Sugar amino acids and related molecules: Some recent developments

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Abstract.   To meet the growing demands for the development of new molecular entities for discovering new drugs and materials, organic chemists have started working on many new concepts that can help to assimilate knowledge-based structural diversities more efficiently than ever before. 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. In recent years, sugar amino acids have been used extensively in the area of peptidomimetic studies. Advances made in the area of combinatorial chemistry can provide the necessary technological support for rapid compilations of sugar amino acid-based libraries exploiting the diversities of their carbohydrate frameworks and well-developed solid-phase peptide synthesis methods. This perspective article chronicles some of the recent applications of various sugar amino acids, furan amino acids, pyrrole amino acids etc. and many other related building blocks in wide-ranging peptidomimetic studies.

Keywords.   Sugar amino acids; furan amino acids; pyrrole amino acids; peptides; NMR; molecular dynamics; hydrogen bonding.

1.   Introduction

The spectacular advances in chemistry in the last century, especially in the area of organic synthesis,[1,2] have given us the ability to design unnatural molecules, to predict their properties, and to build them in the laboratory, providing alternate ways to supplement the traditional methods of finding bioactive molecules from nature.[3–6] The traditional methods are not adequately equipped to rapidly assimilate new molecular structures, the increased demand for which is being critically felt today due to the alarming decline in the number of new chemical entities introduced every year as drugs in the past decade.[7] This has prompted chemists to work on alternate concepts to create new molecules in the laboratory to meet theirs growing demands. The expertise gained over the years in the areas of organic synthesis, biological sciences, the advances made in spectroscopic and computational methods, rational drug-design concepts etc. are cleverly orchestrated to create *de*

novo designer structures to provide leads in discovering new drugs as well as new materials.[8] However, the failure of the new techniques, like combinatorial chemistry and high throughput screening processes, to rapidly produce the much desired lead molecules in large numbers forced chemists to redefine their strategies.[7,9] The initial assumption that diversity relies on numbers is gradually being replaced today by generation of diversity based on detail knowledge of biological processes. It is being increasingly realized that, instead of creating abstract molecules in millions, it is better to design new molecules by emulating the basic principles followed by Nature to build its vast repertoire of biomolecules. The fundamental building blocks used by nature, like amino acids, sugars and nucleosides, can be amalgamated to produce nature-like, and yet unnatural, structural entities with multifunctional groups anchored on a single ensemble, based on which new molecules can be created.

Sugar amino acids represent an important class of such designer templates that have found an important place in the area of peptidomimetic studies. The

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emergence of these molecules as versatile and multifunctional synthetic building blocks has been reviewed by us and others few years back.[10] In this perspective article, we wish to chronicle further developments in the wide-ranging applications of sugar amino acids and related building blocks in designing molecules since then.

The sugar amino acids have a general structure **1** as shown in figure 1. 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- or 2,6-anhydro sugar frameworks. There are several advantages of sugar amino acids as building blocks.

(1) The rigid furan and pyran 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 several 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.

The versatilities of these hybrid molecules named sugar amino acids, which were first reported in 1955,[11] and used in few occasions as peptide building blocks thereafter,[12] were essentially first demonstrated in 1994 by Kessler who used pyranoid sugar amino acids to make analogs of Leu-enkephalin and somatostatin.[13] The details of that study were later
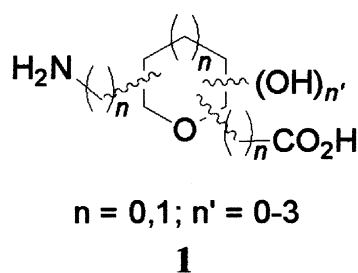
reported by them in 1996.[14] In our laboratory, we focused our attention on the uses of furanoid sugar amino acids (**2** in figure 2) in related studies[15] and these were synthesized following a novel reaction path in which the oxidation of a primary hydroxyl group in a hexose-derived acyclic aziridinyl compound with pyridinium dichromate was accompanied by an interesting rearrangement involving 5-exo S_{N2} opening of the terminal aziridine ring by *g*-benzyloxy oxygen with concomitant debenzylation, leading to the furanoid framework of sugar amino acids (see figure 3).[15] However, the credit for the first synthesis of furanoid sugar amino acids, to the best of our knowledge, goes to Merrer and coworkers who reported their preparation by a different route in
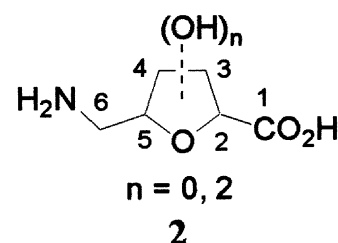

Figure 2. The general structure of the furanoid sugar amino acids used by us.
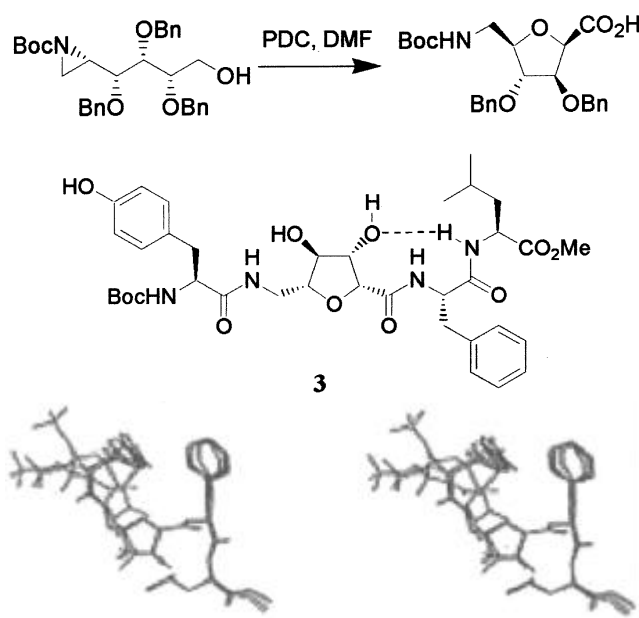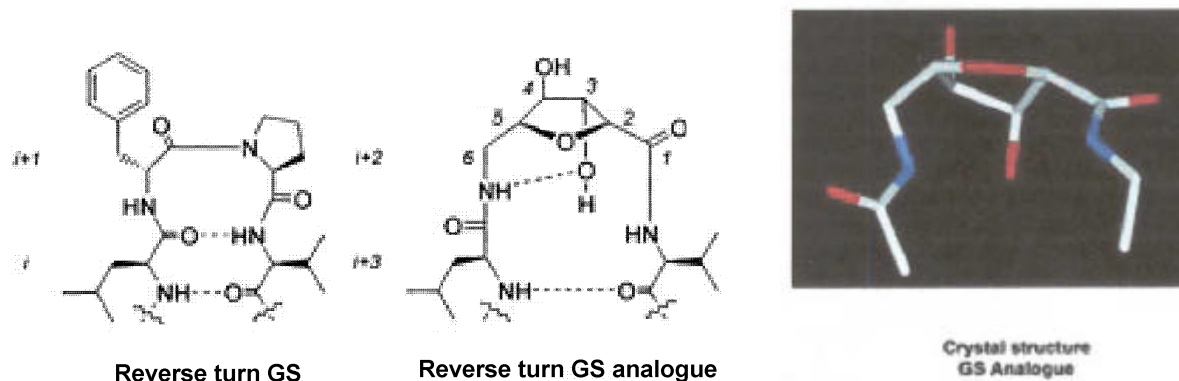

Figure 3. Synthesis of Gaa from its linear precursor (top), Gaa containing Leu-enkephalin analog **3** (middle) and the stereo view of the superimposed energy-minimized structures (bottom) sampled during the constrained MD simulations of **3**.[15]

Figure 1. The general structure of sugar amino acids.

Figure 4. Gaa containing gramicidin S analog **4** and its crystal structure.[19] (Crystal structure has been reprinted with permission from *J. Am. Chem. Soc.* (2004) vol. 126(11), pp 3444–46, © 2004, American Chemical Society.)
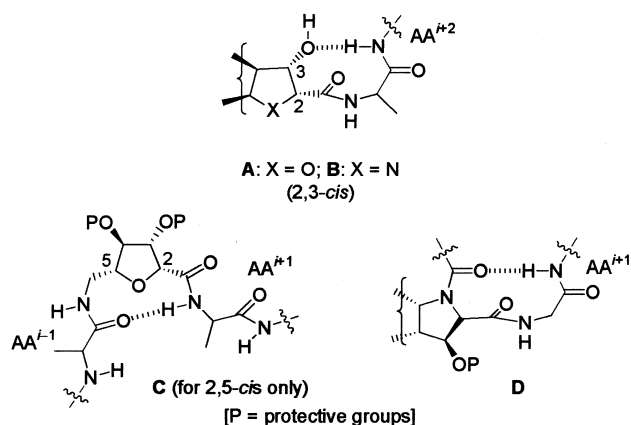

Figure 5. General trends of the intramolecular H-bond forming propensities of the 2,5-anydro (**A** and **C**) and 2,5-imino (**B** and **D**) furanoid sugar amino acid containing peptides: **A** and **B** with free OH and 2,3-*cis* relationship only; **C** with protected-OH, 2,3-*cis* or *trans* and 2,5-*cis* isomers only; **D** with protected-OH and 2,3-*cis* or *trans* isomer.

1995.[16] Many other methods for the synthesis of both furanoid and pyranoid sugar amino acids have been developed by various groups and discussed in detail earlier.[10]

2. Sugar ring OHs as H-bond acceptors in furanoid sugar amino acids

What distinguishes furanoid sugar amino acids from their pyranoid counterparts is the propensity of the ring hydroxyls in the former to participate in intramolecular hydrogen bonds with the main chain amides.

