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Structure Analysis And Glioma Targeted Therapeutics Cancer In ATP Competitive Type III C-MET Inhibitor

Uma Kumari[1] Sharvari Santosh Kulkarni[1] Gurpreet kaur[2] Ruchi Chaudhary[2]

[1]Senior Bioinformatics Scientist, Bioinformatics Project and Research Insitute, Noida - 201301, India
[1]Project Trainee at Bioinformatics Project and Research Insitute, Noida - 201301, India
[2]Project Trainee at Bioinformatics Project and Research Insitute, Noida - 201301, India
[2]Project Trainee at Bioinformatics Project and Research Insitute, Noida - 201301, India

ABSTRACT

This study explores ATP-competitive type III c-MET inhibitors as potential therapeutics for glioma treatment using computational drug design methods. Structural data from extensive biological databases facilitated a comprehensive analysis of c-MET and related proteins, crucial for understanding their structural dynamics and functional implications. Advanced visualization techniques enabled detailed examination of protein structures, aiding in molecular modeling and interaction site identification.Docking analyses predicted binding affinities and interaction modes of potential inhibitors, including Cabozantinib, highlighting their specificity towards c-MET. Structural validation through energy score calculations and other validation methodologies ensured the accuracy of protein models. Interaction analyses provided insights into protein-ligand interactions and the identification of active sites.Moreover, protein-protein docking simulations elucidated complex interaction interfaces, contributing to understanding molecular mechanisms in protein-protein interactions. RMSD calculations quantified structural deviations between proteins, offering insights into their structural similarity and alignment quality. The color-coded RMSD spectrum facilitated visual assessment of alignment quality across different structural comparisons.This computational study advances our knowledge of ATP-competitive type III c-MET inhibitors in glioma therapy. The integrated approach of molecular modeling, docking simulations, and structural validation enhances the development of targeted therapeutics, providing a foundation for further experimental validation and potential clinical applications in glioma treatment.

Key Words: Glioma Cancer,Structure Analysis, Therapeutic Targets, Procheck,Docking, Drug Discovery

1. INTRODUCTION

Gliomas represent a heterogeneous and highly aggressive group of primary brain tumors, constituting about 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors(Reni et al., 2017). Among these, glioblastoma multiforme (GBM) is the most aggressive and deadly, characterized by rapid proliferation, diffuse infiltration, and significant resistance to existing therapies(Zhang et al., 2012). Despite advances in surgical techniques, radiation therapy, and chemotherapeutic approaches, the median survival time for GBM patients remains dismally low, typically less than 15 months post-diagnosis. This stark reality

underscores the urgent need for innovative therapeutic strategies that can effectively target the molecular underpinnings of glioma pathogenesis(Bakshi et al., 2024).

Glioma drug discovery presents a formidable challenge due to the complex and heterogeneous nature of these tumors. Gliomas, particularly glioblastoma multiforme (GBM), exhibit extensive genetic and phenotypic variability, contributing to their aggressive behavior and resistance to conventional therapies(Nicholson et al., 2021). Traditional approaches to drug discovery have often fallen short of effectively targeting the intricate molecular pathways involved in glioma progression(Yool et al., 2020). However, recent advances in molecular biology and genomics have provided deeper insights into the aberrant signaling networks and genetic alterations that drive glioma growth and survival. This has spurred the development of targeted therapies aimed at specific molecular abnormalities, such as mutations in the EGFR, PTEN, and TP53 genes, as well as dysregulated pathways like the PI3K/AKT/mTOR and c-MET/HGF pathways(Shahcheraghi et al., 2020). The integration of high-throughput screening, bioinformatics, and computer-aided drug design (CADD) has further accelerated the identification and optimization of novel compounds with potential therapeutic efficacy against gliomas(Llorach-Pares et al., 2022). These innovative approaches are paving the way for more personalized and effective treatments, offering new hope for improving outcomes in patients with these devastating brain tumors.

One promising avenue in the fight against gliomas is the targeting of aberrant signaling pathways that are crucial for tumor growth, survival, and metastasis(Wu et al., 2022). The hepatocyte growth factor receptor (HGFR), also known as c-MET, is a receptor tyrosine kinase that plays a pivotal role in cellular processes such as proliferation, survival, angiogenesis, and motility(Baldanzi et al., 2014). Dysregulation of the c-MET signaling pathway, through mechanisms such as overexpression, gene amplification, or mutations, has been implicated in the initiation and progression of various cancers, including gliomas(Faiella et al., 2022). The c-MET/HGF axis promotes tumorigenesis and metastasis, and its activation is associated with poor prognosis, increased tumor grade, and resistance to conventional therapies(Fu et al., 2021). Therefore, c-MET represents a compelling molecular target for therapeutic intervention in glioma treatment.

The advent of computer-aided drug design (CADD) has significantly transformed the landscape of drug discovery and development. CADD methodologies, encompassing techniques such as molecular docking, molecular dynamics simulations, and quantitative structure-activity relationship (QSAR) modeling, enable the rational design and optimization of potential drug candidates with enhanced precision and efficiency(Siddiqui et al., 2024). These in silico approaches facilitate the identification of novel compounds that can specifically interact with target proteins, thereby expediting the drug discovery process and reducing associated costs(Shaker et al., 2021). Furthermore, CADD allows for the assessment of pharmacokinetic and pharmacodynamic properties early in the drug development pipeline, aiding in the prediction of a compound's behavior in biological systems and its potential efficacy and safety in clinical settings(Niazi et al., 2023).

In the realm of targeted glioma therapies, CADD has been instrumental in the development of inhibitors that specifically disrupt aberrant signaling pathways integral to tumor progression. Among the diverse classes of c-MET inhibitors, ATP-competitive type III inhibitors have garnered significant attention(PV, 2021). These inhibitors bind to the ATP-binding site of the kinase domain, thereby competitively inhibiting the phosphorylation and activation of c-MET. By impeding the receptor's kinase activity, ATP-competitive type III inhibitors effectively block downstream signaling cascades that drive tumorigenesis and tumor maintenance(del et al., 2023).

