In silico study and virtual Drug Screening of the FDA-approved approach with Molecular Docking.

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Research Article

Keywords: Velpatasvir, Virtual screening, COVID-19, Molecular Docking, Repurpose, main protease inhibitor

Posted Date: April 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-433785/v1

Abstract

Aims: Coronavirus disease 2019 (COVID-19) has emerged in Wuhan, China, and because of fast transmission, it has led to its extensive prevalence in almost all countries, which has made it a global crisis. This study aims to recognize a possible small molecule as a main protease inhibitor versus the main protease protein of SARS-CoV-2 by the computational program.

Methods: Virtual screening procedures like using molegro virtual docker, auto dock tools, and auto dock Vina, was done for more than 1600 FDA-approved medicines that download from the ZINC database, were employed to characterize new implied molecule inhibitors for the recently published crystal structure of the main protease protein of SARS-CoV-2.

Result: The result indicates that Velpatasvir, angiotensin receptor blockers, cephalosporins, and also atorvastatin could fit adequately to the binding site of the main protease. Because of some other beneficial features, including anti-infectious, anti-inflammatory properties, and ADME profile, they might be a promising drug nominee for repurposing to the treatment of COVID-19.

Discussion: Velpatasvir was selected by combining some virtual screening methods for furthers studies to find a suitable ligand for the treatment of COVID-19.

Introduction

The appearance of the new coronavirus (new CoV-19) has influenced human health and also human lifestyle on a global scale. Discovery of the novel targeted drug(s) is needed quickly and has taken center step in combating the coronavirus disease-19 (COVID-19) pandemic. [1]

The SARS-CoV-2 caused an efficacious supplementary strange global public health warning, with comparably high mortality and high transmission speed. The SARS-CoV-2 main protease is necessary for viral replication and an important drug target. [2]

It’s more than 1 year WHO announced that COVID-19 has become a pandemic, and until now there are more than 125,500,000 Confirmed cases, more than 2,755,000 Confirmed deaths and finally 223 Countries, areas or territories with cases are involved with this crisis. [3]

One of the most critical proteins for transcription and replication is the virus's main protease, which cleaves the polyproteins into smaller fragments proteins for transcription and replication are the main protease of the virus, which cleaves the polyproteins into smaller fragments Drug repurposing is considered as a way to discover new applications of the current drugs in handling several diseases. The main protease of a virus, like the new coronavirus, plays an essential role in Reproduction and expansion. [4]

in-silico drug repurposing is an alternative efficacious additional approach to neutralize COVID-19. This procedure may speed up the process of determining the therapeutic compounds for the newly emerged

sicknesses. [5]

Under the current emergency situation, it operated virtual screening tools to search for drugs and natural products that have been deposited in the Drug data Bank to stimulate the drug discovery method. [6]

This research was analyzed to estimate and determine whether FDA-approved medicines might be probable to COVID-19 main protease inhibitors and, Specially, most recently, the SARS-CoV-2 main protease, a key coronavirus enzyme, which is a potential drug purpose, has been fortunately crystallized.

Henceforward, this study's purpose and objective were to explore whether FDA approved drugs could help manage COVID-19 by directly affecting the virus particle. So, A rapid and relatively high accuracy method for screening a large number of the ligand is in silico methods such as molecular docking.

Method

To identify the suitable ligand with the desirable interaction with the main protease of SARS-CoV-2, 1615 FDA-approved were screened with molecular docking simulations over the main protease's binding site SARS-CoV-2.

The crystal structure of the main protease of SARS-CoV-2 that recently has been published was downloaded as a PDB file from a website related to protein data bank (http://www.rcsb.org) with PDB ID: 6wtt [6].

In this study, as mentioned above, the Crystals Structure of the SARS-CoV-2 (COVID-19) main protease with inhibitor GC-376 with 6wtt code used.

- This protein classification is viral protein, and the related organism is Severe acute respiratory syndrome coronavirus 2, which Expression in the Escherichia coli System.

First, databases such as zinc database were used to download SDF format small molecules for searching the Drug bank database and further followed by molecular docking. Auto Dock Tools (ADT, Ver.1.5.6) was used to prepare the input files and analyze the result. [8]

3D structures of FDA approved drugs were downloaded from the ZINC database [9] in structure-data file (SDF) format.

Molegro Virtual Docker (MVD), ver. 6, was used for the first step of the molecular docking study. The docking was performed in these rounds and with these situations and states: importing SDF file of ligands and PDB format related to protein file; searching for all probable cavities on the protein surface and five cavities selected. [10]

Then binding site and grid space established with 0.3 Å; setting the search algorithm on the energy-minimization and hydrogen bonds optimization; run the software and saving the docking results for the following analysis. Docking scores represent calculated ligand-receptor (protein) interaction energy; hence, more negative scores indicate better binding bias. [11]

In next step, a screening procedure screen 1615 ligands. Every ligand was dock ten times with each cavity. After in silico screening of drug space, we identified 18 drugs as potential SARS-CoV-2 main protease inhibitors to propose further experimental testing. All docking results were sorted from the lowest docking score to the highest.

