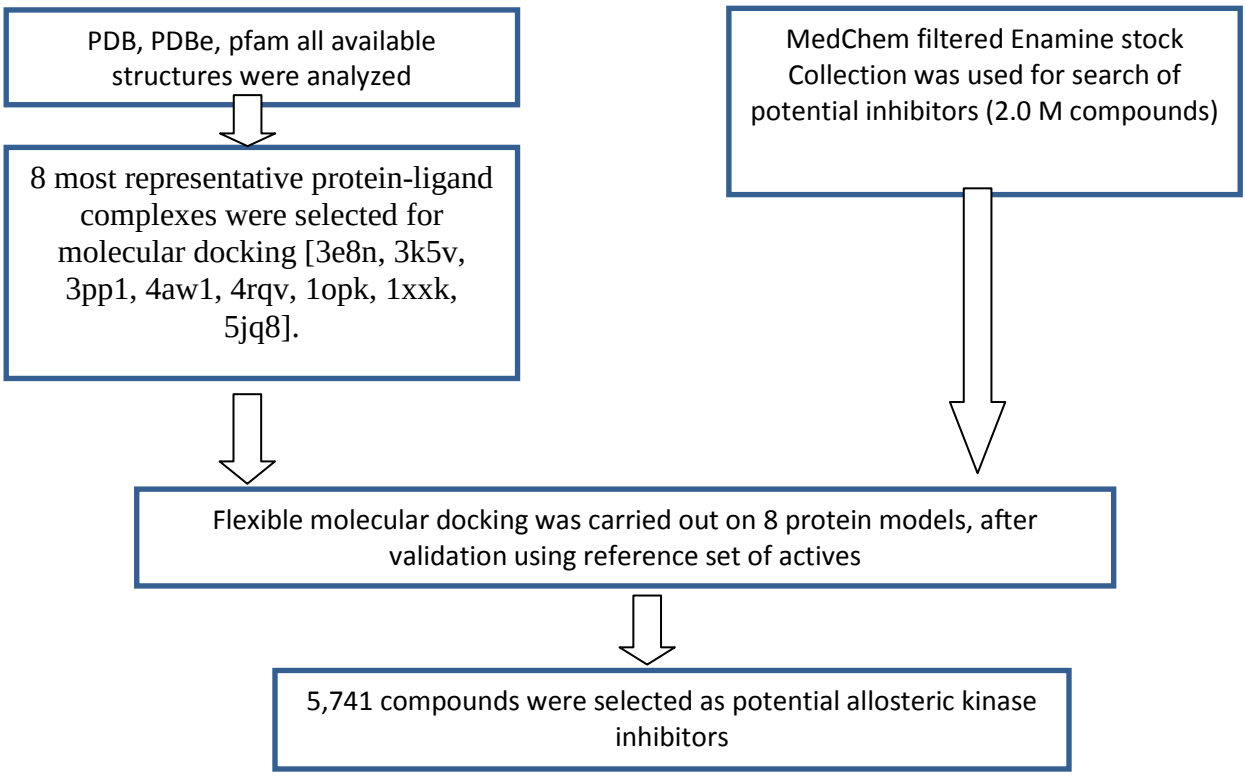
Allosteric Kinase Library

5,678 compounds

Development of efficient kinase inhibitors has been a long-standing challenge in drug development. The structural and mechanistic characterization of kinase inhibitor provides new strategies to develop specific kinase inhibitors by targeting a binding pocket adjacent or not adjacent to the ATP binding pocket.[1]

Allosteric kinase inhibition is among the most promising and sensitive deactivation mechanism of kinase activity. Four type of possible allosteric kinase pockets were determined by now:[2-9] 1) Myristoyl pocket; 2) Inhibitor binding mode that occupies part of binding pocket adjacent to the ATP-site; 3) PIF-pocket (regulatory site targeted); 4) pocket type $I^{1/2}$ relatively allosteric regulators of kinases (library contains 500 such compounds, only).
All available PDB structures with kinase allosteric inhibitors were analyzed. Most representative structures were used for molecular docking calculation. General algorithm of library design represented on the scheme below:



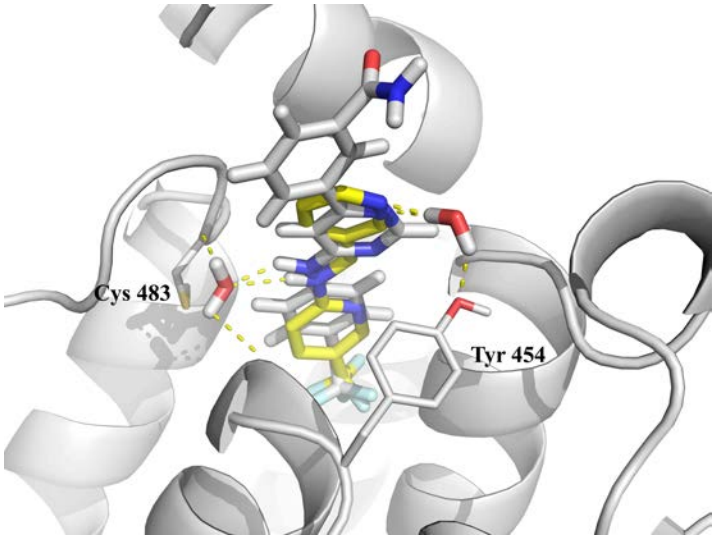


Fig. 1. Example of molecular docking result into the Myristoyl pocket (4aw1 PDB entry). Native ligand represented in grey sticks, docked ligand – in yellow.