This was first demonstrated by us by inserting a glucose-derived furanoid sugar amino acid Gaa into the Gly–Gly segment of Leu-enkephalin to give an analog **3** (figure 3) that had structure very similar to the bioactive conformation of Leu-enkephalin. It was concluded by us based on extensive structural analysis of various peptidomimetic molecules containing furanoid sugar amino acid scaffolds that the free hydroxyl groups on sugar rings prevent short linear peptides containing these molecules from adopting regular *b*-turn structures as these hydroxyl groups themselves act as hydrogen bond acceptors. Free hydroxyl groups on carbohydrate rings form intramelecular hydrogen bonds with adjacent hydroxyls, but in most of the cases they act as both H-bond donor and acceptor in the same molecule.[17] Amino acids with hydroxyl groups in their side-chains (serine, threonine) serve as acceptors only about 30% of the time.[18] Moreover, an H-bond between main-chain NH → side-chain OH leading to this type of turn structure is also very rare, mainly because of the free rotation about c_1 in these amino acids. In sugar amino acids, unlike in serine and threonine, the hydroxyls are conformationally restricted forcing them to participate in the formation of unusual secondary structures. Our finding has recently been corroborated by Overhand *et al*[19] who have reported that in the X-ray structure (figure 4) of a furanoid sugar amino acid containing gramicidin S analog **4** (figure 4), an intramolecular hydrogen bond between the sugar ring **OH** and the **GaaNH** helps the molecule to adopt a well-defined reverse-turn structure.
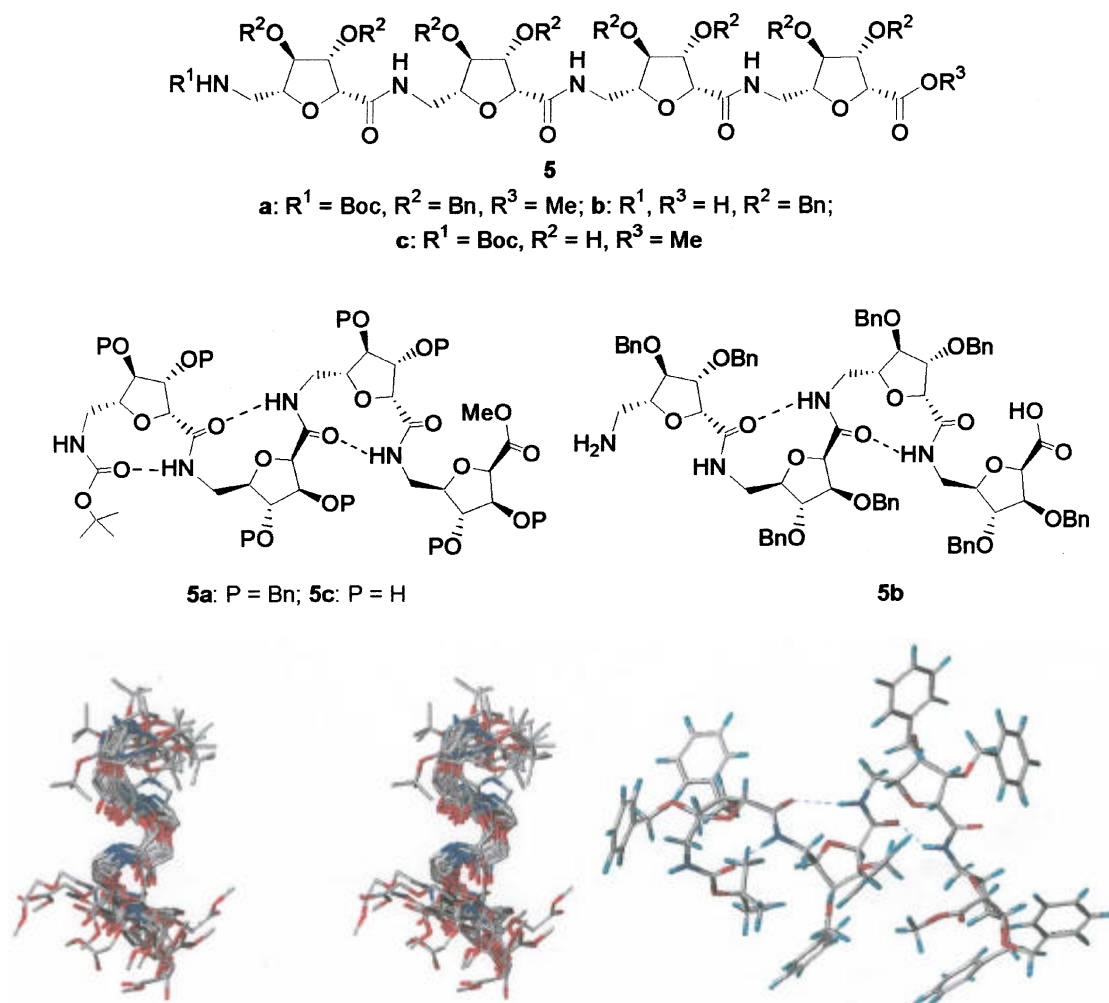
Figure 6. Linear tetramers of Gaa **5** (**top**) and their structures determined by NMR and constrained MD studies. **Middle**: Schematic representation of the proposed consecutive 10-membered **b**-turn like structures of **5**; **Bottom-left**: Stereo view of the backbone-superimposed energy-minimized structures of **5a**, sampled during the constrained MD simulation studies (for clarity, the C3 and C4 atoms of the sugar rings carrying the O-Bn groups are not shown); **Bottom-right**: Full view of the energy-minimized structure of one of the samples from the MD studies of **5a**.[20]

Based on the conformational studies carried out by us and others, today we can generalize the structural preferences in peptides containing furanoid sugar amino acids and their imino-congeners as shown in figure 5. Peptides with 2,5-anhydro furanoid sugar amino acids **A** (figure 5), or having their imino congeners **B**, adopt 9-membered pseudo *â*-turn structures in which the AA^{i+2}-NH form intramolecular hydrogen bond with the AA^i (Saa) ring hydroxyl, C3-OH, only when the ring hydroxyl groups are free and have a *cis*-relationship with the adjacent carboxyl function, i.e. in 2,3-*cis* sugars.

However, when these ring hydroxyls are protected, or even absent as in their 3,4-dideoxy versions,

the peptides containing these scaffolds show the propensity to form regular **b**-turn structures stabilized by intramolecular hydrogen bond between AA^{i+1}-NH $\rightarrow AA^{i-1}$-CO (AA^i is Saa) in those with 2,5-anhydro sugars having either 2,3-*cis* or *trans*, but strictly a 2,5-*cis* relationship (**C** in figure 5) and between AA^{i+2}-NH   pyrrolidine-N-CO in 2,5-imino sugar containing peptides having either 2,3-*cis* or *trans* orientation (**D** in figure 5).

In the Gaa homooligomers **5** (figure 6),[20] even when the ring hydroxyls are free they do not participate in intramolecular H-bonds, like in **A** in figure 5, because the AA^{i+2}-NH is absent in these molecules. They, however, form the regular **b**-turn structures as

shown in figure 6 with intramolecular hydrogen bond between $Gaa^iNH \rightarrow Gaa^{i-2}CO$, irrespective of whether the hydroxyls are free or protected, provided the Saa units maintain the required 2,5-*cis* relationship. Detailed NMR and constrained molecular dynamics (MD) simulation studies support the presence of consecutive 10-membered *b*-turn like structures in **5**, which resemble a helical conformation throughout the molecule. Similar structures with repeating *b*-turns were found earlier by Fleet and co-workers in their conformational studies with the acetate and acetonide protected oligomers of Gaa and other Saa with 2,5-*cis* junctions, the details of which have been recently reported.[21]

Similar structures are expected for the homooligomers of other "2,5-*cis*" furanoid sugar amino acids and also possibly in those furanoid sugar amino acid-containing peptides with no AA^{i+2} amide proton. This generalized concept as detailed above is very helpful in designing analogs of biologically active peptides based on these multifunctional scaffolds and mimic their secondary structures.

Further guidance for designing sugar amino acid containing analogs of small peptides to mimic their bioactive conformations can be provided by the finer details of the structural elements, especially the propensities of the *j*, *y* torsional angles shown by various sugar amino acids in these peptides, which could be generalized based on the conformational studies, already carried out by us and others, of many such substrates. For example, the *j*, *y* torsional angles of **Gaa** and some other furanoid sugar amino acids in various peptidomimetic analogs whose structures were studied by us are shown in table 1.

It was observed by us earlier[15] that in the four average structures (like **A** in figure 5) of Leu-enkephalin analog Boc–Tyr–Gaa–Phe–Leu–OMe **3** (figure 3) obtained during its constrained MD studies, *y*(Tyr) and *j*$_1$(Gaa) variations are coupled and two of the four average structures show flip in the corresponding amide plane (figure 3). The *y*(Tyr) and *j*$_1$(Gaa) of the first two are around –80° and 85° respectively, while the same for both the 3rd and the 4th are around 105° and –92° respectively. Thus, the flip of the amide bond takes place due to Gaa through a 180° change of sequential *y* and *j* dihedral angles. Such flips are responsible for changes in conformations of proteins through switch in turn structures. The *j*, *y* torsional angles of the corresponding Iaa containing analog, Boc–Tyr–Iaa–Phe–Leu–OMe, in its five average structures obtained
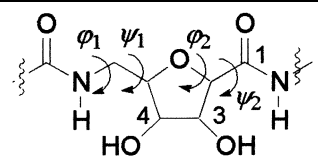
during the MD studies do not show any amide bond flip as is observed in the Gaa-based analog.[15]

In the regular *b*-turn structures (like **C** in figure 5) with protected ring hydroxyls as in compound **5a**, Gaa displays *j*, *y* torsional angles –81·2, 62·7, −133·7, 4·1.[20] More interestingly, in a related study recently carried out by us (last two entries in table 1), and the results of which are yet to be published, the dideoxy sugar amino acid (2*S*,5*R*)-ddSaa displays torsional angles −96·6, 149·0, 110·0, −14·3, which are, to a certain extent, comparable to those for an ideal type II *b*-turn, −60, 120, 80, 0. Insertion of (2*S*,5*R*)-ddSaa is, thus, expected to induce structures having *j*, *y* torsional angles in the *b*-region of the Ramachandran plot. The (2*R*,5*S*)-ddSaa, on the other hand, have *j*, *y* torsional angles similar to those displayed by **5a**, having the same stereochemistries at 2- and 5-positions of the sugar ring. Similar information about the structural preferences shown by other members of the family helps in choosing the appropriate sugar amino acid to mimic the receptor-bound conformations of small peptides.
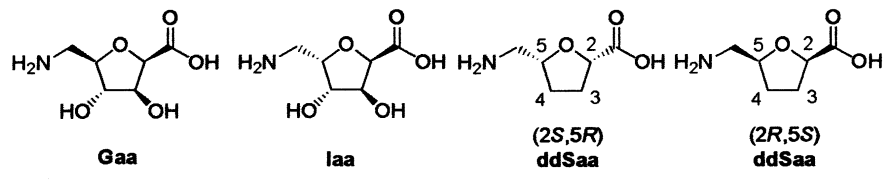
3. Changes in the ^{1}H NMR chemical shifts of the ring hydroxyl protons due to the participation of the hydroxyl oxygens in H-bondings

Another interesting observation made for the first time by us was that the chemical shifts of the protons of the ring hydroxyl groups involved in the intramolecular hydrogen bonds, as depicted in **A** and **B** in figure 5, consistently show significant downfield shifts by up to 0·6 ppm in DMSO-d_6 in the ^{1}H NMR spectra of the furanoid sugar amino acid containing peptidomimetic molecules compared to the chemical shifts of the non-hydrogen bonded hydroxyl protons present on the same sugar ring. The downfield shifts of the H-bonded hydroxyl protons are probably due to the decreased electron density on the hydroxyl hydrogens when the oxygen atoms act as H-bond acceptors to the amide protons. The extent of the downfield shift of the proton signal of the H-bonded OH is directly dependent on the strength of the H-bond, measured by the temperature coefficients of the amide proton chemical shifts ($\Delta d/\Delta T$). Lower the value of the temperature coefficient, stronger is the H-bond and consequently, the larger is the downfield shift of the OH proton signal. The ^{1}H NMR chemical shifts, in DMSO-d_6, of the protons of H-bonded and non-H-bonded hydroxyl groups in

Table 1. The average φ,ψ torsional angles of Gaa and some other furanoid sugar amino acids in various peptidomimetic analogs.

