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Molecular Docking Studies on Synthetic Therapeutic Agents for COVID-19 †

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Abstract: Coronavirus disease (COVID-19) is an infectious disease caused by coronavirus 2 (SARS CoV-2) who have been detected for the first time in Wuhan China in December 2019. The rapid spread of this highly contagious and pathogenic virus led to the declaration of the pandemic by the World Health Organization (WHO) on March 11, 2020. In these conditions, the discovery of new antiviral agents is extremely important. For the development of the anti-SARS-CoV-2 drugs, the fastest way is to find potential molecules from the marketed drugs by molecular docking studies.

Keywords: COVID-19; SARS CoV-2; molecular docking; anti-viral agents; anti-inflammatory agents

1. Introduction

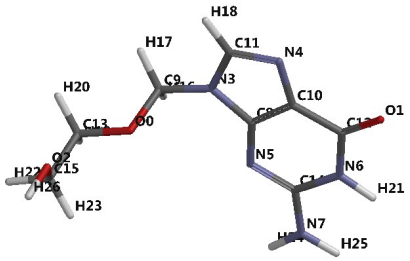
Coronavirus disease (COVID-19) is an infectious disease caused by coronavirus 2 (SARS CoV-2) who have been detected for the first time in Wuhan China in December 2019 [1]. The rapid spread of this highly contagious and pathogenic virus led to the declaration of the pandemic by the World Health Organization (WHO) on 11 March 2020.

The scientific community around the world is concerned with finding an effective treatment for the new coronavirus. Short-term efforts are focused on developing vaccines or inhibitors that act as protection against infection with the new coronavirus [2].

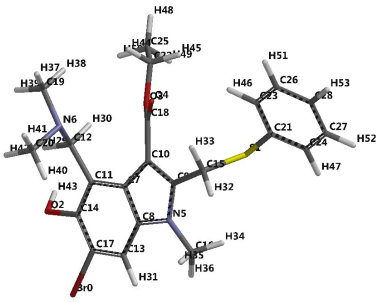
To develop new drugs with antiviral activity, the concern of many research groups is focused on the repositioning of already approved drugs [3–6] and the fastest way is to find potential drugs by molecular docking studies [7–13].

2. Molecular Docking Studies

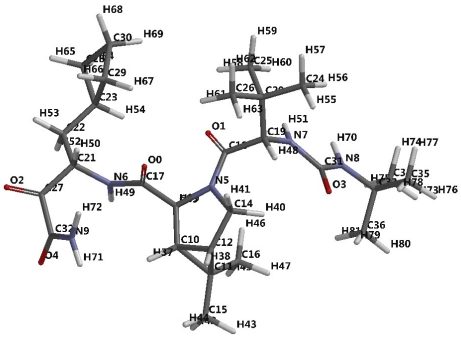
Molecular docking studies have been performed to identify and visualize the most likely interaction of the ligand with the protein receptor [14]. The docking score and hydrogen bonds formed with the amino acids from of the group interaction atoms are used to predict the binding modes, the binding affinity, and the orientation of the docked ligands in the active site of the protein/enzyme receptor. The docking study have been carried out with synthetic anti-viral agents (13) and anti-inflammatory agents (2) (Figure 1) prepared using Spartan 14 Software [15].



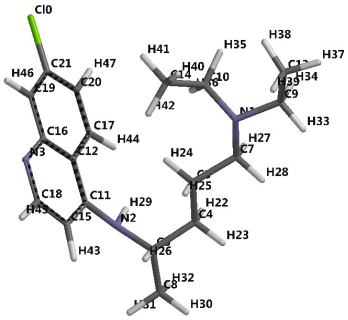
Acyclovir [6]



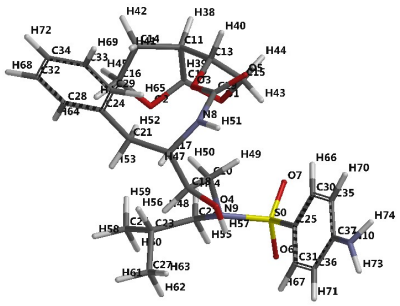
Arbidol [5]



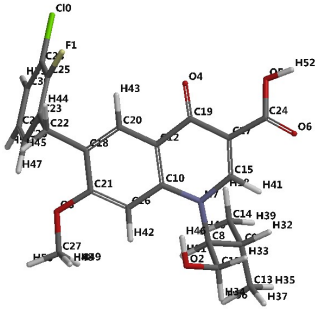
Boceprevir [18]



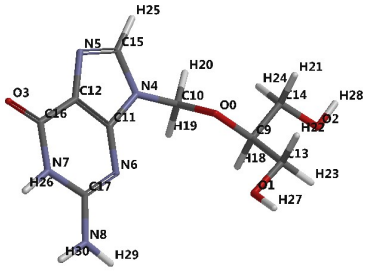
Chloroquine [5]



