



## Drug reposition of Amoxicillin by molecular docking

Sruthi N<sup>1\*</sup>, Nithyasree R<sup>2</sup>, Sathya A<sup>3</sup>

<sup>1-3</sup> Department of Bio-Informatics, SCBT, SASTRA University, Tamil Nadu, India

### Abstract

Molecular docking has become an increasingly important tool for drug discovery. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The present work was aimed to reposition the drug molecules for therapeutic effects other than their approved activity. The target site was Penicillin binding protein 1A. Swiss similarity online platform was used for the shape based virtual screening of FDA approved drugs. PyRx tool was used for molecular docking of all the screened drugs and the binding pocket of the target protein was confirmed from CASTp online tool. Gephi tool was used for the designing of pharmacogenomics network. The repositioned drug interaction was different from the original interactions and the properties were studied from the network model.

**Keywords:** Molecular docking, PyRx tool, Amoxicillin, Target protein 1A, CASTp online tool

### Introduction

The completion of the human genome project has resulted in an increasing number of new therapeutic targets for drug discovery. High-throughput protein purification, crystallography and nuclear magnetic resonance spectroscopy techniques have been developed and contributed to many structural details of proteins and protein–ligand complexes [1]. These advances allow the computational strategies to permeate all aspects of drug discovery today. As to structure-based drug design, molecular docking is the most common method which has been widely used ever since the early 1980s [2]. Programs based on different algorithms were developed to perform molecular docking studies, which have made docking an increasingly important tool in pharmaceutical research [3].

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes [4]. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as *pose*) and assessment of the binding affinity [5].

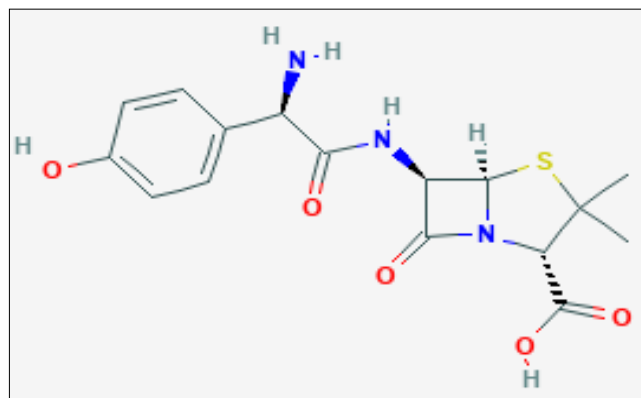
Knowing the location of the binding site before docking processes significantly increases the docking efficiency. In many cases, the binding site is indeed known before docking ligands into it. Also, one can obtain information about the sites by comparison of the target protein with a family of proteins sharing a similar function or with proteins co-crystallized with other ligands [6].

Docking has been performed with a flexible ligand and a rigid receptor for a long time, and remains the most popular method in use [7]. Molecular docking has been the most widely employed technique. Though the main application lies in structure-based

virtual screening for identification of new active compounds towards a particular target protein, in which it has produced a number of success stories [8].

Generally, the drug development is a time consuming, over priced process with a lower success rate. To overcome these difficulties, multiple computational approaches including drug repositioning are used in recent days.<sup>9</sup> Drug repositioning minimizes the cost and time in the drug development process due to the known efficacy and therapeutic potential against other ailments. Development of new broad spectrum antibiotics is increasingly difficult and thus it is essential to utilize such therapeutic alternatives to combat the infections. This involves the investigation of existing drugs for new therapeutic purposes [10, 11].

Amoxicillin is an antibiotic often used for the treatment of a number of bacterial infections such as skin infection, pneumonia and urinary tract infections. The routes of administration include oral or less commonly intravenous [12].



**Fig 1:** Structure of Amoxicillin

The Target protein is Penicillin-binding protein 1A with a general function of transferase activity and transferring glycosyl groups. The specific functions include cell wall formation, synthesis of cross-linked peptidoglycan from the lipid intermediates. The enzyme has a penicillin-insensitive transglycosylase N-terminal domain.

Pharmacogenomics attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient's genes, the functionality of these genes, and how this may affect the efficacy of the patient's current or future treatments.

To screen FDA drugs for shape based similarity with Amoxicillin using drug repositioning approach and screening the drugs for possible therapeutic effects other than their approved activity to generate drug-gene interaction networks for better pharmacogenomics understanding<sup>[13]</sup>.

### Materials and Methods

The Workflow used for Drug Repositioning Method is shown in Figure 2.

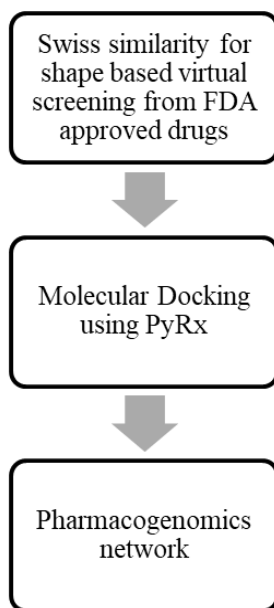


Fig 2: Workflow

### Retrieval of Protein Structure

The protein structure of penicillin binding protein 1A was studied (PDBID:2ZC5).

