Aquaporins Targeted Library

Aquaporins are integral membrane proteins from a larger family of major intrinsic proteins with previously unknown structures. Aquaporins selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes. Known inhibitors that display high activity against aquaporin 1, 4 and 5, are Acetazolamide, Zonisamide, Bumetanide, AQB013, Arbidol and Tamarixetin (Fig.1).

When designing the Life Chemicals Aquaporins Targeted Library, our interest was focused on binding sites 3 and 1 [1, 2]. To delimit possible ligand binding sites, FTMap server was used. FTMap is an on-line tool for binding site search, visual localization of molecular probes (small molecules or functional groups) in the site volume and solvent mapping of the surfaces. Overlapping of molecular probe clusters points to the potential binding site location.

Flexible Glide docking was used to prepare aquaporin 1, 4 and 5 docking grids and constraints for subsequent ligand screening mode. After that, three ligand binding sites were processed and prepared for docking of a test compound set. Minimization of docked ligand poses and binding site amino acids within contact distance was carried out in SYBYL-X.

Based on docking poses of a test set of compounds, 4 docking models have been built for site1 and site3 of aquaporin 1, 4 and 5 (Fig. 1, 2). Selected compounds were sorted by score value and binding site accessory - aq1,4 (these two were combined as their structures are too similar) site1 - 607, site3 - 340, aq5 site1 - 724, site3 – 343.

Total number of compounds in the library is more than **2,000**. Subsets of compounds related to each target are presented separately.

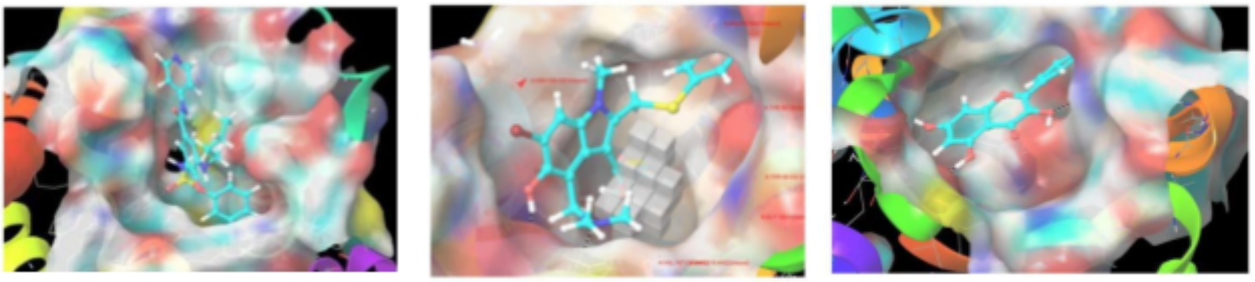

Fig.1. Docked conformation of known aquaporin inhibitors AQB013 (left), Arbidol (center) and Tamarixetin (left) in the binding site of Aquaporin 4. Atoms and regions that are predicted to form donor/acceptor interactions with ligand atoms and hydrophobic cores are indicated.

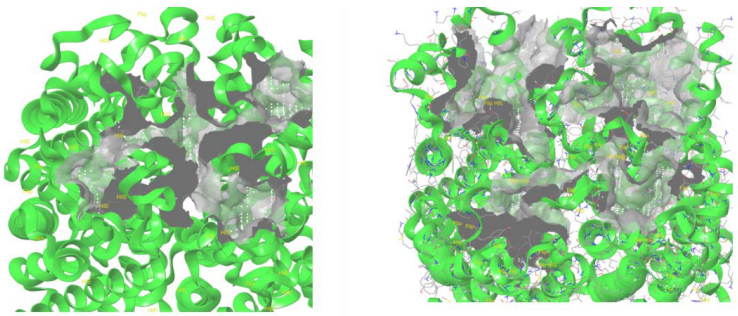

Fig.2. Solvent-accessible surface representation of the binding site cavities of Aquaporin-4 (left) and Aquaporin-5 (right).

References

1. Small-molecule inhibitors of NMO-IgG binding to aquaporin-4 reduce astrocyte cytotoxicity in neuromyelitisoptica. LukmaneeTradtrantip, Hua Zhang. 0892-6638/12/0026-2197 © FASEB
2. Inhibition of Aquaporin-1 and Aquaporin-4 Water Permeability by a Derivative of the Loop Diuretic Bumetanide Acting at an Internal Pore-Occluding Binding Site. Elton Migliati, Nathalie Meurice. Molecular pharmacology Vol. 76, No. 1