High-throughput virtual screening of drug databanks for potential inhibitors of SARS-CoV-2 spike glycoprotein

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ABSTRACT

COVID-19, which is caused by a novel coronavirus known as SARS-CoV-2, has spread rapidly around the world, and it has infected more than 29 million individuals as recorded on 16 September 2020. Much effort has been made to stop the virus from spreading, and there are currently no approved pharmaceutical products to treat COVID-19. Here, we apply an in silico approach to investigate more than 3800 FDA approved drugs on the viral RBD S1-ACE2 interface as a target. The compounds were investigated through flexible ligand docking, ADME property calculations and protein–ligand interaction maps. Molecular dynamics (MD) simulations were also performed on eleven compounds to study the stability and the interactions of the protein–ligand complexes. The MD simulations show that bagrosin, chidamide, ebastine, indacaterol, regorafenib, salazosulfadimidine, silodosin and tasosartan are relatively stable near the C terminal domain (CTD1) of the S1 subunit of the viral S protein. The relative MMGBSA binding energies show that silodosin has the best binding to the target. The constant velocity steered molecular dynamics (SMD) simulations show that silodosin preferentially interacts with the RBD S1 and has potential to act as an interfering compound between viral spike-host ACE2 interactions.

Abbreviations: ACE2: angiotensin converting enzyme 2; HR1: heptad repeat region; HR2: second heptad repeat region; MD: molecular dynamic; MMGBSA: molecular mechanics energies with the generalized Born and surface area continuum solvation; RBD: receptor-binding domain; SMD: steered molecular dynamics; ADT: autodock tools; MMFF: Merck molecular force field; RMSD: root-mean-square deviation; RMSF: root-mean-square fluctuation

INTRODUCTION

A recent coronavirus pandemic leading to COVID-19 caused by a coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China, and has led to thousands of fatalities across the globe (Huang et al., 2020). As the world races against time in search of coronavirus therapeutics and prophylactics, no effective vaccine or antiviral therapeutic agents have been approved for COVID-19 to date. So far, more than 29 million cases have
been confirmed with more than 940 thousand deaths all over the world (Coronavirus disease, 2019).

The SARS-CoV-2 virus uses human angiotensin converting enzyme 2 (ACE2) to enter our cells, replicate and spread efficiently (Babadaei et al., 2020; Hoffmann et al., 2020). A quick look at the structure of the virus and its replication and infection cycle reveals several points of intervention (see Figure 1) (Astuti, 2020).

The spike glycoprotein (S) is comprised of two functional subunits, S1 and S2, that are responsible for binding of the virus to the host cell receptor (Bosch et al., 2003; Ou et al., 2020; Shang et al., 2020), the S1 subunit contains the receptor-binding domain (RBD) that binds to the host cell receptor, and S2 contains the fusion machinery (Tortorici & Veesler, 2019). An obvious strategy in the design of therapeutics is to block the binding of S1 to human ACE2 or to block the fusion machinery of S2. The fusion of viral and host membranes is triggered by proteolysis of S2, a site within S2 containing heptad repeat region (HR1) and second heptad repeat region (HR2). Proteolysis of S2’ that is followed by conformational changes in HR1 and HR2 facilitates fusion and release of the viral genome into the host cell (Kirchdoerfer et al., 2018). Before this detailed understanding of the fusion machinery came to light, Simmons et al demonstrated that endosomal proteolysis of the S glycoprotein of SARS-CoV is required for fusion of the virus and its subsequent infection. Based on this information they developed cathepsin L inhibitors which prevented SARS-CoV infection (Simmons et al., 2005). Amin and coworkers reported a computational comparative study between both SARS-CoV and SARS-CoV-2. They concluded that the S protein of SARS-CoV-2 has a higher affinity to the ACE2 human cell receptor than of SARS-CoV (Amin et al., 2020).

