In silico virtual screening of known drugs against SARS-CoV-2 3CL protease: A drug repurposing approach for COVID-19

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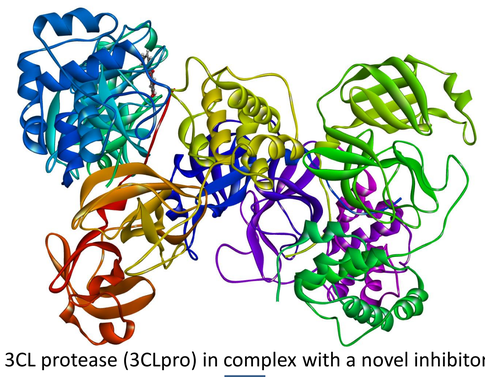
Abstract

Since the outbreak of the novel coronavirus disease (COVID-19) in late December 2019, it rapidly spread throughout the world. Besides, no specific treatment has been reported so far against the disease. In such cases, the drug repurposing approach can be an effective way to determine potential candidates to treat COVID-19. Therefore, this study is focused on screening drugs that could inhibit the viral receptor. Structure of SARS-CoV-2 3CL protease with a complex (baicalein) was employed for the generation of pharmacophore hypothesis using Schrödinger Maestro. Initially, 8820 approved, investigational and experimental drugs from DrugBank database were screened on the basis of generated hypothesis features. Among those, 1000 drugs were subjected to molecular docking-based virtual screening to evaluate the glide score and glide energy. Moreover, receptor-ligand interactions of the best hits were analyzed using discovery studio software. The virtual screening revealed several drug classes including CYP3A4 inhibitor, anti-tumor, anti-platelet, antiviral, neurological, anticancer, Vit-B2 deficiency, anti-inflammatory, antidiabetic, and anti-asthmatic which are capable of inhibiting viral receptor. In particular, six drugs namely rutin, fosifloxuridine-nafalbenamide, eluxadoline, telmisartan, fostemsavir, and capmatinib demonstrated extra precision docking with promising binding affinities. Interaction analysis revealed several hydrogens and hydrophobic bonds with the amino acids of the active site. Additionally, 19 experimental drugs were found to possess higher docking scores than the bound complex with the receptor indicating a possibility of discovering novel drugs to treat COVID-19. However, further *in vitro* and *in vivo* studies are required for the evaluation of the antiviral activity of the mentioned drugs.

Methodology

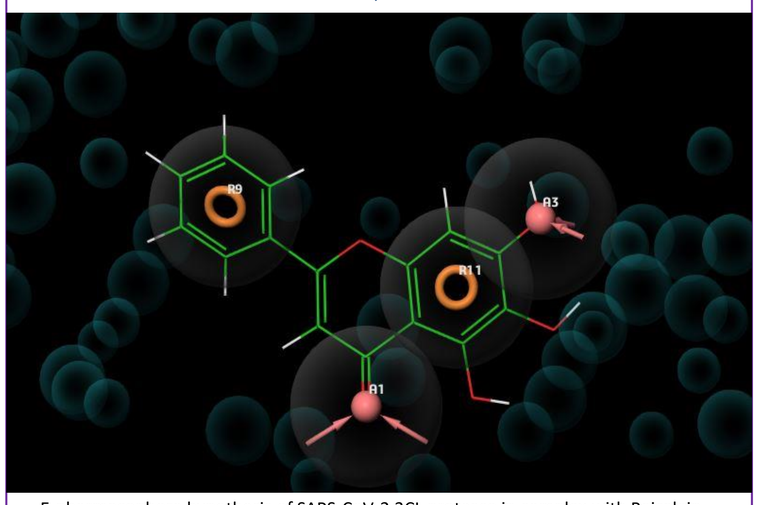


SARS-CoV-2 3CL protease (3CLpro) in complex with a novel inhibitor (Baicalein)

1. Structure Refinement
2. Structure Optimization

Schrödinger Maestro

3. Restrained Minimization
4. Hypothesis Generation



E-pharmacophore hypothesis of SARS-CoV-2 3CL protease in complex with Baicalein

DrugBank Database (8820 Molecules)

Pharmacophore Based Virtual Screening (1000 Molecules)

Docking Based Virtual Screening

Extra Precision Docking

Results

Table-1: Top 30 potential drugs obtained virtual screening.

