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Computational screening and identifying binding interaction of anti-viral and anti-malarial drugs: Toward the potential cure for SARS-CoV-2.

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Abstract: Since the emergence of 2019 novel coronavirus (also known as SARS-CoV-2) to date, effective treatment for the patients was reported to be some anti-viral for flu and HIV-1 or anti-malaria drugs. To understand the finer details of the molecular interactions and complexation between these proteinase inhibitors and the COVID-19, virus sequence analysis in comparison to SARS coronavirus and molecular docking were carried out. Results showed favourable binding for the current treatment of drugs and 7 additional possible effective drugs, DB06290 (Simeprevir, Hepatitis C drug), DB09183 (Dasabuvir, Hepatitis C drug), DB01232 (Saquinavir, HIV-1 drug), DB00254 (Doxycycline, Malaria drug), DB01117 (Atovaquone, Malaria drug), DB04835(Maraviroc, HIV-1 drug), DB08930 (Dolutegravir, Hepatitis C drug) with good binding affinities towards COVID-19 in the range of -8.7 to -8.0 kcal/mol. Analysis of the interaction residues of the docked complex was mapped in a 2D diagram to explain the interaction with the proteinase binding pocket. Repurposed drugs from our recommendation may help battle the new coronavirus and subject for additional examination.

Keywords: *SARS-CoV-2; Anti-viral; HIV-1, Anti-malaria; COVID-19, Molecular Docking*

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Introduction

Novel coronavirus 2019-CoV poses a very grave threat to the global community. The Chinese authorities are scrambling to find the mysterious cause of this virus that emerged in early December 2019[1]. Cluster cases of coronavirus-induced pneumonia was notified to World Health Organization (WHO)'s Chinese office on 31st December 2019, which resulted in closing of Huanan Seafood Wholesale Market on 1st January 2019[1]. On 11th February 2020, WHO officially named this virus as COVID-19 [2].

The COVID-19 shares the similar coronavirus family tree with Severe Acute Respiratory Syndrome (SARS) that infected 8,096 people and 744 deaths in 2002–2003[3]. There are several genome sequence of COVID-19 that been deposited on GenBank and Global Initiative on Sharing All Influenza data (GISAID)[4,5]. The sequence information revealed COVID-19 belongs to betacoronavirus originated from bats. However, the exact wildlife host as virus reservoir is yet to be confirmed as many live animals were sold at the market, where the virus originated and transmitted[6,7]. There is an ongoing debate on possible wildlife host, either bats or snakes based on the complete genome analysis. Recently, scientist reported

that pangolins could act as intermediate host to pass the virus to humans. Its science is still suggestive rather than conclusive[8].

COVID-19 has emerged into an epidemic that paralyzed many provinces in China, and still on rise. Wuhan and several other cities across China were completed lock-down with aim to control and contain the spread of the virus[9]. This fast-spreading COVID-19 has claimed 1115 lives and infected over 80,000 people in 37 countries (as of 25th February 2020)[10]. Hubei, the worst hit province in China recorded over 64,000 infected cases and 2560 death[11]. In Thailand, a total of 37 infected cases have been detected and 21 patients recovered from the virus infection. The virus has a transmission rate (Ro) of 3 (2–3 newly infected from 1 case) with 2% fatality rate (CFR)[11]. While parts of China begin to lower their emergency response level, the coronavirus is spreading more quickly to other parts of the world, Middle East, Europe, Latin America. More deaths have been reported in Iran and Italy[13–14]. In addition, experts have declared 24 days incubation period for COVID-19 rather than the previously believed 14 days, based on the clinical symptoms presented by the patients[12].

The community raises concern on COVID-19 as transmission to other countries besides China is mainly by people who had travelled from outbreak area or had close contact with an infected person. The Chinese along with WHO implemented precaution measures to control the spread of this virus. In the process of rapid identification, BGI Group has been granted the approval to manufacture and sell two virus detection kits and a sequencing system[15]. The community too are aware of the precaution and hygiene measures to avoid been infected with COVID-19.

Now researchers and scientists are racing against time to discover an effective drug or vaccine to treat the flu caused by this coronavirus. Doctors in Thailand reported to have successfully treated a 71-year-old patient with a cocktail of antivirals that are used to treat flu (oseltamivir) and HIV (lopinavir and ritonavir)[16]. Malaysia also has some cases which cured patients with treatment of antiviral medicine, Kaletra (a commercial name for lopinavir)[17]. Likewise, in the United States (US), doctors administrated remdesivir to treat a 35-year-old patient and his symptoms improved. Remdesivir is a Gilead Sciences drug that been used for emergency treatment of patients with Ebola[18]. Further tests should be done in order to confirm the effectiveness of these antivirals.