In the next step, 18 ligands chosen in molegro virtual docker were prepared for docking with autodock tools. For protein input file preparation, all water molecules, ligands, and ions were removed from the PDB file. Then polar hydrogens were added; then the Kollman-united charge was used to determine the partial atomic charge, and the prepared file was saved in pdbqt format to use in the following steps. Ligand with structure-data file (SDF) format should be converted to PDB format.

Then Open Babel (version 2.3.1) [12] was used to convert SDF format to PDB.

Rotatable bonds were assigned to all ligands and saved in pdbqt for further docking process using AutoDock 4.2, and the PDB format of ligands was converted to PDBQT and was saved.

Then protein with PDB format chose as a macromolecule and save as a PDBQT file. Later 90× 90× 90Å (x, y, and z) grid box was centered on the protease binding pocket with 0.375 nm spacing for each dimension and a grid center at dimensions (x, y, and z, respectively): -15.845, 30.799, and 11.939 was designated. AutoGrid 4.2 was used to create grid maps.

Docking parameters were set as follows: energy range was set 4 and exhaustiveness was set 20, other parameters were set in their default value, and finally, docking was performed by AutoDock 4.2.

The procedure of docking was done automatically by codes and scripts written in-house.

Visualization of docking results has been done by PyMol version 1.1evel [13]. All complexes with the were used for additional investigation as input files for final check-in autodock vina.

Result

Initially, a screening procedure was used to screen 1615 ligands. After docking, those ligands with a mol MolDock score lower than 160 were selected and chosen for the next steps. therefore 18 compounds were found and then chose for next step. Auto dock tools was run and binding energy of them sorted.

For working with Autodock vina, PyRx was used, and all of 18 ligands were selected in PDB format, and PyRx converted them to pdbqt, and all of them were selected as ligands. Also, a protein with PDB format was selected and converted to PDBQT and chosen as protein.

2D interaction between ligand and protein was shown in fig.2 and fig.4; and as we can show, some amino acids are more responsible for interaction between ligands and active site of main proteas, such as: Tyr 237, Glu 288, Lue287, Ile 249, Arg 4 and Phe 294.

However, Trypan Blue, Venetoclax, Indocyanine green has the highest score among the chosen drugs, but others could be better choices because of the side effects and lower availability of these three drugs.

Statins like atorvastatin have been suggested as useful drugs in COVID-19 patients mainly. In addition to the different helpful effects of atorvastatin, it is a high ability to inhibit the main protease enzyme causes it to be an ideal choice for further studies. [14]

Zafirlukast was indicates asthma and Upper respiratory problems. Because of this and because of the high affinity of zafirlukast to the main protease of new coronavirus, scientists could think about this medicine and similar medicine to find a suitable medicine.

Many cephalosporins have a high affinity to protein examined; for example, Cefotetan, Ceftazidime, Ceftolozane, Ceftaroline, Cefditoren, and Ceftriaxone has been shown a high affinity to 6wtt protein. These medicines have an excellent anti-Upper respiratory infection and could be considered satisfactory prophylaxis and treatment pneumonia caused by covid-19. But because of possible Antibiotic Resistance it could not be a good option.

Velpatasvir also has a good affinity to main protease of new-coronavirus. It's a NS5A inhibitor, that is used in combination with sofosbuvir in the treatment of hepatitis C. It's just shown that could be useful for treatment of COVID19 with in silico study before. [15]

As Shown in figures 5, 6 and 7 we can figure out that there are 4 amino acids that have a role in interaction between Velpatasvir and main protease, include: GLY 275, MET 276, LEU 286 and ALA 285.

As shown above, some ARBs like losartan and Azilsartan, and Candesartan have a high affinity to the main proteas of new coronavirus that make them a potential medicine for managing this crisis. 3D interaction and Spatial position could be seen in fig3.

Many studies disused about interaction between ARBs and COVID-19. [16, 17, 18] and there was no significant different in hospitalization or death rate; So, for now these drugs could not be good choice. Although other studies should be done for fining ARB like drugs that inhibit main protease of new coronavirus.

The investigational medication of COVID-19: Some particular medicines have been studying in various clinical trials for the treatment of covid-19.

As seen in the table 2, the affinity of Remdesivir to the main protease of new coronavirus is higher than other drugs that are investigating in clinical trials, and FDA has been recently emergency approved this

drug for this illness fig 5 and fig 6 (and for more Emphasis in this study, evaluate in this part of the article).

We can also see Lopinavir, which has an excellent affinity to the main proteas, but not the same as ritonavir or other drugs mentioned above, but it could be a suitable choice for COVID-19.

So, Ritonavir/lopinavir (with brand name Kaletra) could be used in the initial phase of lines of COVID-19 19 that viral load is high an antiviral medicine could be more useful than other phases;

Among these medicines, favipiravir has the lowest affinity to the main protease of new coronavirus.

Conclusions

In this study, an in silico molecular docking experiment was completed on the interaction of FDA-approved with the main protease enzyme of SARS-CoV-2. Virtual screening procedure employing Docking of 1615 FDA approved drugs were performed over the main protease.

The virtual screening result consisted of many drugs include 3 ARBs, 5 cephalosporins, a kinase inhibitor and an HMG CoA reductase and leukotriene receptor antagonist, and some other medicines. All of the drugs suggested above indicate proper interaction with the main protease. Moreover, a challenging Discuss in the treatment of COVID-19 is related to the angiotensin-converting enzyme and ACEIs and ARBs medicine. More research is need for effectiveness of cephalosporins, ARBs, Statins and leukotriene receptor antagonist for treatment of COVID-19.