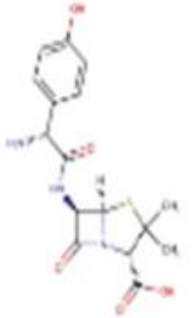
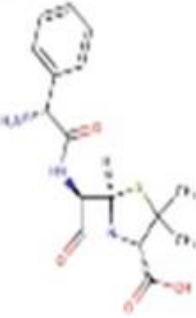
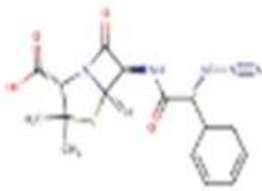
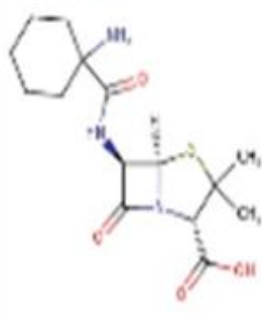
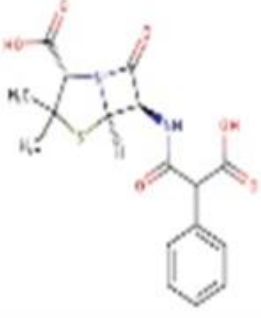
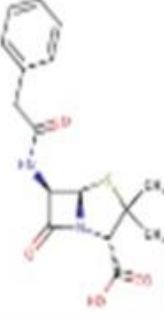
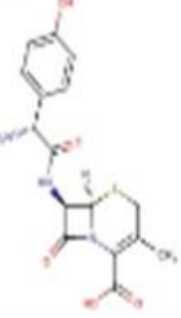
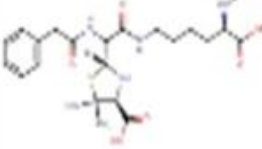
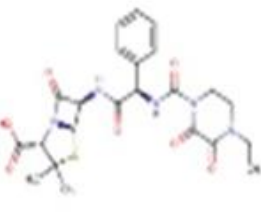
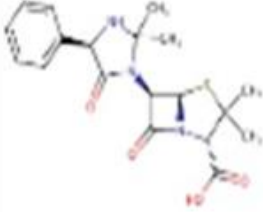
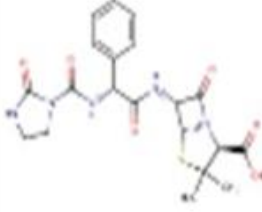
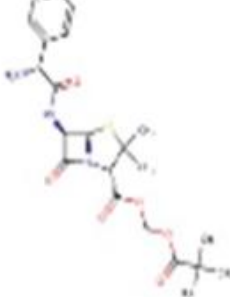
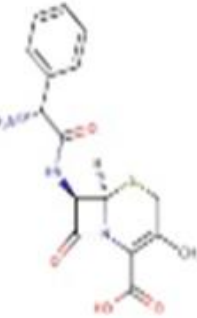
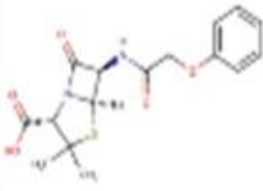
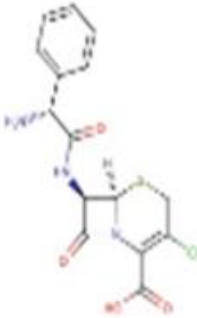
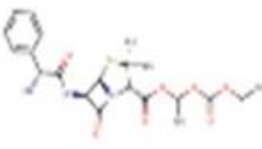


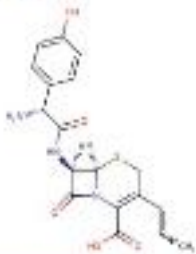
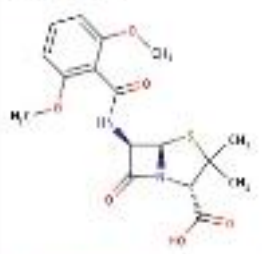
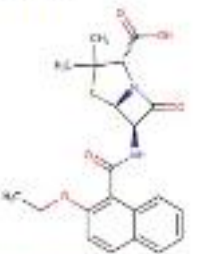
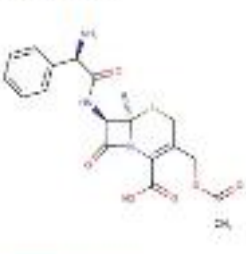
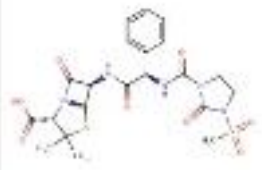
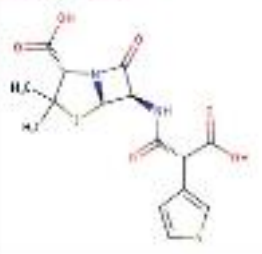
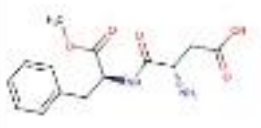

