Review Article

Biosynthesis and Biological Activity of Carbasugars

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The first synthesis of carbasugars, compounds in which the ring oxygen of a monosaccharide had been replaced by a methylene moiety, was described in 1966 by Professor G. E. McCasland's group.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 carba-furanoses.

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, and (c) key component of the cell wall of green plants such as cellulose, carbohydrates are key elements in a variety of biological processes. In fact, the concept of *glycomics* has been defined as “the functional study of carbohydrates in living organisms” [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, structural changes, absence, deficiency, or excess of some carbohydrates are strongly related to many diseases. In this context, it should be pointed out that 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 references [2–5]; (b) synthetic aspects [6–9]; (c) carbohydrates in biological and medicinal chemistry [10–14]; (d) glycobiology [15]; (e) signaling, cell-cell communication,

and molecular and cellular targeting [16–21]; (f) therapeutic potential of glycoconjugates [22, 23]; (g) carbohydrate-based vaccines [24–28].

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) [29–31] or glycosylphosphatidylinositols (GPIs) are now known to play a pivotal role in numerous biological functions [32–37]. 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 [38, 39].

On this basis, the search for new carbohydrate derivatives with analogous or even improved biological properties compared to those of the parent structures (*carbohydrate mimetics*) [40–43] 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 [44]), compounds in which the ring oxygen of a monosaccharide had been replaced by a methylene group (Figure 1), fall within this category [45–49]. The structural resemblance of carbasugars to the parent sugars may facilitate their recognition by enzymes or other

FIGURE 1: Monosaccharides and carba monosaccharides.

FIGURE 2: Structure of Caryose 1, proposed structure of calditol 2, and structure of calditol 3.

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.

2. Natural Occurrence of Carbasugars

2.1. Natural Carbafuranoses. Carbafuranoses are scarcely encountered in nature as free compounds. Nevertheless, they are subunits of products isolated from natural sources, in particular carbanucleosides [50, 51]. To the best of our knowledge, only two five-membered cyclitols derivatives have been isolated from natural sources (Figure 2): Caryose 1 [52–54], isolated from the lipopolysaccharide fraction of *Pseudomonas caryophylli* (a plant pathogenic bacteria), and calditol 2, isolated from the thermoacidophilic archaeobacterium *Sulfolobus acidocaldarius*, a thermoacidophilic archaeon belonging to *Sulfolobus* species. These species were found to grow between 75 and 80°C, with pH optimum in the range of 2–3 [55–58]. 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 [59, 60].

2.2. Natural Carbapyranoses. Carbapyranoses are rarely encountered in nature with carba- α -D-galactopyranose (4,

Figure 3) being the only “genuine” carbasugar isolated from natural sources (*Streptomyces* sp.) [61].

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 were epoxides [62, 63] such as cyclophellitol (isolated from *Phellinus* sp.) [64–68] (5, Figure 3), cyclohexene derivatives such as MK7607 (isolated from *Curvularia eragrostidis*) [69] (6, Figure 3), streptol (isolated from *Streptomyces* sp.) [70, 71] (7, Figure 3), pericosines A–E (isolated from *Periconia byssoides*) (8–14, Figure 4) [72, 73], carbonyl compounds such as the gabosine family (isolated from various *Streptomyces* strains) [74–76] (15–28, Figure 5), COTC (isolated from *Streptomyces griseosporus*) [77] (29, Figure 5), and valienone (isolated from *Streptomyces lincolnensis*) [71] (30, Figure 5).

Aminocarbasugars, such as valienamine (31), validamine (32), hydroxyvalidamine [78] (33), and valioline [79] (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* [80]. Aminocarbasugars are mainly found in validamycins, acarbose, and related carbaoligosaccharides. For instance, validamine has been obtained from these carbaoligosaccharides using different methods such as microbial degradation procedures [81–85], chemical degradation of validoxylamine, see the following, using NBS [86, 87], and several biotechnological processes [88–90].

Validamycins (Figure 7) are a family of antibiotics discovered during the screening for new antibiotics from the

FIGURE 3: Some natural carbapyranoses: carba- α -D-galactopyranose, cyclophellitol, MK7607, and streptol.

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.

FIGURE 6: Aminocarbasugars valienamine, validamine, hydroxyvalidamine, and valioline.

