PREPARATION OF COMBINATORIAL LIBRARIES BY USING SCAFFOLD'S PROTEIN LIGAND INTERACTION FINGERPRINTS (PLIF)

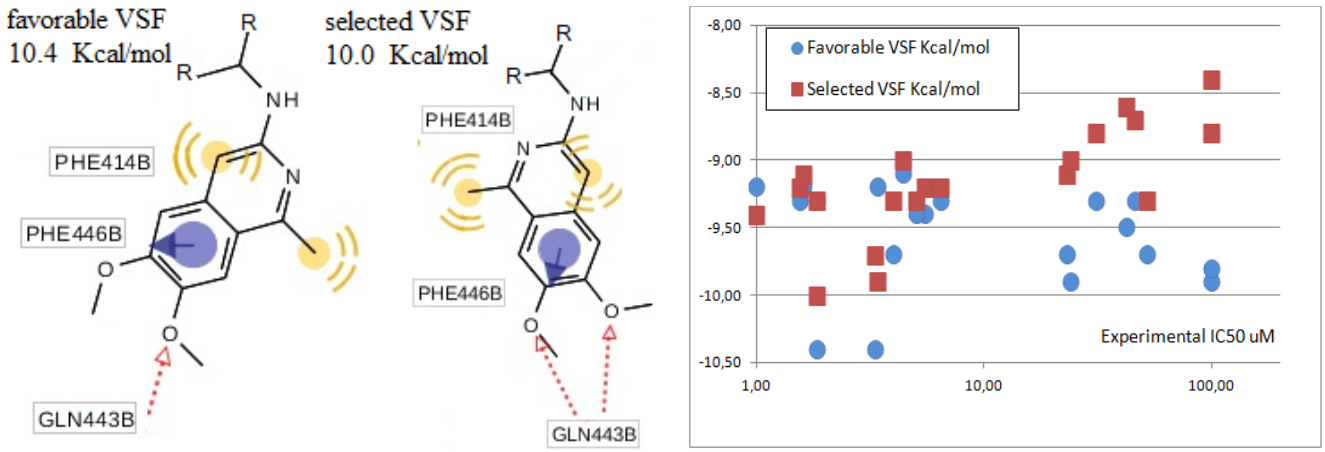
G.B. Lapa

Pirogov Medical University (RSMU), Moscow, Russia

Protein-ligand interactions fingerprints (PLIF) allow to constraint docking scoring functions for more rational evaluation and cross validation of docking results, etc [1]. Compounds of combinatorial library (CL) contain some "main scaffold" and "decorative elements" like side radicals, additional cycles, pseudo-cycle, etc. Obviously both parts are critically important to provide sufficient input in protein-ligand interactions. We believe that the PLIF approach has a limitation in some situations since operate with information about whole molecule. Comparison of complete PLIF and separation similar or dissimilar compounds could reduce chemical diversity of CL. We were trying to avoid this limitation when used only "partial PLIF" for scaffold only. We were trying to answer to c117ouple of questions. How to separate constant part of scaffold's PLIF from variable part? Would be beneficial to use only scaffold's PLIF to design of combinatorial libraries?

We used simplest rules to determine PLIF of ligands and phosphodiesterase of cyclic nucleotide PDE4B [2]. Scaffold's PLIF were determined from several files: piclamilast-1xm4.pdb ciclomilast-1xlx.pdf and papaverine-3iak.pdb as a combination of F414-HP (hydrophobic bond), Q443-HB (two hydrogen bonds) and F446-PP (pi-pi-interactions). Compounds of CL were docked into PDB4B 1xm4.pdb by the Vina-protocol. It was selected set of compounds with appropriate scaffold's PLIF only. Figure shows that selected way of proposed ligand and the most favorable pose by the Vina-protocol were different. The diagram shows that Vina scoring function (VSF-binding energy Kcal/mol) of selected compounds were less than most favorable VSF of those compounds. Nevertheless the correlation between VSF of selected compounds and experimental IC_{50} [3] was much better than between favorable VSF and experimental IC_{50}: R2=0.51 vs R2=0.07.

This approach based on scaffold's PLIF could be used as a general way to select, range and score new virtual compounds for new CL. Chemical diversity of CL made by this approach would be compared with traditional approaches of CL planning.



1. Tran-Nguyen., V.-K., Ballester, P.J. J. (2023) *Chem. Inf. Model.* 63, 1401.
2. Chupakhin, V., Marcou, G., Gaspar, H., et al. (2014) *Comput. and Struct. Biotechnol. J.,* 10, 33.
3. Lapa, G.B., Moiseeva, N.I., Tsunoda T. (2021) *Uspechi Mol. Oncol*. 8, 4, 138.