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Research Article

In Silico Investigation of Ligand Binding Mechanisms in PDGFR-A

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ABSTRACT

Platelet-Derived Growth Factor Receptors A (PDGFR-A) are transmembrane receptor tyrosine kinases critical in cell proliferation, migration, and survival, implicated in various pathological conditions including multiple forms of cancer. Given its critical involvement in oncogenic pathologies, the development of novel inhibitors targeting its kinase domain is of significant therapeutic interest. The primary goal of this research was to determine the preferred orientation and conformation of potential drug molecules within the ATP-binding pocket of PDGFR-A and identify the key amino acid residues involved in drug binding using a structure-based drug design strategy. Molecular docking simulations were performed using Autodock Vina on five standard kinase inhibitors: Dasatinib, Imatinib, Pazopanib, Sorafenib, and Sunitinib. The docking protocol was validated by reproducing the binding mode of the native ligand5. The study recorded binding poses and energies6. Binding affinities ranged from -13.73 kcal/mol (Imatinib) to -8.457 kcal/mol (Sunitinib). Imatinib showed the highest binding affinity, suggesting the strongest interaction. The number of hydrogen bonds varied, with Imatinib and Dasatinib forming two, while others formed one9. Key amino acids involved include PHE 837, VAL 607, ALA 625, and LEU 599 in aromatic interactions, suggesting a hydrophobic pocket, and ASP 836 in hydrogen bonding. Imatinib's high affinity is likely due to two hydrogen bonds with ASP 836 and THR 674. This study provides insights into drug-PDGFR-A interactions, helping explain affinity differences and identify key residues for drug binding. These findings can guide the design of new inhibitors. However, acknowledging limitations of molecular docking, further molecular dynamics and in vitro studies are warranted.

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1. Introduction

Platelet-Derived Growth Factor Receptors A (PDGFR-A) is a transmembrane receptor tyrosine kinases (RTKs) that play essential roles in the regulation of cell proliferation, migration, survival, and differentiation. These receptors are critical mediators in various pathological conditions, including multiple forms of cancer, immune-mediated diseases such as systemic sclerosis (SSc), and viral infections. PDGFR-A is frequently overexpressed in various solid tumors, including glioblastoma, where it drives tumor growth and angiogenesis, making it a critical therapeutic target. [1,2]

PDGFR-A is composed of an extracellular domain with five immunoglobulin (Ig)-like domains responsible for ligand binding, a single transmembrane α-helix, and an intracellular tyrosine kinase domain. This kinase domain consists of a bilobal structure, a juxtamembrane (JM) regulatory region, and an activation loop (A-loop). The activation loop begins with a conserved DFG (Asp-Phe-Gly) motif, which plays a key role in regulating access to the ATP-binding pocket.[3,4]

In the inactive state, the JM domain occludes the active site, and the A-loop partially blocks ATP and substrate access. Activation leads to conformational changes that reposition the DFG motif within a hydrophobic pocket adjacent to the ATP-binding site. This transition is essential for kinase activation. Inhibitors targeting this site can induce structural rearrangements that inhibit receptor function by blocking ATP access either reversibly or irreversibly.[5,6]

Overexpression or aberrant activation of PDGFRα is associated with the progression of various cancers, including prostate, breast, ovarian, pancreatic, and liver cancers. In these contexts, PDGFRα signaling promotes tumorigenesis by activating downstream pathways involved in angiogenesis, proliferation, and metastasis.[7-9]

Given the critical involvement of PDGFRα in oncogenic pathologies, the identification and development of novel inhibitors targeting its kinase domain is of significant therapeutic interest. Structure-Based Drug Design (SBDD) has emerged as a powerful and cost-effective approach for rational drug discovery, particularly when structural information about the target is available.[10,11] Structure-based drug design offers a rational approach to identify novel inhibitors by leveraging the three-dimensional structure of the target protein to predict and optimize drug binding.