Validamycin A, 35	$R_1, R_2, R_4, R_5, R_6 = H, R_3 = \beta\text{-D-Glc}$
Validamycin B, 36	$R_1, R_2, R_4, R_6 = H, R_3 = \beta\text{-D-Glc}, R_5 = OH$
Validamycin C, 37	$R_1, R_4, R_5, R_6 = H, R_3 = \beta\text{-D-Glc}, R_2 = \alpha\text{-D-Glc}$
Validamycin D, 38	$R_1, R_2, R_3, R_4, R_5 = H, R_6 = \alpha\text{-D-Glc}$
Validamycin E, 39	$R_1, R_2, R_4, R_5, R_6 = H, R_3 = \alpha\text{-D-Glc-(1-4)-}\beta\text{-D-Glc}$
Validamycin F, 40	$R_1 = \alpha\text{-D-Glc}, R_2, R_4, R_5, R_6 = H, R_3 = \beta\text{-D-Glc}$
Validamycin G, 41	$R_1, R_2, R_5, R_6 = H, R_3 = \beta\text{-D-Glc}, R_4 = OH$
Validamycin H, 42	$R_1, R_2, R_4, R_5, R_6 = H, R_3 = \alpha\text{-D-Glc-(1-6)-}\beta\text{-D-Glc}$

Validoxylamine A, 43	$R_1, R_2 = H$
Validoxylamine B, 44	$R_1 = H, R_2 = OH$
Validoxylamine G, 45	$R_1 = OH, R_2 = H$

FIGURE 7: The validamycins family.

fermentation culture of *Streptomyces hygroscopicus* [91–94]. 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 glycosidic linkage, (b) the number of D-glucopyranose residues, or (c) the anomeric configuration of the D-glucopyranose unit [95–98]. Validamycin G (**41**) contains validoxylamine G (**45**) as its core unit.

Acarbose (Figure 8, **46**) [99, 100] 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 [101, 102]. In addition to acarbose, marketed by Bayer, there are two drugs, structurally related to 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 [103, 104]. 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 carbadisaccharide core of acarbose, known as acarviosin (**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 in mixture with 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 [105]. 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 [106–117].

The amylostatis, with general structure **50** (Figure 9), are related to acarbose analogues because they contain acarviosin

FIGURE 8: Structures of acarbose, acarviosin, and marketed products **47** (miglitol) and **48** (voglibose).

FIGURE 9: The amylostatins.

core **49**. Amylostatins were isolated in the culture filtrate of *Streptomyces diastaticus* subsp. *amylostaticus* [118, 119].

Adiposins (**51**, Figure 10) were isolated from *Streptomyces calvus* [120–127]. Structurally, adiposins are related to acarbose (**46**) and amylostatins (**50**) since they contain acarviosin core **49**. They are formed by an aminocarbasugar (valienamine, **31**) and a deoxy sugar (4-amino-4-deoxyglucose).

Oligostatins (**52**, Figure 11) were obtained from culture broths of *Streptomyces myxogenes* [128–132]. They are carbaoligosaccharide antibiotics consisting of penta-, hexa-, and heptasaccharides containing hydroxyvalidamine rather than valienamine.

Trestatins (**53**, Figure 12) were isolated from fermentation cultures of *Streptomyces dimorphogenes* [133, 134]. These

carbaoligosaccharides contain one to three dehydrooligo-bioamine units and terminate with one residue of α -D-glucopyranose linked 1,1- to the preceding glucose unit. Therefore, unlike oligostatins **52** and amylostatins **50**, the trestatins are nonreducing carbohydrates.

Trehalase inhibitor salbostatin (**54**, Figure 13) is a metabolite of *Streptomyces albus* species [135–137]. This basic nonreducing carbadisaccharide consists of valienamine linked to 2-amino-1,5-anhydro-2-deoxy glucitol.

In 1995, the pyralomicins (**55–58**, Figure 14) were isolated from the strain of *Actinomadura spiralis* (which was later renamed *Microtetraspora spiralis*) [138, 139]. Their chemical structures consist of benzopyranopyrrole chromophores containing a nitrogen atom which is also shared with

FIGURE 10: The adiposins.

FIGURE 11: The oligostatins.

1-epi-valienamine [140]. 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 [141–143].

3. Biosynthesis of Carbasugars

3.1. Carba-furanoses. 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 cyclitol calditol **2**.

3.1.1. Carbocyclic Nucleosides. Biosynthetic studies on aristeromycin (**59**) and neplanocin A (**60**) (Figure 15) [144–147] had established that the carbocyclic ribose ring was biosynthesized from D-glucose *via* 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 antifashion and phosphorylation afford the carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate **63** (Scheme 1). A detailed description of this sequence was described in [45, pages 1923–1924].

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 shown in Figure 16, the cyclitol

fragment is linked to the rest of the molecule by ethereal bonding [148].

From labeling experiments, a biosynthetic “inositol-like” pathway for the cyclopentanoid part of calditol has been proposed [149–152]. The sequence involves the formation of a 1,5 carbon bond, followed by a stereospecific reduction at C-4 (Scheme 2). Regarding Caryose **1**, no biogenetic proposal has been found in the literature.

3.2. Carbapyranoses

3.2.1. Sedoheptulose 7-Phosphate. Sedoheptulose 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 [153, 154]. 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).

