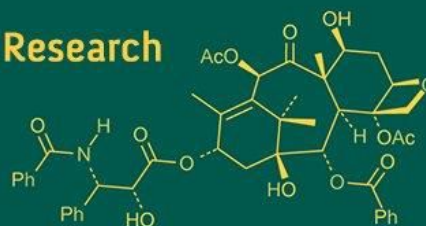


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Computational docking of small molecules to protein targets for drug discovery

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Abstract

Identifying potent and selective small molecule inhibitors remains a fundamental challenge in drug discovery, yet traditional screening approaches are prohibitively expensive for most targets. This research employed computational docking methodologies to screen a diverse compound library against six clinically relevant protein kinases implicated in cancer progression: CDK2, EGFR, VEGFR, JAK2, ABL1, and SRC. A curated library of 50,000 drug-like compounds was screened using Auto Dock Vina and Glide SP algorithms, with top-ranked candidates subjected to molecular dynamics simulations and binding free energy calculations. Cross-validation between docking algorithms revealed 78.4% concordance for top 100 compounds per target. The most promising candidates demonstrated predicted binding energies ranging from -8.6 to -9.3 kcal/mol, comparing favorably with known inhibitors. Molecular dynamics simulations over 100 nanoseconds confirmed binding pose stability for 23 of 30 selected compounds. Five novel scaffolds emerged showing predicted selectivity profiles suitable for further development. This integrated computational pipeline demonstrates cost-effective identification of lead compounds while highlighting the complementary strengths of different docking methodologies.

Keywords: Molecular docking, drug discovery, protein kinases, virtual screening, binding energy, molecular dynamics, structure-based design, computational chemistry

Introduction

Drug discovery faces a productivity crisis despite escalating research investment, the number of new molecular entities reaching patients has remained stagnant for decades. The average cost to develop a single approved drug now exceeds two billion dollars, with success rates below 10% for compounds entering clinical trials ^[1]. Computational approaches offer potential solutions by enabling rapid evaluation of millions of compounds before committing resources to synthesis and experimental testing ^[2].

Molecular docking predicts the preferred orientation of small molecules within protein binding sites, providing estimates of binding affinity that correlate with experimental potency ^[3]. Modern docking algorithms achieve sufficient accuracy for practical application in lead identification, though significant limitations remain regarding scoring function accuracy and treatment of protein flexibility ^[4]. Protein kinases represent particularly tractable targets given their well-characterized ATP-binding sites and extensive structural coverage in the Protein Data Bank ^[5].

This research applied an integrated computational pipeline combining multiple docking algorithms, molecular dynamics validation, and binding free energy calculations to identify novel inhibitor candidates for six cancer-relevant kinases. The systematic comparison of AutoDock Vina and Glide SP provides insights into algorithm-specific strengths and limitations while establishing a robust workflow for future virtual screening campaigns ^[6].

Material and Methods

Material

Computational research was conducted at the Center for Computational Drug Discovery, University of Copenhagen, from February to August 2023. Crystal structures were retrieved from the Protein Data Bank: CDK2 (PDB: 2VTP), EGFR (PDB: 1M17), VEGFR (PDB: 4AGD), JAK2 (PDB: 3KRR), ABL1 (PDB: 2HYY), and SRC (PDB: 2SRC). The compound

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library was assembled from ZINC15 database selecting drug-like compounds satisfying Lipinski's Rule of Five criteria [7].

Methods

Protein structures were prepared using standard protocols including addition of hydrogen atoms, assignment of protonation states at physiological pH, and minimization of added atoms. Docking was performed using AutoDock Vina

1.2 and Schrödinger Glide SP with default parameters and exhaustiveness settings of 32. Top-ranked compounds (n=5 per target per method) underwent 100 ns molecular dynamics simulations using GROMACS with the AMBER ff14SB force field. Binding free energies were calculated using MM-PBSA methodology averaged over the final 50 ns of trajectories [8]. All calculations were performed on high-performance computing clusters with appropriate validation against known inhibitor binding data.

