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# Effectivity of Remdesivir and some compounds as therapeutic potential drugs for anti-SARS-CoV-2: in silico study

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## ABSTRACT

Coronavirus Disease 2019 (COVID-19) pandemic by the infection of the new SARS-CoV-2 has been spread quickly worldwide. Since then, an effort has been made to find a therapeutic drug candidate to prevent and cure the infection. An **in silico** study is one of the most effective ways to do a screening of potential drugs by studying the interaction of the drug compounds with the protein target of the viruses theoretically. In this work, we reported the **in silico** study of 17 drugs candidates as anti-SARS-CoV-2 based on molecular docking. Three of the protein target used were crystal proteins of coronavirus with PDB ID of 2GX4, 6FV1, and 4LMT. The result showed that redemsivir showed the most promising drug candidate followed by hesperidin and chloroquine based on the CDOCKER energy and interaction formed form the molecular docking.

**Keywords:** Coronavirus, docking, *in silico*, Redemsivir, SARS-CoV-2.

## 1. INTRODUCTION

In late December 2019, an outbreak of pneumonia with an unknown cause was reported in Wuhan, China (Zhu et al., 2020; Hui et al., 2020; Lu et al., 2020). The World Health Organization (WHO) was then affirmed the outbreak as the Public Health Emergency of International Concern by the end of January 2020. The status was later declared as Pandemic on March 11, 2020, with the name of Coronavirus Disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Guan et al., 2020; Huang et al., 2020; Wu et al., 2020; Paraskevis et al., 2020). The COVID-19 has spread quickly around the world, as of May 8, 2020, about 3,759,967 positive cases and 259,474 mortality have been reported globally (WHO, 2020).

Currently, there are no registered antiviral drugs for treating COVID-19 (Verma et al., 2020). Research and development of new preventive and therapeutic agents are needed immediately to prevent the uncontrolled number of deaths. Early prevention can be done by isolation or quarantine and followed by treatment according to the symptoms as to minimize the transmission (Zhang et al., 2020). Another possible solution to overcome this pandemic is to search and develop of broad-spectrum antiviral drugs by targeting the main protease of viruses (Xu et al., 2020). Repurposing some available drugs is one of the choices to search for the therapeutic agents for the treatment of COVID-19 as they reduce the time for drug development (Pandey et al., 2020).

Drug repurposing is an approach to search therapeutic agents for COVID-19 by using the current drugs that have been used in a different disease. Antimalarial agents (quinine, chloroquine, hydrochloroquine), antiviral

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(Lopinavir, ritonavir, remdesivir, ribavirin, Oseltamivir), and antibiotics (azithromycin, Tetracycline) are reported to be potential candidates for repurposing against SARS-CoV-2 (Pandey et al., 2020). Some flavonoids such as hesperidin, myricetin, curcumin, thymol, eugenol, quercetin with broad biological activity also have been studied as the therapeutics compound against COVID-19 (Adem et al., 2020; Ngwa et al., 2020; Zahedipour et al., 2020; Kulkarni et al., 2020; Colunga Biancatelli et al., 2020). Based on the literature, several flavonoid-based phytomedicines show a high binding affinity to the spike protein, helicase, and protease on the Angiotensin-converting enzyme (ACE) 2 receptor (Ngwa et al., 2020; Kulkarni et al., 2020).

Generally, coronavirus consists of structural (spike, membrane, envelope, and nucleocapsid protein) and non-structural proteins (Papain like protease/PLpro, Main protease/Mpro, and RNA-dependent RNA polymerase/RdRp) (Lavecchia and Fernandez, 2020). The chymotrypsin-like cysteine protease (3CLpro) is the main protease that can be found in all generations of coronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The main protease 3CLpro has an essential role in replication and also gene expression of the virus (Lokhande et al., 2020). Thus, 3CLpro is proposed as the potential targets against SARS-CoV-2 (Chen et al., 2020). The crystal structures of coronavirus main protease such as 6LU7.pdb (Peele et al., 2020), 6M03.pdb (Singh and Florez, 2020), 1LVO.pdb (Hall and Ji, 2020), 6W01.pdb (Chikhale et al., 2020), and 5R7Y.pdb (Kumar et al., 2020), 6YB7 (Vijayakumar et al., 2020) have been reported as the protein target in the *in silico* study of some repurposed drug against COVID-19. Inhibition of some spike proteins with crystal structure 2GHV.pdb (Hall and Ji, 2020), 6M0J. pdb (Chikhale et al., 2020), and 6LZG.pdb (Vijayakumar et al., 2020) also have been studied using molecular docking. Spike protein is chosen as the target in the reduction of the infection of COVID-19 because it plays a role in the transmission and virulence of the virus (Hall and Ji, 2020). Meanwhile, nucleocapsid proteins in coronavirus can also be used as the target of the therapeutic drug because it is important in replication, transcription, and to build the structure (Tok and Tatar, 2017). Some studies have presented the *in silico* result of the crystal structure of SARS-CoV-2 nucleocapsid protein such as 6M3M.pdb (Kang et al., 2020; Bhowmik et al., 2020).

