 doi:10.20944/preprints202004.0146.v1

Virtual screening of potential inhibitors for SARS-CoV-2 main protease

Carlos Javier Alméciga-Díaz[1,*], Luisa N. Pimentel-Vera[2,3], Angela Caro[4,5], Angela Mosquera[6], Camilo Andrés Castellanos Moreno[5], Juan Pablo Manosalva Rojas[5], Diana Carolina Díaz-Tribaldos[7]

[1] Institute for the Study of Inborn Errors of Metabolism, Faculty of Sciences, Pontificia Universidad Javeriana, Bogotá D.C, Colombia

[2] Centro de Terapia Gênica, Serviço de Pesquisa Experimental - Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil.

[3] Programa de Pós-Graduação em Genética e Biologia Molecular da Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

[4] Chemistry Department, Faculty of Sciences, Pontificia Universidad Javeriana, Bogotá D.C, Colombia

[5] Colombian Pharmacovigilance Association, Bogotá D.C., Colombia

[6] Gimnasio Campestre Marie Curie, Bogotá D.C., Colombia

[7] Internal Medicine, Faculty of Medicine, Universidad Nacional de Colombia, Bogotá D.C., Colombia

* Corresponding author: **Carlos J. Alméciga-Díaz, BPharm, Ph.D.**, Institute for the Study of Inborn Errors of Metabolism, Pontificia Universidad Javeriana, Cra. 7 No. 43-82 Building 54, Room 305A. Bogotá D.C., 110231, Colombia. Tel: +57-1 3208320 Ext 4140; Fax: +57-1 3208320 Ext 4099; E-mail: cjalmeciga@javeriana.edu.co.

 doi:10.20944/preprints202004.0146.v1

Abstract

Coronavirus Disease 2019 (Covid-19) was first described in December 2019 in Wuhan, Hubei Province, China; and produced by a novel coronavirus designed as the acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Covid-19 has become a pandemic reaching over 1.3 million confirmed cases and 73,000 deaths. Several efforts have been done to identify pharmacological agents that can be used to treat patients and protect healthcare professionals. The sequencing of the virus genome not only has offered the possibility to develop a vaccine, but also to identified and characterize the virus proteins. Among these proteins, main protease (M^{pro}) has been identified as a potential therapeutic target, since it is essential for the processing other viral proteins. Crystal structures of SARS-CoV-2 M^{pro} and inhibitors has been described during the last months. To describe additional compounds that can inhibit SARS-CoV-2 M^{pro}, in this study we performed a molecular docking-based virtual screening against a library of experimental and approved drugs. Top 10 hits included Pictilisib, Nimorazole, Ergoloid mesylates, Lumacaftor, Cefuroxime, Cepharanhine, and Nilotinib. These compounds were predicted to have higher binding affinity for SARS-CoV-2 M^{pro} than previously reported inhibitors for this protein, suggesting a higher potential to inhibit virus replication. Since the identified drugs have both pre-clinical and clinical information, we consider that these results may contribute to the identification of treatment alternative for Covid-19. Nevertheless, *in vitro* and *in vivo* confirmation should be performed before these compounds could be translated to the clinic.

Keywords: Coronavirus Disease 2019; SARS-CoV-2; Main protease; molecular docking-based virtual screening

 doi:10.20944/preprints202004.0146.v1

Introduction

Coronavirus Disease 2019 (Covid-19) was first described in December 2019 in clusters of patients with pneumonia of unknown cause in Wuhan, Hubei Province, China [1]. The agent producing Covid-19 was identified as a novel coronavirus, designed as the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which share a high similarity with other previously described betacoronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Covid-19 has become a pandemic that has reached over 1.3 million confirmed cases in 184 countries and 73,000 deaths [3].

Since the early stages of SARS-CoV-2 pandemic, several efforts have been done to identify pharmacological agents that inhibit the virus entry, avoid the virus replication or blocks the assembly of new viruses [4-6]. A randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, was performed to evaluate the impact of lopinavir (a protease inhibitor) and ritonavir (which enhance the half-life of lopinavir by inhibiting cytochrome P450) treatment for 14 days, in addition to standard of care [7]. Remdesivir, an inhibitor of the RNA-dependent RNA polymerase, originally developed for Ebola and related viruses has been also considered as an alternative to treat Covid-19, due to some case reports [8]. Chloroquine and hydroxychloroquine, which decrease acidity in endosomes probably affecting the entry of the virus to the cell, are also under consideration due to encouraging results in China and France [9, 10]. However, currently, none of these strategies have shown a clear and significant impact on the clinical improvement of treated patients.

On the other hand, a run has begun for the development of a SARS-CoV-2 vaccine, boosted for the fast sequencing of the virus genome, the identification of virus receptor, and the structure of the spike protein of the virus [6]. Some strategies are currently under development including mRNA-, recombinant proteins-, and gene therapy-based vaccines; as well as live attenuated and inactivated virus vaccines [6]. Nevertheless, several issues may suggest that a SARS-CoV-2 vaccine will not be

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

available before 1 year since 1) both preclinical and clinical trials are still necessary to confirm safety and efficacy, 2) the large-scale manufacturing capacity needed to cover demand; and 3) lack of appropriate animal models to evaluated the protective capacity of the vaccines [6].

