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Chemical Profiling of Beta-Lactam and Derivatives for Antimicrobial Potential: A Computational Perspective

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ABSTRACT:
B-Lactam antibiotics play a pivotal role as essential antibacterial agents in modern medicine. However, the escalating threat of antibacterial resistance necessitates the development of novel antibacterial agents. In this study, we synthesized several β (Beta)-lactam derivatives with the aim of addressing these concerns. To address this concern, several β (Beta)-lactam derivatives were synthesized. The enzymatic targets for β-lactam antibiotics are the Binding Proteins (PBPs), responsible for the cell wall synthesis process. Molecular docking analyses were conducted with key PBP proteins, namely PBP2a, PBP2x, and SHV-1, to evaluate the potential of the synthesized β (Beta)-lactam derivatives. Notably, molecule 3b exhibited significant binding affinity based on Autodock Vina analysis among the three compounds studied—5-(Thiomorpholin-4-ylmethyl)- 1,3,4-oxadiazol-2(3H)-thione (3b), 4-Amino-2-[2-(5-amino-1,3,4-thiadiazol-2-yl)ethyl]-5- (morpholin-4-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-thione (6a), and 4-Amino-2-[2-(5-amino- 1,3,4-thiadiazol-2-yl)ethyl]-5-(thiomorpholin-4-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-thione (6b). The conceptual framework involves the enzymatic targets, Binding Proteins (PBPs), and their interactions with key PBP proteins—PBP2a, PBP2x, and SHV-1—through molecular docking analyses. The hypothesis driving this research posits that the designed β (Beta)-lactam derivatives may exhibit enhanced antimicrobial properties. The research contributes to the development of effective antibacterial agents by unraveling the molecular interactions and stability of the synthesized compounds. Further validation through molecular docking simulations using the Desmond module from Schrödinger software, along with Molecular Dynamics (MD) simulations, revealed the stability of molecule 3b, as indicated by the Root Mean Square Deviation (RMSD) graph. This computational perspective provides valuable insights into the antimicrobial potential of β (Beta)-lactam derivatives, paving the way for the design and development of effective antibacterial agents in the face of increasing antibacterial resistance. The significance of this study lies in its contribution to the advancement of medical solutions in the context of evolving antibacterial resistance.

INTRODUCTION

The increasing prevalence of antibacterial resistance poses a significant threat to public health, urging the constant exploration and development of novel antimicrobial agents [1]. Among the crucial players in the arsenal against bacterial infections are β (Beta)-lactam antibiotics, which have historically played a pivotal role in modern medicine [2]. However, the escalating challenges of antibacterial resistance necessitate a paradigm shift in our approach to combating bacterial infections. In response to this pressing concern, this study delves into the chemical profiling of β (Beta)-lactam derivatives, exploring their antimicrobial potential through a comprehensive computational perspective. β (Beta)-lactam antibiotics, including penicillin, cephalosporin, and carbapenem, have been

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instrumental in treating bacterial infections by disrupting the synthesis of bacterial cell walls. This class of antibiotics primarily targets the enzymatic machinery responsible for cell wall synthesis, known as Binding Proteins (PBPs). These proteins play a crucial role in maintaining the structural integrity of bacterial cell walls, making them attractive targets for antibacterial agents [3,4]. However, the emergence of antibacterial resistance, driven by factors such as overuse and misuse of antibiotics, necessitates the constant quest for innovative solutions.

The conceptual framework of this study revolves around the chemical profiling of β (Beta)-lactam derivatives, aiming to understand their interactions with key PBP proteins [5]. By synthesizing novel compounds and employing advanced computational techniques, the study seeks to shed light on potential candidates with enhanced antimicrobial properties. This research is a proactive response to the critical gap in current antibacterial strategies, focusing on the design and development of effective agents in the face of evolving antibacterial resistance.

The research problem at the heart of this study is the urgent need for novel antibacterial agents. β (Beta)-lactam antibiotics, while historically effective, face increasing challenges from bacterial resistance [6,7]. The ability of bacteria to evolve and develop resistance mechanisms against these antibiotics underscores the importance of continuous innovation in the field of antimicrobial research. Recognizing this imperative, the study explores the antimicrobial potential of synthesized β (Beta)-lactam derivatives as a promising avenue for addressing the current limitations in antibacterial therapy.