In this work, we performed *in silico* study of some commercial drugs such as remdesivir, chloroquine, hesperidin, and also proposed some candidate compounds against SARS-CoV-2 by targeting the main protease and nucleocapsid proteins of coronavirus. It has been reported that SARS-CoV-2 shows a 96% similarity with the protein sequences of SARS-CoV (Liu et al., 2020). Therefore, it is predicted that compounds with good activity against SARS-CoV would have good potential against SARS-CoV-2. The main protease of SARS-CoV (2GX4.pdb) (Xu et al., 2020), human coronaviruses (HCoV) NL63 (6FV1.pdb) (Zhang et al., 2020), and nucleocapsid protein (NP) of HcoV OC43(4LMT.pdb) (Chang et al., 2016) was used as the protein targets. The binding energy and interaction of the compounds against the coronavirus protein were evaluated to determine the best candidate compounds for SARS-CoV-2.

## MATERIALS AND METHODS

### Material

In this research, all of the docking studies were performed in a personal computer with Intel® Inside Core™ i7 processor (4 GHz, 8 GB RAM, 64-bit system type, and Windows® 10 Ultimate Operating system). The molecular structure of the compounds was drawn using ChemDraw Pro.15.0 software and the molecular docking was executed on the Discovery Studio 2016 (Accelrys, San Diego, USA) software.

### Methods

Molecular docking was performed to the crystal proteins of coronavirus that were retrieved from Protein Data Bank (https://www.rcsb.org/) with PDB ID of

2GX4.pdb (resolution of 1.93 Å); 6FV1.pdb (resolution of 2.30 Å); and 4LMT.pdb (resolution of 1.71 Å). Protein and co-crystal ligands were separated first before the docking process in Discovery Studio software. Docking preparation of the protein was carried out by adding hydrogen atoms and adjusting the ionizable amino acids (residues) at default protonation (pH 7.4). The ligands were prepared to build 3-dimensional geometrics and to minimize the energy before the docking process. All of the docking processes were carried out following the standard protocol implemented from Discovery Studio software (Syahri et al., 2020).

During the docking process, the ligands were allowed to flex and the receptor was rigidly maintained. The docking tolerance from the docked conformer of ligand-receptor was set in 0.25 Å and the number of the nonpolar or polar hotspots in the receptor (to start the conformer fitting) was set at 500. The conformations of the ligands obtained from the docking process were fixed at 500 within the relative energy threshold of 20. Interactions of the ligand-receptor were observed in a grid box size of 90×90×90 with a grid map in Table 1. The validity of the docking methods was determined based on the *root mean square deviation* (RMSD) value <2.0 Å. The RMSD value obtained from the re-docking results of the co-crystal ligands to each protein of 2GX4, 6FV1, and 4LMT were 1.133; 1.850; and 1.890 Å, respectively.

**Table 1. Grid map and radius applied in the docking process**

| PDB ID | X(Å) | Y(Å) | Z(Å) | Radius (Å) |
|---|---|---|---|---|
| 2GX4 | 17.480279 | 1.480907 | 22.008395 | 9.00 |
| 6FV1 | 53.612154 | 12.144000 | 48.989128 | 10.00 |
| 4LMT | 62.809955 | 15.413273 | 7.969364 | 9.00 |

## RESULTS AND DISCUSSION

Preliminary stages using molecular docking is beneficial as it can predict the binding affinity between the compound (ligand) and protein. In this work, a molecular docking study of 17 compounds as a therapeutic candidate toward SARS-CoV-2 was performed to three different coronavirus crystal proteins such as 2GX4, 6FV1, and 4LMT (Table 1). The 2GX4 is a crystal structure of 3C-Like (3CL) protease inhibitor complex of SARS coronavirus and 6FV1 is the main protease from the human coronavirus NL63. Meanwhile, 4LMT is a crystal structure of nucleocapsid (N) protein of human coronavirus OC43.

