

Potentially highly effective drugs for COVID-19: Virtual screening and molecular docking study through PyRx-Vina Approach

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ABSTRACT

Introduction: The World Health Organization (WHO) has declared the novel coronavirus (COVID-2019) infection outbreak a global health emergency. Drug repurposing, which concerns the investigation of existing drugs for new therapeutic target indications, has emerged as a successful strategy for drug discovery due to the reduced costs and expedited approval procedures.

Material and Methods: The crystal structure of a protein essential for virus replication has been filed in the Protein Data Bank recently. Based on this structure and existing experimental datasets for SARS-CoV2 (COVID-19) we present results deriving from the virtual screening of a database of more than 1000 drugs in the DrugBank that have been approved by Food and Drug Administration (FDA).

Results: Results showed that some of the known protease inhibitors currently used in HIV and Cancer infections might be helpful for the therapy of COVID-19 also. Results also showed that Levomefolic acid, or vitamin B9, is recommended therapy because of its oral sources and no side effects.

Conclusion: Between all studied FDA-approved drug, VitaminB9 and Etoposide which used for HIV 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, therefore there is a hope that this drug, could be a potential drug to treating the COVID-19.

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INTRODUCTION

A pneumonia of unknown cause detected in Wuhan; China was first reported to the WHO Country Office in China on 31 December 2019. By April 8, 2020, more than one million individuals were infected and more than 82000 fatalities had been reported. The World Health Organization (WHO) has declared this novel coronavirus outbreak a global health emergency. Currently, there is no specific antiviral drug for this epidemic. Considering the severity of this widespread dissemination and health threats, panic patients misled by media flocked to the pharmacies for Chinese Medicine herbs which were reported to “inhibit” the COVID-19, despite no clinical evidence supporting the claim. Many researchers are engaged in developing anti- COVID-19 drugs [1, 2]. However, new drug discovery and development is a long, costly and rigorous scientific process. A more effective

approach is to search for anti- COVID-19 therapies from the existing FDA-approved drug database.

Drug repurposing, which concerns the investigation of existing drugs for new therapeutic target indications, has emerged as a successful strategy for drug discovery due to the reduced costs and expedited approval procedures [3-5]. Considerable prosperous examples unveil its great values in practice: Nelfinavir, initially developed to treat the human immunodeficiency virus (HIV), is now being used for cancer treatments and Hydroxychloroquine initially is used to prevent or treat malaria caused by mosquito bites now is being used for coronavirus treatment. Amantadine was firstly designed to treat influenza caused by type A influenza viral infection and is being used for the symptoms of Parkinson later on [6]. In recent years, the rapid growth of drug-related datasets, as well as open data initiatives, has led to new developments for computational drug

repositioning, particularly, structural-based drug repositioning (SBDR). Machine learning, network analysis, and text mining and semantic inference are three major computational approaches commonly applied in drug repositioning [7]. The rapid accumulation of genetic and structural databases [8], the development of low-dimensional mathematical representations of complex biomolecular structures [9, 10], and the availability of advanced deep learning algorithms have made machine learning-based drug repositioning a promising approach [7]. Considering the urgent need for anti-COVID-19 drugs, a computational drug repositioning is one of the most feasible strategies for discovering COVID-19 drugs.

Study shows that COVID-19 genome is very close to that of the severe acute respiratory syndrome (SARS)-CoV [11]. The sequence identities of COVID-19 3CL protease, RNA polymerase, and the spike protein with corresponding SARS-CoV proteins are 96.08%, 96%, and 76%, respectively [12]. We, therefore, hypothesize that a potent SARS 3CL protease inhibitor is also a potent COVID-19 3CL protease inhibitor. Unfortunately, there is no effective SARS therapy at present. Nevertheless, the X-ray crystal structure of SARS 3CL protease has been reported [13] and the binding affinities of 115 potential SARS 3CL protease inhibitors are available in ChEMBL database [13]. Additionally, there are 15,843 protein-ligand complexes in PDBbind 2018 general set with binding affinities and X-ray crystal structures [14].