In a recent study, a series of lipopeptides based on the pan-coronavirus fusion inhibitor peptide EK1 were generated and demonstrated that the derived lipopeptide EK1C4 was the most potent fusion inhibitor against SARS-CoV-2 S (Xia &
Table 1. List of the top docking scored ligands and some of their ADME properties.

| Ligand       | Best docking score kJ/mol | TPSA \( ^{b} \) | mLogP \( ^{c} \) | Hydrogen bonds (acceptor/donor) |
|--------------|---------------------------|-----------------|-------------|---------------------------------|
| Sitagliptin  | –33.47                    | 97.06           | 2.91        | 7/4                             |
| Risperidone  | –32.64                    | 29.45           | 6.56        | 3/0                             |
| Lumacaftor   | –32.64                    | 154.41          | 3.86        | 10/3                            |
| Bagrosin     | –34.31                    | 85.34           | 3.64        | 1/2                             |
| Tasosartan   | –33.89                    | 100.56          | 2.48        | 8/1                             |
| Bagrosin     | –32.64                    | 58.2            | 3.3         | 4/2                             |
| Lumacaftor   | –33.05                    | 97.76           | 4.96        | 7/2                             |
| Risperidone  | –32.64                    | 64.17           | 2.96        | 6/0                             |
| Sitagliptin  | –32.64                    | 77.05           | 2.06        | 6/2                             |

\( ^{a} \)All given compounds are with zero Lipinski violations.

\( ^{b} \)TPSA: topological polar surface area of a molecule.

\( ^{c} \)mLogP: molinspiration’s octanol–water partition coefficient.

e et al., 2020). Many therapeutic options are being considered to combat COVID-19; more information about ongoing clinical trials has been summarized by Tu et al (Tu et al., 2020). Whisnant and Burgess (Whisnant & Burgess, 2020) have highlighted possible strategies that utilize the availability of the crystal structure of S and of human ACE2, and also indicated the possibility of human defensin proteins protecting the human GI tract from infection. In silico approach is still revolutionizing the drug discovery development (Aminpour et al., 2019; Macalino et al., 2015; Njogu et al., 2016). Han and Kral (Han & Král, 2020) have designed, computationally, peptide inhibitors of S derived from the interacting region of the ACE2 receptor. Moreover, Wei et al performed a virtual screening for FDA-approved drugs and natural compounds that may target viral spike proteins (Wei et al., 2020). Ahuja and coworkers also implemented a virtual screening approach for identifying possible antiviral compounds that can target the spike protein, main protease and the SARS-CoV-2 RBD-ACE2 complex (Panda et al., 2020). Senathilake et al (Senathilake et al., 2020) performed a virtual screening for FDA approved drugs and they show that zorubicin, aclacinomycin and food dye E 115 were predicted to be potent inhibitors of the RBD–ACE2 interaction. Trezza and coworkers (Trezza et al., 2020) combined docking, molecular dynamics and steered molecular dynamic simulations to show that simprevir and lumacaftor could be potential initial inhibitors of the RBD of the spike protein.

In this paper, we discuss a virtual high-throughput screening of known drug databases to identify lead compounds that could interrupt the viral RBD S1-ACE2 interface. We utilized the reported X-ray crystal structure of the spike glycoprotein complexed with the ACE2 human receptor (PDB ID: 6LZG) to perform a flexible ligand docking on more than three thousand previously known drugs (Wang et al., 2020). The top 200 compounds with the best docking scores were taken for ADME property calculations. MD simulations were further employed to study the dynamical behavior and stability of the ligands between the S and ACE2 protein and to understand the pharmacophoric features of the ligands.

Ligand-RBD-ACE2 interactions were analyzed in detail for the best 190 hits. Interacting residues from RBD and ACE2 were identified. We filtered the top eleven compounds with good ADME properties and good contacts with S and ACE2. The interactions and binding of the eleven best molecules were further studied with MD simulations. The one-average molecular mechanics energies with the generalized Born and surface area continuum solvation (MMGBSA) was used to rescore the binding energy of the ligand-RBD-ACE2 interactions. This study aims to provide insights to find potential inhibitors that may block the RBD S1 subunit of the viral S protein, and therefore, prevent the viral infection. The overall filtering procedure is shown in Figure 2.

Methods

Ligands and protein preparation

Several structures of the SARS-CoV-2 spike glycoprotein interacting with the human ACE2 are available. A recent high-
resolution X-ray crystal structure of the RBD S protein (Wang et al., 2020), PDBID: 6LZG, was taken as a target. The SMILES of FDA approved drugs and some of the compounds under trial for COVID-19 treatment were obtained from the drugcentral (Ursu et al., 2017) and drugbank (Wishart et al., 2006) databases. A total of 3828 compounds (in SMILES format) were converted to 3D coordinates using OpenBabel (O’Boyle et al., 2011) followed by geometry optimization using the MMFF94 force field (Halgren, 1996a, 1996b, 1996c, 1996d Halgren & Nachbar, 1996). The proteins (viral spike and human ACE2) were prepared using AutoDock tools (ADT) (Morris et al., 2009). The zinc ions, unrelated complexes and waters were removed from the protein and polar hydrogens were added. Kollman United Atom charges were assigned for the protein and Gasteiger charges for the ligands.

