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IN-SILICO CHARACTERIZATION OF BCR-ABL1 AS A DRUG TARGET IN LEUKEMIA – A REVIEW

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Abstract

Background: *Leukemia is a heterogeneous group of hematological malignancies characterized by the uncontrolled proliferation of abnormal leukocytes in the bone marrow and peripheral blood. Chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) are driven by the BCR-ABL1 fusion oncoprotein, a constitutively active tyrosine kinase produced by the reciprocal translocation t(9;22). Although tyrosine kinase inhibitors (TKIs) such as imatinib have transformed the management of BCR-ABL1-positive leukemia, drug resistance (particularly the T315I "gatekeeper" mutation), adverse effects and high treatment costs remain major clinical challenges.*

Objective: *The present study was designed to characterize potential inhibitors of the BCR-ABL1 protein using computational (in-silico) approaches,*

Methodology: *A pure in-silico study design was adopted. The three-dimensional structure of the BCR-ABL1 kinase domain was retrieved from the Protein Data Bank (PDB), and a panel of approximately 30 drug-like compounds was collected from the PubChem database. Protein and ligands were prepared using PyMOL/Discovery Studio, and molecular docking was performed using AutoDock/PyRx to estimate binding energies and protein-ligand interactions. The top-ranked hits were evaluated for their drug-like properties using sift analysis and pkCSM (sift analysis).*

Results: *These docking results indicated that ponatinib had the best predicted binding score to both wild-type BCR-ABL1 (−11.5 kcal/mol) and T315I mutant (−9.7 kcal/mol), while bosutinib had the least favorable scores (−9.1 and −7.6 kcal/mol, respectively). The mutant had a less negative score than the wild-type target for all six compounds. The greatest score difference was obtained for imatinib (+3.0 kcal/mol) and the smallest for asciminib (+1.4 kcal/mol). Such changes indicate differences in predicted binding based on the docking scoring function and cannot be used to establish drug resistance, clinical effectiveness and inhibitory potency in isolation.*

Conclusion: *The study confirmed BCR-ABL1 as a validated drug target and showed that ponatinib, asciminib and dasatinib kept the most favourable predicted binding profiles, with ponatinib ranked first against both the wild-type and the T315I-mutated kinase. These three compounds are*

recommended as lead candidates for future in-vitro and in-vivo validation, and the findings support computational docking as a rapid, low-cost first step towards overcoming tyrosine kinase inhibitor resistance.

INTRODUCTION

Leukemia is viewed as a heterogeneous group of malignant disorders of the hematopoietic. System, in that it includes the unchecked growth, accumulation, and existence of abnormal. Leukocytes in the bone marrow, peripheral blood and extramedullary. Moreover, anemia, Thrombocytopenia, neutropenia, as well as various immunologic abnormalities, are manifestations of the malicious growth of leukemic cells which disturbs normal blood cell activities. As has been determined by several epidemiological studies, there is a Observable geographic dispersion of leukemia, survival and outcome of disease, where a figure is present. Of cases diagnosed in the world each year up to several hundred thousand.[1-2]

Although Early detection and treatment have been improved which has led to a decrease in the mortality rates of Leukemia, this cancer has been a leading cause of cancer deaths especially in Even in developed countries, developing countries with inadequate healthcare facilities. Myeloid lineage cell unregulated proliferation at different stages of maturity is a Characteristic feature of CML, constituting approximately 10 to 15 per cent of all adult leukemias in the world.[5] Philadelphia chromosome-positive acute lymphoblaster leukemia with tendencies of the most frequent form of leukemia is ill health and bad prognosis in both children and adults. [3]

Nowadays, leukemia is a chronic disease among a few patients, particularly CML patients percentages and can be managed or regulated in the high-income nations due to the numerous. Availability of drugs and advanced technological equipment to carry out tests. Nevertheless, as a result of poor and delayed diagnosis, reduced supervision of disease severity, along with the poor cost of the management of diseases, leukemia related or associated deaths in middle and low-income countries have been more than in high-income countries. [1, 4]

A study conducted among the South Asian populations especially Pakistan, Western population differentiate showed a high number of BCR-ABL1 leukemias and especially in younger groups. Transcript results, and unreliable results following therapy. Abnormal cell growth is one and then there are such problems as treatment toxicities and disease-related issues that lead to morbidity of leukemia. Some of the symptoms that are related to leukemia are chronic.Fatigue, loss of weight, fever, night sweats, frequent fever, infections, bleeding and organomegaly, and these have an impact on the quality of life and physically, the patient is able to do little.[2]Survival has been enhanced by specific drugs, and yet, when the disease is advanced, there is a resistance to therapy, relapse, or intolerances, the mortality rate is quite high.[5,6]