Virtual *in silico* screening has repeatedly proven to be useful to meet the special challenges of antiviral drug discovery (Figure 1). Recently, four antiviral drugs (Nelfinavir, oseltamivir, lopinavir, ritonavir)[19,20] and antimalaria drug, Chloroquine Phosphate, have been reported to be effective[21]. A combination of HIV (lopinavir and ritonavir) and flu (oseltamivir, commercial name as Tamiflu) drugs for the treatment of patients infected with the new coronavirus has been used at Rajavithi Hospital in Bangkok, Thailand and gives a better outcome.

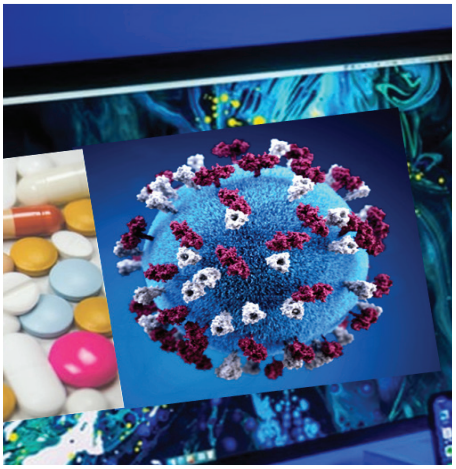


Figure 1. Modern drug discovery using in silico screening techniques in the search of anti-viral and anti-malarial drugs for COVID-19 (created from royalty free images from https://www.shutterstock.com/).

Our previous work on severe acute respiratory syndrome (SARS) during the outbreak in 2003 indicated the primary key enzyme, coronavirus proteinase, to be a good target for designing and screening for anti-SARS drug[22]. In this paper we compare the genetic sequence of SARS-CoV and COVID-19 main proteinase and explored the potential uses of anti-viral and anti-malarial approved FDA drugs to gain insights and understanding on the binding interactions for COVID-19.

Methods

Computational details

Protein target and drug models

The crystal structure of 2019-nCoV main proteinase in complex with a peptide-like inhibitor N3 (PDB ID: 6LU7) and the structure of SARS Coronavirus (SARS CoV) Main Proteinase (PDB ID: 1Q2W) were retrieved from protein databank. Protein X-ray crystal structures were first prepared under Discovery Studio programme v4.5 (Accelrys Inc., San Diego, CA, USA), with heteroatoms including waters and ions removed. Missing residues, ^{45}TAED^{48} in chain A and ^{46}AEDMLN^{51} in chain B of SARS proteinase were added to close the gap. Proteins were then minimized with 500 steps of steepest descent and 500 steps of conjugate gradient in the presence of water and ions using AMBER14 forcefield[23].The protein sequence were analyzed using Discovery Studio programme v4.5 and the protein conformational dynamics based on contact topology in a coarse-grained presentation were compared using Gaussian Network Model (GNM, http://enm.pitt.edu/)[24–26] to observe overall protein flexibility.

49 Approved FDA anti-viral drugs (Table 1), 2 experimental anti-viral drugs (Table 1), and 16 anti-malarial drugs (Table 2) in 3D-SDF file format were downloaded from DrugBank[27] for screening. Drug models were retrieved from protein databank (PDB) if no available 3D-SDF file was found in DrugBank database.

Molecular docking and Interaction analysis

Molecular docking was performed with local search algorithm using Autodock Vina in PyRx virtual screening software (http://pyrx.scripps.edu/). PyRx with easy-to-use user interface can be used to screen libraries of compounds for computational drug discovery against potential drug targets and enables to run in any platform and helps users in every step of the drug discovery process - from data preparation to job submission and analysis of the results. The amino acid binding site located at His41 and Cys145 was selected as the binding center with the box size about 30.0 x 40.0 x 30.0 Å. The Ghemical force field is similar to the Tripos-5.2 force field method which performs acceptably on providing geometries of organic-like molecules. The docked complex is then mapped to clarify the interacting residues using PoseView[28] (Wallace AC, 1995).

Table 1. Details on antiviral FDA approved drugs in this study.