**Molecular docking**

The ligands were prepared for docking using ADT. The backbone and amide bonds were rendered flexibility by allowing them to be rotatable. The prepared protein and ligand structures were saved as PDBQT file format. The flexible ligand docking was performed using AutoDock Vina (Trott & Olson, 2009). The grid was generated at RBD near the C terminal domain (CTD1) of the S1 subunit. After grid generation, the different conformations of the compounds were docked one by one to generate the best five docking score poses; the exhaustiveness parameter was set to 10, to increase the probability of finding the minimum binding affinity pose.

**Protein–ligand interactions**

The active residues of protein interactions with the top 190 docking score ligands were analyzed using LigPlot+ (Laskowski & Swindells, 2011). The 2D and 3D ligand-protein interaction diagrams were generated using the ligand interaction diagram script as implemented in Maestro and the desktop PyMOL 2.4, respectively (DeLano, 2002; Maestro, 2020).

**MD simulations**

MD simulations were performed using the nanoscale molecular dynamics (NAMD) package (Phillips et al., 2005) and the CHARMM36 force field (Best et al., 2012; Klauda et al., 2010). The system was solvated using the TIP3P water model (Mark & Nilsson, 2001) and neutralized by a 0.15 molar concentration of NaCl to mimic the physiological conditions. The energy minimization was performed for 1 ns. The system was then subjected to annealing and equilibration for 10 ns followed by a production run of 100 ns at 300 K using the Langevin thermostat (Grest & Kremer, 1986) with a damping frequency of 1 ps⁻¹. The isothermal-isobaric (NPT) ensemble was used for all MD simulations. The pressure was maintained at 1 atm using the Nose–Hoover barostat (Martyna et al., 1994). Long-range interactions were treated using the particle-mesh Ewald (PME) method (Darden et al., 1993) with a grid spacing of 1.0 Å. For all simulations, a 12.0 Å cutoff distance for the Coulomb and van der Waals interactions was set, and a 10.0 Å cutoff was set for a switching function. The equations of motion were integrated using the rRESPA algorithm.
multiple time-step schemes (Tuckerman et al., 1992) to update short-range interactions for every step and long-range electrostatic interactions for every two steps. The time step of integration was chosen to be 2 fs. The root-mean-square deviation (RMSD) of all heavy atoms with respect to the initial frame was analyzed to determine the stability of the complex over time. In addition, the average deviation of the protein residues were analyzed by the root-mean-square fluctuations (RMSF) over the simulation time.

The relative binding energies

The binding affinity between the ligand and protein can be determined by the binding energy, \( \Delta G_{\text{bind}} \). To estimate the relative binding energies, the molecular mechanics generalized Born surface areas (MMGBSA) were calculated from the MD trajectories using one trajectory scheme, \( \Delta G_{\text{MMGBSA}} \) (Genheden & Ryde, 2015),

\[
\Delta G_{\text{MMGBSA}} = \langle G_{ PL} \rangle - \langle G_{ P} \rangle - G_{L}
\]  

Figure 4. RMSD analysis for a) bagrosin, b) chidamide, c) ebastine, d) indacaterol, e) regorafenib, f) salazosulfadimidine, g) silodosin and h) tasosartan. The light green represents the ligand, blue color represents ACE2, and red color represents the SARS-CoV-2 Spike RBD.
where, $G_{PL}$, $G_P$ and $G_L$ are the Gibbs energies of the protein—ligand complex ($G_{PL}$), protein ($G_P$) and ligand ($G_L$), respectively. The $G$ values can be estimated as below,

$$G = E_{bond} + E_{elec} + E_{vdW} + G_{polar} + G_{nonpolar} - TS$$

The $E_{bond}$, $E_{elec}$ and $E_{vdW}$ are standard molecular mechanics (MM) energy terms of bonded, electrostatic and van der Waals interactions. $E_{bond}$ is canceled in the case of one trajectory scheme. $G_{polar}$ is the polar contributions obtained by

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**Table 3.** The relative MMGBSA binding energies (kJ/mol).

