

P029 Harnessing Chaperones to Generate Potent Small Molecule Inhibitors of Amyloid β Aggregation
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The misassembly of soluble proteins into conformationally altered aggregates is thought to underlie the pathogenesis of neurodegenerative diseases and is considered an attractive target for therapeutic intervention. However, protein-protein interactions, such as those between amyloid beta ($A\beta$) peptide, have proven exceedingly difficult to inhibit. Small molecules lack sufficient steric bulk to prevent interactions between relatively large peptide surfaces. We have synthesized small molecules that increase their steric bulk by binding at nanomolar affinity to the FKBP class of chaperones, but have a moiety available for interaction with $A\beta$ aggregates. This Trojan horse strategy yields the most potent inhibitors of $A\beta$ aggregation yet described. The tripartite molecules made of targeting, linker and FKBP binding moieties are highly compatible with combinatorial synthesis and could yield new therapeutics for Alzheimer's Disease and other forms of neurodegeneration.