Repurposing of FDA Approved Drugs for the Identification of Potential Inhibitors of SARS-CoV-2 Main Protease

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Abstract

COVID-19, responsible for several deaths, demands a cumulative effort of scientists worldwide to curb the pandemic. The main protease, responsible for the cleavage of the polyprotein and formation of replication complex in virus, is considered as a promising target for the development of potential inhibitors to treat the novel coronavirus. The effectiveness of FDA approved drugs targeting the main protease in previous SARS-COV (s) reported earlier indicates the chances of success for the repurposing of FDA drugs against SARS-COV-2. Therefore, in this study, molecular docking and virtual screening of FDA approved drugs, primarily of three categories: antiviral, antimalarial, and peptide, are carried out to investigate their inhibitory potential against the main protease. Virtual screening has identified 53 FDA drugs on the basis of their binding energies (< -7.0 kcal/mol), out of which the top two drugs Velpatasvir (-9.1 kcal/mol) and Glecaprevir (-9.0 kcal/mol) seem to have great promise. These drugs have a stronger affinity to the SARS-CoV-2 main protease than the crystal bound inhibitor α-ketoamide 13B (-6.7 kcal/mol) or Indinavir (-7.5 kcal/mol) that has been proposed in a recent study as one of the best drugs for SARS-CoV-2. The *in-silico* efficacies of the screened drugs could be instructive for further biochemical and structural investigation for repurposing. The molecular dynamics and viral inhibition assay studies on the shortlisted drugs are underway.

Keywords: COVID-19, SARS-CoV-2, Main protease, Repurposing, Antiviral, Virtual screening

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged from the Wuhan city of China in late 2019, has drawn considerable attention from the scientific community worldwide, because of its severity and rapid spread of the disease (Zhu et al., 2020; Muralidharan et al., 2020; Gupta et al., 2020). An increasing number of cases and death from the coronavirus (COVID-19) worldwide certainly has an adverse impact on health and economics (Zhu et al., 2020). Thus, the identification of antiviral agents against SARS-COV-2 for the treatment of COVID-19's infection is of utmost urgency. Since the identification, development, and clinical trial in humans of any new drug takes enormous time, the repurposing of already available FDA approved drugs seems the fastest route to combat with the current novel COVID-19 pandemic.

The main protease (Mpro), also known as 3CLpro, consists of three domains, with amino acid sequences 8-101 (Domain I), 102-184 (Domain II), and 185-306 (Domain III). Domains I and II constitute the antiparallel ß barrel that forms the substrate-binding between them and Domain III is a globular cluster that helps in dimerization of Mpro [J. Shi et al.,2006]. The loop region connects Domain II to Domain III by residues within 189-191. The protease structure has a chymotrypsin-like fold that can be described as an augmented serine-protease forms a His41-Cys145 catalytic dyad at the catalytic cleavage; other important substrate-binding residues within S1-S5 subsites are Thr25, Met49, Phe140, Leu141 Asn142, Gly143, Ser144, Cys145, His163, Met165, Glu166, His172, Gln189, and Thr190 [Jin at al.,2020 and L. Zhang et al.,2020], **Figure** 1.

To date, among all coronaviruses, SARS-CoV-2 is the largest in size, approx. 27-34 kb, which belongs to a family of positive-sense, single-stranded RNA viruses. Its replicase genome encodes two polyproteins, pp1a and pp1ab, overlapping by ribosomal frameshifting [Zhou et al,2020 and Wu et al.,2020]. Proteolytic cleavage produces non-structural proteins, which form the replicase transcriptase complex. Non-structural protein 5 (nsp5) or the main protease (Mpro) exists in the polyprotein pp1a.

Among all the therapeutic targets in SARS-COV-2, Mpro is a vital as well as the best-characterized drug target for rational drug designing [Xia B et al.,2011 and Lu I-L et al.,2006]. Protease has a key role in infecting host cells [C. Steinkühler et al.,2008 & Y. Wan et al.,2020]. It has also an important role in processing the polyproteins that are translated from the viral RNA [R. Hilgenfeld et al.,2014]. Thus, inhibiting the activity of this enzyme would block the viral replication. Moreover, since no proteases with a similar cleavage specificity are known in humans, such inhibitors are unlikely to be toxic. Therefore, the replication process of the virus can be inhibited by designing a novel inhibitor against the SARS-CoV-2 Mpro.