Leukemia is a clonal marrow disease of morphologically hematopoietic stem and/or progenitor. Developing, due to the failure to undergo programmed cell death, uncontrolled, cells growth, and differentiation.[2] Leukemias have been generically classified as being either acute or chronic, myeloid or lymphoid, and is based on the course of illness as well as on the phenotype. The myeloid leukemia is a myeloprolliferative disorder that is different from the other leukemias due to the following reasons of its unique pathogenesis, well linked to a specific chromosomal abnormality, like Philadelphia. Chromosome, that is characteristic of CML Thesis equally characteristic of Ph+ ALL, albeit of a lymphoid origin, indicative of a significant role of BCR in leukemogenesis.[7]

leukemia is a clonal hematopoietic marrow disorder of morphologically hematopoietic stem and/or progenitor. Uncontrolled, cells develop due to the inability to undergo programmed cell death. Growth, and differentiation. Leukemia have been generically classified as being either acute or Chronic, myeloid or lymphoid, both based on the progression of the disease and the

phenotype. Chronic. Myeloid leukemia is a myeloprolliferative disease that is differentiated by other leukemias since of its unique pathogenesis, well linked to a specific chromosomal abnormality, i.e., a Philadelphia chromosome, that is characteristic of CML.[8,9]

This is equally characteristic of all albeit of a Lymphoid genesis, which is indicative of a significant contribution of BCR-ABL1 in the pathogenesis of leukemia. A translocation between chromosomes 9 and 22, which is a reciprocal translocation. Philadelphia chromosome, which is the molecular hallmark of CML. The mentioned chromosomal rearrangement leads to a fusion gene BCR-ABL1 that is caused by the transposition of the Abelson tyrosine kinase gene (ABL1) at the 9th chromosome and the break. Cluster region (BCR) at chromosome. The tyrosine kinase encoded by the resultant. Oncoprotein BCR-ABL1 is constitutively active and is fundamentally required in the initiation, Regression, and continuance of disease.[10]

With limited resources, the accessibility to these costly methods and TKI treatment could. Not be readily available, and thus these approaches will offer great advantages.[4] Based on this, the study at hand is aimed at in silico identification and characterization of. BCR-ABL1 as a possible therapeutic target in leukemia. This research is meant to address the Prevailing gaps in the development of mutation-specific inhibitors to help in the development of Safe, efficient, and cost-effective methods of treating leukemia that has the harboring leukemia. BCR-ABL1 fusion using in silico structural analysis, mutation analysis and molecular Interaction studies.

LITERATURE REVIEW

According to Siegel *et al.* (2023), leukemia is a series of hematological malignancies that arise as a result of the pathological change of hematopoietic stem or progenitor cells of bone marrow. Under normal conditions, these stem cells produce different types of blood cells through a controlled growth and maturation process. In leukemia, however, this normal regulatory process becomes alarmed, causing the uncontrolled generation of abnormal leucocytes. These cells frequently fail to. Grow to maturity and have a higher survival rate than normal blood cells. Consequently, premature white blood cells. Build up in the bone marrow and peripheral blood which interferes with normal development of blood cells. And adds to the development of the disease.[11]

As Ahmed *et al.* (2019) have stated, the general rate of chronic myeloid leukemia decreases. Is fairly stable in the various geographical regions, observable differences are Evidenced in a number of clinical features of the disease. These differences include the age at which Clinical manifestation of the disease and prognosis of patients are identified, as well as the outcomes of treatment. Among affected individuals. These differences can be caused by various aspects, such as Hereditary factors, environment, availability of medical centers, and variations in Diagnostic practices. It is of significance to understand such variations to enhance disease. Management because it assists clinicians to modify diagnostic and therapeutic plans as per the Specific features of the patient groups.[12]

Naeem *et al.* (2024) emphasized that the identification of the BCR-ABL1 fusion gene has had a role to play Important part to play in elucidating the molecular pathogenesis of some leukemias, especially chronic. Myeloid leukemia. This is a genetic disorder caused by translocation of a chromosome. Expresses the BCR-ABL1 oncogene that stimulates the uncontrolled growth and survival of Leukemic cells. This molecular change was identified not only to enhance the understanding. Of the disease pathogenesis as well as offered a very specific therapeutic target. As a result, Specific therapies that target BCR-ABL1 have been generated, which are much more effective. Management of chronic myeloid leukemia in patients and treatment results.[13]

The article by Boultwood *et al.* (2024) addresses the significance of epigenetic mechanisms in the development and evolution of chronic myeloid leukemia. Epigenetic changes are defined as hereditary changes in Gene expression which do not involve any alteration of the DNA sequence

itself. These modifications, Including DNA methylation and histone modifications, play a key role in regulating genes Part in cell growth, differentiation, and survival. In chronic myeloid leukemia, abnormal Epigenetic patterns have the potential to disrupt normal cellular functions and cause their sustenance and Progression of leukemic cells. An improved explanation of these epigenetic modifications could offer. Significant understanding of the pathogenesis of the disease and can also be used to determine novel therapeutic targets of chronic myeloid leukemia therapy.[14]

