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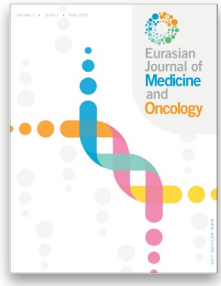


Research Article

# The Molecular Docking Study of Potential Drug Candidates Showing Anti-COVID-19 Activity by Exploring of Therapeutic Targets of SARS-CoV-2

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## Abstract

**Objectives:** The novel human coronavirus which has been designated as SARS-CoV-2 was firstly emerged in late 2019 in Wuhan, China causing respiratory illness called COVID-19. This virus has spread rapidly around the globe. In view of the potential threat of epidemic, scientists around the world have been running to understand SARS-CoV-2 and investigate the pathophysiology of this disease to find out potential treatment and discover effective therapeutic drug candidate. The disorder caused due to the outbreak of coronavirus is an intense need for the development of potential agents against the SARS-CoV-2.

**Methods:** In this study, we have measured the virtual interaction of COVID-19 main protease in complex with an inhibitor N3 (PDB ID 6LU7) with antiviral and antimalarial drug as well as SARS Spike glycoprotein-Human ACE2 complex (PDB ID 6CS2) with antimalarial drugs currently in the market using the AutoDockVina suite.

**Results:** The binding energies obtained from the docking of 6LU7 with ligand, oseltamivir, ritonavir, remdesivir, ribavirin, favipiravir, chloroquine and hydroxychloroquine were found to be -4.7, -7.3, -6.5, -5.6, -5.4, -5.1, -5.3, kcal/mol, respectively. Similarly the binding energies obtained from the docking of 6CS2 with ligand, chloroquine and hydroxychloroquine were -7.1 and -6.8kcal/mol. The docking result suggest a higher affinity of the drug molecule such as oseltamivir, ritonavir, remdesivir, ribavirin, favipiravir, against SARS-CoV-2 since they attributed high affinity interactions withCOVID-19 main protease in complex with an inhibitor N3. In addition, chloroquine and hydroxychloroquine show prominent binding interaction with SARS Spike glycoprotein-Human ACE2 complex.

**Conclusion:** From this study, we can be suggested that these drugs are promising candidates for antiviral treatment with high potential to fight specially against SARS-CoV-2 strain.

**Keywords:** Antiviral drugs, hydroxychloroquine, SARS-CoV-2 protease

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Since December 2019, majority of world population is suffering from COVID-19 outbreak. WHO has changes the name of virus from 2019-nCoV to SARS-CoV-2 (severe acute respiratory syndrome corona virus 2).[1] With a exception of Antarctic, it is vigorously transmitting and spreading from Wuhan city to nearly about every nation in the world. [2] On 14 Apr 2020 around 19.24.679 cases of persons infected worldwide byCOVID-19 out of which 119.955 death have been reported and 4.45.405 patients have been recovered.[3] Since COVID-19 is rapidly spreading worldwide, World Health Organization (WHO) has declared it as a pandemic disease.

Since COVID-19 is a major outbreak in almost all the nations worldwide, novel approaches of drug design and discovery can utilized as promising tool for discovery the some therapeutic drug candidates against COVID-19. Molecular dock-

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ing has become a promising tool for drug discovery and development. By utilizing this tool, we study interaction of ligand (drug) molecules inside the binding pocket of target protein (receptor).[4] It offers study of all the factors that are being utilized for drug discovery such as identification of hit molecules, optimization of lead compound and virtual screening.[5–8]

Since it has been reported that the several existing drug showed potential against COVID-19 including oseltamivir,[9] lopinavir,[10] ritonavir,[10] remdesivir,[11] favipiravir,[12] ribavirin,[12] chloroquine and hydroxychloroquine.[13] Since most of the drugs are HIV protease inhibitors[14] we have performed their docking with COVID-19 main protease in complex with an inhibitor N3.[15] It have been also reported that chloroquine and hydroxychloroquine showed Anti-SARS-CoV-1 action may be attributed by depletion in glycosylation of angiotensin-converting enzyme 2 (ACE2).[16] At low pH, these drug are also belived to interfere in post translational modifications in viral protease and glycosyl transferases in endoplasmic reticulum or vesicles of trans Golgi complex.[16] Therefore, we have also performed the docking of chloroquine and hydroxychloroquine with COVID-19 main protease (in complex with an inhibitor N3)[15] and SARS Spike glycoprotein-Human ACE2 complex.[17]

## Some of the Potential Therapeutic Target Against SARS-CoV and SARS-CoV-2

Several similarities between SARS-CoV-2 and SARS-CoV have been reported. Since the sequencing of SARS-CoV-2 has been done,[18] it have given rise to various molecular modeling experiments in order to find the potential candidate against novel coronavirus SARS-CoV-2. The SARS-CoV-2 is originated from bat has been revealed by the phylogenetic analysis. Xu et al.[18, 19] have performed some molecular modeling experiments which revealed similarity in the 3-D structures of SARS-CoV-2 and SARS-CoV in the RBD (receptor binding domain). This leads to designing of various approaches to find out the potential target for development of potential drug candidate against SARS-CoV-2. The analysis of crystal structure and several biochemical studies, it has been revealed that the S protein (spike protein) of SARS-CoV possess strong affinity for binding to human ACE-2 rceptors.[20] Some of the potential targets for drug design spike protein, envelop protein, membrane protein, protease, nucleocapsid protein, hemagglutinin esterase, and helicase have been identified.[21]

## S Protein

The S protein (spike protein) consisting of ectodomain region (ED), intracellular domain and TM region has been identified.[22] The S protein is type I-transmembrane (TM) protein which appear as clove shaped.[22] The ED region consists of two receptor binding domains (RBD), S1 and trimeric stalk containing S2 subunit associated on C-terminal. By association of S proteins, the virion appear as trimeric form which give rise to crown like structure , thus it is called as coronavirus.[22] The S protein is found to have potential role in viral entry inside the host.[23] The activation of host immune repose against the virus by S protein has been reported. This proteins is considered as a potential target for drug discovery because S1 domain and host ACE2 for SARS-CoV and dipeptidyl peptidase-4 (DPP4) for MERS-CoV associated with host and viral membrane fusion mediated by S2 segment potentiate the CoV to release its RNA in host cell.[23]

