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Docking of 100 Virtual Organic Compounds Against Mycobacterium tuberculosis: A Molecular Modeling Study

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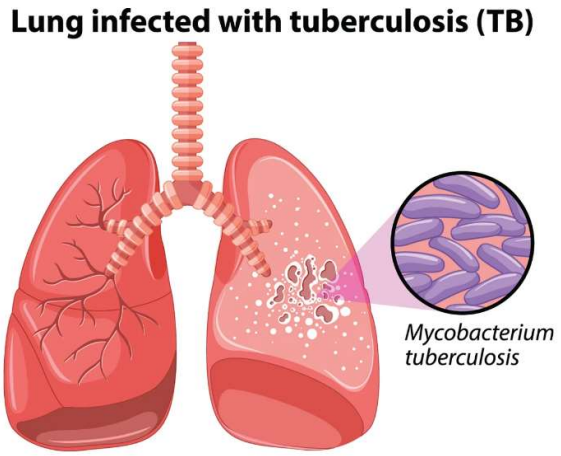
Abstract

In this study, molecular-docking techniques were used to evaluate the effectiveness of a group of virtual compounds against Mycobacterium tuberculosis with selected protein targets(6p9k) using RCSB PDB database agglutination studies (molecular docking). Virtual molecular structures were taken from the ZINC database (100 organic molecular), They were selected based on the stereo symmetry of the Co-crystallized Ligand, as well as the shape of the pocket in the protein and their ability to bind to target proteins was evaluated by simulating molecular docking. The research results showed that 17 virtual compounds show strong and potential binding to binding sites on proteins, suggesting they could be used as alternative medicines. This study provides valuable insights into the design of virtual organic compounds and the evaluation of their effectiveness using molecular modeling techniques, contributing to developing new drug discovery strategies.

Keywords: Mycobacterium tuberculosis, antimicrobial resistance, Dynamic simulation, Molecular Docking.

Introduction

The situation has worsened in recent years regarding antibiotics against some viruses, bacteria, and other causes of some diseases due to these biological organisms gaining resistance against some drugs[1–7]. In a way that calls for caution in the future and the effectiveness of manufactured medicines and compounds in taking their role as anti-biology [7–12].



In recent years, Mycobacterium tuberculosis, the leading cause of tuberculosis, has become a major concern globally due to the emergence of drug-resistant strains[3,6,7,12–19]. Despite advances in the development of diagnostic and treatment strategies, TB remains a major public health challenge[20]. An increase in cases of multidrug-resistant TB (MDR-TB) and severe drug-resistant TB (XDR-TB) has been recorded, complicating therapeutic efforts and increasing the need to develop new and effective drugs[2,7,20]. At the research level, recent studies have focused on better It is possible to use medications for specific diseases and apply them to Mycobacterium tuberculosis, as the difference in partial bonding and spatial structure allows to gives effectiveness, instead of the routine medications used. This reduces the trouble of preparing new medications, which require a long-term study to know the extent of their effect on the human body in general and also studying its toxicology[21–33].

Methodology

protein forment:

Get structure: The 3D crystal structure of the **6p9k** protein receptor (figure1) was obtained from the RCSB PDB database.

Cleaning and preparation:

Removal of small molecules: small ions and other unnecessary organic molecules have been removed from the crystal structure, in order to remove any interference that may affect the Docking process.

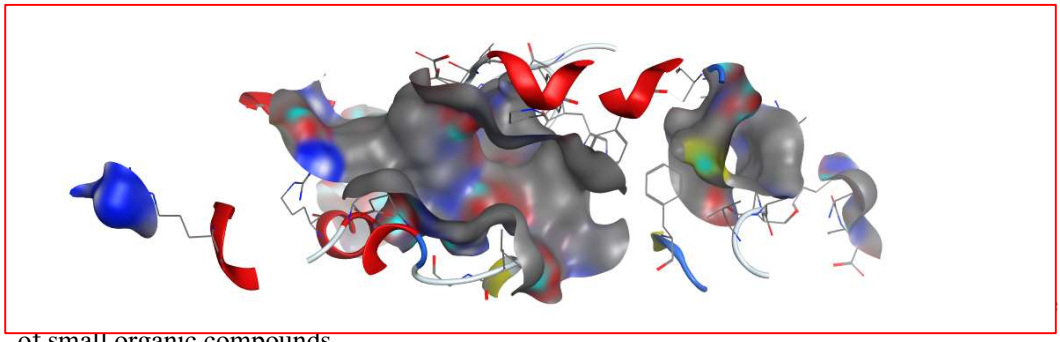
Adding hydrogen bonds: The hydrogen bonds lost during the cleaning process were added, to ensure the accuracy of the electronic representation of the receiver.