The primary goal of this research is to determine the preferred orientation and conformation of potential drug molecules within the ATP-binding pocket of PDGFR-A. Further, to identify the key amino acid

residues in PDGFR-A involved in drug binding through various non-covalent interactions (e.g., hydrogen bonds, hydrophobic interactions, electrostatic interactions) using a structure-based drug design strategy, providing a molecular basis for understanding their inhibitory activity and guiding the development of next-generation therapeutics.

2. Materials and Methods:

Selection and preparation of the ligands

For comparative analysis, the 3D structures of 5 standard PDGFRA inhibitors, Dasatinib (PubChem CID: 3062316), Imatinib (PubChem CID: 5291), Pazopanib (PubChem CID: 10113978), Sorafenib (PubChem CID: 216239) and Sunitinib (PubChem CID: 5329102) were also downloaded in SDF format (Figure 1). The selection of these 5 ligands was based on their clinical relevance as kinase inhibitors and their structural diversity, allowing for a broad exploration of the PDGFR-A binding site. All ligands were converted to PDB format using discovery studio visualizer version [21.1.0.20298], Free Download: BIOVIA Discovery Studio Visualizer - Dassault Systèmes (3ds.com)) to ensure compatibility with docking software. Subsequently, rotatable bonds were defined using AutoDockTolls-1.5.7.[12]

Protein Preparation for Molecular Docking: The three-dimensional structures of PDGFRA in complex with imatinib (PDB ID: 6JOL) was downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB, http://www.rcsb.org/). Protein preparation for docking involved the removal of water molecules, addition of polar hydrogen atoms, and assignment of Kollman charges using AutoDockTolls. The processed protein structures were saved in PDBQT format.

Molecular Docking Analysis

Molecular docking simulations were performed using Autodock Vina 1.2.[13,14] "Grid" menu is used to set up the grid box of 50 × 50 × 50 Å with a grid spacing of 0.375 Å was centred on the predicted active site of the target protein with centre coordinates (x = -38.413, y = 157.049, z = 0.794) to encompass potential ligand binding conformations. The Configuration text file was created containing the information about receptor, ligand, co-ordinates and dimension of the box. The vina was executed by the following command: *vina --config config.txt* using the command prompt in the directory where AutoDock Vina and the input files are located. The docking methodology was validated by assessing the ability of the software to reproduce the binding mode of the native ligand. The resulting docked pose exhibited a high degree of similarity to the crystallographically determined conformation, as evidenced by a minimal

RMSD value (0.4134 ^{0}A), indicating the robustness of the chosen parameters (Figure 2). Docking calculations were carried out using the globally searching exhaustiveness of 20. The resulting docking poses and their associated energies were recorded in .pdbqt files. The binding interactions between the docked ligands and the target proteins, including interacting residues, and binding energies, were extracted from the .pdbqt files. Visualization and analysis of the ligand-protein complexes were performed using Discovery Studio visualizer [21.1.0.20298], Dassault Systemes (Figure 3 and 4).

Binding parameters between ligands and target protein PDGFR-A

Ligands	**Binding Affinity (kcal/mol)**	**Number of hydrogen bonds**	**Amino acids involved in bonding**	**Amino acids involved in hydrogen bonding**	**Amino acids involved in bonding with aromatic rings**
Dasatinib	-9.793	2	LEU:825, LEU:599, VAL:607, CYS :835, LYS:627, ASP:836, VAL:658, ILE:647, CYS:814, VAL:815, ILE:657, PHE:837, MET:648, ALA:625.	VAL 815, ASP 836	PHE:837, VAL:607, ALA:625, LEU:599, LEU:825, CYS:835, LYS:627, VAL:658, MET:648
Imatinib	-13.73	2	MET:648, ASP:836, THR:674, PHE:837, VAL:607, ALA:625, LEU:825, CYS:677, TYR:676, LEU:599, LYS:627, ILE:672	ASP 836, THR 674	VAL:607, LEU :825, PHE:837, ALA:625, TYR:676, LEU:599, LEU:825, MET:468
Pazopanib	-9.69	1	CYS:814, MET:648, VAL:658, GLU:644, LYS:627, PHE:837, LEU:825, LEU:599, ALA:625, VAL:607.	CYS 814	VAL:607, ALA:625, LEU:825, LEU:599, PHE:837, LYS:627, GLU:644, MET:648

