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Drug repurposing approach to combating coronavirus: Potential drugs and drug targets

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Abstract

In the past two decades, three highly pathogenic human coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus, and, recently, SARS-CoV-2, have caused pandemics of severe acute respiratory diseases with alarming morbidity and mortality. Due to the lack of specific anti-CoV therapies, the ongoing pandemic of coronavirus disease 2019 (COVID-19) poses a great challenge to clinical management and highlights an urgent need for effective interventions. Drug repurposing is a rapid and feasible strategy to identify effective drugs for combating this deadly infection. In this review, we summarize the therapeutic CoV targets, focus on the existing small molecule drugs that have the potential to be repurposed for existing and emerging CoV infections of the future, and discuss the clinical progress of developing small molecule drugs for COVID-19.

Keywords

anti-CoV; coronavirus; COVID-19; drug repurposing; drug targets; MERS-CoV; SARS-CoV; SARS-CoV-2; small molecule drugs

1 | INTRODUCTION

Coronaviruses (CoVs) are a large family of enveloped and nonsegmented positive-sense RNA viruses which can infect a wide range of hosts, including human and animals.[1] CoVs belong to the family *Coronaviridae* of the order *Nidovirales* and can be classified into four genera (alpha, beta, gamma, and delta).[2] Human coronaviruses (HCoVs) were first

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CONFLICT OF INTERESTS

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discovered in the 1960s and since, there have been seven identified HCoVs, including two α-CoVs, HCoV-229E and HCoV-NL63, as well as five β-CoVs HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.[1–4] All HCoVs are believed to cross species barriers and emerge originally as zoonoses.[4–7] Human strains HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 usually cause mild symptoms of common cold.[8] However, in the past two decades, three highly pathogenic HCoVs, SARS-CoV, MERS-CoV, and SARS-CoV-2, have emerged with human-to-human transmission, causing severe acute respiratory diseases with alarming morbidity and mortality.[2,9]

SARS-CoV emerged initially in southern China in November 2002 and spread to 29 countries and regions through international air travel, resulting in 8098 cases and 774 deaths with a fatality rate of 9.6% by the end of the pandemic in July 2003.[10] MERS-CoV was first identified in Saudi Arabia in 2012. Dromedary camels are the major reservoir host for MERS-CoV which are involved in direct or indirect transmission to humans.[1,11–14] At the end of January 2020, there were a total of 2519 laboratory-confirmed cases including 866 associated deaths (34.3% of cases) reported in 27 countries, the majority of which were reported from Saudi Arabia (2106 cases including 783 associated deaths).[15] At the end of 2019, the third highly pathogenic HCoV, named SARS-CoV-2 (2019-nCoV), was reported in Wuhan, China, as the cause of coronavirus disease 2019 (COVID-19) outbreak.[16] Human-to-human transmission of SARS-CoV-2 was confirmed, mainly through respiratory droplets and indirect contact via contaminated surfaces.[17–19] Most people with COVID-19 suffer mild to moderate respiratory illness and recover without special treatment; however, older people and those with comorbidities such as cardiovascular disease and diabetes are more likely to develop severe disease with high mortality.[20] Although SARS-CoV-2 possesses a relatively lower case-mortality rate as compared with SARS-CoV and MERS-CoV, it can be transmitted more efficiently, even by infected people in mild condition or asymptomatic carriers, making it challenging to control.[21,22] The World Health Organization declared the COVID-19 outbreak a public health emergency of international concern on January 30 and a pandemic on March 11, 2020, successively. As of November 29, 2020, there are more than 61 million reported cases of COVID-19, including more than 1,448,990 deaths in over 180 countries and regions.[23] Despite the significant clinical impact and the availability of very recently FDA-approved Veklury (remdesivir), there remains an urgent need for more approved antiviral therapeutics effective for CoV infections.

