Combining structure-based and ligand-based approaches for the design of new MTDLs with potential interest for Alzheimer's disease

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Abstract text: Alzheimer's disease (AD) is the most common form of dementia affecting 50 million of patients worldwide, for which the current treatments produce only symptomatic benefits. Among the biological targets implied in the physiopathology, and especially among the G-protein coupled receptors (GPCRs), melatonergic MT_1 and MT_2 receptors (MT_1R and MT_2R) and serotonergic 5-HT_{2c} receptors (5-$HT_{2C}R$) present a growing interest. For example, these receptors have been shown to promote the non-amyloidogenic cleavage of Amyloid Protein Precursor (APP) and to alleviate the symptoms through several actions such as anti-oxidant effect and regulation of the transmission of other neurotransmitters.[1,2] As AD is a multifactorial disorder, a simultaneous action on these receptors with Multi-Target Directed Ligands (MTDLs) could represent a novel therapeutic approach. With this objective, we performed docking studies into the crystal structures of these three receptors[3-5]. In parallel, we computed pharmacophore models from MT_1R agonists, MT_2R agonists and 5-$HT_{2C}R$ antagonists, using Norns[6], an in-house chemoinformatics tool, in order to understand the polypharmacological profile of a promising new series of compounds (Figure 1). These results will be presented in this communication.

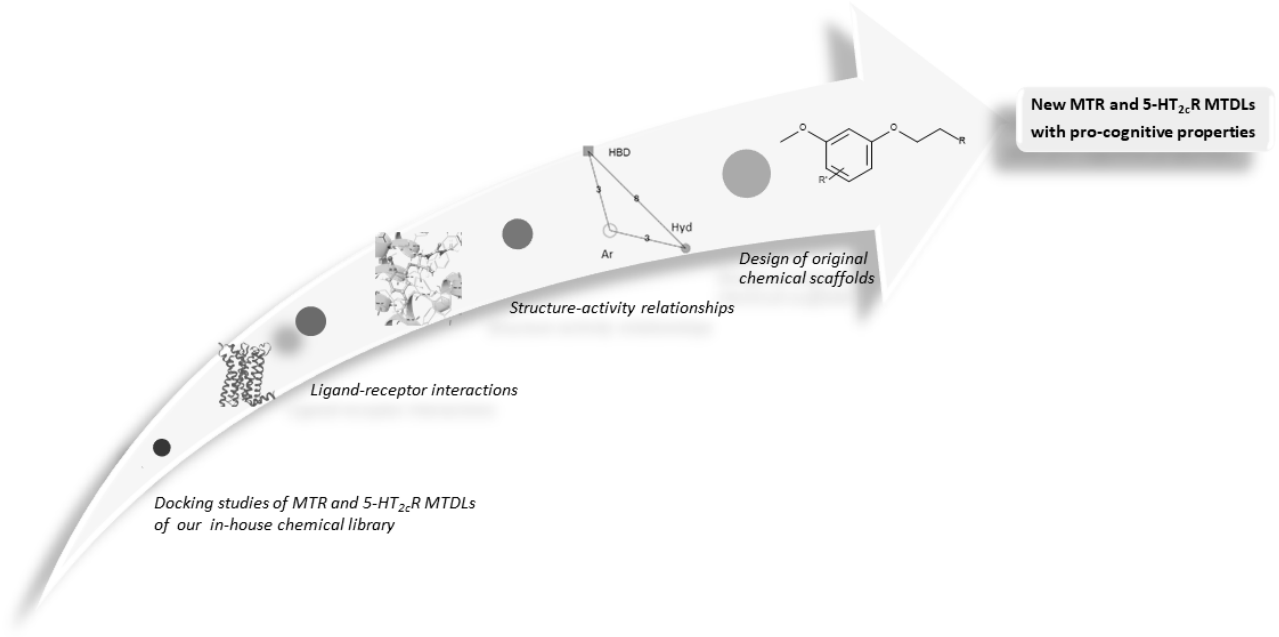

Figure 1. Design of new MTR and 5-$HT_{2C}R$ MTDLs

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