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Original Article

Structure-Based Design of Novel Peptidomimetics Targeting the SARS--CoV-2 Spike Protein

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Abstract
Purpose—SARS-CoV-2 is a SARS-like novel coronavirus strain first identified in December 2019 in Wuhan, China. The virus has since spread globally, resulting in the current ongoing coronavirus disease 19 (COVID-19) pandemic. SARS-CoV-2 spike protein is a critical factor in the COVID-19 pathogenesis *via* interactions with the host cell angiotensin-converting enzyme 2 (ACE2) PD domain. Worldwide, numerous efforts are being made to combat COVID19. In the current study, we identified potential peptidomimetics against the SARS-CoV-2 spike protein.
Methods—We utilized the information from ACE2-SARS-CoV-2 binary interactions, and based on crucial interacting interface residues, novel peptidomimetics were designed.
Results—Top scoring peptidomimetics were found to bind at the ACE2 binding site of the receptor-binding domain (RBD) of SARS-CoV-2 spike protein.
Conclusions—The current studies could pave the way for further investigations of these novel and potent compounds against the SARS-CoV-2.

Keywords—COVID-19, SARS-CoV-2 spike protein, Virtual screening, Molecular docking, Peptidomimetic.

INTRODUCTION

Coronaviruses are a group of RNA viruses that cause diseases in mammals and birds. In humans, these viruses cause respiratory tract infections that can range from mild to lethal. Mild illnesses include some cases of the common cold (which is also caused by certain other viruses, predominantly rhinoviruses), while more lethal varieties can cause SARS, MERS, and COVID-19.[1] COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has a case-fatality rate of 2:3%, with higher rates among elderly patients and patients with concurrent medical conditions (WHO, May.[31] During attachment and penetration, the SARS-CoV-2 attaches itself to a host cell ACE2 PD domain through its spike (S) protein (Li *et al.*[15,18]

Structurally, the coronavirus has the most massive known RNA genome of 26 to 32 kb amongst other known viruses, characterized by non-segmented, positive-sense single-stranded RNA.[6] This genome encodes for four major structural proteins of the virus, including; Nucleocapsid (N), Envelope (E), Membrane (M), and Spike (S) proteins (Li *et al.*[15,18] The membrane and envelope proteins are associated with virus assembly. In contrast, the Spike (S) protein plays the primary role in facilitating the virus entry *via* mediating its interaction with the transmembrane surface receptor on the host cells.[6,14] The Spike (S) protein directly interacts with the peptidase domain (PD) of Angiotensin-converting enzyme 2 (ACE2) receptor (Li *et al.*[16,33,32] which technically marks the virus entry inside the cells.[10] Hence, inhibition of this interaction could be a promising strategy to combat the SARS-CoV-2 infection.

With the current epidemiology of SARS-CoV-2, a vaccine might be considered a highly anticipated therapy. However, the fact that vaccine development and production is a highly challenging and time-consuming task, the need of the hour is to develop potent therapeutic agents which could effectively curb the infection in the early stages. Several approaches such as decoy soluble ACE2 proteins, antibodies from the serum of infected patients, repurposing of drugs, and

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designing of blocking peptides are underway [26,21]; Li *et al.*[15,12–9]; Robson.[27] Peptides possess several attractive features when compared to small molecules and protein therapeutics, including high structural compatibility with target proteins, the ability to disrupt protein-protein interfaces, *etc*. This study attempts to design the peptidomimetics (peptide derivatives) based on the circle residues involved in the interaction of the SARS-CoV-2 spike protein and ACE2 PD domain. Peptidomimetics can respond to peptide limitations of displaying higher metabolic stability, good bioavailability, and enhanced receptor affinity and selectivity.[28] Thus, the main objective of this study is to identify efficient peptidomimetics, which could inhibit ACE2 interaction with SARS-CoV-2 *S*-glycoprotein, thereby blocking the cellular entry of the virus.