Energy Optimization: Structure energy is optimized using the molecular dynamics method (Molecular Dynamics) to ensure a stable structure close to its natural state.

Active Positioning (Pocket):

Structure analysis: The crystal structure of the receptor has been analyzed to determine the active site (Pocket) to which the Co-crystallized Ligand binds (figure2).

Coordinate determination: The exact coordinates of the active site, which represents the target area for vehicle Docking, have been determined.



of small organic compounds.

Figure2. Active Positioning (Pocket)

Selection criteria: Compounds were selected based on their physical and chemical properties, such as molecule size, polarity, and the presence of specific functional groups, to ensure library diversity and increase the chances of finding bioactive compounds.

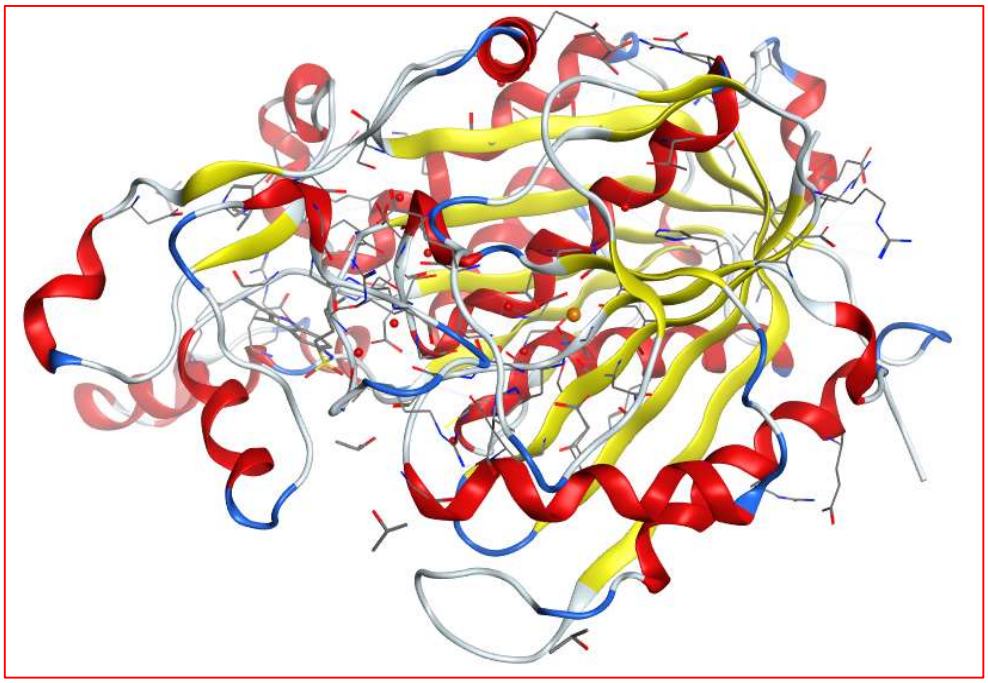


Figure1. 3D crystal structure of the **6p9k** protein receptor

