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Review

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

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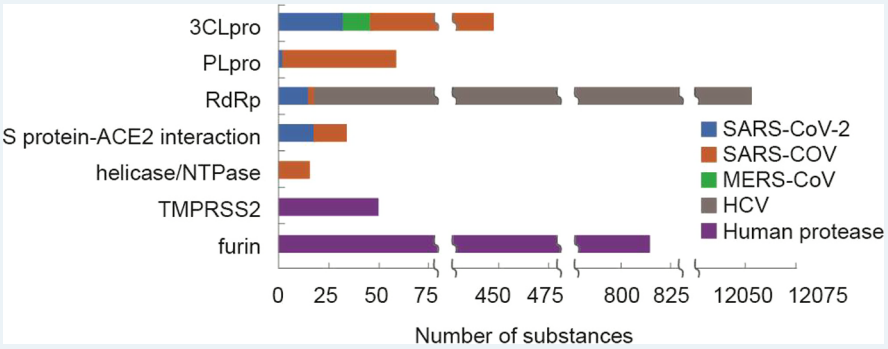

ABSTRACT: The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has led to several million confirmed cases and hundreds of thousands of deaths worldwide. To support the ongoing research and development of COVID-19 therapeutics, this report provides an overview of protein targets and corresponding 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),[1] 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.[2] 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.[3] 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.[4] In particular, SARS-CoV-2 and SARS-CoV share high levels of sequence homology and protein structural similarities.[5] They both use cell membrane protein angiotensin-converting enzyme 2 (ACE2) as their receptor and need host serine proteinase TMPRSS2 to cleave or "prime" their spike (S) protein in order to fuse with the host cell membrane and enter the cells.[6,7] 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.[8−11] In some cases, an excessive immune response called a cytokine storm may contribute to the further development of pulmonary edema, acute respiratory distress syndrome (ARSD), and systemic inflammation. Mean-

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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.[23]

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.[27−29] 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-19[30] 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.

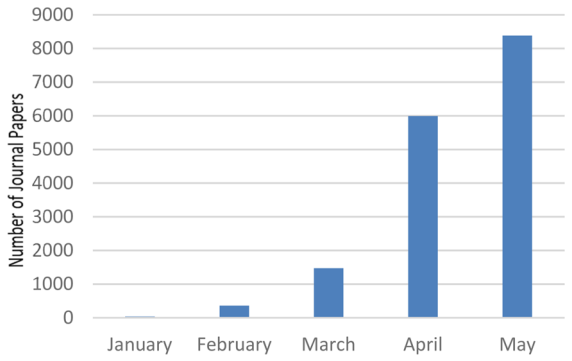

Figure 1. Monthly number of journal articles published related to COVID-19 in 2020.

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 remdesvir, 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 EC_{50} 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 EC_{50} 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

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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-ketoamide inhibitors	*Science* (April 24, 2020)	small molecules (peptidomimetic α-ketoamides)	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 CRIPSR 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	class
CN111184708A[107]	3CLpro	Application of silver monoethyl fumarate in resisting novel coronavirus infection	small molecules
CN111184707A[108]	3CLpro	Use of tolfenamic acid or a pharmaceutically acceptable salt thereof in the preparation of medicament for preventing and/or treating novel coronavirus inflammation	small molecules
CN111150833A[109]	RdRp	Application of LTX-315 in preparing products for inhibiting coronavirus	small molecules
CN111135184A[110]	RdRp	Application of GS-441524 in preparing novel coronavirus SARS-CoV-2 inhibitor	small molecules
CN111135167A[111]	3CLpro	Application of GC376 in preparing novel coronavirus SARS-CoV-2 inhibitor	small molecules
CN111135166A[112]	RdRp, 3CLpro	Pharmaceutical composition consisting of GC376 and GS-441524 and application thereof in inhibiting novel coronavirus	small molecules
CN111053909A[113]	3CLpro, IL-6	Application of 2019-nCoV 3CL hydrolase inhibitor and IL-6 monoclonal antibody in preparing medicament for treating coronavirus disease 2019	small molecules
CN110960532A[114]	RdRp	Composition containing benzylisoquinoline alkaloid and *trans*-resveratrol for treating coronavirus infection	small molecules
CN111166768A[115]	ACE2	Overexpression ACE2 mesenchyma cell in the preparation of medicine for treating new coronavirus application of drugs and preparation method thereof	biologics
CN111172195A[116]	SARS-CoV-2, ORF1ab, nucleocapsid protein	Preparation method of gene therapy product for treating COVID-19	biologics
CN111153991A[117]	nucleocapsid protein	A human SARS-CoV-2 monoclonal antibody and preparation method and application thereof	biologics
CN111139242A[118]	SARS-CoV-2	Small-interfering nucleic acid, and its application for preparing pharmaceutical composition for preventing and/or treating new coronavirus pneumonia	biologics
CN111139241A[119]	SARS-CoV-2	Small interfering nucleic acid for inhibiting new coronavirus and its composition and application	biologics
KR2020032050[120]	SARS-CoV-2	COVID-19 virus customized triple knockout DNA treatment	biologics

accessory proteins. The 16 NSPs are released by autoproteolysis of two large polyproteins by viral proteases, 3CLpro/NSP5 and PLpro/NSP3.[5]

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

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Table 3. SARS-CoV-2 Proteins and Their Roles in Viral Infection