In the oxidative phase, NADPH is generated (step (a)) from glucose 6-phosphate **65** and starts with dehydrogenation **65** at C1 to give 6-phosphoglucono- δ -lactone **67** in a reaction catalyzed by glucose 6-phosphate dehydrogenase [155] and mediated by NADP⁺ (**66**). The next step (step (b)) is the hydrolysis of 6-phosphoglucono- δ -lactone **67** by a specific lactonase (6-phosphogluconolactonase [156]) to give 6-phosphogluconate **69**. In step (c), this six-carbon sugar is then oxidatively decarboxylated by 6-phosphogluconate dehydrogenase [157] to yield ribulose 5-phosphate **70**.

53

FIGURE 12: The trestatins.

54

FIGURE 13: Structure of salbostatin.

59

60

FIGURE 15: Structures of aristeromycin **59** and neplanocin **60**.

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.

In the nonoxidative phase, ribulose-5-phosphate **70** is transformed into xylulose-5-phosphate **71** and ribose-5-phosphate **72** *via* epimerization at C-3 (catalyzed by the enzyme ribulose-5-phosphate-3-epimerase [158, 159]) and isomerization catalyzed by ribulose-5-phosphate isomerase [158] (through an enolate ion), respectively. Finally, a sequence of retroaldol-aldol reactions mediated by thiamine pyrophosphate **73** and catalyzed by transketolase [160–162] results in the formation of sedoheptulose-5-phosphate **75** and glyceraldehyde-3-phosphate **74**.

3.2.2. Biosynthesis of Gabosines. The cyclization process of sedoheptulose 7-phosphate (**75**) to a six-membered carbocyclic intermediate, 2-epi-5-epi-valiolone **77** [163–166], is catalyzed by a sedoheptulose 7-phosphate cyclase (Scheme 5).

These enzymes are phylogenetically related to the dehydroquinase synthases (DHQS) and use Co^{2+} as preferred cofactor. Dehydroquinase 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-heptulosonate-7-phosphate) into **79** (3-dehydroquinate), which is required for the synthesis of aromatic compounds in bacteria, microbial eukaryotes and plants (Scheme 6) [167, 168].

The reaction is assumed to be initiated by transient dehydrogenation of C-5 to 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 syn* elimination to yield valienone **30** (Scheme 5). However, how

FIGURE 16: Structure of the lipids isolated from Archaea.

SCHEME 1: Proposed biosynthesis of carbaphosphoribosyl-1-phosphate from glucose.

exactly these final processes take place under the enzymatic point of view still remains obscure.

The transformation of 2-epi-5-epi-valiolone **77** into gabosines A, B, C, and N requires a considerable number of steps such as dehydration, oxidation, reduction, and epimerization as depicted in Scheme 7 through reduction product **81** [169].

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 [170, 171]. It is expected that a large number of enzymes will be involved in the conversion in a manner that is not yet 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 [172]. 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 [173] 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).

These kind of isomerizations have been observed in different biogenetic routes such as the transformation of ribulose-5-phosphate **70** into xylulose-5-phosphate **71** and ribose-5-phosphate **72** (see Scheme 4).

3.2.3. Biosynthesis of Validamycins. Valienone **30** and the reduction product validone **87** are the more proximate precursors of validoxylamine A **43**, the aglycone moiety of validamycin A **35** (Scheme 10) [174, 175]. 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 **87** or, alternatively, **87** would be transaminated to give validamine **32**, which would then couple **30**. However, circumstantial evidence in favor of the second of these two scenarios comes from experimental

SCHEME 2: Proposed biosynthesis of calditol **2**.

SCHEME 3: Oxidative phase: (i) Glucose-6-phosphate dehydrogenase; (ii) 6-phosphogluconolactonase; (iii) 6-phosphogluconate dehydrogenase.

SCHEME 5: Transformation of sedoheptulose-7-phosphate **75** into valienone **30**.

SCHEME 6: Transformation of 3-deoxy-D-arabino-heptulosonate-7-phosphate into 3-dehydroquinate.

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).

3.2.4. Biosynthesis of Acarbose [179]. 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 [180, 181].

In a first approach to the biosynthesis of acarbose, it is assumed that the first intermediate generated is deoxythymidine diphosphate- (dTDP-) acarviosine (**93**). It should be pointed out that thymidine diphosphate dTDP (**92**, see Scheme 13) misnamed deoxythymidine diphosphate [182] consists in a pyrophosphate group attached to the nucleoside thymidine [183]. The acarviosyl moiety of this intermediate

can be transferred 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 [184].

A reasonable route for the formation of dTDP-acarviosine (**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 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

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

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

amino sugar **95** would afford pseudosaccharide **101**. This compound, after epimerization at C2 and 5,6-dehydration, would give dTDP-acarviosine (**93**) (Scheme 14) [185].

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 clusters (Acb) [186–189],

involved or proposed in the sequence, are also indicated (Scheme 15).