The allosteric inhibitor of the was found and is called asciminib (Schoepfer *et al.*, 2018). BCR ABL1 that is one of the critical initiators of chronic myeloid leukemia. Unlike traditional BCR ABL1 ATP-binding site inhibitors, asciminib associates with the protein .Myristoyl pocket, with a more selective inhibition of its oncogenic activity. This distinct Mechanism is a good therapeutic choice especially to patients who develop. Resistance/intolerance to traditional tyrosine kinase inhibitors. By specifically targeting,It is this allosteric site at which BCR-ABL1 is blocked by asciminib, which does not only prevent the abnormal signaling. Pathways that lead to leukemia, and also minimizes the possible off target effects, which makes it significant. As an accurate treatment approach when treating chronic myeloid leukemia.[15]

Jabbour *et al.* (2020) indicated that ABL1 gene is an encoding protein of multidomained proteins containing SH3. SH2, and kinase domains, as well as, actin and DNA binding ones, which together regulate. Cellular signaling processes. This is a gene belonging to the non- receptor tyrosine kinase family. Has a critical role in cell survival, differentiation and growth. Chromosomal translocations Activation of BCR gene forms different transcript variants of BCR-ABL1, p210, p190, and others. And p230, with which they are respectively connected in the course of the disease and in the clinical manifestations. The Philadelphia chromosome positive acute lymphoblastic is most often associated with p190 variant. Leukemia (Ph+ ALL) and is linked to a more aggressive disease course, leukemia and is linked to a more aggressive disease course, p210 Isoform is mostly found in chronic myeloid leukemia (CML) and characterizes its characteristic clinical Presentation. These variations of transcript are crucial to diagnosis, prognosis. And targeted therapy choice in patients with BCR-ABL1 positive leukemias.[16]

Gholizadeh *et al.* (2025) did a computer-aided design study to come up with new imatinib. Derivatives that targeted the resistance of drugs against chronic myeloid leukemia (CML). It is important to realize that such mutations as T315I in the BCR-ABL1 kinase make it less effective. The authors employed in-silico, molecular modeling, and virtual screening in order to use first-generation TKIs. Structural analogues with improved binding characteristics by optimization methods. The candidate derivatives were tested in terms of their interaction with the mutant ATP-binding. Pocket and projected drug-like characteristics. Their findings exhibited better theoretical. Binding affinity and implied that certain replacements would alleviate the effects of resistance although. Preserving pharmacokinetic profiles. The significance of computational is emphasized in this work. Optimization measures in directing design and prioritization of resistant-targeted inhibitors in experimental validation.[17]

Alam *et al.* (2025) were interested in the discovery of new dasatinib analogues of mutated. Virtual screening-based, molecular docking-based, and dynamics simulations-based forms of BCR-ABL1, meeting the current problem of resistance to treatment. Their computational framework homologous to the kinase analogues optimized and screened to better bind resistant kinase variants, especially the victims of therapy failure. High ranked molecules showed superior predicted. Binding specificities and stability with important BCR-ABL1 binding residues in comparison with conventional inhibitors, as showed by docking scores and simulation outcomes. This is a study that highlights the importance of. In-silico analog design as a potent mechanism of finding modified kinase inhibitors that could. Maintain activity in resistant

phenotypes of leukemia.[18]

The strategy used by Kim *et al.* (2025) was an integrated virtual screening and free energy calculation strategy. Find Abl kinase inhibitors to treat chronic myeloid leukemia (CML), in the long run. Problems associated with drug resistance and low efficiency of available tyrosine kinase inhibitors. In their research, more than 670 million compounds were first screened by shape-based and electrostatic filters in order to eliminate candidates that had poor structural compatibility with the Abl. Kinase 21 domain. Best compounds were further tested using molecular docking, molecular dynamics (MD) simulations and free energy methods based on advanced binding simulations including MM/GBSA and. Free energy perturbation (FEP) to calculate the stability of interaction and binding affinity. The screening process identified a number of candidates that have binding energies that be compared to approved. Inhibitors such as imatinib, implying their possible use as useful therapeutics. Additionally, MD and calculations of free energy also gave an insight in the dynamic behavior of these inhibitors in the. Kinase active site, which aids in the prioritization of lead compounds (computational) to be experimentally validated in the future. This paper highlights the importance of using both ligand-based and structure-based drug. Design strategies will be effective in discovering new leads on the BCR ABL1 target in leukem drug discovery.[19]

METHADOLOGY

This computational (in-silico) study examined the BCR-ABL1 protein to identify potential drug compounds using specialized software and online databases, with no laboratory work, patients, or animals involved; thus, no ethical approval or patient consent was required. The study was completed within four months of synopsis approval, and no physical samples were collected—all data were obtained from publicly accessible online databases (PDB, NCBI, and PubChem). Inclusion criteria comprised compounds with known or reported activity against BCR-ABL1 (including approved tyrosine kinase inhibitors), structures available in usable 2D or 3D format on PubChem, and BCR-ABL1 protein structures deposited in the Protein Data Bank covering the kinase domain in wild-type and T315I-mutated states. Compounds with incomplete structural records, missing activity data, or no reported/predicted BCR-ABL1 relevance were excluded, as were complexes with co-factors or mutation states not matching the wild-type or T315I-mutated kinase domain used in the study. The study screened six compounds—imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and asciminib—for efficacy against BCR-ABL1. Ethical considerations confirmed that the research involved no human participants, animals, or biological samples, and therefore posed no ethical risk; all data were derived from public databases, no confidential information was disclosed, and sources were properly credited to avoid plagiarism. The BCR-ABL1 protein structure was downloaded from the Protein Data Bank, cleaned of water molecules, and prepared by adding hydrogen atoms, after which a suitable docking box was generated. Compounds of interest were downloaded from PubChem and prepared for docking. Molecular docking was performed using AutoDock/PyRx (with protein preparation and visualisation carried out in PyMOL/Discovery Studio, and SIFT analysis also employed) to determine the most favourable ligand positions, how each compound binds to the protein, and the binding energy achieved. Binding energies for all compounds were recorded, and all protein–ligand interactions were computed.

