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A REVIEW ON:MOLECULAR DOCKING OF ANTIBACTERIAL AGENT

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ABSTRACT:

The emergence of antibiotic-resistant bacterial strains poses a significant danger to public health worldwide, necessitating the exploration of novel strategies for the development of effective antibacterial agents. Molecular docking, a computational technique, has become an invaluable tool in the drug discovery process by facilitating the exploration of interactions between ligands and target proteins. This review provides a comprehensive analysis the how molecular docking is used in the design and optimization of antibacterial agents, focusing on key studies and advancements in the field.

KEYWORDS:

Antibacterial agents, molecular docking, drug discovery, antibiotic resistance, computational biology.

INTRODUCTION

A substance that either destroys bacteria (microbicide) or inhibits their growth (bacteriostatic agent) is called an antibiotic.[1] Antimicrobial drugs can be categorized based on the bacteria they mostly target. Antibiotics are applied treat bacteria, whereas antifungals are applied to treat fungi. Additionally, they can be categorized based on their purpose. Antimicrobial prophylaxis is the use of antimicrobial medications to avoid infection, and antimicrobial chemotherapy is the use of antimicrobial medications to treat infection.[2]

The primary categories of agents with antibacterial properties are antiseptics, which are applied to living tissue to lessen infection during surgery, disinfectants (non-selective agents, like bleach), which eliminate a variety of microorganisms on inanimate surfaces to stop the spread of disease, and antibiotics, which eradicate microorganisms.

Aim:

The aim of this project is to employ molecular docking techniques to investigate and optimize the interaction between selected antibacterial agents and specific target proteins associated with bacterial survival.

1.1 Antibiotic Resistance: A Growing Global Concern

The rise of antibiotic-resistant bacteria has become a critical issue in healthcare, leading to increased mortality rates and healthcare costs. Traditional antibiotic development approaches are often time-consuming and costly. Molecular docking, a computational method, offers an efficient and cost-effective alternative by predicting the binding affinity between potential drug candidates and their target proteins.

The "magic bullets" for combating bacteria, antibiotics are regarded as the greatest medical advancement of the 20th century. Antibiotics have revolutionized medicine and have prevented bacterial infections from killing millions of people. Antibiotics are unquestionably a blessing for humanity; in addition to their medical applications, they have been used for decades in many developing and impoverished nations for a variety of purposes, such as animal husbandry and animal production, as preventative measures [3]. Antimicrobial resistance has been created by bacteria due to their increasing use and misuse. Antimicrobial resistance is the capacity of microbes, including parasites, fungi, viruses, and bacteria, to survive and proliferate in the presence of medications meant to destroy them. Antimicrobial-resistant organism infections are not only hard to cure, but they also carry a constant risk of serious sickness and

possibly even death. Antibiotics, antifungals, antivirals, disinfectants, and food preservatives are a few examples of antimicrobial agents. These compounds either kill or inhibit the growth and multiplication of microorganisms. Compared to all other classes of antimicrobials, antibiotics are the ones that are most frequently utilized in the management of bacterial infections and antibiotic resistance.

concerning due to the "superbugs"—microorganisms that are not susceptible to the majority of known antimicrobials—spreading quickly around the world.

Even though antibiotics are crucial for treating bacterial infections, decades of improper use and abuse, along with the wrong dosage and length of time, have led to selection pressure and the emergence of resistant bacteria. AMR's emergence and spread, which have been largely attributed to the unscientific use of antibiotics in livestock feed in many developing nations, have contributed to the problem in addition to the state of human healthcare. Reducing the prevalence of drug-resistant bacteria in animal feed requires closer monitoring of the effects of overuse and uncontrolled use of antibiotics [4]. The effects of antibiotic resistance on human health can be both therapeutic and preventive.