Sorafenib	-10.74	1	GLY:680, CYS:677, LEU:599, LEU:825, ALA:625, VAL:607, PHE:837, VAL:658, CYS:835, ASP:836, ILE:647, GLU:644, MET:648.	ASP 836	PHE:837, VAL:607, VAL:658, ALA:625, LEU:825, LEU:599, CYS:835, MET:648
Sunitinib	-8.457	1	SYS:677, TYR:676, ILE:657, ILE:834, LEU:809, HIS:816, GLU:644, ASP:836, THR:674, VAL:658, ALA:625, VAL:607, LEU:825, LEU:599.	CYS 677	PHE:837, VAL:607, ALA:625, LEU:599, LEU:825, LEU:599, ILE:657, TYR:676

3. Results and discussion:

Binding Affinity: The binding affinities of the different ligands span a range, from -13.73 kcal/mol (Imatinib) to -8.457 kcal/mol (Sunitinib). Imatinib exhibits the highest binding affinity (-13.73 kcal/mol), suggesting the strongest interaction with PDGFR-A among the tested drugs. Sorafenib (-10.74 kcal/mol) and Dasatinib (-9.793 kcal/mol) show intermediate binding affinities. Sunitinib has the lowest binding affinity (-8.457 kcal/mol).

Hydrogen Bonds: Hydrogen bonds are important for drug-receptor interactions because they provide specificity and stability. The number of hydrogen bonds formed varies between the drugs. Dasatinib and Imatinib form two hydrogen bonds each, while Pazopanib, Sorafenib, and Sunitinib form only one. The presence of two hydrogen bonds in the Dasatinib and Imatinib complexes may contribute to their binding affinity.

Amino Acid Interactions: A range of amino acids are involved in the binding of these drugs to PDGFR-A. Some amino acids participate in hydrogen bonding, while others interact with the drugs through aromatic ring interactions. Specific amino acids involved in bonding vary across the different drug-PDGFR-A complexes. The table highlights key residues that are crucial for drug interactions. For example, the frequent involvement of PHE 837, VAL 607, ALA 625, and LEU 599 in aromatic ring interactions suggests these residues may form a hydrophobic pocket that is important for drug binding. The consistent involvement of ASP 836 in hydrogen bonding with Imatinib and Sorafenib

suggests this residue plays a key role in the binding of multiple drugs.

The binding affinity is a crucial parameter in drug design, as it indicates the strength of the interaction between the drug and its target protein. Imatinib's high binding affinity suggests it forms a stable complex with PDGFR-A, which could contribute to its efficacy as an inhibitor of this receptor. The other drugs also show reasonable binding affinities, indicating they can interact with the target, although perhaps with less stability compared to Imatinib.

The involvement of specific amino acids in the binding provides insights into the binding site of PDGFR-A. Some ligands exhibit unique amino acid interactions that might contribute to their specific binding characteristics: Imatinib interacts with THR 674 and CYS 677, Pazopanib interacts with GLU 644, Sunitinib interacts with SYS 677, ILE 834, LEU 809, LEU 825 and HIS 816. These unique interactions could explain some of the differences in binding affinity or selectivity profiles of these drugs.

The high binding affinity of Imatinib (-13.73 kcal/mol) suggests a stable complex formation, which is likely driven by the two observed hydrogen bonds with the key active site residues ASP 836 and THR 674." (Connects affinity to specific interactions).

In contrast, Sunitinib's lower binding affinity (-8.457 kcal/mol) may be attributed to the formation of only a single hydrogen bond with CYS 677 and potentially less favourable hydrophobic interactions compared to Imatinib." (Comparative analysis)

The frequent involvement of PHE 837 in aromatic interactions with all ligands highlights the importance of this residue in forming a hydrophobic pocket that accommodates the aromatic moieties of the inhibitors. Notably, the involvement of ASP 836 and PHE 8374 corresponding to the Asp and Phe residues expected in the DFG motif (Asp-Phe-Gly). This molecular modelling analysis provides valuable information for understanding the interactions between these drugs and PDGFR-A.

