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IN-SILICO STUDIES ON POTENTIAL INHIBITORS OF SARS-CoV2

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Abstract: The emergence of the SARS-CoV-2 virus, responsible for the COVID-19 pandemic, has spurred extensive research to identify effective treatments and preventative measures. One promising avenue is the repurposing of existing anti-malarial and anti-viral compounds, which have shown potential through molecular docking studies. These studies provide crucial insights into how these compounds interact with viral proteins and can aid in the development of novel therapies. In this article, authors will delve into the world of molecular docking studies concerning anti-malarial and anti-viral compounds for SARS-CoV-2.

Keywords: AUTODOCK, Molecular docking, SARS-CoV2.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 is the new virus, formerly known as the 2019-novel corona virus (2019-nCoV). The family Corona Viridae includes enveloped viruses with incredibly long single-stranded RNA genomes that range in size from 26 to 32 kilo bases (CoVs) (Su *et al.,* 2016). Prior to the emergence of the corona virus that causes severe acute respiratory syndrome (SARS-CoV) in late 2002 (Zhong *et al.*, 2003; Drosten *et al.*, 2003; Ksiazek *et al.,* 2003; Fouchier *et al.*, 2003), CoVs were thought to only cause mild illnesses in immune-competent people.

However, CoVs have been found in both avian hosts and a variety of mammals, including bats, camels, dogs, and masked palm civets. The only symptoms that the viruses of 229E, OC43, NL63, and HKU1 produce are mild versions of the common cold. The remaining three viruses, SARS-CoV, which caused the SARS outbreak in 2002 and 2003 (Zhong *et al.*, 2003; Drosten *et al.*, 2003), MERS-CoV, which appeared in 2012 and is still circulating in camels (Zaki *et al.*, 2012) and SARS-CoV-2, which first surfaced in December 2019 in Wuhan, China, and is currently the target of intense containment efforts (Zhu *et al.*, 2020), can all cause severe illness. It gradually became a pandemic and badly affected the education, humanity, environment and society (Verma and Prakash, 2020; Kumari and Shukla, 2020; Roy *et al.*, 2020; Roy and Chaube, 2021; Kumar, 2021).

The research and development of the diagnostics, therapeutics, and vaccines for this novel corona virus have been ongoing since the breakthrough of the COVID-19. It has been reported that some anti-malarial and anti-viral medications have a curative effect on COVID-19 based on the findings of some clinical trials. In order to thoroughly examine the biological activities and pharmacological effects of some anti-malarial and anti-viral medications against COVID-19 main protease receptor, authors have performed molecular docking studies.

MATERIALS AND METHODS

Ligand Preparation

All the ligands (anti-malarial and anti-viral compounds), three-dimensional structures were obtained in SDF format from the PubChem database. Using Pymol, the ligands' specified 3D structures in SDF format were converted to PDB formats. The ligand preparation process entails a number of steps that result in structure variation and optimization, and the results are saved in .pdbqt format. All of the anti-malarial and anti-viral medications' modified structures were then put through a molecular docking study to determine how they might bind to the COVID-19 main protease target.

Protein Preparation

From the RCSB Protein Data Bank database, the three-dimensional crystal structure of the COVID-19 main protease [PDB-ID: 6LU7] was obtained. Before docking, the COVID-19 main protease [PDB-ID: 6LU7] water molecules, unwanted hetero atoms, cofactors were eliminated, and polar hydrogens, Kollaman charges were then added to the protein molecule. The charged protein molecule was then saved in the .pdbqt format using Pymol.

Receptor Grid Generation

With the help of the Lamarackian Genetic Algorithm and an empirical force field, the AutoDock software (Morris *et al.,* 2009), predicts the bound conformation based on free binding energies (Morris *et al*., 1998). Active residues were found to be located in the grid box that was used for molecular docking, with dimensions as: center x=-26.283, center y= 12.599, center z=58.966, size x=80, size y=80, size z=80, spacing=0.475. The hydrogen bond (inter-molecular) interaction between the functional group of the ligands and the amino acid residues available on the target side was taken into account in order to determine the binding affinity between the ligand and target receptor.

