirza, S.; Molleyres, L. P.; Vasella, A. Synthesis of a glyoxalase I inhibitor from *Streptomyces griseosporeus* Niida et Ogasawara. *Helv. Chim. Acta* **1985**, *68*, 986-996.
257. Takayama, H.; Hayashi, K.; Koizumi, T. Enantioselective total synthesis of glyoxalase I inhibitor using asymmetric Diels-Alder reaction of a new chiral dienophile, (S)S-3-(3-trifluoromethylpyrid-2-ylsulfinyl)acrylate. *Tetrahedron Lett*. **1986**, *27*, 5509-5512.

258. Shing, T. K. M.; Tang, Y. Enantiospecific synthesis of 2-crotonyloxy-(4R,5R,6R)-4,5,6-trihydroxycyclohex-2-enone (COTC) from quinic acid. *J. Chem. Soc. Chem. Comm.* 1990, 312.
259. Huntley, C. F. M.; Wood, H. B.; Ganem, B. A new synthesis of the glyoxalase-I inhibitor COTC. *Tetrahedron Lett*. **2000**, *41*, 2031-2034.
260. Arthurs, C. L.; Wind, N. S.; Whitehead, R. C.; Stratford, I. J. Analogues of 2-crotonyloxymethyl-(4R,5R,6R)-4,5,6-trihydroxycyclohex-2-enone (COTC) with anti-tumor properties. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 553-557.
261. Arthurs, C. L.; Raftery, J.; Whitby, H. L.; Whitehead, R.C.; Wind, N. S.; Stratford, I. J. Arene cis-dihydrodiols: Useful precursors for the preparation of analogs of the antitumor agent, 2-crotonyloxymethyl-(4R,5R,6R)-4,5,6-trihydroxycyclohex-2-enone (COTC). *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5974-5977.
262. Arthurs, C. L.; Morris, G. A.; Piacenti, M.; Pritchard, R. G.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Williams, K. F.; Wind, N. S. The synthesis of 2-oxyalkyl-cyclohex-2-enones, related to the bioactive natural products COTC and antheminone A, which possess antitumor properties. *Tetrahedron* **2010**, *66*, 9049-9060.
263. Shing, T. K. M.; Wu, H. T.; Kwok, H. F.; Lau, C. B. S. Synthesis of chiral hydroxylated enones as potential anti-tumor agents. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 7562-7565.
264. Arthurs, C. L.; Lingley, K. F.; Piacenti, M.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Wind, N. S. (-)-Quinic acid: a versatile precursor for the synthesis of analogs of 2-crotonyloxymethyl-(4R,5R,6R)-4,5,6-trihydroxycyclohex-2-enone (COTC) which possess antitumor properties. *Tetrahedron Lett.* **2008**, *49*, 2410-2413.
265. See: Dowling, P. M., Aminoglycosides and aminocyclitols. Antimicrobial Therapy in Veterinary Medicine. 5th Edition. Giguere, S.; Prescott, J. F.; Dowling, P. M. eds. Wiley, **2013**, p. 233-255. See also: Kudo, F.; Eguchi, T. Aminoglycoside Antibiotics: New Insights into the Biosynthetic Machinery of Old Drugs. *Chem. Record* **2016**, *16*, 4-18.
266. Lewwellyn, N. M.; Spencer, J. B. Biosynthesis of 2-deoxystreptamine-containing aminoglycoside antibiotics. *Nat. Prod. Report.* **2006**, *23*, 864-874.
267. Nango, E.; Eguchi, T.; Kakinuma, K Active Site Mapping of 2-Deoxy-scyllo-inosose Synthase, the Key Starter Enzyme for the Biosynthesis of 2-Deoxystreptamine. Mechanism-Based Inhibition and Identification of Lysine-141 as the Entrapped Nucleophile. *J. Org. Chem*. **2004**, *69*, 593-600.
268. Dykes, D.; Waud, W. Murine L1210 and P388 leukemias. Tumor Models in Cancer Research. Teicher, B, ed. Humana Press, Inc., **2002**, pp.23-40.
269. Herbst, R. S. Review of epidermal growth factor. *Int. J. Radiat. Oncol. Biol.* **2004**, *59*, 21-26.
270. See Chanpoux, J. J. DNA topoisomerases: structure, function, and mechanism. *Annu. Rev. Biochem*. **2001**, *70*, 369-413.
271. Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. Novel antitumor metabolites produced by a fungal strain from a sea hare. *Tetrahedron Lett*. **1997**, *38*, 8215-8218.
272. Javitt, N. B. Hep G2 cells as a resource for metabolic studies: lipoprotein, cholesterol, and bile acids. *FASEB J.* **1990**, *4*, 161-168.
273. Bach, G.; Breiding-Mack, S.; Grabley, S.; Hammann, P.; Huetter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. Secondary metabolites by chemical screening. 22. Gabosines, new carba-sugars from Streptomyces. *Liebigs Ann. Chem*. **1993**, 241-250.
274. Tang, Y.-Q.; Maul, C.; Hofs, R.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Zeeck, A.; Thiericke, R. Gabosines L, N and O: new carbasugars from Streptomyces with DNA-binding properties. *Eur. J. Org. Chem*. **2000**, 149-153.
275. Maier, A.; Maul, C.; Zerlin, M.; Grabley, S.; Thiericke, R. Biomolecular-chemical screening. A novel screening approach for the discovery of biologically active secondary metabolites. II. Application studies with pure metabolites. *J. Antibiot*. **1999**, *52*, 952-959.
276. Tsushiya, T.; Mikami, N.; Umezawa, S.; Umezawa, H.; Naganawa, H. KD16-U1, a new metabolite of Streptomyces. Isolation and structural studies. *J. Antibiot*. **1974**, *27*, 579-586.
277. Winchester, B. Role of α-D-mannosidases in the biosynthesis and catabolism of glycoproteins. *Biochem. Soc. Trans.* **1984**, *12*, 522–524.
278. Vidyasagar, A.; Sureshan, K. M. Total Synthesis and Glycosidase Inhibition Studies of (-)-Gabosine J and Its Derivatives. *Eur. J. Org. Chem*. **2014**, 2349-2356.
279. Smetanina, O. F.; Kalinovskii, A. I.; Khudyakov, Y. V.; Moiseenko, O. P.; Pivkin, M. V.; Menzorova, N. I.; Sibirtsev, Y. T.; Kuznetsova, T. A. Metabolites of the marine fungus *Aspergillus varians* KMM 4630. *Chem. Nat. Compd*. **2005**, *41*, 243-244.

