An *in silico* study on inhibitory ability of Baloxavir marboxil, Baricitinib, Galidesivir, Nitazoxanide, and Oseltamivir against SARS-CoV-2

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Submitted September 29, 2021; Revised November 22, 2021; Accepted November 25, 2021

Abstract

Baloxavir marboxil (D1), Baricitinib (D2), Galidesivir (D3), Nitazoxanide (D4), and Oseltamivir (D5) are well-known performing broad-spectrum activity against a variety of viruses, thus holding high potentiality towards SARS-CoV-2. Quantum properties were examined using density functional theory (DFT). The inhibitory ability of the drugs towards Angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2 main protease (6LU7) was evaluated by molecular docking simulation, while their bio-compatibility was justified by physicochemical properties obtained from QSARIS-based analysis in reference to Lipinski's rule of five. Quantum analysis suggests that the compounds are highly favourable for intermolecular interaction towards protein structures. Given ligand-ACE2 systems, the inhibitory effectiveness follows the order D3-ACE2 > D4-ACE2 > D2-ACE2 > D5-ACE2 > D1-ACE2; and the corresponding order for ligand-6LU7 systems is D2-6LU7 > D4-6LU7 > D3-6LU7 > D5-6LU7 > D1-6LU7. Galidesivir is predicted as the most effective inhibitor towards both targeted protein structures (DS_average -13.1 kcal.mol⁻¹) and the most bio-compatible molecule (Mass 264.9 amu; LogP -0.9; Polarisability 26.8 Å³). The theoretical screening suggests all drugs, especially Galidesivir (D3), promising for treatment of SARS-CoV-2 infection and encourages in-related clinical trials.

Keywords. SARS-CoV-2, ACE2, 6LU7, quantum chemical calculation, molecular docking simulation.

1. INTRODUCTION

SARS-CoV-2 is a new strain of the family Coronaviridae, typically causing pneumonia in humans. The Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and Severe Acute Respiratory Syndrome coronavirus 2019 (SARS-CoV-2) are well-known as severe examples.[1,2] The latest has been causing a worldwide pandemic; thus, the demands for sufficient medicines to treat or prevent are of great and urgent concern to all scientists around the world.

The infection of the virus is based on the critical roles two well-determined proteins. Firstly, angiotensin-converting enzyme 2 (ACE2), an integral membrane glycoprotein, known for its expression of high intensity in kidney, endothelium, lungs, and the heart.[3] Unfortunately, the protein was found to be the host receptor of SARS-CoV-2 and SARS-CoV.[4] On the other side, the main protease of SARS-CoV-2 (6LU7) functions as a proteolytic enzyme, cutting polyproteins into functional units. This means an effective inhibition of 6LU7 can restrain the replication of SARS-CoV-2. Hence, these proteins have been considered as promising targets by experimental studies and clinical trials, resulting in their well-established structures existing in the literature. For example, PDB-1R4L (DOI: 10.2210/pdb1R4L/pdb) and PDB-6LU7 (DOI: 10.2210/pdb6LU7/pdb) are well-determined crystal structures of the two proteins published to the literature at Worldwide Protein Data Bank.

Despite the discovery of effective vaccines approved by the World Health Organisation (WHO), such as ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer), and BBIBP-CorV (Sinopharm), temporary inhibitors are still needed in order to temporise the viral spread for human immune system. This helps human immune system have more time to produce enough antibodies responding against the pathogen, especially for unvaccinated cases with serious symptoms. The immune response includes neutralization, agglutination, or phagocytosis.[5] In this approach, a variety of commercial anti-retroviral drugs for infection of Respiratory Syncytial Virus
Infection (RSV) infection, C hepatitis and dengue have been tested, e.g. C hepatitis and dengue include, among others, the Ribavirin, Remdesivir and Favipiravir (T-705).\textsuperscript{[6-8]} They are often considered as versatile antiviral drugs thanks to their high efficacy towards enzymatic structures. In common, these types are known usually consisting aromatic 5- or 6-rings in their molecular structure. In particular, T-705 is a pyrazine-carboxamide derivative, first-time used for treatment of tuberculosis.\textsuperscript{[9,10]} Base on demonstrated inhibitory mechanism of efficacy towards viral protein structures, the drug was clinically studied in China as an emergent treatment for infection caused by SARS-CoV-2. The results obtained revealed its strong prohibitory effects on the viral replication, along with other candidates T-1105 and T-1106.\textsuperscript{[11]}

