Research Article

Virtual Screening of Compounds with Potential Anti-Asthmatic and Anti-Tuberculosis Activity Using CADD

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ABSTRACT

Asthma is a respiratory syndrome with wheezing, Shortness of breath, chest tightness, and cough, together with variable expiratory airflow limitation with symptoms that vary in severity and intensity. Whereas Tuberculosis (TB) mainly caused by Mycobacterium tuberculosis is a multisystemic disease causing the increasing global amount of morbidity and mortality. This research discusses about the Insilico studies of antiasthma and antituberculosis by using CADD techniques. Compounds were identified by using two different receptors namely 1IJZ and 3IG0. The 1IJZ was used for an Antiasthmatic drug whereas 3IG0 was used for tuberculosis drug. The ligand was selected based on Pass prediction, acute toxicity studies, Swiss ADME, and Docking studies for asthma and tuberculosis drugs. The selection of protein and Ligand preparation was taken based on the research studies. The experiment was performed using docking software such as Argus Lab and viewed by Discovery Studio viewer. 12 compounds with anti-asthmatic and 18 compounds with anti-tuberculosic were chosen and predicted for toxicity and physicochemical properties and the results were tabulated. Docking simulation between the protein 1IJZ and 3IG0 were done and the chosen 30 compounds were optimized to achieve the best fit for the ligand in the active site of the target. Docking score between -15 and -10 showed the highest binding energy. Zafirlukast showed the highest binding energy of -13.5127 kcal/mol for Interleukin-13 receptor of Asthma and Bedaquiline showed highest binding energy of -15.0097 kcal/mol for DNA gyrase subunit B receptor for Tuberculosis. Based on the docking scores, it is evident that these compounds have the potential to combat the aforementioned diseases. In future, the compounds with the strongest binding affinity can be selected for further research, including in vitro and in vivo studies against Asthma and Tuberculosis.

Keywords: Asthma, Tuberculosis, 1IJZ, 3IG0, Pass prediction, Acute toxicity, SwissADME, Docking.

INTRODUCTION

Asthma is a heterogeneous chronic airborne inflammatory disease. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable expiratory airflow limitation. Physical activity often provokes asthma-related symptoms reflecting the nature or insufficient control of asthma. This is complex, as disease severity is assessed indirectly and disease manifestations are partly dependent on individual behaviour. Asthma is the third most common reason for consultations in general people with general practitioners. It is a comorbid psychiatric disorder and has been reported to have poorer asthma control and higher healthcare utilization.

Asthma is one of the most common chronic conditions for both childhood and adolescence (WHO 2015), affecting about 10% of adolescents in Germany and a major public health problem in the overall world. Over the past several decades, the prevalence of asthma has increased substantially in several countries due to the western lifestyle [1]. Tuberculosis infection is said to be positive, if QuantiFERON-TB Gold In-Tube test (Interferon-γ- response is ≥ 0·35 IU/mL after subtracting the nil value), ELISpot test (>8 spot-forming cells (SFCs) per well), or tuberculin skin test (TST; ≥10 mm induration). Preventive therapy may be assigned to participants according to each study protocol or local guidelines and practices[2] and it is caused by Mycobacterium tuberculosis[3]. Tuberculosis remain as a leading infectious case of global childhood morbidity to mortality[4]. The present study aims to investigate antiasthma and antituberculosis effect by using CADD techniques.

MATERIALS AND METHOD

Software and Hardware

The computer system with AMD Ryzen 5 5600H CPU processor having 8GB RAM and 512 GB SSD and Geforce GTX 1650 graphics card with Windows 11 as the operating system was used. All the computational studies were carried out in various software such as Argus Lab, ChemDraw Ultra version 12.0, and Discovery studio Visualiser v21.1.0. Online tools like PASS, SwissADME, GUSAR, and Chemical Databases such as Protein Data Bank were used (Open Sources).

Target Selection:

In our current study, Target identification was also studied through network-based drug discovery, a field integrating different levels of information in drug-protein and protein-disease networks. This approach involves a highly collaborative scheme between databases and correlations across genomics, transcriptomics, proteomics, metabolomics, microbiome, pharmacogenomics, which

highly depends on the development of relevant computational and systems biology tools for such data interpretation.[5] The three-dimensional (3D) crystal structure of INTERLEUKIN-13 (PDB ID: 1IJZ) and DNA gyrase subunit B (PDB ID: 3IG0) was obtained from the Protein Data Bank (www.rcsb.org/pdb) in PDB format (Fig.1).

