From homology models on raw templates to a set of ALiBERO binding pockets – a 5-HT_{1A} receptor case study

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Introduction. ALiBERO (Automated Ligand-guided Backbone Ensemble Receptor Optimization) [1] is a new computational tool which expands the pocket selection from single to multiple in an automatic way. Pocket selection procedure uses comprehensive combinatorial search enriching final receptor ensemble by only those that maximize the discrimination of active compounds from decoys. ALiBERO framework is a heuristic search composed from two main steps: generation of multiple receptor conformations and selection of the best individual conformations according to the flexible-docking static-receptor small-scale docking performance. Then, the best performing pockets are selected for the next generation of receptor conformers. This iterative process is repeated until the threshold for the fitness function is reached. AliBERO algorithm was applied for 5-HT1A receptor, a well-recognized therapeutic target [2,3] intensively studied in our laboratory [4-7].

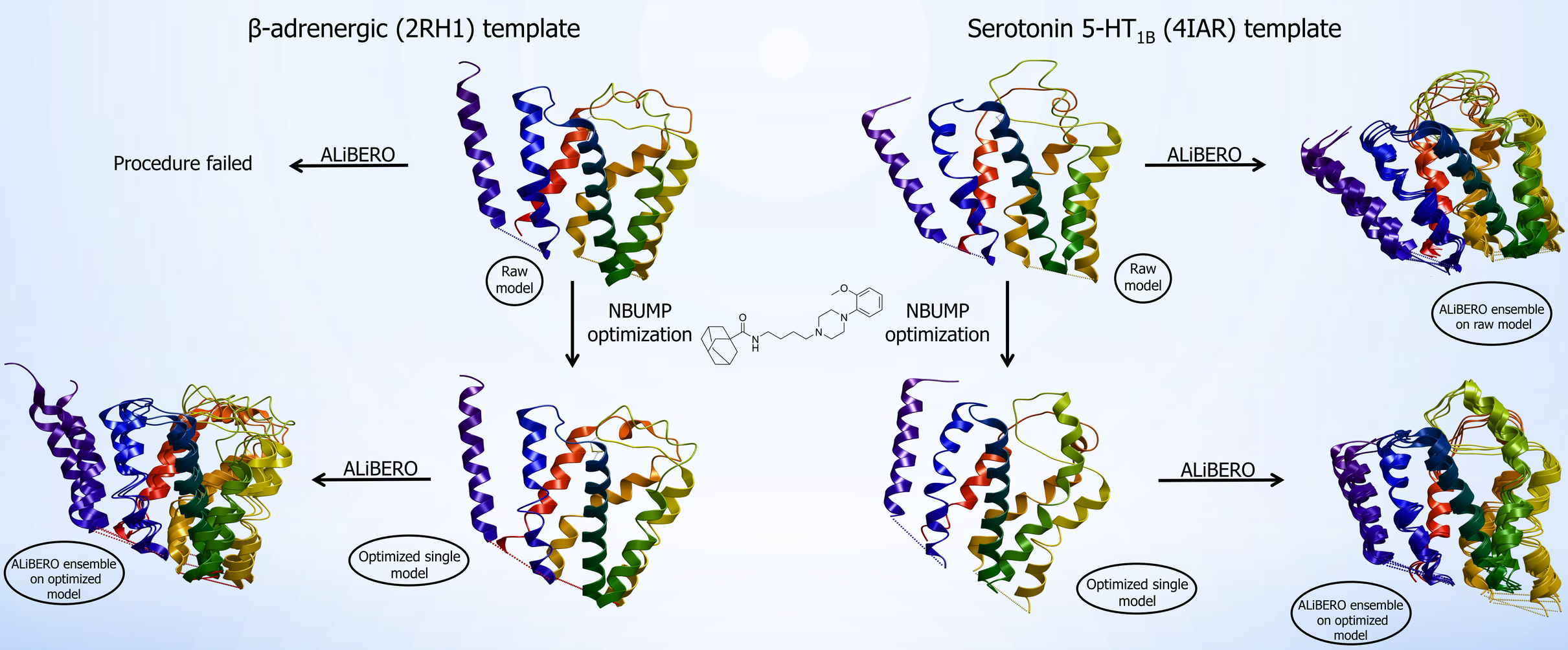

Figure 1. For each template raw models were first optimized on a highly active compound (NBUMP). Single models (both raw and optimized) were used for ALiBERO ensembles generation on training set (Figure 2a) and validated on test set (Figure 2b).