Developing new highly effective anti-CoV drugs may require several years of drug development efforts. However, facing the urgency of the ongoing pandemic COVID-19, screening the existing broad-spectrum antiviral drugs or other drugs targeting viral or host proteins involved in the virus life cycle may serve as a fast and efficient approach for combating this deadly infection.[1] This repurposing strategy offers diverse advantages over de novo drug discovery including a less time-consuming development process, reduced costs and risks, as well as available pharmacokinetic (PK) and safety profiles.[24] In this review, we discuss the potential drugs and drug targets against CoV, focusing on the existing small molecule drugs that may be repurposed for existing and emerging CoV infections of the future, and highlight the clinical progress in developing small molecule drugs for the ongoing pandemic of COVID-19.

2 | CORONAVIRUS TARGETS FOR DRUG DEVELOPMENT

2.1 | Coronavirus genomes and structures

Coronaviruses possess a positive-sense, single-stranded RNA genome, and a helically symmetrical nucleocapsid. The RNA genome contains a 5′-methylated cap and a 3′-polyadenylated tail ranging from 26.4 to 31.7 kb in size.[25,26] CoVs share similar genome organization of 5′-leader-UTR-replicase (ORF1a/b)-spike (S)-envelop (E)-membrane (M)-nucleocapsid (N)-3′-UTR-poly(A) tail (Figure 1).[1,27,28] The open reading frames (ORFs) 1a and 1b take up two-thirds of the genome and encode two large replicase-transcriptase polyproteins (pp1a and pp1ab).[26] Self-cleavage of pp1a and pp1ab produces 16 nonstructural proteins (nsp1–16), including two viral cysteine proteases, nsp3 (papain-like protease [PL^{pro}]) and nsp5 (3C-like or main protease [$3CL^{pro}$]), nsp12 (RNA-dependent RNA polymerase [RdRp]), nsp13 (helicase) and other nsps with known or unknown functions which are likely involved in viral transcription and replication.[26,29–31] The later ORFs encode four main structural proteins: S, E, M, and N proteins and accessory proteins, the number and function of which may vary depending on specific CoV.[26] The S protein is a class I fusion protein that comprises two subunits, the amino-terminal receptor-binding S1 and carboxy-terminal membrane fusion S2.[32] It forms homotrimers which make up the spike structure on the viral surface and mediates host attachment and membrane fusion during entry, determining host range and cell tropism.[33] The E and M proteins play an important role in forming the viral envelope and maintaining its structural shape, whereas the E protein also has ion channel activity required for pathogenesis.[26,34] The N protein is the only protein that exists in the nucleocapsid. It contains two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), and both domains can bind to RNA by using different mechanisms. The N protein was found to be involved in processes associated with viral genome and replication cycle as well as host cellular response to viral infections.[35,36]

2.2 | Life cycle and key targets

The CoV life cycle includes several essential steps, which can be targeted for the development of anti-CoV therapeutics. The first step is viral entry that is initiated by the binding of the surface S1 unit of the S protein to a cellular receptor (Figure 2).[26,28,37] The S1 subunit consists of two independent domains, NTD and CTD. Most CoVs, such as SARS-CoV and MERS-CoV, use CTD as the receptor binding domain (RBD).[38] Many CoVs recognize peptidases as their cellular receptors and cell entry even occurs without the enzymatic domain of these proteins; however, the molecular mechanism of virus entry remains elusive.[39] SARS-CoV and SARS-CoV-2 utilize angiotensin-converting enzyme 2 (ACE2) as their cellular receptors,[40,41] whereas MERS-CoV binds to dipeptidyl peptidase 4 (DPP4) for virus entry.[42] Once RBD of the S1 subunit binds to the host receptor, it will induce conformational changes in the S2 subunit (the stalk region of S), approximate viral and cell membrane via inserting the fusion peptide of S2 into target cell membrane, and finally enable fusion.[1,43] This process requires two proteolytic cleavages by host proteases, including priming cleavage at the S1/S2 junction site for separating the RBD and fusion domains of the S1/S2 proteins and activating cleavage at the S2′ site for exposing the fusion peptide.[38,44,45] These host receptors (ACE2 and DPP4), RBD of the S1 subunit and the S2 subunit can serve as potential anti-CoV targets, but anti-CoV therapeutics such as

monoclonal antibodies (mAbs) and antiviral agents targeting these proteins should avoid inducing immunopathological effects and antibody-dependent enhancement.[46]