MATERIALS AND METHODS

Structure-Based Design of Peptidomimetics

In our previous studies, we designed an 18 amino acid (18aa) SARS-CoV-2 inhibitory peptide.[2] To achieve this, we retrieved the crystal structure of the SARS-CoV2-ACE2 complex (PDB ID: 6M17)[32] from the Protein Data Bank (https://www.rcsb.org/). We examined interface and critically essential residues involved in interactions between RBD of SARS-CoV-2 spike protein and PD domain of ACE2 protein using UCSF Chimera[25] and Arguslab 4.0.1[29] visualizers. We performed alanine scanning for the stretch present in the ACE2 PD domain interacting with SARS-CoV-2 spike protein. After alanine scanning, we designed the 18 amino acid long inhibitory peptide masking ACE2 PD domain binding site on the SARS-CoV-2 spike protein.

Further, novel peptidomimetics were designed based on the critically interacting residues present in the 18 aa inhibitory peptides. The residues "28F, 32F, 40F, 41Y, 43S, 44S, and 45L" of 18aa peptide inhibitor sequence "28-FLDKFNHEAEDLFYQSSL-45" from ACE2 were used for designing and screening of best peptidomimetics. The critically important residues involved in binding were submitted to pep:MMs:MIMIC server (http://mms.dsfarm.unipd.it/pepMMsMIMIC/) to obtain 200 pharmacophore similarity-based peptidomimetics conformations.[7]

Molecular Docking Studies and DFT Validation of Peptidomimetics

Compounds retrieved from the pep:MMs:MIMIC server were used for molecular docking based screening using virtual screening workflow in Discovery Studio version 4.0 (Accelrys, San Diego, USA; BIOVIA.[4] 3D structures of the peptidomimetics were prepared as executable pdbqt files, and to assign the suitable protonation state, ionization and tautomerization were performed for each compound at physiological pH 7.2 ± 0.2. The 3D structure of the SARS-CoV-2 spike protein (PDB ID: 6M17) was retrieved from the protein data bank. Retrieved SARS-CoV-2 spike protein was refined by removing unwanted water molecules, and co-factors from the crystal structure and the hydrogen atoms were added, and then energy minimized until the average root mean square deviation (RMSD) of the non-hydrogen atoms reached 0.3 Å.[17] The induced-fit docking (IFD) is comprised of the combined protocol of docking/dynamics studies.[20] In addition to LibDock from Discovery Studio, Autodock Vina 1.1.2 was also used to validate the molecular docking.[30] The best active conformations of finally screened four compounds from the virtual screening process were used to analyze the density functional theory (DFT) calculations. Becke's three-parameter with Lee–Yang–Parr correlation functional (B3LYP) and basis set 6–31G** was used to Hybrid DFT calculation.[23,22]

Toxicity and ADMET Validations of Peptidomimetics

The molecular dynamics simulation of selected peptidomimetics was carried out using the GROMACS 5.1 package with the recent GROMOS96 (53a6) force field, which plays an important role in protein dynamics.[19] We further predicted the drug-likeness property of the screened compounds by examining its ADMET using MedChem Designer (https://www.simulations-plus.com/) and pkCSM (http://biosig.unimelb.edu.au/pkcsm/). This gives the physicochemical description of possible drug-like compounds and is also used to find the druggable nature of the screened compounds which satisfy Lipinski's rule of 5, as a prerequisite for rational drug design.[5] By predicting these properties helps in filtering active compounds and reduces the experimental procedures to evaluate the screened compounds.

RESULTS AND DISCUSSION

Identification of Critical Residues for Peptidomimetics Preparation and Its Screening

The designing of high potential, stable, and novel peptidomimetics to mask the ACE2 PD domain binding site on a SARS-CoV-2 spike protein is an advancement to our previous study. We examined the interface residues between the SARS-CoV-2 spike

protein and ACE2 PD domain (PDB: 6M17), and a small stretch of the ACE2 PD N-terminal region was found to be interacting majorly with SARS-CoV-2 spike protein. Based on the critically interacting residues between RBD of SARS-CoV-2 spike protein and ACE2 PD domain, we designed 18 amino acid long inhibitory peptide, which can block the ACE2 binding site on the SARS-CoV-2 spike protein. In the current study, the inhibitory peptide was used to design stable and potent peptide derivatives (peptidomimetics), which can bind to the receptor-binding domain (RBD) of SARS_CoV-2 spike protein more efficiently than the peptide. The critically interacting residues (28F, 32F, 40F, 41Y, 43S, 44S, and 45L) of 18 amino acid peptide were taken to design the potential peptidomimetics.

