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REVIEW

Sugar amino acids in designing new molecules*

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Emulating the basic principles followed by Nature to build its vast repertoire of biomolecules, organic chemists are developing many novel multifunctional building blocks and using them to create 'nature-like' and yet unnatural organic molecules. Sugar amino acids constitute an important class of such polyfunctional scaffolds where the carboxyl, amino and hydroxyl termini provide an excellent opportunity to organic chemists to create structural diversities akin to Nature's molecular arsenal. This article describes some of our works on various sugar amino acids and many other related building blocks, like furan amino acids, pyrrole amino acids etc. used in wide-ranging peptidomimetic studies.
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Keywords: **sugar amino acids, furan amino acids, pyrrole amino acids, peptides, NMR, molecular dynamics, hydrogen bonding**

Introduction

Unlike peptides and oligonucleotides, solid-phase synthesis of oligosaccharides have not yet achieved enough efficiency for generating oligosaccharide-based libraries due to their structural diversities arising out of variations in their sequences, position and configuration of linkages and heterocyclic ring sizes [1]. If efficiently exploited these diversities can lead to libraries of astronomically large number of carbohydrate-based structures since carbohydrates carry much more information per unit mass than do either nucleotides or amino acids. Carbohydrates also play very important role in cell-cell recognition processes. Many pathogens use carbohydrate-binding proteins to attach themselves to cell surfaces and initiate disease. Oligosaccharides and sugar molecules may have potential therapeutic values against many of these diseases. Combinatorial libraries of novel carbohydrate-based molecules may find useful applications in new drug discoveries in the coming years. Keeping in mind the growing importance of glycobiology and the problems associated in the synthesis of carbohydrate-based libraries, we envisaged a novel hybrid design represented by a class of compounds called sugar amino acids (Saa). Detailed uses of these sugar amino acids in our laboratory in the development of a large variety of molecules will be discussed here. These sugar amino acids have great potential as multifunctional building blocks in the development large varieties of designer molecules. Today when organic synthesis has reached a state of great excellence [2], it is being increasingly felt by many organic chemists that a time has come to look for new concepts to supplement the traditional methods of finding bioactive molecules from nature, especially as the demand for finding new molecules for discovering new drugs and new materials is increasing day by day. The expertise gained over the years in the area of organic synthesis and the rational drug-design concepts can be combined together, to create *de novo* structures that are expected to provide important leads in discovering new molecules. Emulating the basic principles followed by nature to build its vast repertoire of biomolecules, organic chemists are developing many novel multifunctional building blocks. These building blocks are assembled rationally to create molecules with well-defined structures and useful properties. These new approaches are expected to make valuable contributions along with conventional methods to enrich our arsenal of bioactive molecules to combat the increasing number of life threatening diseases [3–6]. Such concepts may also find useful applications in the development of new materials [7].

Some examples of designer organic molecules [8–22]

In the past 10–15 years, large number of publications appeared from various groups on a wide variety of designer molecules. Some representative examples of such molecular designs are listed here for one to get a feeling for the kind of work that

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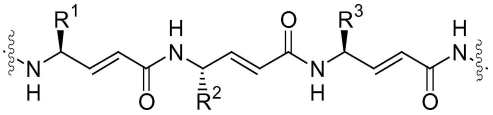


Figure 1. Vinylogous peptides (Schreiber, 1992).

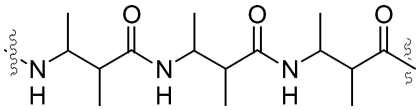


Figure 2. β-Peptides (Seebach, 1996; Gellman, 1996).

is being carried out in this area of research. During the total synthesis of cyclotheonamide, a thrombin inhibitor, isolated from marine source, having an α,β-unsaturated-γ-amino acid, Schreiber developed a new class of vinylogous peptides (Figure 1), which showed excellent helical structures [8].

An entirely new area of research was opened up by the work initiated almost simultaneously by two groups (Seebach and Gellman) on β-peptides [9] (Figure 2) that showed very ordered 3D structures and many of them are also having very useful biological properties, like, for example, antimicrobial properties (Figure 3) [9d,e].

There are many reports on the studies on amide-linked oligonucleotides where the normal phosphate linkages of oligonucleotides are replaced with peptide bonds (Figure 4) [10]. These molecules and Peptide Nucleic Acids (PNA) [11] are finding useful applications in antisense-oligonucleotide therapies. Large varieties of modified PNAs have also been developed [11,12].

Another class of interesting compounds called "Peptoids", developed by Zuckermann and Cohen, are composed of polymeric *N*-alkylated glycines (Figure 5) [13]. They also exhibit helical structures, which are reminiscent of those formed by some β-peptides developed by Gellman and Seebach as described above. Some peptoids also have useful properties. Cationic peptoids can act as DNA-delivery system and reported to be more efficient than lipid-based DNA-delivery vehicles, which do not unpack well.

On carbohydrate-based hybrid molecules, some of the notable examples are carbonucleotoids by Nicolaou [14], carbopeptoids by Ichikawa [15], and also other amide-linked oligosaccharides reported by Wessel (Figure 6) [16].