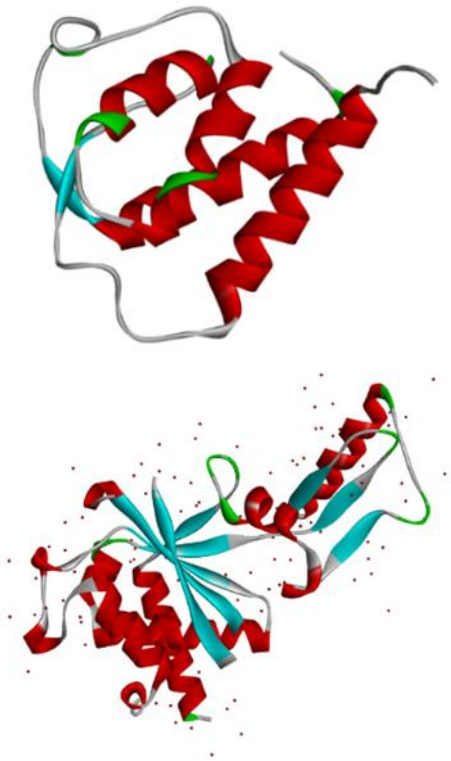


Figure 1: Protein structure Retrieved from PDB with PDB ID: 1IJZ and 3IG0 (www.rcsb.org/pdb)

Pass Prediction:

The PASS computer program allows to estimate the probable profile of biological activity of a drug-like organic compound (whose molecular mass ranges from 50 to 1250 Da) based on its structural formula. The estimation is based on an analysis of the structure-activity relationships for a broad training set entailing drug substances, drug-candidates in various stages of clinical and preclinical investigation, pharmaceutical agents and chemical probes, and compounds, for which specific toxicity information is known[6]. The PASS algorithm was based on the concept of the "biological activity spectrum", which is an intrinsic property of a compound. It reflects all its different biological activities that arise from interactions with biological entities[7]. The categorical description of biological activity as "active" or "inactive" is used in the PASS program.

The PASS user obtains output information with a list of predicted types of activity with the estimated probability for each type of activity "to be active" Pa and "to be inactive" Pi, which vary from zero to one. The probabilities Pa and Pi also indicate the estimated probabilities of first- and second-kind errors, respectively. If we limit ourselves only to activity types predicted with the highest values of Pa, the compounds selected by the prediction may prove to be analogues of known pharmacological agents. For example, when Pa > 0.7, the chances of finding experimental activity are rather high but the compounds found may be close structural analogues of known drugs. If we select in the range 0.5 < Pa < 0.7, the chances for detecting experimental activity will be lower but the compounds will be less similar to known pharmaceutical agents. For Pi < Pa < 0.5, the chances of detecting experimental activity will be even lower but if the prediction is confirmed, the compound found may prove a parent compound for a new chemical class for the biological activity examined.[6]

Acute toxicity studies:

Acute toxicity is considered as the adverse effects occurring within a given time, following a single exposure to a substance. LD_{50} value is one of the important characteristics of acute toxicity that corresponds to the dose causing 50% mortality within 24 hours of administration. The accuracy and predictability of the novel QSAR approach for consensus prediction of rat acute toxicity in comparison with other methods were analysed. Utilization of PASS-predicted biological activity profiles as the basis for QSAR modelling provides the possibility for biological interpretation of the models, which corresponds to the OECD recommendations for QSAR models.

GUSAR- General Unrestricted Structure Activity Relationship

GUSAR is a web-based software that uses a machine learning approach to predict the environmental toxicity of chemicals. GUSAR uses self-consistent regression for model building[8] and it is based on the regularized least-squares method.. It uses a combination of quantitative structure-activity relationship (QSAR) models and genetic algorithms to analyse the chemical structures of the compounds and predict their toxicity.

In-Silico Evaluation of Physiochemical Properties

Drug Likeness

Drug-likeness is a concept used in drug discovery to assess the likelihood that a given molecule will have the pharmacological properties necessary to become a successful drug. It involves a complex evaluation of a variety of factors related to the molecule's structure, properties, and behaviour, such as molecular weight, lipophilicity, solubility, chemical stability, and the presence of specific functional groups. The goal of assessing drug-likeness is to identify molecules that are most likely to be effective as drugs while minimizing the risk of toxicity or other undesirable effects.

