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Research Article

Design, In Silico Evaluation, Synthesis and Biological Evaluation Of 4-Nitroimidazole Derivatives

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ABSTRACT

This study aimed to design and evaluate novel antitubercular agents using computational methods. Four derivatives of isoniazid and acyclovir were designed and subjected to molecular docking studies against the 3IX2 protein. The results showed that the first derivative had the lowest binding energy (-11.58) and formed three hydrogen bonds with the protein. ADMET analysis was performed to evaluate the pharmacokinetic properties of the designed compounds. Based on the molecular docking and ADMET analysis, the first derivative was identified as the most promising compound for further development as an antitubercular agent. The study suggests that this derivative could be a potential lead compound for the treatment of tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by bacteria from the Mycobacterium tuberculi complex. The primary causative agent, *Mycobacterium tuberculi*, is a slow-growing, aerobic, non-motile bacillus that is acid-fast due to its high mycolic acid content. Discovered by Robert Koch in 1882, TB is transmitted person-to-person via aerosol droplets. While M. tuberculosis is the main culprit, other species in the complex, such as *M. bovis*, *M. africanum*, *M. microti*, *M. Canetti*, *M. caprae*, and *M. pinsnipedii*, can also cause TB in humans and animals. TB primarily targets the lungs (pulmonary TB) but can also affect other parts of the body like the brain, kidneys, spine, lymph nodes, and bones (extrapulmonary TB). The pathogenesis of TB begins with inhalation of bacilli from an infected person, which reach the alveoli and are engulfed by macrophages. Instead of being destroyed, the bacteria multiply inside macrophages, and the immune system responds by forming granulomas to contain the infection. TB can be latent, with no symptoms and no contagiousness, or active, with

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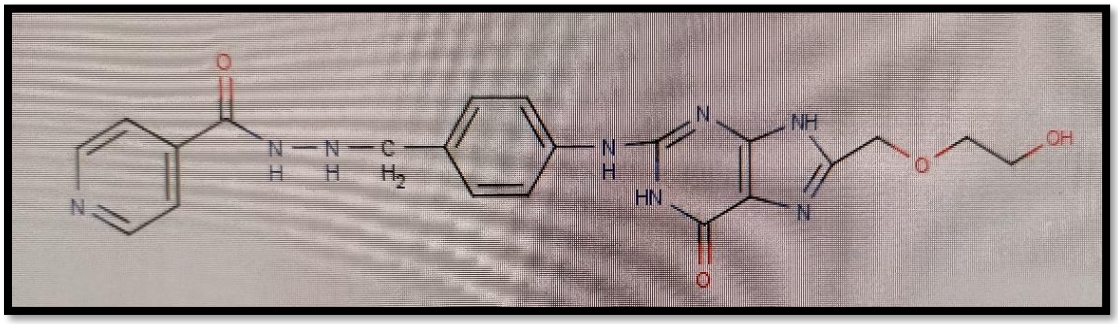
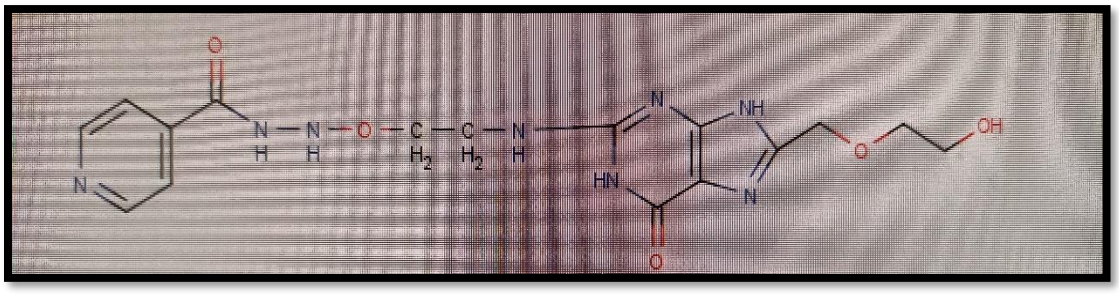
symptoms and contagiousness. Diagnosing TB involves various tests, including the Tuberculin Skin Test (TST), Interferon-Gamma Release Assays (IGRAs), sputum smear microscopy, sputum culture, chest X-ray, and molecular tests like GeneXpert MTB/RIF. Treatment typically follows a standard 6-month regimen, consisting of an intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a continuation phase with isoniazid and rifampicin. However, drug-resistant TB requires longer and more complex treatment with second-line drugs. TB can weaken the immune system, making individuals more susceptible to other opportunistic infections like cytomegalovirus (CMV) , Cancer , Candidiasis , Hepatitis , Herpes Simplex virus (HSV) , Herpes zoster (Shingles) Human Papilloma Virus (HPV), Kaposi Sarcoma , Mycobacterium Avium Complex , Non-Hodgkin Lymphoma (NHL). Despite being preventable and curable, TB remains one of the top infectious disease killers globally. According to the World Health Organization's 2023 reports, approximately 10.6 million people fell ill with TB in 2022, and 1.3 million deaths occurred among HIV-negative individuals. Access to timely diagnosis and treatment remains a significant challenge in many parts of the world.