While drug repurposing can be realized to offer a faster solution to prevent the rapid ever-spreading infection of COVID-19 [T. T. Ashburn et. al.,2004 & J. Xu et. al.,2020], the recently solved high-resolution structure of the SARS-CoV-2 Mpro in complex with a modified α-ketoamide inhibitor (α-ketoamide 13B) can be used for the screening of the potential inhibitors from the existing FDA approved drugs [Linlin Zhang et al.,2020]. The location in which α-ketoamide binds to the main protease is regarded as the binding site in the current study. Here we employ a combination of DFT, docking, and virtual screening methods for the repurposing of FDA approved drugs to identify the drug molecules that could potentially bind to the SARS-CoV-2 Main protease. The findings of this study, we believe, can provoke the designing of experiments of the

best-screened drugs for the antiviral assay study against the novel SARS-CoV-2 and subsequently clinical trial at a rapid pace. This study has therefore been undertaken to explore the molecular interaction of Antimalarial, Protease, and Nucleoside inhibitors with Mpro through molecular docking study.

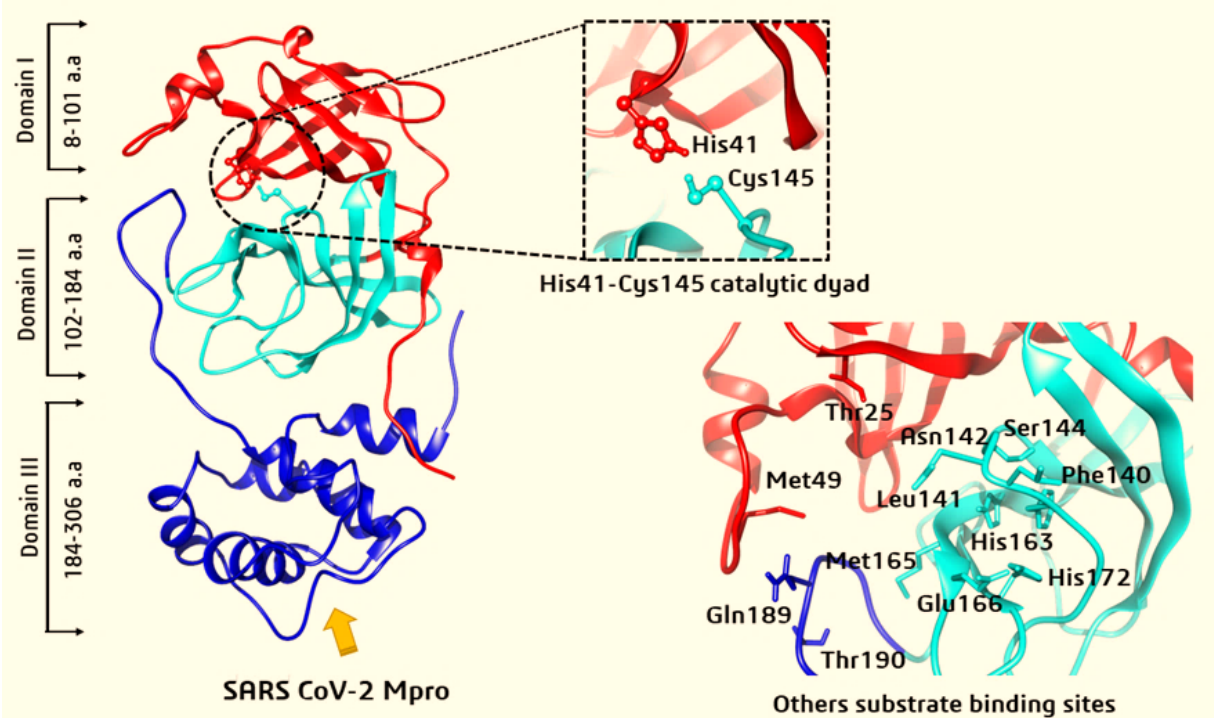

Figure 1. Three domains of the SARS-CoV-2 main protease (Mpro), with highly conserved catalytic dyad His41-Cys145 and other important catalytic residues displayed separately.

