**Journal of Computational Methods in Molecular Design, 2015, 5 (4):120-128**

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**ISSN : 2231- 3176**
**CODEN (USA): JCMMDA**

# Molecular docking studies on mycobacterial tuberculosis-6-oxopurine phosphoribosyltransferase EMRB with pyrimidine derivatives

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**ABSTRACT**

Pyrimidine derivatives are associated with broad spectrum of biological activities including anti-microbial, anti-*cancer, anti-inflammatory etc. This prompted us to use compounds containing pyrimidine moiety and to evaluate for anti microbial activity. The present study is an in silico approach that aims at finding out the potency of pyrimidine derivatives against multidrug resistant protein of Mycobacterium tuberculosis. In the present work, a complete molecular docking and visualisation of the interaction between multidrug resistance protein (MTB) and pyrimidine derivatives are performed. Drug discovery and development involves ligand selection, protein target identification, protein modeling and molecular docking studies. Molecular docking of the active compounds 'pyrimidine' into Mycobacterial tuberculosis-6-oxopurine phosphorisbosyltransferase was carried out using 'Flexible Docking' protocol of Discovery Studio 4.0 software in order to predict the affinity and orientation of the synthesized compounds at the active site of the protein. ADMET properties of the compounds were also found to be satisfactory. 5-(4-methoxybenzyl)-6-aminopyrimidine-2,4 (3H,5H)-dione showed good interactions with Mycobacterial Tuberculosis – 6-Oxopurine Phosphoribosyltransferase protein and had good libdock score (47.244) and ligscores1 &2 (4.85, 5.07).*

**Keywords:** Pyrimidine, Mycobacterium tuberculosis, Discovery Studio, libdock score, hydrogen bond interaction, molecular docking.

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## INTRODUCTION

Heterocyclic compounds carrying pyrimidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature. Pyrimidine nucleus is an important core of many drug molecules pyrimidine and its analogues are reported in literature for varied pharmacological activities like antihistamine and antibacterial inhibitors, and anti tubercular agents. It is known that clinically oxiconazoe having an imidazole moiety exhibits strong antimicrobial activity [1-3].

Pyrimidine are an important class of heterocyclic compounds which possess a wide range of biological activities such as anticancer, antibacterial, anti inflammatory, antiviral, anti tubercular, antihypertensive and anticonvulsant. Biological activity of these heterocycles has helped the medicinal chemist to plan, organize and implement newer approaches towards discovery of newer drugs [4-6].

Docking is an important methodology that can be used in the study of protein ligand interaction properties such as binding energy, geometry complementarity, electron distribution, hydrogen bond donor/acceptor, hydrophobicity and polarizability. Docking is the formation of non dent protein-ligand complexes. Given the structures of a ligand

and a protein, the task is to predict the structures of the resulting complex. This is the so-called docking problem. Because the native geometry of the complex can generally be assumed to reflect the global minimum of the binding free energy, docking is actually an energy-optimization problem [7-10].

In recent years the search for novel drugs has evolved from a process of trial and error into a sophisticated procedure including several computer based approaches. In structure-based design the structures of known target proteins are used to discover new compounds of therapeutic relevance. Hence, molecular docking contributes a major role in drug discovery, in the identification of innovative small scaffold exhibiting the important properties with selectivity for the target together with reasonable ADME profile, lead and or drug likeness [10-13].

*Mycrobacterium tuberculosis* (MTB) is a pathogenic bacterial species of the genus Mycobacterium and the causative agent of most cases of tuberculosis. Tuberculosis (TB), a lung injection and is a contagious and deadly disease which has added to the woes of mankind. The main reason for the prevalence of this disease is emergence of multi-drug resistance.

*Mycrobacterium tuberculosis* strains poses financial burden in the developing countries and attempt to synthesize a new drug with novel mechanism of action has been unsuccessful [14-15].

