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Study on SARS-CoV-2 inhibition of some potential drugs using molecular docking simulation

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Abstract

Inhibitory capabilities of six old drugs selected from the DrugBank database including Losartan, Triazavirin, TMC-310911, Verapamil, Clevudine and Elbasvir, which are promising for the treatment of an infectious disease caused by SARS-CoV-2, were examined on the host receptor Angiotensin-converting enzyme 2 (ACE2) and the main protease (PDB6LU7) of SARS-CoV-2 using molecular docking simulation. Results reveal that both proteins ACE2 and PDB6LU7 are in strong inhibition by the drugs and the inhibitory effectiveness is in the order: Clevudine > Triazavirin > TMC-310911 > Elbasvir > Losartan > Verapamil. In particular, the inhibitability highly correlates with the average docking score energy of inhibitory complexes, and drug-protein active interactions. Regarding inhibitory ligands, their polarizability, molecular size, and dispersion coefficient logP are also significant indicators for inhibition potential. The drugs are suggested as valuable resources for selecting potential pharmaceuticals to prevent SARS-CoV-2 invasion into human body given theoretical demonstration of molecular docking simulation.

Keywords. SARS-CoV-2, potential drugs, ACE2, PDB6LU7, docking simulation.

1. INTRODUCTION

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is a new strain of *coronaviruses* family. It causes human diseases such as respiratory, gastrointestinal and neurological disorders, assembling the symptoms of the known diseases including Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS).[1-3] It has only been about 4 months since the World Health Organisation (WHO) officially announced the first cases of infection with

SARS-CoV-2. They were recorded in Wuhan, Hubei, China. Nevertheless, there have been more than 3 million people worldwide confirmed positive with SARS-CoV-2 so far. Therefore, early finding of an effective treatment, conducive to the race of vaccine proliferation is of the goal to scientists.

There have been hundreds of drugs applied to tackle acute respiratory illnesses, or infectious diseases. For example, Losartan is an angiotensin II receptor blocker (ARB), which is suggested by The Food and Drug Administration (FDA) of The United States to treat hypertension.[4] Especially, it is similarly used for Angiotensin-converting enzyme (ACE) inhibitors when a patient has a cough.[4,5] Similarly, Verapamil is used to treat high blood pressure.[6] Clevudine, also known under the trade names Levovir and Revovir, is an antiviral drug for hepatitis B treatment in South Korea and the Philippines. Triazavirin has been proved performing high efficacy towards influenza A and B, including the highly developed H_5N_1 strain[7-10] in Russia. Because of the structural similarities between SARS-CoV-2 and H_5N_1, health officials are conducting studies on Triazavirin as a potential drug candidate to combat SARS-CoV-2.[8] TMC-310911 (known as ASC-09) is being investigated for fighting against various strains of HIV-1.[11] Like other anti-HIV drugs, TMC-310911 is also being screened as a promising candidate to tackle SARS-CoV-2 infection.[12] Elbasvir is a direct-acting antiviral drug used to treat infectious liver disease resulted from hepatitis C virus infection.[13] According to Balasubramaniam and Reis (2020), elbasvir was theoretically calculated to create the best and most stable binding with the three important proteins essential for SARS-CoV-2 replication.[14]

However, there has not been any further official announcement about potential drugs to directly treat SARS-CoV-2 or its vaccine. Therefore, a study on the interaction mechanism between cytological receptors and potential drugs by docking simulation may initially provide useful information guiding preclinical experiments with a time-effective manner. Angiotensin-converting enzyme 2 (ACE2) is an integral membrane glycoprotein. It is well-known as a host-cell receptor whose is targeted by SARS-CoV-2 and SARS.[15-17] From UniProtKB,[18] we can reference the structural database of ACE2 shown in figure 1. Therefore, if ACE2 can be inhibited, the viral prevention is achievable because of the loss its host.[19] Moreover, PDB6LU7 protein is the main protease of SARS-CoV-2 and its struture has been recently determined from Worldwide Protein Data Bank.[20]

At the present, there have been no precedented research related to SARS-CoV-2 resistance of the six studied drugs. This is either theoretical- and experimental-based. Thus, this study is an attempt for determination of the inhibitory capacity of six potential well-developed drugs (figure 2) against the ACE2 protein and SARS-CoV-2 main protease PDB6LU7 using docking simulation approaches. Characteristic parameters including docking score energy, site-site active interactions of drug-protein, polarizability and volume of potential drugs predict the inhibitory capacity.