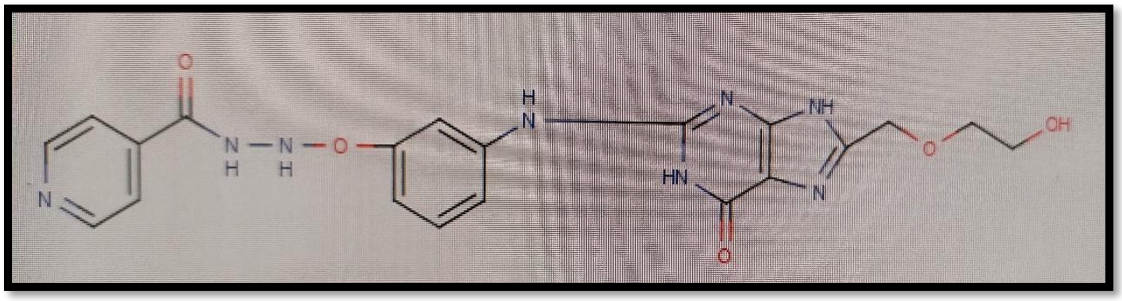
2. MATERIAL AND METHODS:

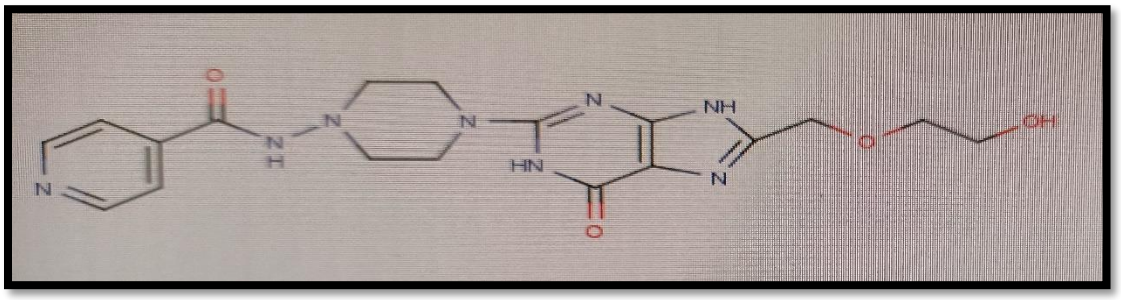
2.1 Design of Ligand:

Here isoniazid and acyclovir introduce as a parent ring in compounds and both are joined via different linkers showing possible antitubercular activity against *Mycobacterium tuberculi*.



