

Virtual Screening of Some Antivirals That Can Be Repurposed As Potential Effective Drugs against SARS-CoV-2

Mohammad Rejaur Rahman^{1*}, Anik Banik³, Ishtiaq Malique Chowdhury², Emran Hossain Sajib³
and Sanchita Sarkar³

1 Assistant Professor, Department of Molecular Biology & Genetic Engineering,

2 MS student, Department of Molecular Biology & Genetic Engineering,

3 Faculty of Biotechnology & Genetic Engineering, Sylhet Agricultural University (SAU),
Sylhet-3100, Bangladesh.

Abstract

SARS-CoV-2 has triggered a big epidemic among people around the world and it is the newest in the sequence to be prevalent among other infectious diseases. Drug repurposing concept has been utilized effectively for numerous viral infections. Considering the situation and the urgency, the idea of drug repurposing for coronavirus infection (COVID-19) is also being studied. Screening with molecular docking method for 29 antiviral drugs was performed against SARS-CoV-2 primary protease proteins (MPP), spike ecto-domain, spike receptor binding domain, Nsp9 RNA binding protein, and HR2 domain. Among these drugs, Indinavir, Sorivudine, Cidofovir and Darunavir show minimum docking scores with all key proteins in terms of least binding energy. For ADME (Absorption, Distribution, Metabolism, and Excretion) analysis, the top 4 drug candidates were further used to examine their drug profiles for suitability against SARS-CoV-2. The toxicity testing of top drug candidates showed no significant carcinogenic, mutagenic or skin irritating impacts. Indinavir may possess some complexity to heart. In addition, the drug similarity prediction revealed several approved structural analogues such as Telbivudine, Tenofovir, Amprenavir, Fosamprenavir etc which also could be used to treat viral infections. The study may speed up the findings of therapeutics against SARS-CoV-2.

Keywords: SARS-CoV-2, Covid-19, Molecular Docking, Drug Repurposing, Antivirals.

*Corresponding author

Mohammad Rejaur Rahman, Department of Molecular Biology & Genetic Engineering, Sylhet Agricultural University, Sylhet-3100, Bangladesh. E-mail: rejaur.mge@sau.ac.bd

1. Introduction

On December 31, 2019, the Health Authority of China notified the World Health Organization (WHO) of multiple cases of pneumonia in Wuhan City of Hubei Province in central China [1, 2]. This emerging infectious disease was later referred to as coronavirus disease 2019 (COVID-19) and the causative agent was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The most renowned Severe Acute Respiratory Syndrome (SARS) scientist, Dr. Zhengli Shi, suggested the bats as the sources of SARS-CoV-2 [4] and other Chinese researchers have claimed that Middle East Respiratory Syndrome (MERS) and (SARS) including coronaviruses are likely to originate from bats in China [5, 6]. This SARS-CoV-2 is a single-stranded, enveloped, positive-sense RNA (+ ssRNA) virus[7]. It belongs to Betacoronavirus such as SARS -CoV and MERS-CoV and shares genetic similarities with them about 79 % and about 50 % respectively [8]. Because of human-to - human transmission through respiratory droplets the virus has become so deadly, particularly when people are in close contact (within 1–2 m) [9, 10, 11]. The COVID-19 disease may be symptomatic, presymptomatic, and asymptomatic [12]. Respiratory symptoms frequently reported include fever, dry cough, dyspnoea, chest pain, fatigue and myalgia, headache , dizziness, stomach pain , diarrhea, nausea , and vomiting are the less common symptoms [13, 14]. The epidemic spread across the world so quickly and widely after emergence that on March 11, 2020, WHO declared the curse as a global pandemic.

The pandemic stymied the strong health sectors of leading countries such as China, the UK, the United States, Russia, Germany, Canada, Italy, Spain, France and others. As of 2 July 10,694,288 people were infected and COVID-19 caused 516,210 deaths worldwide [15]. Researchers from different countries are making every attempt to develop new vaccines and anti-illness medications. Numerous laboratories around the world, as well as research and pharmaceutical companies, are developing new medicines and vaccines [16, 17]. However, it is required nearly one year before drugs and/or vaccines to be available for administration to patients, as it is incredibly time consuming process. In that case, repurposing current medications may play a major role in reducing symptoms or curing the disorder. Some medications such as antimalarial drugs (e.g. chloroquine, hydroxychloroquine) or anti-HIV drugs (e.g. lopinavir, ritonavir, saquinavir) have shown substantial positive results against COVID-19 in many countries[18, 19, 20].

Drug repurposing, also known as repositioning, is an important approach to the speedy identification of therapeutic drugs with a proven safety profile to fight novel infectious diseases [21, 22, 23]. This repurposing strategy has been effective in identifying potential drug candidates against many diseases such as Ebola disease, hepatitis C virus and infection with the zika virus [24, 25, 26, 27]. Moreover, in-silico based screening has become a highly significant tool to mitigate the drawbacks of antiviral drug discovery. Screening of drugs by computational methods via docking approach saves expenditure as well as time [28, 29, 30,31, 32]. Besides, existing drugs approved for some diseases are safe for human consumption [22], and only their efficacy against the targeted disease needs to be proved [33]. So, in silico drugs repurposing strategy can be a great approach in which SARS-CoV-2 significant proteins, such as proteins required for viral replication or binding to human receptor (ACE2: angiotensin-converting enzyme 2), will be targeted.

Our present research focused on virtual screening and protein-ligand docking of a variety of Food and Drug Administration (FDA) — approved antiviral drugs against the promising target drug SARS-CoV-2 main protease (Mpro, PDB ID-6W63), very necessary for viral replication, and spike receptor binding domain (PDB ID-6MOJ), needed to bind to human receptor ACE2. Other drug targets include Nsp9 (Non structural protein-9) RNA binding protein, Spike Ecto domain and HR2 domain which involve in viral replication by binding with single stranded RNA, receptor binding as well as fusion and virus-cell membrane fusion respectively. Here, screened FDA approved antiviral drugs, such as Sorivudine, Tipranavir, Zalcitabine, Zidovudine, Indinavir, Nelfinavir, Nevirapine etc. are applied against human immunodeficiency virus (HIV). Other drugs like Trifluridine, Valganciclovir, Vidarabine, Pritelivir etc. are used for human herpes virus disease. Besides, we also tested drugs that are effective against Influenza A and Influenza B Virus, Hepatitis B and Hepatitis C virus, Respiratory Syncytial Virus (RSV) and other RNA/DNA viruses to detect their effectiveness against the selected drug targets of SARS-CoV-2.

2. Materials and Methods

2.1. Retrieval of SARS-CoV-2 proteins/protein-domains and antiviral drugs

The RCSB Protein Data Bank [34] was used for the retrieval of 3D structures of SARS-CoV-2 main protease (PDB ID: 6W63), Nsp9 (Non-structural protein-9) RNA binding protein (PDB ID: 6W4B), Spike receptor binding domain (PDB ID: 6M0J), spike ecto-domain (PDB ID : 6VYB), and HR2 Domain (PDB ID : 6LVN). A total of 29 antiviral drugs, used against different virus (e.g. HIV, HSV etc.), were extracted from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) [35] in SDS (3D) format (Supplementary file 1). These drugs were also crosschecked in DrugBank database (<https://www.drugbank.ca/>) [36] (Supplementary file 2). Then the retrieved SDS structures were converted into PDB format by OpenBabel v2.3 software for further analysis [37].

2.2. Molecular docking of antiviral drugs against SARS-CoV-2 proteins/protein-domains

Molecular docking is a necessary tool in drug discovery that simplify the way of screening out the appropriate therapeutics against specific drug targets of infectious pathogens [38]. This effective approach provides rankings of docked compounds according to the binding affinity of ligand-receptor complexes [39, 40]. PatchDock server was used to measure the binding affinity of 29 antiviral drugs with different SARS-CoV-2 protein / prorein domains (drug targets / macromolecules) [41, 42]. To refine the docked complexes, FireDock refinement tool [43] was employed. An experimental study claimed alpha-ketoamide (CID 6482451) as a primary protease inhibitor for SARS-CoV-2 [44]. Thus, it was docked against all five macromolecules being used as positive control in this study. Finally, the ligand-receptor complexes were visualized by Discovery Studio v3.1 [45] and PyMOL v2.0 [46].

