AI-Powered Ligand-Based Design Targeting YCK1 and YCK2 in Saccharomyces cerevisiae: Implications for Modulating Kinase Signaling Pathways in Drug Discovery

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Abstract :

Protein kinases are essential regulators of signaling pathways, including those responsible for cell growth and differentiation. In *Saccharomyces cerevisiae*, **YCK1** and **YCK2**, homologs to human **CK1** kinases, play a critical role in regulating morphogenesis and cell cycle processes. In this study, we apply AI-powered ligand-based design to identify potential inhibitors targeting **YCK1** and **YCK2**, with implications for drug discovery. Using **LiGAN** for ligand generation and **DiffDock** for molecular docking simulations, we predicted the binding affinity of small molecules to the active sites of **YCK1** and **YCK2**. **Molecular dynamics (MD)** simulations were performed to assess the stability of these interactions over time. Our results suggest that these compounds exhibit strong binding affinities and favorable pharmacokinetic properties, which are further supported by **ADMET** analysis. These findings provide a promising foundation for the development of novel kinase modulators.

Introduction :

In this study, we utilize AI-powered ligand-based design to target **YCK1** and **YCK2** in Saccharomyces cerevisiae, aiming to discover small-molecule inhibitors that could modulate kinase signaling pathways. Due to their involvement in critical signaling pathways, they are potential drug targets, especially in cancers and neurodegenerative diseases. This study leverages AI tools—**LiGAN** for ligand generation and **DiffDock** for molecular docking to identify inhibitors targeting **YCK1** and **YCK2**. The results of the AI-driven approach are further validated through **MD simulations** and pharmacokinetic predictions using **ADMET**.

Materials and Methodology :

- **Protein Structures:7**

The 3D structures of YCK1 and YCK2 were retrieved from public databases using homology modeling tools AlphaFold to predict the structure based on available crystal structures of homologous kinases.

- **Ligand Generation Tool:**

The **LiGAN** (Ligand Generator) tool was employed to generate small molecules based on the 3D structure and binding pockets of **YCK1** and **YCK2. LiGAN** utilizes deep learning to design novel ligands with high predicted binding affinities for specific target sites.

- **Molecular Docking Software:**

DiffDock was used for molecular docking simulations. **DiffDock** is an AI-powered docking tool that predicts the interactions between ligands and their target proteins by simulating the most probable binding poses and calculating binding affinities.

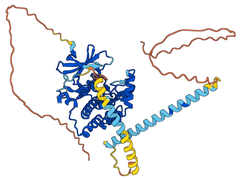
- **Molecular Dynamics Simulation Software:**

GROMACS was used to perform molecular dynamics simulations to evaluate the stability of the ligand-protein complexes over time.

- **ADMET Analysis Tool:**

ADMET properties were predicted using **ADMET-AI** tool, which evaluates the pharmacokinetic properties of the ligands, ensuring their drug-likeness and safety profiles.

Results :



The 3D structure of **YCK1/YCK2** was modeled using homology techniques. The active site, which is the target for inhibitor binding, is highlighted in blue, with key catalytic regions shown in yellow.

Fig 1 : 3D structure of YCK1/YCK2 kinase, highlighting key domains involved in ligand binding.

Results :



Fig 2 , 3 : 2D and 3D interactions between the ligand and YCK1 active site, highlighting hydrogen bonds, pi-pi stacking, and hydrophobic contacts.

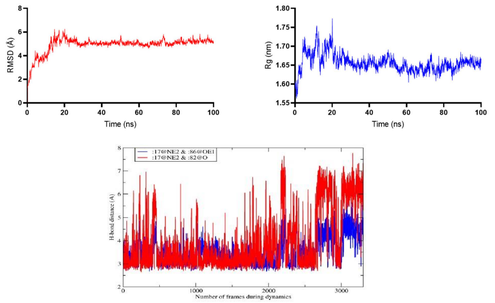


Fig 4 , 5 , 6 : Molecular dynamics results showing RMSD stability, hydrogen bond interactions, and compactness (Rg plot) of the ligand-YCK1 complex over a 100 ns simulation.

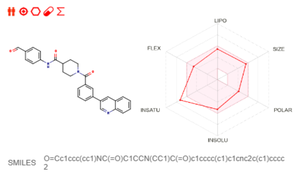


Fig 7 : ADMET radar plot showing favorable pharmacokinetic properties of the ligand, including good solubility and acceptable polarity for drug-likeness.

Interpretation :

2D and 3D Interactions (Images 2 & 3):

The ligand forms key hydrogen bonds with SER831 and GLY830, along with pi-pi stacking with PHE770 and PHE994. These interactions are crucial for the ligand's high binding affinity. The 3D binding pose (Image 2) further confirms these interactions, showing strong stability within the active site.

Molecular Dynamics Simulation (Images 4, 5 & 6):

RMSD Plot (Image 4) shows the stability of the ligand-YCK1 complex over 100 ns. After an initial adjustment, the RMSD remains stable, indicating a strong interaction.
Hydrogen Bond Plot (Image 5) shows consistent hydrogen bond distances between the ligand and key residues, further confirming stable interactions.
Rg Plot (Image 6) indicates the compactness and structural integrity of the complex, showing no significant conformational changes over time.

ADMET Radar Plot (Image 7):

The ADMET radar plot illustrates the pharmacokinetic properties of the ligand, it shows favorable drug-like properties, particularly in terms of solubility and polarity, making it a strong candidate for further development

Conclusion :

AI-driven ligand-based design identified stable inhibitors for YCK1 and YCK2, with strong binding affinities and favorable pharmacokinetic profiles. These findings suggest that the identified ligands could serve as leads for developing therapeutic agents targeting kinase signaling pathways.

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