COMPUTATIONAL APPROACH FOR SELECTIVITY INVESTIGATION OF HOMOLOGOUS KINASES

Nicoleta Stoian, Liliana Halip

Department of Computational Chemistry, "Coriolan Dragulescu" Institute of Chemistry, 24 Mihai Viteazu Ave., 300223 Timisoara, Romania
e-mail: lili.ostopovic@gmail.com

Abstract

Janus Kinases (JAKs) are tyrosine kinases central to cytokine-mediated signaling pathways and play vital roles in chronic inflammatory diseases such as rheumatoid arthritis and psoriasis [1,2]. Within this family, JAK1 represents an attractive therapeutic target due to its involvement in immune signaling. However, the high structural similarity between JAK1 and JAK2 complicates the design of selective inhibitors, raising the need for refined analytical approaches. In this work, we applied an intricate computational workflow combining molecular docking, interaction fingerprint analysis, and statistical validation to explore subtle structural differences between JAK1 and JAK2. Bioactivity data for about 2000 kinase inhibitors were retrieved from activity databases and filtered into active and inactive subsets. Structural alignments revealed six critical residue differences near the ATP-binding site, including substitutions in the glycine loop and gatekeeper region, which modify binding pocket shape and electrostatic properties.
A validation set of known actives and inactives was used to benchmark docking protocols in Schrödinger Maestro[3]. Receiver operating characteristic (ROC) analysis identified the energy scoring of superior enrichment, supporting its use as a decisive ranking metric [4]. Interaction profiling of the resulting data highlighted JAK1-specific hydrogen bonding and side-chain interactions in β-sheet regions, suggesting opportunities for exploiting larger ligand scaffolds.
Subsequent virtual screening of an in-house library of bioactive compounds identified the top candidates with preferential JAK1 selectivity. Notably, the set included clinically relevant kinase inhibitors, thereby validating the robustness of the workflow. These results underline that even subtle amino acid differences between homologous kinases can be analytically harnessed to predict selective binding.

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