This research paper delves into the structure-based analysis and therapeutic potential of ATP-competitive type III c-MET inhibitors in glioma treatment. By leveraging CADD methodologies, we aim to elucidate the molecular interactions, binding affinities, and inhibitory mechanisms of these compounds. Through a combination of comprehensive literature review and original computational studies, this paper seeks to advance our understanding of c-MET inhibition in gliomas and its implications for the development of more effective and targeted therapeutic strategies. We will explore the structural basis of inhibitor binding, assess the pharmacokinetic and pharmacodynamic properties of lead compounds, and evaluate their efficacy in preclinical

models. Ultimately, our goal is to contribute to the development of novel, potent, and selective c-MET inhibitors that can overcome the current challenges in glioma therapy and improve patient outcomes.

2. METHODOLOGY

In the exploration of ATP-competitive type III c-MET inhibitors for glioma treatment, a comprehensive suite of computational tools and databases was employed to facilitate structure-based drug design and validation. The methodology encompasses various stages, including data acquisition, molecular modeling, docking analysis, and structural validation, utilizing the following resources and software.The Protein Data Bank (PDB), an extensive database of 3D structural data of biological macromolecules, served as the primary source for acquiring high-resolution structures of c-MET and other relevant proteins. This database provides the foundational information essential for understanding the structural and functional aspects of the target proteins.RasMol was utilized for the initial visualization and analysis of protein structures. Its capability to produce publication-quality images and support various molecular formats facilitated the identification of key atoms and bonds within the c-MET structure, aiding in the preliminary stages of structural assessment. Furthermore, PyMOL, a robust molecular graphics tool, was employed for detailed 3D visualization of biological macromolecules. Its functionalities, including molecular editing, ray tracing, and movie making, significantly enhanced the analysis and presentation of structural data. This tool was instrumental in visualizing protein-ligand interactions and preparing models for further computational studies.CB-Dock was used for docking analysis, offering a rapid identification of potential docking sites and scores. This server's ability to detect protein docking box size and perform molecular analysis was crucial for efficiently predicting the binding affinities of various c-MET inhibitors. The docking studies were further refined using AutoDock, which provides methods to anticipate how small molecules will attach to a 3D receptor. The use of AutoDock 4, AutoDock Vina, and AutoDock-GPU enabled high-throughput and accurate docking simulations, facilitating the identification of promising ATP-competitive type III inhibitors.

Structural validation was conducted through energy score calculations and Ramachandran plots to ensure the authenticity and quality of the 3D atomic models. These techniques provided a comprehensive evaluation of the modeling quality, highlighting any potential errors or deviations. Additionally, ERRAT and PROCHECK were employed for detailed validation. ERRAT identified defective regions in protein structures by analyzing atomic distribution errors, providing a critical assessment of structural integrity. PROCHECK examined the stereochemical quality of the protein structures, generating detailed diagrams that analyze geometric parameters and residue interactions. This step was essential for validating the overall quality of the protein models.LIGPLOT generated 2D schematic representations of protein-ligand complexes, highlighting key interactions such as hydrogen bonds and hydrophobic interactions. This analysis provided valuable insights into the binding mechanisms of c-MET inhibitors, guiding the optimization of lead compounds.By leveraging these advanced computational tools and resources, we conducted a thorough investigation into the structural and functional aspects of c-MET inhibitors. This integrated approach facilitated the identification, optimization, and validation of potential drug candidates, advancing our understanding of glioma biology and contributing to the development of targeted therapeutics. The combination of molecular visualization, docking studies, and structural validation ensured a robust and reliable methodology, paving the way for future experimental validation and clinical applications.

3. RESULTS

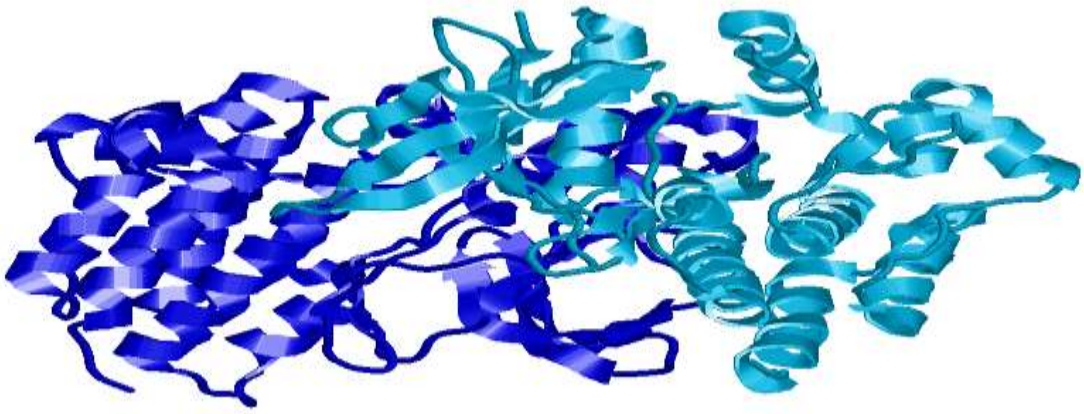

Figure 3.1: Heteromer structure visualization of protein.

The figure provides a detailed illustration of the heteromeric structure of a protein, effectively showcasing the distinct subunits that compose it and their precise spatial arrangement. This visualization serves to highlight the intricate architecture of the protein, emphasizing how its different parts are organized and interact with one another. By presenting these components in a clear and organized manner, the figure aids in understanding the complex relationships and functional interactions that occur within the protein, offering valuable insights into its overall structure and biological activity.