CoVs were found to utilize the endosomal pathway and/or the cell surface nonendosomal pathway for host cell entry.[1] In the endosomal pathway, the pH-dependent endosomal cysteine protease cathepsins mediate the proteolytic processing that, together with low pH, overcomes the energetic barrier for fusion and facilitates CoV cell entry.[47–49] In addition, other host protease, such as transmembrane protease serine 2 (TMPRSS2) and TMPRSS11D (also known as airway trypsin-like protease), were reported to activate S protein for cell surface nonendosomal virus entry at the plasma membrane via cleaving S into the S1 and S2 subunits.[50] Accumulated studies showed CoVs enter the cell directly from the cell surface in the presence of protease such as TMPRSS2 and trypsin.[41,51,52] Inhibitors targeting these host proteases such as cathepsins and TMPRSS2 are also potential anti-CoV agents and their combination use is a rational strategy to fully block the entry of CoVs by inhibiting both endosomal and nonendosomal entry pathways.[41,53]

After cell entry, CoVs disassemble and release the nucleocapsid and viral RNA into the cytoplasm followed by translation of ORF1a/b into viral pp1a and pp1ab.[26] The polyproteins pp1a and pp1ab are self-cleaved by PL^{pro} and $3CL^{pro}$ which are encoded within nsp3 and nsp5, respectively, and subsequently produce nsp1 to nsp16.[1,26] Many of these nsps form replicase-transcriptase complex (RTC) for viral RNA synthesis of which the core component is the catalytic subunit of RdRp (nsp12).[54] RTC transcribes the full-length positive genomic RNA to form a full-length negative-strand template and overlapping subgenomic negative-strand templates for synthesis of genomic and subgenomic RNAs, respectively.[1,26] Positive-sense subgenomic RNAs are subsequently translated to afford structural and accessory proteins. Structural proteins S, E, and M are then moved to endoplasmic reticulum-Golgi intermediate compartment (ERGIC) and interact with the helical nucleocapsid which is originally produced by the assembly of the N protein with genomic RNA in the cytoplasm, finally resulting in the form of mature virions.[28] The viral life cycle is completed once the assembled virions are transported to the cell surface and released through exocytosis.[28]

These nsps and structural proteins, E, M, and N, are also potential targets for anti-CoV drug discovery.[55] $3CL^{pro}$ and RdRp are of particular interest and substantial efforts have been made towards these two targets.[56,57] $3CL^{pro}$ is conserved among CoVs and has no human homolog, making it an ideal anti-CoV target.[58] Currently, the crystal structures of SARS-CoV-2 $3CL^{pro}$ with peptide-aldehyde inhibitors (PDB: 6LZE and 6M0K) or peptide with a Michael receptor **N3** (PDB: 2H2Z) have been solved which are anticipated to facilitate the design and development of other $3CL^{pro}$ inhibitors through molecular docking studies (Figure 3A).[58,59] RdRp plays an essential role in viral replication and transcription and is a major target of many existing drugs of the nucleotide class.[57] The cryo-EM structures of SARS-CoV-2 RdRp either in the apo form (PDB: 7BV1 and EMDB: EMD-30209) or in complex with a template-primer RNA and remdesivir (PDB: 7BV2 and EMDB: EMD-302010) have also been determined, providing excellent models to elucidate how RdRp inhibitors work and also solid templates for modeling and optimizing the existing nucleotide drugs (Figure 3B).[60]