The list of such notable examples of designer organic molecules will not be complete if Eschenmoser's works on "Homo-DNA" or hexose-derived oligonucleotides (Figure 7) are not included [17].

Many cyclic molecules have also been designed and synthesized (Figure 8). The unusual chemical and biological properties of synthetic cyclic DNAs and RNAs have attracted lot of attention in recent years leading to the development of many such compounds from various groups [18]. Besides, many cyclooligosaccharides have been developed as model receptors mimicking cyclodextrins [19,20].

I have tried to give an essence of the kind of research being carried out world wide on the new trends of designing molecules with novel three dimensional structures and interesting properties which inspired us to start working in this area.

Our work on designing molecules based on sugar amino acids and related molecules [21–32]

Carbohydrates and amino acids constitute two important classes of building blocks used by nature to build its vast repertoire of biomolecules. While carbohydrates present in nucleotides, glycopeptides and glycolipids play very important roles in various biological processes, especially in cell-cell recognition processes, proteins derived from amino acids perform myriad cellular functions. Hybridization of these two important natural building blocks gave rise to a very useful class of novel peptidomimetic scaffolds called Sugar Amino Acids (Saa). Sugar amino acids have emerged, in recent years, as versatile templates used extensively as conformationally constrained scaffolds in many peptidomimetic studies and as an important class of synthetic monomers leading to many de novo oligomeric libraries [33–37].

The sugar amino acids prepared by us have a general structure as shown in Figure 9. They are basically hybrids of carbohydrate and amino acids where amino and carboxyl functional groups have been incorporated at the two termini of regular 2,5-anhydro sugar frameworks. There are several advantages of sugar amino acids as building blocks.

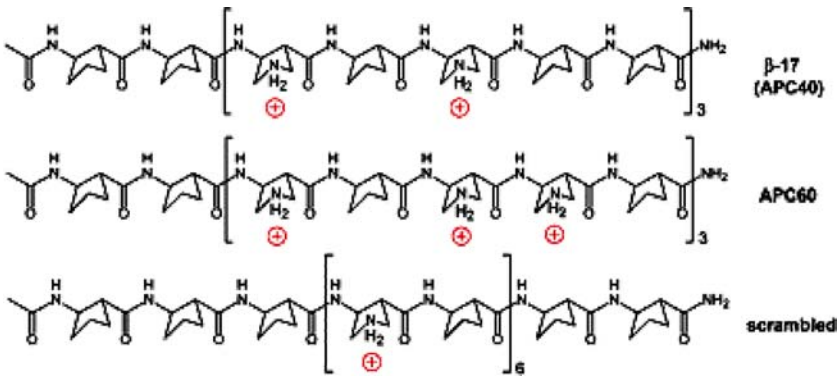


Figure 3. Antimicrobial β-peptides (Gellman 2002).

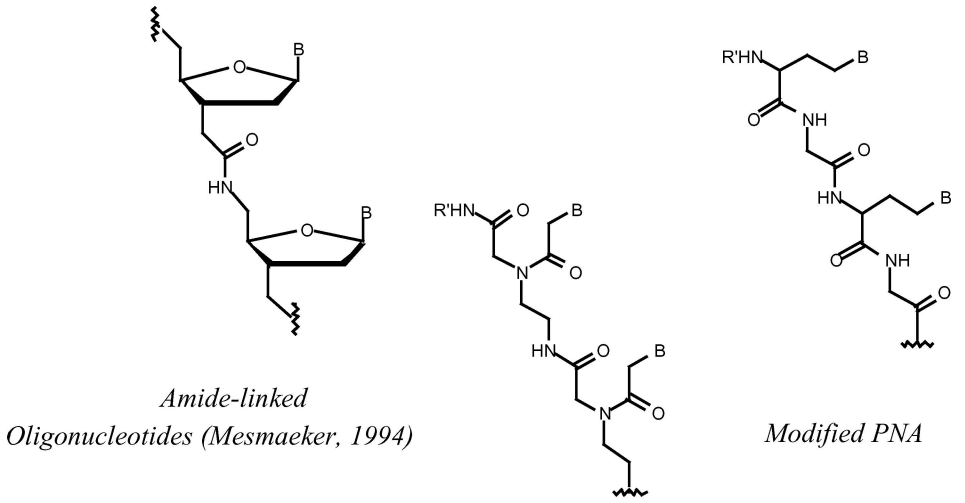


Figure 4. Amide-linked oligonucleotides, PNAs and modified PNAs.

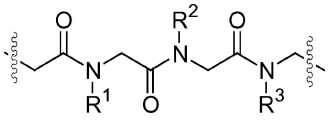


Figure 5. Peptoids (Zuckermann and Cohen, 1992).

1. The rigid furan rings of these molecules make them ideal candidates as non-peptide scaffolds in peptidomimetics where they can be easily incorporated by using their carboxyl and amino termini utilizing well-developed solid-phase or solution-phase peptide synthesis methods.
2. At the same time, it allows efficient exploitation of the structural diversities of carbohydrate molecules. The presence of five chiral centers in these molecules can give rise to large number possible isomers that can be used to create combinatorial libraries of sugar amino acid based molecular frameworks predisposed to fold into architecturally beautiful ordered structures, which may also have interesting properties.
3. The protected/unprotected hydroxyl groups of sugar rings can also influence the hydrophobic/hydrophilic nature of such molecular assemblies.