Aiming to give our contribution, we designed a Virtual Screening campaign of currently FDA approved drugs in the DrugBank for COVID-19 protease inhibition. This choice was driven by the need to provide a therapy quickly, since the development of a new drug might take years to complete. Two separate targets, the COVID-19 main protease. we report the top 10 potentially highly potent anti-COVID-19 inhibitors, which provide timely guidance for the further development of anti-CORONA drugs.

MATERIAL AND 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: 6yb7. AutoDockTools (ADT, Ver 4) [15] was used for generation the input files and analyzing the result. For preparation of protein input files, all water molecules, ligands were removed from pdb file. Then polar hydrogens were added and prepared file was saved in pdbqt format to use in following steps.

3D structures of FDA-approved drugs were

downloaded from Zinc database [16] in structure-data file (SDF) format which contains 1615 compounds. Then OpenBabel (version 2.3.1) [17] 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 PyRx 0.8 virtual screening tool- Vina. Active sites of protein were recognized from COVID-19 main protease pdb file so a $24 \times 36 \times 45$ 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 was used to prepare grid maps.

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 [18] with redocking of co-crystal structure as an inhibitor in main protease of COVID-19 with above mentioned parameters and values. Visualization of docking results has been done by Discovery Studio visualizer version 17.2 [18] and Pymol version 1.1level. [19].

RESULTS

The following structural similarities have been found using the jFATCAT-rigid algorithm [20]. To reduce the number of hits, a 40% sequence identity clustering has been applied and a representative chain taken from each cluster. If the representative chain consists of multiple domains, each domain is included in the search. If available, the SCOP 1.75 domain assignment [21] is used. Otherwise, algorithmic domain assignments are computed using the ProteinDomainParser [22].

Since the sequences are highly identical, the COVID-19 protease structure can be built by homology modeling with the SARS-CoV 3CL protease (PDB ID: 2A5I) [23] as a template. It turns out, as shown in Fig. 2, the homology structure of the COVID-19 protease is essentially identical to the X-ray structure of SARS-CoV 3CL protease. Particularly, the RMSD of two structures at the binding site is 0.21 Å. The high structural similarity between the two proteases suggests that anti-SARS-CoV chemicals can be equally effective for the treatment of COVID-19.

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 were omitted [24]. 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. As a result, there were some compounds left after applying this filter which are listed in Table 1.

Table 1. A summary of potentially highly potent anti-COVID-19 drugs with predicted binding free energies (unit: kcal/mol) and corresponding trade names.

Compound	Type	Trade Name	Predicted Binding Energy	Therapeutic Categories
ZINC169746649	Bortezomib	Velcade	-12.2	Proteasome inhibitors for mantle cell lymphoma
ZINC000001612996	Irinotecan	Camptosar, Campto, Onivyde	-10.6	Liver glucuronidation
ZINC000052955754	Ergotamine	Ergomar,	-10.1	Anti-migraines
ZINC100037101	Clofazimine	Lamprene	-9.4	Leprostastics
ZINC3939013	Fosaprepitant	Emend, Ivemend	-9.4	NK1 receptor antagonists
ZINC000003920020	Etoposide	Actitop, Bo Rui	-8.6	Hodgkin's Lymphoma
ZINC000001612996	Irinotecan	Onivyde	-8,2	pancreatic cancer, lung cancer
ZINC000002005305	Levomefolic acid	Actif,Biofolic	-8,1	L-methylfolate (IS)
ZINC000100003902	Maraviroc	Celsentri	-7.7	Anti-virus AIDS
ZINC000100070954	Glimepiride	Amaryl	-7.4	Anti Diabetes drug
ZINC000003833846	Nelfinavir	Emnel	-7.4	Anti-virus AIDS
ZINC000000592419	Roflumilast	Daliresp	-7.3	Bronchial dilators and anti-asthma drugs

