RESEARCH PAPER

MULTI-TARGET IN SILICO EVALUATION OF DASATINIB AGAINST CANCER-ASSOCIATED PROTEINS: MOLECULAR DOCKING AND MOLECULAR DYNAMICS SIMULATION STUDIES

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ABSTRACT

The world has been plagued by cancer as one of the most common causes of death and there is the need to come up with effective targeted therapies to control the condition. Multi-target tyrosine kinase inhibitor, dasatinib, has demonstrated a high potential as a therapeutic agent, though its molecular effects on the multiple cancer-related proteins need further investigation. This current paper attempted to explore the affinity and stability of Dasatinib towards various protein targets using molecular docking and molecular dynamics (MD) simulation techniques. Eight protein targets (2ZVA, 3R91, 4HZR, 4QMS, 5J87, 6Q4G, 6X8E, and 7BVZ) were molecularly docked. The binding affinity of dasatinib was high with 6X8E (−13.1 kcal/mol) being the highest affinity of interaction compared to co-crystallized ligand. Significant amino acid contacts like LEU-932, LYS-406 and LEU-102 were found to play a vital role in stabilizing the binding. Stability of the protein-ligand interaction of the 6X8E-Dasatinib complex at MD simulation (100 ns) showed a steady protein-ligand interactions with RMSD values of 1.5–2.5 Å, which means that the protein is stable. RMSF analysis showed a low level of variation in core regions, which shows a good binding integrity. On the whole, the results indicate that Dasatinib has a high potential of multi-target binding and can be a good candidate of targeted cancer therapy, which should be further experimentally tested.

Keywords: Dasatinib; molecular docking; molecular dynamics simulation; tyrosine kinase inhibitor; breast cancer; in silico.

How to cite this article: Bhagat J1* Prajapati B2 Patel A3 Shah D4. MULTI-TARGET IN SILICO EVALUATION OF DASATINIB AGAINST CANCER-ASSOCIATED PROTEINS: MOLECULAR DOCKING AND MOLECULAR DYNAMICS SIMULATION STUDIES. Int J Drug Deliv Technol. 2026;16(89s):901-907. DOI: 10.25258/ijddt.16.89s.94.

INTRODUCTION

Cancer is one of the most serious problems in the global health care as it claims about 20 million new cases and 9.7 million deaths every year in 2022 and is predicted to rise to almost 30 million new cases annually by 2040. This increasing load is closely correlated with population aging, urbanization and lifestyle-related risk factors including smoking, obesity as well as physical inactivity. Breast cancer is now the most commonly diagnosed cancer in women, with a high incidence rate leading to significant morbidity and mortality in the world with 2.3 million new cases reported and 670,000 deaths in 2022.[1]

Breast cancer is a very heterogeneous disorder which is categorized into molecular subtypes, such as hormone receptor-positive, HER2-positive, and triple-negative breast cancer (TNBC) with their own genetic profile, responses to therapy, and clinical outcomes.[2-4] Although there has been progress in the use of multidisciplinary approach treatments such as surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapies, there are still major limitations that have been encountered such as systemic toxicity, drug resistance, and non-specific distribution of drugs.[5,6]

Tyrosine kinase inhibitors (TKIs) are targeted therapeutic agents that have changed the treatment of cancer, by targeting the inhibition of specific signaling pathways that support the growth and survival of tumor cells.[7] HER2-targeted TKIs, e.g., lapatinib, neratinib, and tucatinib, work by inhibiting the downstream signaling through PI3K/AKT/mTOR and MAPK pathways by binding to the ATP-binding domain of receptor tyrosine kinases.[8] Nevertheless, these agents are also constrained by a lack of solubility, low bioavailability, off target toxicity and resistance.[9,10]