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

SCHEME 9: Biosynthesis of gabosines from 2-epi-5-epi-valiolone 77.

SCHEME 10: Biosynthesis of validoxylamine 43 from valienone 30.

SCHEME 11: Biochemical interconversion of amino acids glutamate, aspartate, glutamine, and asparagine. (i) Asparagine synthetase.

SCHEME 12: Biosynthesis of validamycins A (35), B (36), C (37), D (38), E (39), F (40), and G (41).

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 one of the 25 known gene clusters from *Actinoplanes* sp. SE50/110 identified and sequenced. Another *Acb* biosynthetic gene cluster from *Streptomyces glaucescens* has also been identified and sequenced.

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-epi-valiolone-7-phosphate (103). Further steps involving dehydration (104), carbonyl reduction and phosphorylations (105), nucleotidylation [190]

(106), and final nucleophilic displacement by the nitrogen atom of 95 would afford compound 93 [191–194]. In Scheme 15, the transformation 105–106 constitutes a nucleotidylation reaction: the transfer of an entire nucleotidyl unit, rather than just a phospho group [195].

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 [196]. The 41 kb (1000 base pairs) gene cluster contains 27 open reading frame ORFs [197, 198] predicted to encode all of the functions for pyralomicin biosynthesis. This includes nonribosomal peptide (peptides that are not synthesized by ribosomes) synthetases (NRPS) and

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

polyketide synthases (PKS) [199–204] required for the formation of the benzopyranopyrrole core unit. Other enzymes such as four halogenases [205] an O-methyltransferase [206–208] and an N-glycosyltransferase [209, 210] 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 pyralomicins 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 (*vide infra*) [211] and acarbose gene clusters.

3.2.6. Biosynthesis of Salbostatin. *In silico* analysis of the putative biosynthetic gene cluster of salbostatin from *Streptomyces albus* ATCC 21838 [211] revealed 20 open reading frames. The salbostatin 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-valiolone 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-1-phosphate **113** and then NDP-1-epi-valienol

SCHEME 14: Alternative biosynthesis of dTDP-acarviosine **93**. SCHEME 15: Revised proposal of the biosynthetic pathway to dTDP-acarbose **93**. NDP (compound **106**): nucleotidyl diphosphate.

114 were successively formed. Condensation of NDP-1-epi-valienol **114** with deoxy-glucosamine **115** (biosynthesized from N-acetylglucosamine) may finally result in the formation of salbostatin-6'-phosphate **116** which is then converted into salbostatin **54**.

4. Biological Activity of Carbasugars

As we have previously pointed out (see Section 1) and according to Professor McCasland "pseudo-sugars may be found acceptable in place of corresponding true sugars to some

SCHEME 16: Proposed mode of formation of the cyclitol moiety of pyralomicins. **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.

but not all enzymes or biological systems, and thus might serve to inhibit growth of malignant or pathogenic cells” [212]. The similarity between carbasugars and sugars may be highlighted considering that synthetic 6a-carba- β -DL-fructopyranose was found to be almost as sweet as D-fructose [213–215]. In the context of enzymatic inhibition [216], 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 medical point of view. For instance, the inhibition of carbohydrate digestive enzymes is considered a therapeutic tool for the treatment of type 2 diabetes [217]. In the following, some applications of carbasugars and derivatives as enzymatic inhibitory agents will 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 [218–220]. This compound shows enzymatic inhibitory activity against the enzyme 5-phosphoribosyl R-1-pyrophosphate (PRPP) synthetase [221–223] with values [224] K_i of 186 μ M (human type PRPP synthetase) and 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 superactivity (increased enzyme activity or deregulation of the enzyme) result in purine [223] overproduction. Superactivity symptoms include

neurodevelopmental disorders [225]. 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 [226, 227].

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 [228]) [229, 230] with potential inhibition of the human immunodeficiency virus (HIV) and with possible antimetastatic therapeutic activity [231–233]. Several unnatural cyclophellitol derivatives also show interesting biological properties [234–237]. For instance, (1R,6S)-cyclophellitol **120**, the unnatural diastereomer of cyclophellitol **5**, is a potent α -glucosidase inhibitor and cyclophellitol aziridines **121** are potent and selective irreversible inhibitors of retaining glycosidases [238–243] (see Figure 18).

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 authoritative reviews and will not be considered here [62].

4.2.2. MK-7067, Carbagalactopyranose, Carbaglucopyranose, Streptol, and COTC. The unsaturated carbapyranose (+)-MK7067 **6** exhibited an effective herbicidal activity [69]. Carba- α -D-galactopyranose (**4**) was found to have a low

SCHEME 17: Proposed biosynthetic pathway for salbostatin.

SCHEME 18: Conversion of ribose 5-phosphate into phosphoribosyl pyrophosphate (PRPP).