In this sense, it is still necessary to identify therapeutic agents that can rapidly be translated from the bench to the clinic, in order to benefit the patients and protect healthcare professionals that are fighting against this pandemic. Virus proteases are potential SARS-CoV-2 treatment targets, since they are essential for the processing of viral proteins. Crystal structures of the main protease (M^{pro}) of SARS-CoV-2 have been reported during the last months (PDB 6Y2E and 6LU7) [11, 12]. In addition, ligands for this protease have been also described ([11, 12], also see https://cdn.rcsb.org/rcsb-pdb/general_information/news_publications/SARS-Cov-2-LOI/SARS-Cov-2-main-protease-LOI.tsv). For instance, Zhang et al. described peptidomimetic α-ketoamide-based inhibitors for SARS-CoV-2 M^{pro} with IC_{50} of 2.39 and 0.67 µM for 13a and 13b compounds, respectively [13]. Similarly, Jin et al. evaluated several SARS-CoV-2 M^{pro} inhibitors, which showed IC_{50} ranging from 0.67 to 125 µM [11]. To describe additional compounds that can inhibit SARS-CoV-2 M^{pro}, in this study we performed a molecular docking-based virtual screening against a library of experimental and approved drugs. We have previously shown the potential of this strategy through the identification of pharmacological chaperones (competitive inhibitors) for lysosomal enzymes [14, 15].

Re-docking of SARS-CoV-2 M^{pro} ligands.

Before performing the virtual screening, we carried out a re-docking analysis for two reported SARS-CoV-2 M^{pro} structures (PDB 6Y2E and 6LU7) and their ligands. Molecular docking was performed as previously described for fungal fructosyltransferases and the human lysosomal enzymes N-acetylgalactosamine-6-sulfate sulfatase and N-acetyl-alpha-glucosaminidase [14-16]. M^{pro} crystal

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

structures and ligands were prepared using UCSF Chimera, candidate version 1.14 (build 42091) [17]. Ligands were retrieved from RCSB-Protein Data Bank and PubChem. Docking was performed using Autodock vina [18], with the grid for the docking centered within the active cavity of SARS-CoV-2 M^{pro} [11, 12] and a size set to 20×20×20 for X, Y and Z axis, respectively. We evaluated the best 20 conformations for each of the ligands inside SARS-CoV-2 M^{pro} active cavity and the results of ligand-protein interaction are reported as the affinity energy (kcal/mol).

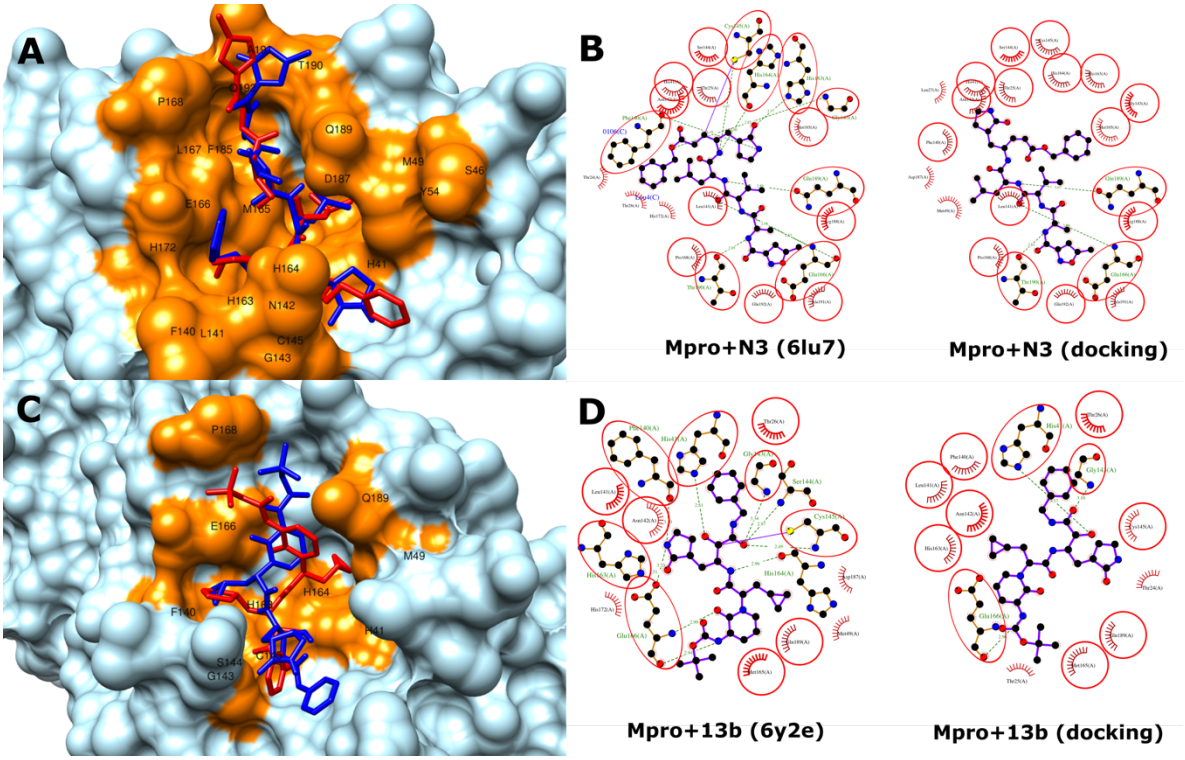


Figure 1. Complexes of SARS-CoV-2 M^{pro} with N3 (A, PDB: 6lu7) and α-ketoamide 13b (C, PDB: 6y2e) after crystallization (red) or re-docking (blue). Reported amino acids interacting with each ligand are colored in orange. Protein-substrate interactions between human SARS-CoV-2 M^{pro} with N3 (B, PDB: 6lu7) and α-ketoamide 13b (D, PDB: 6y2e). Circle residues correspond to conserved interactions among all the substrates. Green and black name residues are amino acids interacting through hydrogen bond and hydrophobic interactions, respectively.