Molecular Docking

To understand, how the compounds bind to the receptor's active site, molecular docking studies were conducted. Protein Data Bank and the PubChem database are used to retrieve the 3D structures of the target enzyme and ligands, respectively. AutoDock Vina was used to carry out molecular docking investigations, and PyMol was used to visualize docking complexes.

RESULTS AND DISCUSSION

The COVID-19 main protease, which has been deposited on RCSB protein data bank [PDB ID: 6LU7] used as a potential target for the molecular docking studies. In this work, authors took anti-malarial drugs namely Chloroquine, Hydroxy-chloroquine, Mepacrine, Quinine, Artemisinin, Phomarin, Proguanil, Mefloquine, Halofantrine, Amodiaquine and eighteen anti-viral drugs viz. Abacvir, Acyclovir, Adefovir, Amantadine, Zanamivir, Oseltavir, Ribavirin, Ganciclovir, Riamilovir, Arbidol/Umiefenovir, Galidesivir, Favipiravir, Ramdisivir, Imatinib, Baricitinib, Ruxolitinib, Anakinra, Isoxzole. These ligands are docked with the COVID-19 main protease receptor target (PDB ID: 6LU7) from AUTODOCK VINA. The results obtained from AUTODOCK docking are depicted in Table 1.

Table1: Docking score/binding affinity of inhibitors as obtained through AUTODOCK.

Sl. No.	Name of the inhibitor	Molecular Formula	Pubchem CID	Binding Affinity (kcal/mol)
Anti-malarial compounds				
1.	Chloroquine	$C_{18}H_{26}ClN_3$	2719	-4.6
2.	Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	3652	-5.5
3.	Mepacrine	$C_{23}H_{30}ClN_3O$	237	-5.6
4.	Quinine	$C_{20}H_{24}N_2O_2$	3034034	-6.4
5.	Artemisinin	$C_{15}H_{22}O_5$	68827	-7.3
6.	Phomarin	$C_{15}H_{10}O_4$	12314177	-7.3
7.	Proguanil	$C_{11}H_{16}ClN_5$	6178111	-5.0
8.	Mefloquine	$C_{17}H_{16}F^6N^2O$	4046	-7.5
9.	Halofantrine	$C_{26}H_{30}CL_2F_3NO$	37393	-6.0
10.	Amodiaquine	$C_{20}H_{22}CLN_3O$	2165	-6.2
Anti-viral compounds				
11.	Abacvir	$C_{14}H_{18}N_6O$	441300	-5.6
12.	Acyclovir	$C_8H_{11}N_5O_3$	135398513	-5.2
13.	Adefovir	$C_8H_{12}N_5O_4P$	60172	-5.1
14.	Amantadine	$C_{10}H_{17}N$	2130	-5.1
15.	Zanamivir	$C_{12}H_{20}N_4O_7$	60855	-6.2
16.	Oseltavir	$C_{16}H_{28}N_2O_4$	65028	-5.6
17.	Ribavirin	$C_8H_{12}N_4O_5$	37542	-6.0
18.	Ganciclovir	$C_9H_{13}N_5O_4$	135398740	-4.2
19.	Riamilovir	$C_5H_4N_6O_3S$	3113817	-5.1
20.	Arbidol/Umiefenovir	$C_{22}H_{25}BrN_2O_5S$	131411	-5.8
21.	Galidesivir	$C_{11}H_{15}N_5O_3$	10445549	-5.6
22.	Favipiravir	$C_5H_4N_3O_2$	492405	-4.6
23.	Ramdisivir	$C_{27}H_{35}N_6O_8P$	121304016	-8.0
24.	Imatinib	$C_{29}H_{31}N_7O$	5291	-8.2
25.	Baricitinib	$C_{16}H_{17}N_7O_2S$	44205240	-6.0
26.	Ruxolitinib	$C_{17}H_{18}N_6$	25126798	-6.8
27.	Anakinra	$C_{20}H_{23}N_5O_7S_2$	139595263	-7.2
28.	Isoxzole	$C_{61}H_{20}C_{l2}N_2O$	21309	-6.7

