In-silico analysis of potential interaction of drugs and the SARS-CoV-2 spike protein

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Abstract

The world is suffering its deadly pandemic in decades from Corona virus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Till the end of April, 2020, the death toll rose to more than 2 lacs worldwide (224 301, on May 1st), affecting 215 countries (source: WHO). Since the invention of a new drug or vaccine takes time, drug repurposing is one of the avenues. Keeping that in mind, we have tried to shed light on some of the drugs, using molecular docking/modeling studies, which could be of immense importance in the current scenario. Using bioinformatic approaches, we have tried to work on the viral spike (S) protein, majorly involved in pathogenicity through its receptor binding event and fusion to the host cells. More emphasis was given on the spike proteins (6vsb) and (6lxt). We predicted the drugs that target to the S proteins by in-silico docking analysis. We determined the functional part of the spike of SARS-CoV-2 and the drugs were predicted by analysis of the functional part using the PDBsum/DrugPort. Molecular Docking unveiled the binding of those drugs to the target spike. This *in-silico* study actually envisions the efficacy of the predicted drugs against the spikes of SARS-CoV-2 and the binding of the drugs might propose the combinatorial effect of the drugs to neutralize the spike effect in the human body.

Introduction

The outbreak of COVID-19 was first noticed in China in December, 2019 and later on it has infected throughout the world, resulting in more than 200,000 deaths up to April end, 2020. The virus causing COVID-19 belongs to beta coronavirus of Coronaviridae family and has similarity with early Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).The new strain is called Severe Acute Respiratory Syndrome- Coronavirus-2 (SARS-CoV-2)[1] The symptoms of COIVD-19 includes different types of illness like fever, cough, respiratory obstruction, enteric, neurologic problems, skin disease, lack of olfaction sense etc.[2]. The entry of Coronavirus in the human body is mediated through the viral spike proteins in an amazing way of receptor recognition and binding of its S1 subunit to the host cells and fusion by its S2 subunit there[3,4]. It has been identified that SARS-CoV-2 transfused its infection via binding with a metallopeptidase, angiotensin converting enzyme-2 (ACE-2) of the host cell[5,6]. Lopinavir, chloroquine, chlorpromazine have been used in COVID-19[7] and success has been found in many cases. Here we approach via *in silico* targeting of the spike protein molecules deposited to Protein Data Bank. The proteins studied here, are possibly good drug targets as suggested by a few studies. Hence, we proceeded with the structures from PDBsum portal (http://www.ebi.ac.uk/pdbsum)[8] to focus on the drugs they bind, using various bioinformatic tools described in the methods and results. Our experimental analysis reveals many drugs, having a potential role for the treatment of COVID-19, explored from the molecular recognition, based on the interaction between macro-molecules and small molecules. So, the interaction between a protein molecule and a ligand molecule likewise protein-drug interaction will explain the various significant biological signaling cascade. And the physicochemical mechanism i.e. binding kinetics (Binding Affinity) and thermodynamics (Global Energy, Free Energy) are the rational for

the understanding of drug-protein interaction study. So, the feasibility of the drug to the target protein could be theoretically/computationally predicted[9].

Methods

Structure retrieved: To study our investigation on COVID-19, structure of spike proteins, pre-fusion spike glycoprotein containing receptor binding site (6VSB)[10] and the post-fusion structure (6LXT)[11] were retrieved from Protein Data Bank (PDB)https://www.rcsb.org/. We retrieved PDB structure of 6VSB and FASTA sequence of both structures. The structures (3D structure) of drugs were retrieved from PubChem. Those 3D structures were converted to a PDB file by SMILES Translator (NCI/CADD group).

Visualization of structures: All the retrieved structures and molecular docking analysis were visualized by PyMOL (Schrodinger/pymol-open-source) and UCSF Chimera[12].

Cluster analysis: To predict the functional part of the 6VSB, chain-C (6VSB is a trimer, we selected chain-c) the cluster was analyzed using the InterProSurf, which predicted the interacting sites on protein surfaces[13-15].

Details of the molecular analysis by PROCHECK (PDBsum and DrugPort): To study more on the functional part, the sequence of the protein (6VSB) of that part and the similar sequence part of 6LXT with 6VSB was analyzed by PDBsum and followed by sequence search on DrugPort, which demonstrated the drug molecules and their target proteins by using PROCHECK (https://www.ebi.ac.uk/thornton-srv/software/PROCHECK/),PDBsum, (http://www.ebi.ac.uk/pdbsum) and DrugPort server[8,16,17].

Pocket analysis: Pockets on the surface of the protein was analyzed by CASTp 3.0 (Computed Atlas Surface Topography of the Protein)[18].

Protein-ligand, Protein-Protein interaction: Entropy-Enthalpy calculation is an important way to analysis binding and here GalaxyWeb server was used for the Binding Affinity calculation and for the analysis of protein-ligand molecular docking[19]. To determine the global energy of the molecular docking between the protein and ligand, PatchDock (based on shape complementarity principle[20,21] was used and further refinement was performedby FireDock[22,23]. Protein-Protein interaction was performed by HDOCK/HADDOCK[24-26]. And the Binding Energy was calculated by the DINC 2.0 (http://dinc.kavrakilab.org)server which is a meta-docking method for the incremental docking based on AutoDock vina[27].

Results And Discussion

Cluster analysis of the SARS-CoV-2 protein

We have worked on a SARS-CoV-2 spike protein (6VSB) from protein data bank[9]. The functional sites of 6VSB, chain-c were predicted by cluster analysis by using InterProSurf and here the amino acids were distributed based on their E1 vector and hydrophobicity, hydrophilicity and polar charged residues in the clusters[13-15].

Identification of pockets by the analysis of surface topography of protein

Pockets on the surface of the proteins are the mouth-opening connection of the interior to the external bulk solution. Those sites are significant for the proteins-ligand interaction or might be the target sites for the therapeutic purpose. Here, we investigated the pockets of SARS-CoV-2 spike protein (6VSB, chain-c) protein by surface topography[18].

Drug interaction to the target sites of the protein

We investigated the drug-target on the spike of SARS-CoV-2 protein by using the PROCHECK, PDBsum and DrugPort[8,16,17] by the protein sequence search which unveiled the drug molecules and their target proteins. We found the drugs targeted to the protein and performed molecular docking analysis by using the docking server[19-27] of those selected drugs to the spike protein of SARS-CoV-2. In each case, we demonstrated the Binding Affinity by GalaxyWeb[12]; Global energy by using PatchDock[20,21] and followed by FireDock[22,23] for the refinement; Binding Energy by using DINC.2 based on AutoDock vina[27].

Docking with Desmopressin (PubChem CID: 16051933):

Desmopressin is a synthetic analogue of Arginine Vasopressin. It helps in the water resorption by binding to the V2 receptors. Desmopressin can induce the eNOS activity. It might inhibit the viral or endotoxin induced septic shock[28,29]. So, Desmopressin might be one of the supportive drugs of choice in COVID-19, even if while the bleeding complicacy.

