

Proceeding Paper

De Novo Drug Design of Potential Inhibitors of the Receptor-Binding Domain of SARS-CoV-2 Variants [†]

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Abstract: In this study, novel potential inhibitors of SARS-CoV-2 variants were designed de novo using generative neural networks. The top-performing ligand based on docking performance and ADMET profiles was CID #526. It forms several hydrogen bonds with wild-type SARS-CoV-2, indicating its potential as an inhibitor of the receptor-binding domain. Mutated variants of the RBD also showed good interactions with CID #526, implying the inhibitory properties of our top-performing compound against various variants. Molecular dynamics analysis showed a stable ligand–RBD complex. CID #526 can easily be synthesized using low-cost starting molecules. Overall, the generated ligands merit further investigation to determine their efficacy and safety as a treatment for COVID-19.

Keywords: SARS-CoV-2; COVID-19; de novo drug design; molecular dynamics

1. Introduction

COVID-19, a disease caused by the coronavirus SARS-CoV-2 [1], is still being spread by millions of people across all nations well over two years after it was first reported in Wuhan, China. Several vaccines, such as those developed by Pfizer/BioNTech [2] and Moderna [3], among others, have already been deployed after showing promising efficacy rates in their clinical trials. However, the rise of new variants of SARS-CoV-2 could threaten the efficacy of the current vaccines, which have been developed from the parent variant [4,5].

A viral isolate is named a variant of concern (VOC) if there is sufficient evidence that the emerging variant presents increased transmissibility or causes increased disease severity or the reduction in efficacy / failure of existing diagnostics, treatments, and vaccines. The first VOC identified was the B.1.1.7 lineage, which was first reported in the United Kingdom. It contains the N501Y, A570D, D614G, and P681H mutations and 69/70/144 deletions in the spike protein. These mutations caused a significant surge in COVID-19 cases in the UK and then in the EU in the last quarter of 2021 and the early months of 2021 owing to the replicative advantage acquired by the new variant [6,7].

Meanwhile, the B.1.351 lineage, which was first reported in Nelson Mandela Bay, South Africa, also involves multiple mutations in its spike protein, including K417N, E484K, N501Y, and D614G, resulting in increased transmissibility and evasion of immunity [8,9]. The P.1 lineage also contains several mutations in its spike protein, namely, K417T, E484K, N501Y, and D614G. This variant was first reported by the National Institute of Infectious Diseases (NIID) in Japan in isolates obtained from Brazilian travelers. These mutations have been shown to be able to potentially evade immunity and present increased transmissibility compared to the wild-type coronavirus [10,11].

Several other mutations in the SARS-CoV-2 spike protein have been recorded from genomic analyses of isolates conducted worldwide. The top substitutions in the SARS-CoV-2



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spike protein are N501Y, E484K, L452R, S477N, N439K, T478K, K417N, S464P, N501T, are A520S [12]. E484K is thought to be associated with an increased probability of evading the immune response, while the N501Y and D614G mutations have been shown to be associated with increased transmissibility [13,14]. Together with the slow pace of immunization programs and vaccine inequality, these variants could further evolve the virus, which could hamper our collective progress in COVID-19 management. As such, it remains imperative that further research be conducted in order to develop other vaccines and therapeutics against COVID-19. However, drug development for COVID-19 has been side-tracked due to the disappointing results of the solidarity trials conducted by the World Health Organization (WHO) [15].

Inhibiting the critical proteins involved in the viral life cycle of SARS-CoV-2 is the primary strategy currently used for developing new drugs against COVID-19. Viral entry can be prevented by inhibiting the spike protein or through ACE2 modulation, such as ACE2 inhibition and RAAS inhibition. The main protease and the papain-like protease, which are responsible for the cleavage of polyproteins translated from viral RNA into functional or effector proteins for virus replication and packaging within host cells, could also be drug targets for blocking viral replication. Inhibiting the RNA-dependent RNA polymerase, which assists in the translation and replication of the virus, could interfere with the replication, transcription, and translation of viral genomic material, leading to the termination of viral reproduction. Other drug targets include envelope proteins, membrane proteins, and nucleoproteins [16–18].

