Development of a novel therapeutic agent for dementia that suppresses the ubiquitination of anti-Alzheimer's disease modulators BRI2 and BRI3

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To develop an innovative therapeutic strategy for Alzheimer's disease, we performed a high-throughput screening (HTS) of a medium-sized molecular library comprising 55,295 compounds to identify specific inhibitors of the NRBP1–BRI2 interaction. Thirteen primary hits were obtained and subsequently subjected to tertiary and advanced characterization in cultured cell models. Two structurally related compounds exhibited concentration-dependent inhibition of BRI2 ubiquitination, elevation of intracellular BRI2 levels, and suppression of Aβ aggregation, although neither compound inhibited Aβ production. Both compounds selectively disrupted the NRBP1–BRI2 interaction without perturbing the BRI2–APP association. These findings suggest that (1) the compounds directly interact with BRI2, inducing a conformational alteration, and (2) this structural modification may modulate BRI2's binding affinity to APP, thereby potentially preventing BRI2 from occluding the β- and γ-secretase cleavage sites on APP.