Nevertheless, continual in-width screening for potential drugs with efficacious activity against the virus is still needed to be carried out and reported to the literature. The information collected can serve as the reservation in situations of either emergency from medical use or antimicrobial resistance from the viral mutation. First, Baloxavir marboxil (BXM) is an antiviral medication for treatment of influenza A and influenza B flu.\textsuperscript{[12]} It was approved for medical use by the U.S. Food and Drug Administration in 2018.\textsuperscript{[13]} The drug is often sold under the brand name Xofluza. Second, Baricitinib inhibits the subtypes JAK1 and JAK2,\textsuperscript{[14]} thus acting as an inhibitor of janus kinase (JAK). This mechanism makes the drug approved for treatment of rheumatoid arthritis (RA) in adults. It was officially approved for use in the European Union\textsuperscript{[15]} and the United States.\textsuperscript{[16]} Recently, a research reported that Baricitinib can reduce hospitalised duration and accelerate positive clinical status among patients with COVID-19, especially among ones with intervention by high-flow oxygen or noninvasive ventilation, although the mechanism was still unknown.\textsuperscript{[17]} The drug is mainly sold under the brand name Olumiant among many others. Third, Galidesivir (BCX4430, immucillin-A) is an antiviral drug, belonging to an adenosine analogue.\textsuperscript{[18]} It is also well-known for broad-spectrum antiviral effectiveness against a variety of RNA virus families, e.g. bunyaviruses, arenaviruses, paramyxoviruses, coronavirus, flaviviruses, and phleboviruses.\textsuperscript{[19]} On 9th April 2021, BioCryst Pharmaceuticals, Inc. opened enrollment for patients with COVID-19 into a randomised, double-blind, placebo-controlled clinical trial (Clinical trial number NCT03891420). This was an attempt to assess the safety, clinical impact and antiviral effects of Galidesivir against the virus. Fourth, Nitazoxanide is a broad-spectrum antiparasitic and antiviral medication, prescribed for a variety of helminthic, protozoal, and viral infections.\textsuperscript{[20-22]} A 3-month period of clinical trials on healthcare personnel with COVID-19 symptoms indicated that Nitazoxanide as an early treatment (with the dosage of 500 mg orally, every 6 hours for 2 days and then 500 mg twice a day for 4 days) can reduce the intensity of COVID-19 outbreaks, in overall.\textsuperscript{[23]} The drug is mainly sold under the brand name Alinia among others. Fifth, Oseltamivir is an antiviral medication often administrated for either treatment or prevention of influenza A and influenza B (flu), approved for medical use by the U.S. Food and Drug Administration in 1999.\textsuperscript{[24]} It is also on the World Health Organization’s List of Essential Medicines.\textsuperscript{[25]} Given its potentiality against COVID-19, clinical profiling carried out during April-May 2020 at a private hospital in Jakarta revealed a synergetic administration of Oseltamivir and Hydroxychloroquine result in an average survival rate of about 83 % after undergoing treatment of about ten days, the highest figure recorded.\textsuperscript{[26]} The drug is often sold under the brand name Tamiflu. Therefore, Baloxavir marboxil, Baricitinib, Galidesivir, Nitazoxanide, and Oseltamivir holding potential activities against SARS-CoV-2.

