Potential Therapeutic Agents and Associated Bioassay Data for COVID-19 and Related Human Coronavirus Infections

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ABSTRACT: The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has led to several million confirmed cases and hundreds of thousands of deaths worldwide. To support the ongoing research and development of COVID-19 therapeutics, this report provides an overview of protein targets and corresponding potential drug candidates with bioassay and structure−activity relationship data found in the scientific literature and patents for COVID-19 or related virus infections. Highlighted are several sets of small molecules and biologics that act on specific targets, including 3CLpro, PLpro, RdRp, S-protein−ACE2 interaction, helicase/ NTPase, TMPRSS2, and furin, which are involved in the viral life cycle or in other aspects of the disease pathophysiology. We hope this report will be valuable to the ongoing drug repurposing efforts and the discovery of new therapeutics with the potential for treating COVID-19.

KEYWORDS: COVID-19, SARS-CoV-2, structure−activity relationship (SAR), bioassay, protein target, drug candidate

1. INTRODUCTION

COVID-19, the infectious disease caused by the newly emerged human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),† was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. As of June 24, 2020, there have been more than 9 million confirmed cases and over 475,000 deaths worldwide.‡ In order to combat this pandemic and prevent future recurrences, scientists around the world have been working tirelessly to elucidate the molecular basis for SARS-CoV-2 infection and to develop effective therapeutic agents and preventative vaccines.

SARS-CoV-2, a member of the Betacoronavirus genus, is an enveloped virus containing a single-stranded, positive-sense RNA genome.§ Two other members of this genus that also cause similar severe acute respiratory diseases in humans are severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV). As RNA viruses, they use their RNA-dependent RNA polymerase (RdRp) to replicate their genomic RNA.¶ In particular, SARS-CoV-2 and SARS-CoV share high levels of sequence homology and protein structural similarities.¶ They both use cell membrane protein angiotensin-converting enzyme 2 (ACE2) as their receptor and need host serine protease TMPRSS2 to cleave or “prime” their spike (S) protein in order to fuse with the host cell membrane and enter the cells.¶† Once inside the host cells, the viral genome is translated by the host cell protein synthesis machinery and the resulting polyproteins are autoproteolytically cleaved by coronavirus proteases 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro) to release smaller functional proteins to continue the viral replication process.¶‡ In some cases, an excessive immune response called a cytokine storm may contribute to the further development of pulmonary edema, acute respiratory distress syndrome (ARDS), and systemic inflammation. Mean-
while, evidence is mounting that multiple organs may be damaged by SARS-CoV-2 infection in severe cases and that excessive blood coagulation may lead to life-threatening conditions.12–14

While there is no specific treatment for COVID-19, over the past few months, significant advances in discovering the molecular mechanisms of SARS-CoV-2 infection have been made, and numerous clinical trials have begun, with many more in the planning stages. For instance, several antiviral drugs or drug candidates already approved for other diseases, such as lopinavir/ritonavir and darunavir (anti-HIV), remdesivir (Ebola), chloroquine and its derivatives (antimalarial), as well as Arbidol and favipiravir (broad spectrum antiviral), were among the first drugs to be tested in multiple clinical trials across the world.15,16 Camostat mesilate and nafamostat, both TMPRSS2 inhibitors, were enlisted in clinical trials shortly after the indispensable function of TMPRSS2 in SARS-CoV-2 infection was discovered.7,17 Since the uncontrolled inflammatory response is one of the major contributing factors to disease severity, anti-inflammatory drugs, such as interferon β, baricitinib, tocilizumab, sarilumab, and acalabrutinib, are also being evaluated in clinical trials for usage either alone or in conjunction with another anti-SARS-CoV-2 agent.18–21 More recently, the potent anti-inflammatory effects of corticosteroids are being explored alone and/or in conjunction with other drugs. Initial reports showed that in patients hospitalized with COVID-19 dexamethasone resulted in a lower 28 day mortality among patients receiving respiratory support but not among those without respiratory support.22 In addition, several clinical trials are either underway or being planned that look at the effects of dexamethasone alone or in combination with other drugs.32

Although there are numerous ongoing clinical trials, only two drugs, remdesivir and favipiravir (avifavir), have so far been conditionally approved in a few countries for limited use,24–26 and these appear to show only modest effects. Moreover, the application of remdesivir is further limited because it can only be administered intravenously to hospitalized patients. Additionally, despite some conflicting results, multiple studies and meta-analyses have concluded that hydroxychloroquine offers either very small or no therapeutic effects in the treatment of COVID-19.27–30 The U.S. Food and Drug Administration (FDA) on June 15, 2020 revoked its Emergency Use Authorization for the use of hydroxychloroquine and chloroquine to treat COVID-1931 and issued cautions against its use due to the risk of incurring heart rhythm problems and other safety issues, including blood and lymph system disorders, kidney injuries, and liver damage and failure.31 However, clinical trials, including those on its use in prophylaxis, are continuing.29 As a result, there is still an urgent need to identify effective therapeutic agents for COVID-19 and possible future coronavirus-related diseases.

To support these efforts, we performed an analysis of the published journal articles and patents related to COVID-19 therapeutics. Herein, we review important viral and human targets and highlight target-based drug candidates with bioassay and structure–activity relationship (SAR) data from the Chemical Abstract Services (CAS)-indexed journal articles and patents.

2. TRENDS IN COVID-19 THERAPEUTIC RESEARCH

2.1. Journal Analysis. Since the beginning of the COVID-19 outbreak, the number of journal articles published on this topic has continued to increase as shown in Figure 1. Over the past 5 months, more than 16 000 articles have been published.

Figure 1. Monthly number of journal articles published related to COVID-19 in 2020.

This trend reflects the tremendous interest in the scientific community in understanding the new virus and in finding methods to combat the pandemic. A large number of publications are related to drug targets and the development of therapeutic agents. Due to the time requirements for de novo drug discovery, most efforts so far have focused on the repurposing of approved drugs, evaluation of investigational drugs (i.e., drugs in clinical trials for other purposes), molecular docking, and virtual screening studies.

Table 1 highlights some notable journal articles, published during this period, which focused on the development and identification of therapeutics against COVID-19. These were selected based on a number of factors, including journal impact factor, the number of citations/downloads, and the type of studies. Because our focus is on newly studied drug candidates, articles on well-known drugs such as remdesivir, hydroxychloroquine, and others that were presented in our earlier report are not included here.32 As shown in the table, both small molecules and biologics have been explored for the identification of COVID-19 therapeutics.

2.2. Patent Analysis. We also analyzed over 100 COVID-19-associated patents published in the first five months of 2020. These are categorized as follows: about 14% development of therapeutics including small molecules and biologics, 4% vaccines, 9% traditional Chinese medicines, and 56% the development of diagnostics.

Table 2 lists specific patent applications related to COVID-19 therapeutics. Patent application CN111135167A discloses that GC376 (CAS Registry Number (RN) 1416992-39-6), a 3CLpro inhibitor, significantly reduces SARS-CoV-2 replication in cells with an EC₅₀ of 3.133 μM. Patent application CN111135166A discloses a pharmaceutical composition, consisting of GC376 and a prodrug, GS-441524 (CAS RN 1191237-69-0), which has a synergistic effect for inhibiting SARS-CoV-2 replication in cells with an EC₅₀ of 1.0 μM. Due to the different examination processes at various patent offices, it is likely that a significant number of COVID-19 therapeutics related patents will be published later this year.