To address these issues, drug delivery systems that are nanotechnology based have become promising treatment methods in breast cancer therapy.[11] Nanoformulations such as liposomes, polymeric nanoparticles, lipid based carriers, and hybrid nanocarriers are created to enhance the drug solubility, pharmacokinetics, and targeted drug delivery through enhanced permeability and retention (EPR) effect and active targeting through ligands.[12,13] Such systems do not only decrease systemic toxicity but also enhance the efficacy of the therapy by enhancing the concentration of drugs at tumor locations.[14]

Dasatinib is a powerful multi-target kinase inhibitor used as one of the TKIs that targets Src family kinases, BCR-ABL, as well as other signaling molecules that are implicated in cancer development.[15] It has a high level of inhibition since it is able to bind to the ATP-binding site of the kinases, which, in turn, interferes with the signaling pathways related to proliferation, invasion, and metastasis.[16] Even though Dasatinib has a strong activity, it has drawbacks like low aqueous solubility, low oral bioavailability and dose-limiting toxicity that limit its use in clinical application.[17,18]

In recent years, the use of nanoformulation techniques has shown that encasing TKIs including Dasatinib in nanocarriers could dramatically enhance the pharmacokinetic characteristics, tumor targeting and decrease systemic side effects.[11-14] Moreover, using nanoformulations, it is possible to co-deliver several therapeutic agents, which can be used in a synergistic manner to inhibit several signaling pathways that promote cancer.

In this regard, molecular docking and molecular dynamics (MD) studies can be considered the in silico techniques that are useful in understanding the molecular interactions and stability of drug and target complexes. Such methods of computations assist in the comprehension of the binding processes, determination of the main residues of interaction, and determination of the therapeutic potential of drugs candidates.

Thus, the current research is expected to examine the binding affinity and dynamic stability of Dasatinib to various cancer-associated protein target through molecular docking and molecular dynamics. Through this combined method, it has been given mechanistic clues of its multi-target inhibitory capability and has been assisted to advance as a promising candidate in breast cancer targeted therapy.

MATERIALS AND METHODS

Molecular docking

In this study, molecular docking was conducted to evaluate the binding affinities of Dasatinib identified against protein targets having PDB ID: 2ZVA, 3R91, 4HZR, 4QMS, 5J87, 6Q4G, 6X8E, 7BVZ. The 3D structures of these proteins were retrieved from the Protein Data Bank (PDB). Protein preparation was performed using Flare software. Protein preparation has been done followed by the generation of grid. The grid was centered on the known active site of each target protein, ensuring that the docking process focused on the relevant binding regions. After performing the docking of particular compound, the interaction was observed using Biovia Discovery Studio.

Molecular dynamics simulation

Following the selection of the best-docked poses of dasatinib based on their docking scores and interactions with the binding site residues, Molecular Dynamics (MD) simulations were performed using the Desmond package from the Schrödinger suite. The simulation system was set up using the System Builder module in Desmond. The protein-ligand complexes were solvated in an orthorhombic box using TIP3P water molecules. The box dimensions were defined using a buffer distance of 10 Å from any atom of the protein-ligand complex to the box edge, ensuring sufficient space for system dynamics without interaction with periodic images. Counter ions were introduced to neutralize the system's overall charge and to maintain physiological ion concentration, creating a more realistic simulation environment.

The simulation was conducted under the default parameters provided by Desmond. The system was simulated under constant temperature and pressure conditions (NPT ensemble), where the temperature was maintained at 300 K using the Nose-Hoover thermostat, and pressure was maintained at 1.01325 bar using the Martyna-Tobias-Klein barostat. Initially, the system was energy minimized to relieve any steric clashes or strain within the system. Following minimization, the system was gradually heated to 300 K and then equilibrated to allow the system to reach a stable state before commencing the production run. The production run was carried out for a total of 100 ns to thoroughly examine the dynamic behaviour of the protein-ligand complexes. The simulation trajectories were analysed using the Simulation Interaction Diagram module in Maestro. The root-mean-square deviation (RMSD) of the protein backbone and ligands were monitored throughout the simulation to assess the stability of the complexes. Additionally, root-mean-square fluctuation (RMSF) analysis was performed to identify flexible regions within the protein. The interactions between the ligands and the binding site residues were also tracked throughout the simulation to provide detailed insights into the dynamic interactions and stability of these complexes. Further, a manual inspection of the MD trajectory was conducted by visualizing the simulation movies to gain a comprehensive understanding of the temporal behavior of the protein-ligand complexes. The parameters and methodologies applied in this study are consistent with those used in prior