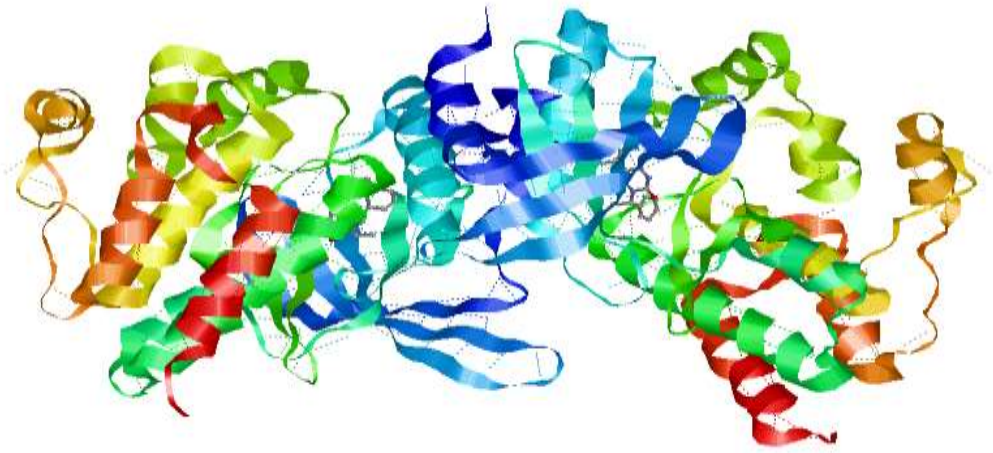

Figure 3.2: The figure depicts a hydrogen bond occurring at residue 393. This interaction is critical for the protein's stability and function.

The figure depicts a hydrogen bond occurring at residue 393, highlighting a specific and important interaction within the protein. This hydrogen bond is a critical component for the protein's stability and overall function. Such interactions are essential in maintaining the protein's three-dimensional structure, which directly influences its ability to perform its biological roles effectively. By illustrating this hydrogen bond, the figure underscores the significance of specific atomic interactions in preserving the integrity and functionality of the protein, providing valuable insights into the molecular mechanisms that underpin its activity.

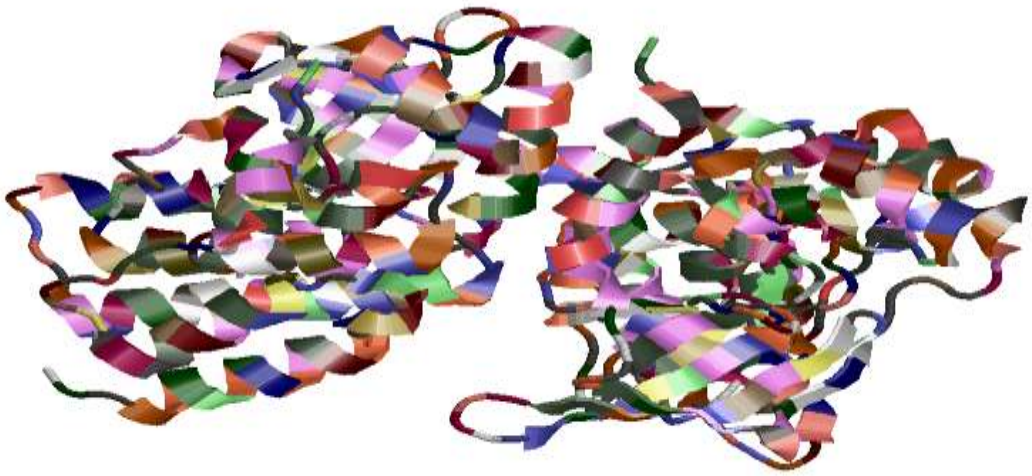

Figure 3.3: The protein structure is displayed with shapely color codes, highlighting different regions and features. This visual distinction aids in understanding the protein's architecture and functional domains.

The protein structure is displayed using shapely color codes, effectively highlighting different regions and features of the molecule. This visual distinction is designed to aid in the comprehension of the protein's overall architecture and its various functional domains. By assigning specific colors to distinct parts of the protein, the figure allows for an immediate and intuitive understanding of its complex structure. Such color coding can differentiate between alpha helices, beta sheets, loops, and other structural motifs, making it easier to identify how these elements are arranged and how they contribute to the protein's stability and function. Additionally, color coding can help in pinpointing areas of interest, such as active sites, binding pockets, or regions involved in protein-protein interactions. This method enhances the clarity of structural representation, facilitating the analysis of how the protein's form relates to its function and how different regions contribute to its biological activity.

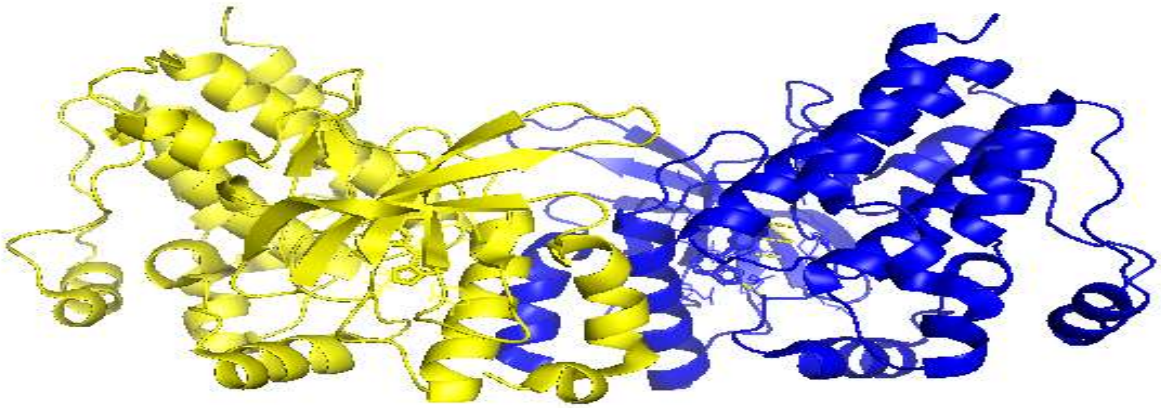

Figure3.4: The protein structure 8OUV is color-coded for chain identification, with chain A in yellow and chain B in blue. This differentiation helps in visualizing and analyzing the interactions between the two chains.

