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

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Abstract

The COVID-19 crisis called for rapid reaction from all the fields of biomedical research. Traditional drug development involve time consuming pipelines that conflict with the urgence of identifying effective therapies during a health and economic emergency. Drug repositioning, that is the discovery of new clinical applications for drugs already approved for different therapeutic contexts, could provide an effective shortcut to bring COVID-19 treatments to the bedside in a timely manner. Moreover, computational approaches can help accelerate the process even further. Here we present the application of different software tools based on transcriptomics data to identify drugs that are potentially able to counteract SARS-CoV-2 infection and also to provide insights on their mode of action. We believe that HDAC inhibitors warrant further investigation. In addition, we found that the DNA Mismatch repair pathway is strongly modulated by drugs with experimental in vitro activity against SARS-CoV-2 infection.

1 Introduction

Drug repositioning or drug repurposing aims to find a new clinical application for a drug already in use but for a different purpose. Usually, in drug repurposing, a known and potentially therapeutic target is selected and an experimental search for existing compounds able to modulate the target activity is performed. Computational drug repurposing offers a complementary approach to prioritise compounds for experimental validation. Several different methods

have been proposed in the literature [1–3] and some have already been applied to SARS-CoV-2 [4]. These can be broadly classified into methods searching for small molecules able to bind an active pocket starting from three-dimensional structure of the target protein [5] and those searching for compounds able to modulate the expression of the target mRNA [6, 7]. While most of the existing drug repositioning pipelines focus on the former approach, her we used the latter to identify FDA approved drugs able to modulate the expression of genes expressed in the airway epithelium and that are known to interact with SARS-CoV-2 proteins. Next, we attempted a completely agnostic approach that tries to identify drugs reversing the gene expression profile induced by SARS-CoV-2 infection. Finally, we investigated potential effective mechanisms of action by identifying molecular pathways that are consistently dysregulated by a set of 24 drugs recently proposed as effective to reduce SARS-CoV-2 N protein levels in treated Vero cells. By the application of the proper computational tools, we were thus able to identify a set of drugs that should further be experimentally validated and that may have a potential beneficial role in COVID19 treatment, together with insights about mechanisms of action that could help to identify the most effective targets against the infection.

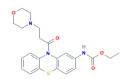
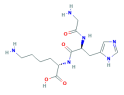
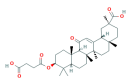
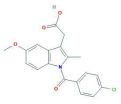
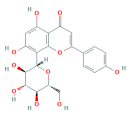
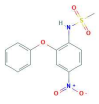
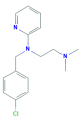
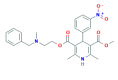
2 Results

2.1 Identification of drugs reducing the expression ACE2 and TMPRSS2

It has been recently shown tha SARS-CoV-2 entry in host cells is mediated by the ACE2 receptor and requires priming by the TMPRSS2 protease [8]. We thus sought to identify drugs that could potentially reduce the expression of both genes, although the benefit of such an approach is being debated [9]. To this end, we applied a computational drug repositioning approach named Gene2Drug[1] [6]. This tool computes an Enrichment Score (ES) and the corresponding P-value for each of 1309 small molecules of the Connectivity Map dataset (Broad Institute), including FDA approved drugs, based on how much they tend to up- or down-regulate the genes of interest (ACE2 and TMPRSS2), as well as other genes involved in the same pathways. Results from the analysis identified 10 drugs shown in Table 1 ($p < 0.05$). Most of these drugs are potentially relevant: **carbenoxolone** has shown antiviral activity against the Dengue virus [10]; **indomethacin** is a non-steroidal anti-inflammatory drug (NSAID) inhibiting Prostaglandin E2 synthase (PTGES2) with a demonstrated efficacy against SARS-CoV [11]. Interestingly, in a recent study, SARS-CoV-2 viral NSP7 was found to interact with PTGES2 [8] and thus the authors suggested indomethacin as potentially useful in treating patients. Here, however, indomethacin was selected by Gene2Drug because it appears to lower expression of genes in the ACE2 pathway, which does not include PTGES2 itself. Therefore indomethacin could be a high priority molecule to be tested as it could have a

[1] http://gene2drug.tigem.it

double effect. Another NSAID is present among the drugs identified in Table 1, **nimesulide** which could have a similar effect as indomethacin. Gene2Drug also identified **nicarpidine**, an angiotensin inhibitor, an obvious candidate but found using a purely data-driven approach.