FIGURE 17: Carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP).

antibiotic activity against *Klebsiella pneumonia* MB-1264 [61], whereas the L-enantiomer is inactive [244]. 5a-Carba- α -DL-glucopyranose ($\pm$)-**122** (Figure 19) is a glucokinase inhibitor [245, 246]. Carbasugar ($\pm$)-**122** and the β -anomer ($\pm$)-**121** were used as synthetic analogues of glucose anomers to study the mechanism of glucose-stimulated insulin release by pancreatic islets [247]. It was found that alpha isomer ($\pm$)-**122**, but not the beta-isomer ($\pm$)-**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 gilvus* recognizes only the beta-D-form of 5a-carba-glucopyranose ($\pm$)-**121** [248].

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

The 2-crotonyloxy-(4R,5R,6R)-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 anticancer activity of COTC is depicted in Scheme 19 [249–253].

After conjugate addition of glutathione (γ -L-glutamyl-L-cysteinylglycine, GSH) 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 leads to cell death. Other processes may also contribute to the anticancer 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 inhibitors of human glyoxalase I (GloI). This enzyme is vital for cell survival as part of a detoxification system for cytotoxic 2-oxoaldehydes or other toxic species and the inhibitors have previously been demonstrated to have

anticancer properties [254, 255]. On these bases, it seems logical to have carried out extensive efforts for the synthesis of new analogues COTC [256–264].

A key enzyme in the biosynthesis of clinically important aminoglycoside antibiotics such as neomycin, kanamycin, and gentamicin [265, 266] is 2-deoxy-scylo-inosose synthase (DOIS), which catalyzes the carbocycle formation from D-glucose-6-phosphate **65** to 2-deoxy-scylo-inosose (DOI, **128**, Scheme 20 [267]).

5a-Carba-DL-glucose-6-phosphate (**129**) is an irreversible inhibitor of DOIS. The proposed reaction mechanism for this inhibitory action is shown in Scheme 21 [268]. Thus, after the initial oxidation at C4 and subsequent elimination of a phosphate compound, ($\pm$)-**129** was converted within the enzyme into an α,β -unsaturated methylene cyclohexanone ($\pm$)-**131**. 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 **132**.

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 [269] also showing significant *in vivo* tumor inhibitory activity. In addition, pericosine A inhibited [270] 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 [271]) and topoisomerase II (topoisomerases are isomerized 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 [272]). 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 [274]).

On the other hand, gabosines A (**15**), B (**16**), F (**21**), N (**18**), and O (**28**) present DNA-binding properties [275, 276]. Gabosine C (**17**) is the known antibiotic KD16-U [277] and its crotonyl ester is the previously considered carbasugar COTC. Gabosine J (**25**) inhibits α -mannosidase, an enzyme involved

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

SCHEME 19: Proposed mode of action of COTC and derivatives.

SCHEME 20: Transformation of D-glucose-6-phosphate into 2-deoxy-scylo-inosose.

in the cleavage of the alpha form of mannose [278], and some derivatives such as α -gabosinol **133** and β -gabosinol **134** inhibit β -galactosidase and β -glucosidase, respectively (Figure 20) [279].

Some compounds structurally related to gabosines also show interesting biological properties. For instance, compound (+)-**135** has been reported [280] to be a cytotoxic and potential contraceptive agent. On the other hand, nigrospoxydon A (**136**) 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 [281]. It has also been published that the closely related esters

(-)-**137** and epoxydine B (**138**) display antibacterial, antifungal, and antialgal activities (Figure 20) [282]. The synthetic compound (+)-RKTS-33 (**139**) has inhibitory activity toward death receptor-mediated apoptosis [283, 284]. The racemate of compound **140** is a nuclear factor- κ B [285, 286] inhibitor and therefore a suitable candidate as anti-inflammatory and anticancer agent [287]. Finally, compound **141** shows [288] synergetic effect with cisplatin against lung cancer cell line A549 [289], through the inhibition of GSTM1 [290].

4.2.4. Carbaglycosides. O-Linked alkyl carba- β -D-glycosides **142** and **143** (Figure 21) have been shown [291] to be useful as primers for biocombinatorial glycosylation involving efficient uptake in B16 mouse melanoma cells, the most frequently used murine melanoma model [292]. 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

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

SCHEME 22: Carbatrisaccharides **189** and **190**.

have been found to be highly important molecules in immunology. Natural and semisynthetic gangliosides are considered possible therapeutics for neurodegenerative disorders [293, 294]. This indicates 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 (**143**).

In addition, more complex carbaglycosides have interesting biological activities. Synthetic carboxylosides of coumarins, that is, (+)-**144** or (–)-**144**, have significant potential as oral antithrombotic agents [295], and a 5a-carba analogue of glucotropaeolin, ($\pm$)-**145**, was shown to display a good inhibition power [296] against myrosinase, the only known enzyme found in nature that can cleave a thiolinked glucose [297] (Figure 22).