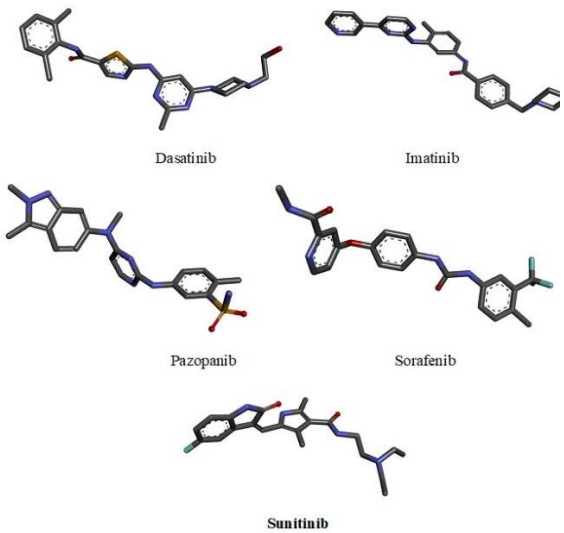


Figure 1: 3D structures of PDGFR-A inhibitors

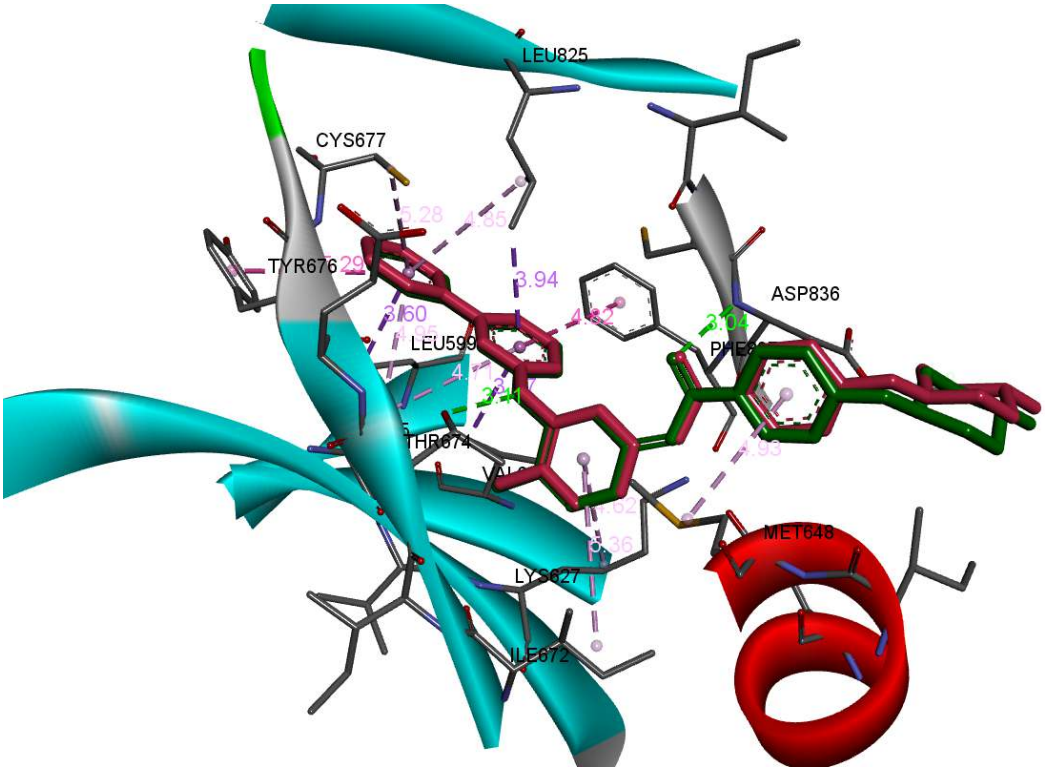


Figure 2: Overlay of the native ligand and docked ligand within the PDGFR-A binding site, validating the docking protocol

