Molecular Docking suggests repurposing of Brincidofovir as a potential drug targeting SARS-CoV-2 "COVID-19" ACE2 receptor and main protease

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Research Article

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Abstract

The current outbreak of the highly transmittable and life-threatening tremen
tense respiratory disorder coronavirus 2 (SARS-CoV-2) has advanced rapidly and posed a
global health emergency. Many clinical trials are now being conducted to test possible
therapies. To assist, the molecular docking was applied on some selected FDA-approved drugs,
previously used in epidemics, and the top ten compounds were selected. These ten
well-characterized drugs, previously used to treat Malaria and Ebola infections, were
screened based on their interactions with the SARS-CoV-2 ACE2 Receptor and 3C-like
Protease. Compared to the other nine medicines, Brincidofovir, an ether lipid ester analog
of cidofovir with potent antiviral activity, showed the highest docking scores and binding
interactions. Therefore, Brincidofovir worth further investigations and clinical trials as a
possible therapeutic agent for the COVID-19 disease.

1. Introduction

Humankind has previously witnessed the outbreak of many life-threatening pathogens including
Ebola, Zika, the Middle East respiratory syndrome (MERS) coronavirus, Severe Acute respiratory
syndrome (SARS) coronavirus and nowadays, the severe acute respiratory syndrome coronavirus 2
(SARS-CoV-2) [1-5]. The novel coronavirus has initially spread from China and propagated
rapidly throughout the globe and has received worldwide attention due to its alarming levels of
transmission and aggressive behavior in causing acute respiratory disease. The virus was then
officially declared pandemic by the World Health Organization (WHO).

Researchers throughout the globe are working around the clock to develop potential vaccines and
drugs to fight SARS-CoV-2 the causative agent of the COVID-19 disease. However, developing a
new drug or vaccine usually takes a long time as it should be intensively tested and confirmed
safe through clinical trials before they can be approved for human use [6]. Therefore, repurposing
FDA-approved drugs seems to be a quicker way to treat patients who otherwise have no option. The
SARS-CoV-2 is a single-stranded positive-sense RNA virus that relies on its spike (S) protein to
attach and enter the target cells [7, 8]. The virus S protein binds to the host cell angiotensin-
converting enzyme 2 (ACE2) receptor allowing the virus particles to enter the cells [7, 9]. Thus,
blocking the ACE2 receptor reveals an effective therapeutic target for drug discovery to prevent
the SARS-CoV-2 transmissibility. Besides, the two coronavirus proteases, designated 3-
chymotrypsin-like protease (3CLpro) and a papain-like protease (PLpro) were previously
considered vital targets to combat the SARS and MERS Coronavirus epidemics [8]. These two
proteases were shown to be highly conserved with the novel SARS-CoV-2, especially in the
functional regions [8]. Viruses use their proteases to breakdown its viral peptides into
functional units essential for its replication and packaging inside the host cells, thus considered
anti-viral drug targets.

Molecular docking is a popular bioinformatic modeling tool broadly used in structure-based
drug design [10]. It is an efficient way to predict the type of interaction, binding affinity and the
appropriate target
binding sites between the drug and corresponding receptor using, for instance, scoring functions [10, 11]. Elucidating the binding behavior has an important role in the rational drugs-design as well as to explicate fundamental biochemical processes [10, 11].

In this study, molecular docking was performed on dozens of FDA-approved drugs and the top ten hits, previously used in the treatment of malarial, fungal/bacterial and Ebola infections and FDA-approved/fast-tracked for human treatment, were selected. The selected drugs used in this study were performed by the MOE modeling program to predict the binding sites and their docking score.

2. Materials And Methods

2.1. Molecular docking Method

2.1.1. Software and machinery used

All docking studies calculated and characterized by the MOE program. Drug Preparation was done by changing the two-dimensional structure of the drugs into a three-dimensional structure. Three-dimensional structure optimization of compounds was done by geometry optimization. Geometry optimization was a process to minimize total energy so that the structure of the most stable test compound was obtained, characterized by a decrease in the overall energy value of the structure of the test drugs. In geometry optimization results a shift in the structure of compounds into the most stable structure, so that there was a decreasing energy value of the structure of the test compound.

2.1.2. SARS-CoV-2 protease and receptor structure.

Generation of the protein structures and the crystal structure of the new COVID-19 Protease (PDB code = 1Q2W) and ACE2 Receptor (PDB code = 6M0J) were retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/welcome.do) [12]. All bound solvent, ligands and metal ions removed from the proteins and then we added hydrogen atoms for optimization.

2.1.3. Molecular docking procedure

The docking protocol was done against the SARS-CoV-2 ACE2 receptor (PDB code = 6M0J), the SARS-CoV-2 3CL protease (PDB code = 1Q2W) and its four active sites. The active sites were isolated and used as dummies atoms. The docking strategy was performed by using MMFF94x force field [13]. The Dock scoring in MOE software was done through the London dG scoring function. flexible rotatable bonds were allowed for all Drugs, and the best five binding poses were used for analysis to get the best score. We used the database browsers to compare the docking poses to the drug inside the receptor structure and to obtain RMSD of the docking pose. To rank the binding affinity of all drugs toward the protein molecule, the binding free energy and hydrogen bonds between the compounds and amino acid in the receptor have been calculated [14]. Also, the RMSD of the drug position compared to the docking pose was used in the ranking. RMSD, as well as the docking score of the native drug within the corresponding receptor, were used [13-16].
3. Results And Discussions

Molecular docking and other computer-related methods are efficient tools broadly used to understand the molecular aspects of protein-ligand interactions during drug discovery against many of previous emerging and fatal diseases including SARS coronavirus [10, 11]. In this study, virtual screening of several FDA-approved/fast-tracked drugs were performed against the SARS-CoV-2 ACE2 host receptor (PDB code = 6M0J), the SARS-CoV-2 3CL protease (PDB code = 1Q2W) and its four active sites, in order to find the most predicated drug-ligand interactions. The presented parameters include the docking scores, ligand binding efficiency and hydrogen bonding interactions. The top ten ranked compounds were selected and presented in Table 1-6 and Figure 1-4. These ten drugs include four antivirals (Favipiravir, Ribavirin, Brincidofovir, and Galidesivir), four anti-malarial (Chloroquine, Mefloquine, Primaquine, and Tafenoquine) and two antimicrobial agents (Doxycycline and Atovaquone). Whether we docked against the ACE2 receptor (PDB code = 6M0J), the SARS-CoV-2 3CL protease (PDB code = 1Q2W) or the four main active sites within the SARS-CoV-2 3CL protease, the docking scores of the 10XC19 drug Brincidofovir or BCV) shown to be the top hit (ranked #1) compared to the other nine drugs. The docking scores for the BCV were -10.83, -8.30 and -9.02 towards the SARS-CoV-2 3CL protease active site 1 (PDB code = 1Q2W), the SARS-CoV-2 3CL whole protease (PDB code = 1Q2W) (Tables 1-2 and Figure 1-2) and the ACE2 receptor (PDB code = 6M0J) (Tables 3-4 and Figure 3-4), respectively. The antimalarial drug Tafenoquine comes second in the rank where it scored -8.15 and -7.76 with the AC2 receptor and the SARS-CoV-2 3CL protease active site 1, respectively (Table 1 and 3).

Tab. 1 Docking score and energy of the Malaria and Ebola drugs and 1Q2W of COVID-19 with site 1 of COVID-19 Protease (PDB code = 1Q2W)

| Drug name      | Score | rmsd_refine | E_conf | E_place | E_score_1 | E_refine | E_score_2 | Log P | Log P |
|----------------|-------|-------------|--------|---------|-----------|----------|-----------|-------|-------|
| Atovaquine     | -6.34 | 2.92        | 60.20  | -69.94  | -10.85    | -32.69   | -6.34     | 6.48  | 6.48  |
| Chloroquine    | -6.98 | 1.88        | -42.83 | -64.37  | -9.70     | -22.01   | -6.98     | 3.98  | 3.98  |
| Doxycycline    | -7.16 | 0.94        | 46.19  | -126.91 | -14.26    | -38.51   | -7.16     | 0.46  | 0.46  |
| Mefloquine     | -6.89 | 0.90        | 119.56 | -74.76  | -10.09    | -33.12   | -6.89     | 3.91  | 3.91  |
| Primaquine     | -6.15 | 1.19        | 2.88   | -70.02  | -9.23     | -32.80   | -6.15     | 2.21  | 2.21  |
| Tafenoquine    | -7.76 | 2.04        | 53.55  | -57.83  | -9.67     | -37.11   | -7.76     | 5.08  | 5.08  |
| Favipiravir    | -5.29 | 1.27        | 51.65  | -63.25  | -9.80     | -26.76   | -5.29     | -0.21 | -0.21 |
| Ribavirin      | -5.91 | 1.45        | 150.55 | -77.89  | -9.55     | -28.37   | -5.91     | -2.27 | -2.27 |
| Galidesivir    | -5.69 | 1.18        | 18.61  | -74.21  | -10.14    | -27.67   | -5.69     | -2.34 | -2.34 |
| Brincidovir    | -10.83| 2.88        | -58.15 | -51.62  | -11.43    | -58.84   | -10.83    | 5.54  | 5.54  |
Tab. 2: interaction table between Malaria and Ebola drugs and 1Q2W of COVID-19 with site 1 of COVID-19 Protease (PDB code = 1Q2W)

