Potential Lead Compounds (small-molecules/peptide/nucleosides) for Training

Repurposing Therapeutics for COVID-19:

---

https://chemrxiv.org/articles/Repurposing_Therapeutics_for_the_Wuhan_Coronavirus_nCov-2019_Supercomputer-Based_Docking_to_the_Viral_S_Protein_and_Human_ACE2_Interface/11871402

Micholas Dean Smith and Jeremy Smith used Summit (IBM AC922 Summit – Oak Ridge Leadership Computing Facility) to screen a small molecule library (~ 8000 compounds) and carried out Docking and Molecular Dynamics simulations to identify hits that could bind to the main "spike" protein (aka S-protein) of the caronavirus. You can read the article, Repurposing Therapeutics for COVID-19: Supercomputer-Based Docking to the SARS-CoV-2 Viral Spike Protein and Viral Spike…, from The Preprint Server for Chemistry, ChemRxiv. You can watch the following video on how the drugs could bind to virus-proteins and disrupt the virus host binding interactions, https://www.olcf.ornl.gov/wp-content/uploads/2020/03/corona_split_video.mp4?_=1. The video link is part of the following ORNL article, ORNL Team Enlists World's Fastest Supercomputer to Combat the Coronavirus – Oak Ridge Leadership Computing Facility.

What software/Database was used?

- **AutoDock Vina**: http://vina.scripps.edu/
- MD software **GROMACS**: http://www.gromacs.org/
- DB: **SWEETLEAD**: https://simtk.org/projects/sweetlead

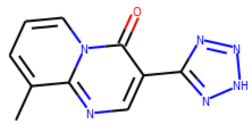
What do we have?

- Ligands (~ 9,120) in AutoDock vina format (pdbqt)
- Receptor structure

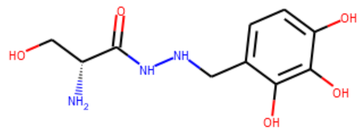
Here is the list of compounds and their chemical structures.

ID	smiles	zinc_id	Name
1	Cc1cccn2c(=O)c(-c3nn[nH]n3)cnc12	ZINC000005783214	Permirolast
2	N[C@H](CO)C(=O)NNCc1ccc(O)c(O)c1O	ZINC000003830273	Benserazide
3	O=c1cc(-c2ccc(O)c(O)c2)oc2cc(O)cc(O)c12	ZINC000018185774	Luteolin-monoarbinoside (NP)
4	C/C(=N\NC(=O)c1ccncc1)C(=O)O	ZINC000004974291	Pyruvic-acid-Calcium-isoniazid
5	O=c1c(O)c(-c2ccc(O)c(O)c2)oc2cc(O)cc(O)c12	ZINC000003869685	Quercetol;quercetin (NP)
6	NC(=O)[C@@H]1CCCN1C(=O)[C@H] (Cc1c[nH]cn1)NC(=O)[C@@H]1CCC(=O)N1	ZINC000004096261	Protirelin
7	CN1C[C@H](O)C2=C/C(=N/NC(N)=O)C(=O)C=C21	ZINC000100029428	Carbazochrome
8	O=C1CN(/N=C/c2ccc([N+](=O)[O-])o2)C(=O)N1	ZINC000003875368	Nitrofurantoin
9	N[C@H](CO)C(=O)NNCc1ccc(O)c(O)c1O	ZINC000003830273	Benserazide
10	CN1C[C@@H](O)C2=C/C(=N/NC(N)=O)C(=O)C=C21	ZINC000100045148	Carbazochrome
11	C[C@H](O)[C@H](O)[C@H]1CNc2nc(N)[nH]c(=O)c2N1	ZINC000013585233	Sapropterin
12	Nc1ncnc2c1ncn2[C@@H]1O[C@H](CO)[C@@H](O) [C@@H]1O	ZINC000000970363	Vidarbine
13	O=C1C[C@@H](c2ccc(O)c(O)c2)Oc2cc(O)cc(O)c21	ZINC000000058117	NP:Eriodictyol
14	C[C@]1(Cn2ccnn2)[C@H] (C(=O)O)N2C(=O)C[C@H]2S1(=O)=O	ZINC000003787060	Tazobactum
15	NC(N)=N/C(N)=N\CCc1ccccc1	ZINC000005851063	Phenformin-hcl
16	CN1C[C@@H](O)C2=C/C(=N/NC(N)=O)C(=O)C=C21	ZINC000100045148	Carbazochrome
17	CN1C[C@@H](O)C2=C/C(=N/NC(N)=O)C(=O)C=C21	ZINC000100045148	Carbazochrome
18	N#C[C@@H]1CCCN1C(=O)CNC12C[C@@H]3C[C@H] (CC(O)(C3)C1)C2	ZINC000100003507	Vildagliptin
19	Oc1ccc(C[C@H]2NCCc3cc(O)c(O)cc32)cc1	ZINC000000896041	Demethyl-coclaurine (NP)

