Ion Channel Targeted Library (Pharmacophore Based)

The sequencing of the human genome has identified more than 400 putative ion channels, but only a fraction of these have been cloned and functionally tested. The widespread tissue distribution of ion channels, coupled with the plethora of physiological consequences of their opening and closing, makes ion-channel-targeted drug discovery highly compelling. However, despite some important drugs in clinical use today, as a class, ion channels remain underexploited in drug discovery and many existing drugs are poorly selective with significant toxicities or suboptimal efficacy [1].

This Ion Channel Targeted Library was designed by a receptor-based approach employing X-ray data for 10 human ion channel targets (complexed with small-molecule ion channel modulators) available from the Protein Data Bank:

- Glutamate receptor ionotropic, kainate 1 (GRIK1)
- Annexin V
- Potassium channel subfamily K member 10
- Small conductance calcium-activated potassium channel protein 2 (SK2)
- Glycine receptor subunit alpha-3
- Glutamate receptor ionotropic, NMDA 2A (GRIN2A)
- Glutamate receptor 2 (GluR2)
- Ionotropic glutamate receptor GluR5
- Excitatory amino acid transporter 1 (EAAT1)
- Cystic fibrosis transmembrane conductance regulator (CFTR)

For each of these complexes, a receptor-based pharmacophore model has been built with various “features” describing the binding mode: H-bond donor, H-bond acceptor, aromatic ring, hydrophobic group, positive or negative charge (Fig.1). Each model contained “excluded volumes” simulating the atoms of the binding site surrounding the ligand and, thus, preventing compounds to be placed in these space points during screening. Next, the Life Chemicals HTS Stock Compound Collection has been screened against each pharmacophore model with pre-generated conformers (up to 50 conformers for each compound) (Fig.1, 2). Resulting compounds were filtered by Rule of Five, presence of PAINS compounds, as well as those with "bad" and reactive groups.

Finally, the focused library comprised almost **6,000** compounds showing the best fit against the corresponding pharmacophore models. Information on the corresponding target and the pharmacophore “ fitness” score is included in the library for each compound.

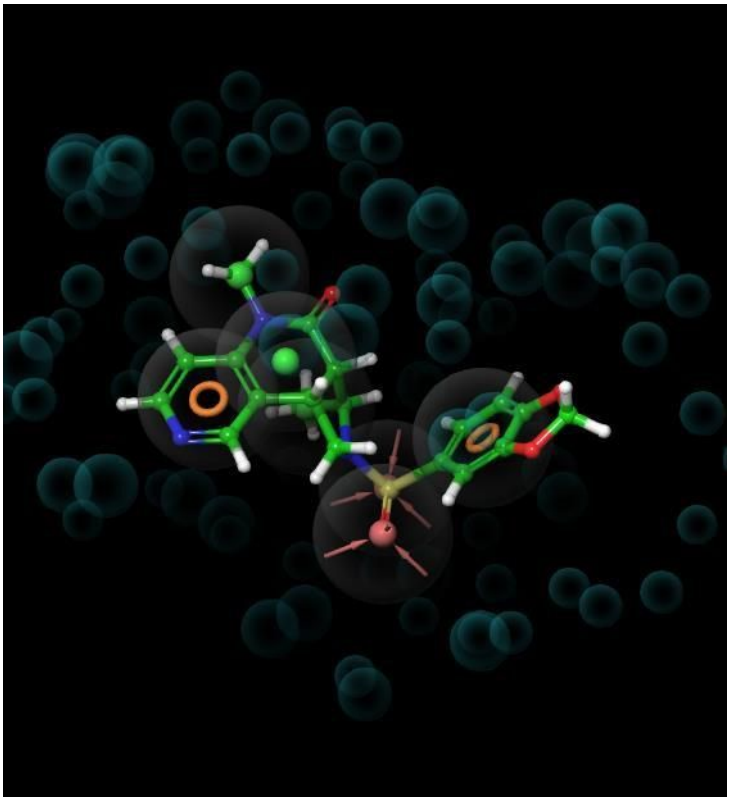

Fig. 1. A pharmacophore model based on Glycine receptor subunit alpha-3 bound to AM-3607. Excluding volumes simulating the receptor atoms are shown as blue-green spheres.