| z    | Ligand | Receptor | Interaction | Distance | E (kcal/mol) |
|------|--------|----------|-------------|----------|--------------|
| Atovaquone | 6-ring | CD       | pi-H        | 4.11     | -0.5         |
| Chloroquine | O 5    | NZ       | H-acceptor  | 3.34     | -0.9         |
|        | 6-ring | CB       | pi-H        | 4.16     | -0.6         |
|        | 6-ring | CA       | pi-H        | 3.49     | -0.5         |
| Doxycycline | N 6    | N        | H-acceptor  | 3.27     | -3.2         |
| Mefloquine | O 41   | OG1      | H-donor     | 3.09     | -0.9         |
| Primaquine | F 1    | N        | H-acceptor  | 3.05     | -0.6         |
|        | 6-ring | CG       | pi-H        | 3.72     | -0.8         |
| Tafenoquine | N 27   | NH1      | H-acceptor  | 3.58     | -1.6         |
|        | 6-ring | CD       | pi-H        | 4.49     | -0.7         |
| Favipiravir | N 13   | O        | H-donor     | 3.16     | -1.6         |
|        | N 9    | N        | H-acceptor  | 3.32     | -2.3         |
| Ribavirin | O 1    | O        | H-donor     | 2.98     | -0.8         |
|        | O 15   | NZ       | H-acceptor  | 3.26     | -1.2         |
|        | O 26   | N        | H-acceptor  | 3.14     | -3.2         |
|        | N 27   | N        | H-acceptor  | 3.32     | -2.1         |
|        | 5-ring | CB       | pi-H        | 3.99     | -0.7         |
| Galidesivir | O 33   | O        | H-donor     | 3.00     | -1.2         |
|        | N 9    | NH1      | H-acceptor  | 3.25     | -4.0         |
|        | N 12   | N        | H-acceptor  | 3.59     | -1.0         |
|        | 6-ring | CD       | pi-H        | 4.39     | -0.7         |
| Brincidovir | O 63   | O        | H-donor     | 3.02     | -2.9         |
|        | O 68   | NH1      | H-acceptor  | 2.95     | -2.4         |
Tab. 3 Docking score and energy of the Malaria and Ebola drugs with ACE-2 Receptor (PDB code = 6M0J)

| No. | Drug name     | Score | rmsd_refine | E_conf | E_place | E_score1 | E_refine | E_score2 | Log P |
|-----|---------------|-------|-------------|--------|---------|----------|----------|----------|-------|
| 1   | Atovaquone    | -6.65 | 1.64        | 64.11  | -76.16  | -10.05   | -28.61   | -6.65    | 6.48  |
| 2   | Chloroquine   | -6.55 | 1.58        | -38.85 | -81.75  | -8.86    | -30.65   | -6.55    | 3.98  |
| 3   | Doxycycline   | -7.11 | 3.84        | 47.57  | -117.63 | -11.62   | -44.11   | -7.11    | 0.46  |
| 4   | Mefloquine    | -6.38 | 1.95        | 120.39 | -78.94  | -12.26   | -28.38   | -6.38    | 3.91  |
| 5   | Primaquine    | -6.10 | 1.44        | 5.46   | -77.03  | -9.45    | -30.29   | -6.10    | 2.21  |
| 6   | Tafenoquine   | -8.15 | 1.57        | 52.07  | -101.66 | -9.88    | -44.36   | -8.15    | 5.08  |
| 7   | Favipiravir    | -4.63 | 1.17        | 49.20  | -63.61  | -9.14    | -21.46   | -4.63    | -0.21 |
| 8   | Ribavirin     | -5.55 | 1.04        | 148.09 | -80.63  | -9.69    | -27.83   | -5.55    | -2.27 |
| 9   | Galidesivir    | -5.78 | 1.35        | 18.31  | -73.22  | -11.53   | -25.24   | -5.78    | -2.34 |
| 10  | Brincidivir    | -9.02 | 2.19        | -52.46 | -57.61  | -8.93    | -49.64   | -9.02    | 5.54  |