Scheme 1 depicts a novel reaction path developed by us for the synthesis of furanoid sugar amino acids **1** from a linear

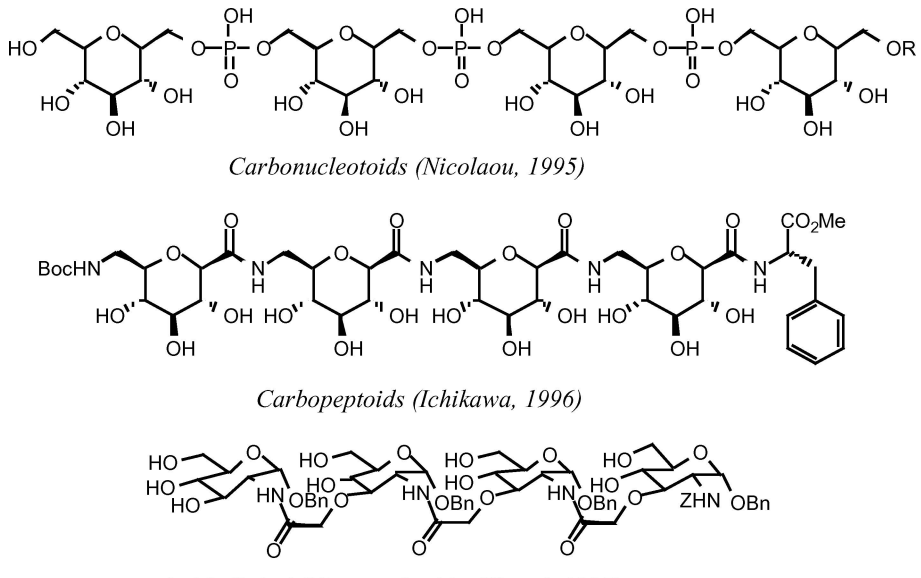


Figure 6. Structures of carbonucleotoids, carbopeptoids and amide-linked oligosaccharides.

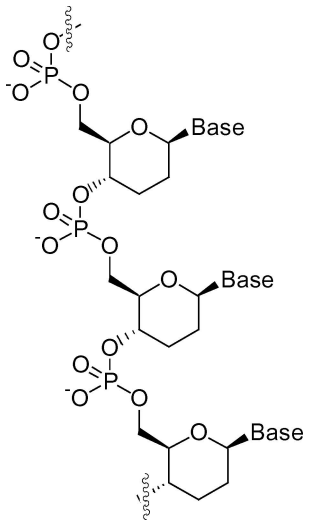
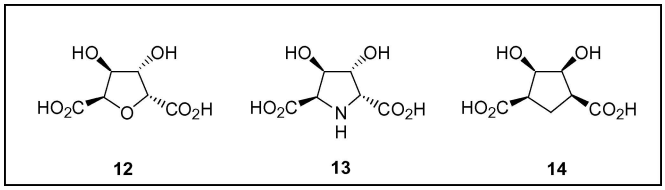


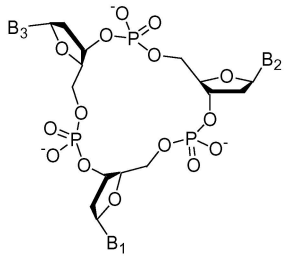
Figure 7. General structure of Homo-DNAs (Eschenmoser, 1992).

precursor **2**. This method was employed for the syntheses of two sugar amino acids, 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid (**3**, Gaa) and its mannonic (**4**, Maa) congeners. Few other members of the family, idonic (**5**, Iaa), 3,4-dideoxyidonic (**6**, ddIaa) and 3,4-dideoxygluconic acid (**7**, ddGaa) congeners were also synthesized. Incorporation of these furanoid sugar amino acids into Leu-enkephalin replacing its Gly-Gly portion gave analogues **8**-**11**.

Detail structural analysis of these molecules by various NMR techniques in combination with constrained molecular dynamics (MD) simulations revealed that one of these analogues, compound **8** has a conformation as shown in Figure 10 that happens to be very similar to the bioactive conformations of opioid peptides in which the two aromatic rings of Tyr and Phe remain in close proximity. The analgesic activities of **8** determined by mouse hotplate and tail-clip methods were similar to that of Leu-enkephalin methyl ester.

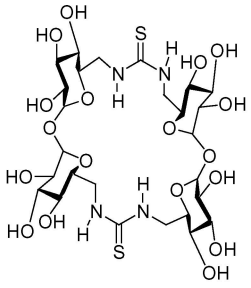
Based on these structural studies, we designed novel molecular scaffolds of various sugar diacids—2,5-anhydro-D-idaric acid (**12**) [22,23], 2,5-dideoxy-2,5-imino-D-idaric acid (**13**) [25] and 4,5-dihydroxy-1,3-cyclopentanedicarboxylic acid [24] (**14**). Each of these designer scaffolds carries, on both sides of their molecular frameworks, the core "*cis*-β-hydroxycarboxyl" motif that was responsible for nucleation of the turn structures in Gaa and Iaa-containing Leu-enkephalin analogs.





