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ADME predictions and molecular docking study of some compounds and drugs as potential inhibitors of COVID-19 main protease: A virtual study as comparison of computational results

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Abstract

There is an urgent need for a drug to be used against COVID-19, which negatively affects human life worldwide and causes pandemic leading to the death of many people. Although some drugs are included in the treatment protocols of health institutions, there are currently no specific drugs against COVID-19 or are unknown, and effective treatment options remain very limited. Since designing a novel drug and testing its pharmacological properties may take long years, here we used a faster virtual study approach for some of our compounds with different chemical structures against COVID-19. Moreover, we included some drugs in this study and compared in silico results obtained. The activity potentials of these compounds were further evaluated through molecular docking studies with AutoDock4 and AutoDock Vina software. Among all the compounds studied, compounds 1a, 1b, and 1c demonstrate significant activity like other prodrugs, particularly against COVID-19. The most promising compound 1a has appropriate ADME prediction values and high binding affinity as a potential inhibitor of COVID-19 main protease.

Keywords: COVID-19, molecular docking, ADME Predictions, favipiravir, remdesivir, hydroxychloroquine

Introduction

Coronaviruses (CoVs) belong to the Coronavirinae subfamily of the Coronaviridae family, from the order Nidovirales [1]. CoVs are enveloped, positive-strand, large RNA viruses, moreover, they are divided into 4 genera as alpha, beta, delta, and gamma, while only alpha and beta Coronaviruses are known pathogenic for humans [2]. CoVs are significant pathogens for vertebrates and these viruses can infect the gastrointestinal, hepatic, respiratory, and central nervous systems of humans and many wild animals [1, 3, 4]. In new animal studies, it has been found that SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) replicates poorly in pigs, dogs, ducks, and chickens but ferrets and cats allow infection. Experimentally, it has been discovered that cats are susceptible to airborne infections, moreover, cats in Wuhan are reported to be seropositive for SARS-CoV-2 [5, 6].

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In the last days of 2019, intense pneumonia was reported in the city of Wuhan. Shortly after reporting the outbreak, local Chinese healthcare workers and the Chinese Center for Disease Control (China CDC) determined that the cause of the outbreak was originally a novel coronavirus, called Wuhan Coronavirus or nCov-2019 (as SARS-Cov-2) [7-9]. This viral infection disease has been officially named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) and, as with other CoVs (SARS (Severe Acute Respiratory Syndrome)-CoV and MERS (Middle East Respiratory Syndrome)-CoV), has been expressed to affect the lower respiratory tract, mostly causing pneumonia. It can also affect the heart, kidney, gastrointestinal tract, and central nervous system, with common symptoms such as cough, fever, and diarrhea [10]. Symptoms range from asymptomatic infections to a lethal form of COVID-19 which is associated with severe pneumonia and acute respiratory distress [11]. According to the World Health Organization data, August 2020 resulted in more than 22,000,000 confirmed cases of COVID-19 with more than ~776,000 deaths. COVID-19 pandemic continues to spread rapidly all over the world. Therefore, drugs and vaccines are in high demand to control this pandemic (https://covid19.who.int/). .

Spike protein is the key for the virus to penetrate the cell via the interaction with Angiotensin-Converting Enzyme 2 (ACE2), which one of the most trend targets for the development of new drugs against SARS-CoV2 due to its crucial role in the transcription and replication of the virus. One of the most important advantages of targeting this protein is that although the mutagenesis rate in viruses is high, the rate here is low because any mutation in this protein can be lethal for the virus [12].

A large number of 3D protein structures for SARS-CoV-2 are available in the Protein Data Bank (http://www.rcsb.org/) and molecular docking studies related to the main protease are increasing in terms of drug screening and protein-inhibitor interactions [13, 14]. More attention was attracted to the phenomenon named repositioning of drugs since the development of the new drug has become more costly in terms of both time and resources [15]. Licensed drugs are more suitable for use in new indications due to their favorable toxicological, pharmacokinetic, and pharmacodynamic properties [16]. In light of all this, it is clear that these approved drugs will be excellent candidates in case of disease emergencies or outbreaks [12]. Binding sites for N3 is well determined in "The crystal structure of COVID-19 main protease in complex with an inhibitor N3" [17]. Potential inhibitor effects with drugs (active metabolite) and synthesized molecules were determined by COVID-19 main protease. The interactions of compounds with the COVID-19 main protease were put forthed via molecular docking studies.

We can define the term drug development as an evaluation of the efficacy and toxicity of novel drug candidates, which includes the target receptor hypothesis for disease and screening of in vitro / in vivo biological activities. With the introduction of early absorption, distribution, metabolism, and elimination (ADME) screening, focusing resources on potential drug candidates has significantly reduced the proportion of compounds that fail in clinical trials and eliminated weak drug candidates in the early stages of drug development [18]. SwissADME free web tool is software used to estimate the absorption, distribution, metabolization, elimination, physicochemical and pharmacokinetic properties of molecules that are more important for clinical research [19, 20].

In this study, it was conducted pharmacokinetics, drug-likeness and medicinal chemistry friendliness with SwissADME web tool [21], molecular modeling studies with Autodock4 [22] software and Autodock Vina [23] software on several FDA approved drugs and 3 different molecules in different chemical structures previously synthesized, so interesting and successful results were achieved.

Material and Methods

ADME Prediction of Ligands

The predictive study of ADME, pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry friendliness properties of ligands were carried out by using the SwissADME free online tool (http://www.swissadme.ch/). The standard SMILES (Simplified Molecular Input Line Entry System) for each chemical was incorporated in the SwissADME tool for the computational simulation.

Molecular Docking Studies

Ligands were energy-minimized using ChemOffice on Windows 10 operating system. Grid box points were determined according to the size of the ligands. The regular space of the Grid box is determined as 0.375 Å, centered on N3. "The crystal structure of COVID-19 main protease in complex with an inhibitor N3" PDB file (PDB ID: 6LU7) was obtained and was modified using the Maestro (Maestro, Schrödinger, LLC, New York, NY, 2020.). Lamarckian Genetic Algorithm was preferred and standard settings were used for all ligands. Docking scores were obtained using AutoDock 4.2 and AutoDock Vina software.

Results

It has been demonstrated that COVID-19 and severe acute respiratory syndrome (SARS) are characterized by an excessive inflammatory response, moreover, viral load for SARS is not associated with worsening of symptoms [24, 25]. It has been previously reported that approximately 15% of patients with COVID-19 disease experience serious illness and 5% can progress to the critical stage that can lead to rapid death [26]. Effective treatment for SARS-CoV-2 infection is still unproven. Apart from supportive care, specific drugs for this disease continue to be explored [27]. In the USA, the first patient infected with SARSCoV-2 has been reported to be treated with supportive care and intravenous Remdesivir [28]. However, it has been stated that randomized clinical trials are needed to evaluate remdesivir in terms of safety and efficacy in the treatment of COVID-19 [27]. Favipiravir, Hydroxychloroquine, and Remdesivir were identified as promising prodrugs against COVID-19 during the literature review [29-32]. Although it is still included in the treatment protocol of some health institutions, it has been explained in a recent academic study that the death rate of COVID-19 patients treated with Hydroxychloroquine or Chloroquine has increased [33].