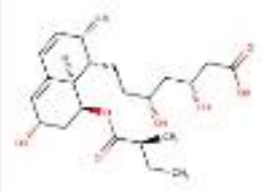
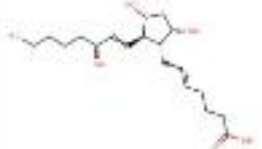
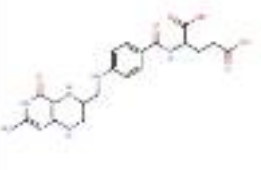
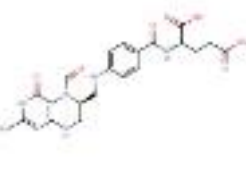
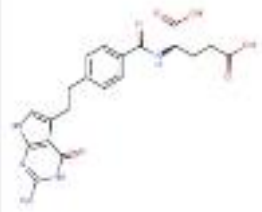
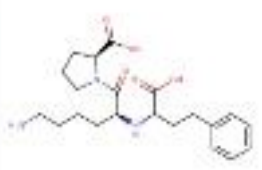
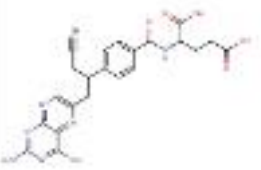
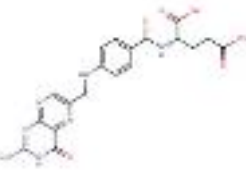
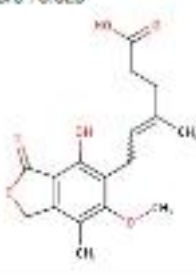
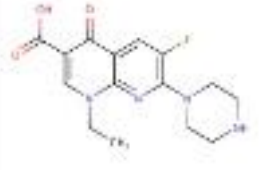
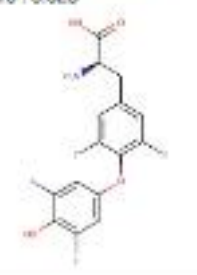
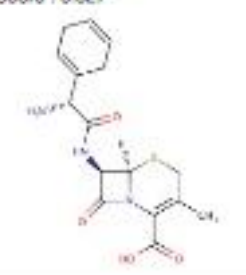
Fig 3: Structure of 2ZC5

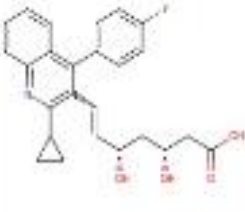
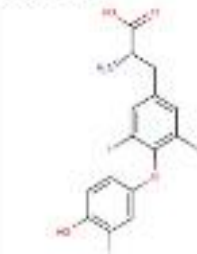
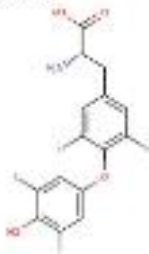
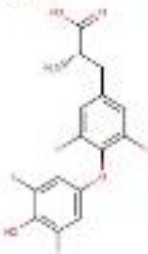
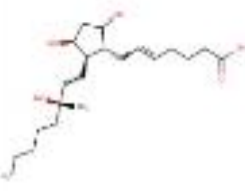
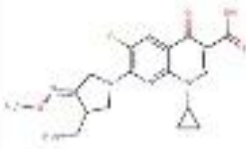
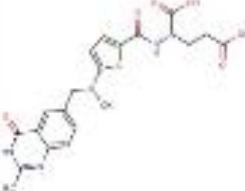
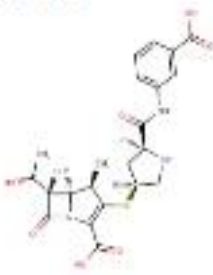
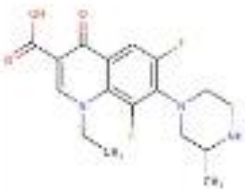
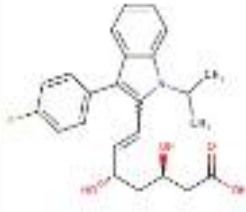
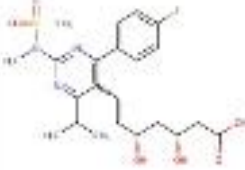
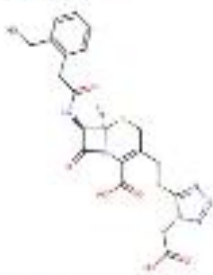
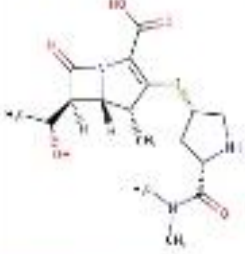
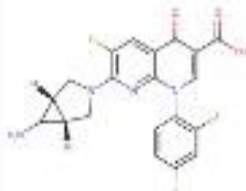
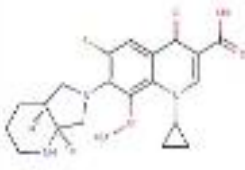
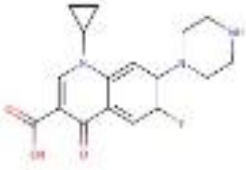
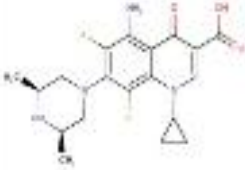
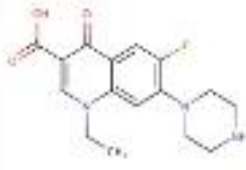

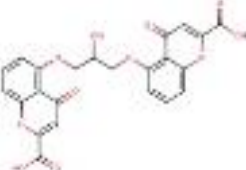
### Shape Based Screening

The smile format and chemical structure of amoxicillin was retrieved from FDA and Swiss Similarity online platform was

