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Computational assessment studies of antiviral drugs against Spike Surface glycoprotein using Bioinformatics Tools

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Abstract

The aim of the current docking study is to assess the inhibitory activity of the antiviral drugs towards the spike surface glycoprotein. The 2D structures of 19 antiviral drugs (Abacavir, Amantadine, Amprenavir, Chloroquine, Delavirdine, Didanosine, Enfuvirtide, Indinavir, Lopinavir, Loviride, Nelfinavir, Nitazoxanide, Peramivir, Ribavirin, Ritonavir, Saquinavir, Zalcitabine, Zanamivir, Zidovudine) were retrieved through literature studies. The 3D structure of the spike surface glycoprotein was modelled using homology modeling technique. Further, the modelled surface glycoprotein structure was validated by Rampage based on Ramachandran plot. Finally, the energy minimization and molecular docking was executed for the modeled protein and 19 drugs using Arguslab software. Thus the result of docking studies predicted that the 5 (Amprenavir, Indinavir, Loviride, Nelfinavir, Lopinavir) antiviral drugs exhibited the better inhibitory action of >-10 Kcal/molwhen compared with other drugs <-8.5 Kcal/mol towards the modeled spike surface glycoprotein.

Keywords: Antiviral Drugs, Spike surface glycoprotein, Homology modeling, Ramachandran plot, Docking.

1. Introduction

The spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins are the four primary structural proteins found in Coronavirus particles [Schoeman D *et al.,* 2019]. When the spike (S) protein's receptor-binding domain (RBD) binds to a host receptor, such as angiotensin-converting enzyme-2 (ACE2) or dipepitdylpeptidase IV (DDPIV), the RBD shape changes, causing the viral membrane to merge with the host membrane [Wu XD*et al.,* 2004]. S is a homotrimeric transmembrane glycoprotein with three monomer units joined together. The S protein has a total of 1282 amino acids in each monomer, which are organized into two major functional domains, S1 and S2.By engaging with the host receptor, it attaches the virion to the cell membrane and starts the infection [Lan J*et al.,* 2020]. The Spike surface glycoprotein undergoes conformational modifications after binding to the human ACE2 receptor and uptake into the host cell's endosomes [Jaiswal G*et al.,* 2020].Virion entrance into the host cell is aided by binding to host NRP1 and NRP2 via the C-terminal polybasic region. This connection could explain why human olfactory epithelium cells, which express high levels of NRP1 and NRP2 but low levels of ACE2, are virus-prone [Kathiravan MK*et al.,* 2021, Xia X 2021].. Three hinges in S's stalk domain give the head unusual orientational mobility. The coiled coil sections assume a trimer-of-hairpins shape during viral and target cell membrane fusion, putting the fusion peptide close to the ectodomain's C-terminal region [Walls AC *et al.,* 2020]. The apposition and subsequent fusing of viral and target cell membranes appears to be triggered by the creation of this structure [Bojkova D*et al.,* 2020].

Homology modeling technique has emerged as a viable option for predicting protein 3D coordinates. The four steps in the modelling process that must be followed in order. The following are the details: 1) template selection, 2) target-template alignment, 3) model construction, and 4) model evaluation are all steps in the model development process [Mahendran R*et al.,* 2017]. The primary goal of modelling studies was to create a structure for protein molecules that act energetically to compound during binding. Based on a template sequence or structure relevant to the target protein, in silico modelling creates a computational 3D structure for the protein [Suganya J*et al.,* 2017].

The purpose of docking experiments was to put the results of the structural relationship of how ligand blocks receptors into action, which is important for lead optimization. The most recent docking tools and algorithms can anticipate the actions of tiny compounds and proteins, which aids researchers in finding more effective medicine candidates [Suganya J *et al.,* 2014].. In a computational program, dock is important for forming complexes between small molecules and target structures, and score is important for determining potential binding interactions between the complexes, which leads to hit detection and small molecule lead optimization. As a result, docking analysis is thought to be particularly important in determining the best medication lead candidate for the target [Suganya J *et al.,* 2016].

