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Ontological and bioinformatic analysis of anti-coronavirus drugs and their implication for drug repurposing against COVID-19

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Abstract

Coronavirus-infected diseases have posed great threats to human health. In past years, highly infectious coronavirus-induced diseases, including COVID-19, SARS, and MERS, have resulted in world-wide severe infections. Our literature annotations identified 110 chemical drugs and 26 antibodies effective against at least one human coronavirus infection *in vitro* or *in vivo*. Many of these drugs inhibit viral entry to cells and viral replication inside cells or modulate host immune responses. Many antimicrobial drugs, including antimalarial (e.g., chloroquine and mefloquine) and antifungal (e.g., terconazole and rapamycin) drugs as well as antibiotics (e.g., teicoplanin and azithromycin) were associated with anti-coronavirus activity. A few drugs, including remdesivir, chloroquine, favipiravir, and tocilizumab, have already been reported to be effective against SARS-CoV-2 infection *in vitro* or *in vivo*. After mapping our identified drugs to three ontologies ChEBI, NDF-RT, and DrON, many features such as roles and mechanisms of action (MoAs) of these drugs were identified and categorized. For example, out of 57 drugs with MoA annotations in NDF-RT, 47 have MoAs of different types of inhibitors and antagonists. A total of 29 anticoronaviral drugs are anticancer drugs with the antineoplastic role. Two clustering analyses, one based on ChEBI-based semantic similarity, the other based on drug chemical similarity, were performed to cluster 110 drugs to new categories. Moreover, differences in physicochemical properties among the drugs were found between those inhibiting viral entry and viral replication. A total of 163 host genes were identified as the known targets of 68 anti-coronavirus drugs, resulting in a network of 428 interactions among these drugs and targets. Chlorpromazine, dasatinib, and anisomycin are the hubs of the drug-target network with the highest number of connected target proteins. Many enriched pathways such as calcium signaling and neuroactive ligand-receptor interaction pathways were identified. These findings may be used to facilitate drug repurposing against COVID-19.

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1. Background

The COVID-19 outbreak, caused by SARS-CoV-2, has become a pandemic and is now spreading worldwide. As of May 29, 2020, over 5,701,000 cases, which includes over 3572,000 deaths, have been reported to WHO. In addition to COVID-19, two other coronavirus-induced diseases, including Severe Acute Respiratory Syndrome (SARS) (Xu, 2013) and Middle East Respiratory Syndrome (MERS) (Zaki et al., 2012), had also caused huge damages previously to public health. SARS emerged in China in November 2002, which lasted for 8 months and resulted in 8,098 confirmed human cases in 29 countries with 774 deaths (case-fatality rate: 9.6%) (Control and Prevention, 2003;Xu, 2013). Approximately 10 years later in June 2012, the MERS-CoV, another highly pathogenic coronavirus, was isolated in Saudi Arabia from the sputum of a male patient who died from acute pneumonia and renal failure (Zaki et al., 2012). MERS-CoV has caused outbreaks with 2,260 cases in 27 countries and 803 deaths (35.5%)(WHO, 2018;Bernard-Stoecklin et al., 2019). To successfully fight against coronavirus infections, intensive studies are required to identify effective and safe measures.

Drug administration is a major way to control coronavirus infections. There have been a large number of studies to discover and develop drugs targeted to these coronaviruses. Many studies have achieved various levels of success *in vitro* and *in vivo* (as detailed in this manuscript later). By integrating the results of previous anti-coronavirus drugs, we may find clues for the development and improvement of drugs to treat COVID19. Existing drugs might be repurposed for treating COVID-19. Enriched patterns extracted from all existing anti-coronavirus drugs may lead to the development of new drugs.

In the informatics field, a formal ontology is a human- and computer-interpretable set of terms and relations that represent entities in a specific biomedical domain and how they relate to each other. Ontology has played a significant role in knowledge and data standardization, integration, and analysis (Ashburner et al., 2000;Bodenreider, 2008;Schulz et al., 2013;Hoehndorf et al., 2015). Three ontologies, including Chemical Entities of Biological Interest ontology (ChEBI)(Hastings et al., 2016), National Drug File – Reference Terminology (NDF-RT) (Peters et al., 2015), and Drug Ontology (DrON) (Hogan et al., 2017), have been frequently used for drug studies (Tao et al., 2016;Liu et al., 2017). ChEBI is a database and ontology of over 56,000 molecular entities with a focus on small chemical compounds. ChEBI ontologically classifies these compounds based on different categories such as structural and

functional features. Produced by the U.S. Department of Veterans Affairs, NDF-RT organizes drugs in a hierarchical and formal representation by modeling drug characteristics including ingredients, chemical structure, physiologic effect, mechanism of action, pharmacokinetics, etc. DrON provides an ontological representation of the drug contents on the RxNorm terminology (Bodenreider and Rodriguez, 2014) that contains all medications available on the US market. Once a list of drugs is identified, tools such as Ontofox (Xiang et al., 2010) can be used to extract these drugs and their related characteristics from an ontology and perform specific analyses (Guo et al., 2016;Xie et al., 2016;Wang et al., 2017;Yu et al., 2019).

In this study, we reported our systematic collection, annotation, and analysis of various anti-coronavirus drugs from the biomedical literature. Over 90 chemical drugs and antibodies against human coronavirus diseases were identified. We mapped the majority of these drugs to the ontologies ChEBI (Hastings et al., 2016), NDF-RT (Peters et al., 2015), and DrON (Hogan et al., 2017). We applied ontology to categorize these drugs and used ontology-based bioinformatics methods to further analyze various features of these drugs. The gene/protein targets of these drugs were also retrieved, and drug-target networks were analyzed to identify hub drug targets. In the end, we will discuss how our results can be used to facilitate rational drug design for COVID-19.

2. Methods

2.1 Literature annotation and data extraction of anti-coronavirus drugs

Reliable peer-reviewed articles in PubMed, Google Scholar, and PubMed Central literature databases were searched using relevant keywords. Chemical or biological drugs that exhibited anti-coronavirus properties were collected. To be included in our list, each drug was required to demonstrate a significant level of viral inhibition *in vitro* or *in vivo*. For each identified drug, we recorded its targeted virus, mechanism, experimental model, assay, and paper citation(s). Antibodies mentioned in this literature were also recorded with their types and antigens.

2.2 Ontology extraction and analysis

The list of identified anti-coronavirus drugs was mapped to ontology IDs from ChEBI(Hastings et al., 2016), NDF-RT(Peters et al., 2015) and DrON(Hogan et al., 2017). The Ontobee ontology

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repository(Ong et al., 2017) was used for the mapping. Using the ontology IDs collected above as input, we extracted subsets of these three ontologies by the ontology extraction tool Ontofox(Xiang et al., 2010). The output ontologies are in the format of OWL. Protégé 5.0 OWL ontology editor (http://protege.stanford.edu/) was used for ontology editing and analysis. The annotated data are stored at the GitHub website: https://github.com/CIDO-ontology/anti-coronavirus-drugs. The GitHub website hosts the information of the community-based Coronavirus Infectious Disease Ontology (CIDO), which is targeted to include the annotated drug information out of this study.

2.3 Clustering of anti-coronavirus drugs using ontology-based semantic similarity analysis

All anti-coronavirus drugs that include ChEBI annotations were used in this study. Suppose that the annotation terms of each drug include the annotation node and all its ancestor nodes as defined by 'is_a' and 'has_functional_parent'. The ontologyIndex R package (Greene et al., 2017) was used to extract the drugs' annotated terms to form a corpus. The frequency of each term Freq(t) in the corpus was calculated. The Information Content (IC) for a term t was defined as: IC (t) = − ln (p (t)), where p(t)=Freq(t)/max(Freq(t')) and t' represent all the terms. The pairwise semantic similarity of 99 drugs based on Lin's similarity method (Lin, 1998) was obtained and a heatmap was prepared based on semantic similarity hierarchical clustering using Euclidean distance and complete linkage.

2.4 Chemical similarity-based analysis of anti-coronavirus drugs

Out of all the anti-coronavirus drugs compiled in the current study, 59 unique small molecules with ChEBI identifiers were manually extracted, wherein structure-data file (SDF) format files were obtained for each compound from ChEBI using their respective ChEBI identifiers and imported into a Molecular Operating Environment (MOE, version 2019.0101) database. If a drug (e.g. chlorpromazine) existed also existed as a salt (e.g. chlorpromazine hydrochloride), only the nonsalt version was used for issues of redundancy. ChEBI entries for mefloquine (ChEBI: 63609) and terconazole (ChEBI: 9451) were racemic mixtures, so thus the (-)-enantiomers were used for both (ChEBI: 63687 and ChEBI: 82980, respectively). All compounds were subjected to the 'Wash' function in MOE to clean up molecular structures, as well as remove salts present. Additionally, the dominant protonation state for each compound was set at pH 7.4. All compounds were then

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saved within a single SDF file and analyzed with ChemmineR (version 3.10) package (Cao et al., 2008). Tanimoto coefficients were calculated between all compounds for chemical similarity using 1,024-bit atom pair fingerprints. Hierarchical clustering with single linkage was performed on the resulting distance matrix, while the heat map was generated with the *gplots* package in R.

2.5 PCA analysis of physicochemical properties of anti-coronavirus drugs

SDF files corresponding to small-molecule drugs with the mechanisms, 'Inhibit viral entry' and 'Inhibit viral replication', were collected from ChEBI and imported into a MOE software database. All compounds were cleaned as in section 2.4. The following descriptors for drug-like compounds were calculated for each compound with MOE: 1) the number of hydrogen bond acceptors, 2) the number of hydrogen bond donors, 3) molecular weight, 4) octanol-water partition coefficient (slogP), and 5) topological polar surface area. PCA was performed on these five physicochemical properties, and the first three principal components were taken for analysis.

2.6 Annotation of drug targets and drug-target network

The known targets of the identified drugs were collected from DrugBank (Wishart et al., 2018). For any drug without a matching DrugBank record, multiple other online resources, including ChEMBL and Wikipedia, to identify any known targets. The collected drug-target interactions as well as protein-protein interactions among these targets, collected from the BioGRID interaction database (Oughtred et al., 2019), were used to construct a drug-target interaction network and visualized using Cytoscape v3.7.2 (Smoot et al., 2011). The collected drug targets were subjected to a pathway enrichment analysis using our in-house functional enrichment tool richR (http://hurlab.med.und.edu/richR) in terms of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (Kanehisa et al., 2017).

3 Results

3.2 151 anti-coronavirus drug compounds effective against viral invasion, replication, and/or in stimulating host immunity

We manually collected and identified 151 chemicals drug compounds, each of which was tested at least in one cell line *in vitro*, and some also tested *in vivo*, and found effective against human coronavirus infections. These 151 chemical compounds include 110 active drug compounds that

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can be mapped to at least one of the three ontologies: ChEBI, DrON, and NDF-RT (Table 1), 15 drugs that do not have any record in these ontologies, and 26 biological drugs (monoclonal or polyclonal antibodies) specifically targeting on coronavirus proteins (e.g., S protein) (Table 2). Note that some listed compounds (e.g., chloroquine phosphate) are the salt forms of some drugs (e.g., chloroquine), and they may be both included in our lists since they have independent ontology IDs and were shown in the literature reports independently. They may also have the same drug bank ID, so our Table 1 includes the drug bank IDs for easy checking.