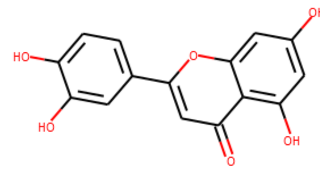
Please note, NP, means Natural Product



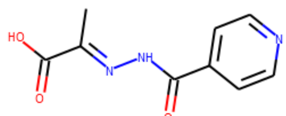
Permirolast



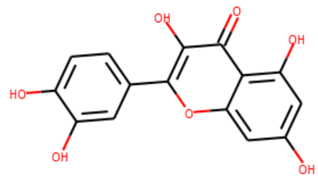
Benserazide



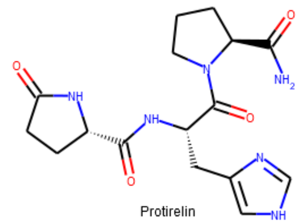
NP-Luteolin-monoarbinoside



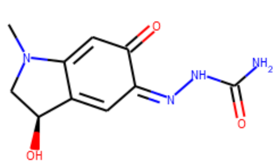
Pyruvic-acid-Calcium-isoniazid



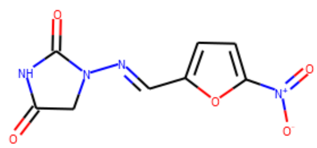
NP-Quercetol;quercetin



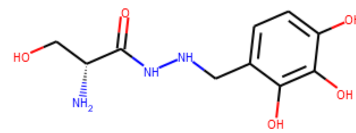
Protirelin



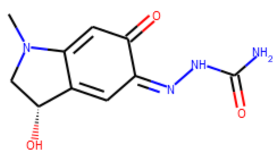
Carbazochrome



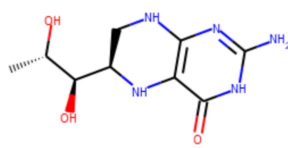
Nitrofurantoin



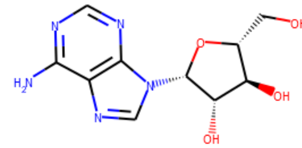
Benserazide



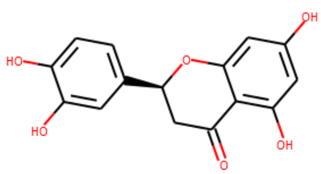
Carbazochrome



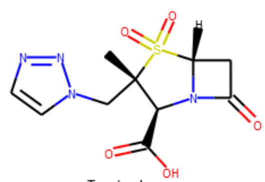
Sapropterin



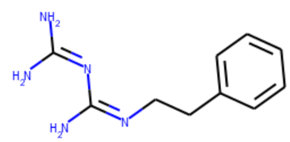
Vidarbine



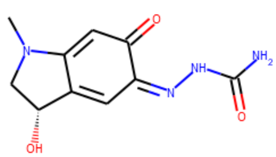
NP:Eriodictyol



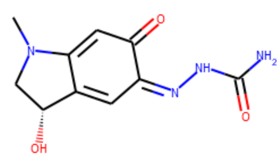
Tazobactum



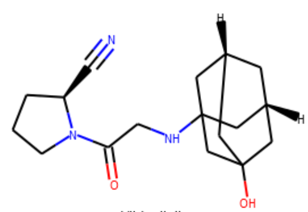
Phenformin-hcl



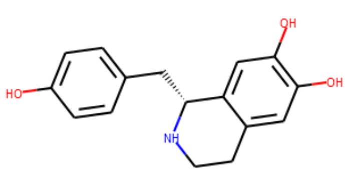
Carbazochrome



Carbazochrome



Vildagliptin



NP:Demethyl-coclaurine

Searching inhibitors for three important proteins of COVID-19 through molecular docking studies

https://arxiv.org/ftp/arxiv/papers/2004/2004.08095.pdf

In this communication, molecular docking studies of 18 ligands were carried out with the three important proteins of SARS-CoV-2, i.e., RNA-dependent RNA polymerase (RdRp), angiotensin-converting enzyme 2 (ACE2) and spike glycoprotein (SGp). From the obtained results, we observed that all the tested molecules showed better dock score in compared to the hydroxychloroquine claimed to be effective against COVID-19. Combining the dock score and other medicinal properties, we believe the limonin can be further explored for potential use against COVID-19.

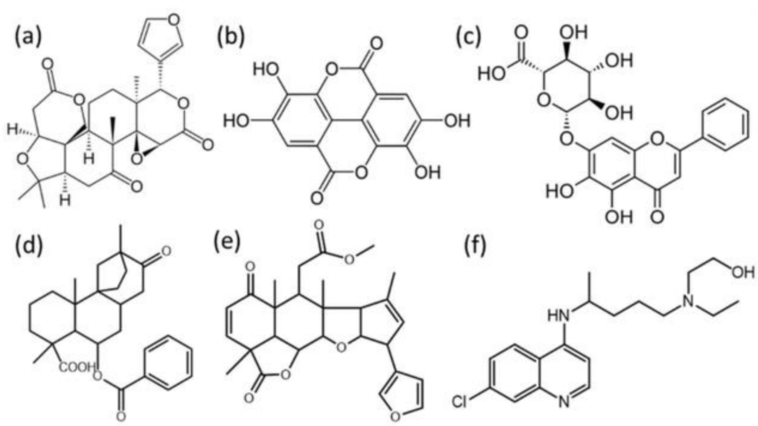


Chart 1. Structure of the ligands (a. Limonin, b. Ellagic acid, c. Baicalin, d. Scopadulcic Acid, e. Nimbolide) that showed high docking score with the three proteins of COVID-19 and (f) hydroxychloroquine claimed to be effective for COVID-19.

Molecular docking and binding mode analysis of selected FDA approved drugs against COVID-19 selected key protein targets: An effort towards drug repurposing to identify the combination therapy to combat COVID-19

https://arxiv.org/ftp/arxiv/papers/2004/2004.06447.pdf

ACE2, RdRp, NSP12, NSP16 Targets to identify Protein AA residues

NOT SURE WHAT THE TARGET IS. THEY USED NSP12, SPIKE and NSP16-10 and docked to all of them

Therefore, many existing viral targets are structurally expected to be similar to SARS-CoV and likely to be inhibited by the same compounds. Here, we selected three viral key proteins based on their vital role in viral life cycle: ACE2 (helps in entry into the human host), viral nonstructural proteins RNA-dependent RNA polymerase (RdRp) NSP12, and NSP16 which helps in replication, and viral latency (invasion from immunity). The FDA approved drugs chloroquine (CQ), hydroxychloroquine (HCQ), remdesivir (RDV) and arbidol (ABD) are emerging as promising agents to combat COVID-19.

Our hypothesis behind the docking studies is to determine the binding affinities of these drugs and identify the key amino acid residues playing a key role in their mechanism of action.

Modelling and docking of Indian SARS-CoV-2 spike protein 1 with ACE2: implications for co-morbidity and therapeutic intervention

---

https://arxiv.org/ftp/arxiv/papers/2004/2004.06361.pdf

Identifying SPIKE-2 - ACE2 interactions

Computational Drug Repositioning and Elucidation of Mechanism of Action of Compounds against SARS-CoV-2

---

https://arxiv.org/ftp/arxiv/papers/2004/2004.07697.pdf

A radical approach to reduce the gene expression (ACE2 etc.)