The selected residues were finally submitted to pep:MMs:MIMIC server (http://mms.dsfarm.unipd.it/pepMMsMIMIC/) to obtain 200 of fingerprint and pharmacophore-based peptidomimetic conformations. The obtained conformations were used for virtual screening study with SARS-COV-2 spike protein in order to get the best peptidomimetics stably binding the RBD of spike protein in accordance with 18aa peptide inhibitor. The 3D coordinates of all the conformations were generated using Open Babel Version 3.0[24] before the virtual screening. Finally, the high-throughput virtual screening of peptidomimetics for SARS-CoV-2 spike protein inhibition was performed using the Discovery studio docking platform along with further validation on other docking platforms, as described below (Fig. 1).

The Virtual Screening and Molecular Docking Studies of Peptidomimetics

A library of 200 peptide derivatives (peptidomimetics), retrieved from pep:MMs:MIMIC server, was used to run the High-Throughput Virtual Screening (HTVS) using the LibDock platform of the BIOVIA Discovery Studio. We screened out the peptidomimetics those who were coming exactly the binding site of 18 amino acid peptide on SARS-CoV-2 spike protein, as illustrated in Fig. 2c. Figure 2a displays the interface of the SARS-CoV-2 spike protein and ACE2 PD domain. Figure 2b is the interaction of inhibitory peptide (18aa) with SARS-CoV-2 spike protein.

To perform blind docking, the whole part of the 3D crystallographic structure of SARS-CoV-2 spike protein was covered, and the generated fingerprint and pharmacophore-based peptidomimetics were supplied as a ligand file in *.sdf* file format. We aimed to screen the peptidomimetics with best docking pose interacting similar to the binding site of the 18aa inhibitory peptide (Fig. 2c). We compared the uniformity of binding mode, and energy scoring pattern of final peptidomimetic residues screened using different molecular docking platforms such as Autodock Vina, Autodock, and iGemdock.[8,11,30] Table 1 displays the results obtained from these docking platforms, and the obtained scores were found to be uniform for the top four peptidomimetic compounds listed here. Thus, we selected these four compounds for further DFT, ADMET, and MESP (Molecular Electrostatic Potentials) calculations.

Further, we analyzed the individual interaction pattern of these peptidomimetics with the key amino acid residues. Figure 3, representing top-scored peptidomimetics, elucidates the structural, functional, and elemental level exchange between amino acid residues/elements of peptidomimetics and SARS-CoV-2 spike protein residues. Obtained results reveal that almost all peptidomimetics showed a strong interaction with these residues. Apart from hydrogen bonds, these compounds were also found to have other non-covalent bonds, such as π–π and cation-π interactions. The non-covalent interactions stabilize a protein-ligand complex as well as the dynamics and thermodynamics of the system, and they differ from covalent bonds in

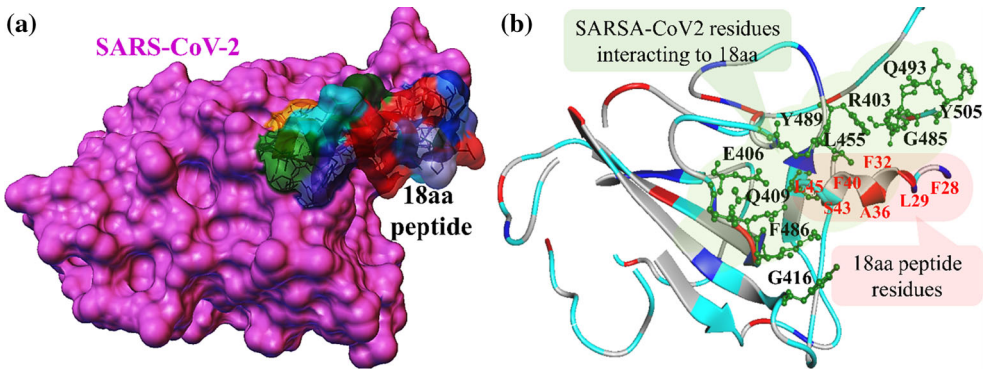

FIGURE 1. Identification of SARS-CoV-2 key residues involved in the interaction with 18aa peptide inhibitor.

