

**STRUCTURE PREDICTION OF TB RPOB AND ITS
MUTATIONS BINDING ANALYSIS**

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AND ITS MUTATIONS BINDING ANALYSIS

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Abstract

Today Tuberculosis is a disease that is still a high-risk categories. Rifampicin is a drug that's used common in the treatment of TB. We know that the effect of this drug in the region of RNA polymerase on TB. Unfortunately, there isn't any three-dimensional crystal structure in the rpo β . In this study, three-dimensional model was created from DNA sequence and applied the resistance mutations of TB for computing resistance .

There are many online tools for three-dimensional modeling with using DNA or amino acid sequences. And the best result of the modeling was used in studying that's more same with the experimental results.

After finding best model, the mutations were applied for computing binding energy of mutations.

Tüberküloz Rpo β protein yapısal modellemesi ve mutasyon dirençlerinin ölçülmesi.

Özet

Tüberküloz bugün hala yüksek risk sınıfında bir hastalıktır. Verem tedavisinde en yaygın kullanılan ilaç rifampisindir. Günümüzde biliyoruz ki bu ilacın TB üzerinde ki etki bölgesi RNA Polimerazdır. Yapılan araştırmalarda ne yazık ki henüz Rpo β için üç boyutlu bir kristal yapısı elde edilememiştir. Bu çalışmada DNA sekansından yola çıkılarak; üç boyutlu model oluşturulması, bu model üzerinden mutasyon dirençlerinin ölçülmesi ve sonuçlarının değerlendirilmesi hedeflenmiştir.

DNA veya Amino Asit sekanslarından yararlanarak üç boyutlu modelleme yapan bir çok online tool arasından yapılan modellemeler sonucunda deneysel sonuçlara en uygun çıkan model kullanılmıştır.

En iyi model bulunduktan sonra, bu model üzerinde TB mutasyonları uygulanarak yeni durumda RIF'in bağlanma enerjileri ölçülmüştür.

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List of Symbols

ΔG_{bind} : Estimation of Binding Affinity

m : sequence of length

n : sequence of length

$m+1$: the matrix dimension

$n+1$: the matrix dimension

$S(i,j)$: score

$i-1$: the score from the cell at position

$j-1$: the score from the cell at position

$s[i,j]$: the new score at position

$s[i,j-1]$: the score one cell to the left

$s[i-1,j]$: the score immediately above the new cell

K, λ : constants

m : length of query sequence

n : length of the entire database

S : score of the alignment

E : expect value

K_i : binding constant

V : pair-wise evaluations

$\rho(\vec{x}_i)(\vec{x}_j)$: probability density function

$\rho(\vec{x}_i)$: the single body distribution function for atom I and is a constant for a given protein

ΔS_{conf} : entropy lost upon binding

L : ligand

P : protein

List of Abbreviations

TB: Tuberculosis

MTB: Mycobacterium Tuberculosis

RIF: Rifampicin

MD: Molecular Dynamics

3D: Three dimension

BLAST: Basic local alignment search

BLOSUM: Blocks of aminoacid substitution matrix

DSSP: Dictionary of Protein Secondary Structure

DOPE: Discrete Optimized Protein Energy

PDF: Probability Density Function

PDB: Protein data bank

RMSD: Root-mean-square deviation

MC: Monte carlo

GA: Genetic algorithm

FF: Force field

SFs: Scoring functions

DS: Discovery studio

gi: Query sequence

E: Expect value

rDAT: rat dopamine transporter

gpf: Grid parameter file

glf: Grid log file

dlf: Docking log file

dpf: Docking parameter file

MC: Monte Carlo

HB: Hydrogen bonding

Chapter 1

Introduction

This thesis is about computational methods of determining the drug resistance of mycobacterium tuberculosis (TB) on it's a First-Line drug; rifampicin (RIF). For examining RIF binding onto the active site of Mycobacterium tuberculosis, this study intends to utilize molecular docking and molecular dynamics (MD) simulations.

Drug	Cellular function inhibited	Target
First-line drugs		
INH	Mycolic acid synthesis	Enoyl reductase
RIF	RNA synthesis	RNA polymerase
Ethambuto (EMB)	Arabinogalactan synthesis	Arabinosyl transferase
Pyrazinamide (PZA)	Unclear	Unclear
Quinolones	DNA supercoiling	DNA gyrase
Ethionamide	Mycolic acid synthesis	Enoyl reductase
STM	Protein synthesis	30S ribosomal subunit
KAN, AMK	Protein synthesis	30S ribosomal subunit
Capreomycin	Protein synthesis	30S/50S ribosomal subuni

Table 1.1 TB Drug Table

RIF affects many bacteria by interacting with the RNA polymerase β - subunit and preventing transcription although it is not specific for mycobacteria. Clinical RIF causes distinct mutations in $rpo\beta$ because its resistance is mostly high- level.[1]

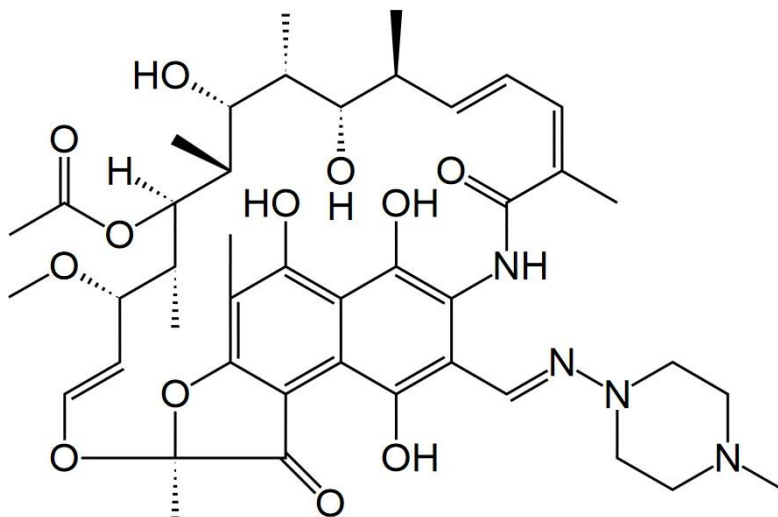


Figure 1.1: Chemical structure of RIF

1.1 Tuberculosis (TB)

TB usually infects the human lower respiratory system as a microbial disease, which has affected human beings for several millennia [2]. *M. tuberculosis*, is the aetiological agent of TB which was extracted 125 years ago by Koch [3]. Although there are many progress in the prevention and treatment of the disease, this ancient chastise still remains as a major pathogen of human and a global tragedy with immense public health and economic implications. World Health Organisation (WHO) identifies a need of US\$47 billion to implement countrywide programmes to stop TB while another US\$9 billion for the research and development of new diagnostics and treatments for TB according to Migliori et al's report (2007).

7% of all deaths in developing countries and 26% of avoidable mature deaths worldwide is based on TB for [4]. 3 million people dying from TB every year in average [5] and of all the infectious bacteria, it is currently the leading killer of adults in the world. WHO has appraise a astounding 8 million new cases globally and has projected about 30 million deaths from TB in this decade according to Manca's report et al. (1997).

There has been a constant rise in notification of TB in Malaysia for over the past 10 years. In year 2000, a terrible 15,057 cases of TB was reported where the incidence rate is 64.7 per 100,000 populations. The TB and HIV co-infection numbers has also escalated from 6 cases in 1990 to 734 cases in 2000. Advanced TB is seen in most patients with TB-HIV co-

infections, therefore the number of deaths due to TB-HIV has also increased. The fast growing numbers of immigrant workers from high TB burden neighbouring countries which might add to the problem of multi-drug resistant TB caused the worries to be further blended [6].

RIF is the prime drug for the treatment of TB [7] since 1952. Anyway its use has been restricted by up to 30% increase of RIF resistant streches [8]. By the increase of multi drug resistant *M. tuberculosis* strains especially amongst HIV infected individuals the problem has further been complicated [9]. A considerable amount of non-TB mycobacteria have been isolated from acquired immune deficiency syndrome (AIDS) patients [10]. In the AIDS patients such opportunistic mycobacteria include the member of *Mycobacterium avium* complex (MAC) caused the prevalent “TB-like” infection. These pathogens are mostly naturally resistant to RIF . When compared, the survival rates of AIDS patients who are not infected are much higher than one’s with MAC infection [11].

The search for alternatives to RIF has prompted by the above declarations. However, the comprehending of drug-receptor interactions is required in order to develop strategies for the design of novel and potent drugs against *M. tuberculosis*. Therefore, there is a compelling need to understand resistance development at the molecular level that remains an enigma until today.

1.2 The significance of molecular modeling in TB research

The efficiency of TB treatment, control and prevention programs have been complicated by the limitation number of efficacious therapeutic agents to treat patients infected with MAC and rise of multi-drug resistant strains these days. The enduring worldwide threat of TB accentuates the importance of the urgent need in more effective diagnosis therapies, which is currently at a very slow process. It’s main cause is the lack of detailed structural features regarding the drug-receptor interactions. Thus, to facilitate the rational development and improvement of anti-TB medications , the comprehending and insights of the molecular events that lead to drug action or resistant in *M. tuberculosis* are important [12].

The pharmacophore hypotheses which derived from those inhibitors with known structures are the top influencer of drug design . The pharmacophore model did not provide the details of the drug-receptor interactions, despite the fact that these hypotheses were able to discover some new inhibitors. Thus, molecular modelling method can predict the binding modes of RIF as well as its derivatives onto rpo β . The search for lead/potential inhibitor(s) and the strategies for the design of new anti-TB compounds can be formulated with the comprehending of binding modes at the molecular level between RIF and rpo β [13].

Acceptor-receptor binding mode predictions have led to a faster discoveries of new lead compounds with impressive improvements in the accuracy and speed of molecular docking. However, there are still many difficulties to over helm. Initially, the binding modes accuracy relies on the correct assessment of acceptor-receptor interaction energies and scoring functions which are simplified for computational efficiency. Secondly, the sampling of acceptor in flexible binding pocket has not been achieved. Third, the involvement of solvent molecules is yet to be addressed in molecular docking method. Fourth because the acceptor might be more mobile in the bound state, the molecular docking method is not able to provide the dynamics data of acceptor within the receptor binding site [14].

Thus, to elucidate a more refined and complete understanding of the binding properties of RIF within the Rpo β binding pocket, MD simulation is also another alternative. MD simulation technique is wasting much time and expensive (regarding large computational storage compared to molecular docking method). However, MD simulation is able to provide the dynamics of RIF-Rpo β complex as well as the detailed insights of intermolecular relationships. MD simulation also able to deal with the docking problems mentioned above, because it uses more accurate force field (a whole atom approach instead of the united atom method in molecular docking simulation). Generally, water molecules play a critical role in determining the conformation of an acceptor in a binding pocket because they are mediating interactions with the protein. Thus, MD simulation allows the involvement of explicit waters (instead of the simplified solvation parameter used in docking simulation) unlike molecular docking. Finally, as RIF and Rpo β 's flexibilities might be critical for recognition between each other, MD simulation methodology will also permit flexibility of both.

