



IJEAST

INTERNATIONAL JOURNAL
OF ENGINEERING APPLIED SCIENCE
AND TECHNOLOGY



VOLUME : 5 ISSUE : 3 Print / Issue Publication Date: 15-Sep-2020



ISSN : 2455-2143



DOI : 10.33564/IJEAST.2020.v05i03.110

Indexed In



WWW.IJEAST.COM

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COMPUTATIONAL METHOD FOR PROTEIN STRUCTURE PREDICTION AND DRUG DESIGN AGAINST COVID -19

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Abstract- In modern drug discovery, a detailed understanding of interactions between small chemical compounds and biomolecular macromolecules (e.g. medicinal agents and their targets) is of crucial importance. The search for drug-like compounds that selectively bind to a molecular target and interfere with its receptor function or enzymatic activity demands a multi- and interdisciplinary approach. Hereby, computer modeling serves as an important tool to understand the relevant ligand-receptor or ligand-enzyme interactions. Nowadays, it is difficult to imagine drug discovery without computation. Almost all critical function in cell rely on specific protein. Understanding these is therefore crucial in investigation of biological system Drug design and drug discovery are critical importance in human health care, Computational approaches have become a major part of structure based drug design. In this review computational method for prediction of protein structure are described and their use toward drug design is discovered.

I. INTRODUCTION

Coronaviruses are a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In 2019, a new coronavirus was identified as the cause of a disease outbreak that originated in China.

The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease it causes is called coronavirus disease 2019 (COVID-19). In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic Coronaviruses

(CoVs) (order Nidovirales, family Coronaviridae, subfamily are enveloped viruses with a positive sense, single-stranded RNA genome. With genome sizes ranging from 26 to 32 kilobases (kb) in length, CoVs have the largest genomes for RNA viruses. Based on genetic and antigenic criteria, CoVs have been organised into three groups: α -CoVs, β -CoVs, and γ -CoVs. The corona virus family is a positive-stranded RNA virus, which mainly causes respiratory and central nervous system disease in humans and animals].

There is an urgent need for the development of anti-viral drugs and vaccines against the 2019-nCov virus due to the high mortality rate of patients. The aim of the study is to use to computational approach to design both anti-viral drug and vaccine candidates. The spike protein in the novel coronavirus sequence is used to design both anti-viral drug and vaccine candidates.

II. MATERIAL & METHOD

NCBI protein database – 6M03-A PDB ID For further analysis the sequence was downloaded as the FASTA sequence.

Homology Modeling using Phyre software
Ligand predicted by Galxy tool, ProBis

III. EXPERIMENT AND RESULT

- analysis show how virus is evolutionary history with bats coronavirus
- Homology modeling using phyre indicate identity with 3C like proteinase
- Ligand predicted by Galxy web – D3F, RFM
- Using probis predicted- Small molecule ligand – 4 Methylbenzene diaminozinc.

