MMSL Military Medical Science Letters Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2018, 87(supplementum 1)
ISSN 2571-113X (Online)

MEETING ABSTRACTS

INSIGHTS INTO THE YIN AND THE YANG OF ACETYLCHOLINESTERASE INHIBITION BY MECHANISTIC X-RAY CRYSTALLOGRAPHY

M. Bartolini [1], M.L. Bolognesi [1], J. Korábečný [2,3], K. Kuca [4], D. Lamba [5], A. Pesaresi [5], X. Zha [6]

[1] Department of Pharmacy and Biotechnology, Alma Mater Studiorum University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy
[2] Department of Toxicology and Military Pharmacy, Faculty of Military Health Sciences, University of Defence, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic
[3] National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic
[4] Biomedical Research Centre, University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic
[5] Istituto di Cristallografia, Consiglio Nazionale delle Ricerche, Trieste Outstation, Area Science Park, Basovizza, S.S. n°14 Km 163.5, I-34149 Trieste, Italy
[6] Department of Pharmaceutical Engineering, Department of Biomedical Engineering, School of Engineering, China Pharmaceutical University, 639 Longmian Avenue, Nanjing 211198, PR China

Drug discovery and development is a complex and expensive process. Thanks to the exponential growth of molecular data and advancement in technologies, efforts have been tremendously amplified. Among new approaches multipotent compounds are emerging as the next paradigm in drug discovery [1] and includes: (i) single drug acting on multiple targets of a unique disease pathway, or (ii) single drug acting on multiple targets pertaining to multiple disease pathways. These compounds are thought to have best beneficial effects in the treatment of complex diseases, like Alzheimer's Disease, in which the simultaneous regulation of various pathological aspects may more efficiently interfere with the disease progression. Systematic integration of the data derived from different disciplines including computational modeling, X-ray crystallography, synthetic chemistry, *in vitro / in vivo* pharmacological tests, is mandatory for the selection of best-in-class compounds. In this context, we report on the key contribution of X-ray crystallography in highlighting peculiar mode of interaction of promising multi-target directed ligands, designed by combining the tacrine fragment to distinct pharmacophores i.e. juglone [2], benzofuran [3] and L-tryptophan with a linker of a suitable length.

Overall, the structural analysis highlights the molecular determinants responsible for the optimal binding of the multi-target ligands to AChE and pinpoints the utility of hybridization strategies in structure-based drug design programs. It also unveils the validity of X-ray crystallographic structures determination at certain milestones along the development of interacting inhibitory drugs based on molecular modeling studies.

Keywords: Acetylcholinesterase Inhibition; Structure-Based Drug Discovery; X-ray Crystallography; Alzheimer's Disease; Multi-target directed ligands

References

1. M.L. Bolognesi, A. Cavalli *ChemMedChem*. **2016**, 11, 1190
2. E. Nepovímová, E. Uliassi, J. Korábečný, L.E. Peña-Altamira, S. Samez, A. Pesaresi, G.E. Garcia, M. Bartolini, V. Andrisano, C. Bergamini, R. Fato, D. Lamba, M. Roberti, K. Kuca, B. Monti, M.L. Bolognesi *J. Med. Chem*. **2014**, 57, 8576
3. X. Zha, D. Lamba, L. Zhang, Y. Lou, C. Xu,, D. Kang, L. Chen. Y. Xu, L. Zhang, A. De Simone A., S. Samez, A. Pesaresi, J. Stojan, M.G. Lopez, J. Egea, V. Andrisano, M. Bartolini *J. Med. Chem*. **2016**, 59, 114