Chapter 2

2.1 Molecular modelling

X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy have arrived to high resolution at the molecular level of three dimensional structures for a numerous proteins with the ease of progresses in molecular biology. However, some proteins cannot easily crystallized, because NMR experiment does not give complete atomic structures. It only gives overviews for proteins with amino acids further than the number of 200 residues. Thus, molecular docking and MD simulation that are computer-based molecular modelling techniques are clearly fascinating methods to predict and derive a molecular insight of the acceptor-protein complex structure[15].

For describing the study of molecules and molecular systems, the molecular modelling term is used generally. It is also a technic that uses theoretical methods to investigate and predict chemical entities and processes. In order to study systems ranging from small chemical molecules to large biological molecules and material assemblies this technique has been used in many ranges such as chemistry, biology, or materials science. The atomistic level description of the studied systems can be gathered with molecular modelling. Inevitably computers are required to study reasonably sized systems while the simplest system can be performed by hand using theoretical calculations. Today's molecular modelling is invariably associated with computer modelling so it's known as computational chemistry. Developments in speed and memory ability of computational power have allowed extensive range of models and up to millions of atoms to be included in the computation[16].

Computer-based molecular modelling simulates the chemical structures and reactions based on the elemental laws of physics in terms of numbers usually. Researchers to study chemical phenomena by running computations instead of wet-lab experiment with this method. Not only stable molecules, but also unstable intermediates and transition states of chemical structures and reactions can be modeled by some simulations. With wet-lab experiment, it is almost impossible to observe molecules and reactions but these hypothetical methods can provide information about them easily. Therefore, molecular modelling is an autonomous research area which could be critical adjunct and alternative to exploratory studies[17].

Chapter 3

Generate 3D model for rpo β protein and its ligand interaction with mutations

Introduction

We are working on a protein (rpo β).

The sequence of rpo β protein (1079 amino acids) was downloaded for structural modeling from NCBI. Multiple alignments of the related sequences were performed using the online available ClustalW program accessible through the European Bioinformatics Institute. There isn't X-ray crystallographic or NMR structure of this protein. Tertiary structures of rpo β protein were modeled on the basis of different template structures from different web based tertiary structures area. Each result of 3D structures was docked with RIF and the results were compared with experimental result. At sum which model is able to get more same result with experimental result, we could accept it for a good research model.[18]

3.1 Working on web based tertiary structures program

First try on swiss-model; An automated knowledge-based protein modelling server. It used 3tiB for based on template.

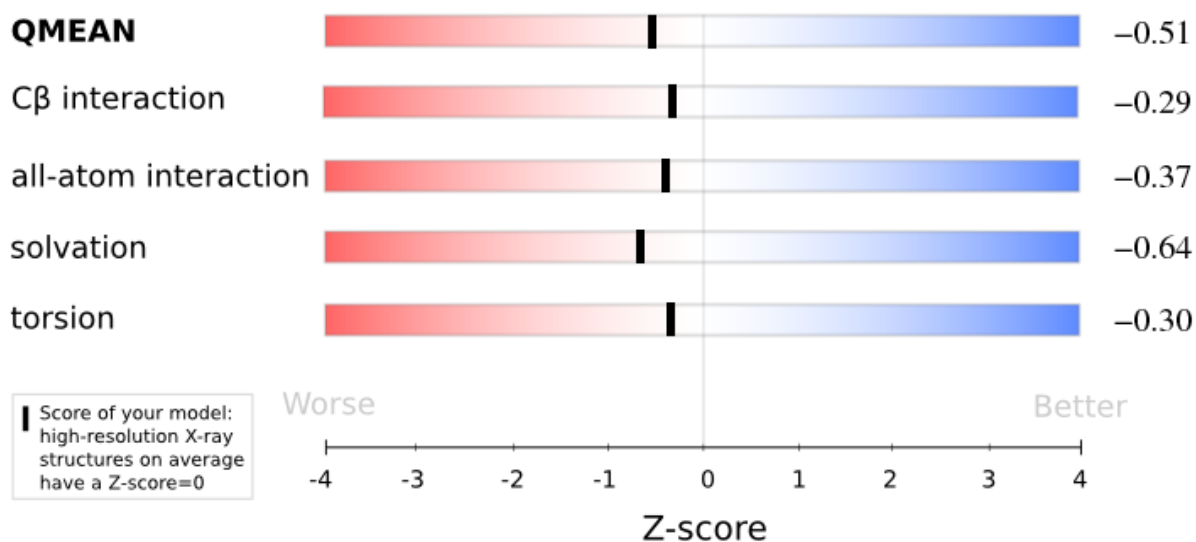


Figure 3.1 Swiss-Model Allignment

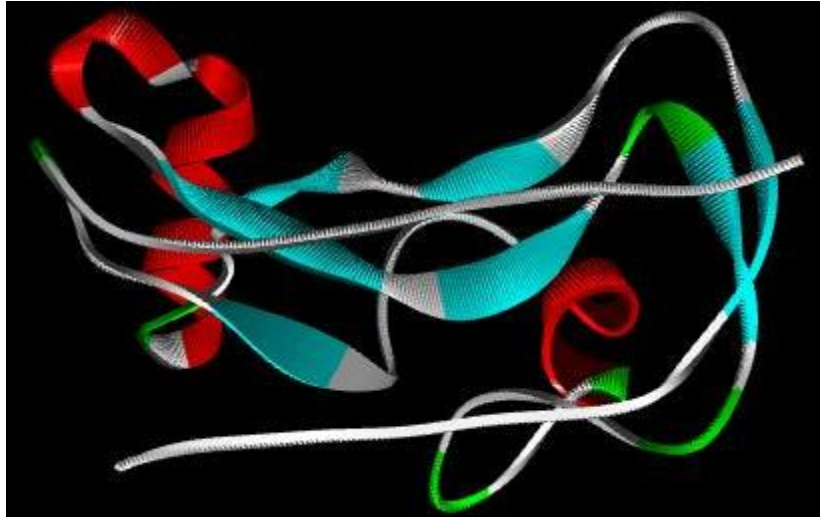


Figure 3.2 Swiss-Model rpoβ model

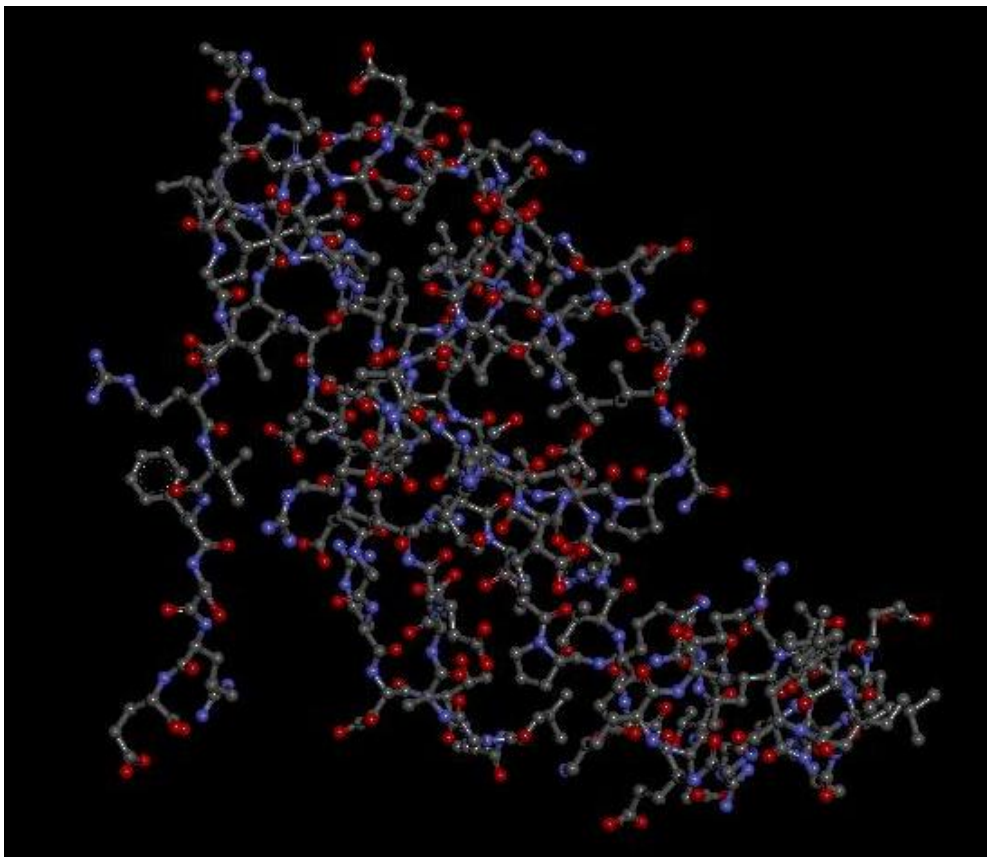


Figure 3.3 Swiss-Model rpoβ Model with atomic view

Secand try on CPHmodels 3.2 Server; CPHmodels 3.2 is a protein homology modeling server. The template recognition is based on profile-profile alignment guided by secondary structure and exposure predictions.

Query sequence:

```
>gi_15607807_ref_NP_215181.1_
MADSRQSKTAASPSRSPQSSSNNSVPGAPNRVVSFAKLRPLEVPGLLDVQTDSEFWLIG
SPRWRESAAERGDVNPVGGLEEVLVELSPIEDFSGSMSLSFSDFPRFDDVKAPVDECKDKD
MTYAAPLFFVTAEFINNTGEIKSQTVFMGDFPMMTEKGTFFIINGTERVVVSQVLRSPGVY
FDETDIKSTDKTLHSVKVIPSARGAWLEFDVDRKRTVGVRIIDRKRQPVTVLLKALGWTSE
QIVERFGFSEIMRSTLEKDNTVGTDEALLDIYRKLKRPGEPTKESAQTLLLENLFFKERY
DLARVGRYKVNKKLGLHVGEPISTLSTEEDVVATIEYLVRLHEGQTTMTVPGGVEVPVE
TDDIDHFGNRRLRRTVGEIIONQIRVGMRSRMRVVRERMTTQDVEAITPQTLINIRPVVAA
IKEFFGTSQLSQFMDQNNPLSGLTHKRRLSALGPGGLSRERAGLEVRDVHPSHYGRMCPI
ETPEGNIGLIGLSVYARVNPFGFIETPYRKVVVDGVVSEIVYLTAEEDRHVVAQANS
PIDADGRFVEPRVLVRRKAGEVEYVPSSEVDYMDVSPRQMVSVATAMIPFLEHDDANRAL
MGANMQRQAVPLVRSEAPLVGTGMELRAAIDAGDVVVAEESGVIEEVSADYITVMHDNGT
RRTYRMRKFARSNHGTCANQCPIVDAGDRVEAGQVIADGFPCTDDGEMALGKNLLVAIMPW
EGHNYEDAILLSNRLVEEDVLTSIHIEEHEIDARDTKLGAEIITRDIPNISDEVLADLDE
RGIVRIGAEVRDGDILVGKVTPKGETELTPEERLLRAIFGEKAREVRDTSKLVPHGESGK
VIGIRVFSREDEDELPAVGNELVRVYVAQKRKISDGDKLAGRHGNKGVIGKILPVEDMPF
LADGTPVDIILNTHGVPRRMNIGQILETHLWCAHSGWKVDAAGVDPDWAARLPDELLEA
QPNAIVSTPVFDGAQEAELQGLLSCTLPNRDGDVLDADGKAMLFDRSGEPFPYPVTVG
YMYIMKLHHLVDDKI HARSTGPYSMITQQPLGGKAQFGGQRFGECECWAMQAYGAAYTLQ
ELLTIKSDDTVGRVKVYEAIVKGENIPEPGIPESFKVLLKELQSLCLNVEVLSSDGAIE
LREGEDEDLERAAANLGINLSRNESASVEDLA
```