Table 2 presented the CDOCKER energy (in kcal/mol) from the ligand-protein complex. Principally, the lower energy produced from the molecular docking process, the more stable interaction between the compounds (ligands) and protein targets. Remdesivir (**1**) showed the lowest CDOCKER energy (-64.4841 kcal/mol) among the 17 tested compounds against 2GX4 crystal strucure protein of SARS-CoV. This docking energy was the closest to the CDOCKER energy of the native co-crystal ligand (NOL) with the energy of -83.2383 kcal/mol. It also can be seen that remdesivir (**1**) showed the lowest CDOCKER energy to 6FV1 (-63.6467 kcal/mol) and 4LMT proteins (-53.0987 kcal/mol), compared with the other 16 compounds. It was revealed that both 2GX4 (from SARS-CoV) and 4LMT proteins (from HCoV-OC43) are categorized as β-coronavirus, while 6FV1 (from HCoV-NL63) is α-coronavirus. Thus, it can be interpreted that remdesivir has broad-spectrum antiviral activity. This result has a good agreement with some reported studies about the antiviral activity of remdesivir (Sheahan et al., 2020; Wang et al., 2020; Wu et al., 2020).

Hesperidin (**2**) displayed the best CDOCKER energy of -61.5854 kcal/mol to the 6FV1 protein, which closes to

the energy of remdesivir (**1**). Hesperidin was also placed as the second candidate of the drug for COVID-19 with lower docking energy against the crystal structure of 2GX4 ( -59.5070 kcal/mol) and 4LMT (-50.1548 kcal/mol). The *in silico* study of hesperidin has been reviewed which is proposing the potential antiviral effect of hesperidin to the proein of SARS-CoV-2 (Bellavite and Donzelli, 2020). It has been published that hesperidin showed the suitable binding against the spike protein also lower binding energy to 3CLpro and Mpro of SARS-CoV-2.

Chloroquine (**3**) has the third-lowest CDOCKER energy of -46.2102 kcal/mol toward 6FV1 protein after remdesivir and hesperidin. Chloroquine (**3**) is widely reported to be the potential drug for the handling of COVID-19 (Colson et al., 2020). The interesting docking result of this compound (**3**) was that it displayed similar CDOCKER energy for all the tested proteins. This result encourages the previous study that proposed the use of Chloroquine (**3**) as an anti-SARS-CoV-2 drug candidate (Rebeaud and Zores, 2020; Devaux et al., 2020; Singh et al., 2020), although it still brings some debates (Touret and de Lamballerie, 2020; Jaffe, 2020). Chloroquine is still used as an antimalarial drug and it might lead to a serious threat concerning the expanding of the antimalarial drug resistance when it is not well-controlled.

**Table 2. The CDOCKER Energy of some potential drugs**

| No | Compounds | CDOCKER Energy (kcal/mol) | | |
|---|---|---|---|---|
| | | **2GX4** | **6FV1** | **4LMT** |
| 1 | Remdesivir | –64.4841 | –63.6467 | –53.0987 |
| 2 | Hesperidin | –59.5070 | –61.5854 | –50.1548 |
| 3 | Chloroquine | –46.2048 | –46.2102 | –45.7560 |
| 4 | Aminoalkylated Chalcone 1 | –45.6236 | –47.9247 | –38.8552 |
| 5 | Aminoalkylated Chalcone 2 | –45.3461 | –46.4737 | –40.0853 |
| 6 | Aminoalkylated Chalcone 3 | –45.3258 | –47.0167 | –40.2087 |
| 7 | Aminoalkylated Chalcone 4 | –45.0230 | –45.4285 | –39.9402 |
| 8 | Myricetin | –43.8472 | –47.8862 | –57.8559 |
| 9 | Curcumin | –43.1526 | –43.7372 | –36.5257 |
| 10 | Oseltamivir | –42.7158 | –42.5152 | –29.2826 |
| 11 | Quercetin | –39.6190 | –44.0359 | –60.6573 |
| 12 | Aminoalkylated Eugenol | –36.4853 | –45.7011 | –30.7630 |
| 13 | Quinine | –34.0921 | –38.1999 | –32.9204 |
| 14 | Ribavirin | –31.6247 | –33.5869 | –31.1901 |
| 15 | Eleutherin | –28.4200 | –36.1497 | –28.3069 |
| 16 | Eleutherinone | –26.1505 | –32.1959 | –26.0152 |
| 17 | Xanthone | –19.5651 | –25.2077 | –19.4864 |

Aminoalkylated chalcone compound (**4-7**), which was reported to be active as antimalarial (Syahri, 2020), showed a CDOCKER energy that closes to the chloroquine (Table 2). This result indicates that the compound (**4-7**) also has the potential to be used as anti-SARS-CoV-2 drug candidates. Meanwhile, myricetin (**8**), curcumin (**9**), oseltamivir (**10**), and quercetin (**11**) exhibited moderate/medium CDOCKER energy to the tested

protein, except compounds (**11**) and (**10**) that displayed low CDOCKER energy of -60.66573 and -57.8559 kcal/mol to the 4LMT protein, respectively. It means that both of the compounds have a specific mechanism of action against the nucleocapsid protein. On the other hand, aminoalkylated eugenol (**12**), quinine (**13**), ribavirin (**14**), eleutherin (**15**), eleutherinone (**16**), and xanthone (**17**) were displaying higher energy for all the tested proteins.