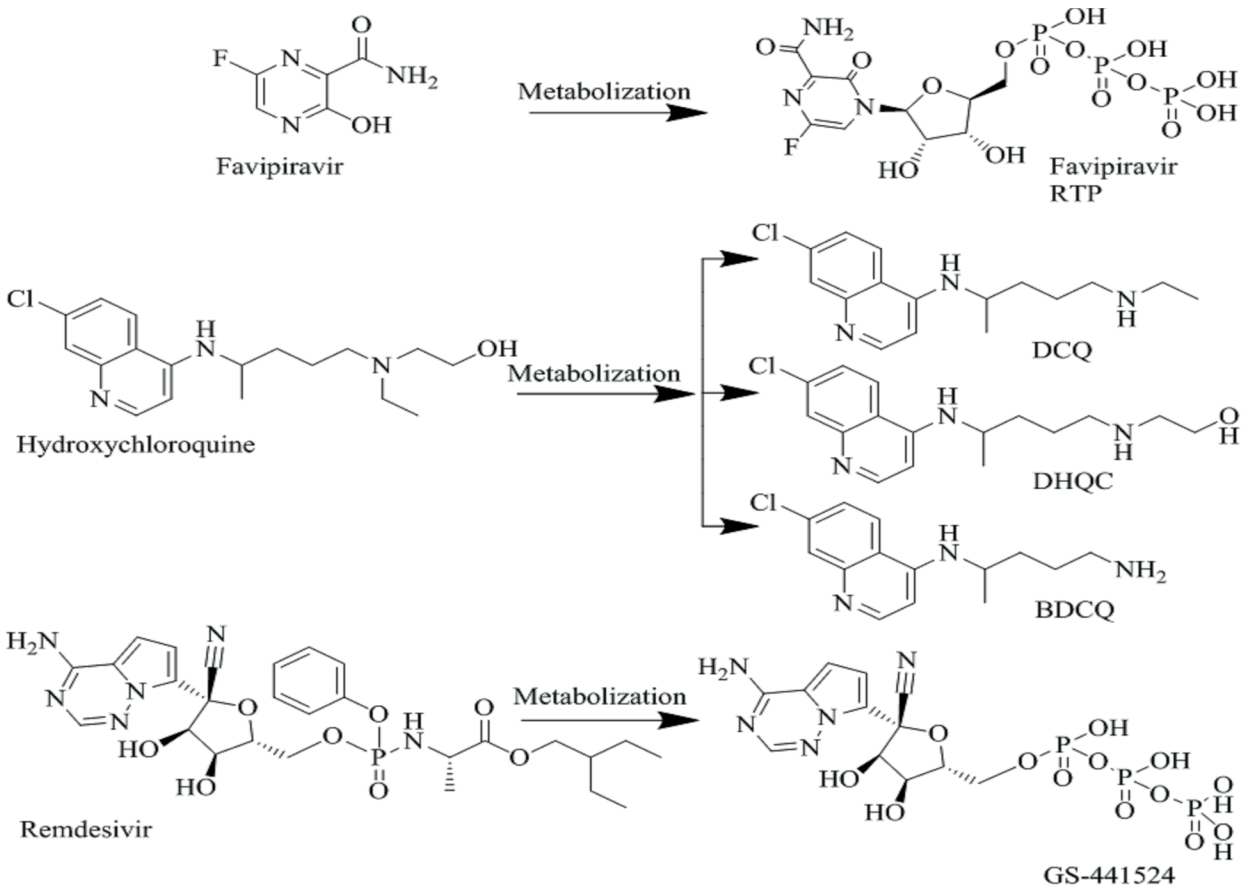
In addition to the base molecules and active metabolites of these prodrugs (Scheme 1), 3 different chemical compounds (pyridine, triazole, thiadiazole, and coumarin ring/rings bearing) were included in silico studies (Scheme 2).

Using the molecular docking approach, the binding interactions of several drug metabolites and other chemical compounds in the active site of the enzyme are understood. Also, here examined the relationships between the chemical structure in these ligands and their efficacy.

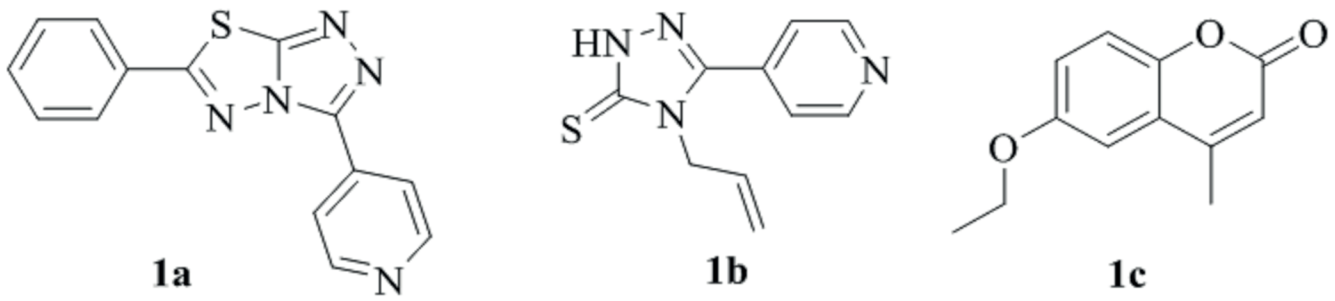
In Silico ADME Prediction

In Silico ADME prediction studies were calculated for compound 1a, compound 1b, compound 1c, Favipiravir, Hydroxychloroquine, Remdesivir, and several active metabolites of these prodrugs (Table 1-4).

Compounds 1a, 1b, 1c, and all prodrugs were found to high for gastrointestinal absorption in terms of pharmacokinetics. There are different results for the blood-brain barrier (BBB). There is a permeation for 1c, Hydroxychloroquine, DCQ, Remdesivir, and GS-441524, but no permeation for all other compounds (Table 1). The fact that Compound 1a does not pass through BBB while



Scheme 1. Molecular structure of Favipiravir [34], Hydroxychloroquine [35], Remdesivir [36], and their some active metabolites



Scheme 2. Molecular structure of 1a [37], 1b [38] and 1c [39].

gastrointestinal absorption is high may indicate low toxic effects.

Water solubility as logS (ESOL) was expressed very soluble for Favipiravir, soluble for all other prodrugs, compounds 1a, 1b, and 1c. Consensus Log Po/w (average of all log P) was expressed negative for Favipiravir and GS-441524, positive for all compounds (Table 2).

