A computational and literature-based evaluation for a combination of chiral anti-CoV drugs to block and eliminate SARS-CoV-2 safely

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Abstract

It has been a great challenge for the scientists to develop an anti-covid drug/vaccine with fewer side effects, since the coronavirus began. Besides, the mechanism of action and the reason of causing side effects, has also become a great challenge for the scientists in the case of chiral drugs. The main reason behind it, is the prescription of chiral drugs in the racemic form. Another hurdle in front of the world, is the positive test of the patient recovered from coronavirus. This positive test of recovered person, shows the demand of such drugs whose mechanism is understandable, and which can block and eliminate SARS-CoV-2 or its material from the body completely, with fewer side effects. The presented computational study explains (i) the mechanism of action of drugs (chloroquine and hydroxychloroquine) that block SARS-CoV-2 (ii) the strength of mefloquine that may eliminate SARS-CoV-2. First, the binding affinities of main protease (M^{pro}) of JC virus for which mefloquine has already shown its strength to remove, were calculated. After that, same method was applied for SARS-CoV-2, and both the results were compared to know the strength of mefloquine against SARS-CoV-2. Till now, the experimental data found in the literature survey, was neither used in the interpretation nor evaluated computationally, in such a way, as I did for the first time to fight against the pandemic situation. Hence, the current study includes the docking results and literature data for the prescription of a combination of only biologically active enantiomers to the patient fighting with coronavirus, with less side effect. Two enantiomers that could do it, are S-(+)-hydroxychloroquine and (+) mefloquine. Of course, one of these two drugs, will block the coronavirus, while another one will eliminate it.

Keywords: Chiral drugs, S-(+)-hydroxychloroquine, (+) mefloquine, computational study and SARS-CoV-2.

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Introduction

To find a suitable drug or vaccine for the coronavirus, has become a great challenge for the researchers in this modern and advanced era. Virologist, microbiologist, clinicians, industrialists, and government authorities are working very hard day-night. Besides, numerous antiviral drugs were employed for the treatment of SARS-CoV-2 infection[1], but an acceptable solution did not come in front of the world yet. Chloroquine blocking the coronavirus from binding to human cells[2], was considered as a suitable drug, but conditions became very critical, when chloroquine was prescribed to the patient fighting with coronavirus (https://edition.cnn.com/2020/03/23/africa/chloroquine-trump-nigeria-intl/index.html). After that, hydroxychloroquine was suggested for the same, because it shows fewer side effects[3], but the question of causing side effects, remained unsolved, which has made these two drugs failed. Hence, one question, why chloroquine and hydroxychloroquine did not give satisfactory results *in vivo*, arises here. The reason behind it, is the prescription of these chiral drugs in the racemic form i.e. enantiomeric form. The main problem is that each enantiomeric form has its own biological activity with different mechanisms[4-13]. Hence, in the case of chiral drugs, the property of existing in different forms, makes the conditions very much complicated, and their mechanism of action also. Therefore, this is a great challenge for the researchers to find out the most biologically active enantiomeric form[14,15]. Nobody knows, which enantiomeric form of chloroquine and hydroxychloroquine, blocked the coronavirus from binding to human cell, and which one caused side effects. Because of the prescription in the racemic form, the mechanism of action of chloroquine and hydroxychloroquine to block the coronavirus remains poorly understood, which the presented study explains for the first time.

Besides the mechanism of action and the side effects of chloroquine and hydroxychloroquine, the most important and notable thing standing in front of the world, is the positive report of the patient recovered from the coronavirus [https://curlytales.com/some-recovered-coronavirus-patients-are-testing-positive-for-it-again/]. All around the world, there have been several cases of people recovering from COVID-19 only to later test positive again. This report clearly shows the existence of coronavirus or its material in the body [https://www.healthline.com/health-news/people-reinfected-with-covid-19-werent-infectious]. This thing raises many questions whose unsolvable chemistry has created another obstacle in front of

the world. The presented study also resolves this problem. Having read the research papers regarding the virus elimination from the body, I found that mefloquine has been used for the same. Mefloquine has given the tremendous results *in vitro*[16] as well as *in vivo*[17]. The virus that was eliminated through mefloquine from the body, was JC virus. Hence, mefloquine has played an important role in the elimination of JC virus from the body completely[16,17], but the problems of causing side effects, with this drug, were same. It was just because of the prescription of this chiral drug in the racemic form. Mefloquine is presently manufactured and vended as a racemate of the (R,S)- and (S,R)-enantiomers by Hoffman-LaRoche, a Swiss pharmaceutical company. It is on the WHO's List of Important Drugs, the harmless and most active drugs desirable in a health system[18]. Hence, if mefloquine is prescribed for the removal of SARS-CoV-2 from the body, we have to face many questions such as experimental data, theoretical or computational data supporting the idea of prescription of this drug. Besides, this drug is chiral in nature, and can not be prescribed as it is i.e. in the racemic form. Therefore, another question related to the prescription of biologically active enantiomeric form of mefloquine to avoid the toxicities, side effects, and other problems, also arises here. The presented study also resolves this question.

Of course, the drugs and their targets should be known, when the mechanism of action, and the strength of drug, is being studied. Hence, a docking study was done using the enantiomers of the chiral drugs taken in the current study, as the ligands, while other things required to inhibit the virus, were selected as the targets.

Results

The docking studies of the enantiomers of chloroquine, hydroxychloroquine and mefloquine with the targets, were performed. The results are given in Tables 1. The representative enantiomeric interactions of chloroquine and hydroxychloroquine with Covid-2 spike attached to its receptor, are shown in Figure 1a and Figure 1b, respectively, while those of mefloquine with JC virus main protease (M^{pro}) as well as SARS-CoV-2 main protease (M^{pro}), are shown in Figure 2 and Figure 3, respectively. These figures show clearly that the enantiomers interacted with targets differently. The most significant and notable point in the docking results (Table 1), was the attachment of enantiomers only with the receptor of Covid-2, not with its spike. The binding affinities of each enantiomer of chloroquine and hydroxychloroquine with the receptor of Covid-2, were same (-4.2 kcal/mol). In the case of chloroquine, R-form of

chloroquine did not form any hydrogen bond, while S-form of chloroquine formed 1-H bond with the receptor of Covid-2 spikes. In the same way, the number of hydrogen bonds, was different in both enantiomers of hydroxychloroquine. It was observed that R-form of hydroxychloroquine formed 3-H bonds, while S-form of hydroxychloroquine did not form any hydrogen bond with the receptor of Covid-2 spikes. On the other hand, the binding affinities of the enantiomers of mefloquine with SARS-CoV-2 M^{pro} and JC virus M^{pro}, were very shocking, because the binding affinities of mefloquine with SARS-CoV-2 M^{pro}, were greater than those with JC virus M^{pro}. The binding affinities ranged from -3.5 to -3.6 kcal/mol in the case of JC virus M^{pro}, while these ranged from -6.8 to -7.3 kcal/mol in the case of SARS-CoV-2 M^{pro}. In the case of JC virus protease, RR-form of mefloquine formed 2-H bonds; RS-form formed no hydrogen bond; SR-form formed 2-H bonds; SS-form formed only 1-H bond. Besides, with SARS-CoV-2 M^{pro}, RR-form of mefloquine formed 2-H bonds; RS-form formed no hydrogen bond; SR-form formed only 1-H bond; SS-form formed only 1-H bond. Additionally, enantiomeric hydrophobic interactions of chloroquine and hydroxychloroquine with the receptor of Covid-2 spike, were also seen as shown in Figure 4a and Figure 4b, respectively, while those of mefloquine with JC virus M^{pro} and SARS-CoV-2 M^{pro}, are shown in Figure 5 and Figure 6, respectively. The common residues involved in enantiomeric hydrophobic interaction of chloroquine and hydroxychloroquine with the receptor of Covid-2 spikes, were Ala533(A), Asp543(A), His535(A), Lys416(A), Ser545(A), Glu430(A), Glu536(A), Asn546(A), His535(A), Lys416(A), Lys534(A), Ser547(A), while those in mefloquine with JC virus M^{pro}, were Gln339(A), Gln340(A), Ser336(A), Trp271(A), OD2, Asn333(A), Asp343(A), OG; with SARS-CoV-2 M^{pro}, were Leu287(A), Leu286(A), Met276(A), Tyr239(A), Tyr237(A), Thr199(A), Asp289(A), Thr199(A).