## Proteases

There are 16 non-structural polyproteins (NSPs) containing PP1a and PP1b present in genome of coronavirus encoded by replicase.[24] The release of NSPs is mediated by the action of protease on polyproteins. The chymotrypsin-like cysteine protease also known as main protease (Mpro) or 3-C like protease (3CLPro) carries out cleavage at C-terminal of polyproteins. The papain like protease (PLpro) facilitate cleavage of polyproteins at N-terminal.[24] The release of 16 NSPs takes place as PLpro facilitate cleavage at first three site of polyproteins whereas CLpro facilitates the cleavage at 11 site.[25]

The Cys-His dyad present on the active sites of 3CLPro is reported to show protease activity.[26] This protease has ability to carry out cleavage at 11 sites in the p1 region of PP1a and PP1ab. It can generate mature protein which facilitates replication[27, 28] and also helps in releasing NSPs.[29] Some of the HIV protease inhibitors including lopinavir and ritonavir, also found to inhibit Mpro.[30]

The papain-like protease (PLpro) potentiate the cleavage polyprotein (PP) at N-terminal to form NSP 1, 2 and 3.[27, 28] The catalytic domain of PLpro consists of 316 amino acids which are known to facilitate cleavage of substrates for replicase mediated by a consensus sequence (LXGG).[29] The inhibition of CLpro and PLpro at higher doses of zinc and its conjugates have been reported. There are several protease inhibitors including combinations of ritonavir and lopinavir are being used for treatment of COVID-19.[31]

## N Protein

The N protein (nucleocapsid protein) consists of N-arm, central linker (CL), and the C-tail which are also known as characteristic intrinsically disordered regions (IDRs).[32] The major structural and functional domains of the N protein are N-terminal domain (NTD) and C-terminal domain (CTD). The NTD is known to facilitate the RNA binding and CTD plays important role in dimerization.[32, 33] Along with the ar-

ginine and serine, the CL region comprises of several phosphorylation sites.[34] The C-tail plays a vital role in interactions of N-M proteins and oligomerization of N protein.[35] N protein is reported to cause inhibition of cell growth in human via inhibition of cytokinesis process.[36] The N protein peptide (N220) has found to have promising activity towards destruction of N protein expressing cells in transgenic animals. Thus, it can be recognized as potential target for developing DNA vaccine.[37] The process of ion channels generation is mediated through oligomerization of E proteins.

### E Protein

E protein (envelop protein) the smallest transmembrane structural protein of coronavirus consists of hydrophobic domain and cytoplasmic tail. It is 8.4-12 kDa size.[38, 39] During viral assembly and release, E protein is known to facilitate viral morphogenesis. In the mammalian cells expressed with SARS-CoV envelop protein, hexamethyleneamiloride has found to inhibit E protein-mediated ion channel activity.[40] Along with assembly and release, E protein is also found to be responsible for virulence of virus.[39, 41]

### M Protein

By virtue of interaction with proteins, introducing Golgi complex in virion and stabilizing the nucleocapsid protein, M proteins modulates shape of envelope of virus.[39, 42] M protein is known to help intracellular homeostasis in virus via various protein interactions.[42] It consists of short N-terminal and long C-terminal.[39] The entry of virus takes place in association with interaction of M–M, M–S, and M–N proteins. The introduction of spike protein in new virus takes place via M-S interactions.[42] The stabilization of nucleocapsid-RNA complex (RNP complex) is associated with M-N interactions. Despite of regulating shape of virus, M and N proteins also facilitates the generation and release of virus like particles. M protein is known to potentiate sensitization of host by virus.[42]

### Helicase

The SARS-CoV Helicase (NTPase) enzyme is a member of the superfamily 1. It facilitates hydrolysis of all NTPs.[43] Helicase can be utilized as potential target for designing numerous drug candidates against various disorders.[44] In order to design the helicase inhibitors, toxicity is major concern as non-specificity leads to precipitation of toxic effects.[43]

### Molecular Docking Study of Some Drug Candidates with Protease of SARS-CoV-2

Due to unavailability of specific treatment for COVID-19are several antiretroviral drugs reported to show effectiveness against COVID-19 including ritonavir,[45, 46] lopinavir,[46] alone or in combination with oseltamivir,[46] remdesivir, chloroquine and hydroxychloroquine.[47] Out of these, ritonavir, remdesivir, chloroquine and hydroxychloroquine has shown efficacy at cellular level[45] which will be evaluated in future by various experimental studies. In drug discovery, molecular docking methodologies is a useful tool as it rapid screening of candidates from drug libraries.[48, 49] In this research, we have performed docking study of some of the potential therapeutic drug candidates that are being used against COVID-19 worldwide by using computational techniques.

## Methods

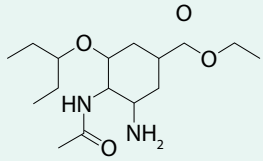
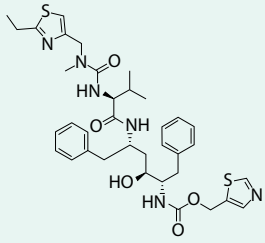
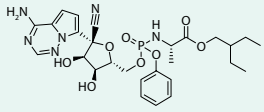
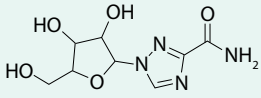
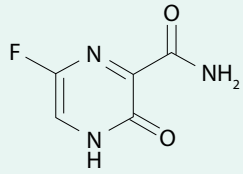
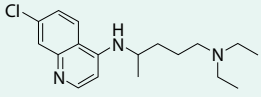
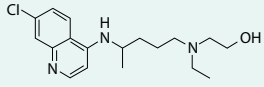
All the docking experiments were performed by using AutoDockVina because (a) it offers more accuracy in predicting ligand-protein interaction compared to its previous AutoDock 4.2 (b) it offers shorter running time because of its multiple core processors (c) it offer more accuracy for ligand processing more than 20 rotatable bonds. Using AutoDockVina 1.0, all the docking experiments were done using method of blind docking (using the grid box large enough to cover whole protein structure to encounter any possible protein-ligand interactions). All dockings were performed as blind dockings (blind docking refers to the use of a grid box which is large enough to encompass any possible ligand-receptor complex) using Autodock Vina 1.050.

