Investigation cell surface glycoprotein CD200 receptor 1 inhibitors against leukemia using in silico approach

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ABSTRACT

Background: Leukemia, a hematological malignancy characterized by the abnormal proliferation of white blood cells, remains a significant challenge in oncology. The investigation into potential therapeutic strategies against leukemia has unveiled a novel approach targeting the cell surface glycoprotein CD200 receptor 1 through ligand inhibition. This study aimed to employ in silico approaches and molecular docking simulations to identify and characterize potential ligand inhibitors that interact with cell surface glycoprotein CD200 receptor 1.
Methods: The study conducted a thorough examination of protein and ligand interactions, focusing on 19 compounds. Canthaxanthin exhibited the most favorable binding affinity to cell surface glycoprotein CD200 receptor 1, and 2D visualizations provided detailed insights into dynamic interactions, revealing hydrogen bonds and hydrophobic interactions with the key amino acid residues involved.
Results: Among the compounds, canthaxanthin emerged as the most promising inhibitor, displaying the highest affinity for binding to CD200 receptor 1. Two-dimensional representations in Figure 3 illustrate receptor-ligand interactions, emphasizing the dynamic engagement between canthaxanthin, CD200 receptor 1, and the anticancer agent doxorubicin. Hydrogen bonds and hydrophobic interactions with specific amino acid residues contribute to the complexity of these interactions.
Conclusion: The study established the potential of targeting CD200 receptor 1 for leukemia treatment, with canthaxanthin identified as a promising lead compound. Molecular docking simulations offer insights into specific interactions, showcasing a diverse network of hydrogen bonds and hydrophobic contacts. The validation of the docking process enhances the study's reliability. The findings not only identify canthaxanthin as a strong candidate but also contribute valuable molecular insights, paving the way for more targeted and effective leukemia therapies. This research signifies a significant advancement in precision medicine for cancer treatment, offering potential breakthroughs in improving outcomes for patients facing hematological malignancies.

Keywords: Leukemia, molecular docking, bioactive compounds, targeting the cell surface glycoprotein CD200 receptor 1

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INTRODUCTION

Leukemia, a cancer of the blood and bone marrow, casts a long shadow across the globe [1]. With millions of cases diagnosed yearly, it disrupts lives and communities in every corner of the world. While current treatments, including chemotherapy and immunotherapy, have led to significant advancements in survival rates, there remains a pressing need for more effective and targeted therapies [2]. This is where ongoing research, like the exploration of cell surface glycoprotein CD200 receptor 1 inhibitors as potential anti-leukemia agents, holds immense promise [3].

Currently, leukemia patients face a diverse landscape of therapeutic options, tailored to the specific type and progression of their disease. Chemotherapy remains a mainstay, harnessing potent chemicals to indiscriminately attack rapidly dividing cells, including cancerous ones [4]. However, these treatments often come with debilitating side effects and struggle to completely eradicate the disease [5].

Amidst this ongoing battle, researchers are actively exploring novel therapeutic avenues, such as targeting specific molecules crucial for cancer cell survival and proliferation. One such target gaining traction is the cell surface glycoprotein CD200 receptor 1. This receptor plays a key role in suppressing the immune system, allowing cancer cells to evade detection and

attack [6]. By developing potent CD200 receptor 1 inhibitors, researchers hope to unleash the immune system's full potential against leukemia, effectively turning it into a powerful ally in the fight against the disease.

This study aimed to identify, design, and optimize potential CD200 receptor 1 inhibitors using uing molecular docking. By exploring the intricate world of CD200 receptor 1 and unlocking its potential as a therapeutic target, researchers are taking a vital step towards a future where leukemia is no longer a formidable foe but a manageable disease.