- Drugs predicted to downregulate ACE2 and TMPRSS2 genes by the Gene2drug tool ($p < 0.05$).
- Drugs predicted to downregulate SARS-CoV-2 human interactors by the Gene2drug tool ($p < 0.05$, top 20 reported).
- Drugs predicted to revert the transcriptional signature induced by SARS-CoV-2 infection through the MANTRA tool

Prediction of potential inhibitors for RNA-dependent RNA polymerase of SARSCoV-2 using comprehensive drug repurposing and molecular docking approach

---

https://arxiv.org/ftp/arxiv/papers/2004/2004.07086.pdf

RdRP Target

Tables

Table 1: Top 5 RdRp Inhibitors with Binding Energy and Involved Amino Acid with Position

Sl. No.	Drug Bank ID	Name	Binding Energy (kcal/mol)	No of Non-Covalent Interactions	Involved Amino Acids with positions
1	DB00615	Rifabutin	-11.8	7	Y32, K47, Y129, H133, N138, C139, T141, S709
2	DB01201	Rifapentine	-11.6	10	V31, Y32, R33,K47, K121, Y122, Y129, H133, N138, C139, D140, T141, S709, N781
3	DB08874	Fidaxomicin	-10.9	16	Y32, K47, Y129, N131, H133, N138, D140, T141, S709, T710, D711, K714, N781, Q773
4	DB03958	7-methyl-guanosine-5'-triphosphate-5'-guanosine	-10	12	Y32, R33, K47,Y122, Y129, H133, D140, T141, A706, S709, T710, D711, , G774, N781
5	DB00602	Ivermectin	-9.9	9	Y32, L49, Y129, H133, S709, T710, K714, G774, N781
Control	DB14761	Remdesivir	-8.8	5	K47, Y129, A130, H133, F134, D135, N138, C139, T141, S709, T710, D711, Q773 and N781
Control	DB12466	Favipiravir	-5.3	6	Y129, H133, S709, K780 and N781

Network Medicine Framework for Identifying Drug Repurposing Opportunities for COVID-19

https://arxiv.org/pdf/2004.07229.pdf

The list of the 81 drugs selected for repurposing.

Table 2: **Drug Repurposing Candidates.** The list of the 81 drugs selected for repurposing. It shows the drugs' name, the final combined rank of each drug, the number of clinical trials in which the drug is being tested for COVID-19 and references to paper, that already noted their potential COVID-19 relevance.

Reference ClinicalTrials.gov

		Drug	C-rank			Drug	C-rank			Drug	C-rank
20	76	Ritonavir	1			Mesalazine	69			Sulfanilamide	265
		Isoniazid	2			Pentamidine	92			Hydralazine	269
		Troleandomycin	3			Verapamil	98			Gemfibrozil	281
		Cilostazol	4		43	Melatonin	109	4		Ruxolitinib	284
76	18,77	Chloroquine	5			Griseofulvin	112			Propranolol	297
		Rifabutin	6			Auranofin	118			Carbamazepine	301
		Flutamide	7	1		Atovaquone	124			Doxorubicin	309
2		Dexamethasone	8			Montelukast	131			Levothyroxine	329
		Rifaximin	9			Romidepsin	138		43	Dactinomycin	335
		Azelastine	10	1		Cobicistat	141			Tenofivir	338
		Folic Acid	16	17		Lopinavir	146			Tadalafil	339
		Rabeprazole	27			Pomalidomide	155			Doxazosin	367
		Methotrexate	32			Sulfinpyrazone	157			Rosiglitazone	397
		Digoxin	33	1		Levamisole	161			Aminolevulinic acid	398
		Theophylline	34			Calcitriol	164			Nitroglycerin	418
		Fluconazole	41	1		Interferon-β-1a	173			Metformin	457
		Aminoglutethimide	42			Praziquantel	176	1		Nintedanib	466
67	13	Hydroxychloroquine	44	1		Ascorbic acid	195			Allopurinol	471
		Methimazole	47			Fluvastatin	199		13	Ponatinib	491
1	13	Ribavirin	49	1		Interferon-β-1b	203	1		Sildenafil	493
1		Omeprazole	50			Selegiline	206			Dapagliflozin	504
		Bortezomib	53	1		Deferoxamine	227			Nitroprusside	515
		Leflunomide	54		78	Ivermectin	235			Cinacalcet	553
		Dimethylfumarate	55	1		Atorvastatin	243			Mexiletine	559
4		Colchicine	57		79	Mitoxantrone	250			Sitagliptin	706
		Quercetin	63			Glyburide	259		80	Carfilzomib	765
		Mebendazole	67	2		Thalidomide	262	1	81	Azithromycin	786

Anti-HCV, Nucleotide Inhibitors, Repurposing Against COVID-19

RdRP TARGET

In this study, sequence analysis, modeling, and docking are used to build a model for Wuhan COVID-19 RdRp. Additionally, the newly emerged Wuhan HCoV RdRp model is targeted by anti-polymerase drugs, including the approved drugs Sofosbuvir and Ribavirin.

Key findings: The results suggest the effectiveness of Sofosbuvir, IDX-184, Ribavirin, and Remidisvir as potent drugs against the newly emerged HCoV disease.

https://pubmed.ncbi.nlm.nih.gov/32119961/

What software was used?

Swiss Model web server is used to build a model for RdRp

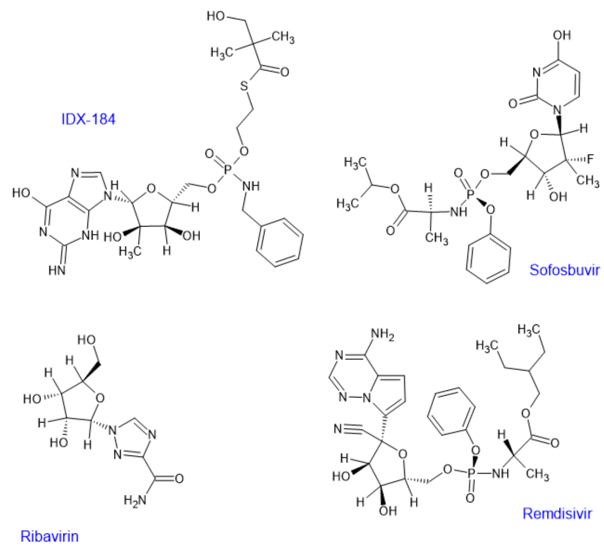
Molprobity web for structure analysis

SCIGRESS, https://www.fqs.pl/en/chemistry/products/scigress, is used to minimize the model and to perform molecular docking experiments.