Tab. 4 : interaction table between Malaria and Ebola drugs with ACE-2 Receptor (PDB code = 6M0J)
| Drug          | Ligand | Receptor | Interaction | Distance | E (kcal/mol) |
|---------------|--------|----------|-------------|----------|--------------|
| Atovaquone    | 6-ring | CA VAL 209 (A) | pi-H        | 3.90     | -1.0        |
| Chloroquine   | N 17   | O GLU 208 (A)  | H-donor     | 3.16     | -0.6        |
|               | CL 1   | NZ LYS 94 (A)  | H-acceptor  | 3.45     | -0.9        |
|               | 6-ring | CA VAL 209 (A) | pi-H        | 4.40     | -0.5        |
|               | 6-ring | CG1 VAL 209 (A) | pi-H       | 4.14     | -0.6        |
|               | 6-ring | N ASN 210 (A)  | pi-H        | 3.62     | -0.6        |
| Doxycycline   | O 24   | OE1 GLU 208 (A) | H-donor    | 3.01     | -1.8        |
|               | 6-ring | CG2 VAL 209 (A) | pi-H       | 4.28     | -0.7        |
| Mefloquine    | N 29   | O ASN 210 (A)  | H-donor     | 2.91     | -0.7        |
|               | N 29   | N ASN 210 (A)  | H-acceptor  | 3.33     | -0.5        |
|               | 6-ring | CB GLU 208 (A)  | pi-H       | 4.42     | -0.5        |
|               | 6-ring | CG2 VAL 209 (A) | pi-H       | 4.46     | -0.6        |
| Primaquine    | 6-ring | CG1 VAL 209 (A) | pi-H     | 4.24     | -0.7        |
|               | 6-ring | CG1 VAL 209 (A) | pi-H     | 4.52     | -0.7        |
| Tafenoquine   |        |           | No measured interaction |        |              |
| Favipiravir   | O 12   | NZ LYS 94 (A)  | H-acceptor  | 3.12     | -3.5        |
| Ribavirin     | O 15   | NZ LYS 562 (A)  | H-acceptor  | 3.03     | -3.6        |
| Galidesivir   | N 14   | O ASN 210 (A)  | H-donor     | 3.05     | -1.0        |
|               | O 29   | CE LYS 562 (A)  | H-acceptor  | 3.16     | -0.7        |
| 5-ring        | CA VAL 209 (A) | pi-H     | 3.79     | -2.1        |
|               | 6-ring | CA VAL 209 (A) | pi-H     | 4.40     | -0.5        |
| 5-ring        | N ASN 210 (A) | pi-H    | 4.25     | -2.7        |
|               | 6-ring | ND2 ASN 210 (A) | pi-H   | 4.58     | -1.3        |
| Brincidovir   | O 63   | OE2 GLU 208 (A) | H-donor | 2.79     | -6.4        |
|               | O 74   | NE2 GLN 98 (A)  | H-acceptor | 3.01     | -1.2        |
Brincidofovir (BCV) is an orally bioavailable, long-acting, nucleotide analog broad-spectrum antiviral developed by Chimerix Inc. of Durham, North Carolina, USA for the treatment of double-stranded DNA (dsDNA) viruses [17]. BCV is less toxic with an enhanced cellular penetration prodrug of cidofovir wherein the cidofovir acyclic nucleoside monophosphate conjugated through its phosphonate group to a lipid, 3-(Hexadecyloxy)-1-propanol [18]. Being linked to a lipid particle, the compound ensures better and higher intracellular releases of cidofovir and lower plasma concentrations of the active drug, effectively increasing its antiviral activity. When intracellular, the released free cidofovir from the BCV is phosphorylated to its active metabolite cidofovir diphosphate which due to its structural similarity to the deoxycytidine triphosphate (dCTP) nucleotides it gets incorporated into the growing viral DNA strands [19]. Once incorporated, it prevents further DNA polymerization and disrupts DNA replication of viruses. The drug received FDA Fast Track Designation and has been evaluated in healthy individuals in Phase I and Phase II/III clinical trials and revealed to be well-tolerated and highly efficacious against adenoviruses, BK virus, herpes simplex viruses, and smallpox but eventually somehow failed for cytomegalovirus [20, 21]. Preliminary in vitro tests have also shown the drug potential for Ebola virus disease treatment, despite that Ebola is an RNA virus, albeit trials eventually discontinued [22]. Being acted on the Ebola RNA virus before, it is encouraging to act as well on the novel RNA SARS-CoV-2 today. And in addition to its intracellular therapeutic strategy of arresting the viral replication and packaging, our study shows here that it also interferes efficiently with the SARS-CoV-2 ACE2 receptor revealing a different therapeutic mode of action through potentially blocking or inhibiting the virus entry to the host cell, thereby slowing the progression of the infection.