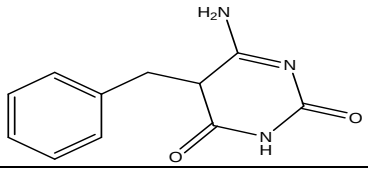
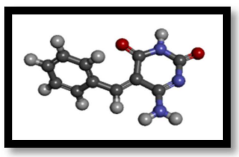
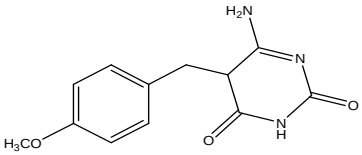
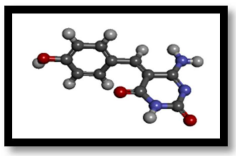
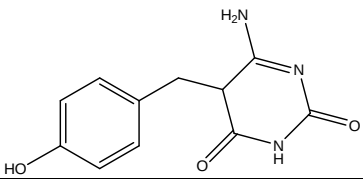
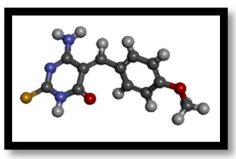
## MATERIALS AND METHODS

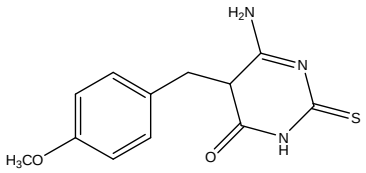
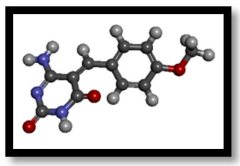
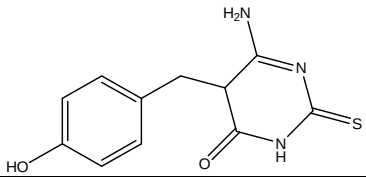
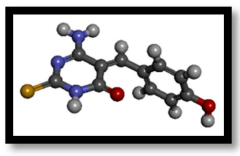
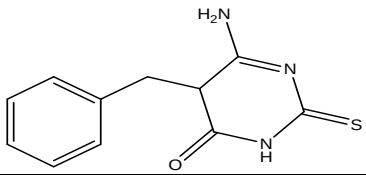
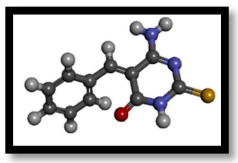
All computational studies were carried out using Discovery Studio 4.0. Discovery Studio is a suite of software which is used for simulating small molecule and macromolecule systems.

### Ligand preparation

The ligands (small molecules) 6-amino-5-benzylpyrimidine-2,4 (3H,5H)-dione (**S1**), 5-(4-methoxy)-6-aminopyrimidine2,4 (3H,5H)-dione (**S2**), 5-(4-hydroxybenzoyl)-6-aminopyrimidine-2,4 (3H,5H)-dione (**S3**), 5-(4-hydroxybenzyl)-6-amino-2,3-dihydro-2-thioxopyrimidin-4-(5H)-one (**S4**), 5-(4-methoxybenzyl)-6-amino-2,3-dihydro-2-thioxypyrimidin-4-one (**S5**), and 6-amino-5-benzyl-2,3-dihydro-2-thioxopyrimidin-4-(5H)-one (**S6**) were synthesized drawn using Chemdraw (8.0) and saved in .mol format. These pyrimidine derivatives satisfy Lipinski's rule of 5. The saved ligands were later imported and minimized using 'Prepare ligands' protocol after adding hydrogen bonds.

**Table 1. Chemical Names of Synthesised Compounds with 2D and 3d Structure Used for Docking**

| S.No | Compound Name | 2D structure | 3D structure |
|---|---|---|---|
| S1 | 6-amino-5-benzylpyrimidine-2,4 (3H,5H)-dione |  |  |
| S2 | 5-(4-methoxybenzyl)-6-aminopyrimidine-2,4 (3H,5H)-dione |  |  |
| S3 | 5-(4-hydroxybenzyl)-6-aminopyrimidine-2,4 (3H,5H)-dione |  |  |

| | | | |
|---|---|---|---|
| S4 | 5-(4-hydroxybenzyl)-6-amino-2,3-dihydro-2-thioxopyrimidin-4 (5H)-one |  |  |
| S5 | 5-(4-methoxybenzyl)-6-amino-2,3-dihydro-2-thioxopyrimidin-4-(5H)-one |  |  |
| S6 | 6-amino-5-benzyl-2,3-dihydro-2-thioxopyrimidin-4 (5H)-one |  |  |

**Preparation of Protein Molecule**

The experiment structure of Mycobacterial tuberculosis-6-oxopurine phosphorisbosyltransferase protein (4RHT) as shown in Figure 1 was retrieved from the RCSB protein data bank in .pdb file format. The protein molecules were prepared by using 'Prepare protein' protocol of the software Discovery Studio 4.0. Active site residues were selected from the protein report given by the software.

