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Molecular Docking of Quinolone against INHA to Treat Tuberculosis

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Abstract: ***Background: Tuberculosis (TB) is one of the most infectious diseases in the present scenario that is caused when Mycobacterium tuberculosis is found in the body. As tuberculosis is a communicable disease or transferrable disease, it is easily transmitted to another person who remains in contact with the infected person through the inhalation process of air droplets carrying that particular bacteria. The in silico study was carried out to inhibit the activity of INHA by drug molecule with the help of molecular docking to treat tuberculosis.***

Methods: All studies were based on molecular docking. Docking was carried out between all the ligands and target protein INHA (PDB ID: 5VRL) with the help of docking software. We selected some natural compounds as ligand like Thiophenes, Sulfonamides, Chalcone, Nitroimidazole, Benzimidazole, Lidamycin and Quinolone and INHA (PDB ID: 5VRL) as a target protein. After the protein preparation by Biovia Discovery Studio Visualizer we imported all the ligand in PyRx software for virtual screening. According to the PyRx result and Lipinski's Rule of Five, Quinolone was the best compound against INHA with its minimum binding energy.

Results: The Biovia Discovery Studio Client 2020 and AutoDockVina software were used for the molecular docking between Quinolone and receptor protein INHA (PDB ID: 5VRL). The result showed 9 poses with different binding affinity, Root means square deviation Lower Bound (RMSD LB) and Root mean square deviation Upper Bound (RMSD UB). The same molecules were further docked through Biovia Discovery Studio Client 2020 and the interaction was visualized under PyMol.

Conclusion: According to the in silicostudy, Quinolone was the only compound which can inhibit the activity of INHA (PDB ID: 5VRL). So in the further studies, Quinolone can be a promising drug for the treatment of tuberculosis after its in vitro and in vivo studies.

Keywords: Tuberculosis, Mycobacterium tuberculosis, Quinolone, INHA

I. INTRODUCTION

Tuberculosis (TB) is one of the most infectious diseases in the present scenario that is caused when *Mycobacterium tuberculosis* is found in the body [1]. As tuberculosis is a communicable disease or transferrable disease, it is easily transmitted to another person who remains in contact with the infected person through the inhalation process of air droplets carrying that particular bacteria. Tuberculosis mainly affects the lungs, but can affect other organs as well. The immune cells test and monitor pathogen when this bacteria encounters within the body. However, this disease remains latent, but after a few years it can become active at any time when the specific immune system becomes compromised [2].It is estimated that the bacterium originated from East Africa. As early humans moved out of East Africa, settling in Europe and Asia, TB infection moved with them and continued throughout the known world to wreak devastation for centuries [3]. *Mycobacterium tuberculosis* is a pathogen transmitted in soil. Droplets bearing the mycobacteria settle all over the airways once inhaled. Most of the bacilli are trapped in the upper parts of the airways where the goblet cells which secrete the mucus are located. The mucus catches the invading bacilli, and the cilia on the cell surface are constantly undulating to move the mucus upwards and trapping foreign particles for removal [4]. This method provides the body with an initial physical protection that in most people exposed to tuberculosis prevents infection [5].

Mycobacterium tuberculosis is a large, non-motile, obligatory aerobic bacterium that grows slowly. This has a predilection as an essential aerobe for the oxygenated environment of the upper lobes of the lungs [6]. *M. Tuberculosis* has an 18-hour doubling period, and clinical cultures can take around 6–8 weeks. It is dehydration resistant and therefore can live in expectorated sputum. Morphologically, the bacterial cell wall contains a range of complex lipids such as mycolic acids, long-chain fatty acids that facilitate acid-fast characteristics; wax D; and phosphatides that contribute to the clinically relevant characteristics of caseating necrosis [7].