2.3. Analyzing drug profiles of active antiviral drugs

A standard drug candidate should have appropriate absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties along with adequate effectiveness against the therapeutic target [47]. These parameters greatly regulate the pharmacological activity and performance of a drug [48]. Among these, the properties of absorption , distribution , metabolism and excretion (ADME) were assessed using SwissADME server [49]. BOILED-Egg model was

used to assess the Blood-brain barrier (BBB) in the studied drugs [50]. After that, pkCSM [51], an online tool, was utilized to predict the relative toxicity of top drugs. It is an effective approach to predict pharmacokinetic properties depending on graph-based signatures that represent distance patterns between atoms [51]. Besides, carcinogenicity of selected top drugs was analysed using admetSAR [52].

2.4. Prediction of drug targets and available drug molecules from DrugBank

Screening of top drugs was performed to find similar potential drugs that can be used against SARS-CoV-2. To predict the probable macromolecular targets of top drugs, SwissTargetPrediction was utilized [53]. The server estimates on about 3000 proteins according to a mix of 2D and 3D uniformity with a library of 370000 recognized bioactive compounds. Furthermore, SwissSimilarity web tool was used to find out the potential drug molecules against SARS-CoV-2 by homology screening of predicted top drugs [54]. The server uses several strategies, such as FP2 fingerprints, electroshape, spectrophores and align-IT to predict experimental, approved or commercially available drugs from DrugBank via virtual screening of numerous libraries of small molecules [54].

3. Results

3.1. Molecular docking of antiviral drugs against SARS-CoV-2 proteins/protein-domains

The retrieved structures of five SARS-CoV-2 proteins/protein-domains (macromolecules) and antiviral drugs (ligands) were optimized and executed for molecular docking to compute the binding affinity between selected macromolecules and ligands. According to binding energy the antiviral drugs were ranked and the drugs which showed minimum binding energy were selected as top scorers (Supplementary File 3). In this way, four top scorers, Indinavir, SorivudineCidofovir and Darunavir, were chosen for further analysis (Table 1, Figure1). Sorivudine, Darunavir and Cidofovir showed highest binding affinity with spike receptor binding domain (-52.99 kcal/mol), spike ecto-domain (-68.01 kcal/mol) and Nsp9 RNA binding protein (-52.74 kcal/mol) respectively, while Indinavir showed best binding affinity with both HR2 Domain (-37.42 kcal/mol) and main protease (-69.23kcal/mol) (Table 1 and Figure 2 and 3). Besides, Sorivudine also experienced excellent binding interactions with spike ecto-domain (-52.28 kcal/mol) and main protease (-59.62 kcal/mol), while Darunavir showed considerable

interactions with spike receptor binding domain (-46.88 kcal/mol), Nsp9 RNA binding protein (-47.62 kcal/mol) and main protease (-55.06 kcal/mol) as well.

3.2. ADME analysis of selected top drugs

To evaluate drug profiles of top antiviral drugs, various ADME properties, such as physicochemical parameters, pharmacokinetics, lipophilicity, water solubility, medicinal chemistry of top drugs were assessed (Table 2, Figure 4). Indinavir showed higher GI absorption, while lower for Sorivudine, Cidofovir and Darunavir. BOILED-Egg model that counted blood-brain barrier (BBB) revealed no BBB permeant within the studied top drugs. Inhibition effects analysis with different CYP isoforms (CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4) expressed that these top drugs had no interaction probability with cytochromes P450 isoforms, except Indinavir with CYP2D6 and Darunavir with CYP3A4. All of the five drugs were water soluble from poor to high level, while Cidofovir showed maximum solubility. Furthermore, these five drugs showed zero alert for pain (Table 2).

3.3. Analysis of Toxicity pattern of top drugs

Different toxicity parameters such as AMES toxicity, Oral Rat toxicity, skin sensitization, T. pyriformis toxicity, minnow toxicity, hepatotoxicity etc. were analysed (Table 3). Result revealed negative outcomes in AMES test for all drugs which indicating the drugs as non-mutagenic. According to the result, all of the drugs acted as hERG I and hERG II inhibitors, except Indinavir which showed positive outcome against hERG II. Besides, they showed negative results for skin sensitization, and oral rat acute toxicity, LD50, values ranged from 1.74 to 2.107 mol/kg for these top drugs. Minnow Toxicity values of all drugs were more than -0.3 log mM proving them non-toxic. Besides, admetSAR predicted carcinogenicity for these drugs was negative, declaring them as non-carcinogen. However, positive hepatotoxicity results of all drugs indicating the possibility for association with the disruption of normal function of liver.

3.4. Prediction of drug targets and available drug molecules from DrugBank

Prediction of effective drug targets against the top drugs revealed some other similar drugs that may be potential against SARS CoV2. Maximum targets belong to protease, transferase and enzyme class. Other target class includes electrochemical transporter, cytochrome p450, family a

g protein-coupled receptor, phosphodiesterase, oxidoreductase, transferase, DNA polymerase alpha subunit, transferase etc (Table 4, Figure 5). To predict structural similar bioactive small compounds against SARS-CoV-2 from DrugBank, a ligand-based screening strategy was employed (Table 5). Quinapril (DB00881) and Sirolimus (DB00877), two approved drugs along with an experimental drug, L-756,423 (DB02009), were found as analogous with Indinavir with score of 0.048, 0.014 and 0.906 respectively. Sorivudine predicted two similar approved drugs Telbivudine (DB01265) and Idoxuridine (DB00249), while Cidofovir predicted Tenofovir (DB00300) and Riboflavin (DB00140) as similar approved drugs. Besides, Darunavir also predicted two similar approved drugs, Amprenavir (DB00701) and Fosamprenavir (DB01319). These results of similarity suggest the efficacy of these related drugs against SARS-CoV-2 and indicate further experimental studies.

4. Discussion

SARS-CoV-2 belongs to a group of viruses that can contaminate humans as well as vertebrate animals. There is no recorded or approved potent drug or vaccine for treating the patient infected with SARS-CoV-2. There are a few candidates within the investigational stages but many of them raised controversy issues [4, 55]. In this study, attempts were taken to screen and suggest to repurpose some FDA approved antiviral drugs as an inhibitory agent of SARS-CoV-2 using molecular docking strategy. The study suggested that Indinavir, Sorivudine, Cidofovir and Darunavir along with their top derivatives, may be effective against SARS-CoV-2.

Drug repurposing is one of the exciting applications of computational pharmacology for finding new uses for existing drugs. Computer-based analysis can speed up the identification of drug targets, screening and refinement of drug candidates. It too facilitate characterization of side effects and foresee drug resistance pattern. Antiviral drugs such as Ledipasvir, Elbasvir, Nelfinavir, Danoprevir, Darunavir, lopinavir and ritonavir were previously used as an inhibiting agent for HCV and HIV [56]. Lopinavir, Ritonavir and Nelfinavir have been reported as potential drug candidates in few earlier studies using repurposing strategy that target Mpro of SARS-CoV-2 [57]. Besides, a recent study emphasized on alpha-ketoamide as a Mpro inhibitor of this virus to determine its efficacy to become a drug candidate [44]. Main protease proteins (Mpro) or RNA-dependent RNA polymerase of SARS-CoV-2 were used as probable drug targets in almost all previous experiments. In this study, we assess the potency of 29 FDA approved