#	Drug	ES	PV	2D structure	Notes
1	moracizine	-1.000	0.0092		Has a role as an anti-arrhythmia drug.
2	Gly-His-Lys	-0.995	0.0184		Has a role as a metabolite, a chelator, a vulnerary and a hepatoprotective agent.
3	carbenoxolone	-0.995	0.0184		Used for the treatment of digestive tract ulcers.
4	indometacin	-0.995	0.0184		Non-steroidal anti-inflammatory drug most commonly used in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute shoulder pains, and acute gouty arthritis.
5	vitexin	-0.995	0.0184		platelet aggregation inhibitor, an alpha-glucosidase inhibitor, an antineoplastic agent and a plant metabolite
6	nimesulide	-0.991	0.0276		Nonsteroidal anti-inflammatory drug, modestly selective COX-2 inhibitor.
7	PNU-0293363	-0.981	0.0461	N/A	N/A
8	chloropyramine	-0.981	0.0461		Antihistamine drug with applications to the treatment of allergic conjunctivitis, allergic rhinitis, bronchial asthma, and other atopic (allergic) conditions.
9	nicardipine	-0.981	0.0461		Calcium channel blocker used in the treatment of hypertension and stable angina pectoris.

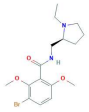
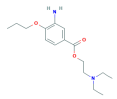
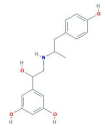
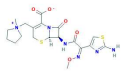
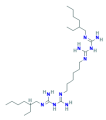
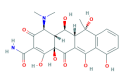
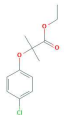
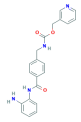
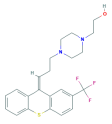
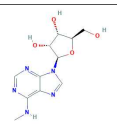
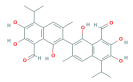
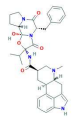
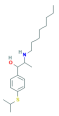
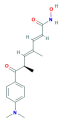
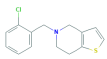
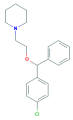
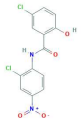
10	remoxipride	-0.981	0.0461		Antipsychotic agent specific for dopamine D2 receptors, effective in the treatment of schizophrenia.

Table 1: Drugs predicted to downregulate ACE2 and TMPRSS2 genes by the Gene2drug tool ($p < 0.05$). Enrichment score (ES) and the corresponding p-value (PV) are reported for each drug.

2.2 Identification of drugs reducing expression of SARS-CoV-2 interactors

Another potentially effective approach to the identification of therapeutic agents counteracting SARS-CoV-2 infection is to target the host-virus interaction. In order to investigate cellular proteins interacting with viral proteins, [8] performed an affinity purification-mass spectrometry analysis which identified a total of 332 protein interactions between 26 SARS-CoV-2 proteins (plus 1 mutant) and human proteins. Since each of these interactions could be key to to hijack the host during the course of infection, we sought to prioritize existing drugs potentially interfering with them. In particular, we applied once more Gene2drug [6], this time exploiting its gene-set wise analysis capability. Specifically, for each viral protein, we generated a corresponding gene-set containing all the host protein interactors, thus obtaining 27 gene-sets. We then applied Gene2Drug to identify those compounds that are able to downregulate the expression of most of the genes across the 27 gene-sets at the same time, which appears a particularly effective strategy given the currently limited understanding of the specific infection mechanisms. The top 20 hits are reported in Table 2. Interestingly, one of the hits is **niclosamide**, an antihelminthic drug, that was found to have antiviral efficacy against SARS-CoV-2 in a recent screening using VERO cells [12]. Other notable candidates found by our analysis are: **fenoterol**, which was also identified as potentially effective in a recent study on computational drug repositioning [13]; **alexidine**, an antibiotic and a selective inhibitor of the mitochondrial phosphatase Ptpmt1, that was found to inhibit replication of the CytoMegaloVirus (CMV) infection [14]; **oxytetracycline**, another antibiotic that has shown antiviral activity against Dengue virus [15] and the ability to reduce HIV-1 RNA transcripts within extracellular vescicles [16]; **clofibrate** is peroxisome-proliferator activated receptor-alpha (PPAR-) agonist previously used as a cholesterol-lowering agent, which was found to have antiviral activity against MDV, an alphaherpesvirus that infects chickens and causes a deadly lymphoma [17]; **flupentixol** is a neuroleptic agent that was found to inhibit hepatitis C virus entry [18] and coxsackievirus replication [19]; **gossypol**, a natural phenol derived from the cotton plan known inhibit spermatogenesis, was shown to have also antiviral activity [20]; **ms-275** and **trichostatin A** are histone deacetylases inhibitors (HDACi), the latter was found to inhibit expression of herpes simplex virus genes[21]; interestingly valproic acid, another HDACi, was proposed for repositioning against SARS-CoV-2, as the viral protein NSP5 was found to interact with HDAC2 [8].