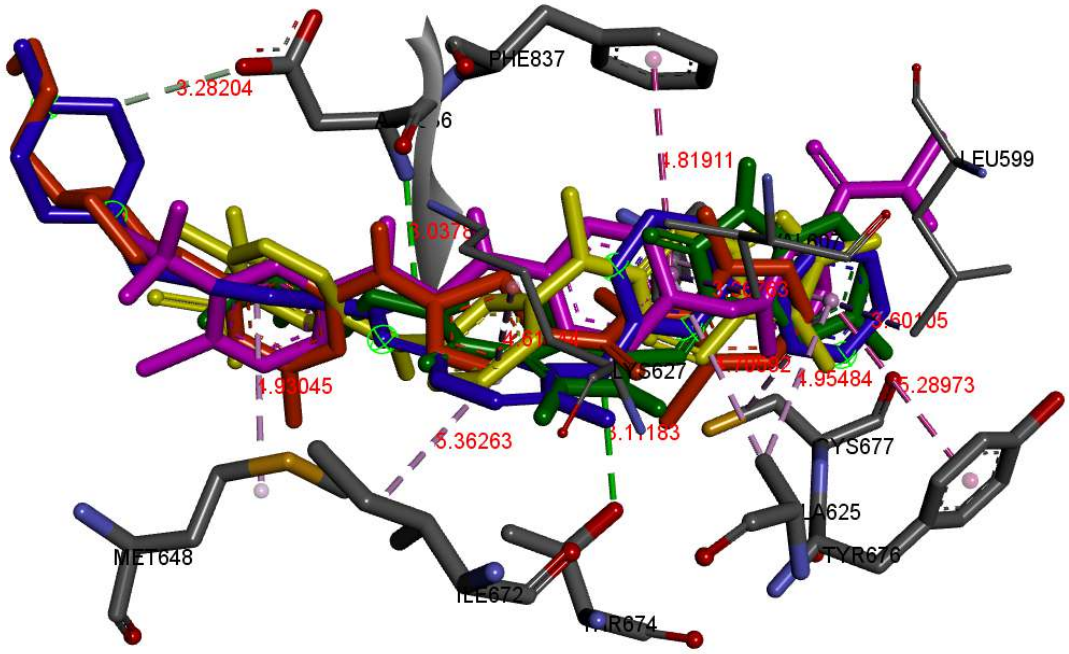
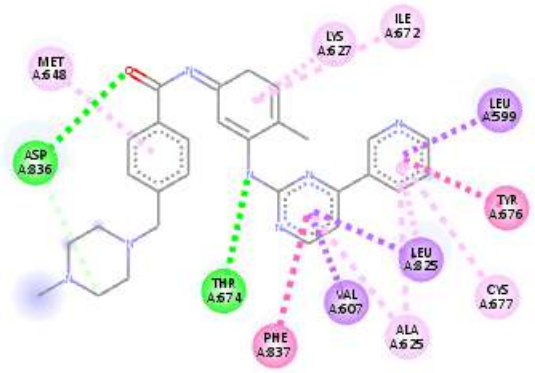
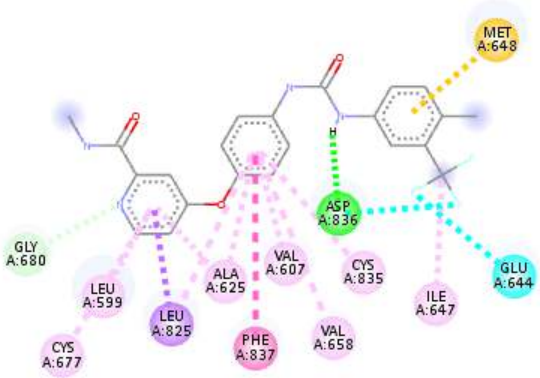