3 | VIRUS-BASED SMALL MOLECULE DRUGS FOR CORONAVIRUS

3.1 | Protease inhibitors

Lopinavir (**1**; Figure 4) and ritonavir (**2**) are antiretroviral drugs of the protease inhibitor class and widely used as a fixed dose combination medication named Kaletra to treat and prevent human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).[61] Typically, ritonavir is used at a lower dose to inhibit the enzyme cytochrome P450–3A4 (CYP3A4) and decrease the metabolism of other combined protease inhibitors including lopinavir. Studies have shown that lopinavir inhibits the replication of SARS-CoV and MERS-CoV with single-digit micromolar EC_{50} values (Table 1) which are in the range of the plasma concentration (8–24 μM) of lopinavir observed in AIDS patients.[62–64] Lopinavir and ritonavir were postulated to inhibit SARS-CoV $3CL^{pro}$ and treatment of lopinavir/ritonavir (LPV/r) alone or combined with ribavirin was associated with improved clinical outcomes in nonrandomized trials of SARS patients.[65–67] LPV/r administration also improved outcome of MERS infection in a nonhuman primate model[68] and a randomized controlled trial of LPV/r and interferon β1b (IFN-β1b; interferons are a group of signaling proteins which can be released by a virus-infected cell and help nearby cells to strengthen their antiviral defenses) for MERS treatment has been underway in Saudi Arabia since November 2016.[69] Recently, lopinavir was reported to inhibit SARS-CoV-2 induced cytopathic effect (CPE) with an half-maximal inhibitory concentration (IC_{50}) value of 9.12 μM[70] and multiple clinical trials of LPV/r treatment for COVID-19 have been initiated. However, a retrospective study that has enrolled 199 adult patients with severe COVID-19 revealed that there was no significant difference between LPV/r-treated group ($n = 99$) and control group with standard care ($n = 100$) in clinical improvement, mortality, and reducing viral loads.[71] Delayed treatment initiation may partially account for the ineffectiveness of LPV/r for COVID-19 treatment. Thus, more clinical data are still needed to confirm or exclude the possibility of a treatment benefit of LPV/r for COVID-19 patients.

Compounds **3**–**6** are also antiretroviral medications that are used to treat HIV infections as protease inhibitors. Nelfinavir (**3**) was found to inhibit the replication of SARS-CoV and SARS-CoV-2 in Vero E6 cells with EC_{50} values of 0.048 and 2.89 μM, respectively.[72,73] When treating patients with nelfinavir at an oral dose of 1875 mg BID, high peak and trough serum concentrations (13.3 and ~5.5 μM, respectively) were observed,[74] higher than its in vitro EC_{50} values against SARS-CoV-2, indicating its therapeutic potential to combat COVID-19. Recently, atazanavir (**4**) was reported to inhibit SARS-CoV-2 replication in Vero and A549 cells with EC_{50} values of 2.0 and 0.22 μM, respectively. It also suppresses cell death and proinflammatory cytokine production in SARS-CoV-2-infected monocytes.[75] Whereas, to date, no in vitro antiviral activities against SARS-COV-2 were reported for darunavir (**5**) and ASC09 (**6**), several clinical trials have been launched to evaluate the efficacy of darunavir/cobicistat, ASC09/ritonavir (ASC09F), and ASC09F/oseltamivir for treatment of COVID-19. Recently, a single-center, randomized, and open-label trial involving 30 patients with mild COVID-19 revealed that a 5-day treatment of darunavir/cobicistat did not increase the proportion of negative conversion at Day 7 compared with standard care alone.[76] It should be noted that HIV protease belongs to the aspartic protease family and its inhibitors were designed to fit its C2 symmetric catalytic site that is lacked in

the cysteine proteases, CoV $3CL^{pro}$ and PL^{pro}.[77] It remains questionable whether HIV protease inhibitors could effectively inhibit $3CL^{pro}$ or PL^{pro} of SARS-CoV-2.

