Design and synthesis of helically constrained peptides to inhibit amyloid aggregation by the stabilization of the monomeric state

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Amyloidoses consist of a group of diseases associated with protein misfolding leading to the formation and accumulation of insoluble fibrils in multiple organs. In fact, few therapeutic approaches exist to treat patients suffering from amyloidosis, and one of the reasons for this is the complexity of the aggregation process, involving many conformations. In this study, using the islet amyloid polypeptide (IAPP) as a model polypeptide, we evaluated a therapeutic strategy based on monomer stabilization. Although IAPP mainly adopts a random conformation in aqueous media, this peptide displays a transient helix-α secondary structure, offering the possibility of stabilizing monomeric IAPP. In this context, a library of helically constrained IAPP derivatives was designed, including fragments of different chain lengths (short, medium or long). Conformational restriction was induced by a stapled technique through the formation of an intramolecular triazole between residues at positions i and i+4 carried out on solid support. By monitoring amyloid formation with the thioflavin T, some compounds showed strong inhibition, a result confirmed by the absence of fibers by atomic force microscopy and by CD spectroscopy. The results obtained suggest that this innovative approach could make it possible to stabilize proteins displaying primarily an natively disordered conformation.