Lipinski's Rule

The 'Rule-of-five' (also known as 'Lipinski's rule') for 'drug-likeness'.[9] A new approach to compound assessment and filtering was described based on known bioavailable small molecules, and a mnemonic was developed (Lipinski et al., 1997) and refined (Lipinski, 2000a) that would strongly influence medicinal chemistry for the subsequent decade.[10]

The original RO5 deals with orally active compounds and defines four simple physicochemical parameter ranges (MWT ≤ 500, log P ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have achieved phase II clinical status.[11] It has raised the awareness of the importance of ADME (absorption, distribution, metabolism, and elimination) and physio-chemical properties for the success of drug discovery among medicinal chemists, and helped to front-load ADME (and later ADME/toxicity) screening in the industrial drug discovery process.[9]

SwissADME

The physicochemical properties and drug-likeness of the designed set of compounds were predicted using the online tool SwissADME in order to determine their design and therapeutic activity. The properties were evaluated based on the Lipinski's rule, in order to predict whether the compounds comply with the criteria of drug-likeness. The molecular properties such as molecular weight, partition coefficient, number of hydrogen bond donors, number of hydrogen bond acceptors and polar surface area were calculated[12].

Molecular Docking

Molecular docking is a kind of computational modelling, which facilitates the prediction of the preferred binding orientation of one molecule (eg. ligand) to another (eg. Receptor), when both interact with each other in order to form a stable complex. The capability of different docking methods is evaluated using docking-based virtual screening protocols to prioritize known active candidates out of several inactive molecules from a database. Ligand and target molecules are separated by some physical distance and then, ligand is allowed to bind into groove/pocket of target molecule after a "definite time of moves" in its conformational space. Comprehensively utilized docking tools employ search algorithms such as genetic algorithm, fragment-based algorithms, Monte Carlo algorithms and molecular dynamic algorithms. Besides this, there are some tools such as DOCK, GOLD, FlexX and ICM, which are mainly used for high throughput docking simulations[13].

There are various kinds of molecular docking procedures involving either ligand/target flexible or rigid based upon the objectives of docking simulations[31]. Rigid body docking produces a large number of docked conformations with favourable surface complementarity, followed by the re-ranking of the conformations using the free energy of approximation. In flexible docking, ligands are freely docked into a rigid receptor. However, it has become increasingly clear that side chain flexibility plays a crucial role in ligand-protein complexes. These changes allow the receptor to alter its binding site according to the orientation of the ligand[14]. In this study, we have used Argus Lab 4.0.1 software to predict the docking score.

I. Protein Preparation

The protein preparation wizard in maestro was used to process the PDB structure of the proteins with PDB IDs 1IJZ and 3IG0. Several typical operations were performed, including:

- Hydrogen atoms were added to the protein structure to ensure that all atoms have appropriate valence and to optimize the hydrogen bonding network.
- Heteroatoms, water molecules, and any unwanted chains or residues were removed from the protein structure to simplify the model and remove unnecessary components.
- Protons were added to the protein structure to optimize the protonation states of amino acid residues, including the titratable side chains, in order to accurately represent the physiological pH conditions of the system.
- Protonation states of amino acid residues were optimized to ensure that the most stable and physiologically relevant protonation states are represented in the model.

Additionally, during the pre-processing step, bond orders were assigned to ensure correct representation of covalent bonds in the protein structure, and the hydrogen bonding network in the protein was optimized and minimized to optimize the stability and conformation of the protein structure.

Overall, these steps in the Protein Preparation Wizard helped to refine and optimize the PDB structures of the proteins for further modelling tasks, resolving common structural issues and ensuring that the protein structure is suitable for accurate simulations or other computational analyses[15,16].

II. Ligand Preparation

The structures from ChemDraw Ultra 12.0 into the LigPrep window and prepared the ligands for further analysis. Since there is no need to change the ionization state, desalt, or generate tautomers in this case, you were able to quickly complete the ligand preparation step in less than a minute, resulting in a file with a. maegz extension. It also generates possible tautomers and different protonation states to minimize the structures for further analysis[17].