	viral protein	role in SARS-CoV-2 infection	sequence similarity to SARS-CoV[5]
NSPs involved in proteolysis	NSP1[5,33]	inhibits production of proteins related to host innate immunity; overexpression increases production of pro-inflammatory chemokines	91.1%
	NSP2[5]	may serve as an adaptor for NSP3; not essential for viral replication	82.9%
	PLpro/NSP3[5,33]	forms complex with NSP4 and NSP6; functions in stripping ubiquitin and blocking host innate immune response	86.5%
	NSP4[33]	forms complex with NSP3 and NSP6; predicted to anchor replication complex to double membrane vesicles	90.8%
	3CLpro/NSP5[5,33,34]	cleaves polyproteins to release individual NSPs	98.7%
	NSP6[5]	forms complex with NSP3 and NSP4; may also limit autophagosome expansion and lysosomal viral degradation	94.8%
NSPs involved in viral RNA modification and replication	primase/NSP7[5,34]	form primase complex as part of the replication complex (NSP7/8/12) capable of both de novo initiation and primer extension	100%
	primase/NSP8[5,34]		99%
	RNA-binding protein/NSP9[5]	single-stranded RNA-binding protein that interacts with replication complex (NSP7/8/12)	98.2%
	NSP10[5,35]	zinc-finger protein that forms complex with NSP16 essential for replication; stimulates NSP16 to execute its methyltransferase activity; may also form complex with NSP14 to carry both exoribonuclease and methyltransferase activities	99.3%
	RdRp/NSP12[5,34]	complexes with NSP7 and NSP8 to form RNA replication complex for viral replication and transcription	98.3%
	helicase/NTPase/NSP13[5,34]	initiates the first step in viral mRNA capping; along with NSP14 and NSP16; installs the cap structure onto viral mRNA in the cytoplasm	100%
	methyltransferase/exoribonuclease/NSP14[5,34]	corrects mutations during genome replication; facilitates capping of viral mRNA	98.7%
	uridylate-specific endoribonuclease/NSP15[5,34]	essential for viral RNA synthesis	95.7%
	2′-*O*-methyltransferase/NSP16[5,34]	forms complex with NSP10; involved in mRNA *S*-adenosyl-L-methionine cap methylation	98.0%
	NSP11[5]	short peptide with unknown function	92.3%
structural proteins	spike (S) protein[5,7,36]	binds to ACE2 receptor on host cells and initiates viral fusion with host cell membrane	87%
	envelope (E) protein[5,36]	plays a central role in viral morphogenesis and assembly	96.1%
	membrane (M) protein[5,36,37]	major driver for viral assembly	96.4%
	nucleocapsid (N) protein[5,36,37]	binds to viral RNA	94.3%
accessory proteins	ORF3a[5]	involved in S protein trafficking and apoptosis	85.1%
	ORF3b[5]	inhibits interferon activities	9.5%
	ORF6[5,38]	interferon I antagonist that binds to karyopherins, alters their localization and reduces interferon/antiviral response	85.7%
	ORF7a[5]	involved in virus-induced apoptosis; inhibits CD317 which prevents release of coronavirus particles	90.2%
	ORF7b[5]	unknown function	84.1%
	ORF8[5]	unknown function but not essential for virus replication	45.3%
	ORF9b[5]	involved in degradation of MAVS signalosome and limits host cell interferon responses	84.7%
	ORF9c[5]	unknown, may not be expressed	78.1%
	ORF10[5]	unknown, may not be expressed	N.A.

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 Orf3*b*/6/9b) may also be potential targets for anticytokine storm drugs.[5]

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 clotting[42] are also listed in Tables 4 and S1.

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Table 4. Selected Human Proteins Involved in SARS-CoV-2 Infection

protein target	acronym	role in SARS-CoV-2 infection	COVID-19 clinical trial?[a]
Host Cell Proteins Involved in Viral Entrance			
angiotensin-converting enzyme 2[43]	ACE2	cell surface receptor for S protein	yes
furin[44,45]	FURIN	cleaves S protein to expose S2 domain needed for virus-plasma membrane fusion	no
transmembrane serine proteinase 2[7]	TMPRSS2	cleaves S protein to expose S2 domain needed for virus-plasma membrane fusion	yes
CD147/basigin[39,40]	BSG	alternative cell surface receptor for S protein	yes
cathepsin L[7,41]	CTSL	cleaves S protein to expose S2 domain needed for virus-endosomal membrane fusion	no
phosphatidylinositol inositol kinase PIKfyve[41]	PIKFYVE	involved in phosphoinositide metabolism, regulates endosomal dynamics; may be involved in facilitating SARS-CoV-2 entry	no
Host Proteins Involved in Viral RNA/Protein Synthesis Processes			
inosine monophosphate dehydrogenase IMPDH2[5,52]	IMPDH2	binds to NSP14; involved in guanine nucleotide metabolism	no
translation initiation factor eIF-4A[5,53]	EIF4A1	binds to NSP2; involved in viral protein translation	no
translation initiation factor eIF-1A[5]	EIF1AX	involved in viral protein translation	yes
translocon protein Sec61[5,54]	SEC61A, SEC61B	involved in viral protein insertion into endoplasmic reticulum	no
splicing factor SF3B1[55]	SF3B1	altered expression in SARS-CoV-2 infection	no
Host Proteins Involved in Inflammatory Response			
protein kinase JAK1 and JAK2[46,47]	JAK1/JAK2	involved in cytokine signaling	yes
interleukin 6[48]	IL6	involved in cytokine storm	yes
complement C3[49]	C3	early complement factor that mediates inflammation and lung injury in COVID-19	yes
chemokine receptor CCR1[15]	CCR1	involved in cytokine signaling	no
chemokine CXCL10[50]	CXCL10	involved in cytokine signaling	
neutrophil extracellular traps[42,51]	N.A.	increased levels in COVID-19 patients, excessive amounts trigger inflammation and blood clotting	yes

[a]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".