The objective of this current research was to perform the homology modeling technique to predict the 3D structure for the Spike Surface glycoprotein. The modelled structure was evaluated for its efficacy and finally docking studies wereexecuted with above described 19 anti-viral drugs to determine the drugs' inhibitory efficacy against the modelled Spike Surface glycoprotein.

2. Materials and Methods

2.1 Target Sequence and Template Structure selection:

The experimental 3D crystal structure of Spike Surface glycoprotein is not available in the Protein Data Bank (PDB); hence, its 3D structure was modelled. TheSequence of Spike Surface glycoprotein protein was retrieved from NCBI protein databaseand the protein sequence was

submitted to Blast P with the cross reference database PDB for the template selection. Finally the protein sequence and predicted template were modelled using Swiss-PdbViewer.

2.2Homology modelling target Sequence:

To load the Fasta file of the protein, open SwissPdbViewer and select "SwissModel" from the Toolbar Menu, then "Load Raw Sequence from Amino Acid."Select "SwissModel" from the "Preferences" menu, and then enter your name, email address, and click "OK."To inspect the residues amino acids and select the suitable residues, go to the "Wind" Menu and select "Control Panel."Select "Submit Template Search Request against EXPDB from current layer" from the "Swiss Model" menu, then input the password in the dialogue box. Select "Open Pdb File" from the "File" menu.For protein structure visualisation, go to the "Wind" menu and select "Contol Panel," then "Visible Checkbox."From the "Fit" menu, select "Magic Fit."Select "Alignment" from the "Wind" menu.Select "Select" from the menu select “Residues Making Clashes”.Quick and dirty, go to the "Tool" menu and pick "Fit Selected SideChain." Select "Submit Modelling Request for Raw Sequence" from the "Swiss Model" menu, then input the Project title in the "Get String" Dialog box. Select "Save" Current Layers and Save Model Structure in.pdb file format from the "File" menu [Andrew Waterhouse*et al.*, 2018].

Result can be viewed in PyMol: Select "file" "Open" in PyMol. **f**ile.pdb (Ex: modelprotein.pdb).Predict the helix, sheet, and loop from the model protein by clicking "C" (Color) by "SS" (Secondary Structure) "Helix Sheet Loop."

2.3 Validation for modelled protein:

The modeled 3D structure of the protein Spike Surface glycoprotein was evaluated through Ramachandran plot via (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php) Rampage server. The Ramachandran plot provides the percentage of residues that are present in either of the favored, allowed and disallowed regions.

2.4 Preparation of Ligand:

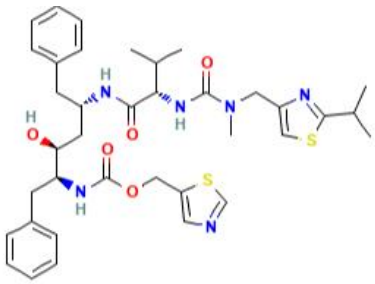
From literature studies, 19 antiviral drugs:Abacavir [Melroy J *et al.*, 2005], Amantadine [TahaNisar*et al.*, 2019], Amprenavir [Halder UC 2021], Chloroquine [Poschet JF *et al.*, 2020], Delavirdine [Caly L *et al.*, 2020], Didanosine [Philippe Flandre*et al.*, 2007], Enfuvirtide [Kapic E *et al.*, 2005], Indinavir [Sohraby F *et al.*, 2021], Lopinavir [Mahdi, M *et al.*, 2020], Loviride, Nelfinavir [Caly L *et al.*, 2020], Nitazoxanide [Mahmoud DB *et al.*, 2020]), Peramivir [AlameMalak M *et al.*, 2016], Ribavirin [Kristina Nystrom *et al.*, 2019], Ritonavir [Mahdi, M *et al.*, 2020], Saquinavir [Pires David *et al.*, 2021], Zalcitabine [AndriFrediansyah *et al.*, 2021], Zanamivir [Caly L *et al.*, 2020], Zidovudine [Alavian G *et al.*, 2021]were used to improve condition on patients with Spike Surface glycoprotein. The 2D structure of the compounds was retrieved from Pubchem database and it is converted into .mol file format using PyMol software (Figure1).