280. Trisuwan, K.; Rukachaisirikul, V.; Sukpondma, Y.; Preedanon, S.; Phongpaichit, S.; Rungjindamai, N.; Sakayaroj, J. Epoxydons and a Pyrone from the Marine-Derived Fungus *Nigrospora* sp. PSU-F5. *J. Nat. Prod.* **2008**, *71*, 1323-1326.
281. Qin, S.; Hussain, H.; Schulz, B.; Draeger, S.; Krohn, K. Two new metabolites, epoxydine A and B, from *Phoma* sp. *Helv. Chim. Acta* **2010**, *93*, 169-174.
282. Kakeya, H.; Miyake, Y.; Shoji, M.; Kishida, S.; Hayashi, Y.; Kataoka, T.; Osada, H. Novel non-peptide inhibitors targeting death receptor-Mediated apoptosis. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3743-3746.
283. Mitsui, T.; Miyake, Y.; Kakeya, H.; Hayashi, Y.; Osada, H.; Kataoka, T. RKTS-33, an epoxycyclohexenone derivative that specifically inhibits Fas ligand-dependent apoptosis in CTL-mediated cytotoxicity. *Biosci. Biotechnol. Biochem*. **2005**, *69*, 1923-1928.
284. Gilmore, T. D. Introduction to NF-kappaB: players, pathways, perspectives. *Oncogene* **2006**, *25*, 6680–6884.
285. Brasier, A. R. The NF-kappaB regulatory network. *Cardiovascular Toxicol*. **2006**, *6*, 111–130.
286. Saitoh, T.; Suzuki, E.; Takasugi, A.; Obata, R.; Ishikawa, Y.; Umewaza, K.; Nishiyama, S. Efficient synthesis of (±)-parasitenone, a novel inhibitor of NF-κB. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5383-5386.
287. Wang, Ch.-H.; Wu, H. T.; Cheng, H. M.; Yen, T.-J.; Lu, I.-H.; Chang, H. Ch.; Jao, S.-Ch.; Shing, T. K. M.; Li, W.-S. Inhibition of Glutathione S-Transferase M1 by New Gabosine Analogs Is Essential for Overcoming Cisplatin Resistance in Lung Cancer Cells. *J. Med. Chem*. **2011**, *54*, 8574-8581.
288. Giard, D. J.; Aaronson, S. A.; Todaro, G. J.; Arnstein, P.; Kersey, J. H.; Dosik, H.; Parks, W. P. *In vitro* cultivation of human tumors: Establishment of cell lines derived from a series of solid tumors. *J. Nat. Cancer Institute* **1973**, *51*, 1417–1423.
289. Engel, L. S.; Taioli, E.; Pfeiffer, R.; Garcia-Closas, M.; Marcus, P. M.; Lan, Q.; Boffetta, P.; Vineis, P.; Autrup, H.; Bell, D. A.; Branch, R. A.; Brockmöller, J.; Daly, A. K.; Heckbert, S. R.; Kalina, I.; Kang, D.; Katoh, T.; Lafuente, A.; Lin, H. J.; Romkes, M.; Taylor, J. A.; Rothman, N. Pooled analysis and meta-analysis of glutathione S-transferase M1 and bladder cancer: a HuGE review. *Am. J. Epidemiol.* **2002**, *156*, 95–109.
290. Ogawa, S.; Aoyama, H.; Sato, T. Synthesis of an ether-linked alkyl 5a-carba-beta-D-glucoside, a 5a-carba-beta-D-galactoside, a 2-acetamido-2-deoxy-5a-carba-beta-D-glucoside, and an alkyl 5a'-carba-beta-lactoside. *Carbohydr. Res*. **2002**, *337*, 1979-1992.
291. Becker, J. C.; Houben, R.; Schrama, D.; Voigt, H.; Ugurel, S.; Reisfeld, R. A. Mouse models for melanoma: a personal perspective. *Exp. Dermatol*. **2009**, *19*, 157–164.
292. David, L. N.; Michael, M. C. Lipids. Lehninger Principles of Biochemistry, 4th edition. W H Freeman, **2005**, p. 357.
293. Mocchetti, I. Exogenous gangliosides, neuronal plasticity and repair, and the neurotrophins. *Cell Mol. Life Sci*. **2005**, *62*, 2283–2294.
294. Jeanneret, V.; Vogel, P.; Renaut, P.; Millet, J.; Theveniaux, J.; Barberousse, V. Carbaxylosides of 4-ethyl-2-oxo-2H-benzopyran-7-yl as non-hydrolyzable, orally active venous antithrombotic agents. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1687-1688.
295. Lefoix, M.; Tatibonët, A.; Cottaz, S.; Driguez, H.; Rollin, P. Carba-glucotropaeolin: the first non-hydrolyzable glucosinolate analogue, to inhibit myrosinase. *Tetrahedron Lett*. **2002**, *43*, 2889-2890.
296. Halkier, B. A.; Gershenzon, J. Biology and Biochemistry of Glucosinolates. *Ann.Rev.Plant Biol.* **2006***, 57*, 303–333.
297. Yuasa, H.; Palcic, M. M.; Hindsgaul, O. Synthesis of the carbocyclic analog of uridine 5′-(α-D4)-galactopyranosyl diphosphate) (UDP-Gal) as an inhibitor of β (1→4)-galactosyltransferase. *Can. J. Chem*. **1995**, *73*, 2190-2195.
298. Cai, S.; Stroud, M. R.; Hakomori, S.; Toyokuni, T. Synthesis of carbocyclic analogs of guanosine 5'-(β-L-fucopyranosyl diphosphate) (GDP-fucose) as potential inhibitors of fucosyltransferases. *J. Org. Chem.* **1992**, *57*, 6693-6696.
299. Norris, A. J.; Whitelegge, J. P.; Strouse, M. J.; Faull, K. F.; Toyokuni, T. Inhibition kinetics of carba- and C-fucosyl analogues of GDP-fucose against fucosyltransferase V: implication for the reaction mechanism. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 571-573.
300. Diaz, L.; Delgado, A. Medicinal chemistry of aminocyclitols. *Curr. Med. Chem*. **2010**, *17*, 2393-2418.
301. Ogawa, S.; Kanto, M. Design and synthesis of 5a-Carbaglycopyranosylamine glycosidase inhibitors. *Curr. Top. Med Chem*. **2009**, *9*, 58-75.