MATERIALS AND METHODS

Materials

CD200 receptor 1, a glycoprotein found on the cell surface, was acquired from the Protein Data Bank Repository (PDB) under the accession number 4BFI [7]. The corresponding files were downloaded in the.pdb extension. Additionally, a 3D conformer file of capecitabine, an anticancer medication, was obtained from the 3D protein structure of its original ligand Nicotinamide adenine dinucleotide (NAD). Furthermore, a compilation of fifteen ligand files was acquired from PubChem [8]. Actinidiolide, altechromone A, amicoumacin A, astaxanthin, canthaxanthin, coelimycin P1, enterocin, flavipin, isopetasin, pyocyanin, syringolin A, thaxton A, thaxtomin B, thaxtomin C, tyrosol, violacein, and zeaxanthin are among the compounds contained in these files. The format of the ligand files was saved as.sdf.

Protein preparation

The protein's.pdb files are obtained after the first ligands and water molecules are removed using Discovery Studio Visualizer [9]. To ensure that a protein is acceptable for docking simulations and to build a protein structure for molecular docking using PyRx [10], there are several crucial steps that must be taken. The procedure involves multiple steps: obtaining the protein structure in a PyRx-compatible format, entering the structure into the software, removing any water molecules, adding hydrogen atoms to any missing residues, assigning atom types to the residues, fine-tuning the structure, and finally saving the finalized protein structure. By following the following steps, researchers can make sure that their protein structures are adequately ready for accurate and reliable docking simulations.

Molecular docking

The protein and ligand were prepared using the PyRx Tools software, which also converted them to the.pdbqt format. To conduct molecular docking simulations, adhere to the subsequent procedures: Import the protein structure into PyRx after obtaining it from a database such as the Protein Data Bank (PDB). In order to assemble the protein, it is necessary to remove water molecules, supplement any absent residues, and introduce hydrogen atoms. An alternative approach to improve precision is to allocate atom types and optimize the structure. Save the protein structure that has been prepared in PDB or PDBQT format. Subsequently, acquire the ligand structure through computational means or obtain it from a chemical database, guaranteeing its compatibility with PDB or SDF formats. Assign atom types, load the ligand into PyRx, supplement with hydrogen atoms as necessary, and convert to PDBQT format if necessary. Ensure that the ligand structure is saved in an appropriate format.

Protein and ligand interaction

Docking data for proteins and ligands were generated based on .pdb files. The PyRx program was employed in the data integration process to ensure a consistent and standardized representation for subsequent analyses. Additionally, 3D structure visualization was conducted using PyMOL [11], enabling a comprehensive examination of conformational changes, binding interfaces, and spatial arrangements. The binding energy (ΔG) value was utilized to assess the strength of ligand-target interactions during molecular docking. Furthermore, inhibition constants (Ki) were calculated using the formula $Ki = e^{(-RT/\Delta G)}$ to determine the binding affinity between a ligand and a target enzyme or receptor.

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, respectively, the inhibition constant and binding energy of the interaction between the ligand inhibitors and the cell surface glycoprotein CD200 receptor 1. Canthaxanthin demonstrated the greatest affinity among the seventeen compounds that were analyzed for its interaction with the cell surface glycoprotein CD200 receptor 1. Docking was validated using the original ligand nicotinamide adenine dinucleotide (NAD), which was extracted from the three-dimensional structure of the protein-ligand complex.

