# An Implementation of Peptide Blocking Method to Disrupt the Cell Infection Caused by SARS-CoV-2:

**Author:**

**Md Mostakim Khan**
**Notre Dame College**
**Email: mkreyn71@gmail.com**

**Affiliation Address: Donia, Dhaka 1236, Bangladesh**

## ABSTRACT:

SARS-CoV-2 is in the class of novel coronavirus, which binds with human cells through its receptor- binding domain (RBD). Angiotensin-converting enzyme 2 (ACE2) has been inaugurated as the functional host receptor for (SARS-CoV-2). ACE2 enzyme activates the binding domain of SARS-CoV-2 and creates cell infection. Blocking the binding residues of ACE2 could retard the binding between ACE2 and RBD, was the presumption of this study. From this context, peptide blocking method was screened to visualize its ability to block the binding residues of ACE2 from interacting with the binding residues of RBD. Peptide blocking method is one of the most effective ways to disrupt the interaction between two proteins, which typically blocks a targeted protein from a certain interaction. These short string amino acids are of interest because of  less toxicity and effectiveness. From that perspective, 16 potential peptides were screened. Molecular docking was conducted to predict these peptides capacity for binding ACE2 at its binding sites. From the result, I found 4 potential peptides which showed the highest celebrity. I propose that these selected peptides are worth further investigation to prevent 2019-nCoV.

**Keywords: Computational Biology, Molecular Docking, Protein Structure, Peptide Modeling, Docking Analysis.**

## 1.1 INTRODUCTION:

**1.1.1**Since the first Covid case was found in Wuhan on 31 December 2019, The SARS-CoV-2 (2019-nCOV), a novel coronavirus, caused the catastrophe outbreak in China and continues to expand. The coronavirus disease 2019 (COVID-19) has emerged as a pandemic. SARS-CoV-2 is a single-stranded RNA virus. SARS-CoV-2 is divergent from SARS-CoV. The closest relationship of SARS-CoV-2 with the bat SARS-like coronavirus strain BatCov RaTG13, with an identity of 96%[Khan et al., 2021]. Coronaviruses use species-specific proteins to mediate the entry in the host cell and the spike S protein activates the infection in human respiratory epithelial cells in SARS-CoV-2[Lan et al., 2020]. Spike S is a trimer protein, and it contains around 1300 amino acids within each unit[Samavati and Uhal, 2020]. The receptor-binding domain (RBD) of Spike S, which contains around 300 amino acids, mediates the binding with angiotensin-converting enzyme (ACE2), attacking respiratory cells.

**1.1.2** Angiotensin-converting enzyme 2 is a zinc-containing metalloenzyme on the surface of intestinal enterocytes, renal tubular cells and other cells(Rathod et al., 2020). ACE2 is a single-pass type I membrane protein. The extracellular region of human ACE2 enzyme is composed of two domains, one is zinc metallopeptidase domain and the other is C terminus[Samavati and Uhal, 2020]. As a transmembrane protein, ACE2 serves as the main entry point into cells for the SARS-coronavirus (CoV), further confirming that human ACE2 is the receptor for the recently emerging 2019-nCoV[Rathod et al., 2020]. As the host cell receptor is critical for the virus entry, targeting ACE2 holds the promise for preventing infection of 2019-nCoV infection(Rathod et al., 2020).

**1.1.3**During this outbreak, traditional drug discovery is not a feasible option because of its long

procedure. Peptides are preferable for their specificity and affinity towards certain targets and minimal toxicity because of their less enhancement tendency in the body[Khan et al., 2021]. Peptides have been developed as drug candidates to disrupt protein-protein interactions (PPIs) and target or inhibit intracellular molecules. Over the past couple of years, the U.S. Food and Drug Administration has approved several numbers of new drugs where notable numbers of molecules were peptides or peptide-containing entities[Khan et al., 2021].