302. Chen, X.; Fan, Y.; Zheng, Y.; Shen, Y. Properties and Production of Valienamine and Its Related Analogues. *Chem Rev*. **2003**, *103*, 1955-1977.
303. Zhang, J.-F.; Zheng, Y.-G.; Shen, Y.-Ch.. Inhibitory effect of valienamine on the enzymatic activity of honeybee (*Apis cerana Fabr.*) α-glucosidase. *Pest. Biochem. Physiol.* **2007**, *87*, 73-77.
304. Zheng, Y.-G.; Shentu, X.-P.; Shen, Y.-Ch. Inhibition of porcine small intestinal sucrase by valienamine. *J. Enzym. Inhibit. Med. Chem*. **2005**, *20*, 49-53.
305. Xue, Y.-P.; Jin, L-Q.; Liu, Z.-Q.; Zhang, J.-F.; Zheng, Y.-G. Purification and characterization of β-glucosidase from Reticulitermes flaviceps and its inhibition by valienamine and validamine. *African J. Biotech*. **2008**, *7*, 4595-4601.
306. Zheng, Y.; Shentu, X.; Shen, Y. Inhibition of porcine small intestinal sucrase by validamine. *Chin. J. Chem. Eng*. **2005**, *13*, 429-432.
307. Ogawa, S.; Oya, M.; Toyokuni, T.; Chida, N.; Suami, T. Pseudo-sugars. VIII. Synthesis of DL-1-Epivalidamine and Related Compounds. *Bull. Chem. Soc. Jpn.* 1983, *56*, 1441-1445.
308. Ogawa, S.; Suzuki, M.; Tonegawa, T. New Synthesis of Penta-N,O-acetyl-DL-validamine and Pseudo-2-amino-2-deoxy-α-DL-mannopyranose, and Their Uronate Analogs. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 1824-1826.
309. Kameda, Y.; Kawashima, K.; Takeuchi, M.; Ikeda, K.; Asano, N.; Matsui, K. Preparation and biological activity of manno- and galacto-validamines, new 5a-carba-glycosylamines as alpha-glycosidase inhibitors. *Carbohydr. Res*. **1997**, *300*, 259-264.
310. Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, K.; Matsui, K.; Horii, S.; Fukase, H. Valiolamine, a new alpha-glucosidase inhibiting aminocyclitol produced by *Streptomyces hygroscopicus*. *J. Antibiot*. **1984**, *37*, 1301-1307.
311. Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. Synthesis and alpha-D-glucosidase inhibitory activity of N-substituted valiolamine derivatives as potential oral antidiabetic agents. *J. Med. Chem.* **1986**, *29*, 1038-1046.
312. Chen, X.; Zheng, Y.; Shen, Y. Voglibose_Basen, AO-128, one of the most important α-glucosidase inhibitors. *Curr. Med. Chem*. **2006**, *13*, 109-116.
313. Dabhi, A. S.; Bhatt, N. R.; Shah, M. J. Voglibose: an alpha glucosidase inhibitor. *J. Clin. Diagnost. Res.* 2**013**, 3023-3027.
314. Konya, H.; Katsuno, T.; Tsunoda, T.; Yano, Y.; Kamitani, M.; Miuchi, M.; Hamaguchi, T.; Miyagawa, J.-i.; Namba, M. Effects of combination therapy with mitiglinide and voglibose on postprandial plasma glucose in patients with type 2 diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* **2013**, *6*, 317-325.
315. Campo, V. L.; Aragao-Leoneti, V.; Carvalho, I. Glycosidases and diabetes: metabolic changes, mode of action and therapeutic perspectives. *Carbohydr. Chem.* **2013**, *39*, 181-203.
316. Derosa, G.; Maffoli, P. α-Glucosidase inhibitors and their use in clinical practice. *Archiv. Med. Sci*. **2012**, *8*, 899-906; (d) Bin, B.-H.; Seo, J.; Yang, S. Ha; Lee, E.; Choi, H.; Kim, K.-H.; Cho, Eun-Gyung; L., Tae R. Novel inhibitory effect of the antidiabetic drug voglibose on melanogenesis. *Exp. Dermatol*. **2013**, *22*, 541-546.
317. Lockhoff, O. Glycolipids as Immunomodulators: Syntheses and Properties *Angew. Chem., Int. Ed*. Engl. **1991**, *30*, 1611-1620.
318. Tsunoda, H.; Sasaki, S.-I.; Furuya, T.; Ogawa, S. Pseudosugars, 36. Synthesis of Methyl 5a′-Carbamaltoses Linked by Imino, Ether and Sulfide Bridges and Unsaturated Derivatives Thereof *Liebigs Ann. Chem.* **1996**, 159-165.
319. Ramstadius, C.; Hekmat, O.; Eriksson, L.; Stalbrand, H.; Cumpstey, I. β-Mannosidase and β-hexosaminidase inhibitors: synthesis of 1,2-bis-epi-valienamine and 1-epi-2-acetamido-2-deoxy-valienamine from D-mannose. *Tetrahedron: Asym*. **2009**, *20*, 795-807.
320. Scaffidi, A.; Stubbs, K. A.; Dennis, R. J.; Taylor, E. J.; Davies, G. J.; Vocadlo, D. J.; Stick, R. V. A 1-acetamido derivative of 6-epi-valienamine: an inhibitor of a diverse group of β-N-acetylglucosaminidases. *Org. Biomol. Chem*. **2007**, *5*, 3013–3019.
321. Frohwein, Y. Z.,; Gatt, S. Isolation of β-N-acetylhexosaminidase, β-N-acetylglucosaminidase, and β-N-acetylgalactosaminidase from calf brain. *Biochem*. **1967**, *6*, 2775–2782.
322. Li, S. C.; Li, Y. T. Studies on the glycosidases of jack bean meal. 3. Crystallization and properties of β-N-acetylhexosaminidase. *J. Biol. Chem.* **1970**, *245*, 5153–5160.
323. Liu, T.; Chen, L.; Ma, Q.; Shen, X.; Yang, Q. Structural insights into chitinolytic enzymes and inhibition mechanisms of selective inhibitors. *Curr. Pharm. Design*. **2014**, *20*, 754-770.
324. Tsunoda, H.; Ogawa, S. Pseudosugars, 33. Synthesis of some 5a-carbaglycosylamides, glycolipid analogs of biological interests. *Liebigs Ann. Chem*. **1994**, 103-107.