3. KEY PROTEINS INVOLVED IN SARS-COV-2 INFECTION

3.1. SARS-CoV-2 Proteins and Their Functions. SARS-CoV-2 contains a 30 kilobase long RNA genome, which encodes 16 nonstructural proteins (NSPs), 4 structural proteins, and 9
accessory proteins. The 16 NSPs are released by autoproteolysis of two large polyproteins by viral proteases, 3CLpro/NSP5 and P/NSP3.

Table 3 summarizes the functions of the SARS-CoV-2 proteins as well as their sequence similarities with those from SARS-CoV. The proteins are grouped based on their functions: (1) NSPs related to viral proteolysis, (2) NSPs related to viral RNA modification or polymerization, (3) structural proteins involved in viral particle assembly, and (4) accessory proteins with various functions. As indicated in the table, most of the SARS-CoV-2 proteins share high sequence similarities with those of SARS-CoV. So far, most attention has been focused on

| Table 1. Notable Journal Articles Related to COVID-19 Therapeutics |
|---|
| title | source | type of potential therapeutics | ref |
| Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketamide inhibitors | Science (April 24, 2020) | small molecules (peptidomimetic α-ketamides) | 59 |
| A human monoclonal antibody blocking SARS-CoV-2 infection | Nature Communications (May 4, 2020) | antibodies | 100 |
| A SARS-CoV-2 protein interaction map reveals targets for drug repurposing | Nature (April 30, 2020) | small molecules with different actions | 5 |
| An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice | Science Translational Medicine (April 29, 2020) | ribonucleoside analog that is also effective against CoV mutations resistant to remdesivir | 91 |
| Computational design of ACE2-based peptide inhibitors of SARS-CoV-2 | ACS Nano (April 14, 2020) | helical peptides that can be attached to nanoparticles and dendrimers | 101 |
| COVID-19: combining antiviral and anti-inflammatory treatments | Lancet Infectious Diseases (February 27, 2020) | baricitinib as an inhibitor of NAK family, especially for AAK1 | 102 |
| COVID-19: immunopathology and its implications for therapy | Nature Reviews Immunology (April 9, 2020) | biologics | 103 |
| Development of CRISPR as an Antiviral Strategy to Combat SARS-CoV-2 and Influenza | Cell (April 29, 2020) | Cas13d-crRNAs | 104 |
| Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody | Nature (May 18, 2020) | human anti-SARS-CoV-2 S protein specific monoclonal antibody | 122 |
| Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2 | Cell (May 14, 2020) | human recombinant soluble ACE2 | 96 |
| Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2 | Cell Discovery (March 16, 2020) | various small molecules | 173 |
| Rapid identification of potential inhibitors of SARS-CoV-2 main protease by deep docking of 1.3 billion compounds | Molecular Informatics (March 11, 2020) | 1000 potential ligands for SARS-CoV-2 3CLpro | 105 |
| Repurposing therapeutics for COVID-19: Supercomputer-based docking to the SARS-CoV-2 viral spike protein and viral spike protein-human ACE2 interface | ChemRxiv (February 27, 2020) | 48 potential small-molecule hits for S-protein-ACE2 interface and 30 hits for S protein alone | 106 |
| Therapeutic options for the 2019 novel coronavirus (2019-nCoV) | Nature Reviews Drug Discovery (February 10, 2020) | various small molecules and biologics | 8 |
| Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients’ B cells | Cell (May 13, 2020) | neutralizing antibodies | 98 |

| Table 2. Patents Related to COVID-19 Therapeutics |
|---|
| patent number | target | title | source | class |
| CN111184708A | 3CLpro | Application of silver monoethyl fumarate in resisting novel coronavirus infection | small molecules | 127 |
| CN111184707A | 3CLpro | Use of tolenamic acid or a pharmaceutically acceptable salt thereof in the preparation of medicament for preventing and/or treating novel coronavirus inflammation | small molecules | 128 |
| CN111150833A | RdRp | Application of LTX-315 in preparing products for inhibiting coronavirus | small molecules | 109 |
| CN111135184A | RdRp | Application of GS-441524 in preparing novel coronavirus SARS-CoV-2 inhibitor | small molecules | 110 |
| CN111135167A | 3CLpro | Application of GC376 in preparing novel coronavirus SARS-CoV-2 inhibitor | small molecules | 111 |
| CN111135166A | RdRp, 3CLpro | Pharmaceutical composition consisting of GC376 and GS-441524 and application thereof in inhibiting novel coronavirus | small molecules | 112 |
| CN1111053909A | 3CLpro, IL-6 | Application of 2019-nCoV 3CL hydrolyase inhibitor and IL-6 monoclonal antibody in preparing medicament for treating coronavirus disease 2019 | small molecules | 113 |
| CN110960532A | RdRp | Composition containing benzylisoquinoline alkaloid and trans-resveratrol for treating coronavirus infection | small molecules | 114 |
| CN111166768A | ACE2 | Overexpression ACE2 mesenchyma cell in the preparation of medicine for treating new coronavirus application of drugs and preparation method thereof | biologics | 115 |
| CN111172195A | SARS-CoV-2, ORF1ab, nucleocapsid protein | Preparation method of gene therapy product for treating COVID-19 | biologics | 116 |
| CN111153991A | nucleocapsid protein | A human SARS-CoV-2 monoclonal antibody and preparation method thereof | biologics | 117 |
| CN111139242A | SARS-CoV-2 | Small-interfering nucleic acid, and its application for preparing pharmaceutical composition for preventing and/or treating new coronavirus pneumonia | biologics | 118 |
| CN111139241A | SARS-CoV-2 | Small interfering nucleic acid for inhibiting new coronavirus and its composition and application | biologics | 119 |
| KR2020030205A | SARS-CoV-2 | COVID-19 virus customized triple knockout DNA treatment | biologics | 120 |
the S protein, 3CLpro/NSP5, PLpro/NSP3, and RdRp/NSP12 as potential drug targets. These proteins not only serve crucial functions in the viral lifecycle of SARS-CoV-2 but also have been well-studied in the related viruses SARS-CoV and MERS-CoV. Although less-studied, other proteins, such as NSP7/8/9/10/13/14/15/16, may also serve as drug targets. Conceivably, those that interfere with host immune regulation (e.g., NSP1 and Orf3b/6/9b) may also be potential targets for anticytokine storm drugs.3

