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In silico Drug Discovery for Novel Inhibitors of DNA Gyrase A as a Potent Drug Candidate for Treatment of Tuberculosis

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ABSTRACT

Computational approaches are an important part of drug discovery research. Computational methods improve the ability to identify and evaluate potential drug molecules. DNA gyrase is a type II topoisomerase that can introduce negative supercoils into DNA at the expense of ATP hydrolysis. It is essential in all bacteria but absent from higher eukaryotes, making it an attractive target for antibacterials. In this study we carried out docking experiment to analyse the interaction of *M. tuberculosis* protein DNA gyrase subunit A with 22 different ligands obtained by pharmocophore building and screening. The new compound can thus prove out to be a best inhibitor for DNA gyarase leading to cure of the disease. We have identified 2 novel compounds with minimum binding energy and their toxicity was predicted.

Keywords: *Mycobacterium tuberculosis*, DNA gyrase, Docking, Multi-drug resistance, Pharmacophore, ADMET Properties.

1. INTRODUCTION

Tuberculosis (TB) is a disease caused by infection from the bacteria M. tuberculosis (Gram-positive bacterium). About 1.5 million people die from tuberculosis each year [1]. Due to the development of Multi-drug resistant Mycobacterium tuberculosis strains, the drugs showed less efficiency on the targets. Most people who are exposed to TB never develop symptoms because the bacteria can live in an inactive form in the body. But if the immune system weakens, such as in people with HIV or elderly adults, TB bacteria can become active. Active TB disease can be fatal if left untreated [2]. The disease has resurfaced in potent new forms -- multidrug-resistant TB and extensively drug-resistant TB. Today, these new and dangerous forms of the disease resistant to some of the commonly used drug treatments have created a public health crisis in many large cities worldwide. Drug-resistant TB is more difficult to treat than ordinary TB. The medicines used against it have a greater number of side effects, and have to be taken for at least 18 months [3]. There are more than twenty drugs that are currently used for the treatment of TB -First line, second line & new TB drugs [4]. Different drugs have different mechanisms of action and different targets and many of them are used in combinations. Mutations in the coding genes have been shown as the molecular basis for drug resistance in an organism [1]. In this study we are searching for novel potent compounds as future tuberculosis drugs which targets bacterial DNA gyrase using pharmacophore based drug designing approach.

2. MATERIALS AND METHODS

2.1 Inhibitors and KNIME data mining tool

11 DNA gyrase inhibitors (Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Norfloxacin, Novobiocin, Ofloxacin, Pefloxacin, Sparfloxacin, Moxifloxacin) were searched from available literature. Sdf files were downloaded from Drugbank database

and opened in marvin view application. All the inhibitor molecules were cleaned in 2D and 3D and saved all as mol2 files (tripos mol2). A complex of all of them was made in Discovery Studio. This complex file was used to configure sdf reader node in the KNIME workflow for similarity check purpose.

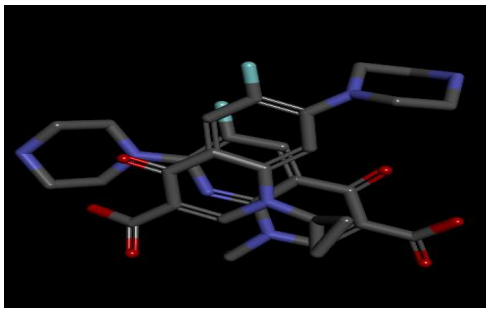

Figure 1. Complex of molecules in Discovery Studio.

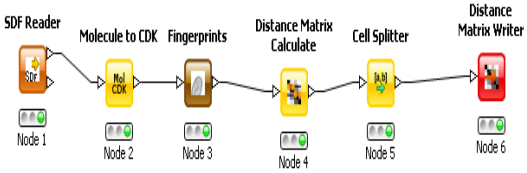

Figure 2. Similarity check knime workflow.

	A	B	C	D	E	F	G	H	I	J	K
1											
2	0.38843										
3	0.180365	0.420152									
4	0.324752	0.480138	0.209581								
5	0.081365	0.379237	0.164319	0.321212							
6	0.275654	0.453125	0.123967	0.275676	0.263918						
7	0.0563	0.374732	0.224256	0.316327	0.101604	0.314516					
8	0.651351	0.652742	0.617918	0.585052	0.666214	0.581841	0.667121				
9	0.324752	0.480138	0.209581	0	0.321212	0.275676	0.316327	0.585052			
10	0.085791	0.39485	0.245413	0.307692	0.126005	0.333333	0.03125	0.676712	0.307692		
11	0.195062	0.435583	0.254464	0.395753	0.154639	0.332673	0.238213	0.682306	0.395753	0.256858	
12											
13											
14	Disimilar	0.33663									
15	Similar	0.66337									
16											