325. Tsunoda, H.; Inokuchi, J.-I.; Yamagishi, K.; Ogawa, S. Pseudosugars, 35. Synthesis of glycosylceramide analogs composed of imino-linked unsaturated 5a-carbaglycosyl residues: Potent and specific gluco- and galactocerebrosidase inhibitors. *Liebigs Ann. Chem*. **1995**, 279-284.

326. Ogawa, S.; Ashiura, M.; Uchida, C.; Watanabe, S.; Yamazaki, C.; Yamagishi, K.; Inokuchi, J.-I. Synthesis of potent β-D-glucocerebrosidase inhibitors:_N-alkyl-β-valienamines. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 929-932.

327. Ogawa, S.; Mito, T.; Taiji, E.; Jimbo, M.; Yamagishi, K.; Inokuchi, J. Synthesis and biological evaluation of four stereoisomers of PDMP-analogue, N-(2-decylamino-3-hydroxy-3-phenylprop-1-yl)-β-valienamine, and related compounds. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1915-1920.

328. Ogawa, S.; Kobayashi, Y.; Kabayama, K.; Jimbo, M.; Inokuchi, J.-I. Chemical modification of beta-glucocerebrosidase inhibitor N-octyl-beta-valienamine: synthesis and biological evaluation of N-alkanoyl and N-alkyl derivatives. *Bioorg. Med. Chem*. **1998**, *6*, 1955-1962.

329. Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. Synthesis and α-D-glucosidase inhibitory activity of N-substituted valiolamine derivatives as potential oral antidiabetic agents. *J. Med. Chem*. **1986**, *29*, 1038-46.

330. Kameda, Y.; Asano, N.; Yoshikawa, M.; Matsui, K.; Horii, S.; Fukase, H. J. N-Substituted valienamines, alpha-glucosidase inhibitors. *J. Antibiot*. **1982**, *35*, 1624–1626.

331. Lysek, R.; Schuetz, C.; Favre, S.; O'Sullivan, A.C.; Pillonel, Ch.; Kruelle, T.; Jung, P. M. J.; Clotet-Codina, I.; Este, J. A.; Vogel, P. Search for α-glucosidase inhibitors: New N-substituted valienamine and conduramine F-1 derivatives. *Bioorg. Med. Chem*., **2006**, *14*, 6255-6282.

332. Kapferer, P.; Birault, V.; Poisson, J.; Vasella, A. Synthesis and evaluation as glycosidase inhibitors of carbasugar-derived spirodiaziridines, spirodiazirines, and spiroaziridines. *Helv. Chim. Acta* **2003**, *86*, 2210-2227.

333. Wang, Y.; Bennet, A.J. A potent bicyclic inhibitor of a family 27 α-galactosidase. *Org. Biomol. Chem*. **2007**, *50*, 1731-1738.

334. Suzuki, Y.; Ogawa, S.; Sakakibara, Y. Chaperone therapy for neuronopathic lysosomal diseases: competitive inhibitors as chemical chaperones for enhancement of mutant enzyme activities. *Persp. Med. Chem*. **2009**, *3*, 7-19.

335. Suzuki, Y. Chemical chaperone therapy for GM1-gangliosidosis. *Cell. Mol. Life Sci*. **2008**, *65*, 351-353.

336. Suzuki, Y. β-Galactosidase deficiency: an approach to chaperone therapy. *J. Inherited Metabolic Dis*. **2006**, *29*, 471-476.

337. Ogawa, S.; Kanto, M.; Suzuki, Y. Development and medical application of unsaturated carbaglycosylamine glycosidase inhibitors. *Mini-Rev. Med. Chem*. **2007**, *7*, 679-691.

338. Matsuda, J.; Suzuki, O.; Oshima, A.; Yamamoto, Y.; Noguchi, A.; Takimoto, K.; Itoh, M.; Matsuzaki, Y.; Yasuda, Y.; Ogawa, S.; Sakata, Y.; Nanba, E.; Higaki, K.; Ogawa, Y.; Tominaga, L.; Ohno, K.; Iwasaki, H.; Watanabe, H.; Brady, R. O.; Suzuki, Y. Chemical chaperone therapy for brain pathology in G_{M1}-gangliosidosis. *Proc. Natl. Acad. Sci. U. S. A*. **2003**, *100*, 15912-15917.