Our collected drugs were organized by three known mechanisms (inhibition of viral entry, inhibition of viral replication, and modulation of host immune response) or unknown mechanism (Table 1). Vero, Vero 6, Huh7, and BHK-21 cells are among the primate cell lines commonly used in *in vitro* anti-coronavirus drug studies (de Wilde et al., 2014;Dyall et al., 2014;Shen et al., 2019). These studies often tested whether the anti-coronavirus effect occurred at the viral entry level or viral replication level. To evaluate the entry level treatment, the drugs were added to the cells before viral attachment, and at a time after infection, the virus-drug mixture was replaced with fresh culture medium and maintained until the end of the experiment. To evaluate the post-entry effect, drugs were added after viral infection (Wang et al., 2020a). For example, chloroquine was found to function at both the entry and post-entry stages against SARS-CoV-2 infection in Vero E6 cells (Wang et al., 2020a), and remdesivir and mefloquine functioned only at a stage post the virus entry (Brickelmaier et al., 2009;Wang et al., 2020a). Often we do not know whether a drug functions at the entry or post-entry stage, but we know that the drug was able to modulate the host immune responses (Table 1). Some drugs' anti-coronavirus mechanisms are unknown (Table 1). Several drug therapies utilized as a combination of two or more drugs. Because it is difficult to evaluate individual drug properties, combination drug therapy studies were not included from our annotations.

Our study found that 33 drugs inhibiting viral entry to host cells, 50 drugs that inhibit viral replications inside host cells, and 12 drugs modulating host immune responses to coronavirus infection (Table 1). At the viral entry-level, the interaction between coronavirus and host-cell receptors can be blocked in multiple ways. For example, chlorpromazine has MoA as dopamine antagonist and adrenergic-alpha antagonist, and it is active against SARS-CoV and MERS-CoV (Zumla et al., 2016). Chlorpromazine also modulates clathrin-coated pits at plasma membrane (Chu and Ng, 2004), which inhibits viral endosomal fusion. Antagonists of adrenergic

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receptors have been shown as potent entry inhibitors of Ebola and Marburg viruses (Cheng et al., 2015). After viral entry, there are potential inhibitors that can suppress coronaviral replication via several pathways. For example, gemcitabine hydrochloride, classified as nucleic acid synthesis inhibitor in NDF-RT, is a deoxycytidine analog, inhibiting DNA replication and repair. Mycophenolic acid and mycophenolate mofetil also function as nucleic acid synthesis inhibitors according to NDF-RT. They all can prohibit MERS-CoV and SARS-CoV by inhibiting viral DNA or RNA replication. Different mechanisms are taken by drugs to modulate host immune responses to coronavirus infection (Table 1). Interferons are biological modifiers that can elicit transcription of hundreds of interferon-induced genes, encoding for anti-viral proteins (Fensterl and Sen, 2009). Interferons have been evaluated to treat coronaviral infections in combination with ribavirin (Chan et al., 2013). Nitazoxanide can inhibit MERS-CoV *in vitro* (Li et al., 2019). Nitazoxanide blocks maturation of the viral hemagglutinin and promotes the production of interferons in virus-infected cells (Rossignol, 2014). By targeting IL-6 receptor, tocilizumab has been found effective in treating moderate to severe rheumatoid arthritis, cytokine storm, and SARS-CoV-2 infection (Xu et al., 2020b) (Table 1).

We have also collected 26 anti-coronavirus antibodies, including 17 monoclonal antibodies and 2 polyclonal antibodies that target on MERS-CoV, and 7 monoclonal antibodies that target on SARS-CoV (Table 2). All of these antibodies were tested for their efficacy *in vitro*, and over half of them were also tested *in vivo*. The SARS-CoV-specific antibodies target for S spike protein, S1 receptor-binding domain (RBD), or S2 protein. For example, S230.15 and m396 were found to compete with the SARS-CoV receptor ACE2 for binding to the RBD as a mechanism of their neutralizing activity (Zhu et al., 2007). The MERS-CoV-specific antibodies specifically target for S spike protein, S1 RBD, or human DPP4 receptor S2. Anti-DPP4 (CD26) is another therapeutic option for fighting MERS-CoV. The anti-CD26 antibodies 2F9, 1F7 and YS110 target the S1-DPP4 interaction from the host side, and prevent the MERS-CoV entry into cells (Rabaan et al., 2017).

3.3 Drugs verified against SARS-CoV-2 infections in vitro or in vivo

Several drugs, including remdesivir, chloroquine phosphate, favipiravir, and tocilizumab (Table 1), have been experimentally or clinically evaluated and found effective at various levels

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against the SARS-CoV-2 infections in vitro or in vivo and have potential in treating COVID-19 (Table 1 and Table 2).

As a drug used to successfully treat the first case of COVID-19 patient in the USA (Holshue et al., 2020), remdesivir has become an highly promising drug for treating COVID-19. Remdesivir is a nucleoside analog which inhibits viral proliferation (Wang et al., 2020a). It has been shown to effectively fight against several kinds of viruses, including SARS-CoV and MERS-CoV *in vitro* (Sheahan et al., 2017). Its anti-viral effects were also identified in the rhesus macaque model infected with MERS-CoV (de Wit et al., 2020). A recent study showed remdesivir can inhibit COVID-19 in vitro (Wang et al., 2020a). Then, remdesivir has been evaluated in two clinical trials (Beigel et al., 2020;Wang et al., 2020b), showing that the hospitalized COVID-19 patients receiving remdesivir treatment recovered faster than similar patients who received placebo. As a result, US FDA has allowed remdesivir to be distributed and used to treat adults and children hospitalized with severe COVID-19 (https://www.fda.gov/media/137564/download).

As an antimalarial drug, chloroquine phosphate has been shown with efficacy in blocking CoVID-19 *in vitro* (Wang et al., 2020a). In addition to treating malaria, chloroquine can also inhibit autophagy and be used to treat skin disorder and rheumatoid arthritis. Some clinical results in China showed that chloroquine phosphate treatment promotes patient recovery as compared to the control treatment (Gao et al., 2020). On March 28, 2020, US FDA issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine sulfate and chloroquine phosphate drugs to be used for certain hospitalized patients with COVID-19 (https://www.fda.gov/media/136534/download).

A new study with a small sample size of COVID-19 patients concluded that the combination of hydroxychloroquine and azithromycin (Gautret et al., 2020) could be used as a very effective treatment of the COVID-19 disease. Like chloroquine, hydroxychloroquine is also an antimalarial medication and possesses a similar antiviral mechanism of action with chloroquine: it both inhibits viral entry and repress viral replication. Hydroxychloroquine was also shown as more effective drug target to CoVID-19 than chloroquine (Yao et al., 2020). Azithromycin is an antibiotic used to treat a number of bacterial infections and malaria as well. It prevents bacterial growth by interfering with their protein synthesis. Azithromycin inhibits the translation of mRNA by binding to the 50S subunit of the bacterial ribosome. While

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azithromycin is used to treat malaria, it was also found with antiviral properties by potentially promoting interferon production *in vitro* (Schogler et al., 2015). Azithromycin has been found to prevent the exacerbations of chronic obstructive pulmonary disease (COPD) (Albert et al., 2011). However, consistent usage of the drug for a long time may cause hearing decrements in a small percentage of subjects (Albert et al., 2011).

Favipiravir, also known as T-705, Avigan, or favilavir, is an antiviral drug being developed with activity against many RNA viruses. Favipiravir resembles nucleoside analogue and inhibits RNA-dependent RNA polymerase. It has been shown that favipiravir is effective to against various RNA viruses, such as Ebola virus, Lassa fever, and other influenzas in animal models and vitro (Shiraki and Daikoku, 2020). Favipiravir has been used in clinical trial as a promising drug to treat COVID-19 (Dong et al., 2020).

Some studies have shown that lopinavir/ritonavir treatment has anti-viral effects in COVID-19 therapy (Lim et al., 2020;Xu et al., 2020a). Lopinavir and ritonavir are enzyme inhibitors that act after viral infection and prohibit viral protein cleavage and production of new viral particles in treating HIV (Kemnic and Gulick, 2020). Several studies have shown that lopinavir can have favorable outcomes in treating SARS and MERS in combination with ritonavir, another enzyme inhibitor, in human and nonhuman primates (Chu et al., 2004;Chan et al., 2015). However, a recent study with a total of 199 adult patients with laboratory-confirmed SARS-CoV-2 infection showed that no benefit in terms of clinical outcomes and mortality was observed with lopinavir–ritonavir treatment beyond standard care (Cao et al., 2020).

A recent study that a triple combination of Interferon beta-1b, Lopinavir-Ritonavir, and Ribavirin in the treatment of mild to moderate COVID-19 patients was safe and superior to lopinavir-ritonavir alone in alleviating symptoms and shortening the duration of viral shedding (Hung et al., 2020). The adverse events for the early triple antiviral therapy included self-limited nausea and diarrhea, which had no difference with the double lopinavir-ritonavir therapy.

3.4 Anti-coronavirus drugs are primarily inhibitors or antagonists, and many having the anticancer role based on ontology analysis

These manually annotated 110 chemical drugs were mapped to and analyzed by three ontologies: ChEBI, NDF-RT, and DrON. Among them, 99 have ChEBI IDs, 70 have NDF-RT IDs, and 60 have DrON IDs. We extracted these terms out from their ontologies using the tool Ontofox

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(Xiang et al., 2010) and built relatively independent subsets of these ontologies. By analyzing these subsets, we were able to identify more scientific insights.

ChEBI can be ontologically and systematically represent various anti-coronavirus drugs and how such representation can be used for advanced analysis. After extracting these drugs and their associations using Ontofox (Xiang et al., 2010), the hierarchical structure among different anti-coronavirus drugs were clearly displayed . For example, we can find that chloroquine, chlorpromazine, dasatinib, and three other drugs all belong to chlorobenzenes (Figure 1A). Chloroquine has many roles including the antimalarial role. Since ontology is computer-understandable, we can query the ontology using different approaches including SPARQL (Group, 2013) and Description Logic (DL) query (Pan et al., 2019). As shown in Figure 1B, we performed a simple DL query on the subset of ChEBI and found three other drugs (i.e., mefloquine, conessine, and lycorine) having the same antimalarial role.

Figure 2 demonstrates another usage of ontology in our drug study. NDF-RT has a unique feature, i.e., representing the mechanisms of action (MoA) for different drugs. Our mapping found that out of 70 anti-coronavirus drugs with NDF-RT records, 57 drugs had their specified MoAs, the hierarchical structure of which are provided by NDF-RT (Figure 2A). By analyzing these MoAs and identifying the drugs that have thee MoAs, we found that 47 of 57 anti-coronavirus drugs had MoAs as inhibitors or antagonists (Figure 2A). Specifically, 23 drugs were inhibitors of enzymes such as kinase or protease. The antagonists were specific for G Protein-coupled receptors. There was only one agonist drug, methylprednisolone, a glucocorticoid hormone receptor agonist that is used to suppress the immune system and decrease inflammation.