OBJECTIVES:

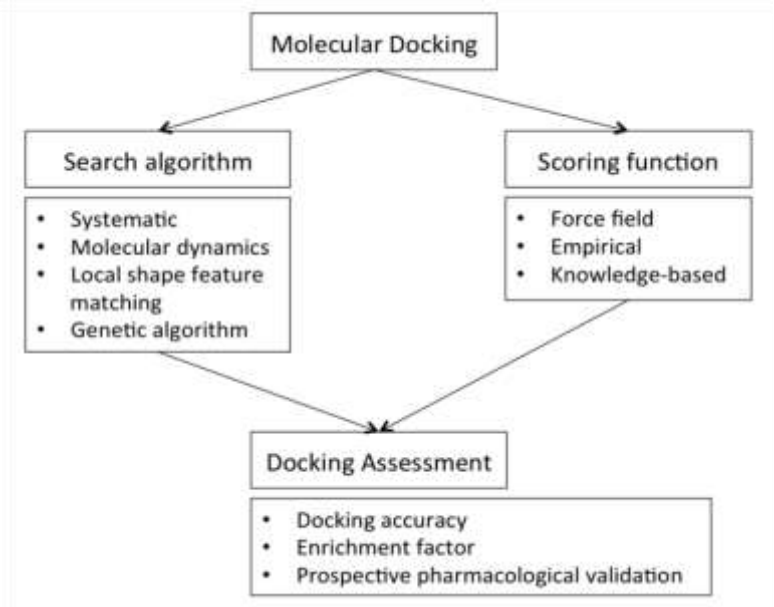
1.Identify potential anti-bacterial agents through virtual screening.

2.Understand the binding modes and interactions between selected anti-bacterial agents and target proteins.

3.Evaluate the binding affinities of the identified compounds.

4.The primary objective of this project is to employ molecular docking techniques to investigate and elucidate the interactions between a set of potential anti-bacterial agents and specific target proteins crucial for bacterial survival. Through a comprehensive computational analysis.

Basics Of Molecular Docking:



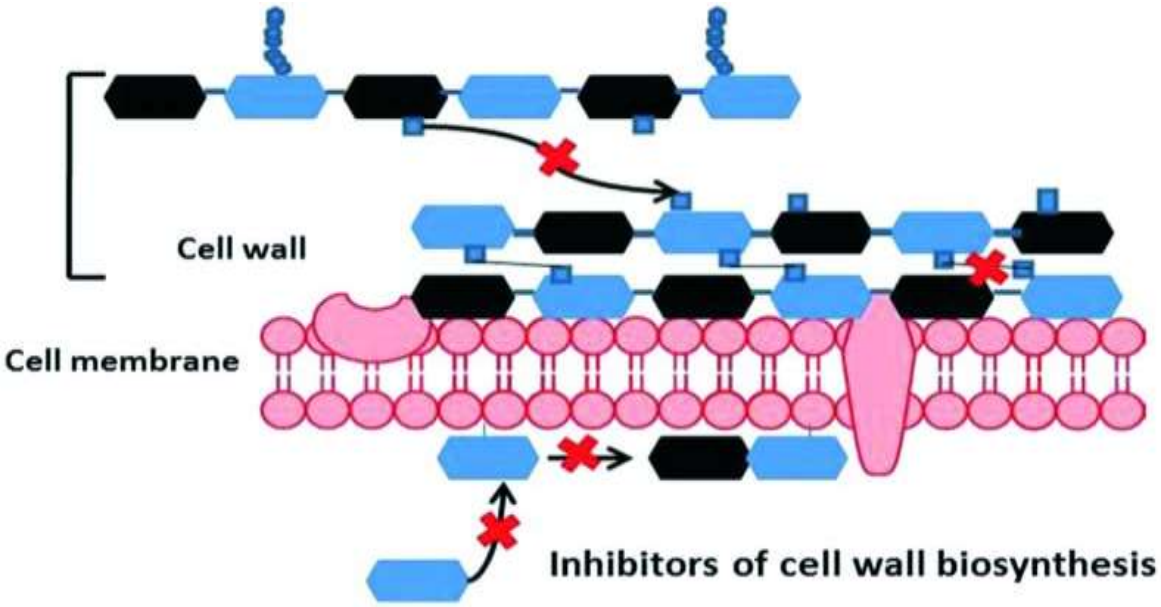
2.1 Principles of Molecular Docking

Docking of molecules involves the forecast for the preferred orientation of a ligand molecule bound to a traget protein, providing insights into the binding affinity and potential biological activity of the ligand. The principles of molecular docking, including scoring funtions and conformtional sampling, are crucial for understanding the accuracy and reliability results.

