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MEETING ABSTRACTS

PLEIOTROPIC PRODRUGS: A NOVEL POLYPHARMACOLOGY APPROACH TO TREAT NEURODEGENERATIVE DISEASES

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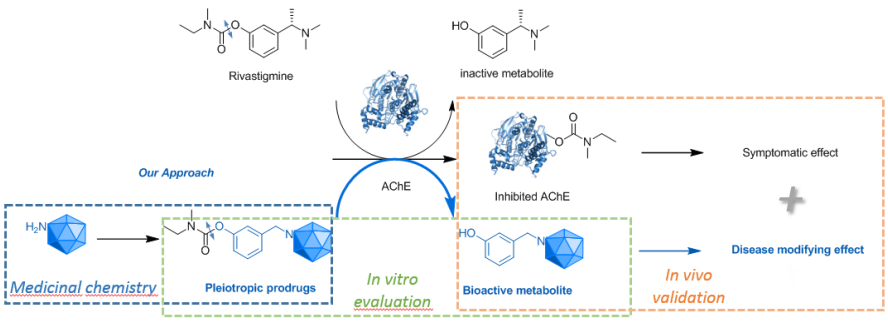
Today, treatment of Alzheimer's Disease (AD) mainly involves acetylcholinesterase inhibitors (AChEIs). AChEIs display solely a symptomatic benefit, alleviating the cognitive disorders associated to AD through a temporary restoration of the cholinergic neurotransmission impaired by the neurodegeneration. The gradual loss of efficiency for AChEIs led to associate them to drugs exhibiting potential disease-modifying properties.

The "Multi-Target-Directed Ligands" (MTDLs) was used in the recent years with a great potential benefit towards multiple targets implicated in the complex AD,[1] as well as other neurodegenerative syndromes, which involve multiple pathogenic factors.

Our contribution to the field led recently to the discovery of Donecopride, the first 5-HT_4R partial agonist, which possesses important acetylcholinesterase (AChE) inhibition properties currently under preclinical development.[2,3] Based on this experience, we have recently developed a novel pleiotropic prodrugs approach to generate promising in vivo active compounds. Based on the structure of rivastigmine, novel MTDLs were designed, acting as prodrugs, able to temporarily covalently bind and inhibit AChE (for a symptomatic effect). and to secondarily release a drug able to selectively reach another AD target (for a potential disease-modifying effect)



This concept was applied to several secondary targets, including different 5-HT receptors of interest[4] for the treatment of AD. The concept, the synthetic development, *in vitro* and *in vivo* evaluation of these candidates and our undisclosed results will be presented for the first time in this communication.

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