Computer Aided Drug Discovery. Case studies

Case study 1. 3D shape workflow

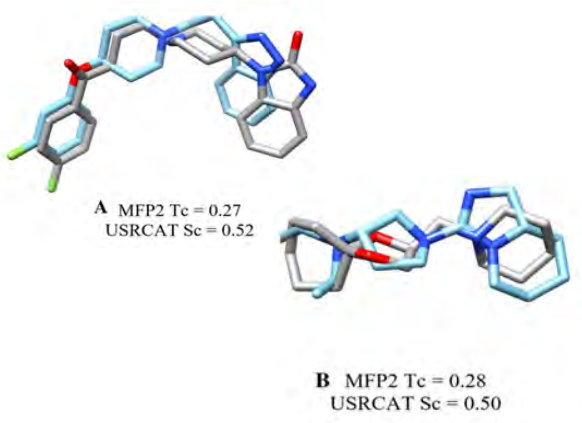
Create of targeted compound libraries based on 3D shape recognition

Methods

Aiming to build a tool for comparing 3D-shapes of small organic bioactive molecules, we used a concept of invariant 3D-fingerprints called Ultrafast Shape Recognition with Credo Atom Types (USRCAT).

Result

Free pipeline for the generation of protein-targeted molecular libraries oriented towards finding novel chemotypes. It maintains a 3D similar but 2D dissimilar structure.



Case study 2. PPI library: PDZ-domains

Methods

2,800 conformations from 163 PDZ domains. Space of shape descriptors: undruggable conformations. Space of shape descriptors: Alignment and analysis of protein binding sites Clustering. 6 conformations selected for virtual screening.

Result

Library of 1,000 compounds validated activity. Method of shape-based library design for a class of PPI domains was further used for other targets because of its effectiveness and high success rate.

Case study 3. Inhibition of syntenin PDZ2

Pharmacological inhibition of syntenin PDZ2 domain impairs breast cancer cell activities and exosome loading with syndecan and EpCAM cargo

Methods

Molecular modelling studies, relying on the X-ray structure of C58 and MOE/Pymol tools, suggested several changes to increase activity :

-addition of one carbon spacer in the compound structure could maintain both the canonical binding mode

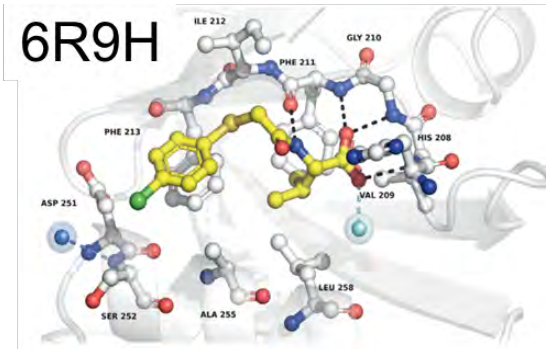
-the face-to-face π-stacking with Phe213, while slightly increasing the distance between the hydrophobic thioether-chlorophenyl moiety and the polar protein backbone

-better torsion angles, closer to optimal geometry (60◦), with favourable staggered conformation on the flexible carbohydrate moiety

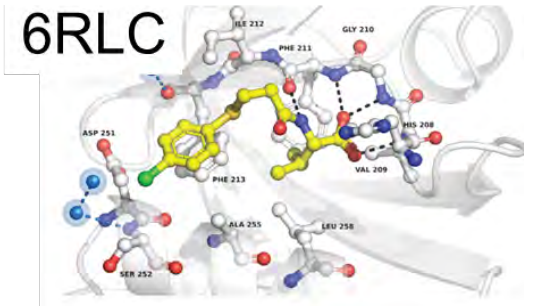
Result

After docking of the PDZ library – 139 compounds were selected and Five structurally related compounds were obtained as hits after biology validation.

An optimization strategy, based on crystallographic data, enabled the development of SyntOFF where the introduction of an additional methylene group improved the affinity 10-fold compared to C58 (IC50 = 37 μM).



X-ray crystal structure of a complex syntenin-PDZ2 domain with one hit (C58) was resolved (PDB code 6R9H).