Discussion

Of course, the results were very complicated, but intriguing as well as exciting. The interpretation was done with the help of docking results, literature data, and experiments done on the presented drugs by others previously. Definitely, the interpretations will play an important role for the solution of coronavirus pandemic. The enantiomers of chloroquine and hydroxychloroquine interacted with the receptor of Covid-2 spikes, in different ways/fashions, that is why the number of hydrogen bonds, was found different in different enantiomers. The similar binding affinities of chloroquine and hydroxychloroquine with the receptor of Covid-2

spikes, show that these drugs bind to the receptor of Covid-2 spikes, with equal strength. The attachment of the enantiomers of chloroquine and hydroxychloroquine only with the receptor of Covid-2 spikes, not with Covid-2 spike, was too much helpful in understanding the mechanism of action of both the drugs. Actually, it means that both the drugs bind with the receptor of Covid-2 spikes, that is why SARS-CoV-2 does not recognize its receptor, and become unable to enter in the human cell. In this way, the mechanism of blocking coronavirus, is resolved. Obviously, the shocking results were observed in the interaction/binding study of mefloquine with both JC virus M^{pro} and SARS-CoV-2 M^{pro}. The different enantiomers of mefloquine interacted with both targets in different modes, that is way the number of hydrogen bonds, was found different in different enantiomers of mefloquine. The most important and notable shocking thing, were the binding affinities of each enantiomer of mefloquine, which were greater for SARS-CoV-2 M^{pro} than that for JC virus M^{pro}. This thing helped too much in understanding the strength of mefloquine for the elimination of SARS-CoV-2 from the body. The diverse binding affinities of the enantiomers of the reported chiral drugs with the targets, were observed due to their dissimilar stereochemical configuration. The docking studies showed that the connections among the enantiomers and targets, were due to hydrophobic interactions as well as hydrogen bonding. The strength of the interaction was based on both binding affinities and the number of hydrogen bonds. Hence, in the coronavirus pandemic, the presented study may prove mefloquine to be a milestone for the removal of coronavirus from the body, as per docking results.

Now, another question arising on the most biologically active enantiomeric form of the respective chiral drugs, is also resolved with the help of literature data. As we know that chloroquine and hydroxychloroquine, both have one chiral center, and exist in two enantiomeric forms that is why the prescription of these drugs in the racemic form, raises many questions related to the side effects. It is already confirmed that hydroxychloroquine is better than chloroquine[3,19]. Now, one question, which enantiomeric form of hydroxychloroquine having less toxicity and side effect, should be prescribed to the patient, arises here. The most biologically active enantiomer of hydroxychloroquine having has less toxicity and side effect, is S-(+)-hydroxychloroquine which has already been patented as an active and effective form[20]. It means that `R` enantiomer of hydroxychloroquine is inactive and causes side effects, that must be avoided. Hence, except the racemic form of hydroxychloroquine, S-(+)-hydroxychloroquine would be a suitable and effective drug in blocking the coronavirus, with less toxicity and side

effect. On the other hand, as per docking results, all the enantiomers of mefloquine interacted with SARS-CoV-2 M^{pro} more strongly, as compared with JC virus M^{pro}, showing the higher capability to remove SARS-CoV-2 from the body. In the prescription of mefloquine, conditions become more complicated. The reason behind it, is the presence of two chiral centers in mefloquine, which confirms the existence of mefloquine in four enantiomeric forms. Hence, the prescription of mefloquine in the racemic form for the elimination of SARS-CoV-2, will raise same questions, as in the case of hydroxychloroquine. The most biologically active enantiomer of mefloquine, that could be prescribed, is (+)-mefloquine, which has already been confirmed as an active and effective form[21]. WRAIR has published several papers outlining ongoing efforts to make mefloquine safer by producing only (+)-mefloquine. The reason behind it, is a shorter half-life of (+)-mefloquine than other enantiomeric forms of it, because this enantiomer has less affinity towards plasma[21]. Hence, (+)-mefloquine would be a suitable and effective drug in eliminating SARS-CoV-2 from the body with less toxicity as well as side effect as per both docking results and literature data[21]. Based on the docking results and literature data[16-21], the prescription of a combination of S-(+)-hydroxychloroquine and (+)-mefloquine, must be suitable for the safest treatment of coronavirus. In these two drugs, S-(+)-hydroxychloroquine would be able to block the coronavirus, while (+)-mefloquine would be able to eliminate it from the body, with less side effect.

Conclusion

After a long discussion based on the docking results, less toxicity of S-(+)-hydroxychloroquine and (+)-mefloquine, and literature data including the work done previously, I found that chloroquine and hydroxychloroquine, both have capability to block the SARS-CoV-2, but not to eliminate it. In these two drugs only hydroxychloroquine, would be suitable to do that, but the prescription of its only S-(+)-form, would make it more suitable and effective with less side effect. On the other hand, as per docking results, mefloquine may exhibit its capability to eliminate the SARS-CoV-2, as mefloquine did in the case of JC virus. The prescription of its (+)-form, would make it more suitable and effective with less side effect. Therefore, the current computational study may prove the prescription of a combination of S-(+)-hydroxychloroquine and (+)-mefloquine to be a troubleshooter in this pandemic situation. Moreover, the prescription of only single enantiomeric form will also be very helpful in understanding the mechanism of

action of both chiral drugs. Hence, the presented study may be acceptable to the scientific community.

Materials and Methods

Software's and Tools

All the software and tools used for studying the interaction between enantiomers and targets, are Discovery Studio Visualizer, MarvinSketch (16.9.12 version), LigPlot, AutoDock Vina 4.2, Protein Data Bank (PDB), MGL tools, PubChem and PyMOL.

Computational study is very helpful not only in understanding the reaction mechanism[22-27] but also in the drug development[28] and mechanism of action in pharmacokinetics[29]. There are three steps following of which, the computational evaluation was done. The first step was the preparation of pdb files of targets and ligands, the second was the molecular docking simulation, and the final step was the data analysis. The experiments done by others on chloroquine[2] and hydroxychloroquine[3], were evaluated computationally, to know the mechanism of action of both chloroquine and hydroxychloroquine in blocking SARS-CoV-2, while the literature data was used to know the most biologically active enantiomer of both chloroquine and hydroxychloroquine. In the same way, the experiments done by others on mefloquine[16,17] for the elimination of JC virus, were also evaluated computationally, and compared with the computationally evaluated docking results for SARS-CoV-2, to know the eliminating strength of mefloquine against it. For this purpose, the main protease (M^{pro}) of both JC virus and SARS-CoV-2, were interacted with mefloquine computationally. In the current study, I took the main protease of both viruses, because it is already understood that the main protease (M^{pro}) of microbes, is considered as an effective target for drug design and development[30]. During drug development strategy, the residues of the targets involving in the interactions with the drugs, assist as a platform for the development of potent and selective inhibitors of microbes such as SARS-CoV-2 M^{pro} [30].

