Kynurenine Pathway Library

12,000 *compounds*

The kynurenine pathway is a metabolic pathway leading to the production of nicotinamide adenine dinucleotide (NAD+) from the degradation of tryptophan. Disruption in the pathway is associated with wide range of diseases and disorders including infectious diseases (e.g. HIV), neurological disorders (Alzheimer's disease (AD), Huntington's disease (HD) and ALS), affective disorders (schizophrenia, depression and anxiety), autoimmune diseases, peripheral conditions and malignancy. The aim of our work was to conduct a search for new potential active compounds for the kynurenine pathway, which, in turn, could be used as convenient and quality starting points for early drug development.

Targets selection

Search of potential actives was performed using all available protein and ligand structural data for the following targets: indoleamine dioxygenase (IDO), tryptophan dioxygenase (TDO), 3-hydroxyanthranilic acid dioxygenase (3-HAO), kynurenine aminotransferases (KATs), kynurenine 3-monooxygenase (KMO).

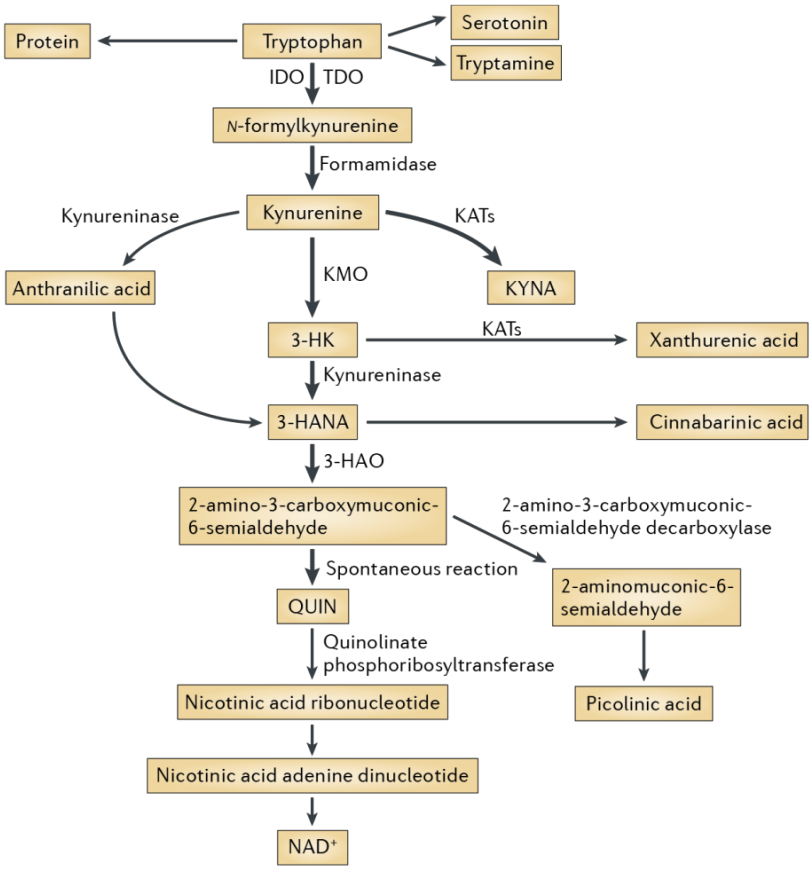


Fig. 1. The kynurenine pathway of tryptophan degradation in mammals.

Screening Models preparation and validation

All available 3D structures of the targets were retrieved from PDB. Alternate superposition and comparison of the protein structures showed high sequence identity in every separate protein target >90 % with RMSD in a range 0.4 - 0.71 $Å^2$. Considering all representative structures only one has been

selected for model preparation taking into account ligand binding parameters (protein- native ligand) and geometric parameters of the binding sites.