DrugBank ID	Drug name	Target
DB00194	Vidarabine	Human Herpesvirus 1, Human Herpesvirus 3, Human Herpesvirus 4
DB00198	**Oseltamivir**	**Influenza A Virus, Influenza B Virus**
DB00220	**Nelfinavir**	**Human Immunodeficiency Virus 1**
DB00224	Indinavir	Human Immunodeficiency Virus 1, Human T-Lymphotropic Virus 1
DB00238	Nevirapine	Human Immunodeficiency Virus 1
DB00249	Idoxuridine	Human Herpesvirus 1
DB00299	Penciclovir	Human Herpesvirus 1
DB00369	Cidofovir	Human Herpesvirus 5
DB00426	Famciclovir	Human Herpesvirus 1, Human Herpesvirus 3
DB00432	Trifluridine	Human Herpesvirus 1
DB00442	Entecavir	Hepatitis B Virus
DB00478	Rimantadine	Influenza A Virus
DB00495	Zidovudine	Human Immunodeficiency Virus 1
DB00503	**Ritonavir**	**Human Immunodeficiency Virus 1**
DB00529	Foscarnet	Human Herpesvirus 1, Human Herpesvirus 5
DB00558	Zanamivir	Human Parainfluenza Virus 3, Influenza A Virus, Influenza B Virus
DB00577	Valaciclovir	Human Herpesvirus 1
DB00625	Efavirenz	Human Immunodeficiency Virus 1
DB00649	Stavudine	Human Immunodeficiency Virus 1
DB00701	Amprenavir	Human Immunodeficiency Virus 1, Human Immunodeficiency Virus 2
DB00705	Delavirdine	Human Immunodeficiency Virus 1
DB00709	Lamivudine	Hepatitis B Virus, Human Immunodeficiency Virus 1
DB00718	Adefovir Dipivoxil	Hepatitis B Virus
DB00787	Aciclovir	Human Herpesvirus 1, Human Herpesvirus 3
DB00811	Ribavirin	Hepatitis C Virus, Human Parainfluenza Virus 2, Influenza A Virus, Influenza B Virus, Respiratory Syncitial Virus
DB00879	Emtricitabine	Human Immunodeficiency Virus 1
DB00900	Didanosine	Human Immunodeficiency Virus 1
DB00915	Amantadine	Influenza A Virus
DB00943	Zalcitabine	Human Immunodeficiency Virus 1
DB01004	Ganciclovir	Human Herpesvirus 1
DB01048	Abacavir	Human Immunodeficiency Virus 1
DB01072	Atazanavir	Human Immunodeficiency Virus 1
DB01232	Saquinavir	Human Immunodeficiency Virus 1
DB01264	Darunavir	Human Immunodeficiency Virus 1, Human Immunodeficiency Virus 2
DB01265	Telbivudine	Hepatitis B Virus
DB01319	Fosamprenavir	Human Immunodeficiency Virus 1
DB01601	**Lopinavir**	**Human Immunodeficiency Virus 1**
DB01610	Valganciclovir	Human Herpesvirus 5
DB04835	Maraviroc	Human Immunodeficiency Virus 1
DB05521	Telaprevir	Hepatitis C Virus, Respiratory Syncitial Virus
DB06290	Simeprevir	Hepatitis C Virus, Respiratory Syncitial Virus
DB06414	Etravirine	Human Immunodeficiency Virus 1
DB06614	Peramivir	Influenza A Virus, Influenza B Virus
DB06817	Raltegravir	Human Immunodeficiency Virus 1
DB08864	Rilpivirine	Human Immunodeficiency Virus 1

DB08873	Boceprevir	Hepatitis C Virus, Respiratory Syncitial Virus
DB08930	Dolutegravir	Human Immunodeficiency Virus 1
DB08934	Sofosbuvir	Hepatitis C Virus, Respiratory Syncitial Virus
DB09183	Dasabuvir	Hepatitis C Virus
DB12466	**Favipiravir**	**Experimental, Novel coronavirus**
DB14761	**Remdesivir**	**Experimental, Novel coronavirus**

Note:*The drugs in highlighted were reported as the current treatment for patients infected with the novel coronavirus.*

Table 2. Details on 16 current anti-malarial FDA approved drugs recognized in Plasmodium falciparum.