2.5 Docking studies:

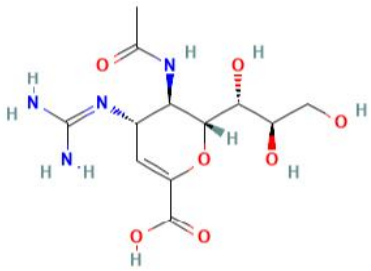
Docking studies with 19 drugs compounds against predicted 3D structure of Spike Surface glycoprotein were performed using Arguslab docking software. Docking procedure was as follows.Open ArgusLab and go to the "File" menu and select "New”.Open a Pdb file of a protein by selecting File > Open (Eg: model.pdb)."Misc" from "Residues" and hide the molecules."Amino acid" is taken from the "Residues" section.Select the protein's active sites, create a group from these Residues Binding sites, name it, and click OK.Open the mol file of the compound from the File menu (eg: Comp.mol)Miscellaneous Residues From this Residue, form a Ligand Group. Calculation is the option to choose. A Ligand is docked.Select GA Dock, adjust the grid size, and click "Start." The result should be saved in.pdb format [Suganya, J*et al.*, 2017].

Figure 1: 2D structure of antiviral drugs along with its Pubchem ID

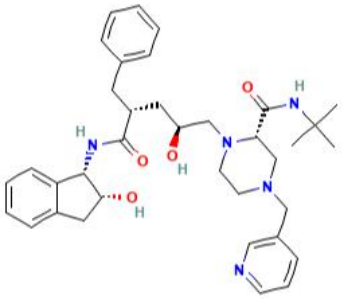
Delavirdine
Pubchem ID: 5625



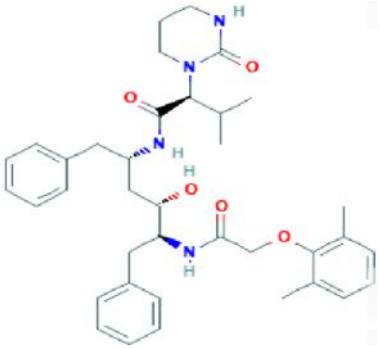
Ritonavir
Pubchem ID:392622



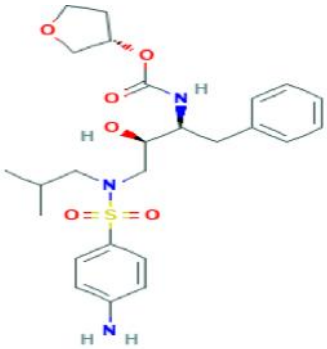
Zanamivir
Pubchem ID: 60855



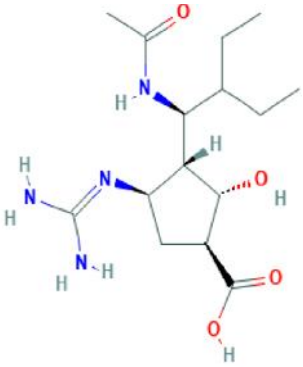
Indinavir
Pubchem ID: 5362440



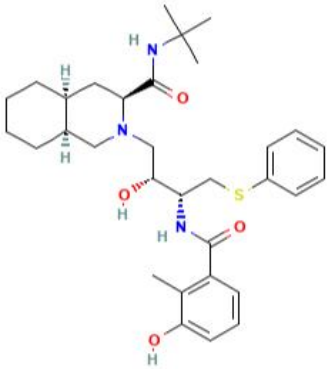
Lopinavir
Pubchem ID: 92727



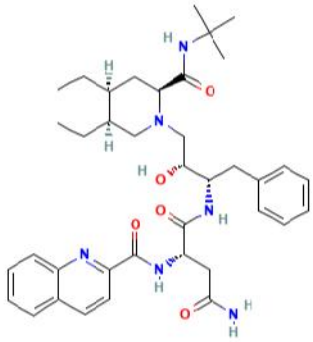
Amprenavir
Pubchem ID:65016



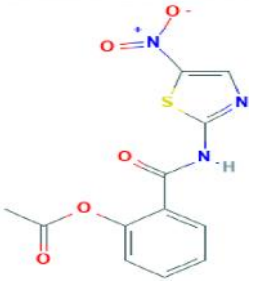
Peramivir
Pubchem ID: 154234



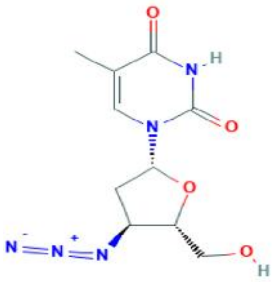
Nelfinavir
Pubchem ID: 64143



Saquinavir
Pubchem ID: 441243

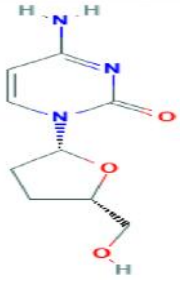


Nitazoxanide
Pubchem ID: 41684

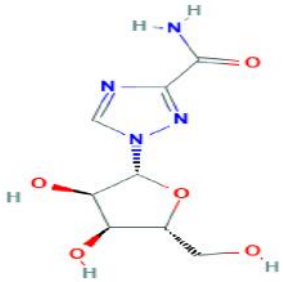


dovudine
Pubchem ID: 35370

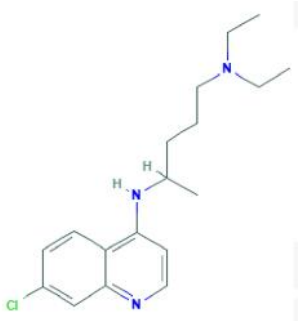
Zi



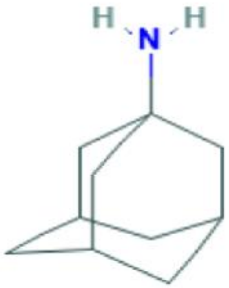
Zalcitabine
Pubchem ID: 24066



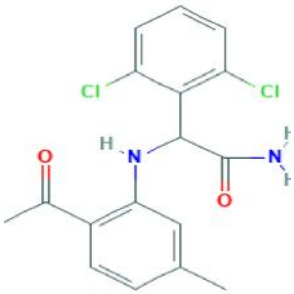
Ribavirin
Pubchem ID: 37542



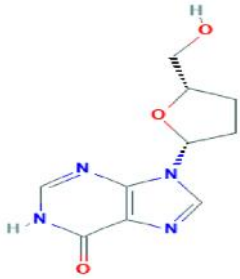
Chloroquine
Pubchem ID:2719



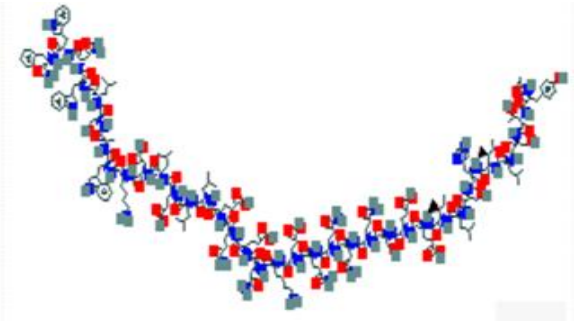