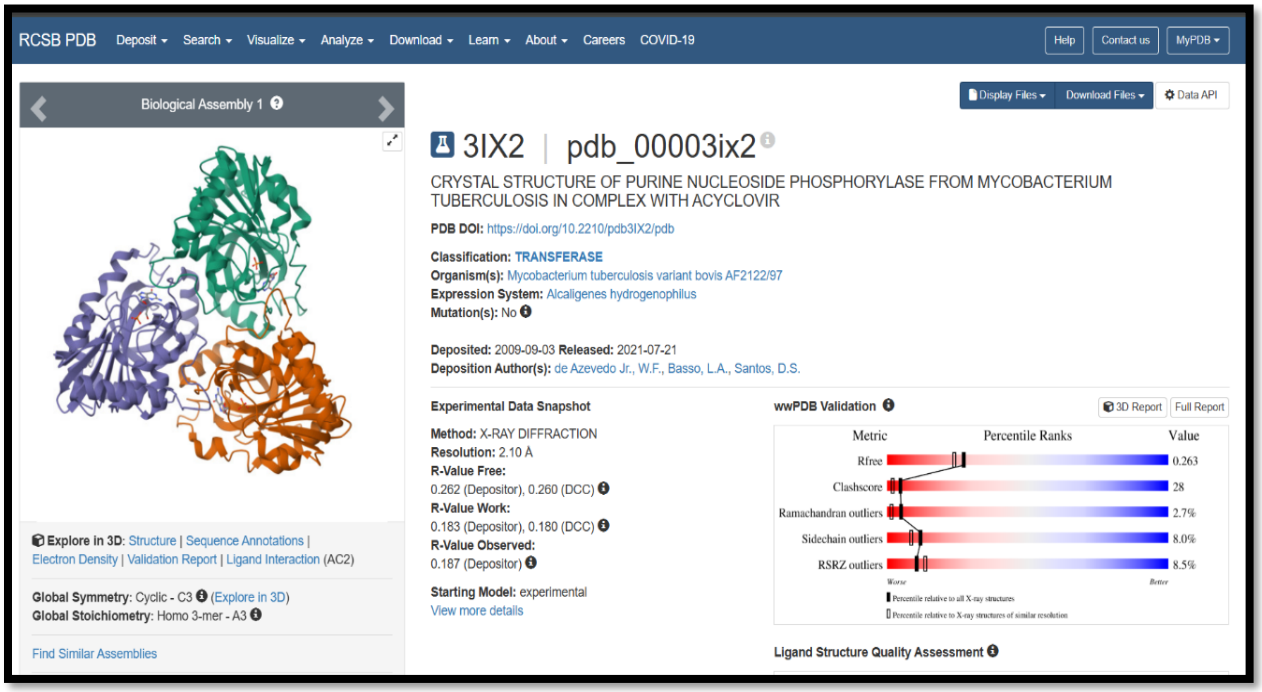






2.1 Selection of Protein For Molecular Docking:

Here isoniazid and acyclovir compounds show possible activity against the adenosine A3 receptor when analysed with Swiss Target Prediction software. We employed the 3IX2 protein from the Protein Data Bank (PDB) for the docking parent compounds. The complete docking procedure makes use of the following software programs: Biovia Discovery Studio, Auto Dock Tools, Marvin View, and Marvin Sketch. Molecular docking is a computational method employed in structure-based drug design to forecast how small molecules (ligands) interact with larger molecules (proteins or receptors). By examining binding interactions, it contributes to the creation of therapeutic compounds. Molecular docking in drug design serves multiple purposes: it aids in identifying possible drug candidates by predicting how a drug molecule (ligand) binds to a protein target (receptor), it enhances our understanding of drug-target interactions, and it eventually supports the development of drugs.



2.3 Chemical Database Search:

The protein data bank (PDB) is a database for the three-dimensional structural data of large biological molecules, such as protein and nucleic acid. The software used for chemical database search is **Swiss Target Prediction**

2.4 Chemical Structure Drawing:

Chemical structure drawing is graphic representation of the molecular structure showing how the atoms are possibly arranged in the real 3D space. The different software's are used for drawing of chemical structure i.e., **Marvin Sketch.**

2.5 Chemical Structure Presentation:

The chemical structure of drug determines its physicochemical properties and further determinates its ADMET properties. The drawn chemical structure should have modified to present in docking. The software used for this is **Marvin View**.