Using a DL-query, 29 chemical entities were identified to have the antineoplastic role (Figure 2B). These 29 chemical entities are used as active ingredients compounds of 23 drugs. To support viral program, viruses often hijack infected cells to have enhanced synthesis of nucleic acids, proteins, and lipids and maintain boosted energy metabolism. The cell patterns are also seen in cancer cells. Therefore, it is likely to use anticancer drugs to inhibit SARS-CoV-2 viral replication (Ciliberto et al., 2020). The 23 antineoplastic or anticancer drugs identified in our study (Figure 2B) have potential to be used for COVID-19 treatment.

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Our identified drugs were also found to have many other roles, including various antimicrobial (e.g., antimalarial, antiviral, and antibacterial) roles. Figure 1B provides an example of the drugs having the antimalarial role.

3.4 Anticoronaviral drug patterns based on ontology classification and heatmap analyses

In this section, we introduce our discovery of different anticoronaviral drug patterns based on ontology-based hierarchical classification, and two different types of heatmap analyses (Figure 3-5).

First, our direct browsing of the anticoronaviral subset of ChEBI ontology identified many enriched ontology hierarchies, including organochlorine compounds, aromatic amides, primary/secondary/tertiary alcohols, phenothiazines, and organofluorine compounds (Figure 3). Many drugs such as chloroquine, chloropromazine, and dasainib are all organochlorine compounds. We found many anticoronaviral drugs are classified as primary, secondary, and tertiary alcohols. For example, bufalin, mefloquine, everolimus, cephalotaxine, cycloheximide, and sirolimus all belong to secondary alcohol group. Those drugs under the same classification likely share similar anticoronaviral functions.

Figure 4 shows the heatmap results based on the semantic relations defined in the ChEBI ontology. Seven clusters were identified. The first cluster colored in red, including imatinib and remdesivir, is enriched with organooxygen compounds. The second cluster in blue is represented by chloroquine and hydroxychloroquine, which appears to be enriched as organohalogen compounds. The third cluster, including benztropine and nelfinavir, is enriched with organic halide salt. The drugs in the fourth cluster, colored purple, including everolimus and sirolimus were mostly heteroorganic compounds. Everolimus is the 40-*O*-(2-hydroxyethyl) derivative of sirolimus (also known as rapamycin), and it works similarly to sirolimus as an inhibitor of mammalian target of rapamycin (mTOR). The drugs in the fifth cluster, colored orange, seem variable including toremifene and tamoxifen. The sixth cluster, including chlorpromazine and fluphenazine, is enriched with heteroorganic compounds The seventh cluster in brown color, have high similarities and were mostly organic halide salt. As ChEBI annotates drugs from both molecular structure and functional radical aspects at a higher level than chemical structure, this similarity clusters may infer potential drug design.

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Figure 5 shows another heatmap patterns detected based on the physicochemical properties of anti-coronavirus drugs. In this study, chemical similarity was calculated between 92 small-molecule anti-coronaviral drugs to determine whether there were clusters of chemically similar drugs. As expected, the drugs grouped into islands representing varying classes of drugs (Figure 5). For example, the glycosides (glycyrrhizic acid, aescin, digoxin, and digitoxin), macrolides (everolimus, sirolimus, and ivermectin), and a polyketides (monensin and salinomycin) were grouped together (Figure 5, red bar). However, there was no clear association in this group between the drugs and mechanism of action; glycyrrhizic acid was shown to modulate immune response and inhibit viral replication, while everolimus only inhibits viral replication (Table 1). It should be noted that the aforementioned glycosides will very likely not be useful as anti-coronaviral drugs due to their high toxicity even in low doses (Cock, 2015). Though not grouped into the cluster, azithromycin was also found to be chemically similar to the aforementioned compounds (Figure 5, asterisk). Interestingly, azithromycin was recently reported to be effective against SARS-CoV-2 (Gautret et al., 2020), suggesting that macrolides could be a potential class of chemical compounds that could be utilized against coronaviruses. Though they are traditionally used in the clinical setting against retroviruses (Pulido et al., 2008), the antiretrovirals, ritonavir, lopinavir, nelfinavir, and SG85 also were observed to have a mixed mechanisms of action (Figure 5, green bar); the former three act as inhibitors of viral entry, while SG85 inhibits viral replication (Table 1). Additionally, the structurally-similar anti-coronavirus drugs, toremifene, tamoxifen, and triparanol (Figure 5, purple bar), all operate as inhibitors of viral entry, as annotated in this study (Table 1). Apart from this function, they have been shown conventionally to inhibit cholesterol biosynthesis (Jordan et al., 2014). However, bazedoxifene was also in the aforementioned cluster, though it has currently an unknown mechanism (Table 1); judging by its chemical similarity to the others, it is likely it could also function as an inhibitor of viral entry.

3.5 Different physicochemical profiles of drugs inhibiting viral entry and inhibiting viral replication

Five common physicochemical properties associated with druggability were examined for anti-coronaviral drugs responsible for: 1) inhibiting viral entry and 2) inhibiting viral replication; there were 25 and 44 small-molecule compounds, respectively. Utilizing PCA analysis on these compounds, no clear separation of mechanism of action was observed among the 69 examined

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drugs (Figure 6A). Interestingly, chloroquine was annotated to work as an inhibitor of both viral entry and replication and was also observed to be located in a dense area of PCA space of mixed efficacy (Figure 6A, arrow), suggesting that it is possible that many of the drugs may possess a dual mechanism of action. Overall, the compounds associated with inhibiting viral replication possessed a greater number of hydrogen bond acceptors and donors and higher topological polar surface area than those that inhibit viral entry after removal of five compounds (valinomycin, telavancin, oritavancin, dalbavancin, and cyclosporine) greater than 1,000 Da (Figure 6B); this removal was performed because these compounds were significantly larger in size than the others, which would have allowed for a more fair comparison between groups. Consequently, compounds that inhibit viral replication also had higher topological polar surface areas. However, octanol-water partition coefficients did not seem to be different between the two groups.

On average, the average number of hydrogen bond acceptors and donors were 2.90 and 1.33, respectively, for drugs that inhibit viral entry. On the other hand, the corresponding values were 5.49 and 2.40 for drugs that inhibit viral replication. However, several outliers were observed for both classes of drugs, as was expected with any generalization. Certain drugs that inhibit viral entry, such as ouabain, had several hydrogen bond acceptors and donors. Additionally, drugs that inhibit viral replication, such as chloroquine, have no hydrogen bond acceptors and donors. Given chloroquine's membership in both drug classes, the physicochemical differences between the two types of drugs are not as clear cut as one would hope. Nonetheless, the present observations can potentially serve as an approximate guideline in the design of anticoronoviral drugs.

3.6 Key drug-targeted biological pathways identified from drug-target network analysis

We generated a drug-target interaction network (Figure 7) that includes all unique drugs and their known targeted proteins according to the records from DrugBank. This network included 68 drugs with their 163 known human protein targets with a total of 428 interactions. Multiple clusters were identified from this network. The biggest one included the majority of the drugs inhibiting viral replication (nodes in violet) and modulating immune response (nodes in green). Another one was centered on the drug chlorpromazine as well as many drugs with unknown mechanisms with respect to their usages in coronavirus treatment.

Three drugs with most connections in Figure 7 are chlorpromazine, dasatinib, and anisomycin. Chlorpromazine has MoA as dopamine antagonist and adrenergic-alpha antagonist

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in NDF-RT. It also interacts with serotonin receptor (HTRs) and histamine receptor (HRHs) (Figure 7). Although how chlorpromazine exhibits anti-coronavirus properties is not fully understood, adrenergic antagonists and histamine antagonists have been shown to inhibit RNA virus such as Ebola and Marburg viruses (Cheng et al., 2015). Dasatinib, together as imatinib (another coronavirus drug as seen in Table 1), is an inhibitor of the Abelson murine leukemia viral oncogene homolog 1 (ABL1) pathway, a signaling pathway involved in cell differentiation, cell adhesion, and cellular stress response. Previous studies showed that dasatinib and imatinib can both inhibit BCR-ABL interaction and prohibit virus fusing with S protein of host cells (Dyall et al., 2014;Sisk et al., 2018).

As another hub drug in Figure 7, anisomycin is an antibiotic that potently inhibits flaviviruses, including Dengue virus and Zika virus, *in vivo*, by mainly affecting viral macromolecular synthesis and replication(Quintana et al., 2020). At non-cytotoxic concentrations, anisomycin strongly inhibited the replication of DENV and ZIKV viruses in Vero cells, and also prevented DENV and ZIKV virus multiplication in human cell lines (Quintana et al., 2020). Anisomycin induces apoptosis (Hori et al., 2008) and can target ribosomes to interfere peptidyl transferase and then block protein synthesis (Barbacid and Vazquez, 1974). However, the exact mechanism of viral replication inhibition by anisomycin is still unclear.

The neurotrophic receptor tyrosine kinase 1 (NTRK1) is notable as a distinct human hub protein in the drug-target network, and it interacts with many drugs and other genes (Figure 7). NTRK1 is a kinase that can be activated by signaling factors. Activated NTRK1 protein phosphorylates other proteins to transmit signals for cell growth and survival. NTRK1 has been found to interact with Ebolavirus transcription- and replication-competent virus-like particles, which are designed to express the Ebola virus proteins required for genome replication and transcription to model Ebola virus life cycles, indicating that NTRK1 may act as an important role in inhibiting viral proliferation (Yu et al., 2018). It is reasonable to assume that drugs in the network can interact with NTRK1 directly or indirectly, leading to the inhibition of coronavirus replication.

To better characterize the biological functions of these known drug targets, a KEGG pathway enrichment analysis on the known targets was performed and the top 30 most significantly enriched KEGG pathways are illustrated in Figure 8. These pathways included

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diverse pathways such as calcium signaling pathway, and neuroactive ligand-receptor interaction. The most significant pathways with the most genes included neuroactive ligand receptor interaction and calcium signaling pathways. The neuroactive ligand receptor interaction pathway is aligned with many mechanisms of action reported in the NDF-RT analysis (Figure 2). A recent study found that NAADP-dependent Ca2+ signaling regulates MERS-CoV pseudovirus translocation through the endolysosomal system (Gunaratne et al., 2018). Calcium signaling pathway is also crucial for viral infection and replication in host cells. Viral infection alters host-cell calcium cation homeostasis and viruses can take over the calcium signaling pathway for their replication (Zhou et al., 2009). Therefore, drugs targeting the calcium signaling pathway have the potential to be effective in fighting against viral infection.

4 Discussion

One novelty of this study is its usage of ontologies. The ontology can logically, hierarchically, and systematically represent various drugs and their characteristics. The usage of the three ontologies in our study significantly enhanced our analysis. For example, our ChEBI analysis enabled us to quickly identify the hierarchical categorization of different anti-coronavirus drugs and query which drugs have the antimalarial role (Figure 1). By systematically analyzing the mechanisms of action of 57 drugs based on NDF-RT, we discovered that the majority of the drugs were inhibitors or antagonists that suppress various biological pathways (Figure 2). The ChEBI was also used for the semantics-based similarity analysis (Figure 3). A pitfall of our ontology-based study is that not all the drugs have annotations in these ontologies, resulting in incomplete analysis power.