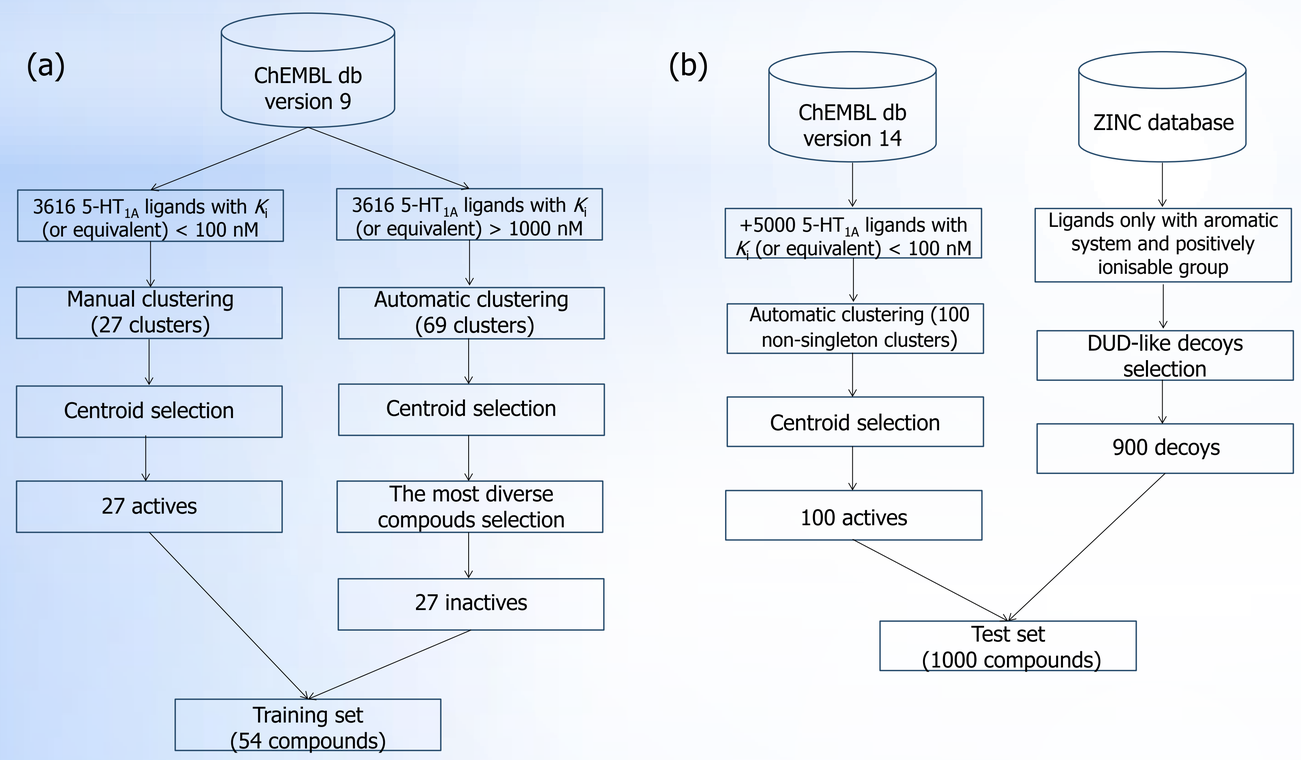

Figure 2. Preparation and composition of (a) training and (b) test sets.