**1.1.4**Many researchers have conducted research on this peptide blocking method against SARS-CoV-2. There is a significant amount of research papers on protein-peptide docking between the main protease of SARC-CoV-2 (Mpro) and potential peptide modules(Rathod et al., 2020), (Khan et al., 2021). But there are a few initiatives which mainly target the entry point of the virus (ACE2) rather than targeting the main protease. In this study, SARS-CoV-2 binding receptor (ACE-2) was targeted with some putative peptide inhibitors. To evaluate the performance of the peptides, molecular dockings were redacted against Angiotensin-converting enzyme .In the end, 4 top candidates according to their global energy score were chosen for non bond interaction analysis.

## 1.2 MATERIALS & METHODS:

### 1.2.1 Peptide Design

Peptides are short strings of amino acids, typically comprising 2–50 amino acids. In this research, 16 peptides were used as ligands. The peptides are the inhibitors of the main protease of HSV-1, HSV-2, DENV-2, RSV, HCV viruses respectively.

Pep-fold 3.5 server were used for peptide designing **.**PEP-FOLD is a de novo approach aimed at predicting peptide structures from amino acid sequences. The number of simulations was set to 200 for better results and the models were sorted by sOPEP. It provided 5 models after running. The ‘Model-1’ was chosen as the best model and used as ligand.

### 1.2.3 Peptide-Protein Docking (Preliminary)

The process of docking involves two basic steps: ligand conformation and assessment of the binding affinity [Khan et al., 2021]. The first step for molecular docking is the preparation of protein structure. There are a lot of water molecules, solvent molecules, ions and other small molecular ligands attached to the main protein. The PYMOL software was utilized to prepare the protein and remove all these byproducts.

For this research, a total of 16 peptides were obtained from Pep-fold 3.5. The protein-peptide dockings were performed using PatchDock and further refinements were done through FireDock. The complex type was set to default and clustering RMSD was 1.5 in this docking process. The binding affinities of the peptides were measured in kcal/mol units and sorted according to the higher negative values, which imply the best binding affinities.

### 1.2.4 Molecular Docking

Based on calculated binding affinities, 4 top-ranked potential peptides were chosen for further analysis. For visualizing and detecting the non-bond interactions in the docked ligand-protein complexes, PyMol and The BIOVIA Discovery Studio software package was used. The docking results of AVP1244, AVP1219, AVP1210,

and AVP1207 peptides were analyzed chronologically. In the analyzing process, intermolecular interactions and unfavorable non-bond interactions were unchecked. After adding hydrogen molecules, the ligands were defined. Then inside the ligand interactions, non-bond interactions panel was selected to get protein-peptide binding data.

## 1.3 RESULTS:

### 1.3.1 ACE2-RBD Interactions:

The non-bond interaction analysis of the titled complex showed that ACE2 interacts with 23 different bonds with the binding residues of RBD glycoprotein. ACE2 had 13 different binding residues with RBD. The Lys, Asp and Tyr residues from ACE2 had a major contribution to these bonds. The residues were LYS31, LYS35, GLU37, TYR83, LYS330, LYS353, ASP30, ASP38, LYS27, GLU24, TYR41, HIS34 and GLY354. There were 7 different types of bonds. The LYS31, LYS27 and LYS353 residues created the highest number of bonds. LYS31 bonded GLU484 residue of RBD with two Salt bridge; Attractive Charge bonds and TYR489 with a Pi-Orbital bond. The LYS27 residue bonded 3 different residues of RBD. It bonded TYR473 with a Carbon Hydrogen Bond, ALA475 with an Alkyl bond and PHE456 with a Pi-Orbital bond. Where LYS353 bonded GLY496 residue of RBD with two different types of bond. One Conventional and one Carbon Hydrogen Bond and TYR505 with a Pi-Stacked bond. HIS34 residue bonded the TYR442 residue of RBD.

LYS35 residue created two different bonds with two unique residues of RBD. LYS35 bonded GLU484 and GLU493 residues with an Attractive Charge Bond and a Carbon Hydrogen Bond, respectively. LYS330 bonded with THR500 residue through a Conventional Hydrogen Bond. ASP30 bonded with LYS417 of RBD through a Salt Bridge; Attractive Charge Bond and ASP38 bonded with GLY498 through a Conventional Hydrogen and a Carbon Hydrogen Bond. GLU37 residue of ACE2 bonded ARG403 through an Attractive Charge Bond. GLU24 bonded GLY476 through a Carbon Hydrogen Bond. GLY354 bonded with GLY502 of RBD through a Carbon Hydrogen Bond. TYR83 bonded with ASN487 and TYR489 through Conventional Hydrogen Bonds and TYR41 bonded ASN501 through a Carbon Hydrogen Bond and THR500 through a Conventional Bond. **(Figure-1 shows the interactions)**.