that no electrons are shared between the participating atoms (Fig. 3). Non-covalent forces are essential in biological function because they are specific without conferring as much rigidity as covalent forces.[13] Non-covalent interactions can be such as electrostatic, π-effects, van der Waals forces, and hydrophobic effects are fairly playing a major role in inter as well as intramolecular communications.[12]

ADMET, DFT, and MESP and Assessments

The 'ToxinPred' server (http://crdd.osdd.net/raghava/toxinpred/) was used to analyze the toxicity of the peptidomimetics, and all compounds showed no toxicity. The obtained ADME score displayed in Table 2 is favorable as well. MlogP scores were revealing the lesser lipophilicity and higher soluble nature of these peptidomimetics naturally. Even though the molecular weight of MMs02471820 and MMs03927283 little higher than the expectation of Lipinski's rule,[19] these compounds have exhibited remarkable *in silico* functional values using lowest binding energy (− 8.4 and − 7.6 kcal/mol respectively) and binding affinity. Hydrogen-bonds play a major role in determining the specificity of drug/ligand binding. The conventional hydrogen bonds established with the key residues ensure the same and the other non-covalent interactions such as π-effects and van der Waals forces making all the peptidomimetics efficient for COVID-19 treatment.

The ionization potential of the peptidomimetics is due to HOMO energies, and electron affinities of the compounds are resultant of LUMO energies (Table 3). In compound MMs02471820, the HOMO region was scattered on the carbonyl end, and LUMO was situated on $-CH_2$ end attached to the aromatic ring (Figs. 4a and a1). In compound MMs03919328, HOMO was around the region of *N*-methyl phenyl end LUMO was spread around nearby the same region (Figs. 4b and b1). In the extended analysis, the HOMO, LUMO pattern was found to be favorable also for the other peptidomimetics MMs03919328 and MMs03919325.

The results of Molecular Electrostatic Potential (MESP) analysis of screened compounds shown in Figs. 5a through 5d. The dark blue color shows the