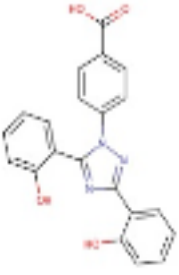

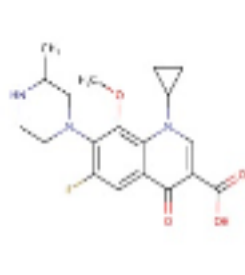
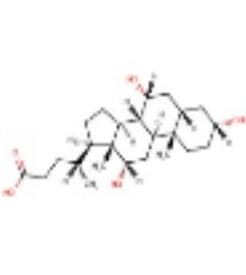
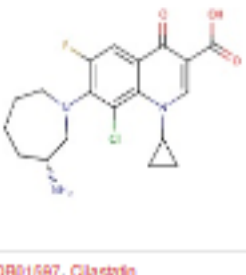
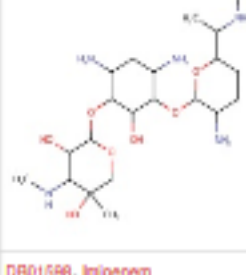
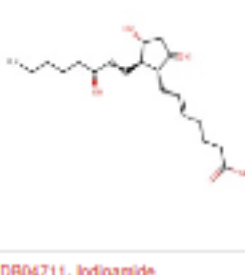
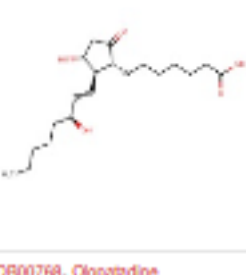
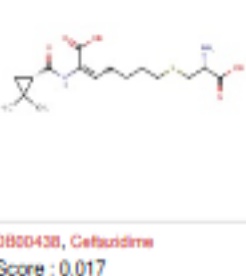
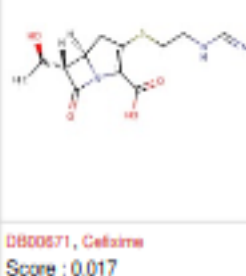
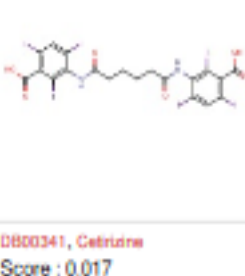
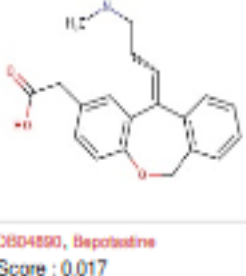
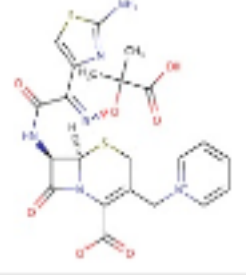
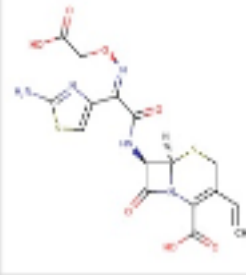
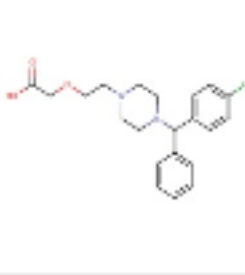
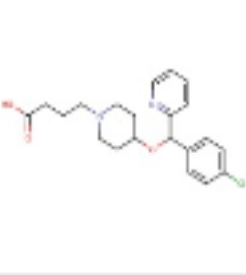
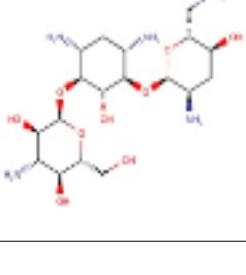
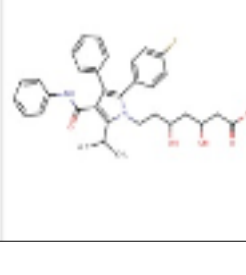
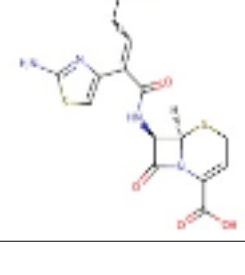
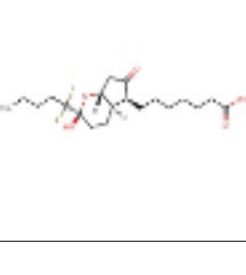
used to identify some chemical hits from FDA and other libraries with respect to the reference structure of amoxicillin. Amoxicillin was used as standard template to screen FDA approved drugs.

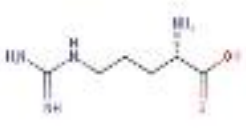
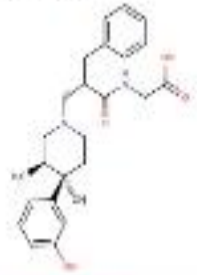
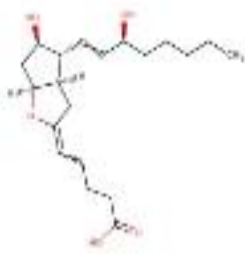
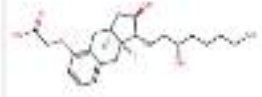
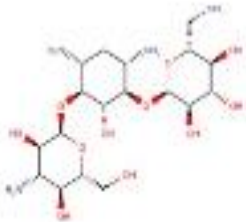