### 3.2. Human Proteins Involved in SARS-CoV-2 Infection

Similar to other viruses, SARS-CoV-2 not only relies on its own proteins but also utilizes many proteins from host cells to achieve its attack on the host cells. These host proteins may also be potential drug targets, since they play crucial roles in one or more aspects of the disease, as shown in Tables 4 and S1. The proteins in Table 4 are grouped into very broad categories such as viral entrance, viral RNA/protein synthesis, host inflammatory response, and other functions. As an example of the human proteins involved in virus entrance, ACE2 functions as the main receptor for the S protein of SARS-CoV-2,7 although other membrane proteins such as CD147/basigin may also be involved.39,40 After binding to a host cell receptor, the S protein needs to be cleaved by human proteases such as TMPRSS2, furin, or endosomal cathepsin L (CTSL) to initiate membrane fusion.41 Additional host proteins involved in various steps of SARS-CoV-2 infection and abnormal host responses such as cytokine storm-mediated inflammation and excessive blood clotting32 are also listed in Tables 4 and S1.
Table 4. Selected Human Proteins Involved in SARS-CoV-2 Infection

| protein target                  | acronym    | role in SARS-CoV-2 infection                                                                 | COVID-19 clinical trial? |
|---------------------------------|------------|---------------------------------------------------------------------------------------------|--------------------------|
| angiotensin-converting enzyme 2 | ACE2       | cell surface receptor for S protein                                                           | yes                      |
| furin                           | FURIN      | cleaves S protein to expose S2 domain needed for virus-plasma membrane fusion                 | no                       |
| transmembrane serine protease 2 | TMPRSS2    | cleaves S protein to expose S2 domain needed for virus-plasma membrane fusion                 | yes                      |
| CD147/basigin                   | BSG        | alternative cell surface receptor for S protein                                               | yes                      |
| cathepsin L                     | CTSL       | cleaves S protein to expose S2 domain needed for virus-endosomal membrane fusion              | no                       |
| phosphatidylinositol inositol   | PIRFYVE    | involved in phosphoinositide metabolism, regulates endosomal dynamics; may be involved in facilitating SARS-CoV-2 entry | no                       |
| kinase PIKfyve                   |            |                                                                                             |                          |

Host Cell Proteins Involved in Viral Entrance

- Angiotensin-converting enzyme 2 (ACE2)
- Furin
- Transmembrane serine protease 2 (TMPRSS2)
- CD147/basigin
- Cathepsin L
- Phosphatidylinositol inositol kinase (PIKfyve)

Host Proteins Involved in Viral RNA/Protein Synthesis Processes

- Inosine monophosphate dehydrogenase (IMPDH2)
- Translation initiation factor eIF-4A
- Translation initiation factor eIF-1A
- Translocon protein
- Splicing factor SF3B1

Host Proteins Involved in Host Proteins Involved in Inflammatory Response

- Protein kinase JAK1 and JAK2
- Interleukin 6 (IL6)
- Complement C3
- Chemokine receptor CCR1
- Chemokine CXCL10
- Neutrophil extracellular traps

Clinical trial data was obtained as of 5/21/2020 from www.ClinicalTrials.gov. "Yes" in the table includes trials with the following status: “Not Yet Recruiting”, “Recruiting”, “Enrolling”, “Active”, or “Completed”.

Figure 2. Distribution of SARS-, MERS-, and COVID-19-associated documents and potential therapeutic substances in relation to specific targets.
4. DISTRIBUTION OF DOCUMENTS ASSOCIATED WITH SARS, MERS, AND COVID-19 AND THERAPEUTIC SUBSTANCES RELATED TO SPECIFIC TARGETS

Sequence homology between SARS-CoV-2 and SARS-CoV indicates that their key enzymes and structural proteins have high similarity. Molecular docking studies have revealed that antiviral agents effective against MERS-CoV and SARS-CoV may have similar affinities to the binding pockets in SARS-CoV2. Repositioning of existing therapeutic candidates developed for SARS and MERS has become a common theme during the past few months in the development of anti-COVID-19 therapeutics. As a result, many studies have explored the effects of potential drug substances initially developed or tested to combat other coronavirus infections. To help facilitate the ongoing repurposing efforts, we analyzed information published from 2003 to May 2020 related to SARS, MERS, and COVID-19 using the CAS content collection.

Of the 20,000 journal articles and 2,200 patents found in our analysis, over 500 patents and more than 500 journal articles were identified that contain potential therapeutic substances against SARS-CoV, MERS-CoV, and SARS-CoV-2 infections. The associations of potential therapeutic substances with specific targets in these documents were determined by data mining of CAS-provided index entries followed by intellectual review of the results. Figure 2 shows some high-frequency document—potential therapeutic substance—protein target relationships. The protein targets are listed according to the number of documents associated with each target. As shown in the figure, the 20 targets include the structural proteins (S and N proteins), nonstructural proteins (3CLpro, RdRp, PLpro, and helicase/NTPase), and human host proteins (ACE2, DPP4, TMPRSS2, and furin). Most of these studies appeared to have focused on the identification and development of small molecule therapeutics, but some biologics (biosequences) have also been developed, including some targeting the S and N proteins. Detailed information about some selected anti-SARS-CoV-2, SARS-CoV, and MERS-CoV substances will be discussed in the subsequent section.

5. BIOASSAY AND STRUCTURE—ACTIVITY RELATIONSHIP DATA FOR SMALL MOLECULES AND BIOLOGICS AGAINST COVID-19 AND RELATED CORONAVIRUS INFECTIONS

5.1. Data Sources. In order to identify drug candidates for COVID-19, we extracted SARS-CoV-2-associated bioassay data related to the development of therapeutics from recently published journals. We also examined bioassay data related to human coronaviruses published in journals and patents from 2000 to 2019, which contain substance information, targets, activity measures (half maximal inhibitory concentration (IC50), half maximal effective concentration (EC50), inhibition constant (Ki), and dissociation constant (Kd)), and assay details. In this section, we focus on five viral proteins, 3CLpro, PLpro, RdRp, helicase/NTPase, and S protein, and two human proteases, TMPRSS2 and furin, that play a key role in S-protein-mediated cell entry of the virus. Selected substances with bioassay information toward these targets are presented in Tables 5–11 and in the Supporting Information. A high level view of the numbers of these substances associated with each protein target is found in Figure 3.

5.2. Small-Molecule Inhibitors of 3CLpro. Of all the SARS-CoV-2 proteins, 3CLpro has the richest history of research data from other coronaviruses. Since 3CLpro is highly conserved among SARS-CoV-2, SARS-CoV, MERS-CoV, and other coronaviruses, previous research on this enzyme can serve as an excellent foundation for drug design of inhibitors of SARS-CoV-2 3CLpro. Table 5 highlights some substances that are active against 3CLpro of SARS-CoV-2 or SARS-CoV. Compounds GC376 and GC373 were designed based on the structures of 3CLpro from other viruses, but these were later shown to be also effective against SARS-CoV-2. Compounds 11a, 11b, 13a, and 13b were designed based on the recently revealed SARS-CoV-2 3CLpro crystal structure. In particular, 13a and 13b displayed longer plasma half-lives, and 13b can be nebulized for potential inhalant formulation. As can be seen in the table, all these compounds share a common pyrrolidinyl structure. Some substances in Table 5 were initially identified in computer-based predictive modeling studies, which have greatly expedited the identification of potential 3CLpro inhibitors. For example, Li et al. performed molecular docking
Table 5. Small-Molecule Inhibitors of 3CLpro in SARS-CoV-2 or SARS-CoV\textsuperscript{15,57−69,77−79}