Another novelty of this study is the usage of bioinformatics and cheminformatics methods in systematic analysis and prediction. The semantic and chemical similarity analyses, as well as the PCA analysis, uncovered various potential drug candidates for COVID-19. The two similarity heatmap clustering analyses provided different but complementary results. For example, both heatmap studies found the group including everolimus and its related drug sirolimus (also known as rapamycin). As ChEBI annotated drugs from both molecular structure and functional aspects, we can sort out all the drugs based on similarity to infer potential new usage of old drugs. The clustered groups from these analyses allowed us to infer possible drug

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development and mechanism study for COVID-19. For example, A clustered group of drugs as anti-retroviral drugs, containing ritonavir and lopinavir also convoluted. Ritonavir and lopinavir are promising drugs in treating coronaviruses. The PCA results demonstrate the two different profiles of the anti-coronavirus drugs associated with the inhibition of viral entry vs the drugs associated with viral replication. Such physicochemical profiles may aid in the design of novel anti-coronaviral drugs based on the intended MoA. These findings also suggest that more refined groups of drugs based on chemical properties and antiviral mechanisms may be required to have the potential to find some hidden relations between them.

How our ontological and bioinformatics analysis of the systematically collected anti-coronavirus drugs provides implication for possible drug repurposing against COVID-19?

Our study found many drugs having similar roles or grouping to chloroquine and hydroxychloroquine. Chloroquine and hydroxychloroquine are both antimalarial drugs. Our collection includes three other antimalarial drugs, i.e., mefloquine, conessine, and lycorine (Figure 1B). These three antimalarial drugs may also be effective against COVOD-19. Meanwhile, our study found that chloroquine, chlorpromazine and dasatinib are all chlorobenzenes (Figure 1A). Chlorpromazine and dasatinib were also found as hubs from our drug-target interaction network (Figure 6). Given that chloroquine and hydroxychloroquine are likely effective anti-COVID-19 drugs (Wang et al., 2020a), it is worth testing the role of chlorpromazine and dasatinib as effective anti-COVID-19 drug as well.

For better therapeutic effect, it is common to use a combination therapy with two or more synergistically acting drugs. The combined usage of two or more drugs may achieve the three main biological processes, including prohibit viral entry, viral replication and induce host immune response (Table 1). Those combinational choices that target these different aspects of the viral lifecycle would be preferred choices. Our identification of the 110 drugs provides choices of drugs for targeting these three areas (Table 1 and 2). 26 monoclonal and polyclonal antibodies appear to be the obvious choices for prohibiting viral entry. Our ontological and bioinformatics analyses in this study provide many possible choices for selecting drugs for combinational therapy.

Various combinations of interferon-alfa or -beta with other antiviral drugs such as ribavirin and/or lopinavir–ritonavir were used to treat patients with SARS or MERS (Al-Tawfiq et al., 2014;Zumla et al., 2016). Corticosteroids were often combined with ribavirin, and

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lopinavir–ritonavir (Zumla et al., 2016). However, the combination therapies consisting of interferons and ribavirin did not generate consistently improved outcomes (Al-Tawfiq et al., 2014;Zumla et al., 2016).

It is interesting that the usage of azithromycin significantly improved the treatment outcome in the combined usage of hydroxychloroquine and azithromycin (Gautret et al., 2020). Like azithromycin, sirolimus, everolimus, and oligomycin are also macrolides that that consist of a large macrocyclic lactone ring. Sirolimus/rapamycin has antifungal role. However, as immunosuppressants, sirolimus and everolimus are typically used to prevent rejection of organ transplants. These two drugs target mammalian mTOR, an important member of the PI3K-related kinase family of protein kinases. Treatment of cells with rapamycin inhibited MERS-CoV infection by 24-61% at 0.1-10 μM (Kindrachuk et al., 2015). How sirolimus and everolimus may be effective against COVID-19 is unclear. However, they may induce strong adverse reactions in the patients. Oligomycin (Shen et al., 2019) is an antibiotic that inhibits ATP synthase by blocking its proton channel necessary for oxidative phosphorylation and energy production.

In addition to azithromycin, our study found other antibiotics, including teicoplanin, anisomycin (Dyall et al., 2014), valinomycin (Dubey et al., 2019), which demonstrated anti-coronavirus functions *in vitro* and/or *in vivo* (Table 1). Anisomycin was introduced earlier in the article. Teicoplanin is an glycopeptide antibiotic used to prevent or treat serious infections caused by Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*. Teicoplanin inhibits bacterial cell wall synthesis. Teicoplanin was also found to potently prevents the entry of Ebola envelope pseudotyped viruses into the cytoplasm, and was able to block the entry of MERS-CoV and SARS-CoV envelope pseudotyped viruses as well (Zhou et al., 2016). Valinomycin is a K^+ ionophore that can change the membrane potential by conducting ions directly through membrane. It can treat *B. gibsoni*, a species of bacterial infection, by changing bacteria's cellular cation concentration *in vitro*(Yamasaki et al., 2009). In a study, TZMbl cells were treated with valinomycin before HIV infection, and valinomycin at 10 nM concentration impeded HIV entry to TZMbl cells by nearly 50% (Dubey et al., 2019). The study also showed that valinomycin inhibits HIV entry by increasing the membrane depolarization, which indicates membrane polarization is crucial for HIV entry. Therefore,

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valinomycin may use the same mechanism against virus and bacteria. However, valinomycin is classified as an extremely hazardous substance in the United States.

It is likely that the antibacterial role of the antibiotics may play a critical role in COVID-19 treatment. Microbiomes exist in many parts of human body such as the gut and lung (He et al., 2020). The lung is now known to hold a large amount of bacteria (Fabbrizzi et al., 2019). Bacterial microbiomes play an important role in human metabolism and immune response to various pathogens. However, in a COVID-19 patient, the normally healthy bacteria inside human lung and other parts of human body may become harmful and cause infections. Therefore, the usage of an antibiotics may support the treatment by killing these previously good but now bad bacteria in the infected lung. Such a hypothesis may still need experimental verification.

A recent study demonstrates that a network-based quantification and analysis of the host-coronavirus interactions and drug targets would help identification of candidate repurposable drugs (Zhou et al., 2020). Their network-based drug repurposing method is aligned with our ontology-based and bioinformatics-based study. Our drug-target network provides a backbone for further network analysis and our ontology approaches provide more logically defined relations between drugs and other types of entities (such as MoA, roles, and diseases). Our ontology-based bioinformatics strategy can enhance the network standardization and computer interpretation in a logical, interoperable, and consistent way, leading to improved prediction of drugs for COVID-19.

As an important part of the network study of interactions among host, host cells, coronavirus, and drugs, we will need to systematically understand the SARS-CoV-2-human protein-protein interactions (PPIs). Recently a bioRxiv paper introduced a SARS-CoV-2-human PPI map that reveals drug targets and potential drug-repurposing (Gordon et al., 2020). This study cloned, tagged, and expressed 26 of the 29 viral proteins in human cells and identified 332 high confidence SARS-CoV-2-human PPIs. The authors identify 67 druggable human proteins or host factors targeted by 69 existing FDA-approved drugs, drugs in clinical trials and/or preclinical compounds. Among their 25 FDA-approved drugs, six drugs are included in our drug list. These six drugs are camostat, chloroquine, mycophenolic acid, nafamostat, rapamycin, ribavirin. How these drugs can be applied for COVID-19 deserves further investigations.

While our systematic collection of experimentally verified anti-coronavirus drugs and ontology and bioinformatics analysis of these drugs identify many new choices of drugs

repurposable for COVID-19 treatment, clinical and experimental studies are required to evaluate these hypothesized choices. Our collection of drugs was primarily verified from experimental settings and most of them came from SARS or MERS studies, which may not reflect the outcome from clinical settings and what to expect for COVID-19. An example is the lopinavir–ritonavir treatment that worked for SARS and MERS but not for COVID-19 treatment as discussed earlier. By using computational methods, FDA-approved drugs, like indinavir and atazanavir, are able to target to viral proteases and potentially can be used for COVID-19 treatment (Chang et al., 2020;Contini, 2020). However, an *in vitro* study on SARS-CoV has shown indinavir has no inhibitory effect on SARS-CoV (Tan et al., 2004). These also demonstrate that we will need to continuously develop new and better algorithms and tools to improve our predictions for clinical and experimental verification.

Ontology has a unique role of providing standard and computer-understandable representation on entities in the host-virus interactions and logic relations among these entities. Such an ontology platform would be able to support advanced computer-assisted machine learning analysis of anti-coronavirus drugs and their mechanisms, and provide more clear clues on drug repurposing against COVID-19. For this purpose, we have recently initiated a community-based Coronavirus Infectious Disease Ontology (CIDO) (https://github.com/CIDO-ontology/cido). The CIDO has also been approved to be an Open Biomedical Ontology (OBO) Foundry library ontology (http://obofoundry.org/ontology/cido.html). The drug information introduced in this article will be included in the CIDO. CIDO will also represent the fundamental host-coronavirus molecular and cellular interaction networks and how the drugs can interact with such interaction networks, and such computer-interpretable mechanism presentation can be used to support different applications. We also welcome more participation from the community to support its deep development and applications.

5. List of abbreviations

ChEBI: Chemical Entities of Biological Interest; DrON: Drug Ontology; NDF-RT: The National Drug File - Reference Terminology.

6. Conflict of Interest

The authors declared that they have no competing interests.

7. Author contributions

YL: Manual collection and annotation, ontology processing. WC: Chemical feature-based clustering and PCA analysis. ZW: ChEBI ontology-based semantic similarity analysis. JH: Drug-target network analysis. JX: Comparative and ontological drug analysis; HY: Clinical expertise in treating coronavirus disease patients, and ontology-based drug effect analysis; YH: Project design, ontology processing, and results integration and analysis. All authors participated in discussion, result interpretation, manuscript preparation and editing, and approved the manuscript.

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Availability of data and material

The data and materials introduced are all openly available in this article or at the GitHub website: https://github.com/CIDO-ontology/anti-coronavirus-drugs.

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Figure Legends:

Figure 1. Demonstration of anti-coronavirus drugs in ChEBI ontology. (A) Demonstration of chloroquine and 6 other anti-coronavirus drugs under halide in ChEBI. Note that terconazole is a racemate consisting of equimolar amounts of (2R,4S)- and (2S,4R)-terconazole. Chlorpromazine, dasatinib, and chloroquine belong to the same group. (B) DL query of anti-coronavirus drugs that has the antimalarial role. The results include chloroquine and 4 other drugs. Note that mefloquine is a racemate composed of (+)-(11R,2'S)- and (-)-(11S,2'R)-enantiomers of mefloquine.

Figure 2. Mechanisms and roles of anti-coronavirus drugs. (A) Mechanisms of action (MoAs) of anti-coronavirus drugs as annotated by NDF-RT. NDF-RT contains the information of mechanism of action (MoA) for 57 anti-coronavirus drugs. These MoAs are mostly inhibitors or antagonists. (B) Drugs having antineoplastic role as annotated by ChEBI. A DL query identified 29 chemical entities that have the antineoplastic role. These chemical entities are active ingredients of 23 anti-coronavirus drugs identified in our study.

Figure 3. Selected hierarchies of anti-coronavirus drugs based on ChEBI classification. The hierarchies include organochlorine compounds, aromatic amides, primary/secondary/tertiary alcohols, phenothiazines, and organofluorine compounds.

Figure 4. Heatmap of anti-coronavirus drugs ChEBI semantic similarity score. The drugs with ChEBI annotations were used in this analysis. The color represents the similarity of drugs or the cluster group as indicated in the color scales on the right upper site. Five groups were classified for all the drugs included in the figure.