### 1.3.2 Peptide-ACE2 Molecular Docking (Preliminary):

In this session, I summarized four peptides that may have therapeutic effects against 2019-nCoV infection. Among the 16 selected peptide-ACE2 complexes obtained from FireDock, I chose 4 complexes according to their FireDock global energy score **(Table-1).** AVP1244-ACE2 complex showed the highest score **(Score: -66.20)**. The PatchDock ranking of selected AVP1244-ACE2 complex was 669. Second highest binding affinity holder was AVP1219-ACE2 complex **(Score: -64.87)**. The PatchDock ranking of selected AVP1219-ACE2 complex was 892. The AVP1210-ACE2 complex was the 3$^{rd}$ highest scorer **(Score: -55.64).** The PatchDock score of selected AVP1210-ACE2 complex was 941. And in my summarization process, the last selected complex with 4$^{th}$ highest global energy score was AVP1207-ACE2 complex **(Score: -52.59).** The PatchDock ranking of selected AVP1207-ACE2 complex was 617.

## 1.3.3 Molecular Docking Analysis:

### 1.3.3.1 AVP1244-ACE2 Complex:

AVP-1244 showed the highest celebrity in my research. There were 2 hydrogen bonds, 3 electrostatic bonds, and 4 hydrophobic bonds. The CYS1-ASP350 bond had the highest bond distance, with a distance of 5.19989**(Figure-2** shows the interaction).

From the non-bond interaction analysis of the complex, I got information on the titled complex in a deeper manner. In the ACE2-AVP1244 complex, a total of 6 different residues of ACE2 protein interacted with AVP1244 peptide residues. There were 3 different residues of AVP1244 peptide which created these bonds. The CYS1 residue of the addressed peptide had bonded with 4 different residues of ACE2 (ASP35, ASP38, ALA348, HIS401). The CYS1-ASP35 and CYS1-ASP38 bonds were Attractive Charge bonds where CYS1-ALA348 bond was a Conventional Hydrogen bond. On the other hand, CYS1-HIS401 bond was a Pi-Alkyl bond. The PHE3 residue of AVP1244 created 2 Pi-Pi Stacked bonds with TRP349 residue and a Conventional Hydrogen Bond with ALA348 residue of ACE2. The last binding residue of AVP1244 was TYR2, which created a Pi-Anion bond with GLU37 of ACE2 and a Pi-Alkyl bond with ALA348 residue of ACE2 protein.

### 1.3.3.2 AVP1219-ACE2 Complex:

AVP1219 was the 2nd best contender in my research. There were a total of 18 hydrogen bonds, 2 electrostatic bonds and 3 hydrophobic bonds. VAL59-VAL34 bond had the highest bond distance, with a distance of 5.46875**(Figure-3** shows the interaction).

I conducted a non-bond interaction analysis on ACE2-AVP1219 protein-peptide complex. In this complex, a total of 12 different residues of ACE2 protein interacted with AVP1219 peptide. I found 10 different binding residues of AVP1219 in these interactions. The GLU27 residue of AVP1219 created 5 interactions with 3 different residues of ACE2. GLU27 created 2 Conventional Hydrogen bonds with TYR50 residue of ACE2, an Attractive Charge bond with LYS341 and 2 Carbon Hydrogen Bonds with HIS34 residue of ACE2 protein. The CYS13 residue of AVP1219 bonded a total of 4 times with LYS31 residue of ACE2. Where it creates 2 Conventional Hydrogen bonds and 2 Carbon Hydrogen Bonds with LYS31. TRP31 residue bonded ASN508 of ACE2 2 times in a Conventional Hydrogen Bond. The GLY39 residue of AVP1219 created 2 Conventional Hydrogen Bonds with ASN121 residue of ACE2. The PHE10 residue of AVP1219 created 2 Carbon Hydrogen Bonds with THR129 residue of ACE2. The VAL34 residue of AVP1219 created 2 Alkyl bonds with VAL59 and MET62 residue of ACE2 respectively. The GLU56 residue of AVP1219 bonded ARG393 residue of ACE2 in an Attractive Charge bond. LEU33 residue of AVP1219 created an Alkyl bond with VAL59 of ACE2 protein. The SER128(ACE2)-ASN29(AVP1219) and ASP67(ACE2)-ASN38(AVP1219) were 2 Conventional Hydrogen Bonds in this complex.