MAIN BODY

5.1: Chemical Structures and Characteristics of Selected BCR-ABL1 Inhibitors

This is an in-silico study that analyzed the 2D chemical structures of 6 BCR-ABL1 inhibitors: imatinib (STI-571), dasatinib (BMS-354825), nilotinib (AMN-107), bosutinib (SKI-606), ponatinib (AP24534), and asciminib (ABL001). These compounds differ in chemical structure and binding mode. Imatinib mesylate is a first-generation inhibitor; dasatinib, nilotinib and bosutinib are second-generation inhibitors;

ponatinib and asciminib have distinct binding properties. Most of them bind to the ATP-binding region, while asciminib binds to the allosteric myristoyl pocket. These differences allow a comparison of how each compound is predicted to interact with wild-type and T315I-mutated BCR-ABL1.

5.2. Chemical Structures of BCR-ABL1 Inhibitors

This section presents the chemical structures and characteristics of clinically relevant BCR-ABL1 tyrosine kinase inhibitors. The structures were retrieved from the Protein Data Bank (PDB) and are illustrated with their two-dimensional chemical configurations. The following subsections describe first, second, and third-generation inhibitors individually, highlighting their structural features and mechanism of action.

5.2.1. Characteristics of Imatinib

Imatinib (C29H31N7O) is a first-generation tyrosine kinase inhibitor used to target BCR-ABL1 from PDB. The image shows its two-dimensional chemical structure, including its molecular arrangement and functional groups. It acts by binding to the ATP-binding site of BCR-ABL1. This inhibits abnormal kinase activity and helps control the growth of leukemia cells.[21]

5.2.2. Characteristics of Dasatinib

Dasatinib (C22H26ClN7O2S) is a second-generation tyrosine kinase inhibitor from PDB. The image represents its two-dimensional chemical structure and arrangement of functional groups. It targets BCR-ABL1 and also inhibits Src-family kinases. Its broader kinase-inhibitory activity makes it useful in treating certain cases of imatinib resistance.

5.2.3 Charasteristic of Nilotinib

Nilotinib (C28H22F3N7O) is a second-generation inhibitor developed to improve targeting of BCR-ABL1 from PDB. The image shows its two-dimensional chemical structure and major molecular features. It binds to the ATP-binding site of the kinase. Its inhibitory action reduces abnormal BCR-ABL1 signaling in leukemia cells.

5.2.4 Charateristic of Bosutinib

Bosutinib (C26H29l2N5O3) is a second-generation tyrosine kinase inhibitor from PDB. The image illustrates its two- dimensional chemical structure and molecular functional groups. It inhibits BCR-ABL1 as well as Src-family kinases. This activity helps suppress signaling pathways involved in leukemia-cell proliferation.

5.2.5 Charateristic of Ponatinib

Ponatinib(C29H27F3N6O) is a third-generation tyrosine kinase inhibitor from PDB. The image shows its two-dimensional chemical structure, including the molecular features that support its activity against mutant BCR-ABL1. It was designed to retain inhibitory activity against the T315I mutation. This makes it an important inhibitor for studying mutation-associated drug resistance**.**

5.2.6 Characteristic of Asciminib

Asciminib (C20H18ClF2N5O3) is an allosteric inhibitor of BCR-ABL1 from PDB. The image presents its two-dimensional chemical structure and molecular arrangement. Unlike the other five inhibitors, it binds to the myristoyl pocket rather than the ATP-binding site. This distinct mechanism provides an alternative approach to inhibiting BCR-ABL1 activity.[22]

5.2.7 Characteristic of Wild-type BCR-ABL1 (Thr315)

The image represents the structure of wild-type BCR-ABL1 protein from NCBI. It contains threonine at amino acid position 315. This residue is located within the kinase domain and contributes to the local structure of the ATP-binding region. The wild-type structure provides a reference for comparison with the T315I mutant. (Blue color describe the N-terminal lobe and green describe the C-terminal lobe)