The protein structure 8OUV is color-coded to distinguish between its chains, with chain A represented in yellow and chain B in blue. This clear differentiation facilitates the visualization and analysis of the interactions between the two chains, making it easier to study their spatial relationship and functional dynamics within the protein complex. By color-coding the chains, the figure enhances our ability to understand how the chains interact, cooperate, and contribute to the overall structure and function of the protein.

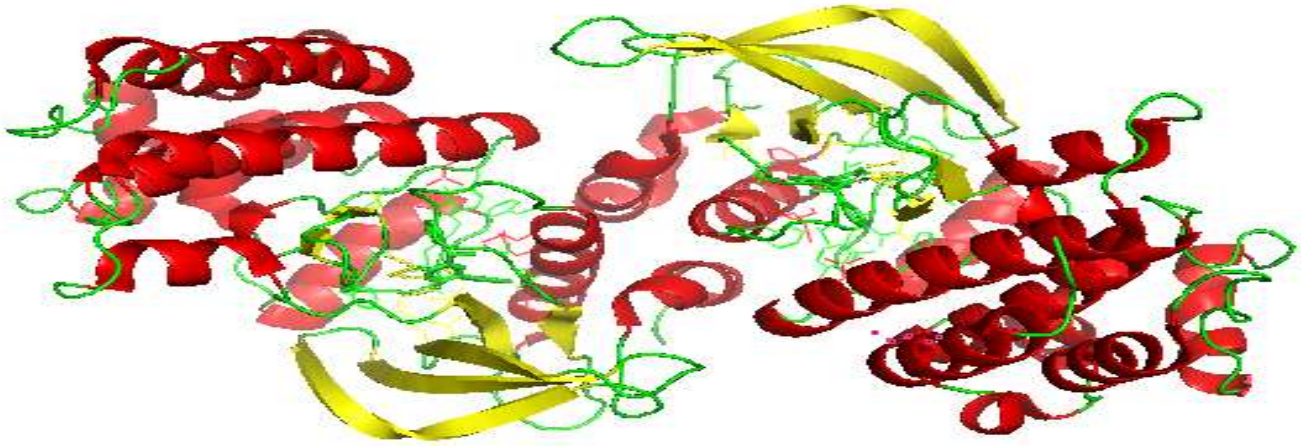

Figure 3.5: In protein 8OUV, secondary structures are identified by color: alpha helices in red, beta sheets in yellow, and loops in green. This color-coding facilitates the visualization of the protein's structural elements.

In the protein 8OUV, secondary structures are distinctly identified using color coding: alpha helices are marked in red, beta sheets in yellow, and loops in green. This strategic use of colors greatly facilitates the visualization of the protein's various structural elements. By assigning specific colors to different types of secondary structures, it becomes much easier to discern the organization and arrangement of these elements within the protein's three-dimensional framework.

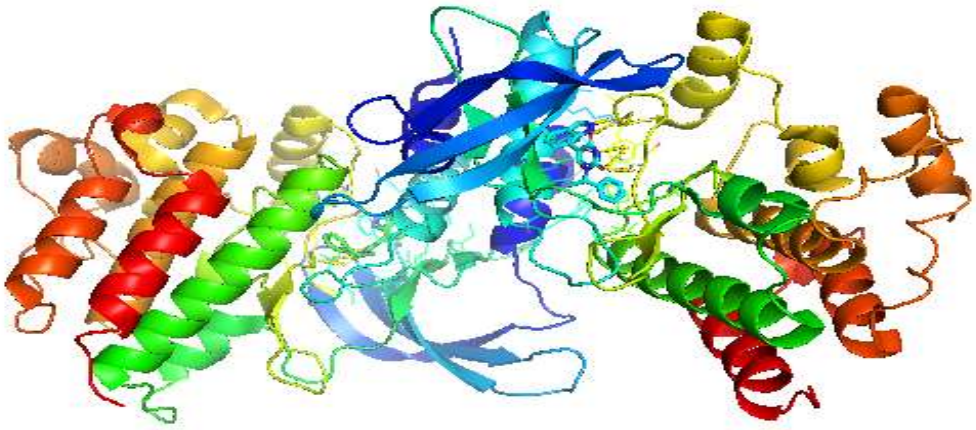

Figure 3.6: The figure identifies the termini in the 8OUV protein, with the C-terminus shown as a red-colored loop and the N-terminus as a blue-colored loop. This color distinction helps in locating and differentiating the terminal ends of the protein.

