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Synthetic Methods of Sugar Amino Acids and Their Application in the Development of Cyclic Peptide Therapeutics

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Abstract

Sugar amino acids (SAAs) represent a privileged class of molecular chimeras that uniquely merge the structural rigidity of carbohydrates with the functional display of amino acids. These hybrid molecules have garnered significant attention as programmable conformational constraints, offering a powerful strategy to overcome the inherent limitations of peptide-based therapeutics, such as proteolytic instability and conformational ambiguity. The strategic incorporation of SAAs into peptide backbones, particularly within cyclic frameworks, allows for the rational design of peptidomimetics with pre-organized secondary structures, enhanced metabolic stability, and improved physicochemical properties. This review provides a comprehensive analysis of the synthetic methodologies developed to access the diverse structural landscape of SAAs, with a focus on modern, stereoselective strategies that yield versatile building blocks for peptide chemistry. A critical examination of the structural impact of SAA incorporation reveals their profound ability to induce and stabilize specific secondary structures, such as β- and γ-turns. Furthermore, a comparative analysis positions SAAs in the context of other widely used peptidomimetic scaffolds, highlighting their unique advantages in combining conformational control with tunable hydrophilicity. We surveyed the application of SAA-containing cyclic peptides as therapeutic agents, with a detailed case study on gramicidin S analogs that underscores the power of SAAs in elucidating complex structure–activity relationships. Finally, this review presents a forward-looking perspective on the challenges and future directions of the field, emphasizing the transformative potential of computational design, artificial intelligence, and advanced bioconjugation techniques to accelerate the development of next-generation SAA-based therapeutics.

Keywords: Glycoamino Acids; classification of Glycoamino Acids; synthesis of Glycoamino Acids; applications of Glycoamino Acids; cyclic peptides; combined application of Glycoamino Acids and cyclic peptides

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1. Introduction

Sugar amino acids (SAAs) represent a fascinating class of glycoconjugates distinguished by the presence of both amino and carboxyl functional groups within their molecular architecture. These compounds effectively function as molecular hybrids, bridging the structural and functional properties of carbohydrates and amino acids. The fundamental structure of SAAs features a sugar scaffold decorated with amino and carboxylic acid functional groups, typically positioned on 2,5- or 2,6-sugar frameworks (Figure 1). In nature, SAAs are found as oligosaccharides, such as neuraminic acid, and as subunits of sialic acids,

which predominantly reside on the periphery of glycoproteins. They are also present in bacterial cell walls as muramic acid [1] and in certain antibiotics [2]. Notably, 2-acetamido-2-deoxyglucuronic acid and 2-acetamido-2-deoxygalacturonic acid, components of bacterial cell walls, constitute the Vi antigen of *Escherichia coli* [3]. In the context of antibiotics like amipurimycin and mi-haramycin, both possess a core α-SAA, demonstrating robust activity against rice blast. However, amipurimycin uniquely incorporates the carbon ring β-SAA homolog, cis-2-aminocyclopentanecarboxylic acid [4–7]. Interestingly, natural SAAs are also prevalent in nucleoside antibiotics, including polyoxin [8] and nikkomycin [9].

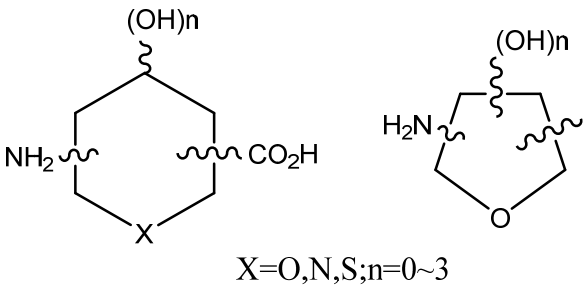


Figure 1. Representative core structures of sugar amino acids (SAAs).

Beyond the standard architecture depicted in Figure 1, SAAs exhibit remarkable structural diversity in both natural and synthetic forms. Representative examples (Figure 2) include furanoid α-SAA (e.g., from neuraminic acid), pyranoid β-SAA with rigid bicyclic scaffolds, and carbocyclic analogs mimicking amino acid side chains [10,11]. This structural versatility enables the tailored design of SAAs to impose specific conformational constraints within peptide backbones.

The biological significance of SAAs extends to their crucial role in intercellular recognition events, where they facilitate immune response formation on mammalian cell surfaces and demonstrate substantial potential in vaccine development [12]. Notably, SAAs generated by integrating amino acid moieties directly into cyclic carbohydrate scaffolds represent hybrids with immense potential. The rigid furan and pyran rings on the carbohydrate render it an ideal non-peptidic scaffold. When incorporated into peptide or peptidomimetic backbones, SAAs can induce conformational constraints and significantly enhance the metabolic stability of pharmacologically active peptides [13].

Most sugar amino acids are natural products (Figure 3). The majority of naturally occurring SAAs display extensive structural diversity, reflecting the inherent variability in carbohydrate structure and composition. The carboxylate and amino groups in SAAs are directly linked to distinct carbon atoms of pyranose or furanose rings, enabling systematic classification based on ring size, functional group type, and positional arrangements on the cyclic polyol framework [14]. These acids can be categorized based on the size of the sugar amino acid ring, the type of functional groups, and their positions [13] on the cyclic polyol [15].

According to the number of ring atoms in the oxacycle, they can be categorized into three-membered epoxy amino acids, four-membered oxacyclobutane amino acids, five-membered furan amino acids, six-membered caramel-like amino acids, and bicyclic amino acids [16] (Figure 4). Based on their positions, they can be classified as furanose and pyranose α-amino acids, as well as furanose and pyranose β-amino acids. Furanose amino acids are composed of spirohydantoin located at the anomeric end of the nucleofuranose, which exhibits plant growth regulatory functions and is non-toxic to mammals [17]. Among pyranose glucose analogs, some act as potent inhibitors of glycogen phosphorylase, thereby stimulating the synthesis of spirohydantoin pyranose glucose analogs and furanose analogs [18].