BLAST SEQUENCE ANALYSIS

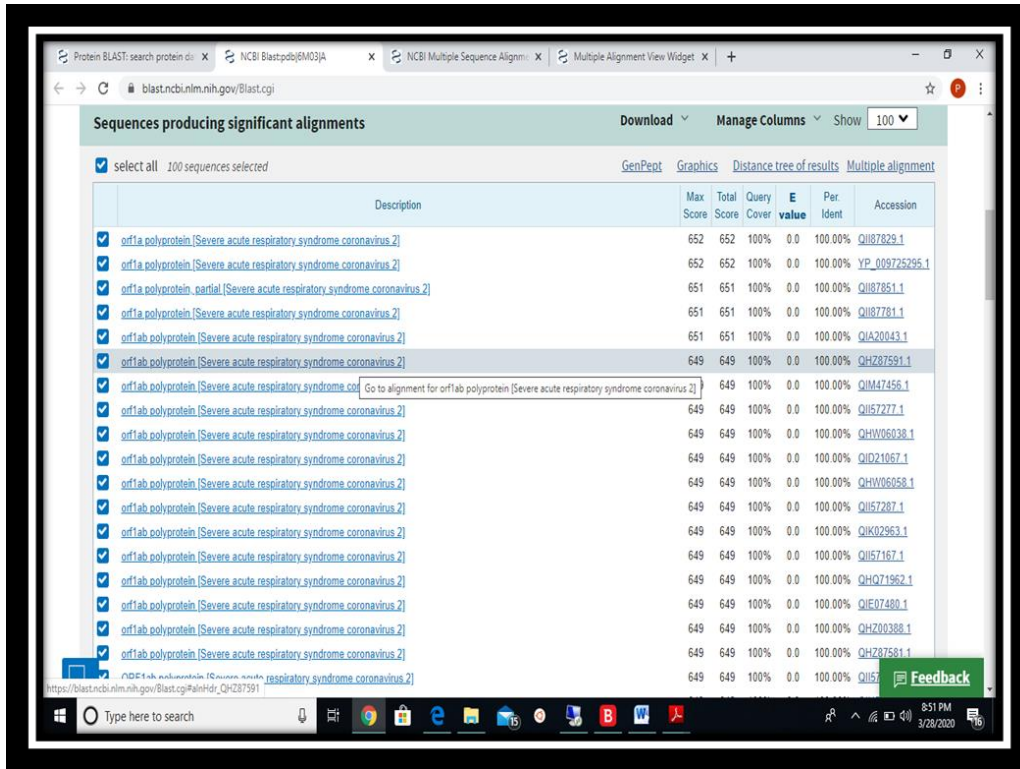


Fig 1 - blast sequence alignments