2. Materials and Methods

2.1. Protein Structure Preparation

The crystal structure of SARS-CoV-2 Mpro having PDB_ID: 6Y2F [Linlin Zhang et al.,2020], with the highest resolution of 1.95 Å was retrieved from RCSB (Protein Data Bank). The missing residues Glu47, Asp48, and Gln306 were added using MODELLER [Šali & Blundell et al.] incorporated into the Chimera UCSF and was accessed using web service [Pettersen et al.,2004].

2.2. Binding Cleft Identification

The interacting residues of the α-ketoamide 13b inhibitor with Mpro have been spotted in Discovery Studio visualizer and used as a binding site in the current study. The active site residues were found to be: 24-27, 41, 49, 54, 140-145, 163-168, 172, and 187-192 amino acids. These residues are thoroughly conserved and make a catalytic His41-Cys145 dyad as mentioned earlier. Cysteine and Histidine are an essential amino acid, which initiate the enzyme catalytic reaction [Jin at al.,2020 and L. Zhang et al.,2020]. Additionally, there was a substrate-binding subsite

positioned in the active site groove of the protease. The specific subsite residues located in the enzyme active site are named as S1 and S2 (buried subsites), S3, S4, and S5 (shallow subsites) depending on their relative positions to the cleavage site [Jin et al.,2020]. In the Mpro active site region of SARS-CoV-2, the S1 subsite is contributed by Phe140, His163, Glu166, Cys145, Gly143, His172, which also serve as the oxyanion (or hydroxyl group) hole of serine protease [Linlin Zhang et al.,2020]. The residues Cys145, His41, and Thr25 are located at the S2 position, amino acids in this position are involved in hydrophobic and electrostatic interactions. The shallow subsites S3-S5 contain Met49, His41, Met165, Glu166, Pro168, and Gln189 amino acid residues (Linlin Zhang et al.,2020). Structural details and interactions are shown in **Figure 1**.

2.3. Protein and Ligand preparation

All available FDA approved antiviral, antimalarial, and protease inhibitor drugs (total 200) were retrieved from DrugBank5.0 [Wishart DS et al.,2018] and SuperDrug2 [Vishal B Siramshetty et al.,2018] to prepare a combinatorial drug library for screening. Mpro and ligands (FDA approved drugs) were prepared for molecular docking by adding missing hydrogens and the Gasteiger charges to atoms using Autodock tools [Morris et al.,2009].

2.4. Molecular docking

Docking study was performed by AutoDock 4.2, AutoGrid and Vina [Trott O et al., 2010], which use a Lamarckian genetic algorithm (GA) in combination with grid-based energy estimation incorporated in PyRx [Dallakyan et al., 2015]. After molecular docking and initial screening, the screened FDA approved drugs were optimized with Gaussian 16 [M. J. Frisch et al.,2016] by the semiempirical PM6 method to improve the screening and docking scores of the drugs. This was repeated again by switching over to DFT B3LYP/6-311G (d, p) based geometry optimization followed by screening. In this manner, docking and re-docking were repeatedly performed between Mpro and the drug molecules optimized at different levels (semiempirical, DFT, etc.) to screen them out. In the docked configurations, different molecular interactions prevail such as the conventional hydrogen bond, π-sulfur, π-sigma, π-anion, π-alkyl, and Alkyl.

3. Results and Discussion

3.1. Molecular docking and binding mode analysis

All the candidates in the drug library prepared were docked at the same active site region where the ligand α-ketoamide 13b was co-crystallized with SARS-CoV-2 Mpro.

Recently, Chang *et al*. reported Indinavir and Remdesivir as the best drug candidates against COVID-19 from the screening of FDA approved drugs for repurposing (Chang et al., 2020). Since Remdesivir is an RNA dependent RNA polymerase (RdRP) inhibitor, we have considered Indinavir (protease inhibitor) as a reference drug for comparison with our screened drugs against the main protease. **Table 1** lists out the best screened FDA approved drugs from this study having the binding energy or docking score ≤ -9.0 kcal/mol along with a reference drug Indinavir and the co-crystallized ligand α-ketoamide 13b, which have been considered for further analyses in this study. **Table S1** contains all the FDA drugs with binding energies ≤ -7.0 kcal/mol, a total number of 53 drugs.