And finally, Velpatasvir is Recommended drug of this study that could be useful for treatment of COVID-19. It can be mentioned that the limitation of this study is related to the reality of in-silico studies. It could be concluded that it needs to be verified by experimental and laboratory studies and, finally, in clinical trials, which may support our judgments and investigations.

Declarations

Competing interests: The authors declare no competing interests.

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Tables

Tables 1-2 are available as a download in the Supplementary Files section.

Figures

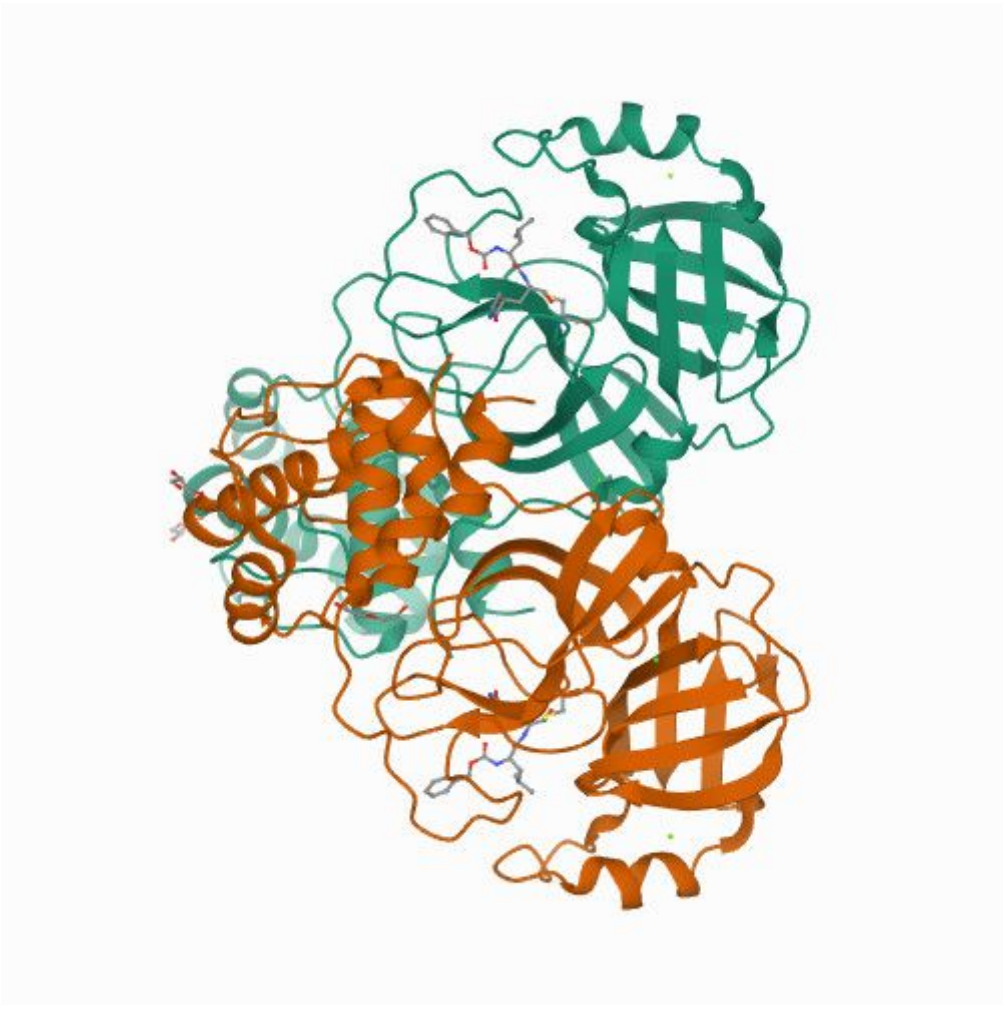

Figure 1

3D View: Structure of main protease of SARS-CoV-2

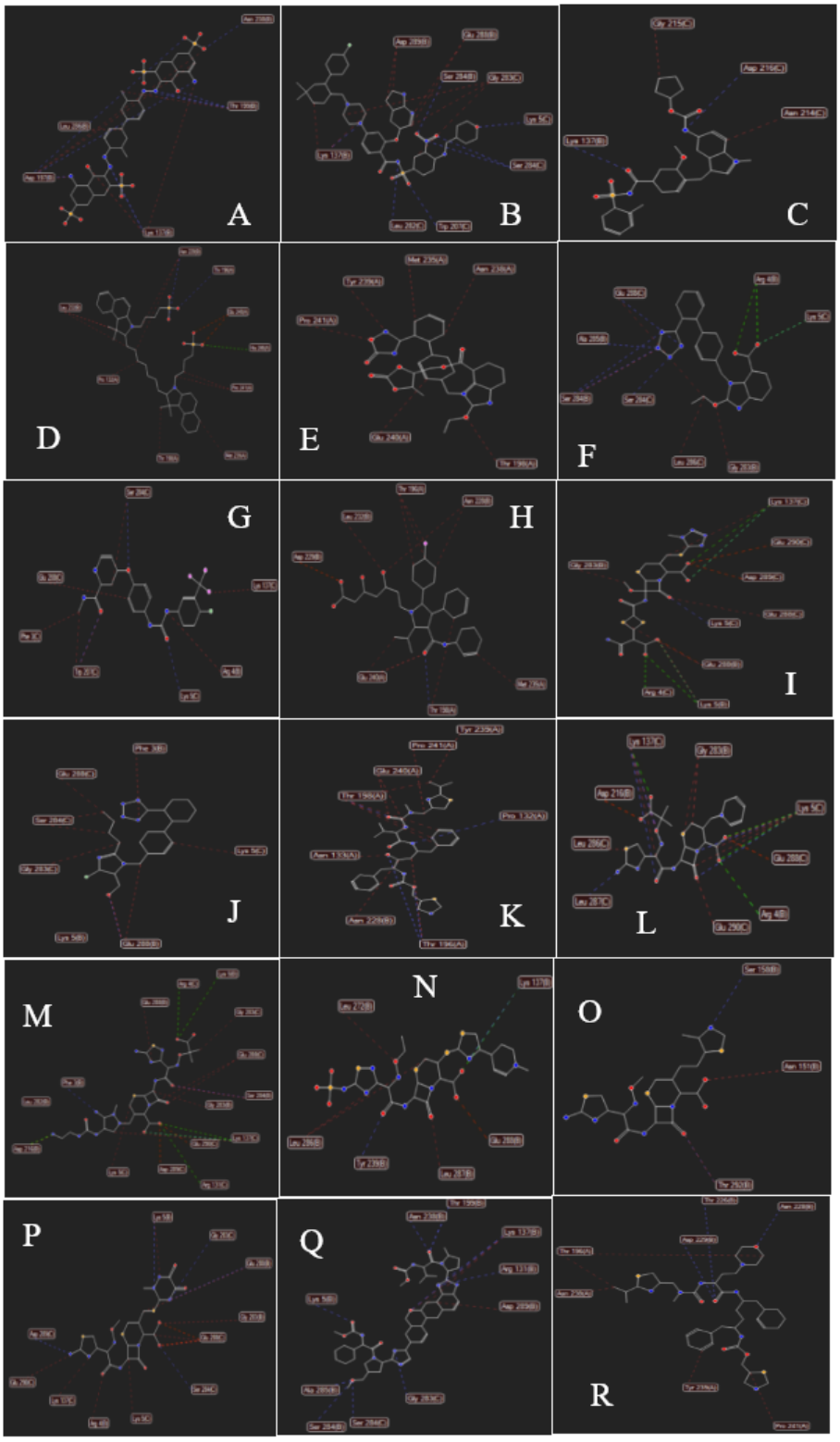

Figure 2

2D interaction between ligand and protein extracted from molegro virtual docker: Docking analysis visualization of 6wtt binding with Trypan Blue (A), Venetoclax (B), Zafirlukast (C), Indocyanine green (d),

Azilsartan (E), Candesartan (F), Sorafenib (G), Atorvastatin (H), Cefotetan (I), Losartan (J), Ritonavir (K), Ceftazidime (L), Ceftolozane (M), Ceftaroline (N), Cefditoren (O), Ceftriaxone (P), Velpatasvir (Q) and Cobicistat (R) designed by MolegroVirtualDocker.