III. Docking

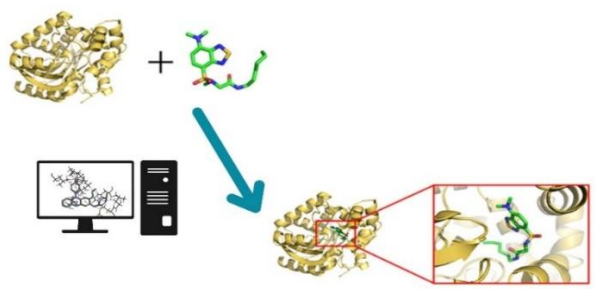


Figure 2: Docking

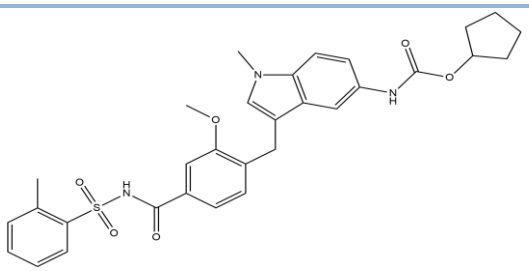
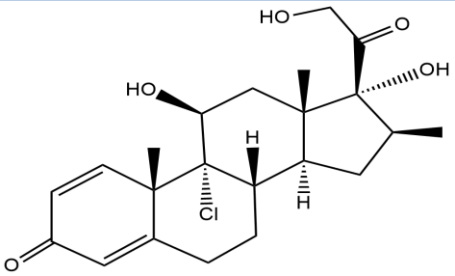
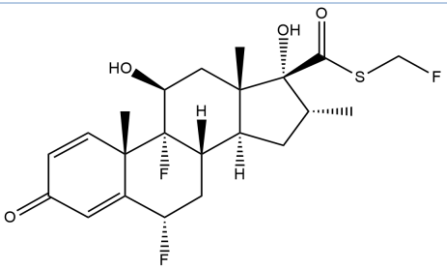
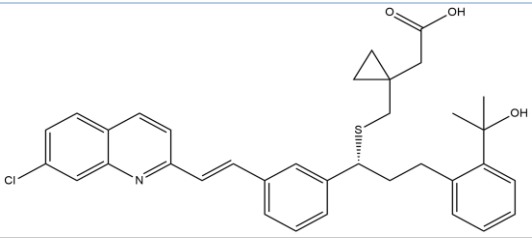
IV. Evaluation of Docking Reports

Using the pose viewer function of Biovia, we were able to obtain 3D interactions of our project results, which were then incorporated into the project table. Afterward, the selected receptor and one of the poses from the project table were visualized in 2D ligand interaction diagrams. This would allow analysing the interactions between the ligand and the receptor in both 3D and 2D representations, providing valuable insights into the molecular interactions and potential binding modes of the ligand with the receptor. This visual representation can aid in understanding the structural details of the ligand-receptor complex and help in further refining and optimizing the ligand design for drug discovery or other applications.

RESULTS AND DISCUSSION

In the present study, the synthetic drugs were evaluated through in silico analysis. Initially the structure of these compounds and their sources were tabulated and screened for their biological activity. 12 compounds with anti-asthmatic and 18 compounds with anti-tuberculosis activity were chosen and predicted for toxicity and physicochemical properties and the results are tabulated in table 1-7. Finally, docking simulation between the protein 1IJZ and 3IG0, the chosen 30 compounds were done to optimize the best fit for the ligand in the active site of the target and the results are shown in Table 8 and 9. From the final results, it was observed that a docking score between -15 and -10 showed the highest binding energy. With that being the case, Zafirlukast showed the highest binding energy of -13.5127 kcal/mol with Interleukin-13 receptor for asthma and Bedaquiline showed highest binding energy of -15.0097 kcal/mol with DNA gyrase subunit B receptor for Tuberculosis. The best 8 compounds were chosen based on the docking score and were visualized. The 2D ligand interactions, 3D docking poses and hydrogen bond interactions of chosen compounds were shown in Figure 3,4,5,6,7,8,9 and 10.

Table 1: Compounds Showing Best Activity

S.NO.	Compound Name	Activity	Structure
1.	Zafirlukast	Anti-asthmatic	
2.	Beclomethasone	Anti-asthmatic	
3.	Fluticasone	Anti-asthmatic	
4.	Montelukast	Anti-asthmatic	

