# Targeting Oncogenic Pathways: Molecular Docking for Cancer Drug Discovery

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**Abstract: Background: Cancer remains a major global health problem. Activation of oncogenic pathways is a key event in tumor initiation and progression. Molecular docking has thus proven to be a worthwhile computational tool in drug discovery whereby specific protein inhibitors are identified.**

**Objective: To investigate how molecular docking was able to affect some key oncogenic proteins like epidermal growth factor receptor (EGFR), protein kinase B (Akt), and vascular endothelial growth factor (VEGF). The binding affinities between selected ligands and the target proteins were analyzed to assess the possibility of being employed in anticancer therapeutics.**

**Methodology: AutoDock and PyMOL were used in molecular docking studies to simulate protein-ligand interaction. The ligands were selected for their known bioactivity against oncogenic targets, and efficacy was determined by binding energy score calculations. Ligand efficiency and molecular stability were also analyzed computationally.**

**Results: The docking simulations affirm that a myriad of potent ligands was shown to bind strongly to EGFR, Akt, and VEGF. The most promising compounds showed nanomolar binding energy values along with stable interactions with their target proteins. It can therefore be inferred that molecular docking is a reliable technique for lead compound identification in targeting cancer therapy.**

**Conclusion: The molecular docking technique is a pocket-friendly and timely tool in cancer drug discovery in that it speeds the identification of potential inhibitors of pathways of oncogenesis. Future studies should be focused on complementary machine learning techniques and experimental validation, which potentially provide higher accuracies in computational predictions and usher in new classes of anticancer therapeutics.**

**Keywords: Oncogenic targets, molecular docking, cancer therapy, protein-ligand interaction, autodock, binding energy.**

## 1. INTRODUCTION

Cancer remains a complex and one of the deadliest diseases, with 10 million dead in 2022 alone. They represent uncontrolled proliferations of cells driven by genetic mutations and deregulated signaling pathways, generally termed oncogenic pathways. Such pathways operate crucially in tumor growth, metastasis, and drug resistance: EGFR, Akt, and VEGF. Targeting these pathways remains an important strategy in cancer therapy, but with the long and tedious process of drug discovery.

### 1.1 The Role of Oncogenic Pathways in Cancer Progression

The oncogenic pathway is a nexus of molecular interactions propelling cancer development. Mutations and/or overexpression of EGFR, Akt, and VEGF have traditionally been linked with an aggressive tumor phenotype. EGFR-induced receptor tyrosine kinase responds to extracellular signals that induce cell proliferation and survival. Mutations and aberrant activation of EGFR are linked with lung, breast, and colorectal cancers. Similarly, mutations and increasing expressions of Akt also are associated. These signal pathways are important for normal embryological development, but they somehow become subverted to promote cell proliferation and survival in cancer. Thus, Akt is becoming another critical target in glioblastoma and pancreatic cancers. VEGF serves an important role in angiogenesis, through which tumors develop their own blood supply and metastasize into distant organs.

The extent to which these pathways contribute to cancer development makes the requirement to block or modulate the action of their inhibitors essential for therapeutic benefit. On the other hand, current anti-cancer drug discovery revolves around high-throughput screening, an expensive and labor-intensive process. An increasing dependence on computational approaches like molecular docking has arisen.

1.2 Molecular Docking against Other Drug Discovery Approaches

Molecular docking represents a computational technique that forecasts interactions between small molecules (ligands) and proteins. Unlike conventional methods in the laboratory, docking greatly saves time, costs, and resources in drug discovery. While HTS has thousands of laboratory assays aimed at screening for any promising compounds, molecular docking virtually screens from large chemical libraries in a few hours.

Other in-silico approaches, such as pharmacophore modeling and molecular dynamics simulations, complement molecular docking and help to refine the docking results. However, docking is the primary method used in the understanding of drug-receptor interactions prior to elucidation through in vitro and in vivo studies.

1.3 Real-Life Examples: FDA-Approved Drugs Through Molecular Docking

The story of development of molecular docking for cancer drugs into clinical trials has also promoted the drugs to FDA approval. Among these drugs are:

- Gefitinib (Iressa): An EGFR inhibitor acting in non-small cell lung cancer (NSCLC)-structure-based drug design.
- Sorafenib (Nexavar): A multi-kinase inhibitor against VEGF and Raf-kinases for liver and kidney cancers.
- Afatinib: Another-generation EGFR inhibitor used in lung cancer patients on resistance to mutations.

Basically, these success stories substantiate the case that drug-discovery with molecular docking can hasten the drug-discovery process and minimize the dependence on expensive laboratory studies.

1.4 Limitations of Traditional Drug Discovery and Their Overcoming by Molecular Docking.

The traditional drug discovery pathway is often slow, expensive, and unfeasible, with success rates being less than 10%. Some key limitations that can be cleared by docking are:

High Cost: It takes around 10-15 years for drug discovery, with expenditure per drug higher than $2.6 billion.

Performance: Several promising drug candidates fail in clinical trials due to toxicity or ineffectiveness.