Furanoid sugar amino acid
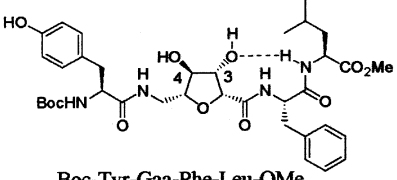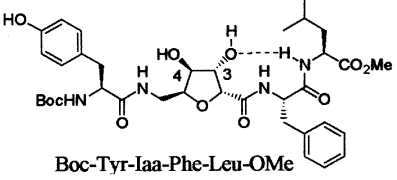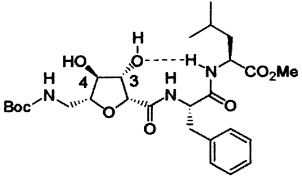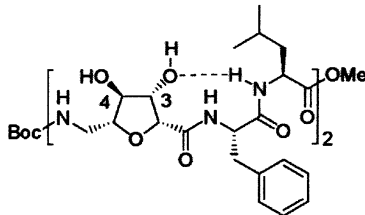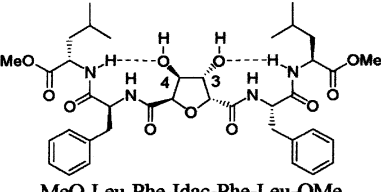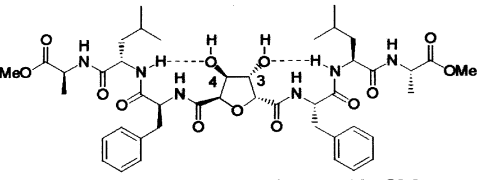
		Torsional angles (in degrees)		
	φ_1	ψ_1	φ_2	ψ_2
Compound **3** containing **Gaa** and with structure as in **A** in figure 5 (ref. 15)				
1st av. structure	80·4	52·9	−153·8	22·1
2nd av. structure	98·1	58·7	−151·8	26·3
3rd av. structure	−93·2	58·8	−127·4	29·1
4th av. structure	−90·9	59·1	−147·2	25·7
Analog of **3** containing **Iaa** and with structure as in **A** in figure 5 (ref. 15)				
Av. values	104·2	−61·4	−105·3	21·0
Compound **5a**, **Gaa** tetramer with structure as in **C** in figure 5 (ref. 20)				
Av. values	−81·2	62·7	−133·7	4·1
Leu–Met-(3,4-dideoxy Saa)-Thr–Tyr–Leu–Lys containing (2*S*,5*R*)-**ddSaa** and with structure as in **C** in figure 5				
Av. values	−96·6	149·0	110·0	−14·3
Leu–Met-(3,4-dideoxy Saa)-Thr–Tyr–Leu–Lys containing (2*R*,5*S*)-**ddSaa** and with structure as in **C** in figure 5				
Av. values	−93·2	61·1	−104·2	3·9

various molecules whose structures have been studied and the temperature coefficients ($\Delta\delta/\Delta T$) of their H-bonded amide proton chemical shifts, wherever they are available, are listed in table 2. It should be noted here that these hydroxyl proton signals are not well detected in CDCl$_3$. To the best of our knowledge, no such finding has been reported earlier on the characteristic downfield shifts of the protons of intramolecularly hydrogen-bonded hydroxyls.[22]

While the amide protons as H-bond donors can be identified easily by variable temperature studies, it is not always easy to locate their correspondi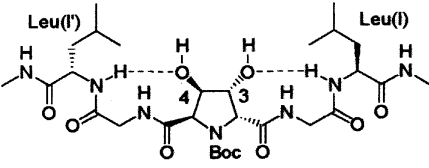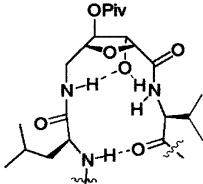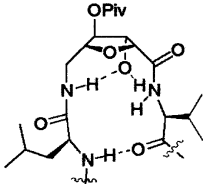ng donors by any direct evidence. The downfield shifts of the hydroxyl protons described here are a very useful diagnostic tool, which, together with the characteristic ROE cross-peaks, can help to establish if such ring hydroxyl groups as in sugar amino acids are indeed involved in intramolecular hydrogen bonding or not. For example, as already stated above in the Gaa homooligomers,[20] even when the ring hydroxyls are free they do not participate in intermolecular H-bond, like the one in **A** in figure 5, because the AA^{i+2}-NH is absent in these molecules. This is evident from the ^{1}H NMR spectrum of Boc-(Gaa)$_4$-OMe **5c** (figure 6) in DMSO-d_6 that does not show any noticeable downfield shift of any of its OH proton signals, which appear in the range of 5·06–

Table 2. Comparison between the ^{1}H NMR chemical shifts of the H-bonded and non-H-bonded hydroxyl hydrogens and the temperature coefficients ($\Delta d/\Delta T$ in ppb/K) of the H-bonded amide protons in furanoid sugar amino acids containing peptides, ~ 2–10 mM in DMSO-d_6.

Peptides	[1]H chemical shift of the H-bonded OH proton (*d*) and $\Delta d/\Delta T$ (ppb/K) of the H-bonded amide proton	[1]H chemical shift of the non H-bonded OH proton (*d*)	Ref.
 Boc-Tyr-Gaa-Phe-Leu-OMe	5·97 (Gaa C3-O*H*) $\Delta d/\Delta T$ (ppb/K) of LeuNH = −1·3	5·34 (Gaa C4-O*H*)	15
 Boc-Tyr-Iaa-Phe-Leu-OMe	5·71 (Iaa C3-O*H*) $\Delta d/\Delta T$ (ppb/K) of LeuNH = −2·0	5·26 (Iaa C4-O*H*)	15b
 Boc-Gaa-Phe-Leu-OMe	5·89 (Gaa C3-O*H*) $\Delta d/\Delta T$ (ppb/K) of LeuNH = −1·7	5·29 (Gaa C4-O*H*)	23
 Boc-(Gaa-Phe-Leu)₂-OMe	5·49 (GaaI C3-O*H*) $\Delta d/\Delta T$ (ppb/K) of LeuINH = −2·7 5·59 (GaaII C3-O*H*) $\Delta d/\Delta T$ (ppb/K) of LeuIINH = −2·2	5·18 (GaaI C4-O*H*) 5·18 (GaaII C4-O*H*)	23
 MeO-Leu-Phe-Idac-Phe-Leu-OMe	5·99 (Idac C3, C4-O*H*) C_2-symmetric $\Delta d/\Delta T$ (ppb/K) of LeuNH = −1·2		15b, 24
 MeO-Ala-Leu-Phe-Idac-Phe-Leu-Ala-OMe	5.96 (Idac C3, C4-O*H*) C_2-symmetric $\Delta d/\Delta T$ (ppb/K) of LeuNH = −2·8		24

Table 2. (*Continued*)

Peptides	^{1}H chemical shift of the H-bonded OH proton (*d*) and $\Delta d/\Delta T$ (ppb/K) of the H-bonded amide proton	^{1}H chemical shift of the non H-bonded OH proton (*d*)	Ref.
	5·75 (sugar C3-O*H*) $\Delta d/\Delta T$ (ppb/K) of Leu(I)NH = −3·4 5·83 (sugar C4-O*H*) $\Delta d/\Delta T$ (ppb/K) of Leu(I′)NH = −3·5		25
	5·90 (sugar C3-O*H*)		19

5·27 ppm, except the C-terminal Gaa(IV)C3-O<u>H</u> proton.[20] The C-terminal Gaa(IV)C3-O<u>H</u> proton in this molecule resonates at 5·52 ppm, possibly due to an intramolecular 6-membered H-bond with the adjacent *cis*-ester group.

4. Furanoid and pyranoid *d*-sugar amino acids and their uses in peptidomimetic studies

Kessler and others[26] reported an improved method for the synthesis of pyranoid *d*-sugar amino acid **6** and used the same in the synthesis of cyclopeptides **7** (figure 7) by a combination of solid-phase synthesis and solution chemistry.[26] Structural analysis reveals that **6** does not act as a *b*-turn mimetic in the cyclopeptide, cyclo (**6**-L-Lys-**6**-D-Phe).

In our laboratory, we have carried out structural studies of a furanoid sugar amino acid based peptide Boc–Gaa–Phe–Leu–OMe **8** and its dimer Boc–(Gaa–Phe–Leu)$_2$–OMe **9** (figure 8).[23] In CDCl$_3$, they display very ordered structure with a repeating *b*-turn-type secondary structure at lower concentrations as shown in figure 8 and start forming aggregates that gradually turn into excellent organogels as the concentrations are increased, a phenomenon observed for the first time in sugar amino acid-containing peptides.
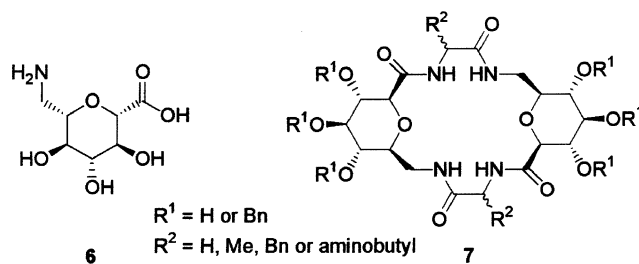

Figure 7. Pyranoid *d*-sugar amino acid **6** and the cyclopeptides **7** prepared from **6**.[26]

While scanning electron microscopic (SEM) analysis of the xerogels from **8** shows porous 3D structure (figure 9, left), SEM images of the gels from **9** (figure 9, right) reveal compact three-dimensional fibrous structures that are wavy and tend to form helices where they are loose.[23]

5. Cyclic homooligomers of furanoid and pyranoid *d*-sugar amino acids

In recent years, chemists have developed a large variety of oligomeric compounds that mimic biopolymers.[3–5,27,28] Such synthetic oligomers are composed of unnatural and yet nature-like monomeric building blocks assembled together by iterative syn-

thetic processes that are amenable to combinatorial strategies. The main objective in developing such oligomers is to mimic the ordered secondary structures displayed by 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.

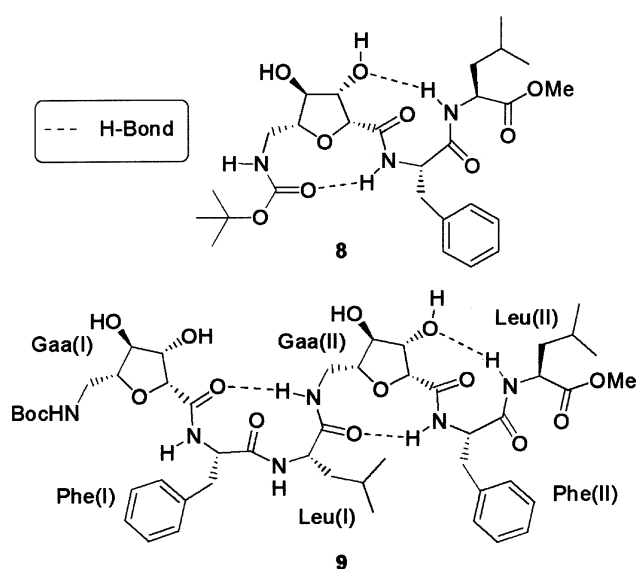In continuation of our work on designing sugar amino acid-based molecules, we were interested in

the synthesis and structural studies of acyclic and cyclic oligomers of furanoid sugar amino acids and related compounds. While the oligomerization of 6-amino-2,5-anhydro-6-deoxy-D-mannonic acid Maa and the structural studies of the oligomers were described earlier,[10a,b] structural studies of the linear oligomers of 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid Gaa[20] has been discussed here in detail above (figure 6). Next, we focused our attention on the synthesis of 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.

In our laboratory, the cyclic homooligomers of mannose-derived furanoid sugar amino acid Maa were synthesized following a novel reaction that converts the sugar amino acid monomer directly into its cyclic homooligomers **10** and **11** (figure 10).[29] The glucose-based sugar amino acid Gaa under the same reaction conditions gives a bicyclic lactam **12** as the major product. Cyclic homooligomers of Gaa were prepared by cyclizing their linear precur-

Figure 8. Glucose-derived furanoid sugar amino acid, Gaa-based peptide Boc–Gaa–Phe–Leu–OMe **8** and its dimer Boc–(Gaa–Phe–Leu)$_2$–OMe **9** and the schematic representation of their structures in CDCl$_3$.[23]
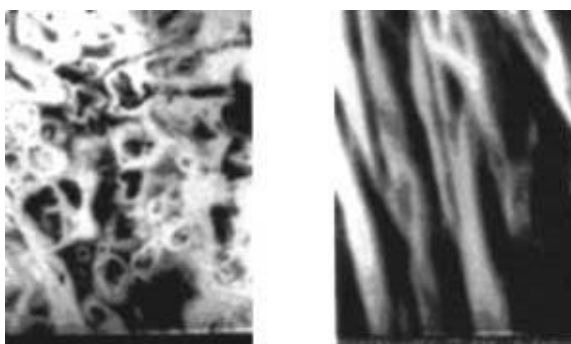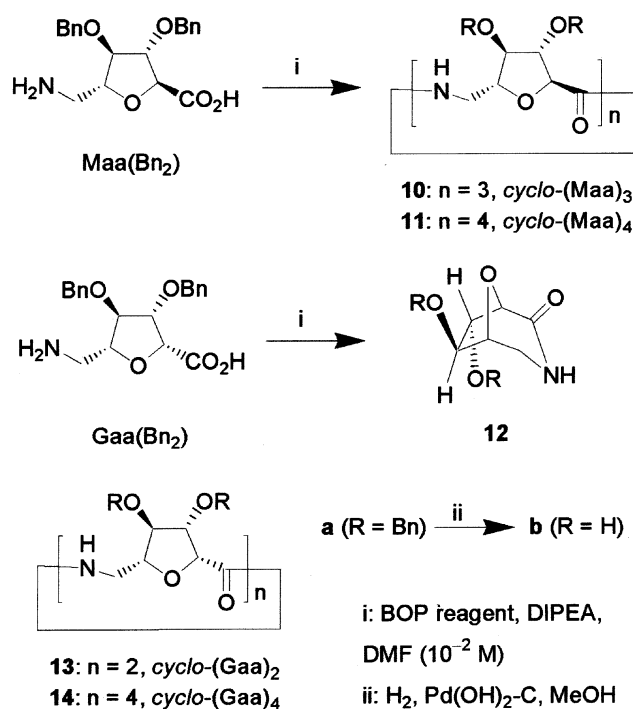