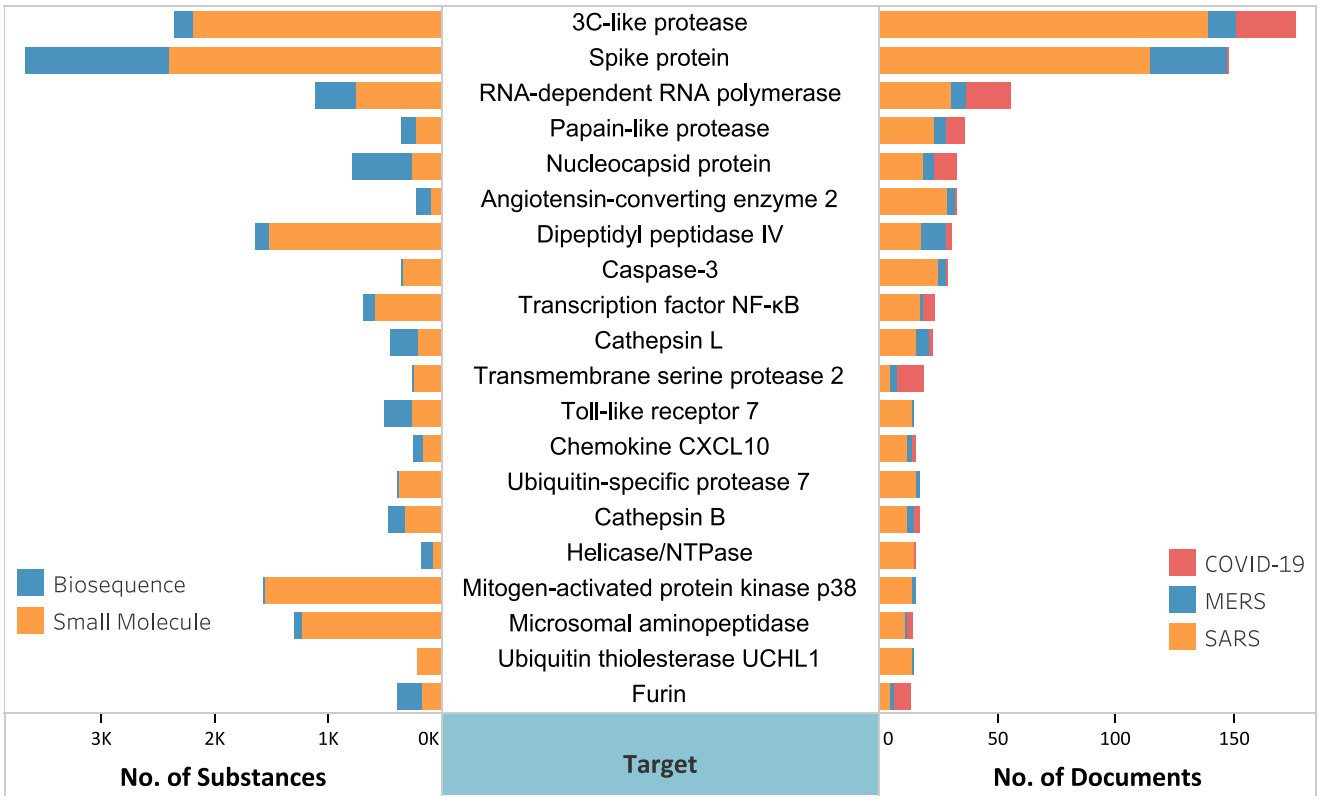

Figure 2. Distribution of SARS-, MERS-, and COVID-19-associated documents and potential therapeutic substances in relation to specific targets.

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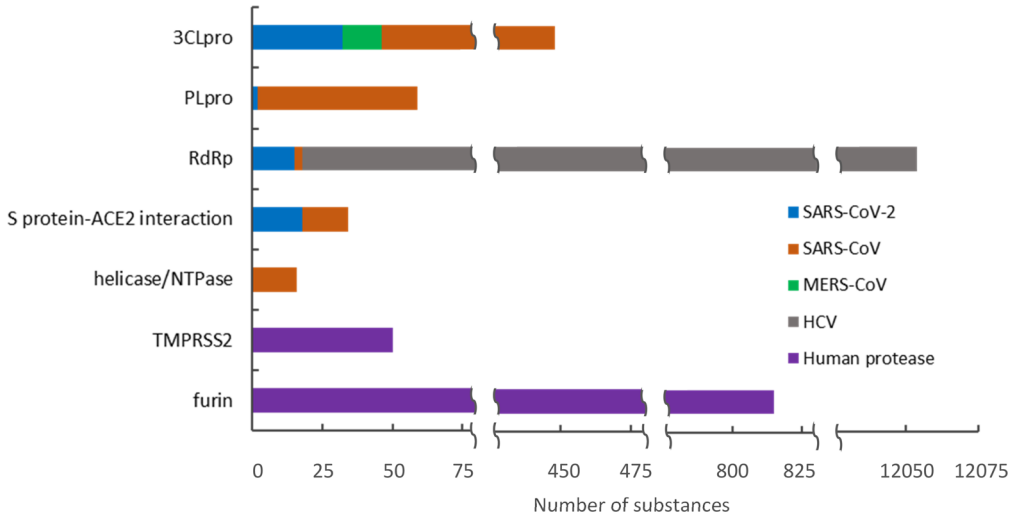

Figure 3. Numbers of substances with bioassay information for specific viral and human protein targets related to COVID-19 or other related viral infections.

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.[5] 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.[56] 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 (IC_{50}), half maximal effective concentration (EC_{50}), inhibition constant (K_i), and dissociation constant (K_d)], 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.[57,58] Compounds **11a**, **11b**, **13a**, and **13b** were designed based on the recently revealed SARS-CoV-2 3CLpro crystal structure.[59,60] In particular, **13a** and **13b** displayed longer plasma half-lives, and **13b** can be nebulized for potential inhalant formulation.[59] 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

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Table 5. Small-Molecule Inhibitors of 3CLpro in SARS-CoV-2 or SARS-CoV[15,57−69,77−79]