 Molecular docking simulation has been demonstrated as a reliable \textit{in silico} approach for prediction of ligand-protein inhibitability. According to the methodology, an associated docking score (DS) represents the static stability, whose value is commonly agreed lower than -3.2 kcal.mol\textsuperscript{-1} for binding capacity.\textsuperscript{[27,28]} In essence, the figure is given by the sum of all free-energy contributed by intermolecular interactions. This affinity includes various hydrogen-bond types (i.e. hydrophilic bonding), and van der Waals forces (i.e. hydrophobic binding). In addition, root-mean-square deviation (RMSD) represents bio-conformational rigidity. The value over 3 Å is commonly referred to failure of inhibition; meanwhile, the threshold for a is widely reported if RMSD ≤ 2 Å.\textsuperscript{[29]}

This study investigates the inhibitability of Baloxavir marboxil (D1), Baricitinib (D2), Galidesivir (D3), Nitazoxanide (D4), and Oseltamivir (D5) towards Angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2 main protease (6LU7). The ligand quantum properties were determined by DFT calculations. The evaluation for their inhibitability towards the targeted protein structures is based on molecular docking simulation. Also, the biocompatibility of the ligands is justified by physicochemical properties obtained from QSARIS-based analysis in reference to Lipinski’s rule of five.
The results are justified by their significance towards the prevention of SARS-CoV-2 infection.

![Structural formula of Baloxavir marboxil (D1), Baricitinib (D2), Galidesivir (D3), Nitazoxanide (D4), and Oseltamivir (D5)](image)

**Figure 1:** Structural formula of Baloxavir marboxil (D1), Baricitinib (D2), Galidesivir (D3), Nitazoxanide (D4), and Oseltamivir (D5)

2. METHODOLOGY

2.1. Quantum chemical calculation

Molecular quantum properties of the potential drugs (D1–D5) and their optimised geometry were examined by density functional theory (DFT) using Gaussian 09 Package (G09) without symmetry constraints\(^\text{[30]}\) at level of theory M052X/6-311++G(d,p).\(^\text{[31]}\) Structural global minimum on the potential energy surface (PES) was confirmed by calculation of vibrational frequencies on the respective molecules. The frozen-core approximation for non-valence-shell electrons with calculation using a larger basis set def2-TZVPP\(^\text{[32]}\) yielded single-point energies at the M052X/6-311++G(d,p)-level-optimised geometries. Resolution-of-identity (RI) approximation was applied for each optimisation run. NBO 5.1 available in Gaussian 09 was utilised frontier orbital analysis at level of theory BP86/def2-TZVPP.\(^\text{[33]}\) The highest occupied molecular orbital (HOMO) energy, \(E_{\text{HOMO}}\), represents intermolecular electron donation tendency; meanwhile, electron-accepting ability of a
molecule can be inferred from its value $E_{\text{LUMO}}$ (for lowest unoccupied molecular orbital - LUMO). By exhibiting molecular electronic excitability, energy gap $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$ can suggest intermolecular reactivity of the host molecule. Koopmans’ theorem$^{[34]}$ was used for calculation of ionisation potential ($I$) and electron affinity ($A$) expressed as: $I = -E_{\text{HOMO}}$ and $A = -E_{\text{LUMO}}$, which further inferred the molecule electronegativity ($\chi$) via equation: $\chi = (I + A)/2$. Figure 1 provides structural formulae of the compounds for the computational input.

2.2. Docking-based prediction

The simulation was implemented on MOE 2015.10 software. The structural information of targeted proteins ACE2 and 6LU7 and docked ligands (D1-D5) were required as the precursors. Typically, a molecular docking simulation follows three steps.$^{[27,28,35,36]}

a) Pre-docking preparation: Structural data for protein ACE2 and protein 6LU7 was downloaded from Worldwide Protein Data Bank at entries DOI: 10.2210/pdb1R4L/pdb and DOI: 10.2210/pdb6LU7/pdb, respectively. Figure 2 provides their crystal assembly. QuickPrep was used to correct the protein structures with 3D protonation; their active regions were set within 4.5 Å of amino acid - ligand distance. As-prepared protein structures were saved in *.pdb as the input for docking simulation. In terms of ligands, D1-D5 were under structure-optimisation by Conj Grad for lowest-energy convergence.

b) Docking investigation: The protein and ligand structures obtained served as the input for molecular docking simulation on MOE 2015.10 environment. The output was the most statically stable intermolecular complexes, stored in the format *.sdf.

c) Post-docking analysis: Docking score (DS) energy was considered as the primary predictor for the ligand-protein inhibitory systems. Root-mean-square deviation (RMSD) represented binding stability of the complex static conformation. Hydrophilic binding (i.e. hydrogen bonds) and hydrophobic interaction (i.e. van de Waals forces) were considered as the contributors for protein-ligand affinity, thus yielding their Gibbs free energy. In addition, ligand-protein interactions are mapped in a 2D projection and the corresponding in-pose orientation is provided by a 3D rendering.