Here, the interaction between Desmopressin and spike was demonstrated by **Binding Affinity:-21.984; Global Energy: - 68.31 and Binding Energy: - 6.7 (kcal/mol).**

Docking with Telaprevir (PubChem CID: 3010818):

Telaprevir is an anti-viral used to treat hepatitis C virus (HCV)[30]. It is the inhibitor of HCV protease[31]. So, we investigated the molecular docking of Telaprevir on spike protein. We found the docking (**Binding affinity: -20.121), Global Energy: - 54.72 and Binding Energy: -6.60 (kcal/mol).**

Docking with Cefpiramide (PubChem CID:636405):

Cefpiramide, a third-generation antibiotic, can interact with penicillin binding proteins (PBP) and inhibits peptodoglycan formation. It can prevent the respiratory tract infection[32] and has the inhibitory role on community acquired pneumonia[33]. We found that Cefpiramide might interact with S protein of SARS-

CoV-2 (**Binding affinity: -18.168**) showed in Fig-5; **Global Energy: -63.41 and Binding energy: -6.4 (kcal/mol).**

Docking with Erythromycin (PubChem CID: 125600):

Broad spectrum antibiotic Erythromycin binds to the bacterial ribosome (50S subunit) and inhibits bacterial protein synthesis by interfering with translocation of amino acids to the protein synthesismachinery during translation. It has been shown to impair the activity of *S. pneumoniae* infection in the respiratory tract[34]. In Fig-6, binding of Erythromycin with COVID was shown with **Binding Affinity: -17.877; Global Energy: -45.45 and Binding Energy: -5.80 (kcal/mol).**

We also found the interaction of Gentamicin with S1 subunit (figure not shown) with the **Binding Affinity: -16.412; Global Energy: -47.62 and Binding Energy: -5.4 (kcal/mol).**

Docking with Fostamatinib (PubChem CID: 11671467):

Fostamatinib is an inhibitor of spleen tyrosine kinase Syk proteinand an immune-modulator.It is used in the treatment of immunethrombocytopenicpurpura (ITP). In immunocompromised individuals, chronic lung infection could be prevented by inhibition of Syk by using Fostamatinib[35]. During infection, virus induced huge cytokine enhancement could be regulated by the Fostamatinib induced inhibition of Syk. So, Fostamatinib could be the target drug for the therapy and **Binding Affinity was found: - 16.259; Global Energy: -35.55 and Binding Energy: -6.2 (kcal/mol).**

Docking with Artesunate (PubChem CID: 6917864):

It is an anti-malarial, anti-viral and anti-neoplastic agent. Artesunate shows its activity through the breakage of the endoperoxide bridge in the presence of heme ion and generates ROS and free radicals, that helps to damage DNA and kill the malaria parasite[36] and is considered to be the best drug against many complicated malaria patients[37]. Artesunate is also effective against herpes virus, hepatitis virus, cytomegalovirus[38]. Fig-8 shows the parametrs for SARS-CoV and Artesunate binding with **Binding affinity (-14.308); Global energy: -44.82 and Binding Energy: -5.50 (kcal/mol).**

Docking with Hydroxychloroquine (PubChem CID: 3652):

Hydroxychloroquine (HCQ) is an anti-malarial drug which is also an immunosuppressive and anti-autophagy drug used in systemic lupus erythematosis and rheumatoid arthritis. HCQ has antiviral and anti-inflammatory activity[39]. It was shown to be effective against coronavirusOC43 in newborn mice[40] and a few recent studies have showed promising results of HCQ against COVID-19 patients[41,42] found. **Binding Affinity of HCQ** with the Spike of SARS-CoV is **-12.803 (Fig-9);**

Docking with Tenofovir alafenamide (PubChem CID: 9574768):

Tenofovir plays immense role against hepatitis B virus (HBV) and potentially against HIV virus by incorporating into viral DNA[43,44]. It can inhibit viral reverse transcriptase, terminating DNA chain elongation and consequently, the replication of virus. We wanted to investigate the binding of the drug with SARS spike in Fig-10, and we found **Tenofovir has Binding affinity (-14.706) with spike of SARS-CoV-2; Global Energy: -42.30; Binding Energy: -5.2 (kcal/mol).**

Docking with Rifabutin (PubChem CID: 135398743):

Rifabutin, an antibiotic is used in HIV infected patients for the controlling of *Mycobacterium*[45].Here, the binding of Rifabutin to spike protein is shown in **Fig-11**(**Binding Affinity: -17.634) in (Fig-14); Global Energy: - 54.04 and Binding Energy: - 7.6 (kcal/mol).**

Docking with Bedaquiline (PubChem CID: 5388906):

Bedaquiline is also an antimycobacterial drug. It is very effective in the drug resistance pulmonary tuberculosis in HIV[46], however, safety concerns remain associated with the usage of it[47]. Bedaquiline binds (**Binding Affinity: - 17.420) with spike is depicted in Fig-12; Global Energy: - 51.46 and Binding Energy: -6.1 (kcal/mol**).

Docking with Phylloquinone (PubChem CID: 5280483):

It is a polycyclic ketone and It has a prothombogenic and antihemorrhagic property. Phylloquinone may inhibit vascular calcification by reducing elastin degradation in COPD patients[48]. So, it could be an effective neutraceutical to combat COVID-19. Phylloquinone bindingto the spike proteinhas been shown in Fig-13. **Binding Affinity, Global Energy, and Binding Energy are respectively- 17.684;: -43.47 and: -5.00 (kcal/mol).**

Docking with Flavin mononucleotide (FMN) (PubChem CID: 643976):

FMN is a cofactor of many oxido-reductase reaction. It can also protect the lungs from toxic compounds[49]. The Binding Affinity of FMN with spike protein is: **-16.080** (Fig-14); **Global Energy is - 56.27 and Binding Energy is - 5.8 (kcal/mol).**

We have also analyzed the docking of **NAD (PubChem CID: 5893)**, NAD binds spike with **Binding Affinity: -15.973; Global Energy: -22.43 and Binding Energy: - 6.4 (kcal/mol).** NAD is an electron carrier and redox reactor. It is also involved in the prevention of HIV and pneumonia[50].

Docking with Aprotinin (3GYM_2|Chains I, J|Pancreatic trypsin inhibitor|Bos Taurus (9913)

Aprotinin is known as BPTI i.e. bovine pancreatic trypsin inhibitor. It is a protein based drug used for the treatment of reducing blood loss during CABG or pericardititis[51,52]. Cleavage of spike protein by host protease is critical for its infection status. So, aprotinin could be therapeutically used to prevent spike protein infection[52,53]. Here we investigated the interaction between spike protein and aprotinin. From

docking analysis, interaction without using template (Docking score: -267.79) could be observed between spike protein and aprotinin.