3.1 Inhibitors of Bacterial Cell Wall Synthesis

The molecular docking studies targeting enzymes involoved within the cell wall of bacteria synthesis, such as penicillin-binding proteins .The inhibition of bacteria's cell wall synthesis is a common and successful strategy for treating a broad range of bacterial

infection. The major inhibitors of cell wall synthesis currently in use are beta-lactams (eg penicillin and cephalosporins), which blocks the formation of the peptidoglycan layer, and glycopeptides which disrupt assembly of the peptidoglycan precursor lipid ll.



Because the wall of the cell is absent from mammalian cells, it presents a viable target for drug development. It's been proven that a number of Bacillus strains target this structure by secreting enzymes (including protease, glucanase, chitinase, amylase, and cellulase) and antimicrobial metabolites.

Antibacterial agents employ various mechanisms to combat bacterial infections, often targeting specific cellular processes or structures essential for bacterial survival. The working mechanics can be broadly categorized into several key strategies:

1.Inhibition of Cell Wall Synthesis:

Antibacterial agents, such as beta-lactam antibiotics (e.g., penicillins and cephalosporins), interfere with the synthesis of bacterial cell walls. They target enzymes like transpeptidases, which are crucial for cross-linking peptidoglycan chains, leading to weakened cell walls and bacterial lysis.

2.Disruption of Cell Membrane Integrity:

Certain antibacterial agents, like polymyxins, disrupt bacterial cell membranes. Polymyxins interact with lipopolysaccharides in Gram-negative bacteria, causing destabilization and permeabilization of the outer membrane, leading to cell death.

3.Inhibition of Protein Synthesis:

Antibiotics such as aminoglycosides (e.g., gentamicin) and tetracyclines interfere with bacterial protein synthesis. Aminoglycosides bind to the bacterial ribosome, causing misreading of mRNA and inhibition of protein synthesis. Tetracyclines inhibit protein production by attachment to the bacterial 30S ribosomal subunit.

4. Interference with Nucleic Acid Synthesis:

Antibacterial agents like fluoroquinolones (e.g., ciprofloxacin) inhibit DNA gyrase or topoisomerase IV, enzymes crucial for bacterial DNA replication and repair. This interference leads to the accumulation of DNA breaks and ultimately bacterial cell death.

5.Disruption of Metabolic Pathways:

Sulfonamides and trimethoprim are antibacterial agents that interfere with bacterial metabolism by inhibiting enzymes involved in the synthesis of essential metabolites. Sulfonamides act as analogs of para-aminobenzoic acid's structure (PABA), a precursor in folic acid synthesis, while trimethoprim inhibits dihydrofolate reductase.

6. Inhibition of RNA Synthesis:

Rifampicin is an antibacterial agent that targets bacterial RNA polymerase, inhibiting RNA synthesis. This disruption leads to a halt in the production of RNA and subsequently protein synthesis, ultimately affecting bacterial viability.

7.Antimetabolite Action:

Antibacterial agents like fosfomycin act as analogs of essential metabolites. Fosfomycin resembles phosphoenolpyruvate, a substrate within the cell wall of bacteria synthesis, and inhibits an enzyme involved in the initial phases of peptidoglycan formation.

8.Targeting Specific Bacterial Components:

Some antibacterial agents specifically target bacterial components without affecting mammalian cells. For instance, daptomycin disrupts bacterial membrane function by binding to bacterial cell membranes and forming pores, leading to membrane depolarization and cell death.