Figure 9. SEM pictures of xerogels from **8** (left) and **9** (right) in CHCl$_3$.[23]

Figure 10. Cyclic homooligomers of furanoid sugar amino acids.[29]

sors leading to the formation of cyclic peptides **13** and **14**. Addition of the bicyclic lactam **12** results in the influx of Na^+ ions across the lipid bilayer leading to the dissipation of valinomycin-mediated K^+ diffusion potential.[29]

Conformational analysis by NMR and constrained MD studies reveal that all the cyclic products have symmetrical structures. While in the Maa trimer **10** (figure 11, 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 **11** point into the ring and the carbonyls to the outside (figure 11, middle). In the Gaa dimer **13** (figure 11, bottom),
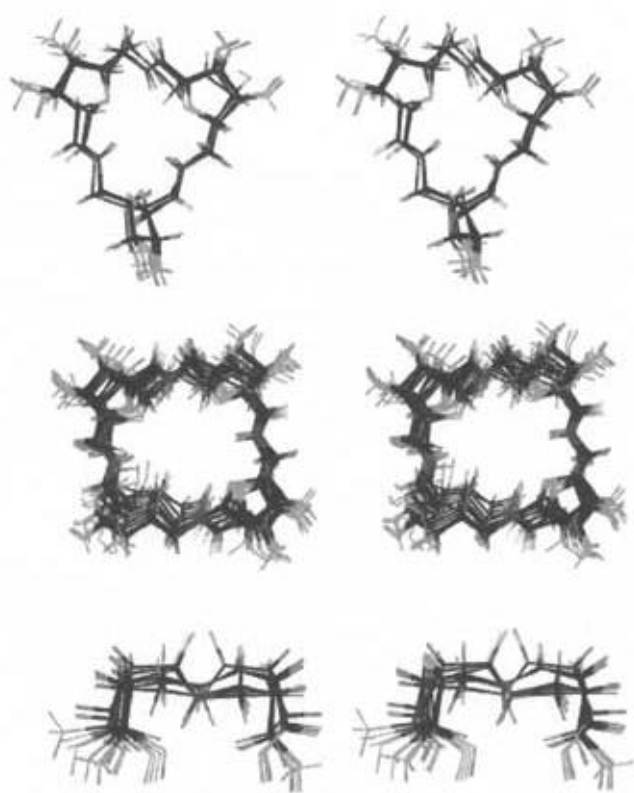
the 12-membered core ring is flanked on two sides by furanoid rings in which the C2-hydrogens and the COs can be seen on one side of the ring and the NHs point to the other side.

Earlier, cyclic homooligomers **15** (figure 12) of pyranoid *d*-sugar amino acid **6** were prepared by Kessler and others[30] by solid- and solution-phase coupling procedures. The compounds show interesting structural properties.[30] The molecular structure of the cyclic oligomer in the all-*syn* conformation for the trimeric sequence generates a hydrophilic exterior surface and a nonpolar interior cavity, which has a cyclodextrin-type molecular shape. Its all-*anti* conformation leads to a flat structure in which the characteristic sequence of alternating ether and amide linkages arranged in a symmetrical array make them ideal macrocyclic chelating agents as revealed by the NMR titration studies of the cyclic hexamer. Specifically, the decrease in the diffusion value of the benzoic acid in the presence of the cyclic hexamer suggests its action as cyclodextrin-like artificial receptor.

6. Furanoid and pyranoid *d*-sugar amino acids (*d*-Saa) with glycosyl amines

Sugar amino acids with glycosyl amines have been prepared by many groups: (i) by reacting a reducing sugar with ammonia or ammonium hydrogen carbonate; (ii) by reducing glycosyl azides; (iii) by acidic ring opening of an *a*-oxazoline.[31] Recently, van der Marel and Overhand's group has synthesized furanoid **16** and pyranoid *d*-Saa **17** (figure 13) bearing an amine group at the anomeric position using the Curtius rearrangement as the key step.[31] These scaffolds are inserted into Leu-enkephalin replacing its

Figure 11. Superimposition of the energy-minimized structures sampled during the constrained MD simulations of **10** (top), **11** (middle) and **13** (bottom).[29]
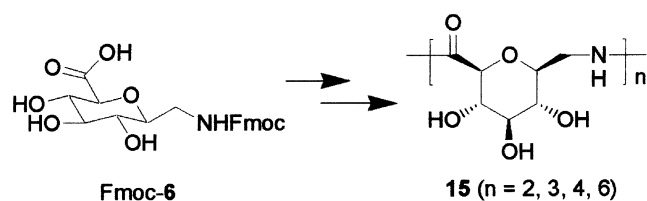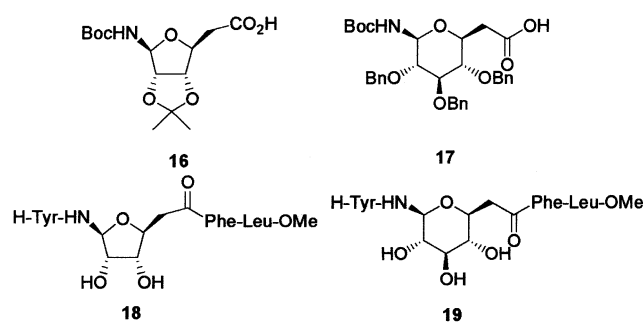

Figure 12. Cyclic homooligomers **15** of pyranoid *d*-sugar amino acid **6**.[30]

Figure 13. Sugar amino acids with glycosyl amines **16** and **17** used to make Leu-enkephalin analogs **18** and **19**, respectively.[31]
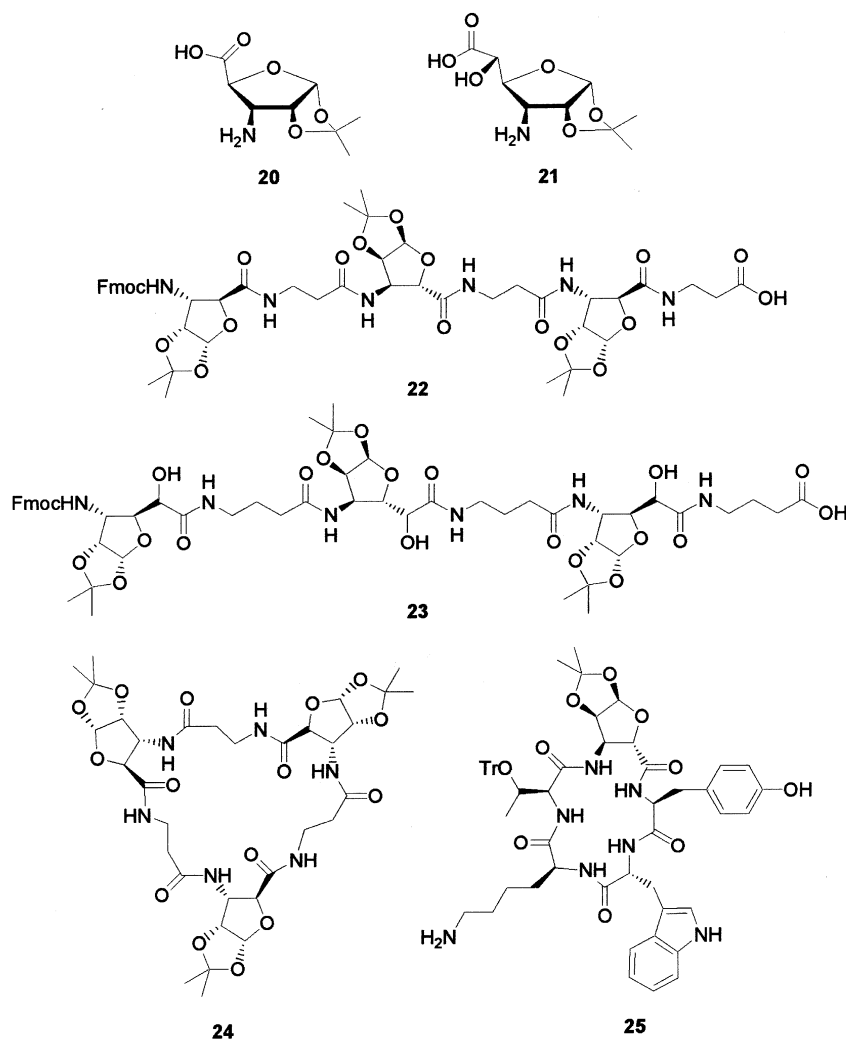
Figure 14. *b*- and *g*-Sugar amino acids (**20** and **21** respectively); the mixed, linear and cyclic oligomers from *b*-Saa and *b*-hGly (**22** and **24** respectively); the mixed, linear oligomer from *ã*-Saa and GABA (**23**) and the somatostatin analog **25** containing the *b*-Saa.[32,33]

Gly–Gly moiety. The resulting analogs **18** and **19** do not show any activity.

7. *b*- and *g*-sugar amino acids

Kessler and coworkers[32] reported the development of two new sugar amino acids – a *b*-Saa **20** and a *g*-Saa **21** (figure 14). The mixed, linear oligomer of *b*-Saa and *b*-hGly (*b*-homoglycine or *b*-alanine), Fmoc-[*b*-Saa-*b*-hGly]$_3$-OH **22** displays the 12/10/ 12-helical structure in CH$_3$CN as determined by NMR studies and subsequent simulated annealing and MD calculations. By contrast, the mixed linear oligomer of *g*-Saa and GABA (*g*-amino butyric acid), Fmoc-[*g*-Saa-GABA]$_3$-OH **23** does not form any stable conformation in solution. The cyclic oligomer

cyclo[*b*-Saa-*b*-Gly]$_3$ **24** exhibits a C_3 symmetric conformation on the NMR chemical shift time scale. Earlier, the *b*-Saa **20** was used by Kessler to prepare the somatostatin analog **25** that showed antiproliferative and apoptotic activity against both multi-drug-resistant and drug-sensitive hepatoma carcinoma cells.[33]

8. Furanoid and pyranoid *e*-sugar amino acids (*e*-Saa)

Overhand's group developed furanoid (**26**) and pyranoid (**27**) *e*-sugar amino acids that were used to prepare their cyclic homooligomers **28** and **29** respectively (figure 15).[34] An unrestrained simulated annealing technique was used to search the entire

conformational space in order to compare the conformational behaviour of these cyclic homooligomers. While the five-membered rings in the cyclic trimer in **28** flip between twist (north, $P = 0°$) and envelope (south, $P = 167°$) conformations, the pyranoid rings in **29** adopt chair conformations stabilized by the equatorial positions of all the hydroxy

groups. The trimer in **29** with pyranoid rings is less flexible than that in **28** with furanoid Saa. In both cyclic trimers the oxygen atoms in the sugar rings are located in their interior and the secondary hydroxyls are oriented outwards. The structure of the furanoid sugar amino acid trimer is compact and does not contain any water-accessible cavity. On the other hand, the pyranoid sugar amino acid trimer does possess a small cavity. Both the furanoid and pyranoid trimers have flat structures.

The furanoid **e**-Saa **26** was used to prepare some cyclic RGD peptidomimetic molecules **30–34** and a cyclic peptide **35** (figure 16) by solid-phase method using a cyclization-cleavage protocol.[35] These molecules were tested to ascertain their abilities to bind to the integrin receptors $a_v b_3$ and $a_{IIb} b_3$. The cyclic tetrapeptide **30** show the most promising activity in an inhibition assay with an IC_{50} of 1·49 *n*M for the $a_v b_3$ receptor and 384 nM for the $a_{IIb} b_3$ receptor. NMR-based molecular dynamics simulations and empirical calculations of the cyclic tetramer **35** show that it is conformationally restrained with the two Saa units adopting different conformations.[36] One of them forms an unusual turn, stabilized by an intra-residue nine-member hydrogen bond as shown in **36**
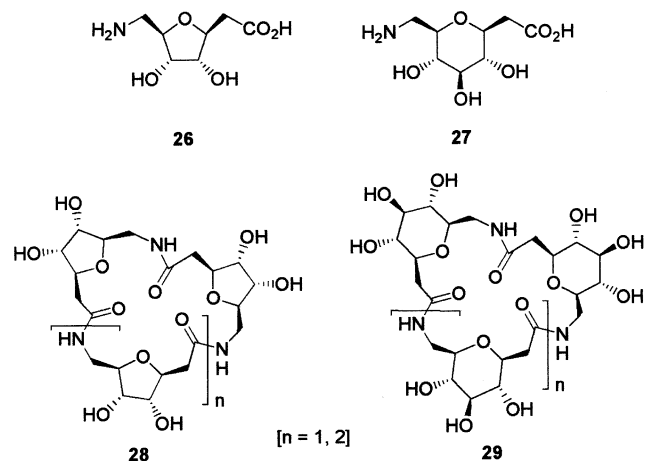

Figure 15. Furanoid and pyranoid **e**-sugar amino acids (**26** and **27** respectively) and their cyclic homooligomers (**28** and **29** respectively).[34]
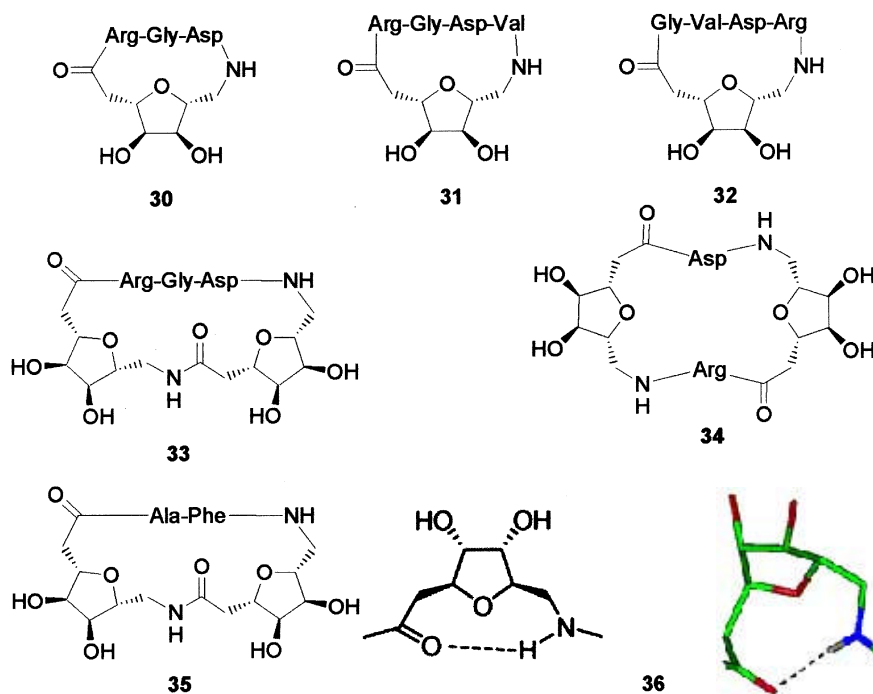

Figure 16. Cyclic RGD peptidomimetic molecules **30–34** and a cyclic tetramer **35** containing furanoid **e**-Saa **26** and the nine-member H-bonded ring structure **36**, nucleated in the cyclic peptides **30** and **35** by the furanoid **e**-Saa.[35,36] (Reprinted with permission from *Am. Chem. Soc.* (2003) vol. 125(36), pp 10822–29, © 2003 American Chemical Society.)
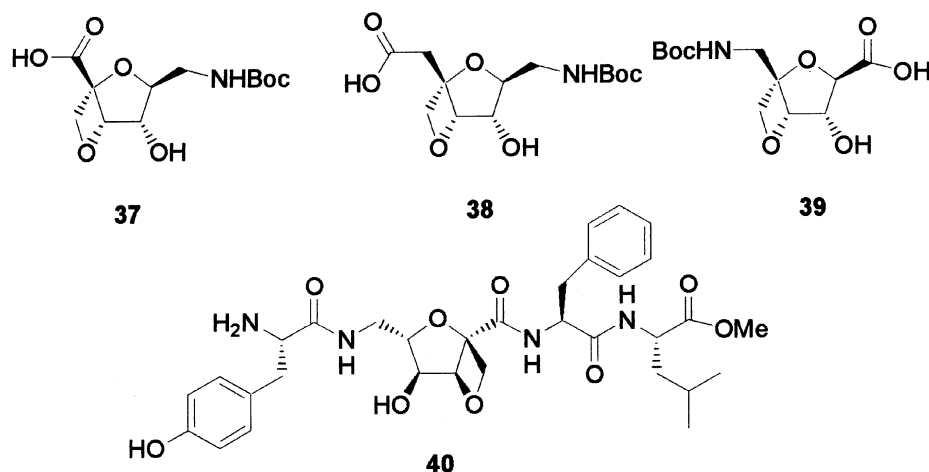
Figure 17. Bridged *d*- and *e*-sugar amino acids **37–39** and the Leu-enkephalin analog **40** containing the *d*-Saa **37**.[37]
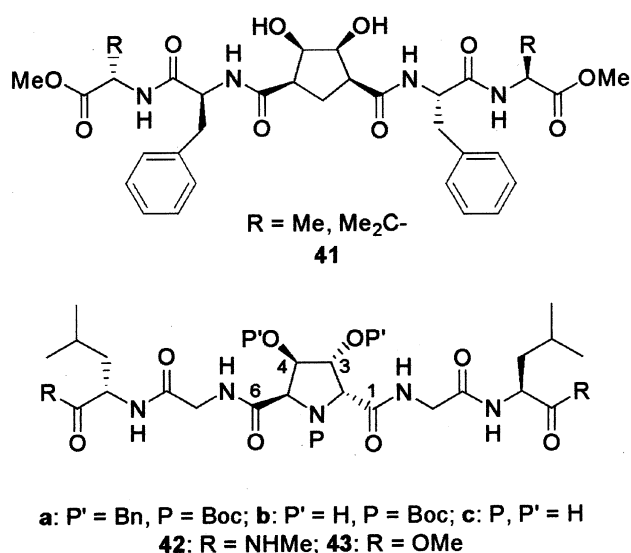

Figure 18. Structures of carbasugar diacid based peptidomimetic molecule **41** and its imino congener based compounds **42–43**.[25,38]

in figure 16. The X-ray crystal structure of **35** strongly resembles its solution conformation. Conformational analysis of the biologically most active RGD analog **30** also reveals the presence of **36**-type H-bonded structure in the molecule.[36]

9. Bridged *d*- and *e*-sugar amino acids

Overhand and van der Marel's group also reported the synthesis of conformationally constrained bridged *d*- and *e*-sugar amino acids **37–39** (figure 17) and one of them (**37**) was used in the synthesis of the Leu-enkephalin analog **40**.[37]

10. Peptidomimetic studies with carbasugar and imino sugar based molecules

Conformational analysis of the furanoid *d*-sugar amino acid based molecules, especially those with 2,5-anhydro framework, as summarized in figure 5, encouraged us to examine the structural behaviour of their carbasugar and 2,5-imino sugar-based congeners. Consequently, we undertook the synthesis and conformational analysis of the carbasugar and imino sugar-based molecules **41** and **42–43** respectively, as shown in figure 18.[38,25] While the former displays a structure which has a folded conformation involving an interstrand H-bond,[38] the latter show two different conformations that switch from one to the other depending on whether the ring hydroxyls are protected or not.[25] The design of the novel molecular framework of pyrrolidine dicarboxylic acid with bi-directional dispositions of "hydroxy-D-proline" moieties will enable us to study the conformational bias conferred by it when inserted in peptides. It is also expected to provide an insight into the role of the hydroxyl groups on the structures of hydroxyproline containing peptides.

Conformational analysis by NMR studies reveals that compounds **42b** and **42c** take interesting turn structures (C_2 symmetric for **42c**) in DMSO-d_6 consisting of identical intramolecular hydrogen bonds at two ends between LeuNH and sugar-OH, as depicted in structure **B** in figure 5 and depicted here schematically in figure 19, whereas **42a** displays structures with regular *b*-turns with hydrogen bonds between LeuNH and Boc-C=O in one half of their molecular framework (structure **D** in figure 5), char-

acteristic of the turn structures commonly observed in "D-Pro-Gly" containing peptides.[25] It is remarkable that the protection–deprotection of the hydroxyl groups on pyrrolidine ring can make these peptidomimetic molecules switch from one conformation to another that has the potential to lead to many useful applications.

The structures sampled during the restrained MD calculations based on the ROESY cross-peaks found
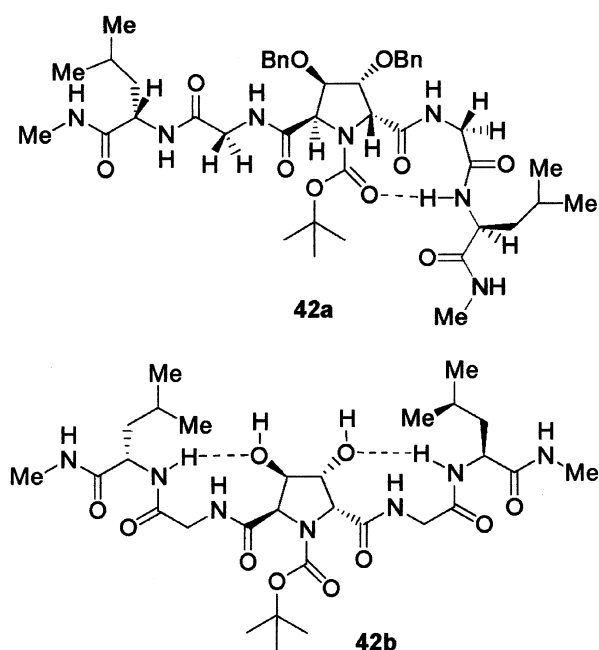

Figure 19. Schematic representation of the H-bonded structures in **42a** and **42b** with type II′ *b*-turn conformation as seen in D-Pro–Gly containing peptides in the former and pseudo *b*-turn involving 9-membered H-bonded structures on both sides of the pyrrolidine ring in the latter. Structure of **42c**, which is C_2-symmetric is similar to that of **42b**.

for **42b** in DMSO-d_6 reveal an ensemble of structures as shown in figure 20, where the two peptide chains form cyclic conformations at both ends involving hydrogen bonds between LeuNH and pyrrolidine-OH with fairly conserved structures observed in the central portion of the molecule and the variations localized mainly at the Leu side-chains.[25]

11. Furan and pyrrole amino acids

In connection with our work on furanoid sugar amino acid, we also developed some new peptide building blocks, for example, a novel furan amino acid, 5-(aminomethyl)-2-furancarboxylic acid **44**,[39] which was formed as a by-product during the preparation of the 3,4-dideoxy furanoid sugar amino acids. Subsequently, we prepared them in large quantities from D-fructose. We were interested in preparing cyclic homooligomers of this furan amino acid as it was envisaged by us that these cyclic homooligomers with structurally rigid molecular scaffolds could be moulded to build predisposed cavities of precise dimensions and thus provide attractive tools for studying diverse molecular recognition processes. The method that we followed for making these cyclic peptides is a novel cyclooligomerization process wherein the monomeric furan amino acid **44** is cyclized directly into its cyclic trimer **45** in 60–75% yield in a single step as shown in figure 21.[39] This avoids the lengthy stepwise assembling of linear precursors, the process conventionally followed for synthesizing similar cyclic products.

