Virtual screening of potential hepatocellular carcinoma inhibitors targeting J-PKAc chimera

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) presents a formidable challenge in oncology, demanding innovative therapeutic avenues. This study aimed to virtual screen the potential inhibitors targeting the J-PKAc chimera, a fusion protein involving DnaJ homolog subfamily B member 1 and cAMP-dependent protein kinase catalytic subunit alpha.
Methods: The assessment employed PyRx gridbox as an intuitive interface to facilitate molecular docking simulations. Figures 1 and 2 depicted the inhibition constant and binding energy, respectively, providing quantitative insights into the interaction between ligand inhibitors and J-PKAc chimera. Seventeen compounds were scrutinized, with fascaplysine exhibiting the highest affinity for binding to the J-PKAc chimera. The original ligand, trans-tetrahydrofuran-3,4-diol(2S)-2-amino-3-phosphonooxy-propanoic acid (SEP), extracted from the protein-ligand complex structure, was used for docking validation.
Results: Among the twenty-one compounds evaluated, fascaplysine demonstrated the most significant affinity for binding to the DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha.
Conclusion: Fascaplysine emerged as a lead candidate, demonstrating high affinity for the J-PKAc chimera. The molecular docking simulations and visualizations elucidate intricate interactions, enhancing our understanding of potential therapeutic interventions. The study not only identifies fascaplysine as a strong candidate but also contributes valuable molecular insights, paving the way for targeted and effective therapies against HCC.

Keywords: Hepatocellular carcinoma, J-PKAc chimera, virtual screening, fascaplysine, molecular docking

Received: 25 October 2023 Revised: 29 November 2023 Accepted: 28 December 2023

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, stands as a significant global health concern, posing a substantial burden on affected individuals and healthcare systems [1]. The multifactorial etiology of HCC, often associated with chronic liver diseases such as viral hepatitis and cirrhosis, contributes to its widespread prevalence worldwide [2].

HCC's global prevalence is substantial, with regions such as Asia and sub-Saharan Africa bearing a disproportionately high burden [3]. According to the World Health Organization (WHO), liver cancer ranks as the sixth most common cancer globally, and HCC accounts for the majority of these cases [2,4]. The rising incidence of risk factors, including viral hepatitis infections and non-alcoholic fatty liver disease (NAFLD), accentuates the urgency of understanding and addressing this formidable malignancy [5].

Current therapeutic approaches for HCC involve a combination of surgery, liver transplantation, local ablation, and systemic treatments such as chemotherapy and immunotherapy [6]. While advances in treatment modalities have improved outcomes for some patients, the heterogeneity of HCC poses challenges, and prognosis remains unfavorable for many [7]. Novel strategies that target specific molecular pathways implicated in HCC progression are actively sought to enhance treatment efficacy and reduce side effects [8].

One emerging avenue in HCC studies involved the exploration of potential inhibitors targeting the J-PKAc chimera [9]. This approach leverages computational methodologies to screen and identify compounds with the potential to inhibit the J-PKAc chimera, a fusion protein involving cAMP-dependent protein kinase (PKAc) and its interacting partner. By employing virtual screening techniques, researchers aim to identify promising candidates that may disrupt the aberrant signaling pathways associated with HCC, offering a targeted and potentially more

effective therapeutic strategy.

This study aimed to utilize virtual screening techniques to identify potential inhibitors targeting the J-PKAc chimera in HCC. By employing computational methods, the research seeks to screen a library of compounds for their binding affinity and potential to disrupt the J-PKAc chimera, thus interfering with the molecular processes driving HCC progression. The ultimate goal is to contribute to the development of targeted and innovative therapeutic interventions for HCC, with a focus on precision medicine tailored to the unique molecular characteristics of this challenging malignancy.