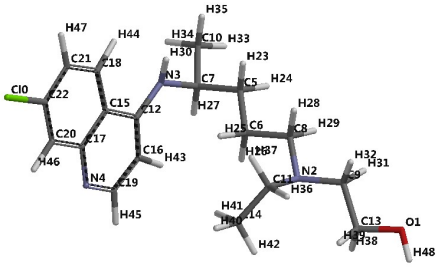
Darunavir [5]



Elvitegravir [17]



Ganciclovir [5]



Hydroxychloroquine [5]

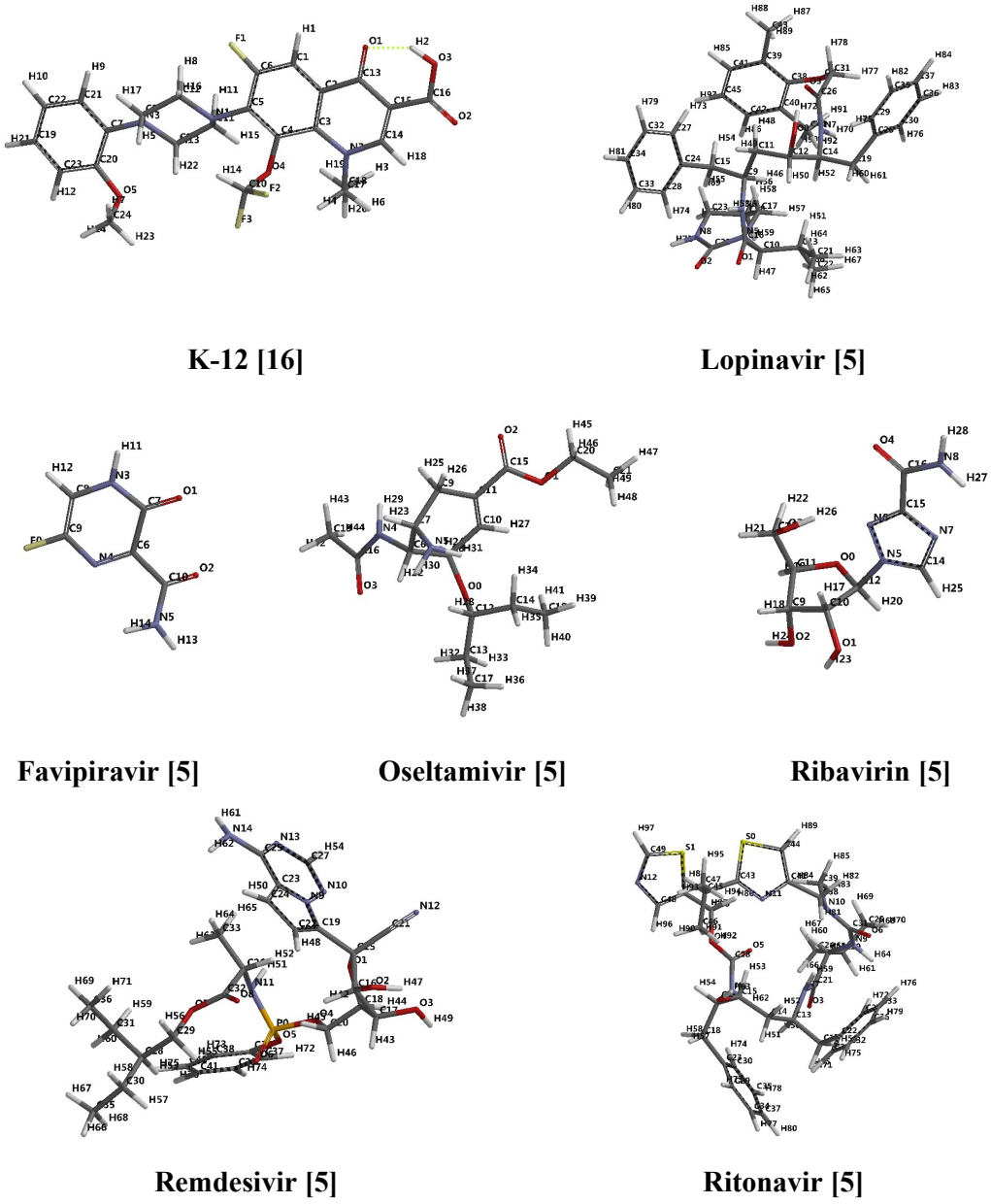


Figure 1. Tube representation of the optimized molecular structure of ligands. (the numbering of the atoms was done according to the software).

In this study are investigated five SARS-CoV-2 targets: main protease (PD ID: 6W63, PD ID: 6WNP), spike glycoprotein (closed state) (PD ID: 6VXX), chimeric receptor-binding domain complexed with its receptor human ACE2 (PD ID: 6VW1), RNA-dependent RNA polymerase (PD ID: 6M71) and 3CL protease (3CL pro) (PD ID: 6M2N).

