The searching of novel PAM of mGluR III by Virtual Screening of commercial chemical databases

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In recent years the Virtual Screening (VS) has become increasingly popular, as an alternative approach to HTS in the pharmaceutical and academic researches, especially in hit discovery and lead optimization [Shoichet, Nature, 2004; Vyas et al., Sci Pharm, 2008]. This *in silico* technology uses high-performance computing to analyze large database of chemical compounds in order to identify possible new ligands of a given target (top-ranked hits) for biological evaluation [Hou and Xu, Curr Pharm Design, 2004].

Here, we show the implementation of multistep virtual screening workflow to the searching of potentially new Positive Allosteric Modulators (PAM) of mGlu receptors family III. To their construction, a broad range of computational techniques (i.e., 2D fingerprints, 1D molecular descriptors, pharmacophore similarity search, docking and scoring, clustering), machine learning (support vector machines, SVM) and statistical (i.e. PCA and data fusion) methods were applied. The protocol was employed to screen the largest chemical databases (i.e., Enamine, ChemBridge, ChemDiv, UORSY and Vitas-M), containing approximately 5.5 million of tangible compounds.

To improve the global performance parameters of VS, such as efficiency, accuracy and hit rate level, a great effort is being made to develop and validate new tools and methods. Additionally, a web-based interface to the database linking results of different research teams will be shown. Detailed aspects and initial results of this study will be presented.

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Design and synthesis of novel metabotropic glutamate receptor allosteric modulators

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Metabotropic glutamate receptors (mGluRs) are members of the group C family of G-protein-coupled receptors (GPCR) and play important roles in a broad range of central nervous system functions, having therapeutic potential in a variety of neurological and psychiatric disorders, such as Alzheimer's disease, Parkinson's disease, anxiety, depression, and schizophrenia [Conn et al., Ann Rev Pharmacol Toxicol, 2010; Urwyler et al., Pharmacol Rev, 2011].

The mGluRs are categorized into three classes (Group I – III), based on their sequence homology, signal transduction profile and ligand binding specificity [Nieswender et al., Curr Top Med Chem, 2009]. Due to the lack of selectivity and physiochemical properties of mGluR orthosteric ligands, a significant effort has been made to identify compounds that can act as active sites' allosteric modulators. Among all mGluRs, group III further divided into subtypes: mGluR4, mGluR6, mGluR7 and mGluR8 still remains the least characterized and explored.

Herein we present the approach to design as well as further structure development of new synthesized molecules as potential innovative allosteric modulators of group III mGlu receptors. Ligands with known

mGluR activity described in recent literature were collected into a constantly supplemented database, and served as a model compounds for elaboration of new structures supported by pharmacophore models generation.

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