This novel 18-membered cyclic homooligomer **45** is found to be an excellent receptor for carboxylate binding having an association constant of $8.64 \times 10^3 \, \text{M}^{-1}$ for tetrabutylammonium acetate in acetonitrile.[39]

Figure 20. (**Left**) Stereoview of the 20 superimposed structures, sampled at 5 ps intervals during 100 ps MD simulations of **42b**, subsequently energy-minimized and superimposed aligning the hydrogen-bonded parts. (**Right**) Energy-minimized structure of one of the samples from MD studies.[25]

We have also designed pyrrole amino acid **46** which is structurally similar to furan amino acids **44** and used it as a conformationally constrained surrogate of the Gly-ΔAla dipeptide isostere in peptidomimetic studies leading to the synthesis of compounds **47–49** (figure 22).[40,41]
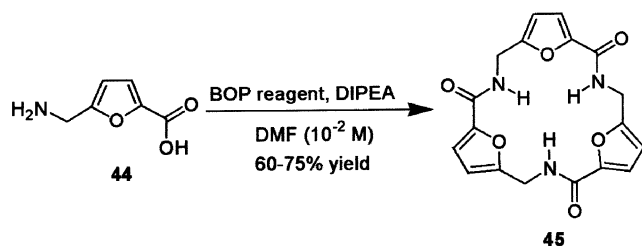

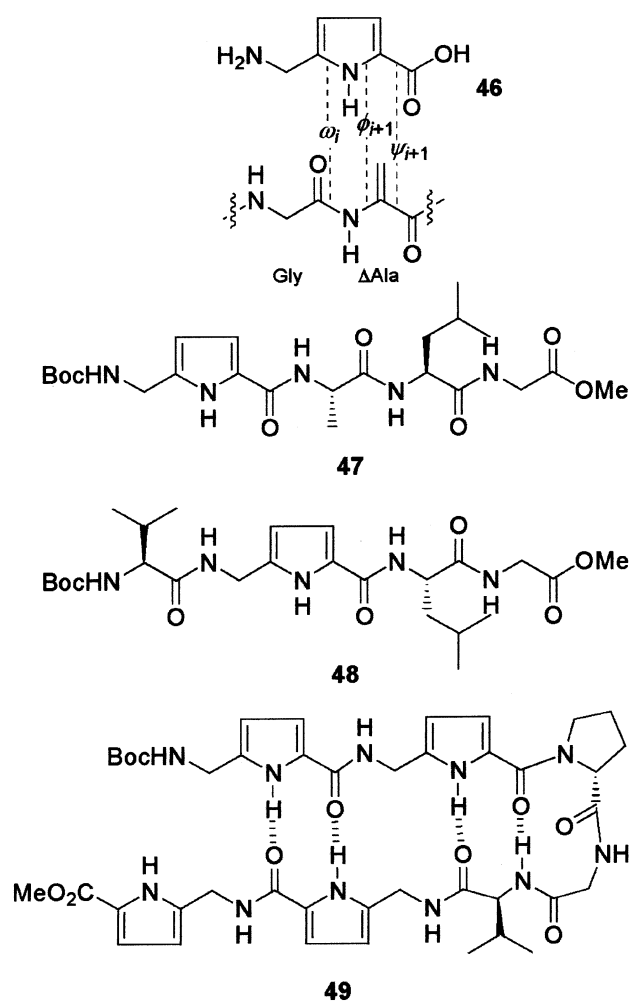**Figure 21.** Single-step cyclooligomerization of furan amino acid **44**.[39]

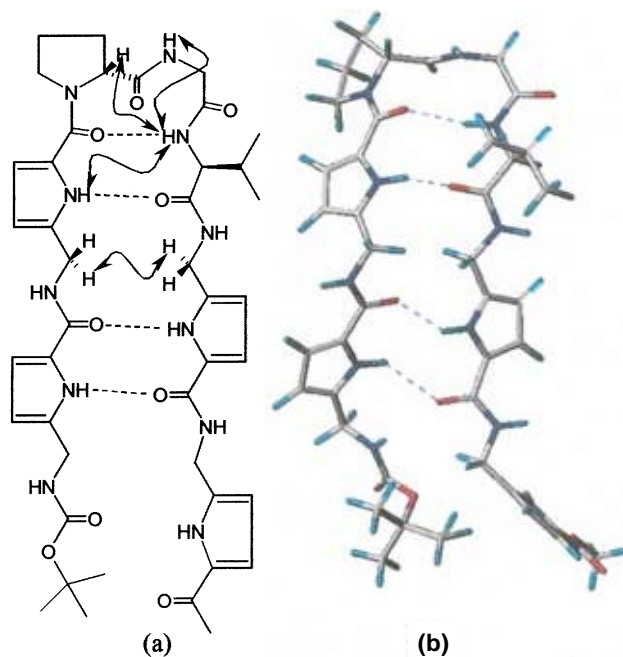**Figure 22.** Pyrrole amino acid **46** and peptides **47–49** based on it.[40,41]

Figure 23. (**a**) Schematic representation of the proposed structure of **49** with the long-range rOes seen in the ROESY spectrum. (**b**) One of the 50 energy-minimized structures of **49** sampled during the 300 ps simulated annealing MD studies.[41]
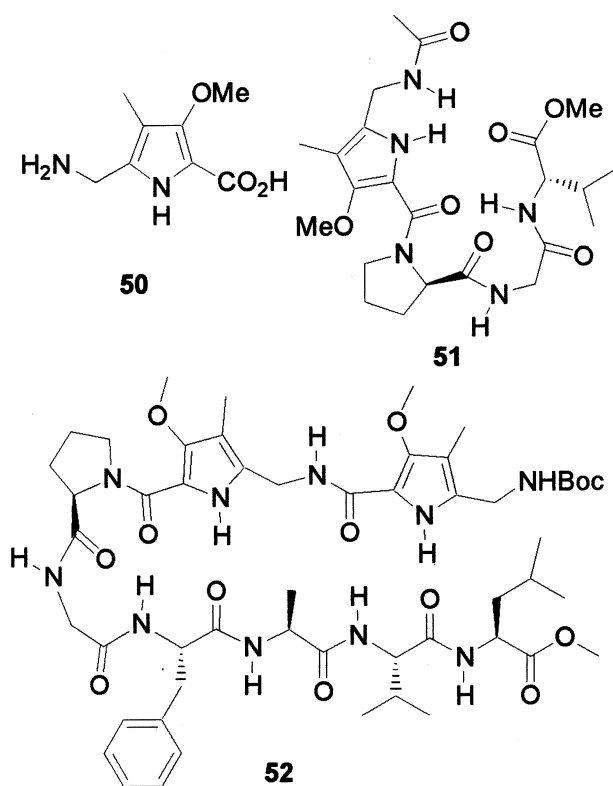

Figure 24. Methoxypyrrole amino acid **50** (MOPAS) and the peptides **51**, **52** based on it.[42]
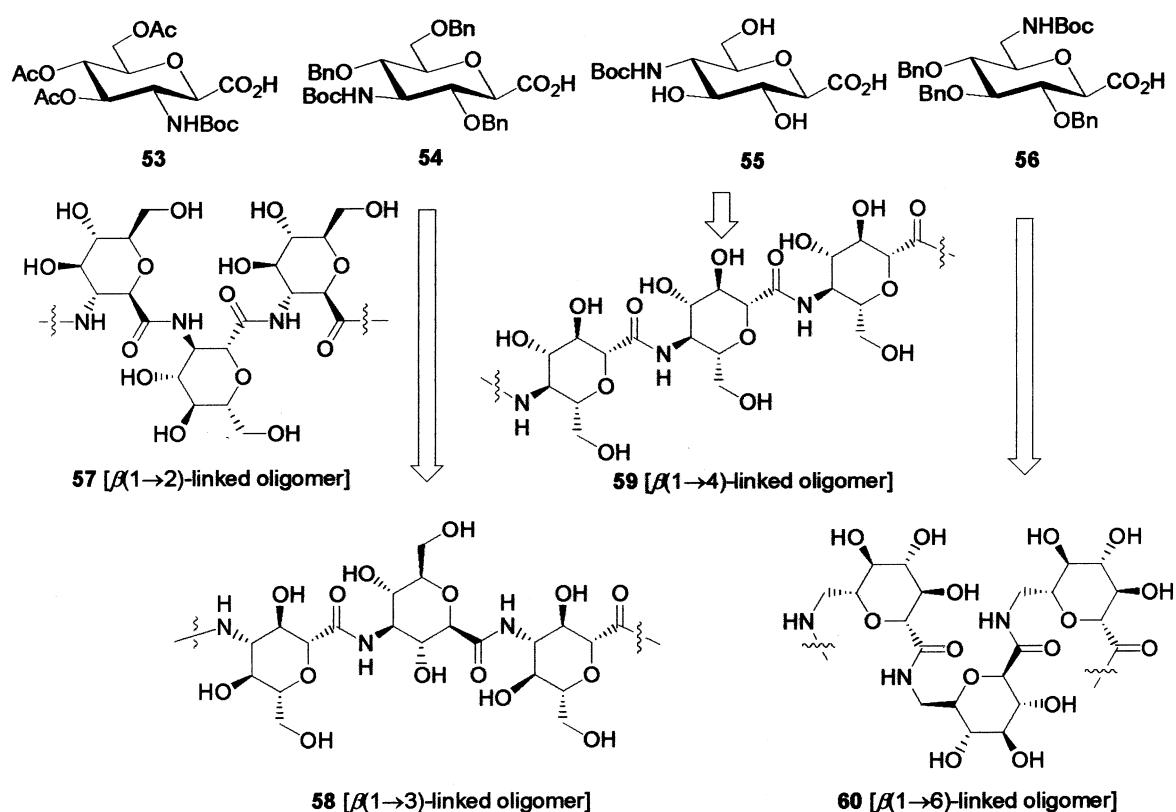
Figure 25. Pyranoid sugar amino acids **53–56** comprising of 2-amino-, 3-amino-, 4-amino- and 6-amino-Glc-*b*-CO$_2$H, respectively and their homooligomers, *b* (1 → 2)-linked **57**, *b* (1 → 3)-linked **58**, *b* (1 → 4)-linked **59**, and *b* (1 → 6)-linked **60**.[43]

The rigid scaffold of the pyrrole amino acid forces compounds **47** and **48** to adopt structures, in CDCl$_3$, that can possibly be attributed to a *g*-turn type structure involving intramolecular hydrogen bonding between the pyrrole NH and the carbonyl of the previous residues.[40] On the other hand, compound **49** with a centrally located type II′ *b*-turn nucleating D-Pro–Gly motif and repeating units of Paa dimers at both N- and C-termini, adopts a well-defined *b*-hairpin conformation in nonpolar solvents, like CDCl$_3$, as shown in figure 23. The D-Pro unit with a *j* value of + 60 ± 20° induces the expected reverse turn in the strand which is further stabilized by non-covalent interactions facilitated by the near planar disposition of the Paa-dimers at both ends leading to the nucleation of the hairpin architecture.[41]

Our work on pyrrole amino acid has recently been extended by König and others[42] who have prepared a substituted Paa, methoxypyrrole amino acids **50** (MOPAS) and introduced them into small peptides **51** and **52** with hairpin structures (figure 24). The intra- and intermolecular binding properties of this

heterocyclic amino acid mimicking a dipeptido, *b*-strand was investigated by NMR titration and X-ray crystal structure analysis. The data reveal a hydrogen-bonding pattern that is complementary to a peptide *b*-sheet.

