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 MT1 and MT2 receptors (MT1R and MT2R) and serotonergic 5-HT2c receptors (5-HT2cR) 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 receptors3–5. In parallel, we computed pharmacophore models from MT1R agonists, MT2R agonists and 5-HT2cR antagonists, using Norns6, 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-HT2cR MTDLs

Bibliography: