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Structure-based Screening of Potential Drugs against SARS-CoV-2 Variants †

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Abstract: SARS-CoV-2 caused the ongoing COVID-19 pandemic, and only a few treatment options are available to mitigate its impact on human health. Hence, there is a need to discover drugs that could be used to treat COVID-19. Several studies have already reported the repurposing of existing drugs to inhibit the receptor-binding domain of SARS-CoV-2. However, the emergence of COVID-19 variants may render current drug candidates ineffective. Here, we report the structure-based drug screening of the DrugBank database against the wild-type, B.1.1.7, B.1.351, and P.1 variants of SARS-CoV-2. Our study revealed that Salmeterol, Abediterol, and Lysophosphatidylglycerol are among the top candidates against all four variants. Furthermore, we showed that Salmeterol forms a stable complex with the receptor binding domain of SARS-CoV-2 variants. Further studies are needed to evaluate the clinical relevance of the drug candidates discovered. Nevertheless, this study provides insight into computational drug design that works against multiple variants of SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; structure-based drug design; drug repurposing; molecular dynamics

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1. Introduction

Since the declaration of a global pandemic by the World Health Organization (WHO) [1], COVID-19 has caused an unprecedented disruption in our daily lives, claiming millions of lives due to complications. While vaccination efforts have successfully prevented COVID-19 in real-world conditions [2], it still causes mild to moderate symptoms when infected by the virus during breakthrough infections [3]. To date, only Molnupiravir [4] and the combination drugs Nirmatrelvir/Ritonavir (Paxlovid) [5] have been granted emergency use authorization for COVID-19 treatment by the Philippine Food and Drugs Authority. However, while generally safe, these drugs are still not widely accessible due to supply chain limitations. Thus, there remains a need to discover drugs that could potentially treat COVID-19 infection.

Several strategies may be done to discover new pharmaceutical compounds. Structure-based drug design uses a database of potential drugs to discover lead compounds based on their docking score [6]. Since it is based on a database of known molecules, drug discovery using this method heavily relies on the database's quality. Meanwhile, *de novo* drug design relies on the shape of the binding site to map out the chemical space for possible drug candidates using deep generative models [7]. While it can generate excellent ligands, it sometimes has the disadvantage of producing difficult-to-synthesize drug-like molecules.

While several studies have already been done in the search for inhibitors of SARS-CoV-2 [8–12], these studies only used the wild-type SARS-CoV-2 variant for drug

screening. It is well-known that SARS-CoV-2 has mutated into several variants, such as the B.1.1.7, B.1.351, and P.1 variants, which were shown to evade immunity [13–16] and caused spikes in COVID-19 cases. To have a "universal drug" that could be used for COVID-19 treatment regardless of the variant involved, we performed a computational structure-based drug design against the receptor binding domain (RBD) of SARS-CoV-2.

2. Computational Details

2.1. Target Preparation

The Protein Data Bank provided the high-resolution crystal structure of the receptor-binding domain (RBD) of SARS-CoV-2 spike protein (PDB 6MOJ) [17]. Its structure was altered with the relevant amino acid alterations for each SARS-CoV-2 variant. All four structures are then pre-processed to obtain their minimum-energy configuration, which is then employed in further docking computations. Missing hydrogens were specifically added, correct bond ordering were validated and assigned, accurate protonation states were predicted, and hydrogen bonds were optimized using systematic and cluster-based techniques. Restrained minimization was also used to relax bonds, angles, and overlaps within each structure.

