Homology modeling of serotonin receptor 5a

***Krzysztof Rataj*, Andrzej J. Bojarski**

Institute of Pharmacology Polish Academy of Sciences, 12 Smętna Street, Kraków, Poland

e-mail: rataj@if-pan.krakow.pl

The 5-HT_{5a} receptor is a rarely considered target for drug designing campaigns, as it is one of the least known class A GPCRs. The 5-HT_{5a} receptor is a pre-synaptic serotonin receptor and it plays an important role in mood control and cognitive functions. Its malfunctioning can be also linked to cognitive impairment in schizophrenia [1].

One of the most reliable methods of computer-aided drug design is the docking methodology, however it requires the complete 3-dimensional structure of the target protein. Since there is no crystal structure available for the 5-HT_{5a} receptor, we resorted to the methodology of homology modeling to acquire putative 3-dimensional structures of the target (Figure 1).

Figure 1: We selected 15 Class A aminergic GPCR proteins with resolved crystal structure as templates for modeling. The alignments were performed automatically using the GPCRdb metaserver [2].

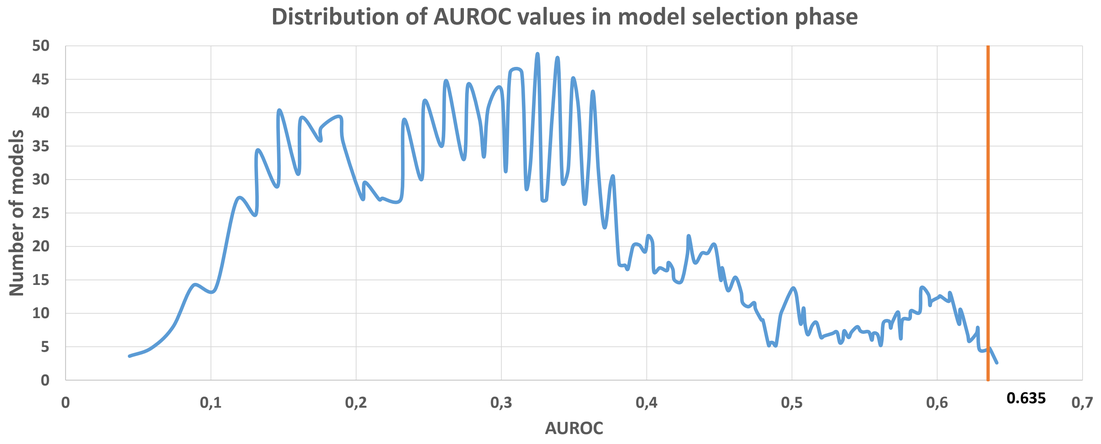

Figure 2: Distribution of AUROC values of the 3000 models created during modeling. The red line represents the cutoff value of AUROC of models that were selected for further research.

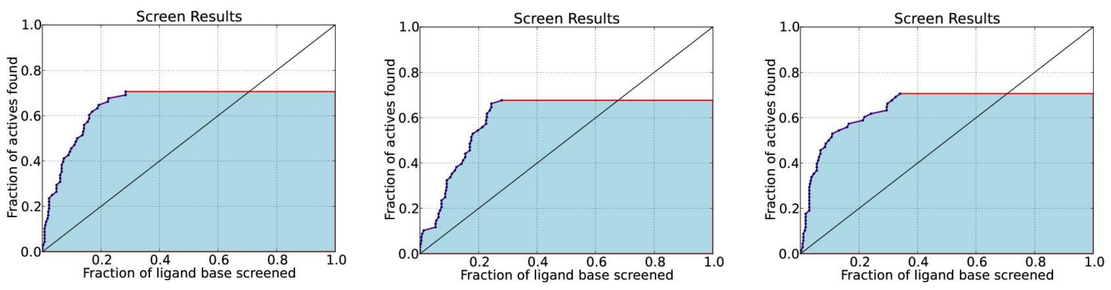

Figure 3: Enrichment results for the 3 best models acquired during the 5-HT_{5a} modeling, based on D3, M2 and M3 templates.

The compounds used for screening were extracted from 5 commercial compound libraries: ChemBridge, ChemDiv, Enamine, Key Organics and Life Chemicals, which gave a total sum of compounds of 2M. Using various ligand-based approaches, the number of compounds was greatly reduced to a total of 5000 (Figure 4).