commercially available antiviral drugs against SARS-Cov-2 main protease (6W63), spike ecto-domain (6VYB), spike receptor binding domain (6M0J), Nsp9 (Non-structural protein-9) RNA binding protein (6W4B), and HR2 domain (6LVN) using molecular docking approach [58]. SARS-CoV-2 Mpro is an appealing pharmacological target for the design of drugs against covid-19 as the Mpro polyprotein cleavage facilitates the formation of the helicase and the RNA-dependent RNA polymerase (RdRp) which are the prerequisite proteins for viral replication initiation [59, 60]. In addition, human proteases have no similar cleavage specificity to that of coronavirus proteases so inhibitors of these proteins are safe [44]. ORF1a encoded Nsp9 RNA binding protein which is involved in the synthesis of viral RNA. Nsp9 has evolved, possibly, from a protease and it's a dimeric protein. Nsp9 communicates with nsp8, actions that may be crucial to its function. Viral replication complexes are also connected with membranes and in this case, nsp9 aids. Nsp9 may likely have an RNA binding activity as a putative component in the Replication complex. In this way it makes a difference in viral replication by binding with single stranded RNA. SARS-Cov-2 moreover have a surface structural spike glycoprotein (S) which plays crucial role in association with the have cell receptor and subsequent virus passage into the cell. The S protein has two subunits, the S1 (receptor-binding) and the S2 (membrane fusion) domains⁴⁰. The attachment of the receptor-binding subunit to the receptor enables interaction between the HR1 and HR2 domains in the membrane fusion subunit and forms a six-helix bundle and this conformational change results in a close apposition of the fusion peptide leading to virus-cell membrane fusion [61]. Thus, spike protein binds to human ACE2 and CLEC4M/DC-SIGNR receptors and internalization of the virus into the endosomes of the host cell induces conformational changes in the S glycoprotein [62]. So, all those macromolecules are potential target for repurposing study.

Docking result revealed that four drug molecules i.e. Indinavir, Sorivudine, Cidofovir and Darunavir scored high for each five macromolecules and bound with lowest global energy (Table 1). Indinavir had highest binding affinity with SARS-CoV-2 main protease (-69.23 kcal/mol) and HR2 Domain (-37.42 kcal/mol). The rest of three drug candidate i.e. Sorivudine, Cidofovir and Darunavir had highest binding affinity with Spike receptor binding domain (-52.99 kcal/mol), Nsp9 RNA binding protein (-52.74 kcal/mol) and Spike ecto-domain (-68.01 kcal/mol) respectively. Indinavir, an alpha-amino acid amide protease inhibitor used to treat Human immunodeficiency virus (HIV) infection. Indinavir inhibits the activity of the enzyme by

binding to the protease active site. This inhibition facilitates the formation of immature non-infectious viral particles through preventing cleavage of the viral polyproteins [63]. Sorivudine, an antimetabolite and synthetic analogue of thymidine. Thymidine kinase activity in the body phosphorylates sorivudine and is absorbed into the viral DNA instead of the correct nucleoside [64]. So the viral DNA cannot be replicated and the virus cannot grow because sorivudine is a competitive inhibitor of DNA polymerase. Cidofovir, a nucleotide analogue and is active against herpes cytomegalovirus (CMV) retinitis infection and chronic hepatitis B which acts through the selective inhibition of viral DNA polymerase. As a result Cidofovir reduce synthesis of viral DNA (10). Darunavir, a non-peptide protease inhibitor, with a distinct chemical structure that enhanced binding affinity of the drug [65]. This antiviral prevents HIV replication by binding to the enzyme, stopping the catalytic activity and dimerization of HIV-1 protease. Specifically, it inhibits the cleavage of HIV encoded Gag-Pol proteins [66] in cells that have been infected with the virus, halting the formation of mature virus particles, which spread the infection.

ADME data is crucial in drug development project whether it is determined by in vitro, in vivo or computational approaches because many drug development project failed during clinical trials due to poor ADME data [67]. Computational analysis of ADME profile of drug candidates is very fast and cost effective compare to other methods. In silico ADME analysis of top four drug candidates did not show any undesirable consequences that could reduce their drug likeliness properties. All of the drug candidates are water soluble and absorbable in GI where cidofovir is highly soluble in water and indinavir has high absorption rate in GI. However, these four drugs are non-permeate to BBB and it would not create any problem as SARS-CoV-2 is a respiratory disease. Most of the target class for the top drug candidates belonged to the categories of enzymes (e.g. Electrochemical transporter, Protease, Transferase, Family A G protein-coupled receptoretc (Table 4). The toxicity pattern of drug molecule is related to their structure. In Europe and the United States structure-activity relationships (SARs) have been widely used to predict toxicity by various bioinformatics tools [68]. The toxicity prediction results of our study showed that all four drug candidates are non-carcinogenic, non-mutagenic and insensitive to skin but these showed hepatotoxicity. Except Indinavir, all the drug candidates are friendly to heart as they showed negative result in hERG I & hERG II inhibitors prediction test. Overall the toxicity prediction test suggested those drugs are safe to take as a medication to treat Covid-19.

Ligand based drug similarity analysis identified three structural analogs of Indinavir where two (Quinapril, Sirolimus) are approved and another one (L-756,423) is in experimental stage. Quinapril is an ACE (angiotensin converting enzyme) inhibitors and used to treat hypertension and heart failure [69]. As we previously know that SARS-CoV-2 entry into the host cell by interacting with ACE receptor, so this analog could be a drug of choice to treat Covid-19. Drug similarity analysis revealed two (Telbivudine&Idoxuridine) approved analog for Sorivudine and both of them act similarly by incorporating into viral DNA in place of thymidine and terminate replication process. Telbivudine&Idoxuridine used to treat hepatitis B virus (HBV) and Herpes simplex virus respectively [70, 71]. Amprenavir and Fosamprenavir are two approved analog of Darunavir and both of them are protease inhibitors. These analogs prevent the processing of viral Gag and Gag-Pol polyprotein and produce noninfectious, immature viral particles that is harmless to host cell [72, 73]. The results encourage that all these compounds could be used as potential drug candidates against SARS-CoV-2.

5. Conclusion

The results suggest that Indinavir, Sorivudine, Cidofovir and Darunavir could be options to end up the SARS-CoV-2 era. Furthermore, several biologically active structural analogs from DrugBank i.e. Telbivudine, Tenofovir, Fosamprenavir, Tenofovir may also be effective and show potency against the viral pathogen. Due to encouraging result we highly recommended these drug candidates as a potential fighter and refers in vivo trials for the experimental validation of our findings against notorious deadly SARS-CoV-2 virus.

6. References

- [1] N.Zhu, D.Zhang, W. Wang,X. Li, B. Yang, J.Song,X.Zhao,B.Huang,W.Shi,R. Lu,andP.Niu, A novel coronavirus from patients with pneumonia in China, 2019, The New England Journal of Medicine 382 (2020) 727-733. doi: 10.1056/NEJMoa2001017.
- [2] C.I. Paules, H.D. Marston and A.S.Fauci, Coronavirus infections—more than just the common cold, The Journal of the American Medical Association 323 (8) (2020) 707-708. doi:10.1001/jama.2020.0757.
- [3] C.C. Lai, T.P. Shih, W.C. Ko, H.J.Tang, and P.R. Hsueh, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the

- epidemic and the challenges, *International Journal of Antimicrobial Agents* 55 (2020)105924.doi:10.1016/j.ijantimicag.2020.105924.
- [4] P. Zhou, X.L.Yang, X.G.Wang , B. Hu, L. Zhang, W. Zhang,H.R. Si, Y.Zhu et al.,A pneumonia outbreak associated with a new coronavirus of probable bat origin, *Nature*579(2020)270-273. doi: 10.1038/s41586-020-2012-7.
- [5] S.Xia,Q.Lan,J.Pu,C.Wang, Z.Liu, W.Xu, Q.Wang, H.Liu, S.Jiang, L.Lu, Potent MERS-CoV Fusion Inhibitory Peptides Identified from HR2 Domain in Spike Protein of Bat Coronavirus HKU4, *Viruses* 11 (2019) 56. doi: 10.3390/v11010056.
- [6] Y.Yuan, J.Qi,R.Peng, C.Li, G.Lu, J.Yan,Q.Wang,G.F. Gao, Molecular Basis of Binding between Middle East Respiratory Syndrome Coronavirus and CD26 from Seven Bat Species, *Journal of Virology* 94 (2020) e01387.doi:10.1128/JVI.01387-19.
- [7] C.Wu, Y. Liu, Y.Yang, P. Zhang, W. Zhong, Y.Wang et al., Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, *Acta Pharm Sin B* 10 (2020) 766-788. doi: 10.1016/j.apsb.2020.02.008.
- [8] R.Lu, X.Zhao, J.Li et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, *The Lancet* 395 (2020) 1033–1034. doi: 10.1016/S0140-6736(20)30251-8.
- [9] CDC, 2020c. Coronavirus Disease 2019 (COVID-19)—Transmission. Centers for Disease Control and Prevention (CDC), United States.
- [10] CDC, 2020h. HowCOVID-19 Spreads. Centers for Disease Control and Prevention (CDC), U.S.
- [11] WHO, 2020q. Q&a on Coronaviruses. World Health Organization (WHO).
- [12] WHO, 2020c. Coronavirus Disease (COVID-2019) Situation Report-73. World Health Organization (WHO).
- [13] C.Huang, Y.Wang, X. Li, L.Ren, J.Zhao, Y.Hu et al., Clinical features of patientsinfected with 2019 novel coronavirus in Wuhan, China, *The Lancet* 395 (2020) 497-506. doi:10.1016/S0140-6736(20)30183-5.
- [14] D.Wang, B.Hu, C.Hu, F.Zhu, X.Liu, J.Zhang et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, *The Journal of the American Medical Association* 323(11) (2020) 1061-1069. doi:10.1001/jama.2020.1585.

