

Honson, Nicolette S., Johnson, Ronald L., Huang, Wenwei, Inglese, James, Austin, Christopher P., Kuret, Jeff, Differentiating Alzheimer Disease-Associated Aggregates with Small Molecules, *Neurobiology of Disease* (2007), doi: 10.1016/j.nbd.2007.07.018

Alzheimer disease is diagnosed postmortem by the density and spatial distribution of  $\beta$ -amyloid plaques and tau-bearing neurofibrillary tangles. The major protein component of each lesion adopts cross- $\beta$ -sheet conformation capable of binding small molecules with submicromolar affinity. In many cases, however, Alzheimer pathology overlaps with Lewy body disease, characterized by the accumulation of a third cross- $\beta$ -sheet forming protein,  $\alpha$ -synuclein. To determine the feasibility of distinguishing tau aggregates from  $\beta$ -amyloid and  $\alpha$ -synuclein aggregates with small molecule probes, a library containing 71,975 small molecules was screened for antagonists of tau-aggregate mediated changes in Thioflavin S fluorescence, followed by secondary screens to distinguish the relative affinity for each substrate protein. Results showed that >10-fold binding selectivity among substrates could be achieved, with molecules selective for tau aggregates containing at least three aromatic or rigid moieties connected by two rotatable bonds.

Source & Full text: [Genome.gov Neurobiology of Disease](#)