Bioinformatics plays an important role in searching the targets and compounds to treat the disease. Computational docking is commonly used to study protein-ligand interactions, and to discover and create drugs. The method typically starts with a well-known structure target, like a crystallographic structure of a catalyst of medicinal interest. Tying up is then used to predicting the conformation of small molecules and binding free energy to the target. Single docking experiments are useful in exploring target performance, and virtual screening, wherever an outsized compound library is docked and ranked, is also used to identifying new drug development inhibitors [8].

II. METHODOLOGY

A. Identification and Selection of Target Protein

Disease causing protein was identified through literature. The structure of protein molecule of INHA (PDB ID: 5VRL) which is a tuberculosis causing protein was downloaded from Protein Data Bank (PDB) (http://www.rcsb.org/). Protein molecule structure was retrieved in .pdb format [9]. The stability of protein molecule was checked through Rampage (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php).

B. Selection of Ligand Molecules

Ligands were chosen from different plant phytochemical constituents. PubChem (https:/pubchem.ncbi.nlm.nih.gov/) has retrieved those ligand molecules. The ligands in.sdf format were downloaded in 3D structure [10]. Through the online SMILES Translator (https:/cactus.nci.nih.gov / translate/), all downloaded ligand structures were further converted into.pdb format. The converted files have been downloaded in the format .pdb. These .pdb files have been used to run various resources and applications.

C. Preparation of Protein Molecule

The overall protein molecule preparations were rendered through Biovia Discovery Studio Visualizer. This program evaluated the various properties of the protein molecule. The protein was loaded in.pdb format and analysed its hierarchy by selecting water molecules and ligands. The ligand molecules bound were separated from the protein molecule, and all water molecules were separated as well. The protein crystal structure was further saved in the.pdb format.

D. Virtual Screening of Ligands

Ligand screenings were performed through PyRx software. This software was used to screen certain ligands that had limited binding energy to the target protein. Ligands that were found to have limited binding energy were screened for property property analysis of drug likeliness. PyRx runs in the format .pdbqt. PyRx's procedure begins with the loading of protein molecule, which was first translated from the.pdb to the.pdbqt format, and then imported ligands in the.sdf format from the specific folder. Ligands' energy was reduced accompanied by the conversion of file.sdf to file.pdbqt. The docking was carried out between the protein target and the ligand molecule, and the minimum binding energy ligands were screened [11].

E. Drug Likeliness Property Analysis

Analysis of the properties of drug likeliness was done via online server i.e. SwissADME. The ligands screened were analyzed for their property on drugs. SMILE screened ligand notations were copied from PubChem and pasted on SwissADME online web server [12]. Drugs for the five-fold Lipinski law were analyzed. Lipinski rule of five states the following points:-

1) Hydrogen bond donors should be less than 5.
2) Hydrogen bond acceptors should be less than 10.
3) The molecular weight should be less than 500 Dalton.
4) Partition coefficient LogP should be less than 5.
5) Not more than 1 rule can be violated.

The ligands which followed the above Lipinski rule of five were selected for final docking through AutoDockVina and Biovia Discovery Studio Client 2020.

F. Final docking through AutoDockVina and Biovia Discovery Studio Client 2020

The best selected ligand was selected for final docking through AutoDockVina and BioviaDiscovery Studio Client 2020.

1) *AutoDockVina*- The protein target in.pdb was loaded on AutoDockVina graphical windows. The protein target in.pdb format was prepared for docking by removing water molecules, adding polar atoms of hydrogen and attaching Kollman charges to the protein molecule and finally saving protein in the format of.pdbqt. Ligand molecule was imported in the format of.pdb and

converted to the format of .pdbqt. After that grid box was chosen for docking of the region. AutoDockVina was executed using the command prompt and the results were analysed [13].

2) *Biovia Discovery Studio Client 2020-* Biovia Discovery Studio Client 2020 also performed protein target docking with the ligand. The target protein (DNMT1) was loaded onto the platform, followed by the ligand in the format of.pdb. The charges were added to the protein molecule, and the ligands minimized energy. The protein molecule and the ligand molecule have both been prepared for docking. Based on Absolute Energy, Confg Number, Mol Number, Relative Energy and Pose Number, the results were analyzed after docking. Under structure visualization tool, i.e. Biovia Discovery Studio Visualizer and PyMol, the protein's interaction with the ligand molecule was analysed.

