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In Silico Screening 2019-Coronavirus Inhibitors by SARS Template-Based Molecular Docking on ANTI-HIV Drugs

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ABSTRACT

Proteases or proteolytic enzymes are effective targets for developing antiviral drugs. The chymotrypsin-like cysteine protease (3CLpro), known as the main protease (M^{pro}) of severe acute respiratory syndrome coronavirus (SARS-CoV) plays an essential role in the proteolytic processing of viruses, and it is an effective target for anti-SARS drug development. An outbreak of novel coronavirus, named 2019-nCoV that occurred in Wuhan, China, has been identified as the cause of the disease and spread rapidly in multiple countries. There are no drugs approved to be an effective treatment for the 2019-nCoV yet. The result of sequence alignment revealed that the 2019-nCov M^{pro} shows 96% similarity with that of SARS-CoV 3CLpro (SARS M^{pro}). This is a potential discovery for developing 2019-nCov inhibitors. In order to find more potential inhibitors of the 2019-nCov M^{pro} protein, we selected SARS-CoV 3CLpro (PDB ID: 2GTB) as a template to perform molecular docking on 10 approved anti-HIV drugs. The docking results revealed that the SARS M^{pro} gave the highest binding affinity for saquinavir with a binding energy of -29.21 kcal/mol. Anti-HIV drugs darunavir (-23.43 kcal/mol), indinavir (-22.87 kcal/mol), and nelfinavir (-21.54 kcal/mol) also showed good binding modes with the active sites of protein, indicating that they may have the potential to be used as anti-COVID-19 clinical drugs. The observations would contribute more drug candidates that could interact with key residues of 2019-nCov M^{pro} similarly to the existing inhibitors against SARS-CoV 3CLpro.

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1. Introduction

The information regarding the current outbreak of coronavirus disease (COVID-2019) was reported from Wuhan, China, on 31 December 2019. Chinese researchers informed the evidence of coronavirus originated from a seafood market in Wuhan. This new type of virus was isolated and named novel coronavirus, 2019-nCoV, on 7 January 2020 [1] – [2]. Unfortunately, the number of infection cases and deaths are still growing rapidly worldwide with various mutations, and no drugs have been approved to be effective for COVID-2019 treatment. The COVID-19 pandemic has increased demand for the discovery and development of drugs to cure the disease.

The main protease (M^{pro}) of coronavirus causing severe acute respiratory syndrome (SARS) plays an essential role in the life-cycle of the virus. Inhibition of M^{pro} can block the synthesis of viral proteins, thus, this enzyme is the most attractive target for the development of anti-SARS drugs. Typically, sequence alignment revealed that 2019-nCov M^{pro} is 96% similar to SARS M^{pro} [3] – [5]. Therefore, *in silico* studies on the inhibitors of 2019-nCov M^{pro} were quickly carried out, and anti-virus drugs are potential candidates as inhibitors of the protein [6] – [11]. Here, we attempted to examine the efficacy of the anti-HIV agents with a computational approach by docking them using SARS M^{pro} (PDB ID: 2GTB) as a template to analyze possible interactions at the active sites of 2019-nCov M^{pro}.

2. Materials and Methods

2.1. Materials

The SMILES of 10 approved anti-HIV virus drugs (Saquinavir: DB01232; Darunavir: DB01264; Indinavir: DB00224; Nelfinavir: DB00220; Fosamprenavir: DB01319; Tipranavir: DB00932; Elvitegravir: DB09101; Ritonavir: DB00503; Remdesivir: DB14761; Lopinavir: DB01601) were received from DrugBank. The SMILES were added to Operating Environment 2008.10 (MOE 2008.10) to convert into 3D structures and saved as *.mol2. The most stable conformation of each ligand was obtained by energy minimization using SYBYL-X 2.0. The minimization procedure was terminated when the energy change between iterations was lower than 10^{-4} kcal/mol. The energy minimized structure of each ligand was finally exported and saved as *.mol2 for further docking simulations.