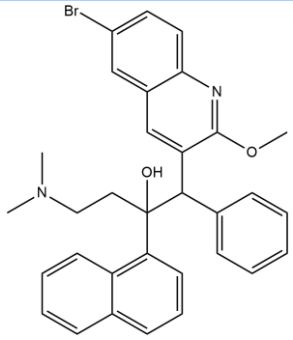
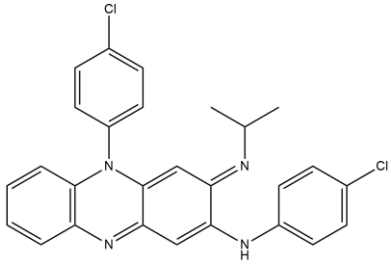
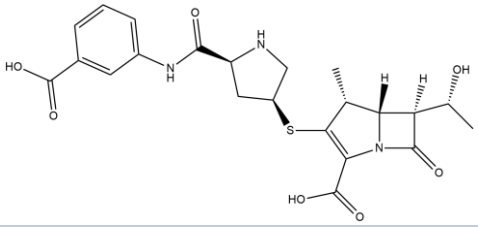
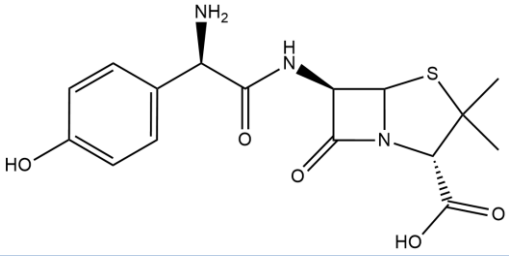
5.	Bedaquiline	Anti-tuberculosic	
6.	Clofazimine	Anti-tuberculosic	
7.	Ertapenem	Anti-tuberculosic	
8.	Amoxicillin	Anti-tuberculosic	

Table 2: PASS Data for Anti-Asthmatic Activity of Selected Compounds

S.NO.	Compound Name	Pa	Pi
1.	Zafirlukast	0.477	0.031
2.	Beclomethasone	0.963	0.004
3.	Fluticasone	0.996	0.002
4.	Montelukast	0.844	0.005
5.	Albuterol (Standard)	0.874	0.004

Table 3: PASS Data for Anti-Tuberculosic Activity of Selected Compounds

S.NO.	Compound Name	Pa	Pi
1.	Bedaquiline	0.532	0.015
2.	Clofazimine	0.383	0.044
3.	Ertapenem	0.777	0.003
4.	Amoxicillin	0.761	0.003
5.	Isoniazid (Standard)	0.810	0.003

Table 4: Acute Toxicity Profile of Selected compounds for Asthma

S.No.	Compound Name	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
1.	Zafirlukast	334,300 in AD	65,970 in AD	1458,000 out of AD	2233,000 in AD
2.	Beclomethasone	1165,000 in AD	32,030 in AD	1593,000 in AD	476,500 in AD
3.	Fluticasone	822,500 in AD	23,740 in AD	1872,000 in AD	721,900 in AD
4.	Montelukast	230,500 in AD	88,140 in AD	1002,000 out of AD	65,110 out of AD
5.	Albuterol (Standard)	302,900 in AD	67,480 in AD	1080,000 in AD	461,500 in AD

Table 5: Acute Toxicity Profile of Selected compounds for Tuberculosis

S.No.	Compound Name	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
1.	Bedaquiline	460,700 in AD	46,660 in AD	653,200 in AD	426,200 in AD
2.	Clofazimine	583,000 in AD	81,150 in AD	2015,000 in AD	1137,000 in AD
3.	Ertapenem	1787,000 out of AD	1112,000 in AD	2375,000 in AD	2864,000 in AD
4.	Amoxicillin	4005,000 in AD	2714,000 in AD	7138,000 in AD	4551,000 in AD
5.	Isoniazid (Standard)	309,600 in AD	256,100 in AD	899,700 in AD	290,200 in AD

Table 6: Predicted Physicochemical Properties and Drug Likeness of Selected Compounds for Asthma

S.NO.	Compound Name	Mol. Wt.	HBD	HBA	logP	TPSA	Lipinski Rule
1.	Zafirlukast	575.68	6	2	3.85	124.11	Yes; 1 violation
2.	Beclomethasone	408.92	5	3	2.27	94.33	Yes; 0 violation
3.	Fluticasone	444.51	7	2	2.82	99.90	Yes; 0 violation
4.	Montelukast	586.18	4	2	4.95	95.72	No; 2 violations
5.	Albuterol (Standard)	239.31	4	4	2.40	72.72	Yes; 0 violation

Table 7: Predicted Physicochemical Properties and Drug Likeness of Selected Compounds for Tuberculosis

S.NO.	Compound Name	Mol. Wt.	HBD	HBA	logP	TPSA	Lipinski Rule
1.	Bedaquiline	555.50	1	4	4.75	45.59	No; 2 violations
2.	Clofazimine	473.40	1	2	4.72	42.21	Yes; 1 violation
3.	Ertapenem	475.51	5	8	1.43	181.57	Yes; 0 violation
4.	Amoxicillin	365.40	4	6	1.40	158.26	Yes; 0 violation
5.	Isoniazid (Standard)	137.14	2	3	0.03	68.01	Yes; 0 violation