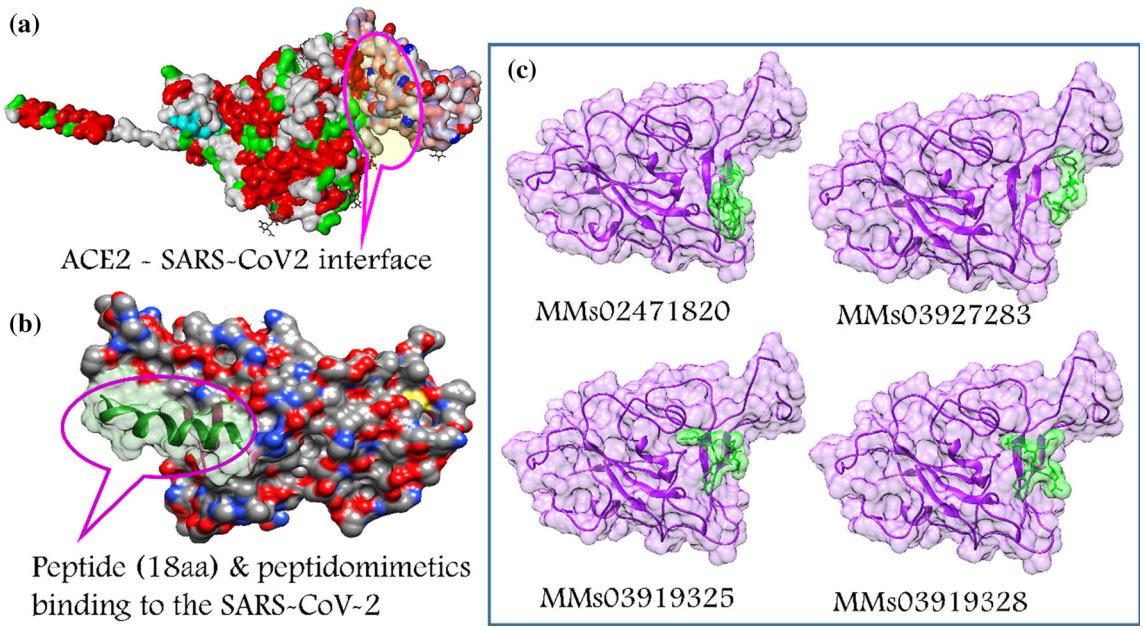

FIGURE 2. (a) Illustration of the binding interface of SARS-CoV-2 and ACE2; (b) 18aa blocks entry point of SARS-CoV-2 to ACE2; (c) Top 4 peptidomimetics docking pose blocking SARS-CoV-2 entry resembling 18aa peptide inhibitor binding mode.

TABLE 1. Molecular mechanistic values of screened peptidomimetics obtained from various molecular docking platforms.

Peptidomimetics	Discovery studio LibDock score	Autodock Vina (BE; kcal/mol)	LE (Autodock)	iGemdock Total energy
MMs02471820	88.7249	− 8.4	− 0.41	− 86.6186
MMs03919328	92.3764	− 7.9	− 0.38	− 84.3075
MMs03927283	99.2277	− 7.6	− 0.35	− 75.5895
MMs03919325	64.6924	− 7.4	− 0.34	− 75.3091

BE Binding Energy, *LE* Ligand Efficiency.