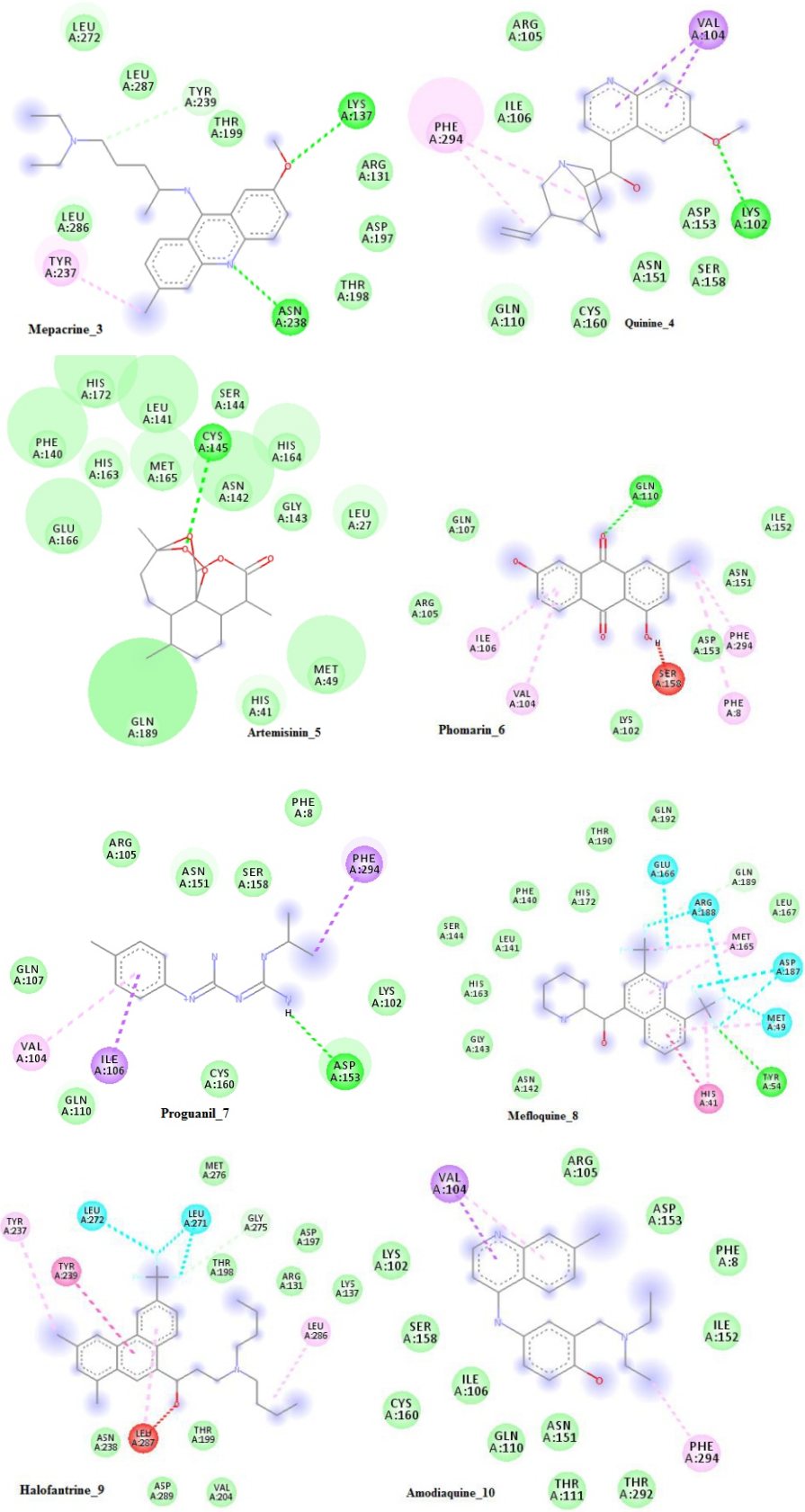
Among all the anti-malarial drugs, Mefloquine shows highest binding affinity of -7.5 kcal/mol while Artemisinin and Phomarin exhibit second highest binding affinity o -7.3 kcal/mol. During docking of eighteen antiviral drugs with COVID-19 main protease, Imatinib shows highest binding affinity of -8.3 kcal/mol while Ramdisivir shows second highest binding affinity of -8.0 kcal/mol, which is slightly lower than the binding affinity of Imatinib. The rest anti-viral drugs show moderate docking score. Table 1 demonstrates that the anti-viral drugs Imatinib and Ramdisivir exhibit better binding capabilities with COVID-19 main protease over all the anti-malarial and anti-viral drugs.

