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Transformation of the amyloidogenic peptide amylin(20–29) into its corresponding peptoid and retropeptoid: Access to both an amyloid inhibitor and template for self-assembled supramolecular tapes

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Abstract—The highly amyloidogenic peptide sequence of amylin(20–29) was transformed into its corresponding peptoid and retropeptoid sequences to design a novel class of β-sheet breaker peptides as amyloid inhibitors. This report describes the synthesis of the chiral peptoid building block of L-isoleucine, the solid phase synthesis of the peptoid and retropeptoid sequences of amylin(20–29), and the structural analysis of these amylin derivatives in solution by infrared spectroscopy, circular dichroism, and transmission electron microscopy. It was found that the peptoid sequence did not form amyloid fibrils or any other secondary structures and was able to inhibit amyloid formation of native amylin(20–29). Although the retropeptoid did not form amyloid fibrils it had only modest amyloid inhibitor properties since supramolecular tapes were formed.

Uncontrolled protein aggregation which leads to the formation of amyloid fibrils and amyloidogenic plaques is a major cause of cell degeneration resulting in cell death in many well-known incurable diseases such as Alzheimer's Disease, Parkinson's Disease, and late onset diabetes (type II diabetes).[1] The latter disease is characterized by the aggregation of human islet amyloid polypeptide (hIAPP) in the insulin producing islet β-cells.[1c] Islet amyloid polypeptide, also known as amylin, is a peptide of 37 amino acid residues, and from structure–activity relationship studies it is known that the (20–29) core region is highly amyloidogenic and rapidly forms amyloid fibrils via a cross β-sheet topology.[2] Based on the seminal papers of Tjernberg et al.[3] and Soto et al.,[4] respectively, in which they describe the design of soluble β-sheet mimics as amyloid fibril inhibitors,[5] we[6] and others[7] used the amylin(20–29) region as a template to design backbone-modified amylin derivatives that are able to inhibit fibril formation of either the (20–29) sequence or full length amylin (Fig. 1).

Previously, we have shown that backbone-modified amylin(20–29) derivatives are promising inhibitors of amyloid formation of native amylin(20–29).[6] Backbone-modified amylin(20–29) derivatives in which one or three amide bonds have been replaced by α-hydroxy acids, *N*-butyl amino acids, *N*-butyl glycines (norleucine peptoid) or β-aminoethane sulfonamides[8] have been designed and successfully synthesized.

Among these β-sheet breaker peptides, we have shown that replacement of an amide bond by a norleucine peptoid derivative is the most effective approach to obtain amyloid inhibitors of amylin(20–29).[6a] Based on these results we designed and synthesized the peptoid and retropeptoid sequences of amylin(20–29) as shown in Figure 2, to study their properties as β-sheet breaker peptidomimetics.

Peptoids[9] are N-alkylated glycine derivatives in which the amino acid side chains are shifted from the α-carbon to the α-amino functionality. A variety of applications in medicinal chemistry[10a] as protease resistant

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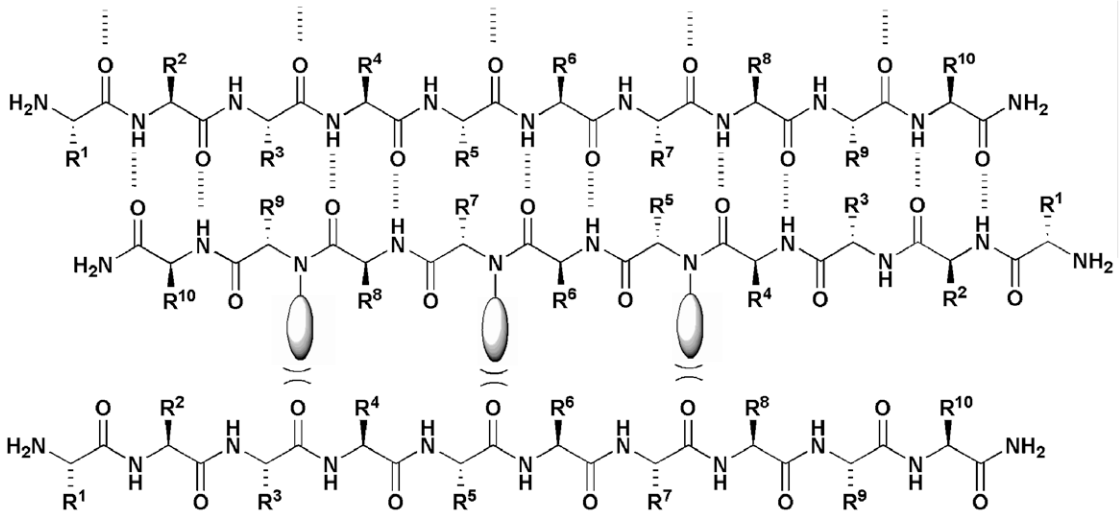

Figure 1. Rationale for design of β-sheet breaker peptides based on the amylin(20–29) sequence. Incorporation of sterical hindrance or removal of essential hydrogen bond donors will disrupt the hydrogen bond network of the (anti)parallel β-sheet and further growth is arrested.