Amantadine
Pubchem ID:2130



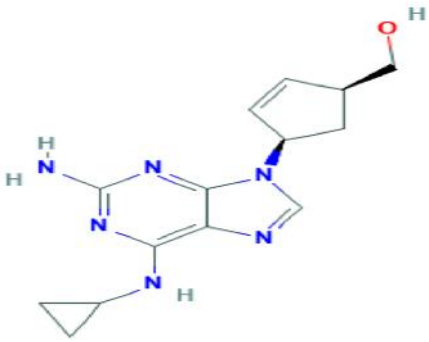
Loviride
Pubchem ID: 3963



Didanosine
Pubchem ID:35398739



Enfuvirtide Acetate
Pubchem ID: 16157631



Abacvir
Pubchem ID:441300

3. Results and Discussion

3.1 Prediction of 3D structure and its validation:

The molecular model generation needs query sequence which was retrieved from Uniprot KB database of spike surface glycoprotein whose 3D structure was not available in PBD.The FASTA format of retrieved protein sequence Spike Surface glycoprotein was submitted to the BlastP program to predict the suitable 3D template from PDB. BLAST search generated a 3D template structure of same protein in same virus and its PDB ID is 6ACD (Figure 2). The protein sequence for the Target and Template protein were showed in Table1. The three dimensional structure of Spike Surface glycoprotein were modelled using the 6ACD chain A with loop region refined, water molecules and heteroatoms present in the structure were removed using PyMol Software.After superimposing the modelled and template structures, the RMSD values obtained by both structures were found to be 0.19Å. The 3D modeled structure of Spike Surface glycoprotein was viewed in PyMol.

Table 1: Protein Sequence of Target and Template protein

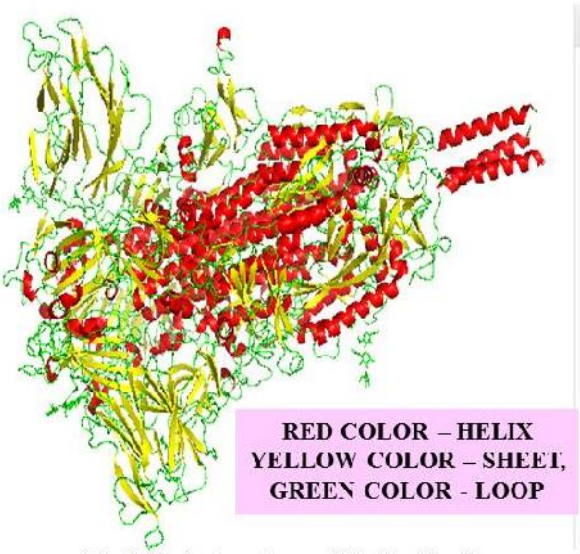
Spike Surface glycoprotein	6ACD:A|PDBID|CHAIN|SEQUENCE
MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFL PFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDS KTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNC TFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSA LEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLK YNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNL CPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL CFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKV GGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTN GVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESN KKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQ DVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGA GICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEIL PVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVF AQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGD CLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQ IPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDV VNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTY VTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVV FLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIIT TDNTFVSGNCDVVIGIVNNTVYDP	MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYYPDEIFRSDTLYLTQD LFLPFYSNVTGFHTINHTFGNPVIPFKDGIYFAATEKSNVVRGWVFGSTMNNKSQS VIIINNSTNVVIRACNFELCDNPFFAVSKPMGTQTHTMIFDNAFNCTFEYISDAFSLD VSEKSGNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGFNTLKPIFKLPLGINI TNFRAILTAFSPAQDIWGTSAAAYFVGYLKPTTFMLKYDENGTITDAVDCSQNPLA ELKCSVKSFEIDKGIYQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWE RKKISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDVRQI APGQTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRYLRHGKLRPF ERDISNVPFSPDGKPCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLNAPA TVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQQFGRDVSDFTDSVRD PKTSEILDISPCSFGGVSVITPGTNASSEVAVLYQDVNCTDVSTAIHADQLTPAWRIY STGNNVFQTQAGCLIGAEHVDTSYECDIPIGAGICASYHTVSLLRSTSQKSIVAYTM SLGADSSIAYSNNTIAIPTNFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQ YGSFCTQLNRALSGIAAEQDRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLK PTKRSFIEDLLFNKVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLLTD DMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKQ IANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLND ILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQ SKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAICHEGKAYFPRE GVFVFNGTSWFITQRNFFSPQIITTDNTFVSGNCDVVIGIINNTVYDPLQPELDSFKE ELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYE QYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDD

Modelled protein validation:

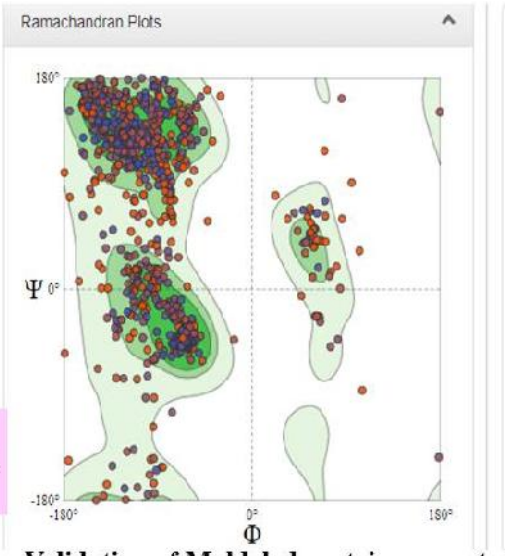
Thegenerated model of3D structure was validated through Rampage. The Ramachandran plot of model protein demonstrated that the majority of the amino acids fall into the Phi-Psi distribution i.e 96% of the amino acids were identified in the plot's favoured regions, 4 % in the plot's allowed regions and none in the plot's allowed regions. Therampage results indicated that the predicted model is both trustworthy and of high quality. The validated 3D protein structure has 16 Alpha helixes, 26 beta pleated sheets. The evaluation of predicted 3D structure of spike surface glycoprotein provides the needed information for further proteomic analysis Figure 3.

Figure2: Result of template search using BlastP

Figure 3: Predicted modeled 3D structure and its validation of Ag85A:



Modelled structure of Spike Surface glycoprotein were viewed in PyMol Software



Validation of Moldeled protein generated by RAMPAGE server.

Docking Studies:

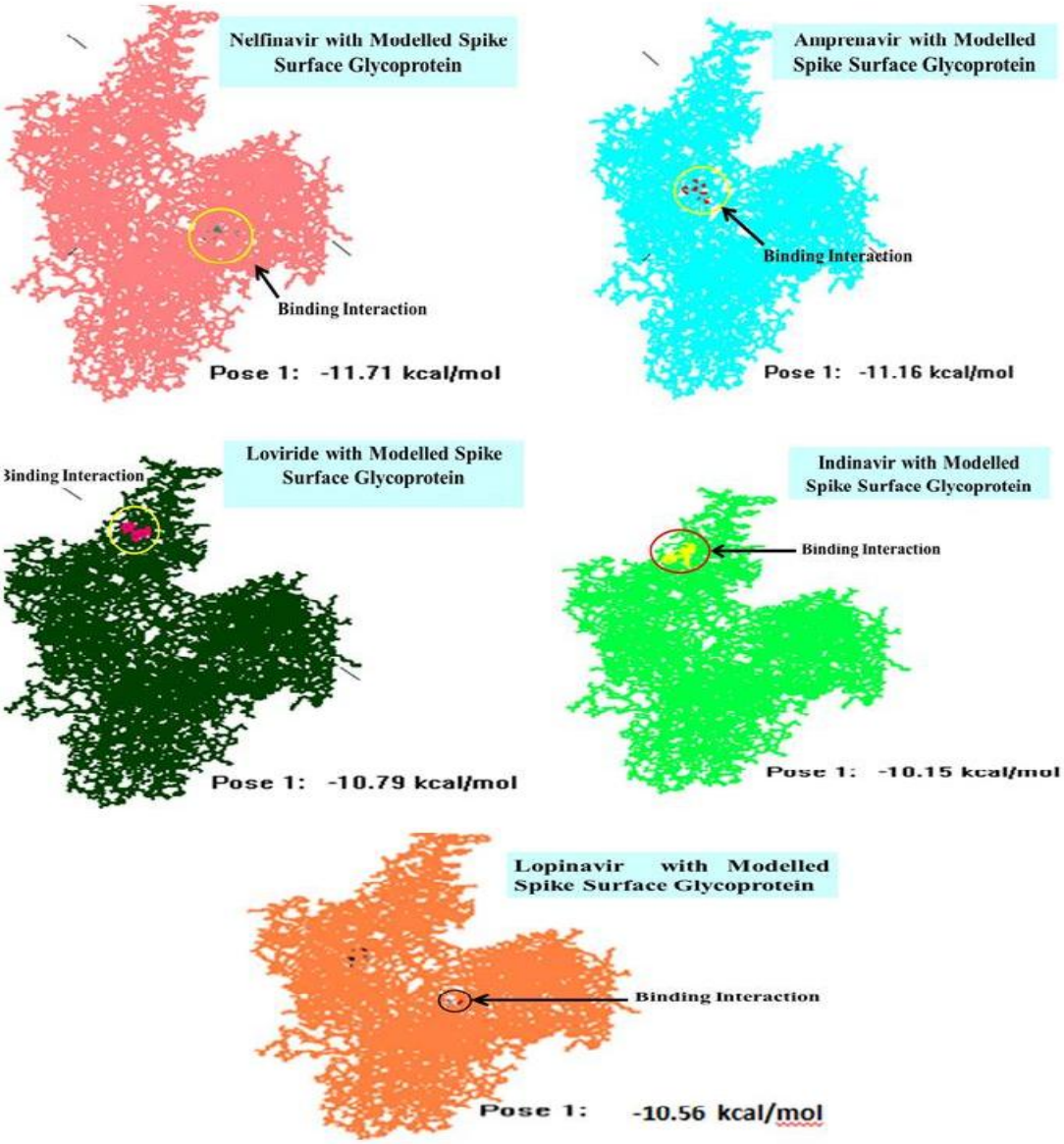
To understand the binding interactions between the 19 antiviral drugs and modelled structure of Spike surface glycoprotein and to explore their binding affinity, docking study was performed using Argus dock available under ArgusLab 4.0.1. The docking scores were highest for 5 drugs: Amprenavir with -11.16 Kcal/Mol, Loviride with -10.79 Kcal/Mol, Nelfinavir with -11.71 Kcal/Mol, Lopinavir with -10.59Kcal/Mol, Indinavir with - 10.15 Kcal/Mol, when compared with other drugs (Table 2). Docking results revealed that above 5 drugs can enter the substrate-binding region of the active site of Modelled protein (Figure 4). Finally, the results revealed clearly that 5 drug accurately interact with Spike surface glycoprotein target.