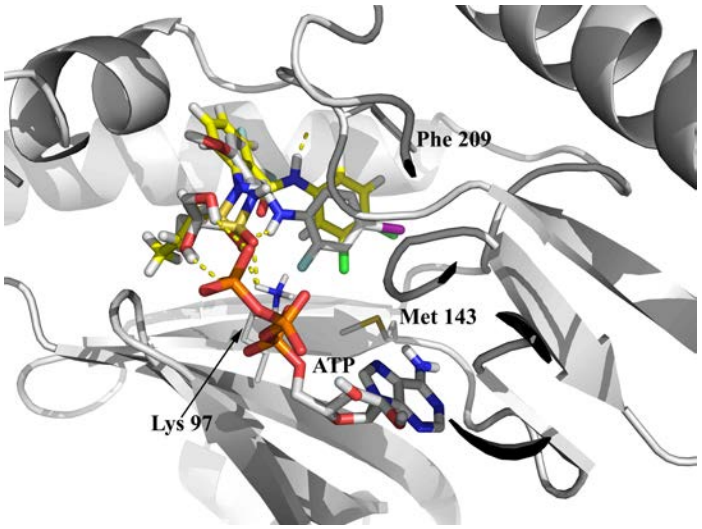


Fig. 2. Example of molecular docking into the ATP-kinase subpocket (3e8n PDB entry). Docking calculations were performed with CoA features.

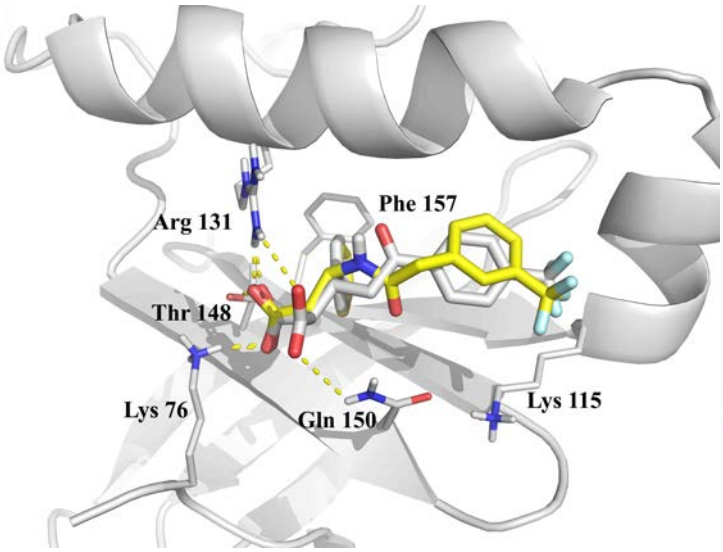


Fig. 3. Example of molecular docking into the PIF pocket (4aw1 PDB entry).

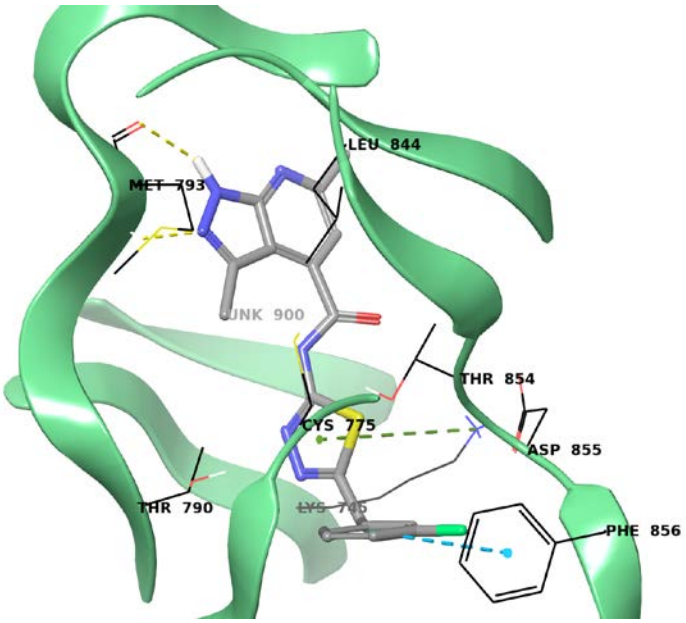


Fig. 4. Example of molecular docking into the PIF $I^{1/2}$ binding site (4aw1). Hit binding mode.

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