2.3. QSARIS-based analysis

Stable structures of potential drugs are evaluated by computing molecular mass (Da), polarizability ($\AA^3$) and volume or size ($\AA$), and dispersion coefficients (logP and logS) implemented on QSARIS system via Gasteiger–Marsili method.$^{[37]}$ They were then prescreened with orally pharmacological compatibility, in-reference to Lipinski’s rule of five predicting their drug-likeness.$^{[38]}$ Accordingly, a certain set of physicochemical properties of a well membrane-permeable candidate is predicted following the requirements: (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).$^{[39,40]}

3. RESULTS AND DISCUSSION

3.1. Quantum chemical property

Geometrically optimised structure of the studied drugs (D1–D5) are shown in figure 3. Overall, all DFT calculations at level of theory M052X/6-311++G(d,p) reach a convergence, validating the in-practice existence of these structures. There are no abnormal constraints (bonding angles) observed in the converged configurations; also, all figures retrieved for bond lengths register within their characteristics, e.g. 1.54 Å for C-C, 1.09 Å for C-H, 1.43 Å for C-O (oxatriquinane), 1.49 Å for C-N (simple amines), and 1.30 Å for S-O (sulphonyl). This indicates their quantum-regarded stability in theory, thus confirming their mass-productivity in application. Besides, a variety of strong-polarised groups such as NH$_2$, N-heterocyclic, OH, or C-O would induce the significance of their dispersibility in physiochemical media and their interactability with biological components.

The frontier molecular orbitals (HOMO and LUMO) of the compounds are presented in figure 4. Base on the interpretation of electron transferability addressed in the methodology, the output can provide a preliminary view on their intermolecular electron transferability, e.g. ligand-protein inhabitation. In particular, HOMO and LUMO electron density of D1 and D5 occupy rather separate parts of their structural planes, thus suggesting their electron-transferring flexibility. This would help the molecules can execute their interactions with vanishing inhabitable approaching manners, yet possibly at the expense of static stability. In contrast, the corresponding configurations for D2-4 seem to implicate the reversed tendency as the HOMO and LUMO occupations are localised about certain parts in their molecular structures, i.e. their heterocyclic functionals in specific. This implies that they are
likely to prioritise either electron-donating or electron-accepting performance through these groups, thus marginising their intermolecular interactions yet with elevated Gibbs free energy.

Quantum chemical parameters retrieved from NBO analysis at BP86/def2-TZVPP are given in Table 1. All structures register their $E_{\text{HOMO}}$ under -7 eV, indicating their electronica stability (commonly agreed by experiment under -5 eV). Another work of ours also signified that the complexes belonging to a tetrylone family are accepted to be highly stable with the corresponding figures ranging from -3 to -7 eV.\[41\] Regarding band-gap energy, the HOMO-LUMO leaps of the compounds, varying between 6.525 and 8.295 eV, lies on the transition of an insulator ($> 9$ eV) and a semiconductor ($< 3.2$ eV).\[42\] This means they are all quantum-favourable candidates for intermolecular binding capability towards protein structures given the well-proven electrical conductivity of the polypeptide molecules.\[43,44\] Also, electronegativity ($\chi$), or the chemical potential ($\mu$) in negative value, could be considered as a reliable inhibition indicator as it presents an electron-attracting tendency. In principle, a higher electronegativity implies stronger attraction of electrons towards the host molecule.

Altogether, the findings from quantum-based investigations on the studied drugs (D1-D5) expects their promising intermolecular interactability in general, and their inhibitability towards protein-structures in particular.