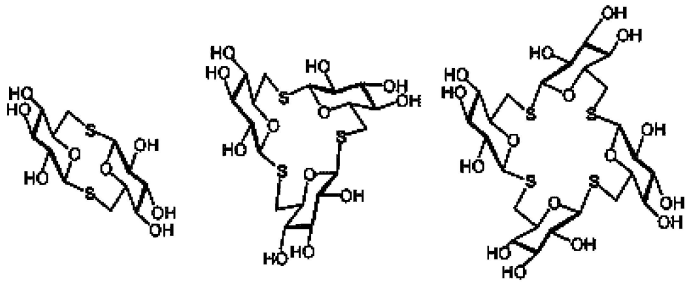
Cyclic DNAs

(Dennis, 1982; van Boom, 1987; Reese, 1989; Kool, 1992)



Cyclooligosaccharides

(Fernandez, 2002)



β-1,6-Thio-linked cycloglucopyranosides
(Hindsgaul, 2002)

Figure 8. Structures of cyclic DNAs and some sugar based designer molecules.

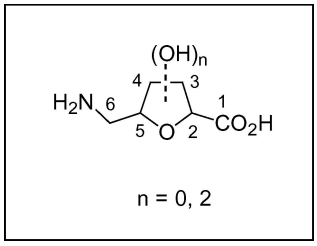


Figure 9. General structure of furanoid sugar amino acids.

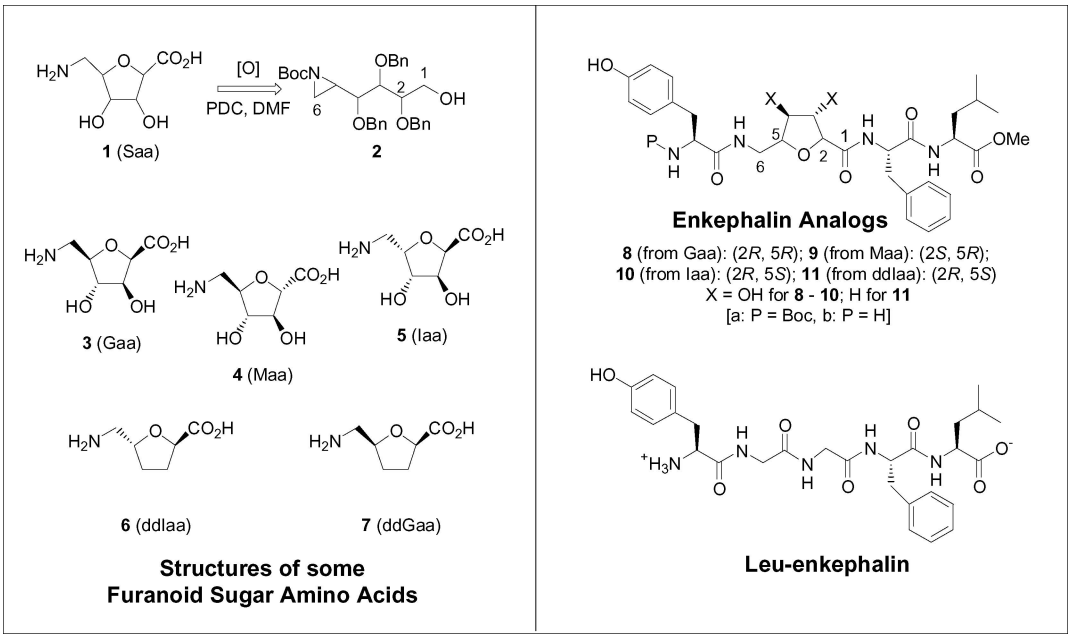
Figure 10. Stereoview of the superimposed energy-minimized structures sampled during the constrained MD simulations of **8** [21,22].

Subsequently, bi-directional elongation of the diacid moieties of these scaffolds with identical peptide strands led to the formation of a C_2-symmetric reverse-turn mimetics. The peptidomimetics molecules **15**-**18** obtained from **12** (Scheme 2) displayed ordered C_2 symmetric structures consisting of identical intramolecular H-bonds at two ends between $AA^2NH \rightarrow$ sugar-OH, same as seen earlier in **8** and **10** [22,23]. These molecules were tested for HIV-1 protease inhibition activities, as they structurally resemble many well-established C_2 symmetric HIV-1 protease inhibitors. Although none of these compounds showed any significant HIV-1 protease inhibitory activity, further refinements in design may lead to protease inhibitors based on these rigid carbohydrate-derived scaffolds.