Boceprevir (**7**) is an NS3 serine protease inhibitor of hepatitis C virus (HCV) which was used to treat hepatitis caused by HCV genotype 1.[78] It inhibits SARS-COV-2 $3CL^{pro}$ with an IC_{50} of 4.13 μM but was not active against the enterovirus A71 (EV-A71) 2A and 3C cysteine proteases (IC_{50} > 20 μM).[79] Boceprevir showed potent antiviral activity against SARS-CoV-2 (EC_{50} = 1.9 μM) in a CPE assay meanwhile displaying low cytotoxicity (CC_{50} > 100 μM), indicating its great potential in COVID-19 treatment. Disulfiram (**8**) is an Food and Drug Administration (FDA)-approved drug used as a second-line treatment of alcohol dependence.[80] It irreversibly inhibits acetaldehyde dehydrogenase (ALDH1A1) by covalently modifying the cysteine residue of the active site and causes uncomfortable hangover symptoms after alcohol consumption.[81] Recent studies showed disulfiram inhibits PL^{pro} of SARS-CoV and MERS-CoV with micromolar IC_{50} values, acting as a competitive (or mixed) inhibitor and an allosteric inhibitor, respectively.[82] Disulfiram exhibited synergistic inhibition with 6-thioguanine or mycophenolic acid (MPA) against MERS-CoV PL^{pro}. Interestingly, disulfiram was also reported to inhibit SARS-CoV-2 $3CL^{pro}$ activity with an IC_{50} value of 9.35 μM.[59] However, the in vitro anti-CoV activity of disulfiram remains to be demonstrated. Ebselen (**9**) is a seleno-organic drug, which can mimic glutathione peroxidase activities and react with peroxynitrite. It possesses anti-inflammatory, antioxidant, antifungal, and cytoprotective properties[83,84] and has been investigated to treat various human conditions such as reperfusion injury[85] and hearing loss.[86] Recently, ebselen was screened out as a potent SARS-CoV-2 $3CL^{pro}$ Mpro inhibitor (IC_{50} = 0.67 μM) and displayed inhibition against SARS-CoV-2 with an EC_{50} value of 4.67 μM in Vero E6 cells using a plaque reduction assay.[59] Cinanserin (**10**) is an antagonist of 5-HT_{2A} and 5-HT_{2C} receptors discovered in the 1960s.[87] It was found to inhibit SARS $3CL^{pro}$ (IC_{50} = 5 μM) and treatment of Vero cells with cinanserin (50 μg/ml) resulted in more than 3log reduction in SARS-CoV RNA production with nontoxic effect.[88] Cinanserin also displays moderate inhibition against SARS-CoV-2 with an EC_{50} of 20.61 μM.[59] Nevertheless, long-term treatment of cinanserin at a high dose (120 mg/kg daily for 59–81 weeks) in rats led to malignant hepatoma.[89] Thus, this molecule may serve as a lead compound for the development of highly effective CoV $3CL^{pro}$ inhibitors with reduced toxicity and antiserotonin activity.

3.2 | Nucleic acid synthesis inhibitors

3.2.1 | RdRp inhibitors—Ribavirin (**11**; Figure 5) is a guanosine nucleoside analog which displays antiviral activity against a wide range of both DNA and RNA viruses in vitro due to its multiple mechanisms of action.[90,91] It has been used to treat respiratory syncytial virus (RSV) infection,[92] HCV infection,[93,94] and some viral hemorrhagic fevers.[95–97] Ribavirin is a prodrug and its metabolized form mimics purine RNA nucleotides and interferes with RNA metabolism required for viral replication by inhibiting messenger RNA (mRNA) capping and viral RNA polymerase and inducing mutations via incorporation into RNA.[91,98,99] Owing to its broad antiviral properties, ribavirin was widely investigated during the SARS and MERS outbreaks. It inhibits the replication of SARS-CoV and MERS-CoV in Vero cells with EC_{50} values of 80 μg/ml (HKU39489) and 41.4 μg/ml (hCoV-EMC/