2.2. Screening of FDA-approved, Investigational, and Experimental Drugs

The e-LEA3D web server [18], which employs the LEA3D method created by Douguet et al. [19], was used to execute structure-based drug design. With a binding site radius of 20 Å, the RBD binding site is described as the region surrounding the centroid of the following amino acids: N501, Q498, E484, T470, L452, N439, P499, Q493, F486, A475, and L455 [20]. FDA-approved (2,356), investigational (2,424), and experimental (5,962) medicines were evaluated for their ability to block the target binding site. DrugBank (release version 5.1.8) was used to retrieve these libraries [21]. Both the protein and the medication molecules are thought to be adaptable. Lipinski's Rule of Five [22] was utilized as a limitation to assure that the compounds created will be drug-like [23]. A docking score was calculated based on the drug molecules' binding to the protease's binding pocket. Virtual screening was carried out against SARS-CoV-2 variants B.1.1.7, B.1.351, and P.1. The docking scores of the therapeutic molecules against each SARS-CoV-2 variant were averaged and then sorted in order to identify the best-performing medicines capable of inhibiting all four forms.

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

The ADMET profiles of all performing drug candidates against the RBD of SARS-CoV-2 were evaluated using the ADMETlab 2.0 platform [24]. Only those that met the following criteria were considered 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 5), low hERG toxicity (p 0.3), low hepatotoxicity (p 0.3), low probability of drug-induced liver damage (p 0.3), low mutagenicity (p 0.3), low acute toxicity (p 0.3), and low carcinogenicity (p 0.3).

2.4. Molecular Dynamics Calculations

The dynamical unbinding process and the manner of ligand-protein interactional binding were explored using molecular dynamics calculations on the top-performing ligand from structure-based drug design. For each protein-ligand complex structure, the calculations were carried out using the Ligand and Receptor Molecular Dynamics (LARMD) website [25].

3. Results and Discussion

3.1. Screening of FDA-Approved Drugs

Drug-repurposing of FDA-approved drugs is the fastest way to look for possible therapies against SARS-CoV-2 since they are already proven safe for use in human beings. Some researchers have done a virtual screening of FDA-approved drugs against the RBD of SARS-CoV-2 in hopes of finding a potential inhibitor to prevent viral entry into the host cells [26–31]. However, those studies focused on the wild-type SARS-CoV-2. The fast emergence of new SARS-CoV-2 variants threatens drug development as the drug candidates previously identified may not be effective when used against the new variants. While we can continually develop new inhibitors for the new COVID-19 variants can always be done, this approach is resource-intensive. Instead, we screened 2,356 FDA-approved drugs for their inhibitory effect against all four SARS-CoV-2 variants. This excludes illicit drugs and those already withdrawn from the market during our drug screening. We then averaged the docking scores of the drugs and identified the top 30 drugs that can potentially inhibit all four variants of SARS-CoV-2 (Table S1). Among the drugs we identified are currently being used to treat ocular hypertension, chronic obstructive pulmonary disease, erectile dysfunction, hypertension, and overactive bladder syndrome, among others. As expected, most FDA-approved drugs have lower docking scores against B.1.1.7, B.1.351, and P.1 variants than wild-type SARS-CoV-2.

Overall, only 730 drugs met our ADMET criteria, i.e., having high human intestinal absorption, low blood-brain barrier permeation probability, and low toxicity. Only 11 drugs met these criteria among those we identified as top-performing drugs. Among them are Latanoprost, Bimatoprost, Salmeterol, Carboprost tromethamine, Tafluprost, Vilanterol, Dopexamine, Labetalol, Silodosin, Treprostinil, Propafenone.