12. Various other oligomers of sugar amino acids

Ichikawa's group prepared a series of pyranoid sugar amino acids **53–56** comprising 2-amino-, 3-amino-, 4-amino- and 6-amino-Glc-*b*-CO$_2$H respectively and constructed four types of homo-oligomers, *b*(1 → 2)-linked **57**, *b*(1 → 3)-linked **58**, *b*(1 → 4)-linked **59**, and *b*(1 → 6)-linked **60** (figure 25).[43] CD and NMR spectral studies of these oligomers suggested that only the *b*(1 → 2)-linked homo-oligomer **57** possesses a helical structure that seems to be pre-determined by the linkage position. Homo-oligomers with *b*(1 → 2)-linkages **57** and *b*(1 → 6)-linkages **60** were also subjected to O-sulphation, and these O-sulphated oligomers are found to be able, in a

linkage-specific manner, to effectively inhibit L-selectin-mediated cell adhesion, HIV infection, and heparanase activity without the anticoagulant activity associated with naturally occurring sulphated polysaccharides such as heparin.

Gervay-Hague's group synthesized ten N-Fmoc-protected pyranoid sugar amino acids that are amenable to solid-phase synthesis.[44] The same group has also recently reported the synthesis of N-Fmoc-protected sugar amino acids derived from *a*-O-methoxy- and 2,3-dehydroneuraminic acids and used them in the preparation of two series of linear oligomers **61** and **62** (figure 26) by solid-phase synthesis.[45] The (1 → 5)-linked amides of 2,3-dehydroneuraminic acid were further subjected to hydrogenation giving a third series of oligomers **63** with a *b*-hydride substituent at the anomeric carbon. A *C*-terminus *e*-amino caproic acid, a hydrophobic linker that diminishes solvation relative to a simple primary amide, was introduced in all these oligomers in order to prevent fraying of the terminal residue, which might disturb important hydrogen-bonding interactions required for stable secondary structure.

Fleet's group has used a furanose sugar amino acid as a library scaffold to illustrate their potential for derivatisation (figure 27).[46] The resulting 99-member library **64** contains three orthogonal points of diversification that allows easy access to ethers and carbamates from a hydroxy moiety, a range of
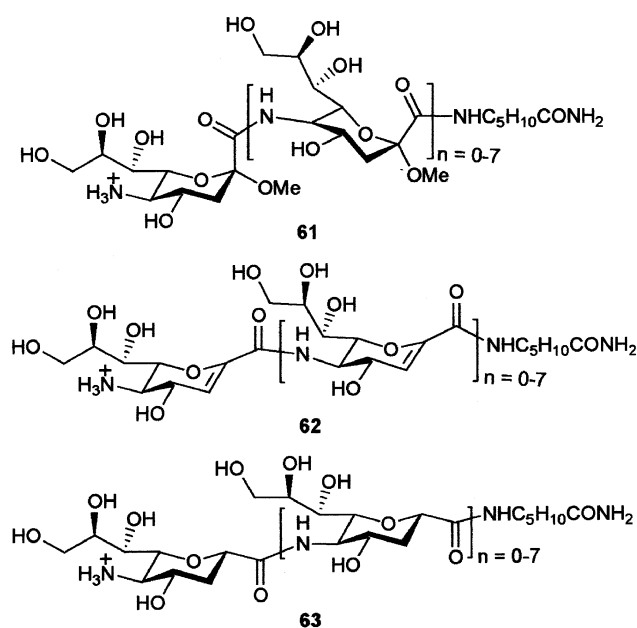
ureas from an azide (via an amine), and a range of amides from a methyl ester.

13. Some other notable works on sugar amino acids

Mazur and others prepared some tetrahydropyran-based peptidomimetic analogs of Phe–Arg–Trp, a truncated version of the melanocortin receptor message sequence.[47] These compounds were tested for their activities at the melanocortin receptors MC4R and MC1R. Two of these analogs **65** and **66** are based on sugar amino acid framework.

Figure 29 summarizes the work carried out by Koert and group.[48] THF–gramicidin hybrids **69–71**, with the L-THF amino acid **67** in positions 11 and 12 and compounds **72–75** with the D-THF amino acid **68** in positions 10 and 11, were synthesized and their ion-channel properties were studied by single-channel-current analysis. The replacement of positions 11 and 12 by the L-THF amino acid **67** gives a strongly reduced channel performance. In contrast, replacement of positions 10 and 11 by the D-THF amino acid **68** gives rise to new and interesting channel properties. For the permeability ratios, the
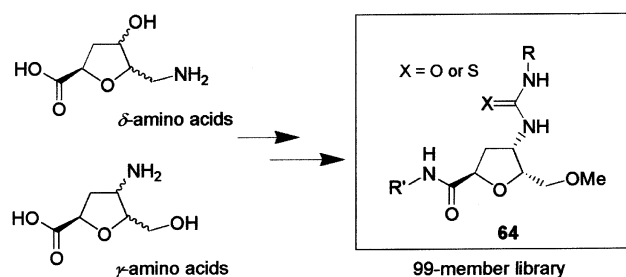

Figure 27. 99-Member library prepared from furanoid sugar amino acid scaffold.[46]

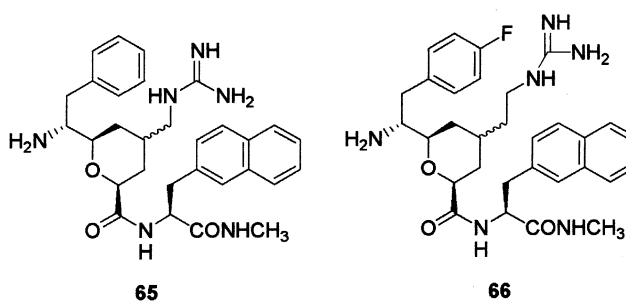**Figure 26.** Various neuraminic acid-derived sugar amino acid oligomers.[45]

Figure 28. Pyranoid sugar amino acid based peptidomimetic analogs **65**, **66** of Phe–Arg–Trp, a truncated version of the melanocortin receptor message sequence.[47]
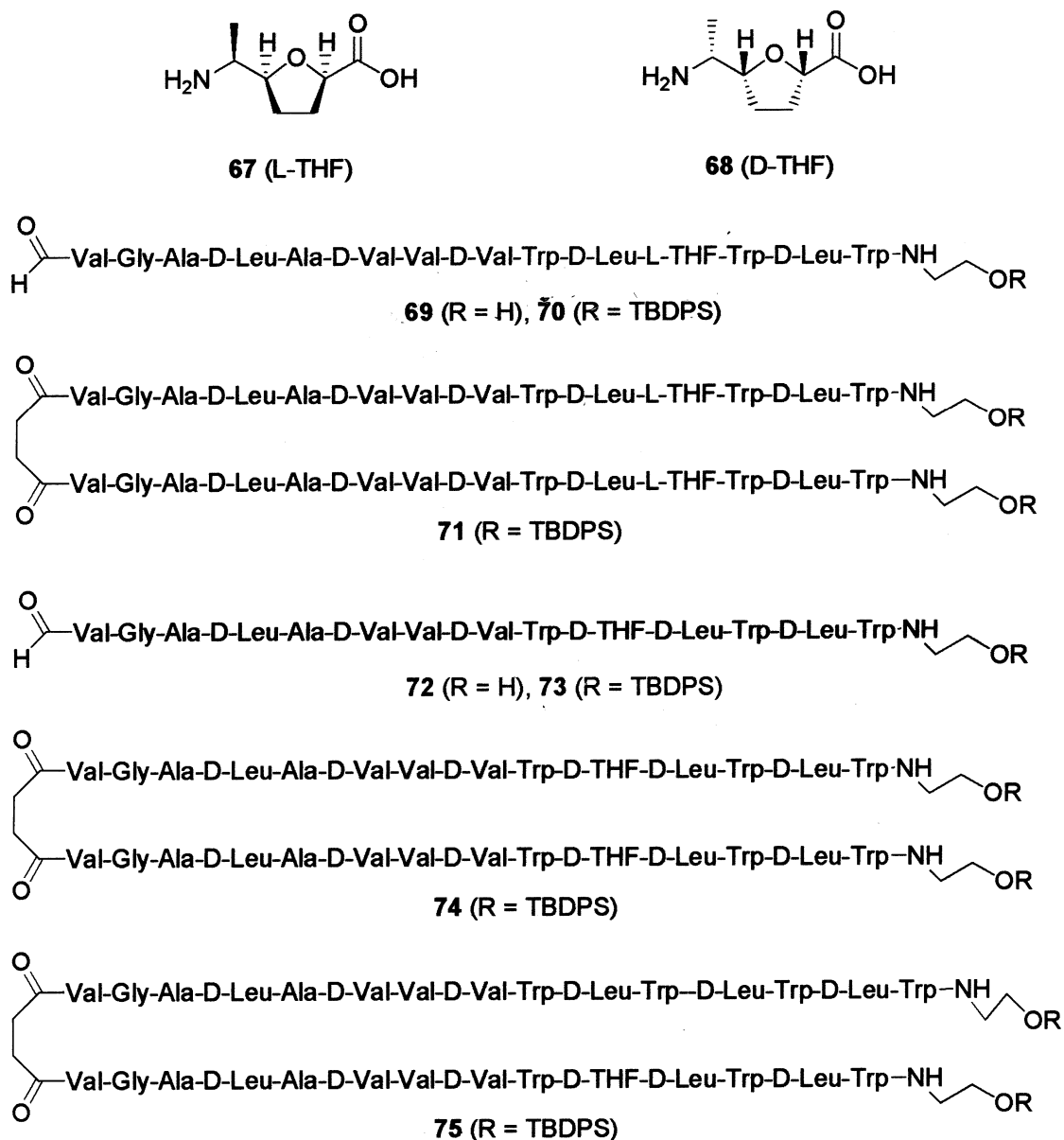
Figure 29. Synthesis and functional studies of THF-gramicidin hybrid ion channels.[48]

ion selectivity shifts from Eisenman I towards Eisenman III selectivity and the channels display ms-dynamics (short closings and openings). Most remarkable is the asymmetric compound **75**, which inserts selectively into a DPhPC membrane and displays voltage-directed gating dynamics.

14. Oligomers of 6-amino-6-deoxyaldonic acids – Hydroxylated nylon 6

Fleet's group has recently reported a new class of sugar amino acids based on open-chain 6-amino-6-deoxyaldonic acids **76**, which can be considered monomeric building blocks for polyhydroxylated nylon 6 derivatives **77** (figure 30).[49–53] They have prepared a large variety of linear and cyclic oligomers, as for example compounds **78–82**, based on these building blocks and studied the X-ray structures of some of these molecules.