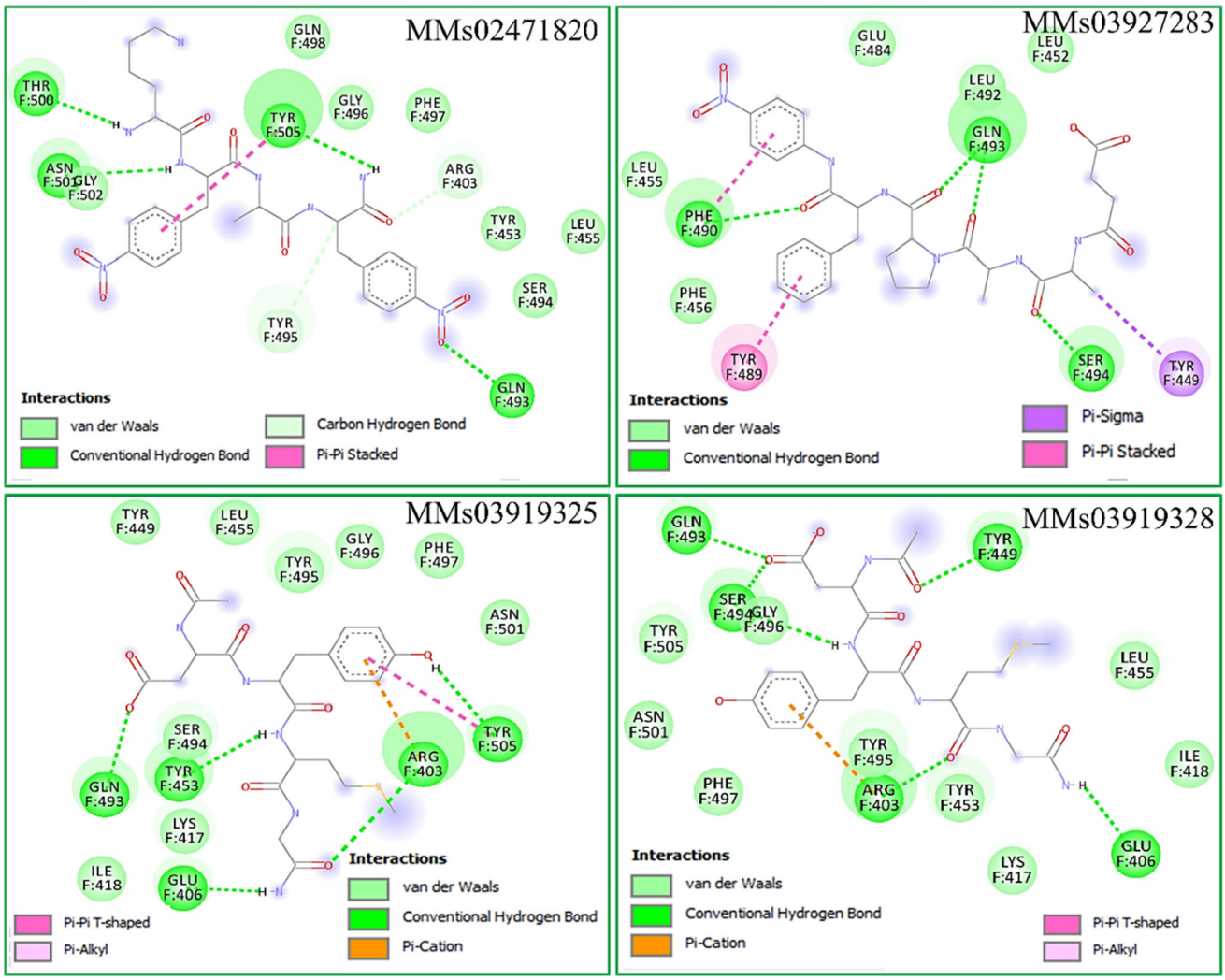

FIGURE 3. Molecular interaction of SARS-CoV-2 spike protein and selected peptidomimetics.

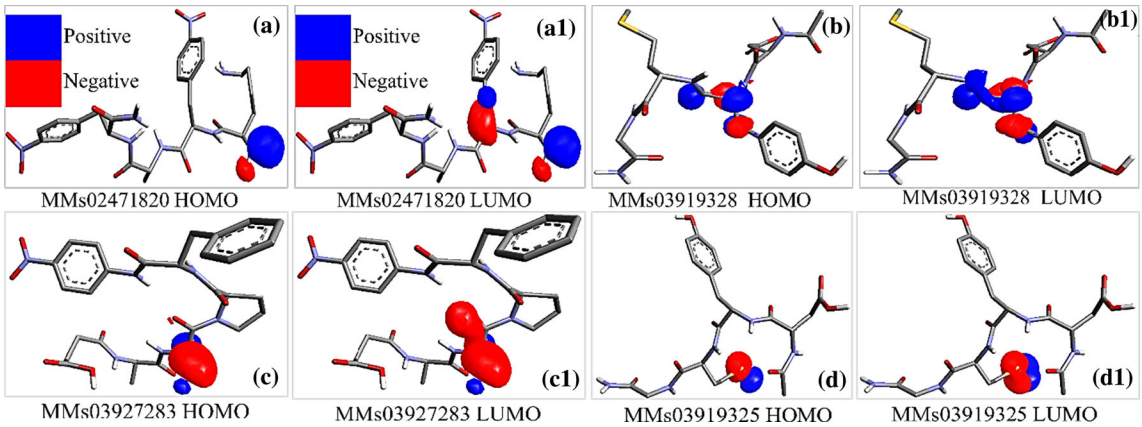

FIGURE 4. The occupied and unoccupied molecular orbital regions representing the HOMO and LUMO surfaces of peptidomimetics MMs02471820 (a and a1), MMs03919328 (b and b1), MMs03927283 (c and c1) and MMs03919328 (d and d1). Blue and red color regions represent positive and negative potential.

TABLE 2. ADMET scores of screened peptidomimetics.