The minimization of the model is performed using the MM3 force field

AutoDock Vina for docking

These small molecules was selected but this can be downloaded from any compound libraries like PubChem, ZINC, DrugBank etc.



The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase.

RdRP Target

https://pubmed.ncbi.nlm.nih.gov/32167173

RNA-dependent RNA polymerase (RdRp) is an important protease that catalyzes the replication of RNA from RNA template and is an attractive therapeutic target. In this study, we screened these chemical structures from traditional Chinese medicinal compounds proven to show antiviral activity in severe acute respiratory syndrome coronavirus (SARS-CoV) and the similar chemical structures through a molecular docking study to target RdRp of SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV).

What software was used?

idock for docking, (https://github.com/HongjianLi/idock)

"Achilles" Blind Docking Server, available at: http://bio-hpc.eu/software/blind-docking-server/.

What database was used for ligands?

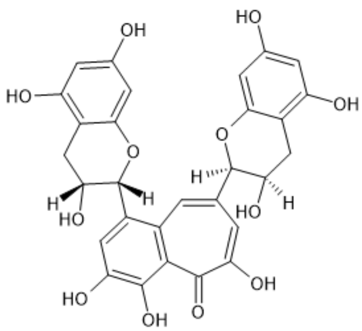
ZINC

What compounds were used for docking?

Eighty-three chemical structures from traditional Chinese medicinal compounds and their similar structures were retrieved from ZINC15 database.

(Ravi: It is not clear what these 80 Chinese Medicinal Compounds are)

Theaflavin was found to be the potent compound



Theaflavin

In Silico Screening of Chinese Herbal Medicines With the Potential to Directly Inhibit 2019 Novel Coronavirus

Proteases Target

Paper doesn't include the list of CHINESE MEDICINES

Objective: In this study we execute a rational screen to identify Chinese medical herbs that are commonly used in treating viral respiratory infections and also contain compounds that might directly inhibit 2019 novel coronavirus (2019-nCoV), an ongoing novel coronavirus that causes pneumonia.

Results: Of the natural compounds screened, 13 that exist in traditional Chinese medicines were also found to have potential anti-2019-nCoV activity. Further, 125 Chinese herbs were found to contain 2 or more of these 13 compounds. Of these 125 herbs, 26 are classically catalogued as treating viral respiratory infections. Network pharmacology analysis predicted that the general in vivo roles of these 26 herbal plants were related to regulating viral infection, immune/inflammation reactions and hypoxia response.

https://pubmed.ncbi.nlm.nih.gov/32113846/

What software were used?

AutoDock (v4.0) and **SwissModel** for Docking and Modeling respectively.

What DB was used for small-molecules?

PubChem: https://pubchem.ncbi.nlm.nih.gov/

No.	Molecular name	Targets or inhibition	Reference	Docking (binding energy)		
				PLpro	3CLpro	Spike
M1	Betulinic acid	Replication, 3CLpro	[16]	Undo	−4.23	Undo
M2	Coumaroyltyramine	PLpro and 3CLpro	[11], [20]	−3.22	−4.18	Undo
M3	Cryptotanshinone	PLpro and 3CLpro	[18]	−5.25	−6.23	Undo
M4	Desmethoxyreserpine	Replication, 3CLpro, and entry	[6]	Undo	−3.52	Undo
M5	Dihomo-γ-linolenic acid	3CLpro	[7]	Undo	−3.88	Undo
M6	Dihydrotanshinone I	Entry, and spike protein	[28]	Undo	Undo	−5.16
M7	Kaempferol	PLpro and 3CLpro	[11]	−2.15	−6.01	Undo
M8	Lignan	Replication, 3CLpro	[16]	Undo	−4.27	Undo
M9	Moupinamide	PLpro	[20]	−3.05	Undo	Undo
M10	N-cis-feruloyltyramine	PLpro and 3CLpro	[11], [20]	−3.11	−4.31	Undo
M11	Quercetin	PLpro and 3CLpro	[20]	−4.62	−6.25	Undo
M12	Sugiol	Replication, 3CLpro	[16]	Undo	−6.04	Undo
M13	Tanshinone IIa	PLpro and 3CLpro	[18]	−5.02	−5.17	Undo

3CLpro: 3C-like protease; PLpro: papain-like protease.

These molecules were reported to inhibit viral entry, and were docked with spike proteins

Rapid Identification of Potential Inhibitors of SARS-CoV-2 Main Protease by Deep Docking of 1.3 Billion Compounds

https://pubmed.ncbi.nlm.nih.gov/32162456/

MPro Protein Target

In the current study we applied DD to all 1.3 billion compounds from ZINC15 library to identify top 1,000 potential ligands for SARS-CoV-2 Mpro protein. The compounds are made publicly available for further characterization and development by scientific community.

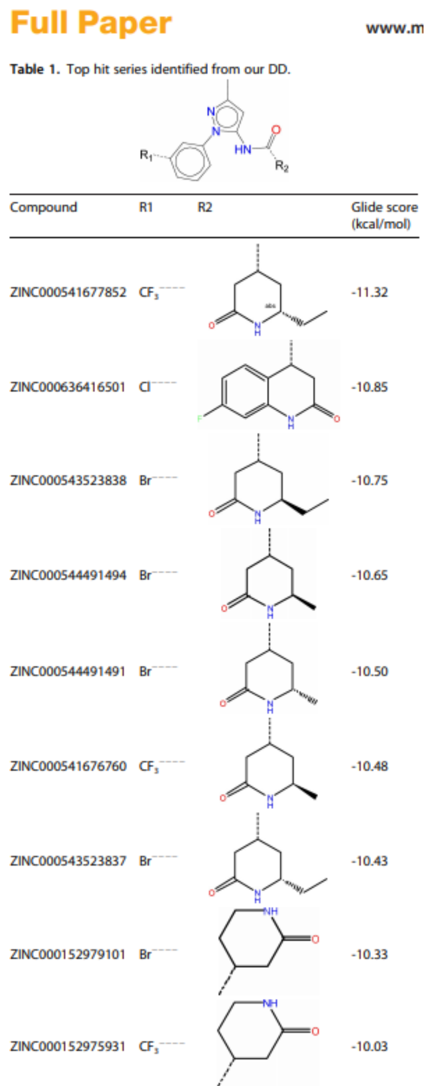

Full Paper www.m

Table 1. Top hit series identified from our DD.