| Substance | CAS Registry Number | Molecular Structure | Bioassay Information | Activity Measure (µM) |
|-----------|---------------------|---------------------|----------------------|----------------------|
| GC376\textsuperscript{57,58} | 1416992-39-6 | forming covalent modification on 3CLpro Cys145, inhibition of SARS-CoV-2 replication in Vero E6 cells | IC\textsubscript{50} = 0.19, EC\textsubscript{50} = 0.92 |
| GC373\textsuperscript{69} | 1333231-44-9 | same as above | IC\textsubscript{50} = 0.40, EC\textsubscript{50} = 1.5 |
| 13a\textsuperscript{59} | 2412965-58-1 | irreversibly reacting with 3CLpro Cys145 | IC\textsubscript{50} = 2.39 |
| 13b\textsuperscript{70} | 2412965-59-2 | irreversibly reacting with 3CLpro Cys145, inhibition of SARS-CoV-2 replication in human Calu-3 cells, being nebulized using an inhalation device | IC\textsubscript{50} = 0.67, EC\textsubscript{50} = 4.5 |
| 11a\textsuperscript{50} | 2103278-86-8 | covalently reacting with Cys145 of 3CLpro, inhibition of SARS-CoV-2 replication in Vero E6 cells | IC\textsubscript{50} = 0.05, EC\textsubscript{50} = 0.53 |
| 11b\textsuperscript{50} | 2413716-71-7 | covalently reacting with Cys145 of 3CLpro, inhibition of SARS-CoV-2 replication in Vero E6 cells | IC\textsubscript{50} = 0.04, EC\textsubscript{50} = 0.72 |
| dipyridamole\textsuperscript{51,62} | 58-32-2 | binding to immobilized SARS-CoV-2 3CLpro, clinical study in patients | IC\textsubscript{50} = 0.55 |
| candesartan cilexir\textsuperscript{81} | 145040-37-5 | binding to immobilized SARS-CoV-2 3CLpro | IC\textsubscript{50} = 2.78 |
| atazanavir\textsuperscript{81,83} | 198904-31-3 | binding to immobilized SARS-CoV-2 3CLpro, inhibition of SARS-CoV-2 replication in Vero cells | IC\textsubscript{50} = 7.53, IC\textsubscript{90} = 2.0, CC\textsubscript{50} = 312 |
| nelfinavir\textsuperscript{84} | 159989-64-7 | inhibition of SARS-CoV-2 replication in Vero E6/TMPRSS2 cells | EC\textsubscript{50} = 1.13 |
| boceprevir\textsuperscript{87} | 394730-60-0 | inhibition of SARS-CoV-2 3CLpro in FRET based enzyme assay, inhibition of SARS-CoV-2 replication in Vero 76 cells | IC\textsubscript{50} = 4.13, K\textsubscript{i} = 1.18, EC\textsubscript{50} = 1.9, CC\textsubscript{50} > 100 |
| danoprevir\textsuperscript{85} (boosted by ritonavir) | 850876-88-9 | clinical study in patient | N.A. |
| calpain inhibitor XII\textsuperscript{86} | 1333312-37-0 | inhibition of SARS-CoV-2 3CLpro in FRET based enzyme assay, inhibition of SARS-CoV-2 replication in Vero 76 cells | IC\textsubscript{50} = 0.45, K\textsubscript{i} = 0.13, EC\textsubscript{50} = 0.49, CC\textsubscript{50} > 100 |
| baicalein\textsuperscript{78,79} | 491-67-8 | inhibition of SARS-CoV-2 3CLpro activity in vitro and the replication of SARS-CoV-2 in Vero cells | IC\textsubscript{50} = 0.39, EC\textsubscript{50} = 2.7 |
studies followed by free energy perturbation (FEP) calculations of FDA-approved drugs and identified 25 drugs, which were further evaluated for their effect on SARS-CoV-2 3CLpro. Out of these 25 drugs, 15 displayed significant inhibitory activity against SARS-CoV-2 3CLpro. Shown in Table 5 are three such drugs with relatively low IC₅₀ values, including dipyridamole, an anticoagulant currently in COVID-19 clinical trial, and atazanavir, an HIV protease inhibitor with both anti-3CLpro and anti-inflammation activities. Other clinically available protease inhibitors for other viruses, such as nefinavir, boceprevir, and danoprevir, were also found to be potent inhibitors of 3CLpro. In particular, danoprevir boosted by ritonavir showed promising results in COVID-19 patients. Ebselen, an investigational drug with anti-inflammatory, antioxidant, and cytoprotective activities, has also been identified as 3CLpro inhibitor for SARS-CoV-2. Other drug candidates that functioned as cysteine protease inhibitors and inhibited SARS-CoV-2 infection include MDL-28170 and ZLVG CHN2, as identified from a large-scale drug repositioning screening of 12,000 FDA-approved and investigational drugs. Carmofur, an antineoplastic drug, covalently binds to 3CLpro Cys145 (a critical residue in the catalytic site) and inhibits viral replication in Vero E6 cells.

3CLpro inhibitors discovered from SARS-CoV and MERS-CoV studies were also examined. A few of these compounds are shown in Table 5, and a more complete list is given in Table S2. Of these, both betulinic acid and savinin not only are 3CLpro inhibitors of SARS-CoV but also may act on other targets, with betulinic acid acting as a cannabinoid receptor (CB) modulator (CB1 antagonist/CB2 agonist) and savinin acting as a tumor necrosis factor α (TNF-α) antagonist. Activation of cannabinoid receptor 2 (CB2), mainly expressed in immune cells, is reportedly linked to inhibition of inflammation and cytokine storms. Thus, activation of CB2 and inhibition of TNF-α would lead to attenuation of cytokine storm commonly observed in severe cases of COVID-19. While seemingly attractive as potential drug candidates for COVID-19, the polypharmacological properties of betulinic acid (inhibition of 3CLpro and activation of CB2) and savinin (inhibition of both 3CLpro and TNF-α) remain to be confirmed. In addition, several oligopeptides with or without chemical modification have been identified as 3CLpro inhibitors. For example, the octapeptide AVLQSGFR inhibited SARS-CoV 3CLpro and yet exhibited no cytotoxicity in Vero cells, indicating its potential as a drug candidate with low toxicity.

5.3. Small-Molecule Inhibitors of PLpro. Besides its protease activity essential for viral replication, PLpro has the additional function of stripping ubiquitin and ISG15 from host-cell proteins to aid coronaviruses in escaping the host innate immune response. Therefore, inhibiting PLpro may be of use in not only inhibiting viral replication but also preventing the inhibition of innate immunity. Table 6 presents selected small molecules shown to inhibit PLpro from SARS-CoV-2 or SARS-CoV. In a study with SARS-CoV-2 PLpro, two clinically safe Zn²⁺ ejectors, disulfiram and ebselein (also inhibit 3CLpro as shown in Table 5), were shown to extract Zn²⁺ from the critical cysteine residues of PLpro and inhibit its enzyme activity. Tioguanine, also known as 6-thioguanine (6-TG), is a chemotherapy agent that is on the World Health Organization’s List of Essential Medicines and could potentially be used to treat COVID-19. A more complete list of substances active against PLpro can be found in Table S3.
undoubtedly help to guide the design of its inhibitors. Ideal RdRp inhibitors will not only terminate RNA synthesis catalyzed by RdRp but also have the potential to block its exonucleolytic proofreading activity. Because of these factors, RdRp inhibitors are often nucleotide analogs with modifications on the sugar or base.