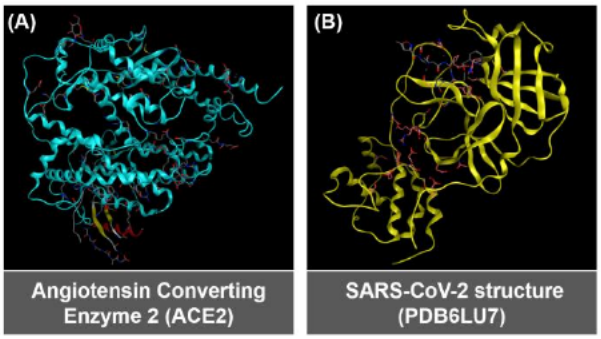

Figure 1: (A) Angiotensin-converting enzyme 2 (ACE2) and (B) SARS-CoV-2 main protease PDB6LU7 referenced from Worldwide Protein Data Bank[20]

2. METHODOLOGY

MOE 2015.10 was utilized for the visual investigation. Structural data of the proteins (ACE2 and PDB6LU7) and 6 potential drugs are needed for molecular docking simulation. They were used to simulate intermolecular interactions with the targeted proteins. Results obtainable include the configuration of inhibitory complexes, their docking score (DS) energy, their root-mean-square deviation (RMSD), binding interaction types, and the ligand-protein distances. In a typical procedure, molecular docking simulation follows 3 steps.[22-25]

a) Protein and ligands preparation: The structural data of proteins ACE2 and PDB6LU7 are obtainable at UniProtKB[18] and Worldwide Protein Data Bank,[20] respectively. Their structure and 3D protonation were prepared by Quickprep tool; meanwhile, their active zones were determined based on ligand-amino acid distance within a radius of 4.5 Å. The information of protein structures was saved in format *.pdb. Also, the 6 potential drugs were optimized. The optimization configuration was: Conj Grad for minima energy; termination for energy change = 0.0001 kcal.mol^{-1}; max interactions = 1000; modify

charge: Gasteiger-Huckel. Finally, intermolecular interactions were performed on MOE 2015.10 system and the inhibitory structures were saved in format *.sdf.

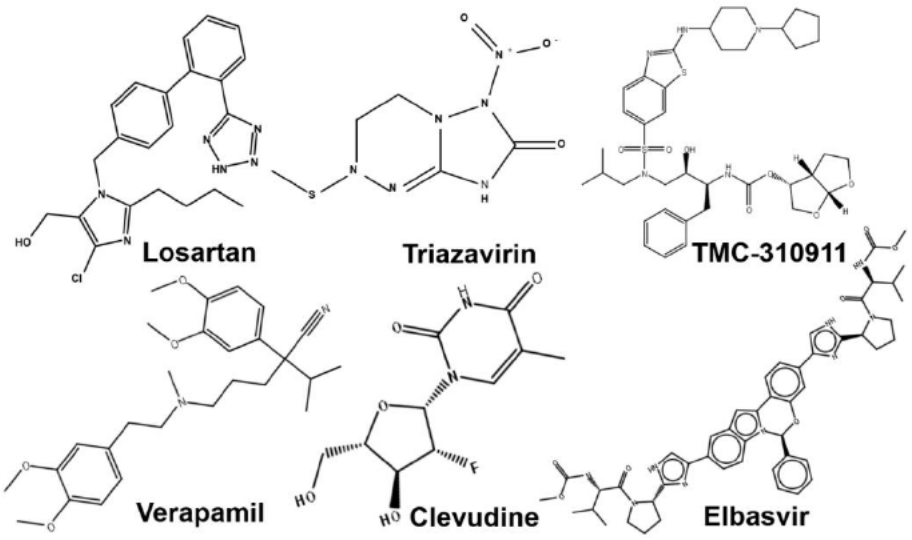

Figure 2: Chemical structures of investigated compounds as the six potential drugs: Losartan, Triazavirin, TMC-310911, Verapamil, Clevudine, Elbasvir

b) Docking investigation: After structural preparation, docking simulation was carried out. The parameters were set: the number of poses retaining further interaction analysis 10; the maximum solutions per iteration 1000; maximum solutions per fragmentation 200.