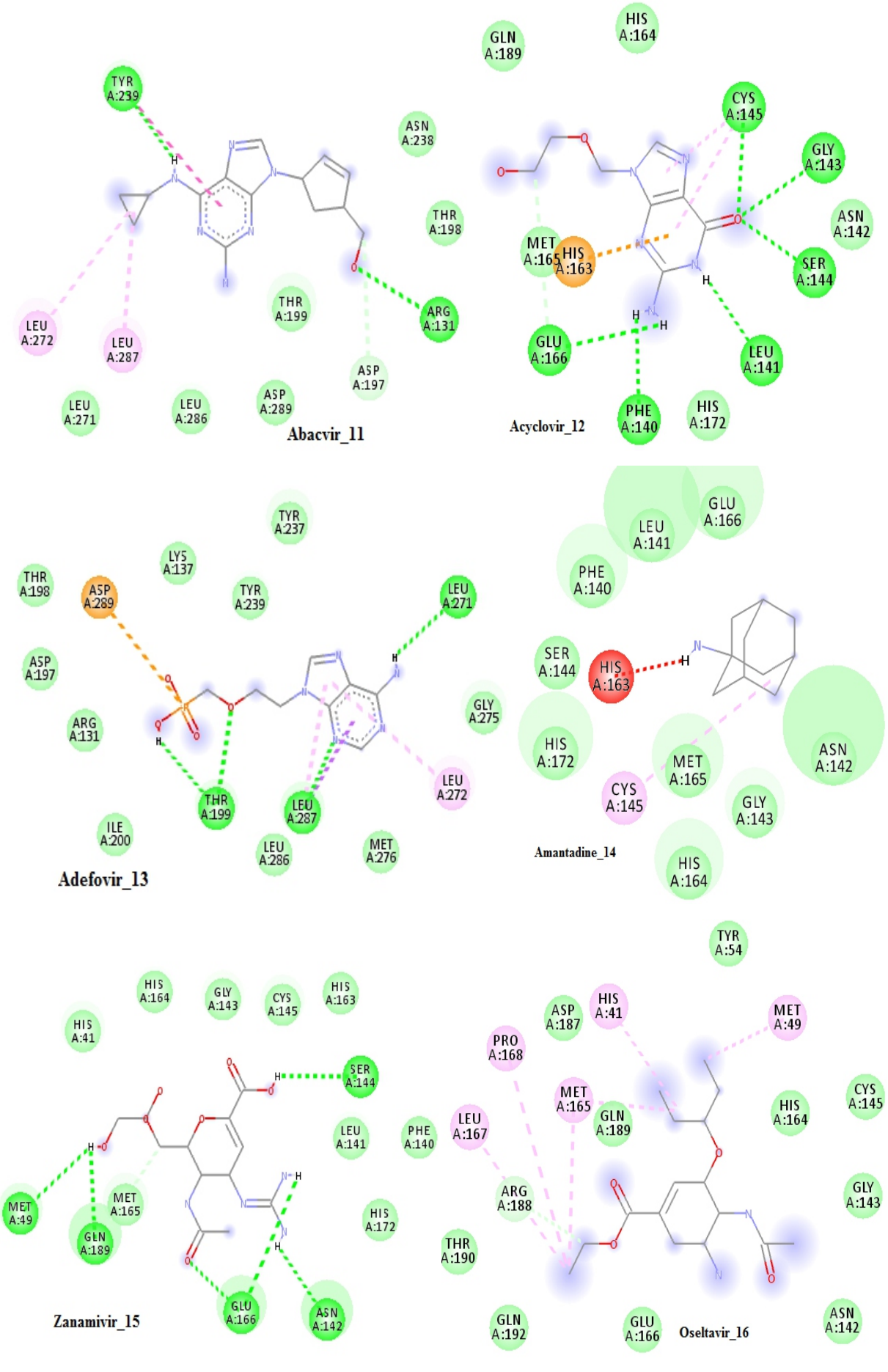
Table 2: Hydrogen bonding interactions in the best docked complexes of ligands.