339. Lin, H.; Sugimoto, Y.; Ohsaki, Y.; Ninomiya, H.; Oka, A.; Taniguchi, M.; Ida, H.; Eto, Y.; Ogawa, S.; Matsuzaki, Y.; Sawa, M.; Inoue, T.; Higaki, K.; Nanba, E.; Ohno, K.; Suzuki, Y. N-octyl-beta-valienamine up-regulates activity of F213I mutant beta-glucosidase in cultured cells: a potential chemical chaperone therapy for Gaucher disease. *Biochim. Biophys. Acta* **2004**, *1689*, 219-228.

340. Hossain, M. A.; Higaki, K.; Saito, S.; Ohno, K.; Sakuraba, H.; Nanba, E.; Suzuki, Y.; Ozono, K.; Sakai, N. Chaperone therapy for Krabbe disease: potential for late-onset GALC mutations. *J. Human Gen*. **2015**, *60*, 539-545.

341. Kuno, S.; Higaki, K.; Takahashi, A.; Nanba, E.; Ogawa, S. Potent chemical chaperone compounds for GM1-gangliosidosis: N-substituted (+)-conduramine F-4 derivatives. *Med. Chem. Med*. **2015**, *6*, 306-310.

342. Suzuki, Y.; Ichinomiya, S.; Kurosawa, M.; Matsuda, J.; Ogawa, S.; Iida, M.; Kubo, T.; Tabe, M.; Itoh, M.; Higaki, K.; Nanba, E.; Ohno, K. Therapeutic chaperone effect of N-Octyl 4-Epi-β-valienamine on murine GM1-gangliosidosis. *Mol. Gen. Metabol*. **2012**, *106*, 92-98.

343. Kuno, S.i; Takahashi, A.; Ogawa, S. Transformation of quercitols into 4-methylenecyclohex-5-ene-1,2,3-triol derivatives, precursors for the chemical chaperones N-octyl-4-epi-β-valienamine (NOEV) and N-octyl-β-valienamine (NOV). *Bioorg. Med. Chem. Lett*. **2011**, *21*, 7189-7192.

344. Luan, Z.; Li, L.; Ninomiya, H.i; Ohno, K.; Ogawa, S.; Kubo, T.; Iida, M.; Suzuki, Y. The pharmacological chaperone effect of N-octyl-β-valienamine on human mutant acid β-glucosidases. *Blood Cell. Mol. Dis*. **2010**, *44*, 48-54.
345. Suzuki, Y.; Ichinomiya, S.; Kurosawa, M.; Ohkubo, M.; Watanabe, H.; Iwasaki, H.; Matsuda, J.; Noguchi, Y.; Takimoto, K.; Itoh, M.; Tabe, M.; Iida, M.; Kubo, T.; Ogawa, S.; Nanba, E.; Higaki, K.; Ohno, K.; Brady, R. O. Chaperone therapy for neuronopathic lysosomal diseases: competitive inhibitors as chemical chaperones for enhancement of mutant enzyme activities. *Ann. Neurol*. **2007**, *62*, 671-675.
346. Lei, K; Ninomiya, H.; Suzuki, M.; Inoue, T.; Sawa, M.; Iida, M.; Ida, H.; Eto, Y.; Ogawa, S.; Ohno, K.; Suzuki, Y. Enzyme enhancement activity of N-octyl-β-valienamine on β-glucosidase mutants associated with Gaucher disease. *Biochim. Biophys. Acta* **2007**, *1772*, 587-596.
347. Hossain M. A.; Shinpo M.; Ozono K.i; Higaki K.Nanba E.; Suzuki Y.Sakai N. Chemical chaperone treatment for galactosialidosis: Effect of NOEV on β-galactosidase activities in fibroblasts. *Brain Develop*. **2016**, *38*, 175-80.
348. Suzuki H.; Ohto U.; Higaki K.; Nanba E.; Mena-Barragan T.; Aguilar-Moncayo M.; Ortiz Mellet C.; Garcia Fernandez, J. M; Suzuki Y.; Shimizu T. Structural basis of pharmacological chaperoning for human β-galactosidase. *J. Biol. Chem*. **2014**, *289*, 14560-14568.
349. Takamura A.; Higaki K.; Ninomiya, H.; Takai, T.; Matsuda J.; Iida M.; Ohno, K; Suzuki, Y.; Nanba, E. Lysosomal accumulation of Trk protein in brain of GM1-gangliosidosis mouse and its restoration by chemical chaperone. *J. Neurochem*. **2011**, *118*, 399-406.
350. Luan, Z.; Ninomiya, H.; Ohno, K.; Ogawa, S.; Kubo, T.; Iida, M.; Suzuki, Y. The effect of N-octyl-β-valienamine on β-glucosidase activity in tissues of normal mice. *Brain Develop*. **2010**, *32*, 805-809.
351. Parenti, G.; Andria, G.; Valenzano, K. J. Pharmacological Chaperone Therapy: Preclinical Development, Clinical Translation, and Prospects for the Treatment of Lysosomal Storage Disorders. *Mol. Ther*. **2015**, *23*, 1138-1148.
352. Parenti, G.; Moracci, M.; Fecarotta, S.; Andria, G. Pharmacological chaperone therapy for lysosomal storage diseases. *Future Med. Chem*. **2014**, 1031-1045.
353. Winchester, B.; Vellodi, A.; Young, E. The molecular basis of lysosomal storage diseases and their treatment. *Biochem. Soc. Trans.* **2000**, *28*, 150–154.
354. Ogawa, S.; Sekura, R.; Maruyama, A.; Yuasa, H.; Hashimoto, H. Synthesis and Glycosidase Inhibitory Activity of 5a-Carba-α-DL-fucopyranosylamine and-galactopyranosylamine. *Eur. J. Org. Chem*. **2000**, 2089-2093.
355. Ogawa, S.; Maruyama, A.; Odagiri, T.; Yuasa, H.; Hashimoto, H. Synthesis and Biological Evaluation of α-L-Fucosidase Inhibitors: 5a-Carba-α-L-fucopyranosylamine and Related Compounds. *Eur. J. Org. Chem*. **2001**, 967-974.
356. Ogawa, S.; Watanabe, M.; Maruyama, A.; Hisamatsu, S. Synthesis of an alpha-fucosidase inhibitor, 5a-carba-beta-L-fucopyranosylamine, and fucose-type alpha- and beta-DL-valienamine unsaturated derivatives. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 749-752.
357. Bernacki, R. J.; Niedbala, M. J.; Korytnyk, W. Glycosidases in cancer and invasion. *Cancer Metastasis Rev.* **1985**, *4*, 81-101.
358. Ogawa, S.; Mori, M.; Takeuchi, G.; Doi, F.; Watanabe, M.; Sakata, Y. Convenient synthesis and evaluation of enzyme inhibitory activity of several N-alkyl-, N-phenylalkyl, and cyclic isourea derivatives of 5a-carba-alpha-DL-fucopyranosylamine. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2811-2814.
359. Ogawa, S.; Fujieda, S.; Sakata, Y.; Ishizaki, M.; Hisamatsu, S.; Okazaki, K. Synthesis and glycosidase inhibitory activity of some N-substituted 6-deoxy-5a-carba-beta-DL- and L-galactopyranosylamines. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3461-3463.
360. Williams, G. J.; Thorson, J. S. Natural product glycosyltransferases: properties and applications. *Adv. Enzymol. Related Areas Mol. Biol.* **2009***, 76*, 55–119.
361. Kajihara, Y.; Hashimoto, H.; Ogawa, S. Galactosyl transfer ability of β-(1→ 4)-galactosyltransferase toward 5a-carba-sugars. *Carbohydr. Res*. **2000**, *323*, 44-48.
362. Qian, H.; Hu, B.; Wang, Z.; Xu, X.; Hong, T. Effects of validamycin on some enzymatic activities in soil. *Environ. Monit. Asses*. **2007**, *125*, 1-8.
363. Ishikawa, R.; Shirouzu, K.; Nakashita, H.; Teraoka, T.; Arie, T. Control efficacy of validamycin A against Fusarium wilt correlated with the severity of phytotoxic necrosis formed on tomato tissues. *J. Pest. Sci*. **2007**, *32*, 83-88.