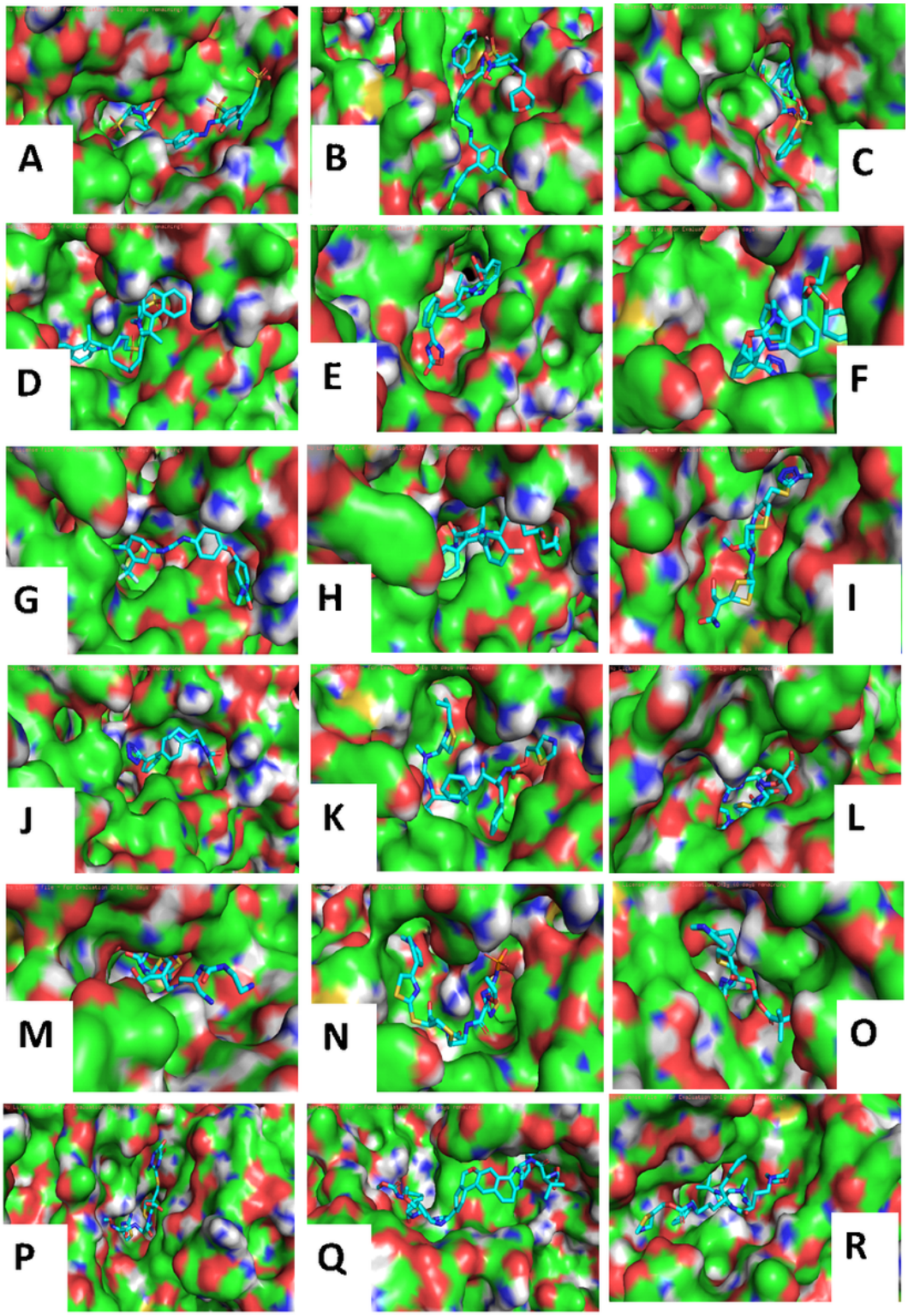

Figure 3

Docking analysis visualization of 6wtt binding with Trypan Blue (A), Venetoclax (B), Zafirlukast (C), Indocyanine green (d), Azilsartan (E), Candesartan (F), Sorafenib (G), Atorvastatin (H), Cefotetan (I),

Losartan (J), Ritonavir (K), Ceftazidime (L), Ceftolozane (M), Ceftaroline (N), Cefditoren (O), Ceftriaxone (P), Velpatasvir (Q) and Cobicistat (R) designed by PyMolWin