c) Docking results analysis: Ligand-protein binding capacity is represented by docking score energy (DS) values. Evaluation of docking score energy (DS) provides the interaction between the potential drugs and the proteins (ACE2 and PDB6LU7). Visual models of the complexes (drug-protein) were plotted on both 2D and 3D planes. The interactions created by the potential drugs and important amino acids of proteins ACE2 and PDB6LU7 within the site-site distance were also analyzed. Hydrogen bonds, ion bonds, π-π interactions, cation-π interactions, and van der Waals ones were detected by connections with hydrophilic, hydrophobic, and solvent interactions. A variety of interaction such as hydrogen bonds, cation-π, π-π bonds, and ionic interactions, interactions distance between amino acids and the active sites of potential drugs were plotted. Additionally, contact with hydrophilic and hydrophobic surfaces between the systems and the bonding point detected Van der Waals interactions. The interactions obtained demonstrate inhibitability of potential drugs into host receptor ACE2 and SARS-CoV-2 main protease (PBD6LU7).

3. RESULTS AND DISCUSSION

The docking score energy (DS) and root mean square deviation (RMSD) values between drugs and the two proteins as well as various interactions for the docking between investigated drugs and ACE2 are presented in figures 3, 4 and table 1. Similarly, figures 5, 6 and table 2 resume the obtained data for 6 studied drugs docked with SARS-CoV-2 main protease (PDB6LU7). Several types of interaction are evaluated including hydrogen bonds, cation-π, π-π bonds, and ionic interactions, interaction distance between amino acids, site-site binding, and Van der Waals interactions.

As can be seen in Figures 3, 4 and Table 1, the ACE2 protein docked with Losartan, Triazavirin, TMC-310911, Verapamil, Clevudin, Elbasvir exhibited the strong inhibitory effects with the values of docking score energy (kcal.mol^{-1}) in the range of -12.6, -14.1, -17.2, -11.7, -15.8 and -16.8, respectively.

The inhibitory intensities of Losartan and Verapamil are almost similar with 4 interactions based on hydrogen bonds for Losartan-ACE2 and 3 hydrogen bonds interactions for Verapamil-ACE2: *(i)* Inhibitory complex Losartan-ACE2 presents DS of -12.6 kcal.mol^{-1} and RMSD of 1.35 Å, while its bonding interaction within site-site distances exhibits the binding sites such as hydrogen bonds between –OH, –NH, N-heterocyclic of Losartan and the amino acids Asp 382 (2.73 Å), Asp 350 (3.25

Å), Asp 350 (2.92 Å), and Arg 393 (3.16 Å); *(ii)* Inhibitory complex Verapamil-ACE2 possesses DS of -11.7 kcal.mol^{-1} and RMSD of 1.89 Å, and bonding interaction within site-site distances between N-atom and aromatic ring of Verapamil and amino acids Thr 371 (3.52 Å), Ser 409 (3.17 Å), Leu 370 (3.60 Å).