From the above stated drug-interaction studies, it could be predicted the possibility of efficacy of those drugs against COVID-19 patients; not only the above drugs and neutraceuticals but also few other drugs, like Sirolimus binds to the spike protein with affinity (table-1); it is an anti-neoplastic, antibiotic, immunosupressive drug and it could be the drug against spike but the drug has a potential pulmonary toxicity. In our analysis, we found some anticonvulsant medicines; Cannabidiol (table-1) is one of them, which can reduce of anxiety disorder. Sucralfate is used for the cure of damaged mucous has a potential Binding Affinity (table-1) with spike protein. Sucralfate could be used a gel to protect from virus/bacteria. Ranolazine/Spiranolactone are the antihypertensive drugs both showed binding affinity (table-1) with spike proteins. Some anticancer antileukemic drugs have potential binding with spike of SARS-CoV-2; for example Vincristine is used for leukemia treatment and As_2O_3 arsenic trioxide (ATO) was also found to be involved against spike of CoV; ATO with anti retroviral therapy (ART) is effective against the viral reservoir of HIV-1 in context of CD4+ T cells[54]. In case of tetraarsenic hexoxide (As_4O_6) could be more effective in human papiloma virus associated cervical cancer[55]. It might be possible that ATO has the ability to induce apoptosis of viral protein by binding on the protein surface[56] (56). Though, use of arsenic could be potentially contraindictory, the dose of 0.15 mg/kg/day is well tolerated in the human body. Beside these, Porfimer sodium, Benzyl penicillin, Tricalabendazole, Oseltamivir, Ribavirin and Tocilizumab antibody and other neutraceuticals like FAD, Ferrous Ascorbate, Glutathione, Zinc Chloride, Zinc acetate, Cu, Zn, Palmitic acid might be the crucial agent to combat against COVID-19 patients (shown in table-1).

It was found that that older persons are more vulnerable to the COVID-19 and the persons who have diabetes, hypertension and cancer, are more susceptible to the complicacy of the disease and death. So, from the above analysis, Fostamatinib/Telaprevir/Hydroxychloroquine/Artesunate/Tenofovir could be used against spike protein and in combination with Cefpiramide/Erythromycin/Rifabutin/Bedaquiline as the protector of pulmonary injury due to the viral induced predisposing bacterial infection or Demopressin/Phylloquinone in case of renal dysfunction/bleeding disorder or Acarbose in hyperglycemia and Ranolazine/Spiranolactone in hypertension or FMN/FAD as neutraceutical and aprotinin as a protease inhibitor might be used to treat COVID-19 patients. It could be possible that various combinations of the those drugs would response better way.

Studies like these are important because, not all drugs work in the same efficacy in all the populations across the world. Disease association also varies in population specific ways, many times. In case of COVID-19 too, data shows, that European or American population have been worstly affected in the world. (In case of infectious diseases, however, other factors like disease containment, health infrastructure etc. also play a crucial role, in addition to genetic makeup. Response to drugs also varied amongst them, eg. China did not find Remdesivir very effective[57], but U.S. Food and Drug Administration (FDA) authorized its emergency use, thinking it as potential drug to treat COVID-19 (https://www.fda.gov/media/137565). So, it is very important to keep eyes on many possibilities, where

our study, could be an important one. It should also be mentioned here that potential drug interaction and contraindication should be followed up and it can be varied from patient to patient (personalized medicine), history of patients. It is a hypothetical *in-silico* analysis by using the Bioinformatically found data which can be confirmed clinically by extended research work/clinical trials.

Table-1: Binding Affinity, Global Energy and Binding Energy score (kcal/mole) of the compounds found from DrugPort analysis

Compound name	Binding Affinity	Global Energy	Binding Energy (kcal/mol)
Desmopressin	-21.984	-68.31	-6.7
Telaprevir	-20.121	-54.72	-6.6
Cefpiramide	-18.168	-63.41	-6.4
Erythromycin	-17.877	-45.45	-5.8
Gentamicin	-16.412	-47.62	-5.4
Fostamatinib	-16.259	-35.55	-6.2
Artesunate	-14.308	-44.82	-5.5
Hydroxychloroquine	-12.803	-45.29	-4.7
Tenofovir alafenamide	-14.706	-42.30	-5.2
Rifabutin	-17.634	-54.04	-7.6
Bedaquiline	-17.420	-51.46	-6.1
Phylloquinone	-17.684	-43.47	-5.0
Flavin mononucleotide	-16.080	-56.27	-5.8
NAD	-15.973	-22.43	-6.4
Aprotinin (docking score)	-267.79		
Sirolimus	-23.454	-58.83	-7.8
Cannabidiol	-14.454	-45.43	-5.0
Sucralfate	-23.002	-42.74	-6.7
Vincristine	-17.552	-44.34	-6.4
Ranolazine	-16.612	-44.36	-5.8
Spiranolactone	-13.365	-52.23	-5.5
Acarbose	-17.850	-49.70	-7.0
Porfimer sodium	-23.239	-58.28	-8.8
Benzyl penicilin	-12.534	-55.76	-4.9
Triclabendazole	-16.593	-45.52	-4.8
Oseltamevir	-12.882	-43.68	-4.1
Ribavirin	-10.964	-38.89	-3.9
FAD	-15.299	-49.06	-6.8
Glutathione	-15.541	-45.59	-4.1
Ferrus ascorbate	-11.371	-30.51	-3.0

Declarations

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Author's contributions: S.B. designed, conceptualized the paper and analyzed the Bioinformatics in the manuscript; S.B and N.B wrote and finalized the manuscript. N.B., G.V.R., S.K.D. and S.M. provided intellectual inputs. All authors reviewed the manuscript.