2.1. SARS CoV-2 Main Protease

2.1.1. SARS CoV-2 Main Protease Receptor PD ID: 6W63

Docking studies were realized to obtaine accurate predictions on the optimized conformations for both the ligands and protein target to form a stable complex. The all compounds have been docked on the crystal structure of SARS CoV-2 main protease (PDB ID: 6W63). The docking pose of the co-crystallized X77 interacting with amino acid residues of the active site and the hydrogen bonds created with GLU 166 (2.721 Å) and GLY 143 (3.202 Å) are shown in Figure 2a. The co-crystallized X77 (**N-(4-tert-butylphenyl)-N-[(1R)-2-(cyclohexylamino)-2-oxo-1-(pyridin-3-yl)ethyl]-1H-imidazole -4-carboxamide**) was taken as reference ligand to compare the docking results of the studied compounds. The docking studies revealed that the docking score of ten compounds are better than of the co-crystallized X77 (docking score: −56.65; RMSD: 0.90 Å) (Table 1, Figure 13): Ritonavir (docking score: −93.42; RMSD: 2.98 Å), Lopinavir (docking score: −83.15; RMSD: 2.15 Å), Remdesivir (docking score: −76.90; RMSD: 1.89 Å), Darunavir (docking score: −70.33; RMSD: 2.14 Å), Elvitegravir (docking score: −67.97; RMSD: 0.23 Å), Arbidol (docking score: −63.32; RMSD: 0.23 Å), K-12 (docking score: −63.05; RMSD: 0.32 Å), Hydroxychloroquine (docking score: −62.66; RMSD: 0.86 Å), Chloroquine (docking score: −59.17; RMSD: 0.85 Å), Boceprevir (docking score: −58.78; RMSD: 4.05 Å). Because, in order to have a prediction as close to reality as possible, the RMSD value must be less than 2 Å [19], for compounds Ritonavir, Lopinavir, Darunavir and Boceprevir it can be considered that the prediction is not very accurate. Also the compound Renedesivir (docking score: −76.90; RMSD: 1.89 Å) shows the occurrence of five hydrogen bonds: with GLU 166 (3.070 Å), HIS 141 (3.205 Å), LEU 141 (2.651 Å), SER 144 (2.768 Å) and with HIS 163 (3.039 Å) (Figure 2b).

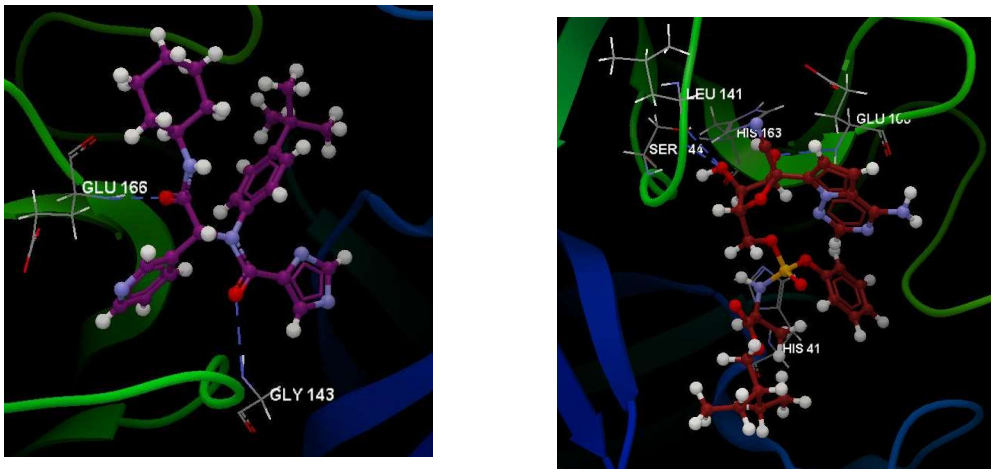


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Figure 2. (**a**) Hydrogen bonds between co-crystallized X77 and GLU 166 and GLY 143 amino acids residues of binding site of 6W63. (**b**). Hydrogen bonds between the Remdesivir ligand interacting with the GLU 166, HIS 141, LEU 141, SER 144 and HIS 163 amino acid residues of binding site of 6W63.

After analyzing the docking study results, it was observed that the all studied ligands were placed in the same binding site (green sphere) of 6W63 as the X77 co-crystallized and was observed they have the same orientation as the co-crystallized ligand (Figure 3).

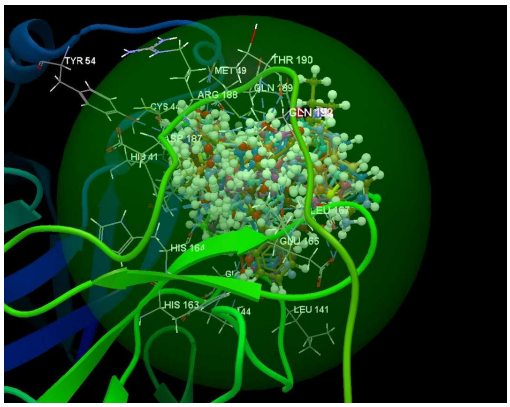

Figure 3. Docking pose of the co-crystallized X77 and all ligands in the binding site of 6W63.