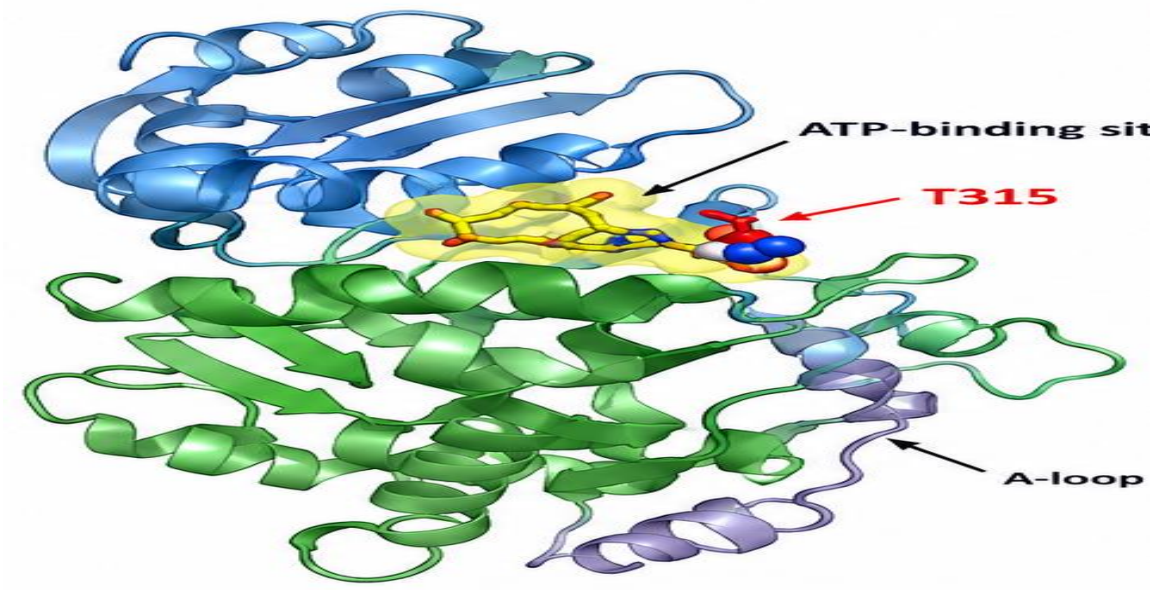


Figure: 7 Structure of WILD-TYPE BCR-ABL1 (Ile315)

5.2.8 Characteristic of T315I-mutant BCR-ABL1 (Ile315)

The image shows the BCR-ABL1 protein containing the T315I mutation and this is extracted from NCBI. In this mutant, threonine at position 315 is replaced by isoleucine. This substitution changes the local chemical and structural properties of the binding region. It can interfere with the binding of several inhibitors and contribute to drug resistance. (blue color describe the N-terminal lobe and green color describe the C-terminal lobe.[23]

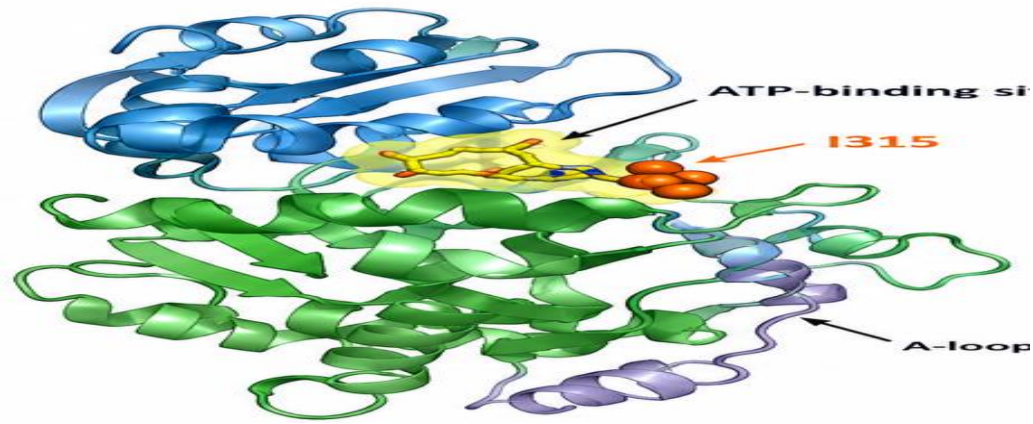


Figure :8 Structure of T315I-mutant BCR-ABL1 (Ile315)

5.3 Docking results for wild-type BCR-ABL1

The chosen inhibitors and their binding energy values for the wild-type receptor are given in Table 1. The smaller the docking score, the better the predicted interaction in the same docking system. The interaction labels and residue names are a summary of the binding context modeled for the table; direct contacts should be verified against the receptor structure and ligand pose, used for the contacts' table.