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Figures

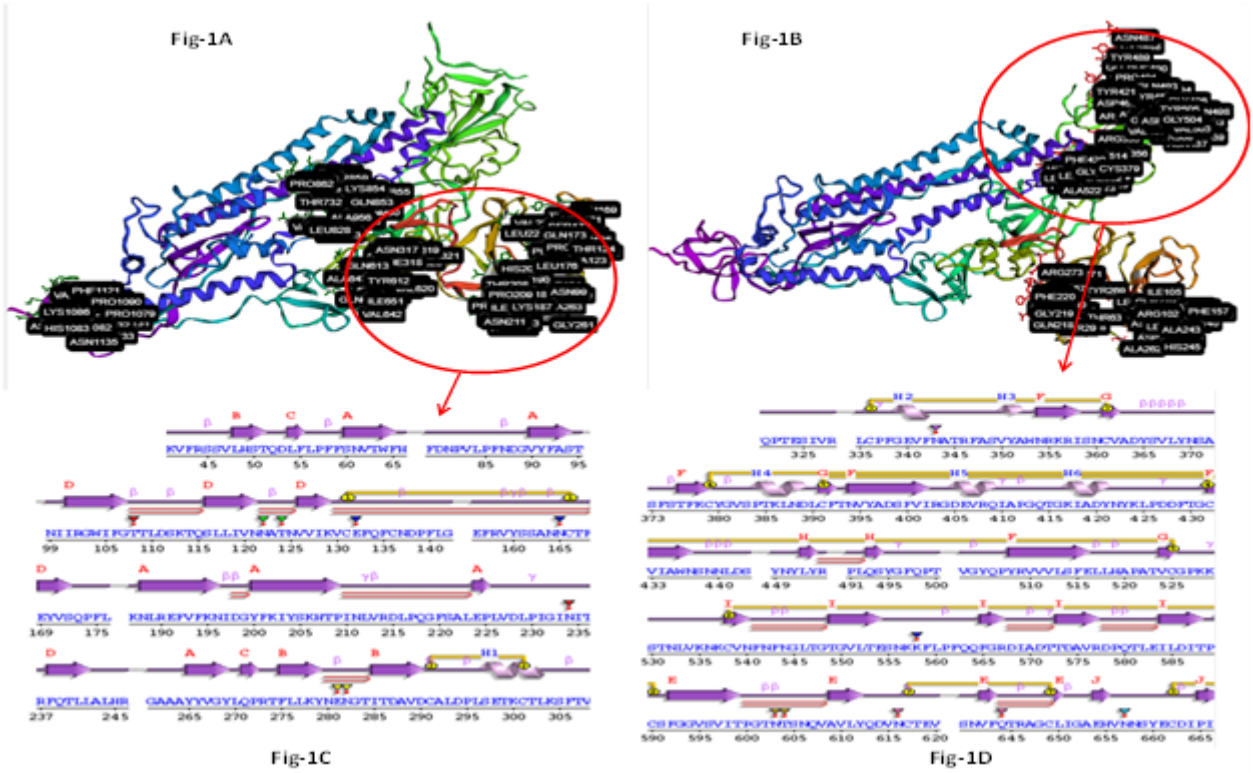

Figure 1

Functional sites of chain-C of 6vsb protein: Fig-1A and 1B represented the distribution of amino acids based on their E1 vector and hydrophobicity, hydrophilicity and polar charged residues respectively. Red circles represent the functional sites; Fig-1C and 1D demonstrated the protein sequence of the red circle sites by entry into the PROCHECK, PDBsum server as described in method.

Poc ID	Area (SA)	Volume (SA)
1	4316.850	17913.101
2	638.916	1723.851
3	144.931	844.729
4	238.799	486.128
5	375.903	207.661
6	215.185	127.554
7	142.090	93.760
8	64.032	58.394
9	88.320	48.780

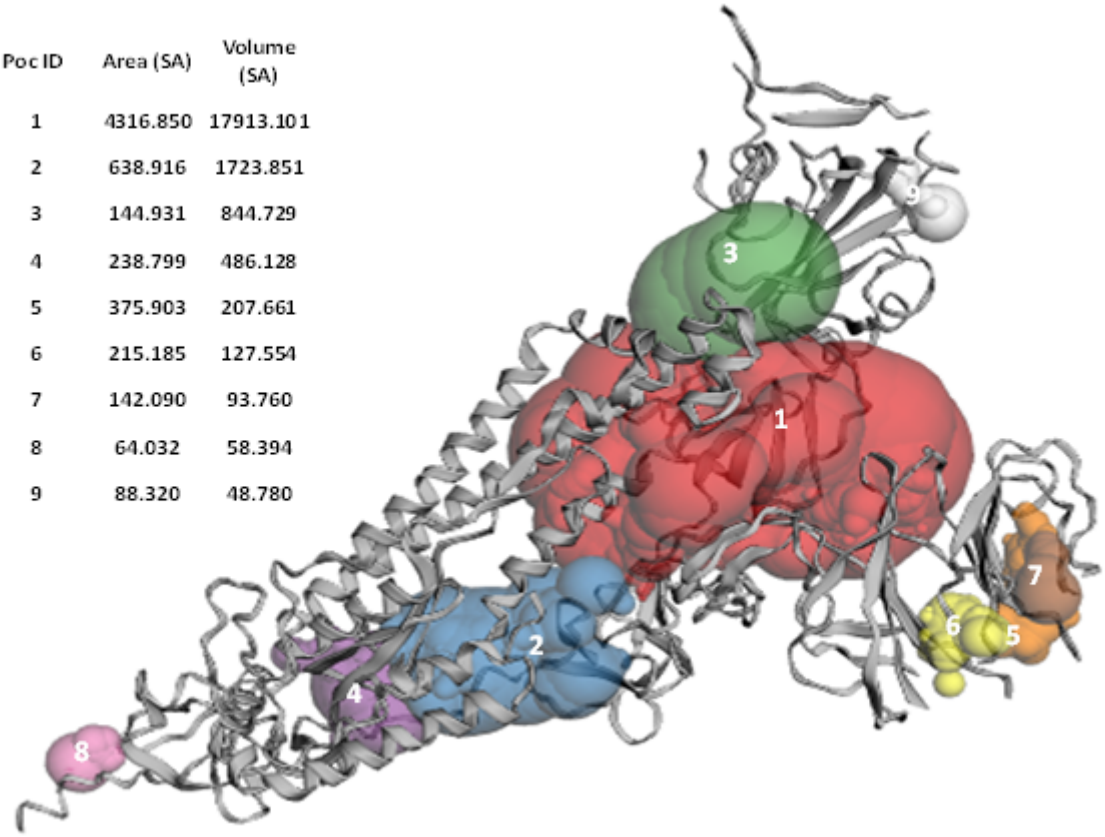

Figure 2

Pocket analysis of 6vsb, chain-C protein: This figure demonstrated thesurface accessible pockets of the 6vsb protein. Nine pockets were selected according to area and volume of the pockets andanalyzed; Poc ID. 1 (red color pocket) possessed maximum area (4316. 850) and volume (17913.101).

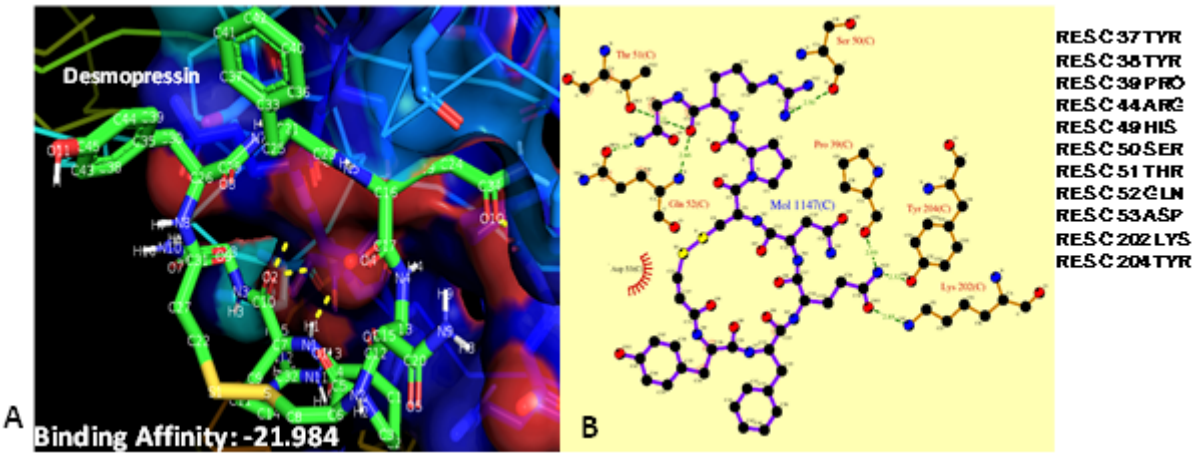

Figure 3

Fig-A represented the binding of desmopression on the surface of S protein of COVID; Fig-B represented the binding site interaction and residues in contact (11 residues).