Table 2: Result of Binding energy between antiviral drugs and Spike surface glycoprotein.

Antiviral drug	Binding energy with the model surface glycoprotein
Abacavir	-6.83 Kcal/Mol
Amantadine	-7.17 Kcal/Mol
Amprenavir	**-11.16 Kcal/Mol**
Chloroquine	-8.14 Kcal/Mol
Delavirdine	-7.80 Kcal/Mol
Didanosine	-5.10 Kcal/Mol
Enfuvirtide	5.90 Kcal/Mol
Indinavir	**-10.15 Kcal/Mol**
Loviride	**-10.79 Kcal/Mol**
Nelfinavir	**-11.71 Kcal/Mol**
Ritonavir	-7.84 Kcal/Mol

Peramivir	-8.20 Kcal/Mol
Ribavirin	-6.40 Kcal/Mol
Saquinavir	-4.92 Kcal/Mol
Zalcitabine	-6.17 Kcal/Mol
Zanamivir	-5.37 Kcal/Mol
Zidovudine	-5.58 Kcal/Mol
Nitazoxanide	-7.96 Kcal/Mol
Lopinavir	**-10.59 Kcal/Mol**

Figure 4: Best Docking interaction between Drugs and Modelled Protein



4. Conclusion

With the threat of a new pandemic ever-present, more surveillance centres are needed around the world to better monitor and sequence circulating viruses and identify new strains, with recent data suggesting that the small number of spike surface glycoprotein severe clinical cases was simply a reflection of a much larger number of undetected subclinical cases. While computer-based techniques and structural modelling will not be able to replace formal viral characterization, they may be beneficial for doing preliminary screenings on spike surface glycoprotein generated by such monitoring tools. Finally, the power of *in silico* structural modelling and docking methods may allow assisting the inhibitory activity of 19 common antiviral drugs. The study was further evaluated to predict the inhibitory activity of the 17 drugs with currently prescribed 2 antiviral drugs to find out lead one. The finding of current research suggested that the 4 anti-viral drugs (Amprenavir, Indinavir, Lovirideand Nelfinavir) could be used as new medication for inhibition of spike surface glycoprotein.

5. Conflict of interest:

The authors declare they have no competing interests.

6. Acknowledgments

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7. References

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