HDAC6

HDAC6 inhibition has long been considered a safe and effective therapy for tau pathology. Sreenivasmurthy et al. identified protopine as a dibenzazecine alkaloid with anti-HDAC6 and anti-AD activities. In a study, they synthesized and tested novel protopine derivatives for their pharmacological action against AD. Among them, bromo-protopine (PRO-Br) demonstrated a two-fold increase in anti-HDAC6 activity and improved anti-tau activities compared to the parent compound in both in vitro and in vivo AD models. Furthermore, molecular docking results showed that PRO-Br binds to HDAC6, with a ΔG value of -8.4 kcal/mol and an IC50 value of 1.51 μM. In neuronal cell lines, PRO-Br reduced pathological tau by inducing chaperone-mediated autophagy (CMA). In 3xTg-AD and P301S tau mice models, PRO-Br specifically decreased the pathogenic hyperphosphorylated tau clumps and led to the restoration of memory functions. In addition, PRO-Br treatment promoted the clearance of pathogenic tau by enhancing the expression of molecular chaperones (HSC70) and lysosomal markers (LAMP2A) via CMA in AD models. Our data strongly suggest that administration of the brain-permeable protopine derivative PRO-Br, could be a viable anti-tau therapeutic strategy for AD [1)]

1)
Sreenivasmurthy SG, Iyaswamy A, Krishnamoorthi S, Reddi RN, Kammala AK, Vasudevan K, Senapati S, Zhu Z, Su CF, Liu J, Guan XJ, Chua KK, Cheung KH, Chen H, Zhang HJ, Zhang Y, Song JX, Kumar Durairajan SS, Li M. Bromo-protopine, a novel protopine derivative, alleviates tau pathology by activating chaperone-mediated autophagy for Alzheimer's disease therapy. Front Mol Biosci. 2022 Oct 26;9:1030534. doi: 10.3389/fmolb.2022.1030534. PMID: 36387280; PMCID: PMC9643865.