MOLECULAR DOCKING

The procedure of molecular docking entails predicting the preferred orientation and conformation of a ligand (the antibacterial agent) when bound to a target receptor, typically a biomolecule associated with the bacterial pathogen. The objective is to elucidate the molecular mechanisms governing the interaction, allowing researchers to identify compounds with the highest therapeutic potential. As we delve into the realm of molecular docking for antibacterial agents, it becomes imperative to explore the different types of molecular docking techniques employed in this endeavor, each tailored to address specific challenges and nuances associated with antibacterial drug discovery.
Molecularly-based docking is a versatile computational technique that encompasses various methods to simulate and predict the binding interactions between a ligand (such as an antibacterial agent) and a target receptor. The choice of docking method depends on factors like the nature of the ligand, the receptor, and the specific research objectives. Here are some common types of molecular docking methods:

1.Rigid Docking:

In rigid docking, both the ligand and the receptor are considered as rigid entities during the simulation.

This method is computationally less intensive and suitable when there is minimal structural flexibility in the binding site.

2.Ligand-Based Docking:

Ligand-based docking methods rely on information derived from the ligand's structure, such as its shape, electrostatic properties, and molecular descriptors.

These methods are useful when the receptor structure is not available or is challenging to model accurately.

3.Receptor-Based Docking:

Receptor-based docking involves utilizing information from the target receptor's structure to predict the binding mode of the ligand.

This approach is beneficial when the receptor structure is well-characterized through experimental methods like X-ray crystallography or NMR spectroscopy.

4.Virtual Screening:

Virtual screening involves the quick screening of a big compound libraries to identify potential ligands that could interact with a target of interest.

It is particularly useful in high-throughput drug discovery campaigns.

5.Molecular Dynamics (MD) Simulation:

Molecular dynamics simulations go beyond docking and involve the simulation of molecular motions over time.

MD simulations provide insights into dynamic behavior, including ligand-induced conformational changes and fluctuations in the binding site.

6. Molecular and Quantum Mechanics (QM/MM) Docking:

QM/MM docking combines quantum mechanics for accurate treatment of the active site with molecular mechanics for the rest of the system.

This method is suitable for studying reactions and interactions involving bond formation and breaking.

7.Homology Docking:

Homology docking involves utilizing homology models of the target receptor when an experimentally determined structure is unavailable.

It is a valuable approach when working with targets closely related to those with known structures.

8. Flexible Docking:

Unlike rigid docking, flexible docking considers flexibility in either the ligand, the receptor, or both.

This accounts for conformational changes that may occur upon binding and provides a more accurate representation of the binding process.

QSAR

A computational tool called the Quantitative Structure-Activity Relationship (QSAR) modelling approach used in medicinal chemistry and drug design to establish a quantitative relationship between the chemical structure of a compound and its biological or pharmacological activity. The underlying idea of QSAR is that variations in molecular structures lead to variations in biological activities. By analyzing these structure-activity relationships, researchers aim to forecast the course of new, untested compounds and guide the design of molecules with desired properties.

Key Components and Steps in QSAR:

1.Molecular Descriptors:

QSAR relies on the calculation of molecular descriptors, which are numerical representations of chemical and physical properties of molecules. Descriptors include parameters like molecular weight, lipophilicity, polarizability, and more.

2.Biological Activity Data:

Experimental data on the biological or pharmacological activity of a set of compounds is essential. This activity could be measured as binding affinity, inhibition, potency, or any other relevant metric depending on the specific context.

3.Data Preprocessing:

The dataset is divided into a training set used to build the QSAR model and a testing set to evaluate its predictive performance. Data preprocessing may involve handling missing values, normalizing descriptors, and addressing outliers.

4.Model Building:

Statistical and machine learning techniques are applied to build a mathematical model that relates the molecular descriptors to the biological activity. Common methods include multiple linear regression, partial least squares (PLS), support vector machines, and quantitative neural networks.

5.Validation:

The QSAR model is validated to ensure its reliability and predictive power. Cross-validation techniques, such as leave-one-out or k-fold cross-validation, are often used to assess the model's performance.

6.Model Interpretation:

Interpretation of the model involves analyzing the coefficients of descriptors to identify which molecular features are correlated with the observed biological activity. This information can guide the design of new compounds with enhanced activity.

7.Model Validation with External Data:

The QSAR model is further tested using external datasets that were not part of the model-building process. This helps assess the model's generalizability to new compounds.