2.1.2. SARS CoV-2 Main Protease Receptor PD ID: 6WNP

Docking studies were realized to obtaine accurate predictions on the optimized conformations for both the ligands and protein target to form a stable complex. The all compounds have been docked on the crystal structure of SARS CoV-2 main protease (PDB ID: 6WNP). The docking pose of the co-crystallized USG A 101 interacting with amino acid residues of the active site and the hydrogen bonds created with CYS 145 (2.900 Å), SER 144 (3.053 Å), GLY 143 (2.783 Å), HIS 41 (2.604 Å), HIS 164 (3.103 Å) and with GLU 166 (3.118 Å, 2.908 Å, 3.229 Å) are shown in Figure 4a. The co-crystallized USG A 101 (Boceprevir -bound form) was taken as reference ligand to compare the docking results of the studied compounds. The docking studies revealed that the docking score of five compounds are better than of the co-crystallized USG A 101 (docking score: −63.95; RMSD: 0.80 Å) (Table 1, Figure 13): Ritonavir (docking score: −97.38; RMSD: 3.54 Å), Lopinavir (docking score: −73.55; RMSD: 3.48 Å), Remdesivir (docking score: −66.87; RMSD: 1.52 Å), Elvitegravir (docking score: −65.81; RMSD: 0.23 Å), and Hydroxychloroquine (docking score: −64.86; RMSD: 1.25 Å). Because, in order to have a prediction as close to reality as possible, the RMSD value must be less than 2 Å [19], for compounds, Ritonavir and Lopinavir it can be considered that the prediction is not very accurate. Also the compound Renedesivir (docking score: −66.87; RMSD: 1.52 Å) shows the occurrence of four hydrogen bonds: two with GLU 166 (3.080 Å and 3.156 Å) and two with GLN 189 (2.936 Å and 2.925) (Figure 4b).

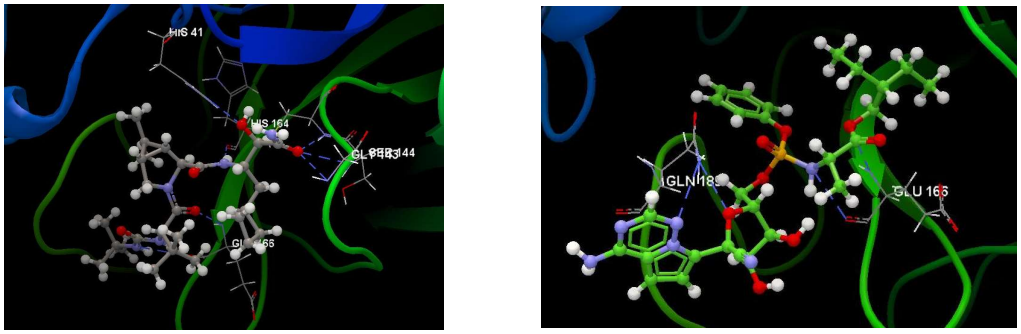

Figure 4. (**a**). Hydrogen bonds between co-crystallized USG A 101 and GLU 166, CYS 145, SER 144, GLY 143, HIS 141 and HIS 164 amino acids residues of binding site of 6WNP. (**b**). Hydrogen bonds between the Remdesivir interacting with the GLU 166 and GLN 189 amino acid residues of binding site of 6WNP.

The docking study results reveals that the all studied ligands were placed in the same binding site (green sphere) of 6WNP as the USG A 101 co-crystallized and was observed they have the same orientation as the co-crystallized ligand (Figure 5) and also it was obseved the corelation of the results

obtained for two X-ray Structures of SARS-CoV-2 main protease (6W63 and 6WNP) downloaded from PDB bank.

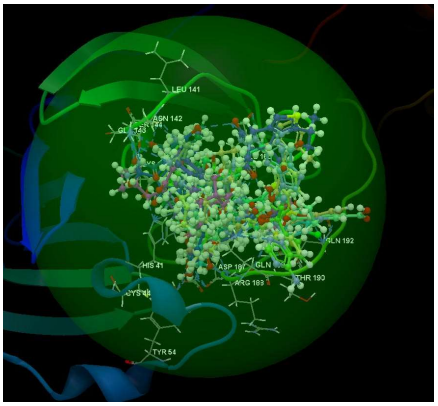

Figure 5. Docking pose of the co-crystallized USG A 101 and all ligands in the binding site of 6WNP.

2.2. SARS CoV-2 Spike Glycoprotein

The all compounds have been docked on the crystal structure of SARS CoV- spike glycoprotein (closed state) (PD ID: 6VXX).The docking pose of the co-crystallized NAG 1302 interacting with amino acid residues of the active site and the hydrogen bonds created with ASN 122 (2.393 Å, 2.441 Å and 2.449 Å) are shown in Figure 6a. The co-crystallized NAG 1302 was taken as reference ligand to compare the docking results of the studied compounds. The docking studies revealed that the docking score of four compounds are smaller than of the co-crystallized NAG 1302 (docking score: −18.42; RMSD: 0.51 Å) (Table 1, Figure 13): Chloroquine (docking score: −15.04; RMSD: 3.71 Å), Favipavir (docking score: −14.26; RMSD: 0.13 Å), K-12 (docking score: −13.45; RMSD: 1.57 Å) and Boceprevir (docking score: −11.41; RMSD: 4.15 Å) and darunavir has the best docking score (docking score: −39.10; RMSD: 4.06 Å). Darunavir is the only compound who shows the occurrence of the hydrogen bonds with the same ASN 122 amino acid (3.092 Å, 2.812 Å and 2.950 Å) like co-crystallized NAG 1302 (Figure 6b). Because, the RMSD value is greater than 2 Å [19], the prediction for Darunavir is not very accurate in this case.

