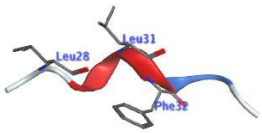
Protein-Protein Interactions

Protein-protein interactions (PPI) represent a very promising class of therapeutic targets, due to their crucial role in regulation of vital cellular processes. The malfunctioning PPI network can lead to the onset and development of various pathological conditions. There is an increasing interest in identifying disease-relevant PPI and developing the corresponding therapeutic agents. Historically the development of small molecule PPI inhibitors has been associated with multiple challenges. Molecular complexity of PPIs involving large and flat interfaces and a lack of appropriate screening libraries that would match the structural requirements of the target protein made many early PPI-directed discovery programs fall short. Further advances in the structural biology, identification of the "hot spot" regions provided a stronger basis for a rational design of small molecule modulators. That coincided with extensive analysis of the PPI-relevant chemical space and development of several strategies for building PPI-focused chemical libraries [Future Med Chem. 2014 Jul;6(11):1291-307].

At Asinex we have developed a holistic approach for the enrichment of our screening libraries with novel chemotypes that would be beneficial for exploring multiple PPIs. That includes the creation of PPI privileged building blocks, fragments and novel structurally sophisticated a-helix mimetic scaffolds, all enhanced by powerful methodologies for their convenient synthesis.

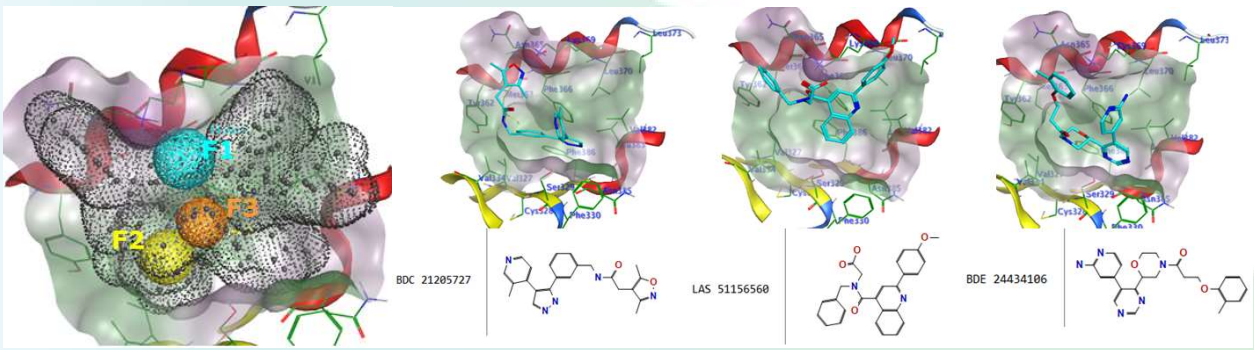
An α-helix is the most common type of secondary structure in proteins. This structure is also quite compact, in contrast to other secondary structural elements, providing the opportunity for the design of drug-like molecules mimicking this important motif. Several α-helix mimetics molecules have proved to be useful for targeting therapeutically significant PPIs including notable examples of HDM2(HDM4) and the BCL-2 family inhibitors. Based on several i*n silico* pharmacophore models we designed and developed synthetic scaffolds that are able to reproduce the substitution geometry of an α-helical motif and display the residual groups toward the hot spot pockets.



An efficiency of this approach can be illustrated by YAP/TEAD protein-protein interaction - a critical component of the Hippo signaling pathway, regulating cell proliferation and apoptosis. The interaction surface of YAP/TEAD complex is relatively flat and majorly governed by helical hydrophobic residues of YAP projected toward hydrophobic pockets of TEAD.

Based on available crystal structures in the PDB database (3JUA, 4NL0, 5GN0, 5OAQ) we created 4 pharmacophore queries that vary by the positions of 3 key recognition features (Figure 1). A pharmacophore search in our PPI/α-helix mimetic library revealed several promising hits that were further prioritized based on docking scoring algorithms.

Figure 1



A systematic study of many other α-helix-mediated protein interactions has allowed for the identification of additional compound classes that might offer a valuable starting point in the discovery of novel inhibitors. Notable examples of some targets where the aforementioned method has been successfully applied include: hSTING, pVHL/HIF-1α, Plk4, Cullin–RING E3. We also have found that adding rigidity to the molecular scaffolds via conformationally constrained combination of rings and linkers can be beneficial for locking compounds into a conformation that best fits into defined pockets.

The resulting PPI library represents a diversity of more than 500 scaffolds, embedding the legacy of our dedicated research in the area of natural product chemistry and improving compounds solubility and cell-permeability properties (BioDesign™).