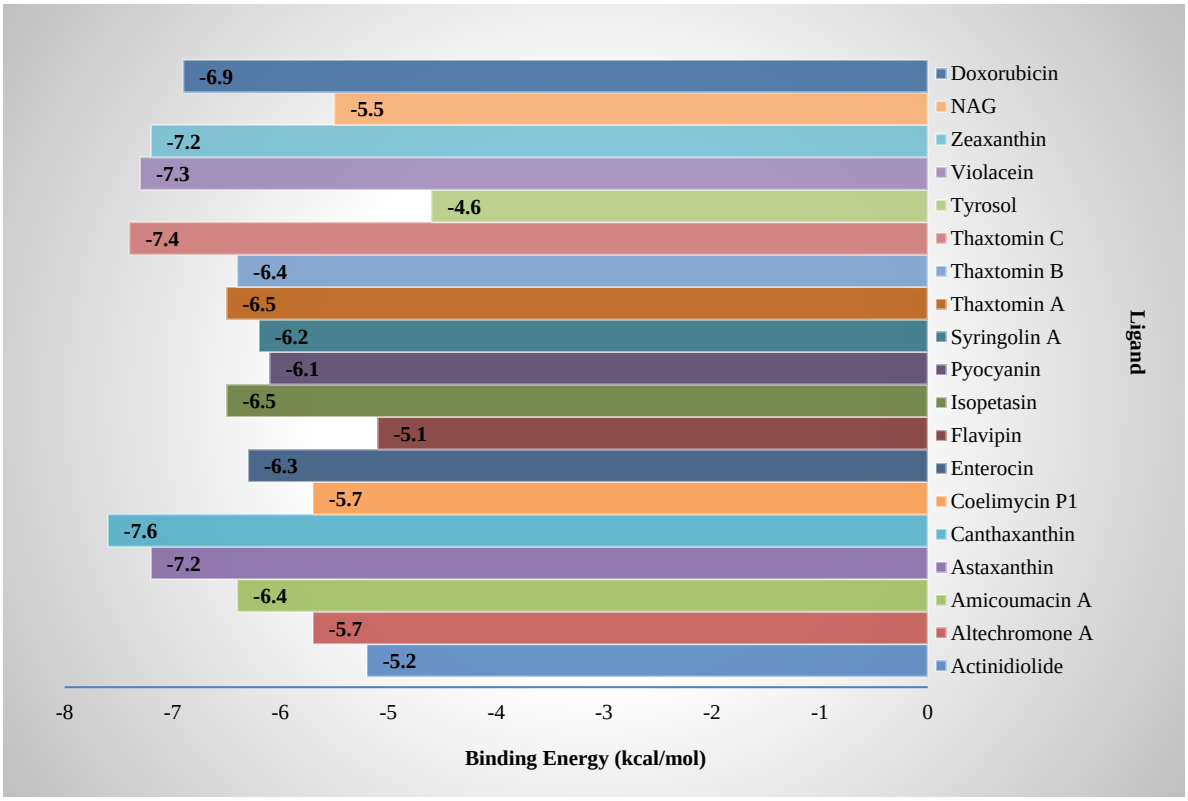

Figure 1. Binding energy between ligands and cell surface glycoprotein CD200 receptor 1.

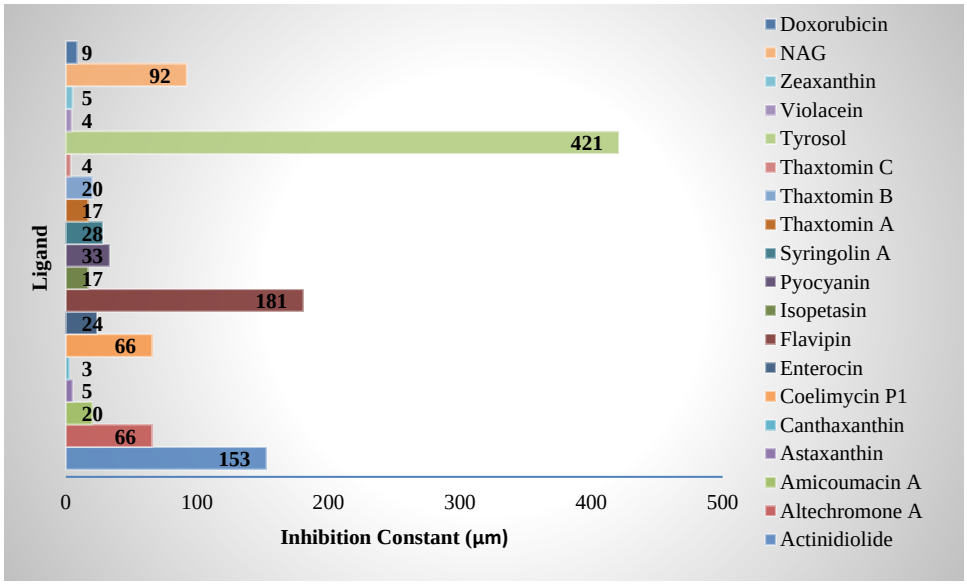

Figure 2. Inhibition constant value (Ki) of ligands and cell surface glycoprotein CD200 receptor 1.