Receptor/Target Preparation

First, all the pdb files of targets with pdb code: 6lzg for covid-2 with its receptor; 6m03 for SARS-CoV-2 M^{pro}; 5j40 for JC virus M^{pro} (Figure 7a), (Figure 7b) and (Figure 7c) respectively, were obtained from the protein data bank (www.rcsb.org). All the pdb files obtained, were not

pure due to the presence of impurities such as ligands and water molecules. Hence, all the pdb files of the targets were made pure by removing the impurities attached to the targets, using Discovery Studio Visualizer so that it could be used for further study. After that, the pdb files were opened one by one in AutoDock Tools (ADT) 4.2 [31] to add the non-polar hydrogen atoms, followed by Gasteiger charges assigned to targets. After the addition of all the things mandatory for the simulation study, the pdb files of targets, were saved as pdbqt format.

Ligands (Enantiomers) Preparation

In the ligands (enantiomers) preparation, MarvinSketch was used. All the enantiomers of chloroquine, hydroxychloroquine, and mefloquine taken in the present study, were saved in pdb files (Figure 7d), (Figure 7e) and (Figure 7f), respectively. All the pdb files of ligands (enantiomers of chloroquine, hydroxychloroquine, and mefloquine), like receptor preparation, were converted into pdbqt format one by one using AutoDock Tools (ADT) 4.2 [31], and the docking was achieved by using ADT considering all the rotatable bonds of the ligand as rotatable, and the receptor as rigid[31]. The grid box size of 60 × 80 × 110 A° with 0.375 A° spacing, was used.

Docking Methods

All the files of enantiomers, formatted as pdbqt, were docked with targets one by one using AutoDock vina[32] program. For docking method, the coordinates of the source were set at x=30.054, y=22.75, and z= 4.171. Fifty autonomous docking runs were applied for each ligand (enantiomer) and targets to find the lowest free energy of binding confirmation from the largest cluster.

Data and Analysis

The analysis of the number of hydrogen bonds, the residues of enantiomers as well as targets involved in hydrogen bondings, mode of interaction, and bond lengths of hydrogen bonds, were studied by PyMOL. On the other hand, LigPlot 1.4.5 [33] was used for the study of enantiomeric hydrophobic interactions with the targets.

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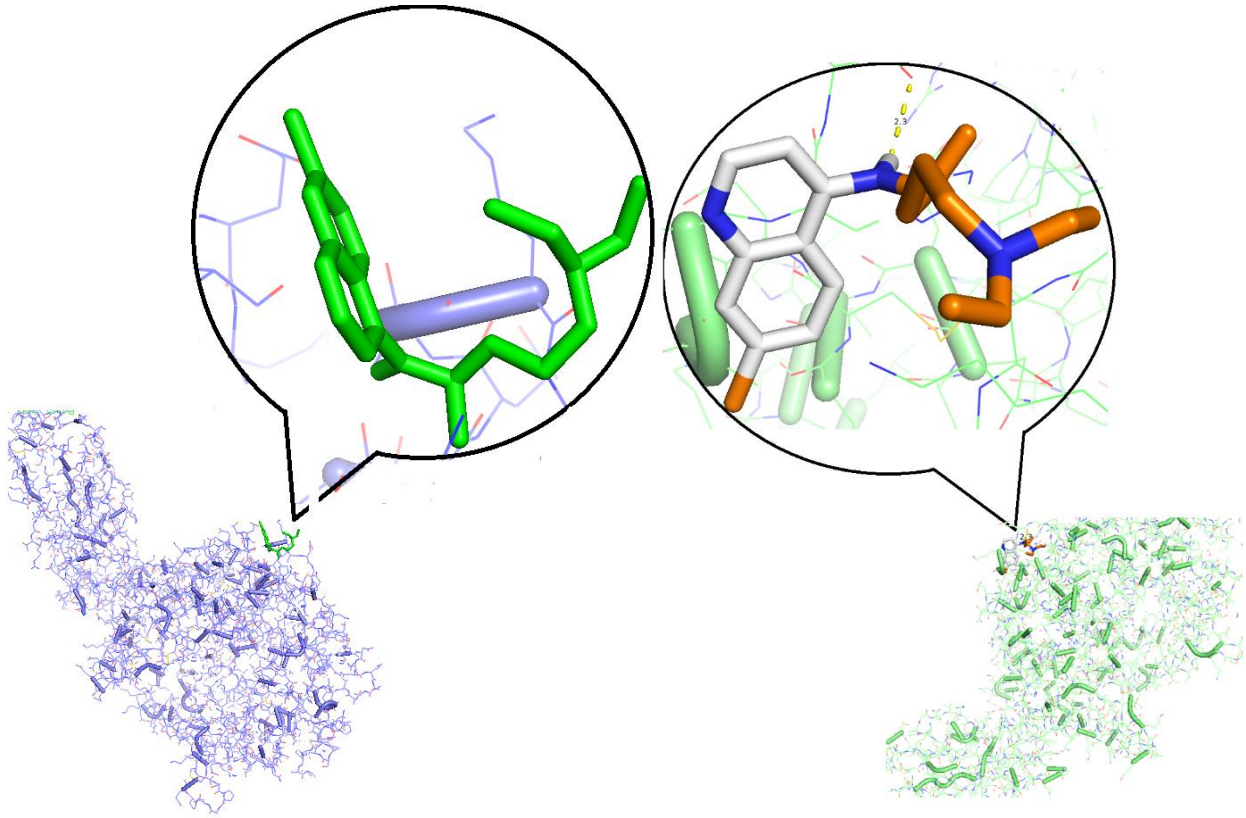
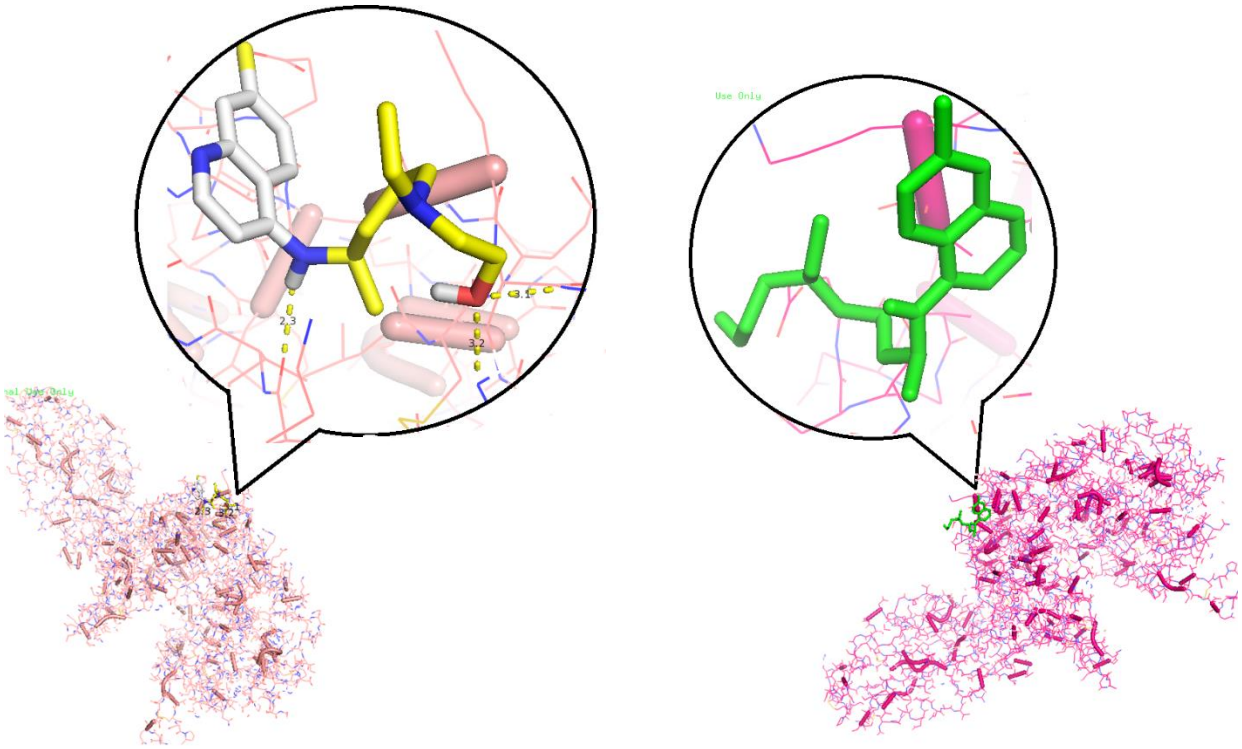