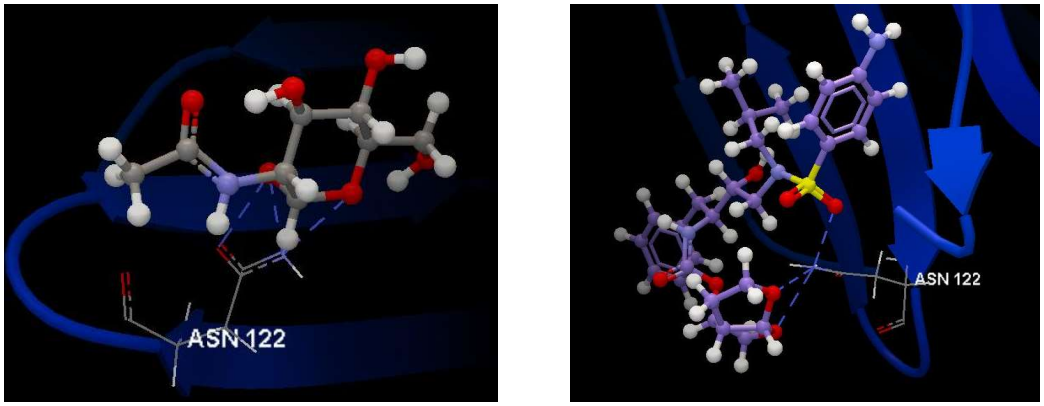

Figure 6. (**a**) Hydrogen bonds between co-crystallized NAG 1302 and ASN 122 amino acid residue of binding site of 6VXX. (**b**). Hydrogen bonds between the Darunavir interacting with the ASN 122 amino acid residue of binding site of 6VXX.

The docking study results reveals that the all studied ligands were placed in the same binding site (green sphere) of 6VXX as the NAG 1302 co-crystallized but only Darunavir has the same orientation as the co-crystallized ligand (Figure 7).

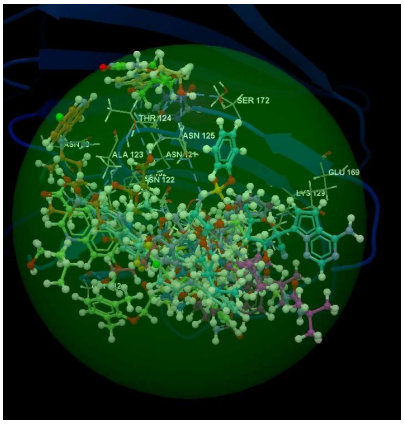

Figure 7. Docking pose of the co-crystallized NAG 1302 and all ligands in the binding site of 6VXX.

2.3. SARS CoV-2 Chimeric Receptor-Binding Domain Complexed with Its Receptor Human ACE2

The all compounds have been docked on the crystal structure of SARS CoV- chimeric receptor-binding domain complexed with its receptor human ACE2 (PD ID: 6VW1). The docking pose of the co-crystallized NAG 714 interacting with amino acid residues of the active site and the hydrogen bonds created with ASN 103 (2.434 Å, 2.310 Å and 2.562 Å) and GLN 81 (2.914 Å and 2.602 Å) are shown in Figure 8a. The co-crystallized NAG 714 was taken as reference ligand to compare the docking results of the studied compounds. The docking studies revealed that only Favipavir (docking score: −32.12; RMSD: 0.01 Å). has the docking score smaller than of the co-crystallized NAG 714 (docking score: −32.77; RMSD: 0.20 Å) (Table 1, Figure 13). Remdesivir compound (docking score: −51.99; RMSD: 2.95 Å) shows the occurrence of hydrogen bonds with the same amino acids ASN 103 (3.007 Å, 3.112 Å and 3.057 Å) and GLN 81 (3.103 Å) like co-crystallized NAG 714 and also with HIS 195 (3.299 Å), ALA 193 (3.078 Å) and with ASN 194 (2.926 Å) (Figure 8b). Because, the RMSD value is greater than 2 Å [19], the prediction for Remdesivir is not very accurate in this case.