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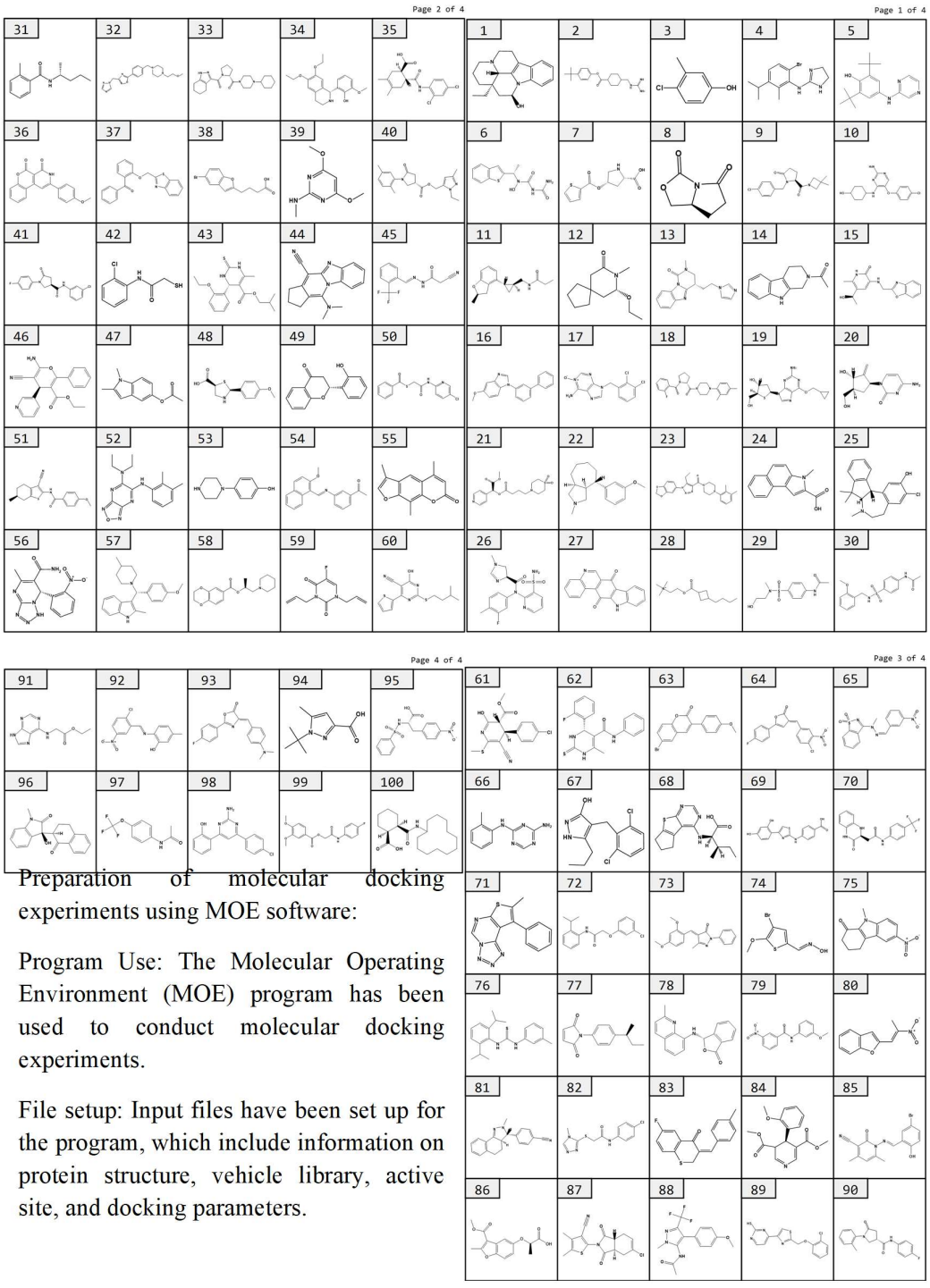
Structure 1. Target compounds



Preparation of molecular docking experiments using MOE software:

Program Use: The Molecular Operating Environment (MOE) program has been used to conduct molecular docking experiments.

File setup: Input files have been set up for the program, which include information on protein structure, vehicle library, active site, and docking parameters.

Table 2. Docking parameters

Center _x = -50.3117	Size _z = 19.4181
Center _y = 8.13636	Size _y = 14.0942
Center _z = -16.9801	Num _modes = 20
Size _x = 11.2784	Energy y_range = 4

Docking results analysis:

Overlapping modes assessment: Overlapping modes of compounds with the receptor have been assessed based on bonding energy, non-covalent interactions (such as hydrogen interactions and polar interactions), and geometric integration between the compound and the active site.