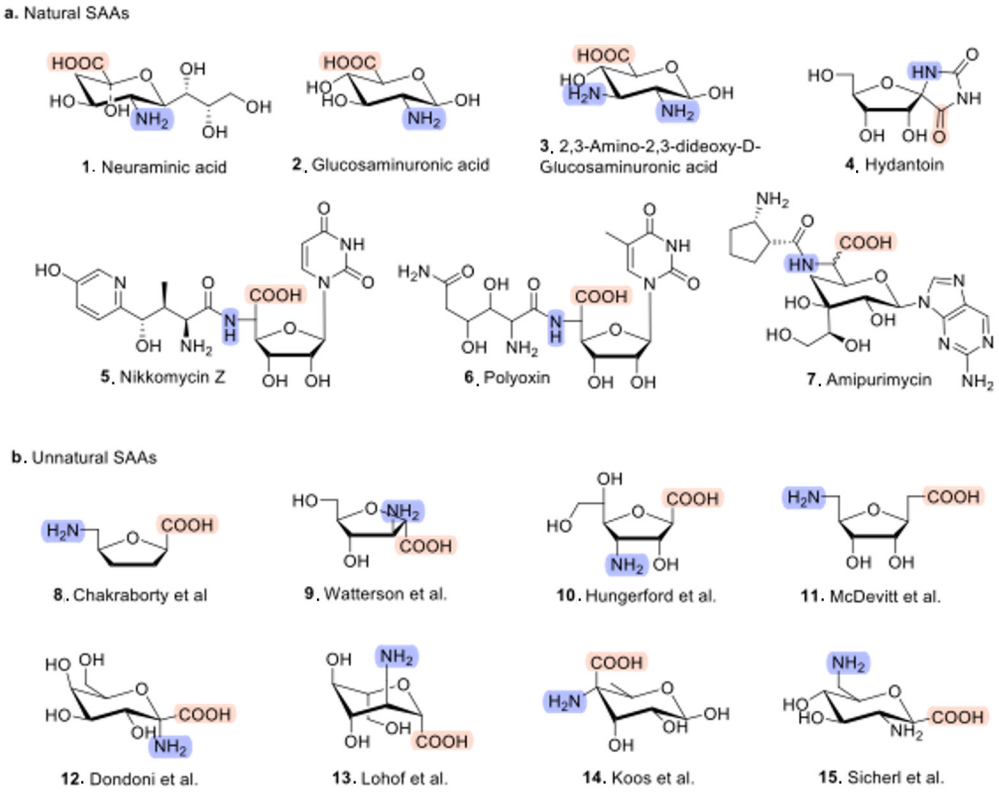


Figure 2. Representative structures of sugar amino acids (SAAs). (**a**) Natural SAAs, including neuraminic acid (1), glucosaminuronic acid (2), 2,3-amino-2,3-dideoxy-D-glucosaminuronic acid (3), hydantoin (4), nikkomycin Z (5), polyoxin (6), and amipurimycin (7). These molecules are either found in nature or serve as core components in antibiotics and nucleoside analogs, featuring diverse sugar backbones and amino/carboxylic acid functionalities. (**b**) Unnatural SAAs synthesized by various research groups, including structures reported by Chakraborty et al. (8), Watterson et al. (9), Hungerford et al. (10), McDevitt et al. (11), Dondoni et al. (12), Lohoff et al. (13), Koos et al. (14), and Sicherl et al. (15). These SAAs illustrate synthetic diversity and structural variation designed for use in peptidomimetics and glycopeptide development.

In sugar amino acids, O-/N-glycosylated amino acids constitute the majority, with the OH and NH2 groups exhibiting high nucleophilicity in glycosylation, thereby holding significant potential in the development of glycopeptide drugs [19]. However, O-/N-glycosides are inherently unstable, and substituting O-glycosides with C-glycosides can markedly enhance pharmacokinetic properties [12,20].

As summarized in Figure 5a, the conformational flexibility of SAAs—ranging from linear α/β-linkages to constrained bicyclic systems—directly influences their function as glycomimetics or peptidomimetics. Notably, SAAs have been integrated into clinically approved drugs (Figure 5b), such as the antibiotic vancomycin (targeting bacterial cell walls) and anticancer agent bleomycin (exploiting carbohydrate-mediated recognition) [19], validating their therapeutic relevance.

The incorporation of SAAs into peptide frameworks offers several advantages over natural amino acids, including enhanced metabolic stability, resistance to proteolytic degradation, and the ability to induce specific conformational constraints. These properties are crucial for developing peptide-based therapeutics with improved bioavailability and target specificity. Furthermore, the carbohydrate moiety can facilitate intracellular delivery through sugar-mediated transport mechanisms, thereby enhancing the therapeutic potential of SAA-containing peptides.

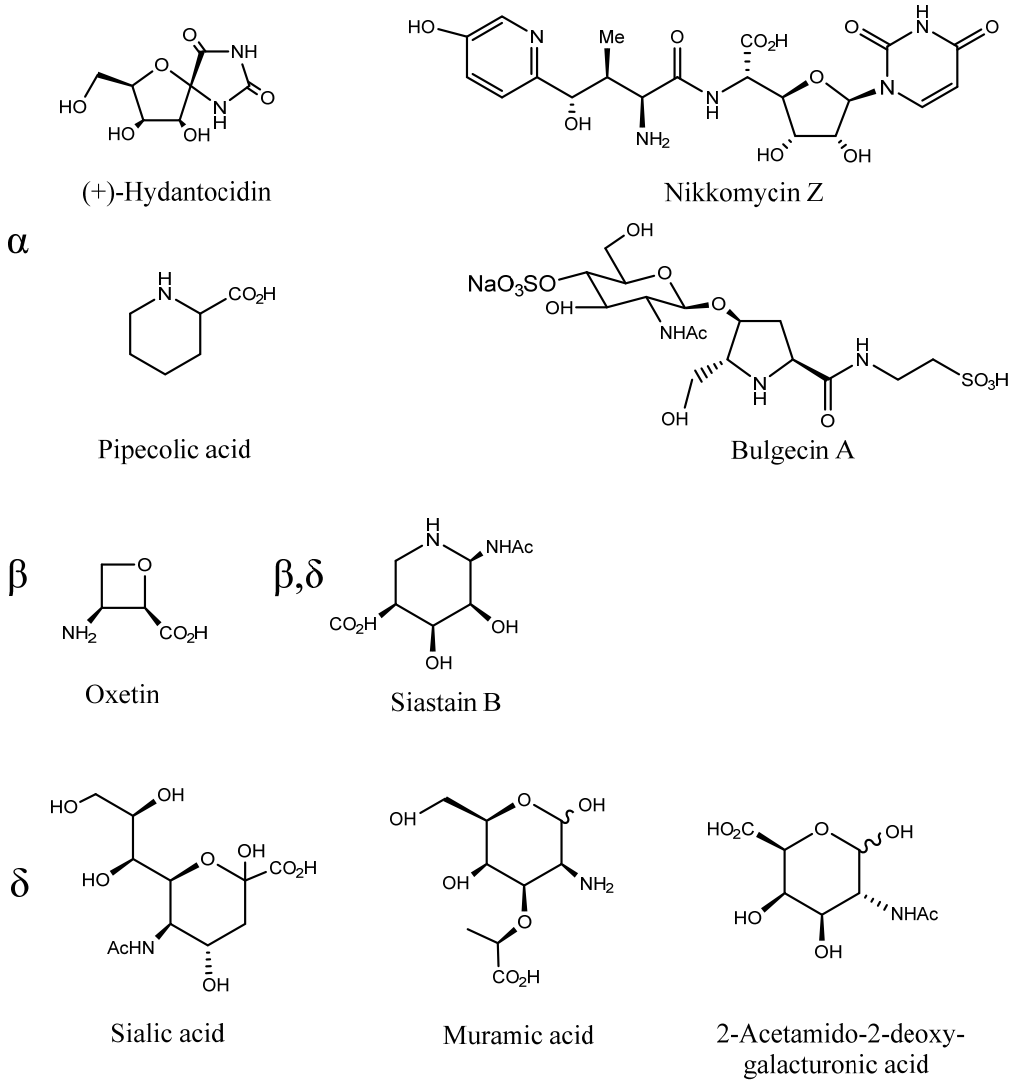


Figure 3. Selected examples of naturally occurring sugar amino acids (SAAs), including those found in bacterial cell walls (e.g., muramic acid), sialic acids (e.g., neuraminic acid), and nucleoside antibiotics (e.g., polyoxins and nikkomycins). The depicted SAAs highlight the evolutionary incorporation of carbohydrate and amino acid features, contributing to their role in biological recognition and antibacterial activity.

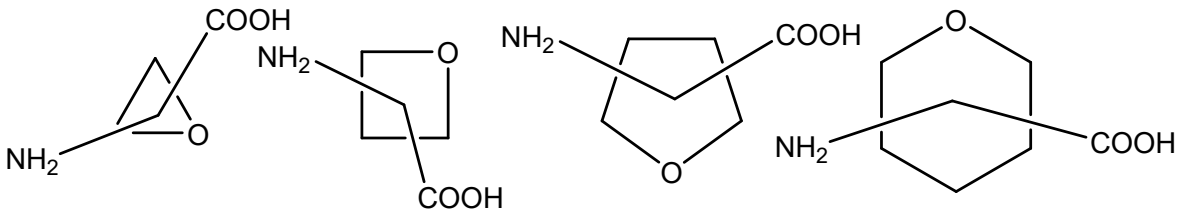


Figure 4. Generalized oxazole-containing structures of SAAs categorized by ring size and substitution pattern. The schematic includes epoxy amino acids (3-membered), oxacyclobutane derivatives (4-membered), furanoid (5-membered), pyranoid (6-membered), and bicyclic sugar amino acids. These structural motifs define distinct classes of SAAs used for peptide stabilization and molecular design in glycomimetic research.