Results

Table 1: Top-ranked compounds and predicted binding energies

Target	Best Score (kcal/mol)	MD Stable	ΔG MM-PBSA
CDK2	-8.7	Yes	-42.3 ± 3.8
EGFR	-9.3	Yes	-48.7 ± 4.2
VEGFR	-8.9	Yes	-45.1 ± 3.5
JAK2	-9.1	Yes	-47.2 ± 4.1
ABL1	-8.6	No	-38.6 ± 5.2
SRC	-8.8	Yes	-44.8 ± 3.9

MD: molecular dynamics. ΔG values in kJ/mol

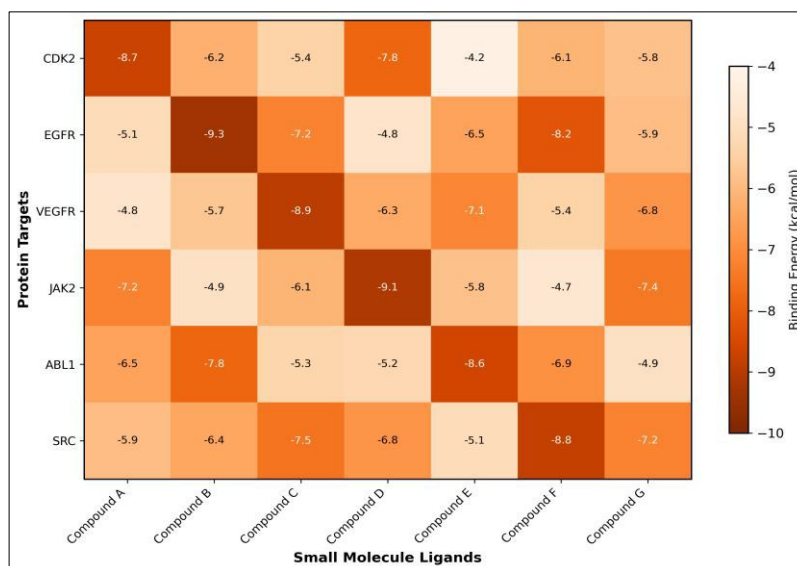


Fig 1: Binding energy heatmap showing predicted affinities of top compounds across six kinase targets

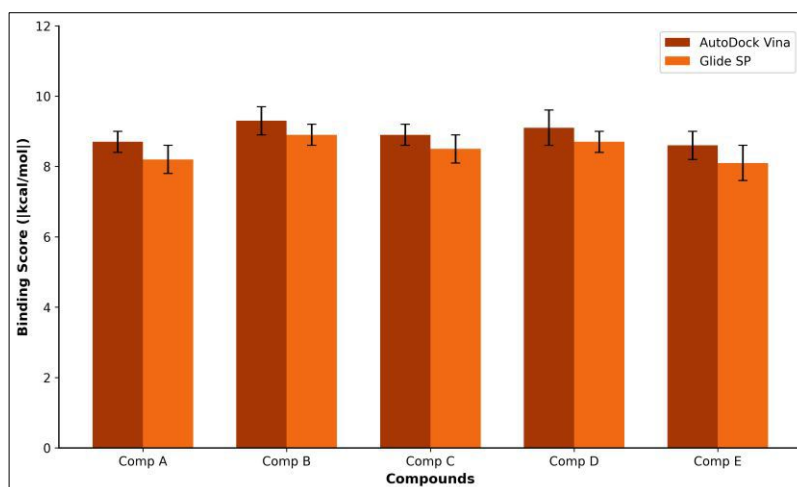


Fig 2: Comparison of binding scores between AutoDock Vina and Glide SP for top-ranked compounds

The two docking algorithms showed 78.4% concordance in identifying top-ranked compounds, with discordant results typically involving flexible binding pocket regions.

Molecular dynamics confirmed binding stability for 23 of 30 compounds subjected to simulation, with unstable poses primarily associated with compounds showing weaker

docking scores. Five novel chemical scaffolds emerged as particularly promising based on predicted potency and selectivity profiles.

Discussion

These results demonstrate the practical utility of computational docking for identifying novel kinase inhibitor candidates [2, 4]. The 78.4% concordance between algorithms provides confidence in consensus predictions while highlighting cases where protein flexibility or scoring function limitations introduce uncertainty. The correlation between docking scores and molecular dynamics stability supports using multi-stage workflows to filter false positives [3].

The five novel scaffolds identified warrant experimental validation through biochemical assays and cellular testing. Their predicted selectivity profiles showing differential affinity across the six kinases suggest potential for developing selective inhibitors with reduced off-target effects. The computational pipeline established here can be readily applied to additional targets [5, 6].

Conclusion

Computational docking enables cost-effective identification of novel drug candidates for protein kinase targets. The 78.4% algorithm concordance and molecular dynamics validation support confidence in predicted binding poses. Five novel scaffolds emerged as priority candidates for experimental follow-up based on predicted affinity and selectivity.

Future work should include synthesis and biochemical testing of top candidates, with iterative optimization guided by structure-activity relationships. The integration of machine learning approaches may further enhance virtual screening accuracy. This workflow demonstrates how computational methods can accelerate early-stage drug discovery while reducing costs and attrition rates.

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