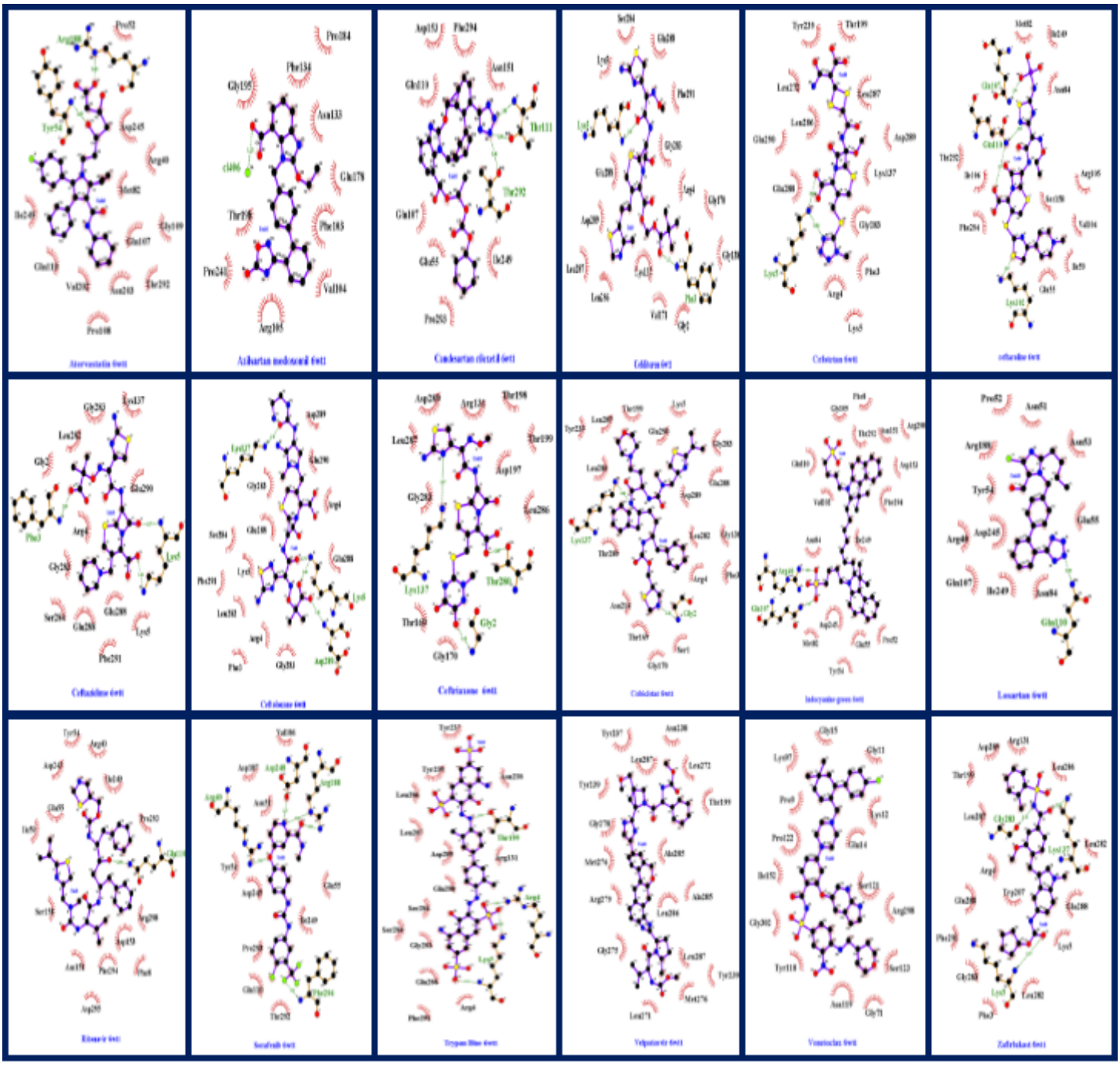

Figure 4

2D interaction ligand protein: integration of 6wtt binding with 18 ligands designed by LigPlus+

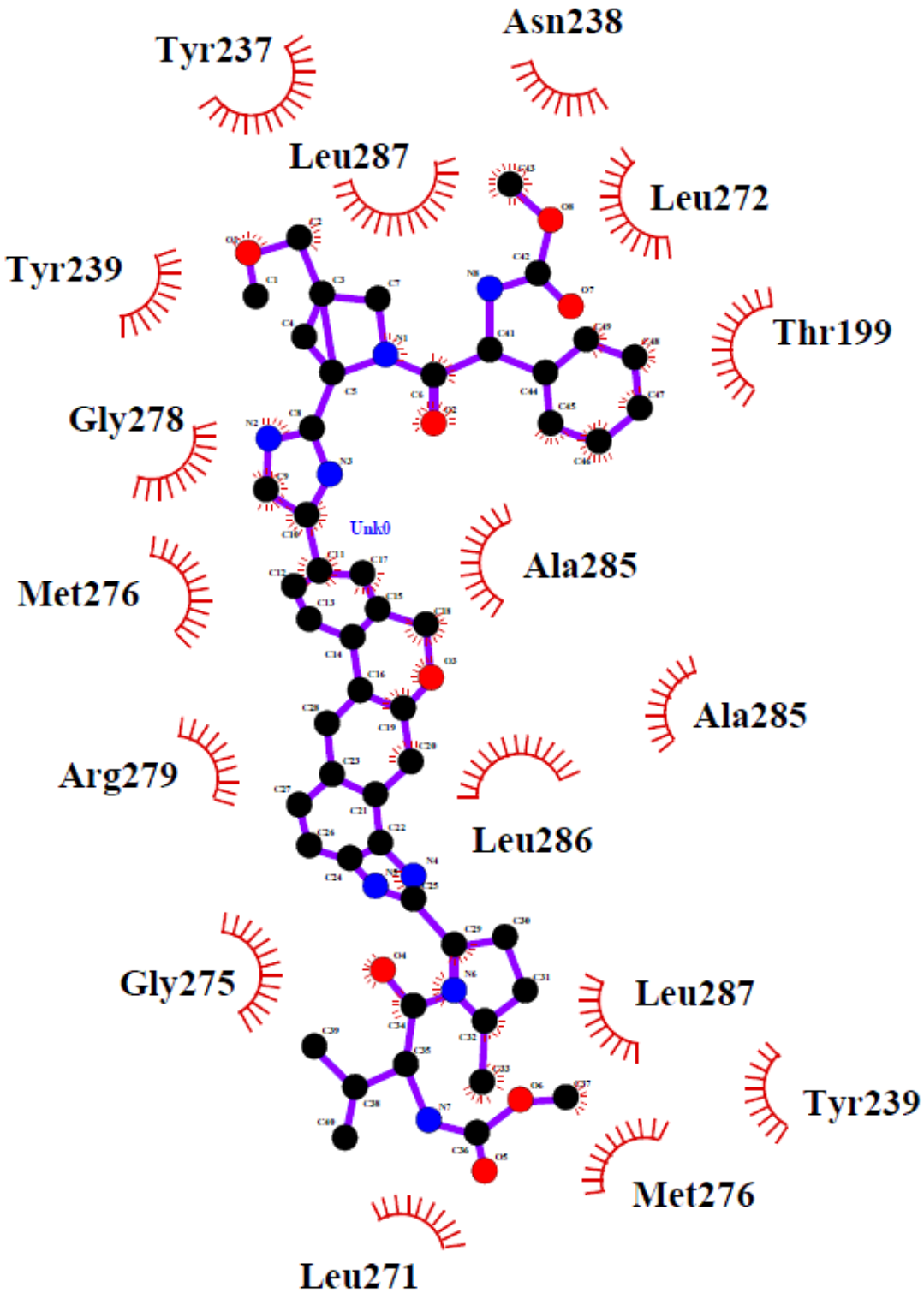

Figure 5

2D interaction ligand-protein: integration of 6wtt binding with Velpatasvir designed by LigPlus+