#	Drug	mean ES	mean PV	2D structure	Notes
1	proxymetacaine	-0.536	0.0002		Benzoic acid derivative anesthetic agent, with local anesthetic activity.
2	fenoterol	-0.492	0.0008		Beta2-adrenergic agonist used in the management of reversible airway obstruction.
3	0179445_0000	-0.498	0.0013	N/A	N/A
4	cefepime	0.473	0.0015		Antibacterial drug.
5	picrotoxinin	-0.473	0.0023		Has a role as a plant metabolite, a GABA antagonist and a serotonergic antagonist.
6	alexidine	-0.485	0.0036		Amphipathic bisbiguanide with a role as an antibacterial agent.
7	oxytetracycline	-0.460	0.0042		Tetracycline used for treatment of infections caused by a variety of Gram positive and Gram negative microorganisms.
8	clofibrate	-0.446	0.0052		Anticholesteremic drug antilipemic drug.
9	ms 275	-0.439	0.0052		Inhibitor of histone deacetylase isoform 1 (HDAC1) and isoform 3 (HDAC3).
10	flupentixol	-0.356	0.0073		Antipsychotic neuroleptic drug, used in schizophrenia.

11	n6 methyladenosine	-0.421	0.0084		methylated adenine residue
12	gossypol	-0.398	0.0086		Orally-active polyphenolic aldehyde with potential antineoplastic activity by inhibiting DNA replication and inducing apoptosis.
13	dihydroergocristine	-0.41	0.0087		Used as the mesylate salt for the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency and in peripheral vascular disease. It has a role as an adrenergic antagonist and a vasodilator agent.
14	suloctidil	-0.398	0.0089		An alkylbenzene.
15	trichostatin A	-0.389	0.0093		Inhibits histone deacetylases. Potent inducer of tumor cell growth arrest, differentiation and apoptosis.
16	ticlopidine	-0.447	0.0093		Has a role as a fibrin modulating drug, a hematologic agent, an anticoagulant, a platelet aggregation inhibitor and a P2Y12 receptor antagonist.
17	cloperastine	-0.461	0.0098		A cough suppressant that acts on the central nervous system.
18	niclosamide	-0.401	0.0103		A member of benzamides with anthelmintic and potential antineoplastic activity.

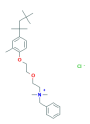
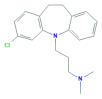
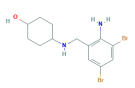
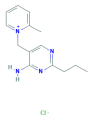
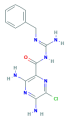
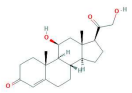
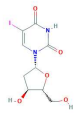
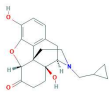
19	methylbenzethonium chloride	-0.454	0.0104		N/A
20	clomipramine	-0.397	0.0106		Has a role as a serotonergic antagonist, a serotonergic drug, a serotonin uptake and trypanothione-disulfide reductase inhibitor, and an antidepressant.

Table 2: Drugs predicted to downregulate SARS-CoV-2 human interactors by the Gene2drug tool ($p < 0.05$, top 20 reported). The mean enrichment score (ES) and the corresponding mean p-value (PV) across different gene-set backgrouns (see Methods) are reported for each drug.