As observed in **Figure 1**, N3 and α-ketoamide 13b docked within the active cavity of SARS-CoV-2 M^{pro} in a similar position and interacted with similar residues, compared to that observed for the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

crystallized structures. These results suggest that the docking protocol used in this study can predict the protein–ligand interactions for SARS-CoV-2 M^{pro}. Docking results predicted that N3 and α-ketoamide 13b bind to SARS-CoV-2 M^{pro} with an affinity energy of -8.2 and 8.0 kcal/mol, respectively. Reported IC_{50} for α-ketoamide is 0.67 μM [12], while for N3 a significant inhibition of SARS-CoV-2 M^{pro} was observed with 0.4 and 1.0 μM [11]. In this sense, both inhibitors have similar inhibition potency, which correlates with the affinity energy predicted after docking. Considering these results, we docked other reported SARS-CoV-2 M^{pro} inhibitors [11, 12] and compared their affinity energies and reported IC_{50}. We also included the reported aldehyde Cm-FF-H (PDB 3SN8), which was described as a potent inhibitor for SARS-CoV M^{pro} [17]. As observed in **Figure 2**, PX-12 (PubChem CID 219104, -4.3 kcal/mol), Shikonin (PubChem CID 479503, -7.0 kcal/mol), Tideglusib (PubChem CID 11313622, -7.9 kcal/mol), α-ketoamide 13a (-8.7 kcal/mol), 14b (-7.8 kcal/mol), and aldehyde Cm-FF-H (-7.6 kcal/mol) docked within the active cavity of SARS-CoV-2 M^{pro}. Noteworthy, we observed a direct correlation between the calculated *K*i [18] and the reported IC_{50} ($R^2 = 0.89$), suggesting that the higher the binding affinity the higher the inhibition potency of the compound (**Figure 2C**). In this sense, these results suggest that a molecular docking-based virtual screening could be used to identify potential inhibitors for SARS-CoV-2 M^{pro}.

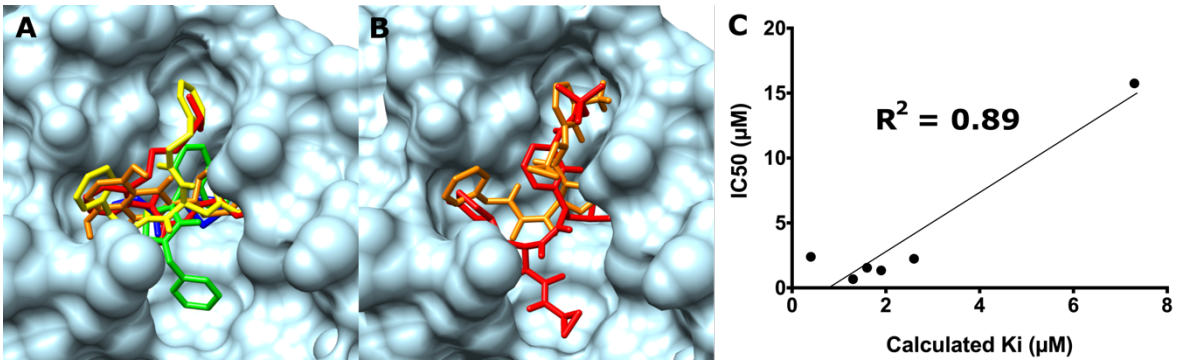


Figure 2. A. Docking of SARS-CoV-2 M^{pro} PDB 6lu7 with PX-12 (blue), Shikonin (orange), Tideglusib (green), and aldehyde Cm-FF-H (yellow, a SARS-CoV inhibitor). **B.** Docking of SARS-CoV-2 M^{pro} PDB 6y2e with α-ketoamide 13a (red) and 14b (blue). **C.** Correlation between the calculate *K*i (μM) and the reported IC_{50} (μM) for each inhibitor.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

Virtual screening of SARS-CoV-2 M^{pro} inhibitors.