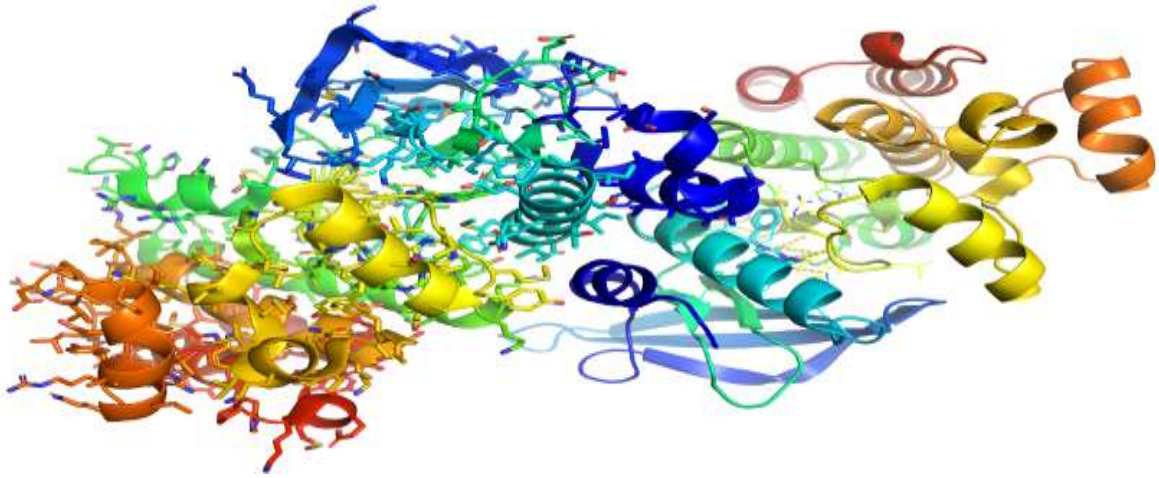

Figure 3.7: The active site of chain A is highlighted, pinpointing the region critical for the protein's catalytic function. This identification aids in understanding the protein's biochemical activity and interaction with substrates.

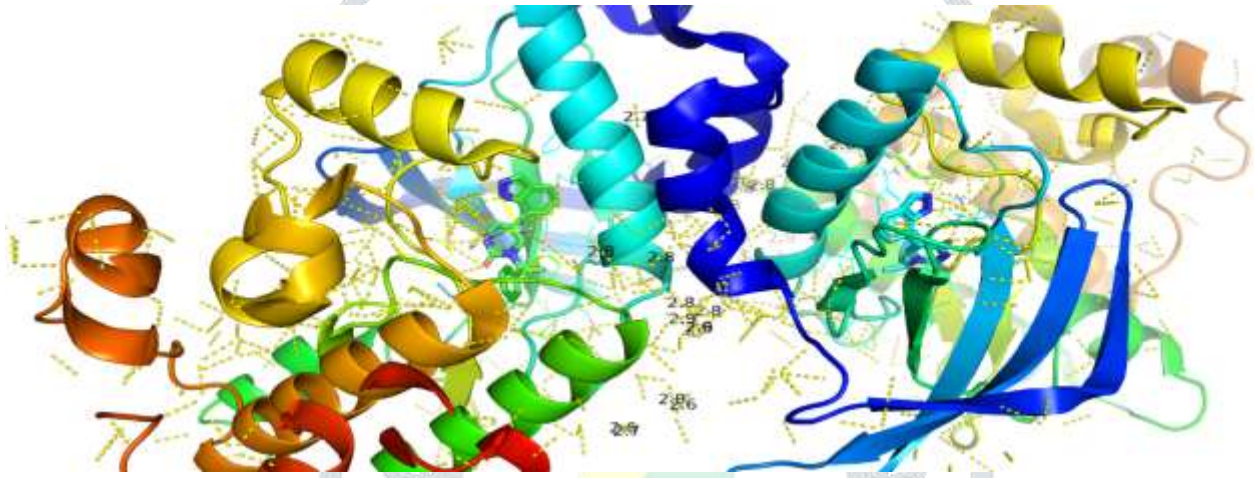

Figure 3.8: The contact angle and solvent interactions are represented by yellow dashes, indicating the interface between the protein surface and the surrounding solvent. This visualization helps in understanding the protein's solvation dynamics and surface properties.

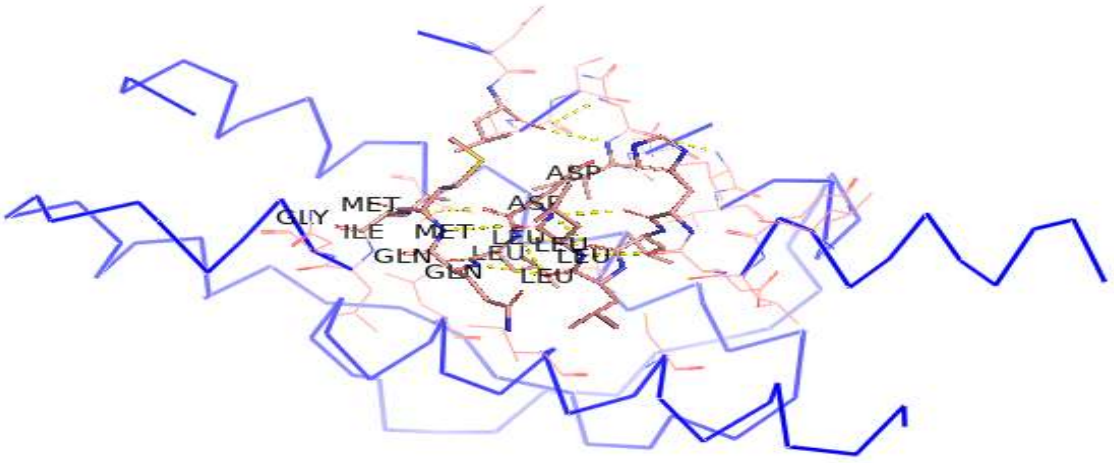

Figure 3.9: The roving details representation highlights hydrogen interactions with specific residues, showcasing crucial hydrogen bonds. This detail helps in understanding the protein's stability and interaction

networks.