- [15] "COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)". ArcGIS. Johns Hopkins University. Retrieved 2 July 2020.
- [16] C.V. Herst, S.Burkholz, J.Sidney, A. Sette, P.Harris, S.Massey, T.Brasel, E.Cunha-Neto, D.Rosa, W.Chao, et al., An Effective CTL Peptide Vaccine for Ebola Zaire Based on Survivors' CD8⁺ Targeting of a Particular Nucleocapsid Protein Epitope with Potential Implications for COVID-19 Vaccine Design, *Vaccine* 38 (2020) 4464-4475. doi:10.1016/j.vaccine.2020.04.034.
- [17] G.Yamey, M.Schäferhoff, R.Hatchett, M.Pate, F. Zhao, K.K. McDade, Ensuring global access to COVID-19 vaccines, *The Lancet* 395 (2020) 1405-1406. doi:10.1016/S0140-6736(20)30763-7.
- [18] J. Gao, Z.Tian, X.Yang, Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies, *BioScience Trends* 14 (2020) 72–73. doi: 10.5582/bst.2020.01047.
- [19] P.Gautret, J.C.Lagier, P.Parola, V.T. Hoang, L.Meddeb, M.Mailhe, B.Doudier, J. Courjon, V.Giordanengo, V.E. Vieira et al., Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial, *International Journal of Antimicrobial Agents* 56 (2020) 105949. doi:10.1016/j.ijantimicag.2020.105949.
- [20] J.Stebbing, A.Phelan, I.Griffin, C.Tucker, O. Oechsle, D.Smith, P. Richardson, COVID-19: Combining antiviral and anti-inflammatory treatments, *The Lancet Infectious Disease* 20 (2020) 400–402. doi:10.1016/S1473-3099(20)30132-8.
- [21] T. T. Ashburn and K. B. Thor, Drug repositioning: identifying and developing new uses for existing drugs, *Nature Reviews Drug Discovery* 3 (2004) 673-683. doi:10.1038/nrd1468.
- [22] J. Li, S.Zheng, B.Chen, A. J. Butte, S. J. Swamidass, and Z.Lu, A survey of current trends in computational drug repositioning, *Briefings in Bioinformatics* 17 (2016) 2-12. doi: 10.1093/bib/bbv020.
- [23] G.Chopra, and R.Samudrala, Exploring Polypharmacology in Drug Discovery and Repurposing Using the CANDO Platform, *Current Pharmaceutical Design* 22 (2016) 3109- 3123. doi:10.2174/1381612822666160325121943.

- [24] J.Kouznetsova,W. Sun, C.Martinez-Romero, G.Tawa,P. Shinn,C.Z. Chen,A.Schimmer, P. Sanderson, J.C.McKew, W.Zheng and A.Garcia-Sastre, Identification of 53 compounds that block Ebola virus-like particle entry via a repurposing screen of approved drugs, *Emerging Microbes & Infections* 3 (2014) 1-7. doi:10.1038/emi.2014.88.
- [25] L. M. Johansen, L. E. DeWald, C. J. Shoemaker, B. G. Hoffstrom, C. M. Lear-Rooney, A. Stossel, E. Nelson, S. E. Delos, J. A. Simmons, J. M. Grenier, and L. T. Pierce, A screen of approved drugs and molecular probes identifies therapeutics with anti-Ebola virus activity, *Science Translational Medicine* 7 (2015) 290ra89. doi: 10.1126/scitranslmed.aaa5597.
- [26] S. He, B. Lin, V. Chu, Z. Hu, X. Hu, J. Xiao, A. Q. Wang, C. J. Schweitzer, Q. Li, M. Imamura and N. Hiraga, Repurposing of the antihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection, *Science Translational Medicine* 7 (2015) 282ra49. doi: 10.1126/scitranslmed.3010286.
- [27] N. J. Barrows, R. K. Campos, S. T. Powell, K. R. Prasanth, G. Schott-Lerner, R. Soto-Acosta, G. Galarza-Munoz, E. L. McGrath, R. Urrabaz-Garza, J. Gao and P. Wu, A screen of FDA-approved drugs for inhibitors of Zika virus infection, *Cell Host & Microbe* 20 (2016) 259-270. doi: 10.1016/j.chom.2016.07.004.
- [28] G. Jones, P. Willett, R. C. Glen, A. R. Leach and R. Taylor, Development and validation of a genetic algorithm for flexible docking, *Journal of molecular biology* 267 (1997) 727-748. doi: 10.1006/jmbi.1996.0897.
- [29] R. A. Friesner, et al., Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy, *Journal of Medicinal Chemistry* 47(2004) 1739- 1749. doi:10.1021/jm0306430.
- [30] J. J. Irwin and B. K. Shoichet, Docking Screens for Novel Ligands Conferring New Biology, *Journal of Medicinal Chemistry* 59 (2016) 4103-4120. doi:10.1021/acs.jmedchem.5b02008.
- [31] N. Mohanasundaram and T. Sekhar, Computational Studies of Molecular Targets Regarding the Adverse Effects of Isoniazid Drug for Tuberculosis, *Current Pharmacogenomics and Personalized Medicine* 16(2018) 210-218. doi:10.2174/1875692116666181108145230.

- [32] M. S.Murgueitio, M.Bermudez, J.Mortier, G.Wolber, Insilico virtual screening approaches for anti-viral drug discovery, *Drug Discovery Today: Technologies* 9 (2012) e219-e225. doi: 10.1016/j.ddtec.2012.07.009.
- [33] M.R.Hurle, L. Yang, Q.Xie, D. K. Rajpal, P. Sanseau and P. Agarwal, Computational drug repositioning: from data to therapeutics, *Clinical Pharmacology & Therapeutics* 93 (2013) 335-341. doi: 10.1038/clpt.2013.1.
- [34] P. W.Rose, A.Prlić, A.Altunkaya, C.Bi, A. R.Bradley, C. H.Christie et al., The RCSB protein data bank: Integrative view of protein, gene and 3D structural information, *Nucleic Acids Research* 45 (2017) D271–D81. doi: 10.1093/nar/gkw1000.
- [35] S.Kim, P. A.Thiessen, E. E.Bolton, J.Chen, G.Fu, A.Gindulyte, L.Han, J.He, S.He, B. A.Shoemaker, J.Wang, PubChem substance and compound databases, *Nucleic Acids Research* 44 (2016) D1202-D13. doi: 10.1093/nar/gkv951.
- [36] D. S.Wishart, Y. D.Feunang, A. C.Guo, E. J.Lo, A.Marcu, J. R. Grant and N.Assempour, DrugBank 5.0: a major update to the DrugBank database for 2018, *Nucleic Acids Research* 46 (2018) D1074-D1082. doi: 10.1093/nar/gkx1037.
- [37] N. M.O'Boyle, M.Banck, C.A.James, C.Morley, T.Vandermeersch, G. R.Hutchison, Open Babel: An open chemical toolbox, *Journal of cheminformatics* 3 (2011) 33. doi: 10.1186/1758-2946-3-33.
- [38] X. Y.Meng, H. X.Zhang, M.Mezei, M.Cui, Molecular docking: a powerful approach for structure-based drug discovery, *Current Computer-Aided Drug Design* 7 (2011) 146-57. doi: 10.2174/157340911795677602.
- [39] S.Y.Huang, X.Zou, Advances and challenges in protein-ligand docking, *International Journal of Molecular Sciences* 11 (2010) 3016–3034. doi: 10.3390/ijms11083016.
- [40] F.López-Vallejo, T.Caulfield, K.Martínez-Mayorga, M.A.Giulianotti, R. A. Houghten, A.Nefzi, J.L. Medina-Franco, Integrating virtual screening and combinatorial chemistry for accelerated drug discovery, *Combinatorial Chemistry & High Throughput Screening* 14 (2011) 475–487. doi: 10.2174/138620711795767866.

