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Simeprevir, potential candidate to repurpose for coronavirus infection: Virtual screening and molecular docking study

Faezeh Sadat Hosseini[a], Massoud Amanlou[a,b*]

[a] Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

[b] Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Coronavirus disease 2019 (COVID-19) has been first appeared in Wuhan, China but its fast transmission, led to its widespread prevalence in various countries and make it a global concern. In addition, lack of a definitive treatment is another concern that needs to be attention. Researchers have come up with several options, which are not certain, but protease inhibitor and some antiviral agent are in the forefront. In this study a virtual screening procedure employing docking of different databases including 1615 FDA approved drugs was used to identify new potential small molecule inhibitors for protease protein of COVID-19. The docking result indicates that among all, simeprevir (Hepatitis C virus (HCV) NS3/4A protease inhibitor) could fit well to the binding pocket of protease and because of some other positive features including ADME profile, might be a helpful treatment option for COVID-19.

Keyword: COVID-19, Simeprevir, Protease inhibitor, Virtual screening, Docking

***Corresponding author:**
Massoud Amanlou,
ORCID: 0000-0002-8559-1668
Tel: +98 21 66959067; Fax: +98 21 64121111
E-mail: amanlou@tums.ac.ir

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Introduction

Novel coronavirus, designated as COVID-19, was first identified in December 2019 in Wuhan, China [1]. COVID-19 is belongs to the Coronaviridae (CoV) family, enveloped positive-sense, single-stranded RNA viruses (+ssRNA) that are spread broadly among humans and other mammals that cause a wide range of infections from common cold symptoms to fatal disease like respiratory syndrome. The CoV genome is constantly changing due to the mutation processes such as insertion or deletion and recombination, therefore COVID-19 is considered distinct from two high pathogenic SARS-CoV and MERS-CoV which are responsible for Severe Acute Respiratory Syndrome in 2002 and Middle East Respiratory Syndrome in 2012 respectively [2]. The fatality rate of this new CoV, seems to be around 2 percent in China [3], which is much less than fatality rate of SARS and MERS. It should be consider that most of the fatal cases are vulnerable populations with medical condition such as immunosuppression, diabetes or heart disease. But the point that has made it the global concern is the efficient transmission from human-to-human leading to its widespread outbreaks in many countries around the world [4].

Up to now, there is no FDA-approved or specific treatment for COVID-19 infection. Clinical guidance of World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) include a prompt supportive care like oxygen therapy, fluid management, empiric antimicrobials (in case of sepsis) and others [5]. Investigational agents reported some potential therapy for COVID-19 such as remdesivir or chloroquine [6] and combined protease inhibitor lopinavir-ritonavir [7] which are previously used to treat against SARS and MERS-CoV but their efficacy is still unclear and need further evaluation. Therefor one of the most important receptors considered as an inhibitory target is the protease, which cleaves the polyproteins into smaller fragments that are necessary for transcription replication. [8] However finding a cure can still be a great help to the international community. In the

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current crisis, in order to achieve the fast and reliable drug, we decided to rely on repurposing concept and consider available FDA-approved drug for use in this disease.

In this regard, virtual screening procedure, employing docking of 1615 FDA-approved drug over binding pocket of protease protein of COVID-19 has been done to find potential small molecule inhibitors to combat the COVID-19 outbreak.

Methods

In order to achieve the mode of interaction of FDA-approved drug with the binding pocket of COVID-19 protease, molecular docking simulations were performed. The newly released crystal structure of COVID-19 main protease as a receptor was retrieved from protein data bank (www.rcsb.org) with PDB ID: 6LU7. AutoDockTools (ADT, Ver.1.5.6) [9] was used for preparation the input files and analyzing the result. For preparation of protein input files, all water molecules, ligands and ions were removed from pdb file. Then polar hydrogens were added and the Kollman-united charge was used to calculate the partial atomic charge and prepared file was saved in pdbqt format to use in following steps.

3D structures of FDA-approved drugs were downloaded from Zinc database [10] in structure-data file (SDF) format which contains 1615 compounds. Then OpenBabel (version 2.3.1) [11] was used to convert SDF to pdb format. Rotatable bonds and Gasteiger-Marsili charges were assigned to all ligands and saved in pdbqt for further docking process using AutoDock 4.2. A 50×50 ×50 Å (x, y, and z) grid box was centered on the protease binding pocket with a 0.375 nm spacing for each dimension. AutoGrid 4.2 was used to prepare grid maps. Docking parameters were set as following: number of Lamarckian job = 40, initial population = 150, maximum number of energy evaluation = 2.5×10^5, other parameters were set in their defaults value and finally docking was performed by AutoDock 4.2.

