GPCR Receptor-Based Targeted Library

Seven-transmembrane receptors, also known as G-protein-coupled receptors (GPCRs) are integral membrane proteins that contain seven membrane-spanning helices. This superfamily of cell surface signaling proteins plays a crucial role in many physiological processes and in numerous diseases, including cancer development.

The design of Life Chemicals GPCR Receptor-Based Targeted Library involved application of several computational methods such as homology modeling, reference compounds set selection and analysis, molecular dynamics, molecular docking and *in silico* version of high-throughput screening (HTS).

Each GPCR target (see the list of targets below) was prepared and optimized with Schrödinger software. Some individual protein structures were further relaxed with molecular dynamics simulation in GROMACS. The reference set of compounds selected for screening validation contained known and proven inhibitors of GPCRs derived from ChEMBL database. Glide Docking (Schrödinger) and Unity modeling (SYBYL-X) protocols were applied for docking and screening procedures (Fig. 1). Docking of the reference set has been done to provide full information about possible conformations of the active ligands and interaction types one can expect as a result of a HTS procedure.

Life Chemicals GPCR Receptor-Based Targeted Library includes about **8,543** compounds with predicted activity against 16 GPCR targets. Hit ranking was based on score values obtained from docking of the reference set.

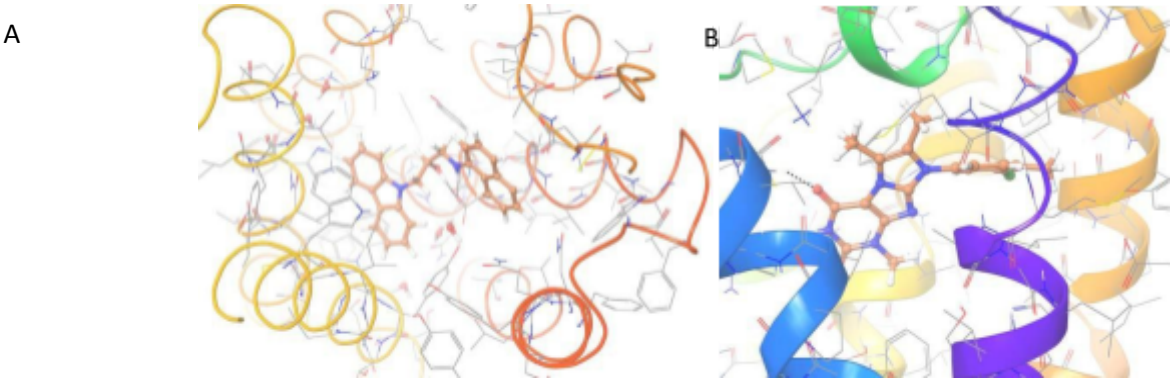

Fig. 1. A. Preparation of the grid map and validation of ergotamine docking conformations in the 5HT-2B receptor binding site considering water molecule orientation. B. Flexible docking of the test compound in histamine binding site of the histamine receptor.

The list of GPCR target proteins and the corresponding number of compounds obtained by means of HTS:

Adenosine receptor

- A2A **197** compounds
- A2B* **1054** compounds
- A3* **149** compounds

Chemokine receptor

- CXCR4 **805** compounds
- CCR5* **367** compounds

Histamine receptor

- H1 **925** compounds
- H3* **149** compounds
- H4* **1,131** compounds

Opioid receptor

- Delta-type **825** compounds
- Kappa-type **696** compounds
- Mu-type **669** compounds
- Dopamine D3 receptor **1,911** compounds
- GABA receptor subunit **295** compounds
- Muscarinic acethylcholine receptor type **21,126** compounds
- Sphingosine 1-phosphate receptor **822** compounds
- Serotonine receptors (type 5HT1B) **650** compounds

**homology modelling approach*