To identify potential inhibitors for SARS-CoV-2 M^{pro}, virtual screening was implemented using an in-house algorithm [14, 15] integrating Autodock vina, the ZINC In Man subset of ZINC (11,421 compounds) [19] and SARS-CoV-2 M^{pro} (PDB 6lu7). Docking for each ligand was run 20 times and constrained to the active cavity. The virtual screening was performed at the High-Performance Computing Center (ZINE) of Pontificia Universidad Javeriana. **Table 1** summarizes the top 10 hits interacting with SARS-CoV-2 M^{pro}, including information about potential targets based on ChEMBL 20 [20]. Pictilisib was predicted as the compound with the highest affinity, followed by Nimorazole. Ergoloid mesylates (Dihydroergotoxine, Ergocristine, and Ergoloid) were ranked 3, 4, and 7, suggesting the high the affinity of these groups of compounds for SARS-CoV-2 M^{pro}. A structure-based clustering was performed for the top 10 hits, by using the multidimensional scaling (MDS) algorithm available at ChemMine Web Tools [21]. The results predicted, as expected, ergoloid mesylates were cluster together; while Nilotimib/Lumacaftor, Cepharenhine/Cefuroxime/Pictilisib, and Nimorazole/2-(n-Morpholino)-Ethanesulfonic Acid, share structural similarities that led to be grouped in three separated clusters (**Figure 3**). These clustering results may shed light on the structure-based design of novel for SARS-CoV-2 M^{pro} inhibitors.

Docking analysis predicted affinity energies between -9.8 and -9.1 kcal/mol (*Ki* between 0.06 and 0.21 μM) for the top 10 hits, which are lower than those predicted for reported SARS-CoV-2 M^{pro} inhibitors (affinity energies ranging from -8.7 to -4.3 kcal/mol and *Ki* between 0.4 and 7.3 μM). By using the linear regression from **Figure 2C**, we predicted that these set of compounds would have similar IC_{50} values to those reported for SARS-CoV-2 M^{pro} inhibitors (**Table 1**), showing their potential to inhibit virus replication.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

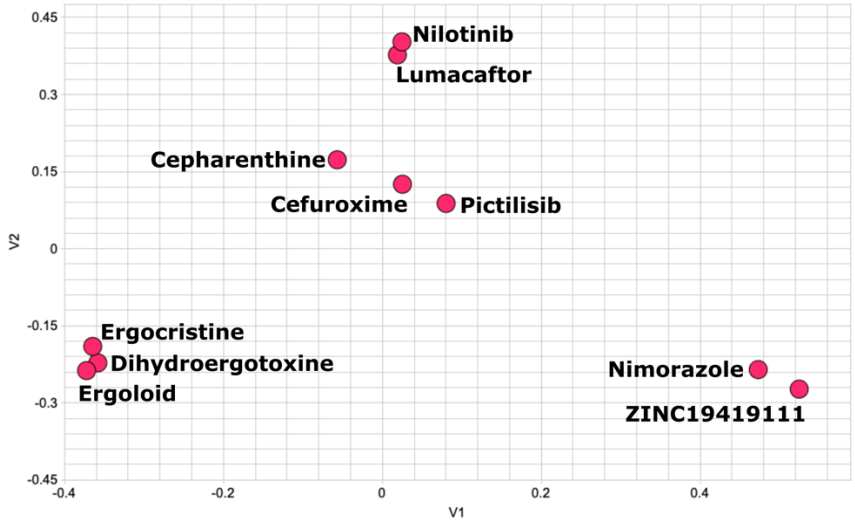
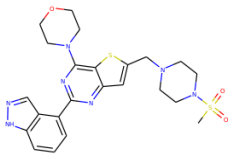
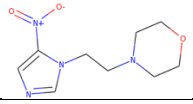
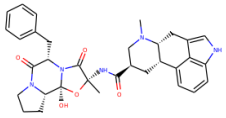
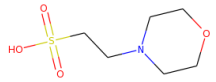
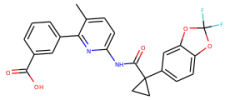
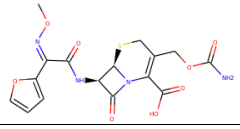
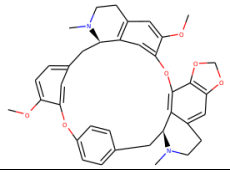
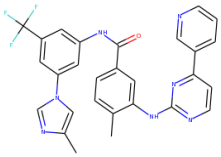


Figure 3. Clustering of top 10 hits interacting with of SARS-CoV-2 M^{pro}. ZINC19419111: 2-(n-Morpholino)-Ethanesulfonic Acid

Table 1. Top 10 hits of the compounds interacting with SARS-CoV-2 M^{pro} (PDB 6lu7) after virtual screening against the ZINC In Man subset from ZINC.

Rank	ZINC ID	Name and structure	Targets (based on ChEMBL 20)	Affinity energy (kcal/mol)	Predicted IC_{50} (μM)
1	ZINC16052714	Pictilisib 	• Phosphatidylinositol 4-phosphate 3-kinase • Casein kinase • Tyrosine kinase • Serine/threonine-protein kinase • Leucine zipper kinase • Cyclin-G-associated kinase	-9.8	1.84
2	ZINC26167988	Nimorazole 	No identified	-9.7	1.86
3, 4, 7	ZINC14880002 ZINC53282743 ZINC03995616	Dihydroergotoxine (Ergocristine, Ergoloid) 	• 5-hydroxytryptamine receptor 5A • Somatostatin receptor type 2 • Somatostatin receptor type 1 • Alpha-2 adrenergic receptor	-9.7 -9.4	1.86 1.98
5	ZINC19419111	2-(n-Morpholino)-Ethanesulfonic Acid	No identified	-9.7	1.86

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

Rank	ZINC ID	Name and structure	Targets (based on ChEMBL 20)	Affinity energy (kcal/mol)	Predicted IC_{50} (μM)
					
