Immuno-Oncology Library

Designed for discovery of novel hits in Immuno-Oncology therapeutic area

52,935 compounds

Immunotherapy has emerged as a transformative approach for cancer treatment being one of the most prospective fields in contemporary drug development. To address growing needs in novel and potent active molecules we have designed special library focused on the most important targets: PD-1/PD-L1 check-points inhibitors, toll-like receptor family (TLR7 and TLR8, as a key players in antiviral response), IRAK4, ALK5 (one of JNK/P38 effectors and initiator of SMAD association), JAK-STAT pathway inhibitors, STING agonists, IDO inhibitors and the number of kinase targets – BTK, MAPK, VGFR and bRAF.

We have carefully selected 52 935 compounds with the most promising features as potential ligands for immuno-oncology targets. All compounds are stored as dry materials and they can be acquired in diverse custom formats. Alternatively, we can promptly supply a copy of the pre-plated Library having 50 240 compounds, that can be also made in a customized ready-to-screen formats. Using our Immuno-Oncology Library for hit discovery you receive multiple benefits allowing you to save on time and costs in lead generation:

- **Hit resupply and hit expansion from dry stock of over 2.6 M compounds.**
- **Straightforward and low-cost analogs synthesis through our REAL Database technology.**
- **Fully customized hit-to-lead project support with broad capabilities available on-site.**

You have also an option to screen the librray directly at Enamine. We will be happy to offer you discount on library cost depending on the collaboration scope.

Most popular library formats available for immediate supply

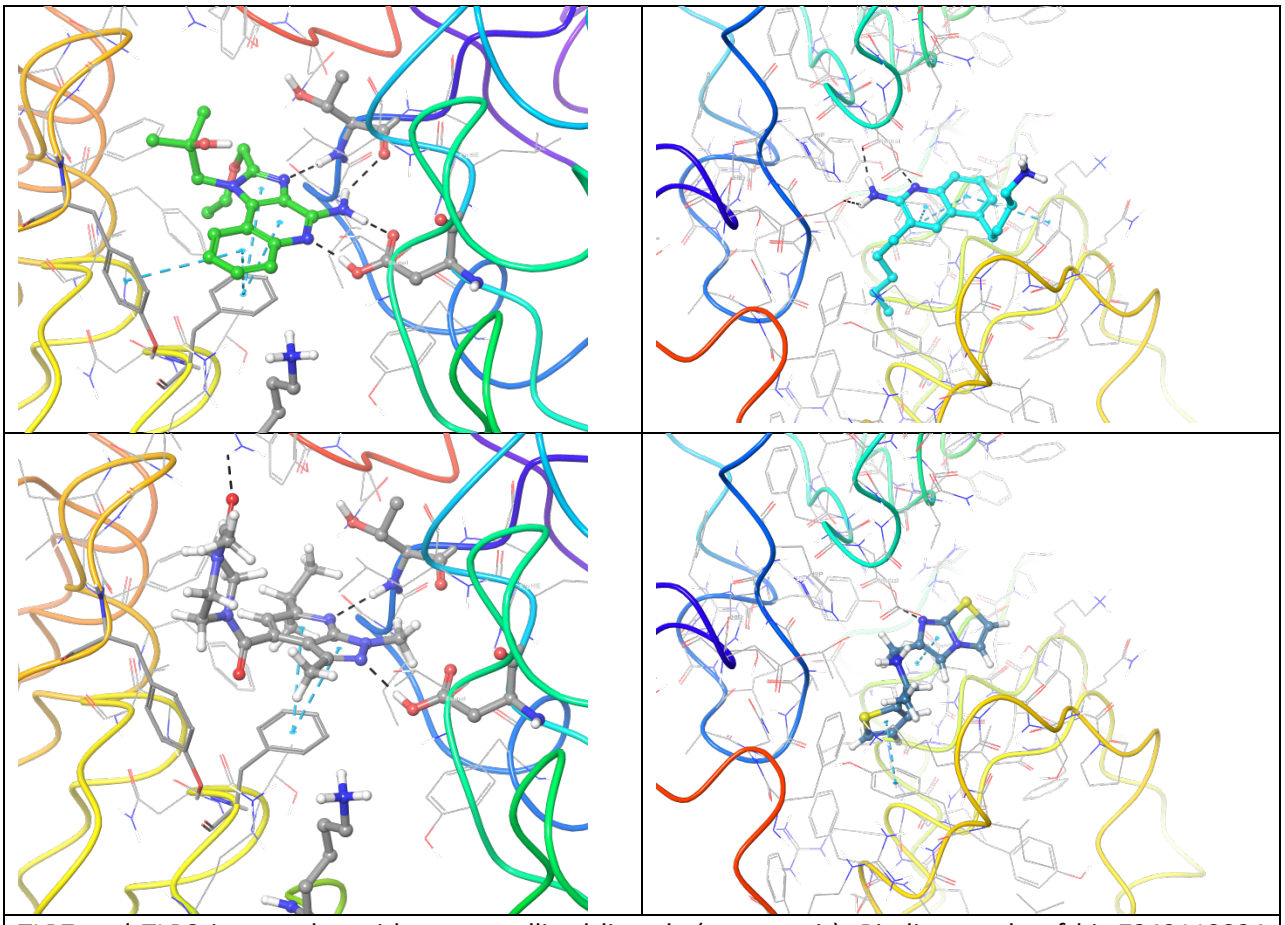
Item	Catalog No.	No of compounds	No of plates	Amount	Plates and format
1	**IMO-50-Y-0**	50 240	157	Any suitable for 1 assay	384-well plates, 320 cpds per plate, first two and last two columns empty
2	**IMO-50-Y-10**	50 240	157	10 µL of 10mM DMSO stock solutions	384-well plates, 320 cpds per plate, first two and last two columns empty
3	**IMO-50-Y-50**	50 240	157	50 µL of 10mM DMSO solutions	384-well plates, 320 cpds per plate, first two and last two columns empty