All docking results were sorted by the binding energy. Docking procedures were done automatically by scripts written in-house. In addition docking validation was carried out using previously published methods [12] with re-docking of co-crystal structure as an inhibitor in main protease of COVID-19

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with above mentioned parameters and values. Visualization of docking results has been done by Discovery Studio visualizer version 17.2 [13] and Pymol version 1.1evel. [14]

Result and discussion

In an attempt to finding potential treating for COVID-19, molecular docking simulation were performed over 1615 FDA-approved drug on the binding pocket of protease protein which play an integral and pivotal role in propagating the virus. Through docking method all compound were compared with each other and the result were sorted from lowest to highest binding energy. In the following the first 25 compounds with lowest binding energy and the highest affinity to the receptor, with cut-off energy -9.5 kcal/mol, were chosen to further investigation. All compounds were evaluated for their clinical applications.

According to the reported by WHO and CDC, COVID-19 mostly affects the respiratory system and leading to the symptoms such as fever, cough and shortness of breath. Therefore, the compounds with specifically effect on other systems like nervous system and skin were omitted (Perampanel, thiothixene and ergotamine). Corticosteroid compounds were omitted because of the special alert by CDC about using them for treatment of viral pneumonia which has no effectiveness and possible harm. Some drugs were ignored because of their side effect (Conivaptan and daunorubicin). As a result, there were 10 compounds left after applying this filter which are listed in Table 1.

In should be mentioned that the ideal compounds are those that could fit well to the binding site with the lowest binding energy. Base on the table provided (Table 1), paclitaxel indicate the great affinity to the binding pocket of protease protein but sometimes, patient condition, does not allow the use of such medicines, in this case, the side effect of bone marrow suppression, lead to a worsening of the condition of the patient which required his strong immune system to overcome the COVID-19.

The same can be said for the rest anticancer such as: Docetaxel, palbociclib, cabazitaxel, imatinib, alectinib and plerixafor. About azelastin it has to be said that it could useful for symptomatic treatment

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of shortness of breath in patient and if it can reach to the protease, make the good interaction and inhibit the protease activity.

Dasabuvir used as chronic Hepatitis C, an infectious liver disease that make the polymerase unable to elongate viral RNA therefore it can through cell membrane and reach to the binding pocket it also has no special side effect. And the last but not the least, simeprevir, which is a hepatitis C virus (HCV) NS3/4A protease inhibitor, it's probably best or ideal choice to repurpose for treatment the COVID-19 because of low binding energy -11.33 kcal/mol, common receptor, ability to reaching the target and minor side effects. The docking conformation of simeprevir indicate three hydrogen bonds with Asn119, His163 and Cys145 and two sigma and pi interactions with His41 that could justify its strong binding energy (Fig. 1).

It's remarkable that two HIV protease inhibitor lopinavir-ritonavir, which have been suggested as one of the therapeutic agents of COVID-19 and recent studies, have been cited them as highly effective drugs [7,15-16], showed less binding energy and affinity (-5.36 and -5.04 kcal/mol respectively) than our proposed drug simeprevir (-11.33 kcal/mol). This means that our proposed drug is not only more efficient but also because of the decrease in the number of medications consumed can lead to a decrease unwanted side effect and can be very promising. Hence, the superimpose of these three protease inhibitor are shown in Fig. 2.

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Table 1. 13 potential compounds to treat the COVID-19

No.	**Compound**	**Drug**	**Binding energy (kcal/mol)**	**Usage**	**Administration**	**Side effects**
1	ZINC000096006020	Paclitaxel	-12.31	Kaposi's sarcoma, cancer of the lung, ovarian, and breast.	intravenous	Bone marrow suppression, neurotoxicity
2	ZINC000164760756	Simeprevir	-11.33	Hepatitis C virus (HCV) NS3/4A protease inhibitor	Oral	Fatigue, headache and nausea
3	ZINC000085537053	Docetaxel	-10.64	Breast, ovarian, and non-small cell lung cancer	Intravenous	Bone marrow suppression, neurotoxicity
4	ZINC000003938686	Palbociclib	-10.62	Breast cancer	Oral	Clastogenic
5	ZINC000085536932	Cabazitaxel	-10.53	Prostate cancer	Intravenous	Neutropenia, hypersensitivity reactions
6	ZINC000066166864	Alectinib	-10.49	Non-small cell lung cancer	Oral	Fatigue, constipation, and edema
7	ZINC000019632618	Imatinib	-10.36	Chronic myelogenous leukemia (CML)	Oral	Edema, nausea, vomiting, muscle cramps
8	ZINC000022443609	Plerixafor	-10.15	Non-Hodgkin lymphoma	Subcutaneous	Nausea and vomiting
9	ZINC000000897240	Azelastine	-9.98	Allergic and vasomotor rhinitis	Nasal	Increased drowsiness
10	ZINC000095616937	Dasabuvir	-9.76	Chronic Hepatitis C	Oral	Nausea and insomnia

*All data retrieved from Drug Bank Databases (www.drugbank.ca).

