

## Design and evaluation of protein kinase inhibitors using ensemble docking and induced-fit optimization of active site

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Incorporation of protein flexibility is especially important for the structure-based design of inhibitors targeting highly plastic active sites of protein kinase. Two approaches are used to account for receptor flexibility: Induced Fit docking that refines protein conformations in the course of docking simulations, and ensemble docking (ED) that involves multiple conformations of the target protein. The ALiBERO method recently proposed by Rueda et al. combines ED with receptor optimization. We will present an ED protocol that retrieves the maximal number of active ligands at a reasonable docking score threshold, while minimizing the number of false positive prediction. We used the 4D Docking protocol developed by Totrov, Bottegioni and others, and implemented in ICM program (MolSoft, LLC). An induced fit procedure was developed for modeling and refinement of complexes with non-cognate ligands. The protocol starts with 4D docking of a training set of active kinase inhibitors into an ensemble constructed from crystal structures or homology models of complexes with the diverse ligands. For the active ligands that failed to return significant docking scores, alternative crystal structures are tested and induced-fit receptor refinement is performed. The best-scoring receptor structures are added to the ensemble. The ensembles that returned high docking scores for the entire training ligand set were selected for virtual screening of test sets containing active ligands, inactive ligands and decoys. We will present validation of this procedure for kinases with multiple crystal structures available in PDB, and for a kinase, which 3D structure was modeled.

### Biography

Mark Shenderovich, Ph.D., CSO of Mol3D research, is computational chemist with 15 years experience of computer-aided drug design in biopharmaceutical industry. He made critical contribution to discovery of drug candidates for Hsp90, protein tyrosine phosphatase, protein kinases and cancer metabolism targets. He is a co-inventor of 9 patents, and co-author of 60+ publications.

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