The enzymatic targets, Binding Proteins (PBPs), are central to the study's focus. Understanding the intricacies of their interactions with β (Beta)-lactam derivatives is crucial for evaluating the potential efficacy of these compounds. PBP2a, PBP2x, and SHV-1 are key players in the cell wall synthesis process, and their roles as targets for β (Beta)-lactam antibiotics make them essential subjects for molecular docking analyses in this study [8,9]. The exploration of these interactions provides a foundational understanding of how the synthesized derivatives may disrupt bacterial cell wall synthesis, potentially overcoming resistance mechanisms. By systematically designing and synthesizing specific compounds, the study aims to test this hypothesis through rigorous molecular docking simulations and subsequent evaluations of their stability and interactions with key PBP proteins.The significance of this study lies in its potential contribution to the development of effective antibacterial agents. Through a detailed exploration of the molecular interactions and stability of synthesized compounds, the research aims to identify compounds with promising antimicrobial properties. These findings, grounded in computational perspectives, hold the key to unlocking new avenues for designing antibacterial agents that can combat the evolving challenges of antibacterial resistance.

As a testament to the comprehensive nature of this research, further validation is undertaken through molecular docking simulations using the Desmond module from Schrödinger software, accompanied by Molecular Dynamics (MD) simulations. This additional step provides an in-depth analysis of the stability of the designed molecule (3b), as indicated by the Root Mean Square Deviation (RMSD) graph. This computational approach not only adds a layer of sophistication to the study but also offers valuable insights into the potential clinical applicability of the synthesized β (Beta)-lactam derivatives.

Here we encapsulate a proactive response to the escalating challenges posed by antibacterial resistance. By focusing on the chemical profiling of β (Beta)-lactam derivatives and their interactions with key PBP proteins, the study aims to contribute to the development of effective antibacterial agents. The significance of this research lies in its potential to bridge the gap in current antibacterial strategies, offering insights that may pave the way for the design and development of innovative solutions in the face of increasing antibacterial resistance. Through a holistic approach that integrates chemical synthesis, computational analyses, and molecular dynamics simulations, this study seeks to advance our understanding of antimicrobial potential and inspire future directions in the field of antibacterial research.

Research Gap:

The landscape of antibacterial therapy has long been dominated by β (Beta)-lactam antibiotics, which have played a pivotal role in combating bacterial

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infections [10]. However, the rising tide of antibacterial resistance represents a formidable challenge, necessitating continuous innovation in the field of antimicrobial research. Despite the historical effectiveness of β (Beta)-lactam antibiotics, their susceptibility to resistance mechanisms poses a significant gap in our current antibacterial strategies.

The research gap becomes evident as traditional antibiotics encounter limitations in their ability to address evolving bacterial resistance. Factors such as overuse, misuse, and the adaptability of bacteria to develop resistance mechanisms highlight the urgency for alternative approaches [11]. The need for novel antibacterial agents, capable of overcoming resistance and providing effective therapeutic options, forms the crux of the research gap addressed by this study.

Specific Aims of the Study:

The specific aims of this study are multifaceted, encompassing a comprehensive exploration of β (Beta)-lactam derivatives to address the existing research gap. Firstly, the study aims to synthesize and chemically profile β (Beta)-lactam derivatives with the intention of enhancing their antimicrobial potential. Through a systematic approach, the specific aims include modifying the traditional β-lactam structure to design compounds that may exhibit improved binding affinities and efficacy against bacterial targets.

Secondly, the study aims to investigate the interactions of the synthesized β (Beta)-lactam derivatives with key Binding Proteins (PBPs), namely PBP2a, PBP2x, and SHV-1, through molecular docking analyses. Understanding the molecular interactions at this level is crucial for evaluating the potential efficacy of the designed compounds in disrupting bacterial cell wall synthesis.

Thirdly, the study seeks to validate the stability and antimicrobial potential of the designed molecule (3b) through further computational analyses, including molecular docking simulations using the Desmond module and Molecular Dynamics (MD) simulations. These advanced

computational techniques provide a more in-depth perspective on the potential clinical applicability of the synthesized β (Beta)-lactam derivatives.