6	ZINC64033452	Lumacaftor 	No identified	-9.5	1.93
8	ZINC03871978	Cefuroxime 	• Beta-lactamase • Solute carrier family	-9.2	2.09
9	ZINC30726863	Cepharanthine 	• Trypanothione reductase • Dopamine receptor • Tissue factor	-9.2	2.09
10	ZINC06716957	Nilotinib 	• Tyrosine-protein kinase • Mast/stem cell • Discoidin domain • Platelet-derived growth factor • Breakpoint cluster region protein • Vascular endothelial growth • Mitogen-activated protein kinase	-9.1	2.16

We then performed a pharmacological analysis of the top 10 hits (**Table 2**). Although the analysis of the biological plausibility showed that under the current evidence the predicted SARS-CoV-2 M^{pro} inhibitors have very-low to medium plausibility in viral activity, this could be an expected result, since up to know anti-viral activity has not been explored for these drugs. Among the top 10 hits, 2-(n-Morpholino)-Ethanesulfonic Acid (ZINC19419111) could be discarded as a potential treatment alternative for Covid-19, since it is currently used as a buffer solution, without clinical studies in humans, in addition to a high cytotoxic potential and a very low biological plausibility (PubChem CID 78165).

 doi:10.20944/preprints202004.0146.v1

Pictilisib, the compound with the highest affinity, binds to phosphatidylinositol 4-phosphate 3-kinase in an ATP-competitive manner, inhibiting the production of the secondary messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3) and activation of the PI3K/Akt signaling pathway. Pictilisib has been studied in the treatment of solid cancers and non-Hodgkin's Lymphoma. Treatment-related adverse events (occurred in ≥10% of patients) included: nausea, diarrhea, vomiting, fatigue, dysgeusia, decreased appetite and rash [22-24]. Nilotinib is a selective tyrosine kinase inhibitor indicated as a treatment alternative for adult patients with chronic myeloid leukemia [25]. The main adverse effects of Nilotinib include cough, increase in alanine aminotransferase, constipation, pruritus, dizziness, upper respiratory tract infection, pyrexia, rash, and headache, among others; in addition to thrombocytopenia and anemia. Co-administration of Nilotinib with CYP3A4 inhibitors should be avoided as they can increase Nilotinib serum concentrations, as well as the concomitant use of drugs that prolong QT interval [26].

Nimorazole is an oral antibiotic used in the treatment of trichomoniasis, which is readily absorbed from the gastrointestinal tract and the main adverse effects include nausea, vomiting, and peripheral neuropathy [27, 28]. Similarly, Cefuroxime is a broad-spectrum, cephalosporin antibiotic used to treat respiratory, urinary, and abdominal infections. This drug is intramuscularly administered, and adverse effects include diarrhea, nausea, vomiting, abdominal pain, headache, and transitory elevation of liver enzymes; in addition to the risk of hypersensitivity and the caution when co-administer with anticoagulants [29].

As mentioned above, Ergoloid mesylates were identified several times among the top 10 hits. These are dihydro-derivatives of naturally occurring ergot alkaloids, which are peripheral vasodilators and have been proposed as treatment alternatives for cerebrovascular disease, geriatric senility, and hypertension [30]. Adverse effects of Ergoloid mesylates may include ergotism (arterial vasospasm or vasoconstriction) and fibrotic reactions [30, 31]. Lumacaftor is an approved drug for the treatment of cystic fibrosis through the correction of the trafficking of the cystic fibrosis transmembrane

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

conductance regulator [32], and it has also been reported as a potential treatment for Stargardt disease [33]. Lumacaftor is absorbed from the gastrointestinal tract and the main adverse effects include cough, fatigue, rash, chest tightness and dyspnea during monotherapy with high doses [34]. Finally, Cepharanthine is a compound extracted from the plant *Stephamia cepharantha* used to treat leukopenia, otitis media, bite of vipers, and androgenetic alopecia. This well-tolerated old Japanese drug has multiple pharmacological properties including anti-oxidative, anti-inflammatory, immuno-regulatory, anti-cancer, anti-viral and anti-parasitic properties; which in some cases are associated to the interference of the AMP-activated protein kinase and NFκB signaling pathways [35, 36].

Conclusions

In the present study, we carried out a molecular docking-based virtual screening of inhibitors for SARS-CoV-2 M^{pro}, a potential target for the development of a therapy for Covid-19. The identified compounds have a higher affinity for SARS-CoV-2 M^{pro} that previously inhibitors and their predicted IC_{50} suggest that they could have a significant impact in controlling virus replication. Drug repurposing has been proposed as a potential alternative to identify drugs to handle Covic-19 pandemic, whereas a specific drug or a vaccine is developed [37, 38]. Several strategies to identify inhibitors of SARS-CoV-2 M^{pro} has been proposed during the last months, which have led to the identification of drugs that could be rapidly translated to the clinics, including antiviral, antibiotics, and natural-derived compounds, among others [11, 39-42]. Based on the pharmacology information available for the predicted SARS-CoV-2 M^{pro} inhibitors we propose Cepharanthine and Nimorazole as potential drugs to be further evaluated both *in vitro* and *in vivo*. Although none of the predicted compounds showed a high biological plausibility in viral activity, the present study offers the possibility to explore novel applications for these drugs. In addition, since the identified drugs have both pre-clinical and clinical information, we consider that the present results could shed light on the rapid identification of a treatment alternative for Covid-19.

 doi:10.20944/preprints202004.0146.v1

Table 2. Pharmacology analysis of potential inhibitors of SARS-CoV-2 M^{pro}.