Chloroquine (R) **Chloroquine (S)**

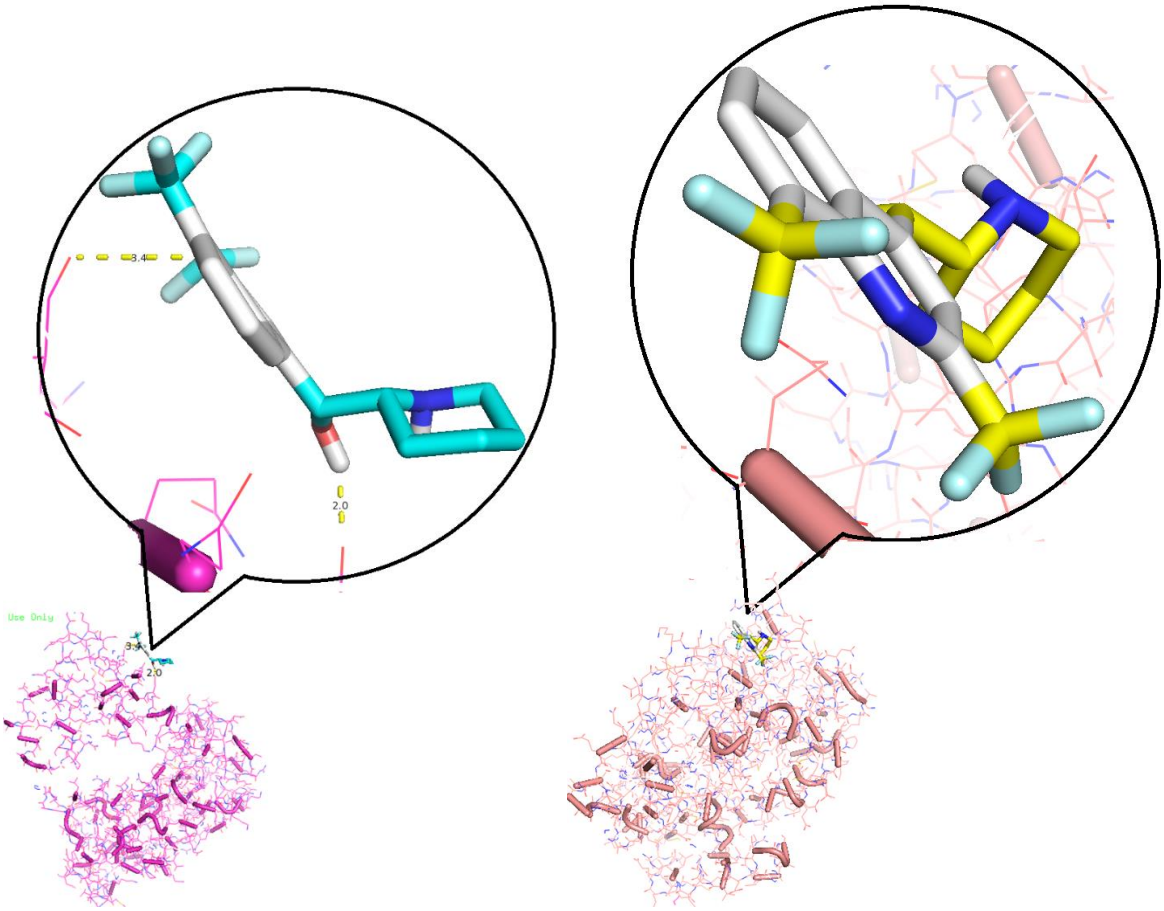
(a)



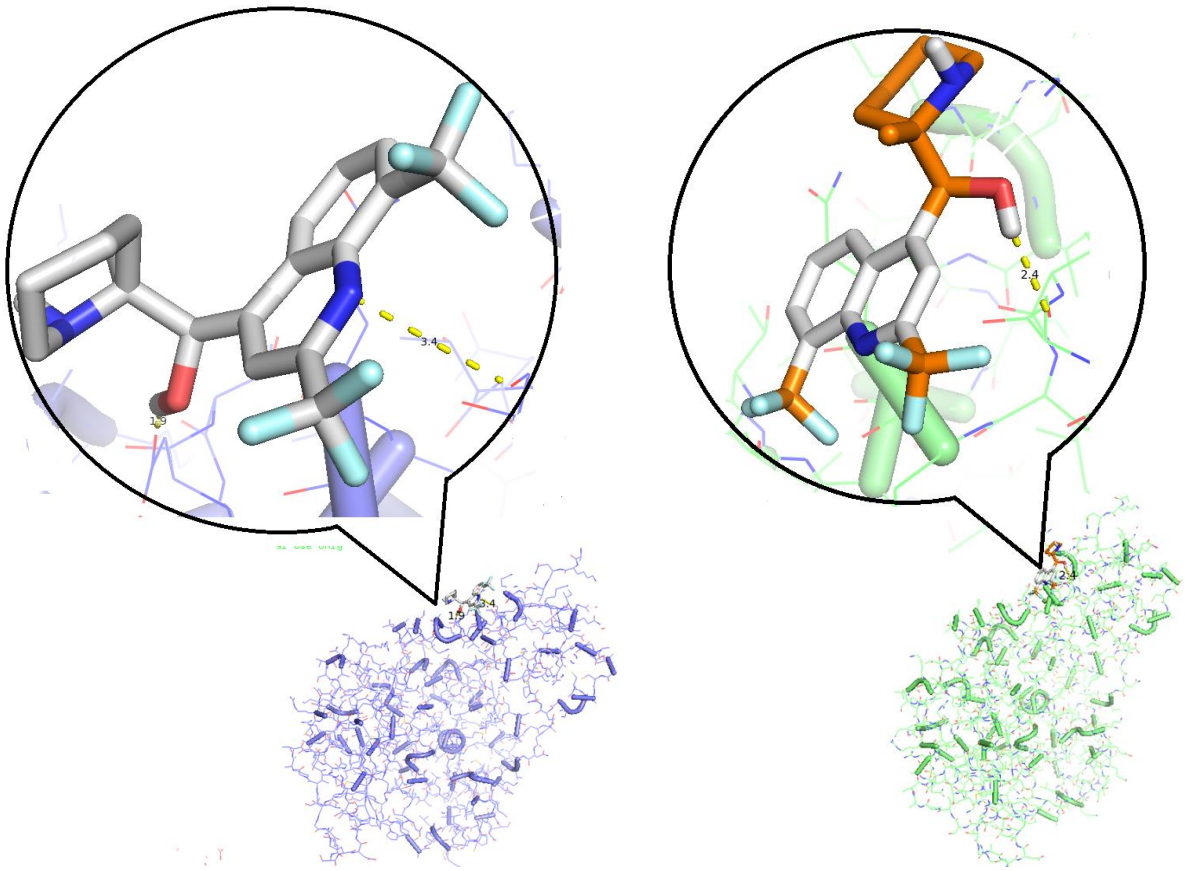
Hydroxychloroquine (R) **Hydroxychloroquine (S)**

(b)

Figure 1: 3D docking images of different enantiomers of (a) chloroquine and (b) hydroxychloroquine with Covid-2 spike attached to its receptor.