2.2. Preparation of receptor and molecular docking

The crystal structure of SARS M^{pro} was retrieved from the protein data bank (PDB ID: 2GTB) [8]. The receptor was prepared by using LigX tool in MOE, the three-dimensional (3D) structure was loaded into MOE and the co-crystallized ligand aza-peptide epoxide (APE) with SARS M^{pro} was used as a reference. Protons and partial charges were added to the receptor to form a 3D protonation form. Sequentially, the receptor atoms were tethered and minimized energy. The unbound water molecules surrounding the active sites were deleted in the next step and finally, the prepared enzyme was saved as *.pdb for the molecular docking procedure. Molecular docking was carried out to analyze the binding interactions of ten anti-HIV drugs and SARS M^{pro} using LeadIT 2.0.2. In order to dock ligands into the binding site of prepared SARS M^{pro}, APE was used as a reference ligand and a binding pocket, including amino acids within a radius of 6.5 Å. The anti-HIV ligands were loaded from the docking library. The pose giving the most negative docking score was ranked as 1 among ten conformations of each ligand. The maximum number of solutions per iteration and fragmentation are 1000 and 200, respectively. Note that, the co-crystallized ligand APE was redocked to its receptor through the same procedure.

3. Results and Discussion

3.1. Redocking

The native conformation of APE was separated from SARS M^{pro} (PDB: 2GTB) and redocked to its binding sites. Figure 1 gave a superposition between the redocked pose of APE and its original one in the binding pocket of SARS M^{pro}. The validity of the molecular docking procedure was based on the Root Mean Square Deviation (RMSD) value, i.e, a deviation between docked pose and the initial co-crystal ligand position. Herein, the redocking RMSD value of 1.0215 Å less than 2 Å suggested that the computational docking has been acceptable for further work on other ligands toward SARS M^{pro} (PDB: 2GTB) [12] – [14].

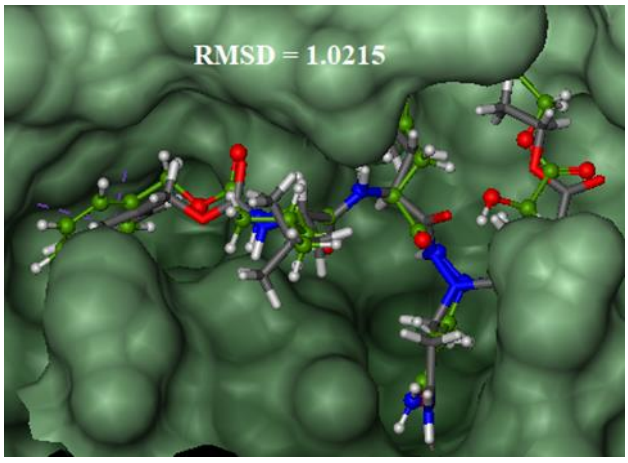

Figure 1. *A superposition of a native APE pose (sticks in green, atoms were exhibited in balls: carbons: green, oxygen: red, nitrogen: blue, hydrogen: white) and a redock APE one (sticks in gray) within SARS Mpro active sites.*

3.2. Molecular docking of HIV inhibitors on SARS Mpro

To screen potential 2019-coronavirus inhibitors, ten approved HIV drugs have been docked on SARS-CoV $3CL^{pro}$ in comparison with APE, a co-crystallized ligand with SARS M^{pro}. Using docking simulation, the inter-molecular hydrogen bonds and hydrophobic interactions between ligands and amino acid residues surrounding the binding site of the enzyme were revealed. Generally, the complexes of HIV inhibitors and SARS M^{pro} have been formed via non-covalent bonds in the binding pocket. Free binding energies of stable ligand- SARS M^{pro} complexes and the number of favorable interactions between the target and ligand were listed in Table 1. These values were calculated based on the number of possible favorable interactions. A much negative value indicates a stable ligand-protein complex and thus, a likely binding interaction. The free binding energies of forming complexes were negative and less than -2.28 kcal/mol (Table 1). We found that there are four inhibitors including saquinavir (-29.21 kcal/mol), darunavir (-23.43 kcal/mol), indinavir (-22.87 kcal/mol), and nelfinavir (-21.54 kcal/mol) showing the best binding energies for SARS M^{pro}. Saquinavir is the best one among 10 inhibitors. The docking pose and 2D ligand-protein interaction of top-ranked saquinavir and SARS M^{pro} were illustrated in Figure 2. This ligand exhibited hydrogen bonds with Glu166, Gln189, Asn142, and 16 hydrophobic/π-π stacking interactions. The most negative binding energy of saquinavir can be attributed to the formation of more interactions with SARS M^{pro}. This observation is consistent with the reported results that better binding affinity was observed with saquinavir docking on the SARS-CoV M^{pro} [9] – [10].