Table 1: A list of the best screened FDA approved drugs, a reference drug (Indinavir), and the co-crystallized ligand with their respective binding energy with Mpro.

S. No.	Repurpose FDA Approved Drugs	Binding Affinity (kcal/mol)
1	Velpatasvir	-9.1
2	Glecaprevir	-9.0
3	Indinavir	-7.5
4	α-ketoamide 13b (co-crystallized ligand)	-6.7

Compared to the α-ketoamide 13b compound as reported in Ref. [Linlin Zhang et al.], notably, the top 2 compounds in the list: Velpatasvir and Glecaprevir have very stronger affinities to the protein target SARS-CoV-2 Mpro of -9.1 kcal/mol and -9.0 kcal/mol, respectively. Velpatasvir is an antiviral agent and NSP5A inhibitor [Ascher DB et al.,2014] used to treat chronic liver infection in the Hepatitis C virus [Lee R et al.,2017]. NSP5A is a viral protein that plays a key role in the replication of the Hepatitis C virus, assembly, and modulation of the host immune response [Mogalian E et al.,2017]. Likewise, Glecaprevir acts as a protease inhibitor of NS3/4A Hepatitis C virus by hijacking the viral replication machinery.

The interacting residues of Velpatasvir with the main protease are shown in **Figure 2**.

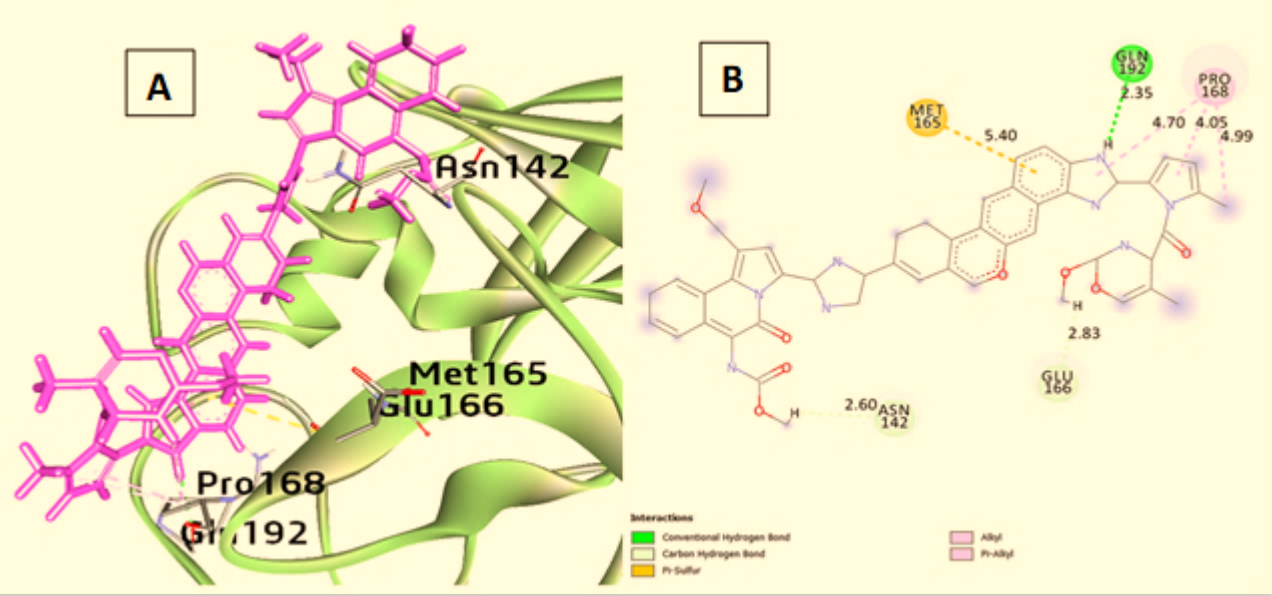

Figure 2: The (A) 3D and (B) 2D diagrams depicting residues contributed majorly to the interaction between Velpatasvir and the main protease.