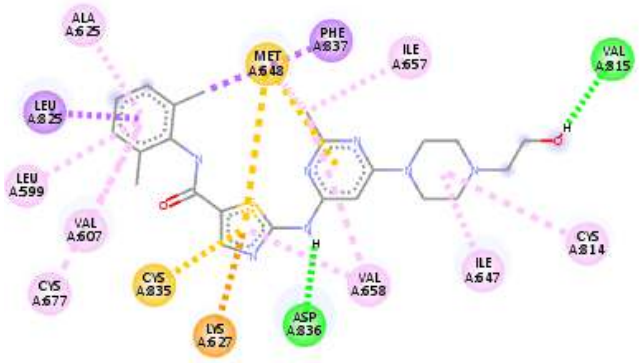
Figure 3: Superimposed Binding Poses of Docked Ligands within the PDGFR-A Binding Site. The figure displays the predicted binding orientations of Dasatinib (red), Imatinib (blue), Pazopanib (yellow), Sorafenib (purple), and Sunitinib (green) within the active site of the PDGFR-A protein (grey sticks). Key interacting amino acid residues are labelled for reference.



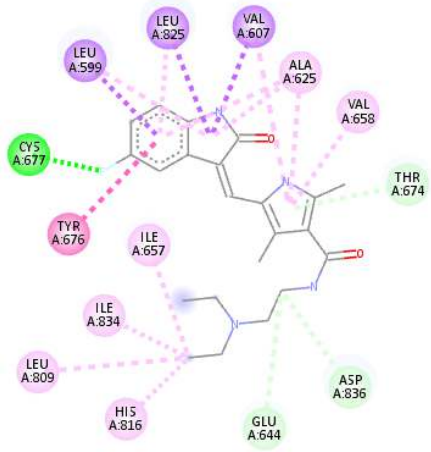
Imatinib 2D interaction



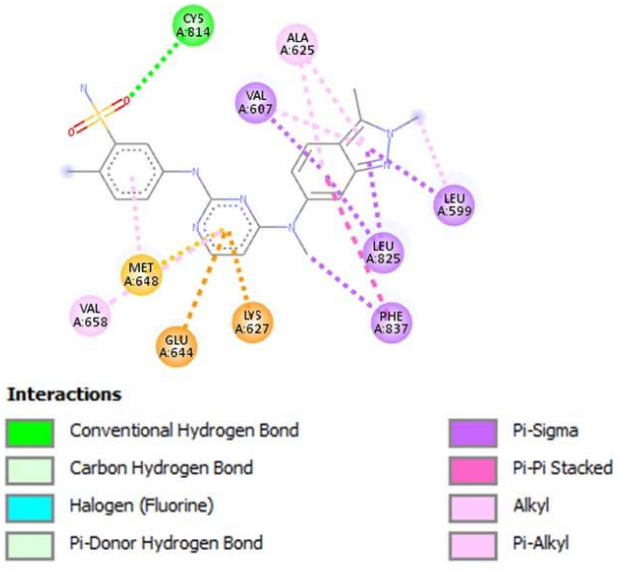
sorafenib 2D interaction



Dasatinib 2D interaction



Sunitinib 2D interaction



Pazopanib 2D interaction

Figure 4: 2D interaction of drugs with the amino acids of the binding site

4. Conclusion

In summary, this molecular modelling study provides valuable insights into the binding interactions of a series of kinase inhibitors with the PDGFR-A protein. The docking results highlight variations in binding affinities and binding modes among the tested ligands, which can be attributed to differences in hydrogen bond formation and specific interactions with key amino acid residues within the PDGFR-A active site. Imatinib, for instance, exhibits a high binding affinity likely due to the formation of two stable hydrogen bonds with ASP 836 and THR 674, while other ligands display distinct interaction profiles. The analysis also underscores the importance of residues such as PHE 837 in forming a crucial hydrophobic pocket for ligand binding. These findings contribute to a deeper understanding of the structural determinants of PDGFR-A inhibition and can be used to:

- Explain the differences in binding affinities among the drugs.
- Identify key amino acids in PDGFR-A that are important for drug binding.
- Guide the design of new and more effective PDGFR-A inhibitors.

However, it is important to acknowledge the inherent limitations of molecular docking, such as the assumption of protein rigidity. Therefore, further studies, including molecular dynamics simulations to account for protein flexibility and in vitro experiments to validate the binding affinities and inhibitory activities, are warranted. Such integrated approaches will provide a more comprehensive understanding of drug-PDGFR-A interactions and facilitate the development of novel therapeutic strategies to combat PDGFR-A-driven diseases."

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