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Cyclic glycopeptidomimetics through a versatile sugar-based scaffold

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ABSTRACT

Cyclic peptidomimetics are attracting structures to obtain a distinct, bioactive conformation. Even more attractive are sugar-containing cyclic peptidomimetics which present turn structures induced by the pyranose ring when incorporated in cyclic peptides. The use of a new and versatile saccharidic scaffold to achieve sugar-based peptidomimetics is here reported together with the successful synthesis of diastereomerically pure cyclic SAA peptidomimetics **15** and **16**.

Low bioavailability, poor stability towards peptidases and rapid excretion displayed by a large number of peptides of therapeutic and biological interest, prompted an intensive search for peptidomimetics.[1–3] As a matter of fact, peptidomimetics molecules, are expected to have the same therapeutic effects as their peptide counterparts, with the added advantages of metabolic stability and bioavailability.

A possible approach of such peptidomimetics is to replace the peptide, or part of the peptide, by a scaffold that distributes in the space the epitopes. Ideally, an attractive scaffold should easily be available as chiral, enantiomerically pure, building block. It should be highly functionalized to introduce various side chains and its flexibility or rigidity could be modulated. Therefore, the use of sugars as scaffolds in mimetic synthesis is a strategy that has been widely studied and which still draws attention.[4–6]

Sugar derivatives can be incorporated in the peptide backbone or in the side chains; modification of peptide skeleton by introducing carbohydrate derivatives is documented leading to a real improvement of the properties of the peptides. Moreover, because of the presence of pyranose ring, sugar aminoacids (SAAs) have been found to introduce turn structures when incorporated in linear or cyclic peptides.[5]

Cyclization of peptides affords structure of special interest to obtain a distinct, bioactive conformation, and several SAAs have been used as building blocks for peptide scaffolds and conformational restrained peptido-mimetics.[2,7] Indeed, this approach has been successfully evaluated for biologically active, cyclic RGD peptides[3] or cyclic peptides with the β-turn motif of somatostatin, containing tetrapeptide Phe-D-Trp-Lys-Thr.[2,8]

Consequently, efficient syntheses and availability of suitable saccharidic scaffolds allowing the systematic modification of the amino acids and the carbohydrate residues, as well as the size of the macrocycle, remain a challenging and attracting target to fully exploit the potential of such hybride structure, in the search of new active compounds.

We report herein the use of the α-O-linked glycohomoglutamate **1**, (Scheme 1), easily obtained as distereomerically pure compound by chemo-, regio- and stereoselective cycloaddition between glucal **2** and aspartic acid derivative **3**,[9] as versatile, multifunctionalized scaffold in the synthesis of cyclic SAA-peptidomimetics **15** and **16** (Scheme 2).

Scaffold **1,** characterized by two orthogonally protected carboxyls, a protected α-amino function and a selectively functionalized monosaccharidic unit, was successfully employed to obtain the monosilyl derivative **4** which, in turn, was oxidized with TEMPO/BAIB to give the glucuronic derivative **5** (see Scheme 1) in 54% yield. No sulfoxide derivative **6** was observed under these reaction conditions (see Supplementary data).[10] Condensation reactions

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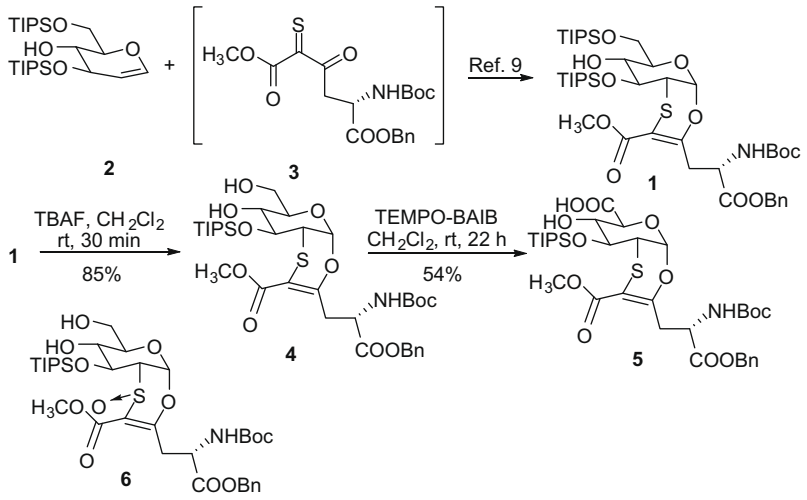

Scheme 1. Synthesis of scaffold **5** and structure of cyclo SAA peptidomimetics **15** and **16**.