Compounds 1a, 1b, 1c, and Hydroxychloroquine were found to comply with all filters and Lipinski rules in terms of drug-likeness, but there were some violations for Favipiravir and Remdesivir. Favipiravir's Ghose filter number of violations is 4: MW<160, WLOGP<-0.4, MR<40, #atoms<20, and Muegge filter number of violations is 1: MW<200. Remdesivir's Lipinski rule number of violations is 2: MW>500, N or O>10, Ghose filter violation number is 3: MW>480, MR>130, #atoms>70, Veber filter violation number is 2: Rotors>10, TPSA>140, Egan filter violation number is 1: TPSA>131.6, Muegge filter number of violations is 3: MW>600, TPSA>150, H-bond acceptor>10 (Table 3.).

Unlike all prodrugs and compound 1b and 1c, compound 1a was found to comply with lead likeness in terms of medicinal chemistry and there were no violations for Structurals Alert. Leadlikeness number of violations for compounds 1b and 1c is 1: MW<250. Among the products and our compounds, the compound with the highest Synthetic Accessibility Score is 1a (Table 4).

Table 1. Comparison between the adenoidectomy and control groups in terms of descriptive statistics (Mann–Whitney U test)

Ligands	Gastrointestinal absorption	Blood-brain permeant	P- glycoprotein substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 3A4 inhibitor	Skin permeation as log Kp (cm/s)
1a	High	No	No	Yes	Yes	No	No	No	-6.22
1b	High	No	No	Yes	No	No	No	No	-6.77
1c	High	Yes	No	Yes	No	No	No	No	-6.01
Favipiravir	High	No	No	No	No	No	No	No	-7.66
Favipiravir RTP	High	No	Yes	No	No	No	No	No	-13.59
Hydroxychloroquine	High	Yes	Yes	Yes	No	No	Yes	Yes	-6.23
DCQ	High	Yes	No	Yes	Yes	No	Yes	Yes	-5.84
DHQC	Low	No	Yes	No	No	No	No	Yes	-8.62
BDCQ	Low	No	No	No	No	No	No	No	-13.27
Remdesivir	High	Yes	No	Yes	No	No	Yes	No	-5.81
GS-441524	High	Yes	No	Yes	Yes	No	Yes	Yes	-5.38

Favipiravir RTP: Favipiravir Ribosyl triphosphate, GS-441524: Remdesivir Active Metabolite, DCQ: Desethylchloroquine, DHQC: Desethylhydroxychloroquine, BDCQ: Bisdesethylhydroxychloroquine.

Table 2. Bioavailability prediction of all ligands

Ligands	Bioavailability score	Water solubility as logS (ESOL)	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log Po/w
1a	0.55	Soluble as -3.92	2.39	2.51	2.91	2.63	3.00	2.69
1b	0.55	Soluble as -2.30	1.79	1.21	2.19	0.55	3.16	1.78
1c	0.55	Soluble as -2.83	2.57	2.16	2.50	1.91	3.25	2.48
Favipiravir	0.55	Very Soluble as -0.80	0.39	-0.56	-0.57	-1.30	0.69	-0.27
Favipiravir RTP	0.11	Highly Soluble as 0.94	-1.24	-5.72	-2.46	-4.91	-5.08	-3.88
Hydroxychloroquine	0.55	Soluble as -3.91	3.58	3.58	3.59	2.35	3.73	3.37
DCQ	0.55	Soluble as -3.95	3.43	3.80	3.89	2.73	3.98	3.57
DHQC	0.55	Soluble as -3.31	3.00	2.75	2.86	1.88	3.38	2.77
BDCQ	0.55	Soluble as -3.40	2.64	2.92	3.24	2.24	3.14	2.83
Remdesivir	0.17	Moderately Soluble as -4.12	3.40	1.91	2.21	0.18	-0.05	1.53
GS-441524	0.11	Highly Soluble as 0.50	-0.99	-5.25	-1.61	-3.89	-5.27	-3.40

Table 3. Druglikeness prediction of all ligands as number of violations

Ligands	Lipinski rule	Ghose filter	Veber filter	Egan filter	Muegge filter
1a	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
1b	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
1c	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
Favipiravir	Yes: 0	No: 4	Yes: 0	Yes: 0	No: 1
Favipiravir RTP	No: 3	No: 2	No: 1	No: 1	No: 4
Hydroxychloroquine	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
DCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
DHQC	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
BDCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
Remdesivir	No: 2	No: 3	No: 2	No: 1	No: 3
GS-441524	No: 3	No: 2	No: 1	No: 1	No: 4
DCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
DHQC	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
BDCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
Remdesivir	No: 2	No: 3	No: 2	No: 1	No: 3
GS-441524	No: 3	No: 2	No: 1	No: 1	No: 4

Table 4. Medicinal chemistry prediction of all ligands

Ligands	Leadlikeness	PAINS Structural Alert	Brenk Structural	Synthetic Accessibility Score
1a	Yes: 0	0	0	2.89
1b	No: 1	0	2	2.16
1c	No: 1	0	1	2.57
Favipiravir	No: 1	0	0	2.08
Favipiravir RTP	No: 2	0	1	4.98
Hydroxychloroquine	No: 2	0	0	2.82
DCQ	No: 1	0	0	2.54
DHQC	No: 1	0	0	2.60
BDCQ	Yes: 0	0	0	2.35
Remdesivir	No: 2	0	1	6.33
GS-441524	No: 2	0	1	4.82
Remdesivir	No: 2	0	1	6.33
GS-441524	No: 2	0	1	4.82

Molecular Docking Studies

According to the X-ray crystallographic structure of COVID-19 main protease in complex with an inhibitor N3 (PDB ID:6LU7), the main binding site has been determined around small molecules as N3 in the receptor. It has been declared that N3 interacts with the active site as binding sites. It has been previously established that N3 interacts with PHE140A, ASN142A, GLY143A, CYS145A, HIS163A, HIS164A, GLU166A, GLN189A, THR190A residues via H-bonds. The covalent bond between N3 and C145A has been reported [17]. Similar H-bonds interactions were observed on all molecules with molecular docking studies except for compound 1a and compound 1c (Table 5). Docking studies were performed for the compound 1a, compound 1b, compound 1c, and several metabolites of all prodrugs. Interaction modes for compounds 1a, 1b, 1c (Figure 1, Figure 3), and metabolites of Favipiravir, Hydroxychloroquine, Remdesivir (Figure S2-S6.) with enzyme active sites were determined (Table 5). Ligands binding types and residues were produced showed by Maestro software (Figure 1, Fig. 2, Figure 3, and Figure. S1-S7) (Maestro, Schrödinger, LLC, New York, NY, 2020.). These compounds' binding modes were similar to N3 (Fig. 1, Fig. S7). The interactions of all compounds, that molecular docking is performed, can be examined in detail with the figures in the Supporting Information Material.

