

A novel dual modulator of class I HDACs and Wnt/ β -catenin signaling with in vitro and in vivo activity in Alzheimer's disease

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ABSTRACT

Inhibition of class I histone deacetylases (HDACs) and restoration of Wnt/ β -catenin signaling are promising therapeutic strategies for Alzheimer's disease (AD). We have recently reported that CI-994, an N-(2-aminophenyl)-benzamide derivative, is a dual modulator of these pathways. Through chemical optimization of CI-994, we herein report the discovery of a novel, potent dual modulator (W2A-16) of class I HDACs and Wnt/ β -catenin signaling. W2A-16 selectively inhibits class I HDAC1, 2 and 3 activities with IC₅₀ values of 130 nM, 201 nM, and 84 nM, respectively, with no inhibitory activities against other HDACs and Sirtuins. In addition, W2A-16 activates Wnt/ β -catenin signaling with an EC₅₀ value of 430 nM in Wnt-3A-expressing HEK293 cells, which is associated with the inhibition of Wnt co-receptor LRP6 degradation. Pharmacokinetically, W2A-16 demonstrates high oral bioavailability and robust brain penetration. In AD patient-specific, iPSC-derived cerebral organoids, W2A-16 significantly increases histone acetylation, enhances Wnt/ β -catenin signaling, and reduces tau phosphorylation. In iPSC-derived neurons, W2A-16 increases spontaneous synaptic firing and network formation. In vivo, W2A-16 treatment significantly attenuates amyloid pathology and gliosis in 5xFAD amyloid model mice, while suppresses tau hyperphosphorylation and neuroinflammation in PS19 tauopathy mice. Therefore, W2A-16 is a high-potency, brain-penetrant dual modulator that addresses multiple AD pathologies, representing a promising candidate for clinical development.