2.7 Ligand Preparation:

- **Step 01:** Open 'Auto Dock Tools'. Click on Ligand→ Input → Open. Browse and Select the mol2 file (Isoniazid and acyclovir.mol2)
- **Step 02:** Ligand → Torsion Tree → Detect Root
- **Step 03:** Go to Ligand → Torsion Tree → Show Root Expansion
- **Step 04:** Ligand → Torsion Tree → Choose Torsions. Then click on 'Done'
- **Step 05:** Ligand → Torsion Tree → Set Number of Torsions. Then click on 'Dismiss'
- **Step 06:** Ligand → Output → Save as PDBQT (Isoniazid and acyclovir. pdbqt)

2.8 Protein Preparation:

- **Step 01:** Open 'Auto Dock tools'. Click on File → Read Molecule. Browse and open 3IX2_edited.pdb
- **Step 02:** Edit → Hydrogen → Add. Select 'Polar Only' and then click 'OK.
- **Step 03:** Click on File → Save → Write PDB. Click 'Browse'. Save the file as 3IX2_H.pdb'. Click 'OK.

2.9 Preparation of Grid:

- **Step01:** Open Auto Dock tools. Go to Grid → Macromolecules → Open. Browse to open 3IX2_H.pdb'. When a 'Save' dialogue box opens, save it as 3IX2_H.pdbqt'
- **Step 02:** Go to Grid → Set Map Types → Directly. In Map Types type in "A C H Cl Br I F S P HD N NA OA SA"
- **Step 03:** Go to Grid → Grid Box
- **Step 04:** Click on Center → Pick an atom. Enter the XYZ coordinates obtained from the PDB file in the boxes marked X, Y and Z centers respectively. If more than one coordinates are found take mean of the coordinates. In the "number of points in x, y and z dimensions", slide to 60, 60 and 60 respectively.
- **Step 05:** File → Close saving current
- **Step 06:** Go to Grid → Output → Save GPF.
- **Step 07:** Enter the file name as <[3IX2].gpf> (3IX2.gpf)

2.10 Executing the commands for Docking:

- **Step 01:** Copy the three files 'autodock4.exe', 'autogrid4.exe' and 'cygwin1.dll' to the folder which contains all the files prepared in the above steps

- **Step 02:** Press Windows (key with windows flag)+R to open RUN command and type 'cmd' and click 'OK' to open the command prompt

- **Step 03:** Go to the directory which contains all the files prepared in the above step. The commands for going in and out of the folder are: 'cd <space><folder name>'. To go out the folder: 'cd..'

- **Step 04**: Type the following command for running autogrid (Note: Change the protein name accordingly) 'autogrid4.exe –p 3IX2.glg' Wait until it shows 'complete' and then enter the following command for running AutoDock (Note: Change the ligand name Accordingly) 'autodock4.exe –p Isoniazid and acyclovir.dpf –l Isoniazid and acyclovir.dlg' Wait until it shows complete

2.11 Docking Analysis:

1. Open docking log file and find RMSD table.

2. Identify runs with highest ranking and minimum binding energy.

3. Analyze docking results in AutoDock Tools.

4. Visualize ligand-receptor interactions and identify hydrogen bonds.

5. Save docked complex and open in Discovery Studio.

6. Visualize ligand binding site atoms and hydrogen bonds.

2.12. ADMET

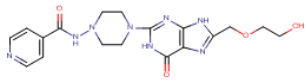
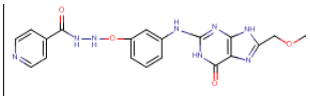
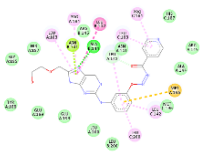
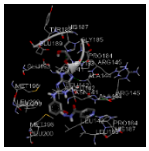
Step 1. Go to admetSAR (http://Immd.ecust.edu.cn:8000/)

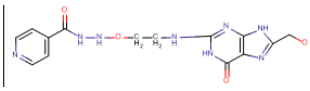
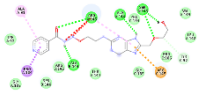
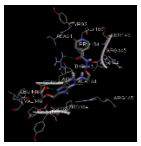
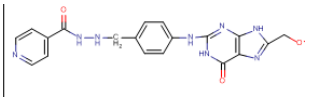
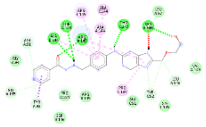
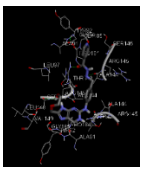
Step 2. Click on " Predict "

Step 3. Copy the SMILES from the database and paste it in search bar

Step 4. After clicking on "Predict" button, following result is displayed.