The X-ray crystal structure of compound SyntOFF in complex with syntenin was also resolved (PDB code 6RLC) indicating.

Case study 4. The mechanism of the ion channel

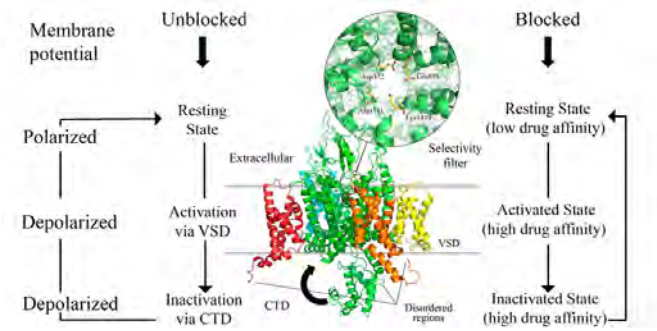
Study of the effect of inhibitors on the mechanism of the ion channel

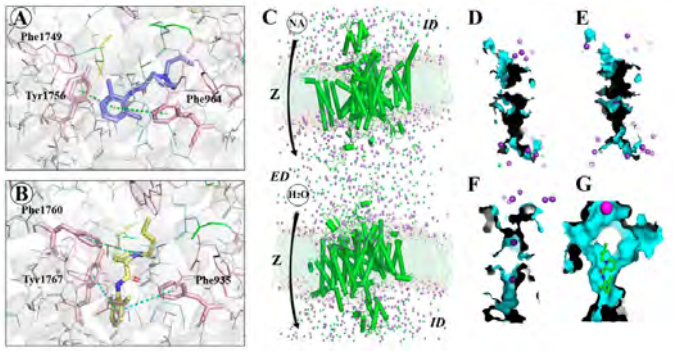
Methods

To prevent a collapse of the system, a trans-membrane protein was embedded in a lipid bilayer. A double membrane system was generated, implying a free of ligand Nav1.5 protein and on the opposite side its copy containing a docked bupivacaine molecule inside the pore channel.

Result

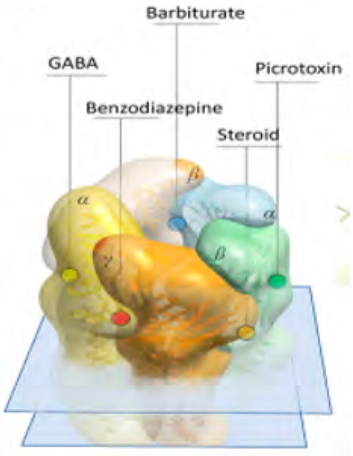
Developing the CompEI swapping protocol to allow understanding molecular binding details and subsequent structural rearrangements, that could give a chance to increase the potency of novel compounds against Nav1.7and avoid the influence on the Nav1.5.





Case study 5. Identification of new GABA modulators

Integrated workflow for the identification of new GABA positive allosteric modulators based on the in silico screening with further in vitro validation. Case study using Enamine's stock chemical space



Methods

Our study represents a convenient and tunable model for the discovery of novel positive allosteric modulators of GABAA receptors.

Result

A High-throughput virtual screening of the largest available database of chemical compounds resulted in the selection of 23 compounds. Further electrophysiological tests allowed us to determine a set of 3 the most outstanding active compounds. Considering the structural features of leader compounds, the study can develop into the MedChem project soon.

Selected publications

1. Creation of targeted compound libraries based on 3D shape recognition. Mol Divers 27, 939–949 (2022). DOI: 10.1007/s11030-022-10447-z
2. Pharmacological inhibition of syntenin PDZ2 domain impairs breast cancer cell activities and exosome loading with syndecan and EpCAM cargo. J of Extracellular Vesicle 10, (2020). DOI: 10.1002/jev2.12039
3. Modelling of an autonomous Nav1.5 channel system as a part of in silico pharmacology study. J Mol Model 27, (2021). DOI: 10.1007/s00894-021-04799-w
4. Integrated workflow for the identification of new GABA positive allosteric modulators based on the in silico screening with further in vitro validation. Case study using Enamine's stock chemical space. Molecular Informatics (2023)