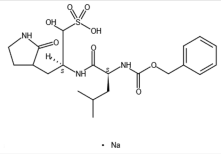
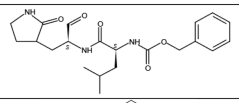
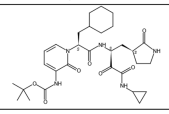
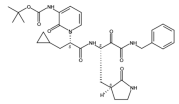
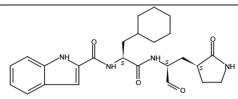
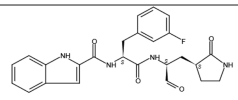
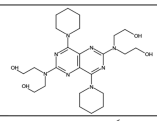
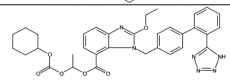
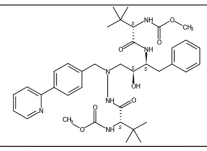
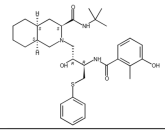
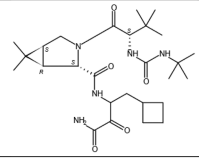
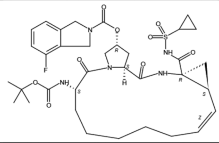
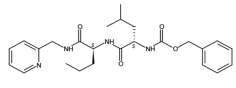
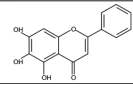
Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure (μM)
Substances with inhibitory effect on 3CLpro of SARS-CoV-2				
GC376[57,58]	1416992-39-6		forming covalent modification on 3CLpro Cys145, inhibition of SARS-CoV-2 replication in Vero E6 cells	IC_{50} = 0.19 EC_{50} = 0.92
GC373[58]	1333231-44-9		same as above	IC_{50} = 0.40 EC_{50} = 1.5
13a[59]	2412965-58-1		irreversibly reacting with 3CLpro Cys145	IC_{50} = 2.39
13b[59]	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_{50} = 0.67 EC_{50} = 4-5
11a[60]	2103278-86-8		covalently reacting with Cys145 of 3CLpro, inhibition of SARS-CoV-2 replication in Vero E6 cells	IC_{50} = 0.05 EC_{50} = 0.53
11b[60]	2413716-71-7		covalently reacting with Cys145 of 3CLpro, inhibition of SARS-CoV-2 replication in Vero E6 cells	IC_{50} = 0.04 EC_{50} = 0.72
dipyridamole[61,62]	58-32-2		binding to immobilized SARS-CoV-2 3CLpro, clinical study in patients	IC_{50} = 0.55
candesartan cilextil[61]	145040-37-5		binding to immobilized SARS-CoV-2 3CLpro	IC_{50} = 2.78
atazanavir[61,63]	198904-31-3		binding to immobilized SARS-CoV-2 3CLpro, inhibition of SARS-CoV-2 replication in Vero cells	IC_{50} = 7.53 EC_{50} = 2.0 CC_{50} = 312
nelfinavir[64]	159989-64-7		inhibition of SARS-CoV-2 replication in Vero E6/TMPRSS2 cells	EC_{50} = 1.13
boceprevir[57]	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_{50} = 4.13 K_i = 1.18 EC_{50} = 1.9 CC_{50} > 100
danoprevir[65] (boosted by ritonavir)	850876-88-9		clinical study in patient	N.A.
calpain inhibitor XII[57]	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_{50} = 0.45 K_i = 0.13 EC_{50} = 0.49 CC_{50} > 100
baicalein[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_{50} = 0.39 EC_{50} = 2.7

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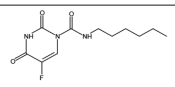
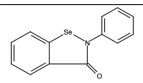
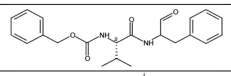
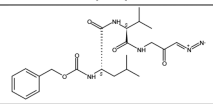
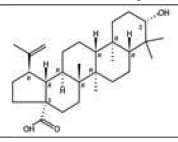
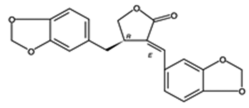
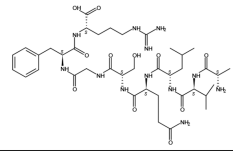
Table 5. continued

Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure (μM)
carmofur[68]	61422-45-5		covalently binding to Cys145 of SARS-CoV-2 3CLpro, inhibition of SARS-CoV-2 replication in Vero E6 cells	EC_{50} = 24.3
ebselen[66,67]	60940-34-3		inhibition of SARS-CoV-2 3CLpro in the high-throughput enzyme inhibition assay, inhibition of SARS-CoV-2 replication in Vero cells	EC_{50} = 4.67 IC_{50} = 0.67
MDL-28170[15]	88191-84-8		inhibition of SARS-CoV-2 replication in Vero E6 cells in a high content imaging assay	EC_{50} = 0.22
Z LVG CHN2[15]	119670-30-3		inhibition of SARS-CoV-2 replication in Vero E6 cells in a high content imaging assay	EC_{50} = 0.19
Substances with inhibitory effect on 3CLpro of SARS-CoV				
betulinic acid[69]	472-15-15-1		*in vitro* binding to SARS-CoV 3CLpro	K_i = 8.2 ± 0.7 IC_{50} = 10 EC_{50} > 10
(-)-savinin[69]	493-95-8		*in vitro* inhibition of SARS-CoV 3CLpro activity, inhibition of SARS-CoV replication	K_i = 9.1 IC_{50} = 25 EC_{50} > 1.13
octopeptide AVLQSGFR[77]	608531-54-0		*in vitro* inhibition of SARS-CoV 3CLpro	IC_{50} = 0.031

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.[61] Shown in Table 5 are three such drugs with relatively low IC_{50} values, including dipyridamole, an anticoagulant currently in COVID-19 clinical trial,[62] and atazanavir, an HIV protease inhibitor with both anti-3CLpro and anti-inflammation activities.[63] Other clinically available protease inhibitors for other viruses, such as nelfinavir,[64] boceprevir,[57] and danoprevir,[65] were also found to be potent inhibitors of 3CLpro. In particular, danoprevir boosted by ritonavir showed promising results in COVID-19 patients.[65] Ebselen, an investigational drug with anti-inflammatory, antioxidant, and cytoprotective activities, has also been identified as 3CLpro inhibitor for SAS-CoV-2.[66,67] Other drug candidates that functioned as cysteine protease inhibitors and inhibited SARS-CoV-2 infection include MDL-28170 and Z LVG CHN2, as identified from a large-scale drug repositioning screening of 12 000 FDA-approved and investigational drugs.[15] Carmofur, an antineoplastic drug, covalently binds to 3CLpro Cys145 (a critical residue in the catalytic site) and inhibits viral replication in Vero E6 cells.[68]

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.[69−72] Activation of cannabinoid receptor 2 (CB2), mainly expressed in immune cells, is reportedly linked to inhibition of inflammation and cytokine storms.[73,74] 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 TNFα) remain to be confirmed.[75] 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.[76,77]

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.[10] 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 Zn^{2+} ejectors, disulfiram and ebselen[66] (also inhibit 3CLpro as shown in Table 5), were shown to extract Zn^{2+} 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[81] and could potentially be used to treat COVID-19. A more complete list of substances active against PLpro can be found in Table S3.