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**Figure 3:** Optimized structures of D1-D5 calculated by DFT at level of theory M052X/6-311++g(d,p)

**Figure 4:** HOMO and LUMO of D1-D5 calculated by DFT at level of theory M052X/def2-TZVPP
3.2. Protein inhibitability

The quaternary structure of the targeted proteins (ACE2 and 6LU7) and their most approachable sites by the potential drugs (D1–D5) are shown in Figure 5; in addition, the screening primary results of the corresponding inhibitability are summarised in Table 2. The sites are assigned as site 1 (yellow), site 2 (green), site 3 (cyan), and site 4 (blue). Overall, both protein structures seem to contain no exceptionally vulnerable sites to the drugs given no significant deviation between their DS values of the inhibitory complexes (ca. ±2.5 kcal.mol⁻¹), i.e. static stability, and their hydrogen bonds, aka. strong interactions. This confirms the versatility as broad-spectrum inhibitors of these selected drugs, which was already well-demonstrated by the experiments and clinical trials. Regarding protein ACE2, different drugs exhibit different affinities to different sites; meanwhile, given protein 6LU7, the susceptibility induced by the drugs is prone to site 1, except for D3. The figures are signified in bold and opted for further justification of their inhibitability.

Table 2: Prescreening results on inhibitability of D1–D5 towards the sites of proteins ACE2 and 6LU7

| P   | D   | Site 1 | Site 2 | Site 3 | Site 4 |
|-----|-----|--------|--------|--------|--------|
|     |     | E      | N      | E      | N      | E      | N      |
| ACE2| D1  | -10.3  | 4      | -9.3   | 2      | -9.8   | 2      | -10.1  | 2      |
|     | D2  | -10.8  | 3      | -12.8  | 5      | -11.3  | 3      | -11.0  | 4      |
|     | D3  | -14.2  | 6      | -11.3  | 4      | -12.1  | 3      | -12.5  | 4      |
|     | D4  | -12.1  | 4      | -10.3  | 3      | -11.5  | 4      | -13.4  | 6      |
|     | D5  | -10.8  | 3      | -11.2  | 5      | -9.7   | 2      | -10.2  | 3      |
|     | D1  | -10.8  | 5      | -9.6   | 3      | -9.7   | 4      | -10.3  | 4      |
|     | D2  | -14.7  | 7      | -12.3  | 4      | -11.8  | 5      | -12.7  | 4      |
|     | D3  | -11.0  | 4      | -12.1  | 7      | -10.9  | 4      | -11.4  | 3      |
|     | D4  | -13.9  | 7      | -12.2  | 5      | -11.8  | 3      | -12.9  | 5      |
|     | D5  | -11.8  | 5      | -9.9   | 3      | -9.2   | 2      | -10.7  | 3      |

P: Protein; D: Drug; E: DS value (kcal.mol⁻¹); N: Number of hydrophilic interactions.

Figure 5: Quaternary structures of proteins (a) ACE2 and (b) 6LU7 with their approachable sites by the investigated drugs: site 1 (grey), site 2 (cyan), site 3 (yellow), and site 4 (blue).
Table 3: Molecular docking simulation results for ligand-ACE2 inhibitory complexes

| Ligand-protein complex | Hydrogen bond | van de Waals interaction |
|------------------------|---------------|--------------------------|
| **Name**               | **DS** (kcal.mol\(^{-1}\)) | **RMSD** (Å) | **L** | **P** | **T** | **D** | **E** | **Interaction**                  |
| D1-ACE2                | -10.3         | 1.39                     | O     | N     | GlnB936 | H-acceptor | 3.36 | -1.8 | AlaA754, LeuA994, IleA752, GlyA751, GluA755, SerA750, GlyB759, LysB297, TyrB300, π-π | 3.96 | -0.1 | IleB299, ValB290, GlyB298 |
| D2-ACE2                | -12.8         | 1.99                     | N     | N     | ArgB996 | H-acceptor | 3.36 | -1.8 | TyrA300, ThrA302, ValA290, SerA289, IleA299, ThrB743, ArgB747 | 4.03 | -1.3 | |
| D3-ACE2                | -14.2         | 1.14                     | O     | O     | GlnB936 | H-donor | 3.00 | -1.2 | LysB929, ArgA1001, GluB999, ArgB996, AlaA754 | 4.04 | -0.9 | |
| D4-ACE2                | -13.4         | 1.45                     | S     | O     | SerB1019 | H-donor | 3.30 | -0.9 | GlnA1018, ValB1022, AspB1023, LysB1020, ArgB1021 | 3.94 | -0.6 | |
| D5-ACE2                | -11.2         | 1.35                     | N     | O     | GlnB936 | H-donor | 3.27 | -2.2 | GluA999, ProA710, LysA929, GluB755, ArgB1001, ValA933, ArgB996, AlaA754 | 3.02 | -2.6 | |