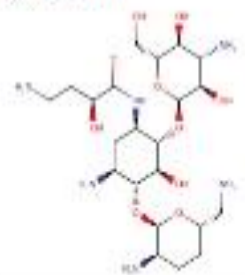
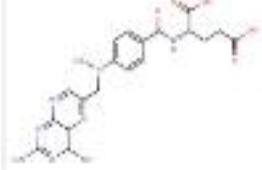
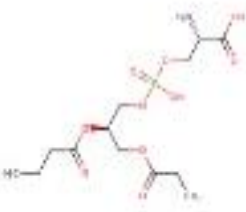
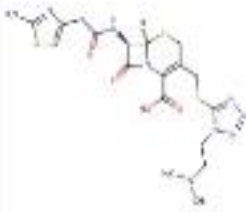
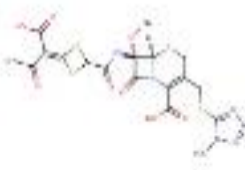
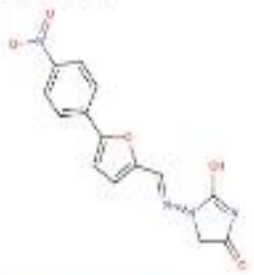
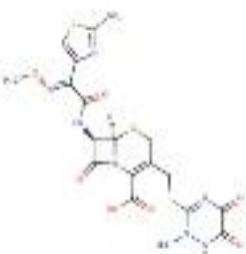
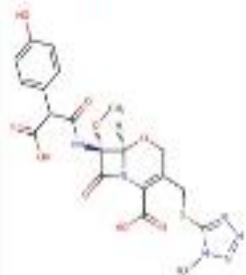
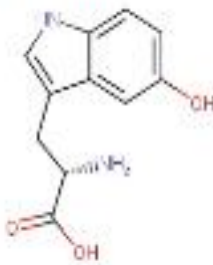
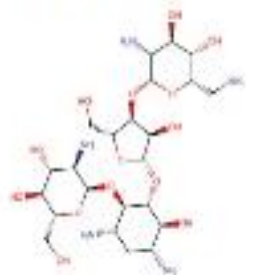
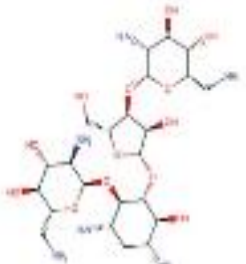
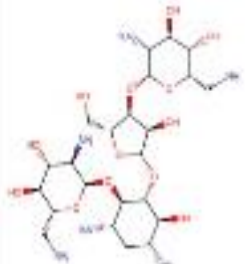
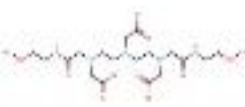
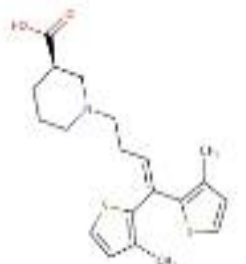
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<p>DB00176, Pravastatin Score : 0.039</p> 	<p>DB01160, Dinoprost Tromethamine Score : 0.037</p> 	<p>DB00116, Tetrahydrofolic acid Score : 0.036</p> 	<p>DB00660, Leucovorin Score : 0.034</p> 
<p>DB00642, Femebedon Score : 0.034</p> 	<p>DB00722, Lisinopril Score : 0.032</p> 	<p>DB00613, Pralsethine Score : 0.031</p> 	<p>DB00158, Folic Acid Score : 0.029</p> 
<p>DB01624, Mycophenolic acid Score : 0.029</p> 	<p>DB00487, Enoxacin Score : 0.029</p> 	<p>DB00509, Dextrothrycine Score : 0.028</p> 	<p>DB01233, Colchicine Score : 0.027</p> 

<p>DB00880, Pivoxacin Score : 0.027</p> 	<p>DB00279, Lidifyranine Score : 0.027</p> 	<p>DB01563, Lixite Score : 0.027</p> 	<p>DB00451, Levofloxacin Score : 0.027</p> 
<p>DB00429, Carbaprost Tromethamine Score : 0.027</p> 	<p>DB01155, Gemifloxacin Score : 0.026</p> 	<p>DB00293, Raltegravir Score : 0.025</p> 	<p>DB00203, Etipanem Score : 0.024</p> 
<p>DB00978, Lomefloxacin Score : 0.024</p> 	<p>DB01066, Fluvastatin Score : 0.024</p> 	<p>DB01066, Rosuvastatin Score : 0.024</p> 	<p>DB00983, Ceftriaxone Score : 0.023</p> 
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<p>DB01597, Cilastatin Score : 0.019</p> 	<p>DB01596, Imipenem Score : 0.018</p> 	<p>DB04711, Iodipamide Score : 0.018</p> 	<p>DB00768, Olopatadine Score : 0.018</p> 
<p>DB00438, Ceftazidime Score : 0.017</p> 	<p>DB00671, Cefixime Score : 0.017</p> 	<p>DB00341, Ceftriaxone Score : 0.017</p> 	<p>DB04890, Bepotastine Score : 0.017</p> 
<p>DB00884, Tobramycin Score : 0.016</p> 	<p>DB01076, Atorvastatin Score : 0.016</p> 	<p>DB01415, Cefibuten Score : 0.015</p> 	<p>DB01046, Lubiprostone Score : 0.015</p> 

<p>DB00125, L-Arginine Score : 0.015</p> 	<p>DB00274, Alvimopan Score : 0.015</p> 	<p>DB01240, Epoprololeol Score : 0.014</p> 	<p>DB00374, Tirozobnol Score : 0.014</p> 
<p>DB01172, Kanamycin Score : 0.014</p> 	<p>DB00470, Amikacin Score : 0.014</p> 	<p>DB00606, Arbekacin Score : 0.014</p> 	<p>DB00583, Mithotrexate Score : 0.014</p> 
<p>DB00144, Phosphatidylserine Score : 0.014</p> 	<p>DB00229, Cefotaxim Score : 0.013</p> 	<p>DB01330, Cefotetan Score : 0.013</p> 	<p>DB01219, Dantrolene Score : 0.013</p> 
<p>DB01212, Ceftriaxone Score : 0.011</p> 	<p>DB04370, Latamoxol Score : 0.011</p> 	<p>DB02259, Octipian Score : 0.011</p> 	<p>DB01421, Paromomycin Score : 0.011</p> 
<p>DB00294, Neomycin Score : 0.011</p> 	<p>DB00452, Framycetin Score : 0.011</p> 	<p>DB00538, Gadoversetamide Score : 0.011</p> 	<p>DB00206, Tiagabine Score : 0.011</p> 