Compound	Indications	Pharmacokinetics	Mechanism of action	Adverse effects and interactions	Reported biological plausibility	Refs
Pictisilib	Pictilisib has been used in trials studying the treatment of solid cancers, breast cancer, advanced solid tumours, metastatic breast Cancer, and non-Hodgkin's lymphoma	---	Selectively binds to PI3K in an ATP-competitive manner, inhibiting the production of the secondary messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3) and activation of the PI3K/Akt signaling pathway.	Treatment-related adverse events that occurred in ≥10% of patients included: nausea, diarrhea, vomiting, fatigue, dysgeusia, decreased appetite and rash.	Low: It is indicated in the inhibition of intracellular PI3K routes, which is a second messenger that could inhibit tumor growth in neoplasic cells. As they are intracellular and non-affecting routes in DNA production and others, it is considered low plausibility in viral activity.	[22-24]
Nimorazole	Antibiotic with similar activity to metronidazole. In the treatment of trichomoniasis, the usual dose of nimorazole is 2 g orally as a single dose with a main meal.	Readily absorbed from the gastrointestinal tract. Peak blood concentrations within 2 hours. It is mainly excreted in the urine as metabolites that also have some antiprotozoal and antibacterial activity. Unchanged drug and metabolites also appear in breast milk.	---	Nausea, vomiting, peripheral neuropathy	Medium: This prodrug has a cytotoxic effect due to the production of nitrogenous free radicals, which also affects DNA, inhibiting its synthesis and causing damage. In the studies carried out, the impact of this drug is more on DNA repair, allowing sensitized cells to die more quickly due to radiotherapy, so that their biological plausibility would be medium, since it would be expected that the damage they cause requires another agent to the death of the microorganism.	[27, 28]

 doi:10.20944/preprints202004.0146.v1

Compound	Indications	Pharmacokinetics	Mechanism of action	Adverse effects and interactions	Reported biological plausibility	Refs
Ergoloid mesylates	Ergoloid mesylates are an equiproportional mixture of three dihydro-derivatives of naturally occurring ergot alkaloids. These include dihydroergocornine, dihydroergocristine, and dihydroergocryptine. They are peripheral vasodilators and have been proposed as treatment alternative for cerebrovascular disease, geriatric senility, and hypertension	---	The mechanism of action of dihydroergotoxine mesylate in geriatric senility is unclear and controversy exists as to whether or not the drug improves cerebral blood flow. The drug has some alpha-blocking activity, but no vasoconstrictor or oxytocic properties. Ergoloid mesylates decrease the concentration of homovanillic acid but not of 5-hydroxyindole acetic acid. The clinical effect may be related to the dopamine-like activity of ergoloid mesylates resulting in depression of dopamine metabolism	Ergotism (arterial vasospasm or vasoconstriction) and fibrotic reactions	Very low. It is a drug whose mechanism of action is not clear, which is believed to be an alpha adrenergic with dopamine agonist effect, which has conferred studies as a neuroprotective in dementia and nootropic effects, for which it is considered very low biological plausibility.	[30, 31]
Lumacaftor	Lumacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) protein corrector.	Lumacaftor is absorbed from the gastrointestinal tract. Following multiple oral doses, peak plasma concentrations occur about 4 hours after dosing when given with food. Plasma-protein binding is about 99%. Lumacaftor is not extensively metabolized, with the majority (about 51%)	Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface.	Cough, fatigue, rash, chest tightness, and dyspnea during monotherapy with high doses.	Very low. Being a drug that improves the conformational stability of certain transmembrane proteins, which in humans are quite specific, it is not considered biological plausibility in the treatment for viral diseases	[32-34]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 April 2020 doi:10.20944/preprints202004.0146.v1

Compound	Indications	Pharmacokinetics	Mechanism of action	Adverse effects and interactions	Reported biological plausibility	Refs
		excreted unchanged in the feces. The half-life of lumacaftor is about 26 hours in patients with cystic fibrosis.				
Cefuroxime	Broad-spectrum, cephalosporin antibiotic used to treat respiratory, urinary and abdominal infections. Indicated treatment of Gonorrhea, uncomplicated or disseminated gonococcal infection, infection of bone and joints, infection of skin and/or subcutaneous tissue, infection of lower respiratory tract infection, and meningitis	Intramuscular administration. Time to peak concentration: 45 min Protein binding: approximately 50% Excretion renal: approximately 89% over 8 h Elimination half life approximately 80 min	It exerts its bactericidal effect by inhibiting bacterial cell-wall synthesis. It has activity against a wide range of aerobic and anaerobic gram-positive and gram-negative organisms.	Diarrhea, nausea, vomiting, abdominal pain, headache, and transitory elevation of liver enzymes; in addition to the risk of hypersensitivity and the caution when co-administer with anticoagulants	Very low. As it is a 2 generation cephalosporin, whose mechanism of action is the inhibition of the bacterial wall by binding of the PBPs, there is no biological plausibility for the management of viral diseases, in addition, it does not have studies that support its use in viral diseases. (1)	[29]
Cepharanthine	This plant extract of *Stephamia cepharantha* is used to treat leukopenia otitis media, the bite of vipers, and androgenetic alopecia. It has multiple pharmacological properties including anti-oxidative, anti-inflammatory, immuno-regulatory, anti-cancer, anti-viral and anti-parasitic properties	---	It interferes with the AMP-activated protein kinase (AMPK) and NFκB signaling pathways. In particular, the anti-inflammatory effects of Cepharanthine rely on AMPK activation and NFκB inhibition.	No adverse effects have been reported.	Medium. This drug has action in DNA since it can bind and stabilize G-quadruplex formed by G-rich sequences in DNA and RNA. It has also been studied as a cancer drug co-assistant due to capacity to modulate drug transporters such as PgP and MRP7, which improves the sensitivity of tumor cells to other antineoplastic agents, so that together with other	[35, 36]