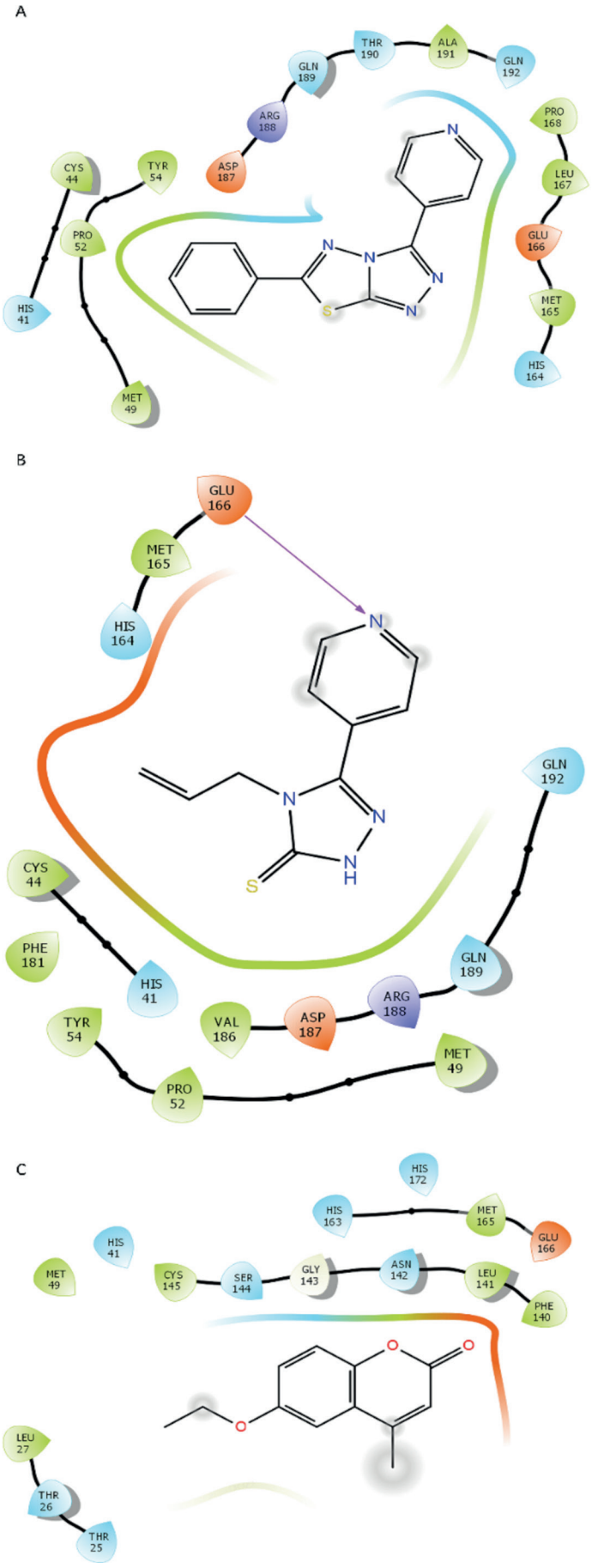


Figure 1. 2D interactions diagram for our compounds (A:1a, B:1b, C:1c) at the active site of 6LU7

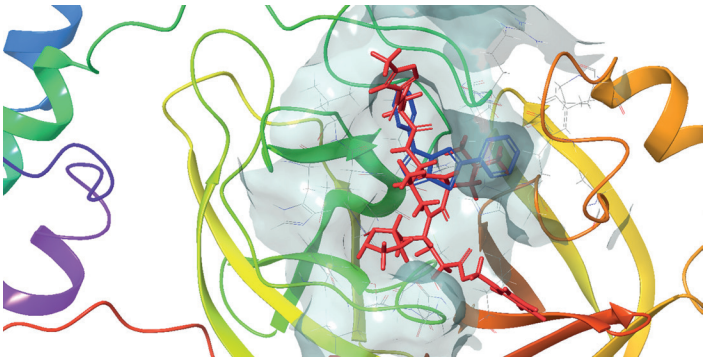


Figure 2. Compounds 1a (blue) and N3 (red) are presented in the COVID-19 main protease (PDB ID: 6LU7) binding cavity (molecular surface rendered in turquoise)

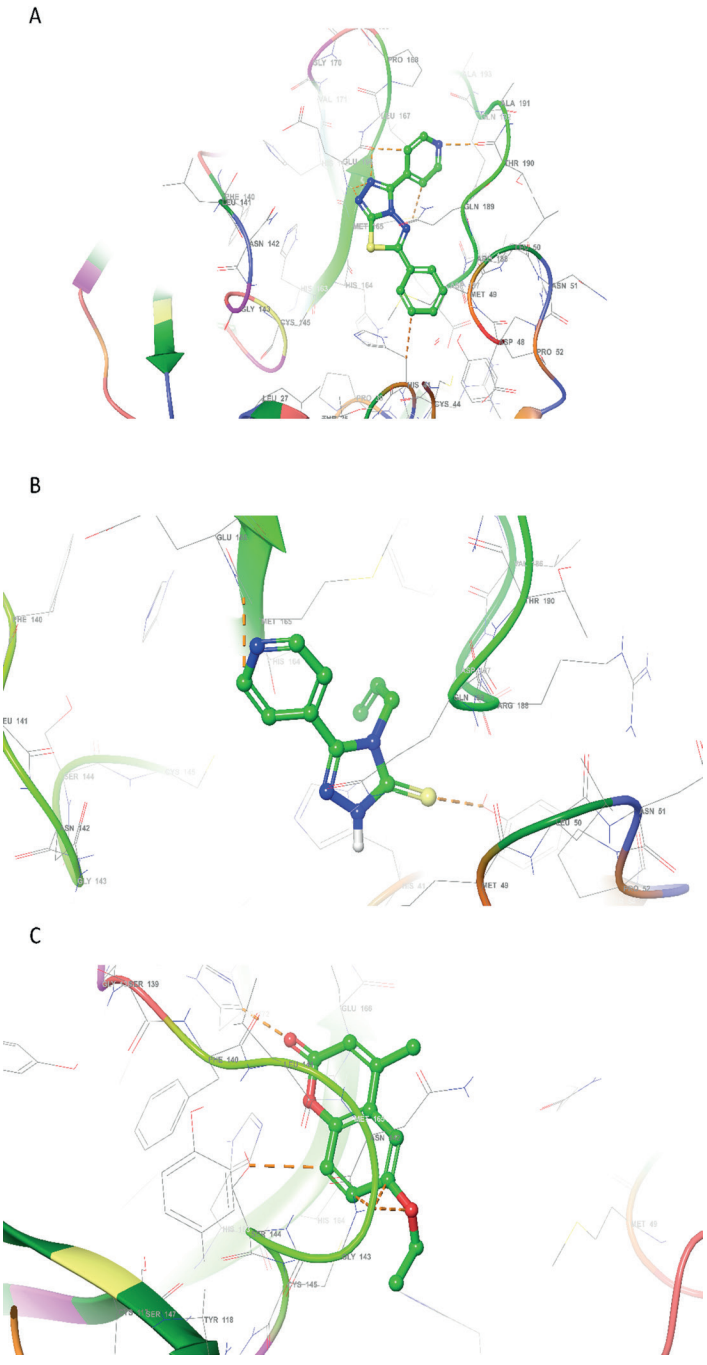


Figure 3. 3D interactions for our compounds (A:1a, B:1b, C:1c) at the binding cavity of 6LU7