**DS**: Docking score energy (kcal.mol\(^{-1}\)); **RMSD**: Root-mean-square deviation (Å). **L**: Ligand; **P**: Protein; **T**: Type; **D**: Distance (Å); **E**: Energy (kcal.mol\(^{-1}\)).

Data on the inhibition simulated at the selected sites of each duo-system is presented in Tables 3 and 4 for ligand-ACE2 and ligand-6LU7 complexes, respectively. In principle, DS values represent the average Gibbs free energy given by the contribution of ligands-protein attractive forces and the compromise for constrained distortion of ligand structures in order to shape into in-pose topographical features; and, RMSD values represent the bio-conformational rigidity. This means the inhibitory potentiality of the ligand-ACE2 systems could be interpreted into the order D3-ACE2 (DS -14.2 kcal.mol\(^{-1}\); RMSD 1.14 Å) > D4-ACE2 (DS -13.4 kcal.mol\(^{-1}\); RMSD 1.45 Å) > D2-ACE2 (DS -12.8 kcal.mol\(^{-1}\); RMSD 1.99 Å) > D5-ACE2 (DS -11.2 kcal.mol\(^{-1}\); RMSD 1.35 Å) > D1-ACE2 (DS -10.3 kcal.mol\(^{-1}\); RMSD 1.39 Å). The results indicate that D3-ACE2 is predicted to possess most static stability given its lowest DS value; whilst, D2 is expected to form loosest inhibitory structure with ACE2 given their highest RMSD value, i.e. root-mean-square deviation of backbone bonding lengths. Furthermore, D2-ACE2 and D3-ACE2 systems are found to form significant hydrophilic bonding between the ligand and the amino acid residues of the protein structures. The former includes two H-acceptor bonds of arginine (viz. ArgB747), with free energy values of -3.6 and -4.5 kcal.mol\(^{-1}\); meanwhile, the latter, there are two different amino acid residues (GluA775 and AspB932) bearing two ionic bonds, with free energy values of -3.6 and -6.2 kcal.mol\(^{-1}\). It can be speculated that these significant interactions might channel sufficient distortion forces to the secondary-tertiary structure of the protein, thus inducing denaturation. This also means a loss of shape-based activity might ensue. In terms of ligand-6LU7 systems, the inhibitory potentiality could be similarly reasoned by the order D2-6LU7 (DS -14.7 kcal.mol\(^{-1}\); RMSD 1.53 Å) > D4-6LU7 (DS -13.9 kcal.mol\(^{-1}\); RMSD 1.10 Å) > D3-6LU7 (DS -12.1 kcal.mol\(^{-1}\); RMSD 1.12 Å) > D5-6LU7 (DS -11.8 kcal.mol\(^{-1}\); RMSD 1.30 Å) > D1-6LU7 (DS -10.8 kcal.mol\(^{-1}\); RMSD 1.22 Å). In particular, the highest DS value means...
**D2-6LU7** complex is most statically stable, and the lowest RMSD value means **D4-6LU7** intermolecular interaction is most rigid in conformation. Although not as predominant as those of ligand-ACE2 systems, there are still significant H-donor-based interactions endured by Asp153 (**D3-6LU7**; E = -3.1 kcal.mol\(^{-1}\)), His164 (**D4-6LU7**; E = -4.9 kcal.mol\(^{-1}\)), and His164 (**D5-6LU7**; E = -4.4 kcal.mol\(^{-1}\)). Besides, the significance on the inhibitability is highly justifiable by comparison to other duo-systems already reported in the literature.[45-47] Consistently, another work using the docking environment given by Patchdock also predicted the fourth-ranked candidate **D5** (aka. Oseltamivir) in this study as a moderate-promising inhibitor towards 6LU7 structure.[48] Therefore, all the studied potential drugs, especially Galidesivir (**D3**), are considered promising inhibitors towards ACE2 and 6LU7 structures, thus issued as an emergency use for SARS-CoV-2 infection.

