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MEETING ABSTRACTS

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

Jan Korabecny [1,2], Katarina Spilovska [1,3], Manuela Bartolini [4], Barbara Monti [4], Doriano Lamba [5], Rosanna Caliandro [5], Alessandro Pesaresi [5], Vendula Hepnarova [2,6], Daniel Jun [2,6], Martina Hrabinova [2,6], Rafael Dolezal [2], Jana Zdarova Karasova [2,6], Ondrej Soukup [1,2], Eva Mezeiova [1,2], Eugenie Nepovimova [3], Maria Laura Bolognesi [4] and Kamil Kuca [2,3]

[1] National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic
[2] Biomedical Research Centre, University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic
[3] Department of Chemistry, University of Hradec Kralove, Rokytanskeho 62, 500 03 Hradec Kralove, Czech Republic
[4] Department of Pharmacy and Biotechnology, Alma Mater Studiorum-University of Bologna, Via Belmeloro 6, I-40126 Bologna, Italy
[5] Istituto di Crystallografia, Consiglio Nazionale delle Ricerche, Area Science Park-Basovizza, S.S. 14-Km 163.5, I-34149 Trieste, Italy
[6] Department of Toxicology and Military Pharmacy, Faculty of Military Health Sciences, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic

e-mail: jan.korabecny@gmail.com

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 (*h*AChE) and human butyrylcholinesterase (*h*BChE) within the series, with nanomolar IC_{50} values (6.31 and 9.07 nM, respectively). Moreover, S K1035 showed good ability to inhibit $A\beta_{42}$ self-aggregation and *h*AChE-induced $A\beta_{40}$ aggregation. The X-ray crystallographic analysis of *Tc*AChE in complex with S-K1035 highlighted the utility of the hybridization approach used in the structure based drug design. 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 also significantly ameliorated performances of scopolamine-treated animals.

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