Because COVID-19 presents a more severe illness in people with comorbidities such as chronic lung disease and hypertension, our discussion will focus more on drugs already being used to treat these diseases. Specifically, Salmeterol is a long-acting β2-adrenergic agonist (LABA) used to treat chronic obstructive pulmonary disease (COPD), chronic bronchitis, and asthma. Figure S1 shows the interaction of Salmeterol with the receptor-binding domain of various variants of SARS-CoV-2. Here, we see that the interaction of Salmeterol's phenol ring with the phenol ring of Tyr 505 via π-π stacking in wild-type SARS-CoV-2 was conserved in the B.1.1.7 and P.1 variants but not the B.1.351 variant. Instead, the π-π interaction occurs between the benzene ring of Salmeterol and the phenyl ring of the B.1.351 variant. The introduction of the N501Y mutation in the RBD of the B.1.1.7, B.1.351, and P.1 variants caused the appearance of a π-π interaction between the phenyl ring of Tyr 501 and Salmeterol. In addition, Salmeterol forms hydrogen bonds between its secondary hydroxyl and amine groups with the carbonyl group of Gly 496 in wild-type SARS-CoV-2. This hydrogen bond is lost in the new COVID-19 variants. Instead, new interactions appeared between Salmeterol and the new COVID-19 variants. In particular, the amino and carbonyl groups of Ser 494 and the carbonyl group of Leu 492 form hydrogen bonds with the hydroxyl group and the hydroxymethyl group of Salmeterol, respectively, in the B.1.1.7 variant.

Meanwhile, the amine and secondary hydroxyl groups form a hydrogen bond with the carbonyl group of Ser 494 in the B.1.351 variant. Moreover, the phenol ring of Salmeterol interacts with the phenol ring of Tyr 449 via π-π stacking in the B.1.351 variant. On the contrary, the benzene ring of Salmeterol interacts with the phenol ring of Tyr 449 in the P.1 variant. Lastly, the hydroxymethyl group of Salmeterol forms a hydrogen bond with the amine group of Gln 498 in the B.1.351 variant but with the amine group of Gly 502 in the P.1 variant.

3.2. Screening of Investigational Drugs

We also screened the DrugBank's database for potential inhibitors of the RBD of SARS-CoV-2 variants. Investigational drugs are those that have already entered clinical trials for a specific indication. Since a drug can have multiple statuses, e.g., an approved drug being studied for a different indication, we trimmed down the database by removing redundant entries already present in the database of FDA-approved drugs. A total of 2,424

investigational drugs were screened, and the top-performing drugs were determined by ranking the average docking scores of the drugs across all four variants (Table S3). Among these, Abediterol came to our attention since it is currently being studied to treat chronic obstructive pulmonary disease (COPD) and asthma.

Figure S2 shows the interaction of Abediterol with the receptor-binding domain of various variants of SARS-CoV-2. Abediterol forms a hydrogen bond between its secondary amine group and the carbonyl group of Ser 494 in wild-type SARS-CoV-2. This hydrogen bond is conserved in the B.1.351 variant but not in the B.1.1.7 and the P.1 variants. An additional hydrogen bond is seen between the phenol group of Abediterol and the carbonyl group of Tyr 505. At the same time, Abediterol's pyridine ring interacts with the phenol ring of Tyr 505 via π-π stacking. Unfortunately, these interactions are not conserved in the new variants of COVID-19. New π-π interactions are seen between the phenyl ring of Tyr 501 and Tyr 505 and the benzene ring of Abediterol in the B.1.1.7, B.1.351, and P.1 variants. π-π stacking is also seen between the phenyl ring and the pyridinone ring of Abediterol with the phenol ring of Tyr 449 in the B.1.351 variant. New hydrogen bonds also emerged in the new COVID-19 variants. The carboxyl group of Glu 406 in B.1.1.7 forms a hydrogen bond with the secondary hydroxyl group of Abediterol. Lastly, the carbonyl group in the side chain of Gln 493 in the P.1 variant forms a hydrogen bond with the phenol group of Abediterol.

3.3. Screening of Experimental Drugs

We further expanded our search for potential inhibitors of the RBD of SARS-CoV-2 by screening the database of experimental drugs obtained from DrugBank. Experimental drugs are those which are being researched pre-clinically but have not yet entered formal clinical trials. Again, we removed the drugs overlapping with the FDA-approved and investigational drugs databases to prevent redundancy. A total of 5,962 drugs were included in the trimmed database. The averaged values of the docking scores of each drug across all four variants were ranked to determine the top-performing inhibitors (Table S5). Among these, Lysophosphatidyl-glycerol emerged as the top candidate. Lysophosphatidylglycerol is a lipid-like molecule belonging to a family of glycerophosphoglycerols are molecules containing a glycerol moiety attached to the phosphate group linked to a glycerol. The fatty acid in Lysophosphatidylglycerol is bonded to the glycerol moiety through an ester linkage.