| Ligand          | MMGBSA    |
|-----------------|-----------|
| Silodosin       | -171.42   |
| Ebastine        | -132.72   |
| Salazosulfadimidine | -106.40   |
| Indacaterol     | -102.63   |
| Chidamide       | -96.61    |
| Regorafenib     | -95.06    |
| Tasosartan      | -86.73    |
| Bagrosin        | -53.93    |
using the generalized Born (GB) model. $G_{\text{nonpolar}}$ is the non-polar contributions obtained from the linear relation with the solvent accessible surface area (SASA) using the NAMD package (Phillips et al., 2005).

$$G_{\text{nonpolar}} = \text{Surface Tension} \cdot \text{Surface Area}$$  \hspace{1cm} (3)

In the last term of Equation (2), T is the temperature, and S is the entropy of the system, which is computed by a normal mode analysis. This term is not computed because we are interested in the relative binding energies and also due to the large computational cost (Sun et al., 2018).

To compute the MMGBSA, 5000 frames of 100 ns MD simulations were evenly extracted from MD trajectories. These trajectories were converted to three subsets of protein–ligand, protein and ligand by removing the water, ions and unnecessary atoms. The generalized Born implicit solvent mode was applied and the SASA was turned on. A solvent dielectric constant of 78.5 was used. The surface tension was assigned to 0.021 kJ/mol/Å, and the alpha-cutoff parameter was set to 11. The $\Delta G_{\text{MMGBSA}}$ values were calculated by taking the averages over the simulations.

Figure 6. Ligand interaction 2D (left) and 3D (right) maps of the top three compounds based on the relative binding energies: a) silodosin b) ebastine and c) salazosulfadimidine obtained using the last frame of 100 ns MD simulations.
**Steered molecular dynamics**

The constant velocity steered molecular dynamics (SMD) (Izrailev et al., 1999) approach was used to compare the interaction of the S protein with ACE2 in presence and lack of ligand and also to give an overview of the interaction between the ligand and the SARS-CoV-2 S protein and between the ligand and ACE2. The protein and the ligand were prepared as described above in the MD simulations section. The system was then solvated using the TIP3P water model with a 15 Å buffer around the protein and then extended to 50 Å in the direction of pulling axis. The system was then neutralized with NaCl. The system was minimized, subjected to annealing, equilibration and then MD simulations for 10 ns. The α carbon atoms of residues HSE519, THR333, ASN360, CYS525, LYS386 and LEU517 are positionally restrained to prevent the SARS-CoV-2 S protein from pulling under the applied force. The restrained force constant is 347.4 pN/Å in only the pulling axis direction. The SMD force

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**Figure 7.** Contact surface area (Å²) for a) bagrosin, b) chidamide, c) ebastine, d) indacaterol, e) regorafenib, f) salazosulfadimidine, g) silodosin and h) tasosartan with ACE2 and SARS-Cov-2 spike RBD. The blue represents the contact area with ACE2, and red color represents the contact area with SARS-Cov-2 spike RBD.
constant of the virtual spring between the dummy atom and the center of mass for all $a$ carbon atoms of ACE2 was 486.4 pN/Å. The pulling was performed at a velocity of 0.005 Å/ps. The SMD simulations were carried out for 10 ns.

**Results and discussion**

All the compounds from the aforementioned drugbanks were prepared for docking. The compounds were docked one by one into the RBD of the SARS-CoV-2 S protein. The ADME properties of the compounds with the top 200 docking scores were estimated utilizing molinspiration webserver (Molinspiration Cheminformatics, 2020). Although all compounds taken from drugbanks have moderate ADME properties, we have chosen the top eleven compounds with zero Lipinski violations (except for ebastine, which has one violation) in our further studies. The top-rank drugs are silodosin, ebastine, salazosulfadimidine, indacaterol, chidamide, regorafenib, tasosartan, bagrosin, lumacaftor, risperidone and sitagliptin. Results of docking scores and some of their ADME properties are collected in Table 1.

A detailed list of the interactions for the top eleven ligands with both the ACE2 residues and the viral spike RBD are shown in Table 2.

Supporting information Figure S1 shows the best docking score poses and their respective ligand interaction 2D maps for some of the compounds with the top docking scores. Although these compounds interact efficiently with S protein RBD and ACE2 residues within 3.9 Å; they would still leave

![Figure 7](image-url)
some interface of S protein and ACE2 open to interact. Figure 3 shows compounds (out of the top 190 docked compounds) interacting with the active site residues of the 6LZG protein within 3.9 Å.