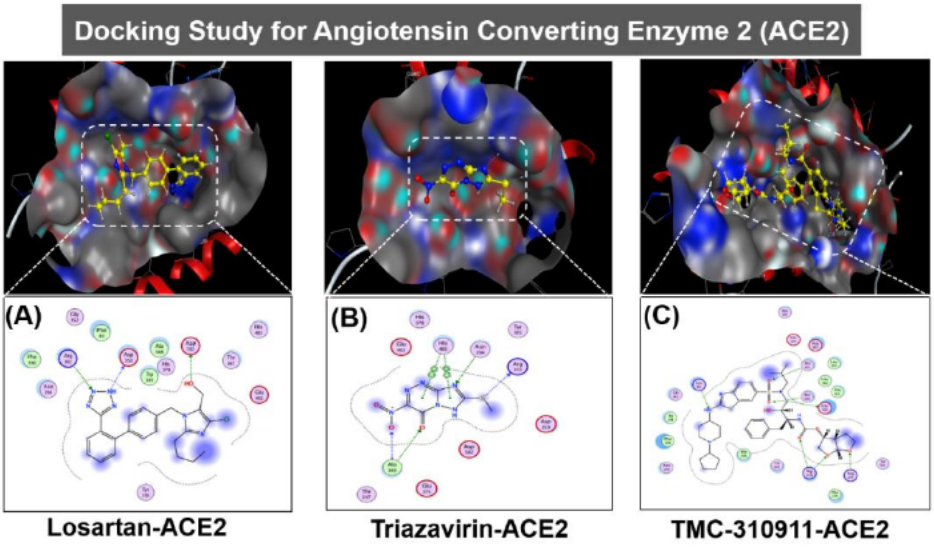

Figure 3: ACE2 protein in human body docked with drugs Losartan, Triazavirin and TMC-310911. Molecular docking simulation with the interactions of (**A**) Losartan-ACE2, (**B**) Triazavirin-ACE2, (**C**) TMC-310911-ACE2

Table 1: Docking simulation results including docking score energy (DS), root-mean-square deviation (RMSD), and the interaction between the potential drugs with ACE2 amino acids. Information on ACE2 protein found at DOI: 10.2210/pdbACE2/pdb

Drug	Complex (Drug-Protein)	DS (kcal·mol^{-1})	RMSD (Å)	Interaction with amino acid (Å)
Losartan	Losartan-ACE2	-12.6	1.35	Asp 382 (2.73), Asp 350 (3.25), Asp 350 (2.92), Arg 393 (3.16)
Triazavirin	Triazavirin-ACE2	-14.1	1.69	Arg 393 (3.70), Ala 348 (3.62), Asn 394 (3.30), Ala 348 (3.31), His 401 (3.67), His 401 (3.92)
TMC-310911	TMC-310911-ACE2	-17.2	1.58	Glu 406 (3.40), Arg 518 (3.34), Arg 518 (3.13), Arg 273 (3.05), Ser 409 (2.96), Thr 371 (3.37), Lys 441 (3.63)
Verapamil	Verapamil-ACE2	-11.7	1.89	Thr 371 (3.52), Ser 409 (3.17), Leu 370 (3.60)
Clevudine	Clevudine-ACE2	-15.8	1.27	His 540 (3.46), Ala 413 (3.10), Ala 413 (3.28), Lys 541 (3.70), Ala 413 (3.20),
Elbasvir	Elbasvir-ACE2	-16.8	1.54	Glu 208 (2.89), Glu 564 (2.95), Tyr 196 (2.89), Arg 219 (3.95), Pro 565 (3.87)

Triazavirin and Clevudine are successfully docked into ACE2 protein and show quite good interactions with its amino acids with 6 interactions (Triazavirin-ACE2) and 7 ones (Clevudine-ACE2) of hydrogen bonds and π-π bonds: *(iii)* Docking of Triazavirin-ACE2 has DS being -14.1 kcal.mol^{-1}, RMSD being 1.69 Å, and site-site bonding interaction between O-, S-, N-heterocyclic of Triazaviri and amino acids Arg 393 (3.70 Å), Ala 348 (3.62 Å), Asn 394 (3.30 Å), Ala 348 (3.31 Å), His 401 (3.67 Å), His 401 (3.92 Å); *(iv)* Docking of Clevudine-ACE2 has DS value being -15.8 kcal.mol^{-1}, RMSD being 1.27 Å, and site-site bonding interaction between –O, –OH, –NH, N-aromatic ring of Clevudine and amino acids His 540 (3.46), Ala 413 (3.10), Ala 413 (3.28), Lys 541 (3.70), Ala 413 (3.20), Pro 415 (3.50), Phe 438 (3.28).