DrugBank ID	Drug name	Drug class
DB00205	Pyrimethamine	Diazines
DB00207	Azithromycin	Macrolides and analogues
DB00254	Doxycycline	
DB00358	Mefoquine	Quinolines and derivatives
DB00468	Quinine	Cinchona alkaloids
DB00608	**Chloroquine**	Experimental, Novel
DB00613	Amodiaquine	Coronavirus
DB00759	Tetracycline	Tetracyclines
DB00908	Quinidine	Cinchona alkaloids
DB01087	Primaquine	
DB01117	Atovaquone	Naphthalenes
DB01131	Proguani,	Diazines
DB01190	Clindamycin	Carboxylic acids and derivatives
DB01218	Halofantrine	Phenanthrenes and derivatives
DB01299	Sulfadoxine,	Benzene and derivatives
DB13132	Artemisinin	Lipids and lipid-like molecules

Note: *The drug in highlighted was reported as the current treatment for patients infected with the novel coronavirus.*

Results and discussion

Sequence alignment of SARS CoV and COVID-19 proteinase were shown in Figure 2 beginning from amino acids residue 3 to 301 and 1 to 306, respectively. Three-dimensional structures superimposed in Figure 3 indicated twelve different positions in amino acids sequence between SARS CoV and COVID-19 proteinase. These positions involve three polar, seven non-polar, two +charge and one -charge amino acids. There is a change in amino acid residue in the binding pocket from alanine (nonpolar in SARS CoV) to serine (polar in COVID-19) at position 46. Several other positions would be less electrostatic owing to replacement of polar by nonpolar group e.g. threonine to valine at residue 35, serine to alanine at residue 94, histidine to phenylalanine at residue 134, and threonine to alanine at residue 285.

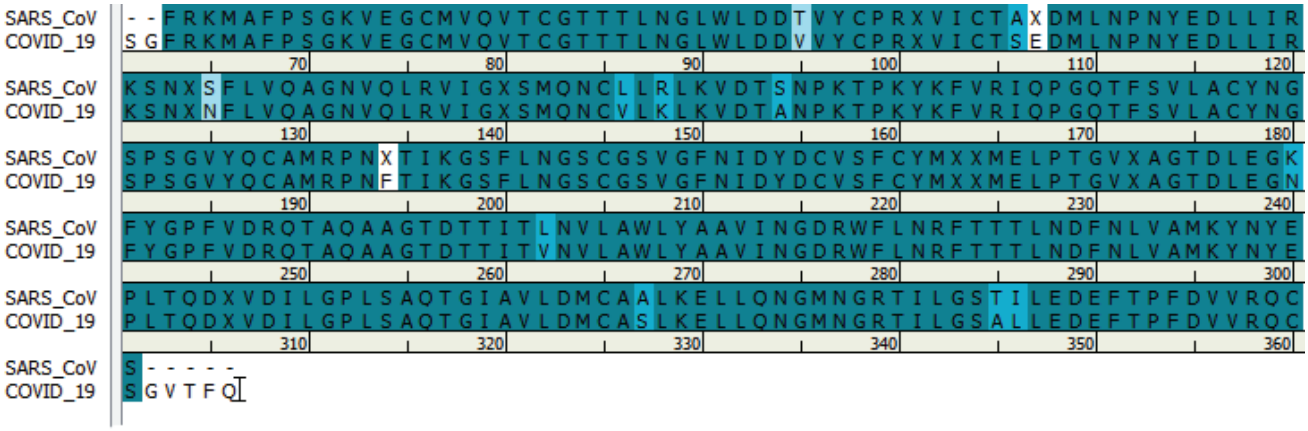
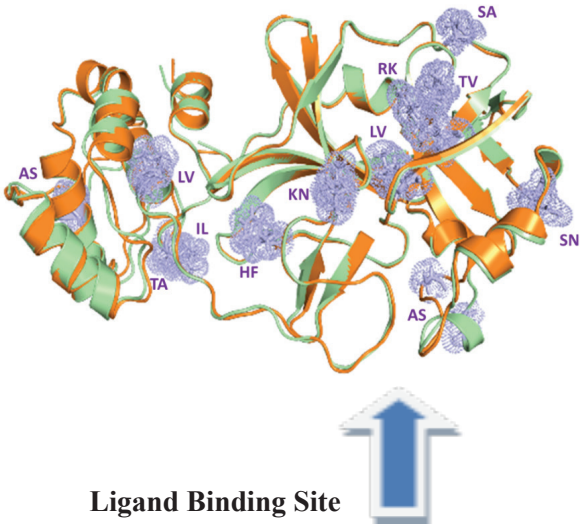


Figure 2. Sequence alignment of proteinase of SARS and COVID-19. Image was generated by Discovery Studio v4.5 where X at the position 46 is protonated glutamine and at the position 136 is Histidine residue