All the protein structures used in docking experiments were retrieved from the protein data bank. All the ligand structure were drawn in ChemDraw 14 and converted into PDB format using Chem3D 12.0. The ligands were converted to energetically most stable structure using energy minimization using Vega ZZ program[51] with SP4 force field and conjugate gradient method. The ligand and protein molecules were converted to their proper readable file format (pdbqt) using AutoDock tools 1.5.6. The docking was done using an exhaustiveness value of 8. All other parameters of software were kept as default and all bonds contained in ligand were allowed to rotate freely, considering receptor as rigid. The final visualization of the docked structure was performed using Discovery Studio Visualizer 2.5.

## Results

The results obtained from these experiments indicated the strong interactions of the potential drug candidates against COVID-19 main protease in complex with an inhibitor N3 and SARS Spike glycoprotein-Human ACE2 complex of SARS-CoV-2. After successful docking of these drugs into the COVID-19 main protease in complex with an inhibitor N3, the results shows various modes of drug-protein inter-

**Table 1.** Various drugs (ligands) used for docking with target protein

| Drug | Structure | Target (Protein) | PDB Code |
|---|---|---|---|
| Oseltamivir |  | COVID-19 main protease in complex with an inhibitor N3[15] | 6LU7 |
| Ritonavir |  | COVID-19 main protease in complex with an inhibitor N3[15] | 6LU7 |
| Remdesivir |  | COVID-19 main protease in complex with an inhibitor N3[15] | 6LU7 |
| Ribavirin |  | COVID-19 main protease in complex with an inhibitor N3[15] | 6LU7 |
| Favipiravir |  | COVID-19 main protease in complex with an inhibitor N3[15] | 6LU7 |
| Chloroquine |  | 1. COVID-19 main protease in complex with an inhibitor N3[15]<br>2. SARS Spike glycoprotein-Human ACE2 complex[17] | 6LU7<br>6CS2 |
| Hydroxychloroquine |  | 1. COVID-19 main protease in complex with an inhibitor N3[15]<br>2. SARS Spike glycoprotein-Human ACE2 complex[17] | 6LU7<br>6CS2 |

actions are generated with particular docking score (binding energy). The binding mode with least binding energy is regarded as best mode of binding as it is most stable for the ligand. The least binding energy which indicates better fit for all the drug is summarized in Table 2. It also revealed the interaction of specific amino acid that taking part in the drug-protein interactions. All the docked structures were visualized in Pymol2.3 and Discovery Studio 4.0.

There are three chains A, B and C present in the structure of SARS Spike glycoprotein-Human ACE2 complex (PDB ID 6CS2) containing central pocket for interaction with ligand. The binding pocket of COVID-19 main protease in complex with an inhibitor N3 (PDB ID 6LU7) consist of two chains, chain A and chain C which may take part in the interactions with the ligand. The ligand may show selective interaction with either of the chain or both depending on the availability of the atoms for the particular interactions (Table 1).

## Visualization of Docking Results

Chloroquine and hydroxychloroquine were docked with both COVID-19 main protease in complex with an inhibitor N3 as well as SARS Spike glycoprotein-Human ACE2 complex. The lowest energy conformations of all the ligand molecules were docked with protein. The ligand is shown as red stick model whereas the protein is shown as surface. The amino acids taking part in the ligand-protein interaction is shown with ligands as blue colour stick with amino acids surrounding them. The interaction shown by green dash lines

**Table 2.** Target (protein) and the drug candidates (ligands) undergoing docking experiment with their best docking score (lowest binding energy)

| Drug (ligand) | Proteins (receptor) | Affinity (kcal/mol) | Distance from rmsdl.b. | Distance from rmsdu.b. |
|---|---|---|---|---|
| Oseltamivir | COVID-19 main protease in complex with an inhibitor N3[15] | -4.7 | 0.000 | 0.000 |
| Ritonavir | COVID-19 main protease in complex with an inhibitor N3[15] | -7.3 | 0.000 | 0.000 |
| Remdesivir | COVID-19 main protease in complex with an inhibitor N3[15] | -6.5 | 0.000 | 0.000 |
| Ribavirin | COVID-19 main protease in complex with an inhibitor N3[15] | -5.6 | 0.000 | 0.000 |
| Favipiravir | COVID-19 main protease in complex with an inhibitor N3[15] | -5.4 | 0.000 | 0.000 |
| Chloroquine | 1. COVID-19 main protease in complex with an inhibitor N3[15] | -5.1 | 0.000 | 0.000 |
| | 2. SARS Spike glycoprotein-Human ACE2 complex[17] | -7.1 | 0.000 | 0.000 |
| Hydroxychloroquine | 1. COVID-19 main protease in complex with an inhibitor N3[15] | -5.3 | 0.000 | 0.000 |
| | 2. SARS Spike glycoprotein-Human ACE2 complex[17] | -6.8 | 0.000 | 0.000 |

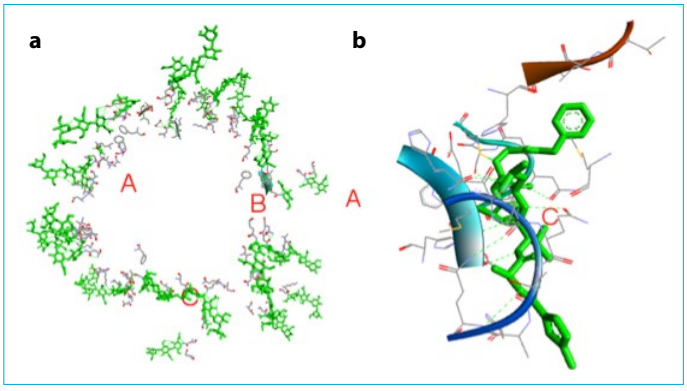



**Figure 1.** The ligand binding site of **(a)** SARS Spike glycoprotein-Human ACE2 complex with chain (labeled by red colour) and **(b)** COVID-19 main protease in complex with an inhibitor N3.

refers to the hydrogen bonding interactions between the ligand and protein. Various amino acids involved in the ligand protein interactions are shown as stick with different colour and labeled by red colour. In order to achieve visibility of the docked ligands into the protein structure, ligands are shown as red colour sticks in the binding pocket of the protein.