15. Conclusion

Sugar amino acids have emerged as an important class of multifunctional building blocks that have
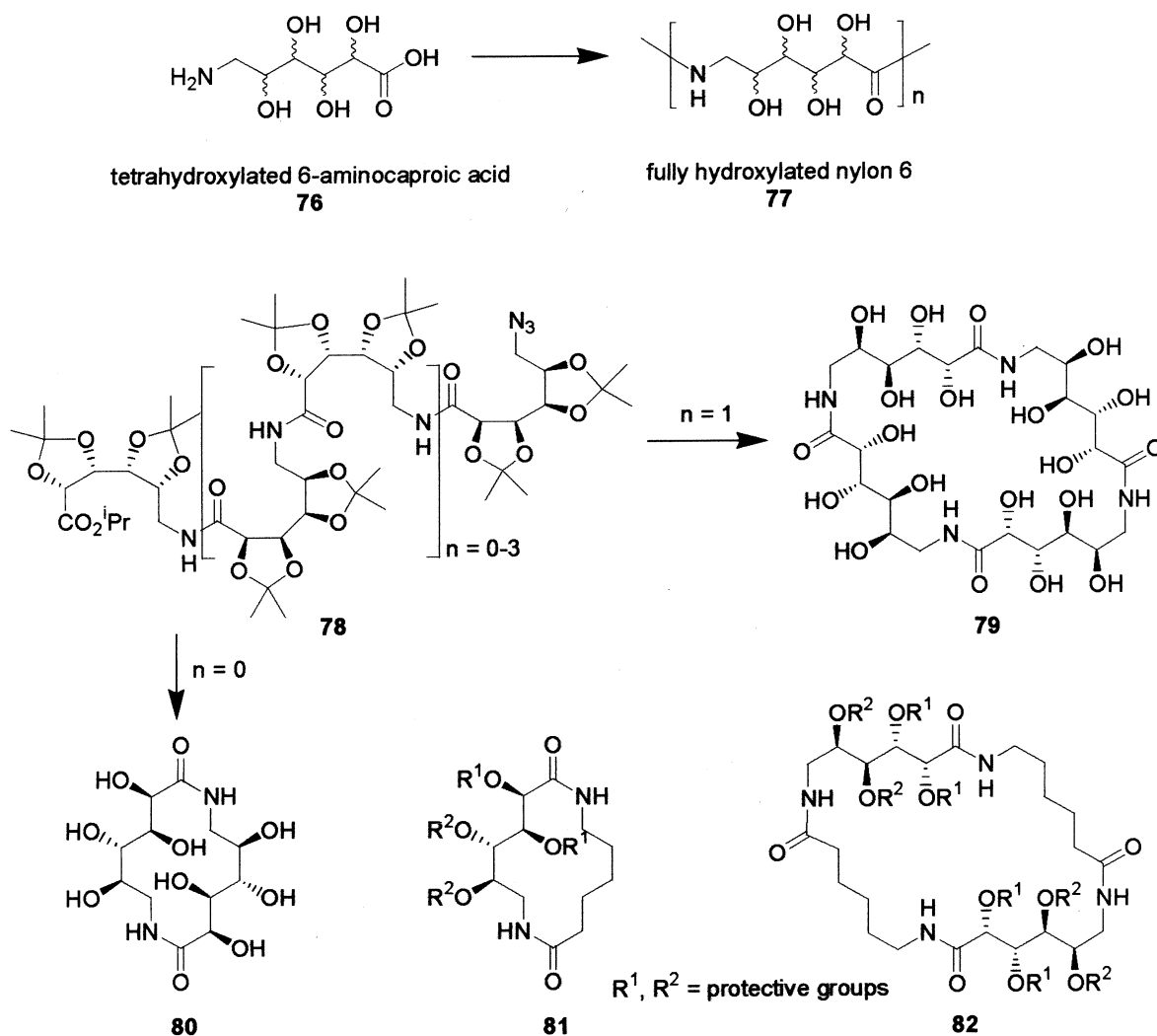
Figure 30. Open-chain sugar amino acids **76** with 6-amino-6-deoxyaldonic acid frameworks as monomeric building blocks for fully hydroxylated nylon 6 derivatives **77** and some of their oligomers.[49–53]

found wide-ranging 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, especially 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 the diversity of biopolymers. Cyclic oligomers of sugar amino acids can be moulded to build predisposed cavities of precise dimensions that are expected to provide useful tools as novel synthetic receptors to study diverse molecular recognition processes. The nonproteinogenic properties of sugar amino acids will render compounds incorporating 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. Designing such molecules on the blackboard, bringing them into existence by synthesising them in the laboratory, studying the three-dimensional structures and properties of these "Designer Molecules" holds much promise for the future of organic synthesis.

Acknowledgements

References

1. Nicolaou K C, Vourloumis D, Winssinger N and Baran P S 2000 *Angew. Chem., Int. Ed.* **39** 44
2. (a) Nicolaou K C and Sorensen E J 1996 In *Classics in total synthesis* (Weinheim: VCH); (b) Nicolaou K C and Snyder S A 2003 In *Classics in total synthesis II* (Weinheim: Wiley-VCH)
3. Soth M J and Nowick J S 1997 *Curr. Opin. Chem. Biol.* **1** 120
4. Kirshenbaum K, Zuckermann R N and Dill K A 1999 *Curr. Opin. Struct. Biol.* **9** 530
5. Barron A E and Zuckermann R N 1999 *Curr. Opin. Chem. Biol.* **3** 681
6. Mehta G and Singh V 2002 *Chem. Soc. Rev.* **31** 324
7. Rouhi A M 2003 *C&En.* **81** 77
8. Fox M A 1999 *Acc. Chem. Res.* **32** 201
9. Newman D J, Cragg G M and Snader K M 2003 *J. Nat. Prod.* **66** 1022
10. (a) Chakraborty T K, Ghosh S and Jayaprakash S 2002 *Curr. Med. Chem.* **9** 421; (b) Chakraborty T K, Jayaprakash S and Ghosh S 2002 *Combinatorial Chem. High Throughput Screening* **5** 373; (c) Schweizer F 2002 *Angew. Chem., Int. Ed.* **41** 230; (d) Gruner S A W, Locardi E, Lohof E and Kessler H 2002 *Chem. Rev.* **102** 491; (e) Peri F, Cipolla L, Forni E, La Ferla B and Nicotra F 2001 *Chemtracts Org. Chem.* **14** 481
11. Heyns K and Paulsen H 1955 *Chem. Ber.* **88** 188
12. (a) Fuchs E F and Lehmann J 1975 *Chem. Ber.* **108** 2254; (b) Fuchs E F and Lehmann J 1975 *Carbohydr. Res.* **45** 135; (c) Fuchs E F and Lehmann J 1976 *Carbohydr. Res.* **49** 267
13. Graf von Roedern E and Kessler H 1994 *Angew. Chem., Int. Ed. Engl.* **33** 687
14. Graf von Roedern E, Lohof E, Hessler G, Hoffmann M and Kessler H 1996 *J. Am. Chem. Soc.* **118** 10156
15. (a) Chakraborty T K, Jayaprakash S, Diwan P V, Nagaraj R, Jampani S R B and Kunwar A C 1998 *J. Am. Chem. Soc.* **120** 12962; (b) Chakraborty T K, Ghosh S, Jayaprakash S, Sarma J A R P, Ravikanth V, Diwan P V, Nagaraj R and Kunwar A C 2000 *J. Org. Chem.* **65** 6441
16. Poitout L, Merrer Y L and Depezay J-C 1995 *Tetrahedron Lett.* **36** 6887
17. Coterón J M, Hacket F and Schneider H-J 1996 *J. Org. Chem.* **61** 1429
18. (a) McDonald I K and Thornton J M 1994 *J. Mol. Biol.* **238** 777; (b) Burley S K and Petsko G A 1988 *Adv. Protein Chem.* 39 125
19. Grotenbreg G M, Timmer M S M, Llamas-Saiz A L, Verdoes M, van der Marel G A, van Raaij M J,

20. Overkleeft H S and Overhand M 2004 *J. Am. Chem. Soc.* **126** 3444
20. Chakraborty T K, Srinivasu P, Madhavendra S S, Kumar S K and Kunwar A C 2004 *Tetrahedron Lett.* **45** 3573
21. Smith M D, Claridge T D W, Sansom M S P and Fleet G W J 2003 *Org. Biomol. Chem.* **1** 3647
22. Davis A P and Wareham R S 1999 *Angew. Chem., Int. Ed.* **38** 2978
23. Chakraborty T K, Jayaprakash S, Srinivasu P, Madhavendra S S, Sankar A R and Kunwar A C 2002 *Tetrahedron* **58** 2853
24. Chakraborty T K, Ghosh S, Rao M H V R, Kunwar A C, Cho H and Ghosh A K 2000 *Tetrahedron Lett.* **41** 10121
25. Chakraborty T K, Srinivasu P, Kumar S K and Kunwar A C 2002 *J. Org. Chem.* **67** 2093
26. Stöckle M, Voll G, Günther R, Lohof E, Locardi E, Gruner S and Kessler H 2002 *Org. Lett.* **4** 2501
27. Gellman S H 1997 *Acc. Chem. Res.* **31** 173
28. Hill D J, Mio M J, Prince R B, Hughes T S and Moore J S 2001 *Chem. Rev.* **101** 3893
29. Chakraborty T K, Srinivasu P, Bikshapathy E, Nagaraj R, Vairamani M, Kumar S K and Kunwar A C 2003 *J. Org. Chem.* **68** 6257
30. Locardi E, Stöckle M, Gruner S and Kessler H 2001 *J. Am. Chem. Soc.* **123** 8189
31. van Well R M, Overkleeft H S, van Boom J H, Coop A, Wang J B, Wang H, van der Marel G A and Overhand M 2003 *Eur. J. Org. Chem.* 1704, and references cited therein
32. Gruner S A W, Truffault V, Voll G, Locardi E, Stöckle M and Kessler H 2002 *Chem. Eur. J.* **8** 4365
33. Gruner S A W, Kéri G, Schwab R, Venetianer A and Kessler H 2001 *Org. Lett.* **3** 3723
34. van Well R M, Marinelli M, Erkelens K, van der Marel G A, Lavecchia A, Overkleeft H S, van Boom J H, Kessler H and Overhand M 2003 *Eur. J. Org. Chem.* 2303
35. (a) van Well R M, Overkleeft H S, van der Marel G A, Bruss D, Thibault G, de Groot P G, van Boom J H and Overhand M 2003 *Bioorg. Med. Chem.* **13** 331; (b) van Well R M, Overkleeft H S, Overhand M, Carstenen E V, van der Marel G A and van Boom J H 2000 *Tetrahedron Lett.* **41** 9331
36. van Well R M, Marinelli L, Altona C, Erkelens K, Siegal G, van Raaij M, Liamas-Saiz A, Kessler H, Novellino E, Lavecchia A, van Boom J H and Overhand M 2003 *J. Am. Chem. Soc.* **125** 10822
37. van Well R M, Meijer M E A, Overkleeft H S, van Boom J H, van der Marel G A and Overhand M 2003 *Tetrahedron* **59** 2423
38. Chakraborty T K, Ghosh A, Nagaraj R, Sankar A R and Kunwar A C 2001 *Tetrahedron* **57** 9169
39. Chakraborty T K, Tapadar S and Kumar S K 2002 *Tetrahedron Lett.* **43** 1317
40. Chakraborty T K, Mohan B K, Kumar S K and Kunwar A C 2002 *Tetrahedron Lett.* **43** 2589
41. Chakraborty T K, Mohan B K, Kumar S K and Kunwar A C 2003 *Tetrahedron Lett.* **44** 471

42. Bonauer C, Zabel M and König B 2004 *Org. Lett.* **6** 1349

43. Suhara Y, Yamaguchi Y, Collins B, Schnaar R L, Yanagishita M, Hildreth J E K, Shimada I and Ichikawa Y 2002 *Bioorg. Med. Chem.* **10** 1999

44. Ying L and Gervay-Hague J 2004 *Carbohydrate Res.* **339** 367

45. Gregar T Q and Gervay-Hague J 2004 *J. Org. Chem.* **69** 1001

46. Edwards A A, Ichihara O, Murfin S, Wilkes R, Whittaker M, Watkin D J and Fleet G W J 2004 *J. Comb. Chem.* **6** 230

47. (a) Mazur A W, Kulesza A, Mishra R A, Cross-Doersen D, Russell A F and Ebetino F H 2003 *Bioorg. Med. Chem.* **11** 3053; (b) Kulesza A, Ebetino F H, Mishra R K, Cross-Doersen D and Mazur A W 2003 *Org. Lett.* **5** 1163

48. Vescovi A, Knoll A and Koert U 2003 *Org. Biomol. Chem.* **1** 2983

49. Hunter D F A and Fleet G W J 2003 *Tetrahedron: Asymmetry* **14** 3831

50. Mayes B A, Stetz R J E, Watterson M P, Edwards A A, Ansell C W G, Tranter G E and Fleet G W J 2004 *Tetrahedron: Asymmetry* **15** 627

51. Mayes B A, Stetz R J E, Ansell C W G and Fleet G W J 2004 *Tetrahedron Lett.* **45** 153

52. Mayes B A, Simon L, Watkin D J, Ansell C W G and Fleet G W J 2004 *Tetrahedron Lett.* **45** 157

53. Mayes B A, Cowley A R, Ansell C W G and Fleet G W J 2004 *Tetrahedron Lett.* **45** 163