G. Structure Visualization through PyMOL

Visualisation of the structure was done through the PyMOL tool. PyMOL is an open-access tool. The protein molecule in the form of.pdbqt was loaded on the graphical screen of PyMOL, followed by the .pdbqt file output. The docked structure was visualized and converted to "molecular surface" under "shown as" option molecule [14].

III. RESULTS AND DISCUSSION

The crystal structure of INHA in .pdb format was retrieved from Protein Data Bank as shown in **Figure 1**. INHA belongs to oxidoreductase class, the resolution of protein was 2.65Å, R- value free was 0.198, R- value observed was 0.173.The stability of protein was analyzed through Rampage as shown in **Figure 2.** Secondary metabolites from different plants were retrieved from PubChem online database. The structures of Thiophenes, Sulfonamides, Chalcone, Nitroimidazole, Benzimidazole, Lidamycin and Quinolonewere downloaded in .sdf format as shown in **Table 1.**The downloaded structure were converted into .pdb format.

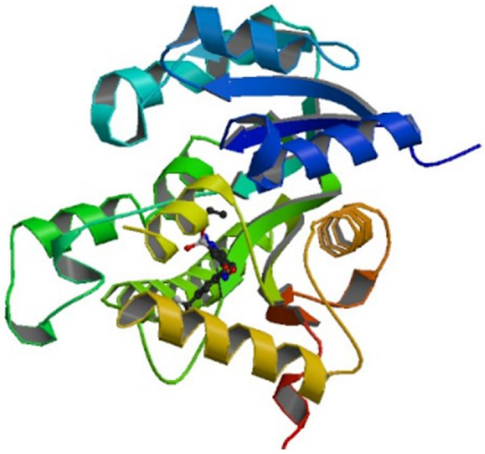
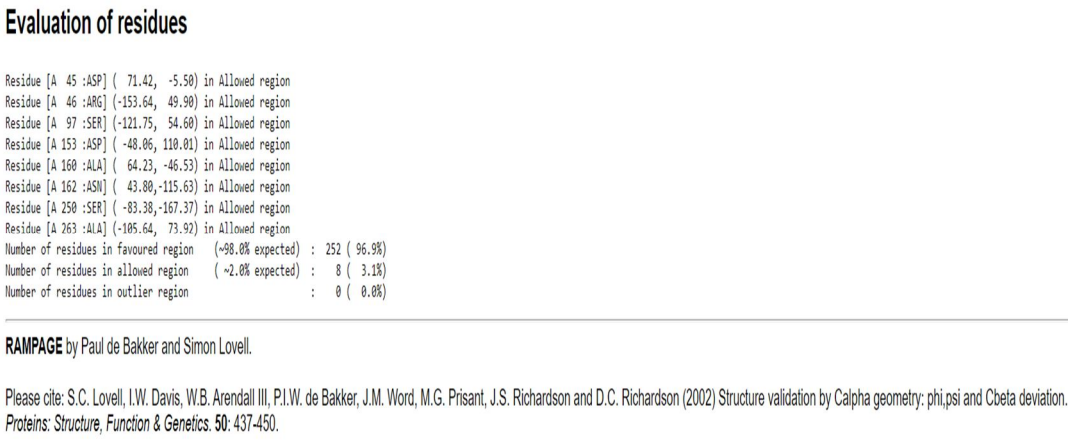