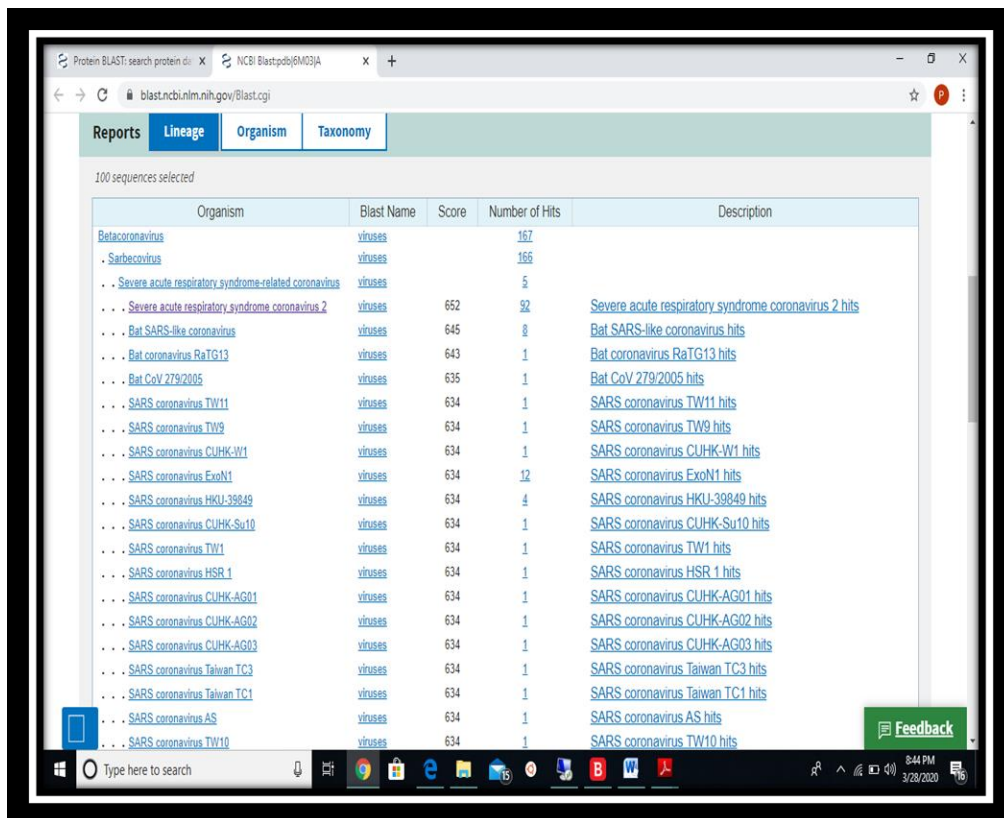


Fig 2- top sequence similarities

HOMOLOGY MODELING USING PHYRE