### 1.3.3.3 AVP1210-ACE2 Complex:

AVP1210 was the 3rd best contender in my research. There were a total of 8 hydrogen bonds, 1 electrostatic bond and 7 hydrophobic bonds. ALA35-LEU320 bond had the highest bond distance, with a distance of 5.29795**(Figure-4** shows the interaction).

I found internal interaction details of this titled complex by operating non-bond interaction analysis. In this complex, a total of 10 different residues of ACE2 protein interacted with 7 different AVP1210 peptide residues. There was a total of 5 Conventional Hydrogen Bond, 4 Pi-Alkyl Bond, 3 Carbon Hydrogen Bond, 3 Alkyl Bond, a Pi-Lone Pair Bond and a Pi-Anion bond. The ASP32 residue of AVP1210 created 2 Conventional Hydrogen Bond with GLN552 and GLY319 residue of ACE2 and a Pi-Anion Bond with PHE555 residue of ACE2 protein. The other Conventional Hydrogen Bonds in this complex were ALA387(ACE2)-ASN38(AVP1210), ALA384(ACE2)-ASN38(AVP1210), and ASN322(ACE2)- VAL140(AVP1210). The TRP31 residue of AVP1210 interacted with the highest number of ACE2 residues. It bonded with 3 different residues of ACE2 with 5 different bonds. TRP31 bonded VAL316 residue of ACE2 with 2 Pi-Alkyl and one Carbon Hydrogen Bond. Also, it bonded GLY319 residue with a Carbon Hydrogen Bond and LEU320 residue with a Pi-Lone Pair Bond. The GLY319 residue of ACE2 could be found in another bond of this complex interacting with ASN30 residue of AVP1210 in a Carbon Hydrogen Bond. ARG559(ACE2)-VAL34(AVP1210), LEU320(ACE2)-ALA35(AVP1210) and PRO321(ACE2)-ALA35(AVP1210) were 3 Alkyl bonds in this complex. Also, there were 2 more Pi-Alkyl bonds in this complex which were PHE555(ACE2)- VAL34(AVP1210) and PHE555(ACE2)- ALA35(AVP1210).

**1.3.3.4 AVP1207-ACE2 Complex:**

AVP1207 was the 4th best contender in my research. There were a total of 5 Hydrogen bonds, 3 electrostatic bonds and 4 hydrophobic bonds. HIS34-VAL40 bond had the highest bond distance, with a distance of 5.40715**(Figure-5** shows the interaction).

AVP1207-ACE2 was my last chosen complex from molecular docking. Like the previous 3, I conducted a non-bond interaction analysis of this complex. Total 7 different residues of ACE2 took part in the interactions of this complex. Also, 7 different residues of AVP1207 peptides took part in these interactions. The GLU27 residue of AVP1207 peptide created the highest number of bonds. It interacted with 2 different residues of ACE2 with 4 different bonds. The GLU27 bonded THR129 residue of ACE2 with one Conventional Hydrogen Bond and one Carbon Hydrogen Bond. Also, GLU27 bonded LYS31 residue of ACE2 with one Salt Bridge; Attractive Force Bond and one Carbon Hydrogen Bond. LYS341(ACE2)-ASP9(AVP1207) and LYS353(ACE2)-ASP2(AVP1207) were 2 Attractive Force Bonds in this complex. The MET1 residue of AVP1207 bonded the CYS344 residue of ACE2 with 3 different bonds. A Conventional Hydrogen Bond, a Sulfur-X bond and an Alkyl Bond. PRO146(ACE2)- 1E23(AVP1207) was another Alkyl Bond in this complex. There were 2 more Pi-Alkyl Bonds in this complex which were HIS34(ACE2)-ALA36(AVP1207) and HIS34(ACE2)- VAL40(AVP1207) bonds.