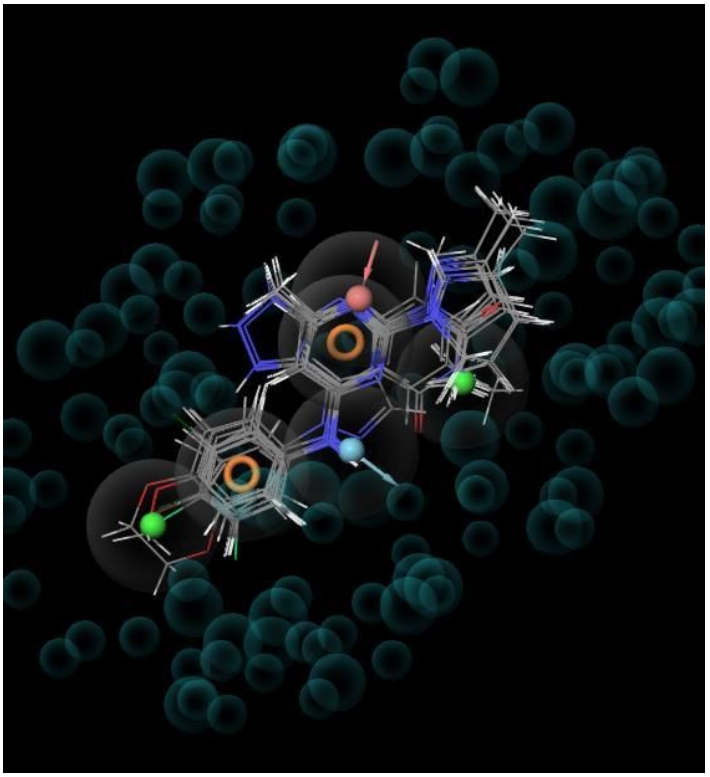

Fig. 2. An example of Life Chemicals compounds matching the SK2 ion channel pharmacophore model. Excluding volumes simulating the receptor atoms are shown as blue-green spheres.

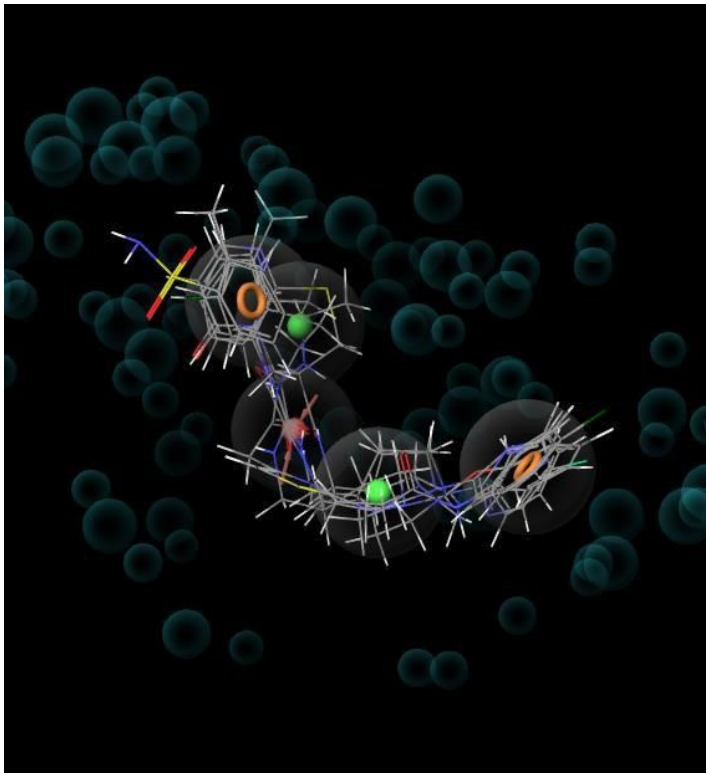

Fig. 3. An example of Life Chemicals compounds matching the Annexin V pharmacophore model. Excluding volumes simulating the receptor atoms are shown as blue-green spheres.

References:

1. Bagal SK, Brown AD, Cox PJ, Omoto K, Owen RM, Pryde DC, Sidders B, Skerratt SE, Stevens EB, Storer RI, Swain NA. Ion channels as therapeutic targets: a drug discovery perspective. *J Med Chem*. **2013,** 56(3), 593-624.