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

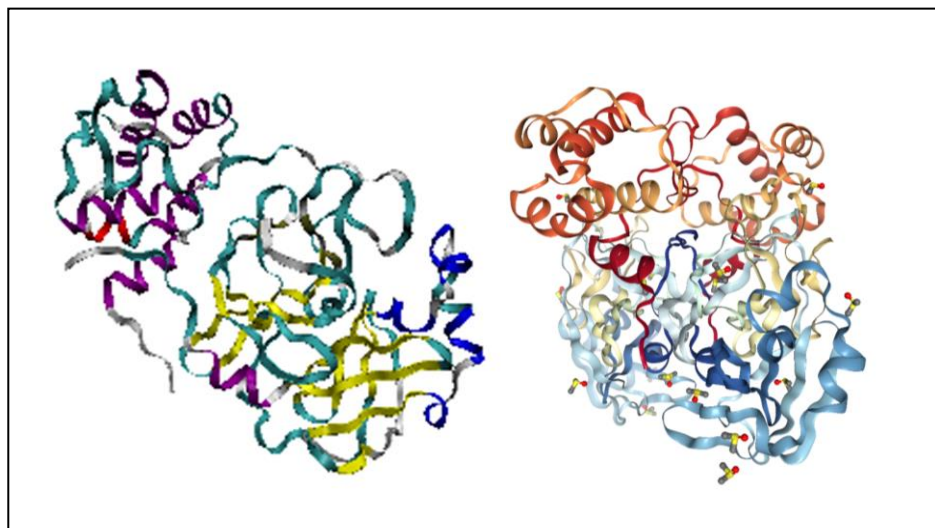


Fig 1: Illustration of the protease structures of COVID-19 protease (left) and the SARS-CoV 3CL protease (right) [Images created with the PDB ID and associated publication, NGL Viewer and RCSB PDB].

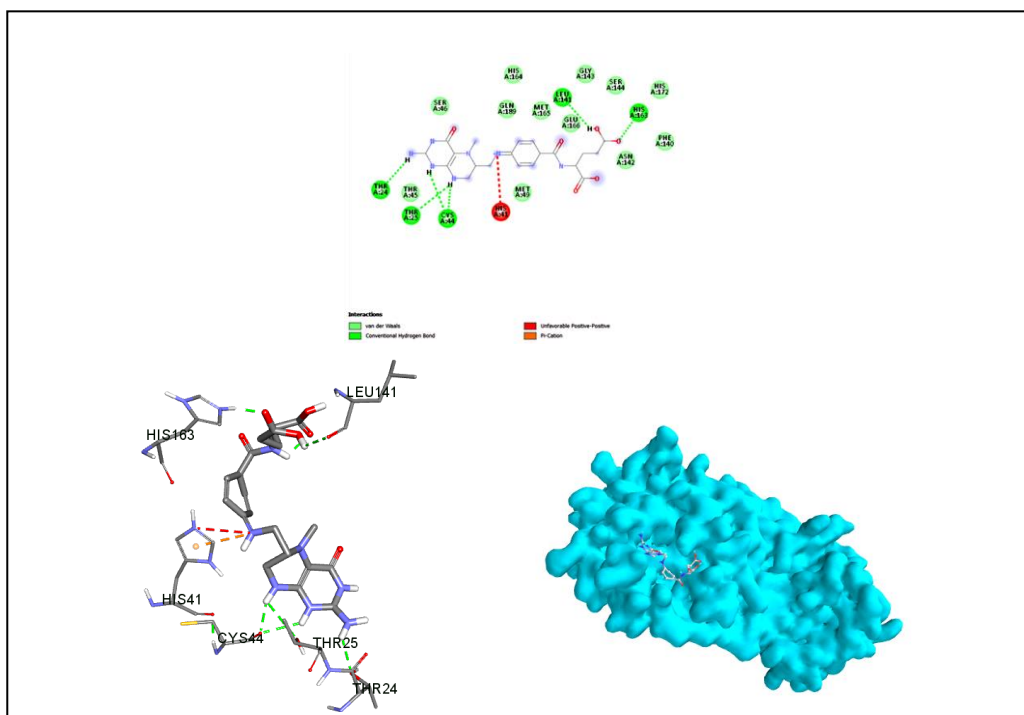


Fig 2: 2D interactions between Vitamin B9 and active site of COVID-19 main protease (a), 3D display of cartoon (b) and surface of protease (c, gray) with Vitamin B9 (yellow)