MATERIALS AND METHODS

Materials

cAMP-dependent protein kinase catalytic subunit alpha, DnaJ homolog subfamily B member 1, was acquired from the Protein Data Bank Repository (PDB) under the accession number BFE2 (https://www.rcsb.org/structure/8FE2). The corresponding files were downloaded in the.pdb extension. Additionally, a three-dimensional conformer file of cabozantinib, an anticancer medication, was obtained from the three-dimensional protein structure of its original ligand, trans-tetrahydrofuran-3,4-diol(2S)-2-amino-3-phosphonooxypropanoic acid (SEP). Furthermore, a compilation of fifteen ligand files was acquired from PubChem [10]. The files contain a variety of compounds, including axisonitrile 3, bromosphaerone, (-)-solenolide A, 8-hydroxymanzamine A, avarone, daryamide B, daryamide C, fascaplysine, geodin, gilvocarcin M, gilvocarcin V, litosterol, meridine, pestalone, plakortide F, puupehenone, and tetramic acid. The format of the ligand files was saved as.sdf.

Protein preparation

After eliminating initial ligands and water molecules with the aid of Discovery Studio Visualizer [11], protein.pdb files are acquired. Preparing a protein structure for molecular docking with PyRx [12] and ensuring the protein's suitability for docking simulations requires the completion of a number of crucial steps. The procedure comprises multiple phases: obtaining the protein structure in a PyRx-compatible format, inputting the structure into the program, potentially removing water molecules, augmenting absent residues with hydrogen atoms, assigning atom types to the residues, optimizing the structure, and ultimately conserving the protein structure that was prepared. By following the steps below, scientists can guarantee that their protein structures are adequately prepared for accurate and reliable docking simulations.

Molecular docking

The PyRx tool was employed to produce both the protein and ligand, as well as to convert them to the.pdbqt format. To perform molecular docking simulations, it is necessary to follow the following protocols: Once the protein structure has been obtained from a database such as the Protein Data Bank (PDB), import it into PyRx. To facilitate the assembly process of the protein, it is imperative to eliminate water molecules, introduce hydrogen atoms, and supplement any absent residues. An additional strategy for enhancing accuracy involves the allocation of atom types and the optimization of the structure. Preserve the prepared protein structure in PDB or PDBQT format. Following this, the ligand structure should be obtained either computationally or from a chemical database, with a guarantee of compatibility with the PDB or SDF formats. Assign atom types, import the ligand into PyRx, augment as needed with hydrogen atoms, and, if required, convert to PDBQT format. Ensure that the format in which the ligand structure is recorded is suitable.

Protein and ligand interaction

The generation of protein and ligand docking data was performed using.pdb files as a reference. The data integration procedure employed the PyRx software to ensure a standardized and consistent representation, upon which subsequent analyses could be constructed. In addition, PyMOL [13] was utilized to visualize the structure in three dimensions, enabling a comprehensive analysis of conformational alterations, binding interfaces, and spatial configurations. Moreover, the extent of the ligand-target interaction during molecular docking was calculated utilizing the binding energy (ΔG) value. To ascertain the degree of binding affinity between a ligand and a target enzyme or receptor, the inhibition constants (Ki) were computed utilizing the formula $Ki = e^{-RT/\Delta G}$.

RESULTS

Protein and ligand interaction

The evaluation utilized a PyRx gridbox, which served as an intuitive interface to generate an individualized receptor docking gridbox in preparation for molecular docking. Figures 1 and 2 illustrate the inhibition constant and binding energy, respectively, of the interaction between the ligand inhibitors and the catalytic subunit alpha of DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase. After analyzing twenty-one compounds, fascaplysine demonstrated the greatest affinity for binding to the catalytic subunit alpha of DnaJ homolog subfamily B member 1, which is a cAMP-dependent protein kinase. Docking was validated using the original ligand trans-tetrahydrofuran-3,4-diol(2S)-2-amino-3-phosphonooxy-propanoic acid (SEP), which was extracted from the three-dimensional structure of the protein-ligand complex.