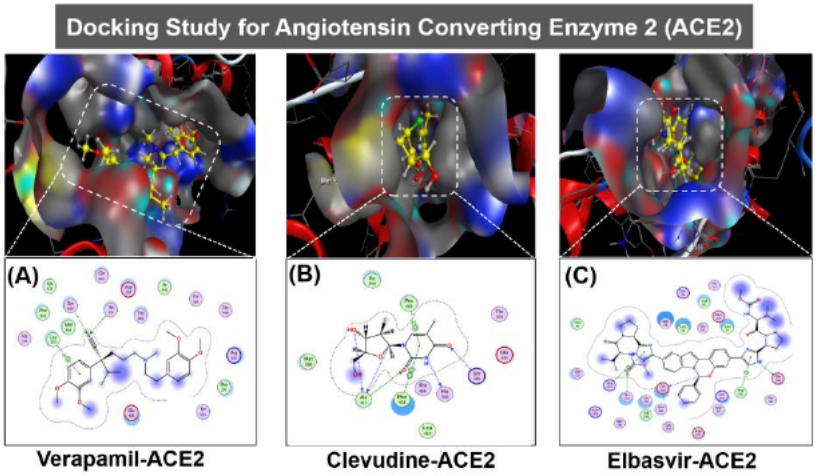

Figure 4: ACE2 protein in human body docked with drugs Verapamil, Clevudine and Elbasvir. Molecular docking simulation with the interactions of (**A**) Verapamil-ACE2, (**B**) Clevudine-ACE2, (**C**) Elbasvir-ACE2

The docking simulations of 6 potential drugs into SARS-CoV-2 protein PDB6LU7 are presented in Table 2, Figures 5 and 6. All potential drugs exhibit as the strong inhibitors for PDB6LU7 and DS values of the studied compounds Losartan, Triazavirin, TMC-310911, Verapamil, Clevudine, Elbasvir are -13.9, -14.1, -16.1, -12.1, -14.6 and -15.7 kcal.mol^{-1}, respectively. It is worthy to note that TMC-310911 and Elbasvir represent the strongest DS energy values. This can be explained that TMC-310911 is a flexible compound consisting of the groups of >S=O, –OH, and six tertiary nitrogens, also display >C=O and –O– in which the two groups >S=O perform significant bonding effects towards amino acids of SARS-CoV-2 main protease PDB6LU7.

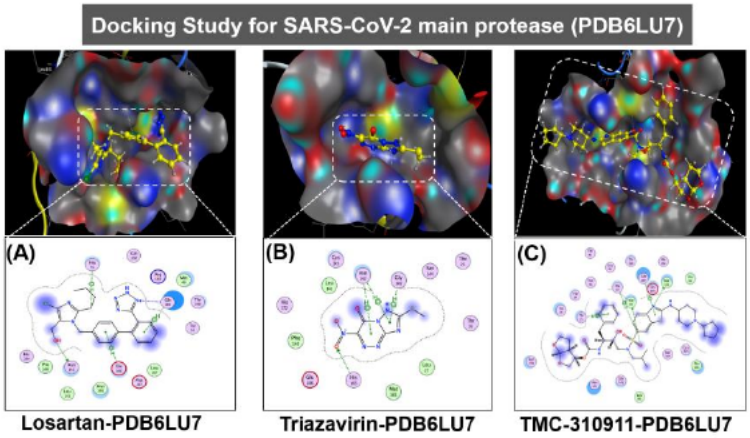

Figure 5: PDB6LU7 protein of the SARS-CoV-2 main protease docked with the potential drugs Losartan, Triazavirin and TMC-310911. Docking simulation with the interaction of (**A**) Losartan-PDB6LU7, (**B**) Triazavirin-PDB6LU7 and (**C**) TMC-310911-PDB6LU7

In addition, Elbasvir has relatively large volume and high molecular mass. These might lead to high binding capacity regarding the monopeptides. The drug has the two groups –NHCOOCH$_3$ and five tertiary nitrogens in the ring along with >C=O, and –O– groups that exhibits the strong inhibitory effects over the PDB6LU7 protein. The site-site binding interactions between six potential drugs and SARS-CoV-2 through the amino acids of PDB6LU7 protein are as follows: *(i)* Losartan forms five hydrogen-bond interactions with amino acids including Asn 142, Gln 189, His 41, Glu 166 and Gln 189; *(ii)* Triazavirin forms four hydrogen interactions with His 163, Asn 142, Asn 142, Gly 143; *(iii)* TMC-310911 exhibits six interactions between the H-atom and amino acids Met 49, Met 165, His 41, Thr 25 and Gln 189 of the main protease; *(iv)* Verapamil has four binding sites with some amino acids such as Cys 145, Met 165, Gly 143, Glu 166; *(v)* while the amino acids Asn 142,

Cys 145, His 163, Asn 142, Gly 143 form hydrogen bonds and π-π bonds of Clevudin; *(vi)* Elbasvir interacts with amino acids included Cys 145, Thr 26, Met 165, Gln 189 of PDB6LU7 protein.