364. Naik, B. M.; John, P.; Solanky, K. U.; Mahatma, L.; Mehta, B. P.; Sabalpara, A. N. Evaluation of newer fungicides for the management of foliar pathogens of banana. *Pestology* **2010**, *34*, 40-43.
365. Lee, Y. H.; Choi, Ch. W.; Kim, S. H.; Yun, J. G.; Chang, S. W.; Kim, Y. S.; Hong, J. K. Chemical pesticides and plant essential oils for disease control of tomato bacterial wilt. *Plant Pathol. J.* **2012**, *28*, 32-39.
366. Guirao-Abad, J. P.; Sanchez-Fresneda, R.; Valentin, E.; Martinez-Esparza, M.; Arguelles, J. C. Analysis of validamycin as a potential antifungal compound against *Candida albicans*. *Int. J. Microbiol*. **2013**, *16*, 217-225.
367. Nwaka, S.; Holzer H. Molecular biology of trehalose and the trehalases in the yeast *Saccharomyces cerevisiae*. *Prog Nucleic Acid Res Mol Biol.* **1998**, *58*, 197-237.
368. Barraza, A.; Sánchez, F. Trehalases: A neglected carbon metabolism regulator?. *Plant Sign. Behav*, **2013**. Published online: www.landesbioscience.com/journals/psb/article/24778.
369. Mueller, J.; Boller, T.; Wiemken, A. Trehalose and trehalase in plants: recent developments. *Plant Sci.* **1995**, *112*, 1-9.
370. Tatun, N.; Wangsantitham, O.; Tungjitwitayakul, J.; Sakurai, S. Trehalase activity in fungus-growing termite, *Odontotermes* feae (Isoptera: *Termitideae*) and inhibitory effect of validamycin. *J. Econ. Entomol.* **2014**, *107*, 1224-1232.
371. Lenka, S.; Bhaktavatsalam, G.; Medhi, B. Fungicidal control of sheath blight of rice. *J. Plant Prot. Environ*. **2010**, *7*, 53-55.
372. Bhuvaneswari, V.; Raju, S. K. Efficacy of new fungicide of strobilurin group against rice sheath blight caused by Rhizoctonia solani. *J. Mycol. Plant Physiol.* **2013**, *43*, 447-451.
373. Wakae, O.; Matsuura, K. Characteristics of validamycin as a fungicide for Rhizoctonia disease control. Review *Plant Protect. Res*. **1975**, *8*, 81-92.
374. Serneels, J.; Tournu, H.; Van Dijck, P. Tight control of trehalose content is required for efficient heat-induced cell elongation in Candida albicans. *J. Biol. Chem*. **2012**, *287*, 6873-36882.
375. Wang, Z.-J.; Ji, S.; Si, Y.-X.; Yang, J.-M.; Qian, G.-Y.; Lee, J.; Yin, S.-J. The effect of validamycin_A on tyrosinase: Inhibition kinetics and computational simulation. *Int. J. Biol. Macromol*. **2013**, *55*, 15-23.
376. Lee, Y. H.; Cho, Y.-S.; Lee, S. W.; Hong, J. K. Chemical and biological controls of balloon flower stem rots caused by R*hizoctonia solani* and *Sclerotinia sclerotiorum*. *Plant Pathol. J.* **2012**, *28*, 156-163.
377. Berg, H.; Tam, N. T. Use of pesticides and attitude to pest management strategies among rice and rice-fish farmers in the Mekong Delta, Vietnam. *Int. J.Pest Manag*. **2012**, *58*, 153-164.
378. Li, H.; Su, H.; Kim, S. B.; Chang, Y. K.; Hong, S.-K.; Seo, Y.-G.; Kim, C.-J. Enhanced production of trehalose in *Escherichia coli* by homologous expression of otsBA in the presence of the trehalase inhibitor, validamycin A, at high osmolarity. *J. Biosci. Bioeng.* **2012**, *113*, 224-232.
379. Qian, K.; Shi, T.; Tang, T.; Zhang, S.; Liu, X.; Cao, Y. Preparation and characterization of nano-sized calcium carbonate as controlled release pesticide carrier for validamycin against Rhizoctonia solani. *Microchim. Acta* **2011**, *173*, 51-57.
380. Best, M.; Koenig, K.; McDonald, K.; Schueller, M.; Rogers, A.; Ferrieri, R. A. Inhibition of trehalose breakdown increases new carbon partitioning into cellulosic biomass in Nicotiana tabacum. *Carbohyd. Res*. **2011**, *346*, 595-601.
381. Biswas, A.; Bag, M. K. Strobilurins in management of sheath blight disease of rice: a review. *Pestology* **2010**, *34*, 23-25.
382. Jin, L.-Q.; Zheng, Y.-G. Inhibitory effects of validamycin compounds on the termites trehalase. *Pest. Biochem. Physiol*. **2009**, *95*, 28-32.
383. Lopez, M; Tejera, N. l A.; Lluch, C. Validamycin A improves the response of Medicago truncatula plants to salt stress by inducing trehalose accumulation in the root nodules. *J. Plant Physiol*. **2009**, *166*, 1218-1222.
384. Gibson, R. P; Gloster, T. M.; Roberts, S.; Warren, R A. J; Storch de Gracia, I.; Garcia, A.; Chiara, J. L; Davies, G. J. Molecular basis for trehalase inhibition revealed by the structure of trehalase in complex with potent inhibitors. *Angew. Chem. Int. Ed*. **2007**, *46*, 4115-4119.
385. Madigan, M.; Martinko J. ed. Brock Biology of Microorganisms (11th ed.). Prentice Hall, **2005**.
386. Nioh, T.; Mizushima, S. Effect of validamycin on the growth and morphology of *Pellicularia sasakii*. *J. Gen. Appl. Microbiol*. **1974**, *20*, 373-383.
387. Uyeda, M.; Ikeda, A.; Machimoto, T.; Shibata, M. Effect of Validamycin on Production of Some Enzymes in *Rhizoctonia solani*. *Agric. Biol. Chem*. **1985**, *49*, 3485-3491.