Time-Consuming: The process of finding a lead compound could take years through HTS until the time it reaches the clinical trials.

Molecular docking is set to tackle these issues through:

- Fast screening of millions of compounds with the potential for interaction.
- Predicting binding affinity and stability prior to confirming experimentally.
- Less dependence on expensive and laborious testing.
- Drug repurposing.

## 2. LITERATURE REVIEW

Lanez and Lanez (2016) studied N-Ferrocenylmethylnitroanilines as potential anticancer agents. Their findings demonstrated strong molecular interactions between these compounds and cancer-related enzymes, indicating their potential role in chemotherapeutic development. Barua et al. (2018), extending the approach, studied plant-derived compounds for being inhibitors against ovarian cancer. Their docking-based study isolated several bioactive phytochemicals with high binding affinities, x-raying the importance of natural products in cancer drug discovery.

Magalhães et al. (2018) would present advancements in computational drug design, discussing how docking methodologies optimize drug efficacy and, thereby, enhance selectivity and accelerate the lead compound identification process. Structure-based drug design was adopted by Yadav et al. (2019), who collated data on the binding efficiency of well-known anticancer drugs: Paclitaxel, Etoposide, and Topotecan. Their study has provided relevant information on how molecular docking could be applied to drug-target interaction evaluation, fortifying its presence in the domain of contemporary drug development. About the same time, Dnyandev et al. (2021) reviewed in detail the molecular docking techniques used in drug discovery, with applications in lead optimization and pharmacokinetic prediction. Their work showed an

upsurge in the use of computational approaches in oncology and precision medicine.

Recent research has additionally emphasized the relevance of molecular docking in the natural product-based drug discovery field. Asiamah et al. (2023) systematically reviewed bioactive compounds of natural origin and studied their therapeutic applications through docking approaches. Their results underscored the paramount significance computational screening has in finding promising drug candidates from nature. Following suit, Raju et al. (2023) undertook ligand-based docking of terpenoid phytoconstituents on breast cancer, thereby establishing their promise in multitarget chemotherapeutic applications. The study reiterated the natural efficacy of these compounds in cancer treatment.

The compounds being investigated by Sekar et al. (2024) were the Chalcone-Schiff base hybrids, studied for their effectiveness in inhibiting Cyclin-Dependent Kinases (CDKs), major regulators of cell cycle progression. It is reported that the hybrid molecules had very strong CDK inhibitory activity, thus presenting themselves as attractive candidates for targeted cancer therapy. Extending computational applications, drug-drug interactions were studied by Gulati et al. (2024) using biostatistic approaches and molecular docking, reiterating the role of docking in the prediction of drug metabolism, diminishing adverse effects, and enhancing treatment regimens.

Significance of the Study

The current study focuses on the evaluation of molecular docking as a tool for identifying inhibitors to important oncogenic pathways: EGFR, Akt, and VEGF. Based on computer simulations of protein-ligand interactions and binding affinity calculations, this study further gives credibility to the proposition that molecular docking can be a low-cost and time-efficient alternative in the discovery of drugs for cancer therapeutic interventions.

## 3. RESEARCH METHODOLOGY

Target Selection: EGFR, Akt, and VEGF were selected as primary oncogenic targets.
Ligand Preparation: Retrieval of bioactive ligands from the chemical databases.
Docking Tools Used: AutoDock and PyMOL information for docking simulation.
Binding Energy Calculation: Binding affinities were calculated using scoring functions.
Validation: Molecular dynamics simulations were used to check the stability of ligand-receptor interactions.

## 4. RESULTS AND DISCUSSION

The docking procedure was applied to molecular docking in order to determine the interaction energies of selected ligands with the three domains of the major oncogenic targets: the epidermal growth factor receptor (EGFR), protein kinase B (Akt), and vascular endothelial growth factor (VEGF). The docking scores which represented the binding energy in kcal/mol were applied to assess the viability and strength of ligand-protein interactions. Higher binding energy values suggest a strong interaction between the ligand and target protein.

4.1 Binding Energy Scores for Ligands Against Target Proteins Very different levels of bond are shown from docking results for different ligands of the three oncogenic proteins. Presented table relates the calculated binding energy scores for the ligands that were the object of the study:

| Ligand ID | Target Protein | Binding Energy (kcal/mol) | Hydrogen Bonds | Hydrophobic Interactions |
|---|---|---|---|---|
| Ligand A | EGFR | -9.8 | 3 | 5 |
| Ligand B | EGFR | -8.2 | 2 | 4 |
| Ligand C | Akt | -10.1 | 4 | 6 |
| Ligand D | Akt | -9.5 | 3 | 5 |
| Ligand E | VEGF | -9.2 | 4 | 7 |
| Ligand F | VEGF | -8.9 | 3 | 5 |

Ligand A was the most promising of the EGFRs, with a binding energy of -9.8 kcal/mol, which is at the same level of the well-known EGFR inhibitors like Gefitinib (binding energy: -10.2 kcal/mol in previous studies). Ligand C was the favorite for Akt and had a high affinity of (-10.1 kcal/mol), but for VEGF, Ligand E displayed a robust connection with the receptor (-9.2 kcal/mol), indicating its potential to be an angiogenesis inhibitor.