## Discussion

After successful docking of all the ligands employed in these docking experiments, the results showed significant binding of the ligands with the target proteins. After visualizing protein in Discovery Studio 12.0 it was found that SARS Spike glycoprotein-Human ACE2 complex and COVID-19 main protease in complex with an inhibitor N3 consist of A, B and C chain as shown in (Fig. 1) in COVID-19 main protease only A and C chain are involved in interaction with ligands. Oseltamivir docked in COVID-19 main protease in complex with an inhibitor N3, showed significant binding with the binding affinity of -6.1. The interaction of olseltamivir with the protease (Fig. 2) showed a high affinity inter-

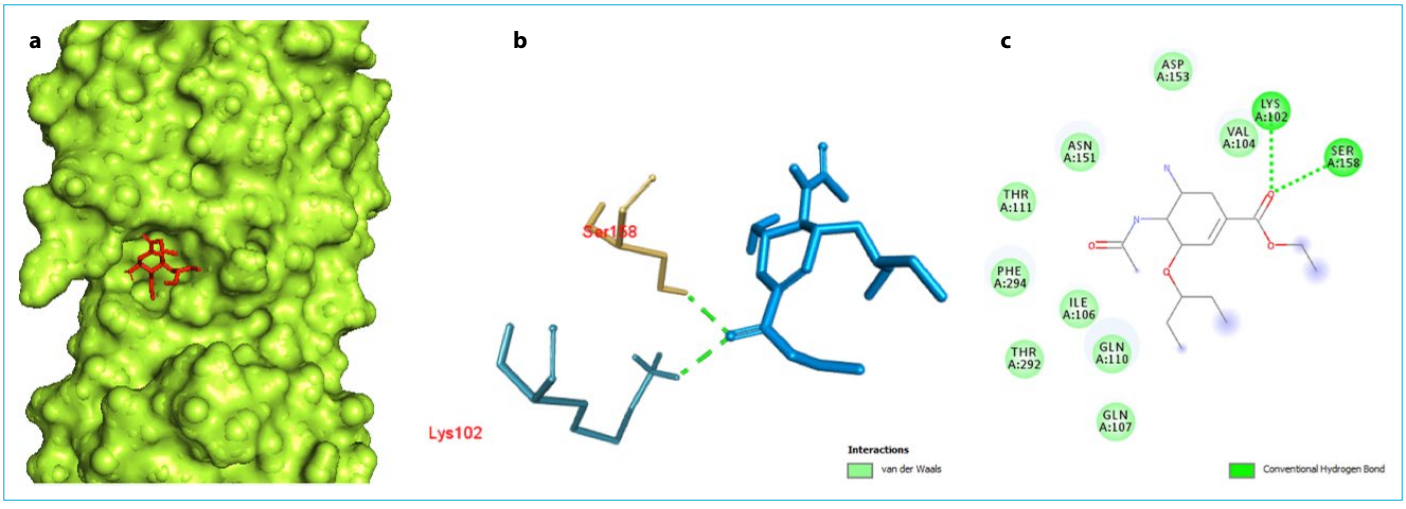



**Figure 2.** Oseltamivir docked in COVID-19 main protease in complex with an inhibitor N3(PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of oseltamivir with amino acid with hydrogen bond (green dash line).

action in chain A as the ligand fits inside the core pocket region of the protease. This is further evidenced by hydrogen bonding between the oxygen of the carbonyl group (ester side chain) of oseltamivir with Lys 102 and Ser 158. Some of the van der Waals interaction of oseltamivir with Val 104, Asp 153, Asn 151, Thr 111, Phe 294, Ile 106, Thr 292, Gln 110 and Gln 107 has been observed.

The docking of ritonavir with the COVID-19 main protease in complex with an inhibitor N3 revealed that ritonavir (ligand) shows high affinity interaction with to the chain A of protein with affinity of -7.3 kcal/mol (Fig. 3). To interact with protein, ritonavir acquire the central pocket surrounded by the chain A, B and C which leads to several interactions between ritonavir and the amino acid residues of the proteins. The interaction results in the form of a hydrogen bond between ritonavir and amino acid residues of protein. The oxygen (in amide group) shows significant hydrogen bonding with Thr 111. The benzene ring shows pi-anion and pi-pi interaction with Asp 153 and Phe 294 respectively.

The docking of remdesivir docked in COVID-19 main protease in complex with an inhibitor N3 shows significant interactions in the central pocket near chain A with the affinity of -6.5 kcal/mol (Fig. 4). The major interaction between remdesivir and the protease is characterized by hydrogen bonding between the nitrogen of cyno group and PHE 294 and oxygen of tetrahydrofuran ring with GLN 110. Some of the pi sigma interactions of aromatic ring and Ile 249 and Val 104 have been observed.