Sl. No.	Name of the inhibitor	No. of H-bonds	Hydrogen bonding interactions
1.	Chloroquine	00	NO
2.	Hydroxychloroquine	00	NO
3.	Mepacrine	02	LYS137, ASN238
4.	Quinine	01	LYS102
5.	Artemisinin	01	CYS145
6.	Phomarin	01	GLN110
7.	Proguanil	01	ASP153
8.	Mefloquine	01	TYR54
9.	Halofantrine	00	NO
10.	Amodiaquine	00	NO
11.	Abacvir	02	ARG131, TYR239
12.	Acyclovir	06	GLU166, PHE140, CYS145, GLY143, SER144, LEU141
13.	Adefovir	03	LEU271, THR199, LEU287
14.	Amantadine	00	NO
15.	Zanamivir	05	MET49, GLN189, GLU166, ASN142, SER144
16.	Oseltavir	00	NO
17.	Ribavirin	04	LEU141, HIS163, GLU166,HIS164
18.	Ganciclovir	00	NO
19.	Riamilovir	04	THR111, THR292, ASN151, GLN110
20.	Arbidol/Umiefenovir	00	NO
21.	Galidesivir	03	GLN110, GLU240,, HIS246
22.	Favipiravir	04	VAL77, GLN74, HIS64, PHE66
23.	Ramdisivir	04	HIS163, LEU141, GLY143, CYS145
24.	Imatinib	01	GLU166
25.	Baricitinib	03	ASP283,LEU287, ARG131
26.	Ruxolitinib	01	HIS41
27.	Anakinra	05	GLY143, SER144, CYS145, HIS163, ASN142
28	Isoxzole	04	LYS137, ASN238, TYR237, LEU287

The non-covalent interactions between lignads and COVID19-main protease are presented in Figure 1 while the H-bonding interactions are given in Table 2. As per Table 2 and Figure 1, Mepacrine shows two H-bonds with LYS137 and ASN 238, Quinine shows one H-bond with LYS 102, Artemisinin shows one H-bond with CYS145, Phomarin shows one H-bond with GLN110, Proguanil Phomarin shows one H-bond with ASP153, Mefloquine shows one H-bond with TYR54, Halofantrine, Oseltavir Amantadine and Amodiaquine does not show any h-bonding, Abacvir shows two H-bond with ARG131, TYR239; Acyclovir shows six H-bond with GLU166, PHE140, CYS145, GLY143, SER144, LEU141; Adefovir shows three H-bond with LEU271, THR199, LEU287; Zanamivir shows five H-bond with MET49, GLN189, GLU166, ASN142, SER144; Ribavirin shows four H-bond with LEU141, HIS163, GLU166,HIS164; Riamilovir four H-bond with THR111, THR292, ASN151, GLN110; Galidesivir shows three H-bond with

GLN110, GLU240,, HIS246; Favipiravir shows four H-bond with VAL77, GLN74, HIS64, PHE66; Ramdisivir with HIS163, LEU141, GLY143, CYS145; Imatinib with GLU166; Baricitinib with ASP283,LEU287, ARG131; Ruxolitinib with HIS41; Anakinra with GLY143, SER144, CYS145, HIS163, ASN142 and Isoxzole shows one H-bond with LYS137, ASN238, TYR237, LEU287.