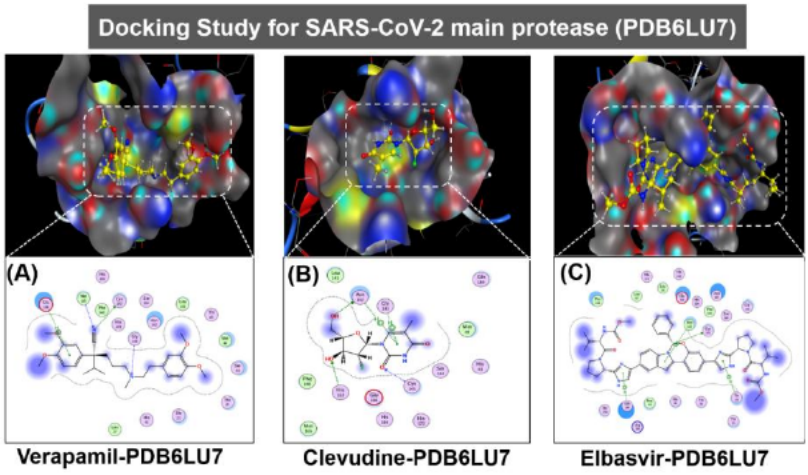

Figure 6: SARS-CoV-2 main protease PDB6LU7 docked with the potential drugs Verapamil, Clevudine and Elbasvir. Docking simulation with the interaction of (**A**) Verapamil-PDB6LU7, (**B**) Clevudine-PDB6LU7 and (**C**) Elbasvir-PDB6LU7

Table 2: Docking simulation results including docking score energy (DS), root-mean-square deviation (RMSD), and the interaction of the 6 potential drugs and PDB6LU7 amino acids (DOI: 10.2210/pdb6LU7/pdb)

Drug	Complex (Drug-Protein)	DS (kcal·mol^{-1})	RMSD (Å)	Interaction with amino acid (Å)
Losartan	Losartan-PDB6LU7	-13.9	1.28	Asn 142 (3.01), Gln 189 (3.55), His 41 (4.03), Glu 166 (4.66), Gln 189 (3.79)
Triazavirin	Triazavirin-PDB6LU7	-14.1	1.16	His 163 (3.05), Asn 142 (3.99), Asn 142 (3.99), Gly 143 (3.51)
TMC-310911	TMC-310911-PDB6LU7	-16.1	1.66	Met 49 (3.67), Met 165 (3.94), His 41 (4.20), Thr 25 (4.01), Thr 25 (3.69), Gln 189 (3.86)
Verapamil	Verapamil-PDB6LU7	-12.1	1.40	Cys 145 (4.19), Met 165 (3.40), Gly 143 (3.55), Glu 166 (4.25)
Clevudine	Clevudine-PDB6LU7	-14.6	1.11	Asn 142 (2.92), Cys 145 (3.01), His 163 (3.04), Asn 142 (4.60), Gly 143 (4.26)
Elbasvir	Elbasvir-PDB6LU7	-15.7	1.40	Cys 145 (3.91), Thr 26 (4.46), Met 165 (4.13), Gln 189 (3.95)

Furthermore, table 3 presents parameters obtained from the simulation, which include $DS_{average}$ (kcal.mol^{-1}), molecular mass (Da), polarizability (Å^3) and volume or size (Å) as well as the logP dispersion coefficient of the potential drugs and the total of hydrogen bonds contained in each drug-protein inhibitory system. They were calculated by Gasteiger-Marsili method using QSARIS system.[26] It is found that the ACE2 and PDB6LU7 inhibition abilities of Losartan, Triazavirin, TMC-310911, Verapamil, Clevudin, Elbasvir exhibit the average DS values of -13.3, -14.1, -16.7, -11.9, -15.2 and -16.3 kcal.mol^{-1}, respectively. Thus, Losartan and Verapamil show the weakest inhibition towards ACE2 and PDB6LU7 with the smallest $DS_{average}$ values of -13.3 and -11.9 kcal.mol^{-1} and the lowest polarizability (5.50 and 0.37 Å^3). Whereas their volume significantly changes from 354.5 to 428.9 Å and the total of hydrogen bonds being 9 and 7 are also small. It is worthy to note that Verapamil shows

a LogP value of 5.7 being higher than 5, the value in which one observes weak inhibitory ability into the SARS-CoV-2.[26]