Result and discussion

Initially, the Co-crystallized Ligand of the target protein for tuberculosis was studied, and the stereo-structure of the ligand was analyzed, compounds almost similar to the stereo-structure and the main active groups were searched; in the figure below shows the structure of the receptor, where it was isolated in a manner consistent with the Co-crystallized Ligand of the protein.

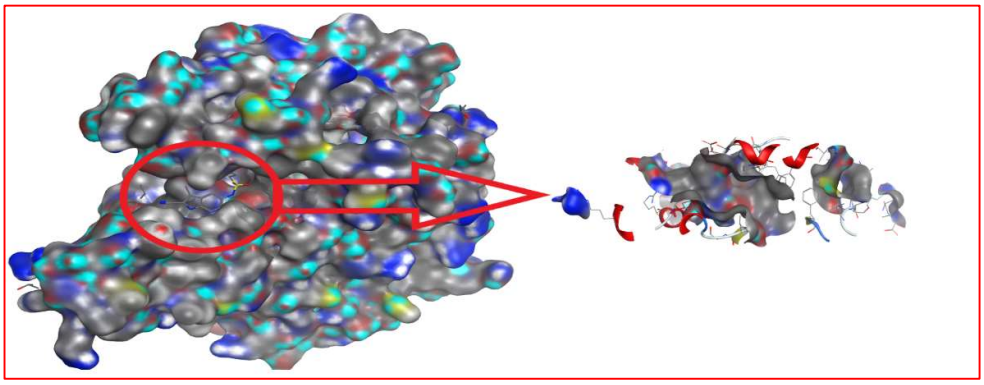


Figure 3. isolated the Pocket (6p9k)

The final results of the S-score and Rmsd values were compared with the resulting data from the docking process between the Co-crystallized Ligand and the receptor:

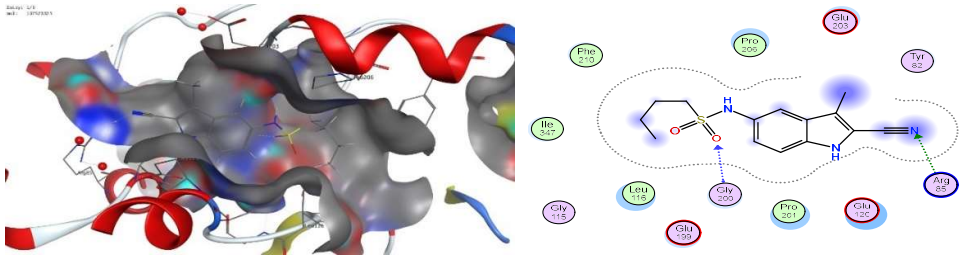
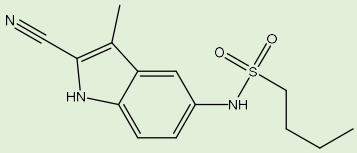


Figure 4. Co-crystallized Ligand interconnection with the receptor (6p9k)

The S-score and Rmsd for Co-crystallized Ligand equals **-6.3091** and **1.1580 respectively** are shown in Table 3, According to the data coming out of the program, these values are considered

Table 3. Results docking Co-crystallized Ligand with receptor (6p9k)

Mol	S	rmsd_refine
	-6.30915	1.1579541
	-5.94871	2.378026
	-5.88192	1.7136604
	-5.80272	2.9733429
	-5.70017	1.1093726

The use of the Co-crystallized Ligand as a comparison unit is considered one of the best natural convergences of the results, and this gives accuracy in selecting alternatives, as well as studying the stereoscopic position of the ligand-receptor structures. The compounds were studied and the results are shown in the table below for each compound.

In the results, some compounds have a small s value, but at the same time the bonding distance R is also high We also find that the ideal value of s and r is achieved, but the bonds between the compound and the receptor are either fewer or ineffective, as the presence of hydrogen bonding is considered one of the most important bonds that can be given the final judgment on its adoption, so all of the above was taken into consideration.