Figure 3. Output of Similarity checking in KNIME data mining tool

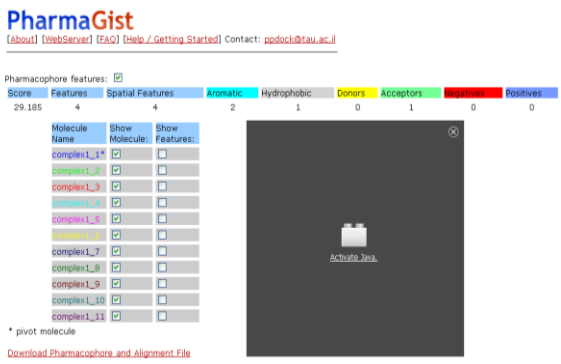

Figure 4. Pharmacophore results

The similarity between inhibitors came out to be 0.66%. Pharmacophore was detected for all 11 inhibitor molecules using PharmaGist giving complex file of molecules in mol2 format as input [5].

ZINCPharmer was used for searching the purchasable compounds of the ZINC database using the Pharmer pharmacophore search technology [6]. 220 hits were obtained. Duplicates were removed using "Split Molecule" executable jar file. 33 hits were obtained.

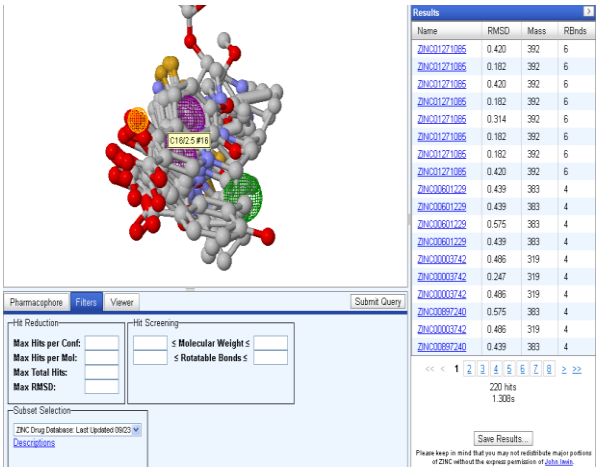

Figure 5. ZINCPharmer results

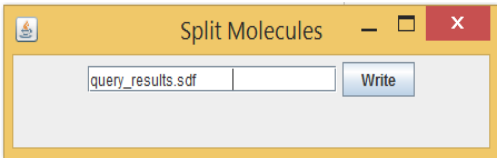

Figure 6. Split Molecule executable jar file.

PDBsum ligplot was checked for pdb Id 5bs8 (*Mycobacterium tuberculosis* DNA gyrase PDB Id). 5bs8 PDB file was downloaded from RCSB protein data bank. Interacting residue was checked from ligplot (Arg128(A)-NH1 and NH2) and corresponding residue was searched in cleaned 5bs8 pdb file (hetero atoms, water molecules and other groups removed) to get x, y, z coordinates. The average of 4 was taken and final coordinates were x=32.22575, y=3.28625, z=27.693.

Docking was performed using Autodock4 [7] for all 11 molecules using above mentioned coordinates for 10 runs. Steps were protein preparation, ligand preparation, grid preparation, docking parameter preparation. Grid and docking commands were run in command prompt window and 1st 10 runs in RMSD Table of dlg file were used in docking analysis. Binding energy, electrostatic energy, torsional energy, number of hydrogen bonds formed, interacting residues were noted in Docking analysis. 5 inhibitors with good binding energy were selected and a complex was made in discovery studio. Pharmacophore was detected in PharmaGist (4 features, SCORE=22.062). ZINCPharmer was used for searching compounds (M.W<=500). 244 hits were obtained. After removing duplicates using

"Split Molecule" 22 hits were obtained. These 22 novel compounds were docked using Autodock4 (genetic algorithm run 35). Results were analysed.