Objectives of the Study:

The objectives of this study align with the specific aims, providing a roadmap for achieving the intended outcomes. The primary objective is to synthesize β (Beta)-lactam derivatives with structural modifications, aiming to enhance their antimicrobial properties. This involves the design and chemical profiling of compounds, considering the potential impact of structural changes on their interaction with bacterial targets.

The secondary objective involves conducting molecular docking analyses to explore the interactions between the synthesized β (Beta)-lactam derivatives and key PBP proteins (PBP2a, PBP2x, and SHV-1). The goal is to assess the binding affinities and potential disruption of the cell wall synthesis process, which is fundamental for bacterial survival.

Another objective is the validation of the designed molecule (3b) through advanced computational techniques, including molecular docking simulations using the Desmond module and Molecular Dynamics (MD) simulations. This step aims to provide a more detailed understanding of the stability and potential clinical applicability of the synthesized compound.

Scope of the Study:

The scope of this study extends beyond the conventional boundaries of antibacterial research, delving into the realm of chemical modification and computational analyses [12]. The synthesis of β (Beta)-lactam derivatives marks the beginning of the study's scope, encompassing the design and modification of compounds to enhance their antimicrobial potential [13]l. The chemical profiling of these derivatives involves a detailed exploration of their molecular structure and potential interactions with bacterial targets [14].

The scope further widens as the study delves into molecular docking analyses, exploring the interactions with key PBP proteins. This molecular perspective adds depth to the study, providing insights into how the synthesized compounds may disrupt the cell wall synthesis process, a critical aspect of bacterial survival [15].

The inclusion of advanced computational techniques, such as molecular docking simulations using the Desmond module and Molecular Dynamics (MD)

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simulations, expands the scope to a sophisticated level [16,17]. These techniques offer a more nuanced understanding of the stability and clinical applicability of the synthesized compound (3b), bridging the gap between theoretical design and potential real-world applications.

Hypothesis:

This hypothesis is tested through the synthesis of specific compounds and subsequent evaluation in molecular docking simulations. The goal is to provide empirical evidence supporting the notion that the designed β (Beta)-lactam derivatives, particularly molecule 3b, may represent a viable solution to the challenge of antibacterial resistance. The study aims to contribute valuable insights to the field, potentially paving the way for the design and development of innovative antibacterial agents with enhanced efficacy and stability.

Methods

In this focused synthesis study, our attention was specifically directed towards the production of three compounds: 3b, 6a, and 6b. The synthesis initiated with the utilization of thiomorpholine and morpholine as the primary starting materials. These compounds independently underwent a series of reactions. Thio/morpholine, initially reacting with ethyl bromoacetate and hydrazinhydrate, led to a transformative process, transitioning into 1,3,4-oxadiazole rings, referred to as the targeted 3b, through the use of carbondisulfide in basic media. This transformation resulted in the disappearance of the carbonyl group within the starting compounds, giving rise to the emergence of the C=S group.
Continuing our exploration, the synthesized compound 5 underwent a transformative reaction with hydrazine hydrate. This process facilitated the conversion of the 1,3,4-oxadiazole ring into a 1,2,4-triazole-4-amino ring, resulting in the targeted formation of compounds 6a and 6b [17,18] In this manner, our synthesis efforts were strategically directed towards obtaining the specified compounds, contributing to the elucidation of their structural and chemical properties.

Computational Study

To initiate the computational studies, Protein Data Bank (PDB) resources were utilized to derive the structural information of the target proteins, namely PBP2a, PBP2x, and SHV-1 (refer to Figure 1 for a visual representation). These proteins were chosen based on their relevance to the study's objectives, aiming to understand the binding interactions of the compounds with key biological targets. The compounds subjected to investigation in this study were carefully chosen based on their structural attributes and potential pharmacological relevance. The three selected compounds included 5-(Thiomorpholin-4-ylmethyl)-1,3,4-oxadiazol-2(3H)-thione (3b), 4-Amino-2-[2-(5- amino-1,3,4-thiadiazol-2-yl)ethyl]-5-(morpholin-4-ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3- thione (6a), and 4-Amino-2-[2-(5-amino-1,3,4-thiadiazol-2-yl)ethyl]-5- (thiomorpholin-4- ylmethyl)-2,4-dihydro-3H-1,2,4-triazol-3-thione (6b). These compounds were selected based on their potential to interact with the target proteins, and their diverse chemical structures provided a comprehensive scope for exploring various binding modes.