Results obtained by docking of ribavirin docked in COVID-19 main protease in complex with an inhibitor N3 showed the binding of ribavirin in the pocket of chain A

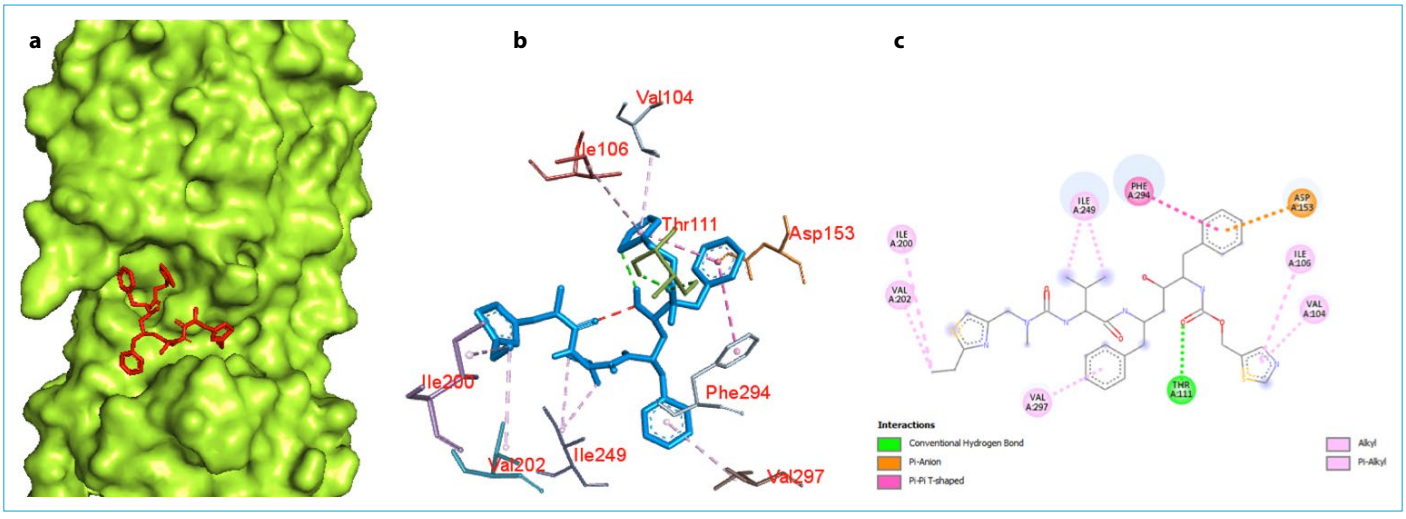



**Figure 3.** Ritonavir docked in COVID-19 main protease in complex with an inhibitor N3 (PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of ritonavir with amino acid with hydrogen bond (green dash line).

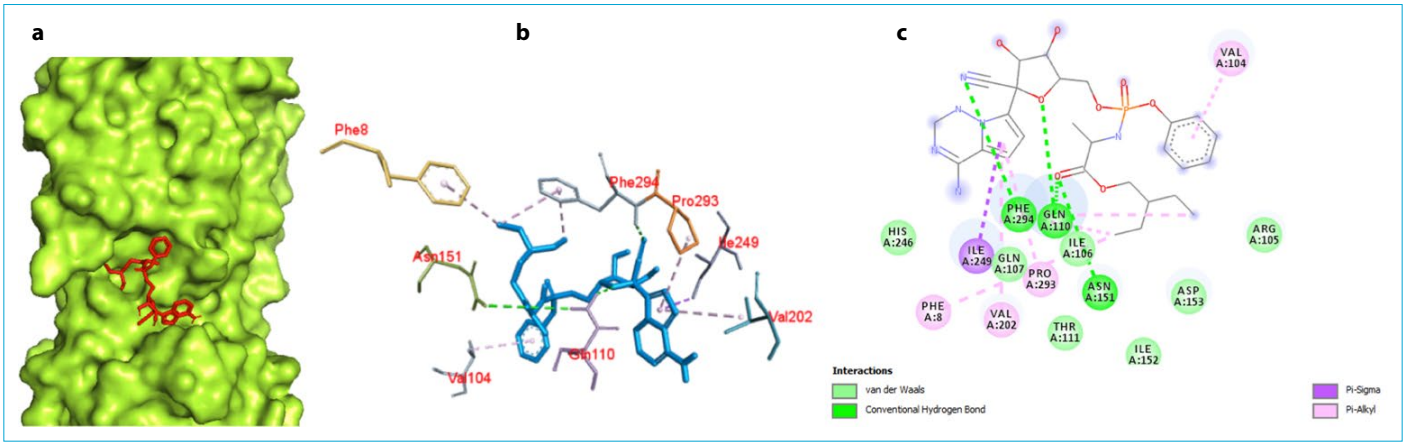



**Figure 4.** Remdesivir docked in COVID-19 main protease in complex with an inhibitor N3 (PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of remdesivir with amino acid with hydrogen bond (green dash lines).

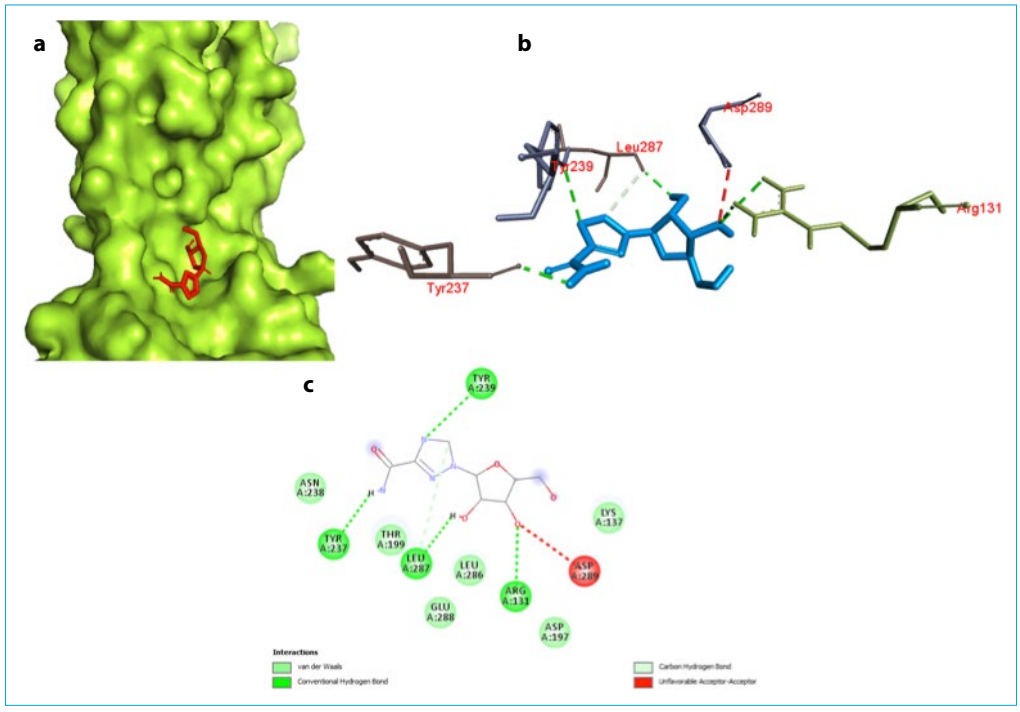



**Figure 5.** Ribavirin docked in COVID-19 main protease in complex with an inhibitor N3 (PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of ribavirin with amino acid with hydrogen bond (green dash lines).