Figure 1: The crystal structure of human INHA



Evaluation of residues

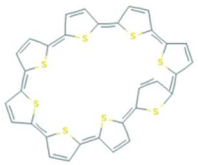
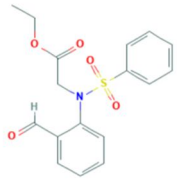
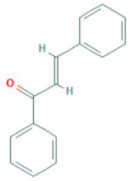
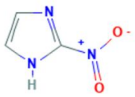
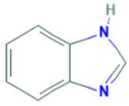
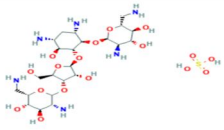
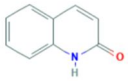
Residue [A 45 :ASP] (71.42, -5.50) in Allowed region
Residue [A 46 :ARG] (-153.64, 49.90) in Allowed region
Residue [A 97 :SER] (-121.75, 54.60) in Allowed region
Residue [A 153 :ASP] (-48.06, 110.01) in Allowed region
Residue [A 160 :ALA] (64.23, -46.53) in Allowed region
Residue [A 162 :ASN] (43.80,-115.63) in Allowed region
Residue [A 250 :SER] (-83.38,-167.37) in Allowed region
Residue [A 263 :ALA] (-105.64, 73.92) in Allowed region
Number of residues in favoured region (~98.0% expected) : 252 (96.9%)
Number of residues in allowed region (~2.0% expected) : 8 (3.1%)
Number of residues in outlier region : 0 (0.0%)

RAMPAGE by Paul de Bakker and Simon Lovell.

Please cite: S.C. Lovell, I.W. Davis, W.B. Arendall III, P.I.W. de Bakker, J.M. Word, M.G. Prisant, J.S. Richardson and D.C. Richardson (2002) Structure validation by Calpha geometry: phi,psi and Cbeta deviation. *Proteins: Structure, Function & Genetics*. **50**: 437-450.

Figure 2: Rampage Result

Table 1: Structure of Ligands

Structure	Ligand	PubChem ID
	Thiophenes	CID: 102188099
	Sulfonamides	CID: 91392493
	Chalcone	CID: 637760
	Nitroimidazole	CID: 10701
	Benzimidazole;	CID: 5798
	Lidamycin	CID: 62403
	Quinolone	CID: 6038

All the seven ligands Thiophenes, Sulfonamides, Chalcone, Nitroimidazole, Benzimidazole, Lidamycin and Quinolone were subjected for virtual screening through PyRx software. The binding affinity of Thiophenes was -7.1Kcal/mol, root mean square deviation lower bound was 2.577(RMSD) and RMSD upper bound was 7.636, Sulfonamideswas -6.1Kcal/mol, root mean square deviation lower bound was 0.053 (RMSD) and RMSD upper bound was 1.94,Chalcone was -4.5Kcal/molroot mean square deviation lower bound was 3.667 (RMSD) and RMSD upper bound was 4.556, Nitroimidazolewas -5.8Kcal/molroot mean square deviation lower bound was 2.834 (RMSD) and RMSD upper bound was 4.232, Benzimidazolewas -7.5Kcal/molroot mean square deviation lower bound was 1.954 (RMSD) and RMSD upper bound was 4.469, Lidamycin was -11.8Lcal/molroot mean square deviation lower bound was 1.965 (RMSD) and RMSD upper bound was 3.422 and Quinolonewas -8.5Kcal/molas shown in **Table 2**. The binding energy of Thiophenes was -7.2, Sulfonamides was -6.1, Chalcone was -4.5, Nitroimidazolewas -5.9, Benzimidazolewas -7.8, Lidamycinwas -11.8 and Quinolone was -8.5 as depicted in Table 3.

Table 2: The Binding affinity, RMSD lower bound and RMSD upper bound of different ligands with protein molecules.

Ligand molecule	Binding affinity(Kcal/mol)	RMSD lower bound	RMSD upper bound
Thiophenes	-7.1	2.577	7.636
Sulfonamides	-6.1	0.053	1.94
Chalcone	-4.5	3.667	4.556
Nitroimidazole	-5.8	2.834	4.232
Benzimidazole;	-7.5	1.954	4.469
Lidamycin	-11.8	1.965	3.422
Quinolone	-8.5	1.445	2.987

Table 3: The Binding energy of different ligands with protein molecules.