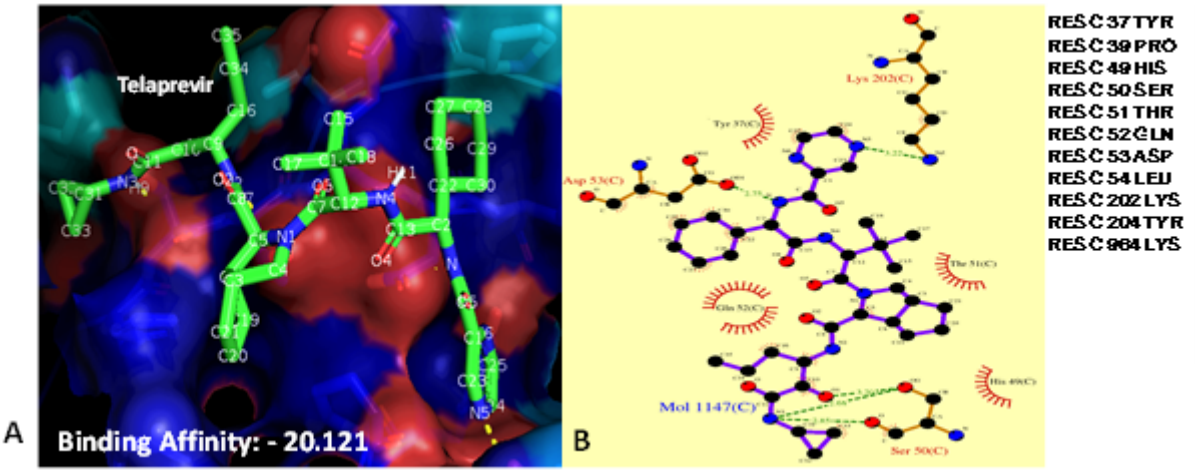

Figure 4

Fig-A represents the binding of Telaprivir with SARS-CoV-2 protein and the Binding affinity is -20.121; Fig-B represents the binding site interaction of Telaprevir and residues in contact.

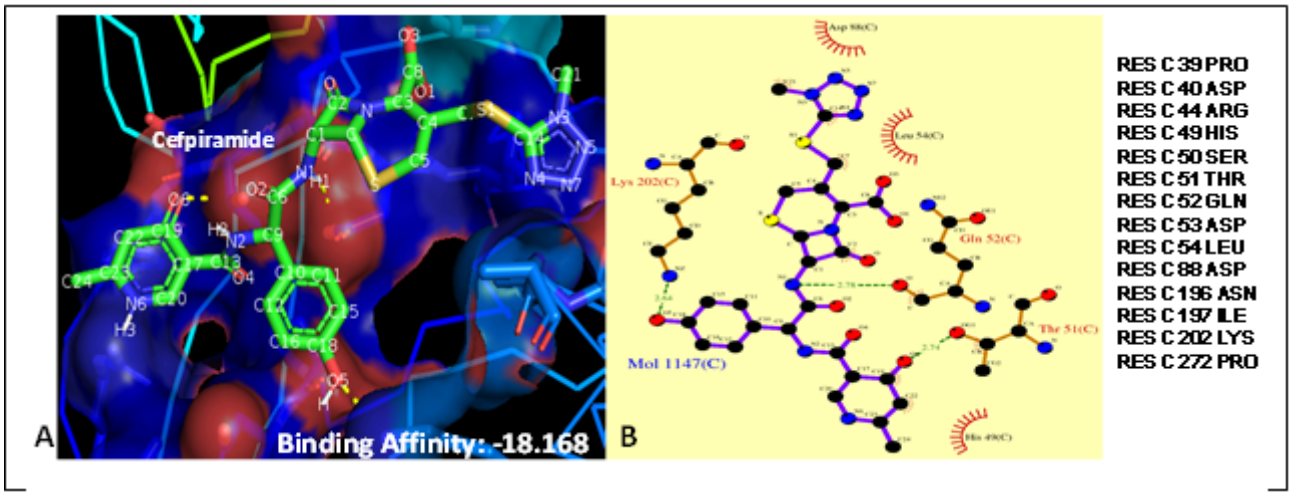

Figure 5

Fig-5A and Fig-6B represents the binding of Cefpiramide and Erythromycin with spike of SARS-CoV-2 respectively, and Fig-B represents the binding site interaction of each drug with their contact residues (Cefpiramide has highest residues in contact).

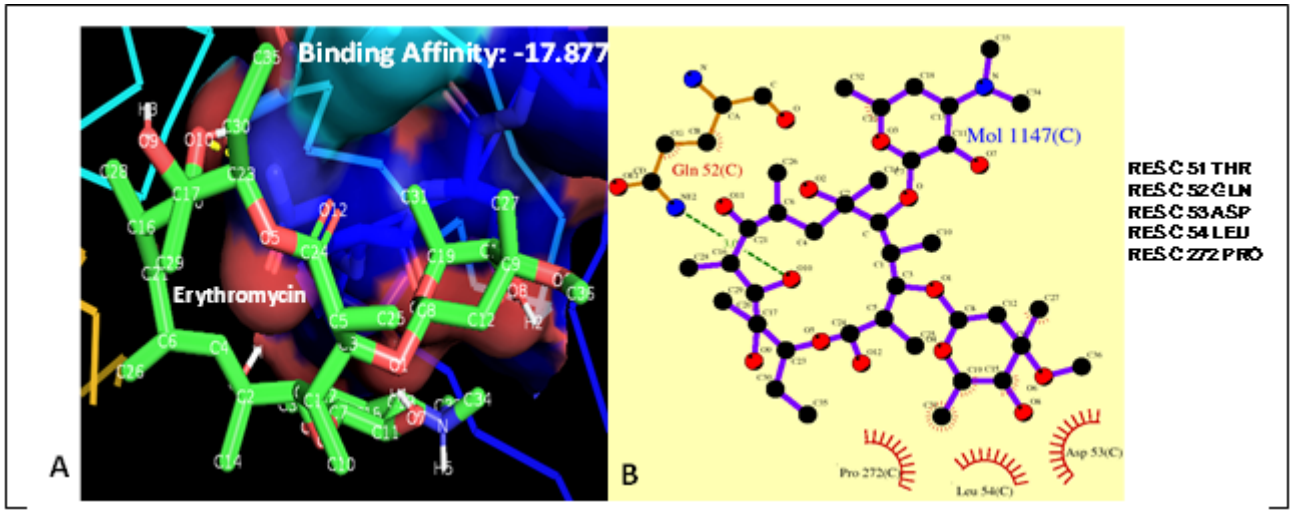

Figure 6

Fig-5A and Fig-6B represents the binding of Cefpiramide and Erythromycin with spike of SARS-CoV-2 respectively, and Fig-B represents the binding site interaction of each drug with their contact residues (Cefpiramide has highest residues in contact).