2012), respectively.[100,101] High-dose treatment of ribavirin as a monotherapy or in combination with corticosteroid or LPV/r was used for SARS patients,[102] but a retrospective, uncontrolled cohort analysis involving 229 cases in Singapore indicated that use of ribavirin did not appear to confer any benefit for SARS patients. Therefore, its clinical benefit remained uncertain.[102–105] Cotreatment of ribavirin and IFN-α2b improves outcome in MERS-CoV-infected rhesus macaques,[106] but no obvious survival benefit was observed in small cohorts of MERS patients.[107–109] Ribavirin was also reported to inhibit the replication of SARS-CoV-2 at high concentration, with an EC_{50} of 109.5 μM.[110] One clinical trial of ribavirin, LPV/r and IFN-β2b combination for COVID-19 treatment has been completed with no reported results yet. However, high-dose ribavirin treatment was associated with significant toxicity such as hemolysis and hemoglobin decrease which hampers its wide clinical application in severe CoV-infected patients.[105]

Remdesivir (**12**, **GS-5734**) is a broad-spectrum antiviral agent of an adenosine analogue that is highly effective against filoviruses, paramyxoviruses, RSV, and pathogenic CoVs.[111,112] It is a phosphoramidate prodrug and metabolized into the active triphosphate form (GS-441524) that inhibits viral RNA polymerase and causes delayed chain termination of nascent viral RNA.[113,114] Remdesivir was originally developed by Gilead Science to combat Ebola virus (EBOV) infection. It inhibits EBOV replication in multiple relevant human cell types with nanomolar to submicromolar EC_{50} values. Although its use achieved significant survival benefit in a rhesus monkey model of EBOV disease (EVD),[115,116] a retrospective analysis involving 673 patients with EVD revealed that the groups with mAb REGN-EB3 or MAb114 administration showed better survival rates than the groups treating with ZMapp or remdesivir.[117] Remdesivir effectively inhibits a wide range of human and zoonotic CoV replication in human airway epithelial (HAE) cells and displays EC_{50}s of 0.069 μM for SARS-CoV and 0.074 μM for MERS-CoV.[114] Both prophylactic and early therapeutic administration of remdesivir reduced lung viral load and improved clinical signs of disease as well as respiratory functions in a SARS-CoV infected mouse model.[112] Similar efficacy was also observed for prophylactic and therapeutic remdesivir treatment in a mouse model and a nonhuman primate (rhesus macaque) model of MERS-CoV infection, respectively.[118,119] As a broad anti-CoV agent, remdesivir was found to inhibit SARS-COV-2 replication in Vero E6 cells with an EC_{50} of 0.77 μM, acting as an RdRp inhibitor as well.[110,120,121] Due to its available PK and safety profiles as well as potent in vitro antiviral activity against SARS-CoV-2, remdesivir was fast advanced into human clinical trials in several countries such as China and the United States to treat COVID-19. Recently, a retrospective study showed compassionate-use of remdesivir was associated with clinical improvement in 36 of 53 patients with COVID-19.[122] However, another randomized, double-blind, placebo-controlled, multicenter study which enrolled 237 adult patients with severe COVID-19 revealed that remdesivir treatment was not associated with significant clinical benefits.[123] Contrarily, according to the final report of a double-blind, randomized, placebo-controlled trial involving 1063 patients hospitalized with COVID-19, patients (538/1063) receiving remdesivir showed a shortened recovery time of 11 days as compared with 15 days of the control group (521/1063) receiving placebo.[124] A press release from Gilead reported that, in a comparative analysis of the phase 3 SIMPLE-Severe trial and a real-world retrospective cohort of patients with severe COVID-19, treatment of remdesivir resulted in an

improvement in clinical recovery and a 62% reduction in mortality compared with standard of care.[125] Very recently, a randomized clinical trial involving 596 patients with moderate COVID-19 showed that patients receiving 5-day treatment course of remdesivir had significantly higher odds of a better clinical status distribution on Day 11 than those receiving standard care, but no statistically significant difference in clinical status on Day 11 was observed between the group receiving 10-day course of remdesivir and the control receiving standard care.[126] Thus, the clinical benefit of remdesivir for COVID-19 remains to be validated by more data from the ongoing human phase 3 randomized, double-blind, placebo-controlled clinical trials.