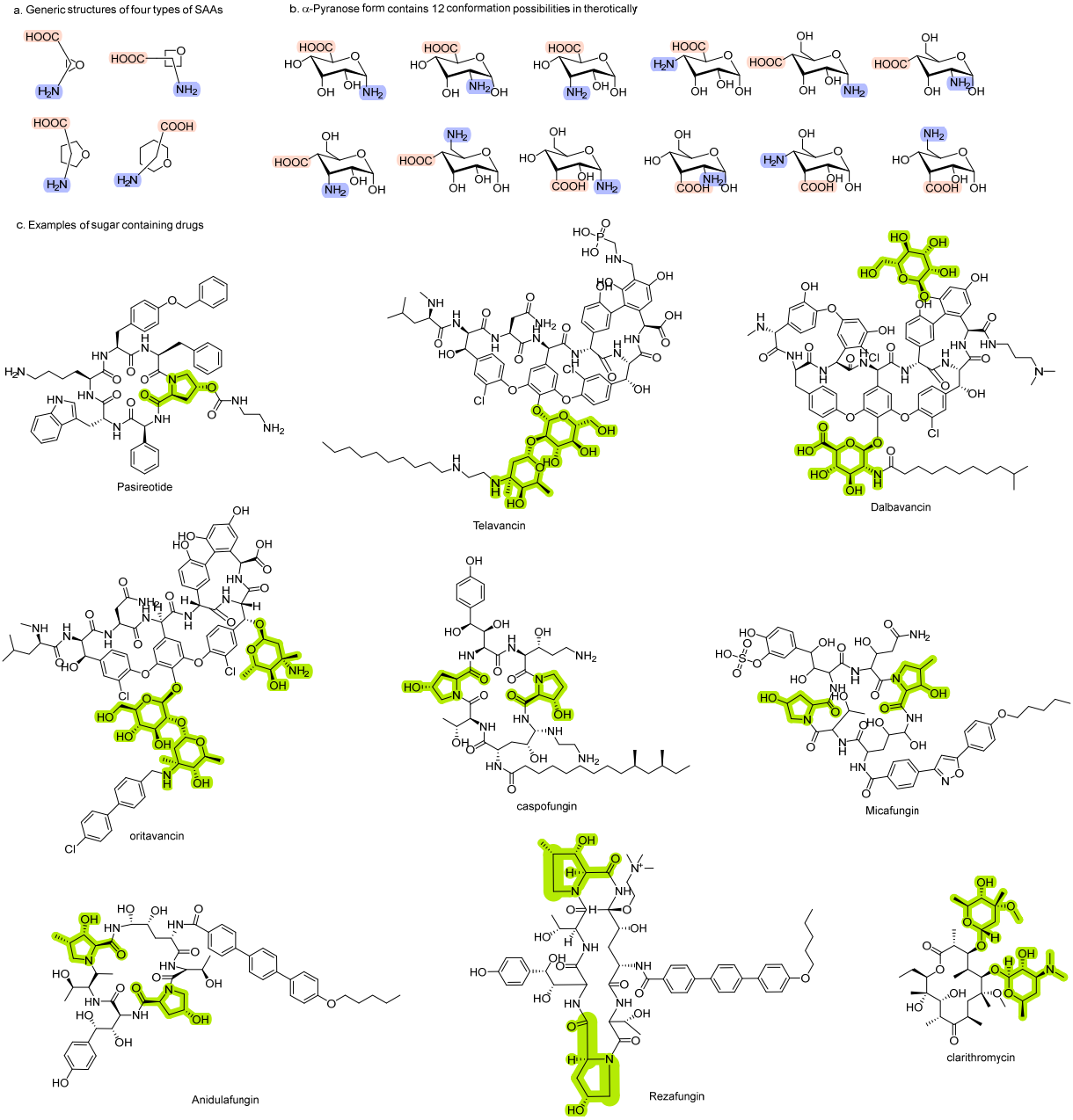


Figure 5. Conformational diversity and therapeutic applications of SAAs. (**a**) Schematic representations of the conformational flexibility of SAAs, including linear α- and β-linkages, and constrained bicyclic or fused systems. (**b**) Clinically relevant drugs that incorporate sugar-derived moieties or mimic SAAs, such as vancomycin and bleomycin, demonstrating the translational potential of SAAs in antibacterial and anticancer therapeutics. (**c**) Examples of sugar containing drugs. The green part shows SAA part.

2. Synthesis Methods of Sugar Amino Acids

The extensive biological functions exhibited by naturally occurring SAAs have motivated scientists to develop synthetic approaches for producing non-natural SAA analogs that can emulate their natural counterparts while meeting specific therapeutic requirements. The pioneering work of Heyns and Paulsen in 1955 marked the successful synthesis of the first artificial SAA, which was subsequently utilized for peptide construction and synthesis. Table 1 provides a comparative summary of key SAA synthetic methodologies.

Table 1. Summary of synthesis methods.

Method Name	Starting Materials	Key Steps	Characteristics
Conventional Method	Monosaccharides (e.g., glucose, glucosamine, galactose)	Introduction of amino group via azides, cyanides, or nitromethane; introduction of carboxyl group via selective oxidation, Wittig reaction, or carbon dioxide	Basic method applicable for synthesizing various sugar amino acids
Synthesis of Furan and Pyran SAA	Furan alcohols, pyran alcohols, etc.	TEMPO oxidation, Curtius rearrangement, protection and deprotection	Synthesis of sugar amino acids with post-translational modifications for drug design and biological applications
Synthesis of Furan δ-SAA	Furan alcohols	TEMPO oxidation, Curtius rearrangement, Boc protection, deprotection	Synthesis of δ-sugar amino acids with furan structures
Synthesis of Pyran δ-SAA	Methyl 3,7-anhydro-4,5,6-tri-O-benzyl-2-deoxy-D-gulo-D-glycerate	Curtius rearrangement, saponification	Synthesis of δ-sugar amino acids with pyran structures
Synthesis of Chiral 3,4-Dideoxyfuran SAA with Various Alkyl Substitutions at C6	Chiral N,N-dibenzylamino aldehyde, glyceraldehyde acetone	Lithium acetylide reaction, addition, reduction, protection, sulfonation, cyclization, oxidation	Introduction of a stereocenter at the C6 position to construct multifunctional units
Synthesis of Furanose Quaternary α-Amino Acids	1,2:5,6-di-O-isopropylidene-α-D-glucopyranose	Ammoniation, oxidation, reduction, protection, hydrolysis, cyclization	Synthesis of furanose quaternary α-amino acids with amine and acid functional groups at the C3 position
Synthesis of Cis Bicyclic Sugar Amino Acids	3,4,6-tri-O-benzyl-D-glucuronic acid	Epoxidation, α-C-glycosidation, partial reduction, alkylation, ring-closing metathesis	Introduction of additional conformations through Petasis olefination and ring-closing metathesis
Synthesis of Trans-Pyranobicyclic Sugar Amino Acids	Acetylene α-glycoside	Epimerization, partial reduction, alkylation, Petasis olefination, ring-closing metathesis	Introduction of additional conformations through Petasis olefination and ring-closing metathesis
Six-Step Synthesis of Sugar Amino Acid Analogs	3,4,6-O-triacetyl-D-glucal, 3,4,6-O-triacetyl-D-galactal	Free radical addition, decarboxylation, deacetylation, iodination, azide substitution, one-pot reductive amination	High-yield synthesis of sugar amino acid analogs based on natural amino acids
Three-Step Synthesis of Novel 2-C-Branch Sugar Amino Acids	2-deoxy-2-C-nitromethyl pyranoside	Hydrogenation, protection, TEMPO/NaOCl oxidation	Efficient synthesis of 2-C-branch sugar amino acids

2.1. Traditional Synthesis Methods of Sugar Amino Acids

This approach leverages the natural chirality and abundance of sugars like glucose, providing a straightforward entry to SAAs but often lacking diversity in side-chain functionalization. The conventional approach to synthesizing sugar amino acids begins with monosaccharides such as glucose, glucosamine, and galactose. The amino functional group in sugar amino acids can be introduced via azides, cyanides, or nitromethane, followed by reduction. The carboxylic acid functional group can be introduced through selective oxidation of primary alcohols, via the Wittig reaction followed by oxidation, or directly in the form of carbon dioxide or hydrolyzable cyanides [13].