2.3 Identification of drugs reversing the transcriptional signature induced by SARS-CoV-2 infection

A data-driven approach to drug repositioning is to identify compounds that are able to revert a disease-related signature [3]. We developed the MANTRA tool exploiting the cMap dataset (Broad Institute) to generate and explore drug networks for drug repositioning [22, 23]. In drug networks, nodes represent drug-induced transcriptional profiles, and edges represent similarities between them. We sought to use this approach to prioritize drugs reverting SARS-CoV-2 induced gene expression at the whole-genome level without assuming any knowledge of molecular mechanisms involved in the disease progression. Recently, gene expression profiles of primary human bronchial epithelial (NHBE) infected with SARS-CoV-2 have been made publicly available [24] (GSE147507 from the GEO database). We obtained the corresponding raw data and computed the differential expression of 15,330 between infected and non infected cells. Out of these, only 37 genes were significantly differentially expressed (adjusted $p < 0.1$), most of which were over-expressed in infected cells and included interleukin 6 (IL6) and 8 (IL8), chemokines and interferon alpha inducible proteins. The MANTRA approach is based on Gene Set Enrichment Analysis and therefore it requires in input a list of all the measured genes ranked according to their differential expression, including both significant and non-significant genes. We thus sorted all the 15,330 genes according to their differential expression, but with genes most down-regulated following infection *at the top of the list* and those most up-regulated *at the bottom*. We then queried the MANTRA drug network with this profile and looked for drugs inducing a similar transcriptional profile, which therefore may potentially induce a profile opposite to that of the infection. We thus found 11 significant drugs (transcriptional distance < 0.8) listed in Table 3. One of the 11 drugs is sirolimus, also known as rapamycin, an inhibitor of mechanistic Target Of Rapamycin Complex 1 (mTORC1), and used clinically as an immunosuppressive agent. This is an obvious candidate for this kind of drug repositioning, where the aim is to find a drug inducing an opposite repsonse to that of the virus, as most of the genes overexpressed during viral infection are immune-related. Of course, this does not mean that it is clinically relevant as suppressing the immune response could be detrimental to the cells. Nevertheless, Rapamycin was also suggested in the SARS-CoV-2 interactors' study based on the nuclecapsid interaction with the mTOR translational repressors LARP1 [8] and on rapamycin reported *in vitro* activity against MERS [25]. Other interesting candidates found by MANTRA are: **ambroxol**, a mucolytic agent with reported antiviral activity against influenza-virus among others [26, 27] and **chlorzoxazone**; **corticosterone**, a glucocorticoid; **idoxuridine**, a nucleoside analogue used to inhibit replication of DNA viruses; **naltrexone**, a mu-opiod receptor antagonist used for opioid and alcohol dependence, with reported antiinflammatory effect [28]; **nordihydroguaiaretic acid** an antioxidant compound found in the creosote bush (Larrea tridentata) with reported antiviral activity against West Nile and Zika viruses [29].

#	Drug	2D structure	Notes
1	ambroxol		Aromatic amine used in the treatment of respiratory diseases associated with viscid or excessive mucus.
2	amprolium		A veterinary coccidiostat that interferes with thiamine metabolism.
3	benzamil		Potent blocker of the ENaC channel and also a sodium-calcium exchange blocker.
4	chlorzoxazone		Centrally acting muscle relaxant with sedative properties used for the symptomatic treatment of painful muscle spasm.
5	corticosterone		Steroid hormone of the corticosteroid type.
6	doxylamine		A first generation ethanolamine with antiinflammatory, sedative and antihistamine properties.
7	idoxuridine		Antiviral drug and DNA synthesis inhibitor, with antiviral activity against herpes simplex virus (HSV) and potential radiosensitizing activities.
8	meptazinol		Opioid analgesic.
9	naltrexone		A mu-opioid receptor antagonist used to treat alcohol dependence. Has also a role as a central nervous system depressant, an environmental contaminant, a xenobiotic and an antidote to opioid poisoning.

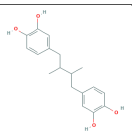
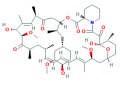
10	nordihydroguaiaretic acid		Has a role as an antioxidant and a plant metabolite.
11	sirolimus		Antibiotic, has a role as immunosupressive, antineoplastic, antibacterial agent, mTOR inhibitor and a bacterial metabolite.

Table 3: Drugs predicted to revert the transcriptional signature induced by SARS-CoV-2 infection through the MANTRA tool (distance to the inverse of the SARS-CoV-2 profile < 0.8.