Table 7 provides compounds recently identified as inhibitors of SARS-CoV-2 RdRp in various bioassays. Included in this table are some FDA-approved drugs, such as sofosbuvir (a key component of hepatitis C drug EPCLUSA), azidothymidine (an anti-HIV drug), tenofovir alafenamide (a drug for HIV and hepatitis B), and tenofovir and emtricitabine (two components in DESCOVY and TRUVADA, two anti-HIV drugs).88,89 In addition, previously discovered SARS-CoV RdRp inhibitor EIDD-1931 was tested in SARS-CoV-2 and exhibited a high potency for infection inhibition.91 Its oral form, EIDD-2801, was also tested in animal models.91 A complete list of substances active against other (+)ssRNA viruses is shown in Table S4.

5.5. Small Molecules and Biologics That Affect Viral Entry Mediated by S-Protein—ACE2 Interactions. Unlike the viral proteases and RdRp, which are more likely to be inhibited by small molecules, inhibitors of the interaction of S protein with receptor ACE2 are predominantly small peptides and recombinant proteins mimicking ACE2 or neutralizing antibodies against the S protein. Recently, many of these biological molecules have been tested with SARS-CoV-2, as shown in Table 8. For example, when EK1, a peptidic pan-coronavirus fusion inhibitor which targets the heptad repeat (HR)1 region of the S protein, was linked to cholesterol (EK1C and EK1C4) or palmitic acid (EK1P), they displayed more potent inhibition against SARS-CoV-2 S-protein-mediated membrane fusion.92 Another lipopeptide, IPB02, is designed based on HR2 sequence and also showed strong activity in inhibiting the SARS-CoV-2 S-protein-mediated viral−cell fusion.93 SBP1, derived from the α1 helix of ACE2 peptidase domain, showed high affinity to the SARS-CoV-2-RBD.94 Recombinant proteins ACE2-Fc and hrsACE2, which act as decoy receptors, also target the S-protein−ACE2 interaction and viral−host-cell membrane fusion.95,96 Furthermore, an increasing number of antibodies, immunoglobulin fragments, or

Table 6. Small-Molecule Inhibitors of PLpro

| Substance | CAS Registry Number | Molecular Structure | Bioassay Information | Activity Measure (µM) |
|-----------|---------------------|---------------------|---------------------|---------------------|
| disulfiram | 97-77-8 | ![Image] | ejecting Zn²⁺ from SARS-CoV-2 PLpro, inhibition of SARS-CoV-2 PLpro in enzyme assay | IC₅₀ = 7.52 |
| eb sales | 60940-34-3 | ![Image] | ejecting Zn²⁺ from SARS-CoV-2 PLpro, inhibition of SARS-CoV-2 PLpro in enzyme assay | IC₅₀ = 2.36 |
| thioguanine (6TG) | 154-42-7 | ![Image] | in vitro target assay of SARS-CoV PLpro 2 using ubiquitin-AMC as substrate | IC₅₀ = 5.0 ± 1.7 |
| N-ethylmaleimide (NEM) | 128-53-0 | ![Image] | same as above | IC₅₀ = 4.4 ± 1.0 |
| bis(2-pyridinethiol-3-sulfonyl) 1-cysteine-zinc | 1698050-37-1 | ![Image] | in vitro target assay of SARS-CoV PLpro | IC₅₀ = 3.3 |
| 5-(aminomethyl)-2-methyl-N-[1R]-1-[1-naphthalenyl]ethyl]-benzamide | 1184301-69-6 | ![Image] | in vitro target assay of SARS-CoV PLpro expressed in E. coli using fluorogenic peptide RLRGGAMC as substrate | IC₅₀ = 0.46 |
| N-[1,3-benzodioxol-5-(methyl)-(1S)-1-[1-naphthalenyl]ethyl]-4-piperidinocarboxamide | 1233939-90-6 | ![Image] | in vitro function assay of SARS-CoV infected Vero E6 cells mediated by PLpro | EC₅₀ = 9.1 |
| in vitro target assay of SARS-CoV PLpro using ubiquitin-AMC | IC₅₀ = 0.56 |
| 5-amino-2-methyl-N-[1R]-1-[1-naphthalenyl]ethyl]benzamide | 1093070-16-6 | ![Image] | in vitro target assay of SARS-CoV PLpro using ubiquitin-AMC | Kᵡ = 0.49 |
| same as above | IC₅₀ = 0.6 |
| N-[1,3-benzodioxol-5-(methyl)-1-[1(R)]-1-[1-naphthalenyl]ethyl]-4-piperidinocarboxamide | 1234198-91-5 | ![Image] | in vitro target assay of SARS-CoV PLpro using fluorogenic peptide RLRGGAMC as substrate | IC₅₀ = 0.32 |
even single-domain antibodies are being developed for this purpose, and their activities have been demonstrated in various assays.97−100,121,122

In addition to the inhibitors mentioned above that have been tested with SARS-CoV-2, we found more compounds from SARS-CoV experiments that could be valuable for SARS-CoV-2 treatment. For example, the small molecule VE607 inhibits both

### Table 7. Small-Molecule Inhibitors of RdRp in SARS-CoV-2

| Substance                        | CAS Registry Number | Molecular Structure | Bioassay Information                                                                 | Activity Measure |
|----------------------------------|---------------------|---------------------|--------------------------------------------------------------------------------------|------------------|
| sofosbuvir                       | 1190307-88-0        | ![Molecular Structure](image1.png) | its triphosphate form inhibiting polymerase extension experiments with SARS-CoV-2 RdRp and cofactors NSP7/8 | 500 µM           |
| azidothymidine                   | 30516-87-1          | ![Molecular Structure](image2.png) | same as above                                                                         | 500 µM           |
| tenofovir alofenamide            | 379270-37-8         | ![Molecular Structure](image3.png) | same as above                                                                         | 500 µM           |
| tenofovir                        | 147127-20-6         | ![Molecular Structure](image4.png) | same as above                                                                         | 500 µM           |
| emtricitabine                    | 143491-57-0         | ![Molecular Structure](image5.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-ganciclovir      | 2416990-53-7        | ![Molecular Structure](image6.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-carbovir         | 2410071-99-5        | ![Molecular Structure](image7.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-cidofovir        | 2416990-54-8        | ![Molecular Structure](image8.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-stavudine        | 2416990-55-9        | ![Molecular Structure](image9.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-entecavir        | 1610358-03-6        | ![Molecular Structure](image10.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-2’-OMe-uridine   | 2416990-56-0        | ![Molecular Structure](image11.png) | same as above                                                                         | 500 µM           |
| phosphoramidate-3’-OMe-uridine   | 1678507-87-3        | ![Molecular Structure](image12.png) | same as above                                                                         | 500 µM           |
| biotin-16-dUTP                    | 86303-28-6          | ![Molecular Structure](image13.png) | inhibiting polymerase extension experiments with SARS-CoV-2 RdRp and cofactors NSP7/8 | 500 µM           |
| undine, 4-oxime (EIDD-1931, NHC) | 3258-02-4           | ![Molecular Structure](image14.png) | inhibition of SARS-CoV-2 replication in Vero cells, Calu-3 cells and human airway epithelial (HAE) cells | IC50 = 0.3 µM (Vero) CC50 > 10 µM (Vero) I50 = 0.08 µM (Calu-3) I50 = 0.14 µM (HAE) |
| undine, 4-oxime, 5’-(2-methylpropanoate) (EIDD-2801) | 2349386-89-4 | ![Molecular Structure](image15.png) | animal model                                                                         | 500 mg/kg        |
Table 8. Small Molecules and Biologics That Affect Viral Entry Mediated by S-Protein—ACE2 Interactions 80,92−100,121,122,127,128