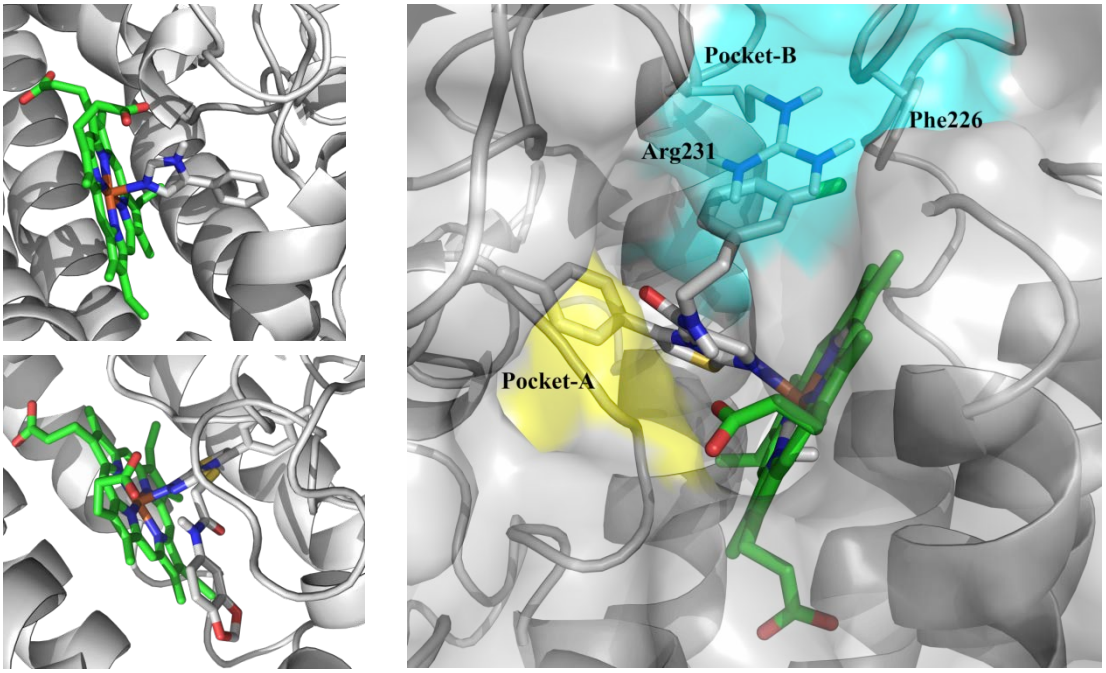


Fig. 2. Binding site of IDO1 (2D0T (top), 4PK5 (bottom) and example two main subpockets (in blue and yellow) used for molecular docking.

Molecular docking & Pharmacophore search

Basing on compounds with known activity and "protein–native ligand" complexes, ligand-based (IDO: 3, TDO: 4, KATs: 3, KMO: 2) and structure-based (IDO: 3, TDO: 6, 3-HAO:2, KATs:3, KMO:4) pharmacophore models were build and validated. Drug-like Enamine database of over 1M compounds were then screened.

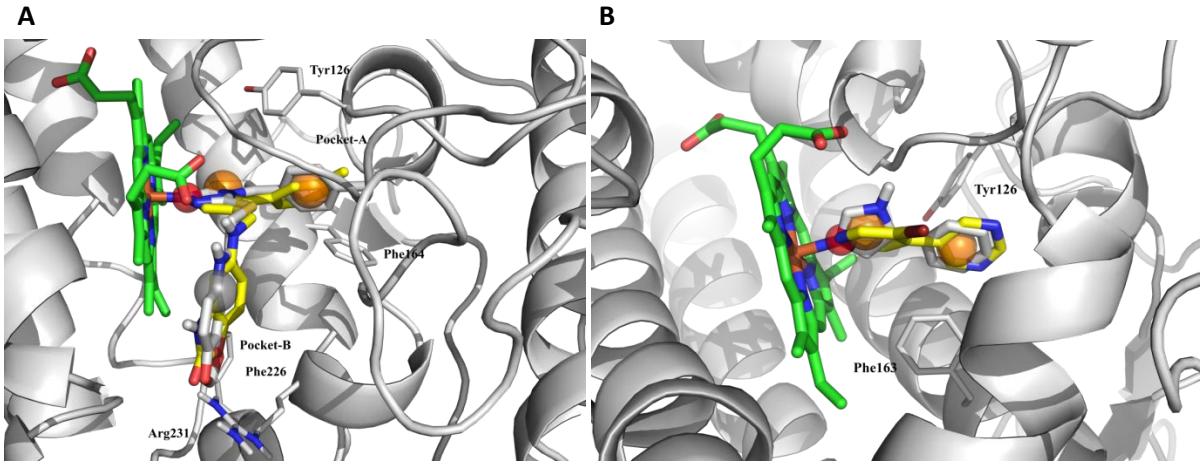
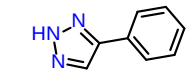
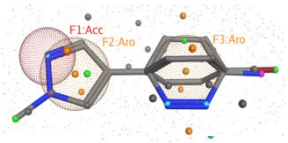


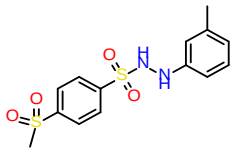
Fig. 3. Results of molecular docking: superposition of native (grey) and hit ligands (yellow) with representation of structure-based pharmacophore features.

Fig. 4. Ligand-based Pharmacophore models used for *in silico* screening.

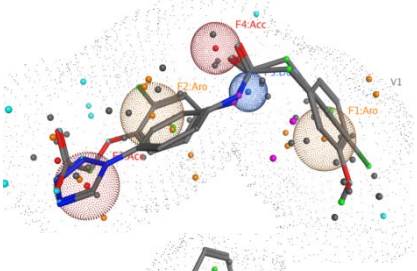


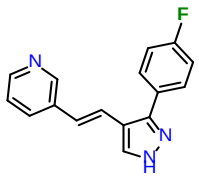
IC_{50}=180 nm



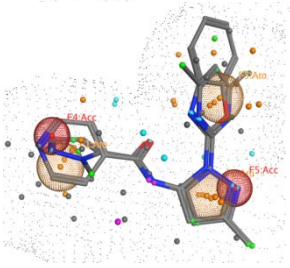


IC_{50}=43 nm





IC_{50}=4200 nm



Number of compounds in targeted libraries after molecular docking calculation and pharmacophore searches:

Target Name	**IDO**	**TDO**	**3-HAO**	**KATs**	**KMO**
Total number of compounds	5 360	6 600	1 000	850	2 840

Careful analyzes of proteins and their ligand interactions involved in kynurenine pathway were performed. The iterative *in silico* searches using all available state-of-the-art methodologies were curried-out to yield unique sets of potentially active molecules. Chemotype control was used to enrich the libraries with structural motifs of true positives and new “patent-free” structural cores .

Developed targeted sets are intended for high-probability initial hit discovery in one step for any particular target.