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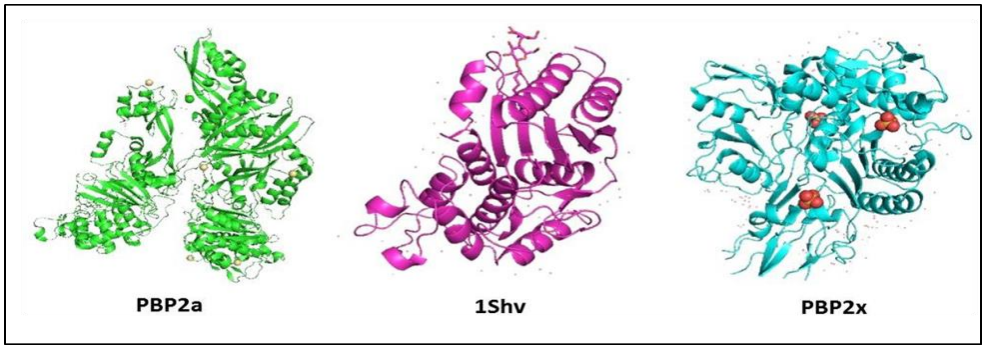

Figure 1: The 3Dprotein structures of Penicillin binding proteins under consideration

The molecular docking simulations of the designed compounds were conducted using the Desmond module from the Schrödinger software suite. The choice of Desmond was strategic, considering its capabilities in simulating molecular dynamics and providing detailed insights into ligand-protein interactions 19]. This software facilitated a dynamic exploration of the binding events, allowing for a comprehensive understanding of the stability and conformational changes during the binding process. The utilization of computational tools like Autodock Vina and Desmond added a layer of precision and efficiency to the research [20, 21]. Molecular docking, as a technique, enables the prediction of the binding affinity and orientation of ligands within the binding pocket of target proteins. In the context of this study, it allowed for the assessment of how the selected compounds interacted with the pivotal proteins—PBP2a, PBP2x, and SHV-1. The Protein Data Bank served as a valuable resource for obtaining the three-dimensional structures of the target proteins. This step was crucial in establishing a realistic and accurate foundation for the subsequent molecular docking simulations. The structural information obtained from the Protein Data Bank ensured that the simulations were based on authentic representations of the proteins under investigation, enhancing the reliability of the study's findings.

The compounds chosen for the study were meticulously selected based on their chemical properties and potential therapeutic relevance. This approach aimed at exploring diverse chemical structures to gain a comprehensive understanding of the interactions between the compounds and the target proteins. The three compounds, 3b, 6a, and 6b, brought unique molecular features to the study, contributing to a more nuanced exploration of the binding modes and potential pharmacological implications.

Result and Analysis Section:

The culmination of the research effort is encapsulated in the Result and Analysis section, where the outcomes of the molecular docking analysis and subsequent simulations are scrutinized and scientifically interpreted. The primary focus revolves around the beta-lactam derivatives' interaction with three significant proteins—PBP2a, PBP2x, and SHV-1. The scientific interpretation of individual results provides valuable insights into the compounds' binding affinities and their impact on the stability of Penicillin binding proteins (PBPs).

The Gibbs free energy (delta G) emerges as a critical parameter in assessing the interaction strengths between beta-lactam derivatives and the target proteins. Figure 2 displays the delta G values for the various derivatives, with a conspicuous standout being compound 3b. The analysis reveals that compound 3b exhibited the most favorable results, signifying a robust binding affinity with PBP2a, PBP2x, and SHV-1 proteins. The lower delta G values indicate more stable interactions, suggesting the potential efficacy of compound 3b in inhibiting these crucial proteins.