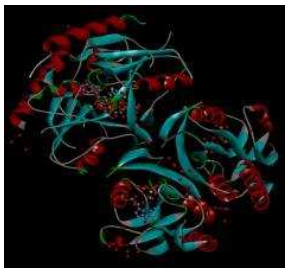


**Figure 1.Structure of mycobacterial tuberculosis-6-oxopurine phosphorisbosyltransferase protein (4RHT)**

**ADME/Toxicity Properties**

Absorption, distribution, metabolism excretion and toxicity (ADMET) determines drug like activity of the ligand molecules.

**Molecular Docking**

The 'Flexible docking' protocol of Discovery Studio was followed for the study of interaction (hydrogen bond, hydrophobic) between Mycobacterium tuberculosis 6-oxopurine phosphoribosyltransferase (4RHT) and molecules S1 to S6.

## RESULTS AND DISCUSSION

Increasing clinical failures of new drugs calls for a more effective use of ADMET technologies, becoming more advanced and reliable in terms of accuracy and predictiveness, and increase in their usage is expected during the initial development and screening phase of innovative drugs.

All the compounds were also found to have good hydrophobic interaction. As an example, the hydrophobic interaction of all compounds is shown in Figure 2 and Table 2 shows that all compounds having good ADME/T values as well as good docking results. These compounds can be easily synthesized and seem to have good

prospectus.

After successful prediction of molecular properties, values are found to be within the required range. The compounds satisfy Lipinski's rule of 5, fulfill the requirements of solubility, low polar surface area, total hydrogen bond donor/acceptor count which are important predictors of good oral bioavailability as shown in Table 2.

The best fit of ligand molecules (MTB inhibitors) in 4RHT, using Discovery Studio 4.0 docking results are recorded. The task is to predict the structure of the interacting complex. A docking method estimates the forces involved in the protein-ligand interactions viz., electrostatic, van der Waal's and hydrogen bonding and place the ligands appropriately in the active site.

The docking studies revealed the receptor-ligand complex was stabilized by hydrogen bonds, hydrophobic and electrostatic interactions. The docking scores of the synthesized compounds are presented in Table 3. In the present study all the six organic compounds were docked with 4RHT protein Mycobacterial tuberculosis–6-oxopurine phosphoribosyltransferase which is an important target of antimicrobial drugs. All the compounds were given a good docking score, though compounds6-amino-5-benzylpyrimidine-2,4 (3H,5H)-dionewere (**S1**) and 5-(4-methoxybenzyl)-6-aminopyrimidine-2,4 (3H,5H)-dione (**S2**)were found to be the best out of these having minimum binding energy i.e. -77.8651 K cal/mole and -35.0072 K cal/mole respectively, with maximum number of hydrogen bonds at the active site residues of Mycobacterial tuberculosis–6-oxopurine phosphoribosyltransferase.

Compounds **S6** & **S2** had good libdock scores (47.244, 34.716), **S1** & **S5** showed minimum binding energy (-77.8651, -60.428). Thus, molecular docking studies showed compound 6-amino-5-benzyl pyrimidine-2,4 (3H,5H)-dione (**S1**) can be considered to be a better inhibitor with stronger activities with mycobacterial tuberculosis-6-oxopurine phosphoribosyltransferase.

The result of the docking studies clearly confirms that compounds S1, S2, S3, S4, S5 and S6 are active against the tuberculosis showing potent antitubercular activity.