Compound	R1	R2	Glide score (kcal/mol)
ZINC000541677852	CF_3		-11.32
ZINC000636416501	Cl		-10.85
ZINC000543523838	Br		-10.75
ZINC000544491494	Br		-10.65
ZINC000544491491	Br		-10.50
ZINC000541676760	CF_3		-10.48
ZINC000543523837	Br		-10.43
ZINC000152979101	Br		-10.33
ZINC000152975931	CF_3		-10.03

Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus

General Peptide based inhibitor design

The goal of this work was to find a short section or sections of viral protein sequence suitable for preliminary design proposal for a peptide synthetic vaccine and a peptidomimetic therapeutic, and to explore some design possibilities

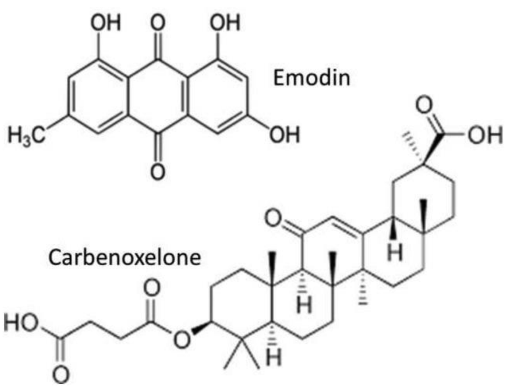
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7094376/

From the point of synthesis of a peptide as a plausible analogue of an immunogenic part ("epitope") of a protein for development of diagnostics and the peptide of interest is:

(NH_3^+)-GPSKRSFIEDLLFNKVTLAC-(COO^-)

The rationale is that the section KRSFIEDLLFNKV is exposed as associated with S2′ at the surface but highly conserved as shown in the second (i.e. "FIEDLL") alignment in Section 4.3.

Potential small molecule inhibitors



The first-in-class peptide binder to the SARS-CoV-2 spike protein

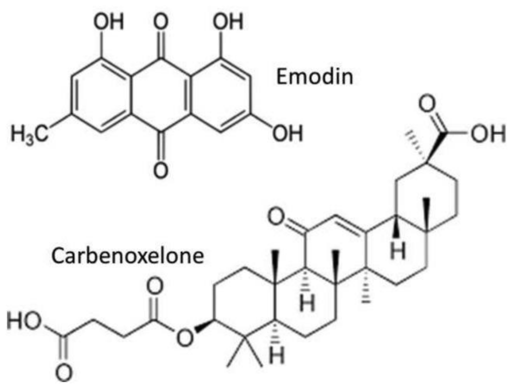
https://www.biorxiv.org/content/10.1101/2020.03.19.999318v1.article-info

Peptide Binder COv-2 SPIKE target

Using molecular dynamics simulations based on the recently solved ACE2 and SARS38 CoV-2-RBD co-crystal structure, we observed that the ACE2 peptidase domain (PD) α1 helix is important for binding SARS-CoV-2-RBD. Using automated fast-flow peptide synthesis, we chemically synthesized a 23-mer peptide fragment of the ACE2 PD α1 helix composed entirely of proteinogenic amino acids. Chemical synthesis of this human derived sequence was complete in 1.5 hours and after work up and isolation >20 milligrams of pure material was obtained. Bio-layer 43 interferometry revealed that this peptide specifically associates with the SARS-CoV-2-RBD with low nanomolar affinity. This peptide binder to SARS-CoV-2-RBD provides new avenues for COVID-19 treatment and diagnostic modalities by blocking the SARS-CoV-2 spike protein interaction with ACE2 and thus precluding virus entry into human cells.

Software used: MD NAMD and LC-MS experiments

Here are the peptide fragments they have reported.



Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19

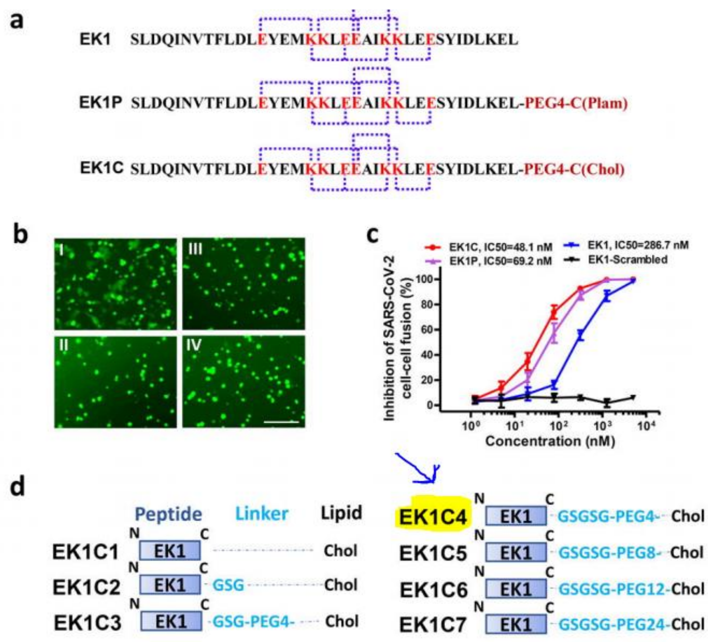
https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/

Collection of Vaccines/drug in the pipeline

Inhibition of SARS-CoV-2 infection (previously 2019-nCoV) by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion

https://www.biorxiv.org/content/10.1101/2020.03.09.983247v1.article-info

We found that one of the lipopeptides, EK1C, exhibited highly 115 potent inhibitory activity against SARS-CoV-2 S-mediated membrane fusion and PsV 116 infection, about 240- and 150-fold more potent than EK1 peptide, respectively



Unrevealing Sequence and Structural Features of Novel Coronavirus Using in silico Approaches: The Main Protease as Molecular Target

https://pubmed.ncbi.nlm.nih.gov/32210741

M-Pro Protease Target

Our results showed that several HIV inhibitors such as lopinavir, ritonavir, and saquinavir produce strong interaction with the active site of SARS-CoV-2 main protease. Furthermore, broad library protease inhibitors obtained from PubChem and ZINC (www.zinc.docking.org) were evaluated. Our analysis revealed 20 compounds that could be clustered into three groups based on their chemical features. Then, these structures could serve as leading compounds to develop a series of derivatives optimizing their activity against SARS-CoV-2 and other coronaviruses.