Figure 5. Heat map of chemical similarity between all small molecule anti-coronavirus drugs. Chemical similarity was calculated between 92 small-molecule anti-coronavirus drugs. Blue denotes no similarity, while white indicates that the compounds being compared are identical.

Figure 6. Analysis of physicochemical properties of anti-coronavirus drugs. (A.) Principal component analysis was applied to physicochemical properties of anti-coronavirus drugs. The chemical features examined were number of hydrogen bond donors, number of hydrogen bond acceptors, molecular weight, octanol-water partition coefficient, and topological polar surface

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area (TPSA). The purple points correspond to anti-coronavirus drugs that inhibit viral entry (25 compounds), while the red points correspond to anti-coronavirus drugs that inhibit viral replication (44 compounds). (B.) Box plots of each physicochemical property are compared between the two drug classes. Drugs over 1,000 Da were removed to make clearer comparisons. Dark gray represents anti-coronavirus drugs that inhibit viral entry, while light gray represents those that inhibit viral replication.

Figure 7. Drug-target network. The network contains 48 unique drugs (hexagons) and 163 their known targets (circles collected primarily from DrugBank) with 428 interactions. Drugs without any known human protein targets were excluded. Node size corresponds to the number of connections each node has, also known as degree. Node color indicates different types of drugs or drug target (gray).

Figure 8. Top 30 most significantly enriched KEGG pathways among the known drug targets. Our in-house enrichment analysis R package RichR was used to perform the enrichment analysis and generate a dot plot. This plot lists the top 30 KEGG pathways with their significance levels. Rich factor is the proportion of known drug targets to all genes in the human genome belonging to each KEGG term. The size of dot corresponds to the numbers of known drug targets annotated with the corresponding KEGG pathways. The color gradient (see color scale right of the figure) indicates the level of significance, represented by –log10(Pvalue).

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989 **Table 1.** Anti-coronavirus drugs with experimental data support

Chemical Ingredients (Drug name)	Targeted virus(es)	Ontology IDs	PUBMED IDs
Inhibit viral entry			
Aloxistatin (E-64d)	S2	C: 101381	32142651
Amodiaquine	S	C: 2674, D: 00012403, N: N0000147704, DB00613	32366720, 30700611
Benztropine mesylate	S, M	C: 3049, D: 00059818, N: N0000146182, DB00245	26202243, 24841273
Bufalin	M	C: 517248	26868298
Camostat	S, M	C: 135632, DB13729	28855003, 25666761
Camostat mesylate	S2	C: 135632, DB13729	32142651
Chloroquine	S, M, S2	C: 3638, D: 00001135, N: N0000147767, DB00608	16837072, 27344959, 27916837, 32150618, 32020029
Chloroquine phosphate	S, M, S2	N: N0000146559, DB00608	24841273, 32150618, 32074550
Chlorpromazine	M, S2	C: 3647, D: 00021685, N: N0000146214, DB00477	27344959, 24841269, 32387014
Chlorpromazine hydrochloride	S, M	C: 3649, D: 00061920, N: N0000146213, DB00477	24841273
Dalbavancin	S, M	C: 82721, N: N0000171775, D: 00750811, DB06219	26953343, 28855003, 16081529
Dasatinib	S, M	C: 49375, D:00018901, N: N0000176043, DB01254	24841273, 26868298
Emetine	O	C: 4781, D: 00017078, N: N0000147834, DB13393	30918074
Hexachlorophene	S	C: 5693, D: 00014863, N: N0000146582, DB00756	32366720, 31027241
Hydroxychloroquine	S2	C: 5801, N: N0000147871, D: 00010111, DB01611	32150618, 32205204
Hydroxychloroquine sulfate	S, M	D: 00061833, N: N0000146583, DB01611	32150618, 24841273
Imatinib	S, M	C: 45783, D: 00018693, N: N0000148698, DB00619	30711575
Imatinib mesylate	S, M	C: 31690, N: N0000148699, DB00619	24841273
Mefloquine	S, M	C: 63609, D: 00022383, N: N0000147900, DB00358	19258267, 24841273
Nafamostat	S, M	C: 135466, DB12598	28855003,30711575, 27550352
Nafamostat mesylate	S2	C: 31890, DB12598	32020029
Nelfinavir mesylate	S2	C: 7497, N: N0000148479, DB00220	32374457
Nilotinib	S	C: 52172, N: N0000176124, D:00018985, DB04868	24841273, 29557770
Oritavancin	S, M	C: 82699, D: 00750820, DB04911	26953343, 28855003, 16081529
Ouabain	S, M	C: 472805, D:00015446, DB01092	26868298
Tamoxifen citrate	S, M	C: 9397, D: 00075906, N: N0000146786, DB00675	23785035, 24841273
Teicoplanin	S, M	D: 00012681, DB06149	26953343, 28855003

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Telavancin	S, M	C: 71229, N: N0000180310, D: 00019459, DB06402	26953343, 28855003, 16081529
Terconazole	S, M	C: 9451, D: 00013976, N: N0000147638, DB00251	30893774, 24841273
Toremifene citrate	S, M	C: 9636, N: N0000148546, DB00539	23785035, 24841273
Trifluprom azine hydrochloride	S, M	C: 9712, N: N0000146110, DB00508	24841273
Triparanol	S, M	C: 135714, N: N0000166394	30893774, 24841273
Valinomycin	S	C: 28545, N: N0000170352, DB14057	30858482, 16837072
Inhibit viral replication			
6-mercaptopurine	S, M	C: 50667, N: N0000006010, DB01033	27344959, 28855003
6-thioguanine	S, M	C: 9555, DB00352	27344959, 28855003
Abemaciclib	S	D: 00803385, DB12001	32366720
Anisomycin	S, M	C: 338412, N: N0000167149, DB07374	24841273
Arbidol	S2	C: 134730, DB13609	32373347
Azithromycin	S2	C: 2955, N: N0000148074, D: 00024808, DB00207	[49]
Cepharanthine	S, O	C: 3546	32366720, 31690059
Berbamine	S	C: 3063	32366720, 29305616
Chloroquine	S, M, S2	C: 3638, D: 00001135, N: N0000147767, DB00608	16837072, 27344959, 27916837, 32150618, 32020029
Chloroquine phosphate	S, M, S2	N: N0000146559, DB00608	24841273, 32150618
Cinanserin	S	N: N0000166641	16837072
Cycloheximide	S, M	C: 27641, N: N0000167211	24841273
Cyclosporine	S, M	C: 4031, D: 00023979, N: N0000147064 DB00091	27478032, 27344959
Digitoxin	S	C: 28544, D: 00016250, N: N0000145817, DB01396	32366720, 29321306
Digoxin	S	C: 4551, D: 00012840, N: N0000146388, DB00390	32366720
Everolimus	M	C: 68478, D:00018224 N: N0000178379, DB01590	26868298
Fangchinoline	O	C: 132893	31690059
Favipiravir	S2	C: 134722, DB12466	32020029; Doi:10.1101/2020.03.17. 20037432
Gemcitabine hydrochloride	S, M	C: 31647, N: N0000022977, DB00441	24841273
Geranylgeranylacetone (GGA)	S	C: 31649	30711575
Gilteritinib	S	C: 145372, D: 00837869, DB12141	32366720
Glycyrrhizin (Glycyrrhizic acid)	S	C: 29807, D: 00723537, DB13751	21762538, 16837072
Hydroxychloroquine sulfate	S, M	D: 00061833, N: N0000146583, DB01611	32150618, 24841273
Indinavir	S	D: 00013621, DB00224	15144898
Ivacaftor	S	C: 66901, D: 00020190, DB08820	32366720
Ivermectin	S2	C: 6078, N: N0000148510, D: 00020654, DB00602	32251768, 21297106
Lopinavir	S, M	C: 31781, D: 00016421, N: N0000148672, DB01601	27344959, 26868298 16837072
Lycorine	O, M, L, V	C: 6601	30918074

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Mefloquine	S, M	C: 63609, D: 00022383, N: N0000147900, DB00358	19258267, 24841273
Mycophenolate mofetil	O, M, L, V	C: 8764, D: 00013779, N: N0000148406, DB00688	30918074
Mycophenolic acid	M	C:168396, D:00016769, N: N0000148832, DB01024	27344959
Niclosamide	S	C: 7553 D: 00015957, N: N0000146594, DB06803	32366720, 32361588
Nitazoxanide	M, S2	C: 94807, D: 00015413, N: N0000148784, DB00507	30918074, 25108173
Nocodazole	M	C: 34892, N: N0000166936, DB08313	27783035, 24841273
Omacetaxine mepesuccinate	S, M	C: 71019, DB04865	24841273
Oxyclozanide	S	N: N0000166893	32366720, 30626902
Penciclovir	S2	C: 7956, N: N0000148462, D: 00013349, DB00299	32020029
Pyrvinium pamoate (Pyrvinium)	O, M, L, V	C: 8688, DB06816	30918074
Rapamycin (sirolimus)	M	C: 9168, DB00877	25487801, 26868298
Remdesivir	S, M, S2	C: 145994, DB14761	30849247, 32275812, 32020029
Ritonavir	S, M	C: 45409, D: 00023321, N: N0000148436, DB00503	27344959, 15226499 16837072
Ribavirin	S, M, O	C: 63580, D: 00025187, N: N0000147496, DB00811	27344959, 26868298 15200845, 16837072
Salinomycin	S	C: 80025, DB11544	32366720, 30282713
SB203580	S, M	C: 90705	24699705, 27344959
SG85	S, M	C: 147346	25039866, 27344959
Selumetinib	M	C: 90227, DB11689	26868298
Silvestrol	M	C: 66484	30711575
Rimantadine	S	C: 49886, N: N0000021902, D: 00017006, DB00478	15288617
Tetrandrine	S, O	C: 49, DB14066	32366720, 31690059
Trametinib	M	C: 75991, D: 00750784, DB08911	26868298
Modulate immune response			
Cepharanthine	S, O	C: 3546	32366720, 31690059
Ciclesonide	S	C: 31397, D: 00019082, N: N0000176150, DB01410	32366720
Corticosteroid	S, M	C: 50858	26868298
Fangchinoline	O	C: 132893	31690059
IFNα2a	M	C: 5937, D: 00016915, N: N0000020127, DB00034	26868298
IFNβ1b	M	C: 5938, D: 00027247, N: N0000021905, DB00068	27344959, 15200845
Wellferon	S	D: 00013637, DB00011	15200845
Glycyrrhizin	S	C: 29807, D: 00723537	21762538, 16837072
Nitazoxanide	M, S2	C: 94807, D: 00015413, N: N0000148784, DB00507	30918074, 25108173
Methylprednisolone	S, M	C: 6888, D: 00025278, N: N0000146409, DB00959	26868298
Tetrandrine	S, O	C: 49, DB14066	32366720, 31690059

