DISCOVERY AND CHARACTERIZATION OF TACRINE/HUPRINE-TRYPTOPHAN HETERODIMERS AS NOVEL MULTIPOTENT COMPOUNDS AGAINST ALZHEIMER'S DISEASE

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Combination of tacrine/huprine, connected through a different linker tether length, with tryptophan led to the generation of a novel, highly-potent family of multi-target directed ligands targeting key molecular mechanisms of Alzheimer’s disease. Based on in vitro biological profile, the 6-chloro-tacrine-(CH 2) 6-L-tryptophan heterodimer S-K1035 was found to be the most potent inhibitor of human acetylcholinesterase (hAChE) and human butyrylcholinesterase (hBChE) within the series, with nanomolar IC 50 values (6.31 and 9.07 nM, respectively). Moreover, S-K1035 also exerted moderate inhibition against neuronal nitric oxide synthase (nNOS). In vivo studies displayed low toxicity profile compared to parent tacrine. S-K1035 significantly ameliorated performances of scopolamine-treated animals.

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