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ASN A:142
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PHE A:140
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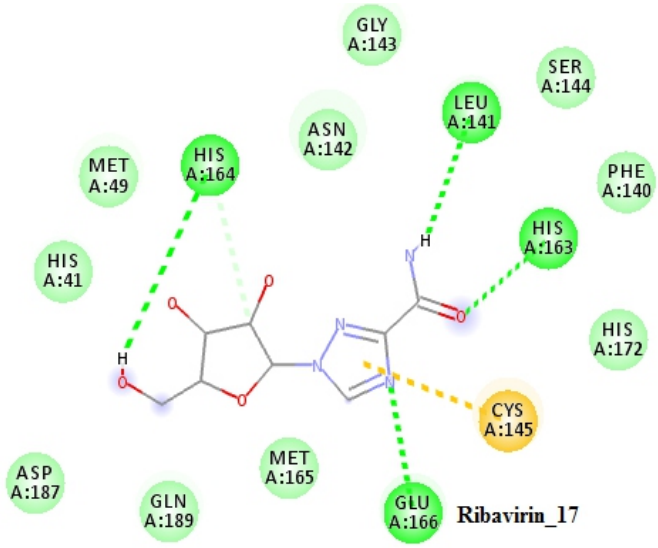
ASN A:142
Oseltavir_16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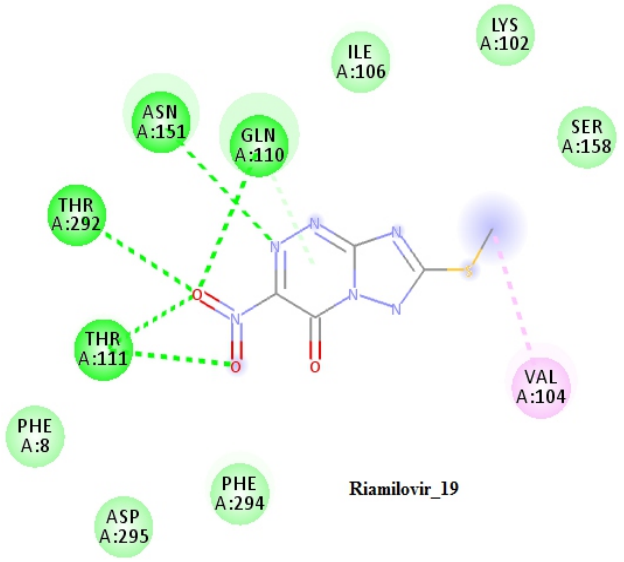
GLU A:166
Ribavirin_17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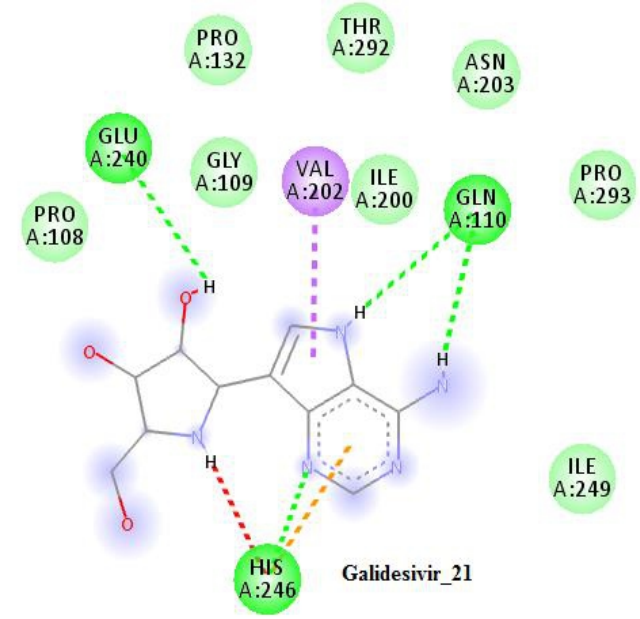