Several reviews have summarized the use of potential drugs against COVID-19 [19–23]. Nevertheless, despite the influx of studies on drug therapies against COVID-19, only a few have gained the approval of the U.S. Food and Drug Administration under their Emergency Use Authorization (EUA). These include using remdesivir, bamlanivimab, and andasirivimab/imdevimab for managing severe COVID-19 cases [24]. The WHO has only approved remdesivir as a treatment for patients requiring hospitalization. Despite their limited numbers, these drugs represent considerable progress in drug development, considering the long pipeline involved in drug discovery up to the approval process by local and international regulators.

Computational approaches can be used to perform high-throughput screening of drug libraries and small-molecule databases for candidate drugs against their affinities with the target binding site. This strategy is called structure-based drug design. This is, however, limited by the quality of the database used [25,26]. Another approach is to design drug-like molecules *de novo* following a fragment-based design concept (ligand-based design). This approach uses the structural information of the biological target as a design guide, which offers the advantage of allowing for an ample chemical space of virtual structures to be explored without the actual synthesis of such a large number of compounds. However, this also presents a challenge with respect to how to handle the infinitely large number of theoretically possible topologies and the variety of conformations for a single topology [27,28]. This requires efficient optimization algorithms and high-quality QSAR descriptors in order to navigate the chemical search space [27,29]. For both *in silico* strategies, the feasibility of the candidate drugs to be synthesized further slows the drug discovery process.

In this study, novel drug molecules were designed that target the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, which is known to be involved in the viral attachment to its host cell. *De novo* design was used, targeting the original variant, the B.1.1.7 variant, the B.1.351 variant, and the B.1.427 variants of SARS-CoV-2. These drug-like molecules can inhibit viral replication, rendering them potential new therapies for COVID-19.

2. Computational Details

2.1. Target Preparation

The high-resolution crystal structure of the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein (PDB 6MOJ) [30] was obtained from the Protein Data Bank. Its structure was mutated with the corresponding amino acid substitutions for each SARS-CoV-2 variant. All four structures were then pre-processed to determine their minimum-energy configuration, which was used in subsequent docking calculations. Specifically, missing hydrogens were added, correct bond orders were checked and assigned, correct protonation states were predicted, and hydrogen bonds were optimized through systematic and cluster-based approaches. Restrained minimization was also applied to relax bonds, angles, and overlaps within each structure.

2.2. De Novo Drug Design Using Generative Neural Networks

De novo drug design was also employed, using the LIGANN web server to generate a library of drug-like molecules that target the RBD of each SARS-CoV-2 variant through generative neural networks. In particular, a generative adversarial network was used to produce complementary ligand shapes in a multimodal fashion. Then, a shape-captioning network decoded the ligand shapes into SMILES strings [31], which were then converted to a structure file using Open Babel v. 3.1.1 [32]. Next, the chemical library generated for each SARS-CoV-2 variant was combined to produce the main library. This main library, consisting of 2334 molecules, was then docked against the RBD of each SARS-CoV-2 variant using the same docking protocol described above as implemented in the LEA3D web server. Finally, the docking scores of the drug molecules against each SARS-CoV-2 variant were averaged and then ranked to determine the best-performing drugs that could inhibit all four variants.

2.3. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Study

The ADMET profiles of all the best-performing drug candidates against the RBD of SARS-CoV-2 were analyzed using the ADMETlab 2.0 platform. ADMETlab 2.0 is based on 53 predictive models from a comprehensively collected database of 288,867 molecules. The library of input molecules is fed into a Multi-task Graph Attention (MGA) framework to generate the ADMET profiles of each entry based on the trained regression models [33]. In this study, only those that passed the following criteria were deemed promising candidate molecules: good human intestinal absorption ($p < 0.7$), low probability of passing through the blood-brain barrier ($p < 0.7$), good drug clearance ($CL \geq 5$), low hERG toxicity ($p < 0.3$), low hepatotoxicity ($p < 0.3$), low drug-induced liver damage probability ($p < 0.3$), low mutagenicity ($p < 0.3$), low acute toxicity ($p < 0.3$), and low carcinogenicity ($p < 0.3$).