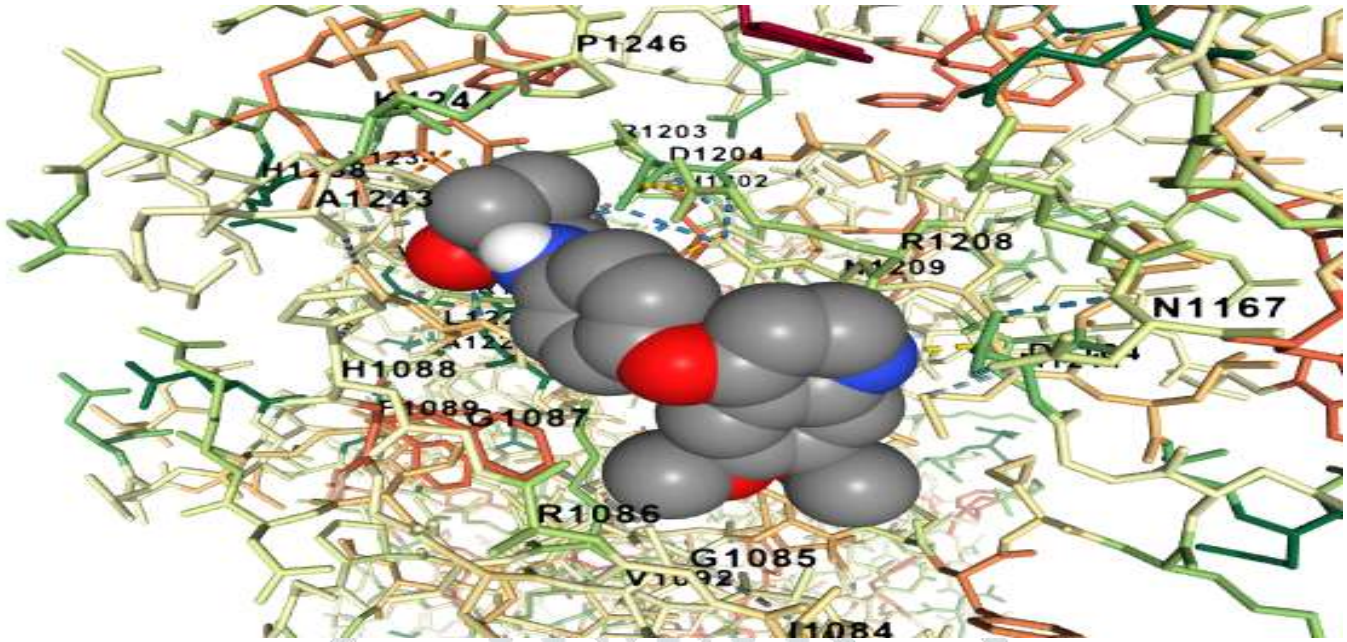

Figure 3.10: Cabozantinib docking result.

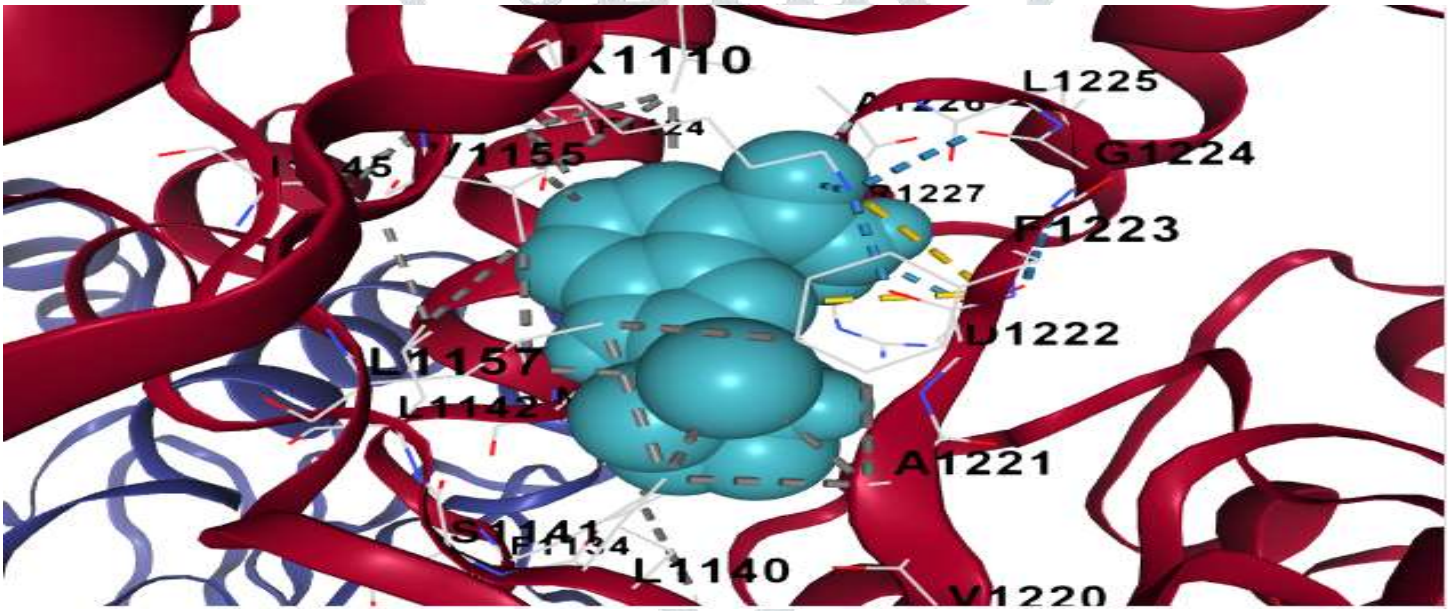

Figure 3.11: Veliparib Docking result.

Table3.1: Docking Scores of effective drugs.