What DB was used?

In order to contribute with further studies related to developing more effective drugs, in this work was evaluated a broad library of protease inhibitors available in the ZINC database (over 100 compounds) and PubChem (over 200 compounds).

What Software was used?

Achilles Blind Docking server: https://bio-hpc.ucam.edu/achilles/

VINA: http://vina.scripps.edu/

VegaZZ 3.1.0.21: https://www.ddl.unimi.it/cms/index.php?Software_projects:VEGA_ZZ

NAMD (for MD simulations): https://www.ks.uiuc.edu/Research/namd/

Binding energy (BE) values of the best 20 compounds selected as potential inhibitors of SARS-CoV-2 protease. Compound structures were obtained from ZINC database (Bold) and PubChem (italics), lowest BE compound of each group are shown in red.

Compound ID	BE (kcal/mol)	Molecular formula	MW	F	S	Br	Cl	RNH2	R2NH	R3N	ROH	RCOR	RCOOR	ROR	RINGS	AROMATIC
213039	-8,1	$C_{27}H_{37}N_3O_7S$	547,6636	0	1	0	0	1	1	0	1	0	1	2	4	2
4369144	-8,2	$C_{30}H_{34}N_6O_3$	526,6294	0	0	0	0	0	1	1	0	0	0	0	5	3
444214	-8,1	$C_{28}H_{31}F_5N_4O_4$	582,5622	5	0	0	0	0	3	1	1	0	0	0	4	3
444603	-8,7	$C_{25}H_{34}N_6O_5S$	530,6397	0	1	0	0	0	1	2	1	0	0	0	4	2
444743	-8,3	$C_{23}H_{29}BrN_6O_5S$	581,4826	0	1	1	0	0	1	1	0	0	0	0	4	2
444745	-9,3	$C_{31}H_{35}N_7O_3$	553,6547	0	0	0	0	0	2	1	0	0	0	0	6	4
444756	-8	$C_{37}H_{55}ClN_8O_5$	727,3362	0	0	0	1	0	2	4	2	0	0	0	5	2
457409	-8	$C_{28}H_{36}N_2O_9S$	576,6584	0	1	0	0	0	1	0	1	0	1	4	5	2
71627394	-7,9	$C_{28}H_{37}N_3O_8S$	575,6737	0	1	0	0	0	1	0	1	0	1	2	4	2
9543419	-8,1	$C_{30}H_{39}N_7O_6$	593,674	0	0	0	0	0	2	1	1	0	0	0	2	1
ZINC001014061065	-7,6	$C_{15}H_{17}N_5O_4$	331,33	0	0	0	0	0	1	1	1	0	0	0	3	2
ZINC001014061063	-7,6	$C_{18}H_{28}N_4O_3$	348,44	0	0	0	0	0	1	1	0	0	0	0	3	1
ZINC001014061081	-8,7	$C_{16}H_{17}N_7O_2$	339,35	0	0	0	0	0	1	1	0	0	0	0	4	3
ZINC000923097446	-7,6	$C_{17}H_{21}N_5O_3$	343,38	0	0	0	0	0	1	2	0	1	0	1	3	2
ZINC001014061043	-7,6	$C_{18}H_{22}N_4O_3$	342,39	0	0	0	0	0	1	1	0	0	0	0	3	2
ZINC001014061084	-8,1	$C_{16}H_{17}N_7O_2$	339,35	0	0	0	0	0	1	1	0	0	0	0	4	3
ZINC001014061083	-8,3	$C_{16}H_{17}N_7O_2$	339,35	0	0	0	0	0	1	1	0	0	0	0	4	3
ZINC000923097334	-7,7	$C_{17}H_{18}N_4O_2$	310,35	0	0	0	0	0	1	1	0	1	0	0	3	3
ZINC001014061082	-7,7	$C_{16}H_{17}N_7O_2$	339,35	0	0	0	0	0	1	1	0	0	0	0	4	3
ZINC001435413766	-7,7	$C_{20}H_{24}FN_3O_2$	357,42	1	0	0	0	0	0	1	0	0	1	0	4	2
ZINC001014061061	-7,8	$C_{18}H_{28}N_4O_3$	348,44	0	0	0	0	0	1	1	0	0	0	0	3	1

F= fluoride, S= sulphurous, Br= bromide, Cl=chloride, RNH2= primary amine, R2NH= secondary amine, R3N= tertiary amine, ROH= alcohol, RCOR= ketone, RCOOR= ester, ROR= ether

Protease inhibitors also identified in the paper

Protease inhibitor	Binding energy (Kcal/mol) for SARS CoV-2 protease	Binding energy (Kcal/mol) for SARS CoV protease	Binding energy (Kcal/mol) for HIV-1 protease
Saquinavir	-9.6	-8.1	-9.7
Lopinavir	-9.1	-8.4	-11.4
Tipranavir	-8.7	-7.7	-10.3
Darunavir	-8.2	-6.7	-10.9
Amprenavir	-7.6	-7.3	-9.2
Atazanavir	-7.2	-7	-9.8
Ritonavir	-6.9	-7.1	-9.4

Structure of M(Pro) from COVID-19 Virus and discovery of its inhibitors

The study was published in Nature, 2020 **(Important Reference)**

MPro Protease Target

The authors have identified MPro, protease, inhibitors and also solved the inhibitor-bound complex using HTS.

Software/Techniques used:

"To understand the binding interaction of these molecules with COVID-19 virus Mpro, two different molecular docking methods, i.e., Glide (v8.2)38 and iFitDock were used to predict their binding poses. Then a 3D molecular similarity calculation method, SHAFTS41, was used for molecular alignment poses enumeration by matching the critical pharmacophore and volumetric overlay between the N3 molecule within the Mpro structure and the six drug candidates. However, the selenium atom of ebselen could not be treated by any of these above methods, so sulfur was used to replace it in the calculations. Then the
obtained optimal superposition of these molecules was used to assess the reasonability of the predicted binding poses from the two docking methods, and only the binding orientations which were consistent among different methods were kept for constructing the initial complexes. Finally, these complexes were further optimized and re-scored by using MM-GBSA module42 of Schrödinger, and the residues within 5 Å around the ligand were refined.