Inversely, Clevudin, Triazavirin, TMC-310911 and Elbasvir display strong inhibition towards either ACE2 or PDB6LU7. The larger $DS_{average}$ values being -14.1 and -15.2 kcal.mol^{-1} exhibit for Clevudin and Triazavirin. Moreover, TMC-310911 and Elbasvir show the strongest inhibitory effects on two studied proteins with the largest $DS_{average}$ values of -16.7 and -16.3 kcal.mol^{-1} by compared with the other drugs in the system. Additionally, the polarizability values of TMC-310911 and Elbasvir are significantly high (i.e. 8.80 and 9.97 Debye). Besides, their large molecular mass and volume might contribute to their high binding capacity with amino acids. However, it is noted that Clevudine and Triazavirin possess the smallest molecular mass and large polarizability values as well as strong site-site binding of interactions referred to hydrogen bonding. Based on these observations, it can be affirmed that Clevudine and Triazavirin bring their flexibilities and large number of interactions as well as impressive docking score energy values. They can be considered as the most potential candidates of six studied drugs. The results may satisfy for drugs screening requirements under the conditions of Lipinski's criteria:[27] *(1)* Molecular mass < 500 Da; *(2)* no more than 5 groups for hydrogen bonds; *(3)* no more than 10 groups receiving hydrogen bonds; *(4)* the value of logP is less than +5 (logP < 5). Based on the obtained results, we suggest the order of the potential drugs into the SARS-CoV-2 resistance as: Clevudine > Triazavirin > TMC-310911 > Elbasvir > Losartan > Verapamil.

Table 3: Molecular docking parameters including the average docking score energy values ($DS_{average}$, kcal.mol^{-1}), molecular mass (Da), polarizability (Å^3), volume or size (Å), logP and the total of hydrogen bonds of the 6 potential drugs docked with proteins ACE2 and PDB6LU7

Drug	$DS_{average}$	Mass	Polarizability	Volume	LogP	Hydrogen bond
Losartan	-13.3	422.9	5.50	354.5	3.2	9
Triazavirin	-14.1	232.2	7.88	165.8	1.1	11
TMC-310911	-16.7	756.0	8.80	542.0	3.7	13
Verapamil	-11.9	454.6	0.37	428.9	5.7	7
Clevudine	-15.2	260.2	9.39	211.7	1.2	12
Elbasvir	-16.3	880.0	9.97	465.8	2.5	9

4. CONCLUSION

Docking simulation results indicate that the selected drugs are potential inhibitors to host receptor ACE2 and SARS-CoV-2 main protease PDB6LU7. Clevudine and Triazavirin perform strongest inhibitability on both proteins. The respective inhibitability order of the active potential drugs towards both ACE2 and PDB6LU7 is summarized as: Clevudine > Triazavirin > TMC-310911 > Elbasvir > Losartan > Verapamil. Docking score energies of the drugs for inhibition of ACE2 vary from -17.2 to -11.7 kcal.mol^{-1} and the corresponding values for PDB6LU7 are from -12.1 to -16.1 kcal.mol^{-1}. The values calculated for root-mean-square deviation are lower than 2Å in all inhibitory systems. The potential drugs structurally are well-bound in their respective binding pose of the host receptor ACE2 and the targeted protease PDB6LU7. This is mainly based on hydrogen bond interactions between the studied compounds and in-pose amino acids. In particular, the inhibitability highly correlates with the average docking score energy of inhibitory complexes, and drug-protein active interactions. Regarding inhibitory ligands, their polarizability, molecular size, and dispersion coefficient logP are also significant indicators for inhibition potential. This study is highly conducive to further research in order to develop appropriate pharmaceuticals for clinical experiments on SARS-CoV-2.

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Conflict of interest. *The authors declare no conflict of interest.*

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