| Substance | CAS Registry Number | Type of Molecule (Sequence/Structure) | Bioassay Information | Activity Measure |
|-----------|---------------------|--------------------------------------|----------------------|-----------------|
| EK1C52    | 2418703-14-5        | cholesterol conjugated lipopeptide with PEG4 linkers AA sequence: SLDOINVFLFDLEYEMKKLEAIKLE ESVYDLKEL | inhibition of SARS-CoV-2 S-mediated cell−cell fusion | IC50 = 48.0 nM |
| EK1C452   | 2428532-99-2        | cholesterol conjugated lipopeptide with GSGSG-PEG4 linkers AA sequence: SLDOINVFLFDLEYEMKKLEAIKLE ESVYDLKEL | same as above | IC50 = 1.3 nM |
| EK1F52    | 2418703-13-4        | palmitic acid conjugated lipopeptide with PEG4 linkers AA sequence: SLDOINVFLFDLEYEMKKLEAIKLE ESVYDLKEL | same as above | IC50 = 69.00 nM |
| IPB0255    | 2415902-12-2       | cholesterol linked small lipopeptide AA sequence: ISGINASVVRQIKREIDRLNEVAKNLNE SLIDQLEK | inhibition of dual split-protein (DSP)-based fusion cell−cell assay in 293T cells | IC50 = 0.025 μM |
| SBP194     | 2416761-69-6        | IEEQAKTFDLKFHNEDAELFLYQS | using bio-layer interferometry to test its binding affinity to glycylated SARS-CoV-2-RBD | Kd = 47.00 nM |
| RBD-Fc55    | 2428540-01-4        | recombinant protein | inhibition of SARS-CoV-2 pseudovirus infection of 293T cells expressing ACE2 orthologs | EC50 = 0.5 μg/ml |
| ACE2-Fc55   | 2428549-36-2        | recombinant protein | same as above | EC50 = 0.3 μg/ml |
| hrsACE2/APN0156 | 328404-18-8 | recombinant protein | inhibition of SARS-CoV-2 infections of Vero-E6 | 26 μg/ml |
| RBD-specific F(ab')2 55 | 2428610-91-5 | immunoglobulin fragment | human capillary organs and kidney organoids | 50 - 200 μg/ml |
| BD-368-256  | 2428617-22-3 | neutralizing antibody | binding to RBD of SARS-CoV-2 S protein measured by surface plasmon resonance (SPR) assay | Kd = 0.82 nM |
| sdAbs 1E255    | 2418703-15-6 | neutralizing single domain antibody | inhibition of SARS-CoV-2 infection in neutralization assay of Calu-3 cells | IC50 = 0.51 μg/ml |
| sdAbs 2F255    | 2418703-16-7 | neutralizing single domain antibody | same as above | IC50 = 0.41 μg/ml |
| sdAbs 3F1150    | 2418703-17-8 | neutralizing single domain antibody | same as above | IC50 = 0.43 μg/ml |
| sdAbs 4D855    | 2418703-18-9 | neutralizing single domain antibody | same as above | IC50 = 0.45 μg/ml |
| sdAbs 5F855    | 2418703-19-0 | neutralizing single domain antibody | same as above | IC50 = 0.24 μg/ml |
| mAb 47D11102 | 2418702-72-2 | neutralizing antibody | inhibition SARS-CoV-2 infection in Vero E6 cells in neutralization assay | IC50 = 0.57 μg/ml |
| IgG1 ab1121 | 2418702-71-1 | neutralizing antibody | neutralization activity assessed in luciferase reporter gene assay | IC50 = 200 ng/ml |
| S309122    | 2418702-70-0 | neutralizing antibody | neutralization assay of SARS-CoV-2 infection in Vero E6 cells | IC50 = 79 ng/ml |
S-protein–ACE2 interaction-mediated SARS-CoV entry and SARS-CoV plaque formation. The flavonoid luteolin has been reported to bind to the S protein and inhibit SARS-CoV entry into host cells. It also has anti-inflammatory and 3CLpro inhibition activities.

5.6. Small-Molecule Inhibitors of SARS-CoV Helicase/NTPase. As mentioned earlier in this report, NSP13 displays both helicase and NTPase activities and initiates the first step in viral mRNA capping. As part of a complex with NSP14 and NSP16, it installs the cap structure onto viral RNA in the cytoplasm. Since the sequence of SARS-CoV-2 helicase/NTPase is almost identical (100% in sequence similarity) to that of SARS-CoV, inhibitors of SARS-CoV helicase/NTPase will most likely work for SARS-CoV-2 as well. Specific examples of such inhibitors are shown in Table 9, and a more complete list is given in Table S5. Some trioxaadamantanetriol compounds, such as bananin and vanillinbananin, inhibited replication of SARS-CoV in cultured cells with low cytotoxicity. Unlike the above mentioned inhibitors, SSYA10–001 demonstrated helicase inhibition without affecting the cellular ATPase activity.

5.7. Small-Molecule Inhibitors of Human Protease TMPRSS2. Human serine protease TMPRSS2 is involved in S protein priming needed for the S2 segment of the S protein to mediate fusion of the viral envelope with the host cell membrane. Selected inhibitors are shown in Table 10, and a more complete list is given in Table S6. In addition to their inhibitory effect on TMPRSS2, these selected inhibitors are known to have other functions that may be beneficial in treating COVID-19. For example, bicalutamide, enzalutamide, dimethycurcin, and CAS RN 2031161−35−8 are nonsteroidal antiandrogen drugs that were shown to inhibit TMPRSS2 expression. Since TMPRSS2 is an androgen-regulated gene that is overexpressed in prostate cancer, speculation has arisen that higher androgen levels could be the reason for more severe outcomes in men with COVID-19. In addition, inhibitors of androgen signaling have been shown to reduce ACE2 levels; therefore, these inhibitors may have dual functions affecting both ACE2 and TMPRSS2. Finally, compounds MI460 and CAS RN 944925−37−5 may also inhibit proinflammatory cytokines and block blood coagulation-related factors, respectively.

