Gurukul International Multidisciplinary Research Journal (GIMRJ)*with* International Impact Factor 8.357
Peer Reviewed Journal
https://doi.org/10.69758/GIMRJ/2504I5VXIIIP0029

e-ISSN No. 2394-8426
Monthly Issue
APR-2025
Issue–IV, Volume–XIII

Molecular Docking Analysis of Reduced Hydrazones of Isoniazid

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Abstract
Tuberculosis remains a major global health challenge, necessitating the development of novel therapeutic agents. In this study, molecular docking analysis was performed using PyRx software to evaluate the binding interactions between the 1ZID protein, a key tuberculosis drug target and reduced bishydrazones of isoniazid and dialdehydes derived from salicylaldehyde. The docking results demonstrated that reduced hydrazones with a spacer of four-carbon chain exhibited the highest binding affinity, emphasizing the role of chain length of spacer in ligand-protein interactions. These findings provide valuable insights into the structural optimization of isoniazid derivatives, potentially enhancing their anti-tuberculosis efficacy.

Keywords: 1ZID, Isoniazid, Hydrazones, etc.

Introduction:

Mycobacterium tuberculosis (Mtb) is the bacterium responsible for causing tuberculosis (TB), a highly serious infectious disease. TB remains a significant global health issue as the second leading infectious cause of death worldwide. The medically important drug isoniazid (INH) was first discovered in 1950 for the treatment of tuberculosis[1]. The treatment of tuberculosis has become more challenging due to medication resistance, which arises from patient noncompliance with treatment protocols and genetic mutations in the organism. Therefore, the development of new INH derivatives is urgently required to address this issue[2]. In order to improve a drug's bioavailability at the ill sites, a lot of research is now being done because many existing treatment options for a variety of diseases require high dosages of a medication, which may have detrimental off-site effects[3]. One novel and possibly useful technique is to use hydrazone linkers to cause the release of drugs in response to certain disease physiologies and environmental factors. One of the physiologically important Schiff bases is hydrazone. "Schiff bases" are substances that are produced when primary amines combine with carbonyl compounds[4]. Since the hydrazone chemical family includes a class of azomethine molecules, hydrazones are a great place to start when creating bioactive heterocycles. In coordination chemistry, pharmacology, and cosmetics, hydrazone molecules are important. Hydrazone's chemical properties are greatly influenced by its carbon and nitrogen atoms. Pharmaceutical and medical chemists are interested in hydrazones because of their special characteristics[5].Certain synthesised hydrazide-hydrazones have been shown to be less dangerous than hydrazides when the NH2 group in hydrazide is blocked. These results add to the increasing importance of the hydrazide-hydrazone chemical synthesis. Hydrazone derivatives have been the focus of a lot of research lately due to their wide variety of biological activities[6-7]. Among the most significant compounds in organic chemistry are heterocyclic hydrazones, which exhibit effective activity in a variety of applications, such as

the creation of novel medications with anti-cancer, antibacterial, analgesic, antituberculosis, antimalarial, antidepressant, anticonvulsant, anti-HIV, and anti-inflammatory properties[8-25]. Part of hydrazones is schiff base. Most Schiff bases are highly susceptible to hydrolysis in the solution phase. By the most a common and gentle reducing agent, such as sodium borohydride, to reduce the imine bond, this issue is resolved[26-27]. According to reports, a reduced Schiff base derivative exhibited notable antibacterial action at low concentrations[28]. By designing and analyzing reduced derivatives of isoniazid using molecular docking studies in PyRx, we identified potential candidates for further research. This approach serves as a cost-effective preliminary screening before conducting expensive anti-tubercular activity assays, aiding in the development of more efficient and targeted therapeutic options against tuberculosis.

Experimental:

Molecular docking is a crucial computational technique in molecular biology and bioinformatics that enables prediction of the mode and affinity of ligand-target protein interaction. PyRx (Python Prescription), an intuitive graphical user interface for the well-known molecular docking application Auto Dock Vina, was utilised in this study. The following methodical procedure guided our docking studies.