Through a dual-pathogen high-throughput screening campaign, EIDD-1931 (**13**, NHC), a pyrimidine ribonucleoside analogue, was identified as a potent inhibitor of RSV, influenza A viruses of human, avian and swine origins, and influenza B viruses.[127] Its active triphosphate form is incorporated into nascent RNA instead of cytidine triphosphate, increasing the chance of viral mutagenesis. This incorporation may also reduce viral RNA polymerase processivity and/or increase the frequency of delayed chain termination. EIDD-2801 (**14**) was developed as an isopropylester prodrug of EIDD-1931 that was orally bioavailable and showed broad ant-influenza virus activity in cultured cells and good in vivo efficacy in the ferret model of influenza infection with high resistance barrier.[128] EIDD-1931 is also highly effective against multiple zoonotic CoVs in HAE cell cultures associated with increased viral mutation rates and shows EC_{50}s of 0.3 μM against SARS-CoV-2 in Vero E6 cells and 0.08 μM against MERS-CoV in Calu-3 cells respectively.[129] Both prophylactic and therapeutic administration of its prodrug EIDD-2801 improved pulmonary function and reduced virus titer and body weight loss in a mouse model of SARS-CoV or MERS-CoV infection. Moreover, EIDD-1931 is active against remdesivir-resistant CoVs as well. These findings together suggested that EIDD-1931 and its prodrug EIDD-2801 have great potential to be developed as a highly effective antiviral to treat MERS, COVID-19 and emerging CoV infections of the future. Currently, two human phase 2 clinical trials with this prodrug EIDD-2801 are ongoing to evaluate its safety, tolerability, and antiviral activity in patients with COVID-19.

Favipiravir (**15**, T-705) is an antiviral drug of a pyrazinecarboxamide derivative which was approved to treat influenza in Japan.[130,131] It is a prodrug which is metabolized to a triphosphate form via intracellular phosphoribosylation targeting viral RNA polymerase. This active form was recognized as an efficient purine nucleoside analogue for incorporation to the RNA, which can lead to lethal mutagenesis. Two consecutive incorporation events efficiently block RNA synthesis.[132–134] Favipiravir does not strongly affect cellular transcription and has a high resistance barrier to influenza virus.[135] However, favipiravir was found inactive against influenza virus A (WSN) in primary human bronchial tracheal epithelial cells, posing a doubt on its efficacy in influenza treatment.[127] In addition to influenza virus, favipiravir was also effective against a wide range of RNA viruses including EBOV and SARS-CoV-2.[110,136–138] It inhibits SARS-CoV-2 replication with an EC_{50} of 61.88 μM in Vero E6 cells.[110] Despite its relatively low in vitro activity against SARS-CoV-2, favipiravir has entered several clinical trials to evaluate its efficacy in COVID-19 treatment. In an open-controlled study, favipiravir/IFN-α treatment group ($n = 35$) showed

better therapeutic effects on COVID-19 in terms of disease progression and viral clearance compared to the control group (n = 45) treated with LPV/r plus IFN-α.[139] In another randomized, controlled, multicenter study involving 240 patients with COVID-19 infection, compared to arbidol (an antiviral medication used to treat influenza infections, see Section 3.3, **24**) group (n = 120), favipiravir treatment (n = 116) did not significantly improve the clinically recovery rate at Day 7, but it shortened the latency to relief for pyrexia and cough and only caused mild and manageable adverse effects.[140] These data support further investigation of the clinical potential of favipiravir for COVID-19 treatment.