with the affinity of -5.6 (Fig. 5). It shows significant binding with four hydrogen bonds between, nitrogen of dihydrotriazole ring and TYR 239, hydrogen of amide group (attached to dihydrotriazole) and TYR 237, hydrogen of hydroxyl group (attached to tetrahydrofuran ring) and ARG 131 and oxygen (attached to tetrahydrofuran ring) with ARG 131. An unfavourable acceptor interaction has also been observed between oxygen (attached to tetrahydrofuran ring) and ASP 289.

With six hydrogen bonds, favipiravir showed promising activity with the protease of COVID-19 with the affinity of -5.4 kcal/mol. It shows strong interaction with protease in the binding pocket near to chain A (Fig. 6). Thus this interaction results in six hydrogen bonds, oxygen (attached to pyrazine

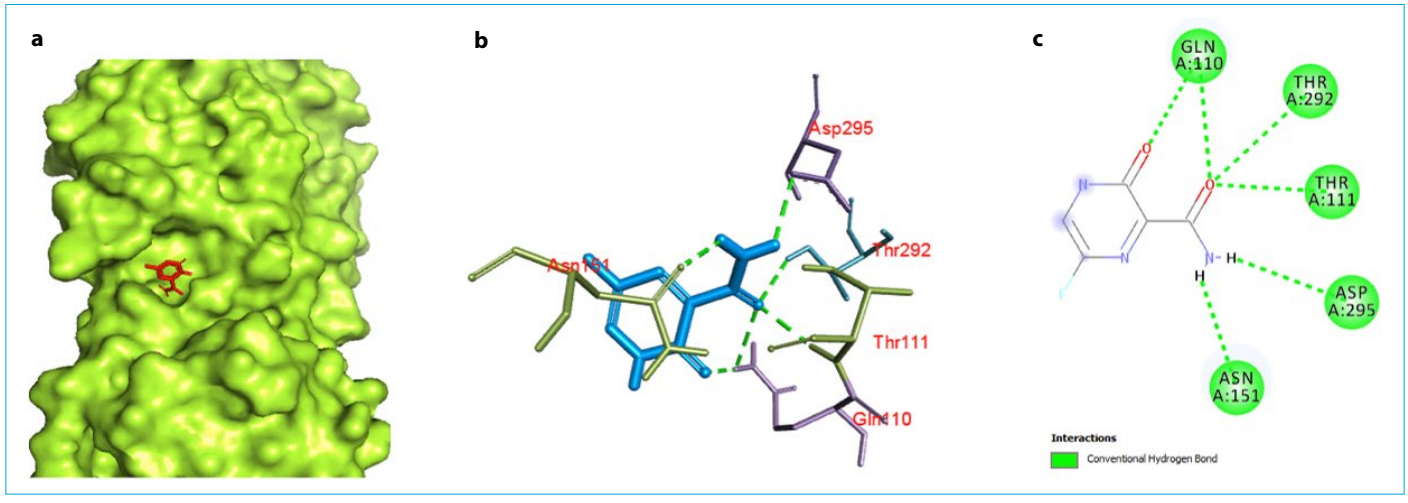



**Figure 6.** Favipiravir docked in COVID-19 main protease in complex with an inhibitor N3 (PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of favipiravir with amino acid with hydrogen bond (green dash lines).

ring) and oxygen carboxamide group (attached to pyrazine ring) with GLN 110, THR 292 and THR 111. Similarly hydrogen of carboxamide group shows hydrogen bonding with ASP 295 and ASN 151. Since the binding is characterized by six hydrogen bonds, this interaction can be recognized as possible mode of binding of favipiravir with the protease of COVID-19.

The docking of chloroquine was performed with both COVID-19 main protease in complex with an inhibitor N3 and SARS Spike glycoprotein-Human ACE2 complex. The binding of interaction of chloroquine with main protease of COVID-19 can be observed in the binding pocket of chain C with the affinity of -5.1 (Fig. 7). The interactions is primarily characterized by pi-alkyl interactions between the chlorobenzene ring with Val 104 and Ile 106. The prominent interaction of chloroquine with SARS Spike glycoprotein-Human ACE2 complex has been observed with the binding affinity of -70 (Fig. 8). The interaction of chloroquine with SARS Spike glycoprotein-Human ACE2 complex attributed by pi-pi and pi-alkyl interaction between the benzene ring and chlorine (attached to benzene ring) with Tyr 738 and Phe 952 respectively. A large number of amino acids involved in van der Waals interaction including Gln 987, Thr 988, Gln 984, Thr 988, Ser 985, Phe 741, Gly 981, Thr 988, Thr 991, Gln 987, Gln 984 and Leu 983. Thus it is observed that chloroquine favors SARS Spike glycoprotein-Human ACE2 complex over COVID-19 main protease in complex with an inhibitor N3.

