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Saccharopeptides and their Triazole Isosteres

Vitalijs Rjabovs, Maris Turks (*Riga Technical University*),
Diana Zelencova and Edvards Liepins (*Latvian Institute of Organic Synthesis*)

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I. Introduction

Oligopeptides arising from synthetic sugar amino acids exhibit interesting self-assembling structures in solution, and were intensively studied as peptidomimetics.[1] After the discovery of click synthesis of 1,2,3-triazoles,[2] the latter were studied as amide bond isosteres as they exhibit similar spatial arrangement and geometry.[3]

Herein, we present synthesis of hybrid building blocks and their synthetic application for the synthesis of saccharopeptides.

II. Discussion

Our synthesized hybrid building blocks contain several structural rigidity elements and several functionalization sites. Structural hybrid **1** (Fig. 1) contains two carbohydrate-based bicyclic rings with defined molecular scaffold, and amide functionality that can participate in intramolecular hydrogen bond formation. It also contains C-terminal alkyne along with masked N-terminal azide for differentiated copper-catalyzed azide alkyne cycloadditions.

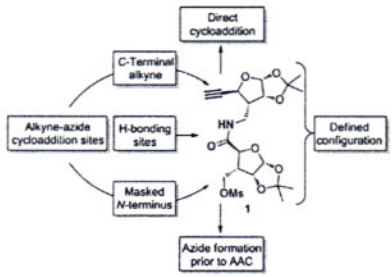

Fig.1. Dimeric structural hybrid **1**

Iterative cycloaddition reaction azidation sequence using this hybrid allows the synthesis of oligomeric saccharopeptides of type **I** (Fig. 2) which has both the amide and triazole linkers between carbohydrate cores.

Substitution of the amide linker in dimeric hybrid with 1,2,3-triazole moiety brings another degree of rigidity and opens the opportunity for the synthesis of type **II** saccharopeptide with all-triazole linkages. 1,2,3-Triazole is considered as weaker both the H-bond donor and H-bond acceptor than amide, thus it is expected that weaker or no intramolecular hydrogen bonds would form.

To find out whether saccharopeptides of types **I** and **II** can acquire certain conformations that are stabilized by intramolecular hydrogen bonds, Nuclear Magnetic Resonance (NMR) studies as well as molecular mechanics (MM) calculations were performed.

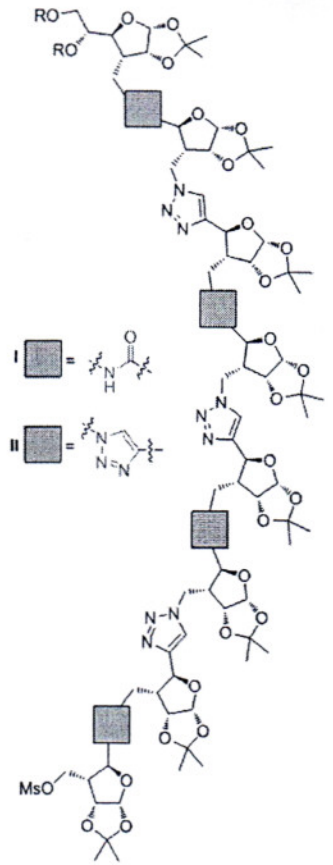

Fig.2. Oligosaccharopeptides of types **I** and **II**

Dimeric structural hybrid studies by NMR allow establishing distances between functional group protons that can help to compare amide and 1,2,3-triazole linkers. This information can be valuable in the analysis of oligomeric structure NMR spectra whereas oligomeric saccharopeptide investigation by NMR establishes intramolecular interactions between protons. Distance comparison of the dimers and oligomers can indicate the formation of secondary structure.

On the other hand, MM calculations give valuable thermodynamic data for the molecules, and can foresee interactions in different solvents.

III. References

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