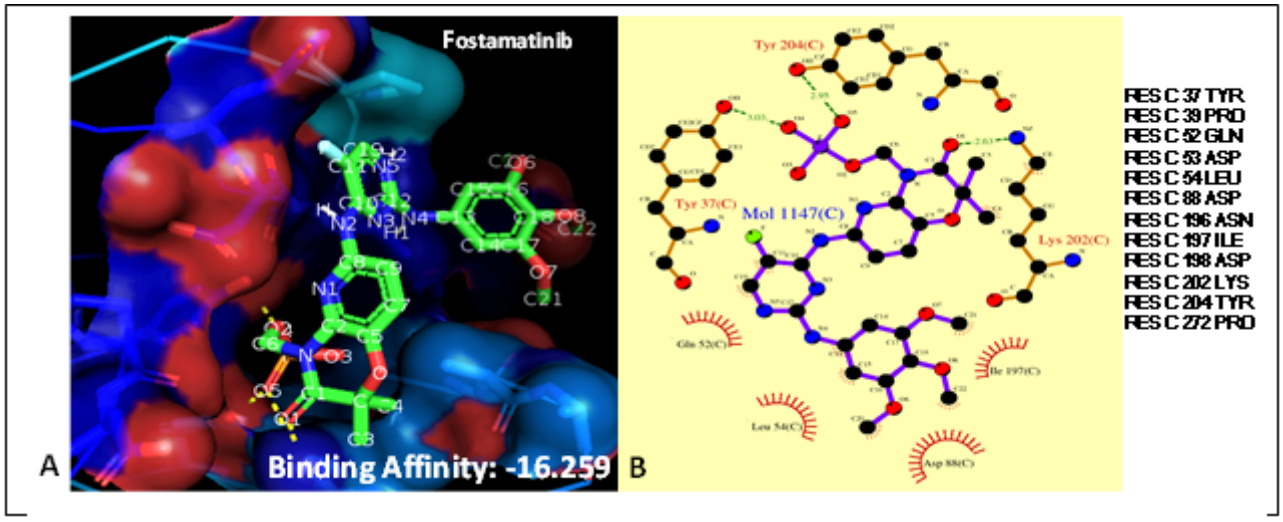

Figure 7

Fig-A represents the binding of Fostamatinib on the surface of SARS-CoV spike and Fig-B represents the binding site interaction of the drug with residues in contact (12 residues).

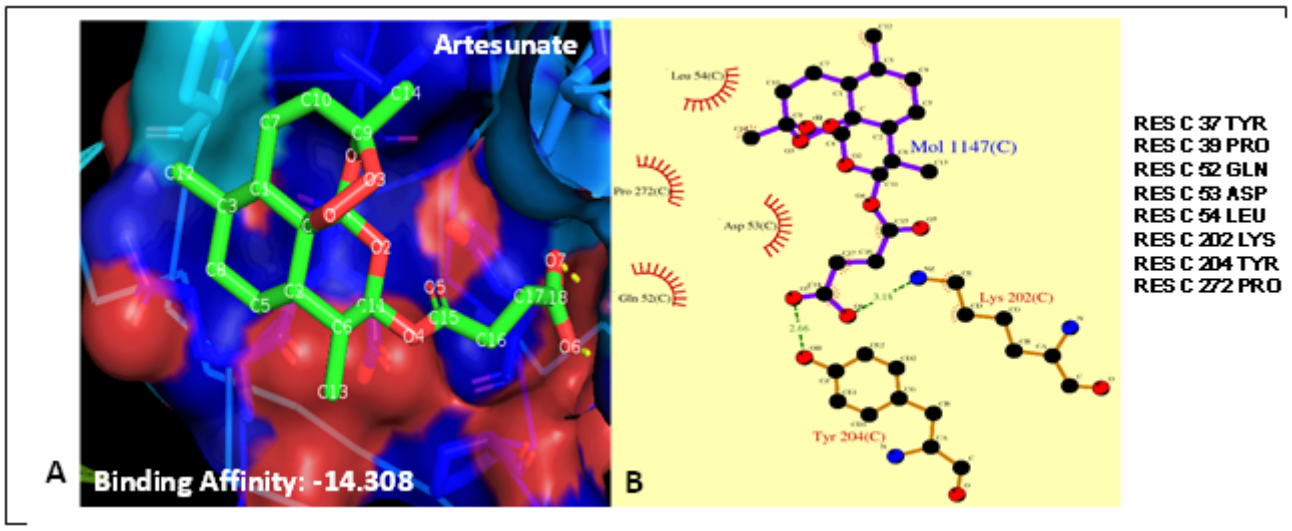

Figure 8

Fig-A respectively demonstrate the Binding of Artesunate and hydroxychloroquine with the spike of SARS-CoV and Fig-B represent the binding site interaction and residues in contact with the drugs.

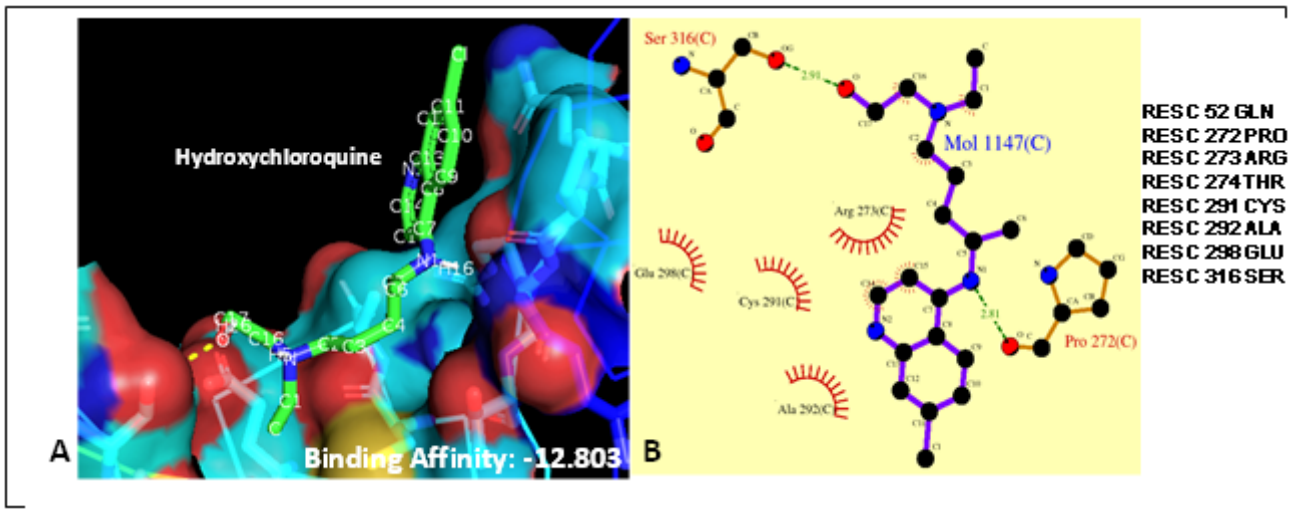

Figure 9

Fig-A respectively demonstrate the Binding of Artesunate and hydroxychloroquine with the spike of SARS-CoV and Fig-B represent the binding site interaction and residues in contact with the drugs.