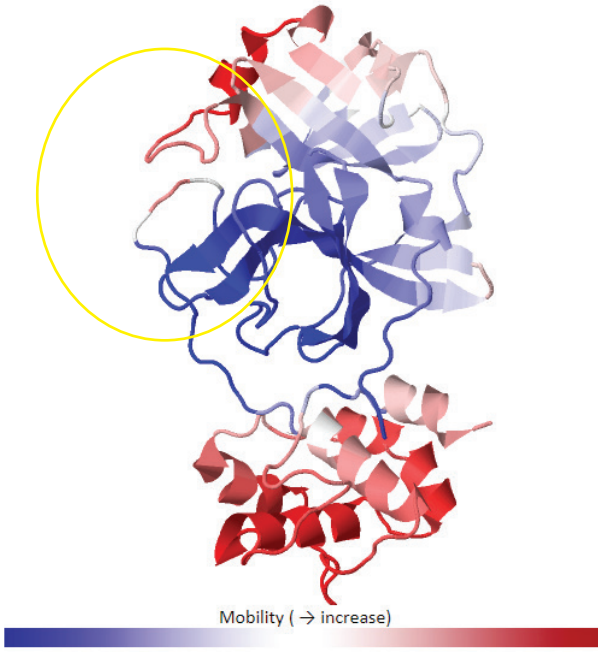


Position	SARS-CoV proteinase	COVID-19 proteinase
35	T	V
46	A	S
47	H	E
65	S	N
86	L	V
88	R	K
94	S	A
134	H	F
180	K	N
202	L	V
267	A	S
285	T	A
286	I	L

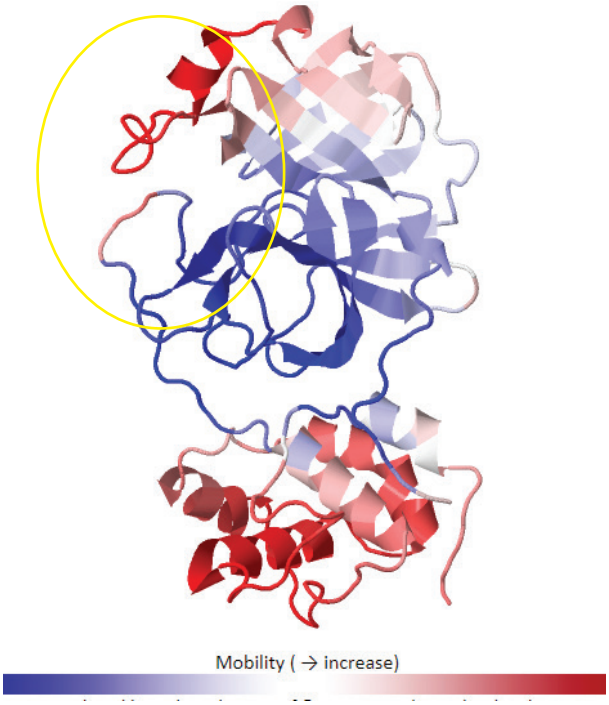
Polar, nonpolar, +charge, -charge

Figure 3. Superimposed proteinase of COVID-19 proteinase (cyan green) to SARS CoV proteinase (orange). Positions of amino acids varied in the two proteinase were surrounded by dots with the amino acids side chain showed in stick model. Amino acids letter code described the change of amino acids, of SARS CoV proteinase to COVID-19 proteinase. Image was generated by Pymol.

In agreement with the GNM model, the binding site of SARS-CoV and COVID-19 proteinase exhibited different flexibilty. Mean-square fluctuation of residues can be predicted from theoretical B-factor (Å^2) in Figure 4. COVID-19 have higher flexibility in the binding site than SAR-CoV. Different activity of drugs could be observed due to this difference in binding toward the binding pocket.