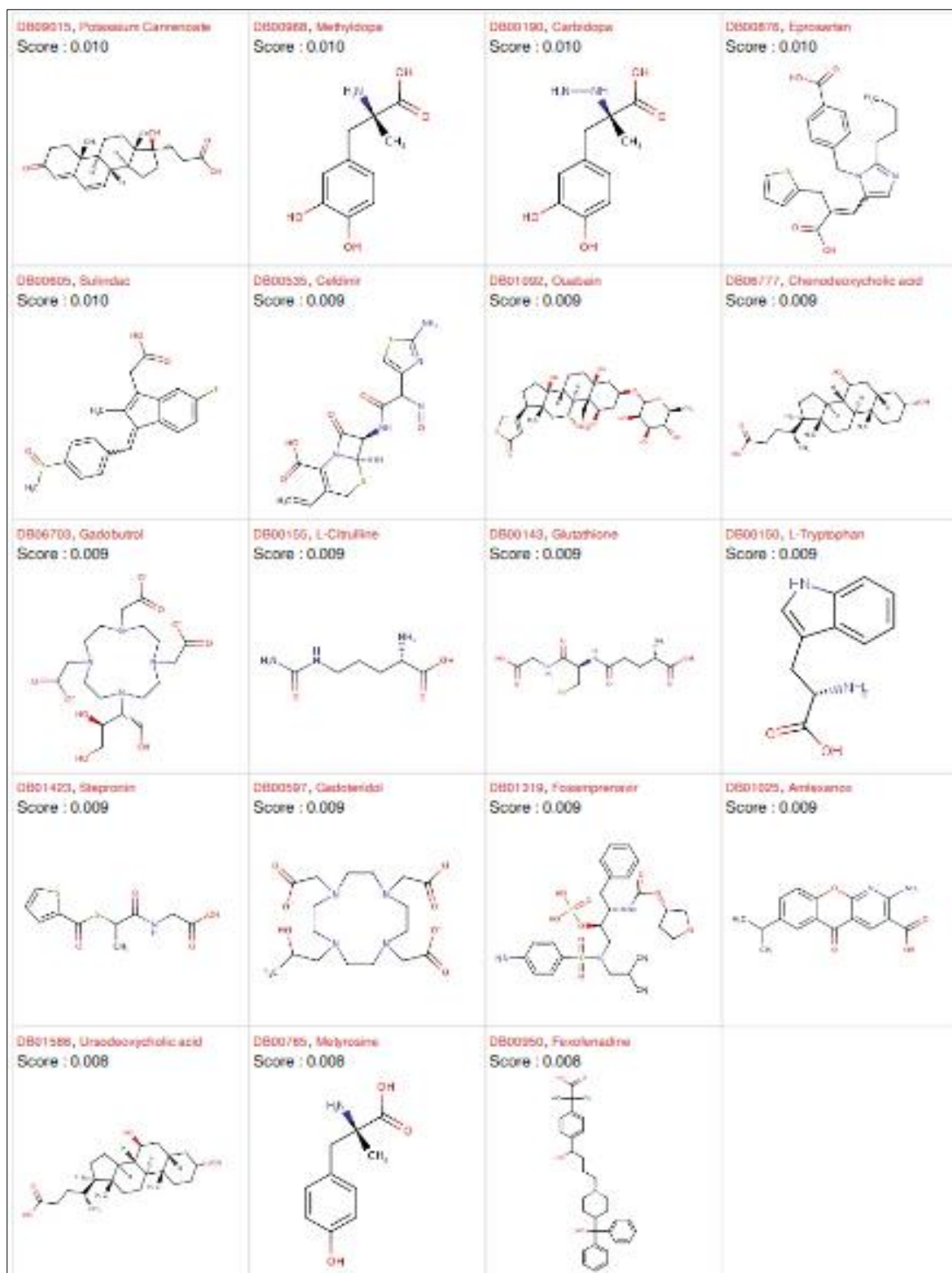


Fig 4: Screened Hits

### Molecular Docking

The aim of molecular docking is to give a prediction of the ligand-receptor complex structure using computation methods. Docking can be achieved through two interrelated steps: first by sampling conformations of the ligand in the active site of the protein; then ranking these conformations via a scoring function.

Ideally, sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it highest among all generated conformations.

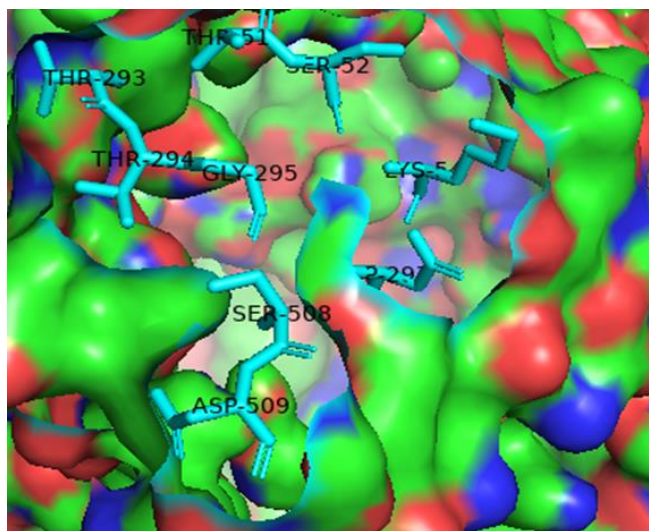
The structure of the screened drugs was obtained from PubChem in their SDF (Structures Data File) file format. Docking was performed on all the screened drugs against the penicillin binding



protein 1A. The binding pocket of the target protein was confirmed from CASTp online tool.