Library Design

In the library design much attention was paid to the search of immune “checkpoint protein” inhibitors, such as PD-1, CTLA-4, CD152, CD279/74 and PD-L1. The other important new as well as some well-known and revised protein targets were screened to identify potential active ligands.

In silico screening of different targets:

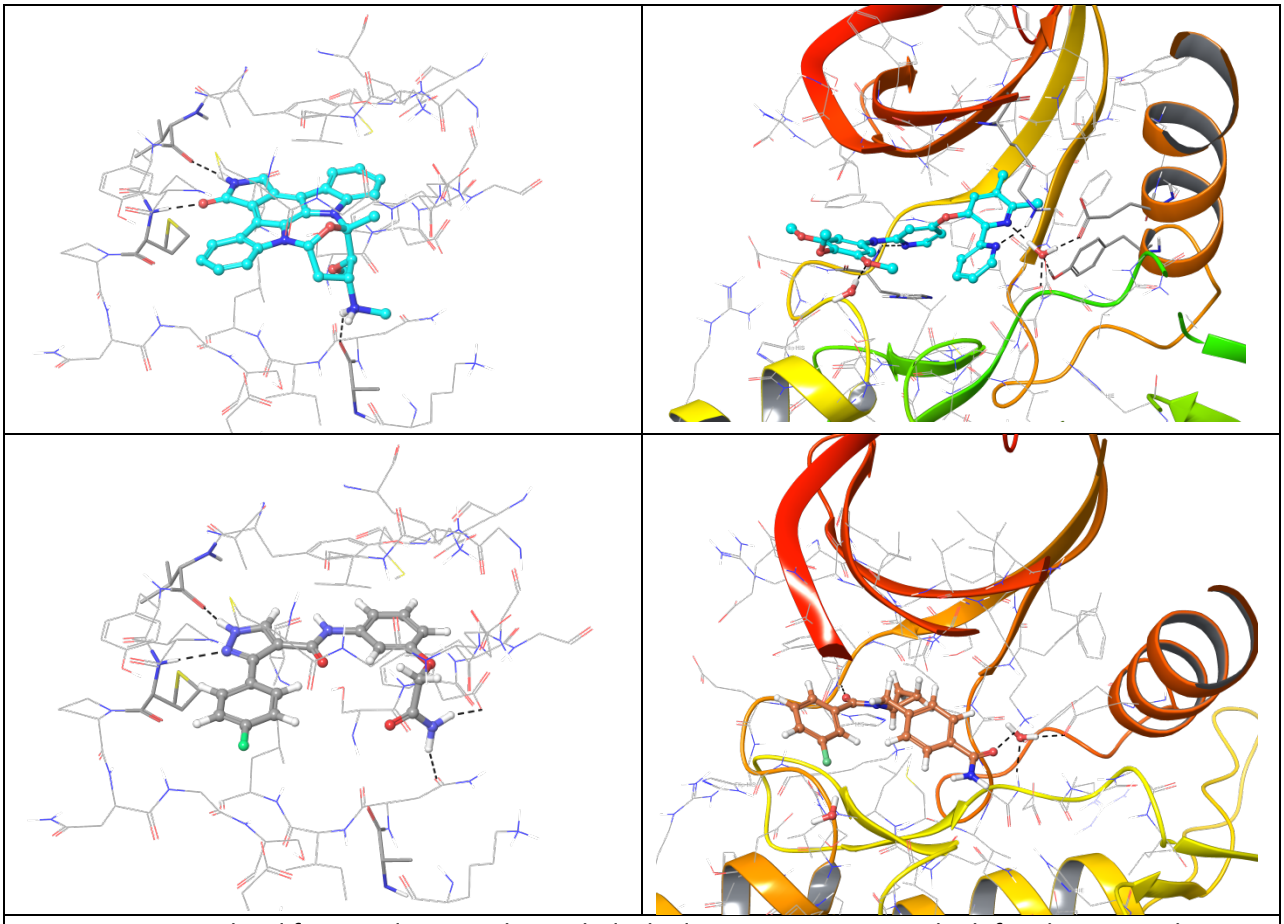
Structure-based approach was applied to search potential inhibitors of TLR7 and TLR8 receptors. All reported in PDB proteins structures were analyzed and superimposed for generation of protein structure-based pharmacophores. Thereafter two models have been validated with reference set of actives and non-active molecules.