Table 3 presented the interaction of the drug compounds (ligands) to the tested protein in the 2-dimension view. Based on the interactions formed, it can be seen that remdesivir (**1**) and hesperidin (**2**) have formed the highest number of hydrogen bonds to all the tested proteins. Remdesivir showed hydrogen bonds to the amino acid residues of Glu166, Gln189, His41, Cys145, and Asn142 (2GX4). The absence of H-bonds to His163 and Gly143 in the docking of **1**-2GX4 complex proposed the reason for the higher CDOCKER energy of remdesivir compared with the co-crystal ligand (NOL). The **1**-6FV1 complex presented the formation of H-bonds to Glu166, Gln164, Gly142, Pro189, Asn141, and Ile165 residues. Meanwhile, 2-D interaction of **1**-4LMT complex displayed the H-bonds to the Glu170, Arg122, Glu56, Tyr124, Ala171, Tyr 63, and Asp165 amino acid residues. Interaction of Hesperidin (**2**) with 2GX4 was formed via H-bonds to Glu166, Asn142, Leu141, Asp187, Met49, His164, and Met165 amino acid residues. Furthermore, H-bonds interaction of **2**-6FV1 can be seen to the Asn141, Glu166, Cys144, Phe139, His163, Ile140, Gln164, Thr47, and Ser190 residues. Lastly, **2**-4LMT complex showed H-bonds interaction to Ala171, Arg164, Asp169, Asp165, Pro166, Glu170, yr124, Tyr63, and Ser64 residues. This result was in agreement with the CDOCKER energy produced by these two compounds, indicating the higher potential as anti-SARS-CoV-2.

Chloroquine (**3**) has produced the most hydrogen bond to the 6FV1 protein compared with the other two tested proteins. It was predicted that chloroquine (**3**) has a specific inhibition mechanism of action to the main protease NL63 of human coronavirus. Meanwhile, compounds (**4-17**) were displayed fewer hydrogen bonds to all of the tested protein that indicates a lower potential as the candidate drugs for treating COVID-19.

Based on the *in silico* study, remdesivir, hesperidin, and chloroquine are highly recommended as candidates for anti-SARS-CoV-2. According to Wang et al. (2020), remdesivir and chloroquine are very effective in inhibiting COVID-2019, proved by the *in vitro* activity of both compounds with $EC_{50}$ values of 3.7 and 10 μM, respectively. Ko et al. (2020) have also reported that remdesivir was a potential drug for COVID-19 therapy. Furthermore, remdesivir was previously reported to be active (*in vitro*) against the Ebola virus with an $EC_{50}$ value of 0.06–0.14 μM (Warren et al., 2016), SARS-CoV with $EC_{50}$ value 0.069 μM, and MERS-CoV with an $EC_{50}$ value of 0.074 μM (Sheahan et al. 2017). Based on the clinical trials on monkey and mouse animals, remdesivir also has a very low toxicity level (Warren et al., 2016).

Hesperidin has been reported the be potential to halt the infection of SARS-CoV-2 based on computational screening (Utomo et al., 2020; Adem et al., 2020). In nature, the high content of hesperidin can be found in the peel of citrus fruits (Bellavite and Donzelli, 2020). As it is abundantly available in nature, hesperidin could be proposed to be used as a therapeutic compound for prevention and also the treatment of COVID-19. Moreover, hesperidin also showed a good safety profile and good tolerability according to human and animal studies (Bellavite and Donzelli, 2020). To conclude, this study strengthens the previous report that recommends remdesivir, hesperidin, and chloroquine as the drug candidates for the treatment of SARS-CoV-2.

## CONCLUSION

This work proposed the potential of Redemsivir as anti-SARS-CoV-2 drug candidates based on the *in silico* studies by observing the CDOCKER energy and the interaction formed to the target protein from the molecular docking. Therefore it is expected that redemsivir could be

considered as the therapeutic drug against COVID-19.

**CONFLICT OF INTEREST STATEMENT**

We declare that we have no conflict of interest.