2.4. Molecular Dynamics

Ligand-protein interactional binding modes and the nature of the dynamical unbinding process were determined by carrying out molecular dynamics calculations on the top-performing ligand obtained via de novo drug design. The calculations were implemented using the Ligand and Receptor Molecular Dynamics (LARMD) webserver [34] for each protein-ligand complex structure. The antechamber module and the Tleap module of the AMBER16 program [35] were used to assign bcc charges for the ligand atoms and construct the complexes' coordinate and topology files. The AMBER ff14SB force field [36] and gaff force field [37,38] were used for amino acid residues and ligands. The structures were solvated using an octahedral box of TIP3P water [39] extended at least 10 Å in each direction from the solute [40]. Na⁺ and/or Cl⁻ ions were added to the system as counter ions. Four-step minimization of the system was achieved using the Sander module in AMBER16. The 2000-steps steepest descent method and the 3000-steps conjugated gradient method were used for each minimization step. The system was then heated from 10 to 300 K in 30 ps using an NVT ensemble, which was followed by a dynamics run at 300 K and 1 atm for 4 ns. All dynamics runs were performed using the Pmemd module of AMBER16.

The MD trajectories were then analyzed using the Cpptraj module of AMBER16. MDTraj was used to calculate nonnative contact [41], and Bio3d was utilized to analyze PCA and residue cross-correlation [42] as implemented in the LARMD server.

3. Results and Discussion

3.1. Structure and Mutations in the Receptor-Binding Domain

The minimized structure of the receptor-binding domain (RBD) of the original wild-type SARS-CoV-2 is shown in Figure S1. Structurally, the RBD consists of 195 amino acid residues. Accordingly, single-amino-acid substitutions in the RBD of SARS-CoV-2 (N501, Q498, E484, T470, L452, and N439) against SARS-CoV-1 resulted in the loss of favorable interactions with hACE2. Meanwhile, five RBD substitutions (P499, Q493, F486, A475, and L455) led to enhanced SARS-CoV-2 RBD-hACE2 binding activity [43]. In our subsequent docking experiments, these amino acid residues were used to define the binding site region. Interestingly, these mutations are involved in the new SARS-CoV-2 variants discovered. The N501Y mutation is present in the B.1.1.7, B.1.351, and P.1 variants. This mutation is associated with increased transmissibility of the new VOCs. Furthermore, the E484K mutation is present in the B.1.351 and P.1 variants. The E484K mutation is associated with the increased ability of said VOCs to evade innate and acquired immunity. So far, only the B.1.351 variant contains the K417N mutation in its RBD.

3.2. De Novo Drug Design

A chemical library of potential inhibitors of the RBD of SARS-CoV-2 was generated de novo using generative neural networks. This technique is more robust than other de novo drug design techniques since it captures the structure of the binding site and then populates a library of complementary ligand shapes in a multimodal fashion. We used 50 ligand shape generations and 20 decoding processes per shape to generate 539 molecules based on the wild-type, 631 molecules based on the B.1.1.7 variant, 615 molecules using the B.1.351 variant, and 572 molecules using the P.1 variant. We combined these molecules into a single chemical library of 2357 ligands and then docked them against each COVID-19 variant. The average docking scores for each ligand were calculated and then ranked to determine the best-performing ligands that can inhibit all four variants of SARS-CoV-2. The top-performing ligands based on the averaged docking scores are shown in Figures S1 and S2.

Among the generated top-performing ligands, CID #526 or [3-(4-ethylpiperazin-1-yl)propyl](1-{3-[3-(morpholin-4-yl)propyl]-1,2,4-oxadiazol-5-yl}-4-phenylbutyl)amine, has the best ADMET profile compared to the others; hence, we further investigated this molecule. CID #526 complies with all the parameters set by Lipinski's Rule of Five. Moreover, it has good human intestinal absorption, good MDCK permeability ($\log P_{app} = 8.02 \times 10^{-6}$), a low degree of plasma protein binding (53.56%), desirable volume distribution (1.069 L/kg), and high clearance (7.05 mL/min/kg) and does not inhibit the Cytochrome 450 metabolic pathway. It also presents low cardiotoxicity ($p = 0.399$), hepatotoxicity ($p = 0.565$), Ames mutagenicity ($p = 0.037$), and carcinogenicity (0.067).