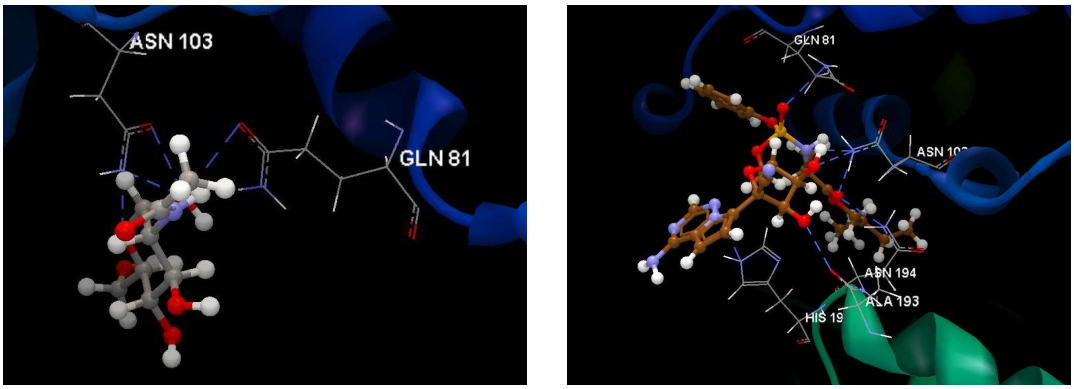

Figure 8. (**a**). Hydrogen bonds between co-crystallized NAG 714 and ASN 103 and **GLN 81 amino acid residues of binding** site of 6VW1. (**b**). Hydrogen bonds between the Remdesivir interacting with the ASN 103, GLN 81, HIS 195, ALA 193 and ASN 194 amino acids residues of binding site of 6VW1.

The docking study results reveals that the all studied ligands were placed in the same binding site (green sphere) of 6VW1 as the NAG 714 co-crystallized and was observed they have the same orientation as the co-crystallized ligand (Figure 9).

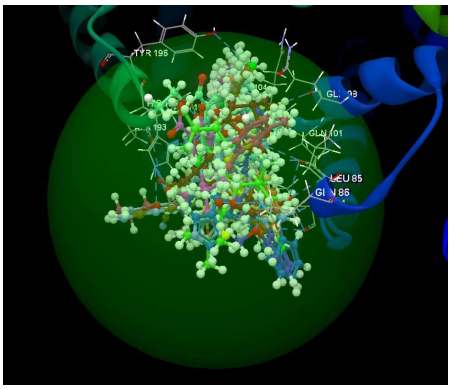

Figure 9. Docking pose of the co-crystallized NAG 714 and all ligands in the binding site of 6VW1.

2.4. SARS CoV-2 RNA-Dependent RNA Polymerase

The all compounds have been docked on the crystal structure of SARS CoV-2 RNA-dependent RNA polymerase (PD ID: 6M71). The docking studies revealed that Remdesivir has the best docking score: −52.51 (RMSD: 2.28) (Table 1, Figure 13) and shows the occurrence of six hydrogen bonds with the ASP 118 (2.792 Å), ASP 760 (2.643 Å), ASN 691 (2.705 Å), ASP 623 (3.320 Å), CYS 522 (3.348 Å) and LYS 621 (2950 Å) (Figure 10a). Because, the RMSD value is greater than 2 Å [19], the prediction for Remdesivir is not very accurate in this case. All studied ligands were placed in the same binding site (green sphere) of 6M71 (Figure 10b).

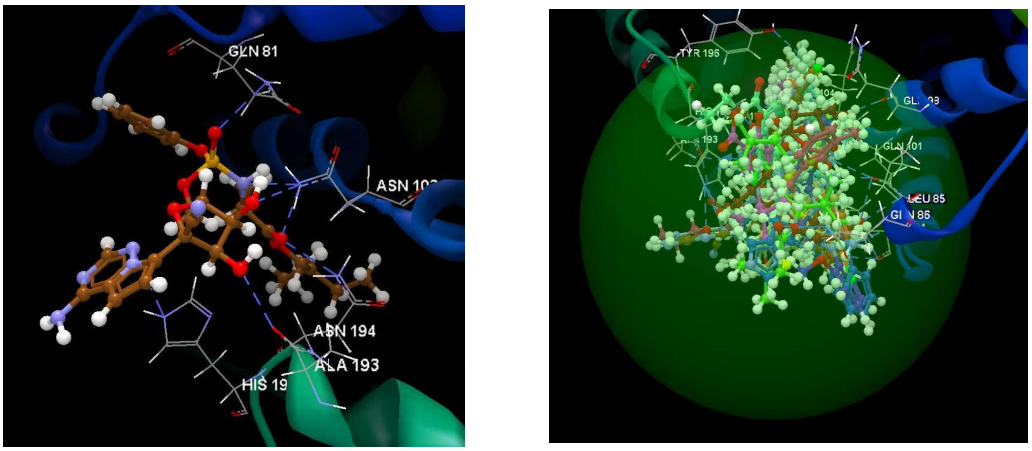

Figure 10. (**a**) Hydrogen bonds between the Remdesivir interacting with the ASP 118, ASP 760, ASN 691, ASP 623, CYS 522 and LYS 621. Amino acids residues of binding site of 6M71. (**b**) Docking pose of all ligands in the binding site of 6M71.