A two-dimensional depiction of receptor-ligand interactions, more specifically the assembly of complexes among diverse entities, was presented in Figure 3. As illustrated in Figure 3A, the dynamic interaction between canthaxanthin and the cell surface glycoprotein CD200 receptor 1 was observed. This interaction results in the formation of three hydrogen bonds with Val-19, Leu-16, and Phe-36, as well as fourteen hydrophobic interactions with the following residues: Leu-32, Leu-33, Tyr-118, Lys-116, Thr-17, Phe-114, Pro-15, Glu-111, Ser-37, and Ile-38. An exhaustive depiction of the interaction between doxorubicin, an anticancer agent, and the cell surface glycoprotein CD200 receptor 1 was provided in Figure 3B.

Seven hydrogen bonds—Gly-196, Gln-198, Pro-126, Met-143, Ala-144, Gln-26, Pro-125—and six hydrophobic interactions—Ile-27, Val-124, Glu-127, His-193, Val-128, and Val-191—were illustrated in the diagram. In conclusion, Figure 3C illustrates the complex interaction that takes place between the ligand NAD and the cell surface glycoprotein CD200 receptor 1. The present analysis provides a comprehensive perspective on the molecular interconnections that exist within the system. These include five hydrophobic interactions with Arg-76, Leu-74, Ile-78, Ile-60, and Thr-71, as well as four hydrogen bonds with Gly-75, Asn-77, Cys-73, and Trp-80. Furthermore, Figure 4 illustrates the 3D visualization of intricate interactions among the subsequent substances: Canthaxanthin and cell surface glycoprotein CD200 receptor 1; the drug canthaxanthin and cell surface glycoprotein CD200 receptor 1; and the initial ligand and cell surface glycoprotein CD200 receptor 1.

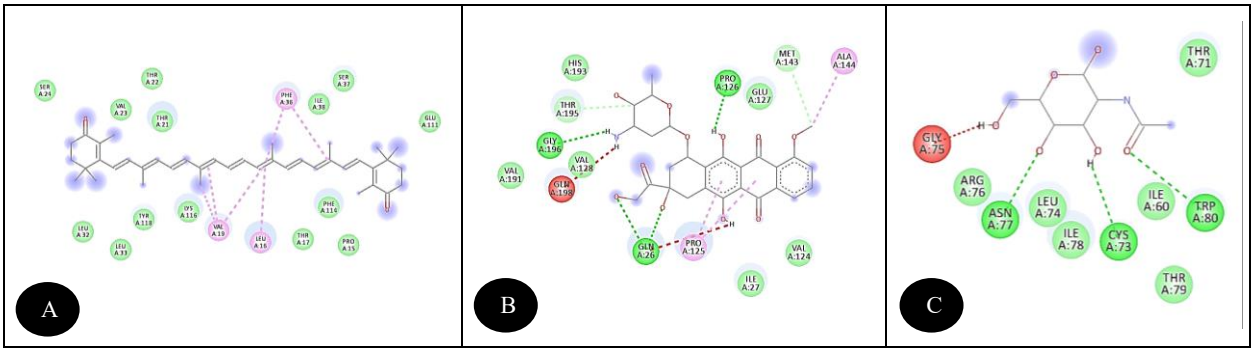

Figure 3. The 2D visualization of interactions complex between: A. cell surface glycoprotein CD200 receptor 1 and canthaxanthin, B. cell surface glycoprotein CD200 receptor 1 and doxorubicin drug, cell surface glycoprotein CD200 receptor 1 and NAD original ligand.