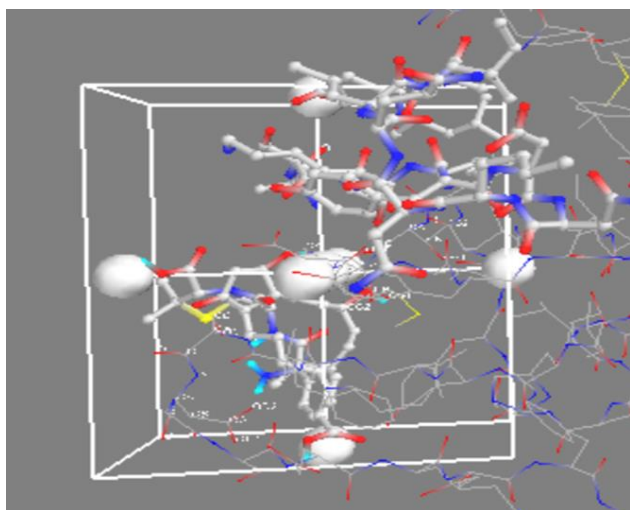
**Table 1:** Residue Interactions

Residue	Residue Number
Lysine (LYS)	54
Serine (SER)	52
Threonine (THR)	51
Threonine (THR)	289
Threonine (THR)	293
Threonine (THR)	294
Glycine (GLY)	295
Aspartic acid (ASP)	297
Serine (SER)	508
Aspartic acid (ASP)	509



**Fig 5:** Binding site of drug

In docking experiments the grid box dimensions were adjusted as X=19.12, Y=20.44, Z=17.10 respectively by default exhaustiveness=8 value. Top ten screened drugs were selected based on the best binding energy.



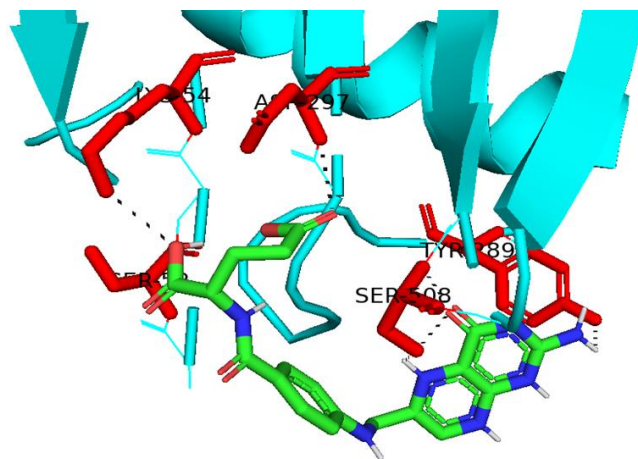
**Fig 6:** Grid Box

## Results and Discussion

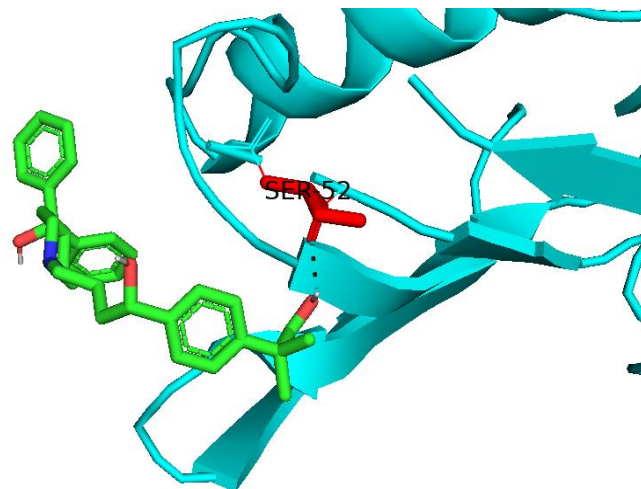
Based on PyRx docking results, the top ten drugs with best binding affinity was selected. The best binding energy (-5.4kcal/mol) was obtained and it was studied that how well different drug molecules bind to the same protein.