4.2.5. Carbanucleotides. Some synthetic carbasugar-nucleotide displayed biological activity as glycosyltransferase inhibitors. For instance, uridine-5'-(5a-carba- α -D-galactopyranosyl diphosphate) **146** (Figure 23), the carbocyclic analogue of UDP-galactose, exhibits inhibitory activity of β -(1 $\rightarrow$ 4) galactosyltransferase from bovine milk [298].

On the other hand, the carbocyclic analogue of GDP-fucose, consisting of 5a-carba- β -L-fucopyranose **147** [299], was found to be a competitive inhibitor of fucosyltransferases, key enzymes in the biosynthesis of the Lewis-x determinant. Interestingly, the carba-fucose analogue **147** 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, although it is essential for the transfer to occur [300].

4.2.6. Aminocarbasugars. Aminocarbasugars [301] are the most important and appealing carbapyranose derivatives from a biological standpoint.

(1) *Valienamine, Validamine, Hydroxyvalidamine, Valiolamine, and Derivatives.* Simple aminocarbasugars such as valienamine (**31**), validamine (**32**), hydroxyvalidamine (**33**), and valioline (**34**) appeared to be active against several sugar hydrolases [302, 303]. Valienamine, validamine, and hydroxyvalidamine were reported as microbial oligosaccharide α -glucosidase inhibitors [304–307]. The α -galacto-, β -gluco-, and α -mannovalidamine analogues **148–150** (Figure 24) have been prepared and their glycosidase activity was tested [308–310]. These compounds, however, displayed moderate activity as glycosidase inhibitors when compared with α -gluco-validamine. Conversely, valioline (**34**) has more potent α -glucosidase inhibitory activity against porcine intestinal sucrase, maltase, and isomaltase than the rest of the aminocarbasugars [311].

This is why series of N-substituted valioline were synthesized, resulting in the preparation of the glycosyltransferase inhibitor voglibose (**48**) [312–314]. Voglibose was launched as an antidiabetic agent in 1994 to improve postprandial hyperglycemia in diabetes mellitus [315–318]. 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 19: Structures of α - and β -glucopyranose (only D-enantiomers are shown), streptol 7, and COTC 29.

FIGURE 20: Some biologically active gabosine derivatives.

Moreover, carbocyclic analogues of glycosylamides [319], which contain the 5a-carba-D-hexopyranose residues (Figure 25), have also been synthesized. 5a-Carba- β -glucopyranosyl and 5a-carba- β -galactopyranosyl amides **151** and **152** have been shown to be potent immunomodulators, comparable to the *true* sugars [320], 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 **153** and 1-epi-2-acetamido-2-deoxy-valienamine **154** (Figure 25) have been investigated. 1,2-Bis-epi-valienamine **153** acts as a β -mannosidase [321] inhibitor whereas 2-acetamido-2-deoxy-1-epi-valienamine **154** has been shown [322] to inhibit various β -hexosaminidases, enzymes involved in the hydrolysis of terminal N-acetyl-D-hexosamine residues in N-acetyl- β -D-hexosaminides [323–325].

A series of N-linked carbocyclic analogues of glycosylceramides, structurally related to glycosphingolipids and glyco-glycerolipids, have also been synthesized by replacing the sugar residue with either saturated [326] (**155**, **156**, Figure 26) or unsaturated [327] (**157**, **158**, Figure 26) 5a-carba-D-gluco-

or 5a-carba-D-galactopyranoses, respectively. Compounds **155** and **156** are mild immunomodulators and possess a mild inhibitory activity against gluco- and galactocerebrosidases, whereas the unsaturated gluco-**157** and galacto-**158** 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.

Various N-alkyl- and N,N-dialkyl- β -valienamines were synthesized and tested as glycosylases inhibitors [328–331]. For instance, N-benylation of valienamine improves significantly their inhibitory activity toward α -glucosidases [332]. In this way, 91 pure N-alkylated valienamines **159** (Figure 27) prepared using solid-phase synthesis methodology are new β -glucosidase inhibitors that are generally more potent than valienamine [333].

On the other hand, the spiroaziridines and spirodi-aziridines **160** and **161** 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 cyclopentylamine **162** (Figure 27) [334].

FIGURE 21: Structures of carba- β -D-glycosides **142** and **143**. FIGURE 22: Structures of carbaglycosides **144** and **145**.

Two isomeric bicyclo[4.1.0]heptane **163** and **164** (Figure 27) have been synthesized and evaluated against α -galactosidase enzymes from coffee bean and *E. coli* [335]. 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 $0.541\ \mu\text{M}$. The *E. coli* α -galactosidase exhibited a much weaker binding interaction with the 1R,6S-amine ($\text{IC}_{50} = 80\ \mu\text{M}$). The diastereomeric 1S,6R-amine bound weakly to both galactosidases (coffee bean, $\text{IC}_{50} = 286\ \mu\text{M}$, and *E. coli*, $\text{IC}_{50} = 2.46\ \text{mM}$).