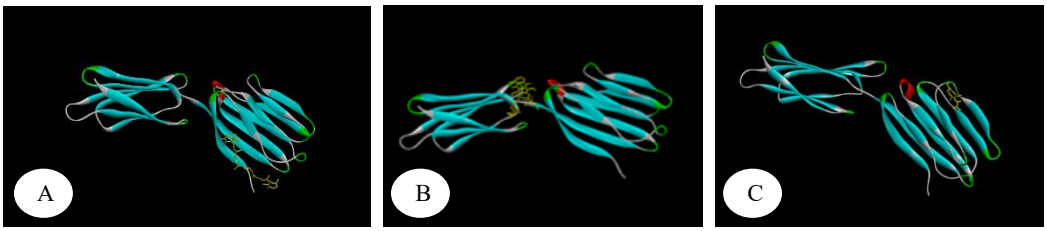

Figure 4. The 3D visualization of interactions complex between: A. cell surface glycoprotein CD200 receptor 1 and canthaxanthin, B. cell surface glycoprotein CD200 receptor 1 and doxorubicin drug, cell surface glycoprotein CD200 receptor 1 and NAD original ligand.

DISCUSSION

The investigation into the potential therapeutic targeting of cell surface glycoprotein CD200 receptor 1 in leukemia treatment through ligand inhibition provides valuable insights into the molecular interactions underlying this novel approach. The use of PyRx gridbox facilitated the establishment of a personalized receptor docking gridbox, allowing for precise molecular docking simulations. The resultant Figures 1 and 2 effectively convey the inhibition constant and binding energy of ligand inhibitors interacting with the CD200 receptor 1.

Among the seventeen compounds examined, canthaxanthin emerged as the most promising candidate, displaying the highest affinity for binding to CD200 receptor 1. This finding suggests its potential as an effective inhibitor in leukemia treatment. The validation of the docking process using the original ligand, nicotinamide adenine dinucleotide (NAD), extracted from the protein-ligand complex structure, further strengthens the reliability of the study.

The two-dimensional representation in Figure 3 offers a clear visualization of receptor-ligand interactions, showcasing the dynamic engagement between canthaxanthin and CD200 receptor 1. Notably, three hydrogen bonds and fourteen hydrophobic interactions play pivotal roles in this interaction, involving specific amino acid residues such as Val-19, Leu-16, Phe-36, Ser-24, and others. Similarly, Figure 3B illustrates the interaction between CD200 receptor 1 and the anticancer agent doxorubicin, revealing seven hydrogen bonds and six hydrophobic interactions with various amino acids. This provides a comprehensive understanding of the molecular intricacies involved in the interaction between the receptor and an established anticancer agent.

Canthaxanthin, an orange carotenoid pigment found in algae, salmon, and crustaceans, has recently emerged as a potential star in the fight against cancer [12]. Beyond its well-established role as a food colorant and antioxidant, research suggests canthaxanthin possesses potent anticancer properties, offering a glimmer of hope for novel and effective in anticancer activities, such as inhibition of cell proliferation, induction of apoptosis, anti-angiogenic effects and antioxidant capacity [13-15].

While research on canthaxanthin's anticancer properties is still in its early stages, the promising preclinical findings warrant

further investigation. Ongoing studies are exploring combination therapy by combining canthaxanthin with existing cancer treatments like chemotherapy or immunotherapy to potentially enhance efficacy and reduce side effects [16]. In delivery systems, it will develop efficient delivery systems to target canthaxanthin specifically to cancer cells, maximize its therapeutic effect while minimizing systemic exposure [17].

CONCLUSION

The study highlighted the potential of targeting cell surface glycoprotein CD200 receptor 1 for inhibition in leukemia treatment, with canthaxanthin emerging as a promising lead compound. The molecular docking simulations and visualizations provide a detailed understanding of the specific interactions between CD200 receptor 1 and ligands, showcasing the diverse network of hydrogen bonds and hydrophobic contacts. The validation of the docking process with the original ligand, NAD, enhanced the study's reliability. The findings not only identify canthaxanthin as a strong candidate for further development but also contribute valuable molecular insights, laying the groundwork for more targeted and effective therapies in the realm of leukemia and related hematological malignancies. This research marks a significant step toward advancing precision medicine in cancer treatment, offering potential breakthroughs in the ongoing quest for improved outcomes for patients facing these challenging diseases.

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