Figure S3 shows the interaction of Lysophosphatidylglycerol with the RBD of SARS-CoV-2 variants. The wild-type SARS-CoV-2 forms five hydrogen groups with Lysophosphatidylglycerol. The carbonyl and amine group of Ser 494 form a hydrogen bond with the terminal secondary hydroxyl group and the ester group of Lysophosphatidylglycerol. The amino and carbonyl groups of Gly 496 form a hydrogen bond with the ester group of Lysophosphatidylglycerol. Finally, the terminal primary hydroxyl group of Lysophosphatidylglycerol is involved in two hydrogen bonds: with the amine group of Asn 501 and the carbonyl group of Gly 496. However, these interactions are not conserved in the new COVID-19 variants.

Lysophosphatidylglycerol forms four hydrogen bonds with the B.1.1.7 variant: its phosphate group with the phenol group of Tyr 453 and the primary amine group of Arg 403, its hydroxyl group with the carbonyl group of Gly 496, and its terminal primary hydroxyl group with the primary amine group of Arg 403. On the other hand, Lysophosphatidylglycerol forms five hydrogen bonds with the B.1.352 variant: its terminal hydroxyl group with the amine group of Gln 409, its carbonyl group with the phenol group of Tyr 453, its terminal hydroxyl group with the carboxylic group of the side chain of Glu 406, and the phosphate group with the primary amine group and the imide group of Arg 403. A salt bridge also exists between the phosphate group of Lysophosphatidylglycerol and the imide group of Arg 403. On the other hand, only two hydrogen bonds are formed between Lysophosphatidyl-glycerol and the P.1 variant: its terminal primary hydroxyl

group with the carbonyl group of Tyr 449 and its phosphate group with the amino group of Ser 494.

3.4. Molecular Dynamics Study

Molecular dynamics simulations were done on Salmeterol to investigate its interaction with the SARS-CoV-2 variants further. Salmeterol forms a stable ligand-receptor complex with the RBD of all SARS-CoV-2 variants. Dynamic cross-correlation analysis of the ligand binding and unbinding process demonstrated the stability of the docked Salmeterol, indicating that it could inhibit the function of the RBD during SARS-CoV-2 pathogenesis. Moreover, we found that the average ligand RMSD in wild SARS-CoV-2 (2.8430 ± 0.8432 Å) is comparable to that of the B.1.1.7 variant (4.3099 ± 1.0177 Å), B.1.351 variant (2.7488 ± 0.7182 Å), and P.1 variant (1.9985 ± 0.4290 Å). The binding energy of the wild-type SARS-CoV-2 (-10.81 kcal/mol), B.1.1.7 variant (-13.10 kcal/mol), B.1.351 variant (-12.85 kcal/mol), and P.1 variant (-12.60 kcal/mol) were calculated using MMPBSA approach. These results show that Salmeterol acts against the wild-type SARS-CoV-2 and is also stable against other variants.