Table 5. Molecular docking binding scores of some compounds, within the COVID-19 main protease in complex with an inhibitor N3 (PDB ID: 6LU7) active site. Residues participating H-bonds with the compounds are shown

Compound	Autodock Result			Vina Result
	H-bonds	Estimated Inhibition Constant, Ki	Best Docking Score Estimated Free Energy of Binding (kcal/mol)	Best Docking Score
1a	-	1.04 μM	-8.16	-7.3
1b	Glu166.	128.59 μM	-5.31	-5.5
1c	-	29.21 μM	-6.19	-5.9
Favipiravir RTP	Asn142, Gly143, Ser144, Cys145, Gln192.	1.13 mM	-4.02	-7.4
DCQ	Glu166.	6.23 μM	-7.10	-6.0
DHQC	Thr190.	7.07 μM	-7.03	-6.1
BDCQ	Asn142, Glu166.	2.87 μM	-7.56	-5.8
GS-441524	Cys145, Glu166.	702.64 μM	-4.30	-7.3

Favipiravir RTP: Favipiravir Ribosyl triphosphate, GS-441524: Remdesivir Active Metabolite, DCQ: Desethylchloroquine, DHQC: Desethylhydroxychloroquine, BDCQ: Bisdesethylhydroxychloroquine, mM: millimolar, μM: micromolar

Discussion

In particular, the reason for the low docking scores of active metabolites with triphosphate may be the reduction of the Autodock4 algorithm power by increasing the number of rotating bonds. On the other hand, there was no such low level for Autodock Vina docking scores [40]. The results of molecular docking studies were exhibited to be convenient for the results of the ADME predictions studies. When Autodock4 docking scores were examined, it was observed that the results of hydroxychloroquine metabolites, which are relatively small among our compounds and prodrug metabolites compared to others, and which do not contain triphosphate so contain less rotatable bonds, are closer.

Conclusion

A COVID-19 main protease inhibitor activities of several promising drugs with them active metabolites and some compounds in different structures that we had previously synthesized, in silico ADME prediction and molecular docking studies, were evaluated. In silico ADME prediction studies showed that the compounds 1a, 1b, and 1c were drug-likeness in terms of most of the physicochemical parameters and they possessed generally favorable pharmacokinetic properties. When the number of H-bond acceptors (1a: 4, 1b: 2, 1c: 3) is evaluated, it can be said to be related to the docking score (1a: -8.16/-7.3, 1b: -5.31/-5.5, 1c: -6.19/-5.9). Molecular docking studies exhibited the interaction mode of all ligands with COVID-19 main protease including hydrophobic interactions and/or hydrogen bonds. It can be expected that the activity will increase as the number of groups that will make H-bond in these previously synthesized compounds bearing the nitrogen atom and carbonyl or ether structure in the ring. When the ADME predictions especially lead-likeness with drug-likeness and docking scores were evaluated, Compound 1a continues to show hope as a COVID-19 main protease inhibitor agent, suggesting that this aspect should be improved.

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Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
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Ethical approval
No ethical approval is needed for this research.

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Supplemental

Supporting Information: Computational Studies Results

ADME Predictions and Molecular Docking Study of Some Compounds and Drugs as Potential Inhibitors of COVID-19 Main Protease: A Virtual Study as Comparison of Computational Results

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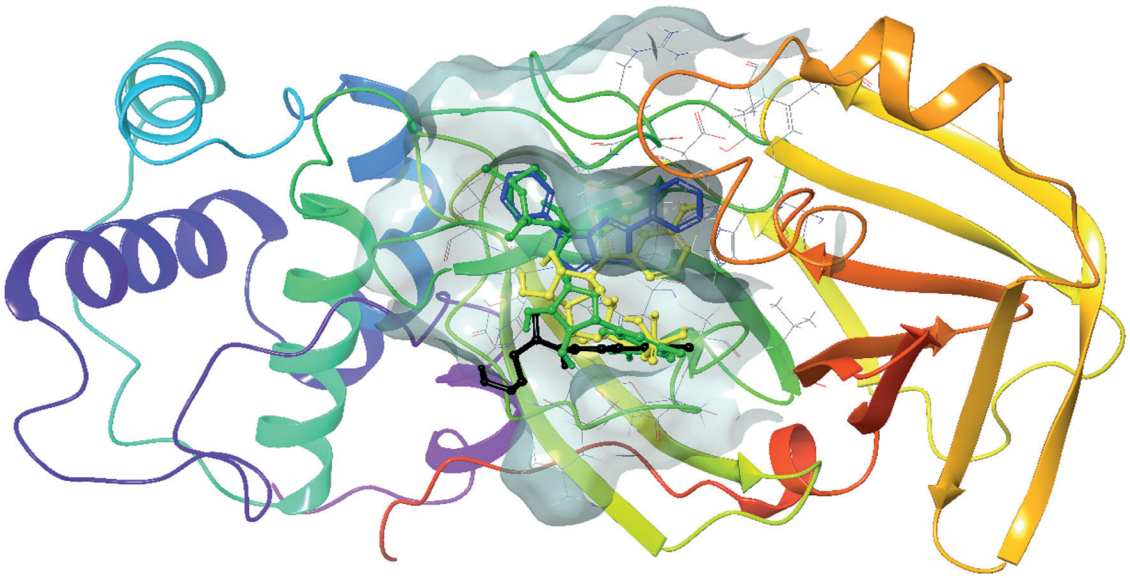

Figure. S1. Compounds 1a (blue), GS-441524 (yellow), Favipiravir RTP (green) and BDCQ (black) are presented in the COVID-19 main protease (PDB ID: 6LU7) binding cavity (molecular surface rendered in turquoise).