2.4 Mechanism of action of compounds with reported *in vitro* antiviral action against SARS-CoV-2 infection.

Understanding the biological mechanisms underlying a pathological condition at the molecular level can greatly help the identification of potentially effective drugs. One way of obtaining such knowledge is the analysis of existing small molecules that have been observed to elicit varying levels of therapeutic effect through automated screening. Although the mode of action of positive hits from large-scale drug screening can be difficult to identify, it is likely that such hidden mechanism is shared among most of the hits. In order to investigate and exploit this assumption, we previously developed the Drug Set Enrichment Analysis (DSEA[2] [30]). DSEA is able to highlight molecular pathways that are consistently and specifically dysregulated by most drugs in a set by analyzing drug-induced expression profiles in the cMap dataset (Broad Institute).

In order to identify compounds that are able to counteract SARS-CoV-2 infection, Jeon et al [12] recently screened a collection of 35 small molecules previously observed as potentially effective against SARS-CoV infection, plus 15 drugs suggested by infectious diseases specialists. Among the 50 screened drugs, 24 showed reduction of the SARS-CoV-2 N protein levels in infected VERO cells[12]. Of the 24 drugs, only ten were present in the cMap dataset used by DSEA (amodiaquine, ciclosporin, desoxycortone, digoxin, loperamide, mefloquine, niclosamide, ouabain, proscillaridin, tetrandrine). We thus sought to analyze these 10 drugs through the DSEA tool in order to understand the common mechanism of action underlying their antiviral effect. These drugs were found by DSEA to modulate targets of transcription factors (TFs) as shown in Table 4 including: **NF-kB**, a master regulator of stress response; **ATF6**, a TF involved in the integrated stress response and with a known role in enhancing herpesvirus gene expression [31]; and **STAT5B**, a member of the STAT family activated in response to cytokines and growth factor. DSEA also highlighted several biological processes as modulated by these drugs (Table 4), among which some related to DNA mistmatch repair pathway (MMR). Interestingly, DNA MMR has been recently reported to be required for the host innate response following influenza virus infection [32].

[2]http://dsea.tigem.it

Transcription Factor / GO Term	**ES**	**PV**
Transcription Factor Targets		
NF-κB (V$NFKAPPAB65_01)	0.704	1.08E-04
ATF6 (V$ATF6_01)	0.675	2.35E-04
OCT (V$OCT_Q6)	0.669	2.77E-04
SREBP1 (TCANNTGAY_V$SREBP1_01)	0.668	2.82E-04
NF-κB (V$NFKAPPAB_01)	0.667	2.94E-04
OCT (V$OCT_C)	0.665	3.07E-04
STAT5B (V$STAT5B_01)	0.658	3.68E-04
NF-κB (V$NFKB_Q6)	0.656	3.89E-04
SREBP1 (V$SREBP1_01)	0.648	4.75E-04
PITX2 (V$PITX2_Q2)	0.646	5.05E-04
Gene Ontology - Biological Process		
RNA modification	-0.731	5.01E-05
response to ischemia	-0.707	9.91E-05
DNA replication	-0.682	1.95E-04
amino acid transport	0.681	2.03E-04
DNA strand elongation involved in DNA replication	-0.679	2.12E-04
intra-Golgi vesicle-mediated transport	0.678	2.16E-04
porphyrin-containing compound biosynthetic process	-0.678	2.16E-04
chlorophyll biosynthetic process	-0.674	2.46E-04
photosynthesis	-0.674	2.46E-04
negative regulation of neuron projection development	-0.660	3.54E-04
Gene Ontology - Molecular Function		
MutLalpha complex binding	-0.795	7.08E-06
polypeptide N-acetylgalactosaminyltransferase activity	-0.726	5.72E-05
mismatched DNA binding	-0.701	1.17E-04
nucleotide binding	-0.686	1.76E-04
magnesium chelatase activity	-0.674	2.46E-04
single-stranded DNA binding	-0.668	2.82E-04
receptor activity	0.659	3.61E-04
antigen binding	0.630	7.64E-04
enzyme regulator activity	-0.629	7.76E-04
ribonuclease P activity	-0.611	1.22E-03
Gene Ontology - Cellular Component		
nucleolus	-0.715	7.94E-05
DNA replication factor C complex	-0.675	2.35E-04
Gemini of coiled bodies	-0.654	4.08E-04
Cul3-RING ubiquitin ligase complex	-0.638	6.27E-04
nucleosome	0.608	1.29E-03
apical plasma membrane	0.601	1.52E-03
mitochondrial small ribosomal subunit	-0.596	1.73E-03

extracellular matrix	0.596	1.74E-03
nucleolar ribonuclease P complex	-0.584	2.31E-03
COPI vesicle coat	0.577	2.72E-03

Table 4: Drug Set Enrichment Analysis results for 24 small molecules showed to lower the level of the N protein in SARS-CoV-2. The reported pathways are consistently dysregulated by most drugs in the set as found by the DSEA based on the analysis of their induced transcriptomes. Top 10 pathways are reported for the Transcription Factor Targets collection and for the three Gene Ontology collections. Enrichment Scores (ES) and the corresponding p-value (PV) are reported for each gene set.