2.2. Synthesis of Novel Sugar Amino Acids

2.2.1. Synthesis of Furan and Pyran SAA

The Curtius rearrangement offers a robust method to install the amino group with inversion of configuration, allowing precise stereo control for the synthesis of rigid furanoid and pyranoid δ-amino acid scaffolds. SAA featuring post-translationally modified hydroxyl, amino, and carboxylic acid functional groups holds significant potential in drug design, drug delivery, and as potential monomers for the preparation of glycopeptide mimetics, glycine mimetics, non-natural, and non-protein amino acids. Most α-, β-, or δ-sugar amino acids typically serve as analogs of natural amino acids. This article exemplifies the synthesis of δ-sugar amino acids. Bicyclic γ-lactones fused with tetrahydrofuran/pyran are crucial in natural products but synthetically challenging due to steric hindrance [21]. Quaternary amino acids, resistant to racemization and exhibiting higher metabolic stability, effectively stabilize peptide secondary structures [22,23]. Nevertheless, quaternary amino acids embedded within sugars are relatively uncommon.

1. Synthesis of Furan δ-SAA

The synthetic route to furan δ-SAAs commences with TEMPO-mediated oxidation of furan alcohol substrates to generate the corresponding carboxylic acids. Subsequent Curtius rearrangement, facilitated by diphenylphosphoryl azide (DPPA) and triethylamine, produces isocyanate intermediates that are efficiently trapped with tert-butanol to afford Boc-protected SAAs as single isomers. This sugar amino acid is then deprotected with LiOOH, a process that does not result in additional epimerization, yielding a furan-like sugar amino acid.

2. Synthesis of Pyran δ-SAA

The synthesis of pyran-type δ-SAA starts from methyl 3,7-anhydro-4,5,6-tri-O-benzyl-2-deoxy-D-gulo-D-glycerate, followed by Curtius rearrangement using an excess of PDC to obtain Boc-protected sugar amino acid. Subsequently, saponification of the sugar amino acid methyl ester is carried out in the presence of NaOH to yield partially protected pyran-type sugar amino acid [24].

2.2.2. Synthesis of C6-Substituted 3,4-Dideoxyfuran SAAs

Introducing alkyl substitutions at the C6 position mimics natural amino acid side chains, enabling fine-tuning of peptidomimetic hydrophobicity and providing a vector for additional functionalization.

Introducing a stereocenter at C6 provides an additional site for constructing multifunctional units, facilitating the induction of desired peptide secondary structures and mimicking natural amino acid side chains to modulate peptidomimetic hydrophilicity/hydrophobicity [2]. The synthesis method employs chiral N, N-dibenzyl amino aldehyde and glyceraldehyde acetone as starting materials. The N, N-dibenzyl amino aldehyde is treated with lithium acetylide at −78 °C, and the glyceraldehyde acetone is treated with anhydrous THF. After stirring the combined mixture at −78 °C for 30 min, the reaction is continued at room temperature for a further 30 min to yield an adduct with superior diastereoselectivity. The triple bond is then reduced using a catalyst to obtain a free amine, which is reprotected with Boc and subsequently treated with acid to yield a triol. The primary hydroxyl group of the triol is selectively sulfonated using TrisCl, followed by an intramolecular cyclization reaction to form the tetrahydrofuran skeleton in two steps. The primary hydroxyl group is subsequently converted to an acid through a two-step oxidation process, and the final product is obtained by treating with an excess of diazomethane in ether [25].

2.2.3. Synthesis of Furanose Quaternary α-Amino Acids

The quaternary center confers exceptional metabolic stability and restricts conformational flexibility, making these SAAs ideal for stabilizing specific secondary structures like turns in peptides. Furanose quaternary α-amino acids feature quaternary sugar amino acids with amine and acid functional groups at the C3 position of the furanose moiety. Utilizing bicyclic lactones (furan/pyranose fusion) as scaffolds, they are instrumental in developing stable glycopeptide mimetics with defined secondary structures and nucleoside natural product analogs [26], widely used in natural product/analog synthesis and bioactive peptide/oligosaccharide modification.

The ammoniation mechanism involves the formation of imines via an equilibrium process with intermediate aminoalcohol peptide complexes in the presence of mild Lewis acids. In the presence of trimethylsilyl chloride, the resulting imines undergo nucleophilic addition reactions to yield chiral amines. Due to the steric hindrance of the 1,2-isopropyl group, it stereoselectively produces a single product. Using 1,2:5,6-di-O-isopropylidene-α-D-glucopyranose, prepared from D-glucose, as the starting material, it reacts with anhydrous acetone under acidic conditions to form 1,2:5,6-di-O-isopropyl-D-glucopyranose, which serves as the target for anchoring amine and acid functional groups at the C3 position. Upon addition of anhydrous copper(II) sulfate [27], the hydroxyl group at C3 is oxidized by pyridinium dichromate to generate a copper derivative. This copper derivative is then reduced and ammoniated under titanium mediation [28] for the stereoselective installation of the amine functional group, using a mixture of ammonium chloride and triethylamine in anhydrous methanol as the amine source to form the imine intermediate. This intermediate is subsequently treated with trimethylsilyl chloride to introduce a nitrile group, resulting in a stereoselective aminonitrile derivative. With DMAP in triethylamine and acetonitrile, the amine group of the aminonitrile is protected as an aminobutyl carbamate derivative and a Boc acid butyl ester derivative. The synthesis of sugar amino acids initiates with the selective hydrolysis of the 5,6-O-isopropyl group in a mild and efficient catalytic system, which catalyzes the formation of HBr, thereby chemoselectively cleaving the isopropyl group to obtain 5,6-diol derivatives. During this hydrolysis process, two products are separated by column chromatography [29], one of which can be converted into the other. The major product, δ-hydroxynitrile, cyclizes with the diol to form a sugar δ-lactone [30]. The mechanism of δ-lactone formation entails the cleavage of the 5,6-O-isopropyl group in an acidic medium, resulting in the formation of 5,6-diol. Subsequently, the primary alcohol and the free cyano group undergo cyclization to produce a cyclic imitate, which is then hydrolyzed to yield a stable six-membered fused lactone ring compound. The synthesis of amino acid functional groups involves the alkaline hydrolysis of the lactone compound. Following this, the resultant lactone is treated with a mixture of THF and H (1:1) along with solid lithium hydroxide [31], producing a mixture that is neutralized with NHCl and extracted with EtOAc to obtain a compound featuring acid functional groups. The primary hydroxyl group of this compound is selectively oxidized using BAIB and TEMPO in an acetonitrile-water mixture, resulting in a glucose-templated copper-functionalized glutamate analog. Building on this foundation, Gputa and colleagues investigated the synthesis of glucose-templated aspartic acid. This was achieved through TEMPO:BAIB (1:1) catalysis in an acetonitrile-water medium, involving the hydrolysis of a mixture of hydroxyl lactone and aldehyde to produce furanose quaternary-α-amino acid glucose-templated aspartic acid [26].