Inhibition of the Main Protease 3CL-pro of the Coronavirus Disease 19 via Structure-Based Ligand Design and Molecular Modelingtitled section

https://arxiv.org/pdf/2002.09937.pdf

A Large-scale Drug Repositioning Survey for SARS-CoV-2 Antivirals ****

https://www.biorxiv.org/content/10.1101/2020.04.16.044016v1.full.pdf

we profiled a library of known drugs encompassing approximately 12,000 clinical-stage or FDAapproved small molecules. Here, we report the identification of 30 known drugs that inhibit viral replication. Of these, six were characterized for cellular dose-activity relationships, and showed effective concentrations likely to be commensurate with therapeutic doses in patients. These include the PIKfyve kinase inhibitor Apilimod, cysteine protease inhibitors MDL-28170, Z LVG CHN2, VBY-825, and ONO 5334, and the CCR1 antagonist MLN-3897.

COVID-19 Docking Server: An interactive server for docking small molecules, peptides and antibodies against potential targets of COVID-19

https://arxiv.org/pdf/2003.00163

READ THE PAPER TO GET ALL THE STRUCTURAL AND NSprotein information

A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug- Repurposing

bioRxiv preprint doi: https://doi.org/10.1101/2020.03.22.002386. **(Important Reference)**

Deciphering the Protein Motion of S1 Subunit in SARS-CoV-2 Spike Glycoprotein Through Integrated Computational Methods

https://arxiv.org/pdf/2004.05256.pdf

Old Drugs for Newly Emerging Viral Disease, COVID-19: Bioinformatic Prospective

https://arxiv.org/ftp/arxiv/papers/2003/2003.04524.pdf

Screening of Therapeutic Agents for COVID-19 using Machine Learning and Ensemble Docking Simulations

https://arxiv.org/pdf/2004.03766.pdf

INTERESTING PAPER

On the Inhibition of COVID-19 Protease by Indian Herbal Plants: An In Silico InvestigationUntitled section

https://arxiv.org/ftp/arxiv/papers/2004/2004.03411.pdf

In Silico Screening of Some Naturally Occurring Bioactive Compounds Predicts Potential Inhibitors against SARS-COV-2 (COVID-19) Protease

https://arxiv.org/ftp/arxiv/papers/2004/2004.01634.pdf

In the present study, we investigated Jensenone as potential inhibitor candidates for COVID-19 Mpro

Molecular docking studies on Jensenone from eucalyptus essential oil as a potential inhibitor of COVID 19 corona virus infection

https://arxiv.org/ftp/arxiv/papers/2004/2004.00217.pdf

In Silico Investigations on the Potential Inhibitors for COVID-19 Protease

https://arxiv.org/ftp/arxiv/papers/2003/2003.10642.pdf

We have calculated log P and log S values in addition to molecular docking and PASS predictions. Among the seven studied compounds, mepacrine appears as the potential inhibitor of the COVID-19 followed by chloroquine, hydroxychloroquine and phomarin. Therefore, these anti-malarial drugs may be potential drug candidate for the treatment of this novel coronavirus

Multidrug treatment with nelfinavir and cepharanthine against COVID-19

https://www.biorxiv.org/content/10.1101/2020.04.14.039925v1.full

FEP-based screening prompts drug repositioning against COVID-19

https://www.biorxiv.org/content/10.1101/2020.03.23.004580v1

Classical drug digitoxin inhibits influenza cytokine storm, with implications for COVID-19 therapy

https://doi.org/10.1101/2020.04.09.034983

Structural basis for the inhibition of COVID-19 virus main protease by carmofur, an antineoplastic drug

https://doi.org/10.1101/2020.04.09.033233

Reversal of Infected Host Gene Expression Identifies Repurposed Drug Candidates for COVID-19

https://doi.org/10.1101/2020.04.07.030734

A data-driven drug repositioning framework discovered a potential therapeutic agent targeting COVID-19

https://doi.org/10.1101/2020.03.11.986836

Nucleotide Analogues as Inhibitors of SARS-CoV-2 PolymeraseUntitled section

https://doi.org/10.1101/2020.03.18.997585

The target landscape of N4-hydroxycytidine based on its chemical neighborhood

https://doi.org/10.1101/2020.03.30.016485

The potential SARS-CoV-2 entry inhibitor

---

https://doi.org/10.1101/2020.03.26.009803

Triphosphates of the Two Components in DESCOVY and TRUVADA are Inhibitors of the SARS-CoV-2 Polymerase

---

https://doi.org/10.1101/2020.04.03.022939

In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication

---

https://doi.org/10.1101/2020.04.03.023846

Molecular Modeling Evaluation of the Binding Effect of Ritonavir, Lopinavir and Darunavir to Severe Acute Respiratory Syndrome Coronavirus 2 Proteases

---

https://doi.org/10.1101/2020.01.31.929695

Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs

---

https://doi.org/10.1101/2020.03.20.999730

Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production

---

https://doi.org/10.1101/2020.04.04.020925

Molecular Docking Analysis of Some Phytochemicals on Two Sars-Cov-2 Targets

---

https://doi.org/10.1101/2020.03.31.017657

Nucleotide Analogues as Inhibitors of SARS-CoV Polymerase

https://doi.org/10.1101/2020.03.12.989186

Discovery of baicalin and baicalein as novel, natural product inhibitors of SARS-CoV-2 3CL protease in vitro

https://doi.org/10.1101/2020.04.13.038687

Evaluation of 19 antiviral drugs against SARS-CoV-2 Infection

https://www.biorxiv.org/content/10.1101/2020.04.29.067983v1.full.pdf

The global pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV) has prompted multiple clinical trials to jumpstart search for anti-SARS-CoV-2 therapies from existing drugs, including those with reported in vitro efficacies as well as those ones that are not known to inhibit SARS-CoV-2, such a Ritonavir/lopinavir and Favilavir. Here we report that after screening 19 antiviral drugs that are either in clinical trials or with proposed activity against SARS-CoV-2, remdesivir was the most effective. Chloroquine only effectively protected virus-induced cytopathic effect at around 30 µM with a therapeutic index of 1.5. Our findings also show that velpatasvir, ledipasvir, litonavir, lopinavir, favilavir, sofosbuvir do not have direct antiviral effect.