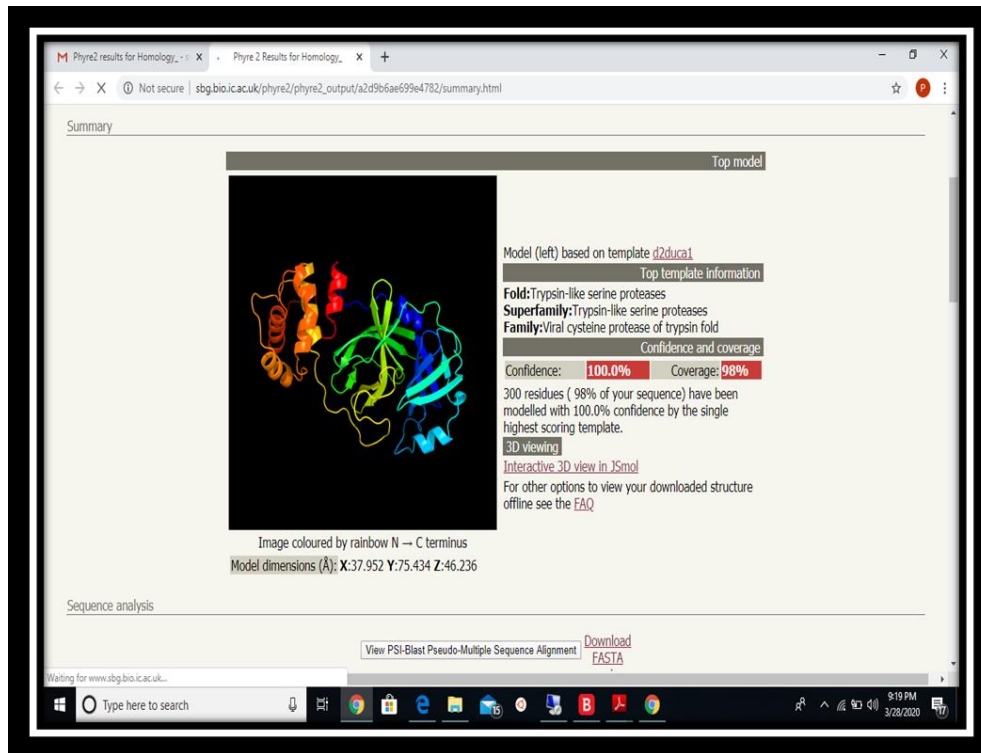
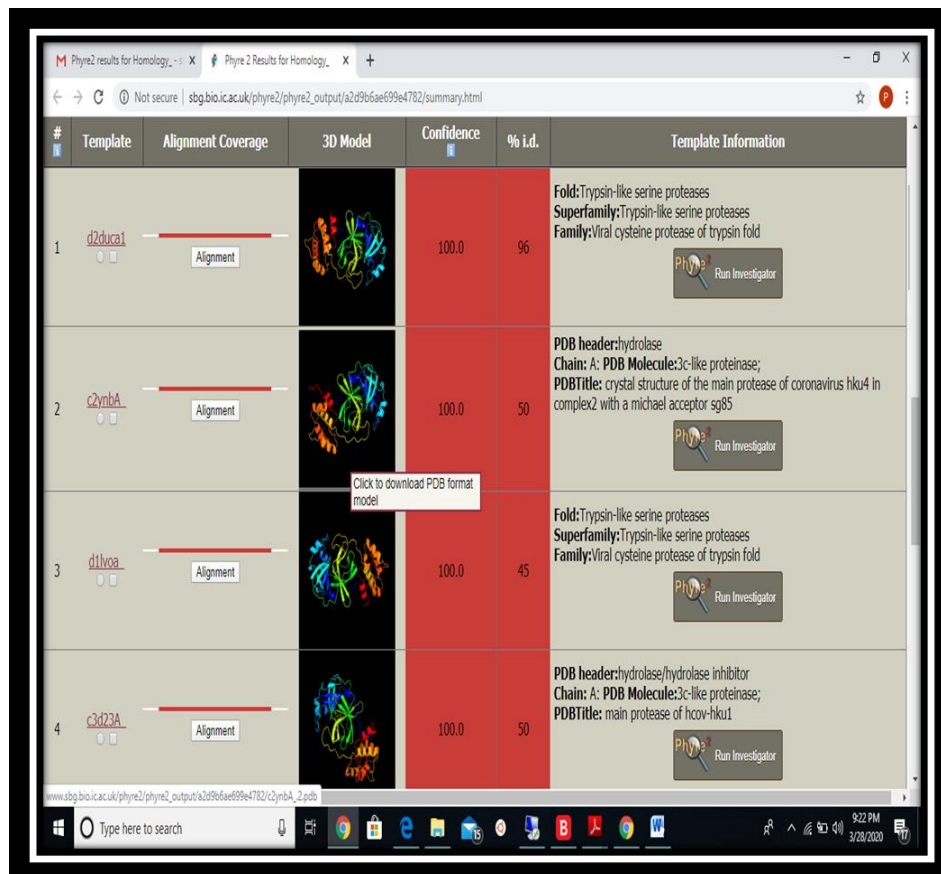