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Tocilizumab	S2	N: N0000180629, D: 00019607, DB06273	32350134
Unknown mechanism			
Fluspirilene	S, M	D: 00014099, N: N0000167366, DB04842	24841273
Thiothixene	S, M	C: 9571, D: 00012220, N: N0000148032, DB01623	24841273
Fluphenazine hydrochloride	S, M	C: 5126, D: 00059506, N: N0000146092, DB00623	24841273
Promethazine hydrochloride	S, M	C: 8462, D: 00061963, N: N0000146203, DB01069	24841273
Astemizole	S, M	C: 2896, D: 00017043, N: N0000147536, DB00637	24841273
Chlorphenoxamine hydrochloride	S, M	C: 135288, DB09007	24841273
Thiethylperazine maleate	S, M	C: 32216, N: N0000147331, DB00372	24841273
Clomipramine hydrochloride	S, M	C: 3755, D: 00058882, N: N0000147612, DB01242	24841273
Monensin	M	C: 27617, N: N0000167131, DB11430	24841273
Aescin	S	C: 2500	15226499
Reserpine	S	C: 28487, D: 00023295, N: N0000145891, DB00206	15226499
Phenazopyridine	O, M, L,V	C: 71416 , D: 00016762, N: N0000147969, DB01438	30918074
Cetylpyridinium chloride (Cetylpyridinium)	O, M, L, V	C: 32915, D:00050843, N: N0000147354, DB11073	30918074
Oligomycin	O,M, L, V	C: 25675, N: N0000168432	30918074
Harmine	O, M, L, V	C: 28121, N: N0000167259, DB07919	30918074
Conessine	O, M, L, V	C: 27965	30918074
Loperamide	S, O, M	C: 6532, D: 00000908, N: N0000147893, DB00836	30918074, 27344959, 32366720
Proscillaridin	S	C: 32065, D: 00012193, N: N0000168447, DB13307	32366720
Hydroxyprogesterone caproate	S	C: 5812, N: N0000145993, DB06789	32366720
Anidulafungin	S	C: 55346, D: 00018854, N: N0000171752, DB00362	32366720
Bazedoxifene	S	C: 135947, D: 00750789, DB06401	32366720
Eltrombopag	S	C: 85010, D: 00019163, N: N0000177933, DB06210	32366720
Baicalin	S	C: 2981, N: N0000179808	15288617
Emetine dihydrochloride hydrate	S, M	C: 146000	24841273, 29557770

** Notation: For targeted virus, M: MERS-CoV, S: SARS-CoV, S2: SARS-CoV 2, O: HCoV-OC43, L: HCoV-NL63, V: MHV-A59. For ontologies, C: ChEBI, D: DRON, N: NDF-RT. Noted that Azithromycin was newly added due to its very recent online publication on May 17, 2020 [49].

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996 **Table 2:** Anti-coronavirus antibodies annotated from the literature and clinical trials

Antibody name	Antigen	Efficacy test	Type	PMID or clinical trial IDs
Targeting SARS-CoV				
S3.1	spike protein	*in vitro*/ *in vivo* mouse	monoclonal	15247913, 17620608
CR3014	spike protein	*in vitro*/*in vivo* ferrets	monoclonal	15220038, 15650189, 17620608
S230.15	S1 RBD*	*in vitro*	monoclonal	17620608
m396	S1 RBD	*in vitro*	monoclonal	17620608
80R	S1	*in vitro*	monoclonal	14983044, 17620608
201	S1 RBD	*in vitro*	monoclonal	15655773, 17620608
scFv B1	S2	*in vitro*	monoclonal	15939399, 17620608
Targeting MERS-CoV				
m332	spike protein	*in vivo* (rabbits)	monoclonal	27344959
311B-N1	spike protein	*in vivo* (rhesus macaques)	monoclonal	27344959
REGN3051	spike protein	*In vitro*/*in vivo* (mouse)	monoclonal	26315600
REGN3048	spike protein	*In vitro*/*in vivo* (mouse)	monoclonal	26315600
4C2	S1 RBD*	*in vitro*/*in vivo* (mouse)	monoclonal	28855003, 26391698
Mersmab	S1 RBD	*In vitro*	monoclonal	28855003
m336	S1 RBD	*In vitro*/*in vivo* (mouse, rabbit)	monoclonal	28855003
m337	S1 RBD	*In vitro*	monoclonal	28855003
m338	S1 RBD	*In vitro*	monoclonal	28855003
MERS-4	S1 RBD	*In vitro*	monoclonal	28855003
MERS-27	S1 RBD	*In vitro*	monoclonal	28855003
hMS-1	S1 RBD	*In vitro*/*in vivo* (mouse)	monoclonal	28855003
LCA60	S1 RBD	*In vitro*/*in vivo* (mouse)	monoclonal	28855003
3B11-N	S1 RBD	*In vitro*/*in vivo* (rhesus monkeys)	monoclonal	28855003
2E6	S1 RBD	*in vitro*	polyclonal	26391698
2F9	DPP4	*In vitro*	monoclonal	28855003
1F7	DPP4	*In vitro*	monoclonal	28855003
YS110	DPP4	*In vitro*	monoclonal	28855003, 26315600
anti-CD26	DPP4	*in vitro*	polyclonal	26315600

997 *RBD: spike receptor-binding domain.

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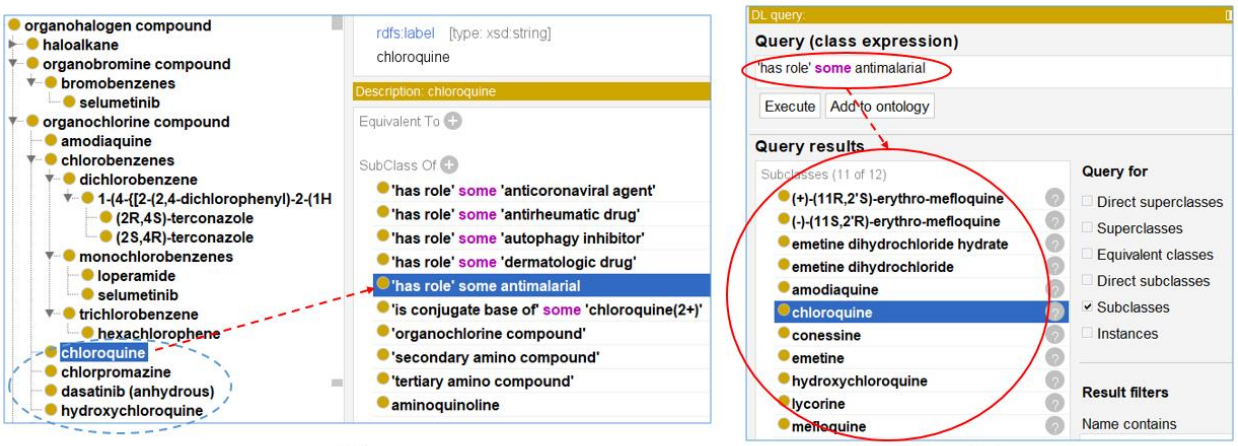

Figure 1. Demonstration of anti-coronavirus drugs in ChEBI ontology. (A) Demonstration of chloroquine and 6 other anti-coronavirus drugs under halide in ChEBI. Note that terconazole is a racemate consisting of equimolar amounts of (2R,4S)- and (2S,4R)-terconazole. Chlorpromazine, dasatinib, and chloroquine belong to the same group. (B) DL query of anti-coronavirus drugs that has the antimalarial role. The results include chloroquine and 4 other drugs. Note that mefloquine is a racemate composed of (+)-(11R,2'S)- and (-)-(11S,2'R)-enantiomers of mefloquine.

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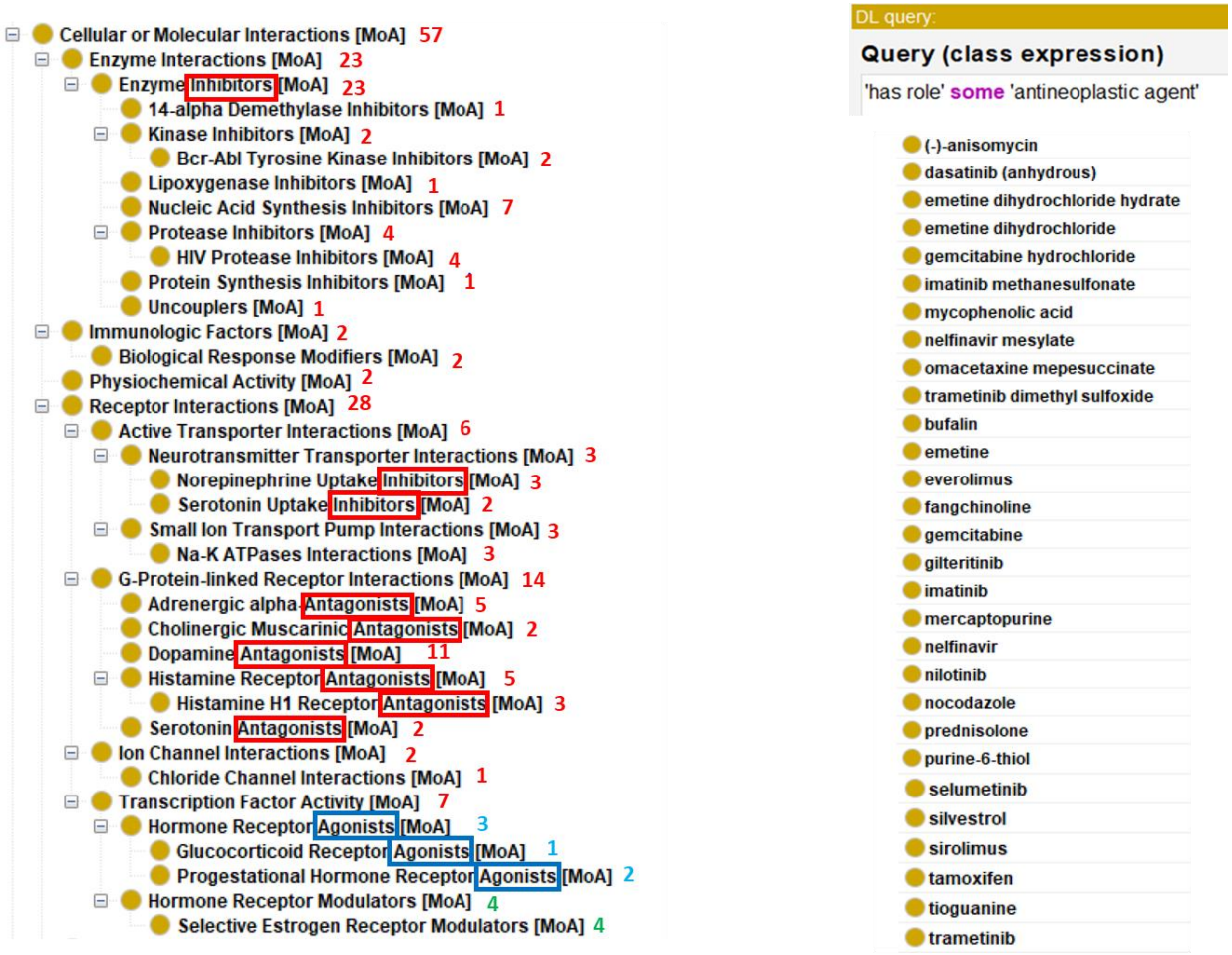

(A) **(B)**

1013

1014 **Figure 2. Mechanisms and roles of anti-coronavirus drugs.** (A) Mechanisms of action
1015 (MoAs) of anti-coronavirus drugs as annotated by NDF-RT. NDF-RT contains the information
1016 of mechanism of action (MoA) for 57 anti-coronavirus drugs. These MoAs are mostly inhibitors
1017 or antagonists. (B) Drugs having antineoplastic role as annotated by ChEBI. A DL query
1018 identified 29 chemical entities that have the antineoplastic role. These chemical entities are
1019 active ingredients of 23 anti-coronavirus drugs identified in our study.