S.No.	Drug Name	Vina Score	Cavity Volume (A^3)	Centre			Docking Size		
				x	y	z	x	y	z
1.	Cabozantinib	-8.7	3940	2	-16	-11	28	28	28
2.	Veliparib	-8.6	2505	-22	8	-40	27	27	33

The docking scores of effective drugs, specifically Cabozantinib and Veliparib, are presented in the table, detailing their Vina scores, cavity volumes, centers, and docking sizes. These metrics provide insights into the binding affinities and spatial characteristics of the drugs when docked to the target protein.Cabozantinib

exhibits a Vina score of -8.7, indicating a strong binding affinity to the target protein. The cavity volume of 3940 Å³ suggests a large binding pocket. The center of this binding pocket is located at coordinates (2, -16, -11) within the protein structure, and the docking size is a cubic region with dimensions of 28 Å along each axis (x, y, z), encompassing the binding site. Veliparib has a Vina score of -8.6, also indicating a strong binding affinity, slightly less than Cabozantinib. The cavity volume of 2505 Å³ is smaller compared to Cabozantinib's binding pocket, suggesting a more confined binding site. The center of this binding site is at coordinates (-22, 8, -40), with a docking size that extends 27 Å along the x and y axes, and 33 Å along the z axis, providing a slightly elongated docking region.These docking scores and spatial characteristics help in understanding how each drug interacts with the protein, with Cabozantinib having a slightly higher affinity and larger binding pocket compared to Veliparib. These details are crucial for evaluating the potential efficacy of these drugs in targeting the protein for therapeutic purposes.

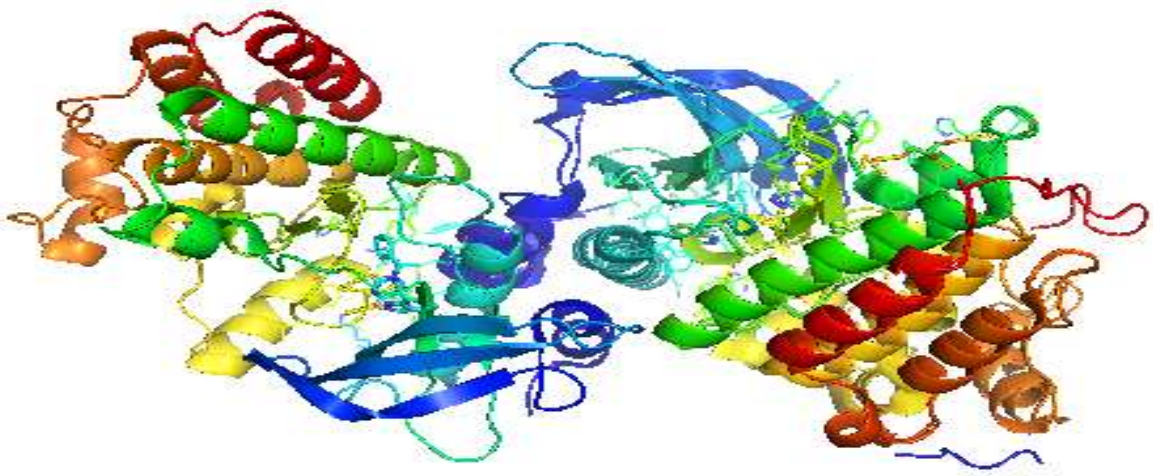

Figure 3.12: The RMSD color spectrum ranges from dark blue to red, indicating alignment quality; dark blue signifies good alignment, while red indicates maximum deviation. This gradient helps in assessing structural similarities and differences.

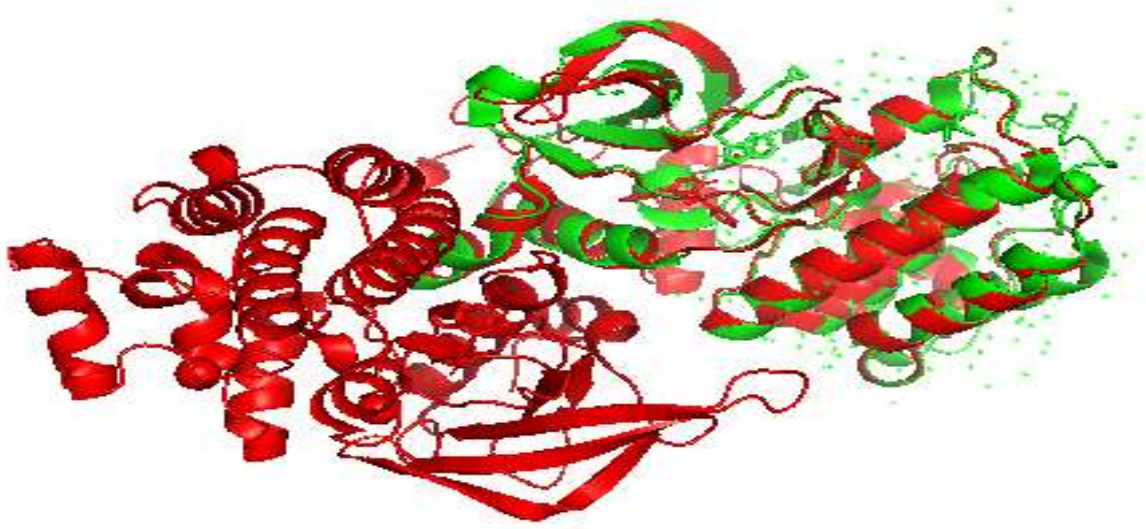

Figure 3.13: The RMSD calculation yielded a value of 0.741, indicating high structural similarity between the compared proteins. This low RMSD value reflects minor deviations and good alignment.