Drug Name	Group	Category	Glide Score (kcal/mol)
Olinciguat	Investigational	CYP3A4 Inhibitor	-7.981
Glumetinib	Investigational	Anti-tumor	-7.963
Prasugrel	Approved	Anti-platelet	-7.615
BMS-488043	Investigational	Antiviral	-7.482
Darapladib	Investigational	Atherosclerosis	-7.473
Emapunil	Investigational	Anxiolytic	-7.447
Fulacimstat	Investigational	Antiinflammatory	-7.441
GSK-364735	Investigational	Antiviral	-7.432
Lucitanib	Investigational	Anticancer	-7.363
Oxyphenisatin acetate	Approved, Investigational, Withdrawn	Anticancer	-7.355
Cianidanol	Approved, Withdrawn	Antiinflammatory	-7.340
Riboflavin	Approved, Investigational, Nutraceutical	Vit-B2 Deficiency	-7.306
Ivosidenib	Approved, Investigational	Anticancer	-7.256
Inarigivir	Investigational	Antiviral	-7.246
Tepoxalin	Vet approved	Antiinflammatory	-7.220
Iguratimod	Investigational	Antiinflammatory	-7.203
Cabotegravir	Investigational	Antiviral	-7.134
MK-0533	Investigational	Antidiabetic	-7.025
Selurampanel	Investigational	Antiepileptic	-6.990
JNJ-39393406	Investigational	Antidepressant	-6.986
Pagoclone	Investigational	Anxiolytic	-6.961
Aplindore	Investigational	Neurologic disorder	-6.936
Deracoxib	Investigational	Antiinflammatory	-6.927
Apararenone	Investigational	Antidiabetic	-6.922
Spebrutinib	Investigational	Anticancer	-6.902
Dolutegravir	Approved	Antiviral	-6.884
Indibulin	Investigational	Anti-tumor	-6.873
Cromoglicic acid	Approved	Anti-asthmatic	-6.871
Sonedenoson	Investigational	Antidiabetic	-6.829
Idelalisib	Approved	Anticancer	-6.8297

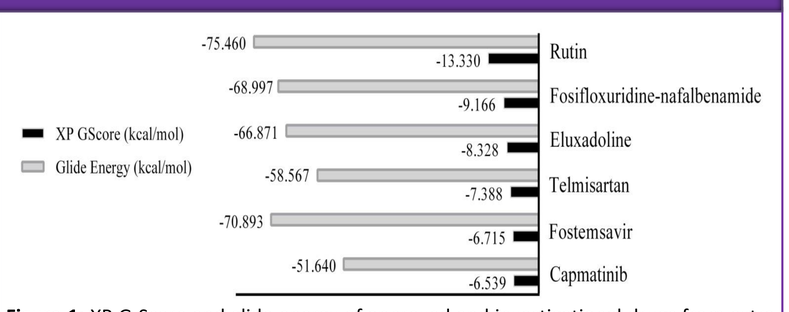


Figure-1: XP G-Score and glide energy of approved and investigational drugs from extra precision (XP) docking.