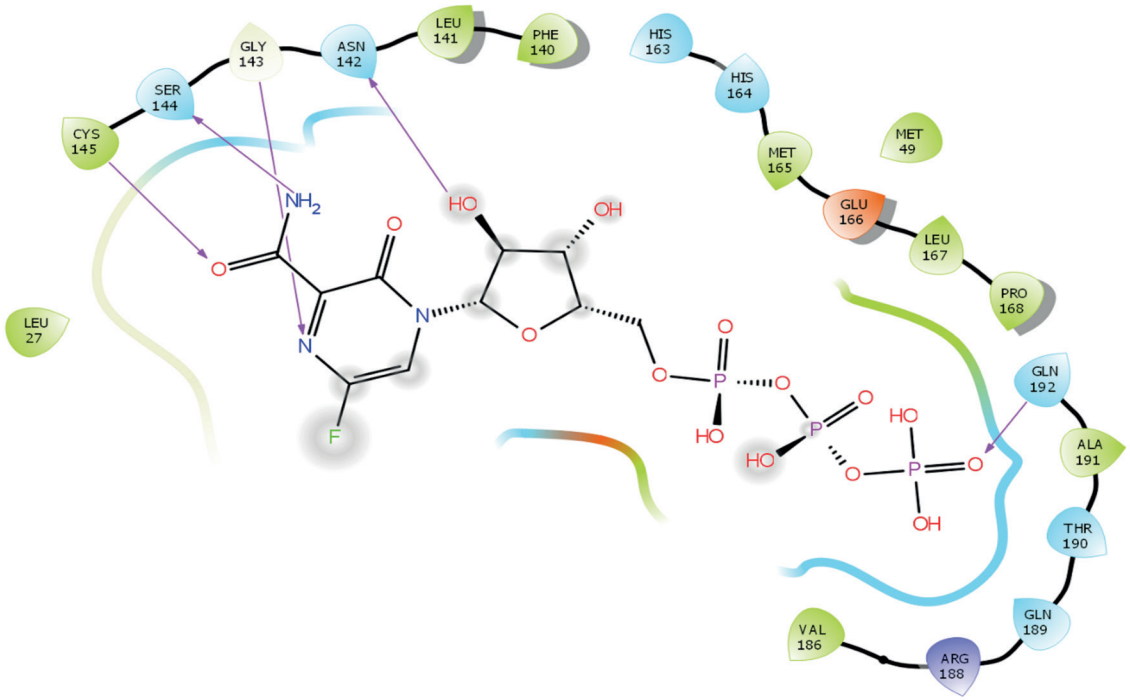

Figure. S2. 2D interactions diagram for Favipiravir RTP at active site of 6LU7

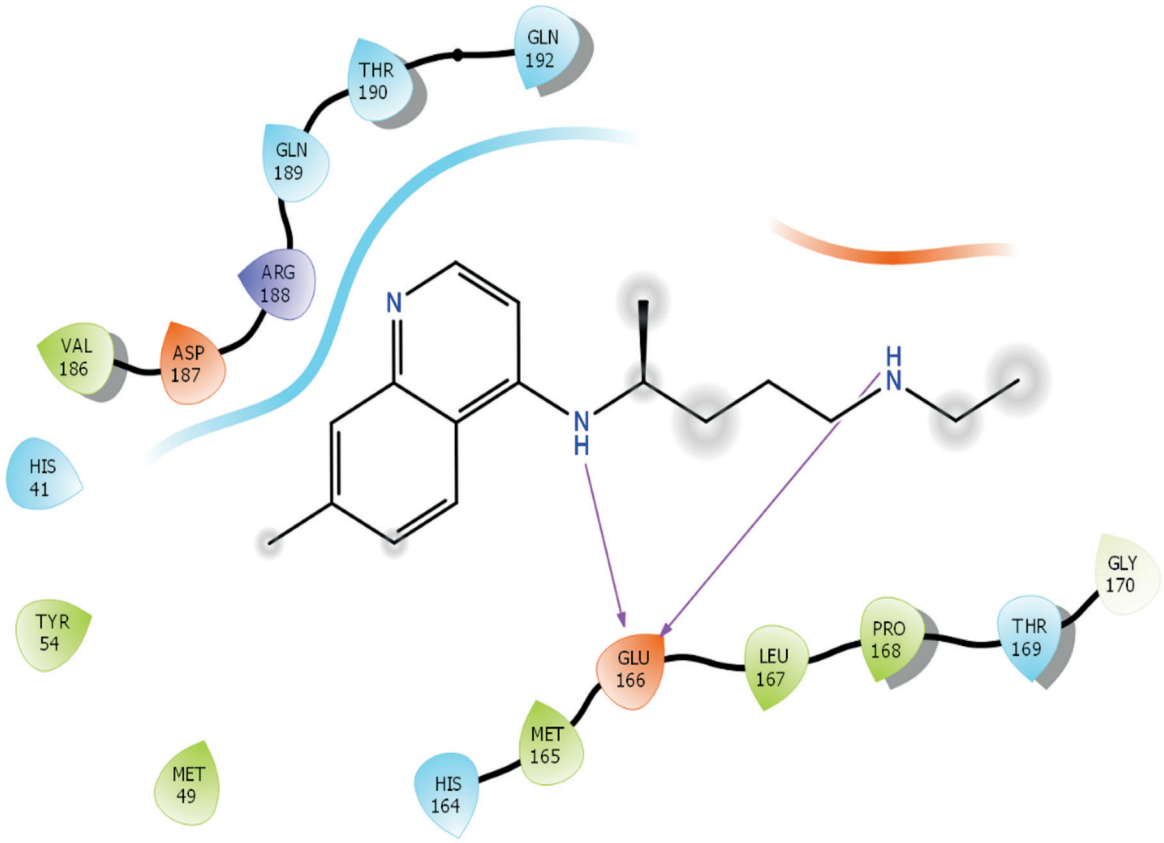

Figure. S3. 2D interactions diagram for DCQ at active site of 6LU7

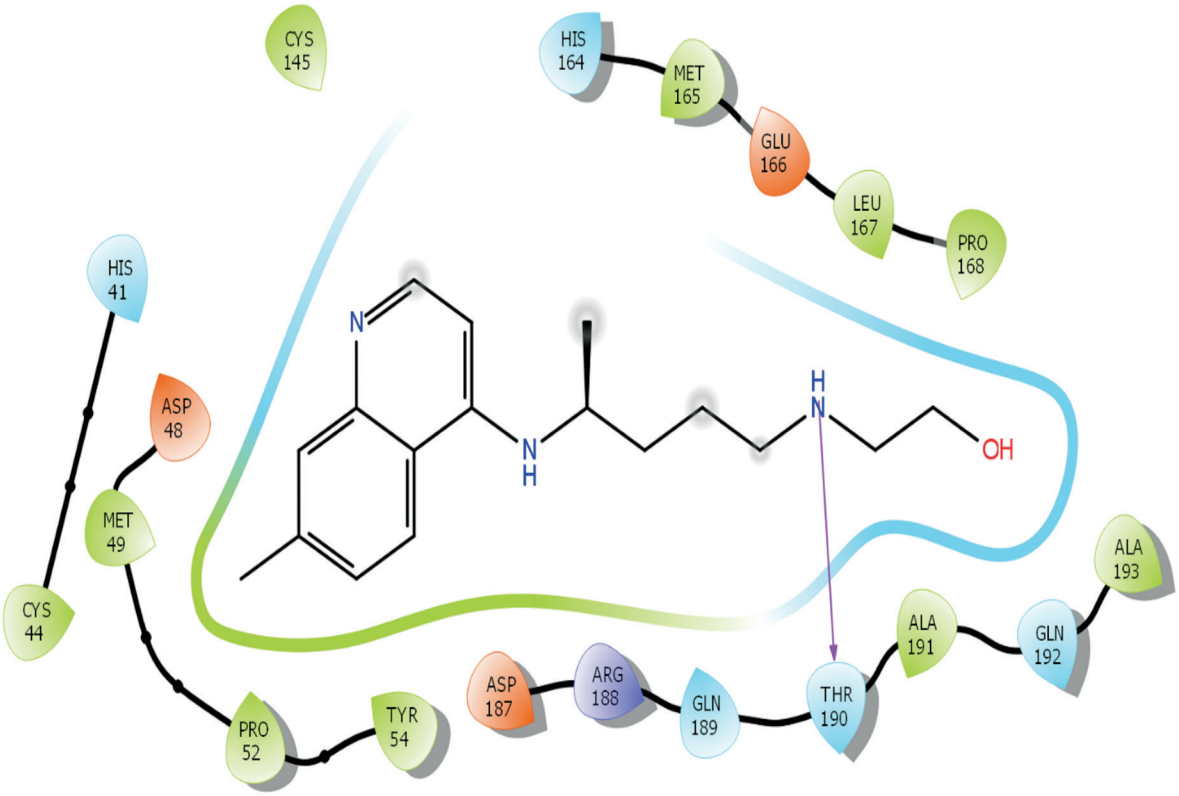

Figure. S4. 2D interactions diagram for DHQC at active site of 6LU7