FIG.1. STRUCTURE OF CI-994 AND W2A-16

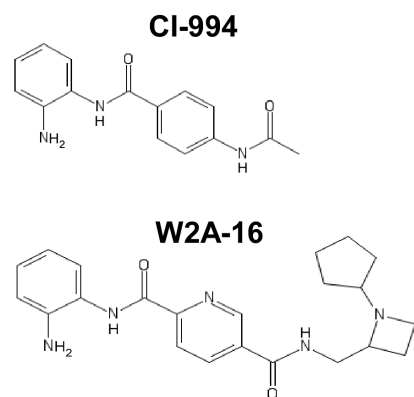


FIG.2. W2A-16 INHIBITS CLASS I HDACs AND ACTIVATES WNT/ β -CATENIN SIGNALING

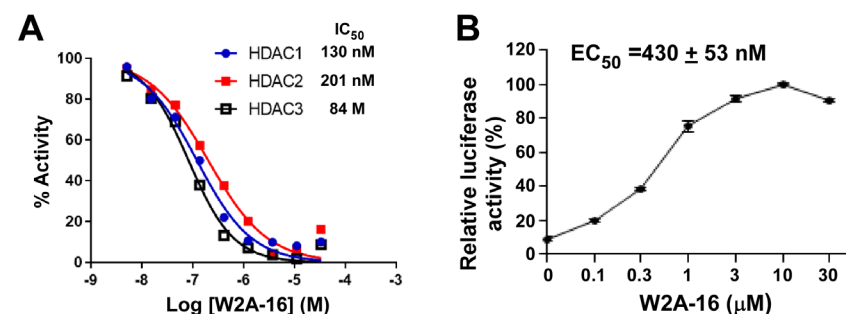


FIG.3. W2A-16 ACTIVATES WNT/ β -CATENIN VIA STABILIZING WNT CORECEPTOR LRP6

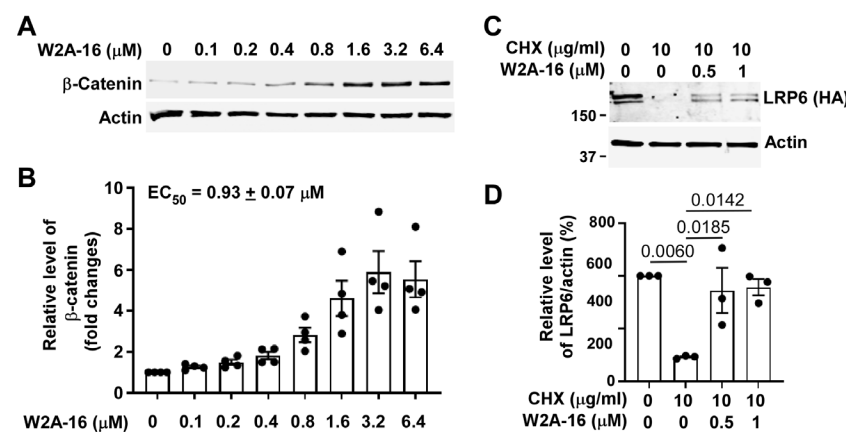


FIG. 4. W2A-16 ENHANCES SYNAPTIC ACTIVITY AND NETWORK FORMATION IN AD PATIENT-SPECIFIC IPSC-DERIVED NEURONS

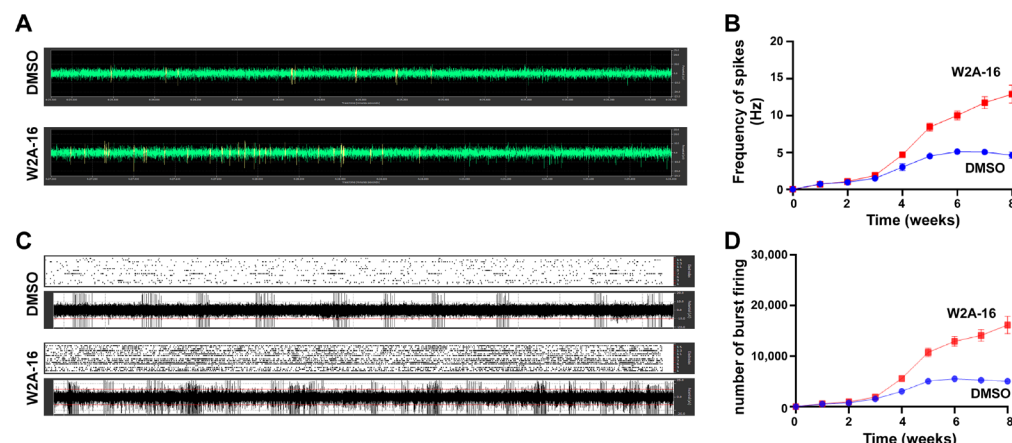


FIG.5. W2A-16 INHIBITS TAU PHOSPHORYLATION IN PATIENT-SPECIFIC IPSC-DERIVED ORGANOIDs

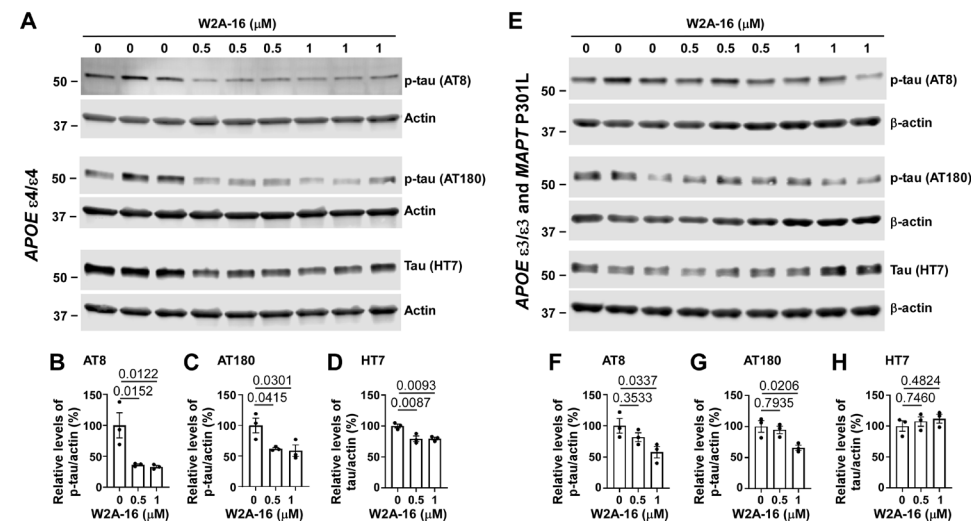


FIG.6. THE PK PROFILE AND BRAIN PENETRATION OF W2A-16

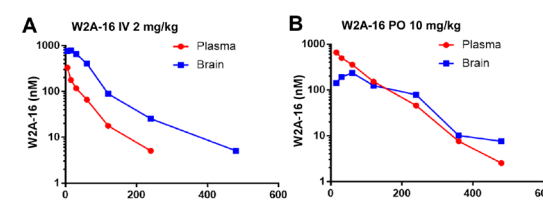


FIG.7. W2A-16 ALLEVIATES AMYLOID PATHOLOGY IN 5XFAD MICE

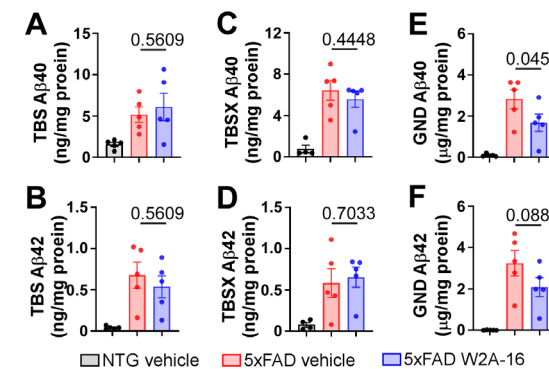


FIG.8. W2A-16 SUPPRESSES TAU PHOSPHORYLATION IN PS19 MICE