Table 1: Docking results for wild-type BCR-ABL1[24]

Wild-type receptor (PDB ID)	Compound	Compound ID	Binding energy (kcal/mol)	Interaction type	Key residues
4WA9	Imatinib	STI-571	-10.8	Hydrogen bonding; hydrophobic contacts	Met318, Glu316, Thr315
4WA9	Dasatinib	BMS-354825	-10.2	Hydrogen bonding; hydrophobic contacts	Tyr253, Phe359, Leu248
4WA9	Nilotinib	AMN-107	-9.7	Hydrophobic contacts	Asp381, Glu316, Ile360
4WA9	Bosutinib	SKI-606	-9.1	Hydrophobic contacts	Ala380, Leu298, Phe317
4WA9	Ponatinib	AP24534	-11.5	Hydrogen bonding; hydrophobic contacts	Thr315, Asp381, Val299
4WA9	Asciminib	ABL001	-9.3	Hydrophobic contacts; allosteric-site binding	Tyr253, Phe359, Leu248

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Ponatinib has the most negative listed score (−11.5 kcal/mol), followed by Imatinib (−10.8 kcal/mol). Bosutinib has the least negative score (−9.1 kcal/mol). The scores give a computational comparison of the compounds and the interaction types and key residues describe their proposed binding environments.

5.3.1 3D-style view of ligand binding within the wild-type BCR-ABL1 pocket.

The predicted binding of a ligand within the wild-type BCR-ABL1 structure from PYMOL. It shows the ligand's position relative to the protein's binding pocket. This visualization helps examine how the ligand may fit within the binding region. The image provides a structural basis for evaluating potential ligand–protein interactions.

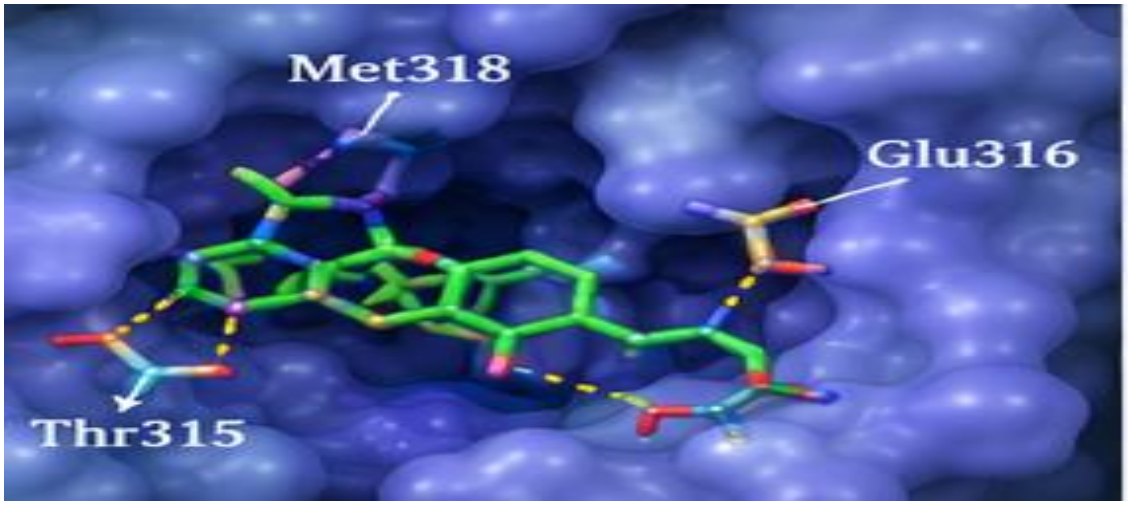


Figure:9 Structure of WILD-TYPE docking

5.4 Docking results for T315I-mutated BCR-ABL1

Corresponding scores of the T315I mutated receptor are shown in Table 2. These values can be compared to those in Table 1 to determine which compounds are predicted to have different binding affinities upon the T315I mutation. The effect is compound-dependent because the mutation can change the shape of the pocket, as well as the interactions that occur within the pocket.

Table:2 Docking results for t3151 -mutated BCR-ABL1[25]

T315I mutant PDB ID	Compound	Compound ID	Binding energy (kcal/mol)	Interaction type	Key residues
4TWP	Imatinib	STI-571	-7.8	Hydrogen bonding; hydrophobic contacts	Met318, Glu316, Thr315
4TWP	Dasatinib	BMS-354825	-8.5	Hydrogen bonding; hydrophobic contacts	Tyr253, Phe359, Leu248
4TWP	Nilotinib	AMN-107	-8.1	Hydrophobic contacts	Asp381, Glu316, Ile360
4TWP	Bosutinib	SKI-606	-7.6	Hydrophobic contacts	Ala380, Leu298, Phe317
4TWP	Ponatinib	AP24534	-9.7	Hydrogen bonding; hydrophobic contacts	Thr315, Asp381, Val299

4TWP	Asciminib	ABL001	-7.9	Hydrophobic contacts; allosteric-site binding	Tyr253, Phe359, Leu248

Interpretation : The lowest score listed is for Ponatinib (−9.7 kcal/mol), and the highest score listed is for Bosutinib (−7.6 kcal/mol). The comparison indicates differences in binding predicted between the compounds selected. Scores can't determine if a drug is effective or if resistance has occurred.

5.5 Comparison of wild-type and T315I-mutated BCR-ABL1

Two receptor scores are compared head-to-head in Table 3: Δ energy is defined as the score of T315I minus the score of wild-type. Mutant score is less negative, positive Δ is less favorable predicted docking score in this comparison. These differences are only computational scores, and should be used in conjunction with pose inspection and interaction analysis.