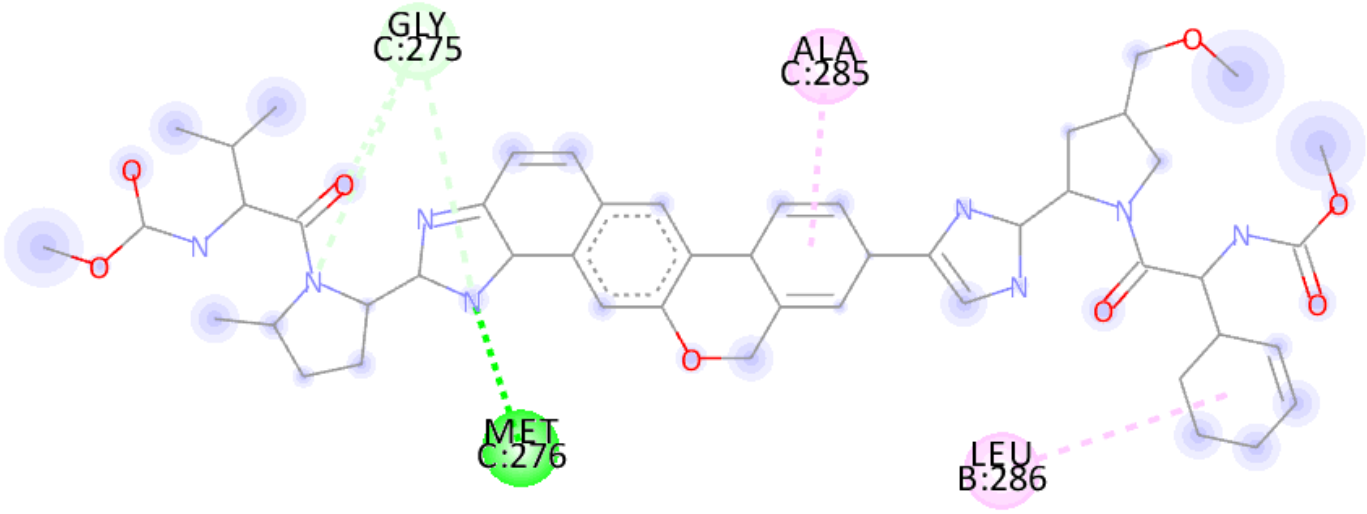

Figure 6

2D interaction ligand-protein: integration of 6wtt binding with Velpatasvir designed by Discovery Studio