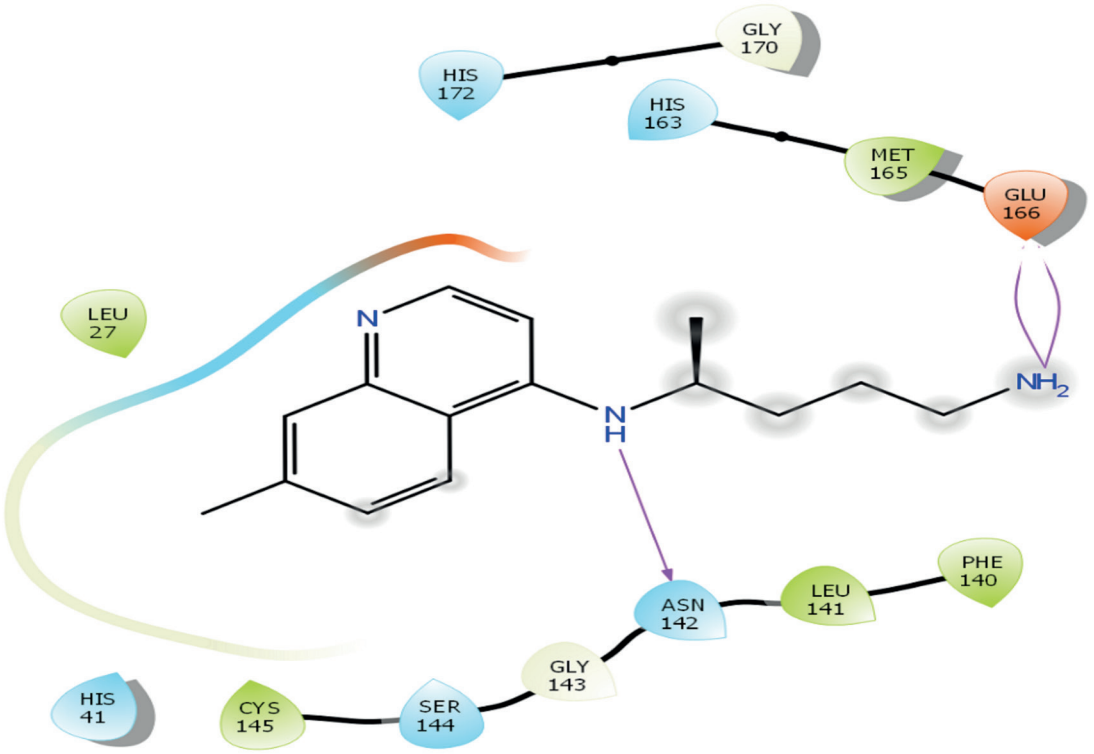

Figure. S5. 2D interactions diagram for BDCQ at active site of 6LU7

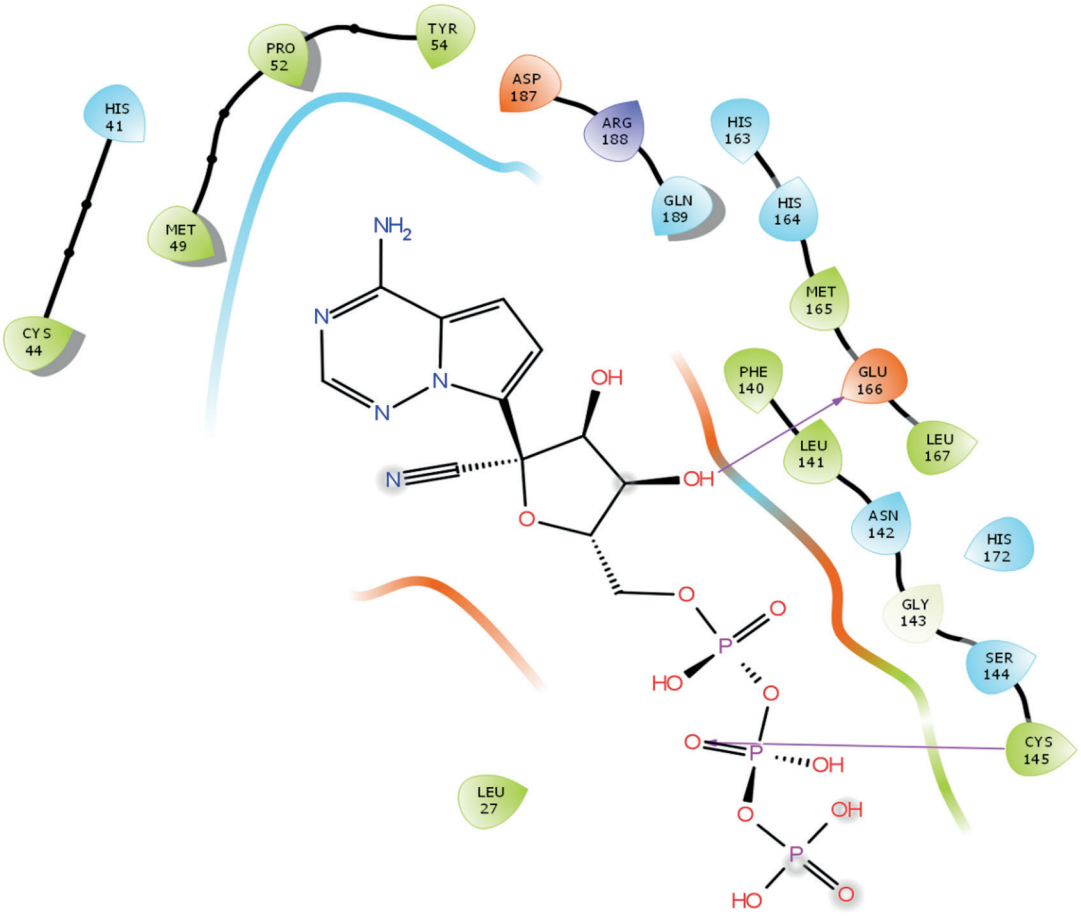

Figure. S6. 2D interactions diagram for GS-441524 at active site of 6LU7

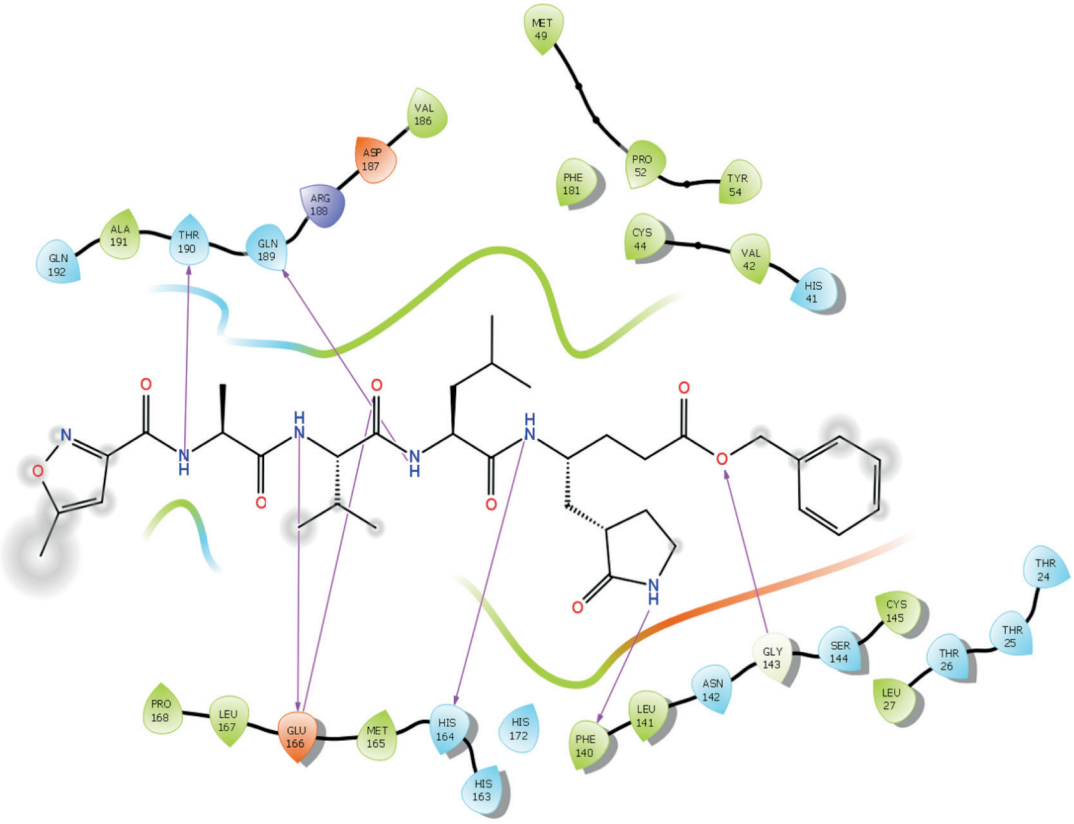

Figure. S7. 2D interactions diagram for N3 at active site of 6LU7