388. Kido, Y.; Nagasato, T.; Ono, K.; Fujimoto, Y.; Uyeda, M.; Shibata, M. Change in a Cell-Wall Component of *Rhizoctonia solani* Inhibited by Validamycin. *Agric. Biol. Chem*. **1986**, *50*, 1519-1525.
389. Uyeda, M.; Ikeda, A.; Ogata, T.; Shibata, M. Effect of Validamycin on β-D-Glucan-degrading Enzymes from *Rhizoctonia solani*. *Agric. Biol. Chem*. **1986**, *50*, 1885-1886.
390. Kameda, Y.; Asano, N.; Yamaguchi, T.; Matsui, K. Validoxylamines as trehalase inhibitors J. *Antibiot.* **1987**, *40*, 563-565.
391. Asano, N.; Takeuci, M.; Kameda, Y.; Matsui, K.; Kono, Y. Trehalase inhibitors, validoxylamine A and related compounds as insecticides. *J. Antibiot*. **1990**, *43*, 722-726.
392. Shigemoto, R.; Okuno, T.; Matsuura, K. Effects of validamycin A on the growth of and trehalose content in mycelia of *Rhizoctonia solani* incubated in a medium containing several sugars as the sole carbohydrate. *Ann. Phytopath. Soc. Jpn*. **1992**, *58*, 685-690.
393. Asano, N.; Yamaguchi, T.; Kameda, Y.; Matsui, K. Effect of validamycins on glycohydrolases of *Rhizoctonia solani*. *J. Antibiot*. **1987**, *40*, 526-532.
394. Ogawa, S.; Sato, K.; Miyamoto, Y. Synthesis and trehalase-inhibitory activity of an imino-linked dicarba-α,α-trehalose and analogues thereof. *J. Chem. Soc., Perkin Trans. 1* **1993**, 691-696.
395. Ogawa, S.; Nishi, K.; Shibata, Y. Synthesis of a carba-sugar analog of trehalosamine, [(1S)-(1,2,4/3,5)-2-amino-3,4-dihydroxy-5-hydroxymethyl-1-cyclohexyl] alpha-D-glucopyranoside, and a revised synthesis of its beta anomer. *Carbohydr. Res*. **1990**, *206*, 352-360.
396. Ogawa, S.; Shibata, Y. Synthesis of biologically active pseudo-trehalosamine: [(1S)-(1,2,4/3,5)-2,3,4-trihydroxy-5-hydroxymethyl-1-cyclohexyl] 2-amino-2-deoxy-alpha-D-glucopyranoside. *Carbohydr. Res*. **1988**, *176*, 309-315.
397. Fukuhara, K.-i.; Murai, H.; Murao, S. Isolation and strusture-activity relationship of some amylostatins (F-1b fraction) produced by *Streptomuces diastaticus* subsp. *Amylostaticus* No. 9410. *Agric. Biol. Chem*. **1982**, *46*, 1941-1945.
398. Namiki, S.; Kangouri, K.; Nagate, T.; Hara, H.; Sugita, K.; Noda, K.; Tarumoto, Y.; Amura, S. Studies on the. α.-glucoside hydrolase inhibitor, adiposin. IV. Effect of adiposin on intestinal digestion of carbohydrates in experimental animals. *J. Antibiot.* **1982**, *35*, 1167-1173.
399. Kangouri, K.; Namiki, S.; Nagate, T.; Hara, H.; Sugita, K.; Omura, S. Studies on the. α-glucoside hydrolase inhibitor, adiposin. III. α-Glucoside hydrolase inhibitory activity and antibacterial activity in vitro. *J. Antibiot*. **1982**, *35*, 1160-1166.
400. Itoh, J.; Omoto, S.; Shomura, T.; Ogino, H.; Iwamatsu, K.; Inouye, S.; Hidaka, H. Oligostatins, new antibiotics with amylase inhibitory activity. I. Production, isolation and characterization. *J. Antibiot*. **1981**, *34*, 1424-1428.
401. Shibata, Y.; Kosuge, Y.; Ogawa, S. Synthesis and biological activities of methyl oligobiosaminide and some deoxy isomers thereof. *Carbohydr. Res*. **1990**, *199*, 37-54.
402. Ogawa, S.; Shibata, Y.; Kosuge, Y.; Yasuda, K.; Mizukoshi, T.; Uchida, C. Synthesis of potent α-glucosidase inhibitors: methyl acarviosin analogue composed of 1,6-anhydro-β-D-glucopyranose residue. *J. Chem. Soc., Chem. Commun*. **1990**, 1387-1388.
403. Shibata, Y.; Kosuge, Y.; Mizukoshi, T.; Ogawa, S. Chemical modification of the sugar part of methyl acarviosin: synthesis and inhibitory activities of nine analogues. *Carbohydr. Res*. **1992**, *228*, 377-398.
404. Ogawa, S.; Aso, D. Chemical modification of the sugar moiety of methyl acarviosin: synthesis and inhibitory activity of eight analogues containing a 1, 6-anhydro bridge. *Carbohydr. Res*. **1993**, *250*, 177-184.
405. Ogawa, S. Chemical synthesis of glycosylamide and cerebroside analogs composed of carba sugars. *Methods Enzymol.* **1994**, *247*, 136-143.
406. Ogawa, S.; Sasaki, S.-i.; Tsunoda, H. Synthesis of carbocyclic analogues of the mannosyl trisaccharide: ether- and imino-linked methyl 3,6-bis(5a-carba-alpha-D-mannopyranosyl)-3,6-dideoxy-alpha-D-mannopyran osides. *Carbohydr. Res*. **1995**, *274*, 183-196.
407. Ogawa, S.; Furuya, T.; Tsunoda, H.; Hindsgaul, O.; Stangier, K.; Palcic, M. M. Synthesis of beta-D-GlcpNAc-(1->2)-5a-carba-alpha-D-Man p-(1->6)-beta-D-Glcp-O$(CH_2)_7CH_3$: a reactive acceptor analog for N-acetylglucosaminyltransferase-V. *Carbohydr. Res.* **1995**, *271*, 197-205.
408. Hakomori, S. I. Aberrant glycosylation in tumors and tumor-associated carbohydrate antigens. *Adv. Cancer Res.* **1989**, *52*, 257-331; (b) Schachter, H. In Molecular Glycobiology; Fukuda, M., Hindsgaul, O., Eds.; IRL Press: Oxford, New York, Tokyo, **1994**; pp 86-162.
409. Prieels, J. P.; Monnom, D.; Dolmans, M.; Beyer, T. A.; Hill, R. L. Co-purification of the Lewis blood group N-acetylglucosaminide alpha 1 goes to 4 fucosyltransferase and an N-