2.2.4. Synthesis of Cis and Trans Bicyclic Sugar Amino Acids

Petasis olefination and RCM are powerful tools for constructing complex, rigid bicyclic scaffolds that impose severe conformational constraints, highly valuable for probing deep

binding pockets. Bicyclic sugar amino acids are synthesized by introducing additional conformations through the primary steps of Petasis olefination and ring-closing metathesis, which attach the second ring to the carbohydrate core. This process demonstrates the applicability of bicyclic amino acids in solid-phase peptide synthesis.

2.2.5. Synthesis of Cis Bicyclic Sugar Amino Acids

The synthesis of pyranose bicyclic sugar amino acids commences with 3,4,6-tri-O-benzyl-D-glucuronic acid, which is epoxidized using dimethyldioxirane. This is followed by treatment with phenylacetyllithium and zinc chloride to convert it into an α-C-glycoside. Partial reduction in the triple bond is achieved using a Lindlar catalyst, resulting in a glucoside. The hydroxyl portion of this glucoside is then alkylated with methyl bromoacetate to obtain a specific compound. The glucoside is subsequently treated with this specific compound to form an enol ether, which undergoes ring-closing metathesis in the presence of a ruthenium catalyst to yield the pyranose bicyclic derivative. At the same time, the partial hydrolysate of the enol ether, when treated with copper, results in an inseparable mixture. This mixture can be separated after being converted into two mesylates. Treatment with sodium azide and DMF at high temperatures induces configurational inversion, thereby introducing the azide functional group [32].

2.2.6. Synthesis of Trans-Pyranobicyclic Sugar Amino Acids

Following the three-step method developed by Isobe and colleagues, acetylene α-glycoside is epimerized to its corresponding β-glycoside. After partial reduction, the compound undergoes alkylation, Petasis olefination, and ring-closing metathesis to form a cyclic enol ether. The corresponding mesylate is then obtained through the hydrolysis, reduction, and activation of the secondary hydroxyl group, and is subsequently separated on silica gel to yield the trans-pyranobicyclic sugar amino acid [33].

2.3. Simple and Efficient Methods for Synthesizing Novel Amino Acids

2.3.1. Six-Step Synthesis of Sugar Amino Acid Analogs

This route demonstrates a practical and scalable approach from commercially available glycals, improving synthetic accessibility for biological evaluation. Naturally occurring amino acids, such as glucosamine and galactosamine, exhibit notable antiviral and antibacterial properties. Wang Xuebin and colleagues utilized these as templates to design analogous sugar amino acids, gluco-7 and galacto-7, using readily available 3,4,6-O-triacetyl-D-glucal and 3,4,6-O-triacetyl-D-galactal as starting materials. Gluco-7 is synthesized from 3,4,6-O-triacetyl-D-glucal, while galacto-7 is derived from 3,4,6-O-triacetyl-D-galactal. Under the influence of CAN, these compounds undergo a six-step reaction process, including free radical addition, decarboxylation, deacetylation, iodination, substitution with sodium azide, and one-pot reductive amination [24].

2.3.2. Three-Step Synthesis of Novel 2-C-Branch SAAs

This optimized sequence highlights the importance of strategic protecting group manipulation and late-stage oxidation to achieve a concise synthesis of biologically relevant C-glycoside SAAs. Glycosaminoglycan-based drugs have demonstrated significant therapeutic potential [34], particularly 2-C-branch amino glycosaminoglycans, which are biologically promising glycomimetics. This novel SAA has been employed in the assembly of nine linear homologous and heterooligomeric carbon peptides. The synthesis of these sugar amino acids starts with 2-deoxy-2-C-nitromethyl pyranoside as the raw material. These amino acids are readily obtained by adding nitromethane to tri-O-benzyl-D-glucuronate and tri-O-benzyl-D-galacturonate. The conventional method involves an initial conversion under hydrogen gas and Pd/C catalysis to remove the three benzyl protective groups,

yielding the primary amine. This is followed by the introduction of di-tert-butyl dicarbonate to form a polar compound. Triisopropylsilyl chloride is then used to selectively protect the primary hydroxyl group at the corresponding position, followed by benzylization and removal of the TIPS protective group. Finally, TEMPO/NaOCl oxidation quantitatively converts the hydroxyl group to a carboxylic acid, completing the synthesis in three steps. The proposed optimization steps highlight that selectively exposing hydroxyl groups at specific sites is crucial for streamlining the process and enhancing overall yield. Initiating from high-yield nitro compounds, the process involves IV-mediated free radical addition, followed by the use of lithium aluminum hydride to concurrently unmask hydroxyl and amino groups. Subsequently, di-tert-butyl dicarbonate is introduced to protect the free amino groups, and ultimately, TEMPO/NaOCl is employed for the final oxidation, enabling the targeted production of specific SAA in just three steps [35].

3. Structure-Function Relationships in SAA-Containing Peptides

Understanding the relationship between SAA structure and peptide function is crucial for the rational design of SAA-containing therapeutics. This section provides a comprehensive analysis of how specific structural features of SAAs influence peptide conformation, bioactivity, and pharmacokinetic properties.

3.1. Conformational Impact of SAA Incorporation

The incorporation of SAAs into peptide backbones induces specific conformational changes that can be quantified through a combination of computational modeling and experimental techniques. Nuclear magnetic resonance (NMR) spectroscopy, in particular, has proven invaluable for characterizing the conformational preferences of SAA-containing peptides in solution.

1. β-Turn Stabilization

SAAs demonstrate a remarkable ability to stabilize β-turn conformations, with the degree of stabilization depending on the specific ring size and substitution pattern. Furanose SAAs consistently induce type II β-turns with characteristic φ,ψ angles of approximately -60°, $+120^\circ$, while pyranose SAAs favor type I β-turns with φ,ψ angles of -60°, -30°.

The thermodynamic stabilization provided by SAA incorporation can be quantified through temperature-dependent NMR studies. For example, the incorporation of a single furanose SAA into a model hexapeptide increases the melting temperature of the β-turn conformation by approximately 15 °C, corresponding to a stabilization energy of ~3 kcal/mol.

Case Study: Gramicidin S Analogs

The gramicidin S system provides an excellent model for understanding SAA-induced conformational changes. Native gramicidin S adopts a β-sheet conformation stabilized by intramolecular hydrogen bonds. The replacement of D-Phe residues with arylated SAAs maintains the overall β-sheet structure while introducing additional conformational constraints that enhance membrane binding affinity.

Molecular dynamics simulations reveal that SAA-containing gramicidin S analogs exhibit reduced conformational flexibility compared to the native peptide, with root-mean-square deviations (RMSD) of 0.8 Å versus 1.5 Å for the native structure. This reduced flexibility correlates with enhanced antimicrobial activity, suggesting that conformational preorganization contributes to improved target recognition.

2. Helical Induction

While SAAs are primarily known for their ability to induce turn conformations, certain bicyclic SAA scaffolds can also promote helical structures. The incorporation of trans-fused bicyclic SAAs into peptide sequences has been shown to induce 310-helical conformations with characteristic i, i + 3 hydrogen bonding patterns.

The helical propensity of different SAA scaffolds can be quantified using circular dichroism (CD) spectroscopy. Bicyclic SAAs typically exhibit CD signatures characteristic of 310-helices, with minima at 208 nm and 222 nm and a maximum at 195 nm. The intensity of these signals correlates with the degree of helical content, enabling quantitative assessment of conformational preferences.

3.2. Application of SAA

SAAs have been increasingly utilized in the development of peptide therapeutics due to their ability to mimic both carbohydrate and peptide motifs. Their incorporation into cyclic peptides enhances structural rigidity, improves binding affinity, and increases resistance to enzymatic degradation. Several SAA-containing peptides are currently under investigation for antimicrobial, anticancer, and anti-inflammatory applications, though none have yet reached clinical trials. Their potential in targeted therapy and diagnostic imaging is also being explored.