As shown in Figure 3, His34, Glu37, Asp38 and Glu35 residues of ACE2 and Arg403, Tyr453, Ser494 and Tyr495 residues of the S protein RBD are the residues with the most interactions and hold the compound in between the two proteins disrupting the viral spike-host interactions.

Classical MD simulations were performed for the protein with and without the eleven filtered drugs to understand the stability of the complex over time and its dynamical behavior. Undoubtedly, the RMSD results of bagrosin, chidamide, ebastine, indacaterol, regorafenib, salazosulfadimidine, silodosin and tasosartan indicate the positional stability of these compounds during the simulations (see Figure 4).

In contrast, the RMSD results for lumacaftor, risperidone and sitagliptin indicate that these three drugs are not positionally stable between the S protein and ACE2 since they moved away from their initial positions; the RMSD for sitagliptin, risperidone and lumacaftor are provided in the supporting information (supporting information Figure S2). The RMSF for these compounds were computed with respect to the α carbon atom of each protein residue to study the local structural stability and flexibility of the protein. As given in Figure 5, the RMSF plots show that the protein residues are stable in the presence of these drugs and the overall structure of the viral protein and host ACE2 is maintained with the drug obstructing their interactions.

The relative MMGBSA binding energies were computed for the stable compounds from the MD simulations, and the results are given in Table 3. Silodosin shows the best relative binding energy while bagrosin depicts the worst relative binding energy.

Figure 6 shows 2D and 3D interactions of the three compounds with the best relative binding energy (i.e. silodosin, ebastine and salazosulfadimidine) with both ACE2 and SARS-CoV-2 S obtained using the last frame of the MD simulations. Supporting information Figure S4 depicts polar histograms for some of orientation torsion angles for silodosin, ebastine and salazosulfadimidine during the MD simulations.

To investigate the non-covalent interactions between the top eight compounds with both ACE2 and SARS-CoV-2 S, the contact areas were computed based on the surface area of the hits exposed to both ACE2 and SARS-CoV-2 S during the MD simulations. Figure 7 depicts the time evolution of contact areas of these compounds with ACE2 and SARS-CoV-2 S. Table 4 summarizes the average contact areas and represents the best three contact residues and the average contact area coming from the residue of both ACE2 and SARS-CoV-2 spike with the top eight compounds during the MD simulations.

As shown in Figure 7 and Table 4, the average contact areas for bagrosin, chidamide, ebastine, regorafenib, silodosin and tasosartan with SARS-CoV-2 S are larger than the average contact areas with ACE2, which shows that the non-covalent interactions for these compounds are mainly with SARS-CoV-2 spike. Table 4 illustrates that most of the compounds share

| Molecule               | Interaction with ACE2 | Interaction with SARS-CoV-2 spike |
|------------------------|-----------------------|----------------------------------|
|                        | Average area (Å²)     | Residue (f)                      | Average area (Å²)     | Residue (f)                      |
| Bagrosin               | 157.73                | HSE34 (51.43), PRO389 (29.37),   | 170.26                | ARG403 (39.62), TYR505 (23.91),  |
|                        |                       | GLU37 (27.99)                    |                       | GLU406 (16.90)                   |
| Chidamide             | 240.81                | HSE34 (74.46), LY535 (36.16),    | 317.48                | TYR505 (38.65), ARG403 (29.69),  |
|                        |                       | ASP38 (32.94)                    |                       | GLN493 (22.50)                   |
| Ebastine               | 214.10                | LYS33 (49.94), HSE34 (44.54),    | 363.57                | TYR505 (61.99), ARG403 (41.07),  |
|                        |                       | ASP38 (30.96)                    |                       | TYR449 (39.31)                   |
| Indacaterol            | 310.42                | HSE34 (48.33), ASP38 (47.47),    | 287.00                | TYR505 (59.21), TYR449 (47.15),  |
|                        |                       | GLU35 (34.42)                    |                       | ARG403 (36.54)                   |
| Regorafenib            | 171.05                | HSE34 (58.86), ASP38 (47.15),    | 287.95                | SER494 (41.91), TYR505 (29.32),  |
|                        |                       | LYS353 (33.46)                   |                       | GLN493 (28.86)                   |
| Salazosulfadimidine    | 244.63                | LYS353 (71.23), HSE34 (42.39),   | 226.13                | TYR505 (45.09), TYR505 (29.70),  |
|                        |                       | ASP38 (38.94)                    |                       | GLN493 (22.16)                   |
| Silodosin              | 312.42                | HSE34 (79.42), GLU33 (60.51),    | 421.91                | TYR505 (50.09), ARG403 (33.40),  |
|                        |                       | ASP38 (35.35)                    |                       | SER494 (33.28)                   |
| Tasosartan             | 185.79                | ALA387 (54.72), HSE34 (45.51),   | 222.36                | TYR505 (56.31), ARG403 (39.98),  |
|                        |                       | PRO389 (33.67)                   |                       | GLU406 (21.23)                   |