Name	DiffCoef	MlogP	S + logP	RuleOf5_Code	MWt	T_PSA	HBDH
MMs02471820	0.502	1.056	0.993	Hb; Mw; NO	600.635	274.07	9
MMs03919325	0.547	− 1.46	− 1.039	Hb; Mw; NO	525.584	217.02	8
MMs03927283	0.496	0.516	1.418	Mw; NO	624.655	219.83	5
MMs03919328	0.547	− 1.46	− 1.039	Hb; Mw; NO	525.584	217.02	8

DiffCoef Differential co-efficient, *MlogP* Moriguchi estimation of logP, *S + logP* Simulated logP, *RuleOf5 (RO5)* Lipinski's Rule of Five: a score indicating the number of potential problems a structure might have with passive oral absorption, *RuleOf5_Code* Lipinski's Rule of Five codes: LP = logP, *Mw* molecular weight.

TABLE 3. Summary of HOMO, LUMO, HLG and MESP parameters of 6 hit peptidomimetics from DFT studies.

					MESP	
Compound	HOMO (eV)	LUMO (eV)	HLG (eV)	SE (kcal/mol)	MNP	MPP
MMs02471820	− 0.18	− 0.05	− 0.18	− 15.95	− 0.2103	0.1836
MMs03919325	− 0.22	− 0.12	− 0.14	− 12.94	− 0.3540	0.3373
MMs03927283	− 0.23	− 0.07	− 0.18	− 20.93	− 0.2544	0.1765
MMs03919328	− 0.20	− 0.07	− 0.19	− 11.88	− 0.4238	0.1747

HLG HOMO-LUMO gap, *SE* Solvation energy, *MESP* Molecular Electrostatic Potential, *MPP* Most Positive Potential, *MNP* Most Negative Potential.

most electropositive region and dark red color depicts the electronegative region. In MMs02471820 the electronegative regions were observed in areas where amine groups present, and highly electropositive regions were observed in prominently protonated regions. In MMs03919328 high electro positivity was seen near the amine group and high electronegativity was observed near the carbonyl group and slight electronegativity was spread throughout the molecule. In MMs03927283 the electronegative region was spread across the entire molecule with the prominent electronegative region around the oxygen atom and slight electro positive region observed at the peripheral hydrogens of the molecule. MMs03919325 had slightly electropositive regions spread across the compound at the protonated sites and a prominent electronegative region was observed at carbonyl residue and the slight electronegative region was observed in the rest of the atoms in the residue. The MESP analysis also revealed that all the compounds had electron transfer. The electron transfer makes a filled valence shell, and therefore the compound becomes more stable.

In drug discovery, predicting the fraction unbound in plasma offers a good understanding of the pharmacokinetic properties of these peptides also helps in candidate selection in the early stages. The unbound fractions are active and bind to proteins to make drug-protein complex. The predicted unbound fraction range (0.412 to 0.581) shows the pharmacological effects of screened four compounds. Total clearance is related to the bioavailability. The total clearance values are predicted as the proportionality constant (CLtot), and it is the combination of renal and hepatic clearance. The obtained value range of 0.289 to 0.386 Log(ml/min/kg) indicates the adaptive nature of these compounds' physiological environment while carrying out therapeutic validations. The maximum recommended tolerated dose (MRTD) provides an estimate of the toxic dose threshold in humans. MRTD less than or equal to 0.477 is low, and higher than 0.477 is high. The obtained value (0.389) indicates that these compounds are still non-toxic to human.

CONCLUSION

The SARS-CoV-2 is the etiological agent of the COVID-19 that emerged in China in late 2019 and causing an uncontrolled pandemic. There is an unmet need for an efficacious medicine to eradicate this current menace. Global multidimensional medicine development approaches against SARS-CoV-2 still under evaluation level. Peptidomimetics being close to natural peptide conformations have been attractive agents against viral infection. In this study, we developed a library of potential 200 peptidomimetics utilizing the sequence F28 to L45 (FLDKFNHEAEDLFYQSSL) of 18aa peptide inhibitor from ACE2. Top lead peptidomimetics were screened for further validation.