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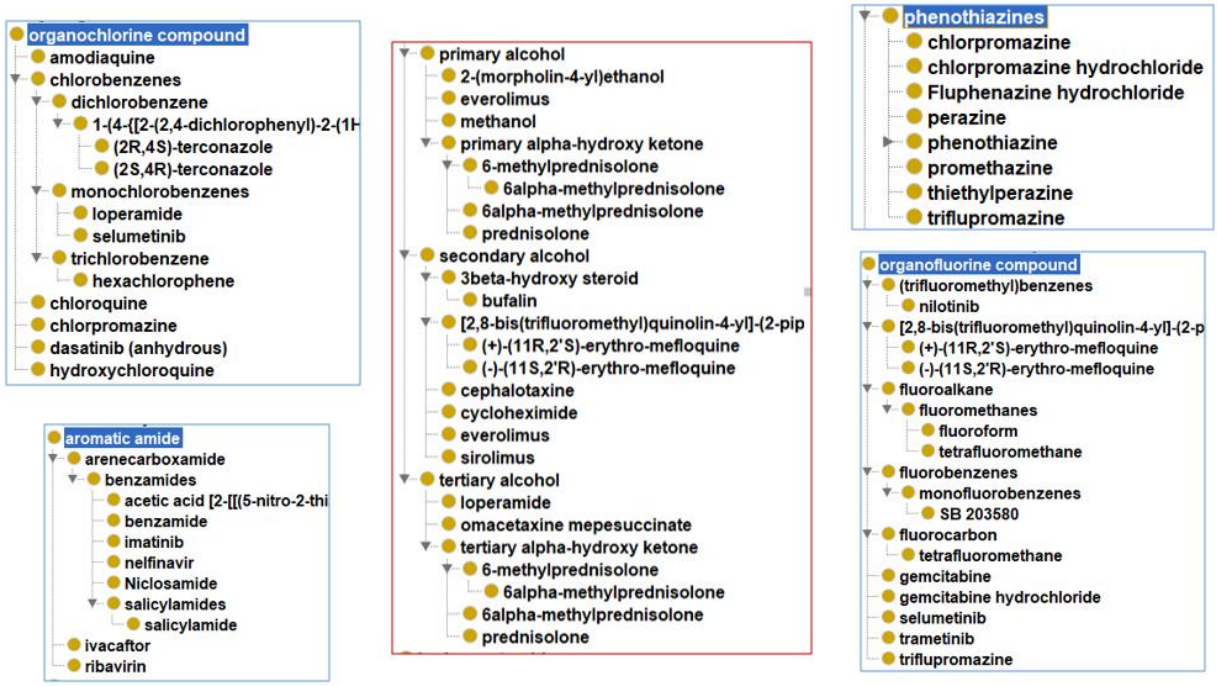

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1023

1024 **Figure 3. Selected hierarchies of anti-coronavirus drugs based on ChEBI classification.** The
1025 hierarchies include organochlorine compounds, aromatic amides, primary/secondary/tertiary
1026 alcohols, phenothiazines, and organofluorine compounds.

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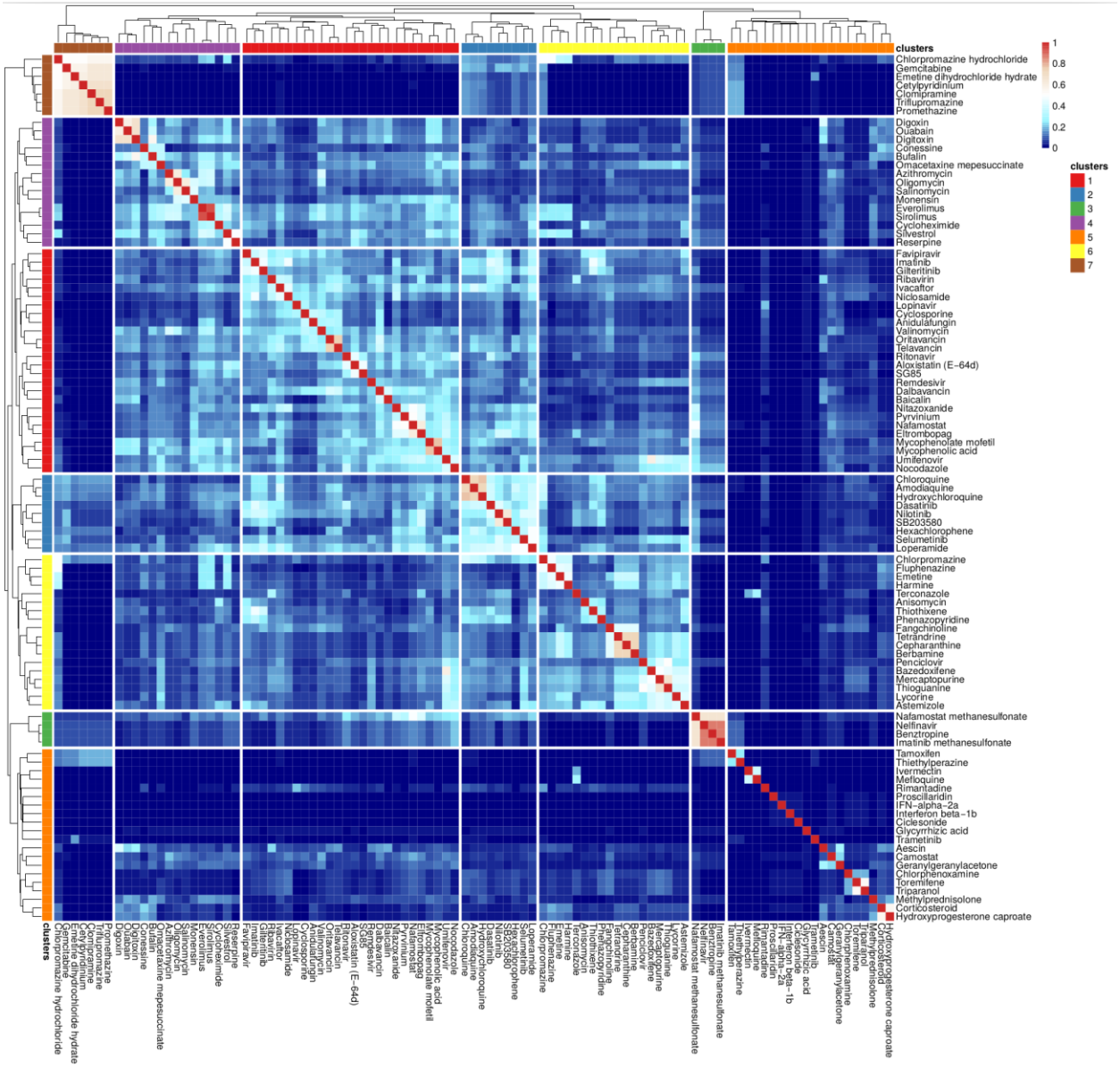

Figure 4. Heatmap of anti-coronavirus drugs ChEBI semantic similarity score. The drugs with ChEBI annotations were used in this analysis. The color represents the similarity of drugs or the cluster group as indicated in the color scales on the right upper site. Five groups were classified for all the drugs included in the figure.

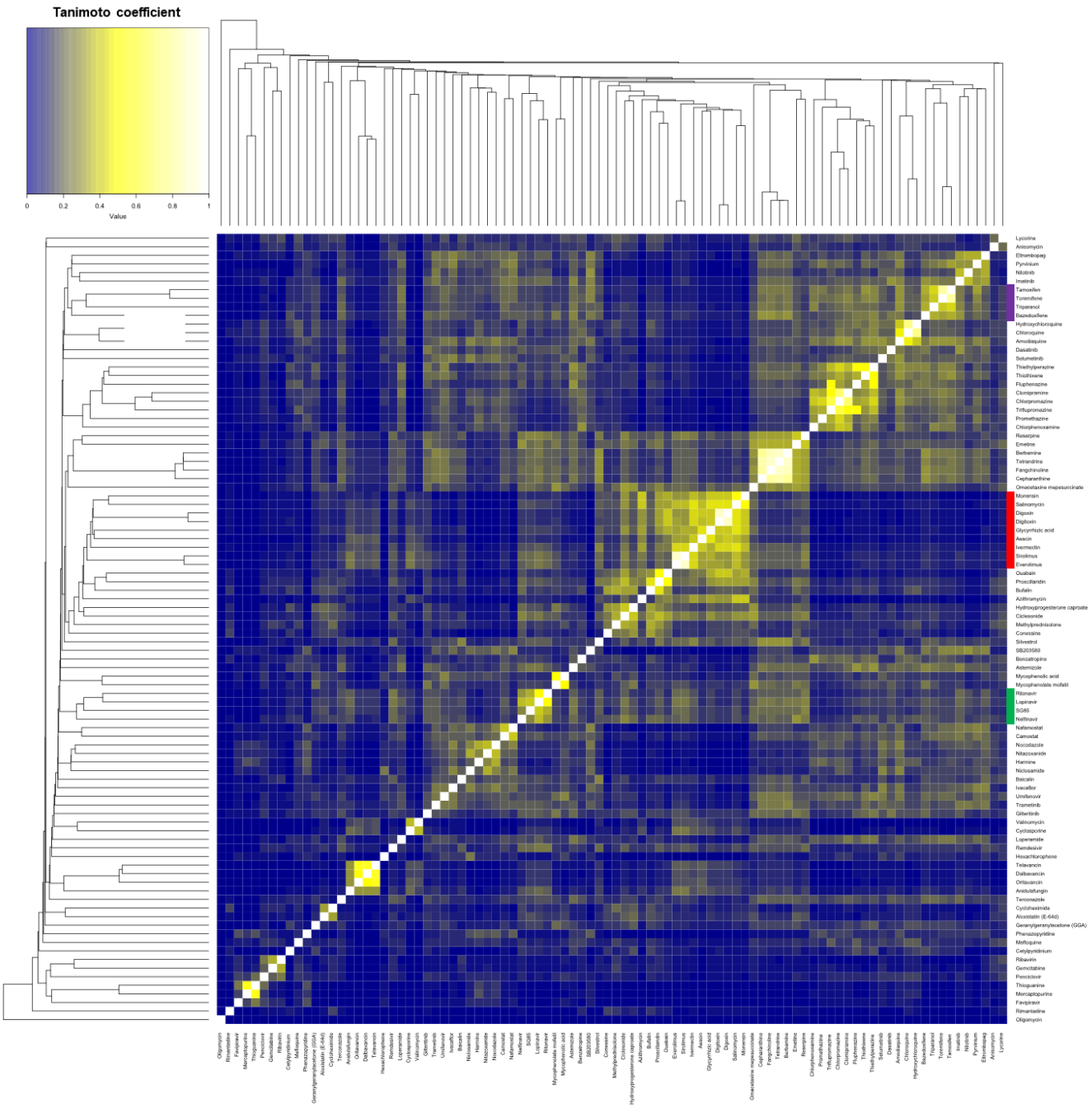

Figure 5. Heat map of chemical similarity between all small molecule anti-coronavirus drugs. Chemical similarity was calculated between 92 small-molecule anti-coronavirus drugs. Blue denotes no similarity, while white indicates that the compounds being compared are identical.