TLR7 and TLR8 in complex with co-crystallized ligands (upper pair). Binding mode of hit Z242112334 found after docking calculations with TLR7 (left) and another hit compound Z1438692506 in the cavity of TLR8 (right).

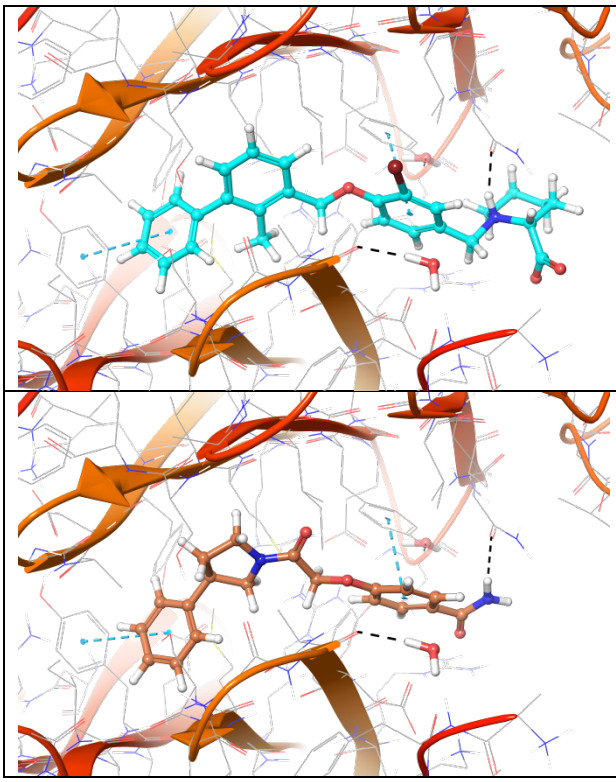
Two types of transmembrane proteins (IRAK4 and TGF beta R1) which possess kinase activity were studied based on 4U97 and 2WOT structures respectively. As all kinases these domains have much in common. Presence of several hydrophobic cores in the ligand structure and its ability to form strong h-

bonds with key amino acids in the binding site were the only reliable requirement for potential inhibitors of these kinases. However, to overlap all possible structures and conformations an alternate combination of hydrophobic cores and h-bonds was used for selection of compounds in these mini libraries. Two subsets of constraints were generated to create the most exhaustive screening model for each kinase. As a result a high scoring was achived.



IRAK4 in its crystalized form and in complex with docked Z243559212 are in the left column. TGF beta R1 in original state from RCSB and in complex with Z316882020 are in the right column.

In the case of PD-1 and PD-L1 binding there are few known compounds which can hit PD-L1, changing surface properties and causing re-arrangements in its interface. Our *in silico* researchers tried to apply some structural and spatial constraints to find compounds, which can modulate the state of PD-L1 structure. To increase selectivity and avoid undesirable conformational similarity a two staged screening was applied. All results have been evaluated visually to define the molecules with best bindings.



Co-crystallized BMS-8 structure (upper left) with indicated interactions and both Z195611316 and Z942299126 ligands, which have similar structure and binding modes.