### Table 4: Molecular docking simulation results for ligand-6LU7 inhibitory complexes

| Ligand-protein complex | Hydrogen bond          | van de Waals interaction |
|------------------------|------------------------|--------------------------|
|                        |                        |                          |
| **C** C S              | Met49                  | H-donor                  | 3.67 -1.0 Val186, Asp187, Glu166, His164, Asn142, Ser144, Gly143, Leu141, Thr25, His41, Arg188, Thr24 |
| **O** O S              | Cys145                 | H-donor                  | 3.97 -1.0                           |
| **O** O C              | Met165                 | H-acceptor               | 3.41 -1.0                           |
| **O** O N              | Gln198                 | H-acceptor               | 3.04 -1.9                           |
| **F** F N              | Thr26                  | H-acceptor               | 3.03 -1.1                           |
| **N** N O              | Arg188                 | H-donor                  | 3.12 -0.8                           |
| **O** O S              | Met49                  | H-donor                  | 3.47 -0.6                           |
| **N** N N              | Ser144                 | H-acceptor               | 3.31 -0.8                           |
| **N** N N              | Cys145                 | H-acceptor               | 3.39 -0.9                           |
| **N** S S              | Cys145                 | H-acceptor               | 3.36 -1.4                           |
| 6-ring C               | Gln189                 | π-H                      | 3.58 -0.9                           |
| 6-ring N               | Gln189                 | π-H                      | 4.56 -0.6                           |
| **O** O O              | Asp153                 | H-donor                  | 2.93 -3.1                           |
| **N** O O              | Asn151                 | H-donor                  | 3.21 -0.9                           |
| **N** O O              | Thr111                 | H-donor                  | 3.23 -0.9                           |
| **N** O N              | Asn151                 | H-donor                  | 3.30 -1.1                           |
| **N** O N              | Asp295                 | ionic                    | 3.87 -0.8                           |
| 5-ring 6-ring          | Phe294                 | π-π                      | 3.91 -0.1                           |
| 6-ring 6-ring          | Phe294                 | π-π                      | 3.80 -0.1                           |
| **S** S S              | Met49                  | H-donor                  | 3.64 -0.1                           |
| **N** S S              | Cys145                 | H-donor                  | 4.08 -1.7                           |
| **N** O N              | His164                 | H-donor                  | 2.88 -4.9                           |
| **O** O N              | Gln189                 | H-acceptor               | 3.08 -1.4                           |
| **O** O N              | Cys145                 | H-acceptor               | 3.34 -1.2                           |
| 6-ring 5-ring          | His163                 | π-H                      | 4.60 -0.6                           |
| 6-ring 5-ring          | His41                  | π-H                      | 3.79 -0.1                           |
| **O** O S              | Met165                 | H-donor                  | 3.42 -0.1                           |
| **N** O N              | His164                 | H-donor                  | 2.74 -4.4                           |
| **C** S S              | Met165                 | H-donor                  | 3.70 -1.1                           |
| **C** 5-ring           | His41                  | H-π                      | 3.91 -1.2                           |

**DS**: Docking score energy (kcal.mol\(^{-1}\)); **RMSD**: Root-mean-square deviation (Å).

L: Ligand; P: Protein; T: Type; D: Distance (Å); E: Energy (kcal.mol\(^{-1}\)).

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Figure 6: Visual presentation and in-pose interaction map of ligand-ACE2 inhibitory structures

Projections for 3D in-pose morphology and 2D interaction map of all ligand-protein inhibitory complexes are visually presented in figures 6 and 7 for ligand-ACE2 and ligand-6LU7 complexes, respectively. In design of specific protein inhibitors, the size- and shape-compatibility between the ligands and the protein sites is also of importance. Although the compounds are observed to be size-fitting (from 3D observation) and shape-complementary (by 2D continuous proximity contours), the sites are unlikely conducive to either simultaneous inhibition or profoundly larger candidates. Hence, the studied drugs could serve as size- and medica-references for further development of a pharmaceutical medicine.