**S1** undergoes hydrogen bonding interactions with [THR130], [LEU129], [GLY128], [VAL124] amino acids respectively in the 4RHT protein as show in Table 3. These interactions of compounds S4, S2 and S5 have better stabilization in the 4RHT protein cavity than S3 and S6 based on the scores obtained and shows enhanced anti tubercular activity. Overall, these six compounds are eligible candidates for chemical compound synthesis in drug designing and development studies.

**Table 2. ADMET Properties**

| Sl. No. | Name | Molecular Weight | Solubility | BBB[a] | CYP2D6[b] | Hepatotoxic | AlogP98 | PSA |
|---|---|---|---|---|---|---|---|---|
| 1 | S1 | 215.214 | -2.458 | -1.159 | -6.90415 | -1.62234 | 1.113 | 85.275 |
| 2 | S2 | 231.214 | -2.195 | -1.563 | -7.94919 | -0.9106 | 0.871 | 106.09 |
| 3 | S3 | 245.241 | -2.729 | -1.306 | -8.9017 | -0.78492 | 1.097 | 94.205 |
| 4 | S4 | 261.307 | -3.344 | -0.814 | -9.12652 | -0.5901 | 1.801 | 76.904 |
| 5 | S5 | 247.28 | -2.809 | -1.072 | -8.43307 | -0.94122 | 1.576 | 88.789 |
| 6 | S6 | 231.28 | -3.073 | -0.668 | -7.38804 | -1.771 | 1.818 | 67.974 |