Query Mw: 129235 (1172 aa)
Searching for template ...

```
Round 0. Hits better than threshold: 0.000010:
entry: 3IYD chain: C score: 1175 E: 0.0
entry: 1IW7 chain: C score: 1088 E: 0.0
entry: 1IW7 chain: M score: 1088 E: 0.0
entry: 2A6E chain: C score: 1088 E: 0.0
entry: 2A6E chain: M score: 1088 E: 0.0
entry: 2A6H chain: C score: 1088 E: 0.0
entry: 2A6H chain: M score: 1088 E: 0.0
entry: 2A68 chain: C score: 1088 E: 0.0
entry: 2A68 chain: M score: 1088 E: 0.0
entry: 2A69 chain: C score: 1088 E: 0.0
entry: 2A69 chain: M score: 1088 E: 0.0
entry: 2BE5 chain: C score: 1088 E: 0.0
entry: 2BE5 chain: M score: 1088 E: 0.0
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entry: 2O5I chain: M score: 1088 E: 0.0
entry: 2O5J chain: C score: 1088 E: 0.0
entry: 2O5J chain: M score: 1088 E: 0.0
entry: 2PPB chain: C score: 1088 E: 0.0
entry: 2PPB chain: M score: 1088 E: 0.0
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entry: 1SMY chain: M score: 1088 E: 0.0
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entry: 1ZYR chain: M score: 1088 E: 0.0
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entry: 3DXJ chain: M score: 1088 E: 0.0
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entry: 3EQL chain: M score: 1088 E: 0.0
entry: 3AOH chain: C score: 1084 E: 0.0
entry: 3AOH chain: M score: 1084 E: 0.0
entry: 3AOH chain: H score: 1083 E: 0.0
entry: 2GHO chain: C score: 1083 E: 0.0
entry: 1YNJ chain: C score: 1083 E: 0.0
entry: 1YNN chain: C score: 1083 E: 0.0
entry: 1HQM chain: C score: 1082 E: 0.0
entry: 1I6V chain: C score: 1082 E: 0.0
entry: 1L9Z chain: C score: 1057 E: 0.0
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```

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entry: 3AOI chain: H score: 1032 E: 0.0
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entry: 2YOS chain: R score: 179 E: 2e-44
entry: 2WAQ chain: B score: 179 E: 2e-44
entry: 2WB1 chain: B score: 179 E: 2e-44
entry: 2WB1 chain: R score: 179 E: 2e-44
entry: 2PMZ chain: B score: 178 E: 4e-44
entry: 2PMZ chain: R score: 178 E: 4e-44
entry: 3HKZ chain: B score: 178 E: 4e-44
entry: 3HKZ chain: J score: 178 E: 4e-44
entry: 3K1F chain: B score: 151 E: 5e-36
entry: 3HOG chain: B score: 150 E: 8e-36
entry: 3HOG chain: N score: 150 E: 8e-36
entry: 2NVX chain: B score: 146 E: 2e-34
entry: 3QT1 chain: B score: 145 E: 4e-34
entry: 3TBI chain: B score: 145 E: 4e-34
entry: 3HOU chain: B score: 145 E: 4e-34
entry: 3HOU chain: N score: 145 E: 4e-34
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entry: 2R92 chain: B score: 145 E: 5e-34
entry: 2R93 chain: B score: 145 E: 5e-34
entry: 2B8K chain: B score: 145 E: 5e-34
entry: 3FKI chain: B score: 145 E: 5e-34
entry: 3HOW chain: B score: 145 E: 5e-34
entry: 3HOX chain: B score: 145 E: 5e-34
entry: 2B63 chain: B score: 145 E: 6e-34
entry: 2JA7 chain: B score: 145 E: 6e-34
entry: 2JA7 chain: N score: 145 E: 6e-34
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entry: 1Y1V chain: B score: 145 E: 6e-34
entry: 1Y1W chain: B score: 145 E: 6e-34
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entry: 4A3E chain: B score: 145 E: 6e-34
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entry: 4A3J chain: B score: 145 E: 6e-34
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entry: 4A3G chain: B score: 145 E: 6e-34
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entry: 3S1Q chain: B score: 144 E: 6e-34
entry: 3S1R chain: B score: 144 E: 6e-34
entry: 3S2D chain: B score: 144 E: 6e-34
entry: 3S2H chain: B score: 144 E: 6e-34

```

entry: 3I4M chain: B score: 144 E: 6e-34
entry: 3I4N chain: B score: 144 E: 6e-34
entry: 3PO2 chain: B score: 144 E: 6e-34
entry: 1I6H chain: B score: 144 E: 6e-34
entry: 1NIK chain: B score: 144 E: 6e-34
entry: 1R5U chain: B score: 144 E: 6e-34
entry: 1R9S chain: B score: 144 E: 6e-34
entry: 1WCM chain: B score: 144 E: 6e-34
entry: 1R9T chain: B score: 144 E: 7e-34
entry: 1SFO chain: B score: 144 E: 7e-34
entry: 2VUM chain: B score: 144 E: 7e-34
entry: 3GTL chain: B score: 144 E: 7e-34
entry: 3GTO chain: B score: 144 E: 7e-34
entry: 3GTP chain: B score: 144 E: 7e-34
entry: 3GTQ chain: B score: 144 E: 7e-34
entry: 3M3Y chain: B score: 144 E: 7e-34
entry: 3M4O chain: B score: 144 E: 7e-34
entry: 2E2J chain: B score: 144 E: 7e-34
entry: 2E2H chain: B score: 144 E: 7e-34
entry: 2NVZ chain: B score: 144 E: 7e-34
entry: 3GTG chain: B score: 144 E: 7e-34
entry: 3GTJ chain: B score: 144 E: 7e-34
entry: 3GTK chain: B score: 144 E: 7e-34
entry: 4A93 chain: B score: 144 E: 1e-33
entry: 3K7A chain: B score: 143 E: 2e-33
entry: 1NT9 chain: B score: 131 E: 6e-30
entry: 1I50 chain: B score: 123 E: 2e-27
entry: 2NVY chain: B score: 123 E: 2e-27
entry: 1TWF chain: B score: 123 E: 2e-27
entry: 1I3Q chain: B score: 123 E: 2e-27
entry: 1K83 chain: B score: 123 E: 2e-27
entry: 1TWA chain: B score: 122 E: 4e-27
entry: 1TWC chain: B score: 122 E: 4e-27
entry: 1TWG chain: B score: 122 E: 4e-27
entry: 1TWH chain: B score: 122 E: 4e-27
entry: 3CQZ chain: B score: 100 E: 2e-20
entry: 3MLQ chain: D score: 92 E: 7e-18
entry: 3MLQ chain: B score: 91 E: 8e-18
entry: 3MLQ chain: C score: 91 E: 9e-18
entry: 3MLQ chain: A score: 89 E: 4e-17
entry: 3LTI chain: A score: 77 E: 2e-13

```

Retrieving template ...

Entry: 3iyd
Chain: C

Making profile-profile alignment ...

Score: 1493.0 bits
Identity: 53.5 %

```

Query: 32  RVSAKLEPVEPLGLLDVQTDSEFWLIGSPRWRESAAERGDVNPVG--GLEEVLYELSP 89
          R F K + L+VP LL +Q DSF+ I + +P G GLE + P
Templ: 3  RKDFGKRPOQLDVPYLLSIQLDSFQKFI-----EQDPEGQYGLEAAFRSVFP 49

Query: 90  IEDFSGSMSLSFSDPRFDDVKAPVDECKDKDMTYAAPLFVTAEFI-----NNNTGEIK 142
          I+ +SG+ L + R + V EC+ + +TY+APL V + +IK
Templ: 50  IQSYSGNSELQYVSYRLGEPVFDVQECQIRGVTYSAPLRVKLRLVIYEREAPGTVKDIK 109

Query: 143 SQTVMGDFPMMTEKGTFIINGTERVVVSQLVRS PGVYFDETDK--STDKTLHSVKVIP 200
          Q V+MG+ P+MT+ GTF+INGTERV+VSQ L RSPGV+FD K S+ K L++ ++IP
Templ: 110 EQEVYMG EIPLMTDNGTFVINGTERVIVS QLHRSPGVFFDS DKGKTHSSGKVLYNARIIP 169

Query: 201 SRGAWLEFDVDRDTPGVVRIDRKRQPVTVLLKALGWTSEQIVERF-----G 247
          RG+WL+F+ D +D + VRIDR+R+ P T++L+AL +T+EQI++ F G
Templ: 170 YRGSWLD FEFDPKDNLFVRIDRRRKL PATIILRALNYTTEQILD LFFEKVDLLAKLSQSG 229