Table 8: Docking Scores of Selected Compounds for Asthma

S.NO.	Compound Name	Binding Energy (Kcal/mol)
1.	Zafirlukast	-13.5127 kcal/mol
2.	Beclomethasone	-11.4572 kcal/mol
3.	Fluticasone	-11.2751 kcal/mol
4.	Montelukast	-11.1807 kcal/mol
5.	Albuterol (Standard)	-8.46428 kcal/mol

Table 9: Docking Scores of Selected Compounds for Tuberculosis

S.NO.	Compound Name	Binding Energy (kcal/mol)
1.	Bedaquiline	-15.0097 kcal/mol
2.	Clofazimine	-11.7034 kcal/mol
3.	Ertapenem	-10.3138 kcal/mol
4.	Amoxicillin	-9.59416 kcal/mol
5.	Isoniazid (Standard)	-6.43385 kcal/mol

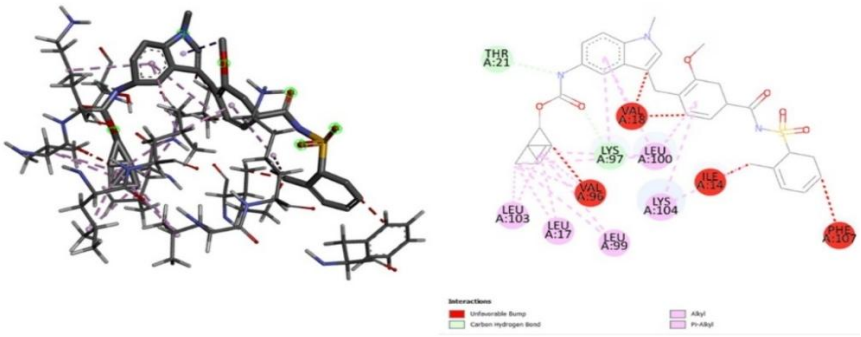


Figure 3: 3D & 2D Docking Poses of Zafirlukast with INTERLEUKIN-13 Receptor (PDB ID: 1IJZ)

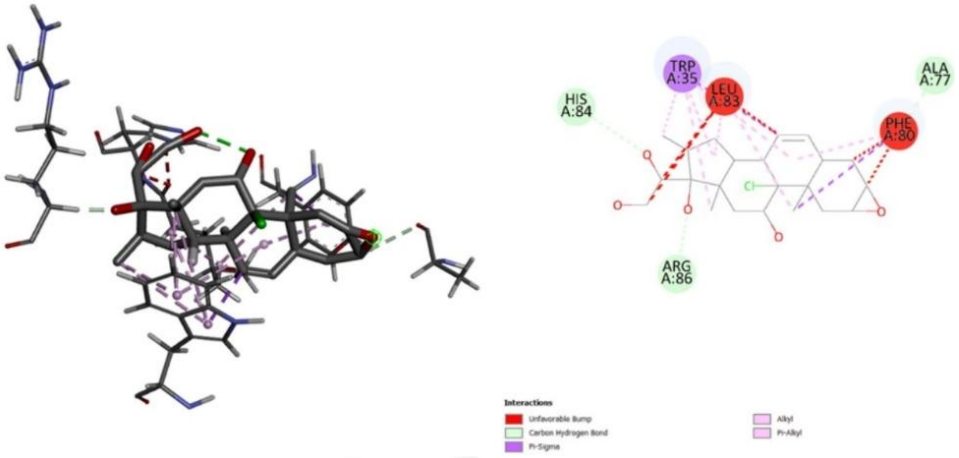


Figure 4: 3D & 2D Docking Poses of Beclomethasone with INTERLEUKIN-13 Receptor (PDB ID: 1IJZ)