*a. Blood Brain Barrier, b. Cytochrome P2D6, c. Polar Surface Area 2D.*

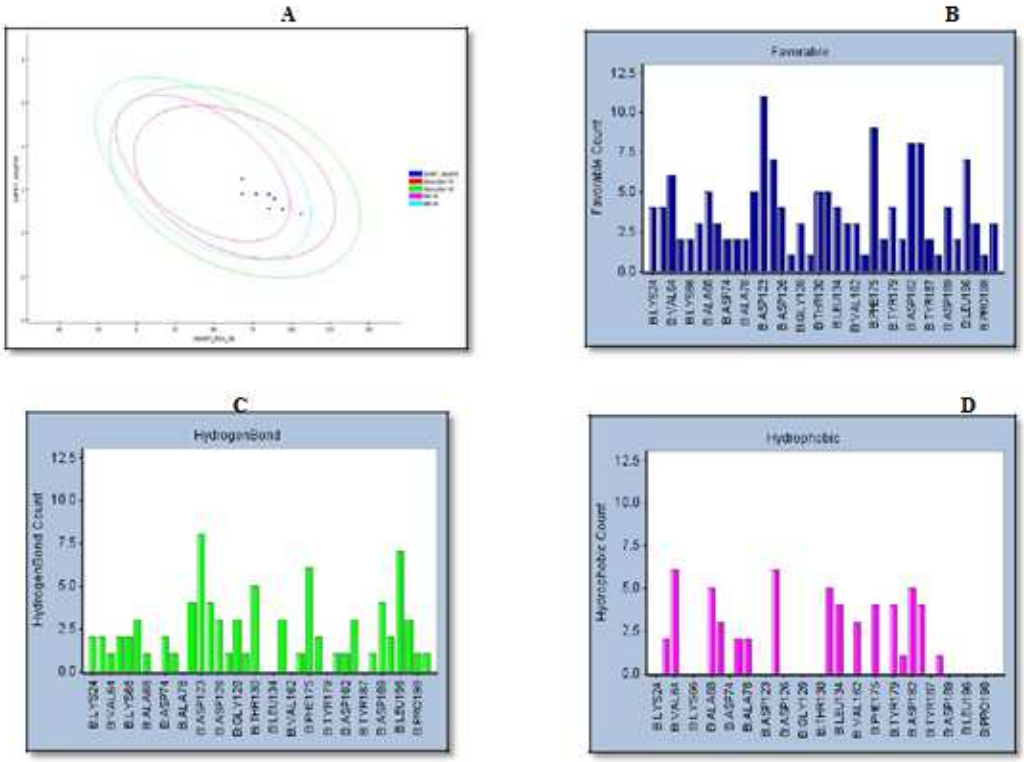
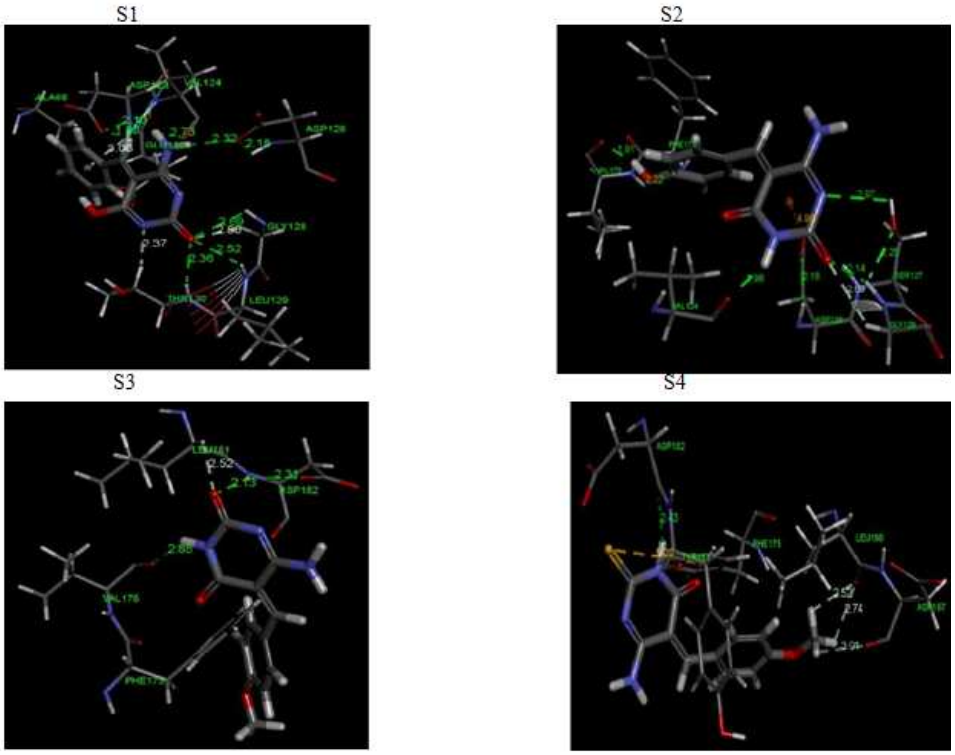
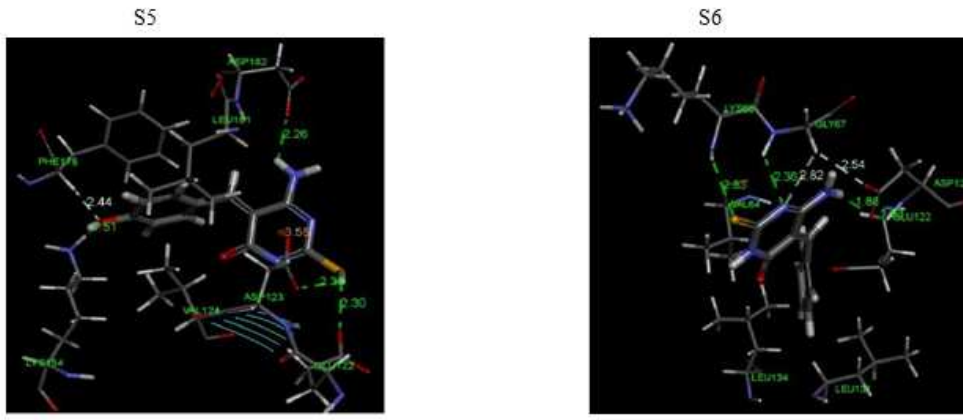



**Figure 2. Summary of Six Compounds of Residue Interaction Histograms. Docked residue Interactions**






(A) ADMET Graph (B) Favorable (C) Hydrogen bond (D) Hydrophobic.

