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POSTER PRESENTATION II-33

HUMAN METABOTROPIC GLUTAMATE RECEPTOR-5 (mGluR5) HOMOLOGY MODELLING: AN INNOVATIVE STRATEGY TO MODEL RECEPTOR FLEXIBILITY

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During the last years, a big effort has been focused on the study of modulators at GPCR allosteric sites. Recordati claimed[1] the possibility to treat Overactive Bladder (OAB) dysfunctions using selective metabotropic glutamate receptor subtype 5 (mGluR5) negative allosteric modulators (NAM). From this patent application, a number of close analogues of MPEP and other hit compounds endowed with good affinity for the receptor became available for our studies, all of them sharing a common phenylethynyl portion.

Using these newly synthesised molecules as training set and available binding pocket mutagenesis data we worked on the validation of a mGluR5 homology model, which was generated using the fragmental approach as recently proposed by some of us.[2] In agreement with previous models and mutagenesis data,[3] the allosteric binding pocket was placed among TM3, TM5, TM6 and TM7 helices.

As recently described, [4] conserved proline residues may play a crucial role in conformational changes of receptor since they can assume two well defined conformations (straight or kinked) switching the receptor between the active and inactive state. An innovative strategy to model the receptor flexibility, considering the conformational effect of Pro-containing transmembrane helices, was defined in this study. This approach allowed the generation of an exhaustive set of mGluR5 homology models (also termed chimeras), which differ for the bending of Pro-containing transmembrane helices and thus for the wideness of the TM bundle.

With such constructed chimeras, we decided to focus the docking studies on three chimeras, which were supposed to be representative of the close, intermediate and open receptor structure. The chimera which afforded the best predictive results was characterized by an intermediate opening of TM bundle, confirming that these ligands, even being allosteric modulators, act with an inverse agonism mechanism based on their ability to prevent the full closure and thus the activation of the receptor.

Specifically, Pro-655 (TM3), Pro-743 (TM5) and Pro-790 (TM6) seem to play a main role in the allosteric binding site. The first one may be directly involved in the binding and all together work as a filtering "proline sieve", discriminating among active and inactive compounds and conferring to the receptor a particular rigidity, that can explain the dramatic loss of affinity obtained with minor molecular changes. In agreement with a pharmacophore model developed in house, the "proline sieve effect" is defined by two main ligand aromatic portions, characterized by a different lipophilicity, and rigidly spaced at a distance of about 10 Å with an optimal angle of about 120°.

In summary, this study emphasized the promising potentialities of chimera modelling, confirming the key role of proline residues, within the TM bundle, and suggesting that improved results can be pursued by considering the often disregarded receptor flexibility. This approach could find fertile applications in GPCR modelling affording relevant results both in rational ligand optimization and in virtual screening.

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[1]Selective mGlu5 Antagonists for Treatment of Neuromuscular Dysfunction of the Lower Urinary Tract, *Leonardi,*

264 18th European Symposium on Quantitative Structure-Activity Relationships