## 1.4 DISCUSSION:

**1.4.1** The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure [Rathod et al., 2020]. The molecular docking approach allowed me to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. which is useful information for lead optimization. The global energy scoring function of molecular docking estimated the binding affinity, adopting various assumptions and simplifications.

From the protein-protein docking analysis between ACE2 and RBD, I found my target residues of ACE2 which helped me design my peptides and screen the effectiveness of those peptides. From my extracted results of firedock and patchdock, I found my top 4 peptides. The global energy represents the binding affinity and rate of successful interactions between ACE2 and modelled peptides. From the comparison of attractive and repulsive van der waal forces, I found a greater attraction rate of these complexes. More attraction force between the frontier interactive electrons denotes a better binding affinity.

**1.4.2** The results of the top 4 peptide-ACE2 dockings showed the binding sites of these complexes. From my first chosen complex according to global energy, it was observed that AVP1244 peptide interacts with several residues from my refined target residues. The CYS1 residue of AVP1244 directly binds the ASP38 residue of ACE2 with a strong attractive charge bond. Also, the TYR2 residue of AVP1244 binds with GLU37 residue of ACE2. GLU37 and ASP38 directly bind the GLY498 and ARG403 residues of RBD. So, AVP1244 could successfully disrupt 2 viral interactions (GLU37-ARG403 and ASP38-GLY498) between ACE2 and RBD. Furthermore, the CYS1 residue of AVP1244 also binds the HIS401 residue of ACE2 which could disrupt the nearby HIS34 residue from binding with RBD. AVP1219 residue binds HIS34 residue of ACE2 with two strong Carbon Hydrogen Bonds. Which could disrupt the HIS34-TYR442 bond interaction. AVP1219 had significant success by binding with LYS31 residue of ACE2 through its CYS13 residue. LYS31 is a dominant residue on the ACE2 surface as it creates 3 different bonds with RBD. The CYS1 residue could disrupt these bonds by creating 2 strong Conventional Hydrogen Bond and 2 Carbon Hydrogen Bond with LYS31. Also, AVP1219 binds 2 nearby residues (TYR50, LYS341) of ACE2-RBD interaction which could partially disrupt those interactions. The AVP1210 residue could not directly bind any interactive residue of ACE2. It binds GLY319 residue of ACE2 with 4 different residues. Which could partially disrupt the interactions. The AVP1207 had the biggest success in binding the interactive residues of ACE2. It binds both LYS31 and LYS353 residues of ACE2 which have a total of 6 interactive bonds with RBD. AVP1207 could disrupt these bonds by creating one Salt Bridge; Attractive Force Bond, one Carbon Hydrogen Bond, and one Attractive Force Bond through its GLU27 and ASP2 residues. Also, AVP1207 could block another direct interactive residue of ACE2 which is HIS34 as it binds HIS34 with 2 residues (ALA36, VAL40).

The docking results revealed that selected peptides could create a huge barrier between ACE2 and RBD interaction.

**1.4.3** From the analysis, we can see AVP1210 had a high binding affinity but it is not so capable to bind the interactive target residues of ACE2 which are actually responsible for ACE2-RBD interaction. But AVP1244, AVP1219 and AVP1207 residues could bind the interactive residues of ACE2 with a high binding affinity and block several catalytic residues of ACE2. AVP1207 could directly block 6 viral interactions and partially block two interactions. AVP1244 could directly block 2 viral interactions and partially disrupt one viral interaction. AVP1219 could directly block 3 viral interactions and partially block 2 viral interactions. These peptides created strong Hydrogen and Pi bonds with ACE2 against the interactive bonds between ACE2 and RBD.