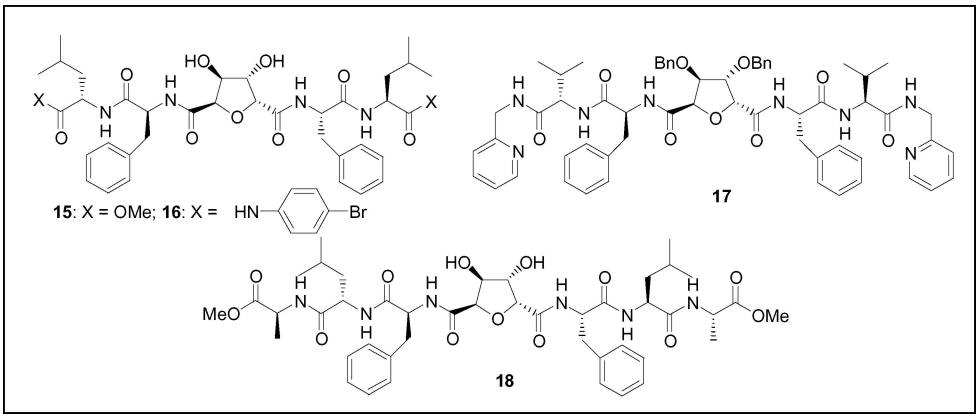
These studies were followed by the synthesis and conformational analysis of the corresponding carbasugar and imino sugar based molecules **19** and **20**-**21**, respectively, as shown in Scheme 3 [24,25]. While the former displayed a structure which had a folded conformation involving an interstrand H-bond [24] the latter showed two different conformations that switched from one to the other depending on whether the ring hydroxyls were protected or not [25].

Conformational analysis by NMR studies revealed that compounds **20b** and **20c** take interesting turn structures (C_2 symmetric for **20c**) in DMSO-d_6 consisting of identical intramolecular hydrogen bonds at two ends between LeuNH $\rightarrow$ sugar-OH as depicted in structure **A** in Figure 11, whereas **20a** displays structures with regular β-turns with hydrogen bonds between LeuNH $\rightarrow$ Boc-C=O in one half of their molecular frameworks (structure **B**), characteristic of the turn structures commonly observed in "D-Pro-Gly" containing peptides [25].

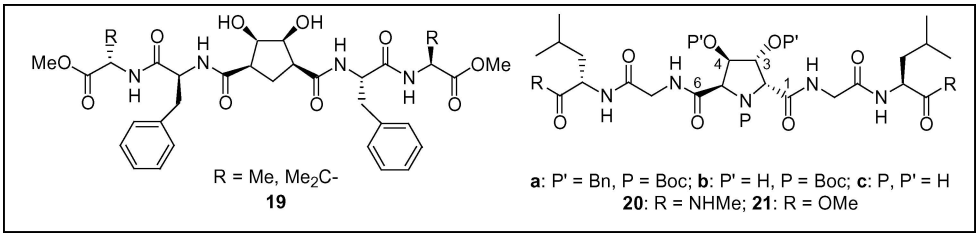
The structures sampled during the restrained MD calculations based on the ROESY cross-peaks found for **20b** in DMSO-d_6 reveal an ensemble of structures as shown in Figure 12, where the two peptide chains form cyclic conformations at both ends involving hydrogen bonds between LeuNH and pyrrolidine-OH.



Scheme 1. Synthesis of furanoid sugar amino acids **3**-**7** and their application in the synthesis of peptidomimetic molecules **8**-**11** [21,22].



Scheme 2. Synthesis of C_2 symmetric peptidomimetics **15**-**18** based on 2,5-anhydro sugar diacid **12** as potential HIV-1 protease inhibitors [22,23].



Scheme 3. Structures of carbasugar diacid based peptidomimetic molecule **19** and its imino congener based compounds **20**-**21**.

Oligomers of sugar amino acids

In recent years chemists have developed a large variety of oligomeric compounds that mimic biopolymers [1,3–5,38,39]. Such synthetic oligomers are composed of unnatural and yet nature-like monomeric building blocks assembled together by iterative synthetic processes that are amenable to combinatorial strategies. The main objective in developing such oligomers is to mimic the ordered secondary structures displayed by the biopolymers and their functions. They are also expected to be more stable toward proteolytic cleavage in physiological systems than their natural counterparts. Rationally chosen monomeric units from the large repertoire of structurally diverse building blocks are woven together in specific sequences by iterative synthetic methods leading to the development of novel homo- and heteropolymers with architecturally beautiful 3-D structures and desirable properties.

In continuation of our work on designing sugar amino acid based molecules, we were interested in the synthesis and structural studies of acyclic and cyclic oligomers of furanoid sugar amino acids and related compounds. Oligomerization of 6-amino-2,5-anhydro-6-deoxy-D-mannonic acid **4** by solution phase peptide coupling methods gave oligomers **22**-**25** as shown in Scheme 4 [26]. Conformations of these oligomers were studied by detailed NMR experiments and also tested for their biological activities. However, all of them were found to be inactive in hypoglyceamic tests in rats.