Table 5. Top Docking Hits: 17 Compounds Identified

RMSD	S	N.CP.
0.46097207	-7.23964	30
0.63394058	-7.10658	10
0.82661986	-7.63152	32
0.86754304	-7.12566	50
0.86963522	-7.28066	11
0.88287371	-7.25343	40
0.90121973	-7.30175	34
0.90369582	-7.22375	2
0.91036838	-7.55891	52
0.92828405	-7.40032	19
0.95477748	-7.05562	81
1.1005673	-7.5867	26
1.1696575	-7.00768	70
1.2144891	-7.51081	33
1.450551	-7.24563	21
1.5156852	-7.25926	99
1.5985621	-7.65423	18

After sorting and analyzing the results according to S-score and Rmsd, the **17** highest effective compounds were obtained out of the **100** items, where the compound gave **30** highest results with a factor of S-score, Rmsd, equals to **-7.23964** and **0.46097207** respectively, which is the highest effectiveness, and when comparing this result with the actual values of the Co-crystallized Ligand, note that the compounds in Table 5 gave higher effectiveness than the Co-crystallized Ligand.

The other important part is the number of bonds and bonding forces between the compounds and the receptor, and this is what we will explain in the figures below, where the number of bonds and forces of the most effective compounds is shown in Figure 5.

Looking at the results in Table 3 and comparing them with the final form of each compound with the receptor, we find several of these compounds form a discouraging link, even though these compounds have a high value for S-score, Rmsd. note that compound **30**, which is considered the best among other compounds according to the values of S-score and Rmsd, did not have any hydrogen bond with the independent, while compound **52** and **19** had more than two hydrogen bonds; figure 5, **cp.52** and **cp.19**.

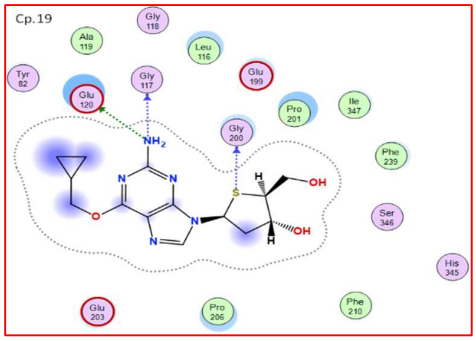


Figure 5. **Cp.19** interconnection with the receptor (6p9k)

Noticeable in the interactions of the ligand with the receptor that the amino acid **Gly200**, as well

as the **Arg85**, are active units in creating the effectiveness of the ligand. Referring to Figure 5 of compound **19**, we find that the amino acid **Gly200** is present in the interaction between compound **19** and the receptor, in addition to **Gly117** and **Glu120**. This provides a hypothetical indication of compound 19's effectiveness. It can be very effective in inhibiting **TB**.