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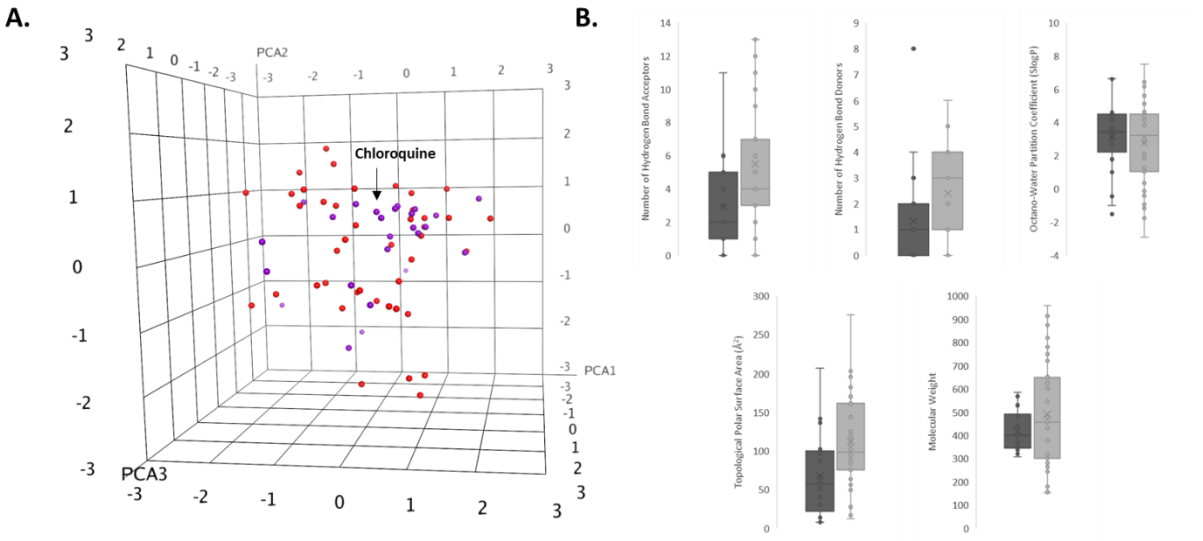

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1043

1044 **Figure 6. Analysis of physicochemical properties of anti-coronavirus drugs.** (A.) Principal
1045 component analysis was applied to physicochemical properties of anti-coronavirus drugs. The
1046 chemical features examined were number of hydrogen bond donors, number of hydrogen bond
1047 acceptors, molecular weight, octanol-water partition coefficient, and topological polar surface
1048 area (TPSA). The purple points correspond to anti-coronavirus drugs that inhibit viral entry (25
1049 compounds), while the red points correspond to anti-coronavirus drugs that inhibit viral
1050 replication (44 compounds). (B.) Box plots of each physicochemical property are compared
1051 between the two drug classes. Drugs over 1,000 Da were removed to make clearer comparisons.
1052 Dark gray represents anti-coronavirus drugs that inhibit viral entry, while light gray represents
1053 those that inhibit viral replication.

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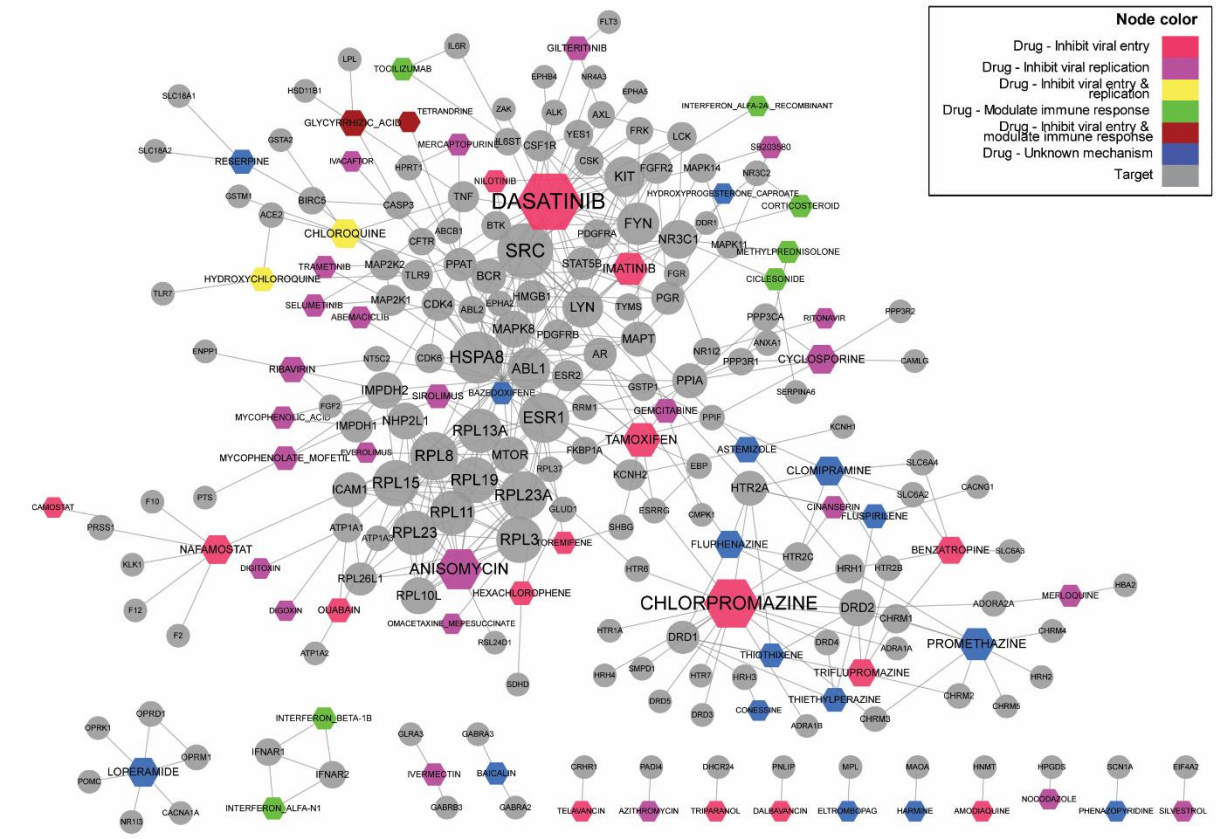

Figure 7. Drug-target network. The network contains 48 unique drugs (hexagons) and 163 their known targets (circles collected primarily from DrugBank) with 428 interactions. Drugs without any known human protein targets were excluded. Node size corresponds to the number of connections each node has, also known as degree. Node color indicates different types of drugs or drug target (gray).

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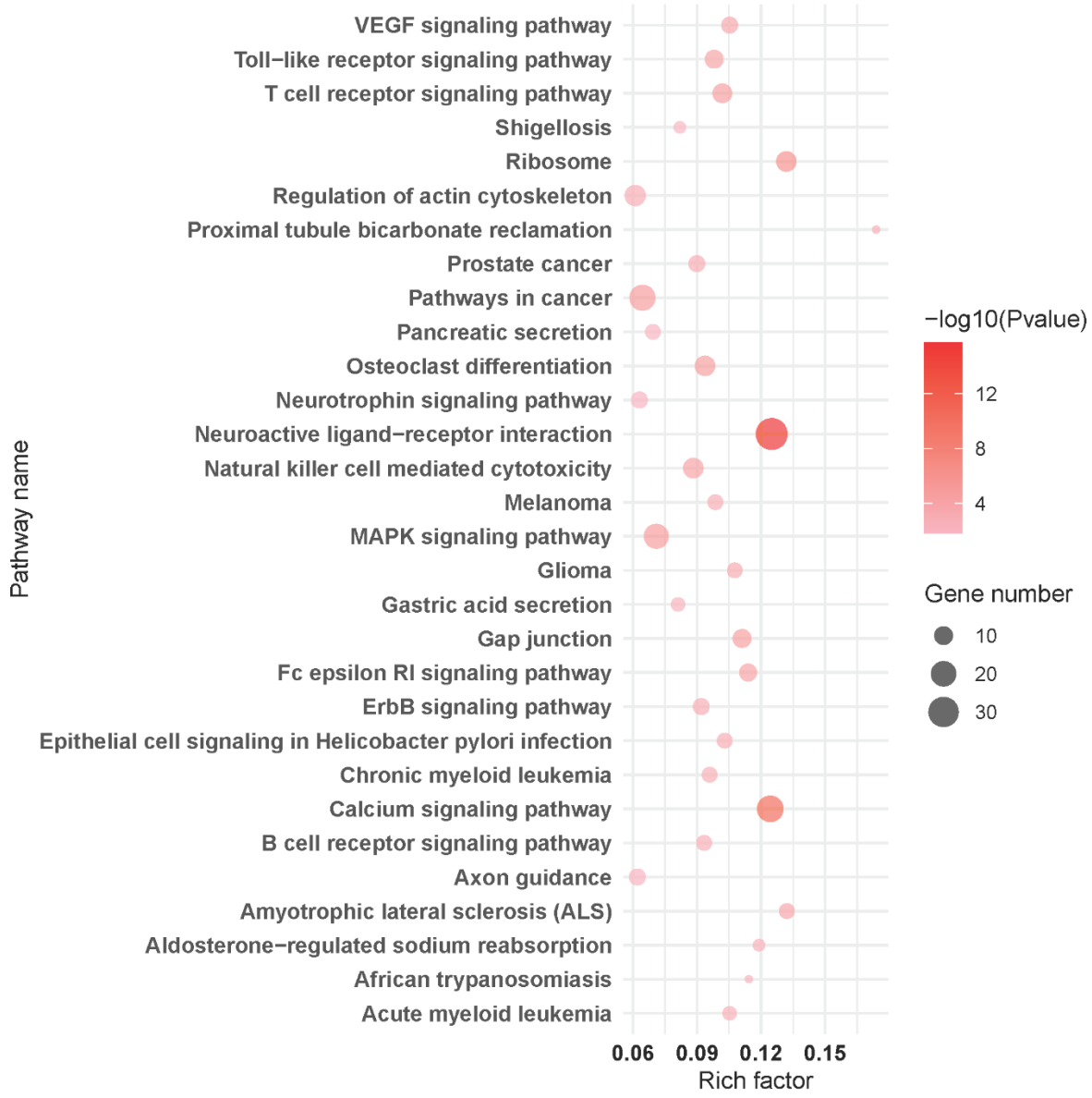

1065

1066 **Figure 8. Top 30 most significantly enriched KEGG pathways among the known drug**
1067 **targets.** Our in-house enrichment analysis R package RichR was used to perform the enrichment
1068 analysis and generate a dot plot. This plot lists the top 30 KEGG pathways with their
1069 significance levels. Rich factor is the proportion of known drug targets to all genes in the human
1070 genome belonging to each KEGG term. The size of dot corresponds to the numbers of known
1071 drug targets annotated with the corresponding KEGG pathways. The color gradient (see color
1072 scale right of the figure) indicates the level of significance, represented by –log10(Pvalue).

1073