 doi:10.20944/preprints202004.0146.v1

Compound	Indications	Pharmacokinetics	Mechanism of action	Adverse effects and interactions	Reported biological plausibility	Refs
					drugs, it could have biological plausibility in the management of viral diseases	
Nilotinib	Indicated as treatment alternative for adult patients with chronic myeloid leukemia	Oral absorption: rapid, reach peak concentration in 3 hours Liver metabolism. Inhibitor of CYP3A4, CYP2C8, CYP2D6, UGT1A1, and P-gp. Excretion fecal: 93% Total body clearance: 29 L/hr [5] Elimination half life in adults: 17 hours.	A selective tyrosine kinase inhibitor	The main adverse effects include cough, increase in alanine aminotransferase, constipation, pruritus, dizziness, upper respiratory tract infection, pyrexia, rash, and headache, among others; in addition to thrombocytopenia and anemia. Co-administration of Nilotinib with CYP3A4 inhibitors should be avoided as they can increase Nilotinib serum concentrations, and the concomitant use of drugs that prolong QT interval should be also avoided	Low. For its activity in selective tyrosine kinase inhibitor that targets BCR-ABL kinase, c-KIT and platelet derived growth factor receptor (PDGFR). It is not considered biological plausibility in diseases where the microorganisms are dependent on DNA-RNA, and without effect on DNA replication processes or on the formation of proteins for splice, and it does not count as an immunomodulatory effect.	[25, 26]

Acknowledgments.

C.J. Alméciga-Díaz is supported by Pontificia Universidad Javeriana (PPTA # 8275) and the Ministry of Science, Technology and Innovation (Grant ID 120380763212 – PPTA # 8352). Luisa N. Pimentel-Vera is supported by the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES). The authors thank IBM for the access to the Micromedex database, and the Colombian Pharmacovigilance Association. The authors declare no conflict of interest.

References

1. Li, Q., et al., *Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia.* New England Journal of Medicine, 2020. **382**(13): p. 1199-1207.
2. Zhu, N., et al., *A Novel Coronavirus from Patients with Pneumonia in China, 2019.* New England Journal of Medicine, 2020. **382**(8): p. 727-733.
3. Johns Hopkins University. *Johns Hopkins Coronavirus Resource Center*. 2020 [cited 2020 April]; Available from: https://coronavirus.jhu.edu.
4. Kupferschmidt, K. and J. Cohen. *WHO launches global megatrial of the four most promising coronavirus treatments*. 2020 [cited 2020 March 22]; Available from: 10.1126/science.abb8497.
5. Baden, L.R. and E.J. Rubin, *Covid-19 — The Search for Effective Therapy.* New England Journal of Medicine, 2020. **In press**(10.1056/NEJMe2005477).
6. Amanat, F. and F. Krammer, *SARS-CoV-2 Vaccines: Status Report.* Immunity, 2020. **In press**(https://doi.org/10.1016/j.immuni.2020.03.007).
7. Cao, B., et al., *A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19.* New England Journal of Medicine, 2020. **In press**(10.1056/NEJMoa2001282).
8. Holshue, M.L., et al., *First Case of 2019 Novel Coronavirus in the United States.* New England Journal of Medicine, 2020. **382**(10): p. 929-936.
9. Gao, J., Z. Tian, and X. Yang, *Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies.* Biosci Trends, 2020. **14**(1): p. 72-73.
10. Gautret, P., et al., *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.* Int J Antimicrob Agents, 2020: p. 105949.
11. Jin, Z., et al., *Structure of Mpro from COVID-19 virus and discovery of its inhibitors.* bioRxiv, 2020: p. 2020.02.26.964882.
12. Zhang, L., et al., *Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors.* Science, 2020. **In press**(10.1126/science.abb3405).
13. Zhang, L., et al., *Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors.* Science, 2020.
14. Almeciga-Diaz, C.J., et al., *Identification of Ezetimibe and Pranlukast as Pharmacological Chaperones for the Treatment of the Rare Disease Mucopolysaccharidosis Type IVA.* Journal of medicinal chemistry, 2019. **62**(13): p. 6175-6189.