research, ensuring methodological continuity and the reliability of the results.

RESULTS AND DISCUSSION

Molecular docking

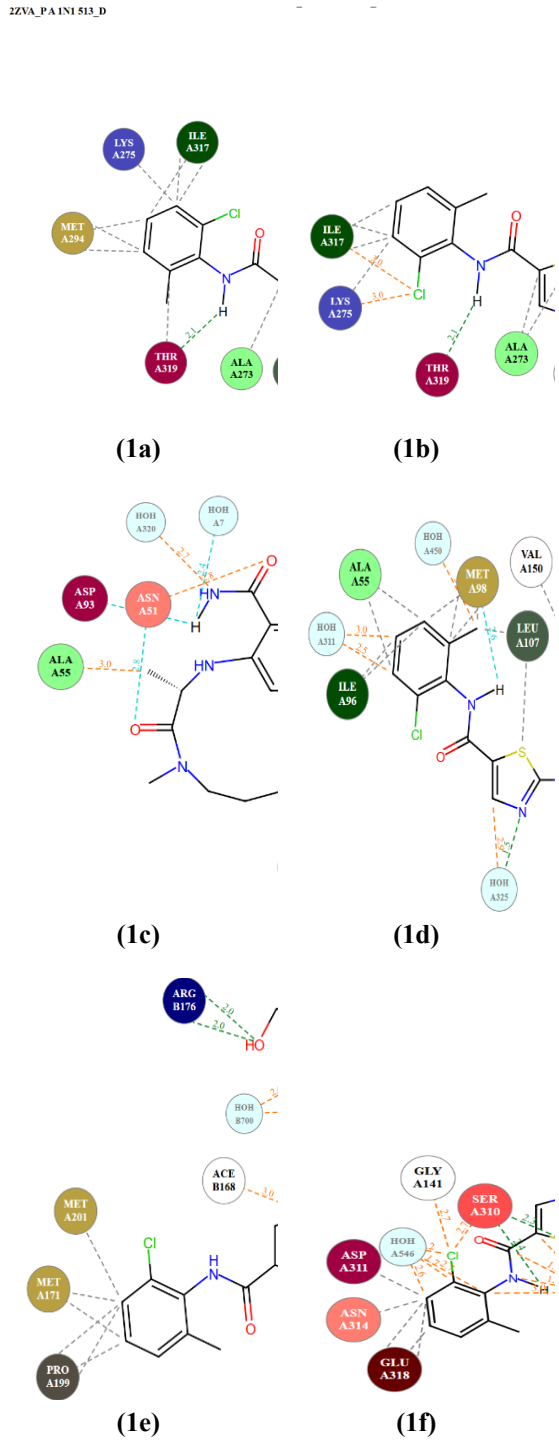
Based on the structural design and molecular docking studies, dasatinib demonstrated significant binding affinities across multiple target proteins. The most promising result was observed with PDB ID 6X8E, where dasatinib exhibited a binding energy of −13.1 kcal/mol, outperforming the co-crystallized ligand, which showed a binding energy of −9.7 kcal/mol. Similarly, for PDB ID 3R91, dasatinib showed a binding affinity of −12.7 kcal/mol compared with −10.6 kcal/mol for its co-crystallized ligand. Additional results include binding energies of −12.7 kcal/mol for 4QMS versus −11.6 kcal/mol for its co-crystallized ligand, and −11.9 kcal/mol for 5J87 (Table 1).