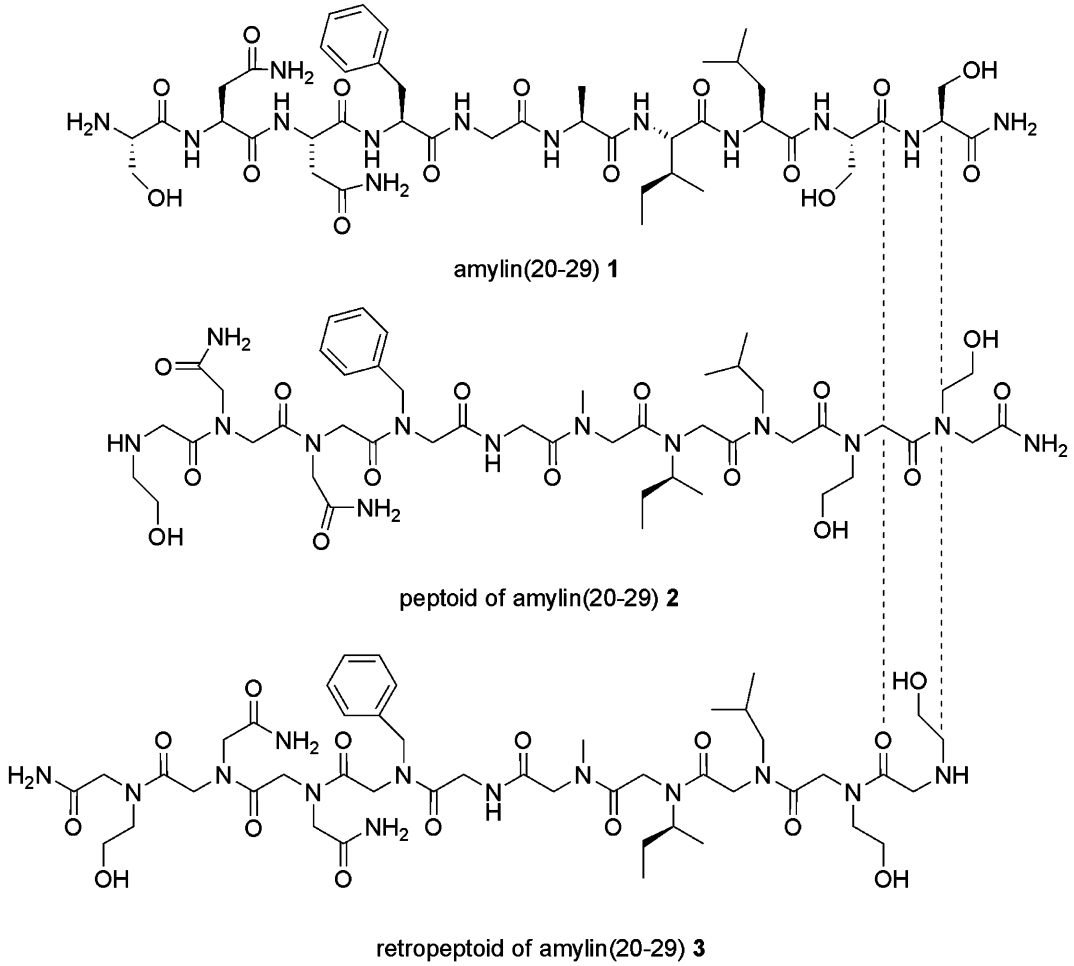

Figure 2. Amino acid sequence of native amylin(20–29) **1** and the corresponding peptoid **2** and retropeptoid **3** derivatives of amylin(20–29).

entities,[10b] antimicrobial agents,[10c] inhibitors of protein–protein interactions,[10d] and artificial protein mimics[10e] have been described in the literature. Peptoids are non-chiral peptidomimetics, except for the chirality of any proline residues or β-carbon atoms of isoleucine and threonine. Moreover, the absence of hydrogen bond donors in the peptide backbone (except for glycine) and the increased flexibility of the backbone due to the presence of tertiary amides which induce ciscoid conformations should abrogate the tendency to form (anti)parallel β-sheets. Translation of a peptide sequence may result either in a peptoid (direct translation) or in a