The second top-ranked drug is Tafenoquine which is an orally-active 8-aminoquinoline, a long-acting analog of primaquine, anti-malarial medicine developed by GlaxoSmithKline and 60 Degrees Pharmaceuticals [23, 24]. The drug was FDA-approved for the radical cure of Plasmodium vivax (P. vivax) malaria and the prophylaxis of malaria in 2018. The drug is active against pre-erythrocytic, erythrocytic forms and the gametocytes of Plasmodium species that include P. falciparum and P. vivax [23, 24]. Clinical trials for this drug may be also recommended. Chloroquine, which is an anti-malaria and immunosuppressive drug, recently shown to improve the outcomes in patients with the novel coronavirus pneumonia which made the FDA issue an Emergency Use Authorization to be tested as a treatment for COVID-19, ranked at the fourth position in this study [25]. Lastly, while we were working in this research, an Australian study showed that Ivermectin, an anti-parasitic drug, to be effective against the COVID-19 disease although, further clinical trials are underway to confirm this effectiveness [26]. We decided to do some investigations using molecular docking to check the binding interaction between Ivermectin and the SARS-CoV-2 protease and receptor. We got comparable data to the antiviral Brincidofovir where the docking scores were -10.31 and -8.84 with the SARS-CoV-2 protease and ACE2 receptor, respectively. But overall, Brincidofovir is superiorly recommended because for its high lipophilicity “5.54” where Ivermectin “2.01”.

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Tab. 5 Docking score and energy of Ivermectin drug and 1Q2W of COVID-19 with site 1 of COVID-19 Protease (PDB code = 1Q2W)

| Ivermectin | S  | rmsd_ref | E_conf | E_place | E_score 1 | E_refine | E_score 2 | Log P |
|------------|----|----------|--------|---------|-----------|----------|-----------|-------|
| B1a        | -10.90 | 1.73    | 85.45  | -72.26   | -8.53     | -57.13   | -10.90    | 2.10  |
| B1B        | -10.31 | 1.29    | 89.61  | -102.28  | -9.56     | -53.44   | -10.31    | 1.59  |

Tab. 6 Docking score and energy of Ivermectin drug with ACE-2 Receptor (PDB code = 6M0J)

| Ivermectin | S  | rmsd_ref | E_conf | E_place | E_score 1 | E_refine | E_score 2 | Log P |
|------------|----|----------|--------|---------|-----------|----------|-----------|-------|
| B1a        | -8.84 | 2.25    | 34.89  | -62.74  | -7.46     | -52.54   | -8.84     | 2.10  |
| B1B        | -8.62 | 3.56    | 60.89  | 2.73    | -7.05     | -47.16   | -8.62     | 1.59  |

In conclusion, molecular modeling tools were used to screen for potential anti-SARS-CoV-2 therapeutic agents. After a virtual screening against SARS-CoV-2 protease and ACE2 receptor, a set of antivirals, antimalarials, and antimicrobials drugs showed a potent binding interaction, wherein Biocidofovir showed to be the top hit. Therefore, repurposing of Biocidofovir against the COVID-19 disease is suggested.

**Declarations**

**Competing Interest**

The authors declare no competing interest.

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**Figures**

![3d Docking of Malaria and Ebola drugs and 1Q2W of COVID-19 with site 1 of COVID-19 Protease (PDB code = 1Q2W)](image-url)

**Figure 1**

3d Docking of Malaria and Ebola drugs and 1Q2W of COVID-19 with site 1 of COVID-19 Protease (PDB code = 1Q2W)
Figure 2

2d Docking of Malaria and Ebola drugs and 1Q2W of COVID-19 with fixing the active site of COVID-19 Protease (PDB code = 1Q2W)

Figure 3

3d Docking of Malaria and Ebola drugs with ACE-2 Receptor (PDB code = 6M0J)

Figure 4

2d Docking of Malaria and Ebola drugs with ACE-2 Receptor (PDB code = 6M0J)