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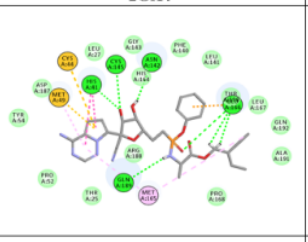
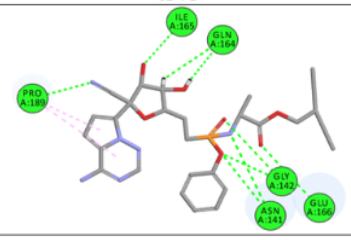
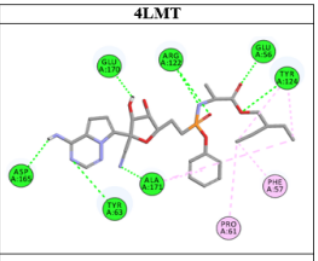
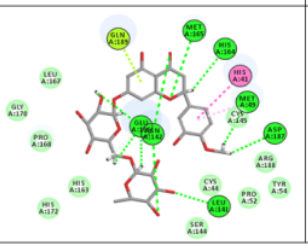
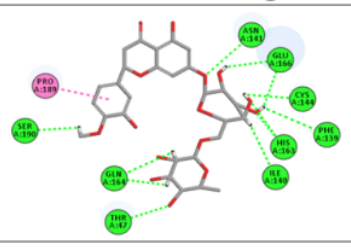
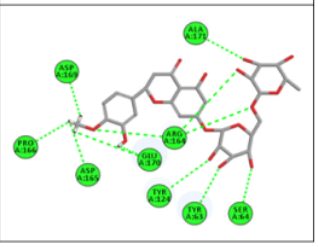
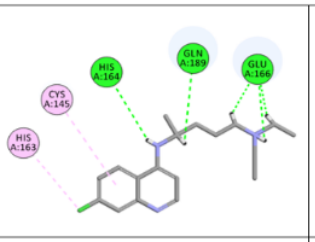
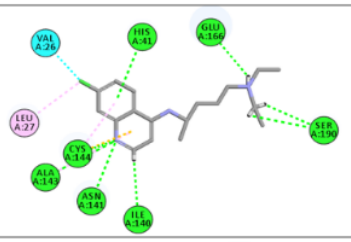
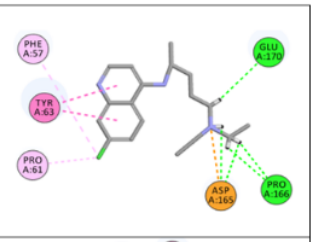
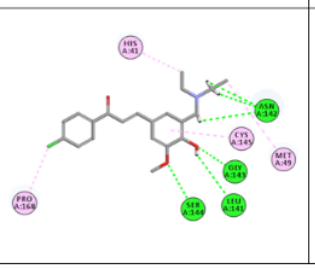
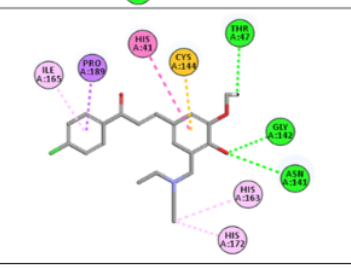
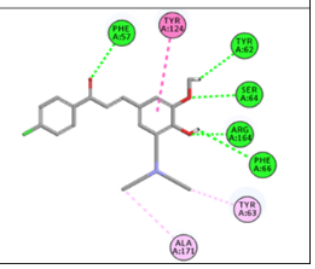
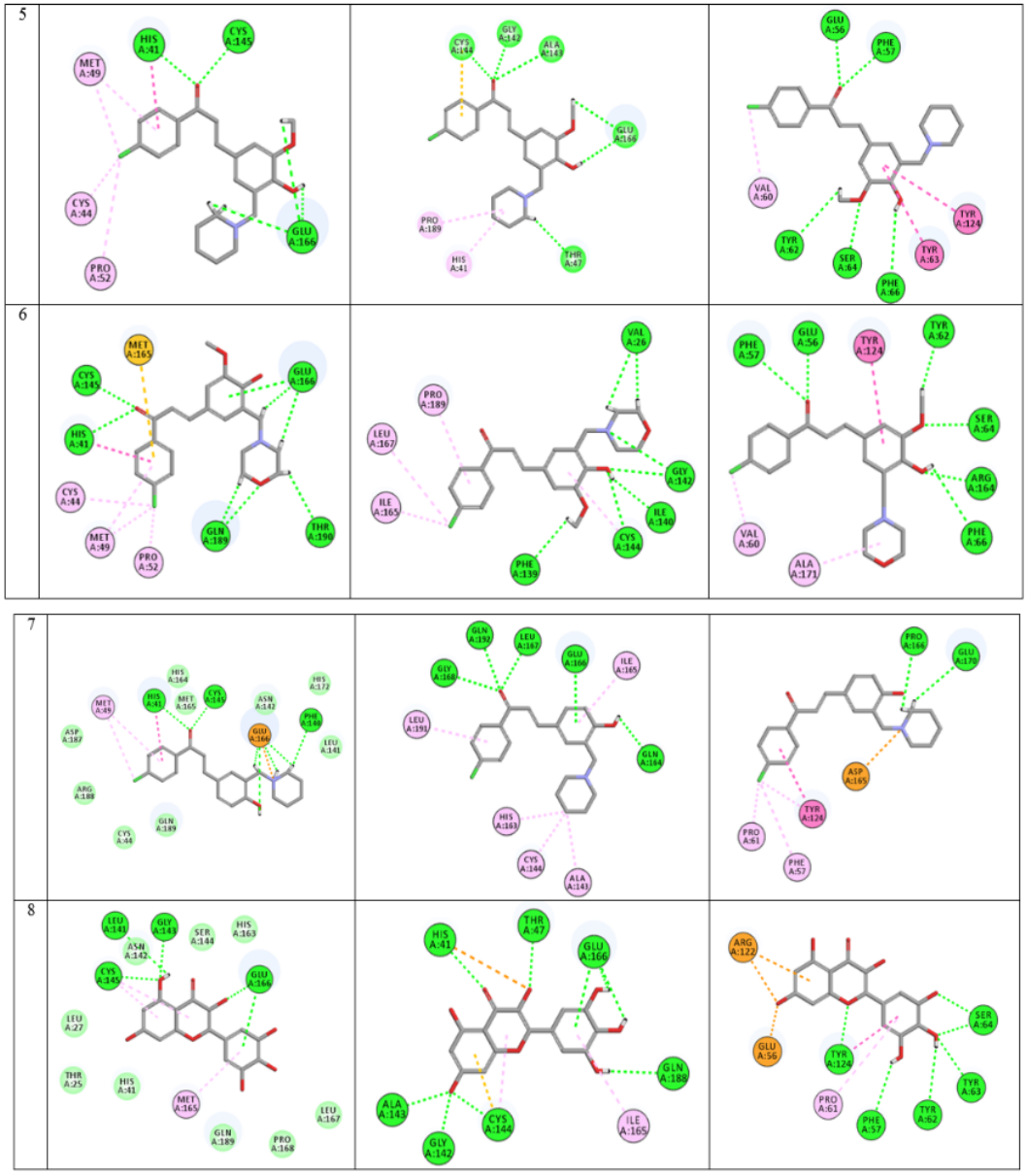
**Table 3. 2-Dimension interaction of some potential drug compounds to the amino acid residues of protein 2GX4, 6FV1, and 4LMT**