5.8. Small-Molecule and Peptide Inhibitors of Human Protease Furin. The human protease furin is a ubiquitously expressed subtilisin/kexin-like proprotein convertase (PC) that...
cleaves the multibasic motif (RX(K/R)R↓) and activates/inactivates a variety of proteins including hormones, cytokines, and enzymes. Similar to TMPRSS2, furin is involved in priming viral S protein to mediate viral fusion with the host cell membrane and subsequent viral entry. Its cleavage site (RRAR↓) at the S1/S2 boundary of the SARS-CoV-2 and MERS-CoV S protein matches the minimal requirement of furin substrate sequence. Many furin inhibitors have been reported in the literature. Selected substances are shown in Table 11, and a more complete list is given in Table S7. The vast majority of furin inhibitors are peptides or peptidomimetics containing polyarginine or their derived analogs that bind to the catalytic site of furin. For instance, phenylacetyl-Arg-Val-Arg-4-amidinobenzylamide is one such substrate analog furin inhibitor. Further modification of this compound with additions of tert-leucine and a basic group, as represented by CAS RN 922732-52-3, improved the potency of furin inhibition. Other examples are peptide inhibitors and peptidomimetics that were synthesized based on the RARRKKRT inhibitory scaffold and the potent furin inhibitor Dec-RVKR-CMK that was shown to inhibit cleavage and viral replication in Vero cells. There are also nonpeptidic furin inhibitors, such as the guanidinylated aryl 2,5-dideoxystreptamine-derived compound represented by CAS RN 922732-52-3. This substance inhibited not only furin but also other PC family members (PC6B, PACE4, and PC7) without significant cytotoxicity to cells. Another inhibitor, oroxylin A, an O-methylated flavone natural product extracted from Scutellaria roots, has anti-inflammatory and anticoagulation activities, which may also be beneficial in treating COVID-19. Baicalein, a flavone from the roots of Scutellaria baicalensis, has been shown to inhibit Dengue virus replication in Vero cells and has also been reported recently to inhibit SARS-CoV-2 3CLpro. In addition, baicalein has antibacterial and anti-inflammatory activities. Although these inhibitors may be used to treat COVID-19 and its associated complications, more study is needed to ensure the safety of these compounds.

### Table 9. Small-Molecule Inhibitors of Helicase/NTPase

| Substance       | CAS Registry Number | Molecular Structure | Bioassay Information | Activity Measure (µM) |
|-----------------|---------------------|---------------------|----------------------|-----------------------|
| myristicin      | 529-44-2            | ![Molecular Structure](image1.png) | ATPase activity      | IC50 = 2.71          |
| scutellarein    | 529-53-3            | ![Molecular Structure](image2.png) | ATPase activity      | IC50 = 0.86          |
| HE6022         | 353488-07-0         | ![Molecular Structure](image3.png) | ATPase activity      | IC50 = 6.9           |
| SSY10-001      | 675104-49-1         | ![Molecular Structure](image4.png) | dsDNA unwinding activity | IC50 = 5.3          |
| banarin         | 665026-57-3         | ![Molecular Structure](image5.png) | RNA unwinding activity | IC50 = 5.7          |
| banilinbanani   | 858956-96-4         | ![Molecular Structure](image6.png) | SARS-CoV rep licon assay | EC50 = 8.95          |
|                 |                     |                     | cytotoxicity assay   | CC50 => 250          |
|                 |                     |                     | ATPase activity      | IC50 = 2.3*          |
|                 |                     |                     | cytotoxicity assay in Vero cells | CC50 = 765.0 |
|                 |                     |                     | helicase FRET assay  | IC50 = 3*            |
|                 |                     |                     | ATPase activity      | IC50 = 0.66          |
|                 |                     |                     | helicase FRET assay  | IC50 = 2             |

*Multiple activity measure values for one substance are from multiple references.*

### 5.9. Small Molecules and Biologics Targeting Other Human Proteins Involved in SARS-CoV-2 Infection

In addition to TMPRSS2 and furin, there are many other human proteins as listed in Table 4 which have been shown to be involved in COVID-19. Table 12 lists several small molecules or biologics targeting these human proteins involved in different steps of SARS-CoV-2 infection. A number of these, including...
meplazumab, merimepodib, plitidepsin, niclosamide, dornase alfa, and AMY-101 are currently in COVID-19 clinical trials.

6. SUMMARY AND PERSPECTIVES

In light of the enormous amount of published information and rapidly evolving knowledge about COVID-19, this report systematically assembles and curates a large amount of data into one resource to support the ongoing research and development of COVID-19 therapeutics. Highlighted are notable journal articles and patents related to COVID-19, important viral and human protein targets, a high-level view of target–substance relationship in documents related to COVID-19, SARS, and MERS, as well as rich lists of target-based potential drug candidates for COVID-19 and related coronavirus infections. The potential drug candidates include both small- and large-molecule biologics. The small molecules are comprised of a wide variety of organic compounds, nucleotide analogs, and peptides, while the biologics are mainly antibodies along with a few recombinant proteins. More importantly, we report bioassay data with detailed structure–activity relationship information extracted from published studies. We hope this report will be valuable to the ongoing drug repurposing efforts and the discovery of new therapeutics with the potential for treating COVID-19. It is worth mentioning that although these preclinical studies provide important information the utility of the listed substances as drugs for COVID-19 or related coronavirus infections would ultimately rely on successful clinical trials.

In addition to the various wet-laboratory-based approaches, computational drug repurposing for COVID-19 also plays a significant role in accelerating therapeutic development for this and other diseases. In this approach, a variety of computational and clinical data are often used and analyzed together for drug repurposing. This approach can help to overcome the challenge of translating basic scientific findings to human applications, because these drugs have passed clinical safety and bioavailability testing, thereby increasing their chances for final approval. For example, in a high-throughput docking approach, after screening a chemical library built from FDA-approved drugs and compounds undergoing clinical trials, Cavasotto and Di Filippo identified several structurally diverse compounds that each displayed antiviral activity against SARS-CoV-2. Another structure-based virtual study suggested that toremifene, an FDA-approved estrogen receptor modulator for treating advanced breast cancer, may inhibit the SARS-CoV-2 S protein and methyltransferase/NSP14. Moreover, melatonin was identified by the network medicine approach as showing a

Table 10. Small-Molecule Inhibitors of Human Protease TMPRSS2

| Substance | CAS Registry Number | Molecular Structure | Bioassay Information | Activity Measure (µM) |
|-----------|---------------------|---------------------|----------------------|----------------------|
| bicalutamide | 90357-06-5 | function assay/expression of TMPRSS2 gene in LNCaP cell | IC₅₀ = 0.831 |
| enzalutamide | 915087-33-1 | same as above | IC₅₀ = 0.072 |
| dimethylcurcin | 52328-98-0 | same as above | IC₅₀ > 10 |
| (αS)-N-[4-cyano-3-[(trifluoromethyl)phenyl]-5-fluoro-o-hydroxy-o-methyl]-1H-indole-1-propanamide | 2031161-35-8 | same as above | IC₅₀ = 0.013 |
| MI460 | 1420977-03-2 | recombinant TMPRSS2 expressed in E. coli BL21 (DE3) with D-cyclohexylalanine-PRO-ARG-AMC as substrate | Kᵢ = 0.001 |
| N2-[(phenyl(methyl)sulfonyl)]-D-arginyln-N-[4-(aminomethyl)phenyl](methyl)-L-prolinamide | 944925-37-5 | TMPRSS2 expressed in E.coli using D-CHA-GLY-ARG-pNA substrate | Kᵢ = 0.003 |
significant association with reduced likelihood of SARS-CoV-2-positive test results. In addition, Zeng et al. demonstrated that deep learning is a powerful methodology to prioritize existing drugs for further investigation. Using a library of commercially available compounds, Elmezayen et al. discovered several potential inhibitors against 3CLpro or TMPRSS2 with virtual screening and further evaluated their absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles. It can be expected that computer-screening of compounds and modeling will be increasingly used in the discovery of drugs for COVID-19 and other viral infections to expedite the drug development process and lower its cost. Nevertheless, experimental evaluation of drug candidates’ efficacy in cell-based assays and animal model studies is still needed to confirm the suggested drug effects of these virtually selected molecules.