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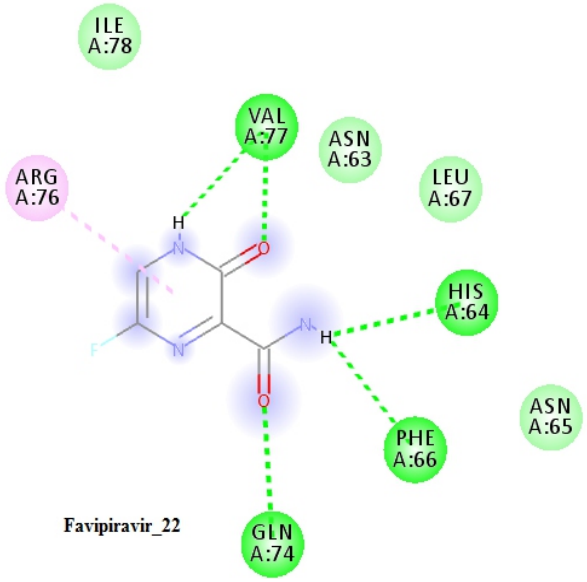
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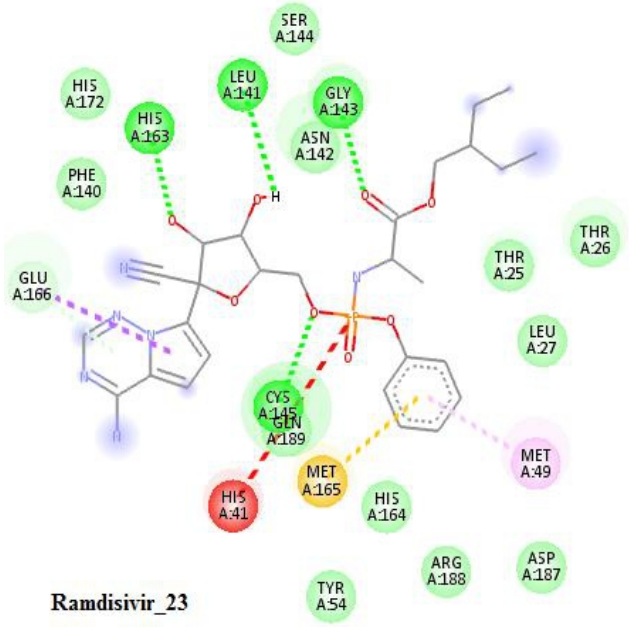
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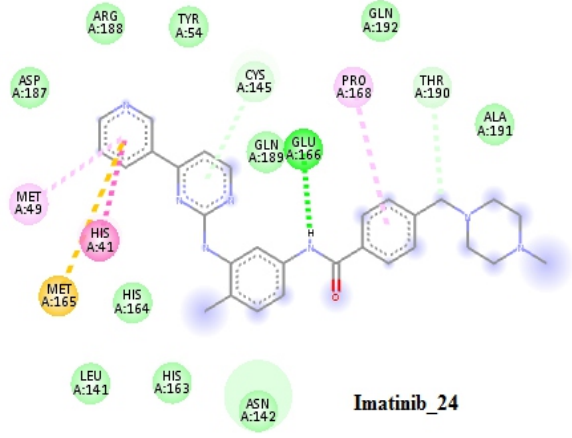
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Imatinib_24