| No | 2GX4 | 6FV1 | 4LMT |
|---|---|---|---|
| 1 |  |  |  |
| 2 |  |  |  |
| 3 |  |  |  |
| 4 |  |  |  |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PRO A:189
HIS A:41
THR A:47
GLU A:56
PHE A:57
VAL A:60
TYR A:124
TYR A:62
SER A:64
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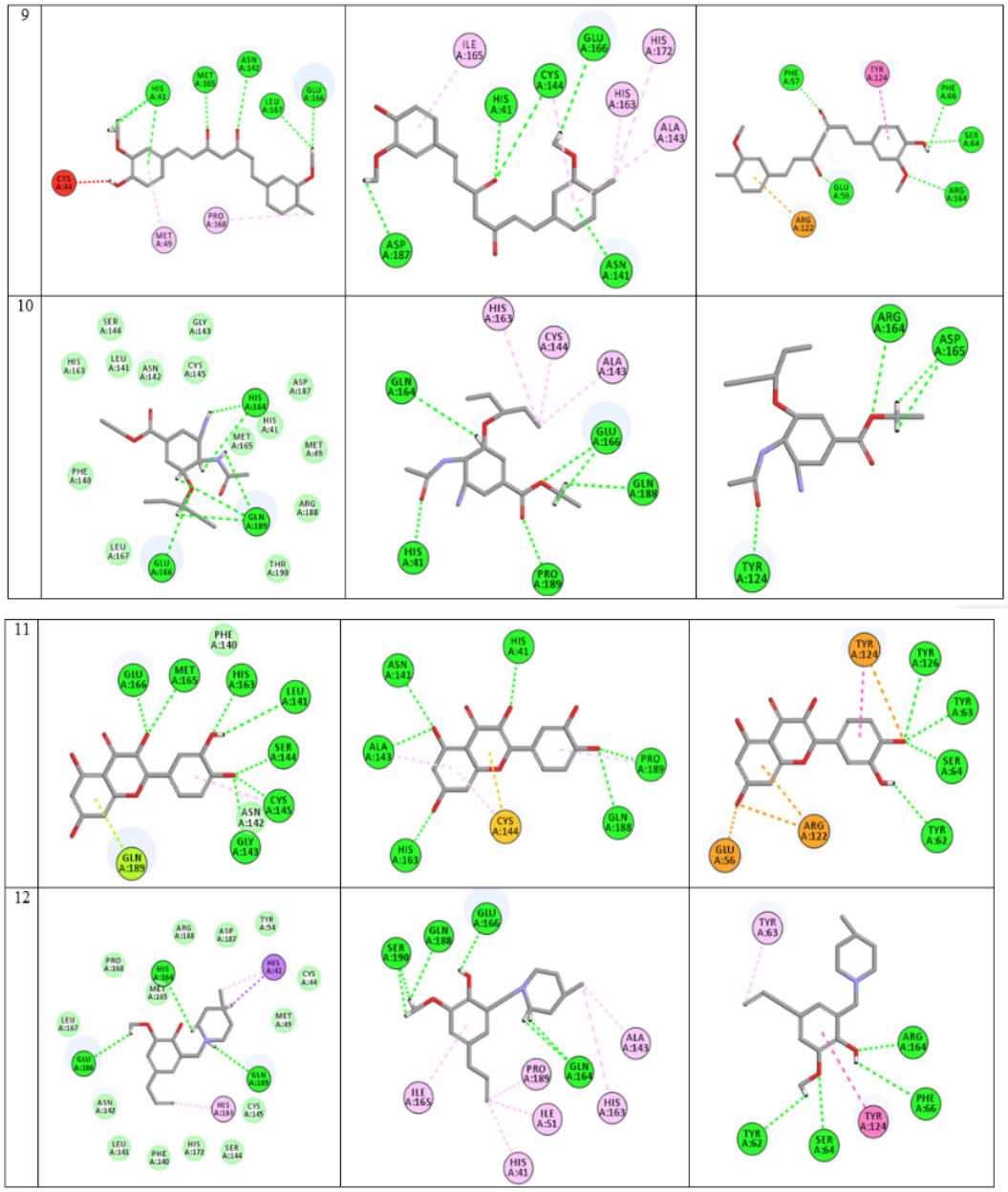
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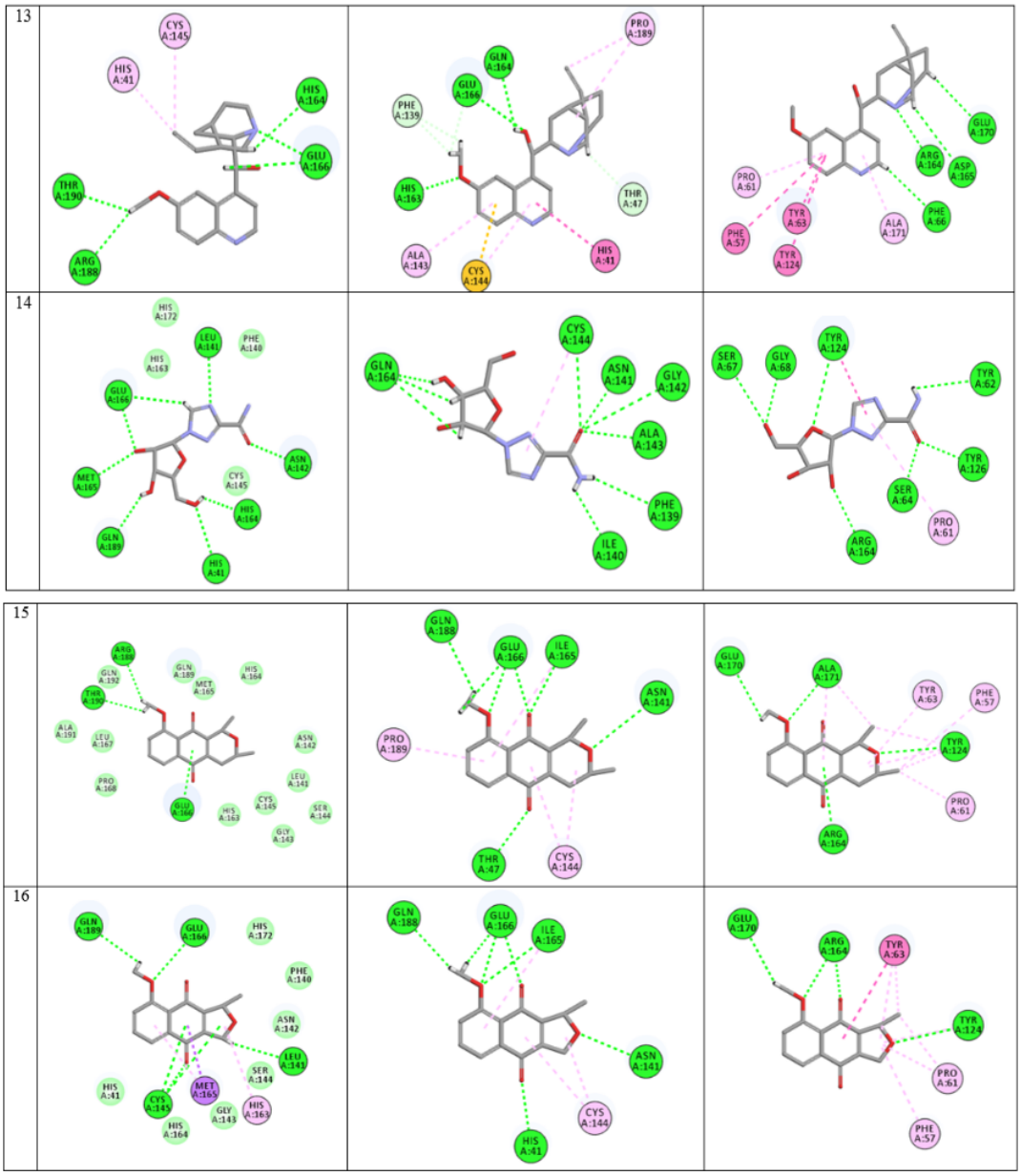
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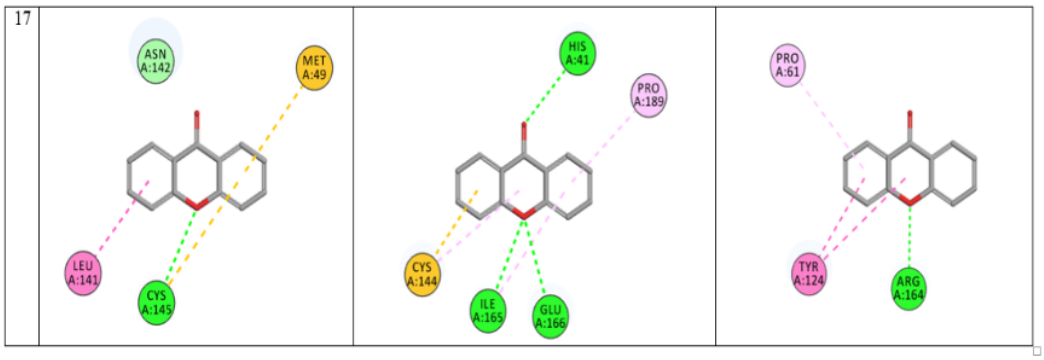