Although this paper focuses on individual therapeutics, therapy regimes that combine various drugs to target multiple pathological processes and/or molecular targets have been evaluated and may play an important role in treating COVID-19. Over 600 documents covered drug combination approaches for COVID-19 in the CAS scientific literature collection. These include studies on the well-publicized hydroxychloroquine and azithromycin combination and on remdesivir with numerous other drugs. Of the latter, one interesting paper that combined in silico and in vitro methods highlighted the combination of remdesivir with nitazoxanide. Since COVID-19 is often characterized by exaggerated inflammatory responses, anti-

Table 11. Small-Molecule and Peptide Inhibitors of Human Protease Furin

| Substance | CAS Registry Number | Molecular Structure | Bioassay Information | Activity Measure (µM) |
|-----------|---------------------|---------------------|----------------------|----------------------|
| oroxylin A | 480-11-5            | ![Molecule Image](image) | recombinant soluble human furin with Boc-RVRR-MCA as substrate | $K_i = 3.3$ |
|           |                     |                     |                      | $IC_{50} = 4.8$     |
| baicalein  | 491-67-8            | ![Molecule Image](image) | recombinant soluble human furin using Boc-RVRR-MCA as substrate | $K_i = 6.2$ |
|           |                     |                     |                      | $IC_{50} = 13.36$  |
| rel-N.N"-[[1R,3S,4S,6R]-4,6-bis(aminominoethyl)amino]-1,3-cyclohexanediyli[bis(oxy-4,1-phenylene)]bis[guanidine] | 922732-52-3 | ![Molecule Image](image) | recombinant vaccinia expressed furin using fluorescent substrate Pyr-RTKR-MCA | $K_i = 0.012$ |
|           |                     |                     |                      | $CC_{50} > 250$    |
| phenylacetyl-Arg-Val-Arg-4-amidinobenzamide | 1206473-15-5 | ![Molecule Image](image) | human recombinant furin with pyroGlu-Arg-Thr-Lys-Arg-AMC as substrate | $K_i = 0.001$ |
|           |                     |                     |                      |                     |
| N2-[2-[4-[[aminominoethyl](aminomethyl)phenyl]acetyl]-L-arginyl-3-methyl-L-valyl-N-[4-(aminominoethyl)phenyl)methyl]-L-argininamide | 1788032-54-1 | ![Molecule Image](image) | same as above | $K_i = 0.006$ |
|           |                     |                     |                      |                     |
| decanoyl-Arg-Val-Lys-Arg-chloromethylketone (Dec-RVKR-CMK) | 150113-99-8 | ![Molecule Image](image) | inhibition of human furin using Boc-RVRR-AMC as a substrate | $K_i = 0.002$ |
|           |                     |                     |                      | $CC_{50} = 712.9$  |
| RARRKKKR | 1104196-79-3        | ![Molecule Image](image) | human recombinant furin with Pyr-RTKR-AMC as substrate | $K_i = 0.011$ |

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inflammatory treatments are often combined with antiviral agents. For example, Zhou et al. found that the mercaptopurine/melatonin and toremifene/emodin combinations were potentially of value in a computational network pharmacology study.  

Table 12. Small Molecules and Biologics Targeting Other Human Proteins Involved in SARS-CoV-2 Infection5,15,40,49,52,53,159−164  

| Substance | CAS Registry Number | Molecular Structure | Known Protein Target | Bioassay Information | Activity Measure |
|-----------|---------------------|---------------------|----------------------|----------------------|-----------------|
| Ticlopidin159 | 61036-62-2 | N.A. | Cathepsin L | Luciferase assay | IC50 = 1.66 μM |
| E624159 | 88321-09-9 | Thiols, protease and cathepsin B, H and L | Cell infection assay | N.A. |
| Aplimost160,161 | 541500-19-0 | PI3Kγ | Cell infection assay | EC50 = 0.023 μM |
| Viciusin-1161 | 35196-65-1 | PI3Kγ | Cell infection assay | N.A. |
| VBY-82515 | 131034-58-9 | Cathepsin A | Cell infection assay | EC50 = 0.3 μM |
| ONO-533415 | 868273-90-9 | Cathepsin K | Cell infection assay | EC50 = 0.5 μM |
| Meplazumab162 | 2413715-21-4 | Antibody CD147 | Cell infection assay | EC50 = 24.88 μg/ml |

Drug or drug candidate inhibiting host inflammatory response

| Substance | CAS Registry Number | Molecular Structure | Known Protein Target | Bioassay Information | Activity Measure |
|-----------|---------------------|---------------------|----------------------|----------------------|-----------------|
| AMY-101163 | 2108782-47-2 | N.A. | Complement C3 | Clinical study in patients | N.A. |
| Ofepramine164 | 481-49-2 | Anti-inflammatory/viral attachment | Cell infection assay | IC50 = 0.35 μM |
| MLN-389715 | 1010731-97-1 | CCR1 | Cell infection assay | EC50 = 0.14 μM |
| 99mTc-MDPe165 | 121524-79-6 | Anti-inflammatory | Clinical study in patients | N.A. |
| Domase alfa164 | 143831-71-4 | N.A. | Neutrophil extracellular traps | Clinical study in patients | N.A. |

Drug or drug candidate inhibiting viral RNA/mRNA/protein synthesis processes

| Substance | CAS Registry Number | Molecular Structure | Known Protein Target | Bioassay Information | Activity Measure |
|-----------|---------------------|---------------------|----------------------|----------------------|-----------------|
| Merimepide15 | 198821-22-6 | IMPDH | Cell infection assay | Inhibition 10 μM | |
| Zotatin13 | 2088191-53-6 | Efr4A1 | Enzyme activity assay | IC50 = 1.5 nM | |
| Pifidip91 | 137219-37-5 | Efr1AX | Clinical study in patients | N.A. |
| Emotina15 | 483-18-1 | 40S ribosome protein S14 | Cell infection assay | IC50 = 0.52 μm |
| Pladienclidate16 | 445493-23-2 | Splicing factor SF3B1 | Cell infection assay | IC50 = 0.007 μm |

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Since COVID-19 patients with an underlying condition, such as cardiovascular disease or diabetes, are more likely to be hospitalized and have life-threatening conditions, it is very likely that COVID-19 patients receiving antiviral drugs are simultaneously on other medications for their pre-existing conditions. Therefore, it is also crucial that COVID-19 drugs given should be compatible with those medications that the patient is already taking in order to prevent undesirable drug–drug interactions.

Currently, it is unknown how long the COVID-19 crisis will last. As different parts of the world become increasingly interconnected, it seems likely that there will be additional pandemics in the years to come, and many of these will be of viral origin. We hope the current focus on antiviral agent research will lead to major breakthroughs and help us to be better prepared for future outbreaks.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsptsci.0c00074.

Table S1: A more complete list of human protein targets involved in COVID-19, Table S2: inhibitors of 3CLpro in SARS-CoV and MERS-CoV, Table S3: inhibitors of PLpro in SARS-CoV, Table S4: inhibitors of RdRp in SARS-CoV, Table S5: inhibitors of RdRp in positive-stranded ssRNA viruses, Table S6: inhibitors of helicase/NTPase in SARS-CoV, Table S7: inhibitors of human protease TMPRSS2, Table S8: inhibitors of human protease furin (XLSX).

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