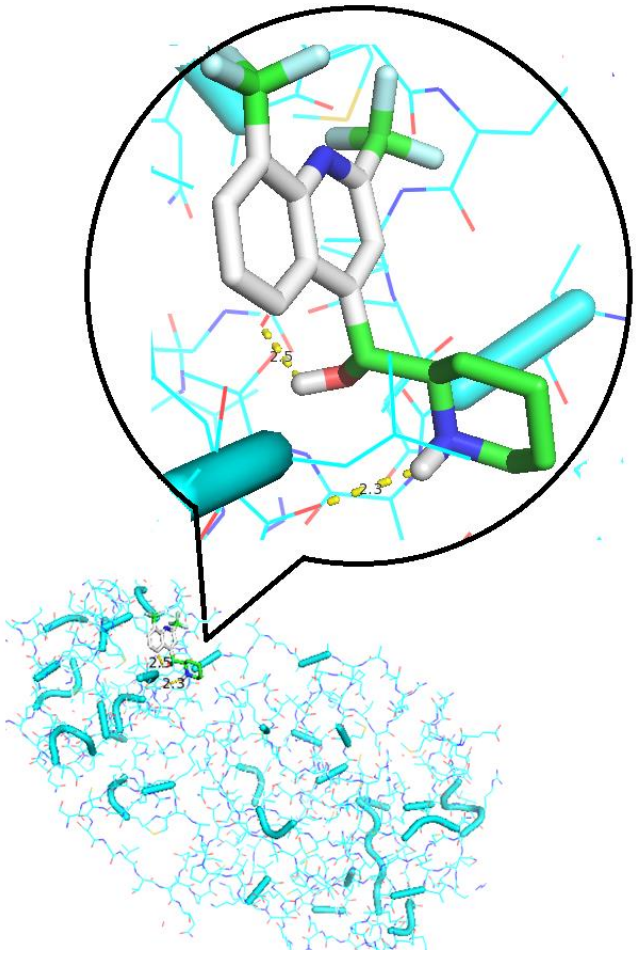


RR **RS**

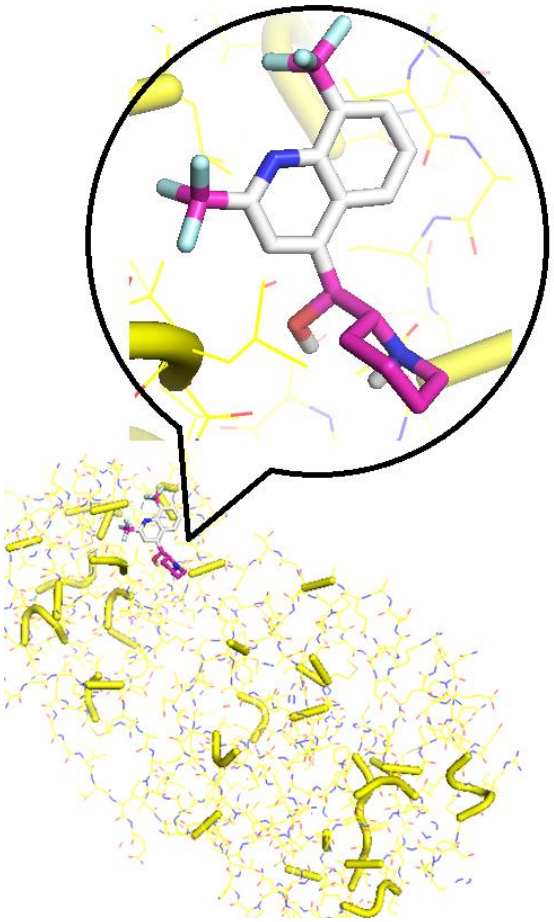


SR **SS**

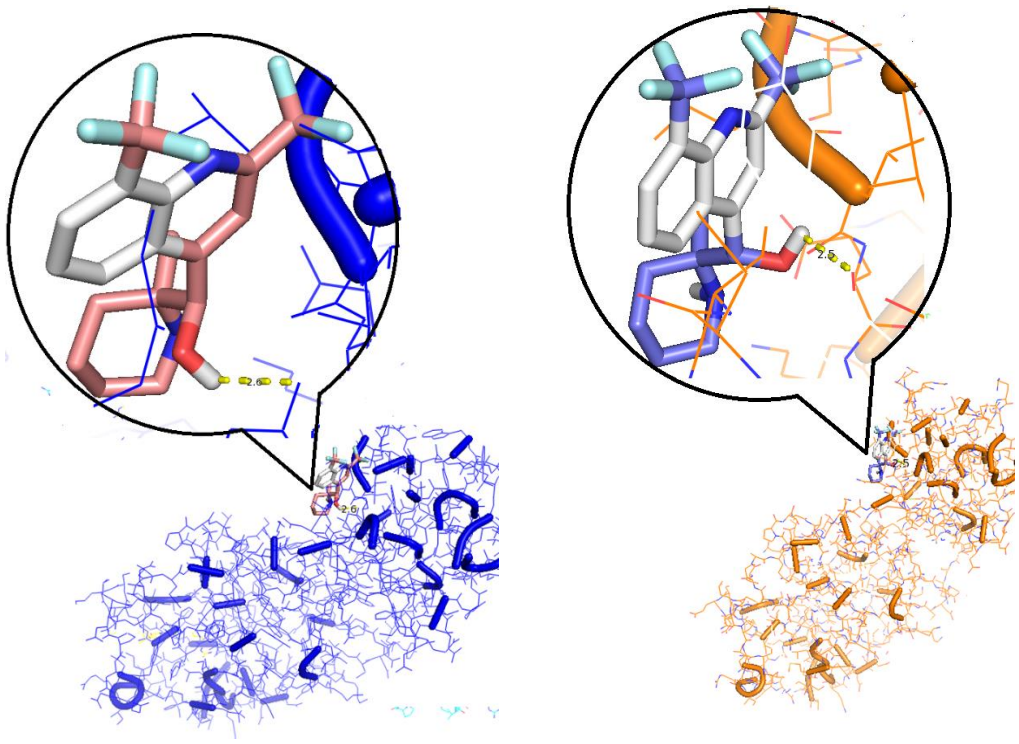
Figure 2: 3D docking images of different enantiomers of mefloquine with JC virus main protease (M^{pro}).