- [41] D. Schneidman-Duhovny, Y. Inbar, R. Nussinov, H.J. Wolfson, PatchDock and SymmDock: servers for rigid and symmetric docking, *Nucleic Acids Research* 33 (2005) W363-W367. doi: 10.1093/nar/gki481.
- [42] K.F. Azim, S.R. Ahmed, A. Banik, M.M.R. Khan, A. Deb and S.R. Somana, Screening and druggability analysis of some plant metabolites against SARS-CoV-2: An integrative computational approach, *Informatics in Medicine Unlocked* 20 (2020) 100367. doi: 10.1016/j.imu.2020.100367.
- [43] E. Mashlach, D. Schneidman-Duhovny, N. Andrusier, R. Nussinov, H. J. Wolfson, FireDock: a web server for fast interaction refinement in molecular docking, *Nucleic Acids Research* 36 (2008) W229-W232. doi: 10.1093/nar/gkn186.
- [44] L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauerhering, S. Becker, K. Rox, R. Hilgenfeld, Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors, *Science* 368 (2020) 409-412. doi: 10.1126/science.abb3405.
- [45] Q. Wang, J. He, D. Wu, J. Wang, J. Yan, H. Li, Interaction of α -cyperone with human serum albumin: Determination of the binding site by using Discovery Studio and via spectroscopic methods, *Journal of Luminescence* 164 (2015) 81-85. doi: 10.1016/j.jlumin.2015.03.025.
- [46] W.L. DeLano, Pymol: An open-source molecular graphics tool, *CCP4 Newsletter on protein crystallography*, 40(1) (2002) 82-92.
- [47] L. Guan, H. Yang, Y. Cai et al., ADMET-score - a comprehensive scoring function for evaluation of chemical drug-likeness, *MedChemComm* 10 (1) (2018) 148-157. doi:10.1039/c8md00472b.
- [48] S. K. Balani, V.S. Devishree, G. T. Miwa, L. S. Gan, J. T. Wu, F.W. Lee, "Strategy of utilizing in vitro and in vivo ADME tools for lead optimization and drug candidate selection", *Current Topics in Medicinal Chemistry* 5 (2005) 1033-8. doi: 10.2174/156802605774297038.
- [49] A. Daina, O. Michielin, V. Zoete, SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Scientific Reports* 7 (2017) 42717. doi: 10.1038/srep42717.

- [50] A.Daina, V. Zoete, A BOILED-Egg to Predict Gastrointestinal Absorption and BrainPenetration of Small Molecules, *ChemMedChem* 11 (2016) 1117–1121. doi: 10.1002/cmdc.201600182.
- [51] D. E.Pires, T. L.Blundell and D. B. Ascher, pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures, *Journal of Medicinal Chemistry* 58 (2015) 4066–4072. doi: 10.1021/acs.jmedchem.5b00104.
- [52] F.Cheng, W.Li, Y.Zhou, J. Shen, Z. Wu, G.Liu, P. W. Lee and Y.Tang, admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties, *Journal of Chemical Information and Modeling* 52 (2012) 3099–3105. doi: 10.1021/ci300367a.
- [53] A. Daina, O. Michielin and V. Zoete, SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules, *Nucleic Acids Research* 47 (2019) W357-W364. doi: 10.1093/nar/gkz382.
- [54] V. Zoete, A. Daina, C. Bovigny and O.Michielin, SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening, *Journal of Chemical Information and Modeling* 56 (2016) 1399-1404. doi: 10.1021/acs.jcim.6b00174.
- [55] L.Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), *Drug Discoveries & Therapeutics* 14 (2020) 58–60. doi: 10.5582/ddt.2020.01012.
- [56] S. G. V.Rosa, and W. C. Santos, Clinical trials on drug repositioning for COVID-19 treatment, *RevistaPanamericana de SaludPública* 44 (2020) 1–13. doi.org/10.26633/RPSP.2020.40.
- [57] T. Sekhar, Virtual Screening based prediction of potential drugs for COVID-19, *Combinatorial Chemistry & High Throughput Screening* 23 (2020). doi: 10.2174/1386207323666200814132149.
- [58] M. W.Chang, C.Ayeni, S.Breuer and B. E. Torbett, Virtual screening for HIV protease inhibitors: a comparison of AutoDock 4 and Vina, *PloS ONE* 5 (2010) e11955. doi:10.1371/journal.pone.0011955.

- [59] V. Thiel, K. A.Ivanov, A.Putics, T. Hertzig,B. Schelle, S. Bayer, andA. E. Gorbalenya, Mechanisms and enzymes involved in SARS coronavirus genome expression, *Journal of General Virology* 84 (2003) 2305-2315. doi: 10.1099/vir.0.19424-0.
- [60] J. F.Chan, S. K.Lau, K. K.To, V. C.Cheng, P. C. Woo and K. Y. Yuen, Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease, *Clinical Microbiology Reviews* 28 (2015) 465-522. doi: 10.1128/CMR.00102-14.
- [61] J. P.MooreandR. W. Doms, The entry of entry inhibitors: a fusion of science and medicine. *Proceedings of the National Academy of Sciences, Proceedings of the National Academy of Sciences of the United States of America* 100 (2003) 10598-10602. doi: 10.1073/pnas.1932511100.
- [62] M. A.Tortorici and D. Veessler, Structural insights into coronavirus entry, *Advances In Virus Research* 105 (2019) 93-116. doi: 10.1016/bs.aivir.2019.08.002.
- [63] R. M. W.Hoetelmans, C. H. W.Koks,J. H.Beijnen, Meenhorst, P. L. Mulder, J. W. and D. M. Burger, Clinical pharmacology of HIV protease inhibitors: focus on saquinavir, indinavir, and ritonavir, *Pharmacy World and Science* 19 (1997) 159-175. doi: 10.1023/A:1008629608556.
- [64] R. B. Diasio, Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase, *British Journal of Clinical Pharmacology* 46 (1998) 1-4. doi: 10.1046/j.1365-2125.1998.00050.x.
- [65] L. J. Pasquau and T. C. Hidalgo, Chemical characteristics, mechanism of action and antiviral activity of darunavir, *EnfermedadesInfecciosas y MicrobiologiaClinica* 26 (2008) 3-9. doi:10.1016/s0213-005x(08)76547-9.
- [66] D. A.Davis, E. E.Soule, K. S.Davidoff, S. I.Daniels, N. E.Naiman and R. Yarchoan, Activity of human immunodeficiency virus type 1 protease inhibitors against the initial autocleavage in Gag-Pol polyprotein processing, *Antimicrobial agents and Chemotherapy* 56 (2012) 3620–3628. doi: 10.1128/AAC.00055-12.
- [67] H. K.Shin, Y. M. Kang and K. T. No, Predicting ADME properties of chemicals, *Handbook of Computational Chemistry* (2017) 1-37. doi: 10.1007/978-94-007-6169-8_59-1