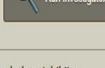


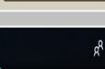


Fig 3 - Homology modeling structure

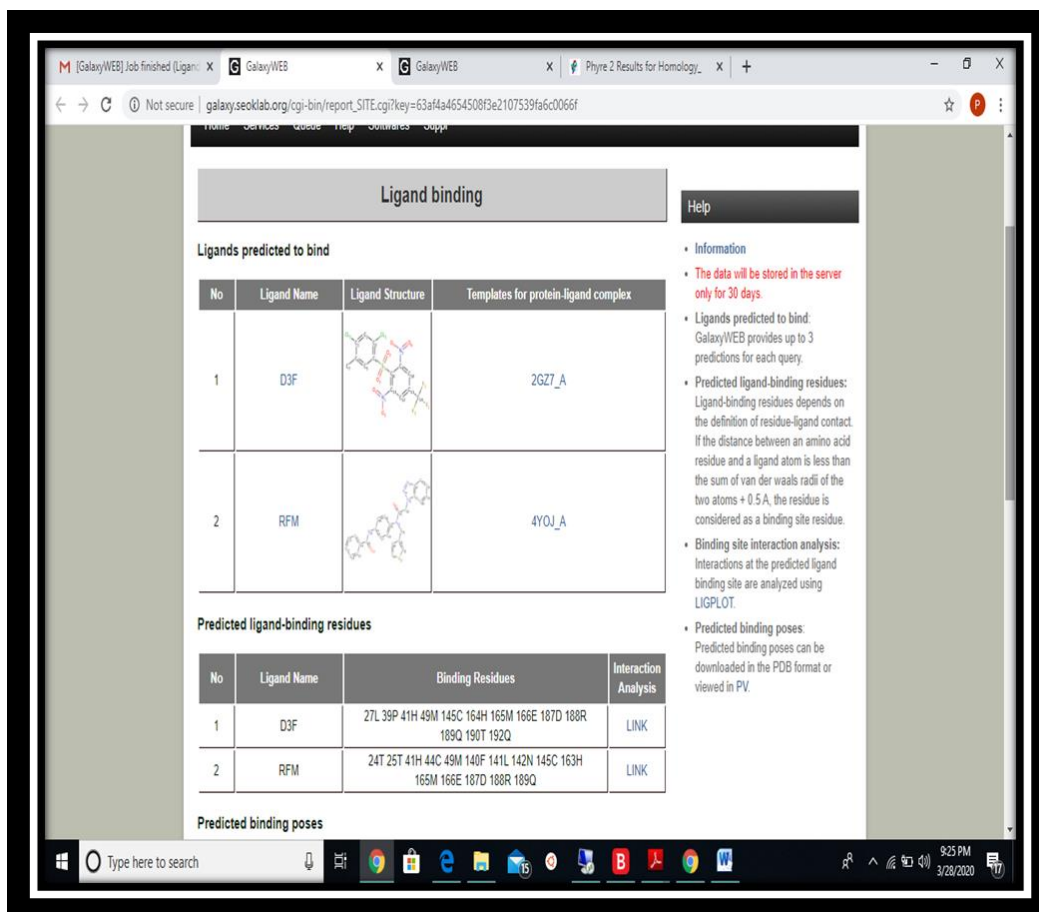


#	Template	Alignment Coverage	3D Model	Confidence	% i.d.	Template Information
1	d2duca1			100.0	96	Fold: Trypsin-like serine proteases Superfamily: Trypsin-like serine proteases Family: viral cysteine protease of trypsin fold 
2	c2ymbA			100.0	50	PDB header: hydrolase Chain: A: PDB Molecule: 3c-like proteinase; PDBTitle: crystal structure of the main protease of coronavirus hku4 in complex2 with a michael acceptor sg85 
3	d1lvoa			100.0	45	Fold: Trypsin-like serine proteases Superfamily: Trypsin-like serine proteases Family: viral cysteine protease of trypsin fold 
4	c3d23A			100.0	50	PDB header: hydrolase/hydrolase inhibitor Chain: A: PDB Molecule: 3c-like proteinase; PDBTitle: main protease of hcov-hku1 

Click to download PDB format model

Fig 4 - top rated alignments


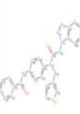
LIGAND BINDING USING GALAXY



The screenshot shows the GalaxyWEB interface with the following data:

Ligand binding

Ligands predicted to bind

No	Ligand Name	Ligand Structure	Templates for protein-ligand complex
1	D3F		2GZ7_A
2	RFM		4YQJ_A

Predicted ligand-binding residues

No	Ligand Name	Binding Residues	Interaction Analysis
1	D3F	27L 39P 41H 49M 145C 164H 165M 166E 187D 188R 189Q 190T 192Q	LINK
2	RFM	24T 25T 41H 44C 49M 140F 141L 142N 145C 163H 165M 166E 187D 188R 189Q	LINK

Predicted binding poses

Help

- Information
- The data will be stored in the server only for 30 days.
- Ligands predicted to bind: GalaxyWEB provides up to 3 predictions for each query.
- Predicted ligand-binding residues: Ligand-binding residues depends on the definition of residue-ligand contact. If the distance between an amino acid residue and a ligand atom is less than the sum of van der Waals radii of the two atoms + 0.5 Å, the residue is considered as a binding site residue.
- Binding site interaction analysis: Interactions at the predicted ligand binding site are analyzed using LIGPLOT.
- Predicted binding poses: Predicted binding poses can be downloaded in the PDB format or viewed in PV.