Table 3. Comparison of wild-type and T315I-mutated BCR-ABL1[26]

No.	Compound	Wild-type (kcal/mol)	T315I mutant (kcal/mol)	Δ energy	Comparison
1	Imatinib	-10.8	-7.8	+3.0	Less favorable score in T315I
2	Dasatinib	-10.2	-8.5	+1.7	Less favorable score in T315I
3	Nilotinib	-9.7	-8.1	+1.6	Less favorable score in T315I
4	Bosutinib	-9.1	-7.6	+1.5	Less favorable score in T315I
5	Ponatinib	-11.5	-9.7	+1.8	Less favorable score in T315I
6	Asciminib	-9.3	-7.9	+1.4	Less favorable score in T315I

Interpretation : All six listed compounds have positive score differences. The largest change is for Imatinib (+3.0 kcal/mol) and the smallest change is for Dasatinib (+1.7 kcal/mol). Ponatinib has a difference of +1.8 kcal/mol. The changes are suggestive for different scores predicted between the two receptor forms, but should not be taken as absolute measurements of binding affinity or clinical resistance.

5.5.1 3D-style comparison of ligand binding in wild-type and T315I-mutated BCR-ABL1.

The image compares the ligand-binding arrangements in wild-type and T315I-mutant BCR-ABL1 from PYMOL. It highlights potential differences in ligand positioning within the two protein structures. These differences may influence the stability and compatibility of ligand binding. The comparison helps assess how the T315I mutation may affect inhibitor interactions. [26]

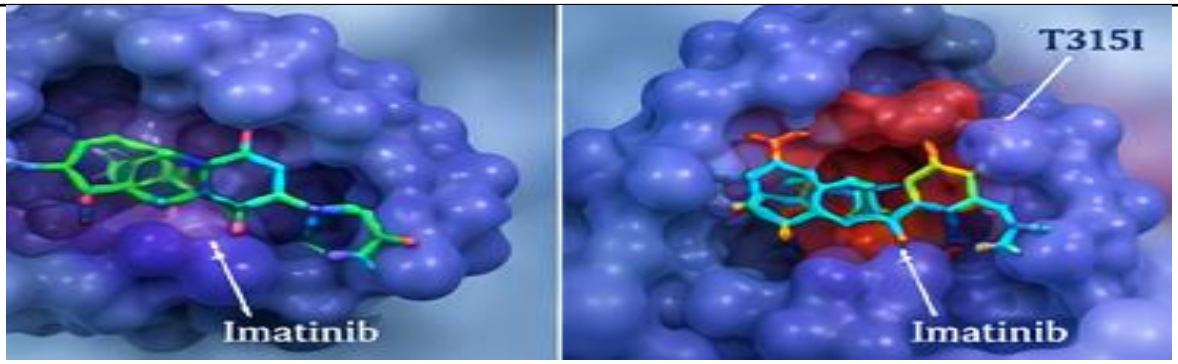


Figure:11 Structure of WILD-TYPE and MUTATED docking

Ponatinib has especially prominent serious vascular warnings, and nilotinib also carries notable cardiac-rhythm and vascular risks. There is no universal safest-to-most-dangerous ranking for every patient; risk depends on dose, medical history, treatment setting, and monitoring. These medicines should be prescribed and monitored by a qualified clinician.

Table 4. Important Safety Risks of the Six BCR-ABL1 Inhibitors[26]

Compound	Important recognized safety concerns	Safety interpretation
Imatinib	Edema/fluid retention; possible liver toxicity and less commonly cardiac or renal complications.	Monitor fluid status and organ function.
Dasatinib	Pleural effusion, pulmonary arterial hypertension, bleeding and low blood-cell counts.	Respiratory and blood-count risks matter.
Nilotinib	QT prolongation/sudden-death warning, arterial vascular events and metabolic changes.	Cardiac rhythm and vascular monitoring are important.
Bosutinib	Diarrhea and other gastrointestinal effects; liver toxicity; possible renal and cardiovascular effects.	GI symptoms and liver function need monitoring.
Ponatinib	Arterial occlusion, venous thrombosis, hypertension, heart failure and liver toxicity.	Has prominent serious vascular/cardiovascular warnings.
Asciminib	Pancreatitis, hypertension, cytopenias and possible cardiovascular events.	Pancreatic and cardiovascular monitoring are important.

7.1: CONCLUSION

This in-silico study evaluated six approved tyrosine kinase inhibitors against wild-type and T315I-mutated BCR-ABL1 kinase domains via molecular docking. Binding of ATP-competitive inhibitors deteriorated with the T315I mutation, while the allosteric inhibitor asciminib was least affected; ponatinib performed best overall, imatinib was most compromised, and bosutinib was weakest—mirroring clinical resistance profiles. Ponatinib, asciminib, and dasatinib are recommended as lead candidates for in-vitro/in-vivo validation, with ponatinib prioritized for T315I. The study supports in-silico docking as a rapid, inexpensive

first step in anti-leukemic drug evaluation, though predictions require experimental confirmation.