5.4. Small-Molecule Inhibitors of RdRp. Recently, the cryo-EM structure of RdRp has been revealed,[87] which will

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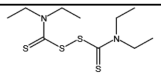
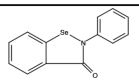
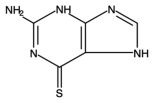
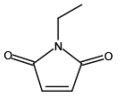
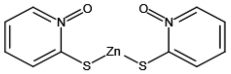
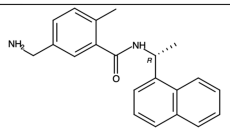
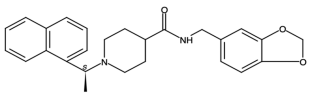
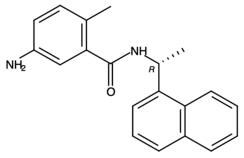
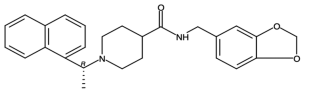
Table 6. Small-Molecule Inhibitors of PLpro[66,80,82−86]

Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure (μM)
disulfiram[66]	97-77-8		ejecting Zn^{2+} from SARS-CoV-2 PLpro, inhibition of SARS-CoV-2 PLpro in enzyme assay	IC_{50} = 7.52
ebselen[66]	60940-34-3		ejecting Zn^{2+} from SARS-CoV-2 PLpro, inhibition of SARS-CoV-2 PLpro in enzyme assay	IC_{50} = 2.36
thioguanine (6TG)[82]	154-42-7		*in vitro* target assay of SARS-CoV PLpro 2 using ubiquitin-AMC as substrate	IC_{50} = 5.0 ±1.7
N-ethylmaleimide (NEM)[82]	128-53-0		same as above	IC_{50} = 4.4 ±1.0
bis[(2-pyridinethiol-κS2) 1-oxidato]zinc[80]	1698050-37-1		*in vitro* target assay of SARS-CoV PLpro	IC_{50} = 3.3
5-(aminomethyl)-2-methyl-N-[(1R)-1-(1-naphthalenyl)ethyl]-benzamide[83]	1184301-69-6		*in vitro* target assay of SARS-CoV PLpro expressed in E. coli using fluorogeneic peptide RLRGGAMC as substrate	IC_{50} = 0.46
N-(1,3-benzodioxol-5-ylmethyl)-1-[(1S)-1-(1-naphthalenyl)ethyl]-4-piperidinecarboxamide[84]	1233939-90-6		*in vitro* function assay of SARS-CoV infected Vero E6 cells mediated by PLpro	EC_{50} = 9.1
			in vitro target assay of SARS-CoV PLpro using ubiquitin-AMC as substrate	IC_{50} = 0.56
5-amino-2-methyl-N-[(1R)-1-(1-naphthalenyl)ethyl]benzamide[85]	1093070-16-6		*in vitro* target assay of SARS-CoV PLpro using ubiquitin-AMC	K_i = 0.49
			same as above	IC_{50} = 0.6
N-(1,3-benzodioxol-5-ylmethyl)-1-[(1R)-1-(1-naphthalenyl)ethyl]-4-piperidinecarboxamide[86]	1234195-91-5		*in vitro* target assay of SARS-CoV PLpro using fluorogenic peptide RLRGGAMC as substrate	IC_{50} = 0.32

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

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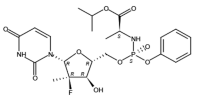
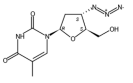
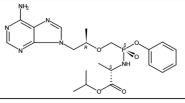
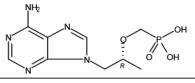
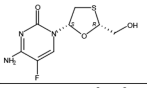
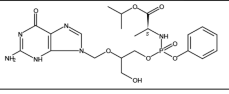
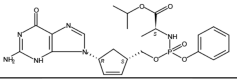
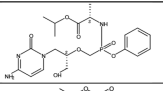
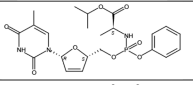
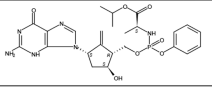
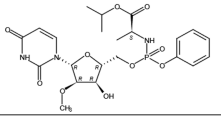
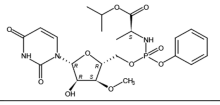
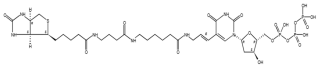
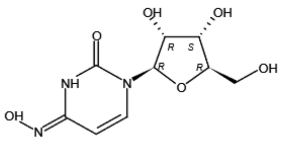
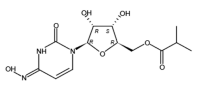
Table 7. Small-Molecule Inhibitors of RdRp in SARS-CoV-2[88−91]

Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure
sofosbuvir[88]	1190307-88-0		its triphosphate form inhibiting polymerase extension experiments with SARS-CoV-2 RdRp and cofactors NSP7/8	500 μM
azidothymidine[88]	30516-87-1		same as above	500 μM
tenofovir alafenamide[88]	379270-37-8		same as above	500 μM
tenofovir[89]	147127-20-6		same as above	500 μM
emtricitabine[89]	143491-57-0		same as above	500 μM
phosphoramidate-ganciclovir[90]	2416990-53-7		same as above	500 μM
phosphoramidate-carbovir[90]	2410071-99-5		same as above	500 μM
phosphoramidate-cidofovir[90]	2416990-54-8		same as above	500 μM
phosphoramidate-stavudine[90]	2416990-55-9		same as above	500 μM
phosphoramidate-entecavir[90]	1610358-03-6		same as above	500 μM
phosphoramidate-2'-OMe-uridine[90]	2416990-56-0		same as above	500 μM
phosphoramidate-3'-OMe-uridine[90]	1678507-87-3		same as above	500 μM
biotin-16-dUTP[90]	86303-26-6		inhibiting polymerase extension experiments with SARS-CoV-2 RdRp and cofactors NSP7/8	500 μM
uridine, 4-oxime (EIDD-1931, NHC)[91]	3258-02-4		inhibition of SARS-CoV-2 replication in Vero cells, Calu-3 cells and human airway epithelial (HAE) cells	IC_{50} = 0.3 μM (Vero) CC_{50} > 10 μM (Vero) IC_{50} = 0.08 μM (Calu-3) IC_{50} = 0.14 μM (HAE)
uridine, 4-oxime, 5'-(2-methylpropanoate) (EIDD-2801)[91]	2349386-89-4		animal model	500 mg/kg