In contrast to the oligomers **22**-**25** derived from Maa **4**, the amide proton signals of the Gaa **3** based linear tetramer **26**, Boc-[Gaa(Bn$_2$)]$_4$-OMe, were very well resolved in $CDCl_3$. Furthermore, these amide proton chemical shifts displayed no concentration dependence and very small changes during the solvent titration studies. Both concentration dependence and solvent titration studies strongly suggested their involvements in intramolecular hydrogen bonds with no aggregation. This was further corroborated by variable temperature studies in $CDCl_3$ recorded between 30 and 55°C. Conformational analysis by NMR and constrained MD studies revealed that compound **26** has a well-defined structure in $CDCl_3$ with repeating β-turns, each involving 10-membered ring structure with intramolecular

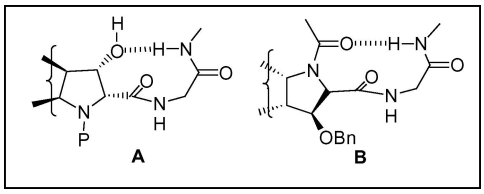
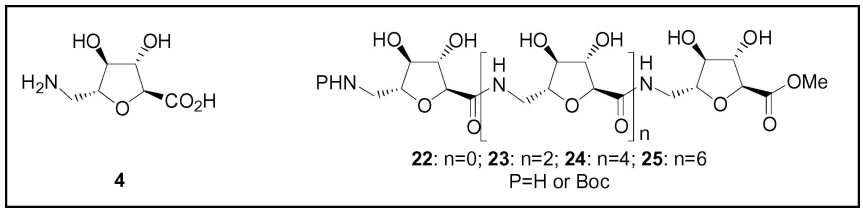
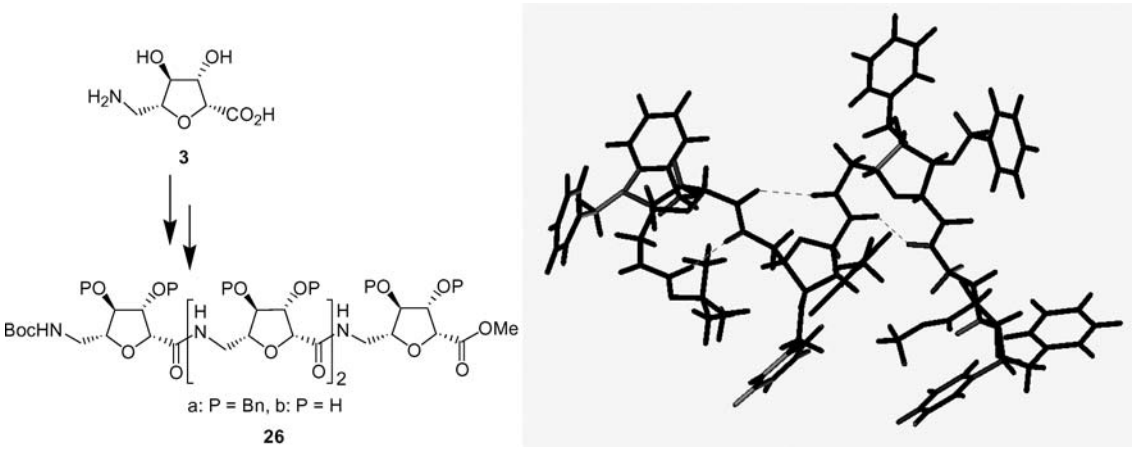


Figure 11. Conformational changes in iminosugar based peptidomimetc molecules.

Figure 12. Stereoview of the constrained MD simulated structures of iminosugar based designer molecule **20b**.



Scheme 4. Oligomerization of 6-amino-2,5-anhydro-6-deoxy-D-mannonic acid **4** [26].



Scheme 5. Acyclic homooligomer **26** derived from 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid **3** (Gaa) and the 3D structure of **26a** in $CDCl_3$ (right) from NMR/constrained MD studies.

hydrogen bond between $NH_i \rightarrow C{=}O_{i-2}$ as shown in the 3D figure in Scheme 5 [27].

We have also prepared and carried out structural studies of a furanoid sugar amino acid based peptide Gaa-Phe-Leu **27** and its dimer **28** [28]. In $CDCl_3$, they displayed very ordered structure with a repeating β-turn-type secondary structure at lower concentrations as shown in Figure 13 and started forming aggregates that gradually turned into excellent organogels as the concentrations were increased, a phenomenon observed for the first time in sugar amino acid containing peptides.

While the scanning electron microscopic (SEM) analysis of the xerogels from **27** showed porous 3D structure (Figure 14, left), the SEM image of the gel from **28** (Figure 14, right) revealed a compact three-dimensional fibrous structure that were wavy and tending to form helices where they were loose [28].

Next, as part of our efforts to develop novel sugar amino acid based foldamers, we were interested in synthesizing cyclic homooligomers of furanoid sugar amino acids. Cyclization of linear peptides or covalent bridging of their constituent amino acids at appropriate places is a widely used method to constrain their conformational degrees of freedom and induce desirable structural biases essential for their biological activities, such as tubular structures for transporting ions or molecules across membranes.