Fig 5-ligand predicted by galxy web

PREDICTED BINDING POSES

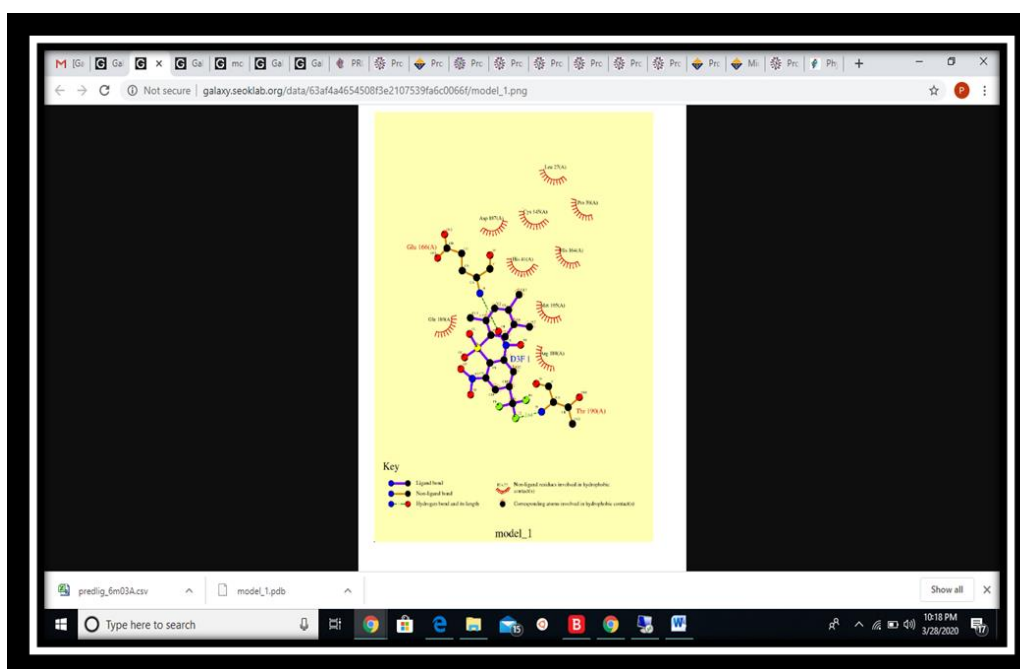


Fig 6 -site predicted by galaxy web model 1

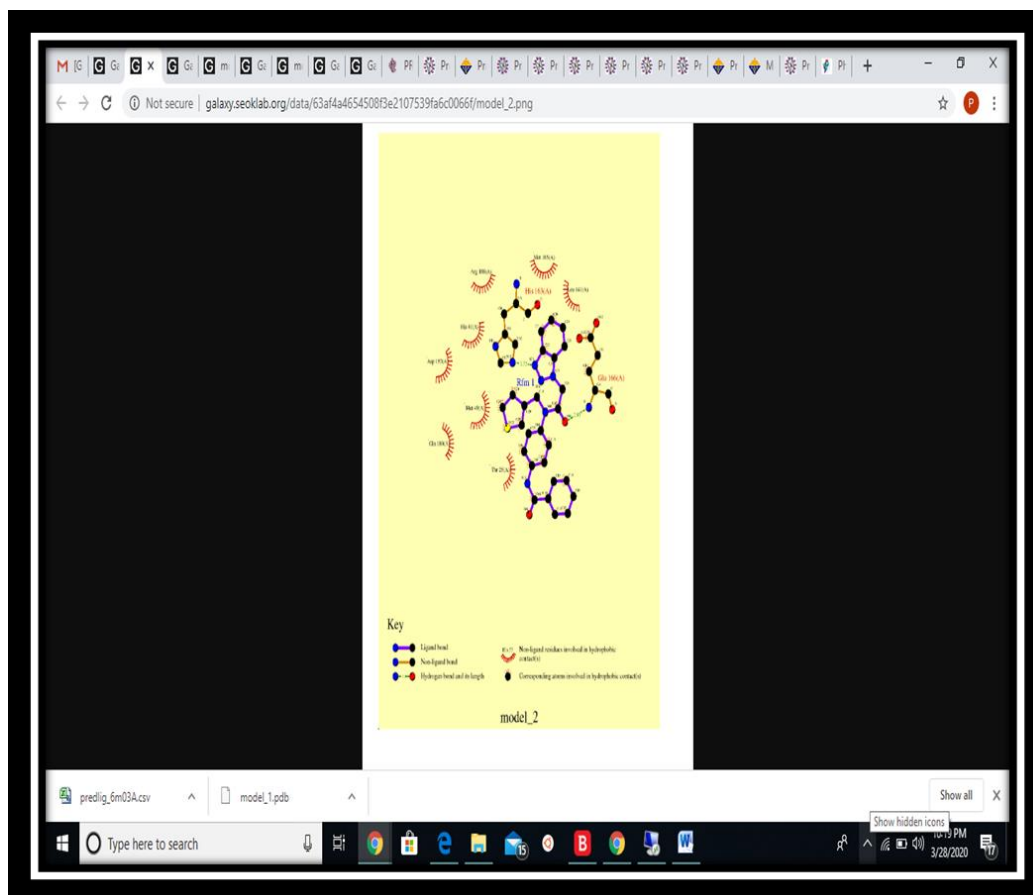


Fig 7 -site predicted model 2

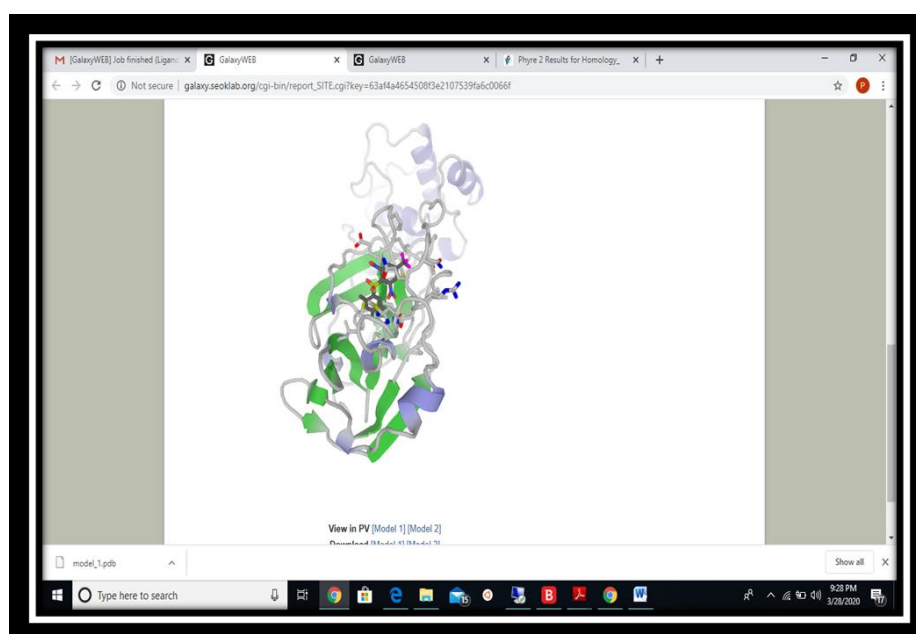


Fig 8 -predicted model

proBis web servers into one functional unit that enables prediction of protein–ligand complexes and allows for their geometry optimization and interaction energy calculation. The ProBiS web server predicts ligands (small compounds, proteins, nucleic acids, and single-atom ligands) that may bind to a query protein

