

MEETING ABSTRACTS

BUTYRYLCHOLINESTERASE INHIBITORS GRAFTED WITH ANTIOXIDANT AND NEUROPROTECTIVE ACTIVITIES: NOVEL MULTIFUNCTIONAL LIGANDS FOR ALZHEIMER'S DISEASE

Damijan Knez¹, Nicolas Coquelle², Anja Pišlar¹, Simon Žakelj¹, Marko Jukič¹, Matej Sova¹, Janez Mravljak¹, Florian Nachon³, Xavier Brazzolotto³, Janko Kos¹, Jacques-Philippe Colletier², Stanislav Gobec¹

Presenting author: Damijan Knez¹

- ¹ Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia
- ² University Grenoble Alpes, IBS, F-38044 Grenoble, France; CNRS, IBS, F-38044 Grenoble, France; CEA, IBS, F-38044 Grenoble, France
- ³ Institut de Recherche Biomédicale des Armées, 91223 Brétigny sur Orge, France

Current symptomatic treatment has only limited clinical efficacy and minute effect on progression of Alzheimer's disease. The research focus has thus shifted from single targets towards multifunctional ligands targeting several pathological processes of the disease [1, 2].

A potent picomolar selective inhibitor of human butyrylcholinesterase [3] was used as the starting point to develop a new series of multifunctional ligands. A focused library of derivatives was designed and synthesized that showed both butyrylcholinesterase inhibition and good antioxidant activity comparable to natural antioxidants. The crystal structure of compound 11 in complex with butyrylcholinesterase revealed the molecular basis for its low nanomolar inhibition of butyrylcholinesterase ($K_i = 1.09 \pm 0.12$ nM). In addition, compounds 8 and 11 show metal-chelating properties as determined by the UV-Vis titrations, and reduce the redox activity of chelated Cu^{2+} ions in a Cu-ascorbate redox system. Compounds 8 and 11 decrease intracellular levels of reactive oxygen species, and are not substrates of the active efflux transport system, as determined in Caco2 cells. Compound 11 also protects neuroblastoma SH-SY5Y cells from toxic $\text{A}\beta_{1-42}$ species. These data indicate that compounds 8 and 11 are promising multifunctional lead ligands for treatment of Alzheimer's disease.

Keywords: Alzheimer's disease; butyrylcholinesterase; multifunctional ligands; 8-hydroxyquinoline

References

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2. Das S. et al., *Curr Top Med Chem* **2017**, 17, 3017.
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