RR

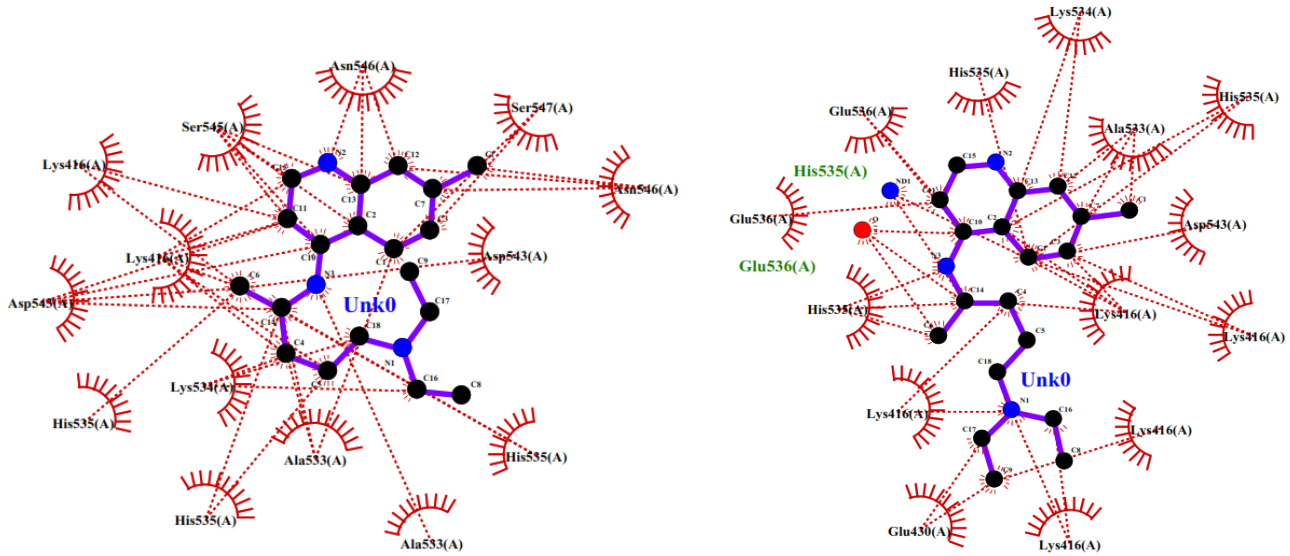


RS



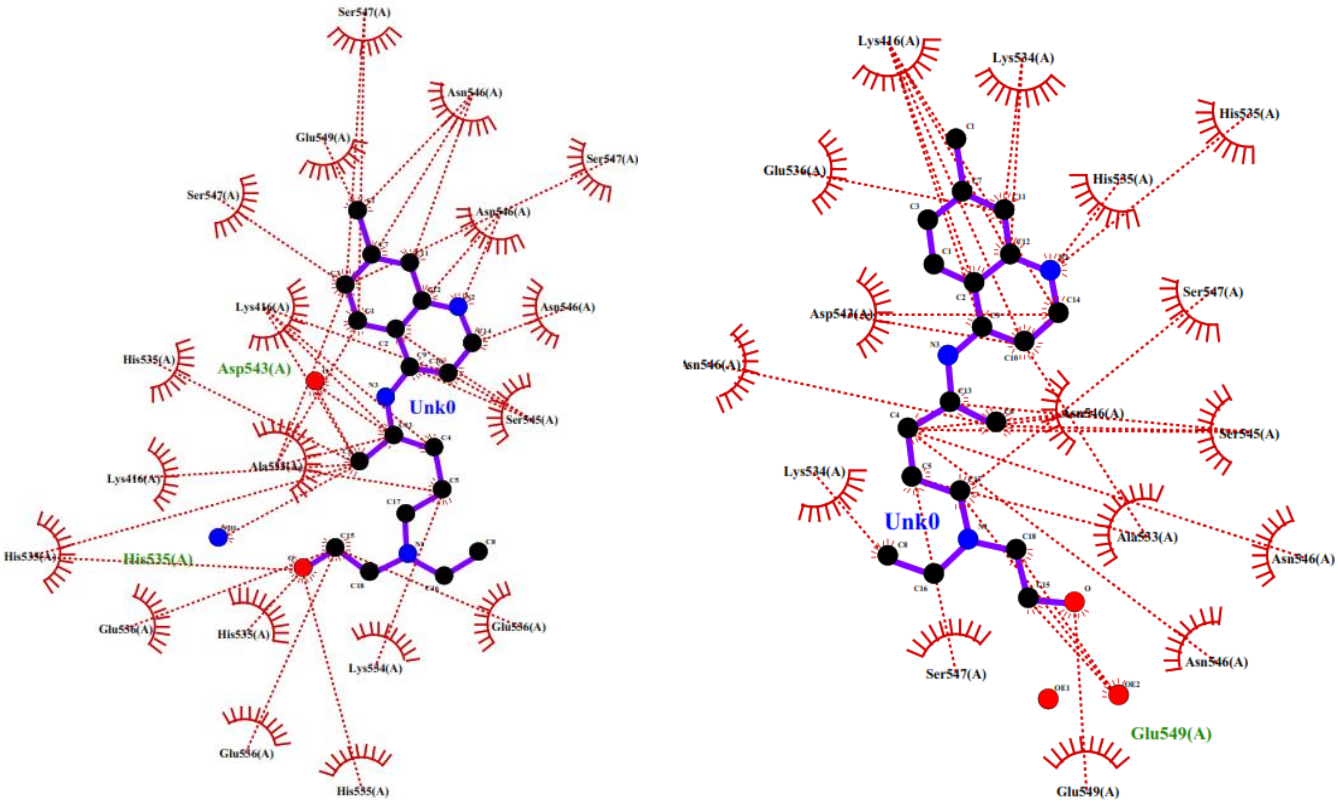
SR **SS**

Figure 3: 3D docking images of different enantiomers of mefloquine with SARS-CoV-2 main protease (M^{pro}).



Chloroquine (R) **Chloroquine (S)**

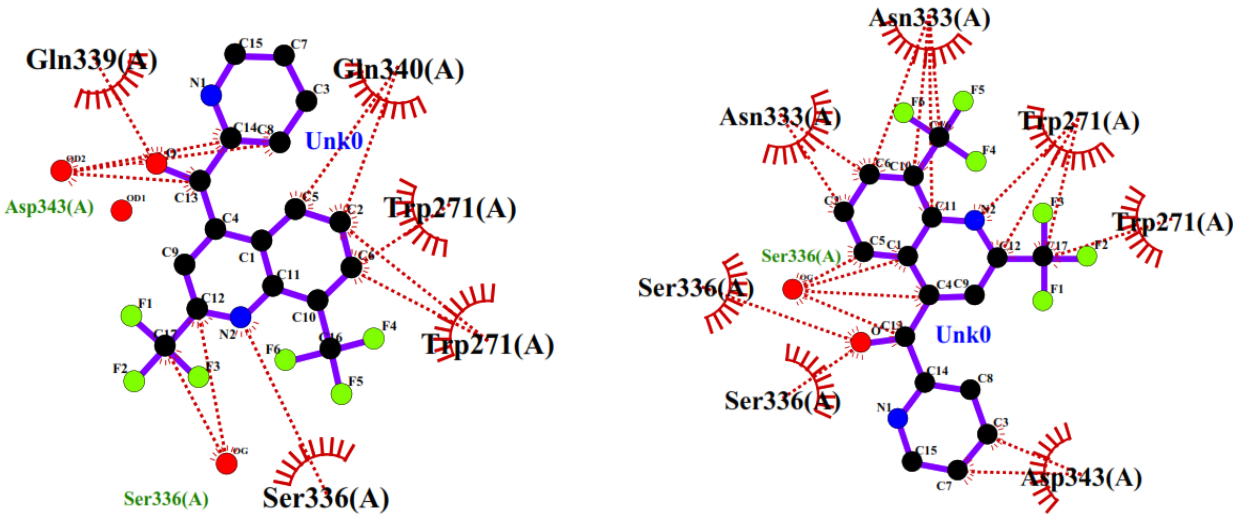
(a)