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

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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
Substances with inhibitory effect in SARS-CoV-2 studies				
EK1C[92]	2418703-14-5	cholesterol conjugated lipopeptide with PEG4 linkers AA sequence: SLDQINVTFLDLEYEMKKLEEAIKKLE ESYIDLKEL	inhibition of SARS-CoV-2 S-mediated cell–cell fusion	IC_{50} = 48.00 nM
EK1C4[92]	2428532-99-2	cholesterol conjugated lipopeptide with GSGSG-PEG4 linkers AA sequence: SLDQINVTFLDLEYEMKKLEEAIKKLE ESYIDLKEL	same as above	IC_{50} = 1.3 nM
EK1P[92]	2418703-13-4	palmitic acid conjugated lipopeptide with PEG4 linkers AA sequence: SLDQINVTFLDLEYEMKKLEEAIKKLE ESYIDLKEL	same as above	IC_{50} = 69.00 nM
IPB02[93]	2415902-12-2	cholesterol linked small lipopeptide AA sequence: ISGINASVVNIQKEIDRLNEVAKNLNE SLIDLQELK	inhibition of dual split-protein (DSP)-based fusion cell-cell assay in 293T cells	IC_{50} = 0.025 μM
SBP1[94]	2416761-69-6	IEEQAKTFLDKFNHEAEDLFYQS	using bio-layer interferometry to test its binding affinity to glycosylated SARS-CoV-2-RBD	K_d = 47.00 nM
RBD-Fc[95]	2428540-01-4	recombinant protein	inhibition of SARS-CoV-2 pseudovirus infection of 293T cells expressing ACE2 orthologs	EC_{50} = 0.5 μg/ml
ACE2-Fc[95]	2428549-36-2	recombinant protein	same as above	EC_{50} = 0.3 μg/ml
hrsACE2/APN01[96]	328404-18-8	recombinant protein	inhibition of SARS-CoV-2 infections of Vero-E6	25 μg/ml
			human capillary organoids and kidney organoids	50 - 200 μg/ml
RBD-specific F(ab')2[97]	2428610-91-5	immunoglobulin fragment	inhibition of SARS-CoV-2 infection of Vero E6 cells in neutralization test	EC_{50} = 0.07 μg/ml
BD-368-2[98]	2428617-22-3	neutralizing antibody	binding to RBD of SARS-CoV-2 S protein measured by surface plasmon resonance (SPR)	K_d = 0.82 nM
			inhibition of SARS-CoV-2 in plaque reduction neutralizing test (PRNT) assay	IC_{50} = 15 ng/ml
sdAbs 1E2[99]	2418703-15-6	neutralizing single domain antibody	inhibition SARS-CoV-2 infection in neutralization assay of Calu-3 cells	IC_{50} = 0.51 μg/ml
sdAbs 2F2[99]	2418703-16-7	neutralizing single domain antibody	same as above	IC_{50} = 0.41 μg/ml
sdAbs 3F11[99]	2418703-17-8	neutralizing single domain antibody	same as above	IC_{50} = 0.43 μg/ml
sdAbs 4D8[99]	2418703-18-9	neutralizing single domain antibody	same as above	IC_{50} = 0.45 μg/ml
sdAbs 5F8[99]	2418703-19-0	neutralizing single domain antibody	same as above	IC_{50} = 0.24 μg/ml
mAb 47D11[100]	2418702-72-2	neutralizing antibody	inhibition SARS-CoV-2 infection in Vero E6 cells in neutralization assay	IC_{50} = 0.57 μg/ml
			ELISA-based binding affinity for the ectodomain of SARS-CoV-2 S protein	EC_{50} = 0.15 μg/ml
			binding kinetics measured by biolayer interferometry	K_d = 0.75 nM
IgG1 ab1[121]	2418702-71-1	neutralizing antibody	neutralization activity assessed in luciferase reporter gene assay	IC_{50} = 200 ng/ml
			binding kinetics to RBD-Fc measured by sensorgrams	K_d = 0.16 nM
S309[122]	2418702-70-0	neutralizing antibody	neutralization assay of SARS-CoV-2 infection in Vero E6 cells	IC_{50} = 79 ng/ml

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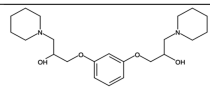
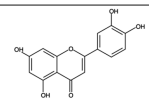
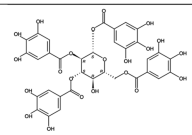
Table 8. continued

Substance	CAS Registry Number	Type of Molecule (Sequence/Structure)	Bioassay Information	Activity Measure
Substances with inhibitory effect in SARS-CoV studies				
VE607[80]	100434-29-5		function assay of S protein-ACE2-mediated entry of SARS-CoV into 293T cell line	EC_{50} = 3 μM
luteolin[80]	491-70-3		function assay of S protein-ACE2-mediated entry of SARS-CoV into Vero E6 cell line	EC_{50} = 9.02 μM
tetra-*O*-galloyl-β-*D*-glucose/TGG[80]	79886-50-3		same as above	EC_{50} = 2.86 μM
P1 (HR2 1153-1189)[127]	1115413-79-0	GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYE	SARS-CoV fusion (F) and infection (I) in HeLa cells expressing S protein and ACE2	IC_{50} = 0.62 μM (F) IC_{50} = 3.04 μM (I)
P4 (HR2 1153-1182)[127]	1114935-17-9	GINASVVNIQKEIDRLNEVAKNLNESLIDL	same as above	IC_{50} = 0.80 μM (F) IC50 = 3.17 μM (I)
P6 (HR2 1153-1175)[127]	1114935-14-6	GINASVVNIQKEIDRLNEVAKNL	same as above	IC_{50} = 1.04 μM (F) IC_{50} = 2.28 μM (I)
N46 (902-947)[127]	1115413-12-1	QKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQ	SARS-CoV fusion in HeLa cells expressing S protein and ACE2	IC_{50} = 3.97 μM
N46eg (902-947)[127]	1115413-38-1	QNQSANQFQKEISQINEVLTTTNTSLGKLQDDVNQNNQSLNTLQKE	same as above	IC_{50} = 5.07 μM
SP-4 (192-203)[128]	882157-75-7	GFLYVYKGYQPI	SARS CoV S protein binding to ACE2 in Vero E6 cells	IC_{50} = 4.30 μM
SP-8 (483-494)[128]	882157-83-7	FYTTTGIGYQPY	same as above	IC_{50} = 6.99 μM
SP-10 (668-679)[128]	882157-88-2	STSQKSIVAYTM	same as above	IC_{50} = 0.002 μM
SP-10-1 (648-659)[128]	2417311-17-0	CDIPIGAGICAS	same as above	IC_{50} > 0.02 μM
SP-10-2 (660-671)[128]	2417311-18-1	YHTVSLLRSTSQ	same as above	IC_{50} = 0.006 μM
SP-10-3 (664-675)[128]	1348040-05-0	SLLRSTSQKSIV	same as above	IC_{50} = 0.005 μM
SP-10-4 (672-683)[128]	1349017-97-5	KSIVAYTMSLGA	same as above	IC_{50} = 0.002 μM
SP-10-5 (676-687)[128]	2417311-19-2	AYTMSLGADSS	same as above	IC_{50} > 0.02 μM