8.Applicability Domain:

Establishing the applicability domain of the QSAR model defines the chemical space within which the model is considered valid. This ensures that predictions are reliable only for compounds with structures similar to those in the training set.

9.Prediction of New Compounds:

Once validated, the QSAR model may be employed to forecast the behavior of new, untested compounds. This is valuable for prioritizing compounds for synthesis and experimental testing.

10.Model Optimization and Refinement:

If necessary, the QSAR model can be optimized and refined by adjusting parameters, incorporating additional descriptors, or updating the model with new data.

QSAR has proven to be a valuable tool in drug discovery and design, facilitating the identification of lead compounds, optimization of molecular structures, and the prediction of biological activities. It enables researchers to make informed decisions in the initial phases of medication development, saving time and resources.

Molecular Docking & Interaction Analysis:

Understanding the protein-ligand bonded structure and providing an explanation of the molecular mechanism underlying small drug-like entities.

The most common process in cellular pathways is molecular docking. pertinent methodology [5]. 17 compounds were found for molecular docking by an ESI-LCMS, and a three-dimensional (3D) PDB format structure of the FabA protein (PBD ID: 4B0C) was brought into the molecular docking program, MOE. examination [6]. Three-dimensional protonation, heteroatoms, and the protein structure's water molecules were eliminated. in order to get it ready for both the default and the docking approach ligand affixed to the protein

of interest. According to earlier research [7], the chosen protein (4B0C) has an active site that is determined, and structural optimization is executed through the utilization of the following variables: energy.

Molecular docking:

Two portions can be distinguished in molecular docking.
Search algorithm:

The formula ought to create an optimum number of combinations that allow for the discovery of binding mechanisms through experimentation. The following are various algorithms applied for docking analysis such as Point complementary, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry etc.

Scoring Function:

The score function provides a way to rank ligand positions in relation to one another. The score should ideally match up exactly with the binding to the binding affinity of the ligand for the protein, so that the best scoring ligands are the best binders. Scoring functions can be empirical, knowledge based, or molecular mechanics based. Scoring is actually compiled for three different expression relevant to medication design and docking:

(1) Rank order of generated configurations using docking search.
(2) Ranking different ligands against protein (virtual screening).
(3) One or more ligands ranking against different proteins by their binding affinity (selectivity and specificity).

Address issues such as ligand flexibility, protein flexibility, and the accuracy of scoring functions -

Proteins are the most significant and well-liked targets in drug discovery. Drug molecules interact to proteins and can cause disruptions in their functioning. This covers potential signal transduction processes, enzymatic actions, macromolecular aggregation, and potentially the start of cellular apoptosis. Computer-aided techniques have grown in significance in recent years for medication creation as well as the assessment and forecasting of molecular docking outcomes. Recent

advancements in the prediction of tiny organic drug-like compounds that target biomolecules of pharmacological relevance, including proteins, are the main topic of
the paper. Particular attention is paid to how to effectively include protein flexibility. An understanding of the target protein's three-dimensional structure is a necessary precondition for computational docking. In actuality, the protein data library contains about 60,000 structures.