The first step was installing PyRx, which required a Python setup beforehand. Auto Dock Vina's workflow integration was made easier by the availability of PyRx for download from its official website. After the software was installed, we prepared the required input files as our next step. To make sure PyRx would work with the target protein's 3D structure, we consulted resources such as the Protein Data Bank (PDB). Using programs like Open Babel, the ligand's 3D structure was simultaneously created in a variety of formats (e.g., PDB, MOL2, SDF), which made the next docking simulations easier.

When we created a new PyRx initiative, we imported the ligand and protein structures. The meticulous setting of the docking parameters was essential to the success of our research. The exhaustiveness, search space specification, and other pertinent parameters were crucial in determining how accurate our predictions were. Then, using the Auto Dock Vina engine built into PyRx, the docking simulation was started. Constant observation made sure the simulation was completed successfully throughout this phase. After the simulation, we turned our attention to analysing the results. The docking data revealed information on the expected binding posture and affinity of the ligand. PyRx's integrated molecular visualisation capabilities enabled a thorough analysis of the binding interactions.

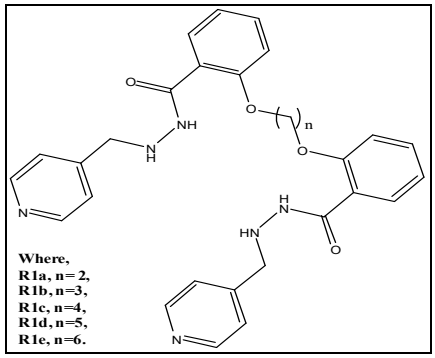

Fig.No.1 Design of Reduced Hydrazones of Isoniazid Derivatives

Results & Discussion:

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We have successfully designed (as shows in fig. No. 1) and analysed five reduced hydrazones of isoniazid by PyRx software. The molecular docking results revealed varying binding affinities for the different ligand-receptor complexes, with binding affinities (as shows in Table No 1) ranging from -8.7 kcal/mol to -9.2 kcal/mol. The docking scores suggest that all ligands exhibit favorable interactions with the target protein(1ZID), with R1c showing the highest binding affinity (-9.2 kcal/mol), followed by R1b (-9.1 kcal/mol), R1d (-9.0 kcal/mol), and R1a and R1e (-8.7 kcal/mol each).

The molecular interactions of the ligands with the target protein were analysed to identify key amino acid residues involved in binding. The residues most frequently involved in interactions across all ligands included ILE21, ALA22, PHE41, SER94, GLY96, PHE97, and ALA198, which suggests that these residues play a crucial role in ligand stabilization within the binding pocket. Notably, R1c demonstrated interactions with the highest number of amino acids (13 residues), including GLY14, ILE15, ILE16, ILE21, ALA22, PHE41, SER94, ILE95, GLY96, PHE97, THR196, and ALA198. This extensive interaction network likely contributed to its highest binding affinity (-9.2 kcal/mol). Various types of molecular interactions were observed among the ligand-protein complexes, including conventional hydrogen bonds, water hydrogen bonds, carbon-hydrogen bonds, pi-pi stacking, pi-alkyl interactions, and pi-cation interactions.

The highest binding affinity was observed for R1c (-9.2 kcal/mol), which can be attributed to its extensive interactions, particularly the presence of both hydrogen bonding and hydrophobic interactions. R1b (-9.1 kcal/mol) followed closely, benefiting from pi-pi stacking and pi-cation interactions. R1d (-9.0 kcal/mol) also displayed a strong binding affinity, enhanced by attractive charge interactions. R1a and R1e exhibited the lowest binding affinities (-8.7 kcal/mol), indicating a relatively weaker interaction with the target protein due to fewer stabilizing interactions.

Table No. 1 Binding affinity and amino acids interactions of docked ligand with types of bonding.