S-protein−ACE2 interaction-mediated SARS-CoV entry and SARS-CoV plaque formation.[123] The flavonoid luteolin has been reported to bind to the S protein and inhibit SARS-CoV entry into host cells.[124,125] It also has anti-inflammatory and 3CLpro inhibition activities.[126]

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,[129] 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.[130,131] In addition, the plant-derived flavonoids myricetin and scutellarein, which are both found in tea, have been shown as active inhibitors with low toxicity.[132,133] Unlike the above mentioned inhibitors, SSYA10−001 demonstrated helicase inhibition without affecting the cellular ATPase activity.[134]

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.[7] 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, dimethylcurcin, and CAS RN 2031161−35−8 are nonsteroidal antiandrogen drugs that were shown to inhibit TMPRSS2 expression.[137] Since TMPRSS2 is an androgen-regulated gene that is overexpressed in prostate cancer,[138] speculation has arisen that higher androgen levels could be the reason for more severe outcomes in men with COVID-19.[139] 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.[140] Finally, compounds MI460 and CAS RN 944925−37−5 may also inhibit proinflammatory cytokines and block blood coagulation-related factors, respectively.[141,142]

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

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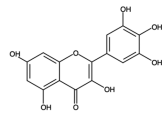
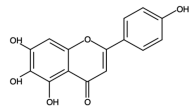
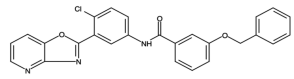
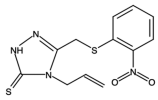
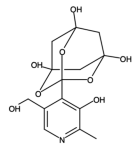
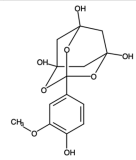
Table 9. Small-Molecule Inhibitors of Helicase/NTPase[80,123,130,133,135,136]

Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure (μM)
myricetin[133]	529-44-2		ATPase activity	IC_{50} = 2.71
scutellarein[133]	529-53-3		ATPase activity	IC_{50} = 0.86
HE602[123]	353488-07-0		ATPase activity	IC_{50} = 6.9
SSYA10-001[135]	675104-49-1		dsDNA unwinding activity	IC_{50} = 5.3
			RNA unwinding activity	IC_{50} = 5.7
			SARS-CoV replicon assay	EC_{50} = 8.95
			cytotoxicity assay	CC_{50} => 250
bananin[80,130,136]	665026-57-3		ATPase activity	IC_{50} = 2.3*
			cytotoxicity assay in Vero cells	CC50 = 785.0
			helicase FRET assay	IC_{50} = 3*
vanillinbananin[80,136]	858956-96-4		ATPase activity	IC_{50} = 0.68
			helicase FRET assay	IC_{50} = 2

[a]"*": multiple activity measure values for one substance are from multiple references.

cleaves the multibasic motif (RX(K/R)R↓) and activates/inactivates a variety of proteins including hormones, cytokines, and enzymes.[145] 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.[146,147] 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.[148] 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 1788032−54−1,[145] improved the potency of furin inhibition. Other examples are peptide inhibitors and peptidomimetics that were synthesized based on the RARRRKKRT inhibitory scaffold[148] and the potent furin inhibitor Dec-RVKR-CMK that was shown to inhibit cleavage and viral replication in Vero cells.[149]

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.[150] 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.[151] 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.[152] In addition, baicalein has antibacterial and anti-inflammatory activities.[79] 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.

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

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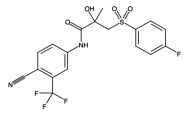
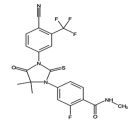
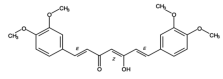
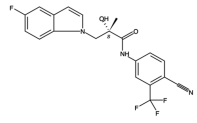
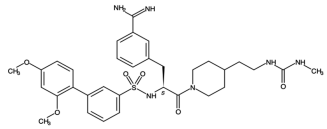
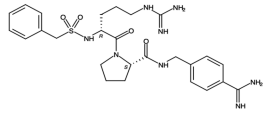
Table 10. Small-Molecule Inhibitors of Human Protease TMPRSS2[137,143,144]

Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure (μM)
bicalutamide[137]	90357-06-5		function assay/expression of TMPRSS2 gene in LNCaP cell	IC_{50} = 0.831
enzalutamide[137]	915087-33-1		same as above	IC_{50} = 0.072
dimethylcurcin[137]	52328-98-0		same as above	IC_{50} > 10
(αS)-N-[4-cyano-3-(trifluoromethyl)phenyl]-5-fluoro-α-hydroxy-α-methyl-1H-indole-1-propanamide[137]	2031161-35-8		same as above	IC_{50} = 0.013
MI460[143]	1420977-03-2		recombinant TMPRSS2 expressed in E. coli BL21 (DE3) with D-cyclohexylalanine-PRO-ARG-AMC as substrate	K_i = 0.001
N2-[(phenylmethyl)sulfonyl]-D-arginyl-N-[[4-(aminoiminomethyl)phenyl]methyl]-L-prolinamide[144]	944925-37-5		TMPRSS2 expressed in E.coli using D-CHA-GLY-ARG-pNA substrate	K_i = 0.003

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.[165] 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.[166] 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.[167] 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.[168] Moreover, melatonin was identified by the network medicine approach as showing a