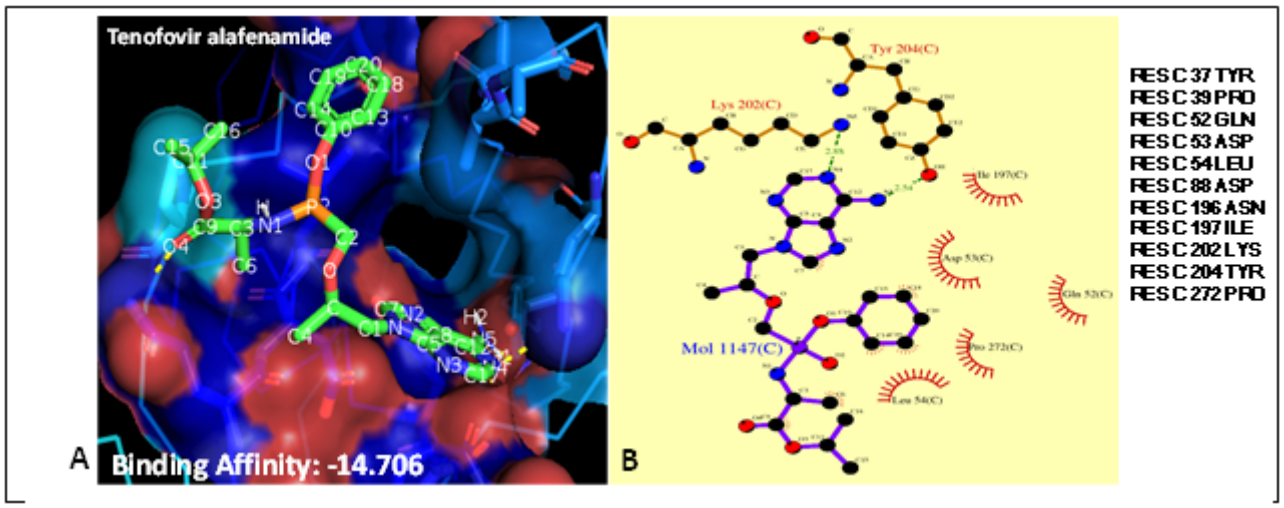

Figure 10

Fig-A demonstrates the binding of Tenofovir with SARS-CoV spike protein; Fig-B represents the binding site interaction and contact residues (11 residues).

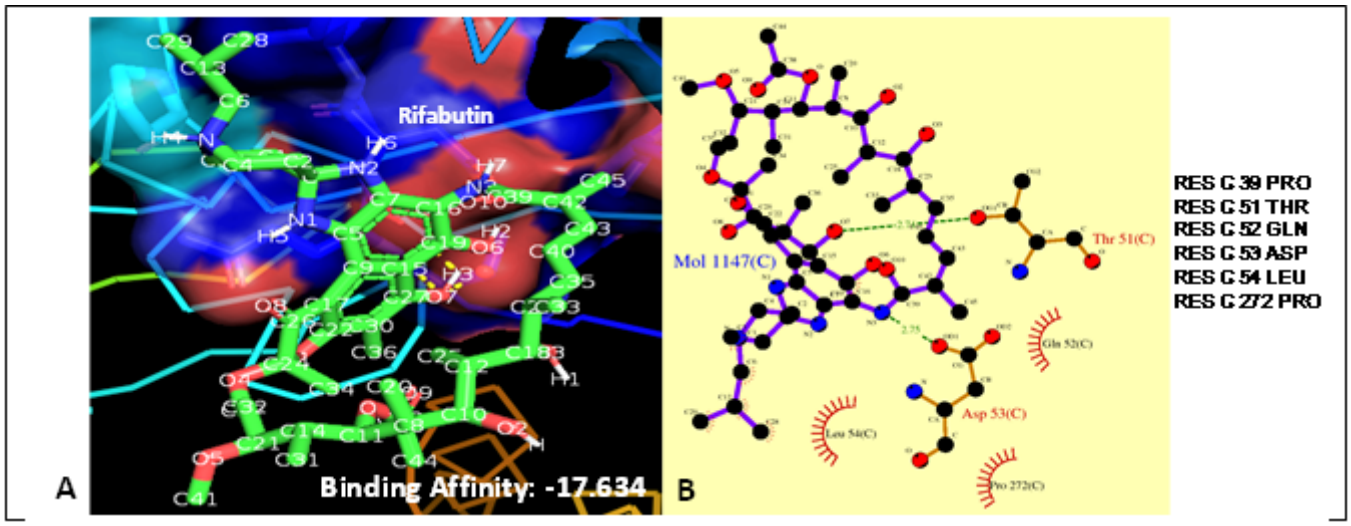

Figure 11

Here, Fig-A demonstrates the binding of Rifabutin and Bedaquiline to the spike respectively. and Fig-B represents the interaction of binding sites and contact residues with the drugs.

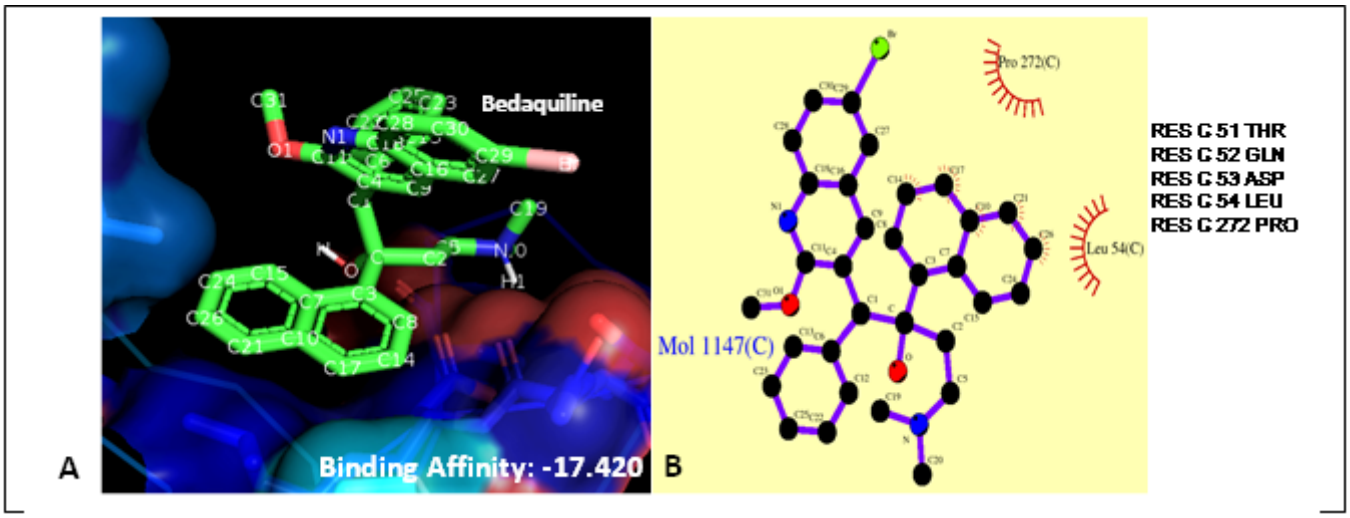

Figure 12

Here, Fig-A demonstrates the binding of Rifabutin and Bedaquiline to the spike respectively. and Fig-B represents the interaction of binding sites and contact residues with the drugs.