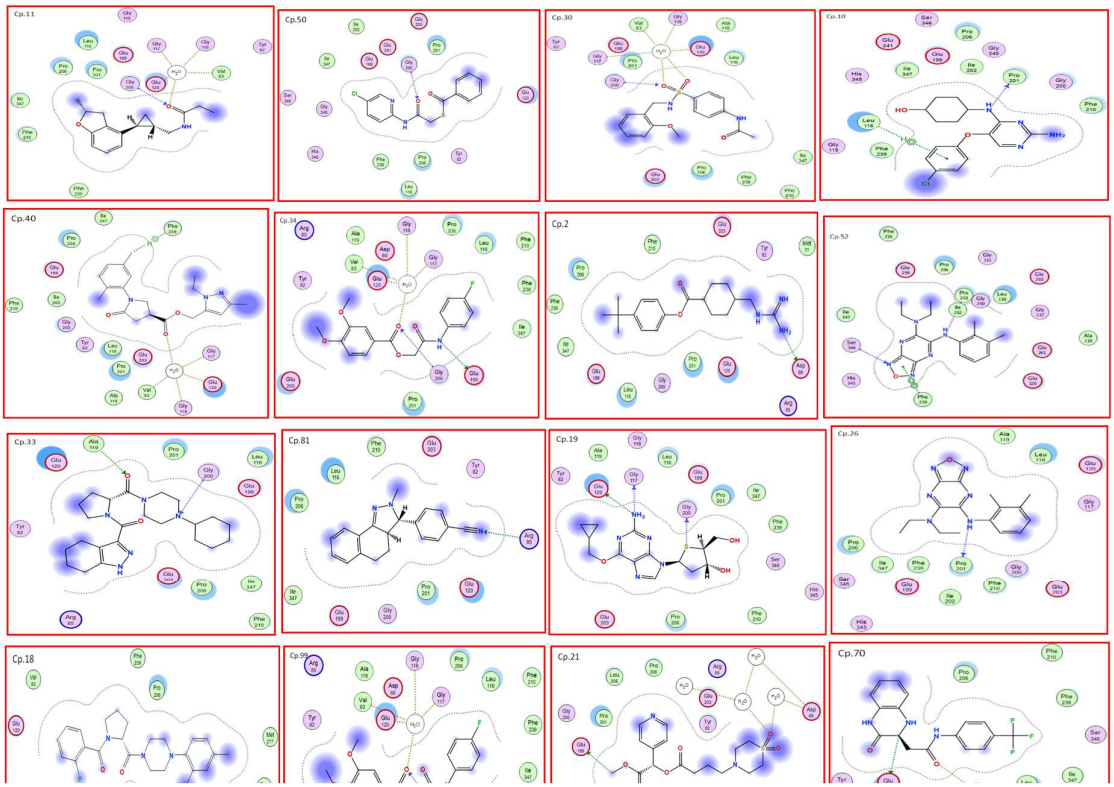


Figure 6. interaction between compounds and receptor (6p9k)

Comparative Analysis of Docking Energies for Selected Compounds

The binding energies (E) of the compounds that underwent docking with their respective target receptors are compared in this section.

Compound 52:

• Interaction 1: In chain A, N 25 engages in H-donor interactions with PRO 201. A distance of 2.89 Å and a binding energy of -1.1 kcal/mol are present. A comparatively strong and stable hydrogen bond is indicated by this interaction.

• Interaction 2: In chain A, N 19 engages in H-acceptor interactions with SER 346. The binding energy at a distance of 3.64 Å is -0.7 kcal/mol. In comparison to the H-donor interaction with PRO 201, this interaction is less advantageous.

• Interaction 3: A pi-pi interaction occurs between the 5-ring and PHE 239 in chain A. The binding energy at a distance of 3.88 Å is -0.0 kcal/mol. There is very little binding energy and this interaction is weak.

Compound 19:

• Interaction 1: As an H-donor in chain A, N 1 interacts with GLY 117. A distance of 2.93 Å and a binding energy of -1.8 kcal/mol are present. This suggests a highly stable and robust hydrogen bond.

• Interaction 2: As an H-donor in chain A, N 1 also interacts with GLU 120. The binding energy at a distance of 2.82 Å is -7.2 kcal/mol. This contact is very persistent and noteworthy since it exhibits a very strong hydrogen bond.

• Interaction 3: As an H-donor in chain A, S 40 engages in interaction with GLY 200. A distance of 3.11 Å and 0.8 kcal/mol are the binding energies. Though it is not as strong as the others, this interaction nevertheless affects the binding profile.

Table 6. Binding Interactions and Energies of Docked Compounds

Compound	Ligand	Atom 1	Receptor	Interaction	Distance (Å)	E (kcal/mol)
cp.52	N 25	O	PRO 201	H-donor	2.89	-1.1
	N 19	CA	SER 346	H-acceptor	3.64	-6.4
	5-ring	6-ring	PHE 239	pi-pi	3.88	-0.0
cp.19	N 1	O	GLY 117	H-donor	2.93	-1.8
	N 1	OE2	GLU 120	H-donor	2.82	-7.2
	S 40	O	GLY 200	H-donor	3.11	0.8

Stability Assessment of Protein Structure Through RMSD Analysis During Molecular Dynamics Simulation

protein RMSD of Cp.19

RMSD is a measure used to evaluate the extent to which the tertiary structure of a protein changes over time compared to a reference structure. Low values indicate stability of the protein structure, while high values indicate significant changes in structure. In this drawing, the RMSD value starts near 0.06 nm and then stabilizes around this value with very slight fluctuations, indicating that the protein structure is relatively stable throughout the simulation period Figure 7.