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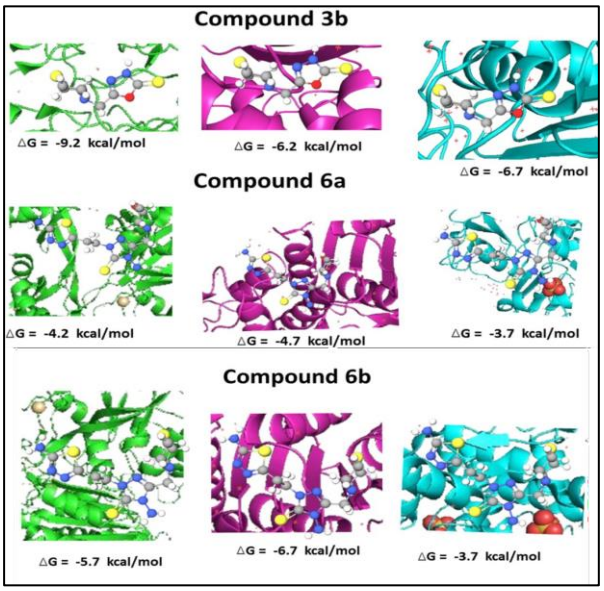

Figure 2: Molecular Docking Results

To delve deeper into the dynamics of the interaction, molecular simulations were extended specifically to compound 3b. This strategic decision was grounded in the exceptional binding affinity observed in the initial docking analysis. The trajectories exhibiting the best binding affinity were subjected to further scrutiny to unravel the intricate details of the binding process.

The Root Mean Square Deviation (RMSD) graph, presented in Figure 3, emerges as a pivotal tool for assessing the stability of the designed molecule (3b) concerning the three Penicillin binding proteins (PBPs). The RMSD values, indicative of structural deviations from the initial conformation, offer a nuanced understanding of the compound's stability over time during the simulation.