To begin with, a novel furan amino acid, 5-(aminomethyl)-2-furancarboxylic acid **29**, was cyclized directly into its cyclic trimer **30** in 60–75% yield in a single step cyclooligomerization process as shown in Scheme 6 [29]. This avoids the lengthy step-wise assembling of linear precursors, the process conventionally followed for synthesizing similar cyclic products. This novel 18-membered cyclic homooligomer **30** derived from furan amino acid **29** was found to be an excellent receptor for carboxylate binding having an association constant

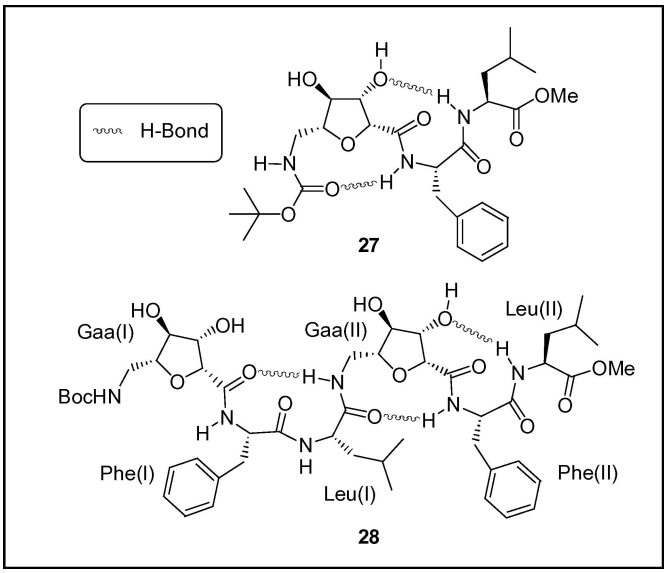


Figure 13. Hydrogen bonded structures of **27** and **28** in $CDCl_3$ under dilute conditions.

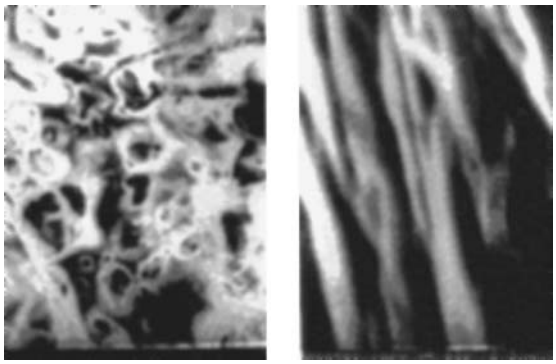
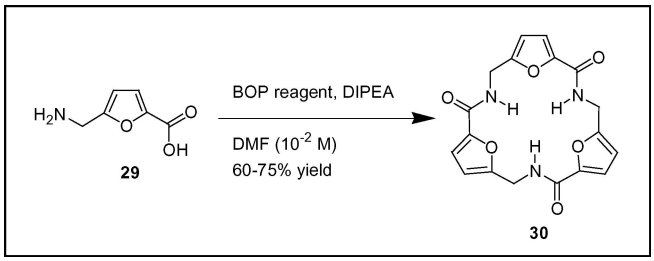
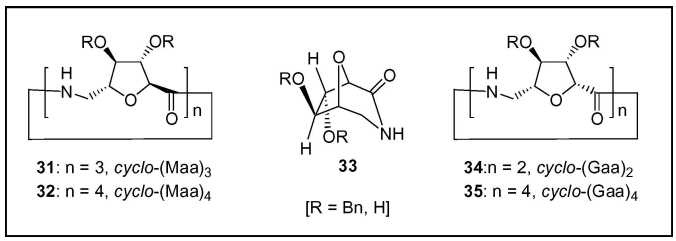


Figure 14. SEM pictures of xerogels from **27** (left) and **28** (right) in $CHCl_3$ [28].



Scheme 6. Cyclooligomerization of furan amino acid **29**.



Scheme 7. Cyclic homooligomers of furanoid sugar amino acids.

of 8.64×10^3 M^{-1} for tetrabutylammonium acetate in acetonitrile [29].

Following the same strategy, cyclic homooligomers of mannose-derived furanoid sugar amino acid **4** were also synthesized that converted the sugar amino acid monomer directly into its cyclic homooligomers **31** and **32** (Scheme 7) [30]. The glucose-based sugar amino acid **3** under the same reaction conditions gave a bicyclic lactam **33** as the major product. Cyclic homooligomers of Gaa were prepared by cyclizing their linear precursors leading to the formation of cyclic peptides **34** and **35**. Addition of the bicyclic lactam **33** resulted in the influx of Na^+ ions across lipid bilayer leading to the dissipation of valinomycin-mediated K^+ diffusion potential [30].

Conformational analysis by NMR and constrained MD studies revealed that all the cyclic products had symmetrical structures. While in Maa trimer **31** (Figure 15, top), the C2-H and CO are placed on one side of the ring and the NHs point to the other side, the amide protons in the Maa tetramer **32** point into the ring and the carbonyls to the outside (Figure 15, middle). In the Gaa dimer **34** (Figure 15, bottom), the 12-membered core ring is flanked on two sides by furanoid rings in which the C2-hydrogens and the COs can be seen on one side of the ring and the NHs point to the other side.