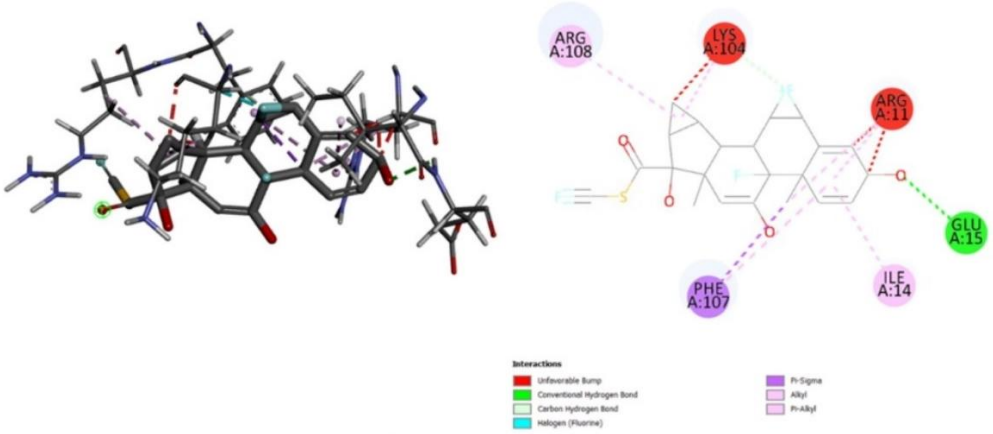


Figure 5: 3D & 2D Docking Poses of Fluticasone with INTERLEUKIN-13 Receptor (PDB ID: 1IJZ)

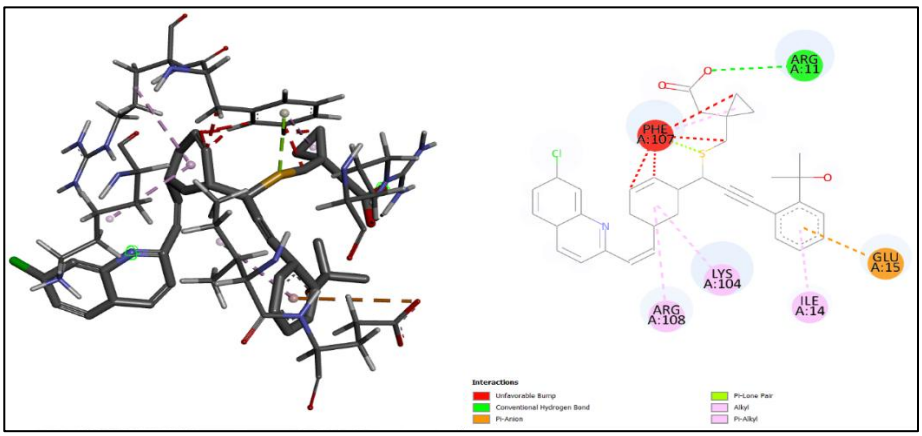


Figure 6: 3D & 2D Docking Poses of Montelukast with INTERLEUKIN-13 Receptor (PDB ID: 1IJZ)

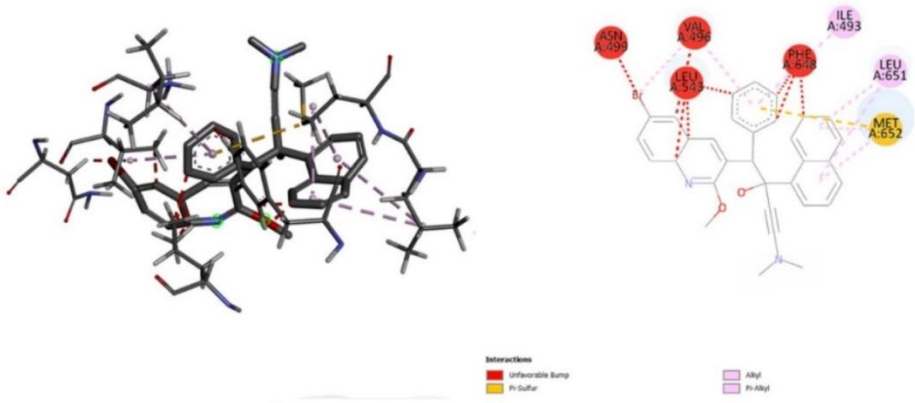


Figure 7: 3D & 2D Docking Poses of Bedaquiline with DNA Gyrase Subunit B (PDB ID: 3IG0)