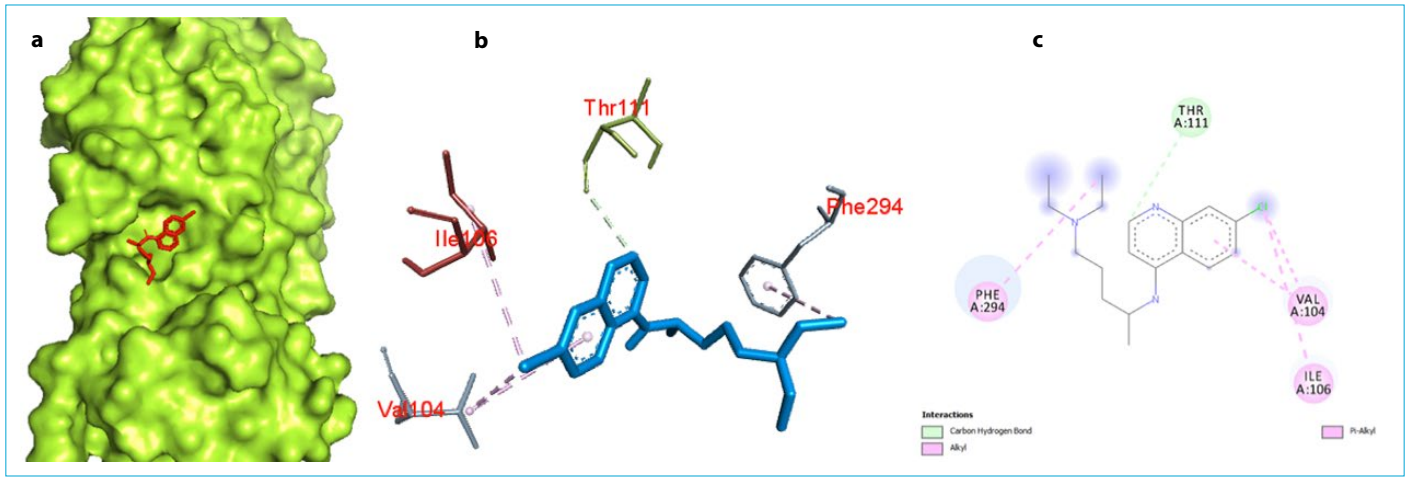



**Figure 7.** Chloroquine docked in COVID-19 main protease in complex with an inhibitor N3(PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of chloroquine with amino acid with hydrogen bond (green dash lines).

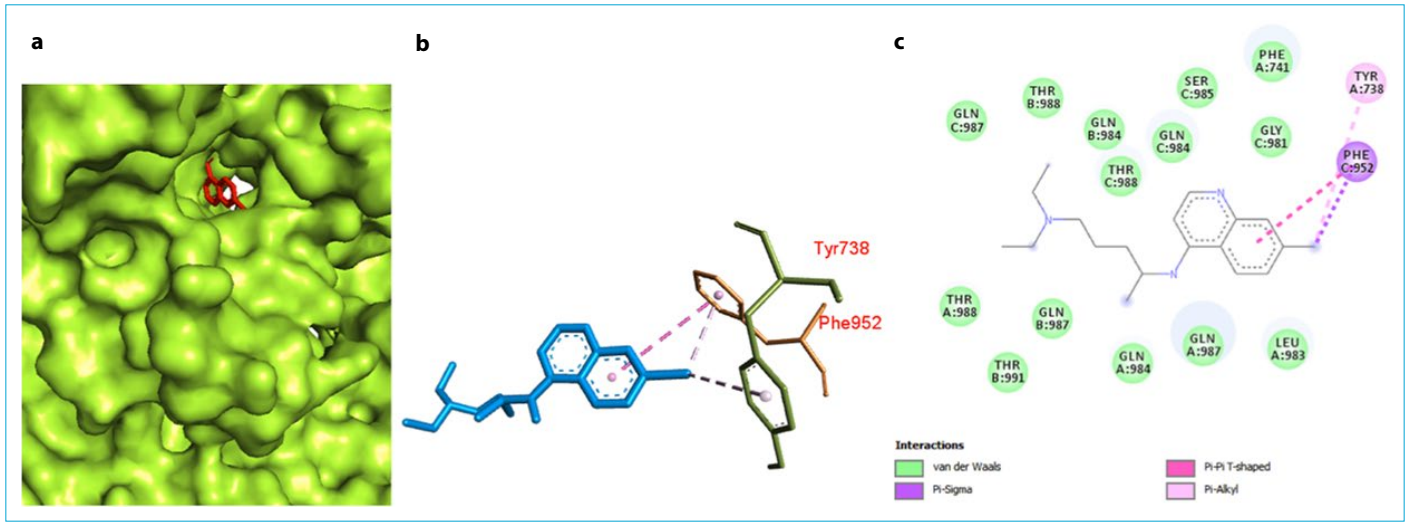



**Figure 8.** Chloroquine docked in SARS Spike glycoprotein-Human ACE2 complex (PDB ID 6CS2) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of chloroquine with amino acid with hydrogen bond (green dash lines).

Similarly, docking study of hydroxychloroquine with both-COVID-19 main protease in complex with an inhibitor N3 and SARS Spike glycoprotein-Human ACE2 complex attributed several facts about the binding interaction. The docking of hydroxychloroquine with COVID-19 main protease showed binding affinity of -5.3 kcal/mol with a hydrogen bonding interaction between hydrogen of hydroxyl group (in aliphatic chain) with Asn 151 (Fig. 9). It also showed pi-pi and pi-alkyl interaction with residues of Val 297, Pro 252 and Ile 249. The van der Waals interactions are taking place with Pro 293, Phe 294, Thr 111and Phe 8. Similar to chloroquine, hydroxychloroquine also showed promising interaction with the SARS Spike glycoprotein-Human ACE2 complex (Fig. 10) with the binding affinity of -6.8 kcal/mol. This interaction is primarily attributed large number of amino acids involved in van der Waals interaction due to better fitting of hydroxychloroquine inside the pocket of the protein. One hydrogen bond between secondary amine hydrogen and Gln 992 has been observed. A pi-sigma interaction takes place between the ring and Thr 943. Based on the results, it can be observed that SARS Spike glycoprotein-Human ACE2 complex acts as a promising target for hydroxychloroquine over COVID-19 main protease in complex with an inhibitor N3. Thus based on this study, it can be said that hydroxychloroquine favor the SARS Spike glycoprotein-Human ACE2 complex over the protease for binding.