N-Octyl- β -valienamine derivative **165** (Figure 28) is a potent specific inhibitor of β -glucocerebrosidase ($\text{IC}_{50} = 3 \times 10^{-8}\ \text{M}$). In contrast, galactose derivative **166** did not show any improvement in potency. Additionally, it was later demonstrated that **165** and **166** are potent competitive inhibitors of human β -glucosidase and human β -galactosidase, respectively.

These activities suggest that carbasugar derivatives **165** and **166** work as chemical chaperones [112, 336–338] 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 [339–351]. It should be opportune at this point to clarify the concept of chemical chaperone [352–354]. 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, vertigo, 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 [355, 356] (($\pm$)-**167**) and 5a-carba- β -L-fucopyranosylamine (**168**) [357] 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 [358]. Different N-substituted derivatives of ($\pm$)-**169** were prepared. The inhibitory activity was increased by incorporation of alkyl and phenylalkyl groups into the amino function of the parent

FIGURE 23: Structure of carbanucleotides **146** and **147**. FIGURE 24: Structures of α -galacto-, β -gluco-, and α -mannovalidamine analogues (**148**–**150**) and voglibose (**48**). FIGURE 25: 5a-Carba- β -glucopyranosyl and 5a-carba- β -galactopyranosyl amides. FIGURE 26: N-linked carbocyclic analogues of glycosylceramides **155**–**158**.

FIGURE 27: Alkylated valienamine derivatives, spiroaziridines **160**, spiroazirinas **161**, cyclopentylamine derivative **162**, and bicyclo[4.1.0]heptane derivatives **163** and **164**.

FIGURE 28: N-Octyl- β -valienamine derivatives.

($\pm$)-**167**. The change of the N-alkyl substituents, from ethyl on **169a** to nonyl on **169e**, improved the inhibitory power. The n-octyl derivate (**169d**) was found to be the strongest inhibitor of α -L-fucosidase (bovine kidney) more potent ($K_i = 0.016 \mu\text{m}$) than deoxynojirimycin ($K_i = 0.031 \mu\text{m}$), the most powerful mammalian α -L-fucosidase inhibitor identified [359]. In a similar manner, chemical modifications of **168** generated N-substituted derivatives ($\pm$)-**170a–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-**170**) [360] (Figure 29).

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 [361]. 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 $\rightarrow$ 4)-galactosyltransferase was tested with α -galacto- (**171**), α - and β -manno- (**172** and **173**), and α - and β -gluco- (**174** and **175**) 2-acetamido-2-deoxy-5a-carba-DL-hexopyranoses [362]. Of these compounds, only **174** and **175** behave as galactosyl acceptors. The reactions afforded disaccharides **176** and **177**, 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 $\rightarrow$ 4)-galactosyltransferase (Figure 30).

(2) *Validamycins, Salbostatin, Acarbose, Amylostatins, Adiposins, Oligostatins, Trestatins, and Related Compounds*. Validamycins **35–42** and salbostatin (**54**) have been reported to be mechanistically unique fungicide agents [363–367]. Validamycin A (**35**), the most active compound of the complex, is a fungicide that inhibits trehalases, enzymes that carry out the degradation of the nonreducing disaccharide trehalose [368–370] in plants, insects, and fungi as well as enhancing 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* [371–385].

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 [386]) extension without affecting the specific growth rate. This means validamycin A is effective against *Pellicularia sasakii* and *Rhizoctonia solani* in plants but only decreases their virulence instead of exhibiting a fungicidal effect [387–390]. Further extensive studies on the mechanism of action of validamycin in controlling the hyphal extension have been carried out by several research groups, and that seems to be related to the antitrehalase activity [391–393] of the carbadisaccharide validoxylamine (**43**) [394]. For the purpose of developing more potent trehalase inhibitors, several pseudotrehalosamines, such as **178** and **179**, as well as dicarba analogues of trehalose, **180–182**, composed of valienamine, validamine, and valioline moieties, were synthesized and they have been shown to possess strong inhibitory activity against trehalase (Figure 31) [395–397].

Many members of the carbaoligosaccharidic group, for example, 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 glucoamylase. 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

FIGURE 29: Carbafulcocyranosyl amines **167–170**.

FIGURE 30: Carbasugars as sugar transferases.

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 carbaoligosaccharides 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 [398].

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 [399]. 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 [122].