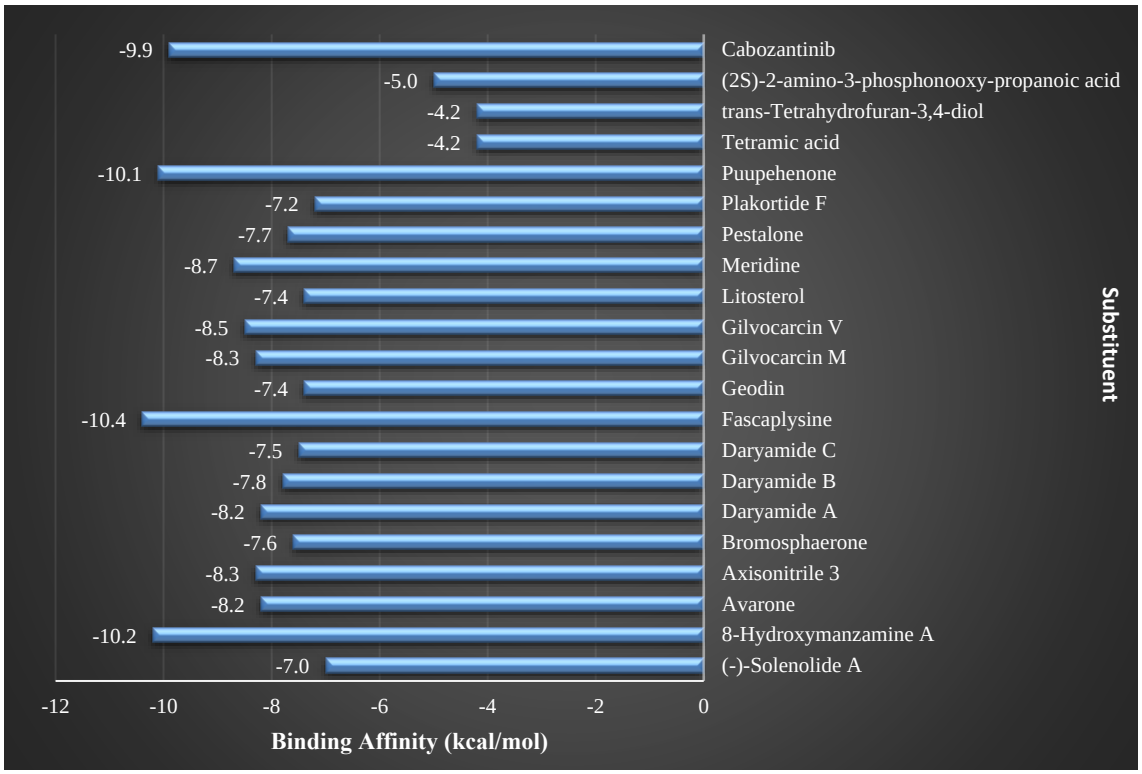

Figure 1. Inhibition constant value (Ki) of natural compounds towards DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha.