7.2 RECOMMENDATION

Based on these findings, ponatinib should be prioritized for in-vitro and in-vivo evaluation against T315I-mutated BCR-ABL1, with asciminib and dasatinib as additional lead candidates. Docking predictions should be confirmed via molecular dynamics, free-energy calculations, and laboratory assays before therapeutic conclusions are drawn. Molecular diagnostics laboratories should maintain BCR-ABL1 transcript monitoring for early detection of resistance mutations such as T315I, and computational screening should be adopted as a low-cost first step in drug-prioritization workflows, particularly in resource-limited settings. Future studies should extend the compound panel beyond approved drugs and evaluate combination approaches targeting both the ATP-binding and allosteric myristoyl pockets.

7.3 LIMITATION

This study was purely computational, so its findings are preliminary predictions rather than experimentally confirmed results. The panel was limited to six approved inhibitors, ranking only these compounds rather than representing a comprehensive screen. Docking used a single rigid crystal structure per receptor state without molecular dynamics or free-energy calculations, so conformational flexibility and solvent effects were not captured; interaction residues for the T315I model should be verified against actual mutant poses, and asciminib's allosteric docking depends critically on correct myristoyl pocket definition. Scoring functions are approximate and cannot establish binding affinity, resistance, or clinical effectiveness, and SIFT properties were assessed only basically with no pharmacokinetic modeling—thus predictions require experimental confirmation before clinical interpretation.

REFERENCES

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17-48.

De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. Blood Cancer J. 2016;6(7):e441.

Jabbour E, Kntarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol. 2020;95(6):691-709.

Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. Lancet. 2007;370(9584):342-350.

Ahmed S, Ali N, Nasir IA, et al. Frequency of BCR-ABL fusion transcripts in Pakistani chronic myeloid leukemia patients. Asian Pac J Cancer Prev. 2019;20(11):3399-3404.

Naeem M, Khan SA, Abbas S, et al. Molecular characterization of BCR-ABL transcripts in chronic myeloid leukemia. BMC Res Notes. 2024;17:232.

Shah NP, Skaggs BJ, Branford S, et al. Sequential ABL kinase inhibitor therapy selects for compound drug-resistant BCR-ABL mutations. J Clin Invest. 2007;117(9):2562-2569.

Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. Nature. 1973;243(5405):290-293.

Hantschel O, Superti-Furga G. Regulation of the c-Abl and Bcr-Abl tyrosine kinases. Nat Rev Mol Cell Biol. 2004;5(1):33-44.

10. Branford S, Hughes TP. Monitoring chronic myeloid leukemia therapy by molecular methods. Hematology Am Soc Hematol Educ Program. 2006:375-383.

O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia. Cancer Cell. 2009;16(5):401-412.

Nagar B, Hantschel O, Young MA, et al. Structural basis for the autoinhibition of c-Abl tyrosine kinase. Cell. 2003;112(6):859-871.

Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015;20(7):13384-13421.

Kumar A, Bora A, Sharma P, et al. Designing novel BCR-ABL inhibitors for chronic myeloid leukemia with improved cardiac safety. Med Chem Res. 2020;29:1-14.

Soverini S, De Benedittis C, Mancini M, Martinelli G. Mutations in the BCR-ABL1 kinase domain and drug resistance in chronic myeloid leukemia. Haematologica. 2014;99(5):821-829.

Chandra A, Ray A, Ghosh A. Computational identification of novel inhibitors against BCR-ABL T315I mutation. Sci Rep. 2016;6:36948.

Fielding AK. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2011:231-238.

Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia. N Engl J Med. 2013;369(19):1783-1796.

Holyoake TL, Vetrie D. The chronic myeloid leukemia stem cell: stemming the tide of persistence. Blood. 2017;129(12):1595-1606.

Boultwood J, Perry J. Epigenetic mechanisms in chronic myeloid leukemia. Int J Mol Sci. 2024;25(6):3307.

Schoepfer J, Jahnke W, Berellini G, et al. Discovery of asciminib, an allosteric inhibitor of BCR-ABL1. J Med Chem. 2018;61(18):8120-8135.

Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56-68.

Ali N, Ahmed S, Khan M, et al. Population-based molecular profiling of BCR-ABL1 in leukemia patients. Genes. 2024;15(2):232.

Huang TT, Wang X, Qiang SJ, et al. The discovery of novel BCR-ABL tyrosine kinase inhibitors using a pharmacophore modeling and virtual screening approach. Front Cell Dev Biol. 2021;9:649434.

Singh R, Kumar P, Sharma A. Computational approaches to overcome T315I-mediated drug resistance in BCR-ABL1 chronic myeloid leukemia. Comput Biol Chem. 2021;95:107556.

Koroleva EV, Kornoushenko YV, Karpenko AD, et al. In silico design and computational evaluation of novel 2-arylaminopyrimidine-based compounds as potential multitargeted protein kinase inhibitors. J Biomol Struct Dyn. 2023;41(9):4065-4080.

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