**Table 2:** Binding Energy of Screened drugs

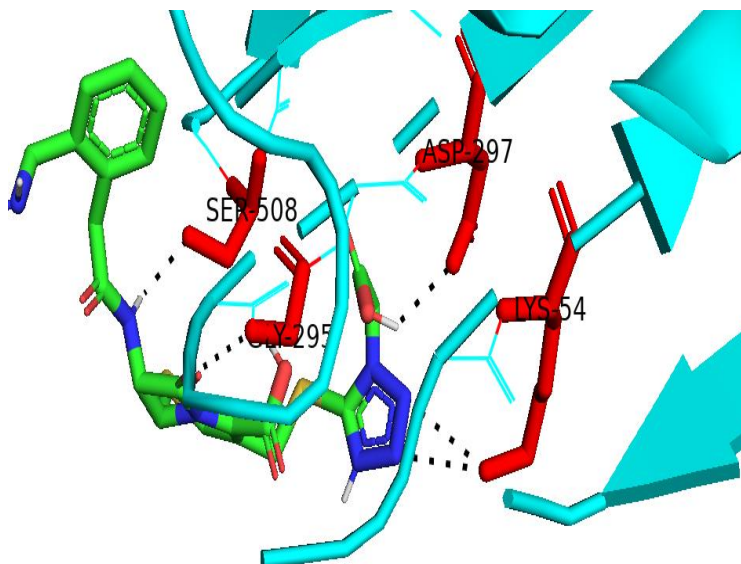
Ligand	Target	Binding Energy (kcal/mol)
Folic Acid	2zc5	-5.9
Fexofenadine	2zc5	-5.8
Cefroanide	2zc5	-5.5
Cefotetan	2zc5	-5.4
Ertapenem	2zc5	-5.4
Leucovorin	2zc5	-5.4
Bacampicillin	2zc5	-5.3



**Fig 7:** Binding pocket of Folic Acid



**Fig 8:** Binding pocket of Fexofenadine



**Fig 9:** Binding pocket of Cefroanide

**Table 3:** Gene interactions

Sl.No	Search Term	Match Term	Match Type	Gene	Drug	Interaction Types
1	Folic Acid	Folic Acid	Definite	FOL R2	Folic Acid	Binder
2	Folic Acid	Folic Acid	Definite	FOLR3	Folic Acid	Binder
3	Folic Acid	Folic Acid	Definite	CHEK 1	Folic Acid	Inhibitor
4	Folic Acid	Folic Acid	Definite	FOL R1	Folic Acid	Binder
5	Folic Acid	Folic Acid	Definite	TYM SOS	Folic Acid	Binder
6	Folic Acid	Folic Acid	Definite	ITPA	Folic Acid	Binder
7	Folic Acid	Folic Acid	Definite	DHFR	Folic Acid	Binder
8	Folic Acid	Folic Acid	Definite	LEP	Folic Acid	Binder
9	Folic Acid	Folic Acid	Definite	ABC B1	Folic Acid	Binder
10	Folic Acid	Folic Acid	Definite	ENOS F1	Folic Acid	Binder
11	Folic Acid	Folic Acid	Definite	TLR4	Folic Acid	Binder
12	Folic Acid	Folic Acid	Definite	SLC19A1	Folic Acid	Binder
13	Folic Acid	Folic Acid	Definite	MYC	Folic Acid	Binder
14	Folic Acid	Folic Acid	Definite	XDH	Folic Acid	Binder
15	Folic Acid	Folic Acid	Definite	AFP	Folic Acid	Binder
16	Folic Acid	Folic Acid	Definite	ABCG2	Folic Acid	Binder
17	Folic Acid	Folic Acid	Definite	ATIC	Folic Acid	Binder
18	Folic Acid	Folic Acid	Definite	DDRKG1	Folic Acid	Binder
19	Folic Acid	Folic Acid	Definite	TYMS	Folic Acid	Binder
20	Folic Acid	Folic Acid	Definite	TNF	Folic Acid	Binder
21	Folic Acid	Folic Acid	Definite	AMPD1	Folic Acid	Binder
22	Folic Acid	Folic Acid	Definite	LPL	Folic Acid	Binder
23	Folic Acid	Folic Acid	Definite	MTR	Folic Acid	Binder
24	Fexofenadine	Fexofenadine	Definite	HR H1	Folic Acid	Antagonist
25	Leucovorin	Leucovorin	Definite	MAP2K1	Fexofenadine	Inhibitor
26	Leucovorin	Leucovorin	Definite	MAP2K3	Leucovorin	Inhibitor
27	Leucovorin	Leucovorin	Definite	MAP2K4	Leucovorin	Inhibitor
28	Leucovorin	Leucovorin	Definite	ERBB2	Leucovorin	Inhibitor
29	Leucovorin	Leucovorin	Definite	BAX	Leucovorin	Inhibitor
30	Leucovorin	Leucovorin	Definite	MET	Leucovorin	Inhibitor
31	Leucovorin	Leucovorin	Definite	ABCC4	Leucovorin	Inhibitor
32	Leucovorin	Leucovorin	Definite	BRAF	Leucovorin	Inhibitor
33	Leucovorin	Leucovorin	Definite	RUNX3	Leucovorin	Inhibitor
34	Leucovorin	Leucovorin	Definite	TYMS	Leucovorin	Inhibitor
35	Leucovorin	Leucovorin	Definite	DPYD	Leucovorin	Inhibitor
36	Leucovorin	Leucovorin	Definite	APC	Leucovorin	Inhibitor
37	Dantrolene	Dantrolene	Definite	RYR1	Dantrolene	Antagonist
38	Dantrolene	Dantrolene	Definite	RYR3	Dantrolene	Antagonist
39	Ceftriaxone	Ceftriaxone	Definite	CXCL8	Ceftriaxone	Antagonist

## Conclusion

Molecular docking has been widely used for discovery of drugs. The present study evaluates the repositioning of amoxicillin for added therapeutic activities. Out of the FDA approved drugs, the best ten drugs with structural similarity were displayed. The repositioned drug interaction was different from the original interactions reported with the respective genes. The interaction of the drug with various genes was studied and the network model was built to know the properties of the drug gene interaction. Further, to improve the study, molecular dynamics simulation using Gromacs and Designing of pharmacogenomics network model using Drug gene interaction database and Drug signatures database would throw light on the unseen portions of the study.

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