- [68] L. Guan, H. Yang, Y.Cai, L.Sun, P.Di, W.LiandY. Tang, ADMET-score—a comprehensive scoring function for evaluation of chemical drug-likeness, *MedChemComm* 10 (2019) 148-157. doi: 10.1039/C8MD00472B.
- [69] A. G.Kieback, S. B.Felix and T. Reffelmann, Quinaprilat: a review of its pharmacokinetics, pharmacodynamics, toxicological data and clinical application, *Expert Opinion on Drug Metabolism & Toxicology* 5 (2009) 1337-1347. doi: 10.1517/17425250903282773.
- [70] A. K.Seth, A.MisraandD.Umrigar, Topical liposomal gel of idoxuridine for the treatment of herpes simplex: pharmaceutical and clinical implications, *Pharmaceutical Development and Technology* 9 (2005) 277-289. doi: 10.1081/PDT-200031432.
- [71] Y. Y.LuiandH. L. Chan, Treatment of chronic hepatitis B: focus on telbivudine, *Expert Review of Anti-infective Therapy* 7 (2009) 259-268. doi: 10.1586/eri.09.6.
- [72] K. Y.Smith, W. G.Weinberg, E. DeJesus, M. A.Fischl, Q. Liao, L. L.RossandC. Lancaster, Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT, *AIDS Research and Therapy* 5 (2008) 5. doi: 10.1186/1742-6405-5-5.
- [73] B. M.Sadler, C. D.Hanson, G. E.Chittick, W. T. Symonds and N. S. Roskell, Safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus (HIV) type 1 protease inhibitor, following oral administration of single doses to HIV-infected adults, *Antimicrobial Agents and Chemotherapy* 43 (1999) 1686-1692. doi: 10.1128/AAC.43.7.1686.

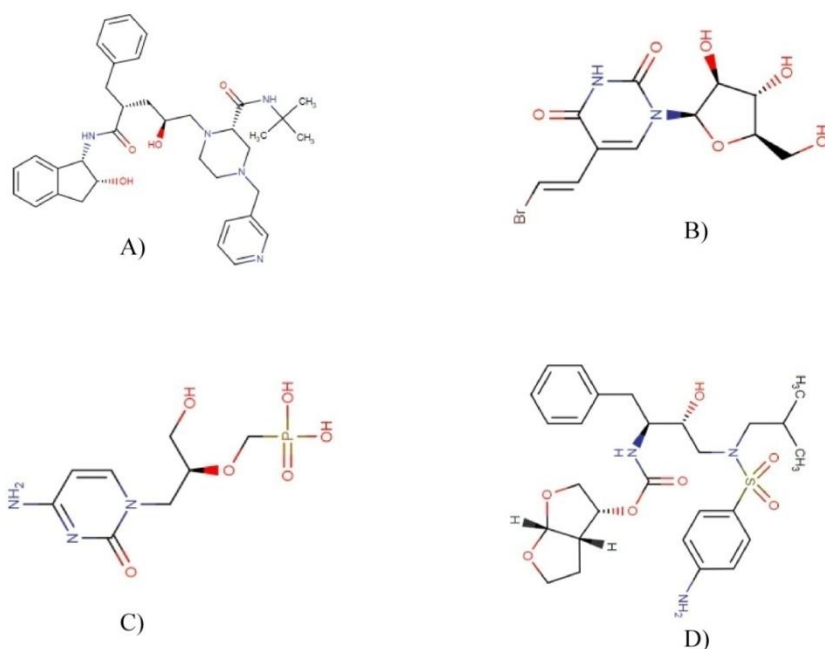


Figure 1: Chemical structures of Indinavir (A), Sorivudine (B), Cidofovir (C) and Darunavir (D)

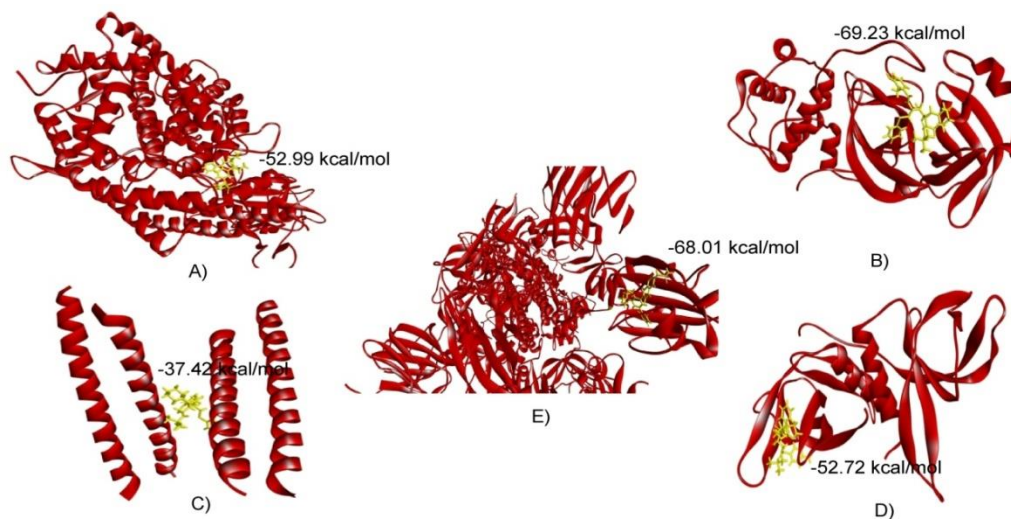


Figure 2: Molecular interaction of Sorivudine with spike receptor-binding domain (A), Indinavir with main protease (B), Indinavir with HR2 Domain (C), Cidofovir with Nsp9 RNA binding protein (D) and (E) Darunavir with spike ectodomain.

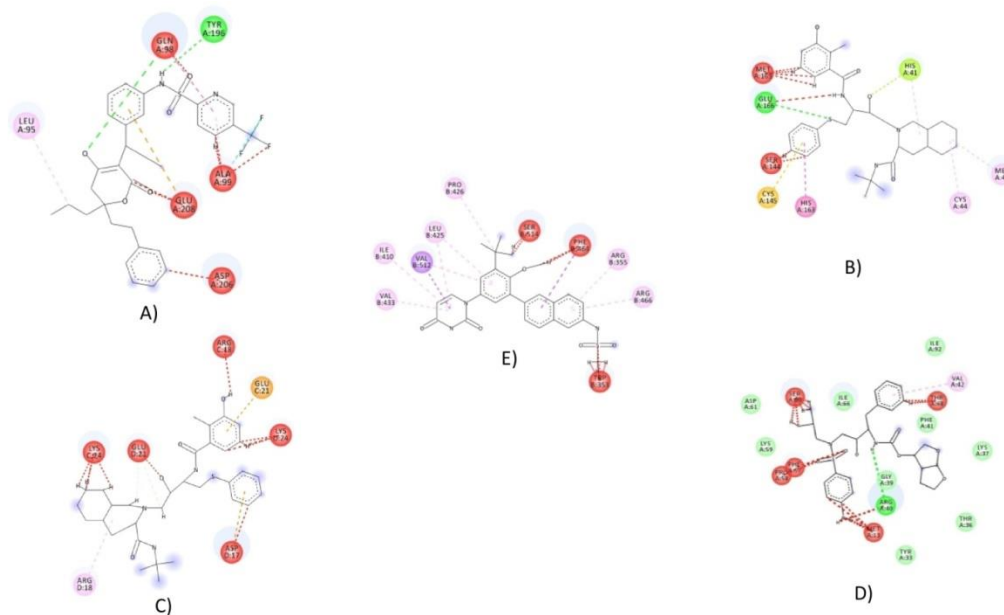


Figure 3: Ligand binding site of Sorivudine with spike receptor-binding domain (A) , Indinavir with main protease(B), Indinavir with HR2 Domain (C), Cidofovir with Nsp9 RNA binding protein (D) and (E) Darunavir with spike ectodomain.