SARS-CoV proteinase



COVID-19 proteinase

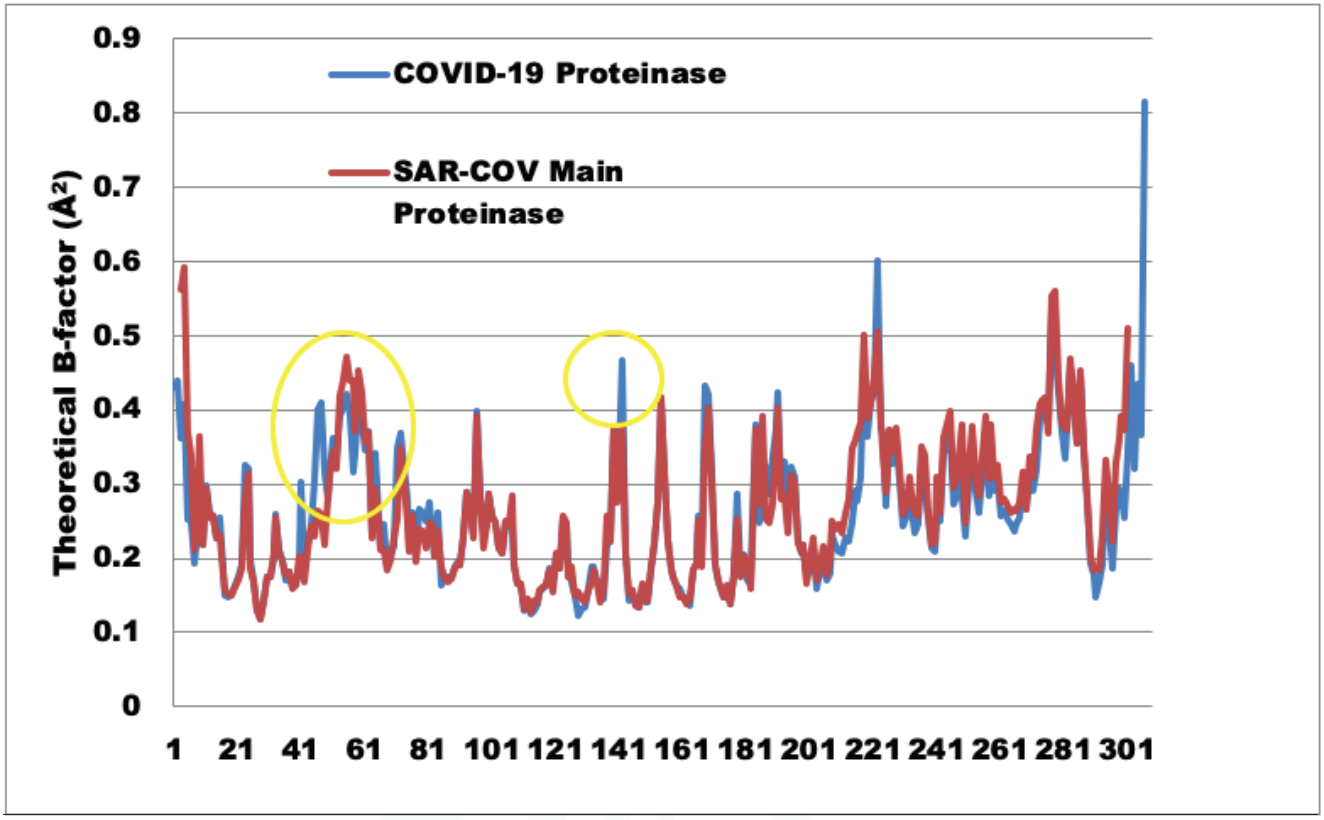


Figure 4. Theoretical B-factor indicate the mean-square fluctuation of residues. His41 and Cys145 are the binding site centre and circled in yellow.

Table 3. Docking study of 67 approved drugs against COVID-19 proteinase.

Ligand	Lowest Binding Energy (kcal/mol)	Ligand	Lowest Binding Energy (kcal/mol)
Strong Interaction		**Weak Interaction**	
DB01601	**-8.7**	DB00705 DB00718 DB01319	-6.9
DB06290 DB09183	-8.4	DB06414	-6.8
DB01232	-8.2	DB00442 DB00900 DB01048 DB00468	-6.7
DB00220 **DB14761** DB00254 DB01117	**-8.1**	DB01610 DB00908	-6.6
DB04835 DB08930	-8.0	DB00577 DB08873 DB13132	-6.5

DB00224 DB06817	-7.9	DB00787 DB00613 DB01299	-6.4
DB08864	-7.8	DB00426 DB00432 DB00558 DB00811 DB00207 DB01131	-6.3
DB01264 DB00759	-7.7	DB00194 DB00299 DB00495	-6.2
DB08934	-7.3	DB00238 DB01004 DB01190	-6.1
DB01072 DB05521	-7.2	DB00625 DB01087	-6.0
DB00503 DB00701 DB00358 DB01218	**-7.0**	**DB00198** DB00369	**-5.9**
		DB00943	-5.8
		DB01265 DB00205	-5.7
		DB00249 DB00879	-5.5
		DB06614 **DB00608**	**-5.4**
		DB00649 DB00709	-5.3
		DB12466	**-4.9**
		DB00478	-4.8
		DB00915	-4.4
		DB00529	-4.3

Note: The drugs in highlighted were reported as the current treatment for patients infected with the novel coronavirus.