Sr. No.	Entry	Binding Affinity Kcal/Mol	Amino Acids	Types of Bonding
1	R1a	-8.7	SER20, ILE21, MET147,PHE149, MET155, GLY192, PRO193, ALA198.	Water Hydrogen Bond;Conventional Hydrogen Bond, Conventional Hydrogen Bond, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl.
2	R1b	-9.1	GLY14, ILE15, ILE21, ALA22, PHE41, SER94, GLY96, PHE97, THR196, ALA198.	Water Hydrogen Bond;Conventional Hydrogen Bond, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Pi Stacked Amide-Pi Stacked,Pi-Alkyl
3	R1c	-9.2	GLY14, ILE15, ILE16, ILE21, ALA22, PHE41, SER94, ILE95, GLY96, PHE97, THR196, ALA198.	Water Hydrogen Bond;Carbon Hydrogen Bond, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Pi Stacked, Amide-Pi Stacked, Alkyl, Pi-Alkyl.
4	R1d	-9.0	ILE16, SER20, ILE21, ALA22, PHE41, ASP64,	Attractive Charge, Water Hydrogen Bond;Conventional Hydrogen Bond,

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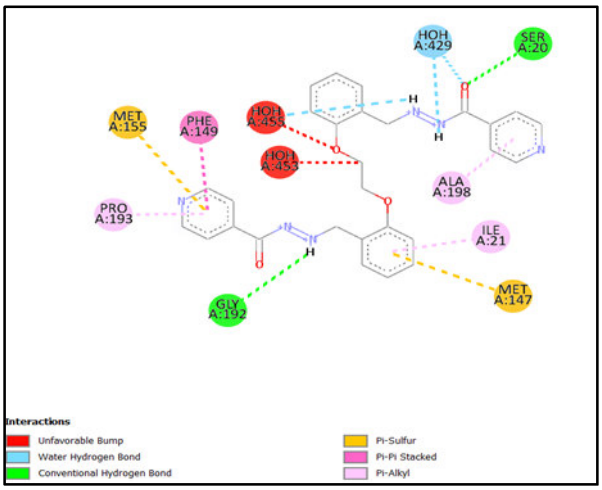
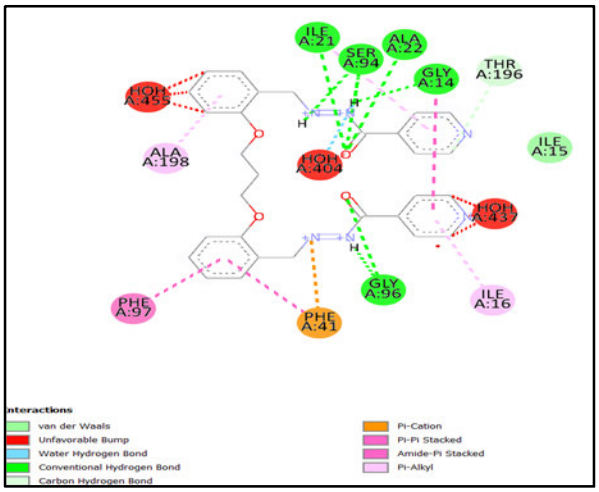
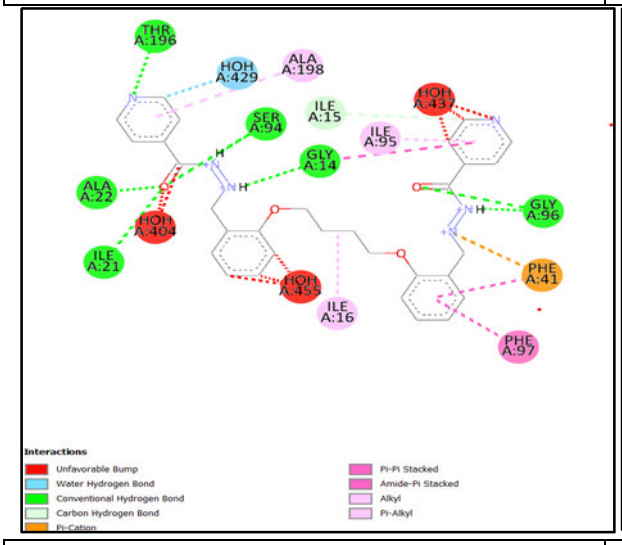
			SER94, ILE95, GLY96, PHE97, ALA198, MET199.	Water Hydrogen Bond;Pi-Donor Hydrogen Bond, Conventional Hydrogen Bond, Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl.
5	**R1e**	-8.7	ILE16, SER20, ILE21, ALA22, PHE41, ASP64, SER94, ILE95, GLY96, PHE97, ALA198, MET199.	Attractive Charge Water Hydrogen Bond;Conventional Hydrogen Bond, Water Hydrogen Bond;Pi-Donor Hydrogen Bond, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl.