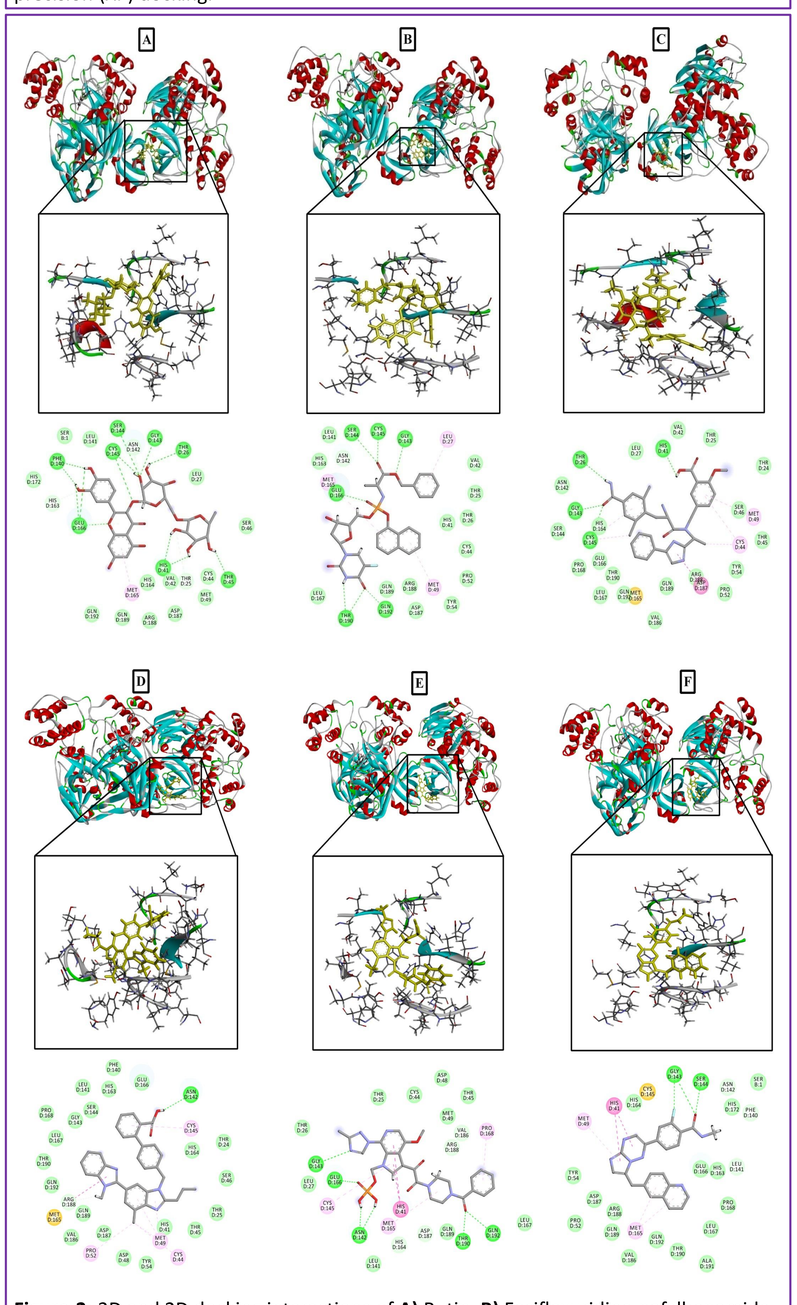


Figure-2: 3D and 2D docking interactions of **A)** Rutin, **B)** Fosifloxuridine-nafalbenamide, **C)** Eluxadoline, **D)** Telmisartan, **E)** Fostemsavir and **F)** Capmatinib with SARS-CoV-2 3CL protease.

Conclusions

In this study, structure based virtual screening identified several categories of drugs against SARS-CoV-2 3CL protease. Among those, five antiviral drugs namely BMS-488043, GSK-364735, Inarigivir, Cabotegravir, and Dolutegravir interacted with the receptor through standard precision docking. However, six drugs specifically Rutin, Fosifloxuridine-nafalbenamide, Eluxadoline, Telmisartan, Fostemsavir and Capmatinib undergone extra precision docking with promising glide scores and interaction with the receptor active site. These drugs might be repurposed for the treatment of novel coronavirus disease.

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