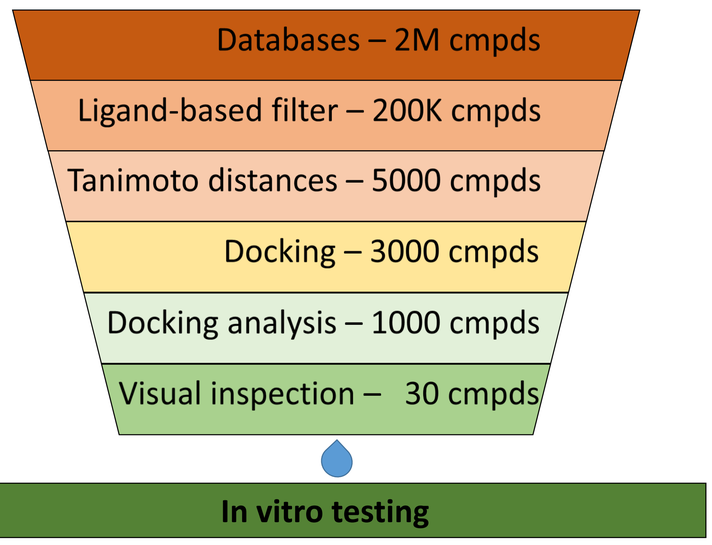

Figure 4: Number of compounds present at each step of the screening cascade

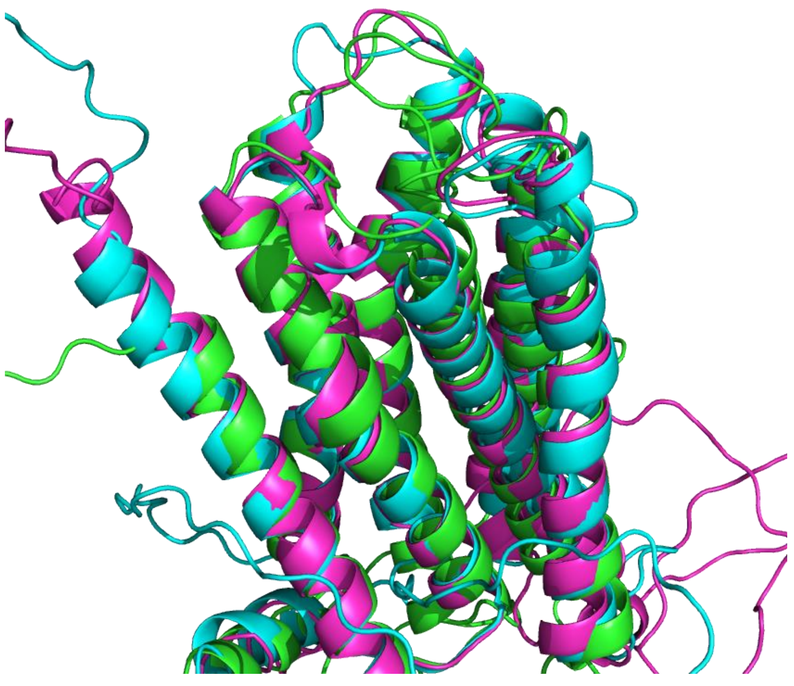

Figure 5: An ensemble of the best models of 5-HT_{5a}, based on D3, M2 and M3 templates

The 5000 compounds from the commercial databases remaining after the ligand-based filtering were finally docked to the 10 selected 5-HT_{5a} models using Schrodinger's Glide software with SP precision. On average, each model was able to dock around 3000 compounds.

In order to ensure that the selected compounds have the highest probability of being active towards 5-HT_{5a}, we considered only those compounds, which were able to dock to all 10 5-HT_{5a} models with GlideScore of at least -3. This resulted in acquisition of 1000 compounds for visual inspection.

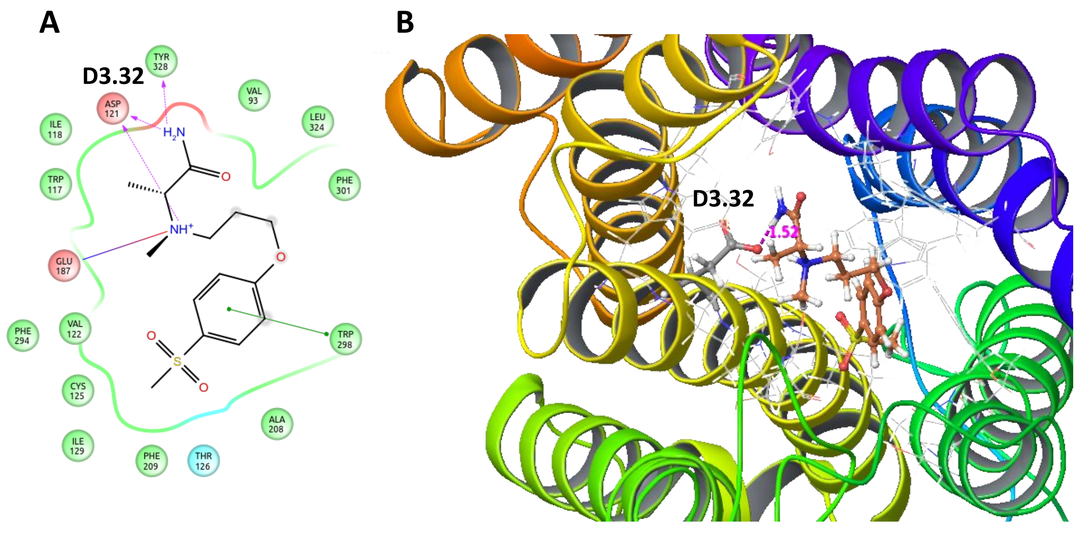

Figure 6: Representation of a docking pose fulfilling the screening criteria, shown as ligand interactions in 2D (A) and in a ligand-receptor complex (B)

The visual inspection was focused on ligand-receptor complexes acquired during the docking phase. In this stage, those complexes were evaluated for their ability to form a charge-assisted hydrogen bond between D3.32 residue of 5-HT_{5a} and a positively charged nitrogen within the compound, as this interaction is deemed to be crucial for proper receptor activation (Figure 6). The secondary criterion was the ability of the compound to interact with the aromatic cluster present within the TM6 domain of the protein.

Finally, a set of 30 compounds was selected for *in vitro* screening, and will be tested for their activity towards 5-HT_{5a} serotonin receptor.

Acknowledgments:

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References:

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