Ligand molecules	Binding energy
Thiophenes	-7.2
Sulfonamides	-6.1
Chalcone	-4.5
Nitroimidazole	-5.9
Benzimidazole;	-7.8
Lidamycin	-11.8
Quinolone	-8.5

According to PyRx results it was concluded that Quinolone,Benzimidazole;,Lidamycinand Thiophenesshowed minimum binding energy. The screened molecules Quinolone,Benzimidazole;,Lidamycinand Thiophenes were analysed for drug likeliness property analysis. The screened three ligands were analysed by SwissADME online web server. Further the ligands were screened on the basis of qualifying Lipinski Rule of five. Theligands were analysed for the its Molecular weight, Hydrogen bond donor, Hydrogen bond acceptor, Partition coefficient and Lipinski rule violation as shown in **Table 4.**It was analysed that Quinolone was having minimum binding energy with protein molecule and it was also qualifying Lipinski's rule of five.

Table 4: Drug Likeliness Property Analysis

Compound name	Molecular weight (g/mol)	Hydrogen donor	Hydrogen Acceptor	Partition coefficient	Violations
Benzimidazole	118.14	1	1	0.98	0 violations
Sulfonamides	347.39	0	5	-1.64	0 violations
Lidamycin	533.95	5	10	-0.85	Yes; 1 violation: MW>500
Thiophenes	656.99	0	0	6.43	No; 2 violations: MW>500, MLOGP>4.15
Quinolone	450.68	1	2	2.77	0 violations

The screened ligand Quinolone was docked with protein target through AutoDockVina and Biovia Discovery Studio Client 2020. Through AutoDockVina software, ligand showed minimum binding energy, and through Biovia Discovery Studio Client 2020 the result was same. Quinolone was considered as the best binding ligand against protein target through AutoDockVinas as shown in Table 5.The results of Biovia Discovery Studio Client 2020 can be depicted in Table 6.

Table 5: AutoDockVina Result

Mode	Affinity	RMSD L.B	RMSD U.B
1	-8.5	0.000	0.000
2	-8.0	1.390	3.133
3	-7.9	17.410	22.081
4	-7.6	11.703	18.464
5	-7.6	7.786	11.328
6	-7.5	3.610	9.680
7	-7.4	10.454	14.666
8	-7.4	3.989	9.621
9	-7.4	6.926	13.094

Table 6: ResultBiovia Discovery Studio Client 2020

Quinolone	Absolute energy	Clean energy	ConfNumber	Mol_Number	Relative energy	Pose_Number
1.	-8.5	-8.6	648	1	2.86621	1
2.	-8.4	-8.4	76	1	2.58367	2
3.	-8.2	-8.2	108	1	1.35342	3

Quinolone showed a strong binding affinity with the drug target. The interaction of ligand and the target protein was visualized through PyMol as shown in Figure 3. In this *in silico* study, Quinolone may act as an inhibitor and it can be used in a form of drug which may control tuberculosis. Thus this drug can prevent tuberculosisand may form effective drug for the treatment of tuberculosis.