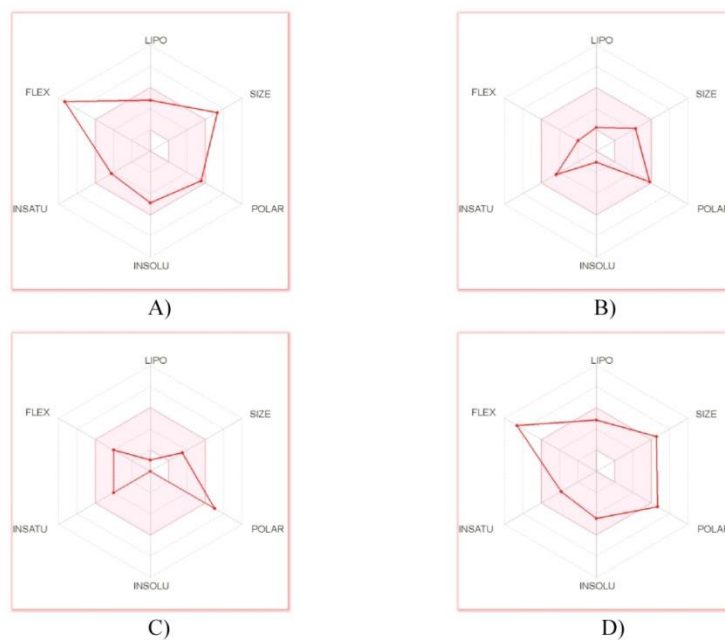


Figure 4: ADME analysis of top four drugs; Indinavir (A), Sorivudine (B), Cidofovir (C) and Darunavir (D)

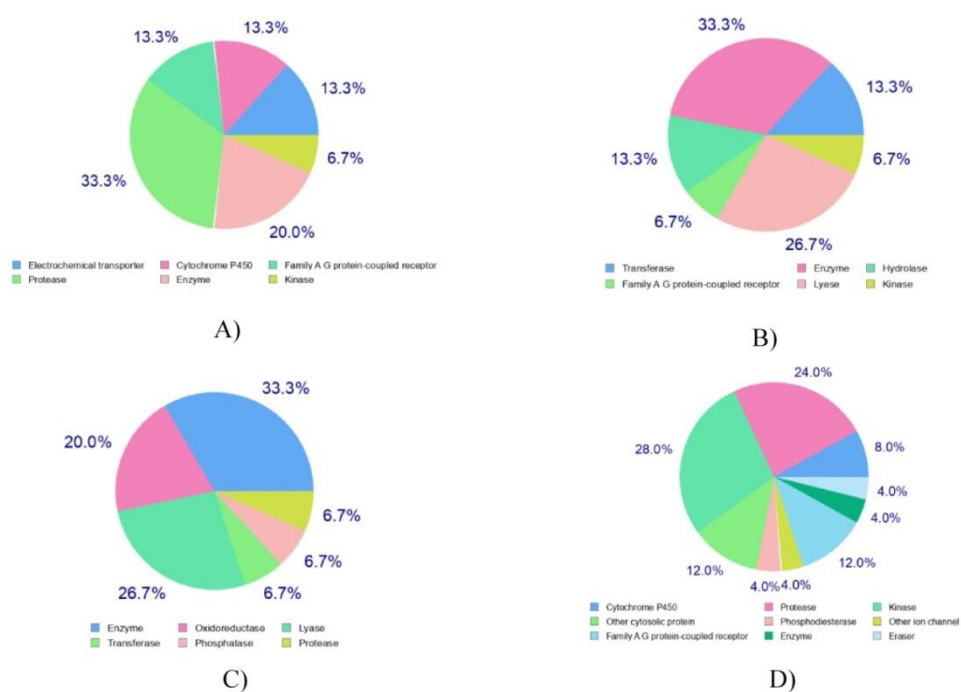


Figure 5: Prediction of drug targets for Indinavir (A), Sorivudine (B), Cidofovir (C) and Darunavir (D)

Table 1: Analysis of binding energy of top four screened drugs (ligands)

Macromolecules	Ligands	Global Energy	ACE	Score	Area	Binding sites
HR2 Domain (6LVN)	α -ketoamide (Control)	-25.52	-2.71	4318	564.20	Ile16, Asn20, Lys24, Asn27, Glu28
	Indinavir	-37.42	-2.33	5148	630.20	Gln13, Lys14, Ile16, Asp17, Arg18, Asn20, Glu21, Lys24
	Sorivudine	-29.12	-1.81	4782	592.80	Gln13, Lys14, Asp17, Arg18, Asn20, Glu21, Lys24
	Cidofovir	-28.02	-2.75	5082	568.60	Lys14, Asp17, Arg18, Asn20, Glu21, Lys24
	Darunavir	-26.27	-0.43	5102	592.10	Lys14, Asp17, Arg18, Asn20, Glu21, Ala23, Lys24, Asn27
Spike receptor binding domain (6M0J)	α -ketoamide (Control)	-60.50	-9.34	5374	655.40	Lys94, Tyr196, Asp206, Glu208, Val209, Asn210

	Indinavir	-49.51	-13.44	6372	765.30	Leu95, Leu97, Gln98, Ala99, Gln101, Tyr196, Tyr202, Trp203, Gly205, Asp206, Glu208, Val209, Asn210, Ala396, Lys562, Glu564, Pro565, Trp566
	Sorivudine	-52.99	-10.46	6254	787.40	Leu95, Gln98, Ala99, Gln102, Tyr196, Gly205, Asp206, Glu208, Val209, Asn210, Ala396, Glu398, Lys562, Glu564, Pro565, Trp566
	Cidofovir	-49.19	-13.26	6206	795.80	Lys94, Leu95, Gln98, Ala99, Gln102, Tyr196, Tyr202, Gly205, Asp206, Tyr207, Glu208, Val209, Asn210, Ala396, Lys562, Glu564, Pro565, Trp566
	Darunavir	-46.88	-14.07	5456	667.50	Leu95, Gln102, Asn103, Asn194, Tyr196, Tyr202, Trp203, Gly205, Asp206, Tyr207, Glu208, Val209, Ala396, Lys562, Glu564, Pro565, Trp566
Spike ecto-domain (6VYB)	α -ketoamide (Control)	-63.94	-17.32	5728	705.10	Thr547, Gly548, Thr549, Asp745, Val976
	Indinavir	-37.29	-4.09	7150	854.60	Arg765, Ala766, Thr768, Gly769, Ile770, Val772, Glu773, Lys776, Glu780, Lys947, Asp950, Gln954, Gln957, Gln1010, Leu1012, Ile1013, Arg1014, Glu1017, Arg1019
	Sorivudine	-52.28	-14.36	6848	824.30	Arg319, Phe541,

						Thr547, Gly548, Thr549, Asp571, Thr572, Thr573, Pro589, Cys590, Phe593, Met740, Cys743, Gly744, Asp745, Ser746, Asn856, Leu966, Ser975, Val976, Leu977, Asn978, Arg1000
	Cidofovir	-42.21	-9.27	6714	774.20	Leu368, Tyr369, Asn370, Ser371, Ala372, Ser373, Phe374, Ser375, Thr376, Phe377, Arg403, Asp405, Glu406, Arg408, Gln409, Thr415, Gly416, Lys417, Asn437, Tyr453
	Darunavir	-68.01	-25.44	6174	845.70	Ser349, Val350, Tyr351, Ala352, Trp353, Asn354, Arg355, Asp398, Ile410, Ala411, Asn422, Tyr423, Lys424, Leu425, Pro426, Phe429, Thr430, Gly431, Cys432, Val433, Pro463, Phe464, Arg466, Val512, Ser514, Phe515
Nsp9 RNA binding protein (6W4B)	α -ketoamide (Control)	-48.60	-16.39	4458	504.60	Phe41, Trp54, Ile66, Thr68, Glu69
	Indinavir	-43.27	-13.58	5908	755.00	Met13, Ser14, Thr36, Lys37, Gly38, Gly39, Arg40, Phe41, Val42, Phe57, Pro58, Lys59, Ser60, Asp61, Ile66, Thr68
	Sorivudine	-25.09	-10.17	5506	643.50	Met13, Gly38, Gly39, Arg40, Phe41, Val42, Phe57, Pro58, Lys59, Ser60, Asp61, Thr63,