4. Conclusions

Structure-based drug design was done by screening the library of FDA-approved, experimental, and investigational drugs in the DrugBank database as possible inhibitors of each variant of SARS-CoV-2. The corresponding docking scores for each variant were average, and the ligands were then ranked. Among the drugs in the database, Salmeterol, Abediterol, and Lysophosphatidylglycerol emerged as top candidates against all four variants with a desirable ADMET profile. In particular, Salmeterol, a drug used for chronic obstructive pulmonary disease, interacts well with the RBD of SARS-CoV-2 by hydrogen bonding and π-π stacking. Molecular dynamics showed that Salmeterol forms a stable complex with the RBD with good binding energies against all four variants. As such, Salmeterol may be repurposed as a treatment for SARS-CoV-2 infection. Further studies are needed to ascertain the efficacy and safety of using these repurposed drugs for COVID-19 treatment.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, **Table S1.** Comparative performance of top-performing FDA-approved drugs as potential inhibitors of the RBD of SARS-CoV-2 variants.; **Figure S1.** Structures of Salmeterol, the top-performing FDA-approved drug, docked in the RBD of SARS-CoV-2 and their corresponding ligand interaction diagrams: (a-b) Wild type; (c-d) B.1.1.7 variant; (e-f) B.1.351 variant; and (g-h) P.1 variant.; **Table S2.** ADMET properties of top-performing FDA-approved drugs as potential inhibitors of the RBD of SARS-CoV-2 variants.; **Table S3.** Comparative performance of top-performing experimental drugs as potential inhibitors of the RBD of SARS-CoV-2 variants.; **Figure S2.** Structures of Abediterol, the top-performing investigational drug, docked in the RBD of SARS-CoV-2 and their corresponding ligand interaction diagrams: (a-b) Wild type; (c-d) B.1.1.7 variant; (e-f) B.1.351 variant; and (g-h) P.1 variant.; **Table S4.** ADMET properties of top-performing experimental drugs as potential inhibitors of the RBD of SARS-CoV-2 variants.; **Table S5.** Comparative performance of top-performing investigational drugs as potential inhibitors of the RBD of SARS-CoV-2 variants.; **Figure S3.** Structures of Lysophosphatidylglycerol, the top-performing experimental drug, docked in the RBD of SARS-CoV-2 and their corresponding ligand interaction diagrams: (a-b) Wild type; (c-d) B.1.1.7 variant; (e-f) B.1.351 variant; and (g-h) P.1 variant.; **Table S6.** ADMET properties of top-performing investigational drugs as potential inhibitors of the RBD of SARS-CoV-2 variants.; **Figure S4.** (a) Principal Component Analysis (PCA) for the MD trajectory of Salmeterol binding into Wild-type RBD.; **Figure S5.** (a) Principal Component Analysis (PCA) for the MD trajectory of the unbinding process between Salmeterol and Wild-type RBD.; **Figure S6.** Dynamical residue cross-correlation map for the MD trajectory of the (a) binding process and (b) unbinding process of the receptor-ligand complex involving Salmeterol docked in Wild-type RBD; **Figure S7.** (a) Principal Component Analysis (PCA) for the MD trajectory of Salmeterol binding into SARS-CoV-2 B.1.1.7 Variant RBD.; **Figure S8.** (a) Principal Component Analysis (PCA) for the MD trajectory of the unbinding process between Salmeterol and SARS-CoV-2 B.1.1.7 RBD.; **Figure S9.**

Dynamical residue cross-correlation map for the MD trajectory of the (a) binding process and (b) unbinding process of the receptor-ligand complex involving Salmeterol docked in SARS-CoV-2 B.1.1.7 RBD.; **Figure S10.** (a) Principal Component Analysis (PCA) for the MD trajectory of Salmeterol binding into SARS-CoV-2 B.1.351 Variant RBD.; **Figure S11.** (a) Principal Component Analysis (PCA) for the MD trajectory of the unbinding process between Salmeterol and SARS-CoV-2 B.1.351 RBD.; **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 Salmeterol docked in SARS-CoV-2 B.1.351 RBD.; **Figure S13.** (a) Principal Component Analysis (PCA) for the MD trajectory of Salmeterol binding into SARS-CoV-2 P.1 Variant RBD.; **Figure S14.** (a) Principal Component Analysis (PCA) for the MD trajectory of the unbinding process between Salmeterol and SARS-CoV-2 P.1 RBD.; **Figure S15.** Dynamical residue cross-correlation map for the MD trajectory of the (a) binding process and (b) unbinding process of the receptor-ligand complex involving Salmeterol docked in SARS-CoV-2 P.1 RBD.

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