RESULT AND DISCUSSION:

Sr. no	IUPAC Name	Binding Energy	No. Of Hydrogen	Structure	2D Structure	3D Structure
1.	N-(4-{8-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1H-purin-2-yl}piperazin-1-yl)pyridine-4-carboxymide	-11.58	3			
2.	N-[3-({8-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1H-purin-2-yl}amino)phenoxy]pyridine-4-carbohydrazide	-10.73	1			

3.	N-[3-({8-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1H-purin-2-yl}amino)ethoxy]pyridine-4-carbohydrazide	-9.69	4			
4.	N-[3-({8-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1H-purin-2-yl}amino)phenyl]methyl}pyridine-4-carbohydrazide	-9.93	5			

According to this table, 1st derivative of isoniazid and acyclovir with binding energy -11.58 occur as most suitable as compare to other 3 derivatives.

CONCLUSION:

According to ADME properties of all 4 derivatives, the derivative 1 with most least binding energy (-11.58) is suitable for docking and synthesis. So, we going to synthesize derivative 1st for our final project.

REFERENCES

1. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. Journal of Computational Chemistry, 30(16), 2785-2791.
2. Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., & Zoete, V. (2014). Swiss Target Prediction: a web server for target prediction of bioactive small molecules. Nucleic Acids Research, 42(W1), W32-W38.
3. Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., ... & Tang, Y. (2012). admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. Journal of Chemical Information and Modeling, 52(11), 3099-3105.
4. Smith, P. J., & Dowd, C. S. (2020). Tuberculosis Pathogenesis. In StatPearls [Internet]. StatPearls Publishing.
5. World Health Organization. (2022). Global Tuberculosis Report 2022.
6. Cole, S. T., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., ... & Barrell, B. G. (1998). Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature, 393(6685), 537-544.
7. Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. Nature Reviews Drug Discovery, 3(11), 935-949.
8. 2. Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. Current Computer-Aided Drug Design, 7(2), 146-157.
9. Wang, Y., Xing, J., Xu, Y., Zhou, N., Peng, J., Xiong, Z., ... & Zheng, M. (2015). In silico ADME/T modelling for rational drug design. Quarterly Reviews of Biophysics, 48(4), 441-457.

10. Dye, C., Scheele, S., Dolin, P., Pathania, V., & Raviglione, M. C. (1999). Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA, 282(7), 677-686.
11. 2. Russell, D. G. (2007). Who puts the tubercle in tuberculosis? Nature Reviews Microbiology, 5(1), 39-47.
12. Steingart, K. R., Henry, M., Ng, V., Hopewell, P. C., Ramsay, A., Cunningham, J., ... & Pai, M. (2006). Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. The Lancet Infectious Diseases, 6(9), 570-581.
13. 4. Zumla, A., Nahid, P., & Cole, S. T. (2013). Advances in the development of new tuberculosis drugs and treatment regimens. Nature Reviews Drug Discovery, 12(5), 388-404.
14. Gandhi, N. R., Nunn, P., Dheda, K., Schaaf, H. S., Zignol, M., van Soolingen, D., ... & Bayona, J. (2010). Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. The Lancet, 375(9728), 1830-1843.
15. Cole, S. T., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., ... & Barrell, B. G. (1998). Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature, 393(6685), 537-544.
16. Congreve, M., Chessari, G., Tisi, D., & Woodhead, A. J. (2008). Recent developments in fragment-based drug discovery. Journal of Medicinal Chemistry, 51(13), 3661-3680.
17. Ekins, S., Mestres, J., & Testa, B. (2007). In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. British Journal of Pharmacology, 152(1), 9-20.

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