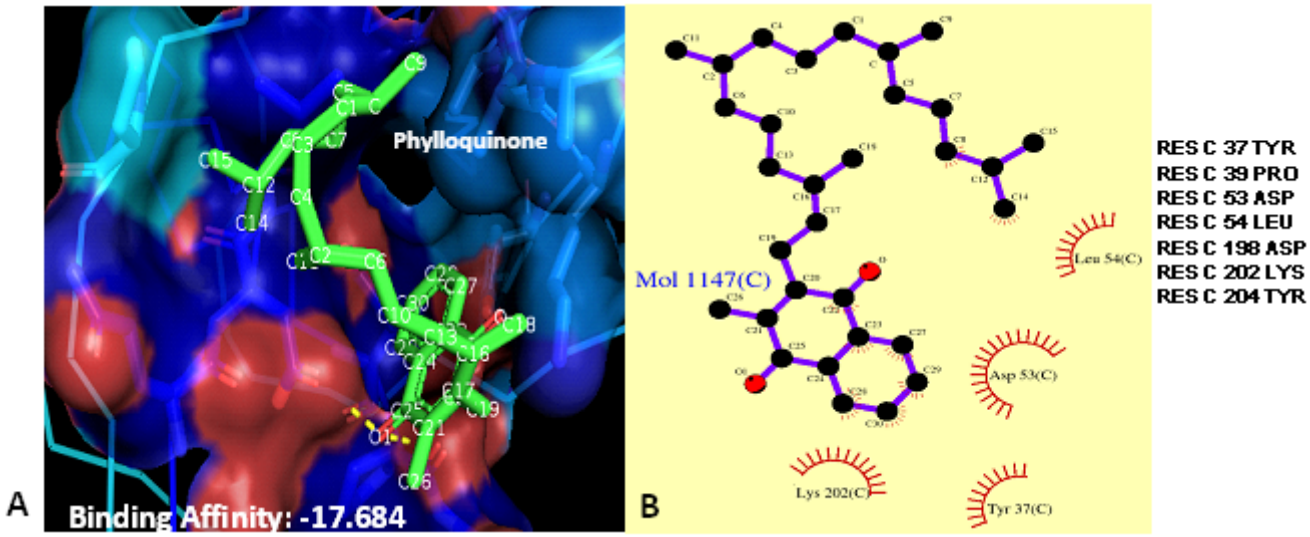

Figure 13

Fig-A demonstrates the Binding Affinity of Phylloquinone and FMN with spike of SARS-CoV-2 respectively and Fig-B represents the binding site interaction and contact residues.

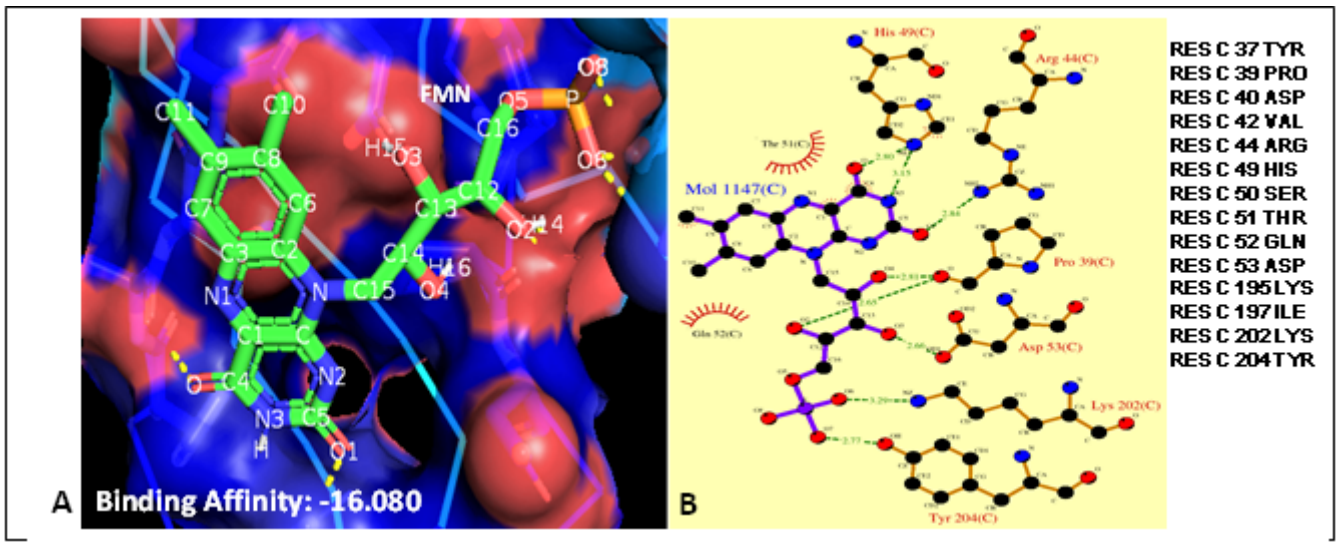

Figure 14

Fig-A demonstrates the Binding Affinity of Phylloquinone and FMN with spike of SARS-CoV-2 respectively and Fig-B represents the binding site interaction and contact residues.

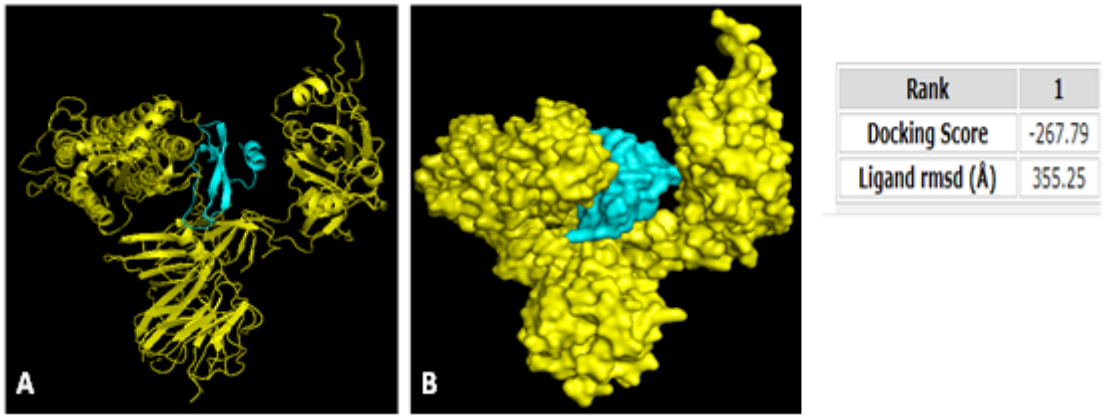

Figure 15

This figure demonstrates the surface interaction between SARS-CoV-2 protein (6vsb) (yellow) and aprotinin (cyan) and the Docking score: -267.79