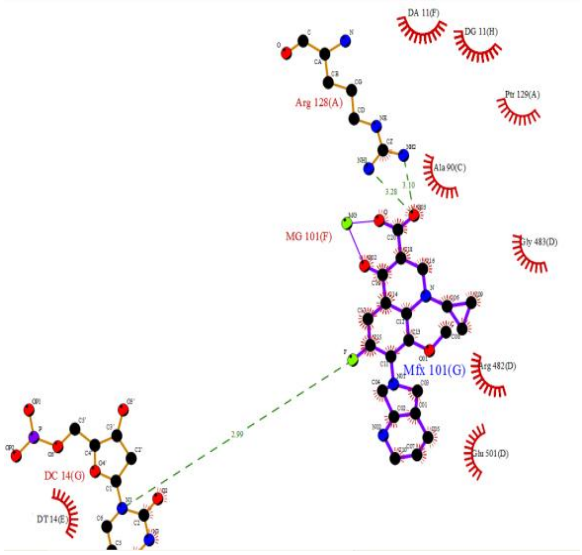

Figure 7. Ligplot

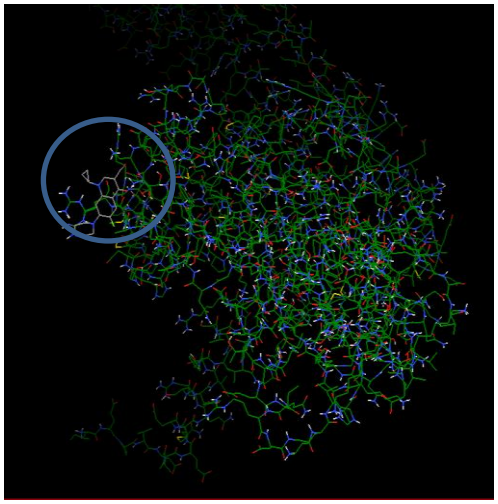

Figure 8. Protein and ligand interaction in Autodock.

3. RESULTS AND DISCUSSION

The most repeating residue was THR130 with minimum binding energy -8.26 and -7.96 for ligand 16 and 14 respectively.

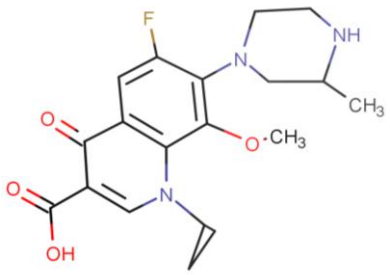

Figure 9. Ligand 16.

Toxicity of both the ligands was predicted using admetSAR using their SMILES notation. These ligands are Gatifloxacin and Moxifloxacin respectively. Gatifloxacin has the minimum binding energy as compared to Moxifloxacin.

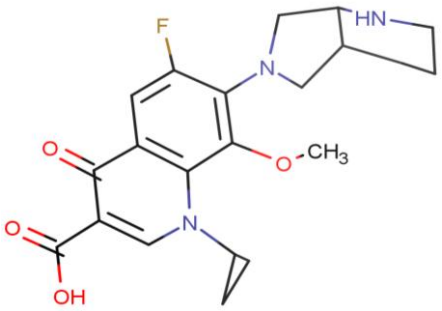

Figure 10. Ligand 14.

4. CONCLUSION

As the cases of Multi drug resistant tuberculosis is increasing, it has become important to find new ways to deal with this problem. The concept of inhibiting DNA gyrase of *Mycobacterium tuberculosis* is good. Many Fourth-generation fluoroquinolones are available for treatment and Gatifloxacin and Moxifloxacin are one among them. In this study we came to know that Gatifloxacin is a better target compared to Moxifloxacin having good interaction and binding affinity found in docking experiments. In future, many Gatifloxacin derivative drugs can be developed for treatment of multi-drug resistant tuberculosis.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

1. A. Sasikalaveni, A. Wilson Aruni et al., (2014), 'Computational Prediction and In Silico Analysis of Gyrase Gene QRDR Region Coding Drug Resistance among *Mycobacterium Tuberculosis* Isolates of India', *International Journal of Computational Bioinformatics and In Silico Modeling*, pp. 362-368.
2. Understanding Tuberculosis -- the Basics. (2016, July 15). Retrieved from http://www.webmd.com/lung/understanding-tuberculosis-basics
3. About the treatment –The Truth About TB. (2016, July 15). Retrieved from http://www.thetruthabouttb.org/treatment/about-the-treatment/
4. TB Drugs – First line, second line & new TB drugs. (2016, July 22). Retrieved from http://www.tbfacts.org/tb-drugs/
5. Schneidman-Duhovny D1, Wolfson HJ et al., (2008), 'PharmaGist: a webserver for ligand-based pharmacophore detection.', *Nucleic Acids Research*, pp. W223–W228.
6. David Ryan Koes and Carlos J. Camacho, (2012), 'ZINCPharmer: pharmacophore search of the ZINC database', *Nucleic Acids Research*, pp. W409–W414.
7. Garrett M. Morris, Arthur J. Olson et al., (2009), 'AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility', *J Comput Chem.*, pp. 2785–2791.

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