2.5. SARS CoV-3CL Protease (3CL pro)

Docking studies were realized to obtaine accurate predictions on the optimized conformations for both the ligands and protein target to form a stable complex. The all compounds have been docked on the crystal structure of SARS CoV-2 3CL protease (3CL pro) (PD ID: 6M2N).The docking pose of the co-crystallized 3WL A interacting with amino acid residues of the active site and the hydrogen bonds created with GLU 166 (3.016 Å), GLY 143 (3.104 Å and 2.969 Å) and ASN 142 (3.341 Å) are shown in Figure 11a. The co-crystallized 3WL A was taken as reference ligand to compare the docking results of the studied compounds. All compounds except Oseltamivir, Ganciclovir, Aciclovir, Ribavirin and Favipavir have a docking score greater than co-crystallized (docking score: −53.49; RMSD: 0.37 Å) (Table 1, Figure 13). Lopinavir has the best docking score: −83.22 (RMSD: 0.98 Å) and

shows the occurrence of hydrogen bonds with the same amino acids GLU 166 (3.013 Å), GLY 143 (2.637 Å) and ASN 142 (2.944 Å) like co-crystallized 3WL A (Figure 11b).

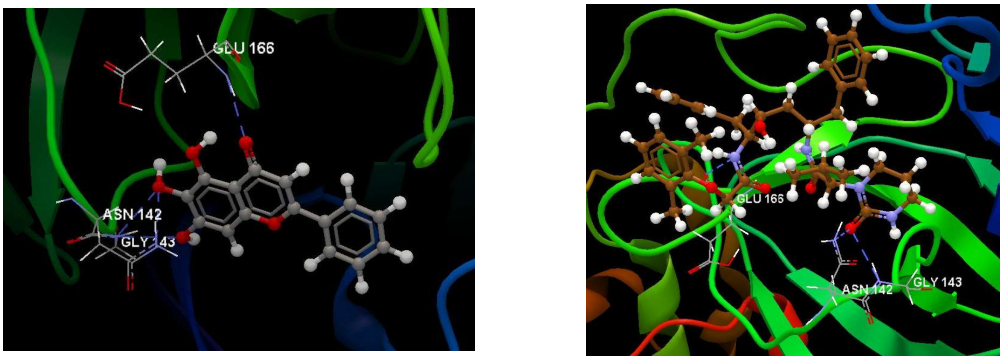

Figure 11. (**a**) Hydrogen bonds between co-crystallized 3WL A and GLU 166, GLY 143 and ASN 142 amino acids residues of binding**.** Site of 6M2N. (**b**). Hydrogen bonds between the Lopinavir ligand interacting with the GLU 166, GLY 143 and ASN 142 amino acid residues of binding site of 6M2N.

After analyzing the docking study results, it was observed that the all studied ligands were placed in the same binding site (green sphere) of 6M2N as the 3WL A co-crystallized and was observed they have the same orientation as the co-crystallized ligand (Figure 12).

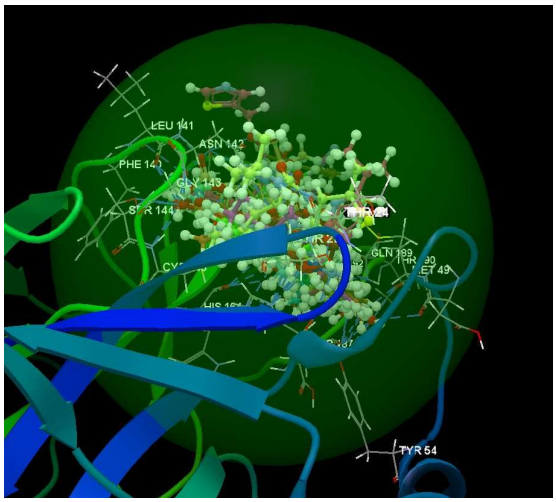

Figure 12. Docking pose of the co-crystallized 3WL A and all ligands in the binding site of 6M2N.

Table 1. Docking score of ligands.