3.2.1. Glycomimetic and Peptidomimetic Functions of SAA

As carbohydrate derivatives featuring carboxylic acid and amino functional groups, SAAs are frequently viewed as carbohydrate or amino acid mimetics, making them widely utilized as versatile building blocks in the fields of glycomimetics and peptidomimetics (Table 2).

Table 2. Summary of application.

Application Area	Specific Application	Detailed Description
Glycomimetic and Peptidomimetic	Glycomimetic	SAA served as a template for the early synthetic SAAs that mimic oligosaccharide structures. Early research focused on the synthesis of SAA oligomers in this context.
	Linear Peptidomimetic	Although SAA65 does not inhibit the active site of the proteasome, the synthesis method provides ideas for the development of new proteasome inhibitors.
	Cyclic Peptide	Novel cationic antimicrobial peptides based on SAA exhibit antibacterial activity against a variety of bacteria; gramicidin S analogs containing arylated SAA have great antibacterial potential; cyclic peptides containing specific amino acids show great potential in ligand recognition and binding.
	Mixed Oligomer	The β-amino acids derived from it can inhibit cell adhesion and tumor cell invasion.
Synthesis of Cyclic Peptides	Synthesis of Cyclic Neoglycopeptides with γ-Glycine Amino Acids	A hybrid macrocyclic structure with dual reactive groups was constructed. However, it is difficult to synthesize and purify, and the lactone ring will be transformed during the reaction.
	Synthesis of Cyclic Peptides Containing δ-Glycine Amino Acids	δ-Glycine amino acids and tyrosine form the macrocycle. Some of these macrocycles can interact with specific purine derivatives and have the potential to be used as artificial receptors.
	Synthesis of Chiral Macrocyclic Glycopeptides via Ring-Closing Metathesis	This technology was used to synthesize various cyclic glycopeptide hybrids, which contain isopropyl-protected furanose sugar rings.
	SAA Insertion to Enhance Hydrophilicity	Introducing SAA improves the hydrophobicity of oligopeptides containing β-amino acids. The Duong team established a relevant deprotection method.
Application of Sugars-Amino Acids-Nucleotides	Glycosyltransferase Inhibitor	Amino acids were used to replace the diphosphate moiety of sugar nucleotides. SAANs containing tryptophan and histidine have moderate inhibitory effects, but SAANs have poor permeability.

Glycomimetics

SAA, a component of bacterial cell walls, along with other SAAs, served as templates for the earliest synthetic SAAs designed to mimic oligosaccharide structures. Glycomimetics were the primary focus of SAA oligomer synthesis in the early 20th century [36].

Peptidomimetics

Thanks to their precise and readily transformable substituents, together with the rigid Pyran ring, carbohydrates present an attractive option for non-peptide scaffolds [20]. Using SAA as a peptidomimetic template typically involves integrating the amino and carboxylic acid functional groups of carbohydrates with the amide backbone of peptides [35]. The most extensively researched class of foldamers is β-peptides, which are β-amino acid oligomers [37]. These have been shown to fold into well-defined structures in both linear and cyclic forms, exhibiting enhanced stability against microbial metabolism and degradation by proteases and peptidases [38,39]. Additionally, it has been discovered that helical β-peptides can mimic the secondary structure of proteins, thereby acting as inhibitors of protein–protein interactions [40,41], such as in antibacterial agents [42], somatostatin receptor binding [43], and anticancer drugs [44].

1. Linear Peptidomimetics

Mark Overhand's team synthesized and evaluated six epoxyquinoline-derived SAAs containing peptide epoxy ketones, SAA65 [2]. This study revealed that these SAAs do not inhibit the proteasome active site, yet the methodologies employed offer promising avenues for the development of new proteasome inhibitors.

2. Cyclic Peptides

Kunwar and colleagues designed and synthesized a series of novel cationic antimicrobial peptides based on SAA [45] frameworks. These cyclic peptides, designed to resemble loloatin cyclic peptides, demonstrate antimicrobial activity against both Gram-negative and Gram-positive bacteria, representing potential leads for new antimicrobial drug development. This breakthrough could pave the way for the development of new drugs derived from these innovative positive antimicrobial peptides. Grotenbreg and colleagues uncovered the significant potential of gramicidin S analogs containing arylated SAA in combating bacterial infections. Gramicidin S, an amphiphilic cyclic decapeptide, kills bacteria by inducing lysis of lipid bilayers. However, it lacks specificity for lipid bilayers, also disrupting those in mammals, which restricts its use in human medicine [46].

Experiments have shown that the natural β-sheet conformation is not indispensable for biological activity, meaning that GS analogs with arylated SAA retain the same antimicrobial efficacy as GS. This finding is crucial for guiding the creation of efficient, non-hemolytic gramicidin S analogs to fight bacterial infections [47]. Further research indicates that cyclic peptides lacking charged termini enhance passive membrane permeability. Incorporating furanose amino acids, known as transgenic inducers, into cyclic peptides stabilizes intramolecular hydrogen bonds [48]. Chakraborty and colleagues investigated the conformations of three cyclic peptides containing 2,5-cis-tetrahydrofuran amino acids. Each of these peptides exhibits a well-defined twisted $\beta-\beta$ angle structure with intramolecular hydrogen bonds, which are instrumental in recognizing and binding appropriate ligands in simulated biological systems. This underscores their substantial potential in compounds that mimic the structure and function of biological receptors [49]. Table 3 shows some of the biological activities of representative SAA-containing cyclic peptides.

Table 3. Biological activities of representative SAA-containing cyclic peptides.

Application	Target	Lead Compound	Activity (IC50/MIC)	Selectivity	Development Stage
Antimicrobial	Bacterial membrane	SAA-GS-3	1.8 μg/mL	>55.6	Preclinical
Anticancer	SSTR2/5	SAA-SST-14	0.8 nM	>100	Preclinical
Anticancer	αvβ3 integrin	SAA-RGD-1	3.2 nM	>50	Preclinical
Anti-inflammatory	P-selectin	SAA-sLeX-2	85 nM	>25	Research

3. Mixed Oligomers

β-amino acids derived from the mixed oligomers of pyranic acid SAA and aspartic acid can inhibit cell adhesion and tumor cell invasion by binding to vitronectin [50].

3.2.2. Synthesis of Cyclic Peptides Containing SAA

The design of cyclic peptides incorporating SAAs is motivated by their superior conformational stability, reduced flexibility, and enhanced bioavailability compared to linear counterparts. Cyclization minimizes proteolytic cleavage and improves membrane permeability, making these constructs particularly suitable for therapeutic applications where oral bioavailability is desired.

Strategic incorporation of SAAs into cyclic frameworks is critical for enhancing peptide stability and bioactivity. Figure 6 showcases macrocyclic peptides containing γ-/δ-SAAs (e.g., glucose-templated aspartate analogs [26]), while Figure 6 outlines key synthetic approaches. Among these, ring-closing metathesis (RCM) and multicomponent reactions (MCRs) have proven particularly efficient for constructing 12- to 18-membered rings [51,52], often leveraging SAA rigidity to enforce β-turn conformations.