**Figure 3.Poses with best interactions of molecules S1 – S6 respectively in Mycobacterium tuberculosis 6-oxopurine phosphoribosyltransferase (4RHT).**

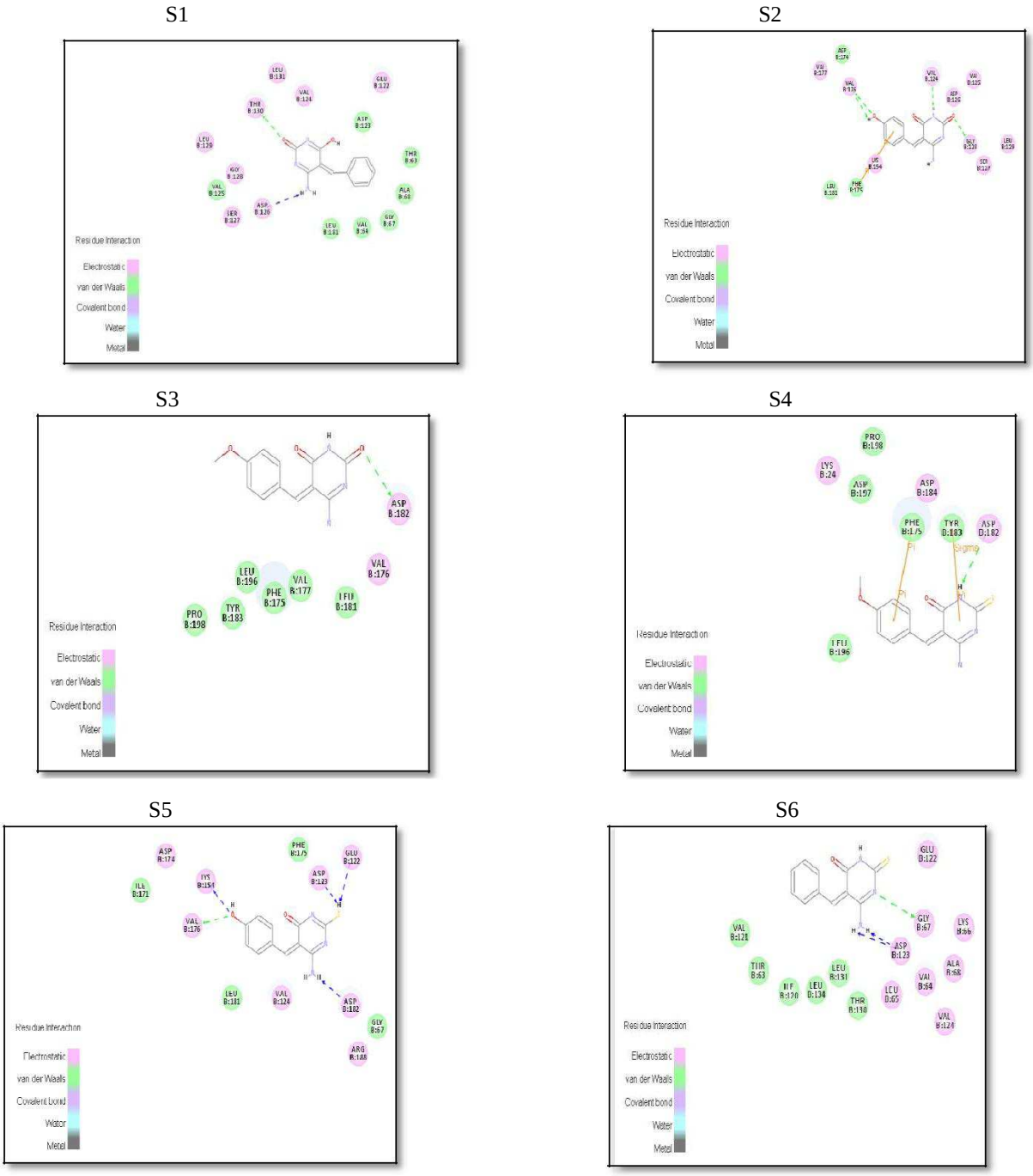



**Figure 4. 2D Diagram of S1- S6 Compound Interactions with 4RHT.**

**Table 3. Results of Protein-ligand Interaction given by Discovery Studio V4.**

| Compound Name | C-Energy | C-Docker Interaction Energy | LibDockScore | LigScore1 | LigScore2 | Binding Energy | Hydrogen Interaction | Distance |
|---|---|---|---|---|---|---|---|---|
| S1 | 14.109 | 29.394 | 15.398 | 3.77 | 4.62 | -77.8651 | [THR130] C-H…N | 2.37 |
| | | | | | | | [THR130] N-H…O | 2.36 |
| | | | | | | | [LEU129] N-H…O | 2.52 |
| | | | | | | | [GLY128]N-H…O | 2.69 |
| | | | | | | | [GLY128] C-H…O | 2.8 |
| | | | | | | | N-H…O[VAL124] | 2.73 |
| S2 | 12.885 | 27.883 | 34.716 | 4.85 | 5.07 | -35.0072 | O-H…O[VAL176] | 1.91 |
| | | | | | | | [VAL176]N-H…O | 2.22 |
| | | | | | | | N-H…O[VAL124] | 1.96 |
| | | | | | | | [SER127] O-H…N | 2.97 |
| | | | | | | | [GLY128] C-H…O | 2.69 |
| | | | | | | | [GLY128]N-H…O | 2.14 |
| S3 | 7.762 | 24.986 | 30.305 | 2.38 | 4.15 | -0.6261 | N-H…O[VAL176] | 2.85 |
| | | | | | | | [LEU181] C-H…O | 2.52 |
| | | | | | | | [ASP182] N-H…O | 2.13 |
| S4 | 2.078 | 19.992 | 30.344 | 1.38 | 3.49 | -40.1704 | N-H…O [ASP182] | 2.43 |
| | | | | | | | C-H…O[ASP197] | 2.52 |
| | | | | | | | C-H…O[ASP197] | 3.01 |
| | | | | | | | C-H…O[LEU196] | 2.743 |
| S5 | 11.751 | 28.613 | 28.919 | 3.45 | 4.14 | -60.428 | N-H…O [ASP182] | 2.26 |
| | | | | | | | [PHE175] C-H…O | 2.44 |
| | | | | | | | [LYS154] N-H…O | 1.51 |
| | | | | | | | S-H…O [ASP123] | 2.38 |
| | | | | | | | S-H…O [GLU122] | 2.3 |
| S6 | 13.327 | 29.318 | 47.244 | 2.59 | 4.49 | -16.9795 | N-H…O [ASP123] | 1.88 |
| | | | | | | | [GLY67] C-H…N | 2.82 |