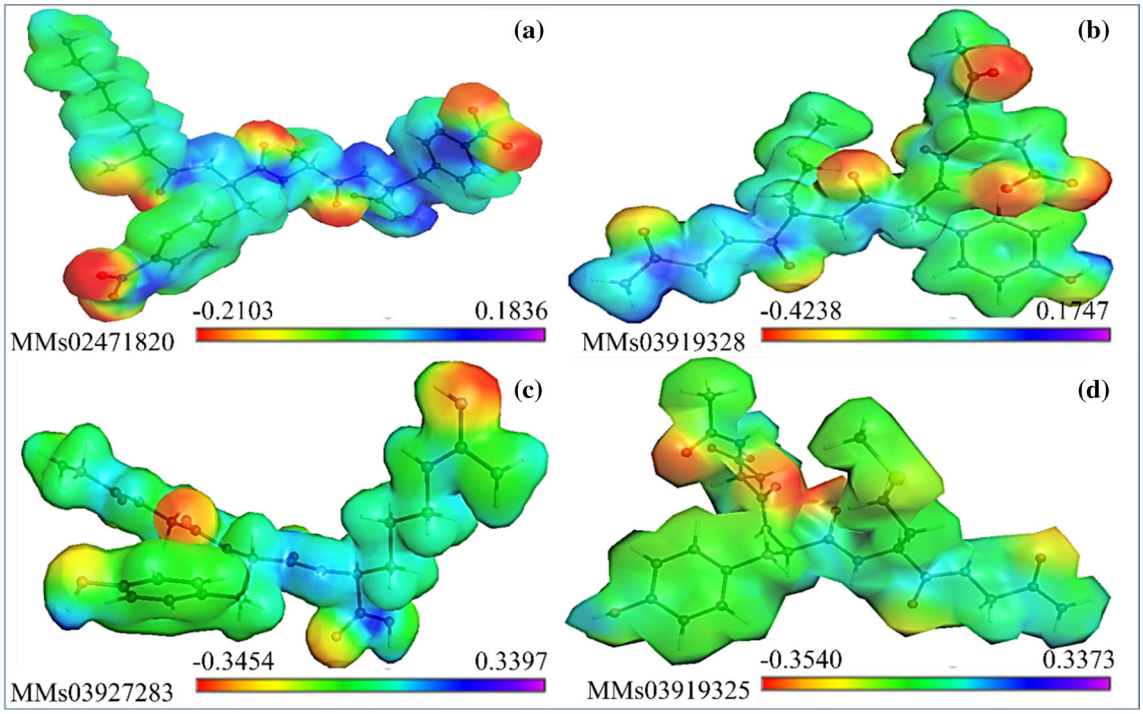

FIGURE 5. Calculated Molecular Electrostatic Potential for the identified ligands (a) MMs02471820; (b) MMs03919328; (c) MMs03927283; (d) MMs03919325.

In conclusion, structure-based and E-pharmacophore based screening was performed to identify potent inhibitors against SARS-CoV-2 spike protein, thereby inhibiting its binding to the ACE2 PD domain. Top six peptidomimetic molecules were identified based on their docking energy with the target protein. The binding efficacy and structural stability of these six molecules were validated through IFD, DFT, and ADMET studies. Finally, 4 lead compounds (MMs02471820, MMs03919325, MMs03919328, and MMs03927283) were found to have a high binding affinity and free energy as well as a suitable interaction pattern at the SARS-CoV-2 spike protein interface. IFD and DFT studies revealed that the aliphatic chain regions attached to aryl rings of the peptidomimetic scaffold play a crucial role in hydrogen bonding and π-π interaction with SARS-CoV-2 spike protein. DFT studies also revealed these regions possessed electron acceptor/donor ability for the inhibition of SARS-CoV-2 spike protein. Further, the 4 lead peptidomimetic compounds have been proposed for SARS-CoV-2 spike protein inhibition studies in cell-based assays.

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AUTHOR CONTRIBUTIONS

MSB conceived and designed the research. MA and SR executed, compiled and analyzed the data. MSB has written, reviewed and edited the manuscript.

FUNDING

There is no funding source available for this study

CONFLICT OF INTEREST

All authors (M.A., S.R., and M.S.B.) declare no competing interest

ETHICAL APPROVAL

Not applicable as this article deals only the computational structural biology studies and no involvement of animal and human subjects.

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