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Chloroquine and hydroxychloroquine, have been used to treat malaria, systemic lupus erythematosus, rheumatoid arthritis, and Q fever, which is effective on the COVID-19 by increasing the endosomal pH which is essential for virus/cell fusion [6, 17]. But, the low binding energy of these drug indicate that they do not interact effectively with the protease in compare with simeprevir. Captopril and enalapril, are also other suggested options, with the assumption that they can inhibit the binding between the COVID-19 and human ACE2, and reduces symptoms of severe pneumonia [18] based on the obtained binding energy, these two drugs are not able to interact properly with the mentioned target.

Finally remdesivir a prodrug of adenosine nucleotide analog, has entered into clinical phases for COVID-19 [19] but is not yet FDA-approved and therefor was reviewed separately. This drug has recently been considered for treatment of COVID-19, with its mechanism of action on viral RNA polymerase and making a mistake in proofreading by viral exoribonuclease (ExoN), which cause a decrease in viral RNA production [20]. The implication stated for the other compounds is also true here, and low binding energy indicates the inability of the compound to interact well with the protease binding pocket. Therefore, it can be concluded that these last five drugs have any effect on the protease and will not lead to drug interactions with our suggested drug simeprevir and they can be used together.

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Table 2. 7 drugs used to treat the COVID-19

No.	**Compound**	**Drug**	Binding energy (kcal/mol)	**Usage**
1	ZINC000003951740	Lopinavir	-5.36	HIV protease inhibitor
2	ZINC000003944422	Ritonavir	-5.04	HIV protease inhibitor
3	ZINC000019144226	Chloroquine	-7.5	Antimalarial agent
4	ZINC000001530654	Hydroxychloroquine	-6.7	Rheumatoid arthritis
5	ZINC000000057001	Captopril	-4.22	Hypertension
6	ZINC000003791297	Enalapril	-5.6	Hypertension
7	-	Remdesivir	-5.8	Antiviral

*All data retrieved from Drug Bank Databases (www.drugbank.ca).

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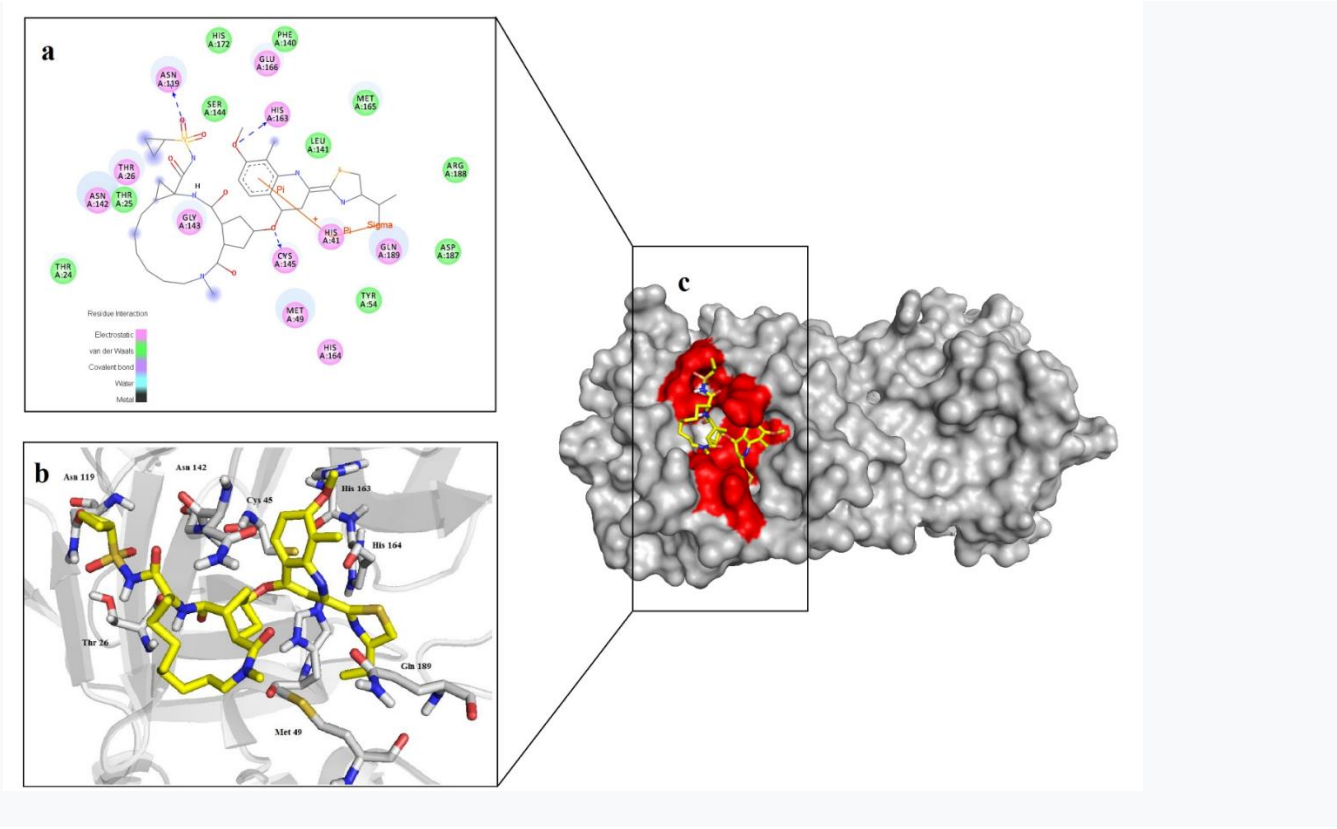

