Phosphodiesterase (PDE10) Targeted Library

Phosphodiesterases (PDE) are a family of enzymes that degrade the phosphodiester bond in the second messenger molecules - cAMP and cGMP, to terminate signal transduction. PDE10, a dual cAMP/cGMP phosphodiesterase, is expressed at high levels in the striatal medium spiny neurons, but at very low levels elsewhere in brain and other tissues. Therefore, it is an attractive target for effective and selective treatment of degenerative CNS disorders. Inhibitors of PDE10 may potentially treat psychiatric and neurological diseases, including schizophrenia, delusional disorder, anxiety disorders, Alzheimer's disease, movement disorders such as Parkinson's and Huntington's diseases. Cognitive dysfunction is responsible for substantial disability in most of these diseases and is not improved significantly by current medications.

We have combined different computational approaches to develop a unique method for *in silico* search of potential PDE10 inhibitors. At the first stage, a general 3D pharmacophore model was created based on the structure of three most potent PDE10 inhibitors (Fig.1). The model was validated using a reference set of 150 active and 10 non-active compounds (ChEMBL DB).

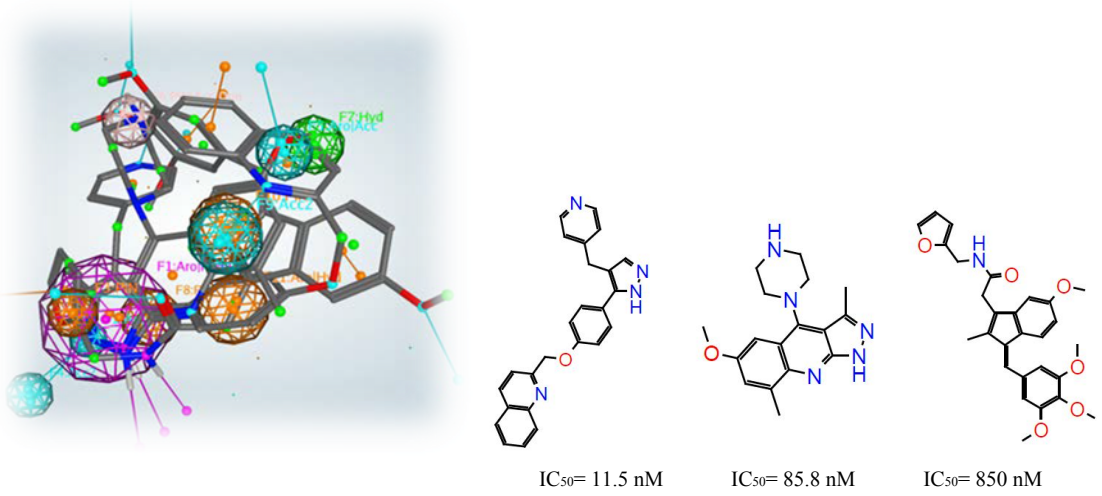

Fig. 1. Pharmacophore model obtained from superposition of 3 potent inhibitors.

TopomerSearch tool implemented in SYBYL-X was used for effective and quick selection of potentially active molecules based on pharmacophore definition. At the next step, the structure of the binding site of PDE10 including water molecules was modeled. Protein structures recorded in 3UI7, 3UUO and 4BBX PDB entries were filled with water molecules and optimized using a series of molecular dynamics simulations (GROMACS). The most stable protein structure during calculations was used for docking. A grid model of PDE10 binding site was created based on features of both key amino acids and a co-crystalized ligand (Glide, Schrödinger). Docking constraints were determined and optimized, using a reference set of molecules with known activities. The scoring rates were brought into conformity to *in vitro* inhibitory data.

Finally, **427 small molecules** were predicted as potential PDE10 inhibitors from Life Chemicals Stock Compound Collection (Fig. 2).

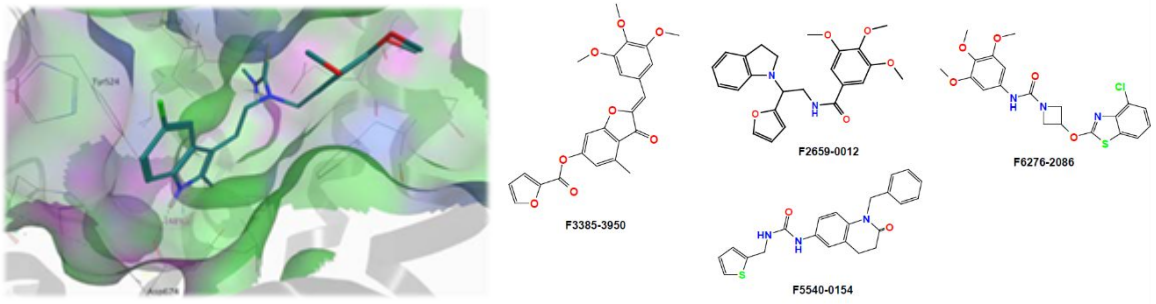

Fig. 2. Example of the binding mode of a hit molecule (left) and some hit structures obtained after docking (right).