						Ile66
	Cidofovir	-52.74	-18.32	5456	683.20	Met13, Tyr33, Gly39, Arg40, Phe41, Val42, Phe57, Pro58, Lys59, Ser60, Asp61, Ile66, Thr68
	Darunavir	-47.62	-17.90	5350	640.90	Met13, Ser14, Gly39, Arg40, Phe41, Val42, Phe57, Pro58, Lys59, Ser60, Asp61, Ile66, Thr68
Main protease (6W63)	α -ketoamide (Control)	-56.92	-16.84	4560	526.40	Asp197, Leu272, Gly275, Leu286, Leu287, Asp289
	Indinavir	-69.23	-21.97	5584	695.70	Thr25, Leu27, His41, Val42, Cys44, Thr45, Ser46, Met49, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, His172, Val186, Asp187, Arg188, Gln189, Gln192
	Sorivudine	-59.62	-19.53	5816	704.90	Thr25, Leu27, His41, Cys44, Thr45, Ser46, Met49, Tyr54, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, His172, Asp187, Arg188, Gln189,
	Cidofovir	-56.49	-18.88	6074	720.90	Thr24, Thr25, Thr26, Leu27, His41, Val42, Cys44, Ser46, Met49, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, His172, Val186,

						Asp187, Arg188, Gln189, Gln192
	Darunavir	-55.06	-19.64	5240	670.40	Thr25, Leu27, His41, Val42, Cys44, Thr45, Ser46, Met49, Phe140, Leu141, Asn142, Ser144, Cys145, His163, His164, Met165, Glu166, His172, Val186, Asp187, Arg188, Gln189, Thr190

Table 2: Drug profile and ADME analysis of top four drugs

Parameter		Top Inhibitors of SARS-CoV-2 Proteins			
		Indinavir	Sorivudine	Cidofovir	Darunavir
Physicochemical parameters	Formula	C ₂₁ H ₃₄ N ₄ O ₂	C ₁₁ H ₁₃ BrN 2O ₆	C ₈ H ₁₄ N ₃ O 6P	C ₂₇ H ₃₇ N ₃ O ₇ S
	Molecular weight	374.52 g/mol	349.13 g/mol	279.19 g/mol	547.66 g/mol
	No. H-bond acceptors	4	6	7	8
	No. H-bond donors	3	4	4	3
	Molar Refractivity	116.07	72.23	61.82	142.20
	TPSA	87.46 Å ²	124.78 Å ²	157.71 Å ²	148.80 Å ²
Lipophilicity	Log <i>P</i> _{o/w} (iLOGP)	2.89	1.02	-0.13	3.20
	Log <i>P</i> _{o/w} (XLOGP3)	1.52	-1.58	-3.61	2.94
	Log <i>P</i> _{o/w} (WLOGP)	0.54	-1.92	-1.65	3.46



	Log $P_{o/w}$ (ML OGP)	1.21	-0.90	-2.25	1.18
	Log $P_{o/w}$ (SIL ICOS-IT)	2.42	-0.19	-2.41	1.46
	Consensus Log $P_{o/w}$	1.71	-0.71	-2.01	2.45
Pharmacokinetics	GI absorption	High	Low	Low	Low
	BBB permeant	No	No	No	No
	P-gp substrate	Yes	No	No	Yes
	CYP1A2 inhibitor	No	No	No	No
	CYP2C19 inhibitor	No	No	No	No
	CYP2C9 inhibitor	No	No	No	No
	CYP2D6 inhibitor	Yes	No	No	No
	CYP3A4 inhibitor	No	No	No	Yes
	Log K_p (skin permeation)	-7.51 cm/s	-9.55 cm/s	-10.57 cm/s	-7.55 cm/s
Water Solubility	Log S (ESOL)	-2.62	-1.03	0.85	-4.46
	Solubility	8.90e-01 mg/ml ; 2.38e-03 mol/l	3.23e+01 mg/ml ; 9.26e-02 mol/l	1.99e+03 mg/ml ; 7.12e+00 mol/l	1.88e-02 mg/ml ; 3.44e-05 mol/l
	Class	Soluble	Very soluble	Highly soluble	Moderately soluble
	Log S (SILIC)	-5.08	-0.15	0.33	-5.33

	OS-IT)				
	Solubility	3.15e-03 mg/ml ; 8.41e-06 mol/l	2.45e+02 mg/ml ; 7.03e-01 mol/l	5.97e+02 mg/ml ; 2.14e+00 mol/l	2.55e-03 mg/ml ; 4.66e-06 mol/l
	Class	Moderately soluble	Soluble	Soluble	Moderately soluble
Medicinal Chemistry	Leadlikeness	No; 2 violations: MW>350, Rotors>7	Yes	Yes	No; 2 violations: MW>350, Rotors>7
	Bioavailability Score	0.55	0.55	0.11	0.55
	PAINS	0 alert	0 alert	0 alert	0 alert
	Synthetic accessibility	3.53	4.23	3.41	5.67

Table 3: Toxicity patterns of top four drugs

Toxicity Parameter	Drug Name			
	Indinavir	Sorivudine	Cidofovir	Darunavir
AMES Test	No	No	No	No
Max. Tolerated Dose (log mg/kg/day)	-0.358	1.274	0.187	-0.763
hERG I inhibitor	No	No	No	No
hERG II inhibitors	Yes	No	No	No
Oral Rat Acute Toxicity, LD50 (mol/kg)	2.914	2.172	1.74	2.107
Oral Rat Chronic Toxicity, LOAEL (log mg/kg_bw/day)	1.428	3.004	3.131	2.775
Hepatotoxicity	Yes	Yes	Yes	Yes
Carcinogen	Non carcinogen	Non carcinogen	Non carcinogen	Non carcinogen
Skin Sensitisation	No	No	No	No
<i>T. pyriformis</i> Toxicity (log µg/L)	0.285	0.285	0.284	0.289
Minnow Toxicity (log mM)	5.061	4.043	4.381	0.61

Table 4: Predicted drug targets for Indinavir, Sorivudine, Cidofovir and Darunavir

Drugs	Drug Targets	Common Name	Uniprot ID	ChEMBL ID	Target Class	Probability*
Indinavir	Multidrug and toxin extrusion protein 1	SLC47A1	Q96FL8	CHEMBL1743126	Electrochemical transporter	
	Multidrug and toxin extrusion	SLC47A2	Q86VL8	CHEMBL1743127	Electrochemical transporter	












	protein 2					
	Neurokinin 2 receptor	TACR2	P21452	CHEMBL2327	Family A G protein-coupled receptor	
	Renin	REN	P00797	CHEMBL286	Protease	
Sorivudine	Thymidine kinase, cytosolic	TK1	P04183	CHEMBL2883	Transferase	
	Cytidine deaminase	CDA	P32320	CHEMBL4502	Enzyme	
	Thymidine kinase, mitochondrial	TK2	O00142	CHEMBL4580	Enzyme	
Cidofovir	Thymidine phosphorylase	TYMP	P19971	CHEMBL3106	Enzyme	
	Hypoxanthine-guanine phosphoribosyltransferase	HPRT1	P00492	CHEMBL2360	Enzyme	
	Purine nucleoside phosphorylase	PNP	P00491	CHEMBL4338	Enzyme	
Darunavir	Cathepsin D	CTSD	P07339	CHEMBL2581	Protease	
	Cytochrome P450 3A4	CYP3A4	P08684	CHEMBL340	Cytochrome P450	
	Complement factor D	CFD	P00746	CHEMBL2176771	Protease	

Table 5: Structural similar bioactive molecules from drug bank

Drugs	Similar structure Drug bank id	Name	Score	Status
Indinavir	Quinapril	DB00881	0.048	Approved
	Sirolimus	DB00877	0.014	Approved
	L-756,423	DB02009	0.906	Experimental
Sorivudin	Telbivudine	DB01265	0.933	Approved
	Idoxuridine	DB00249	0.863	Approved
Cidofovir	Tenofovir	DB00300	0.811	Approved
	Riboflavin	DB00140	0.127	Approved
Darunavir	Amprenavir	DB00701	0.983	Approved
	Fosamprenavir	DB01319	0.503	Approved

Graphical Abstract :