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# فعالية ريمديسيفير والعديد من المركبات كأدوية علاجية محتملة لمقاومة SARS-CoV-2: دراسة في السيليكو

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## ملخص

وباء فيروس كورونا 2019 (COVID-19) بالعدوى فيروس SARS-CoV-2 ينتشر بسرعة في جميع أنحاء العالم. منذ ذلك الحين، بذلت الجهود للبحث عن الأدوية المرشحة للوقاية من العدوى وعلاجها. تعد دراسات السيليكو واحدة من أكثر الطرق فعالية لإجراء فحص محتمل للأدوية من خلال دراسة التفاعلات النظرية لمركبات الدواء مع البروتينات المستهدفة الفيروسية. في هذا البحث ، أبلغنا عن دراسة في السيليكو لـ 17 عقارًا مرشحًا كمضاد لـ SARS-CoV-2 على أساس إرساء الجزيئي. كانت البروتينات المستهدفة الثلاثة المستخدمة عبارة عن بلورات بروتين فيروس كورونا برمز PDB 2GX4 و FV16 و LMT4. أظهرت النتائج أن ريمديسيفير كان أكثر الأدوية المرشحة الواعدة يليه الهسبريدين والكلوروكين بناءً على طاقة CDOCKER والتفاعلات المتكونة من نتائج إرساء الجزيئي.

**الكلمات الدالة:** كورونا فيروس، إرساء، السيليكو، ريمديسيفير ، SARS-CoV-2.

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