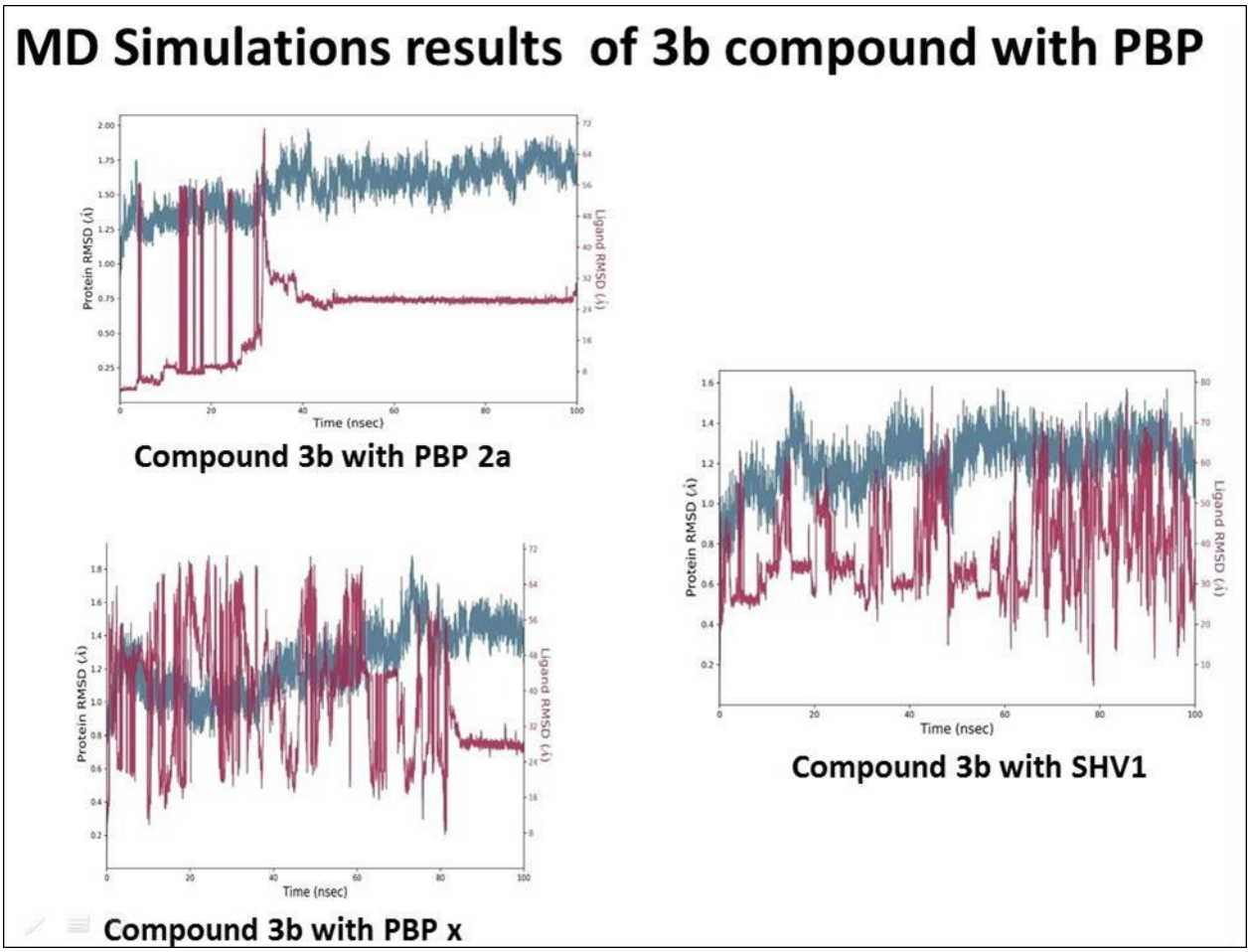

Figure 3: MD-Simulations Results

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The analysis of the RMSD graph illuminates a compelling narrative. It is evident that compound 3b showcases superior stability across all three PBPs—PBP2a, PBP2x, and SHV-1. The consistently lower RMSD values signify minimal structural deviation, indicating a robust and sustained binding interaction. This outcome aligns with the earlier observation of compound 3b's remarkable binding affinity, affirming its potential as a promising candidate for inhibiting the target proteins.

The scientific interpretation of individual results goes beyond the mere identification of the most potent compound; it delves into the molecular intricacies governing the interactions. The lower Gibbs free energy for compound 3b substantiates its efficacy by suggesting stronger and more stable binding with the target proteins. Furthermore, the RMSD analysis reinforces this finding by demonstrating the compound's ability to maintain structural integrity over the course of the simulation.

In a broader context, these results contribute substantively to the understanding of ligand-protein interactions, especially in the realm of antibacterial drug design. The efficacy of compound 3b in inhibiting crucial proteins involved in bacterial cell wall synthesis positions it as a potential lead compound for further drug development. The scientific interpretation provided here lays the groundwork for future studies, opening avenues for the refinement and optimization of compound 3b and its derivatives for enhanced therapeutic outcomes