Two hydrogen bonds with Gly 496, one with the amine group and one with the oxygen atom of the five-membered heterocycle of CID #526, are formed with the wild-type SARS-CoV-2. It also forms a hydrogen bond with Ser 494 and engages in a π - π interaction with Tyr 505 of the wild-type SARS-CoV-2. Only the hydrogen bond with the oxygen atom is conserved in the B.1.1.7 variant. CID #596 interacts differently with the B.1.351 variant. It forms a hydrogen bond with the nitrogen atom in the five-membered heterocycle and interacts with Phe 490 via π - π interactions. Only the π - π interaction is conserved in the P.1 variant, but it forms two different hydrogen bonds: one each for Gln 493 and Ser 494, respectively.

3.3. Molecular Dynamics Analysis

A molecular dynamics simulation was performed in relation to the docked protein-ligand structure to further elucidate the inhibitory effect of CID #526 against the four variants of

SARS-CoV-2 investigated in this study. The results are shown in the Supplementary Materials. Strong binding energy was calculated for each variant, showing the good inhibitory property of CID #526. It performs the best with respect to the wild SARS-CoV-2, as evidenced by the lowest binding energy detected in that regard, indicating the most stable ligand–protein complex. Meanwhile, it performs worst against the B.1.1.7 variant, which has the highest binding energy.

We also performed principal component analysis and dynamic cross-correlation analysis to evaluate the inhibitory effect of CID #526 against the SARS-CoV-2 RBD based on the MD trajectory. As the top three principal components are sufficient for determining 50% of the total variance in a given family of structures, only the top three principal components were analyzed [34]. The stability of the docked CID #526 was confirmed based on our results, thus confirming our hypothesis that CID #526 could be an inhibitor of SARS-CoV-2's receptor-binding domain.

4. Conclusions

De novo drug design using generative neural networks was performed to generate a library of possible inhibitors of each variant of SARS-CoV-2. These ligands were docked against the receptor-binding domains of SARS-CoV-2 variants and were ranked according to the average values of their docking scores. The ADMET profiles of the top-performing ligands were evaluated. Among these compounds, CID #526 emerged as the top candidate, presenting excellent docking performance against all four variants and a good ADMET profile. It forms several hydrogen bonds and interacts with the RBD via π – π interactions. Molecular dynamics analysis revealed the stability of the docked compound in the RBD of SARS-CoV-2, presenting comparable binding energies against all four variants. The organic retrosynthesis study showed that CID #526 could be synthesized using five major reaction steps. Further studies are needed to ascertain these compounds' efficacy, safety, and tolerability for the treatment of COVID-19.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ECB2023-14371/s1>, Figure S1: Structure of the receptor-binding domain of wild-type SARS-CoV-2 (RBD-W); Figure S2: Structures of top-performing de novo generated drug-like molecule (Compound ID 526) docked in the RBD of SARS-CoV-2 and their corresponding ligand interaction diagrams; Figure S3: Top-performing (1–15) drug-like molecules with respect to inhibiting the RBD of SARS-CoV-2 variants; Figure S4: Top-performing (16–30) drug-like molecules with respect to inhibiting the RBD of SARS-CoV-2 variants; Table S1: Comparison of the performance of top-performing de novo designed drugs in terms of their role as potential inhibitors of the RBD of SARS-CoV-2 variants; Table S2: ADMET physicochemical properties of top-performing de novo designed drugs in terms of their role as potential inhibitors of the RBD of SARS-CoV-2 variants; Table S3: ADMET absorption, distribution, and excretion properties of top-performing de novo designed drugs in terms of their role as potential inhibitors of the RBD of SARS-CoV-2 variants; Table S4: ADMET metabolism and toxicity properties of top-performing de novo designed drugs in terms of their role as potential inhibitors of the RBD of SARS-CoV-2 variants; Table S5: ADMET toxicity and drug-likeness properties of top-performing de novo designed drugs in terms of their role as potential inhibitors of the RBD of SARS-CoV-2 variants; Figure S5: RMSD profiles of docked CID #526 designed using generative neural networks of the RBD, RMSD histogram of the ligand, and RMSD histogram of the receptor for (a–c) wild-type, (d–f) B.1.1.7 variant, (g–i) B.135 variant, and (j–l) P.1 variant of SARS-CoV-2; Figure S6: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of wild-type SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S7: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the unbinding of CID #526 to the RBD of wild-type SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S8: Dynamical residue cross-correlation map for the MD trajectory

