Designing peptidomimetics to inhibit protein-protein interactions involving beta-sheet structures

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Modulating protein-protein interactions (PPIs) is a promising strategy to obtain next-generation drugs to treat major human diseases such as cancer and neurodegenerative diseases. However it is still a challenging issue because PPIs involve rather large and not well defined protein surfaces. However, the hot-spot residues involved in PPIs adopt generally secondary structures, and peptides analogues able to mimic secondary structures could be a relevant strategy to modulate PPIs. Helix mimics have been mainly designed to inhibit PPIs involving helix-helix interactions mediating pathological processes in cancer. Peptidomimetics adopting secondary structures to inhibit PPIs involving β-sheet structures are much more scarcely reported. These PPIs concern cancers but also amyloidoses that are diseases associated with the abnormal β-sheet aggregation of at least 30 known proteins.
The question we would like to answer is: can we prevent PPIs involving β-sheet structures with peptide derivatives and analogues adopting β-hairpin or helical conformations? The proof of concept will be brought with the design of acyclic β-hairpin and helix mimics for the inhibition of Aβ1-42 and hIAPP proteins aggregation in cause in Alzheimer's disease (AD) and type II diabetes (T2D), that are still untreated diseases affecting more than 40 and 300 million people respectively. Design, synthesis and biophysical evaluations will be described.

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