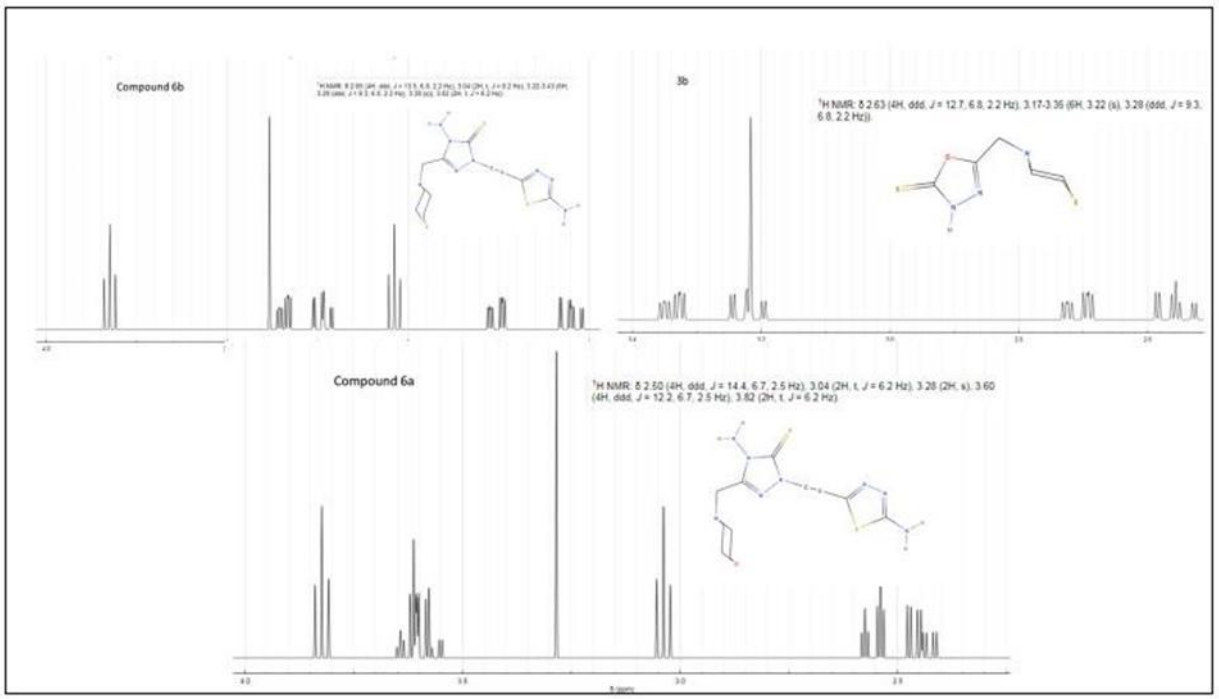

Figure 4: NMR Spectrum Results

Conclusion:

In drawing a comprehensive conclusion from this study, it is evident that the molecular docking analyses and subsequent simulations have provided valuable insights into the interactions between beta-lactam derivatives and key proteins—PBP2a, PBP2x, and SHV-1. Compound 3b has emerged as a standout candidate, displaying superior binding affinity and stability across all three Penicillin binding proteins. The Gibbs free energy and RMSD analyses collectively support the robust nature of compound 3b's interaction with the target proteins, positioning it as a promising lead for further exploration in antibacterial drug development.

The compelling results underscore the significance of computational approaches in elucidating molecular interactions, paving the way for rational drug design. The identification of compound 3b as a potent

inhibitor opens avenues for future investigations, emphasizing the potential impact of this research on advancing antibacterial therapeutics.

Limitation of the Study:

Despite the promising outcomes, it is crucial to acknowledge the limitations inherent in this study. The computational nature of the research, while powerful, relies on various assumptions and approximations. The molecular docking simulations, while informative, may not perfectly mirror the complex physiological conditions within a living organism. Additionally, the reliance on crystal structures from the Protein Data Bank introduces an element of static representation, overlooking potential conformational changes that might occur in a dynamic biological environment.

Moreover, the study focuses primarily on in silico analyses, and the absence of in vitro or in vivo validations necessitates cautious extrapolation of the findings to real-world applications. The limitations underscore the need for a holistic approach, integrating computational insights with experimental validations for a more robust understanding of the compounds' therapeutic potential.

Implication of the Study:

The implications of this study extend beyond the realm of beta-lactam derivatives and protein interactions. The identification of compound 3b as a potent inhibitor holds significant promise for antibacterial drug development. The study's findings provide a foundation for further exploration of compound 3b and its derivatives, potentially catalyzing the development of novel therapeutics for combating antibiotic-resistant bacterial strains.

Furthermore, the methodology employed in this research can serve as a template for similar studies targeting other biological processes or drug classes. The implications stretch into the broader field of computational biology, emphasizing the efficacy of molecular docking and simulation techniques in the rational design of pharmaceutical agents.

Future Recommendations:

To build upon the current study and address its limitations, several avenues for future research are recommended. First and foremost, experimental validation through in vitro assays and, eventually, in vivo studies should be prioritized. This would provide a more comprehensive understanding of the compounds' bioactivity, pharmacokinetics, and potential toxicity profiles.

Furthermore, exploring a broader range of derivatives and structural modifications of compound 3b could enhance the understanding of structure-activity relationships, facilitating the optimization of lead compounds. Incorporating dynamic simulations that consider protein flexibility and environmental factors could provide a more accurate representation of in vivo conditions.

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