The amide hydrogen (H-N) of Velpatasvir forms a conventional hydrogen bond (h-bond) with the oxygen of Gln192 residue with NH···O within a distance of 2.35 Å. Asn142 and Glu166 amino acid residues are involved in carbon-hydrogen bond formation with the Velpatasvir within a distance of 2.60 Å and 2.83 Å respectively. Met165 residue forms a π-sulfur bond with Velpatasvir. Pro168 amino acid residue is also involved in π-alkyl interaction with Velpatasvir within the proximity of 4.05 Å and 4.70 Å. These interactions give rise to -9.1 kcal/mol energy as mentioned before.

Glecaprevir binds strongly to the target site of the main protease with four conventional h-bonds with residues, namely: Thr25 (2.71 Å), His41 (2.97 Å), Asn142 (2.73 Å), and Cys145 (2.36 Å), please see **Figures 3A and B**. Apart from these h-bonds, there exists one carbon-hydrogen bond interaction with His41(3.74 Å). There is -9.0 kcal/mol interaction energy between Glecaprevir and the main protease as shown in **Table 1**. Glu166 side chain residue is also interacting in close proximity with two aromatic rings within 3.23 Å and 3.68 Å distances. Moreover, residues like Pro168 and Thr26 interact with an alkyl group and the halogen atom of Glecaprevir as seen in **Figure 3**. For all drugs listed in **Table 1**, which includes two shortlisted FDA approved drugs, a reference drug, and the co-crystallized ligand, the details of various interactions present are provided in Table S1.

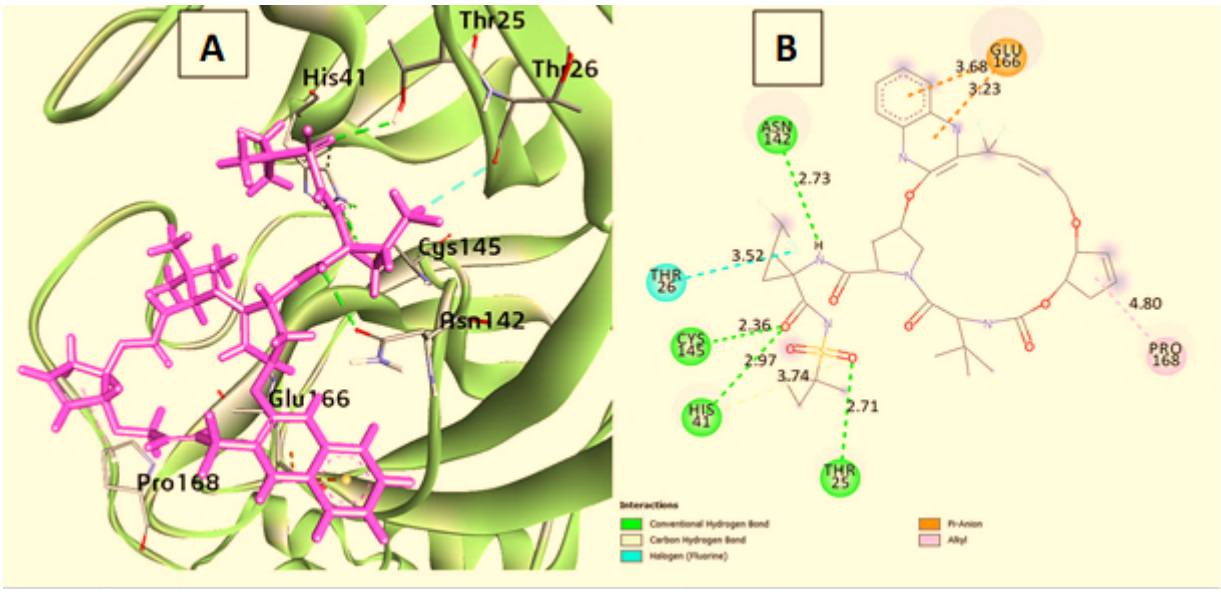

Figure 3: The (A) 3D and (B) 2D diagrams depicting residues contributed majorly to the interaction between Glecaprevir and the main protease.