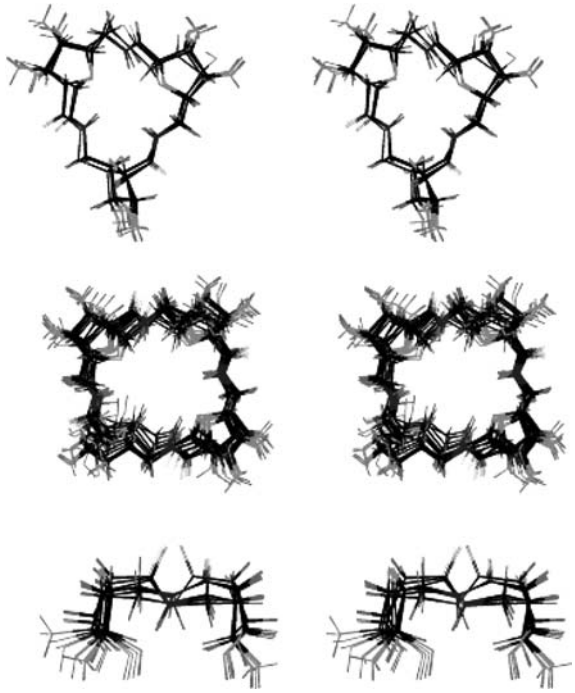
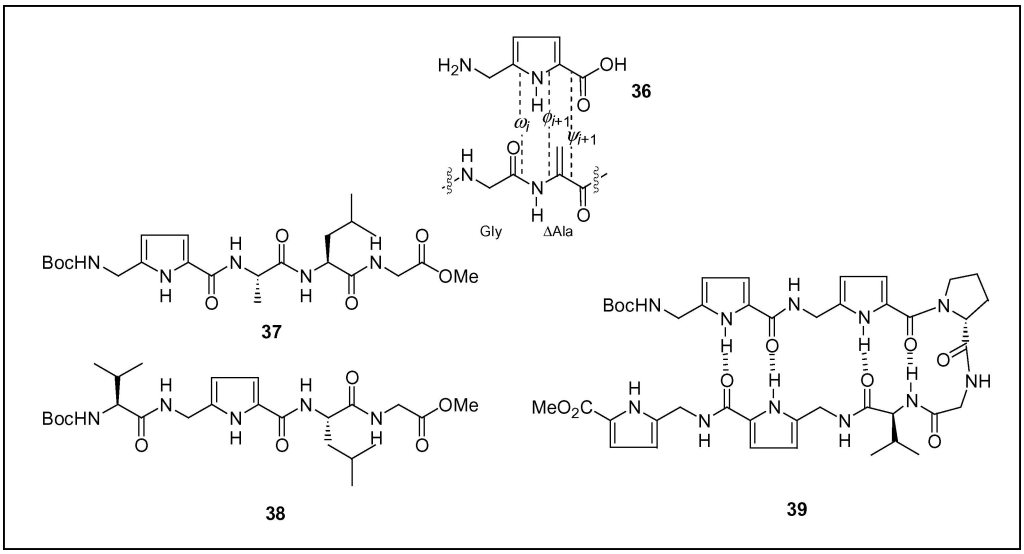


Figure 15. Superimposition of the energy-minimized structures sampled during the constrained MD simulations of **31** (top), **32** (middle) and **34** (bottom).

We have also designed pyrrole amino acid **36** that are structurally similar to furan amino acids **29** and used it as a conformationally constrained surrogate of the Gly-ΔAla dipeptide isostere in peptidomimetic studies leading to the synthesis of compounds **37**-**39** (Scheme 8) [31,32].

The rigid scaffold of the pyrrole amino acid forces compounds **37** and **38** to adopt structures, in $CDCl_3$, that can possibly be attributed to a γ-turn type structure involving intramolecular hydrogen bonding between the pyrrole NH and the carbonyl of the previous residues [31]. On the other hand, compound **39** with a centrally located type II′ β-turn nucleating D-Pro-Gly motif and repeating units of Paa dimers at both N- and C-termini, adopted a well-defined β-hairpin conformation in nonpolar solvent, like $CDCl_3$. The D-Pro unit with a φ value of $+60 \pm 20^\circ$ induced the expected reverse turn in the strand that was further stabilized by noncovalent interactions facilitated by the near planar disposition of the Paa-dimers at both ends leading to the nucleation of the hairpin architecture [32].



Scheme 8. Pyrrole amino acid **36** and peptides based on it.

Conclusions

Sugar amino acids are fast emerging as an important class of multifunctional molecular scaffolds that can find wide range of applications. Besides being used in peptidomimetics as rigid templates capable of inducing secondary structures in peptides, the various functional groups on each of these sugar amino acids, specially their amino and carboxyl termini can serve as adapters for solid-phase synthetic methods providing opportunities to create libraries of multifaceted molecules that may emulate diversities of biopolymers. Besides, the cyclic oligomers developed by us that can be moulded to build predisposed cavities of precise dimensions are expected to provide useful tools as novel synthetic receptors to study diverse molecular recognition processes. The nonproteinogenic properties of sugar amino acids will make compounds having them physiologically more stable. Optimum utilization of the molecular diversities of sugar amino acids and the efficiency and speed of solid-phase chemistry will lead to the development of more and more bioactive molecules.

As the demand for discovering new molecules is increasing day by day, the need to explore new methods to create them at much faster rate is felt today more than ever before. Designing molecules on chemists' blackboard, bringing them into existence by synthesizing them in the laboratory, studying the three dimensional structures and properties of these "Designer Molecules" hold lots of promises for the future of organic synthesis.

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