Query: 248 FSEI-----MRSTLEKDNVTGDEALLDIYRKL RGPPEPTKESAQT LLENLF 294
          I + TL D T AL++IYR +RGPPEPT+E+A++L ENLF
Templ: 230 HKRIETLFTNDLDHGPYISETLRVDPTNDRLSALVEIYRMMRPGPEPTTREA AESLFENLF 289

```

Query: 295 FKEKRYDLARVGRYKVNKKLGLHVGEPIISS-TLTEEDVVATIEYLVRLHEGQTTMTVPG 353
 F E RYDL+ VGR K N+ L + E I S L+++D++ ++ L+ + G+

Templ: 290 FSEDRYDLSAVGRMKFNRSL---LREEIEGSGILSKDDIIDVMKKLIDIRNGKG----- 340

Query: 354 GVEVPVETDDIDHFGNRRRLTVGELIQNQIRVGMSSRMERVVREMTTQDVEAITPQTLIN 413
 E DDIDH GNRR+R+VGE+ +NQ RVG+ R+ER V+ER++ D++ + PQ +IN

Templ: 340 -----EVDDIDHLGNRRIRSVGEMAENQFRVGLVVRVERAVKERLSLGDLDLTLMPQDMIN 394

Query: 414 IRPVVAAIKEFFGTSQLSQFMDQNNPLSGLTHKRRLSALGPGGLSRERAGLEVRDVHPSH 473
 +P+ AA+KEFFG+SQLSQFMDQNNPLS +THKRR+SALGPGGL+RERAG EVRDVHP+H

Templ: 395 AKPISAAVKEFFGSSQLSQFMDQNNPLSEITHKRRISALGPGGLTRERAGFEVRDVHPTH 454

Query: 474 YGRMCPIETPEGPNIGLIGLSVYARVNPFFGIETPYRKVVDGVVSDIEVYLTADEEDRH 533
 YGR+CPJETPEGPNIGLI SLSVYA+ N +GF+ETPYRKV DGVV+DEI YL+A EE +

Templ: 455 YGRVCPJETPEGPNIGLINSLSVYAQTNEYGFLETPYRKVTDGVVTDIEHYLSAIEEGNY 514

Query: 534 VVAQANSPIADGRFVEPRVLVRRKAGEVEYVPSSEVDYMDVSPRQMVSATAMIPFLEH 593
 V+AQANS +D +G FVE V R K GE +VDYMDVS +Q+VSV ++IPFLEH

Templ: 515 VIAQANSNLDEEGHFVEDLVTCRSK-GESSLFSRDQVDYMDVSTQQVVSQVSLIPFLEH 573

Query: 594 DDANRALMGANMQRQAVPLVRSEAPLVGTGMELRAAIDAGDVVVAEESGVIEEVSADYIT 653
 DDANRALMGANMQRQAVP +R++ PLVGTGME A+D+G VA+ GV++ V A I

Templ: 574 DDANRALMGANMQRQAVPTLRADKPLVGTGMEAVAVDSGVTAVAKRGGVVQYVDASRIV 633

Query: 654 VMHDNGTRRT-----YMRKFARSNHGTCANQCPIVDAGDRVEAGQVIADGPTDDGE 706
 + + Y + K+ RSN TC NQ P V G+ VE G V+ADGP TD GE

Templ: 634 IKVNEDEMYPGEAGIDIYNLTKYTRSNQNTCINQMPCVSLGEPVERGDVLDGPTDLDGE 693

Query: 707 MALGKNLLVAIMPWEHNYEDAIILSNRLVEEDVLTSIHIEEHEIDARDTKLGAEIITRD 766
 +ALG+N+ VA MPW G+N+ED+I++S R+V+ED T+IHI+E +RDTKLG EEIT D

Templ: 694 LALGQNMRFVAFMPWNGYNFEDSILVSERVVQEDRFTTIHIQELACVSRDTKLGPEEITAD 753

Query: 767 IPNISDEVLADLDERGIVRIGAEVRDGDILVGKVTPKGETELTPEERLLRAIFGEKAREV 826
 IPN+ + L+ LDE GIV IGAEV GDILVGKVTPKGET+LTPEE+LLRAIFGEKA +V

Templ: 754 IPNVGEAALSKLDESGIVYIGAEVTTGGDILVGKVTPKGETQLTPEEKLLRAIFGEKASDV 813

Query: 827 RDTSLKVPHGSGKVIIGIRVFSRED-EDELPAQVNLVRYVVAQKRKISDGDKLAGRHGN 885
 +D+SL+VP+G SG VI ++VF+R+ E +L GV ++V+VY+A KR+I GDK+AGRHGN

Templ: 814 KDSSLRVPNGVSGTVIDVQVTRDGVVEKDLAPGVKIVKIVYLAVKRRIQPGDKMAGRHN 873

Query: 886 KGVIGKILPVEDMPFLADGTPVDIILNTHGVPVPRMNIGQILETHLWCAHSGWKVDAAGK 945
 KGV I KI P+EDMP+ +GTPVDI+LN GVP RMNIGQILETHLG AAKG

Templ: 874 KGVISKINPIEDMPYDENGTPVDIVLNLPLGVPSRMNIGQILETHLGM-----AAKG 924

Query: 946 VPDWAARLPDELLEAQPNAIVSTPVFDGAQEAELQGLSCTLPNRDGDVLDADGKAMLF 1005
 + +P ++TPVFDGA+EAE++ LL GD+ G+ L+

Templ: 925 IG-----MP-----IATPVFDGAKEAEIKELLKL-----GDL--PTSGQIRLY 960

Query: 1006DGRSGEFPYPVTVGYMYIMKLHHLVDDKIHARSTGPYSMITQQPLGGKAQFGGQRFGEM 1065
 DGR+GE F PVTVGYMY++KL+HLVDDK+HARSTG YS++TQQPLGGKAQFGGQRFGEM

Templ: 961 DGRTGEQFERPVTVGYMYMLKLNHLVDDKMHARSTGSYSLVTTQQPLGGKAQFGGQRFGEM 1020

Query: 1066ECWAMQAYGAAYTLQELLTIKSDDTVGRVKVYEAIVKGENIPEPGIPESFKVLLKELQSL 1125
 E WA++AYGAAYTLQE+LT+KSDD GR K+Y+ IV G + EPG+PESF VLLKE++SL

Templ: 1021EVWALEAYGAAYTLQEMLTVKSDDVNGRTKMYKNIVDGNHQMEPGMPESFNVLLKEIRSL 1080

Query: 1126CLNVEV 1131
 +N+E+

Templ: 1081GINIEL 1086

Modeling ...

Summary: Query= gi_15607807_ref_NP_215181.1_Template= 3IYD.C Id= 53.5 Qlen= 1172
 Model_len= 1100 Coverage= 93.9 Q_Mw= 129235 Model_Mw= 121855 Method= 'PDB Blast' E-
 value= 0.0

Table 3.1 CPHmodels 3.2 Server Alligment Results

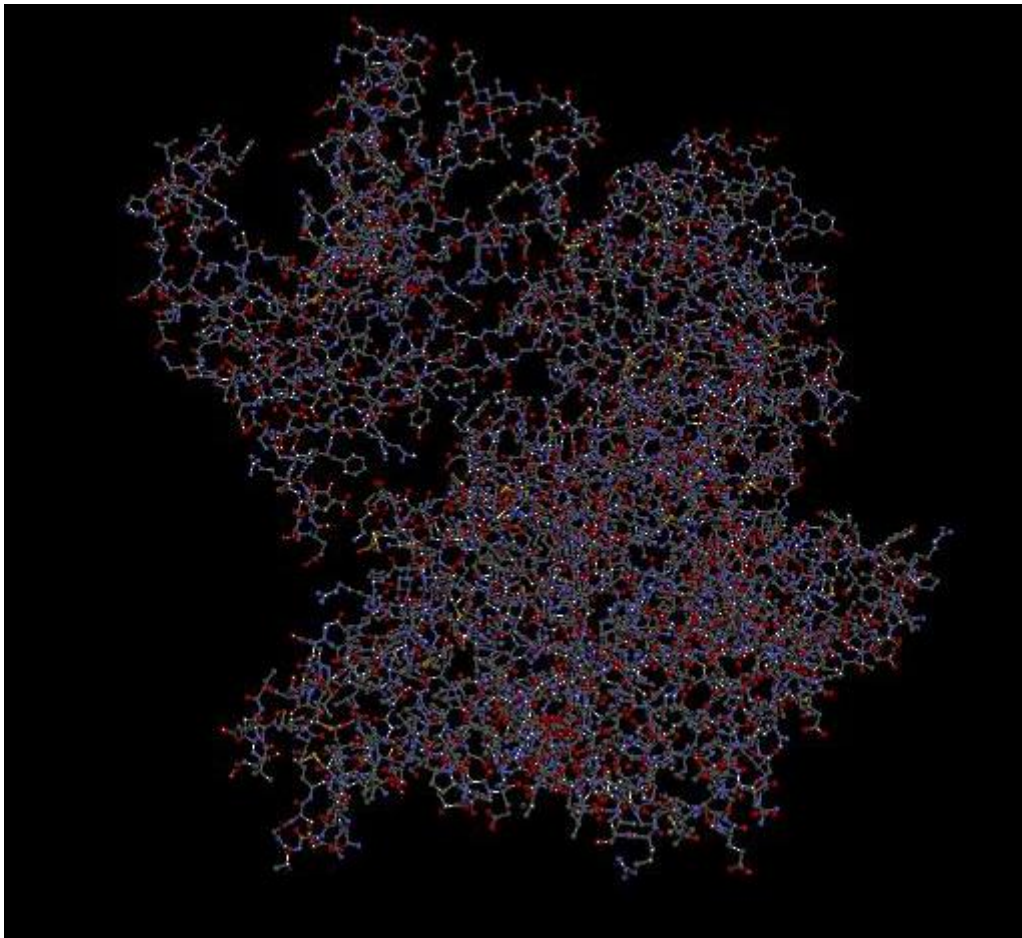


Figure 3.4 CPHmodels 3.2 Server rpo β model atomic view

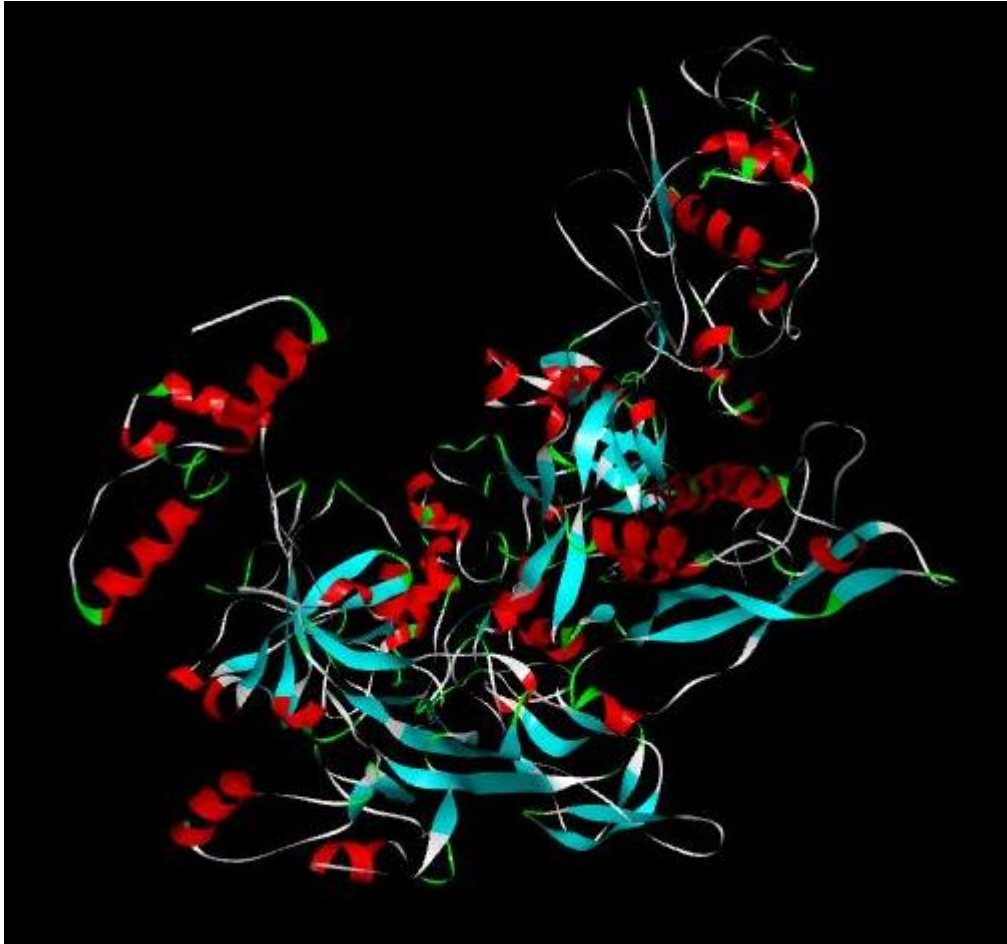


Figure 3.5 CPHmodels 3.2 Server Protein Chain View

3.2 Protein structure prediction on the Web: a case study using the Phyre server

Phyre server is an Automated homology modeling program using neural networks.

Query gi|15607807|ref|NP_215181.1| (seq=MADSRQSKTA...NESASVEDLA Len=1172 Neff=6.9 Nseqs=213)
Parameters score SS:yes search:local realign with MAP:no

No Hit	Prob	E-value	P-value	Score	SS	Cols	Query	HMM
1 2a6h_C	100.0	5E-272	2E-276	2556.4	60.2	1059	31-1145	2-1115 (1119)

2	3lu0_C	DNA-directed RNA polyme	100.0	1E-268	4E-273	2551.1	45.5	1065	29-1134	9-1342 (1342)
3	2waq_B	DNA-directed RNA polyme	100.0	6E-221	2E-225	2091.2	49.5	940	31-1134	10-1119 (1131)
4	1twf_B	DNA-directed RNA polyme	100.0	7E-219	3E-223	2081.0	55.3	940	35-1136	31-1221 (1224)
5	3h0g_B	DNA-directed RNA polyme	100.0	3E-215	1E-219	2048.7	13.9	941	35-1137	18-1210 (1210)
6	3mlq_A	DNA-directed RNA polyme	100.0	3.6E-40	1.3E-44	345.1	19.6	184	46-434	2-188 (188)
7	3lti_A	DNA-directed RNA polyme	100.0	1.4E-28	5.3E-33	274.2	19.2	177	172-362	1-296 (296)
8	3tbi_B	DNA-directed RNA polyme	99.8	2.8E-20	1E-24	199.2	13.2	128	743-870	1-228 (228)
9	3qqc_A	DNA-directed RNA polyme	97.2	0.0001	3.8E-09	86.7	3.2	57	1097-1153	25-86 (436)
10	2lmc_B	DNA-directed RNA polyme	92.2	0.12	4.4E-06	47.1	4.5	57	633-699	23-84 (84)
11	2xha_A	NUSG, transcription ant	81.9	0.95	3.5E-05	47.2	4.2	57	633-699	100-159 (193)
12	2xhc_A	Transcription antitermi	75.4	1.7	6.3E-05	49.4	4.2	58	633-700	140-200 (352)
13	3it5_A	Protease LASA; metallo	60.0	6.9	0.00025	40.4	4.5	53	633-697	48-100 (182)
14	2xha_A	NUSG, transcription ant	56.0	1.4E+02	0.005	31.1	13.4	142	636-873	43-191 (193)
15	1ax3_A	Iiaglc, glucose permeas	49.2	17	0.00063	36.7	5.3	82	632-718	48-132 (162)
16	1f3z_A	EIIA-GLC, glucose-speci	37.5	37	0.0014	34.2	5.6	65	632-698	48-114 (161)
17	3our_B	EIIA, phosphotransferas	34.5	44	0.0016	34.4	5.6	65	632-698	70-136 (183)
18	2gpr_A	Glucose-permease IIA co	34.2	42	0.0015	33.5	5.3	65	632-698	43-109 (154)
19	3nyy_A	Putative glycyl-glycine	30.3	44	0.0016	36.0	5.1	58	627-697	129-197 (252)
20	2xhc_A	Transcription antitermi	30.0	2E+02	0.0075	32.3	10.7	109	636-797	83-197 (352)
21	2hsi_A	Putative peptidase M23;	25.7	66	0.0024	35.2	5.5	77	627-718	184-265 (282)
22	2gul_A	Zinc peptidase; alpha/b	20.8	1.1E+02	0.0042	34.2	6.4	77	627-718	236-317 (361)

2a6h_C DNA-directed RNA polymerase beta chain; RNA polymerase holoenzyme, streptolydigin, antibiotic, transcription regulation; HET: STD; 2.40A {Thermus thermophilus} SCOP: e.29.1.1 PDB: 1smy_C* 1zyr_C* liw7_C* 2a69_C* 2a6e_C 2a68_C* 2be5_C* 2cw0_C 2o5i_C 2o5j_C* 2ppb_C* 3aoh_C* 3aoi_C* 3dxj_C* 3eql_C* 1ynj_C* 1ynn_C* 2gho_C 1hqm_C 119u_C ... Probab=100.00 E-value=5.5e-272 Score=2556.40 Aligned_cols=1059 Identities=53% Similarity=0.908 Sum_probs=0.0