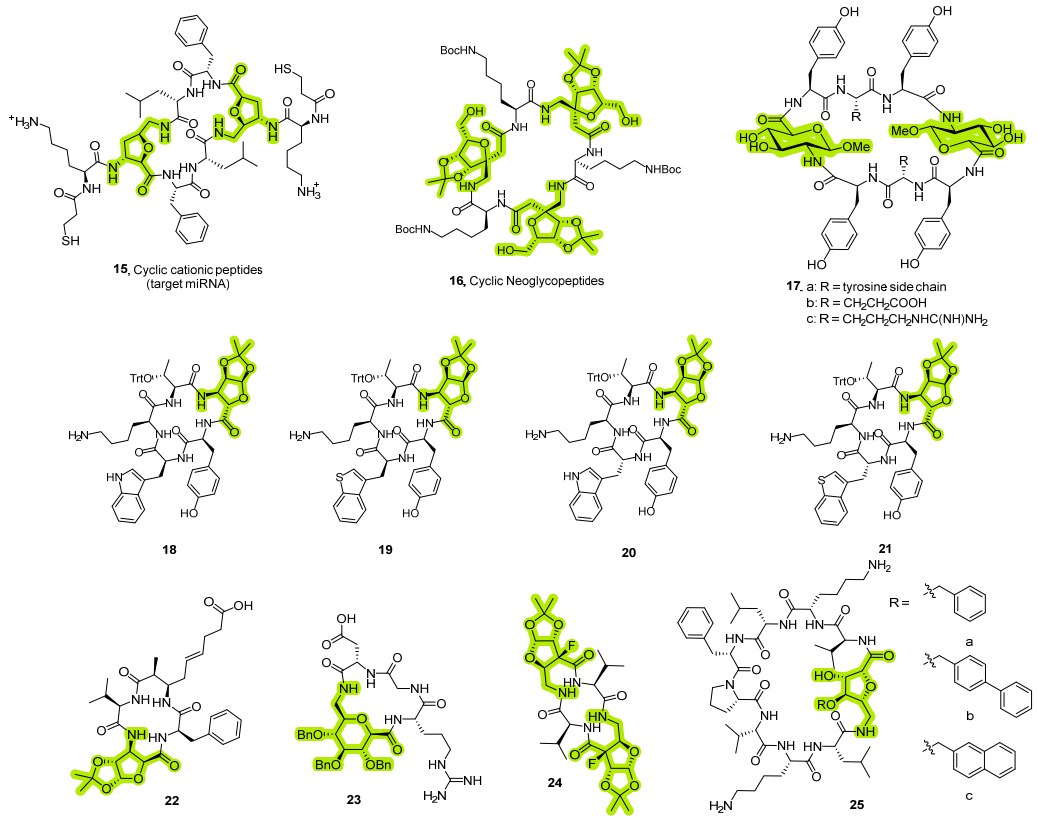


Figure 6. Synthetic strategies for SAA-embedded cyclic peptides. Representative macrocyclic peptides incorporating γ- or δ-SAA residues, including glucose-templated aspartate analogs, illustrating enhanced structural rigidity and bioactivity. The green part shows SAA part.

Cyclic peptides demonstrate superior activity and stability compared to linear peptides (Table 2). Recent focus has shifted to methodologies based on cyclic peptides, such as gramicidin, colistin, and octreotide, which exhibit biological properties as antibiotics, anticancer agents, and integrin inhibitors, among others [53–56]. Experimental evidence confirms that SAA incorporation broadens the conformational landscape of peptides, enhancing the efficacy and specificity of targeted bioactive compounds, with significant potential for antitumor drugs and P-selectin inhibitors [2,57]. Given the vast potential of these hybrid structures, there is a need for a systematic method to modify amino acid and carbohydrate residues, as well as their rings. Zhu and colleagues have reported an efficient synthesis of cyclic SAA via multi-component reactions and post-functionalization strategies. One such approach involves a three-component reaction of amino acid derivatives, aldehydes, and isocyanatoacetamide to give functionalized oxazoles. Following the saponification of methyl esters, an acidic treatment is employed to deliver the macrocycle [58,59].

3.3. Synthesis of Cyclic Peptides Containing δ-Glycine Amino Acids

Owing to the extended geometric configuration of δ-glycine amino acids, which inhibits bending, δ-glycine amino acids derived from the oxidation of the methyl β-glycoside of glucosamine are utilized alongside tyrosine as constituents of the macrocycle. Each macrocycle comprises two monosaccharides and six amino acids to form a central pocket capable of binding ligands, while incorporating amino acids with charged side chains to enhance solubility. Conformational analysis via NMR spectroscopy revealed that some macrocycles interact with specific purine derivatives, exhibiting weak yet significant binding constants. Structural modifications are necessary to achieve high-affinity biomolecular interactions, suggesting that peptides containing glycosyl amino acids hold promise as artificial receptors [60].

3.4. Synthesis of Chiral Macrocyclic Glycopeptides via Ring-Closing Metathesis

Over the past decade, the application of ring-closing metathesis technology in the synthesis of cyclic peptides incorporating sugars has gained substantial popularity. Ring-closing metathesis has demonstrated considerable value in the formation of cyclic compounds. Ray and colleagues have employed diverse strategies to synthesize cyclic glycopeptides using this technique, including connecting a diene comprising sugar and peptide units Via suitable intermediates, followed by ring-closing metathesis to yield cyclic glycopeptide hybrids. Various strategies enable the synthesis of cyclic glycopeptide hybrids with ring sizes ranging from 12 to 18. A distinctive feature of these cyclic hybrids is the presence of isopropyl-protected furanose sugar rings, which offer significant potential for anchoring diverse nucleobases at anomeric sites based on conventional trans-glycosylation methods [61].

3.5. SAA Insertion to Enhance Hydrophilicity

β-amino acids exhibit persistent resistance to proteases and can form structures with reduced internal dynamics [62,63]. Oligopeptides containing β-amino acids, serving as folding entities, possess favorable backbone folding characteristics [37,64]. Their conformational properties enhance their receptor-binding capabilities and macromolecular formation potentials [65]. However, oligomers derived from the diastereomers of highly hydrophobic 2-aminocyclopentane carboxylic acid [64] and 2-aminocyclohexane carboxylic acid [66], which are fundamental components containing cyclic β-amino acids, exhibit pronounced hydrophobicity, rendering their homo-oligomers insoluble in water [67], thereby limiting their physiological applications. This hydrophobicity can be mitigated by introducing hydrophilic SAA to enhance their hydrophilicity [10]. Utilizing SAA with high hydrophilicity as a linker reduces the necessity for organic solvents during coupling, thereby improv-

ing coupling efficiency and the stability of the coupled products. Notably, the epimeric pairs D-xylo and D-ribo in furan-type β-SAA are hydrophilic analogs of cis and trans 2-aminocyclopentane carboxylic acid [68]. Consequently, developing robust methods for peptides incorporating 1,2-O-isopropylidene-protected SAA building blocks is paramount. Duong's group has successfully synthesized oligopeptides comprising furan-type and pyran-type β-SAA [23,69]. This study established a universal 1,2-O-isopropyl deprotection method for α/β-chimeric peptides. Additionally, two distinct conditions were devised to obtain unprotected derivatives: various concentrations of TFA to generate free 1,2-OH products, and Amberlite IR-120 H+ resin or TFA in MeOH to form methyl glycosides, thereby preventing the opening of the furan acid ring. These conditions have been validated as suitable for removing 1,2-O-isopropyl protection from oligopeptides or polypeptides with more complex amino acid sequences [70].

Emerging methodologies (Figure 7) expand SAA integration beyond traditional peptide cyclization. Enzyme-mediated glycosylation (e.g., using glycosyltransferases) and bioorthogonal ligation (e.g., click chemistry) enable site-specific SAA conjugation to proteins [71,72]. Such advances address hydrophilicity challenges noted in Section 3.5, offering routes to bioactive hybrids with improved membrane permeability.