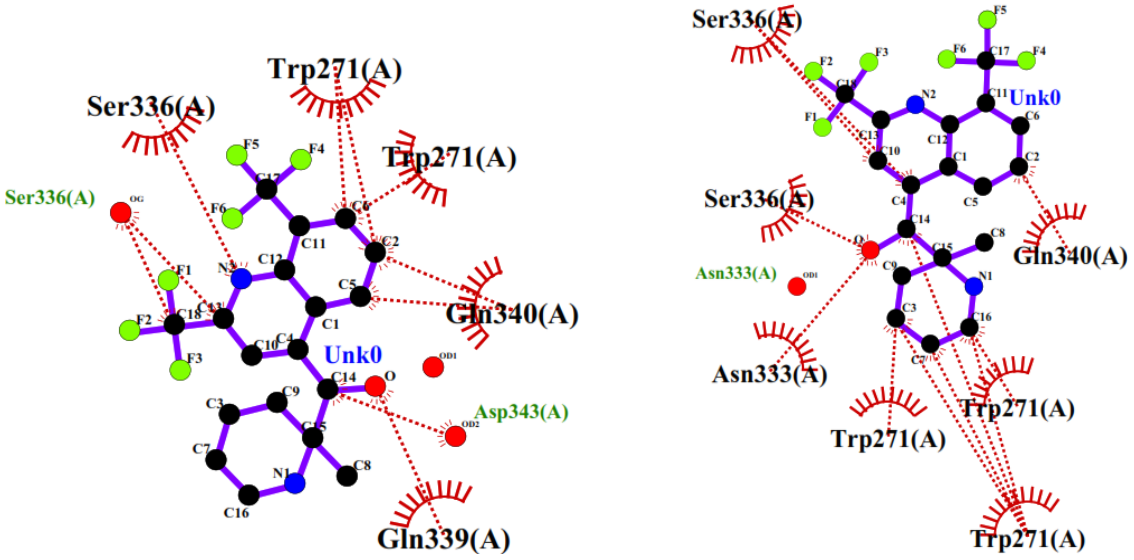
Hydroxychloroquine (R) **Hydroxychloroquine (S)**

(b)

Figure 4: 2D docking images of enantiomeric hydrophobic interaction of (a) chloroquine and (b) hydroxychloroquine with Covid-2 spike attached to its receptor.

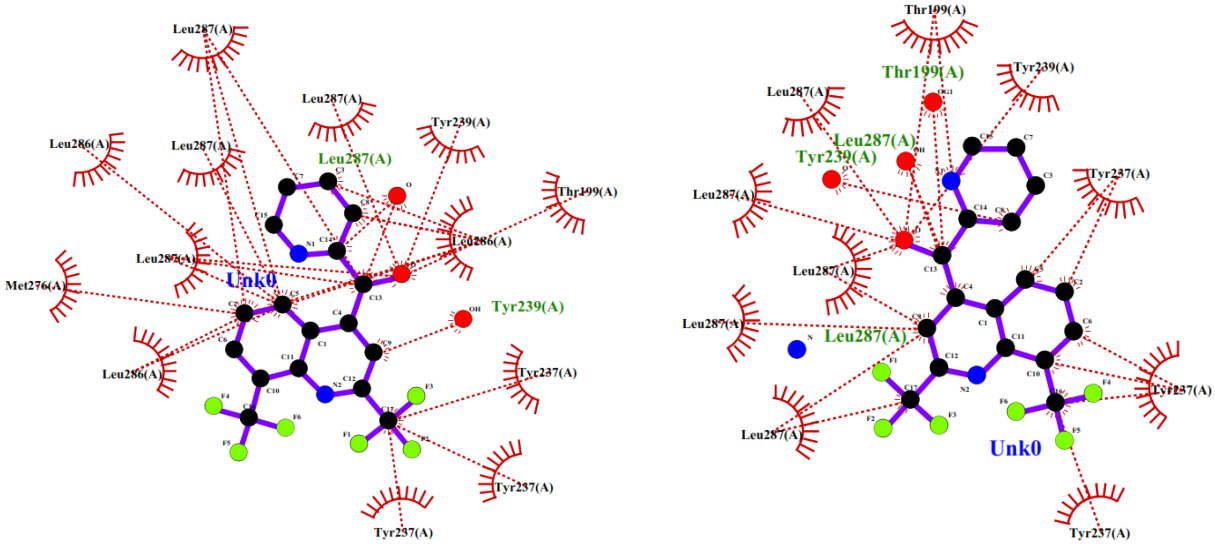


RR **RS**

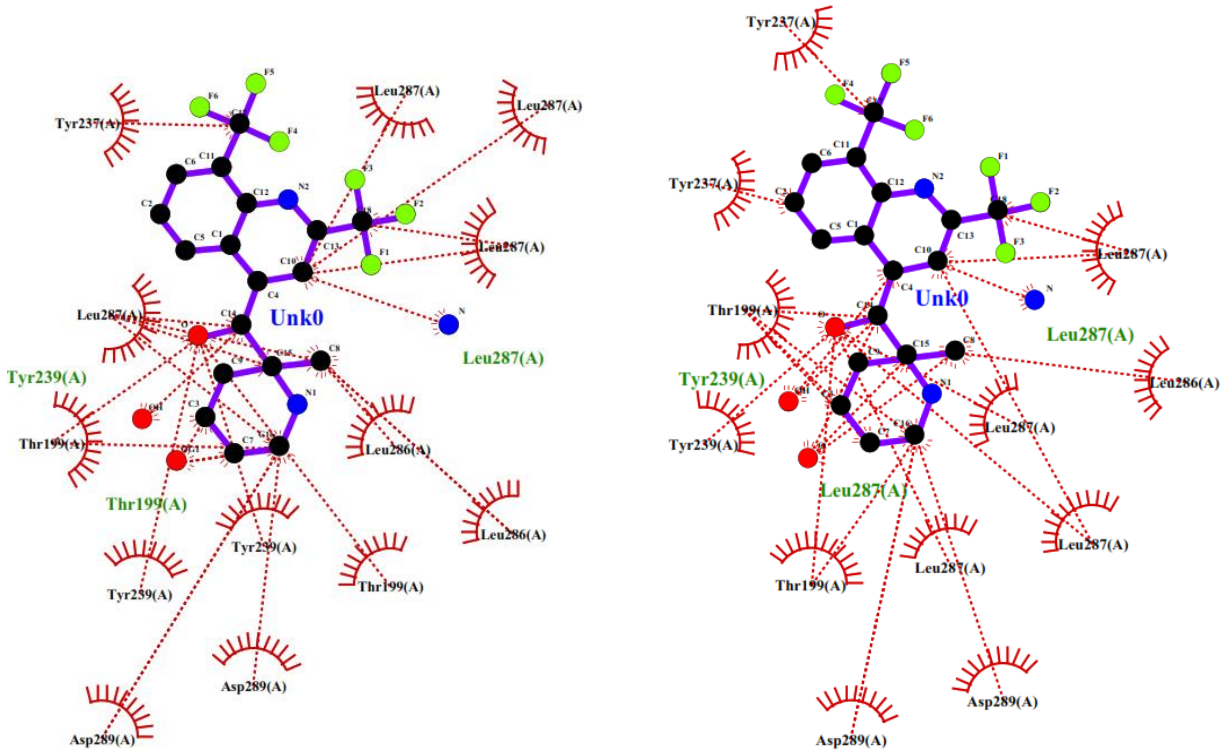


SR **SS**

Figure 5: 2D docking images of enantiomeric hydrophobic interaction of mefloquine with JC virus main protease (M^{pro}).



RR **RS**



SR **SS**

Figure 6: 2D docking images of enantiomeric hydrophobic interaction of mefloquine with SARS-CoV-2 main protease (M^{pro}).