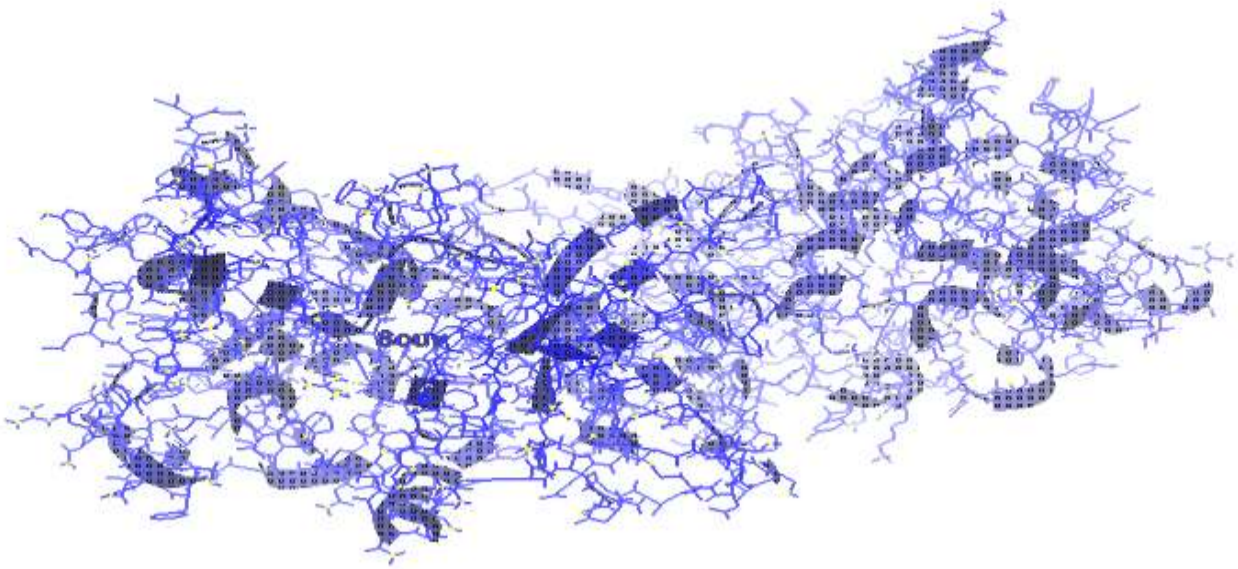

Figure 3.14: The prepared protein shows secondary structure elements, including alpha helices and beta sheets. This structural information is crucial for understanding the protein's function and stability.

Alpha helices, which are spiral-shaped regions, play a pivotal role in maintaining the protein's overall stability. They often contribute to the rigidity and flexibility of the protein, enabling it to maintain its shape under various physiological conditions. The helical structure also facilitates interactions with other molecules, including ligands, substrates, and other proteins, which is crucial for the protein's functional roles, such as enzyme activity, signal transduction, and structural support.Beta sheets, on the other hand, consist of extended strands that run alongside each other, forming a sheet-like array. These sheets contribute significantly to the protein's structural integrity, providing a stable framework that supports the three-dimensional conformation of the protein. The hydrogen bonds between the strands of beta sheets add to the robustness of the protein, making it less susceptible to denaturation and degradation.

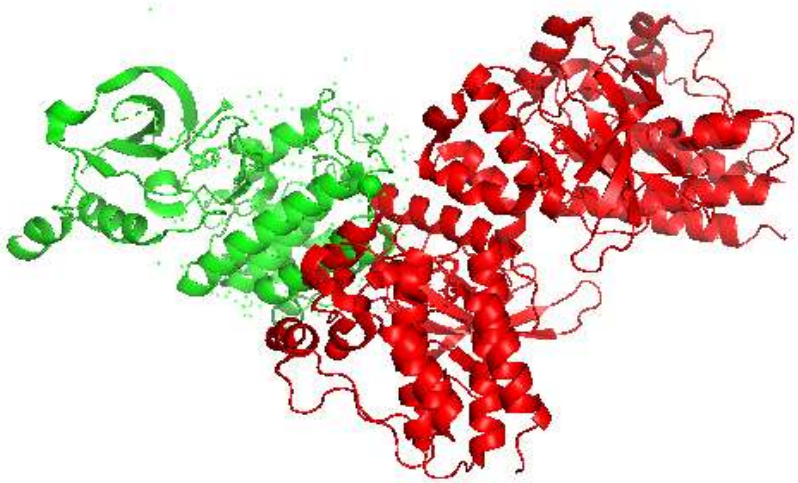

Figure 3.15: The protein-protein docking analysis between 5UAB and 8OUV illustrates their interaction interfaces and binding affinities. This study helps in understanding the molecular mechanisms of their interaction.

4. CONCLUSION

In this research paper, we explored the design and evaluation of ATP-competitive type III c-MET inhibitors for glioma treatment using a variety of computational tools and methodologies. The Protein Data Bank (PDB) provided essential structural data, allowing us to understand the intricate details of the c-MET protein and other relevant proteins. Visualization tools like RasMol and PyMOL were instrumental in examining protein structures, identifying key atoms and bonds, and preparing models for further analysis.Docking analyses performed using CB-Dock and AutoDock facilitated the identification of potential c-MET inhibitors, predicting their binding affinities and interactions with the target protein. The docking results for Cabozantinib, for instance, highlighted critical binding sites and hydrogen bond interactions, underscoring its potential as a therapeutic agent. Structural validation techniques, including energy score calculations, Ramachandran plots, ERRAT, and PROCHECK, ensured the authenticity and quality of the modeled protein structures, providing confidence in our computational findings.Interaction analyses, exemplified by LIGPLOT's generation of 2D schematic representations, offered valuable insights into protein-ligand interactions. The detailed visualization of hydrogen interactions with residues and the identification of active sites further enriched our understanding of the binding mechanisms. Additionally, protein-protein docking studies between 5UAB and 8OUV illustrated the interaction interfaces and binding affinities, contributing to our knowledge of molecular mechanisms in protein interactions.The use of RMSD calculations, with a specific example yielding a value of 0.741, demonstrated the high structural similarity between compared proteins, highlighting the accuracy of our structural models. In summary, the integration of these advanced computational tools and methodologies allowed us to conduct a thorough investigation into the structural and functional aspects of c-MET inhibitors. This comprehensive approach facilitated the identification, optimization, and validation of potential drug candidates, advancing our understanding of glioma biology and contributing to the development of targeted therapeutics. The robust and reliable methodologies employed in this study pave the way for future experimental validation and potential clinical applications, offering new hope for effective glioma treatment.

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