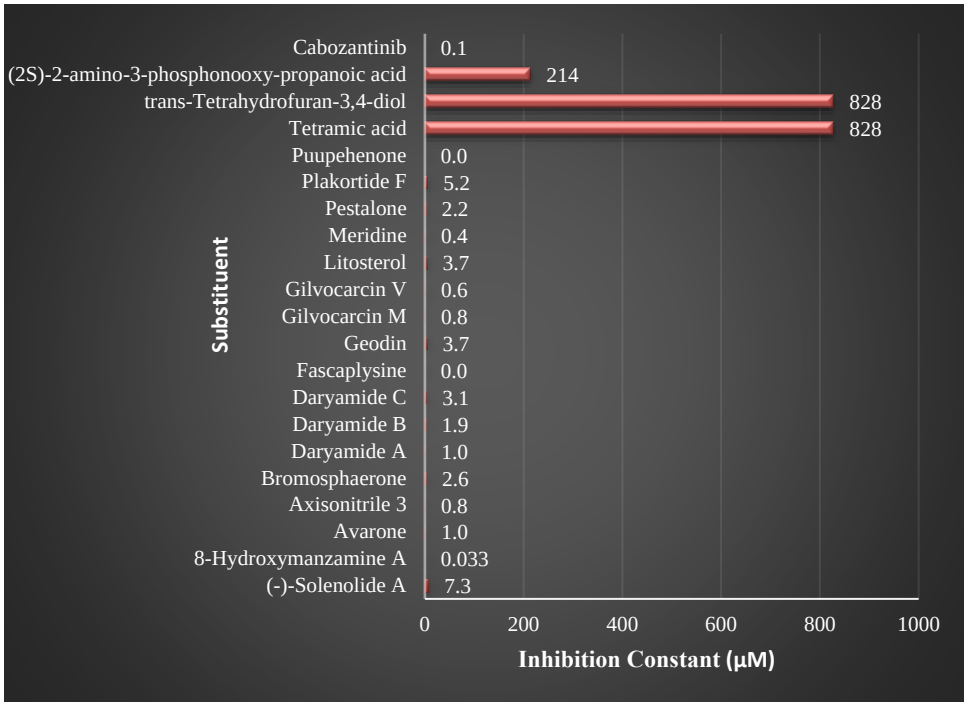

Figure 2. Binding energy between natural compounds and DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha.

Figure 3 depicts a visual representation of receptor-ligand interactions in two dimensions, specifically highlighting the

development of complexes between different entities. The Figure 3A illustrates the dynamic interaction between fascalypsine and the receptor of the DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha. This interaction involves the formation of five hydrogen bonds with specific amino acids, namely Ala-125, Val-178, Leu-228, Thr-238, and Val-112. Additionally, twelve hydrophobic interactions occur with Val-159, Glu-176, Tyr-177, Leu-104, Phe-382, Gly-105, Glu-182, Thr-106, Phe-109, Asp-239, Lys-127, and Met-175. Figure 3B provided a detailed depiction of the interaction between DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha, and the anticancer drug cabozantinib. The image showed eight hydrogen bonds between the two components: Leu-228, Thr-106, Lys-223, Phe-109, Asp-239, Ser-108, Val-112, and Val-134. Figure 3C illustrates the complex interaction between the ligand SEP and the protein DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha. This research provides a comprehensive perspective on the molecular interactions within the system, including two hydrogen bonds formed between Ala-273 and Gly-337. Furthermore, Figure 4 showcased the 3D representation of intricate interactions among the aforementioned components. A. The first combination consists of DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha, and fascalypsine. B. The second combination consists of DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha, and the drug cabozantinib. C. The third combination consists of DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha, and the initial ligand.

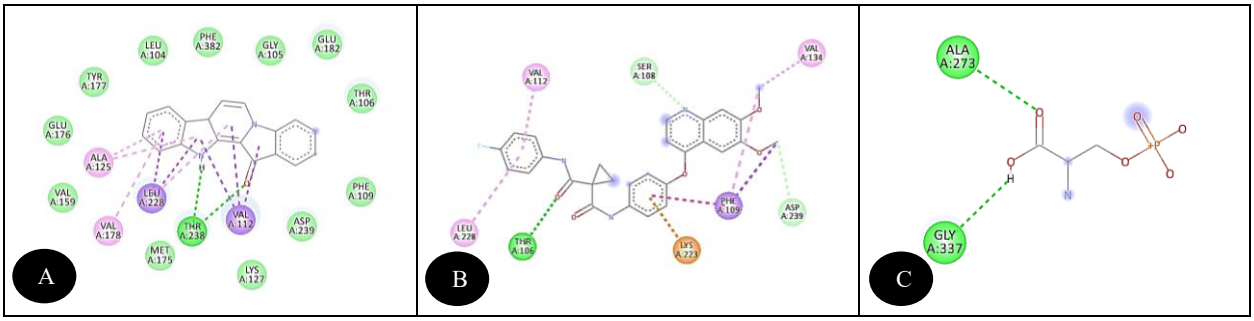

Figure 3. In a two-dimensional display, the intricate relationships between A. The fascalypsine, cAMP-dependent protein kinase catalytic subunit alpha, and DnaJ homolog subfamily B member 1, B. Subfamily B member 1 of the DNAJ gene, alpha subunit of the cAMP-dependent protein kinase, and cabozantinib Alpha subunit of cAMP-dependent protein kinase, the initial ligand, and C. DnaJ homolog subfamily B.