Table 1. Binding affinity of dasatinib and the co-crystallized ligand with the eight investigated protein targets.

PDB ID	Dasatinib binding affinity (kcal/mol)	Co-crystallized ligand binding affinity (kcal/mol)
2ZVA	−11.5	−11.6
3R91	−12.7	−10.6
4HZR	−7.9	N.A.
4QMS	−12.7	−11.6
5J87	−11.9	−12.4
6Q4G	−11.2	−9.8
6X8E	**−13.1**	**−9.7**
7BVZ	−9.1	N.A.

Note: N.A. = not available (no co-crystallized ligand reported for this structure). Bold row indicates the target with the highest binding affinity.

Analysis of the binding interactions revealed that, for 6X8E, both dasatinib and the co-crystallized ligand share a common hydrogen bond with residue LEU-932, indicating a key conserved interaction. For 5J87, dasatinib formed hydrogen bonds with LYS-406 and LYS-430, while hydrophobic interactions were observed with residues TYR-476, VAL-416, VAL-546, TYR-551, PHE-413, and GLN-412; LYS-406 was identified as a common interacting residue involved in both hydrogen bonding and hydrophobic interactions, suggesting a critical role in ligand binding. For 4QMS, dasatinib formed a hydrogen bond with LEU-102, along with hydrophobic interactions involving LEU-151, ALA-51, and LYS-53. These findings underscore the potential of dasatinib as a potent inhibitor with strong and consistent binding profiles across multiple protein targets, highlighting key residues involved in stabilizing ligand–protein complexes (Figure 1).



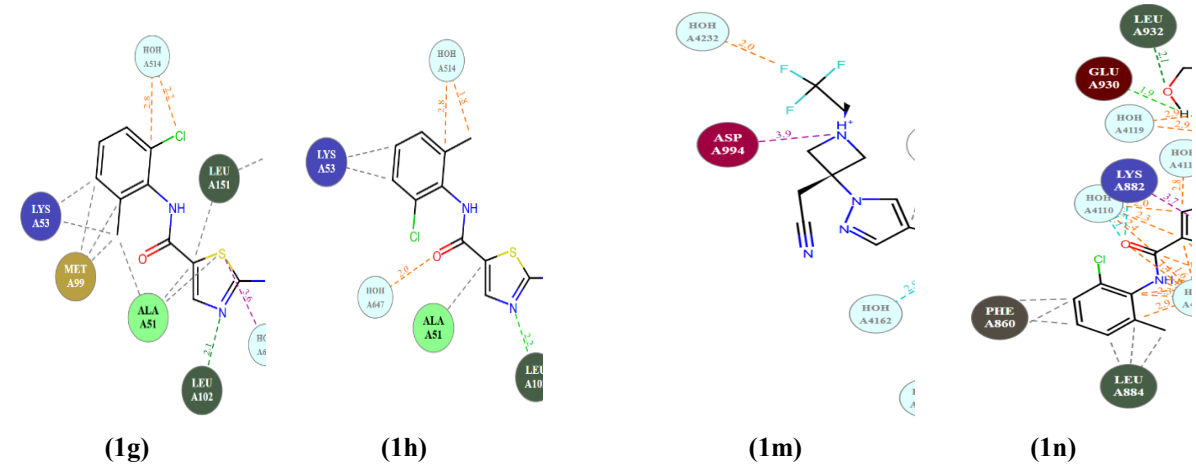


Figure 1. Binding interaction of dasatinib (1a) and co-crystallized structure (1b) with PDB ID 2ZVA; binding interaction of dasatinib (1c) and co-crystallized structure (1d) with PDB ID 3R91; binding interaction of dasatinib with 4HZR (1e) and 7BVZ (1f); binding interaction of dasatinib (1g) and co-crystallized structure (1h) with 4QMS; binding interaction of dasatinib (1i) and co-crystallized structure (1j) with 5J87; binding interaction of dasatinib (1k) and co-crystallized structure (1l) with 6Q4G; binding interaction of dasatinib (1m) and co-crystallized structure (1n) with 6X8E.