## Conclusion

The docking results attributed various kind of binding interaction of the drug with protein among which some interac-

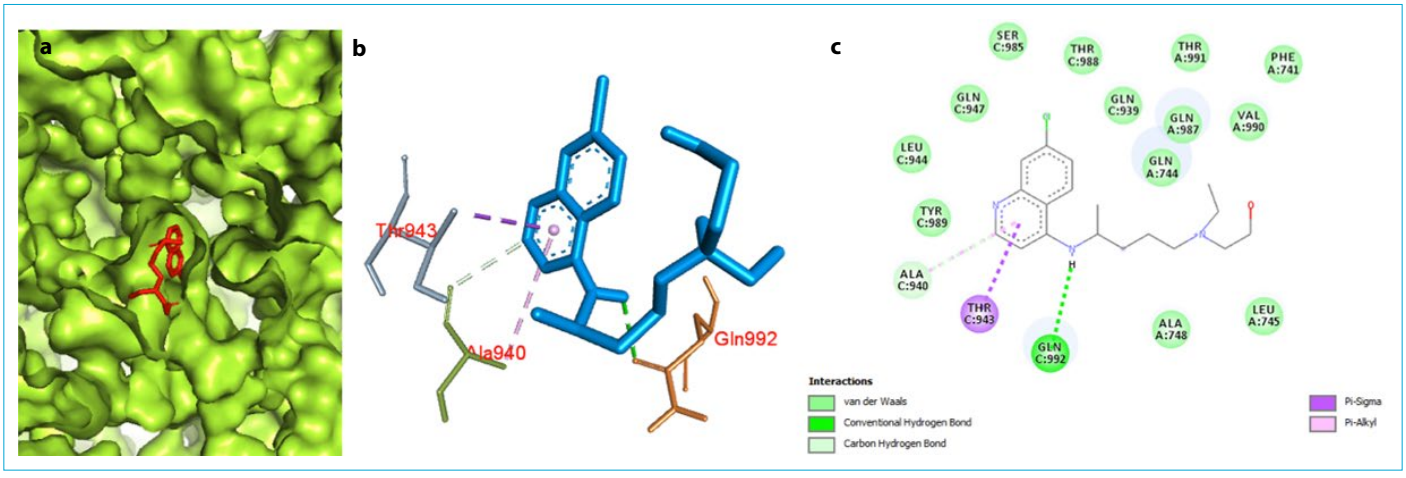



**Figure 10.** Hydroxychloroquine docked in SARS Spike glycoprotein-Human ACE2 complex(PDB ID 6CS2) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of hydroxychloroquine with amino acid with hydrogen bond (green dash lines).

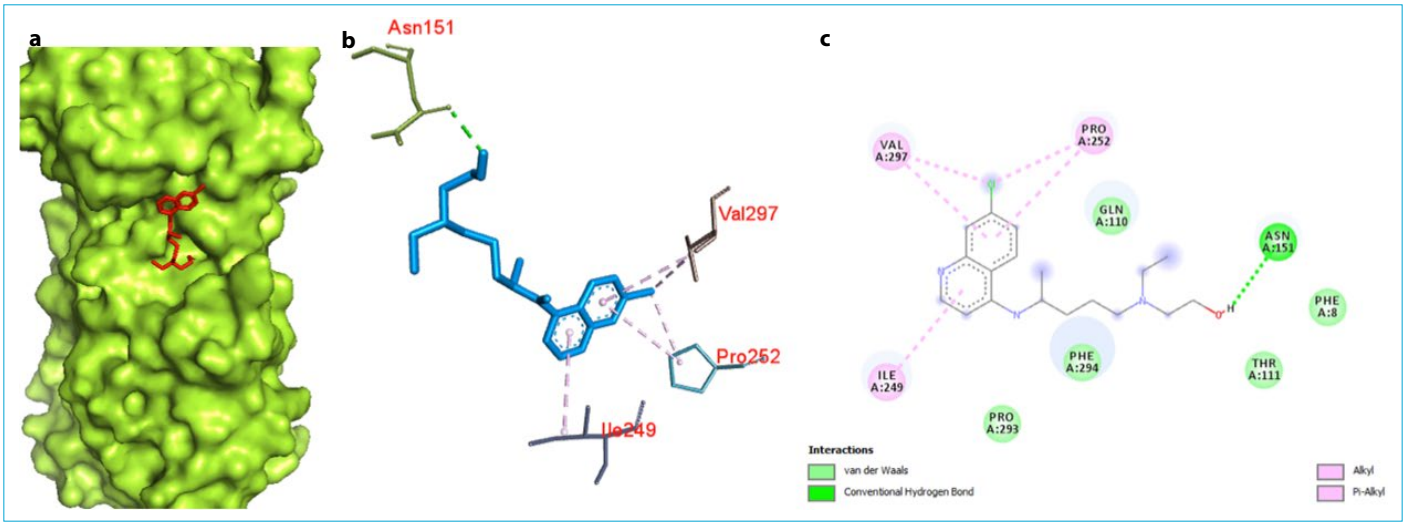



**Figure 9.** Hydroxychloroquine docked in COVID-19 main protease in complex with an inhibitor N3(PDB ID 6LU7) with **(a)** Best binding mode in the pocket of protein (with ligand as red color sticks), **(b)** Amino acid residues involved in interaction (with ligand as blue sticks) and **(c)** Binding interaction of hydroxychloroquine with amino acid with hydrogen bond (green dash lines).

tions are said to be favorable. The antiviral drugs including oseltamivir, ritonavir, remdesivir, ribavirin and favipiravir show high affinity interactions with the both COVID-19 main protease in complex with an inhibitor N3 whereas the anti-malerial drugs such as chloroquine and hydroxychloroquine show prominent interaction with SARS Spike glycoprotein-Human ACE2 complex. Thus it may be possible that, the anti COVID-19 activity of several antiviral drugs is attributed by interaction of them withCOVID-19 main protease. It can also make conclude that the anti COVID-19 effect of chloroquine and hydroxychloroquine is attributed by high affinity interaction with SARS Spike glycoprotein-Human ACE2 complex.

**Disclosures**

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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