Table 1. *Docking scores, number of hydrogen bonds, hydrophobic contacts of APE, and 10 HIV inhibitors toward SARS Mpro.*

Inhibitor	Binding energy (kcal/mol)	Number of hydrogen bonds	Number of hydrophobic interactions
APE	-32.72	09	14
Saquinavir	-29.21	07	16
Darunavir	-23.43	09	08
Indinavir	-22.87	07	09
Nelfinavir	-21.54	04	10
Fosamprenavir	-18.52	06	14
Tipranavir	-15.44	07	15
Ritonavir	-14.94	05	12
Elvitegravir	-14.92	03	12
Remdesivir	-13.89	05	10
Lopinavir	-2.28	05	15

When compared to saquinavir, the binding energies of the darunavir (-23.43 kcal/mol), indinavir (-22.87 kcal/mol) and nelfinavir (-21.54 kcal/mol) are higher than that of saquinavir, indicating that the binding affinities of these inhibitors toward SARS M^{pro} might be lower than saquinavir. The binding modes of drugs in their docking complexes are shown in Figure 3. Compared to saquinavir, these structures formed fewer interactions with contact residues at the active site of SARS-M^{pro}. The number of established interactions likely strengthens the binding affinity between ligand and protein, probably explaining why the binding energy value between darunavir (indinavir, nelfinavir) and SARS-M^{pro} is higher than saquinavir. Although SARS M^{pro} gave lower binding affinities for darunavir, indinavir and nelfinavir, the inhibitors have been proven to be potential candidates against 2019-nCov M^{pro} based on the docking results [5] – [9]. In addition, darunavir formed 9 hydrogen bonds, which play an essential role in the stability of the ligand-protein complex, and thus, darunavir might be suggested for treatment of COVID-19 [9] – [15].

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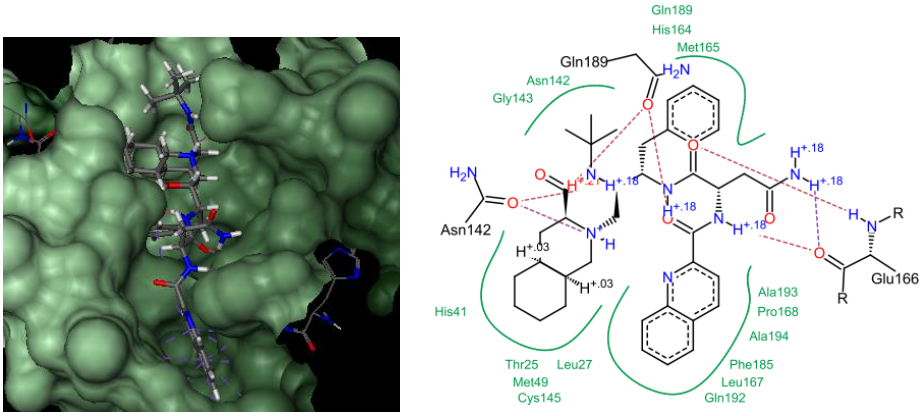
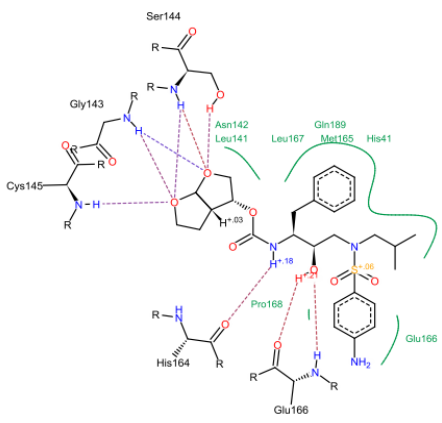
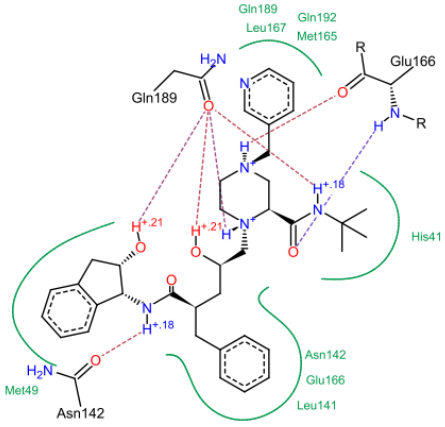