Ligand	PDB ID: 6W63		PDB ID: 6WNP		PDB ID: 6VXX		PDB ID: 6VW1		PDB ID: 6M71		PDB ID:6M2N	
	Score	**RMSD [**Å]	**Score**	**RMSD [**Å]	**Score**	**RMSD [**Å]	**Score**	**RMSD[**Å]	**Score**	**RMSD[**Å]	**Score**	**RMSD[**Å]
Co-crystallized	−56.65	0.90	−63.95	0.80	−18.42	0.51	−32.77	0.20	–	–	−53.49	0.37
Ritonavir	−93.42	2.98	−97.38	3.54	−38.40	5.17	−55.89	3.16	−46.55	2.49	−80.80	3.24
Lopinavir	−83.15	2.15	−77.35	3.48	−38.48	4.69	−57.81	2.67	−48.13	2.35	−83.22	0.98
Remdesivir	−76.90	1.89	−66.87	1.52	−28.58	3.78	−53.28	2.95	−52.21	2.28	65.68	1.33
Darunavir	−70.33	2.14	−60.18	1.84	−39.10	4.06	−51.99	1.94	−48.80	1.34	−63.32	1.94
Elvitegravir	−67.96	0.23	−65.81	0.58	−28.54	2.10	−50.89	0.40	−48.76	0.06	−66.27	0.07
Arbidol	−63.32	0.23	−61.55	0.48	−30.23	1.38	−47.62	0.87	−43.11	0.49	−65.76	0.04
K-12	−63.05	0.32	−57.90	0.61	−13.45	1.57	−48.82	0.63	−50.55	0.40	−59.31	0.52
Hydroxychloroquine	−62.66	0.86	−64.86	1.25	−20.44	3.08	−53.26	0.71	−45.68	1.06	−67.91	1.07
Chloroquine	−59.17	0.85	−57.90	1.07	−15.04	3.71	−47.22	1.17	−41.10	0.96	−62.53	1.85
Boceprevir	−58.78	4.05	−59.43	0.80	−11.41	4.15	−41.46	1.41	−34.82	1.07	−61.26	1.80
Oseltamivir	−48.68	0.51	−44.43	0.45	−26.16	3.82	−37.56	0.63	−40.48	1.25	−47.34	0.48
Ganciclovir	−48.13	0.81	−44.73	0.55	−23.18	0.80	−41.17	0.62	−36.56	0.48	−45.90	0.25
Ribavirin	−40.96	0.03	−40.13	0.75	−20.79	0.19	−34.76	0.08	−32.89	0.02	−39.01	0.03
Acyclovir	−40.94	0.77	−37.72	0.72	−19.23	1.15	−38.45	0.22	−29.47	0.52	−43.91	0.04
Favipiravir	−30.58	0.03	−30.56	0.01	−14.26	0.13	−32.12	0.01	−21.65	0.04	−33.28	0.09

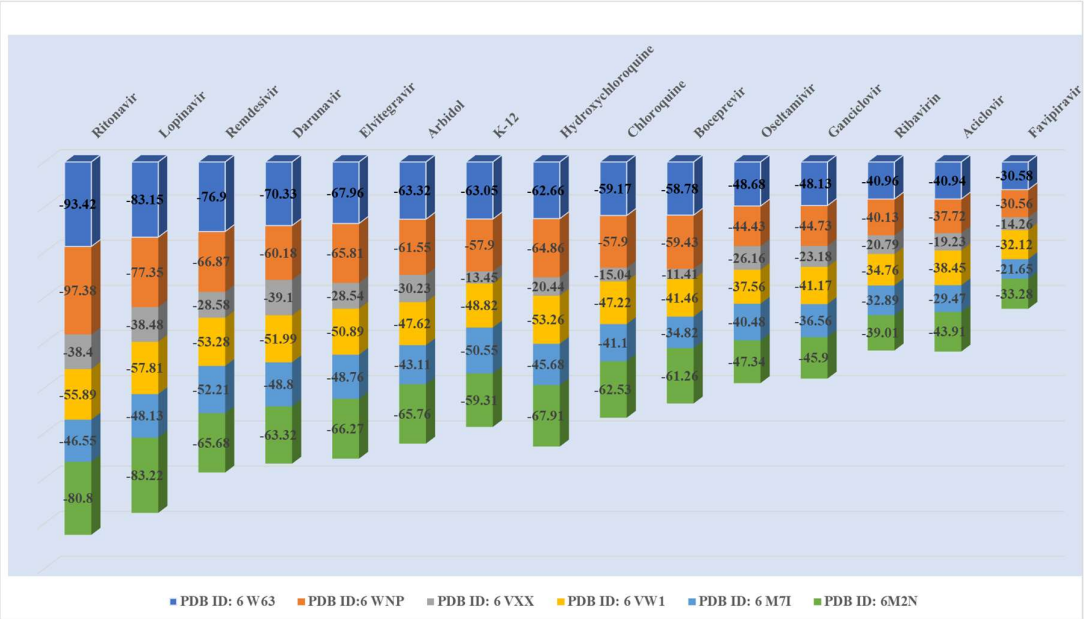

Figure 13. Docking score of the studied molecules.

3. Conclusions

The docking study have been carried out with synthetic anti-viral agents (13) and anti-inflammatory agents (2) as ligands against the SARS-CoV-2 main protease (PD ID: 6W63, PD ID: 6WNP), SARS-CoV-2 spike glycoprotein (closed state) (PD ID: 6VXX), SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2 (PD ID: 6VW1), SARS-CoV-2 RNA-dependent RNA polymerase (PD ID: 6M71), SARS-CoV-2 3CL protease (3CL pro) (PD ID: 6M2N).

The study indicates the possibility of using approved drugs in the treatment of coronavirus disease (COVID-19).

The best results were obtained for antiretrovirals:

- protease inhibitors: Lopinavir, Ritonavir, Darunavir
- integrase inhibitors: Elvitegravir and for Remdesivir, originally developed for the treatment of Marburg virus, Ebola virus and Cueva virus infections.

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