```

Q ss_pred          eeeehhccccccCCCCHHHHHHHHHHHHhCccccccccccccccchHHHHHHhCCCEe--
-cCCcEEEEEEEEEEc
Q gi|15607807|re   31 NRVSFAKLREPLEVPGLLDVQTDSEFWLIGSPRWRESAAERGDVNPVGGLEEVLYELSPIED--
-FSGSMSLSFSDPRFD 107 (1172)
Q Consensus       31 ~r~~~~i~~~~~p~Lv~~qi~SFn~Fl~~~~~GL~~ii~~~~pI~~~
~~~~~l~f~~i~i~  107 (1172)
                    +|++|+++++|++|+|+++|++|||+|||.+++      |++|+++|+++++|++
.++++|+|++++|+
T Consensus       2 ~r~~~~~L~v~~qi~SFn~Fl~~~~~
~~~~~GL~~i~~~~pI~~~~~L~f~~i~i~  74 (1119)
T 2a6h_C          2 EIKRFGRTREVIPPLPTEIQVESYRRALQADVP-----
PEKRENVGIQAAFRETFFIEEDKGGGLVLDLFLEYRLG  74 (1119)
T ss_dssp          EEECCCCCCCCSCCCTTHHHHHHHHHHSCCTTSC-----
TTSSCCCHHHHHHHHHCSEEECCSSSCCEEEECCECCBC
T ss_pred         cceccccccccCcHHHHHHHHHHHccCCc-----
cccchhhHHHHHHhCCCEccccCCcEEEEEEEEEEc

```




Figure 3.6 Amino Acid chain base viewing by Phyre Server

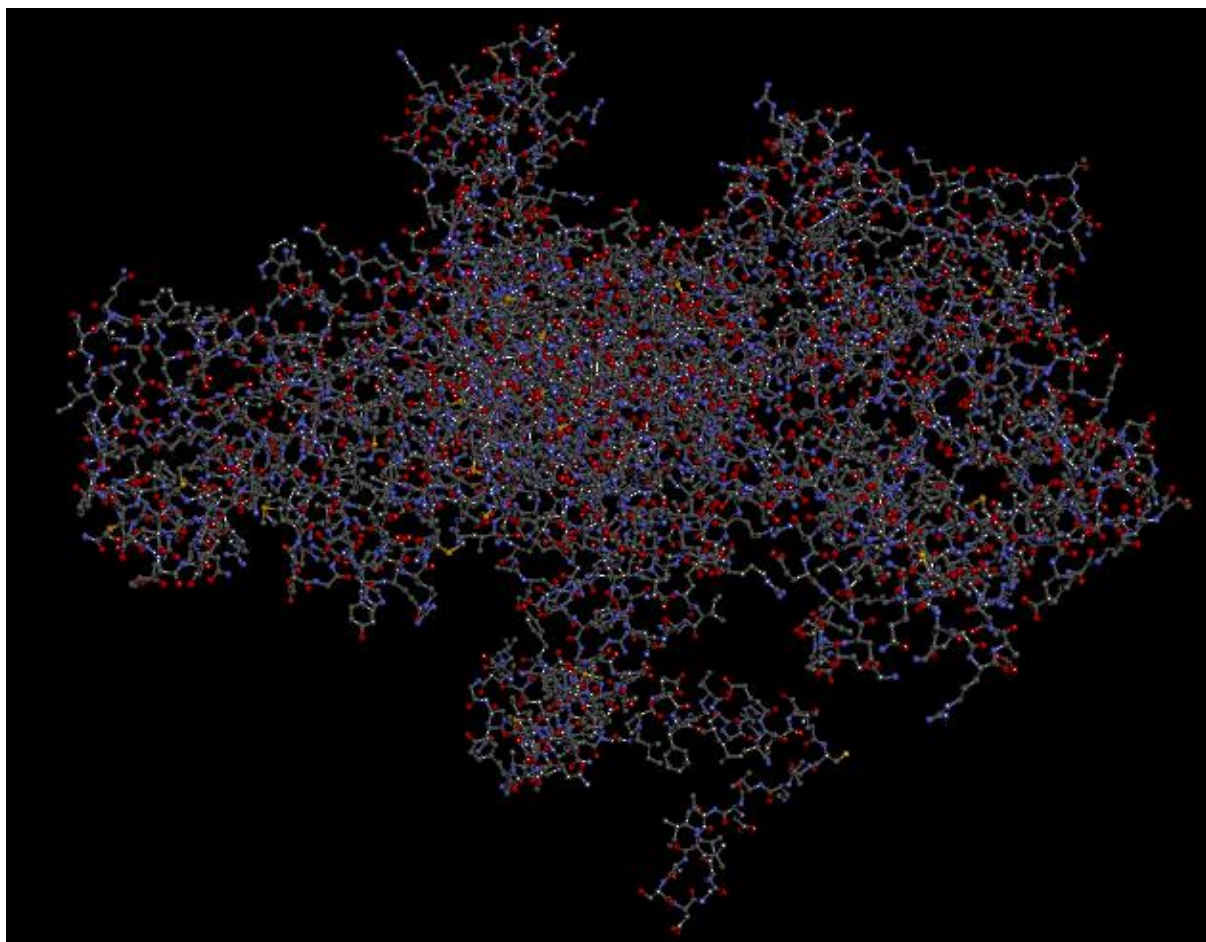


Figure 3.7 Atomic base viewing by Phyre Server

3.3 Docking result for rpoβ

We know that experimental docking energy is -13.3 kcal/mol.

We used autodock for docking process. We used it with that's configuration:

x-y-z coordinates: -41.936 ; 176.086 ; -3.12

maximum number of energy evaluations : 5000000 ,

num.grid points in xyz: 120 120 120 .

Source	ΔG
Experimental	-13.3 kcal/mol.
swiss-model	-6.27 kcal/mol.
Phyre server	-12.64 kcal/mol.
CPHmodels 3.2 Server	-9.43 kcal/mol.

Table 3.3 Docking result for each modeling server

So Phyre server is given better result for docking. We used it for mutation resistance calculation.

Enzyme	AA	Mut	ΔG	Ki
rpo β			-12.64 kcal/mol	542.08 pM
rpo β	S 456 (Ser)	L (Leu)	-11.44 kcal/mol	4.08 nM
rpo β	D 441 (Asp)	V (Val)	-10.89 kcal/mol	12.10 nM
rpo β	H 451 (His)	D (Asp)	-10.19 kcal/mol	1.16 nM
rpo β	H 451 (His)	R (Arg)	-12.22 kcal/mol	1.11 nM
rpo β	H 452 (His)	Y (Tyr)	-12.43 kcal/mol	552.11 pM
rpo β	Q 438 (Gln)	K (Lys)	-10.84 kcal/mol	11.40 nM
rpo β	S 447 (Ser)	Q (Gln)	-11.69 kcal/mol	3.87 nM
rpo β	S 456 (Ser)	W (Trp)	-11.61 kcal/mol	3.07 nM

Table 3.4 Docking result for each mutation for Phyre Server Result

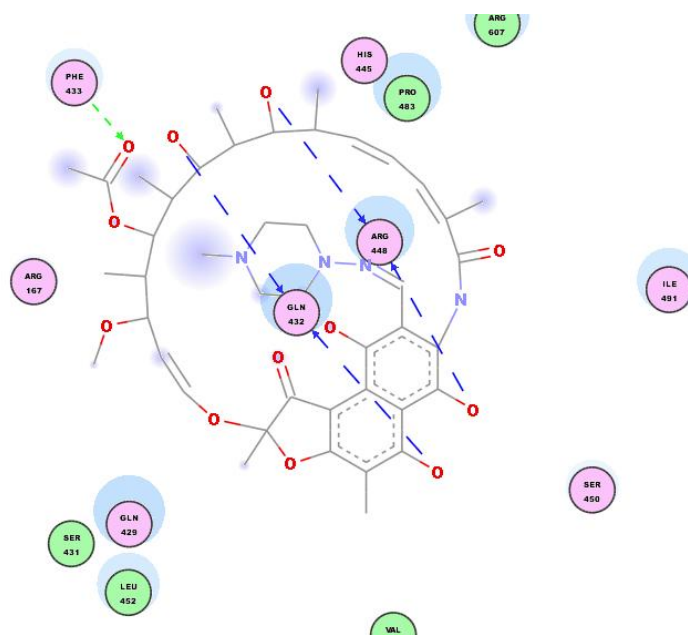


Figure 3.8 2D viewing RIF docking side with no mutation

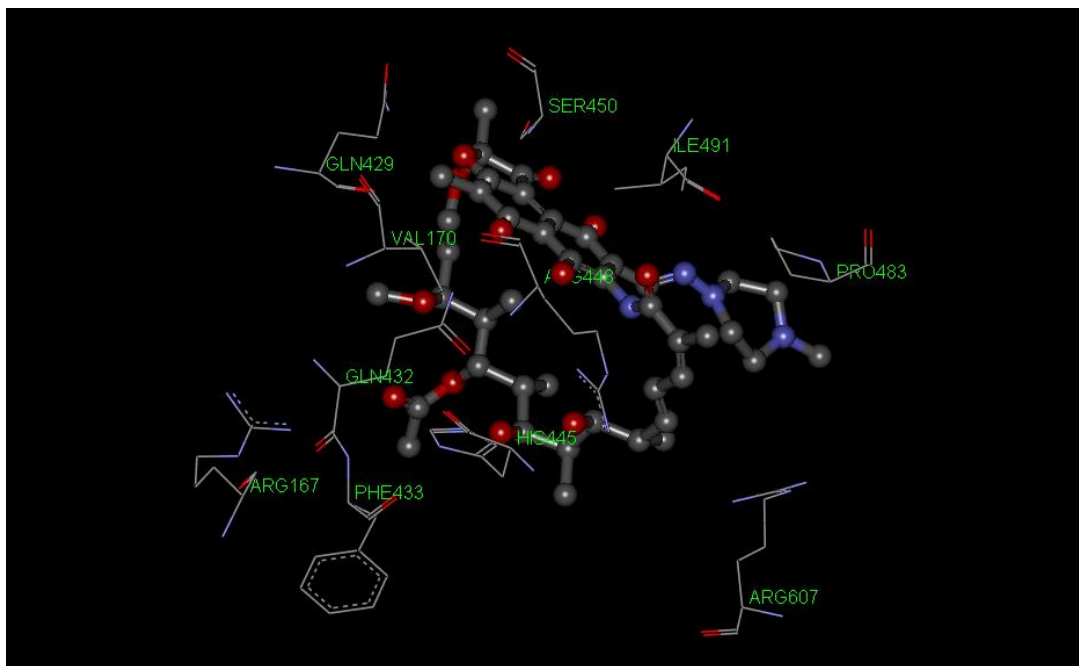


Figure 3.9 3D viewing RIF docking side with no mutation

