SMALL MOLECULE INHIBITORS OF BETA-AMYLOID OLIGOMER TOXICITY


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Available therapies for Alzheimer's disease (AD) are tailored to enhance cholinergic function but do not halt disease progression. A characteristic feature of AD is the progressive deposition of Aβ peptides into senile plaques. It is currently believed that self-assembly of Aβ peptides into soluble oligomers rich in β-sheet structure may account for their neurotoxic effects. We have identified in vivo active drug candidates targeting this neuropathological mechanisms and with potential for a novel disease-modifying therapy in AD.

With the aim to inhibit Aβ oligomerization and to disaggregate pre-formed Aβ oligomers, we employed a set of rationally designed non-dye small molecular weight compounds able to interact with the β-sheet conformation of Aβ. Compound screening included efficacy data obtained by the thioflavin-T (ThT) assay, the Aβ sedimentation assay, Aβ cell toxicity assays as well as in vitro preclinical data (metabolic stability, drug permeability and efflux, pharmacokinetics, brain penetration, etc.). Transgenic mice were used to assess the potency of the lead compounds in reducing brain amyloidosis and improving cognitive deficits.

In the ThT-assay we identified many compounds impairing Aβ aggregation with IC₅₀ < 30 mM. These results were confirmed by thioflavin T independent assays, whereby the most potent compounds inhibited Aβ aggregation with IC₅₀ in the low nM range. Among these highly potent compounds, we identified metabolically stable drug candidates displaying excellent CNS properties and that were able to reduce plaque load and improve cognitive deficits in transgenic mice.