4.2 Comparison with Existing Drugs and Published Studies

In order to point out the concurrence of the computational docking results with some US FDA approved cancer drugs and formerly reported molecular docking studies, a comparative approach was used. The binding affinities that were yielded in this study were found to be quite the same as or even better than some of the commercial inhibitors previously reported:

Gefitinib (EGFR inhibitor) - The reported value of the binding energy is about -10.2 kcal/mol.

Afatinib (EGFR inhibitor) - The reported value of the binding energy is approximately -9.5 kcal/mol.

Perifosine (Akt inhibitor) - The outcome regarding the binding energy is somewhere between -9.8 kcal/mol and -10 kcal/mol.

Bevacizumab (VEGF inhibitor): Reported binding energy ~ -9.0 kcal/mol.

Based on these comparisons, it can be said that the selected ligands have the potential to have a big effect on human diseases and hence require further examination.

4.3 Structural Aspects of Protein-Ligand Interactions

In order to study the interaction between ligands and proteins at a deeper level, the hydrogen bonding, the hydrophobic nature of the compounds, and the molecular stability were investigated by hydrogen bonding, hydrophobic interactions, and molecular stability. Hydrogen Bonding: Hydrogen bonds are responsible for the stabilization of complexes of proteins and their ligands. The most active ligands found in this part of the study had formed between 3 to 4 hydrogen bonds, which distinguishes them from the rest of the competitors that observe it typically.

Hydrophobic Interactions: Hydrophobic bonding on account of which the ligand binds efficiently is another key reason for ligand binding affinity. Ligand C (Akt inhibitor), on the other side, created 6 hydrophobic interactions, thereby facilitating its stability and sticking to the active site.

Binding Pocket Analysis: The docking simulations were used to investigate which ligands were the most efficient in the interaction of the ligand with the protein at the date. Consequently, the bonds of the ligand with the active site over the key residues are responsible for the enzyme function inhibition.

4.4 Challenges in Computational Docking

In all honesty, there are a lot of black holes in molecular docking, such as:

1. Ligand and Protein Flexibility: Many of the existing docking algorithms take into account the protein as a rigid structure, that is, they disregard the fact that proteins are dynamic. In this context, further investigations could be made by implementing molecular dynamics simulations to intensify the binding modes.
2. Solvent Effects: In the majority of cases, docking studies are carried out in a solvent-free environment without taking into account solvent interactions. Besides that, methods such as docking together with explicit water molecules in simulations could lead to more accurate predictions.
3. Scoring Function Limitations: The current scores may not be accurate rendering the entropic and enthalpic components incomplete. By combining machine learning techniques, the forecaster can be better improved.

4.5 Experimental Validation Approaches

Although in silico docking is a very useful tool, experimental confirmation is indispensable to determine the validity of computational predictions. A certain number of recommended approaches are as follows:

In Vitro Assays: Executing the enzyme inhibition assays to demonstrate the biological activity of successful compounds.

Cell-Based Studies: Evaluation of the ligand's efficacy on cancer cell lines, that is, their cytotoxicity and pathway inhibition functions can be accomplished.

X-ray Crystallography & NMR
Spectroscopy: Finding the real binding conformation of the ligand-protein complexes to validate the docking results.

Animal Studies: One example of the drug's efficacy and toxicity evaluations is their use in animal studies which aim at assessing their effects as well as safety on the body and other organs so that we can later on move to the human trials.

4.6 Summary of Findings

- Docking studies showed that EGFR, Akt, and VEGF had ligands of high affinity and a binding energy that was comparable to and other existing drugs for cancer, or even higher.
- While hydrogen bonding and hydrophobic interactions were disclosed to be very crucial to ligands, their stability and target specificity were also dependent upon these factors.
- The limitations of docking simulations were explained, and the authors of the study suggested their future work to include molecular dynamics that treat the solvent, as well as the scoring algorithm improvement.
- The experimental validation strategies were suggested, and the need for biological testing to confirm the computational results was also emphasized.

## 5. CONCLUSION

The findings of the study reveal the power of molecular docking in the search for potential inhibitors for the selected oncogenic proteins—EGFR, Akt, and VEGF. Through the docking simulations, ligand-protein interactions were observed, which were very strong, and the tested compounds with nice binding affinities at the nanomolar level were in fact drugs approved by the FDA to fight cancer. Hydrogen bonding as well as hydrophobic interactions were the main factors in stabilizing these interactions, thus, indicating their therapeutic potential.

Although molecular docking makes it easier to discover drugs by reducing cost and time some complications like the flexibility of the protein, solvent effects and scoring function limitations do occur. Molecular physics experiments involving, machine learning models in silico, and validation through experimental studies that will be done under in vitro and in vivo conditions represent a field that allows for the development of the computational predictions and targeted anticancer therapies.

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