In consideration of intermolecular interactions in drugs against COVID-19 proteinase, results from the Autodock Vina using local search algorithm for virtual screening are shortlisted based on the lowest docking energy score along with the capability of the drug making a chemical interaction with the His41 and Cys145 (Table 3 & Figure 5) . Among effective approved drugs in this virtual screening, antiviral lopinavir (DB01601) bound best toward COVID-19 proteinase with a promising lowest binding energy of -8.7 kcal/mol, followed by Nelfinavir (DB00220), Remdesivir (DB14761), Ritonavir (DB00503), respectively. However, Oseltamivir (DB00198), Chloroquine (DB00608) and Favipiravir (DB12466) considered having a weaker interaction with respect to binding site. Their effectiveness may be due to the interaction with other receptor targets.

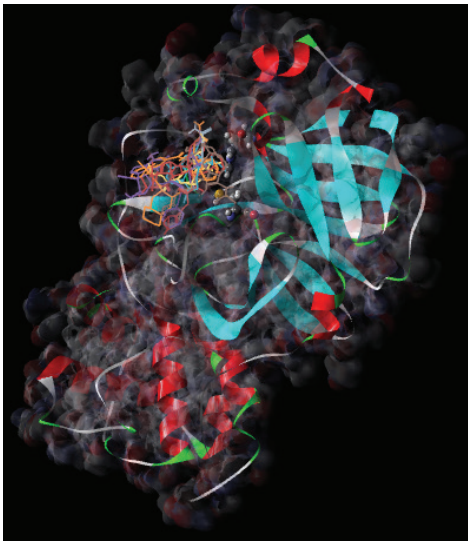


Figure 5. Seven current treatment drugs; lopinavir (DB01601, orange), Nelfinavir (DB00220, grey), Remdesivir (DB14761, purple), Ritonavir (DB00503, pink), Oseltamivir (DB00198, yellow), Chloroquine (DB00608, blue) and Favipiravir (DB12466, white). in stick model in binding with the binding pocket of COVID-19 proteinase. His41 and Cys145 binding site were in ball and stick model.