**1.4.4 Negative Finding:**

In this research, I have targeted Angiotensin-Converting- Enzyme -2. ACE2 is a protein on the surface of many cell types. It is an enzyme that cuts the larger protein and produces small proteins. ACE2 plays a protective role in the cardiovascular system. Also, ACE2 saves the lung from several vital injuries, as ACE2 has several physiological functions in the lung. In the endothelial site, ACE2 degrades the octapeptide Ang II. Octapeptide is vasoconstrictive and proapoptotic for lung epithelial cells [Samavati and Uhal, 2020]. So, it seems like even though I am treating ACE2 enzyme as nefarious in my research, I can't deny the fact that ACE2 has some vital role in our system as well. Targeting ACE2 receptor protein may solve the Covid problem, but it may cause some side effects as well. So, it is advisable that we should conduct some controlled initiative against this main binding receptor of SARS-CoV-2, Angiotensin- Converting- Enzyme -2.

## 1.5 CONCLUSION:

From the context of my study, I suggest that AVP1244, AVP1219, and AVP1207 are potential candidates for Covid-19 treatment. The docking results showed that these 3 peptides fit in the binding pocket of ACE2 near-perfectly embedding the ACE2-RBD interaction. Since ACE2 is the primary media for SARS-CoV-2 virus to enter the cell and affect the whole human body, proposed candidates may show their effectiveness of working against other corona viruses as well. Further studies are needed to verify my results and test the anti-2019-CoV effects of these peptides.


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## 1.8 ARTWORK and TABLES:

**Figure. 1:** Interactive bonds between ACE2 and RBD**(Left)** H-bonds on the receptor surface of RBD(**Right)**

**Figure 2:** AVP1244-ACE2 interacting bonds**(Left)** H-bonds on the receptor surface**(Right)**

**Figure 3:** AVP1219-ACE2 interacting bonds**(Left)** H-bonds on the receptor surface**(Right)**

**Figure 4:** AVP1210-ACE2 interacting bonds**(Left)** H-bonds on the receptor surface**(Right)**

**Figure 5:** AVP1207-ACE2 interacting bonds**(Left)** H-bonds on the receptor surface**(Right)**

| Protein | Peptide AVPid | Peptide Length | Attractive VdW | Repulsive VdW | Global Energy | Peptide Sequence |
|---|---|---|---|---|---|---|
| | AVP-1244 | 33 | -27.26 | 3.61 | -66.20 | GCASRCKAKCAGRRCKGWASAFRGRCYCKCFRC |
| | AVP-1219 | 33 | -31.29 | 12.47 | -64.87 | GLEDELVYLLDGPGYDPIHCDVVIRGGSRLFNF |
| | AVP-1210 | 9 | -30.01 | 9.60 | -55.64 | ASLRVRIKK |
| | AVP-1207 | 8 | -20.87 | 4.39 | -52.59 | AGKRKSG |
| | AVP-1118 | 10 | -28.07 | 11.36 | -52.31 | ASLRVRIKKQ |
| | AVP-1216 | 15 | -34.07 | 17.32 | -49.33 | HCIYATTNDALIFSV |

| | | | | | | |
|---|---|---|---|---|---|---|
| | AVP-1212 | 18 | -31.13 | 11.59 | -47.68 | GELGRLVYLLDGPGYDPI |
| Angiotensin-Converting- Enzyme -2 | AVP-1202 | 6 | -26.85 | 6.72 | -46.71 | CGYKGC |
| | AVP-0766 | 43 | -23.79 | 8.01 | -46.64 | GCASRCKAKCAGRRCKGWASAFRGRCYCKCFRC |
| | AVP-1211 | 33 | -26.28 | 2.52 | -46.01 | GELGRLVYLLDGPGYDPIHCSLAYGDASTLVVE |
| | AVP-1208 | 12 | -38.25 | 23.88 | -45.11 | CAGKRKSG |
| | AVP-1120 | 10 | -36.80 | 11.44 | -45.03 | ASLRVRIKKQ |
| | AVP-1214 | 33 | -21.75 | 24.47 | -44.76 | GELGRPVYVLGDPGYYATHCIYATTNDALIFSV |
| | AVP-1205 | 7 | -22.90 | 10.27 | -43.58 | CGKRKLC |
| | AVP-1221 | 20 | -26.24 | 5.85 | -41.83 | GELDELVYLLDGPGDPIHS |
| | AVP-1200 | 7 | -27.84 | 17.21 | -41.21 | CGYGLC |

**Table-1:** Result analysis of PatchDock and FireDock refinement.

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