between **5** and **7** as well as between **5** and **8** were performed using standard conditions (see Supplementary data) affording respectively compounds **9** and **10** (Scheme 2). Peptidic chains **7** and **8** as well as SAA derivatives **9** and **10** have been obtained relying on standard solid-phase strategy, using 2-chlorotrityl resin. Removal of the resin, gave linear glycopeptides **11** (62%, over 10 steps) and **12** (25%, over 11 steps) which were treated with trifluoroacetic acid to take off the Boc protecting group quantitatively affording derivatives **13** and **14**, as trifluoroacetic salts. Intramolecular condensation of the latter, and suitable deprotection, gave the cyclo glycopeptides: *cyclo*(SAA**5**-Ala-Phe-Phe-Phe-Ala) **15**, and *cyclo*(SAA**5**-Glu-Ile-Leu-Asp-Val) **16**, (see Supplementary data) which were prepared to be tested as tachykinin NK_2 receptor ligand and integrin ($\alpha4\beta1$) inhibitor respectively (Scheme 2).

In a previous paper[11] we have shown how insertion of aromatic groups on a suitable sugar derived scaffold can mimic the structure of highly active tachykinin NK_2 antagonists such as the small monocyclic pseudopeptide **17**[12] (Fig. 1).

Indeed, some of the compounds we obtained showed binding affinities at the human tachykinin NK_2 receptor at submicromolar concentrations, while molecular dynamics calculations indicated that the structures of **17** and that of one of the best sugar derived compounds were quite well superimposable. As tachykinin NK_2 antagonists continue to raise interest as potential new drugs for the therapy of gastrointestinal and CNS diseases,[13] we turned our attention to the synthesis of compounds in which small peptide sequences, containing aromatic aminoacids (Phe) and alanine residues as chiral spacers, are linked to the sugar derived rigid scaffold **5** in order to distribute the aromatic moieties in suitable space regions. We thus synthesized compound **15** which showed some, although limited, activity in the binding assay at the human tachykinin NK_2 receptor. Affinity of compound **15** at the human NK_2 receptor was determined in binding experiments by using membranes of Chinese Hamster Ovary (CHO) cells stably transfected with the human NK_2 receptor.[14] The compound was tested for its ability to displace the radioligand [^{125}I]-neurokinin A (0.15 nM) after 30 min incubation at room temperature, resulting in 25% inhibition of the radioligand binding at 10 μM concentration.

Capitalizing on this encouraging result, further work is ongoing in order to increase the biological activity through the modulation of the peptide sequence assisted by molecular dynamics calculations.

It is known that a requisite for a good recognition by NK_2 receptors is the presence of two close aromatic rings in the axial position about the backbone ring.[15] We performed a preliminary modeling study of compound **15** to locate its allowed conformations;[16] the molecule showed a high degree of conformational flexibility and several populated geometries. Among them, two significant conformations show two of the three phenyl rings oriented in the same region of the space, though they do not belong to adjacent aminoacidic residues as in **17**. These conformations, reported in Figure 2, are stabilized by a β-turn motif and support the potential interest in such cyclic glycopeptidic structures.

Integrins are a family of membrane-spanning adhesion receptors composed of non- covalently linked α and β subunits which combine to give a wide amount of heterodimers. In recent years antagonists of very late antigen-4 (VLA4, also known as integrin $\alpha4\beta1$) have shown great promise in treating inflammatory disorders.[17–19] VLA4 recog-

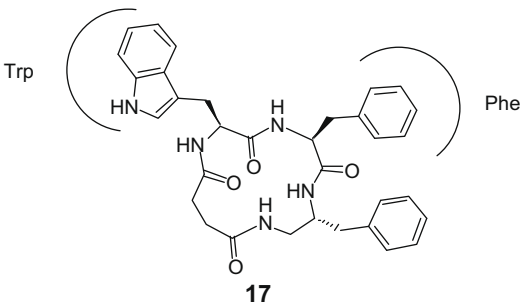

Figure 1. Structure of compound **17**.

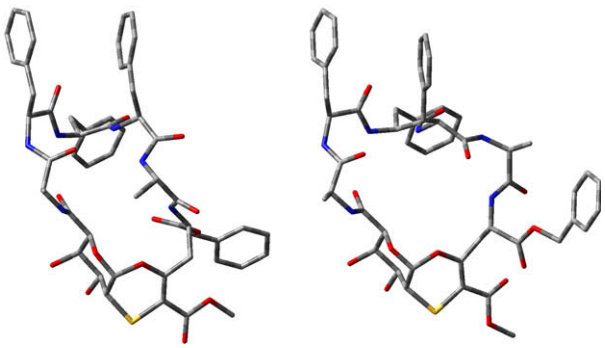

Figure 2. 3D plot of representative conformations for compound **15**.