Table 5: Physicochemical properties of studied compounds D1-D5

| Drug | DSaverage | Mass  | Polarisability | Size   | Dispersion coefficients | Hydrogen bond (ACE2/6LU7) |
|------|-----------|-------|----------------|--------|-------------------------|---------------------------|
|      |           |       |                |        | LogP | LogS | H-acceptor | H-donor |
| D1   | -10.6     | 572.7 | 54.6           | 603.9  | 2.3  | -4.2 | 3/3        | 0/2     |
| D2   | -13.8     | 370.8 | 36.2           | 391.5  | 1.9  | -3.1 | 3/3        | 0/2     |
| D3   | -13.1     | 264.9 | 26.8           | 270.3  | -0.9 | -1.7 | 2/0        | 1/4     |
| D4   | -13.7     | 308.1 | 26.7           | 334.2  | 2.5  | -4.4 | 3/2        | 2/3     |
| D5   | -11.5     | 312.9 | 33.8           | 475.6  | 1.4  | -3.2 | 4/0        | 1/4     |
3.2. Physicochemical properties

Table 5 summarises QSARIS-based physicochemical properties of the investigated ligands, including molecular mass (amu), polarisability (Å$^3$) and size (Å) as well as the logP and logS dispersion coefficients. These parameters can be thought to represent pre-docking conditions, i.e. the interactions between the ligands and potential plasmatic components in the polarised media of biological bodies. As Baloxavir marboxil (D1), Baricitinib (D2), Galidesivir (D3), Nitazoxanide (D4), and Oseltamivir (D5) are all approved for commercial use, there is no anomalousness retrieved, except for D1 whose mass (572.7 amu) is slightly larger than first Lipinski's criterion ($M_a < 500$ amu). Significantly, D3, already proving its inhibitory potentiality by molecular docking simulation, also exhibits its bio-compatibility via analysis on QSARIS; in fact, the molecule possesses the lowest figures of molecular mass ($M_a = 264.9$ amu) and dispersion coefficient (LogP = -0.9). Also, no more than five hydrogen bonds, either donor- or acceptor-type, regardless of targeted proteins (ACE2 or 6LU7) preliminarily implies that Galidesivir would satisfy the third and fourth criteria of Lipinski's rule of five. In addition, its polarisability constant is of significance, i.e. 26.8 Å$^3$, likely inducing the formation of molecular dielectric moments.$^{[49]}$ This is thought to be highly conducive to both inhibition towards a polarised protein structure and fluidity in body-based hydrophilic media.

4. CONCLUSIONS

This report reviews the theoretical efficacy of Baloxavir marboxil (D1), Baricitinib (D2),
Galidesivir (D3), Nitzoxanide (D4), and Oseltamivir (D5) as protein inhibitors towards Angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2 main protease (6LU7). Quantum properties of the ligand molecule suggest favourableness for intermolecular activity in general and inhibition towards protein structures in particular. Galidesivir is predicted as the most effective inhibitor towards both ACE2 and 6LU7 protein structures by molecular docking simulation. Given D3-ACE2, DS value is -14.2 kcal.mol⁻¹; RMSD value is 1.14 Å; Gibbs free energy values of GluA755- and AspB932-based ionic bonds are -3.6 and -6.2 kcal.mol⁻¹, respectively. Regarding D3-6LU7, DS value is -12.1 kcal.mol⁻¹; RMSD value is 1.12 Å; Gibbs free energy value of Asp153-based H-donor bond is -3.1 kcal.mol⁻¹. The drug is also demonstrated most bio-compatible by QSARIS-based analysis (in reference to Lipinski’s rule of five), with molecular mass of 264.9 amu (< 500 amu) and dispersion coefficient of -0.9 (< 5). The screening results especially suggest Galidesivir (D3) as a promising inhibitor in treatment of SARS-CoV-2 infection and encourage further tests, either in-laboratory or in-clinical, to validate the findings.

Acknowledgments. This research was funded by the Ministry of Education and Training for the development of Science and Technology, with code of B2021-DHH-13.

Conflicts of interest. The authors declare no conflict of interest.

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