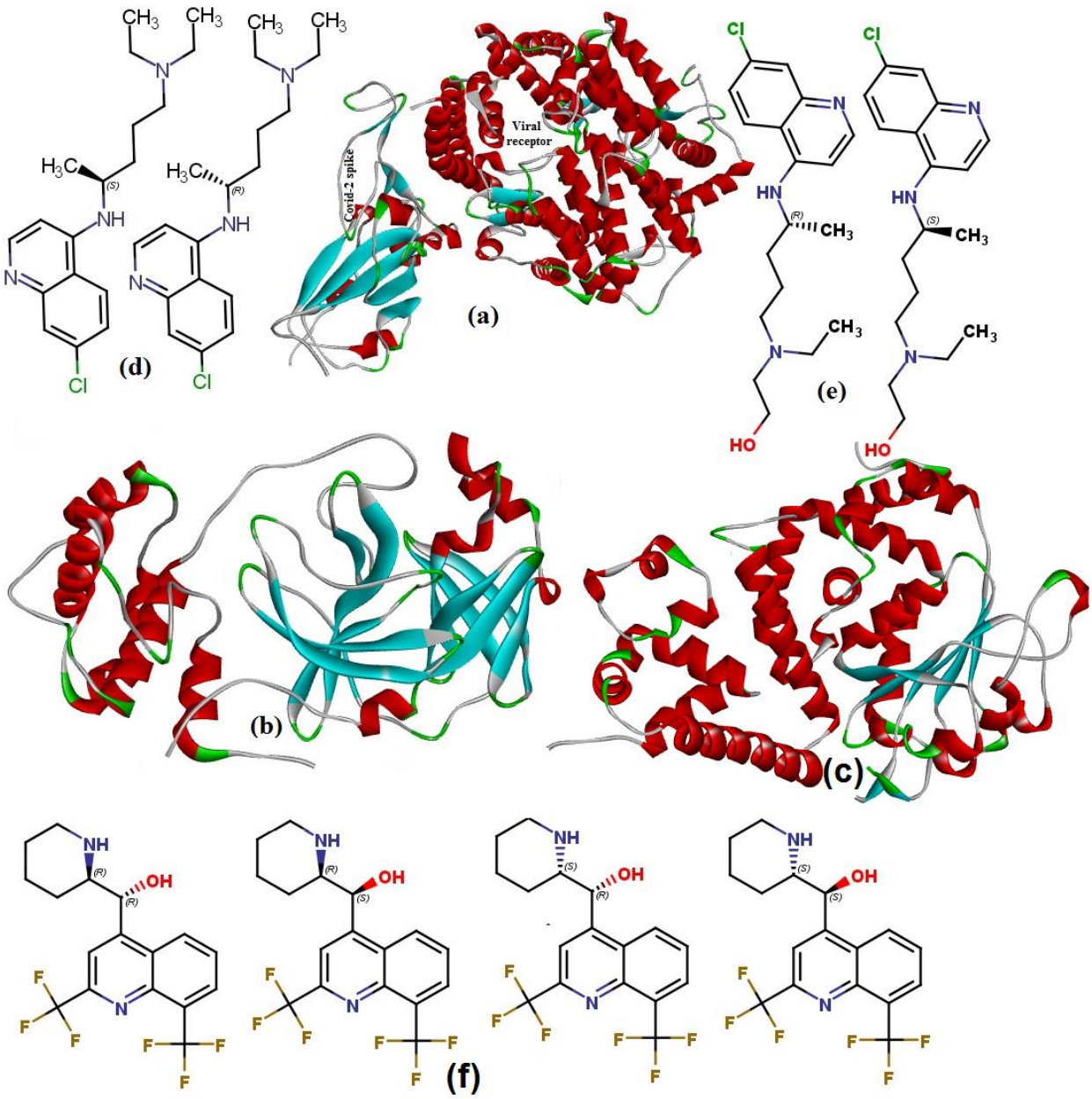


Figure 7: Structures of three-dimensional (a) Covid-2 spike with its receptor, (b) SARS-CoV-2 main protease (M^{pro}) and (c) JC virus main protease (M^{pro}) & (d) chloroquine (e) hydroxychloroquine and (f) Mefloquine.

Table 1. The simulation studies of different enantiomeric interactions of chloroquine, hydroxychloroquine and mefloquine with their targets.

Targets (pdb code)	Chiral drugs	Enantiomers	Binding affinities	No. of H-bond	Residues involved in H-bonding (Bond length in A°)	Residues involved in hydrophobic interaction
Covid-2 spikes with its receptor (6LZG) (A)= viral receptor	Chloroquine	R	-4.2	Nil	-	Ala 533(A)::C1,C4,C14&N3 Asn546(A)::C1,C7,C12,C13&N2 Asp543(A)::C6,C10,C11&C14 His535(A)::C5,C6&C14 Lys416(A)::C4,C5,C6,C11,C15 Lys534(A)::C4,C16&C18 Ser545(A)::C2,C10,C11&C13 Ser(A)::C1&C3
		S	-4.2	1	.268/A/GLU`536/O & H of -NH- group (2.3)	Ala 533(A)::C1,C7&C12 Asp543(A)::C3 His535(A)::C1,C2,C6&C14 Lys416(A)::C1,C2,C3,C4,C8,C9&N1 Ser545(A)::C2,C10,C11&C13 Glu430(A)::C9&C17 Glu536(A)::C10&C11
	Hydroxychloroquine	R	-4.2	3	.268/A/ASP`543/O & H of -NH- group (2.3) .229/A/GLU`536/N & O of -OH group (3.1) .227/A/HIS`535/ND1 & O of -OH group (3.2)	Ala 533(A)::C1,C3,C5&C13 Asn546(A)::C1,C7,C11,C12C14&N2 His535(A)::C6&O Lys416(A)::C3,C4,C6&C10 Lys534(A)::C5 Ser545(A)::C2,C9&C10 Ser547(A)::C1&C3 Glu536(A)::C15 Glu549(A)::C1
		S	-4.2	Nil	-	Ala 533(A)::C5&C10 Asn546(A)::C4&C6 His535(A)::N2 Lys416(A)::C2,C9,C10,C12,&C14 Lys534(A)::C8,C11&C12 Ser545(A)::C4,C6&C13 Ser547(A)::C5&C17 Glu536(A)::C11 Glu549(A)::O
JC Virus M^{pro} (5j40)	Mefloquine	RR	-3.6	2	.647/A/ASP`343/OD2 & H of -OH group (2.0) .218/A/SER`336/OG & H of -NH- group (3.4)	Gln 339(A)::O Gln340(A)::C2&C5 Ser336(A)::N2 Trp271(A)::C2&C6 OD2::C8,C14&C13
		RS	-3.5	Nil	-	Asn333(A)::C2,C6,C10,C11&C16 Asp343(A)::C3&C7 Ser336(A)::O Trp271 (A)::C12,C17&N2

						OG::C1,C4,C5&C13
		SR	-3.5	2	.647/A/ASP`343/OD2 & H of -OH group (1.9) .218/A/SER`336/OG & H of -NH- group (3.4)	Gln 339(A)::O Gln340(A)::C2&C5 Ser336(A)::N2 Trp271(A)::C2&C6 OG::13&C18 OD2::C14
		SS	-3.6	1	.218/A/SER`336/OG & H of -OH group (2.4)	Asn333(A)::O Gln340(A)::C2 Ser376(A)::C10,C13&O Trp271(A)::C3C7C14&C16
SARS-CoV-2 M^{pro} (6m03)	Mefloquine	RR	-6.8	2	.268/A/LEU`287/O & H of -NH- group (2.3) .190/A/TYR`239/OH & H of -OH group (2.5)	Leu 287(A)::C2,C5,C13&O Leu 286(A)::C2,C3,C5&C8 Tyr 239(A)::O Tyr 237(A)::C17 Met276(A)::C2 Thr199(A)::O
		RS	-7.0	Nil	-	Tyr 239(A)::O Tyr 237(A)::C2,C5,C6,C10 &C16 Thr199(A)::N1&O
		SR	-7.2	1	.190/A/TYR`239/OH & H of -OH group (2.6)	Leu 287(A)::C8,C10,C14,C15, C16&C18 Tyr 239(A)::O Tyr 237(A)::C17 Asp289(A)::C16 Thr199(A)::C16&O
		SS	-7.3	1	.190/A/TYR`239/OH & H of -OH group (2.5)	Leu 287(A)::C8,C10,C18&O Tyr 239(A):: O Tyr 237(A):: C2&C17 Asp289(A)::C16 Thr199(A)::C3,C7,C14,C16& O