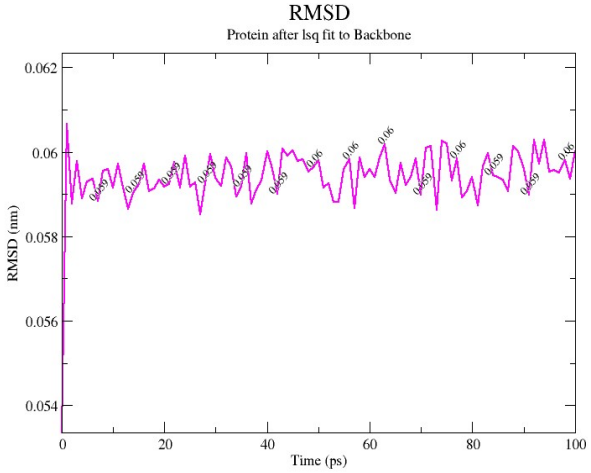


Figure 7. protein RMSD of Cp.19

The small fluctuations you see reflect small movements in the protein, but they do not indicate any fundamental structural changes. This indicates that the protein maintains its original structure well after the overlay is performed on the spine.

ligand RMSD of Cp.19

In this drawing, the RMSD of the ligand starts near 0.04 nm and continues to oscillate within a range between 0.04 and 0.08 nm throughout the simulation period. This constant oscillation reflects noticeable but not drastic structural movements, suggesting that the ligand retains its overall structure but shows certain structural flexibility during the simulation Figure 8.

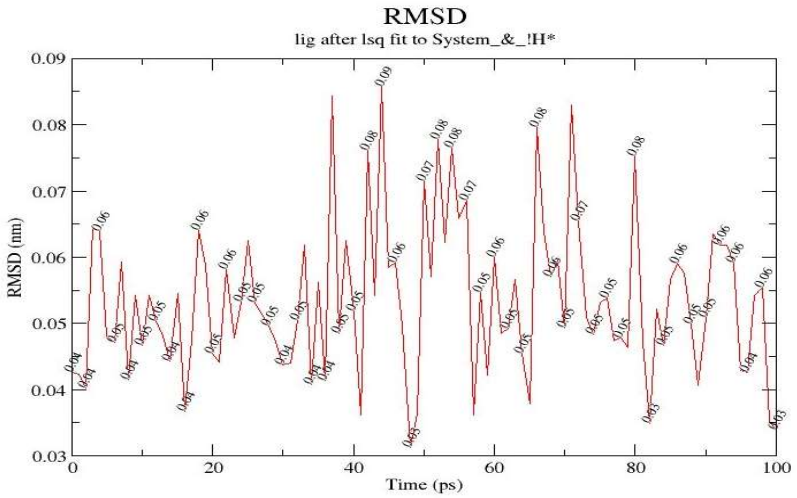


Figure 8. ligand RMSD of Cp.19

These fluctuations may indicate ongoing interactions between the ligand and the active site of the protein or dynamic changes that may occur within the active site or due to interactions between the ligand and the surrounding environment. Overall, these results show that ligand is relatively stable with some structural movements that may be important for understanding its reactive behavior with the target protein.

Amino acids RMS of receptor

Low values of RMS flotation (about 0.015 to 0.025 nm) indicate that those parts of the protein are relatively stable with slight movements during the simulation period. Higher values (up to 0.03 nm or more) indicate that there are certain regions in the protein that show greater flexibility or movement Figure 9.

In this graph, we observe several major peaks at values of 0.03 nm, indicating that these regions in the protein are the most mobile and elastic. This elasticity may be related to functionally active regions of the protein, such as binding sites or sites that undergo structural changes during interaction with other molecules.