Methods. The experiments were performed on two different templates: β-adrenergic (2RH1) [8] and the recently published 5-HT1B (4IAR) [9] - the closest 5-HT1AR homologue (Figure 1). Raw models were first optimized on NBUMP – compound with a very high affinity for the 5-HT1A receptor (Ki=0.1 nM) [10]. Then, both raw and the optimized single models were used as input structures for ALiBERO algorithm. Optimization process were performed on the training set of 27 active and 27 inactive diversified compounds (Figure 2a). The effectiveness of individual approach was checked in virtual screening-like experiment with 100 diverse 5-HT1AR ligands and 900 DUD-like decoys (Figure 2b). Each experiment was assessed by area under the receiver operating characteristic curve (ROC) [11] describing ability of classification procedure to recognize true positive and negatives. Normalized Square root AUC (NSQ_AUC) metric [12] which is especially sensitive on early hit enrichment was also calculated (Table 1).

Table 1. Summary of the results before and after ALiBERO optimization of 5-HT1A receptor models.

Model	AUC	NSQ_AUC
4IAR raw single model	0.716	0.402
2HR1 raw single model	0.682	0.308
4IAR optimized single model	0.775	0.541
2HR1 optimized single model	0.829	0.605
4IAR ALiBERO ensemble on raw model	0.815	0.572
4IAR ALiBERO ensemble on optimized model	0.851	0.675
2HR1 ALiBERO ensemble on optimized model	0.826	0.625

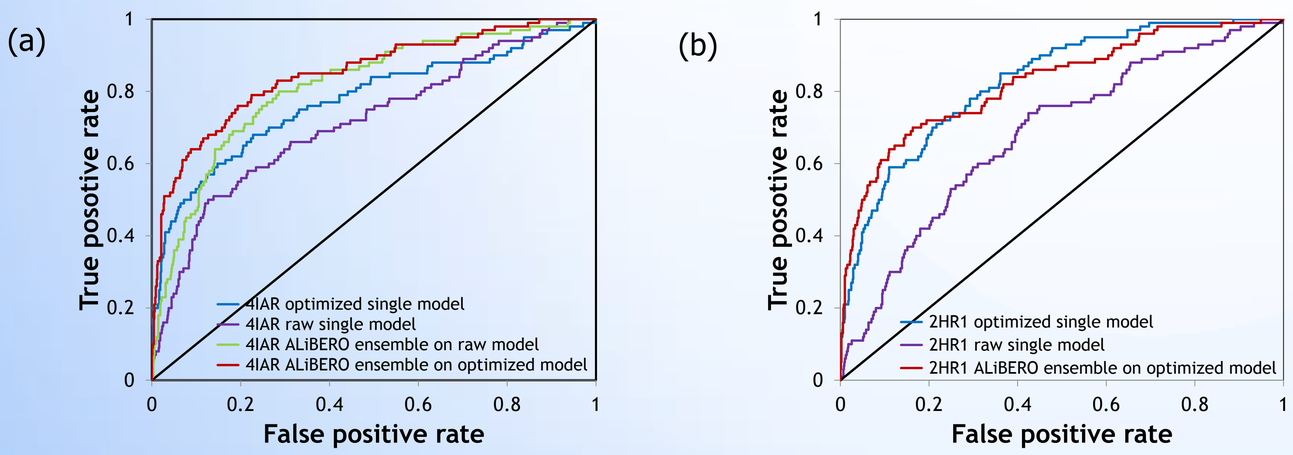

Figure 3. ROC curves for models based on (a) 4IAR and (b) 2HR1 templates.

Results and discussion. The results (Table 1. and Figure 3.) show expected superiority of ALiBERO ensembles over the raw or pre-optimized single models. Interestingly, quite satisfactory level of discrimination between actives and inactives was reached for a single model, optimized only on one highly-potent ligand. While the ensemble of receptors always outperformed single model, the impact of template is ambiguous. 4IAR template raw model worked better then raw 2HR1 model. However, optimization on NBUMP ligand reversed this trend. Nevertheless, ALiBERO ensembles were more efficient when 4IAR template was used.

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Acknowledgements

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