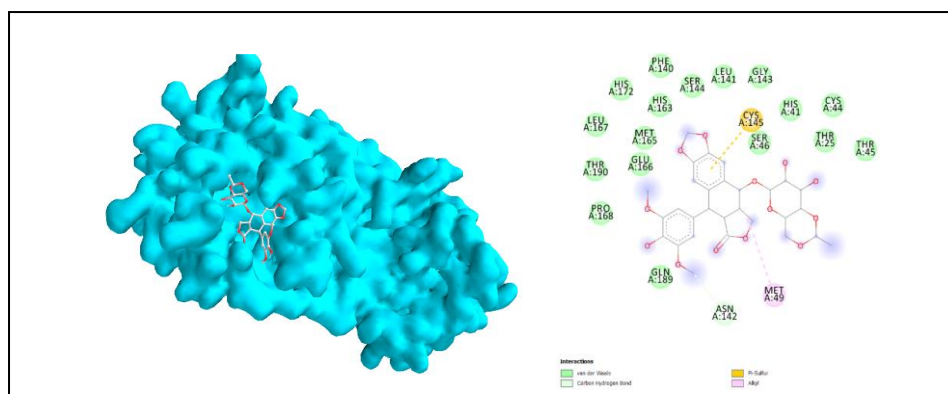


Fig 3: 2D interactions between Etoposide and active site of COVID-19 main protease (a), 3D display of cartoon (b) and surface of protease (c, gray) with Etoposide (yellow).

Dimethyl Sulfoxide is a ligand that has been experimentally found in the released crystal structure of COVID-19 main protease. A search of the zinc15 database of FDA drugs with this ligand in their structure has been identified. In an attempt to finding potential treating for COVID-19, molecular docking simulation were performed over these 1000 FDA-approved drugs on the binding pocket of protease protein which play an integral and pivotal role in propagating the virus.

The docking conformation of Vitamin B9 indicate five hydrogen bonds with THR 24, THR 25, CYS 44, HIS 163, and LEU 141 and twelve van der waals interactions with that could justify its strong binding energy.

DISCUSSION

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 compounds with lowest binding energy and the highest affinity to the receptor, with cut-off energy -7.3 kcal/mol, were chosen to further investigation. All compounds were evaluated for their clinical applications.

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). Irinotecan has an acceptable bonding affinity but is not recommended because of its high

cost and side effects.

Levomefolic acid, or vitamin b9, is recommended because of its oral sources and no side effects, especially for the treatment or prevention of coronary artery disease.

Etoposide, a semi-industrial drug for the treatment of lung cancer, has a bonding affinity. It is acceptable that it is extracted from the root of the medicinal plant *Pseudophilum*. Therefore, the medicinal plant *Podophyllum* can also be a candidate for coronary artery disease.

About Roflumilast it has to be said that it could be useful for symptomatic treatment of shortness of breath in patient and if it can reach to the protease, make the good interaction and inhibit the protease activity. Nelfinavir and Maraviroc medications are antiviral drugs used to treat and control the symptoms of AIDS.

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, showed less binding energy and affinity (-5.36 and -5.04 kcal/mol respectively) than our proposed drug Levomefolic acid (-7.7 kcal/mol).

This means that our proposed drug is not only more efficient but also it has no side effect and can be very promising. Hence, the superimpose of these three-protease inhibitors are shown in Fig. 3.

Finally, remdesivir a prodrug of adenosine nucleotide analog, has entered into clinical phases for COVID-19 [25] but is not yet FDA-approved and therefore 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, which cause a decrease in viral RNA production [26]. 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 Vitamin B9 and they can be used together.

CONCLUSION

The current pneumonia outbreak caused by a new coronavirus (COVID-19), has evolved into a global health emergency declared by the World Health Organization. Although there is no effective anti-viral medicine for the COVID-19. According to the predicted binding affinities, we recommend some FDA-approved drugs as potentially highly potent medications to COVID-19, which serve as a crucial step for the development of anti-COVID-19 drugs. A virtual screening procedure employing docking of 1000 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 studied FDA-approved drug, Vitamin B9 and Etoposide which used for HIV 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, therefore there is a hope that this drug, could be a potential drug to treating the COVID-19.

AUTHOR'S CONTRIBUTION

All authors contributed to the literature review, design, data collection and analysis, drafting the manuscript, read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this study.

FINANCIAL DISCLOSURE

No financial interests related to the material of this manuscript have been declared.

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