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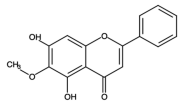
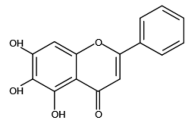
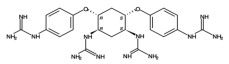
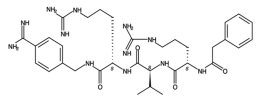
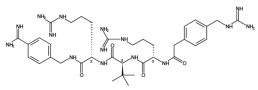
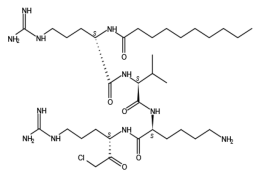
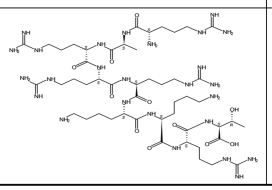
Table 11. Small-Molecule and Peptide Inhibitors of Human Protease Furin[145,153−158]

Substance	CAS Registry Number	Molecular Structure	Bioassay Information	Activity Measure (μM)
oroxylin A[153]	480-11-5		recombinant soluble human furin with Boc-RVRR-MCA as substrate	K_i = 3.3 IC_{50}= 4.8
baicalein[154]	491-67-8		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[(aminoiiminomethyl)amino]-1,3-cyclohexanediyl]bis(oxy-4,1-phenylene)]bis[guanidine][150,155]	922732-52-3		recombinant vaccinia expressed furin using fluorescent substrate Pyr-RTKR-MCA	K_i = 0.012 CC_{50} >250
phenylacetyl-Arg-Val-Arg-4-amidinobenzylamide[156]	1206473-15-5		human recombinant furin with pyroGlu-Arg-Thr-Lys-Arg-AMC as substrate	K_i = 0.001
			human recombinant soluble furin using Phac-Arg-Val-Arg-Arg-AMC as substrate	K_i = 0.66
N2-[2-[4-[[(aminoiiminomethyl)amino]methyl]phenyl]acetyl]-L-arginyl-3-methyl-L-valyl-N-[[4-(aminoiiminomethyl)phenyl]methyl]-L-argininamide[145]	1788032-54-1		same as above	K_i = 0.006
decanoyl-Arg-Val-Lys-Arg-chloromethylketone (Dec-RVKR-CMK)[157]	150113-99-8		inhibition of human furin using Boc-RVRR-AMC as a substrate	K_i = 0.002 CC_{50} = 712.9
RARRRKKRT[158]	1104196-79-3		human recombinant furin with Pyr-RTKR-AMC as substrate	K_i = 0.011

significant association with reduced likelihood of SARS-CoV-2-positive test results.[169] In addition, Zeng et al. demonstrated that deep learning is a powerful methodology to prioritize existing drugs for further investigation.[170] 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.[171] 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.[172] Since COVID-19 is often characterized by exaggerated inflammatory responses, anti-

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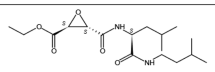
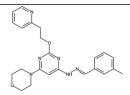
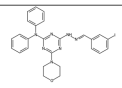
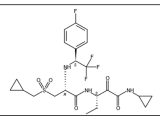
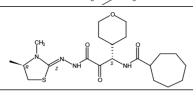
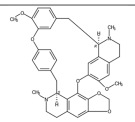
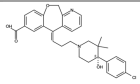
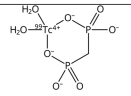
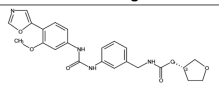
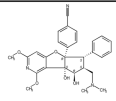
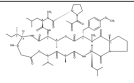
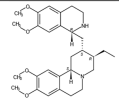
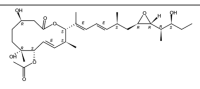
Table 12. Small Molecules and Biologics Targeting Other Human Proteins Involved in SARS-CoV-2 Infection[5,15,40,49,52,55,159−164]

Substance	CAS Registry Number	Molecular Structure	Known Protein Target	Bioassay Information	Activity Measure
Drug or drug candidate inhibiting host proteins involved in viral entrance					
teicoplanin[159]	61036-62-2	N.A.	cathepsin L	luciferase assay	IC_{50} = 1.66 μM
E64d[160]	88321-09-9		thiol protease and cathepsin B, H and L	cell infection assay	N.A.
apilimod[15,161]	541550-19-0		PIKfyve	cell infection assay	EC_{50} = 0.023 μM
vacuolin-1[161]	351986-85-1		PIKfyve	cell infection assay	N.A.
VBY-825[15]	1310340-58-9		Cathepsins	cell infection assay	EC_{50} = 0.3 μM
ONO-5334[15]	868273-90-9		Cathepsin K	cell infection assay	EC_{50} = 0.5 μM
meplazumab[40]	2413715-21-4	antibody	CD147	cell infection assay	EC_{50} = 24.86 μg/ml
				binding assay	IC_{50} = 15.16 μg/ml
Drug or drug candidate inhibiting host inflammatory response					
AMY-101[49]	2108782-47-2	N.A.	Complement C3	clinical study in patients	N.A.
cepharanthine[162]	481-49-2		anti-inflammatory/viral attachment	cell infection assay	IC_{50} = 0.35 μM
MLN-3897[15]	1010731-97-1		CCR1	cell infection assay	EC_{50} = 0.14 μM
99mTc-MDP[163]	121524-79-6		anti-inflammatory	clinical study in patients	N.A.
dornase alfa[164]	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					
merimepodib[52]	198821-22-6		IMPDH	cell infection assay	Inhibition 10 μm
zotatifin[5]	2098191-53-6		EIF4A1	enzyme activity assay	IC_{50} = 1.5 nM
plitidepsin[5]	137219-37-5		EIF1AX	clinical study in patients	N.A.
emetine[55]	483-18-1		40S ribosome protein S14	cell infection assay	IC_{50} = 0.52 μm
pladienolide b[55]	445493-23-2		splicing factor SF3B1	cell infection assay	IC_{50} = 0.007 μm

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.[173]

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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 positive-stranded ssRNA viruses, Table S5: inhibitors of helicase/NTPase in SARS-CoV, Table S6: inhibitors of human proteaseTMPRSS2, Table S7: inhibitors of human protease furin (XLSX)

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Notes

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