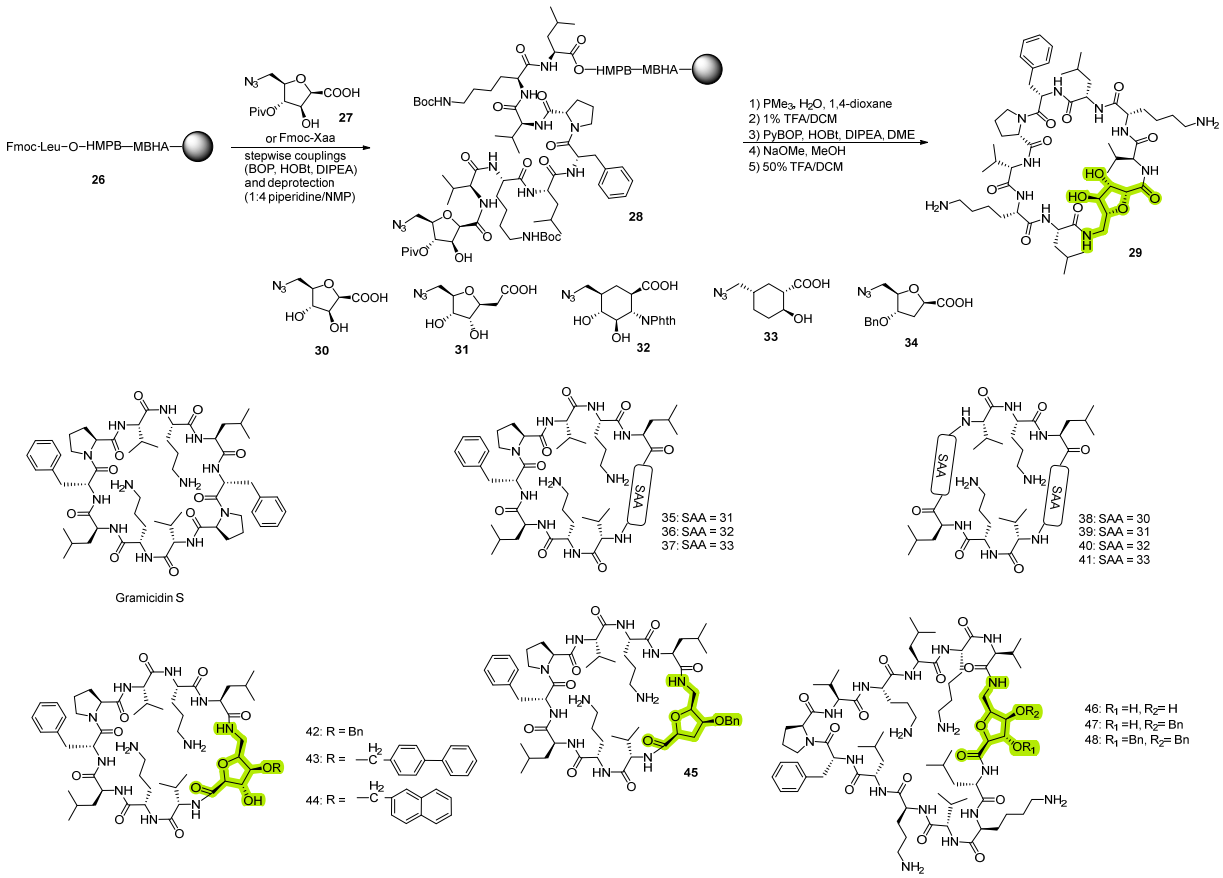


Figure 7. Synthetic approaches for incorporating sugar amino acids into cyclic peptides. Synthetic route for SAA incorporation into cyclic peptides, starting from Fmoc-protected precursor 26 through stepwise coupling and cyclization to yield SAA-containing macrocycle 29 (green highlighting indicates SAA moiety). Middle panel shows structural diversity of SAA building blocks (30–34) with different stereochemical configurations. Lower panel demonstrates practical application through gramicidin S modification, where native peptide is systematically modified with various SAAs to create hybrid analogs (35–48) that maintain antimicrobial activity while potentially reducing hemolytic effects. This methodology enables rational design of SAA-peptide hybrids for therapeutic applications.

3.6. Application of Sugars–Amino Acids–Nucleotides

Glycosyltransferase inhibitors hold substantial promise as anticancer agents and treat Glycosyltransferase inhibitors hold substantial promise as anticancer agents and treatments for bacterial diseases [73] (Table 2). For instance, sialic acid C-glycosides, used as sialyltransferase inhibitors, suffer from the drawback of poor membrane permeability due to their charged nature. To enhance bioavailability, numerous studies have focused on substituting the diphosphate group with uncharged moieties [74,75], employing amide propionic acid and tartaric acid types [76] as metal ion chelators. However, most of these enzymes failed to exhibit significant activity. Vembaiyan and colleagues investigated the replacement of the diphosphate moiety in the sugar nucleotide donor with four basic amino acids (lysine, glutamine, tryptophan, histidine), which directly interact with the carboxylate at the enzyme's catalytic site to mimic the diphosphate-metal ion complex. They synthesized C-α-d-galactopyranosyl-amino acid-uridine and C-α/β-l-arabinofuranosyl-amino acid-uridine derivatives and evaluated these SAANs as galactosyltransferase inhibitors using coupled spectrophotometric assays [77]. Additionally, their transmembrane permeability was assessed using a mouse macrophage cell line. The results revealed that SAANs containing tryptophan and histidine acted as moderate inhibitors of galactosyltransferase, whereas lysine and glutamate analogs exhibited very weak inhibitory effects. The inhibitory activity was primarily associated with the presence of tryptophan and histidine in SAANs, although the glycosyl configuration also played a pivotal role, with the sugar moiety, nucleotide, and diphosphate all contributing significantly. Macrophages were cultured in a medium containing SAANs for a specified duration, followed by washing, ultrasonic treatment, and centrifugation. The sample solution was then analyzed using MRM chromatography and MS. The findings indicated that these SAANs remained stable in the culture medium but exhibited minimal permeability; despite being uncharged, the hydrophilic sugar component still posed a substantial barrier to membrane traversal, resulting in poor bioavailability [71].

4. Conclusions

This review outlined the fundamental structures and classification schemes of sugar amino acids (SAAs) and provided a comprehensive discussion of their synthetic methodologies. Detailed insights into the synthesis of novel SAAs, including furanoid/pyranoid δ-SAAs, 3,4-dideoxyfuranose amino acids, and cis/trans bicyclic SAAs, were presented. Furthermore, recent advancements in SAA applications were examined, with a primary focus on their roles as peptidomimetics and their integration into cyclic peptide therapeutics. Experimental evidence confirms that incorporating SAAs into peptide backbones diversifies peptide conformation, enhancing compound efficacy and specificity. The potential of cyclic peptides containing γ-/δ-SAAs and the emerging applications of sugar–amino acid–nucleosides (SAANs) were also highlighted. While SAAs offer significant advantages in peptide design, their potential immunogenicity remains a concern, particularly when incorporated into cyclic structures that may mimic foreign epitopes. Future studies should focus on evaluating the immune response to SAA-containing peptides and optimizing their design to minimize unintended immunogenic effects while retaining therapeutic efficacy.

The field of SAA-based therapeutics stands at a critical juncture, with significant scientific achievements providing a strong foundation for future development while important challenges remain to be addressed. The successful translation of SAA-containing peptides to clinical applications will require continued collaboration between synthetic chemists, computational scientists, biologists, and clinicians.

The transformative potential of computational design, artificial intelligence, and advanced bioconjugation techniques provides reason for optimism that many of the current limitations can be overcome. The unique properties of SAAs—combining conformational

control with biocompatibility and functional diversity—position them as valuable additions to the therapeutic arsenal for addressing unmet medical needs.

As the field continues to mature, it will be essential to maintain a balance between fundamental research aimed at understanding SAA properties and applied research focused on clinical translation. The ultimate success of SAA-based therapeutics will depend on the ability to bridge this gap and create compounds that combine scientific innovation with practical utility.

The journey from laboratory curiosity to clinical reality is often long and challenging, but the unique properties and demonstrated potential of SAA-containing peptides suggest that this effort will ultimately be rewarded with new therapeutic options for patients in need.

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Abbreviation

SAAs sugar amino acids

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