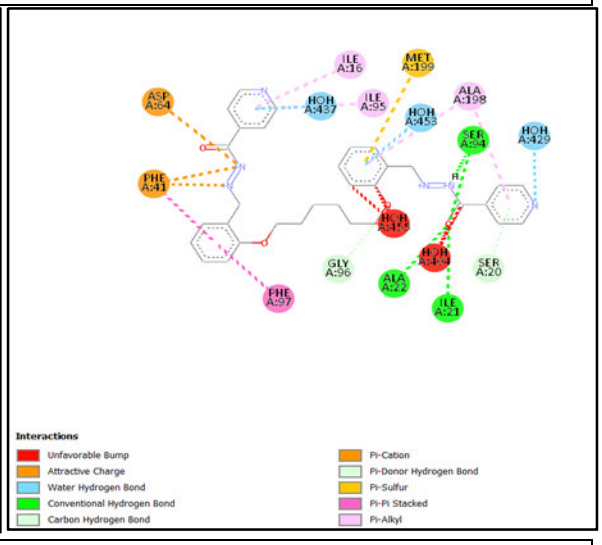
2d Interaction of R1a ligand with protein



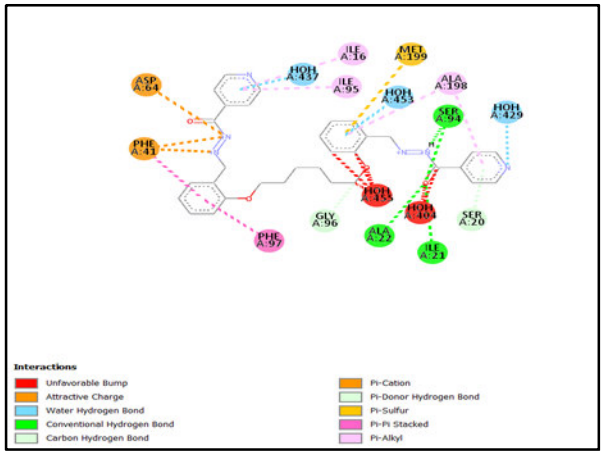
2d Interaction of R1b ligand with protein



2d Interaction of R1c ligand with protein



2d Interaction of R1d ligand with protein



2d Interaction of R1e ligand with protein

Conclusions:

In summary, our molecular docking study revealed that among the tested ligands, R1c exhibited the strongest binding affinity to the 1ZID protein, followed by R1b and R1d. The interactions observed, including hydrogen bonding, pi-pi stacking, and pi-alkyl interactions, played a crucial role in stabilizing the ligand-protein complexes. These findings provide valuable insights into the rational design of novel inhibitors with enhanced binding efficiency against the target protein. Our study highlights the potential of reduced hydrazones of isoniazid as promising candidates for tuberculosis therapy. Future studies, including molecular dynamics simulations and in vitro validation, are necessary to further assess the stability, bioavailability, and therapeutic potential of these compounds.

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Acknowledgement:

We would like to express our gratitude to the Department of Chemistry, Sant Gadge Baba Amravati University, Amravati for providing the necessary facilities for conducting this research.