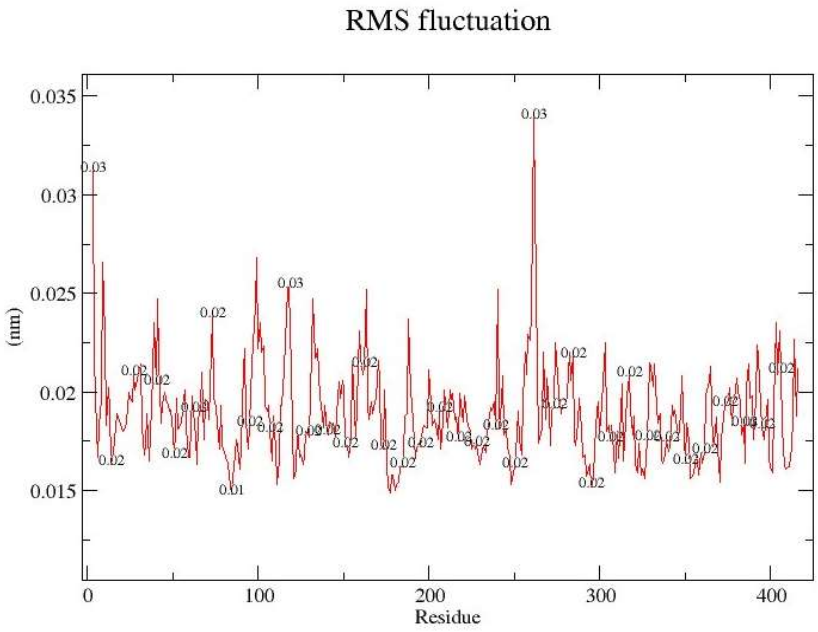
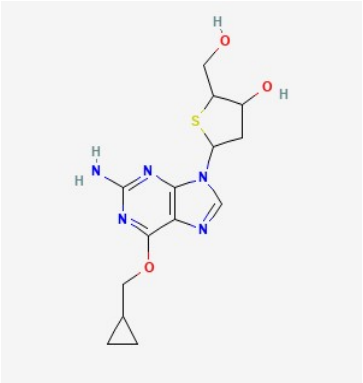


Figure 9. Amino acids RMS of receptor

Physicochemical and Pharmacokinetic Profile of Cp.19



The compound with the SMILES notation "OCC1SC(CC1O)n1cnc2c1nc(N)nc2OCC1CC1" has the molecular formula C14H19N5O3S and a molecular weight of 337.40 g/mol. It consists of 23 heavy atoms, including 9 aromatic ones, and has a fraction Csp3 of 0.64. The compound possesses 5 rotatable bonds, 6 hydrogen bond acceptors, and 3 hydrogen bond donors. The topological polar surface area (TPSA) is 144.61 Å², and the molar refractivity is 86.82. Its lipophilicity is reflected in various Log P values, with a consensus Log P of 0.60. The compound is classified as soluble with varying solubility values depending on the prediction method. Regarding pharmacokinetics, it exhibits low GI absorption, is not BBB permeant, and is a substrate of P-gp. It does not inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4 enzymes. The compound has a skin permeation coefficient (Log Kp) of -7.70 cm/s. In terms of drug-likeness, it complies with Lipinski's rule with no violations and meets the Ghose criteria. It shows no alerts for PAINS or Brenk, with a synthetic accessibility score of 4.42, indicating moderate ease of synthesis. The data were obtained from SwissADME.

Conclusion:

The analysis shows that **Compound 19** exhibits significantly better binding properties than **Compound 52**. Specifically, **Compound 19** has notably lower binding energies, particularly with GLU 120 (-7.2 kcal/mol), indicating a stronger and more stable interaction. In contrast, **Compound 52** has weaker overall binding energies, with its most significant interaction being with PRO 201 (-1.1 kcal/mol). Thus, **Compound 19** is identified as the more promising

candidate for further evaluation. **Compound 19, to our knowledge, has not been previously explored for the treatment of TB Disease. This opens up new avenues for therapeutic research and potential drug development.**

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