Figure 4 shows the interacting residues of the main protease with the reference FDA drug Indinavir. Indinavir interacts with the main protease to form three h-bonds involving GLU166, HIS164, and THR45 within 2.26 Å, 2.20 Å, and 2.15 Å distances, respectively. Residues involved in π -interactions are LEU141 and MET165, which are situated 3.82 Å and 5.13 Å, respectively, vicinal to the nearest interacting sites of Indinavir. Altogether, these interactions result in -7.5 kcal/mol binding energy between Indinavir and the main protease given in **Table** 1 as mentioned before.

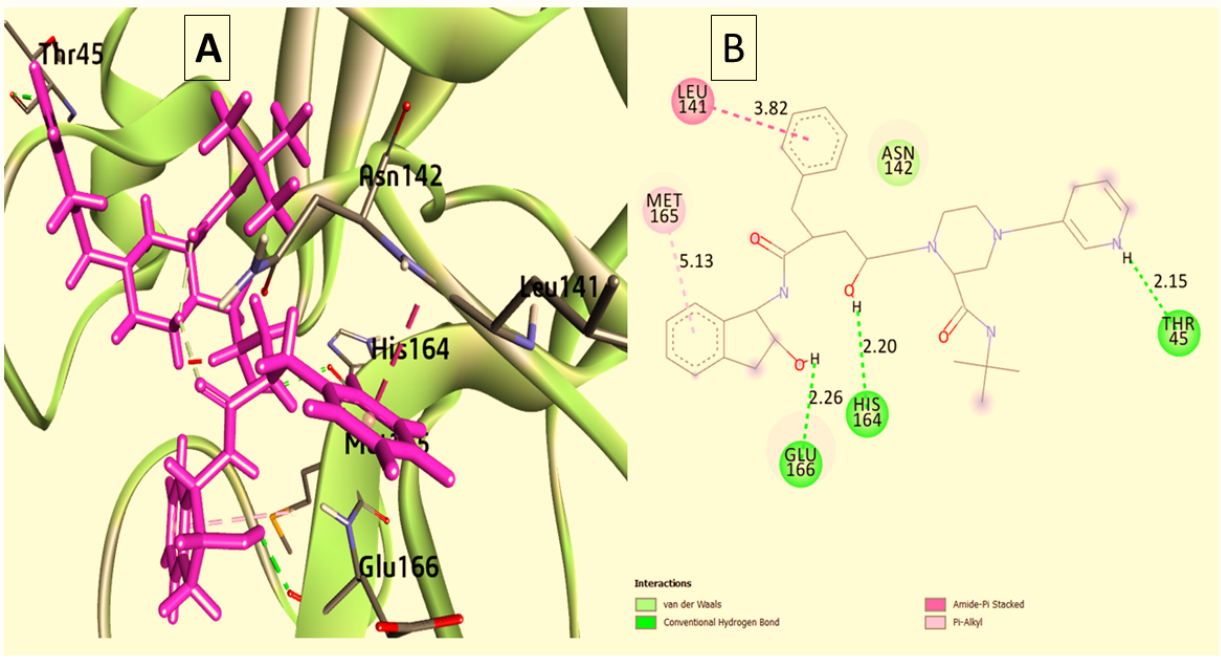

Figure 4: The (A) 3D and (B) 2D diagrams depicting residues contributed majorly to the interaction between Indinavir and the main protease.

Interestingly, the FDA approved drug Velpatasvir having the best docking score seems to possess a less number of interactions than Glecaprevir and others (**Tables 1** and **S2**). What are the factors responsible for the lowest binding energy of Velpatasvir than others? After careful observation, it is recognized that the involvement of a large number of amino acid residues participating in the van der Waals interaction and their additive effect might be the reason of the lowest binding energy. Molecular dynamics simulation and free energy calculation may further insight into this and validate the screening results.

Conclusion

The present study deals with the screening of existing antiviral, antimalarial, and protease inhibitor FDA approved drugs against a crucial target of SARS-COV-2, the main protease, to find a faster remedy to the ever-spreading infection of COVID-19. Molecular docking and virtual screening of 200 FDA approved drugs revealed Velpatasvir and Glecaprevir could be the best choices to treat COVID-19 because of their strongest binding affinities around -9.0 kcal/mol with the SARS-COV-2 target. The FDA approved drug Indinavir being reported recently as one of the best inhibitors of SARS-COV-2, we have compared Indinavir with our screened-out drugs which outperform the former. To further validate the screening results, molecular dynamics and free energy calculation are underway. Post-molecular dynamics simulation, Velpatasvir and Glecaprevir will undergo antiviral assay study here against the main protease of SARS-CoV-2 (COVID-19) that will be

decisive for the next clinical trial step. The structural insights, key interacting residues, and the binding mechanisms of the screened drugs would further help in designing a better inhibitor of the main protease.