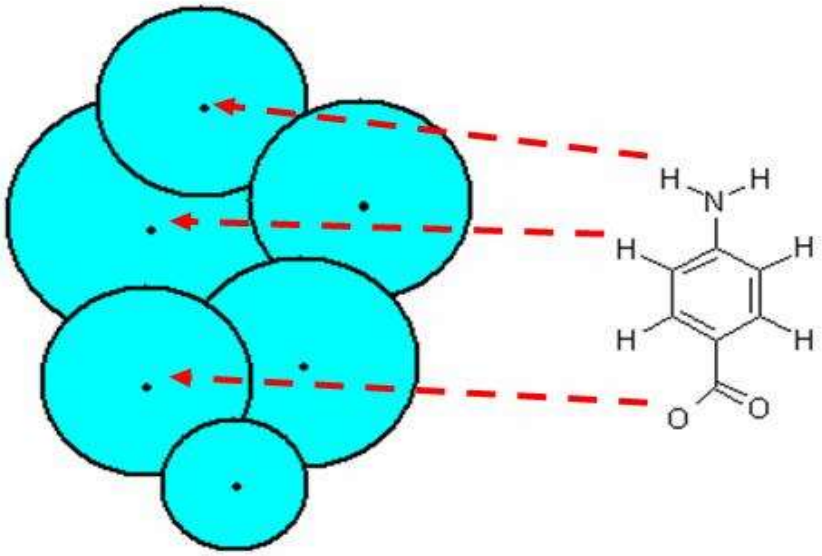
Docking and Scoring-

Putative binding locations for a set of suggested ligands on a receptor molecule are predicted using computational docking techniques. The target molecule's binding location is frequently known to some degree. However, a number of methods, such as active sites or cofactor binding pockets, have been created to offer techniques to pinpoint possible drug binding sites and reviewed in[8]. The majority of these techniques anticipate binding locations by using particular surface descriptors, such as the protein's curvature and hydrophobicity [9]. Recently, Seco et al. reported an intriguing method based on MD simulation in which a 20% (v/v) isopropyl alcohol-water combination surrounds the protein. Isopropyl alcohol's preferred resident sites at the protein surface are revealed by the MD trajectory [10]. These locations may also serve as "hot spots" for the binding of medications or other less polar biomolecules.

Various types of Docking:

The main docking methods that are used are as follows:

Look and Key\Rigid Docking The ligand and receptor are kept stationary & docking is executed Induced fit\Flexible Docking-In induced fit docking both the ligand and the receptor are conformationally flexible. The surface cell occupancy and energy are calculated with each rotation, and the most optimal position is then chosen.



Important actions done in mechanisms of molecular docking:

The procedure known as "molecular docking" is where the intermolecular interaction between 2 molecules was study in In-silica. In this process; the Macromolecule is the protein receptor. The micro molecules is the Ligand molecules which can be acted as an inhibitor.so, the Docking process involves the following steps:

Step 1 -Preparation of protein:

The three-dimensional configuration of the protein should be retrieved from data bank (PDB); afterward the retrieved structure should be pre-processed. This should admit removal of the water molecules from the cavity, stabilizing the charge, filling the missing residues, generation the side chains etc. according to the parameters available.

Step 2-Active site prediction:

After the preparation of protein, the operational website of protein should be predicted. The receptor might possess lots of active sites merely the one of the concern should be picked out. The majority of the heteroatoms and water molecules are eliminated if present.

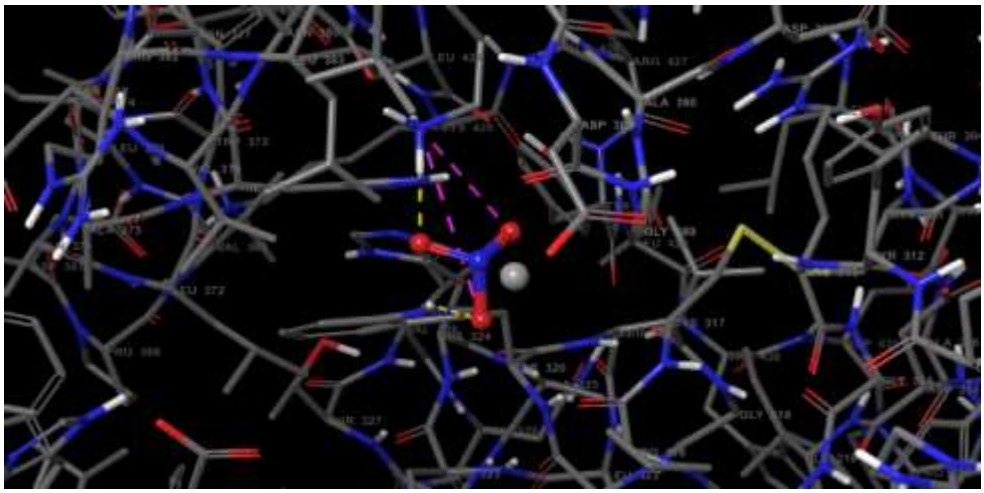
Step 3-Preparation of ligand:

Ligands can be obtained from several databases, including ZINC and Pub Chem, or they can be drawn using the Chem Sketch tool. While picking out the ligands the LIPINSKY' You should apply the RULE of 5. The Lipinski Rule of Five helps distinguish between candidates who are drug-like and those who are not. It offers a high probability of success or failure because the molecules it resembles are similar to drugs & 2 or more than of the complying rules. For selecting a ligand that permits the LIPINSKY'S RULE to:

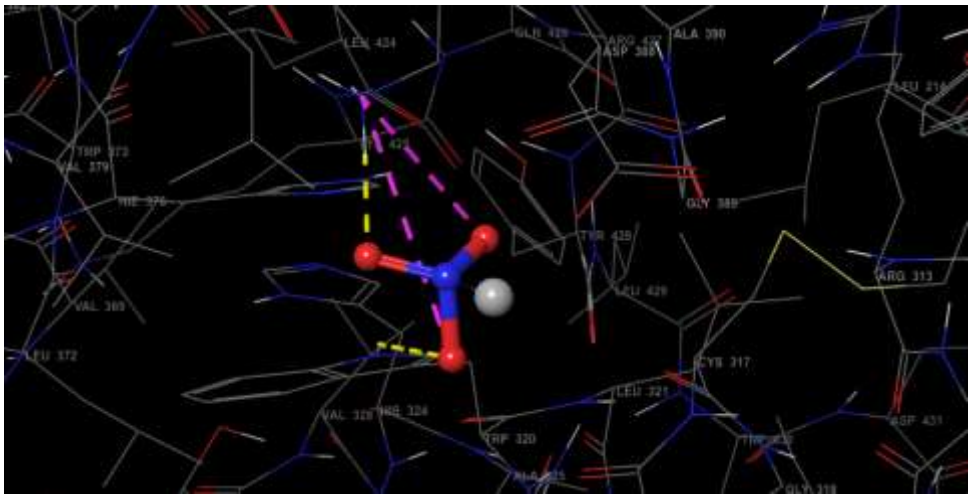
(1) Less than five donors of hydrogen bonds
(2) Fewer than 10 acceptors of hydrogen bonds
(3) Molecular mass less than 500 Da
(4) Molar-refractivity should be between 40-130

Step 4–Molecular Docking Study:

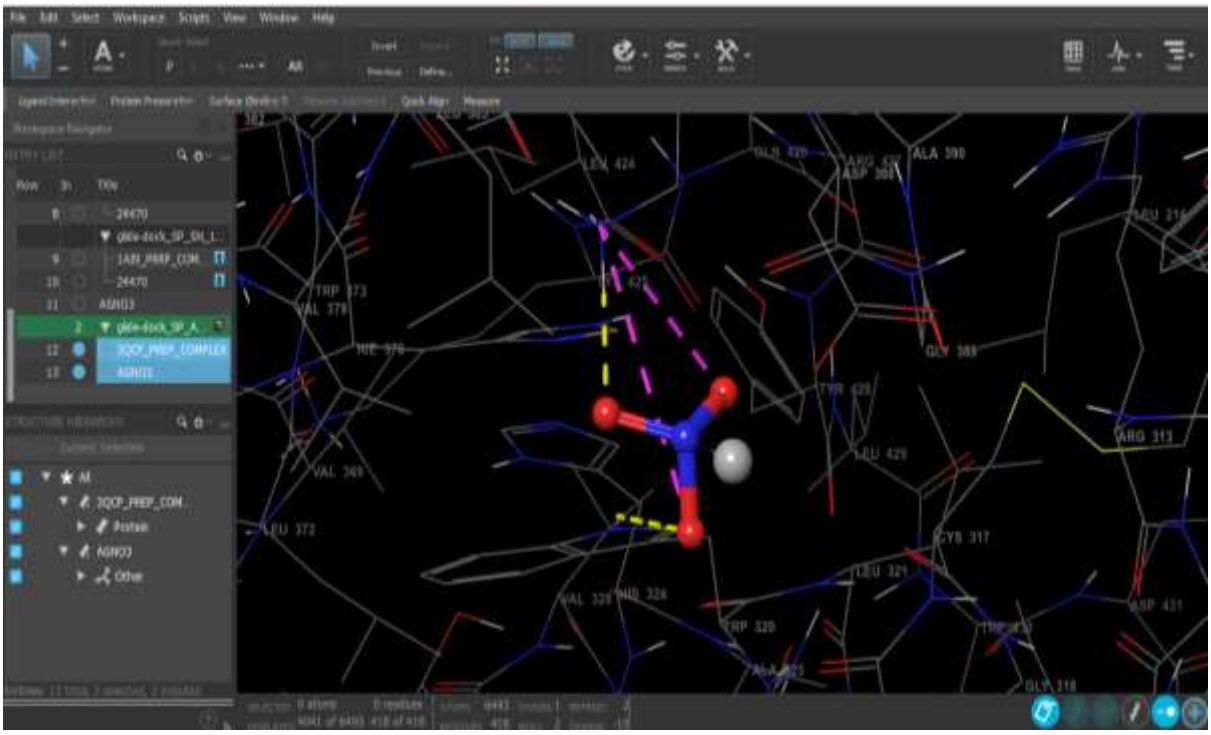
Fosfomycin



Binding of ligand and amino acid residue present on receptor I.



Binding of ligand and amino acid residue present on receptor II.



Docking study of silver nitrate using Schrodinger docking software.

After the docking study, the results were obtained for different protein interactions, and from the below score it was confirmed that protein binding was very strong between ligand AgNO3 and bacterial receptor protein 3QCP.

Dock protein and their score.

Dock protein	Dock score
5BNR	-4.351
1AI9	-6.055
3QCP	-6.487

Bacterial strains:

The bacterial strains used in the present study were,

1. E. coli

2.Staphylococcus aureus

3. Pseudomonas

USES:

Treat urinary tract infection.

Application of molecular docking:

Molecular docking interactions may lead in activation or inhibition of the protein. Whereas ligand binding may lead in agonism or antagonism. Perhaps using molecular docking to:

- Hit Recognition (Online Screening)
- Optimization of Leads in Drug Discovery
- Bioremediation
- Prediction of K (Biological activity)
- De-orphaning
- Binding site prediction (blind docking)
- Protein-Protein /Nucleic acid interactions
- Searching for lead structure for protein targets
- Studies of Structure- function
- Mechanisms of Enzymatic reactions
- Protein engineering

New algorithms from industry and academia are quickly incorporated in to the high-end packages. Public domain packages are becoming more stable and offering functionality that rivals some of the commercial offering computers continue to double in speed every year and half while graphic displays became more sophisticated and intuitive. All of this Molecular docking plays a crucial role in drug design due to certain factors [11]. It keeps playing a bigger part in innovative new methods like proteomic search engines, genomics, and computational enzymology.

Challenges in Molecular Docking for Antibacterial Agents:

Discuss the limitation & challenges associated with molecular docking context of antibacterial agent development. Address issues such as ligand flexibility, protein flexibility & the accuracy of scoring function.

CONCLUSION:

The docking project aimed at identifying potential antibacterial agents against antibiotic-resistant bacteria has provided valuable insights into the realm of combating antimicrobial resistance. Through computational docking simulations, we explored the interactions between selected compounds and target bacterial proteins, gaining a deeper understanding of their potential efficacy.

The results indicate promising candidates that exhibit strong binding affinity and interactions with key bacterial targets associated with resistance mechanisms. These results open the door for further experimental validation and optimization of the identified compounds, potentially leading to the development of novel antibacterial agents.

Addressing antibiotic resistance is crucial for global public health, and this docking project contributes to the ongoing efforts to discover new therapeutic strategies. While the

computational predictions offer a starting point, rigorous experimental studies, including in vitro and in vivo assays, are essential to validate the efficacy and safety of the identified compounds.

In the broader context, the success of this docking project highlights the significance of interdisciplinary approaches, combining computational biology with experimental research, to accelerate the drug discovery process. As we confront the challenges posed by antibiotic-resistant bacteria, ongoing collaboration and innovation are essential to bring effective treatments to fruition and ensure a sustainable future for healthcare.

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