Aminopyrazole β-sheet Ligands – Design and Binding to $A\beta_{42}$

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Alzheimer's disease (AD) is a steadily increasing threat especially for industrialized countries with a growing percentage of old individuals. Despite the last decades' research on potential therapies, no one single drug has been developed which is able to cure the disease. Since AD is accompanied by many diverse pathologic mechanisms, numerous avenues have been exploited in the search for a therapy.

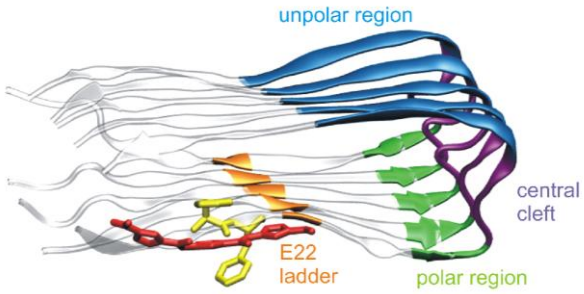
Valuable insight into Aβ aggregation came from structures of $A\beta_{40}$[1] and $A\beta_{42}$[2] in the fibril state, that were determined by NMR spectroscopy. With respect to the monomeric subunits, both structures consistently reveal two β-strands connected by a turn, thus forming a U-shaped topology. The monomeric subunits form a longitudinal stack, thereby creating two parallel in-register β-sheets.

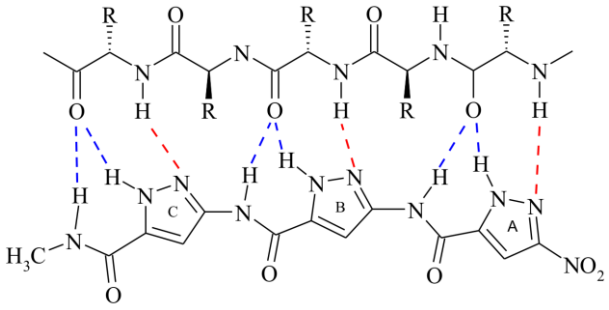
A plethora of small molecules has been screened for their antiaggregation potential against Aβ. Among these are colored heterocyclic compounds (e.g. Congo Red), Zn- and Cu-chelators, or peptides, sometimes taken directly from putative nucleation sites within the Aβ molecule.

Aminopyrazoles (AP) are rationally designed β-sheet ligands with a specific sequence of hydrogen bond donors and acceptors, perfectly complementary to that of a β-sheet.[3] It has been shown by experiment that they bind selectively to the backbone of misfolded peptides in which the predominant structural element is a cross-β-sheet conformation.

In this work we address two questions by means of molecular dynamics simulations:[4]

1, Where is the preferred binding position of the basic AP trimer scaffold?
2, What kind of interactions are formed by different classes of functionalized AP trimers?





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