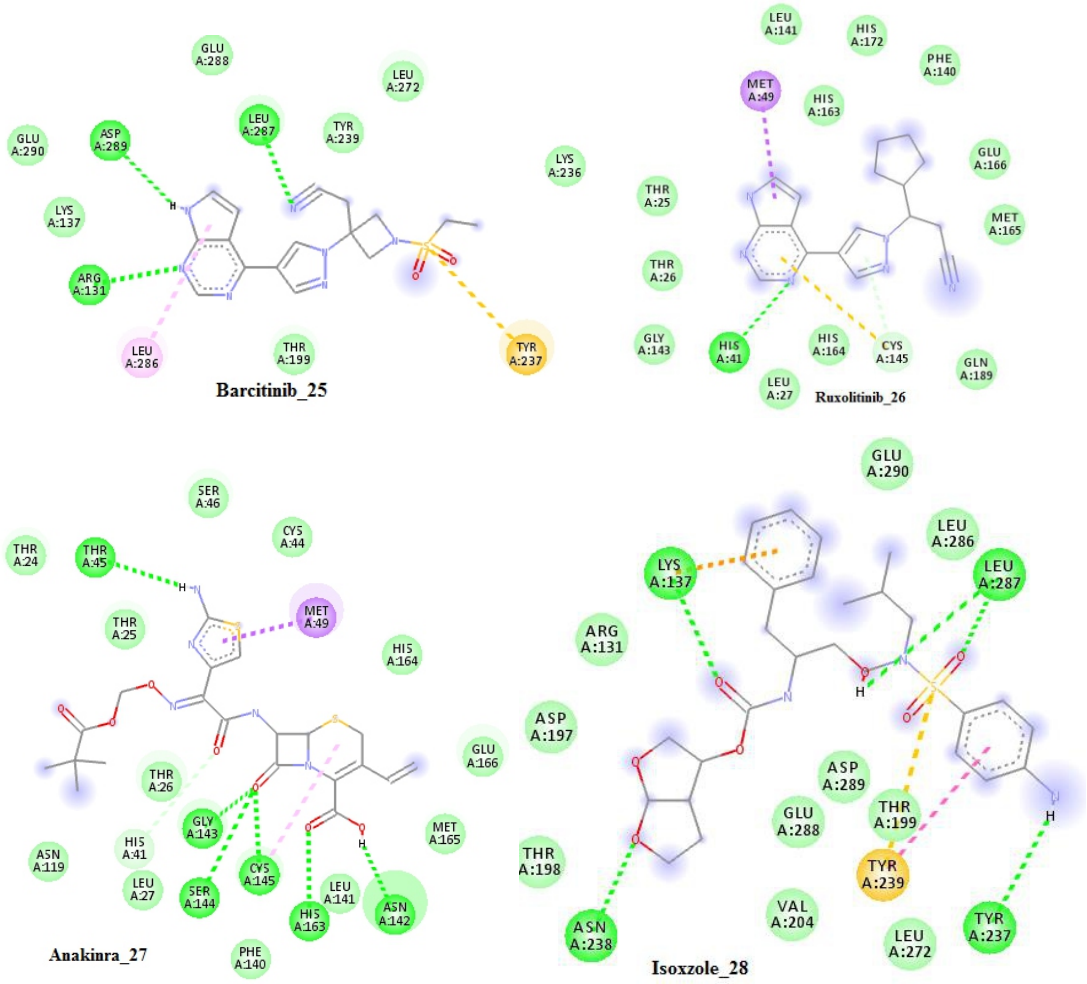

Fig.1: Hydrogen bonding and other non-covalent interactions in the best docking poses of ligands.

CONCLUSION

Molecular docking studies on anti-malarial and anti-viral compounds have shed light on potential treatments for COVID-19. The docking results of anti malarial and antiviral drugs against COVID-19 main protease receptor suggest that Imatinib and Ramdisivir exhibit better binding capabilities with COVID-19 main protease over all the anti-malarial and anti-viral drugs. While these studies provide a valuable starting point, they must be followed by rigorous experimental testing to confirm the effectiveness and safety of these compounds.

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