Figure 1. 2D interactions between simeprevir and active site of COVID-19 main protease (a), 3D display of cartoon (b) and surface of protease (c, gray) with simeprevir (yellow).

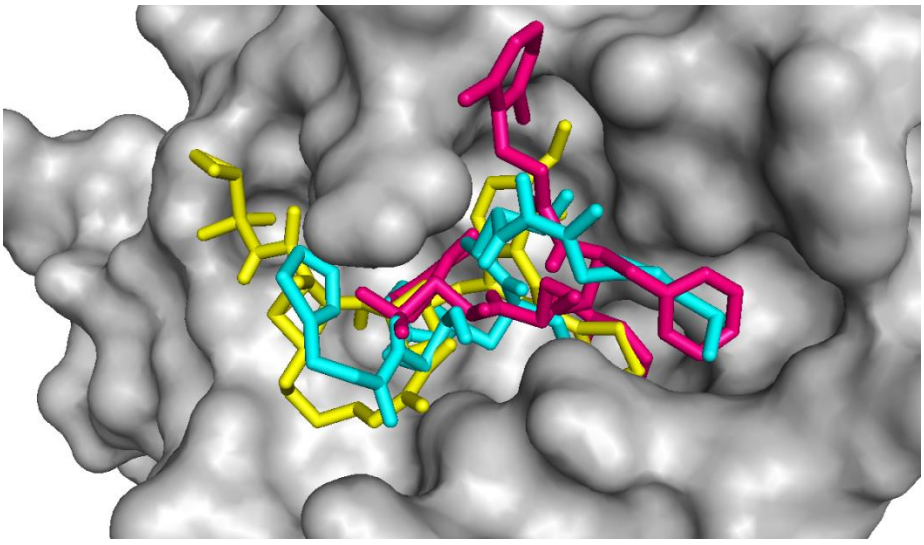

Figure 2. Superimpose of simeprevir (yellow), lopinavir (magenta) and ritonavir (cyan) in the binding pocket of protease

Conclusion

As noted before, COVID-19 has become a global concern, due to widespread outbreaks and lack of treatment. Therefore, it is necessary to find and evaluate treatment methods more quickly in this case computer methods are very effective and helpful. Relying on this topic and repurposing concept, a virtual screening procedure employing docking of 1615 FDA approved drugs was used to identify new potential small molecule inhibitors for protease protein of COVID-19 and the result indicates that between all FDA-approved drug, simeprevir which used for Hepatitis C virus (HCV) NS3/4A protease inhibitor, revealed strong interaction with protease binding pocket and placed well into the pocket even better than the lopinavir-ritonavir, and since this compound is FDA-approved and successfully passed various testing steps, therefor there is a hope that this drug, could be a potential drug to treating the COVID-19.

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Conflicts of Interest: The authors declare no conflict of interest.

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