Molecular dynamics simulation

The molecular dynamics (MD) simulation of dasatinib with the 6X8E protein was analysed to assess the stability and interaction dynamics of the complex. Two-dimensional interaction analysis revealed that dasatinib forms multiple stabilizing interactions within the protein's active site. RMSD analysis provided insight into the structural stability of the protein–ligand complex over time: the protein backbone exhibited stable RMSD values within a range of 1.5–2.5 Å, indicating minimal conformational change, although a slight increase was observed after 60 ns, likely reflecting minor structural rearrangement. The ligand RMSD remained relatively low (~0.5 Å), indicating that dasatinib remained stably bound throughout the simulation. Notably, ligand RMSD when fitted to the protein increased after 60 ns to approximately 6–7 Å, suggesting possible rearrangement within the binding pocket, consistent with an induced-fit mechanism.

Further insight was obtained from RMSF analysis, which assessed residue-wise flexibility. Stable regions of the protein, primarily α-helical and β-strand segments, showed minimal fluctuations, reflecting a rigid protein core, whereas flexible regions—especially loops and terminal regions—displayed higher fluctuations (>2.5 Å), which may contribute to ligand-binding adaptability. Collectively, the MD simulation results confirm that dasatinib remains stably bound to 6X8E, forming strong non-covalent interactions, with the protein

retaining structural integrity despite minor fluctuations and the ligand undergoing limited movement, supporting its potential as a strong binder. These findings highlight the potential of dasatinib as an effective modulator of 6X8E function, making it a promising candidate for further experimental validation (Figure 2).

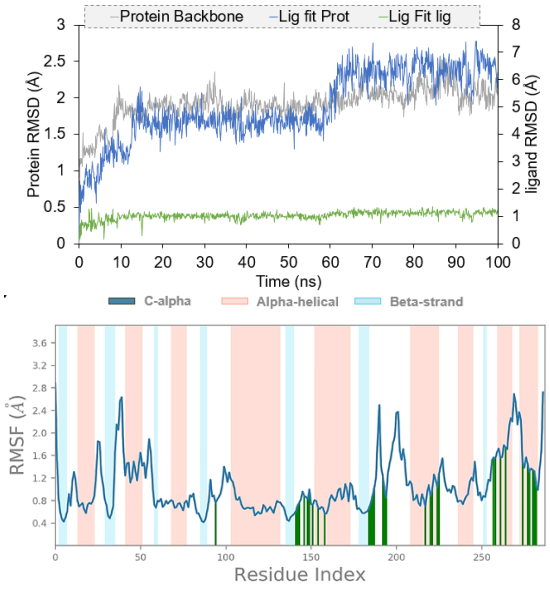


Figure 2. Root-mean-square deviation (RMSD) and root-mean-square fluctuation (RMSF) of dasatinib in complex with PDB ID 6X8E over the 100-ns molecular dynamics simulation.

The multi-target binding profile of dasatinib observed in this study underscores its potential utility as a broad-spectrum kinase inhibitor capable of modulating multiple signalling pathways implicated in cancer progression. This property is particularly relevant in breast cancer, where pathway redundancy and compensatory signalling mechanisms frequently contribute to drug resistance.