(a) *(b)*

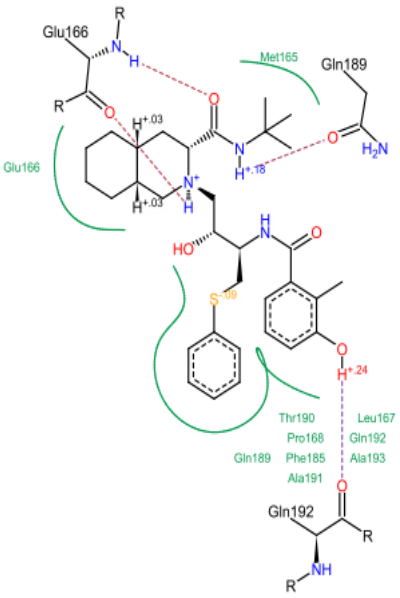
Figure 2. *(a) The docking pose and (b) 2D ligand-protein interaction of top-ranked saquinavir and SARS Mpro (PDB ID: 2GTB).*



(a) Darunavir-SARS M^{pro}



(b) Indinavir -SARS M^{pro}



(c) Nelfinavir -SARS M^{pro}

Figure 3. *Two-dimensional (2D) binding interactions of docking poses of darunavir, indinavir and nelfinavir and active sites of SARS Mpro (PDB ID: 2GTB).*

Remdesivir formed a protein-ligand complex with a binding energy of -13.89 kcal/mol. Protein targets such as main protease (M^{pro}) and RNA dependent RNA polymerase (RdRp) are important in different stages of viral replication. Remdesivir was found to show the best binding energy on RdRp [10] – [16]. The lower binding affinity of remdesivir compared to saquinavir/darunavir can be attributed to the formation of the unfavorable complex of remdesivir and SARS M^{pro} (PDB: 2GTB). Currently, the use of remdesivir alone for patients who are hospitalized with COVID-19 is not likely to be sufficient. To improve patient outcomes in COVID-19, the future strategies are the use of remdesivir in combination with other antiviral agents [17]. The binding energies of ritonavir and lopinavir on SARS M^{pro} are -14.94 and -2.28 kcal/mol, respectively, which indicates that these inhibitors might not be effective enough for COVID-19 treatment. The result is consistent with the report that treatment with ritonavir-lopinavir on patients with COVID-19 infection gave no clinical improvement [18].

4. Conclusions

A data set of 10 approved anti-HIV inhibitor drugs was selected to evaluate their binding affinities with SARS-M^{pro} by molecular docking. Our work demonstrated that among inhibitors, saquinavir exhibits the lowest binding energy toward SARS-M^{pro}, suggesting that it should be the best candidate among the 10 docked drugs. Even though the binding energies of darunavir, indinavir and nelfinavir for SARS-M^{pro} are not as good as that of saquinavir, these drugs are also proposed to be potential inhibitors for SARS-M^{pro} via virtual screening. Their binding modes are clues to discovering more effective drugs for COVID-19 treatment. The results in the present work were obtained by *in silico* screening, i.e, without experimental confirmation. Nevertheless, the docking results provided hints and/or clues for drug discovery and development process, which consists of several steps and is difficult to be done in a single project.

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