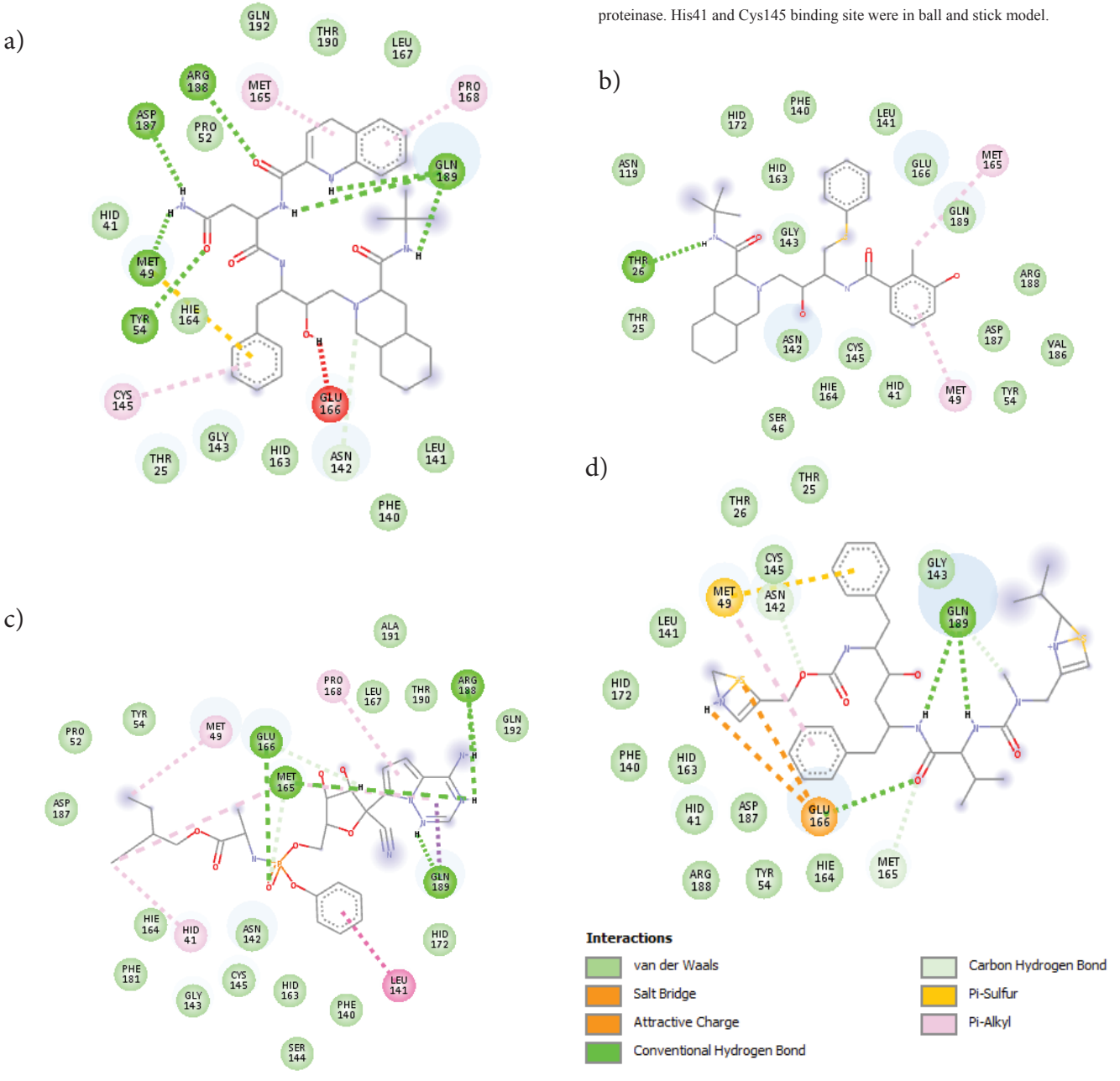


Figure 6. Schematic representation of the binding interactions between COVID-19 proteinase and a) Lopinavir (DB01601), b) Nelfinavir (DB00220), c) Remdesivir (DB14761) and d) Ritonavir (DB00503) (within 4.0 Å). Hydrogen bonds interactions are depicted with green dotted lines.

To explore contributing interactions in the active sites of high potent drugs, the possible binding interactions between COVID-19 proteinase and currently used antiviral drugs lopinavir (DB01601), Nelfinavir (DB00220), Remdesivir (DB14761) and Ritonavir (DB00503) were mapped into 2D diagram using PoseView as shown in Figure 6. Residues i.e., Thr26, Met49, Tyr54, Met165, Glu166, Asp187, Arg188 and Gln189 were involved in hydrogen bonding whereas residues such as His41, Met49, Cys145, Met165 and Pro168 were contributed to to alkyl and pi-alkyl interactions. Additionally, the analysis have indicated that some *van der Waals* interactions were found between these drugs and the binding residues Thr25, Thr26, His41, Ser46, Tyr54, Pro52, Asn119, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, His172, Leu167, Phe181, Val186, Asp187, Arg188, Thr190, Ala191 and Gln192. Further investigations using PoseView (Figures are not shown) have revealed that residues such as Thr25, Met49, Leu141, Glu166, Met165, Met168, Asp187 and Gln189 were due to non-polar interactions. Based on these observations, 7 new potential drug candidates, DB06290 (Simeprevir, Hepatitis C drug), DB09183 (Dasabuvir, Hepatitis C drug), DB01232 (Saquinavir, HIV-1 drug), DB00254 (Doxycycline, Malaria drug), DB01117 (Atovaquone, Malaria drug), DB04835(Maraviroc, HIV-1 drug), DB08930 (Dolutegravir, Hepatitis C drug) which have the favourable interactions similar to the current treatment drug (< -8.0 kcal/mol) can be further studied experimentally.

Conclusion

In order to search for potent COVID-19 drugs, molecular docking studies of 67 approved drug were explored and preliminary results show that the binding affinities for current treatment drug toward coronavirus proteinase were -8.7 to -4.9 kcal/mol. Sequence alignment and binding site flexibility indicate the different binding mode of interaction between SARS-CoV and COVID-19. From our results, lopinavir bound best to COVID-19 protienase and *in silico* screening suggests seven more potential FDA approved drugs for HIV-1, hepatitis C and malaria which can be repurposed and further investigated experimentally.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgements

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