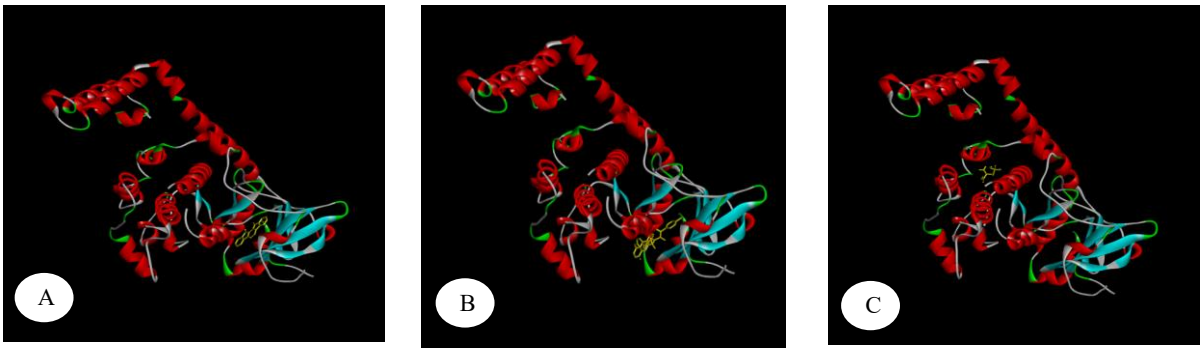

Figure 4. In a three-dimensional display, the intricate relationships between A. The fascalypsine, cAMP-dependent protein kinase catalytic subunit alpha, and DnaJ homolog subfamily B member 1, B. Subfamily B member 1 of the DNAJ gene, alpha subunit of the cAMP-dependent protein kinase, and cabozantinib Alpha subunit of cAMP-dependent protein kinase, the initial ligand, and C. DnaJ homolog subfamily B.

DISCUSSION

The investigation into targeting DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha for inhibition in HCC treatment provides valuable insights into potential therapeutic strategies [14]. Among the twenty-one compounds assessed, fascaplysine demonstrated the highest affinity for binding to DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha. The validation of the docking process using the original ligand, SEP, extracted from the protein-ligand complex structure, added credibility to the study. The dynamic interaction between fascalypsine and the receptor, depicting five hydrogen bonds and twelve hydrophobic interactions involving specific amino acid residues such as Ala-125 and Val-112. A comprehensive interaction between DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha, and the anticancer agent cabozantinib, revealing eight hydrogen bonds with various amino acids. The intricate interaction between SEP and the receptor, emphasizing two hydrogen bonds with Ala-273 and Gly-337.

These detailed illustrations provide a holistic understanding of the molecular connections in the system.

Fascaplysine is a fascinating natural compound isolated from the Fijian sponge *Fascaplysinopsis Bergquist* sp. [15]. It has attracted significant attention for its potential as an anticancer agent due to its diverse biological activities, including antiproliferative, proapoptotic, anti-angiogenic, anti-metastatic, inhibits epithelial-to-mesenchymal transition (EMT), and immunomodulatory [16].

These pleiotropic effects against cancer cells make fascaplysine a promising candidate for anticancer drug development [17]. Several mechanisms of action have been proposed for its anticancer activity, including inhibition of cell cycle kinases, modulation of signaling pathways, and interference with DNA replication [18]. However, further research is needed to fully elucidate its precise molecular targets and optimize its therapeutic potential.

CONCLUSION

This study suggests that fascaplysine holds promise as a lead compound for further development in targeted leukemia therapies directed at DnaJ homolog subfamily B member 1, cAMP-dependent protein kinase catalytic subunit alpha. The detailed molecular insights gained from the protein-ligand interactions contribute to the ongoing efforts in advancing precision medicine and targeted therapies for leukemia and related hematological malignancies. Further exploration of these compounds and interactions may pave the way for the development of innovative and effective treatments in the realm of leukemia.

ACKNOWLEDGEMENT

We extend our appreciation for the continuous support extended by the Directorate of Research and Development at UI and the Institute for Research and Community Service at UNAS.

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