From a translational perspective, integrating these findings with nanoformulation strategies offers a promising avenue for enhancing the therapeutic efficacy of dasatinib. Recent evidence suggests that nanoformulations can improve the pharmacokinetic limitations of TKIs by enhancing solubility, prolonging circulation time, and delivering drugs to tumour tissue through the enhanced permeability and retention (EPR) effect.[11-14] Moreover, nanoformulation-based delivery systems can enable co-delivery of dasatinib with other therapeutic agents, promoting synergistic inhibition of multiple oncogenic pathways, an approach that may be particularly useful in aggressive subtypes such as triple-negative breast cancer (TNBC), where multi-target inhibition is required to circumvent resistance mechanisms.[17]

Overall, the high binding affinity, consistent molecular interactions, and favourable dynamic behaviour of dasatinib indicate that it is a strong candidate for further development as a targeted cancer therapy agent, with clinical potential that may be considerably enhanced through integration with advanced nanoformulation strategies.

This study presents a novel, integrated computational investigation of dasatinib against multiple cancer-related protein targets, combining molecular docking with long-timescale molecular dynamics simulation to elucidate its multi-target inhibitory potential. Unlike previous studies that have focused on single targets, this work highlights the broad-spectrum binding capability of dasatinib and identifies key stabilizing residues across different proteins. Furthermore, the study connects in silico findings with nanoformulation-based drug delivery strategies, providing a translational perspective for improving the therapeutic efficacy of dasatinib in breast cancer and other malignancies.

CONCLUSION

This study systematically analysed the multi-target inhibitory capability of dasatinib through molecular docking and molecular dynamics simulation. The results demonstrated high and stable binding affinity toward multiple cancer-related proteins, with the strongest interaction observed for PDB ID 6X8E. Key amino acid interactions and consistent non-covalent binding patterns were identified, providing structural insight into the basis of dasatinib's inhibitory effect.

The stability of the protein–ligand complex over 100 ns was further confirmed by molecular dynamics simulation, which showed limited conformational deviation and sustained interactions, supporting the reliability of the docking results. The observed multi-target binding profile suggests that dasatinib may effectively modulate a range of oncogenic signalling pathways, which is particularly relevant for complex and heterogeneous diseases such as breast cancer.

From a translational standpoint, integration of nanoformulation approaches may help overcome the pharmacokinetic limitations of dasatinib. Targeted nano-delivery systems could enhance solubility and tumour accumulation and facilitate co-delivery for combination therapy, thereby improving therapeutic efficacy while reducing systemic toxicity.

Future work should focus on experimental validation of these findings through in vitro and in vivo studies, alongside the development of optimized nanoformulations, to translate this in silico potential into clinical therapeutic outcomes.

ACKNOWLEDGEMENTS

The authors would like to express their great thanks to the Faculty of Pharmacy, Parul University, Vadodara, Gujarat, India for providing the required facilities and support for this research work. The authors are also thankful to all the people who gave technical guidance and gave support during the molecular docking, molecular dynamics simulation and during preparation of the manuscript. They have

played an important role in the successful completion of this study.

AUTHOR CONTRIBUTIONS

Jenish Bhagat contributed to the conceptualization of the study, literature investigation, preparation of the introduction, manuscript drafting, and visualization. Ashish Patel contributed to the study methodology, molecular docking, molecular dynamics (MD) simulation, formal data analysis, data curation, validation, and review and editing of the manuscript. Bijal Prajapati contributed to supervision, project administration, critical review and revision of the manuscript, and final approval of the version to be published. Drashti Shah contributed to the validation of the molecular docking and molecular dynamics simulation studies. She also assisted in the analysis and interpretation of the computational data, ensuring the accuracy and reliability of the results. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in accordance with the ICMJE authorship criteria.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

This study is a purely computational (in silico) investigation and did not involve human participants, human data, or animal subjects; therefore, ethical approval was not required.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study (docking scores, MD trajectories) are available from the corresponding author on reasonable request.

ABBREVIATIONS

TKI: tyrosine kinase inhibitor; TNBC: triple-negative breast cancer; MD: molecular dynamics; RMSD: root-mean-square deviation; RMSF: root-mean-square fluctuation; PDB: Protein Data Bank; EPR: enhanced permeability and retention; NPT: constant number, pressure, temperature (ensemble).

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