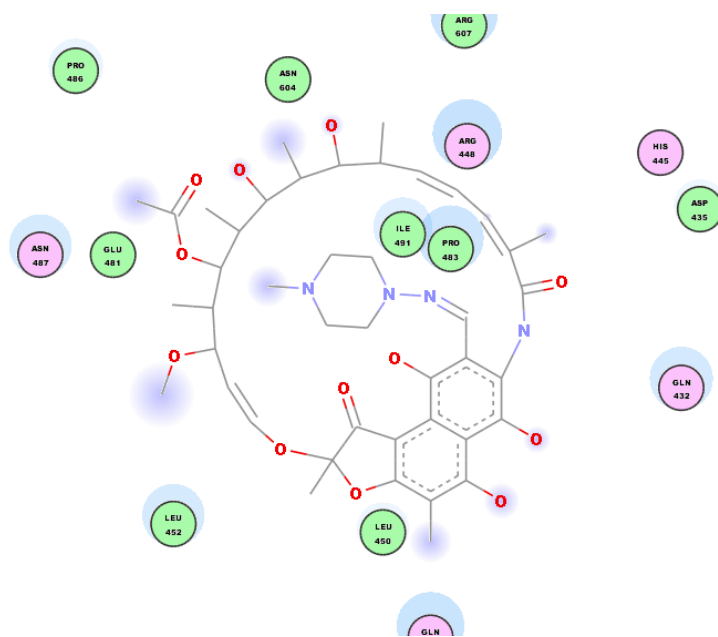


Figure 3.10 2D viewing RIF docking side with 456 S – L mutation

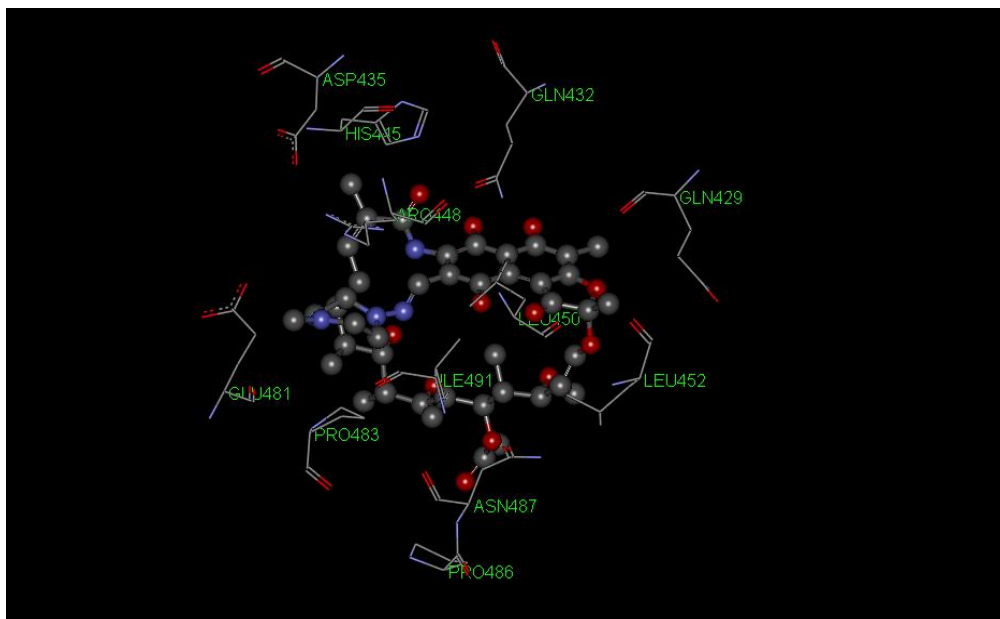


Figure 3.11 3D viewing RIF docking side with 456 S – L mutation

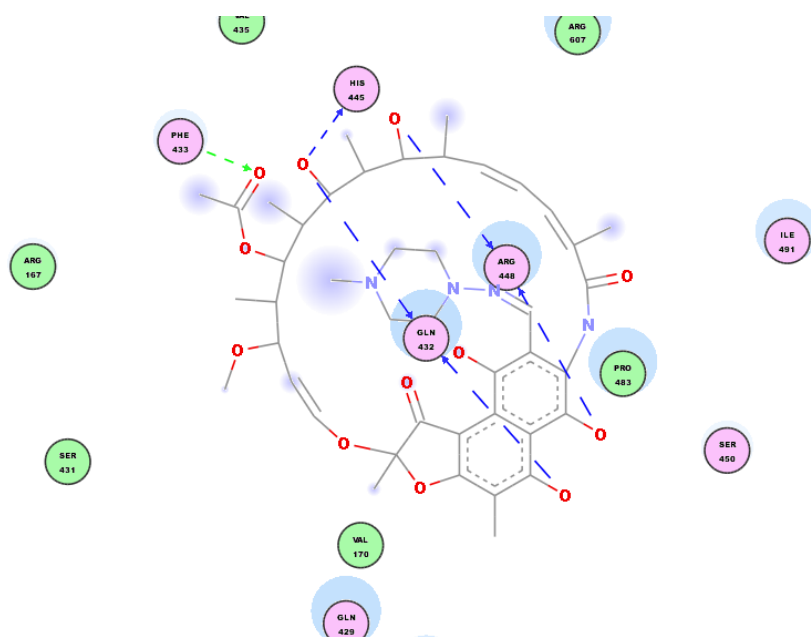


Figure 3.12 2D viewing RIF docking side with 441 D – V mutation

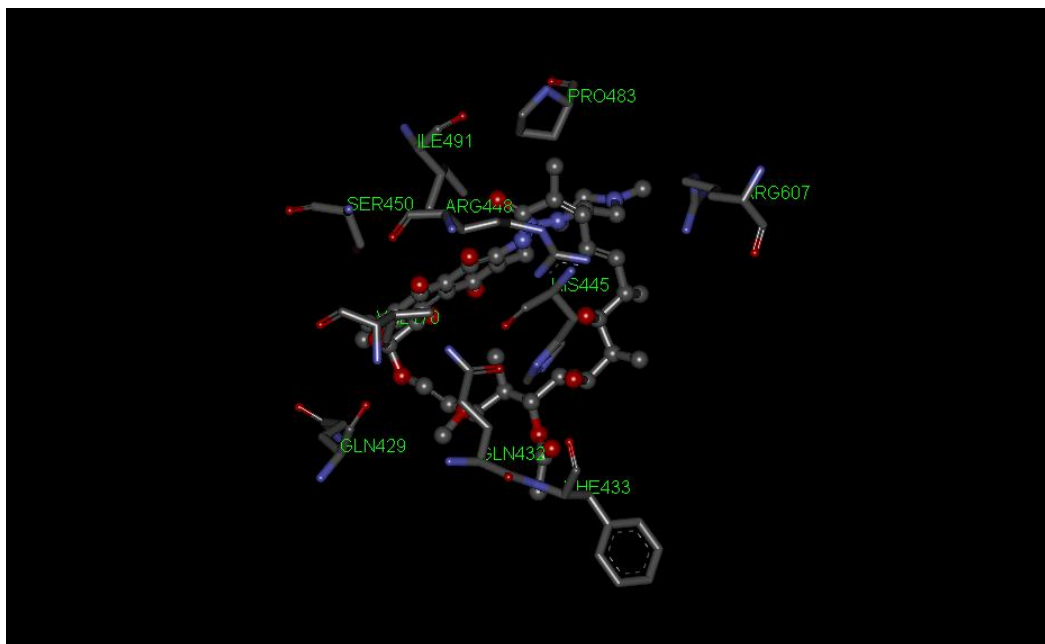


Figure 3.13 3D viewing RIF docking side with 441 D – V mutation

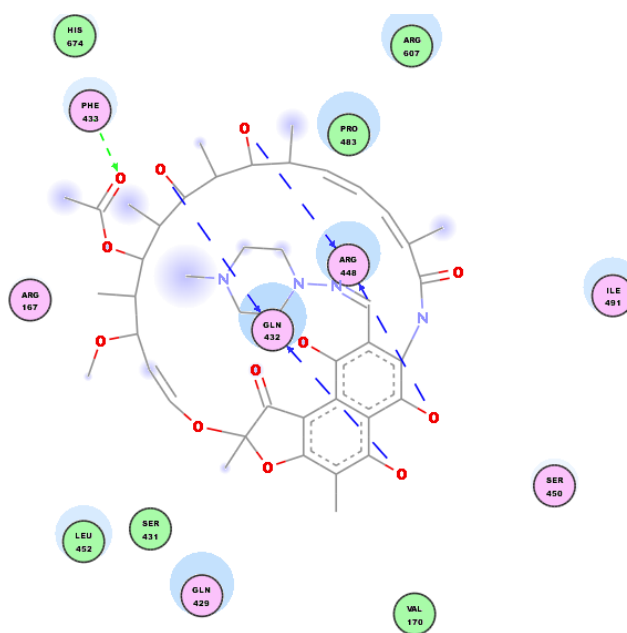


Figure 3.14 2D viewing RIF docking side with 451 H – D mutation

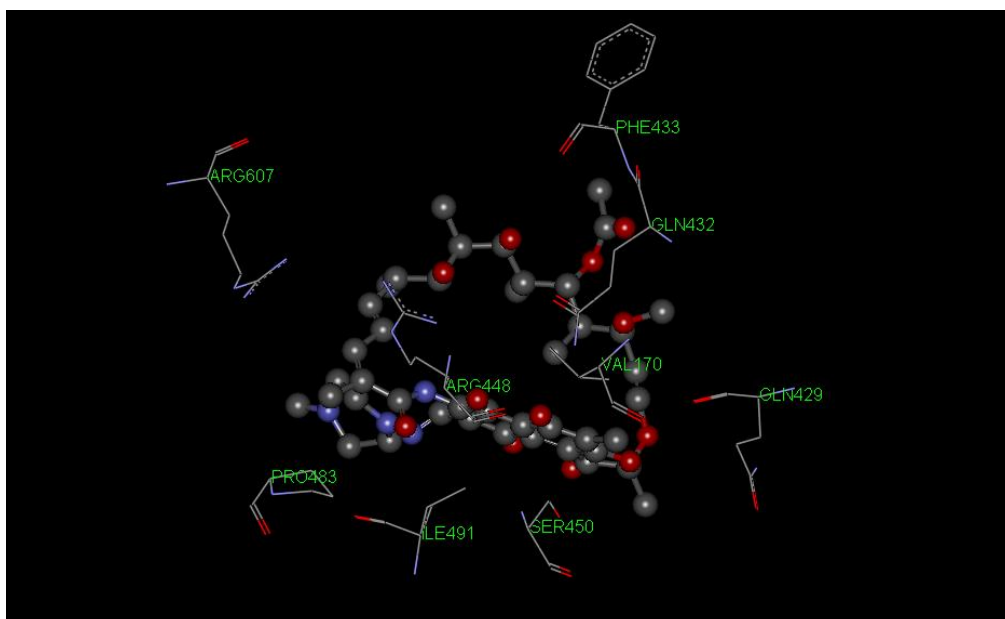


Figure 3.15 3D viewing RIF docking side with 451 H – D mutation

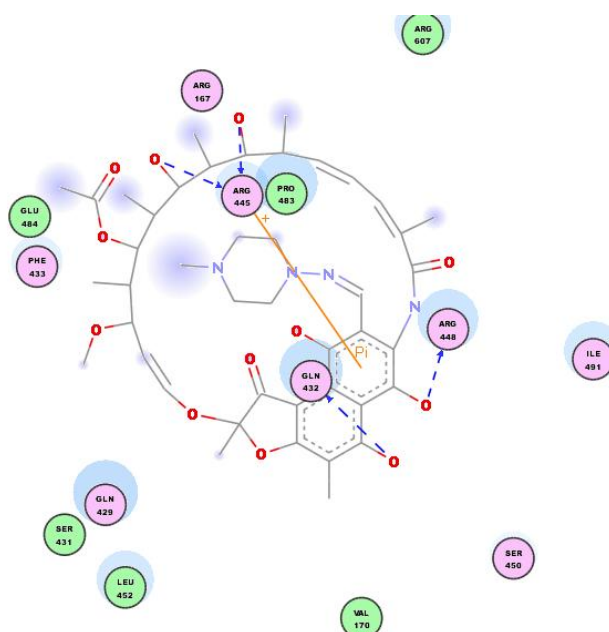


Figure 3.16 2D viewing RIF docking side with 451 H – R mutation

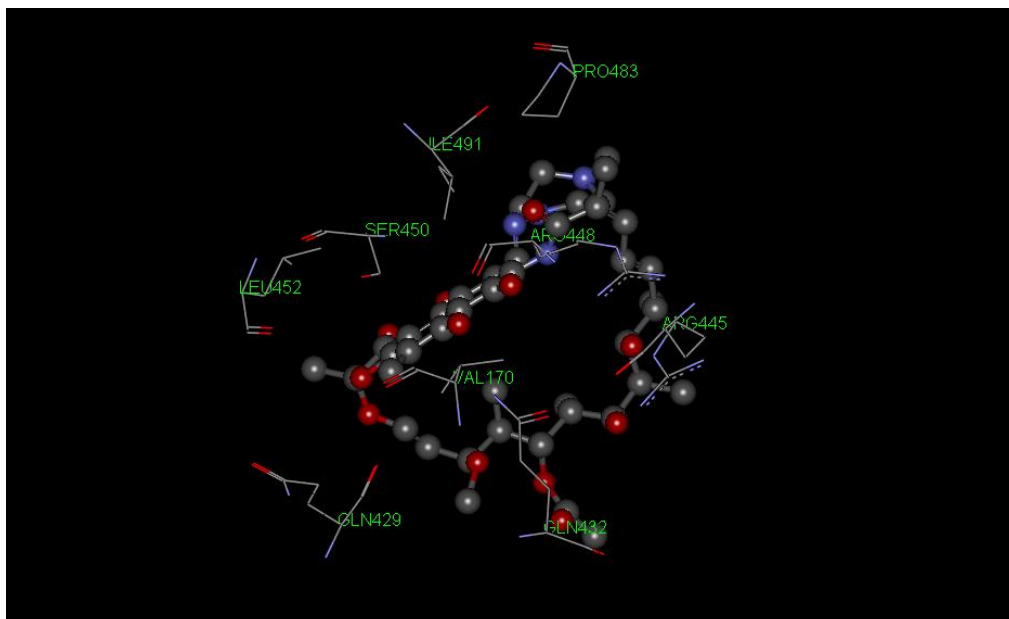


Figure 3.17 3D viewing RIF docking side with 451 H – R mutation

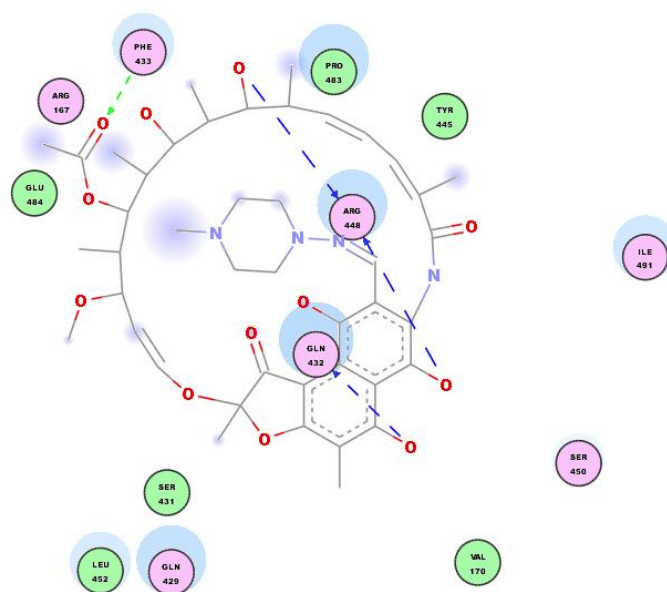


Figure 3.18 2D viewing RIF docking side with 452 H – Y mutation

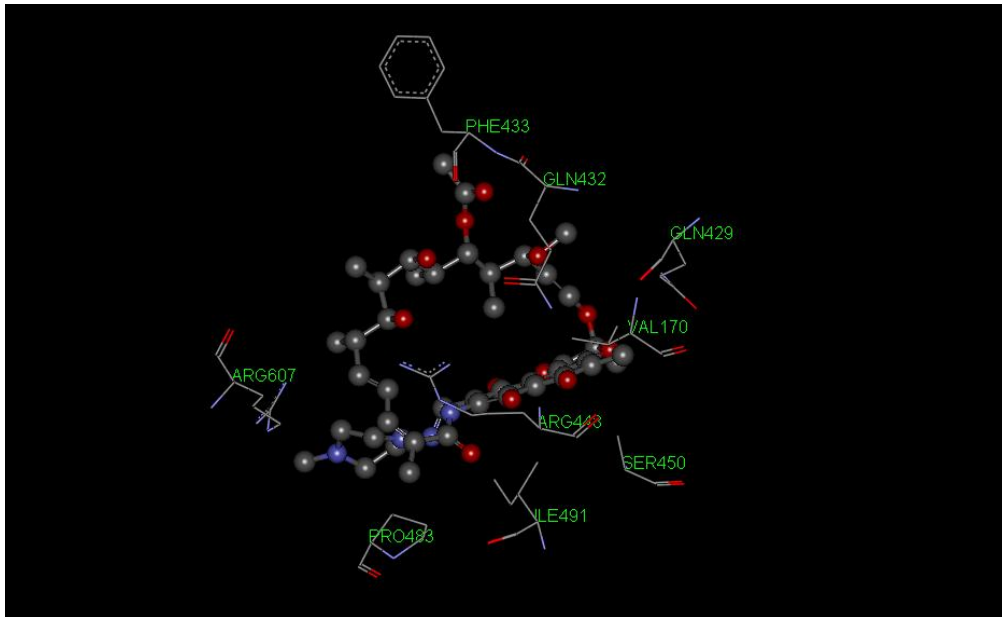


Figure 3.19 3D viewing RIF docking side with 452 H – Y mutation

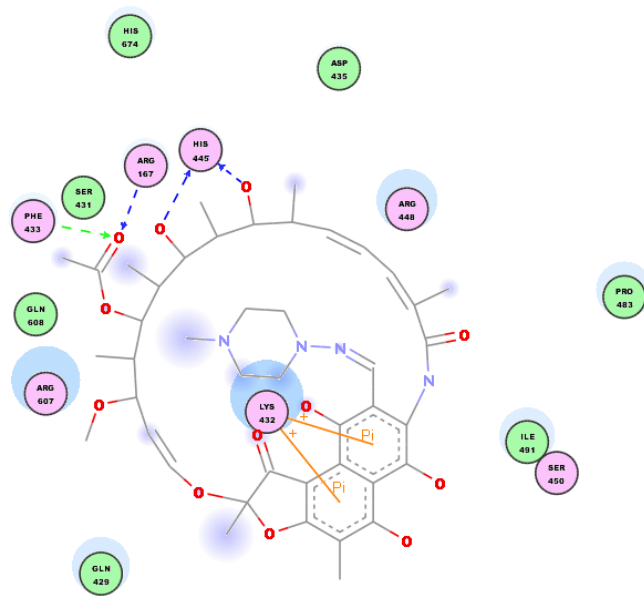