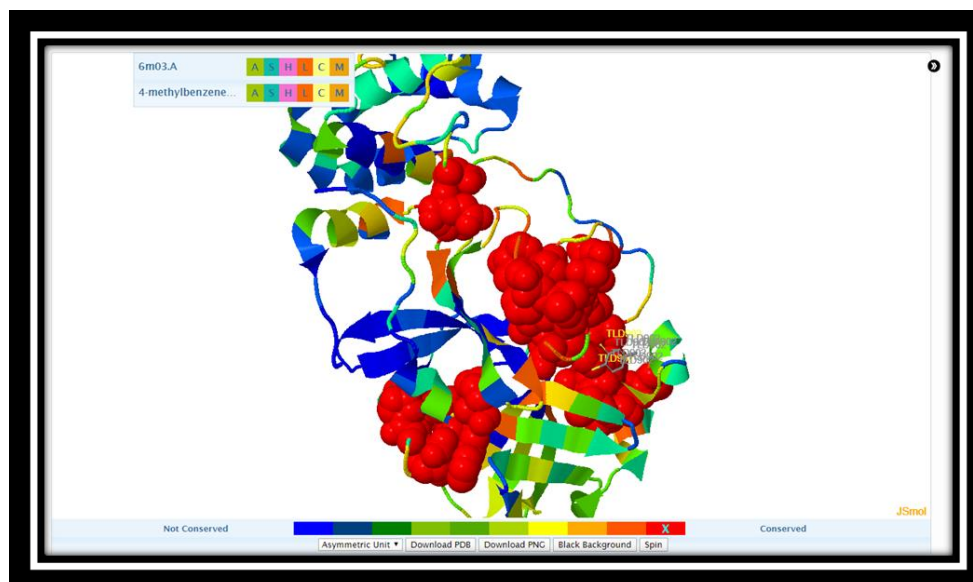


Fig 9- showing 4 methylbenzene binding geometry

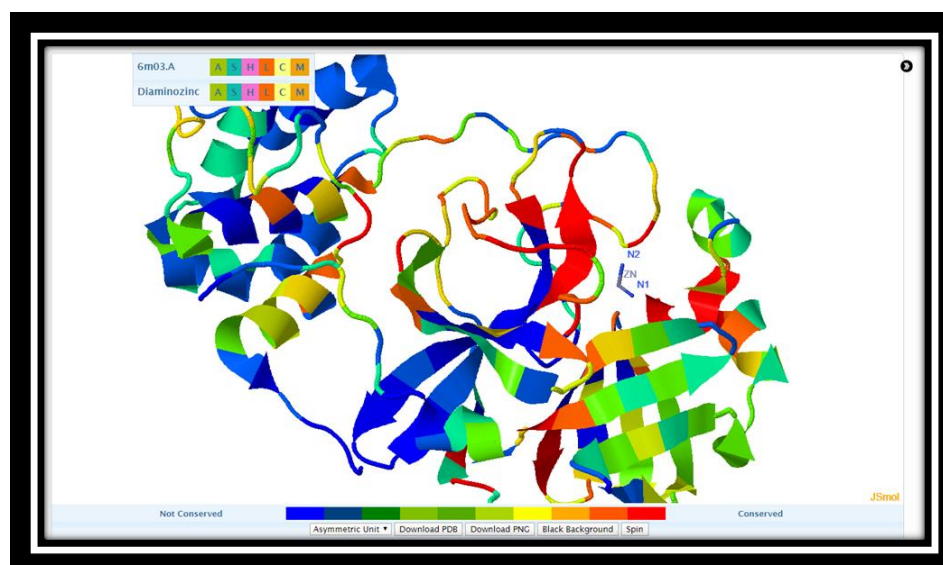


Fig 10 - showing diaminozinc binding geometry

IV. CONCLUSION

Due to the scarcity of experimental and clinical data, as well as the urgency to understand the infectivity of the deadly coronaviruses. computational analyses to study the 2019-nCoV virus in terms of protein structures, functions, phylogeny, and interactions at both molecular and organismal levels. In the present study, both drug and vaccine design was applied to identify drug and vaccine this approach will be cost effective and can save time in the design of drugs.

V. ACKNOWLEDGEMENTS

I thanks to Shri. N.V. Ingole Assistant Professor. AGRIBIOTECHNOLY COLLEGE AMRAVATI for lending her expertise and encourage to me. Deepest gratitude to Dr,P,D Shirgave Coordinater department of Agrochemicals

and Pest Management, Devchand College, Arjunnagar whose sincerity and encouragement I will never forget

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2455-2143