acetylglucosaminide alpha 1 goes to 3 fucosyltransferase from human milk. *J. Biol. Chem*. **1981**, *256*, 10456-10463.

410. Macher, B. A.; Holmes, E. H.; Swiedler, S. J.; Stults, C. L. M.; Srnka, C. A. Human α-1–3 fucosyltransferases. *Glycobiology* 1991, *1*, 577-584; (c) de Vries, T.; Knegtel, R. M. A.; Holmes, E. H.; Macher, B. A. Fucosyltransferases: structure/function studies. *Glycobiology* **2001**, *11*, 119R-128R

411. Becker, D. J.; Lowe, J. B. Fucose: biosynthesis and biological function in mammals. *Glycobiology* **2003**, *13*, 41R-53R.

412. Ogawa, S.; Matsunaga, N.; Palcic, M. M. Synthesis of biological interest: ether linked octyl 5a'-carba-β-lactosaminide and related compounds *Carbohydr. Lett*. **1997**, *2*, 299-306.

413. Ogawa, S.; Matsunaga, N.; Li, H.; Palcic, M. M. Synthesis of Ether- and Imino-Linked Octyl N-Acetyl-5a′-carba-β-lactosaminides and -isolactosaminides: Acceptor Substrates for α-(1→3/4)-Fucosyltransferase, and Enzymatic Synthesis of 5a′-Carbatrisaccharides. *Eur. J. Org. Chem*. **1999**, 631-642.

414. Ogawa, S.; Gamou, K.; Kugimiya, Y.; Senba, Y.; Lu, A.; Palcic, M. M. Synthesis of octyl-N-acetyl-5a-carba-lactos-aminide ans –isolactosminide: acceptor substrates for α1,3-fucosyltransferase V and α2,3-(N)-sialyltransferase. *Carbohydr. Lett*. **2000**, *3*, 451-456.

415. Okazaki, K.; Nishigaki, S.; Ishizuka, F.; Kajihara, Y.; Ogawa, S. Potent and specific sialyltransferase inhibitors: imino-linked 5a'-carbadisaccharides. *Org. Biomol. Chem.* 2003, *1*, 2229-2230.

416. Kawamura, N.; Kinoshita, N.; Sawa, R.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. Pyralomicins, novel antibiotics from Microtetraspora spiralis. I. Taxonomy and production. *J. Antibiot*. **1996**, *49*, 706−709.