15. Losada, J.C., C.J. Alméciga, and J. Gonzalez, *In silico identification of pharmacological chaperones for mucopolysaccharidosis type IIIB.* Molecular Genetics and Metabolism, 2020. **129**(2): p. S101.
16. Olarte-Avellaneda, S., et al., *In Silico Analysis of the Structure of Fungal Fructooligosaccharides-Synthesizing Enzymes.* Interdiscip Sci, 2018. **10**(1): p. 53-67.
17. Pettersen, E.F., et al., *UCSF Chimera--a visualization system for exploratory research and analysis.* J Comput Chem, 2004. **25**(13): p. 1605-12.
18. Trott, O. and A.J. Olson, *AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading.* Journal of computational chemistry, 2010. **31**(2): p. 455-61.
19. Irwin, J., et al., *ZINC: a free tool to discover chemistry for biology.* Journal of chemical information and modeling, 2012. **52**(7): p. 1757-68.
20. Davies, M., et al., *ChEMBL web services: streamlining access to drug discovery data and utilities.* Nucleic Acids Res, 2015. **43**(W1): p. W612-20.
21. Backman, T.W., Y. Cao, and T. Girke, *ChemMine tools: an online service for analyzing and clustering small molecules.* Nucleic Acids Res, 2011. **39**(Web Server issue): p. W486-91.
22. Sarker, D., et al., *First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors.* Clin Cancer Res, 2015. **21**(1): p. 77-86.
23. Leong, S., et al., *A Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of Pictilisib in Combination with Erlotinib in Patients with Advanced Solid Tumors.* Oncologist, 2017. **22**(12): p. 1491-1499.
24. Han, N., et al., *C-Labeled Pictilisib (GDC-0941) as a Molecular Tracer Targeting Phosphatidylinositol 3-Kinase (PI3K) for Breast Cancer Imaging.* Contrast Media Mol Imaging, 2019. **2019**: p. 1760184.
25. Branford, S., et al., *Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase treated with nilotinib.* J Clin Oncol, 2012. **30**(35): p. 4323-9.
26. Kuo, C.Y., et al., *Safety and efficacy of nilotinib in routine clinical practice in patients with chronic myeloid leukemia in chronic or accelerated phase with resistance or intolerance to imatinib: results from the NOVEL study.* Ther Adv Hematol, 2018. **9**(3): p. 65-78.
27. Henk, J.M., K. Bishop, and S.F. Shepherd, *Treatment of head and neck cancer with CHART and nimorazole: phase II study.* Radiother Oncol, 2003. **66**(1): p. 65-70.
28. Timothy, A.R., J. Overgaard, and M. Overgaard, *A phase I clinical study of Nimorazole as a hypoxic radiosensitizer.* Int J Radiat Oncol Biol Phys, 1984. **10**(9): p. 1765-8.
29. Dallmann, A., et al., *Physiologically Based Pharmacokinetic Modeling of Renally Cleared Drugs in Pregnant Women.* Clin Pharmacokinet, 2017. **56**(12): p. 1525-1541.
30. Bicalho, B., et al., *Identification and human pharmacokinetics of dihydroergotoxine metabolites in man: preliminary results.* Biopharm Drug Dispos, 2008. **29**(1): p. 17-28.
31. European Medicines Agency. *Ergot derivatives containing medicinal products*. 2013 [cited 2020 April]; Available from: https://www.ema.europa.eu/en/documents/referral/assessment-report-ergot-derivatives-containing-medicinal-products-dihydroergotoxine_en.pdf.
32. Van Goor, F., et al., *Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809.* Proc Natl Acad Sci U S A, 2011. **108**(46): p. 18843-8.
33. Liu, Q., et al., *The CFTR Corrector, VX-809 (Lumacaftor), Rescues ABCA4 Trafficking Mutants: a Potential Treatment for Stargardt Disease.* Cell Physiol Biochem, 2019. **53**(2): p. 400-412.
34. Talamo Guevara, M. and S.A. McColley, *The safety of lumacaftor and ivacaftor for the treatment of cystic fibrosis.* Expert Opin Drug Saf, 2017. **16**(11): p. 1305-1311.

 doi:10.20944/preprints202004.0146.v1

35. Bailly, C., *Cepharanthine: An update of its mode of action, pharmacological properties and medical applications.* Phytomedicine, 2019. **62**: p. 152956.
36. Rogosnitzky, M. and R. Danks, *Therapeutic potential of the biscoclaurine alkaloid, cepharanthine, for a range of clinical conditions.* Pharmacol Rep, 2011. **63**(2): p. 337-47.
37. Li, G. and E. De Clercq, *Therapeutic options for the 2019 novel coronavirus (2019-nCoV).* Nat Rev Drug Discov, 2020. **19**(3): p. 149-150.
38. Phadke, M. and S. Saunik, *COVID-19 treatment by repurposing drugs until the vaccine is in sight.* Drug Dev Res, 2020.
39. Liu, S., Q. Zheng, and Z. Wang, *Potential covalent drugs targeting the main protease of the SARS-CoV-2 coronavirus.* Bioinformatics, 2020.
40. Khan, S.A., et al., *Identification of Chymotrypsin-like Protease Inhibitors of SARS-CoV-2.* J Biomol Struct Dyn, 2020: p. 1-13.
41. Chen, Y.W., C.B. Yiu, and K.Y. Wong, *Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL.* F1000Res, 2020. **9**: p. 129.
42. Fan, H.H., et al., *Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model.* Chin Med J (Engl), 2020. **In press**(10.1097/CM9.0000000000000797).