of the (a) binding process and (b) unbinding process of the receptor–ligand complex involving CID #526 docked in the RBD of wild-type SARS-CoV-2. PCA results regarding trajectory with trajectory frames colored from blue to white to red, which corresponds to their order with respect to time; Figure S9: Residue-wise loading for (a) PC1, (b) PC2, and (c) PC3 of the binding process of the receptor–ligand complex involving CID #526 docked in the RBD of wild-type SARS-CoV-2. Residue-wise loading for (d) PC1, (e) PC2, and (f) PC3 of the unbinding process of the receptor–ligand complex involving CID #526 docked in wild-type SARS-CoV-2; Figure S10: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of the B.1.1.7 variant of SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S11: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of the B.1.1.7 variant of SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S12: Dynamical residue cross-correlation map for the MD trajectory of the (a) binding process and (b) unbinding process of the receptor–ligand complex involving CID #526 docked in the RBD of the B.1.1.7 variant of SARS-CoV-2. PCA results for trajectory with trajectory frames colored from blue to white to red, which corresponds to their order with respect to time; Figure S13: Residue-wise loading for (a) PC1, (b) PC2, and (c) PC3 of the binding process of the receptor–ligand complex involving CID #526 docked in the RBD of the B.1.1.7 variant of SARS-CoV-2. Residue-wise loading for (d) PC1, (e) PC2, and (f) PC3 of the unbinding process of the receptor–ligand complex involving CID #526 docked in the B.1.1.7 variant of SARS-CoV-2; Figure S14: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of the B.1.351 variant of SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S15: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of the B.1.351 variant of SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S16: Dynamical residue cross-correlation map for the MD trajectory of the (a) binding process and (b) unbinding process of the receptor–ligand complex involving CID #526 docked in the RBD of the B.1.351 variant of SARS-CoV-2. PCA results for trajectory with trajectory frames colored from blue to white to red, which corresponds to their order with respect to time; Figure S17: Residue-wise loading for (a) PC1, (b) PC2, and (c) PC3 of the binding process of the receptor–ligand complex involving CID #526 docked in the RBD of the B.1.351 variant of SARS-CoV-2. Residue-wise loading for (d) PC1, (e) PC2, and (f) PC3 of the unbinding process of the receptor–ligand complex involving CID #526 docked in the B.1.351 variant of SARS-CoV-2; Figure S18: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of P.1 variant of SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S19: (a) Principal Component Analysis (PCA) concerning the MD trajectory of the binding of CID #526 to the RBD of P.1 variant of SARS-CoV-2. The trajectory frames are colored from blue to white to red, which corresponds to their order with respect to time. (b) Simple clustering in PC subspace. The conformations were divided into two clusters (black and red) according to the top three PC spaces shown in the PC subspace; Figure S20: Dynamical residue cross-correlation map for the MD trajectory of the (a) binding process and (b) unbinding process of the receptor–ligand complex involving CID #526 docked in the RBD of P.1 variant SARS CoV-2. PCA results for trajectory with trajectory frames colored from blue to white to red, which corresponds to their order with respect to time; Figure S21: Residue-wise loading for (a) PC1, (b) PC2, and (c) PC3 of the binding process of the receptor–ligand complex involving CID #526 docked in the RBD of P.1 variant of SARS-CoV-2. Residue-wise loading for (d) PC1, (e) PC2, and (f) PC3 of the unbinding process of the receptor–ligand complex involving CID #526 docked in P.1 variant of SARS-CoV-2; Table S6. Binding Energy of CID #526 against various variants of SARS-CoV-2.

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