* f is the average contact area coming from the residue. Only the best three contact residues are reported.
the same contact residues; HSE34, PRO389, ASP38, LYS353, GLU37, GLU35, and ALA387 of ACE2, and ARG403, TYR505, GLU406, GLN493, TYR449, and SER494 of SARS-CoV-2 spike.

In addition, hydrogen bond interactions of the top eight filtered compounds with ACE2 and SARS-Cov-2 spike RBD were also analyzed during the 100 ns NPT ensemble. An analysis of the hydrogen bonds interaction of the top 8 compounds revealed that silodosin had the highest number of hydrogen bonds during the MD simulations. Silodosin formed hydrogen bonds mainly with GLU37, ARG393, SER494 and GLN493 with 51%, 31%, 27% and 18% occupancy, respectively. It should be mentioned that not all the top ligands formed a high occupancy of hydrogen bonds on S1-RBD interface during the simulation. For instance, indacaterol formed hydrogen bonds with LI41 with 15.2% occupancy and chidamide formed hydrogen bonds with LI31 and GLY496 with 9.1% and 4.0% occupancy, respectively. The ligands that do not form many hydrogen-bonds, the main force holding them may be due to the electrostatic interactions with ionized residues.

We performed constant velocity SMD simulations to study the extent of the interactions between silodosin and SARS-CoV-2 S protein and between silodosin and the ACE2. SMD forces were applied on the center of mass of the α carbon atoms of ACE2, no constraints were applied on the silodosin, and positional restraint was used only in the pulling axis direction on six α carbon atoms at the end of SARS-CoV-2 S protein. Similarly, we performed another constant velocity SMD simulation for the protein in absence of the ligand. The SMD results are given in Figure 8. The force vs. time for the SMD simulations is given in Figure 8a. The position of the center of mass of ACE2 during the SMD simulations is shown in Figure 8b. Snapshots of SMD simulations are given in Figure 8c. Interestingly, the study shows that the drug silodosin preferentially remains interacting with the SARS-CoV-2 S protein as opposed to ACE2. Figure 8a shows that the...
force needed for breaking the RBD S₁-ACE2 interface is lower in the presence of silodosin. Silodosin has a large binding energy with many hydrogen bonds interactions, a high positional stability during the MD simulation, and the lower force in SMD analysis suggests silodosin to be a promising candidate for the inhibition of SARS-CoV-2.

Conclusions

While writing this manuscript, several repurposing studies that target the S subunit of spike or ACE2 were published (Calligari et al., 2020; Cavasotto & Di Filippo, 2020; CelIK et al., 2020; Krishnasamy et al., 2020; Senathilake et al., 2020; Trezza et al., 2020); herein, we are targeting the RBD S₁-ACE2 interface. The structure-based docking screening, MD and SMD simulations, and binding energy calculations were conducted on the viral RBD S₁-ACE2 as a drug target. From our results, the known drugs, bagroisn, chidamide, ebastine, indacaterol, regorafenib, salazosulfadimidine, silodosin and tasosartan are shown to be potential candidates for interrupting the viral RBD S₁-ACE2 interface. Among these drugs, silodosin shows the best binding energy and has the greatest number of hydrogen bonding interactions during the MD simulation. The relative binding energy, the positional stability and hydrogen bond interactions between the silodosin and spike on S1-RBD interface, altogether, are suggested as a possible mechanism of action. Silodosin may therefore successfully disrupt the viral spike and host ACE2 interactions.

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Author contributions

I.E.A.: conceptualization, performing the computations, analysis, investigation, writing – original draft; A.A.A.: presenting ideas, review and editing; S.S.: preparing Figures 1 and 2; A.Y.: conceptualization, writing and supervision; R.A.P.: conceptualization, review and editing, supervision, project administration and funding acquisition.

Disclosure statement

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