3 Conclusions

Computational methods for drug repositioning could narrow down the search for effective drugs to counteract novel epidemics. Here we showed how a number of existing tools can be used towards this aim, covering different approaches such as targeting of host proteins interacting with viral proteins, reversion of disease-induce transcriptional and mode of action investigation for drugs with *in vitro* activity against SARC-CoV-2 infection. Overall, we found 39 compounds that could be tested experimentally among which NSAIDs, antihistamines, antibiotics and antihelmintics, antipsychotics, corticosteroids and HDAC inhibitors (HDACi). Of interest, HDAC2 was found to interact with SARS-CoV-2 proteins[8] and the screening on inhibitors of infection on VERO cells identified several members of the cardiac glycosides as effective [12]. Cardiac glycosides have been recently found to have strong HDACi activity [33, 34]. It will be therefore interesting to verify experimentally whether HDACi have beneficial role in reducing viral replication in host cells. Finally, by interrogating the possible mode of action of positive hits of a drug screening in VERO cells [12], we identified the DNA MMR pathway as possibly involved in the mode of action of these drugs, and therefore hinting that this pathway could be involved in the host response to the viral infection.

4 Methods

All the used computational tools share the same database of 6,100 drug induced gene expression profiles included in the Connectivity Map 2.0 (CMap [35]). CMap data were produced using Affymetrix Micrarrays, which we pre-processed to abtain the expression values for 12,012 genes. Moreover, expression profiles induced by the same drug across different replicates and experimental conditions were merged together into a single consensus profile. Details of the preprocessing are reported in [30].

Both Gene2drug and DSEA use a pathway-based version of the Cmap. A Pathway-based Expression Profiles (PEP) is obtained from a Gene Expression Profiles (GEP) by iteratively applying Gene Set Enrichment Analysis (GSEA [36]) to the GEP for each pathway in a database such as the Gene Ontology or KEGG. In particular, both tools use all the pathway collections included in the MSigDB v6.1. See [30] for the details of the process.

The publicly available online implementation of Gene2drug[3] was used to identify drugs downregulating ACE2 and TMPRSS2. The tool automatically identifies all the gene sets involving the input genes across all of the pathway databases. Also for the DSEA analysis, we used the online tool[4].

Since the Gene2drug analysis applied to the SARS-CoV-2 human molecular interactors required customization, it was performed offline using the gep2pep

[3]http://gene2drug.tigem.it

[4]http://dsea.tigem.it

Bioconductor package [37]. In particular, the interactors of each of the 27 SARS-CoV-2 proteins were used to define a gene set. The 27 obtained gene sets were then added to each of the pathway collections included in the latest version of the MSigDB [36], that is v7. Finally, the CMap GEPs were converted to PEPs based on these newly created gene set collections. In order to prioritize drugs according to their PEPs, Gene2drug analysis was performed for the 27 SARS-CoV-2 related gene sets, using all the MSigDB gene sets as statistical background. Since the statistical background was different for each gene set collection, the average scores were computed to obtain the final prioritization.

Drugs predicted to reverse SARS-CoV-2 induced signature were identified using the publicly avaliable MANTRA tool[5]. RNA-seq raw counts for the identification of differentially expressed genes (DEGs) in response to SARS-CoV-2 were downloaded from GEO database (accession number GSE147507). Raw counts were first normalized using edgeR while DEGs identified by using the limma package with its voom method in the R statistical environment 3.6.The obtained GEP was added to the MANTRA network using the "reverse node" feature. In this way the GEP is reversed (most up-regulated genes appear as the most down-regulated and vice-versa) and the closest nodes in the network correspond to drugs inducing the opposite GEP as compared to that of SARS-CoV-2.

Two-dimensional structure images and annotations reported in the tables were obtained from the PubChem database [38].

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