Figure 3.20 2D viewing RIF docking side with 438 Q – K mutation

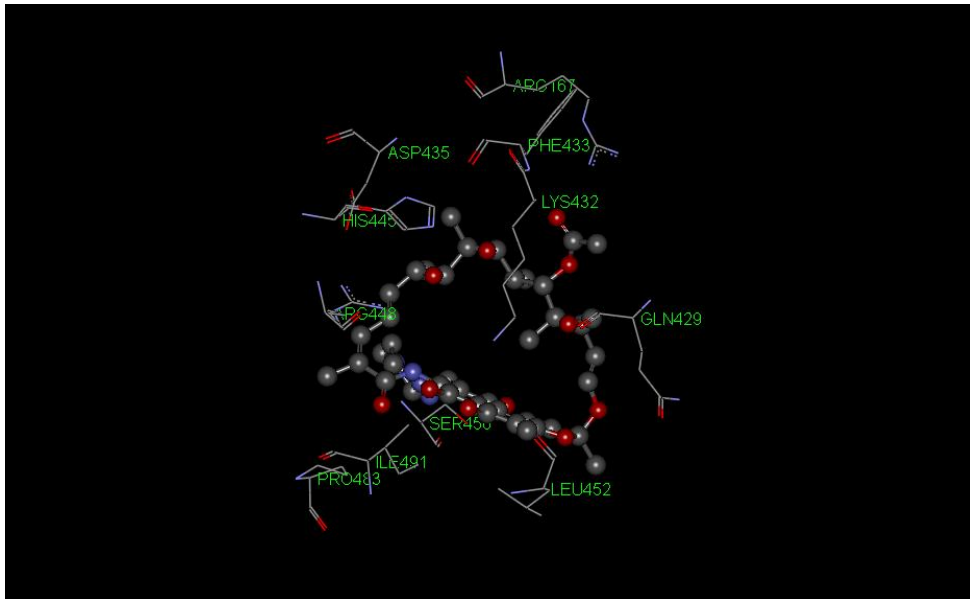


Figure 3.21 3D viewing RIF docking side with 438 Q – K mutation

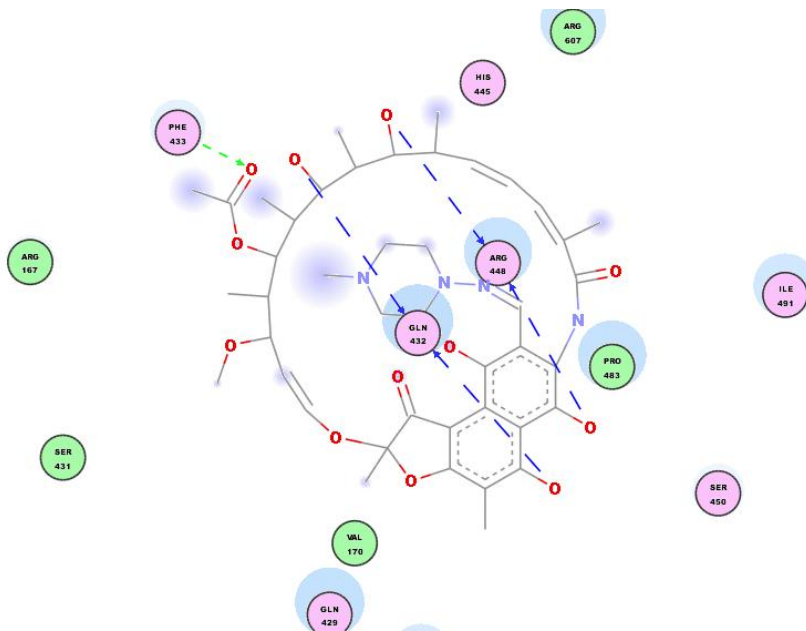


Figure 3.22 2D viewing RIF docking side with 447 S – Q mutation

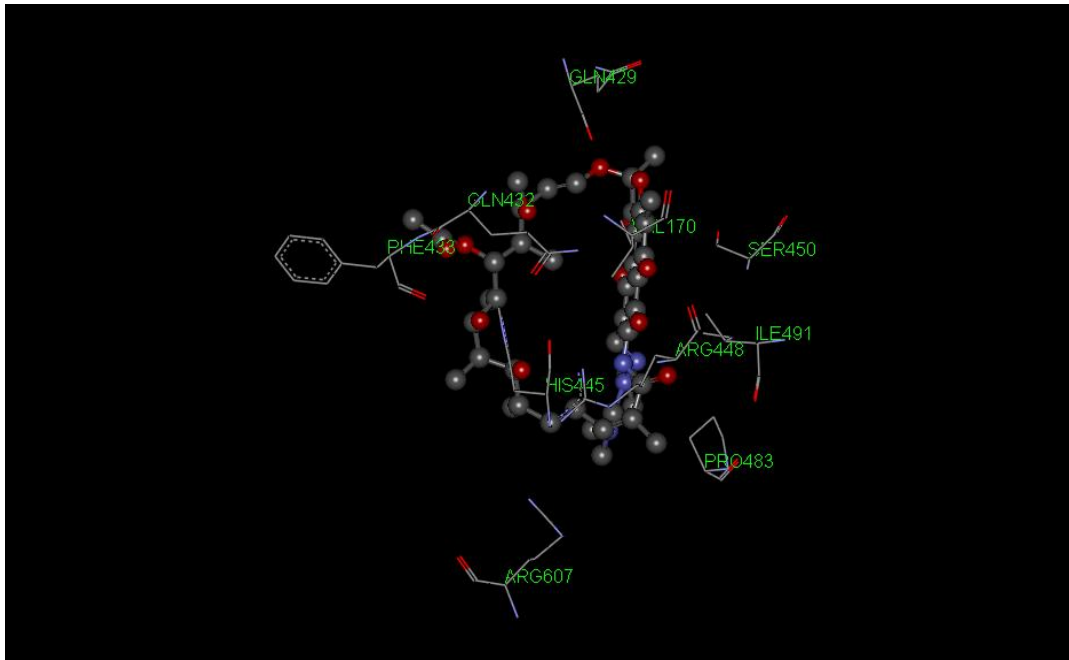


Figure 3.23 3D viewing RIF docking side with 447 S – Q mutation

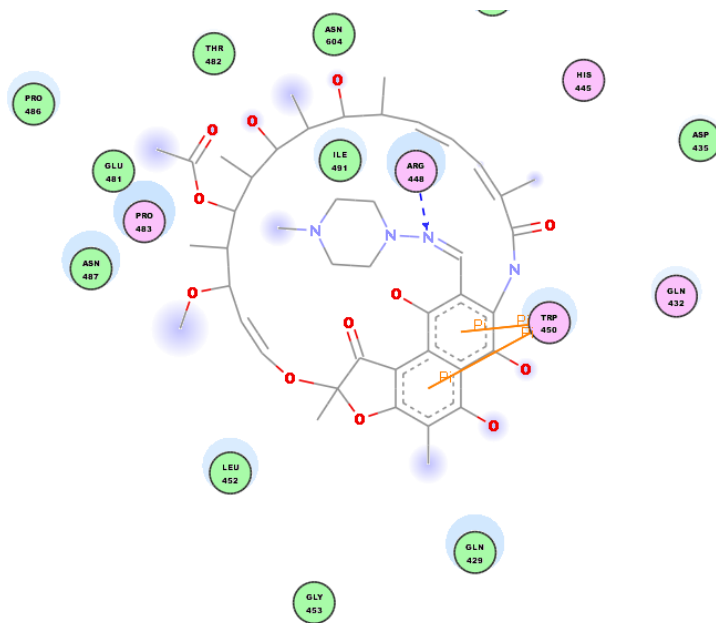


Figure 3.24 2D viewing RIF docking side with 456 S – W mutation

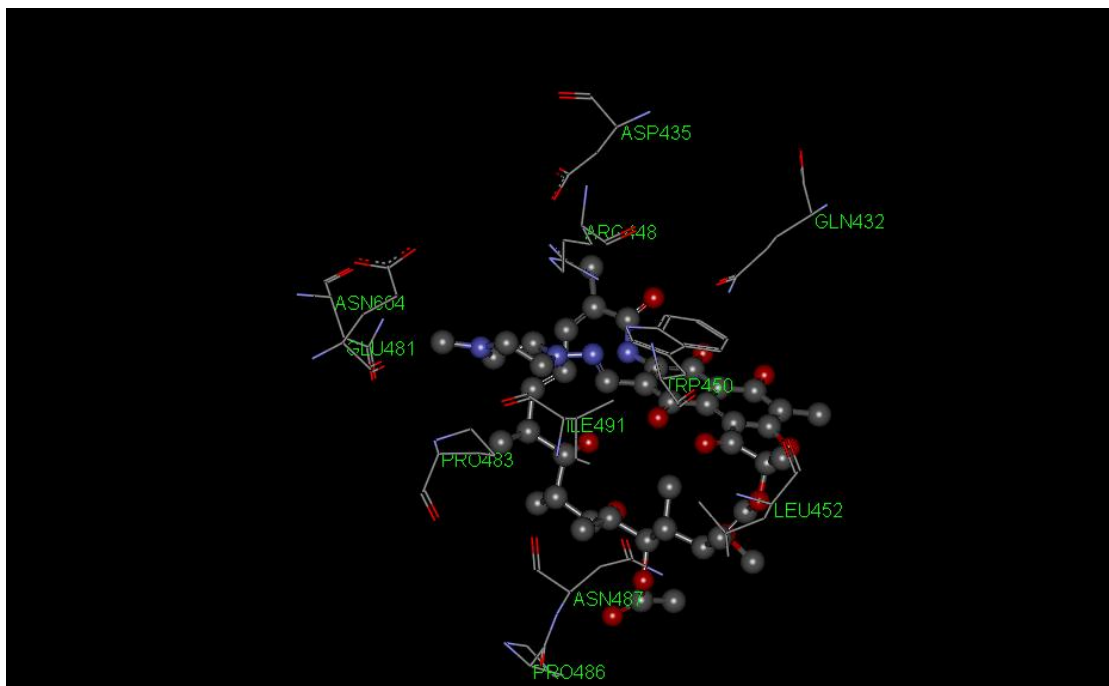


Figure 3.25 3D viewing RIF docking side with 456 S – W

Chapter 4

Conclusion

We understand that computational science method is good starting for computing mutation resistance to drug for TB with RIF. The changing amino acid characters with mutation reflect to the effect of drug. Next step could be tried of changing RIF for breaking resistance of mutations.

About rpo β protein modelin we can say that I couldn't locate its co-factor (Mg $^{++}$). We know that rpo β is need Mg $^{++}$ for starting working. But it is not possible located an atom on modeling.

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