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Alzheimer disease is diagnosed postmortem by the density and spatial distribution of β-amyloid plaques and tau-bearing neurofibrillary tangles. The major protein component of each lesion adopts cross-β-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-β-sheet forming protein, α-synuclein. To determine the feasibility of distinguishing tau aggregates from β-amyloid and α-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.