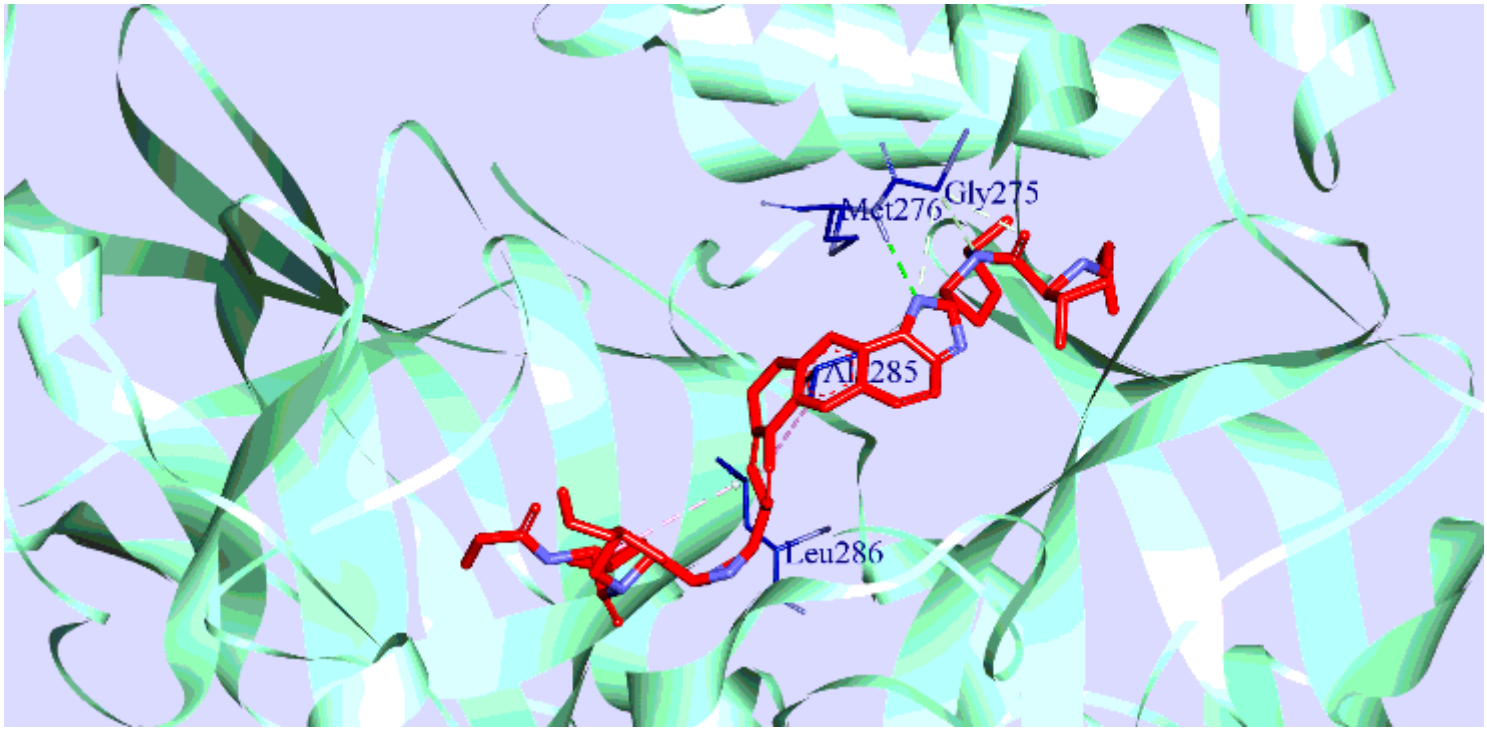

Figure 7

3D interaction ligand-protein: integration of 6wtt binding with Velpatasvir designed by Discovery Studio

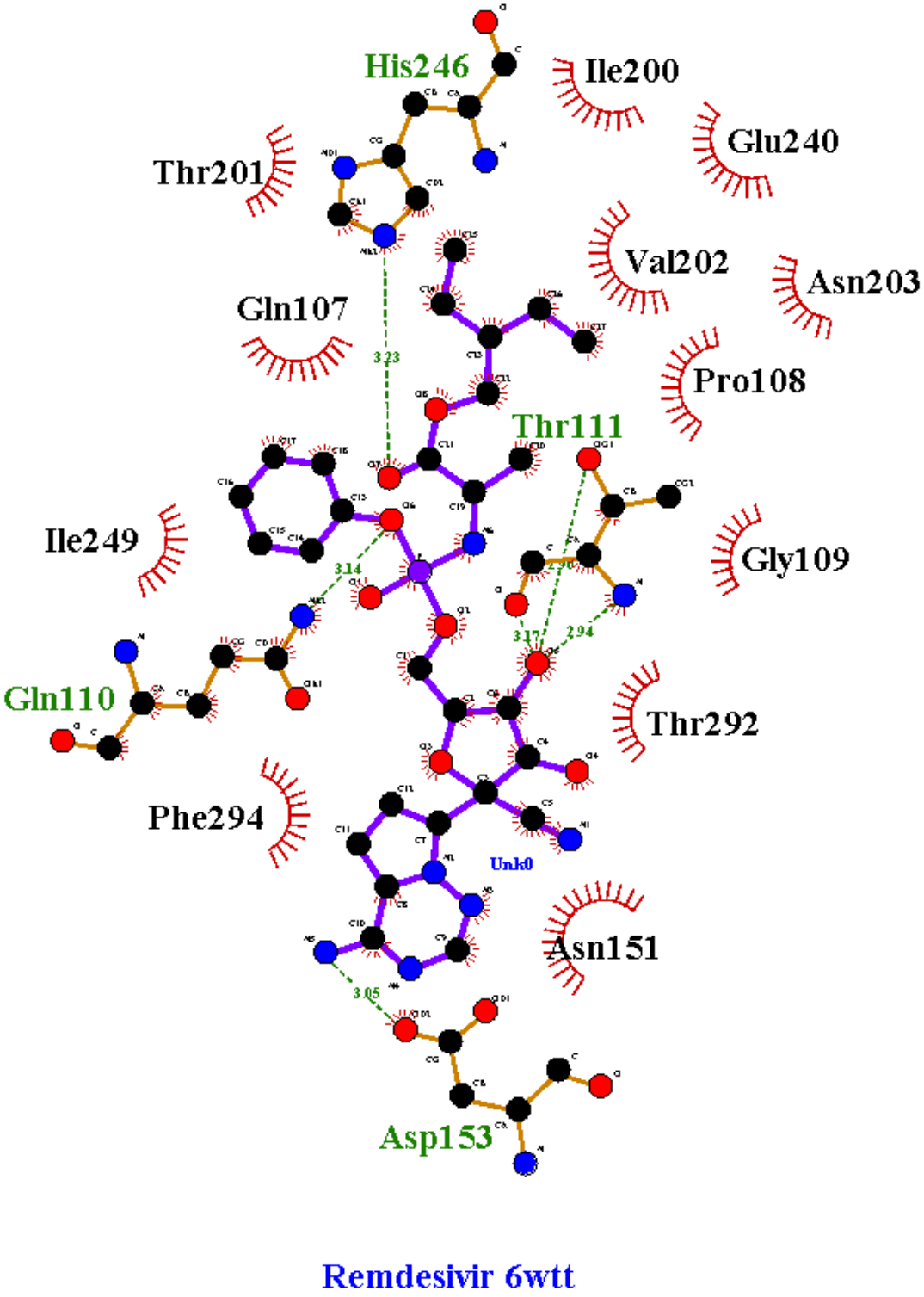

Figure 8

2D interaction ligand-protein: integration of 6wtt binding with Remdesivir designed by LigPlus+

Supplementary Files

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- Tables.docx