Evolutionary Multi-Objective Design of SARS-CoV-2 Protease Inhibitor Candidates

https://arxiv.org/pdf/2005.02666.pdf

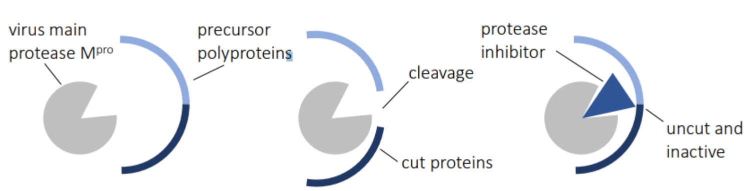


Fig. 1: Illustration of (left) protease enzyme with uncut precursor polyproteins, (middle) the cleavage progress, and (right) protease inhibition preventing the cleavage.

Alpha 1 Antitrypsin is an Inhibitor of the SARS-CoV2–Priming Protease TMPRSS2

https://www.biorxiv.org/content/10.1101/2020.05.04.077826v1.full.pdf

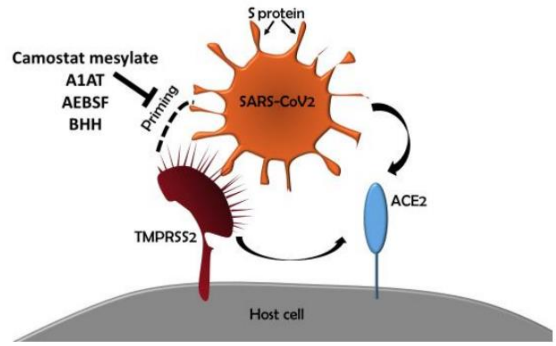


Figure 3. Model of SARS-CoV2 entry and the role of protease inhibitors. TMPRSS2 processes the S protein on the SARS-CoV2 envelope in a process called priming. Priming of the S protein is necessary for binding between the S protein and the host receptor ACE2. TMPRSS2 inhibitors, such as camostat mesylate, A1AT, AEBSF, and BHH prevent the priming of the S protein and therefore block virus entry. In addition, inhibition of TMPRSS2 prevents processing of ACE2, which decreases the infectivity of the coronavirus.

The race to find a SARS-CoV-2 drug can only be won by a few chosen drugs: a systematic review of registers of clinical trials of drugs aimed at preventing or treating COVID-19

https://www.medrxiv.org/content/10.1101/2020.05.05.20091785v1.full.pdf

The objective of this comprehensive systematic review is to gather and synthesize the information included in the clinical trial registers of candidate drugs to prevent and treat COVID-19 according to the pharmacological group and specific drugs name, study design, main outcomes, number and characteristics of participants recruited, and It is made available under a CC-BY-NC-ND 4.0 International license . (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: https://doi.org/10.1101/2020.05.05.20091785.this version posted May 9, 2020. The copyright holder for this preprint expected completion date. In addition, we graphically represent which drugs are most likely to achieve consistent results over the coming months of 2020

Protein-ligand interaction study to identify potential dietary compounds binding at the active site of therapeutic target proteins of SARS-CoV-2

https://arxiv.org/ftp/arxiv/papers/2005/2005.11767.pdf

Objective: Total 186 biologically important phenylpropanoids and polyketides compounds from different Indian medicinal plants and dietary sources were screened to filter potential compounds that bind at the active site of the therapeutic target proteins of SARS-CoV-2. Method: The molecular docking studies were carried out by using the Autodock Vina. The in silico ADMET and drug-likeness properties of the compounds were predicted from SwissADME server.

Result: The molecular docking study of the 186 compounds with the therapeutic target proteins (Mpro, PLpro, RdRp, SGp and ACE2) of SARS-CoV-2 resulted 40 compounds that bind at the active site with dock score above -8.0 kcal/mol.

Virtual Screening of Plant Metabolites against Main protease, RNA-dependent RNA polymerase and Spike protein of SARS-CoV-2: Therapeutics option of COVID-19

https://arxiv.org/ftp/arxiv/papers/2005/2005.11254.pdf

Covid-19, a serious respiratory complications caused by SARS-CoV-2 has become one of the global threat to human healthcare system. The present study evaluated the possibility of plant originated approved 117 therapeutics against the main protease protein (MPP), RNA-dependent RNA polymerase (RdRp) and spike protein (S) of SARS-CoV-2 including drug surface analysis by using molecular docking through drug repurposing approaches. The molecular interaction study revealed that Rifampin (-16.3 kcal/mol) were topmost inhibitor of MPP where Azobechalcone were found most potent plant therapeutics for blocking the RdRp (-15.9 kcal /mol) and S (-14.4 kcal/mol) protein of SARS-CoV-2. After the comparative analysis of all docking results, Azobechalcone, Rifampin, Isolophirachalcone, Tetrandrine and Fangchinoline were exhibited as the most potential inhibitory plant compounds for targeting the key proteins of SARS-CoV-2.

Repurpose Open Data to Discover Therapeutics for COVID-19 using Deep Learning

https://arxiv.org/ftp/arxiv/papers/2005/2005.10831.pdf

Supplemental data is not yet available

Repositioning of 8565 existing drugs for COVID-19

https://arxiv.org/pdf/2005.10028.pdf

Supplemental data is not yet available

Targeting the SARS-CoV-2 Main Protease to Repurpose Drugs for COVID-19

https://www.biorxiv.org/content/10.1101/2020.05.23.112235v1.full.pdf

Repurposing of Miglustat to inhibit the coronavirus Severe Acquired Respiratory Syndrome SARS-CoV-2

https://www.biorxiv.org/content/10.1101/2020.05.18.101691v1.full.pdf

Identification of five antiviral compounds from the Pandemic Response Box targeting SARS-CoV-2

https://www.biorxiv.org/content/10.1101/2020.05.17.100404v1

Identification of five antiviral compounds from the Pandemic Response Box targeting SARS-CoV-2

https://www.biorxiv.org/content/10.1101/2020.05.17.100404v1

Comparative analysis of antiviral efficacy of FDA-approved drugs against SARS-CoV-2 in human lung cells: Nafamostat is the most potent antiviral drug candidate

https://www.biorxiv.org/content/10.1101/2020.05.12.090035v1.full.pdf