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Conflict of interest

The authors report no conflicts of interest.

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Supporting Information

Repurposing of FDA Approved Drugs for the Identification of Potential Inhibitors of SARS-CoV-2 Main Protease

Table S1: A list of FDA approved drugs and their binding energies with the SARS-CoV-2 main proteas.

S. No.	Repurpose FDA approved Drugs	Binding affinity (kcal/mol)
1	Alpha Ketoamide 13b (co-crystallized ligand)	-6.7
2	Velpatasvir	-9.1
3	Glecaprevir	-9.0
4	Grazoprevir	-8.7
5	Baloxavir marboxil	-8.4
6	Danoprevir	-8.4
7	Betulinic Acid	-8.3
8	Fostemsavir	-8.2
9	Ledipasvir	-8.2
10	Paritaprevir	-8.2
11	Daclatasvir	-8.1
12	Faldaprevir	-8.1
13	Lonafarnib	-8.1
14	Ravidasvir	-8.1
15	Voxilaprevir	-8.1
16	Nelfinavir_mesylate	-8.1
17	Beclabuvir	-8.0
18	Dolutegravir	-8.0
19	Saquinavir	-8.0
20	Bictegravir	-7.9
21	Nelfinavir	-7.9
22	Raltegravir_potassium	-7.9
23	Tetrandrine	-7.9
24	Calanolide_A	-7.8
25	Letermovir	-7.8
26	Telaprevir	-7.8

27	Pimodivir	-7.7
28	Pyronaridine	-7.6
29	Dasabuvir	-7.5
30	Inarigivir	-7.5
31	Indinavir	-7.5
32	JE_2147	-7.5
33	Presatovir	-7.5
34	Elsulfavirine	-7.4
35	Tecovirimat	-7.4
36	Vedroprevir	-7.4
37	Adafosbuvir	-7.4
38	Asunaprevir	-7.3
39	Delavirdine	-7.3
41	Doxycycline	-7.3
42	Doravirine	-7.3
43	Uprifosbuvir	-7.3
44	Artefenomel	-7.2
45	Maraviroc	-7.2
46	Rupintrivir	-7.2
47	Darunavir_ethanolate	-7.1
48	Ombitasvir	-7.1
49	Rilpivirine	-7.1
50	TMC_310911	-7.1
51	Etravirine	-7.1
52	Pleconaril	-7.1
53	BMS_488043	-7.0

Table S2: Different types of interactions present between the SARS-CoV-2 main protease and the amino acid residues of selected FDA approved drugs for repurposing. Also, the distances of the amino acid residues from the nearest interaction site of the drugs are reported in Å.

Name of the drugs	Hydrogen bond interaction	Carbon-hydrogen bond interaction	π-sigma interaction	π-sulfur interaction	π-alkyl interaction	Alkyl interaction	π-anion interaction	Halogen interaction
α-Ketoamide 13b	Asn142 (2.38); Gly143 (2.47); Cys145 (2.60)	Glu166 (2.41)	Met49 (3.65)	Met49 (4.08)	His41 (5.11) Cys44 (5.12) Met165 (5.04)	Met165 (4.17)		
Velpatasvir	Gln192 (2.35)	Asn142 (2.60) Glu166 (2.83)		Met165 (5.40)	Pro168 (4.70) Pro168 (4.05)	Pro168 (4.99)		
Glecaprevir	Thr25 (2.71) His41 (2.97) Asn142 (2.73) Cys145 (2.36)	His41 (3.74)				Pro168 (4.80)	Glu166 (3.23) Glu166 (3.68)	Thr26 (3.52)
Indinavir	Thr45 (2.15) His164 (2.20) Glu166 (2.26)		Leu141 (3.82)		Met165 (5.13)			