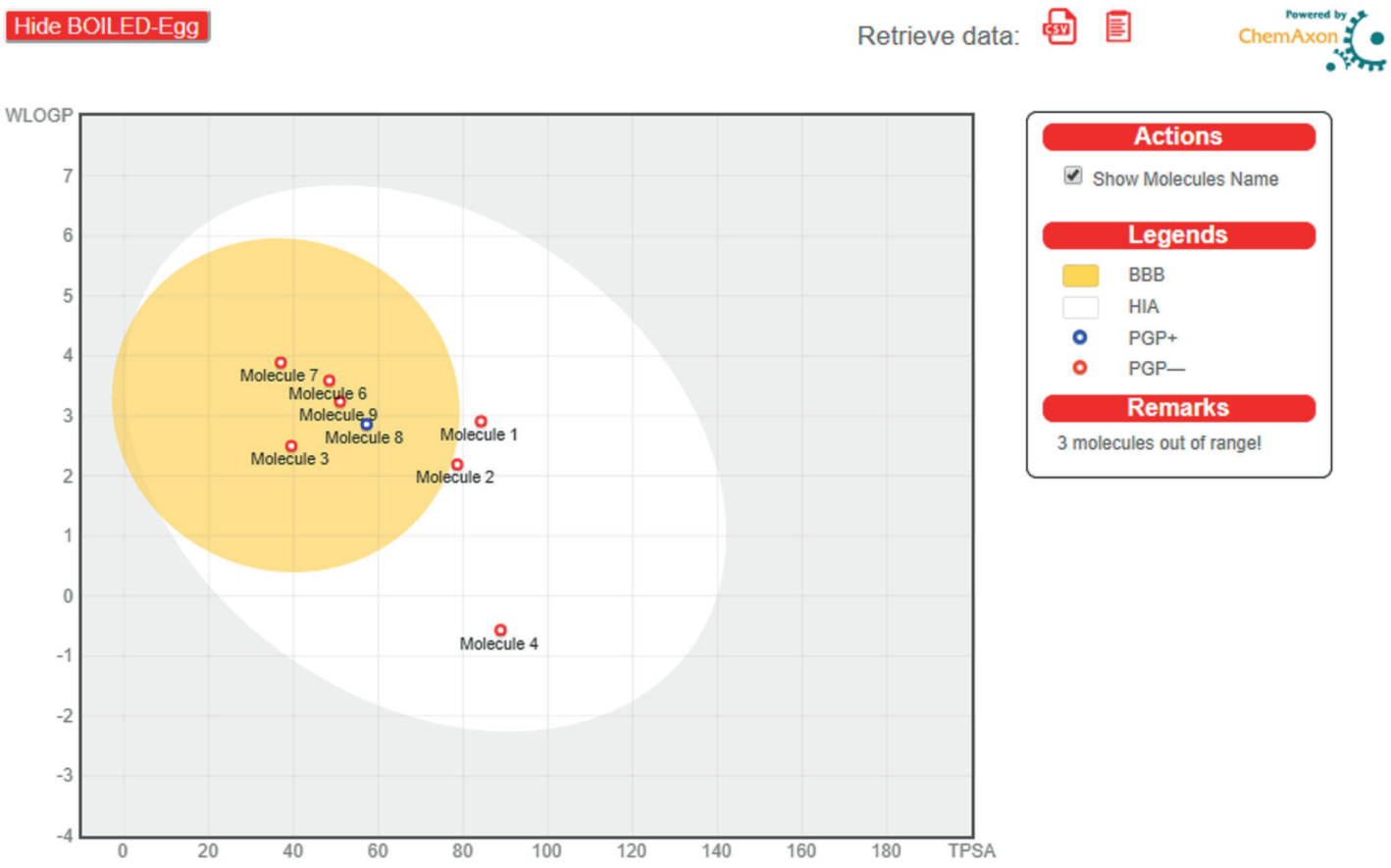

Figure. S8. BOILED-Egg for all ligans

Table S1. Number of Compounds for ADME Predictions (SwissADME)

1a	Molecule 1
1b	Molecule 2
1c	Molecule 3
Favipiravir	Molecule 4
Favipiravir RTP	Molecule 5
Hydroxychloroquine	Molecule 6
DCQ	Molecule 7
DHQC	Molecule 8
BDCQ	Molecule 9
Remdesivir	Molecule 10
GS-441524	Molecule 11