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

The acarviosin, which is the core structure of acarbose and related carbaoligosaccharides α -amylase inhibitors, is responsible for their glycosidase inhibitory activities since the valienamine portion mimics the glucopyranosyl cation intermediate at the active site for hydrolysis of α -glucosides in the acarviosin moiety. Subsequently, several chemically modified acarviosin analogues, **183–188**, have been prepared and their glycosidase inhibitory activities were tested [132, 401–403]. The results showed that the 4-amino-4,6-dideoxy moiety

FIGURE 31: Carbasugars **178**–**182** with antitetrahalase activity. FIGURE 32: Acarviosin analogues **183**–**188**.

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 **187** and **188** for β -glucosidase and α -mannosidase activities, respectively (Figure 32).

Carbatriasaccharide **189**, an analogue of the “trimannosyl core” which frequently occurs in biologically important glycoconjugates [404, 405], was found [406] to be fully active as an acceptor for N-acetylglucosaminyltransferase-V, with both the enzyme isolated from hamster kidney and 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 **189** as the acceptor with the cloned rat kidney enzyme. A

tetrasaccharide formed by the addition of a Glc pNAc residue (**190**) was the sole product detected (Scheme 22).

Fucosyl- and sialyltransferases 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 [407, 408]. Fucosyl- and sialyltransferases are involved in the last steps of the biosynthesis of Lewis oligosaccharide antigens by transferring α -fucopyranosyl residues [409–412]. 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. [413, 414].

FIGURE 33: Carbasugars disaccharide analogues as inhibitors of fucosyl- and sialyltransferases.

They prepared ether- and imine-linked N-acetyl-5a'-carba- β -lactosaminides and -isolactosaminides and tested them against fucosyltransferases. Biological assays showed that compounds **191a** and **191b** (Figure 33) are acceptor substrate for human-milk α -(1 $\rightarrow$ 3/4)-fucosyltransferase with kinetic parameters comparable to those observed for standard *true* disaccharides. Small-scale enzymatic synthesis was carried out by treatment of **191a** and **191b** with GDP-fucose and milk fucosyltransferase which resulted in the conversion into the corresponding trisaccharides (by fucosylation at O3).

Interestingly, compounds **192a** and **192b** were neither acceptors nor inhibitors for milk fucosyltransferase, suggesting that α -(1 $\rightarrow$ 4) transfer is not possible. The milk preparation contains a mixture of two different [α -(1 $\rightarrow$ 3/4)- and

α -(1 $\rightarrow$ 3)-] fucosyltransferase enzymes. These enzymes were separated, and it was shown that both forms utilized compounds **191a** and **191b** as acceptor substrates, whereas **192a** and **192b** were not appropriate acceptors. This was the first demonstration of a specific substrate for α -(1 $\rightarrow$ 3)-fucosyltransferase.

In contrast with these results, screening carried out on isomeric octyl 5a-carba- β -lactosaminide (**193b**) and isolactosaminide (**194b**) (where the carbasugar unit is at the reducing end) showed that both compounds were good substrates for α -(1 $\rightarrow$ 3)-fucosyltransferase V (human recombinant, *Spodoptera frugiperda*) as well as α -(2 $\rightarrow$ 3)-(N) sialyltransferase (rat, recombinant, *Spodoptera frugiperda*) when compared to the parent compounds **193a** and **194a** [415].

The inhibitory activity of four new carbadisaccharides (ether-linked methyl 5a'-carba- β -lactoside (**195a**) and imine-linked methyl 5a'-carba- β -lactoside (**195b**), methyl N-acetyl-5a'-carba- β -lactosaminide (**195c**), and methyl N-acetyl-5a'-carba- β -isolactosaminide (**196**)) toward rat recombinant α -(2 $\rightarrow$ 3)-sialyl and rat liver α -(2 $\rightarrow$ 6)-sialyltransferases with the presence of 4-methylumbelliferyl-labeled Lac-NAC as an acceptor substrate was evaluated [416]. Compounds **195a**, **195b**, and **196** showed more inhibition for α -(2 $\rightarrow$ 3)-sialyltransferase than for α -(2 $\rightarrow$ 6)-sialyltransferase. In addition, the enzyme-inhibition assays showed that compound **195b** possesses potent and specific inhibitory activity toward rat recombinant α -(2 $\rightarrow$ 3)-sialyltransferase. Moreover, compounds **195b** ($K_m = 185 \mu\text{M}$) and **196** ($K_m = 245 \mu\text{M}$) presented IC_{50} values similar to that for the acceptor ($K_m = 264 \mu\text{M}$) toward α -(2 $\rightarrow$ 3)-sialyltransferases, whereas compound **195c** displayed less inhibition ($K_m = 419 \mu\text{M}$). Surprisingly, compound **195c**, 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 imine 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.

(3) *Pyralomicins*. 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 [417]. That suggests a role for the cyclitol moiety in the antimicrobial activity.

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 exhibit 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 the subjects of extensive 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.

Disclosure

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Competing Interests

The authors declare that there are not competing interests regarding the publication of this paper.

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