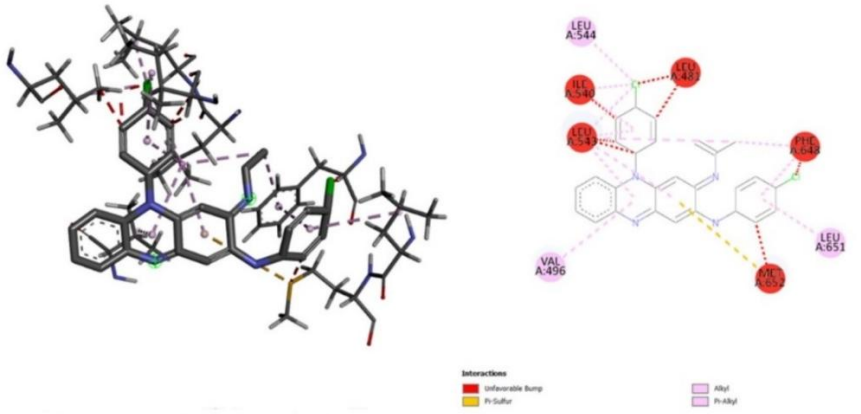


Figure 8: 3D & 2D Docking Poses of Clofazimine with DNA Gyrase Subunit B (PDB ID: 3IG0)

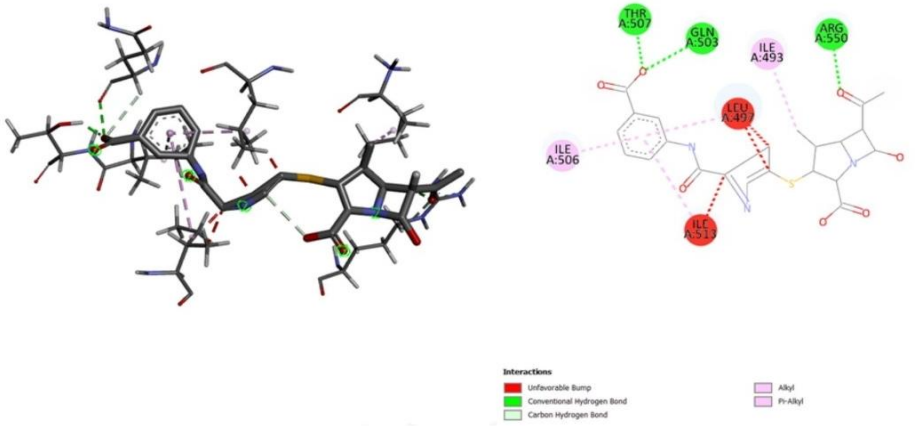


Figure 9: 3D & 2D Docking Poses of Ertapenem with DNA Gyrase Subunit B (PDB ID: 3IG0)

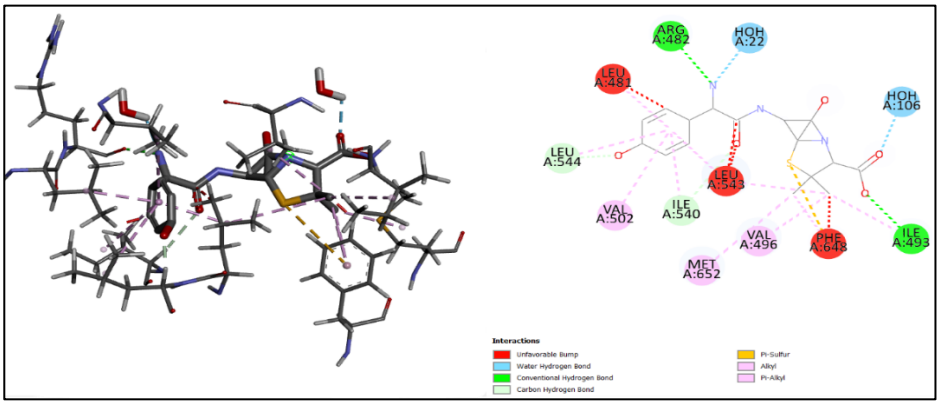


Figure 10: 3D & 2D Docking Poses of Amoxicillin with DNA Gyrase Subunit B (PDB ID: 3IG0)

CONCLUSION

The compounds that have been chosen were assessed for their pharmacological effectiveness against Asthma and Tuberculosis. To determine this, several studies were conducted, including predictions of biological activity, toxicity evaluations, assessment of physicochemical properties, and molecular docking analyses. Ultimately, the compounds Zafirlukast, Beclomethasone, Fluticasone, and Montelukast demonstrated the greatest potency and binding affinity to the Interleukin-13 receptor, while Bedaquiline, Clofazimine, Etrapenem, and Amoxicillin exhibited the highest potency and binding affinity to the DNA gyrase subunit B receptor. Based on the docking scores, it is evident that these compounds have the potential to combat the aforementioned diseases. In future, these compounds with the strongest binding affinity will be selected for further research, including in vitro and in vivo studies against Asthma and Tuberculosis.

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