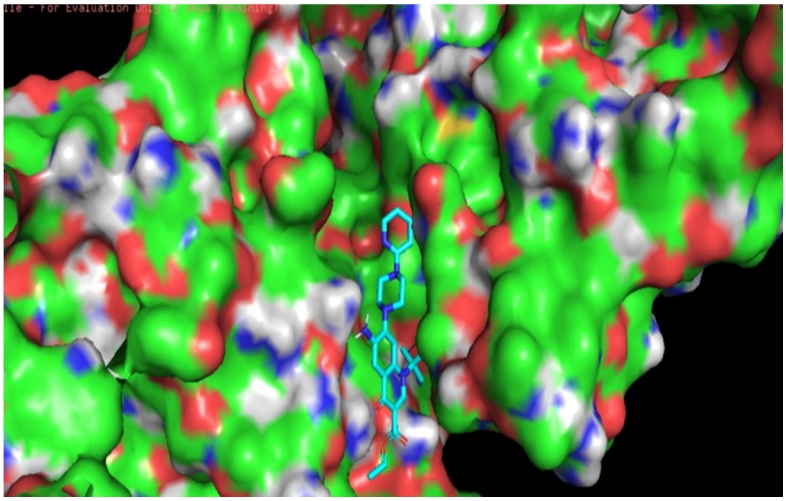


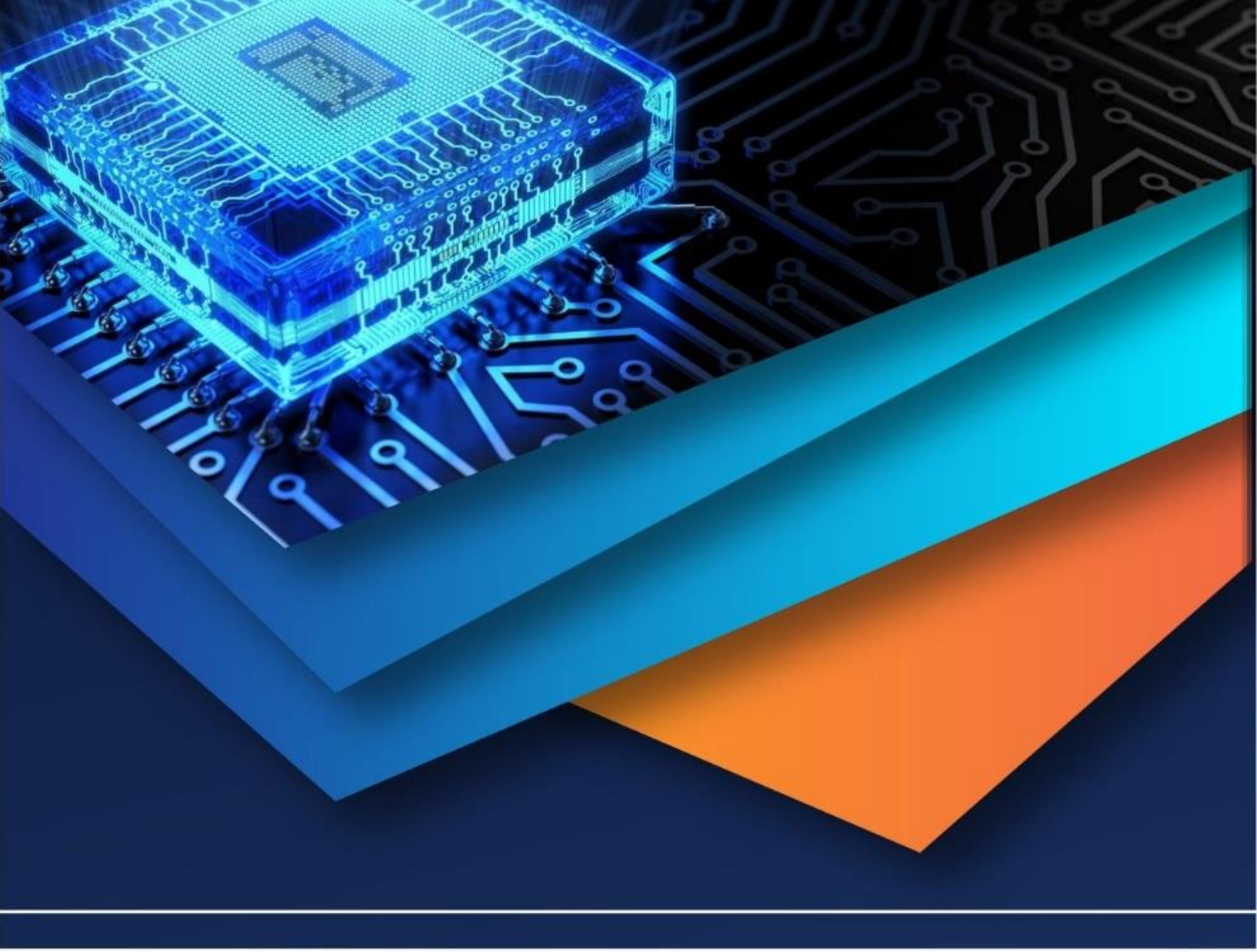
Figure 3: Interaction of INHA with Quinolone