| | | | | | | | [GLY67] N-H…N | 2.36 |
| | | | | | | | [LYS66] N-H…S | 2.83 |

## CONCLUSION

In our study, a successful strategy of molecular modeling based on hydrogen bond interaction was reported using docking studies. The docking studies revealed that the orientation and hydrogen bonding interactions of pyrimidine derivatives inside the active site of Mycobacterium tuberculosis 6-oxopurine phosphoribosyltransferase are similar to those in the crystal structure of Mycobacterium tuberculosis 6-oxopurine phosphoribosyltransferase as found in PDB. Drug discovery is a challenging process due to complexity of biological systems. The docking study for the anti tuberculosis activity against 4RHT was done using Discovery Studio 4.0 software. The possible number of ligand interactions and the binding ability of the derivatives were predicted. In conclusion, treatment of drug-resistant TB should aim for a high proportion of treatment success. The results obtained will be helpful in designing of new series of drugs especially for the resistant tubercular bacteria. Insilico approach helps in screening the appropriate molecules as drug targets.

Conflict Of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

Contribution of the Authors

S. Srinivasan made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data. S. Srinivasan, Dr. R. Girija and Dr. S. Aruna participated in revising it critically for important intellectual content; and Dr. R. Girija and Dr. S. Aruna gave approval of the final version of the manuscript to be submitted for publication.

**Acknowledgement**

Authors are thankful to Bioinformatics Infrastructure Facility (funded by DBT), Queen Mary's College and Chennai. I am also thankful to Ms. R.P. Sasikala & P.G. Stella for their guidance and support.

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