Aquaporins Targeted Library

1,500 *compounds*

Designed using docking and 2D similarity search to target water channels

Enamine's Aquaporins Targeted Library includes compounds for targeting end-chains and internal central pore of water channels (Aquaporins) AQ1, AQ4, and AQ5. Since limited number of ligands is known for this type of targets to date, docking approach was used to search new potential inhibitors. In addition to that, 2D similarity search was performed to enrich the library with compounds similar to the reported actives.

Library Design

Three protein structures (3D9S, 1IH5, 3GD8) were chosen after analysis of 11 available X-Ray structures (1H6I, 1IH5, 2ZZ9, 3GD8, 4NEF, 3D9S, 5DYE, etc.). Mutation studies published in the literature allowed identification of several hot-spots located inside the channel; these data were used for preparation of docking models on the initial stage of the protein structure refinement if the corresponding amino acid residues were involved in interaction directly. Additionally, the whole surface of each protein monomer was probed with FT-MAP server – a tool which is based on evaluation of energy interaction between small organic probes (solvents, saturated and unsaturated rings etc.) and the surface of interest. This method showed itself as very accurate and trustworthy for binding site identification.

Design of the library was performed using two different approaches: flexible docking and high throughput virtual screening. Flexible docking protocol assumed a partially-free rotatable motion of the side-chains, which are located at the entrance of both cavities in AQ5/AQ4/AQ1 proteins. The area of flexibility covered about 5 $Å^2$ around the center of the channel in one unit of the tetrameric structure. The center of a Grid box (defining the binding area) was selected using the data from the above-mentioned residue mutation studies and FT-MAP calculations. To expand the volume of putative binding sites, a set of confirmed inhibitors disclosed in publications and ChemBL database were docked, together with some other compounds which were shown to interact with the target. Specifically, AqB013, Bumetanide, Zonisamide, Arbidol and Acetazolamide were taken from the literature data, and some neurotransmitters (*e. g.* dopamine, epinephrine and serotonine) were chosen based on the results obtained in our previous collaboration with academic groups.

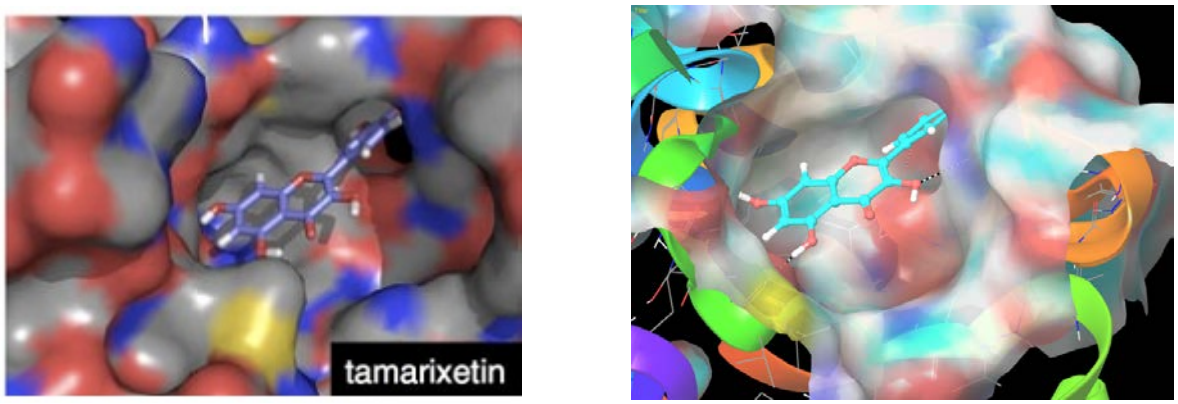

Figure 1. Reported binding mode of tamarixetin (left) and representation of a hit molecule obtained after the docking (right)

In this way, optimized structures of the active sites were obtained, which were used for the screening procedure with slightly less exhaustive parameters of pose estimation and lower number of generated conformers (Figures 1 and 2). Compounds which possessed a hydrophobic moiety and formed 2–3 hydrogen bonds with the key amino acid residues of the active sites were subjected to more accurate and time-consuming docking procedure. The highest-scoring hits were included into the final Library; the score used for the selection was a combination of empiric values, post-processing calculation of energy, as well as steric and H-bonding impacts.

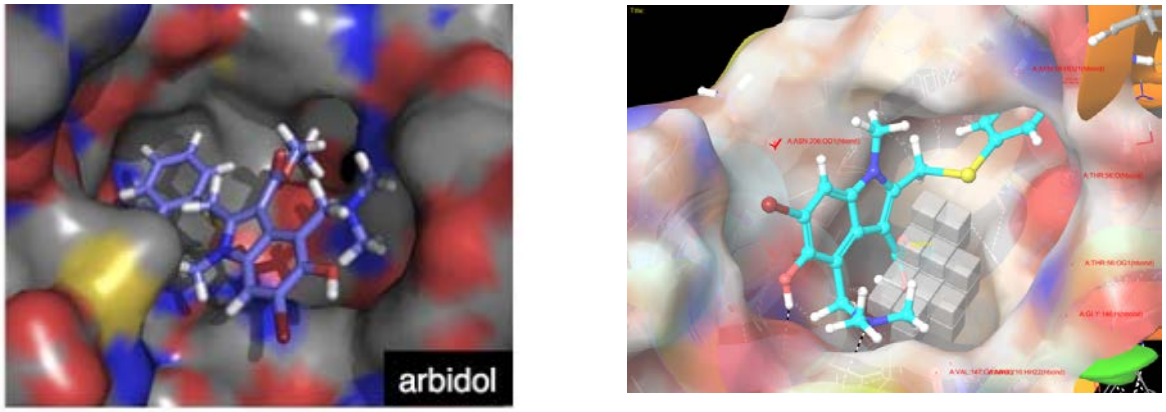

Figure 2. Several residues responsible for the substrate/inhibitor binding (G146, V147, R216, T56, Asn58, Gly209, and Val141) (right); they are also important for binding of arbidol (left)