IV. CONCLUSION

The Tuberculosis disease is the airborne disease that is caused by *M. tuberculosis.* The vaccine called Bacillus Calmette Guerin was one of the most effective therapies to prevent tuberculosis in the human. Tuberculosis is treated with several different types of antibiotics. To protect the body from the encounter of these bacteria, various new techniques are being used to improve the tuberculosis vaccines. Molecular docking was carried out to identify the interactions of different compounds with target protein. Docking studies showed that the strong affinity of Quinolonetoward tuberculosis related protein. Thus, according to the *in-silico* study, Quinolonemay act as an inhibitor and it may be used in a form of drug which may control tuberculosis and may be used as a promising antituberculosis agent for the treatment of tuberculosis. Thus, this drug may prevent tuberculosis and may form effective drug for the treatment of tuberculosis.

REFERENCES

[1] Trial, T. P. (1980). Trial of BCG vaccine in South India for tuberculosis prevention. *Indian J Med Res*, *72*, 1-74.
[2] Khare, N., Khare, P and Singh, D. (2018). A Review: History, Structure, Diagnosis and Treatment of Tuberculosis Disease. Mycobacterial diseases, 8(2).
[3] Pavan, F. R., &Leite, C. Q. F. (2009). What is "Mycobacterium tuberculosis"?. *Tuberculosis*, *27*, 28.
[4] Van Crevel, R., Ottenhoff, T. H., & Van Der Meer, J. W. (2002). Innate immunity to Mycobacterium tuberculosis. *Clinical microbiology reviews*, *15*(2), 294-309.
[5] Parrish, N. M., Dick, J. D., &Bishai, W. R. (1998). Mechanisms of latency in Mycobacterium tuberculosis. *Trends in microbiology*, *6*(3), 107-112.
[6] Russell, D. G. (2001). Mycobacterium tuberculosis: here today, and here tomorrow. *Nature reviews Molecular cell biology*, *2*(8), 569-578.
[7] Fitzgerald, D. H. D. W., Sterling, T. R., & Haas, D. W. (2005). Mycobacterium tuberculosis. *Principles and practice of infectious diseases*, *6*, 2852-2886.
[8] Morris, G. M., & Lim-Wilby, M. (2008). Molecular docking. In *Molecular modeling of proteins* (pp. 365-382). Humana Press.
[9] Bank, P. D. (1971). Protein data bank. *Nature New Biol*, *233*, 223.
[10] Kim, S., Thiessen, P. A., Bolton, E. E., Chen, J., Fu, G., Gindulyte, A., ...& Wang, J. (2016). PubChem substance and compound databases. *Nucleic acids research*, *44*(D1), D1202-D1213.
[11] Dallakyan, S., & Olson, A. J. (2015). Small-molecule library screening by docking with PyRx. In *Chemical biology* (pp. 243-250). Humana Press, New York, NY.
[12] Zhang, M. Q., & Wilkinson, B. (2007). Drug discovery beyond the 'rule-of-five'. *Current opinion in biotechnology*, *18*(6), 478-488.
[13] Goodsell, D. S., Morris, G. M., & Olson, A. J. (1996). Automated docking of flexible ligands: applications of AutoDock. *Journal of molecular recognition*, *9*(1), 1-5.
[14] DeLano, W. L. (2002). PyMOL.



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