Alzheimer's Disease and Amyloid-β Oligomers: An Endeavor in Rational Drug Design

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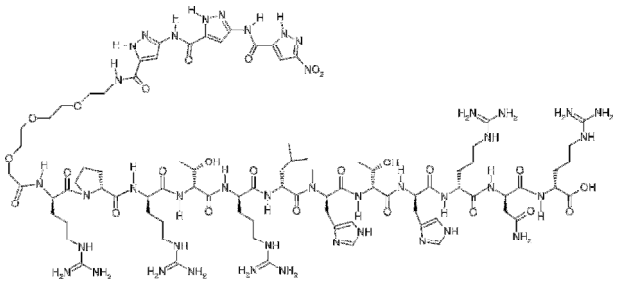
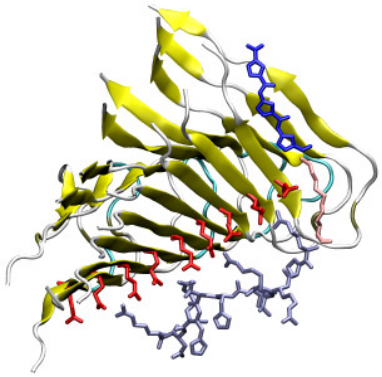
Alzheimer's disease (AD) has become a major threat to public health. Notwithstanding the impressive research efforts in many areas over the last years, a viable medication to AD is still not available to date. As converging lines of evidence suggest amyloid-β (Aβ) peptide oligomers to be the main neurotoxic species in AD,[1] investigation of the interaction of potential drug candidates with these species has gained much interest.[2]

This contribution will summarize our findings from molecular dynamics (MD) simulations about the conformational stability of small fibrillar Aβ oligomers (up to the pentamer).[3]

In the second part we present results from rational drug design of ligands targeting fibrillar Aβ oligomers. Starting point for this development was the aminopyrazole trimer ligand, which is known to possess β-sheet-breaking properties. By the design of suitable substituents which target different regions of the Aβ peptide the binding properties of the trimer ligand were significantly improved.[4]

A major activity enhancement of the trimer ligand-class was achieved, when it was covalently linked to another anti-Aβ substance, the D3-peptide.[5] This can be rationalized, as both molecules, the aminopyrazole trimer and the D3 peptide, target distinct Aβ regions in spatial proximity. The resulting hybrid ligand showed anti-Aβ properties superior to the isolated educt molecules.[6]





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