Galidesivir (**16**, BCX4430), a novel synthetic adenosine analog, is an antiviral agent, which was developed as a potential treatment for EBOV and Marburg virus (MARV) infection. Its active triphosphate form suppresses viral RNA polymerase function, acting as an RNA chain terminator. Postexposure intramuscular administration of BCX4430 led to significant protection against EBOV and MARV disease in rodent models.[141] Galidesivir displays broad-spectrum antiviral activities against a wide range of viruses including flaviviruses, bunyaviruses, arenaviruses, paramyxoviruses, and CoVs.[141–143] It inhibits SARS-CoV and MERS-CoV replication with EC_{50} values of 57.7 and 68.4 μM, respectively.[141] Additionally, galidesivir was found to bind to SARS-CoV-2 RdRp tightly via molecular docking.[144] Although no in vitro activity against SARS-CoV-2 was reported, it has been advanced into a human phase 1 clinical trial to evaluate its safety, PKs and antiviral effects in COVID-19 treatment.

Penciclovir (**17**) is an antiviral medication of a guanosine analogue, which is used to treat various herpesvirus infections.[145–147] Penciclovir is first mono-phosphorylated by viral thymidine kinase which is a rate-limiting step in its activation. Further phosphorylation by cellular kinase yields the active triphosphate form, thereby inhibiting viral DNA polymerase and leading to chain termination, with less influence on the normal cellular processes.[148] Penciclovir has low toxicity and good selectivity and is often used as a topical treatment due to its poor oral absorption. Through screening existing antiviral drugs, penciclovir was also found to inhibit SARS-CoV-2 replication with an EC_{50} of 95.96 μM in Vero E6 cells.[110]

3.2.2 | Other nucleic acid synthesis inhibitors—MPA (**18**, Figure 6), also called mycophenolate, is an immunosuppressant drug, which is used to prevent draft rejection in organ transplantation and treat Crohn's disease.[149,150] It is commonly administered as the mycophenolate sodium salt form or the prodrug mycophenolate mofetil (**19**, MMF). MPA is a potent, noncompetitive inhibitor of the enzyme inosine-5′-monophosphate dehydrogenase (IMPDH) that catalyzes the de novo synthesis of guanosine-5′-monophosphate (GMP) from inosine-5′-monophosphate (IMP).[151] It inhibits the proliferation of T and B lymphocytes, and antibody formation as well as the glycosylation, expression, and function of adhesion molecules.[150,151] MPA exhibits broad antiviral activities against different viruses such as flavivirus,[152–155] Chikungunya,[156] and HCV.[157,158] MPA was reported to significantly inhibit MERS-CoV replication with EC_{50} values of 0.17 μg/ml and 2.87 μM in different assays.[159,160] However, in a common marmoset model of MERS-CoV infection, MME treatment resulted in a worse outcome with more severe disease and higher viral loads compared to the untreated group.[161] MPA was also found to be inactive against SARS-CoV up to 30 μM in vitro and in a mouse model.[162] In addition, cases were reported that renal

transplant recipients developed severe or fatal MERS when receiving immunosuppressant medication MMF.[163,164] Recently, MPA was reported to be effective against SARS-CoV-2 with an EC_{50} of 0.87 μM.[165] However, it remains to be validated whether treatment with the IMPDH inhibitor MPA really works for CoV infections.

Merimepodib (**20**, VX-497) is another novel, specific, reverse, and noncompetitive IMPDH inhibitor which selectively suppresses lymphocyte proliferation and immunoglobulin production.[166] Merimepodib possesses broad-spectrum antiviral activities,[167–169] highly effective against HCV, hepatitis B viru (HBV), human cytomegalovirus (HCMV), encephalomyocarditis virus (EMCV), and RSV with EC_{50}s ranging from 0.38 to 1.14 μM.[167,170] A phase 2 clinical trial has been completed to evaluate its efficacy in combination with PEG-IFN-β2a and ribavirin for the treatment of chronic hepatitis C. Intriguingly, merimepodib inhibited SARS-CoV-2 replication in vitro in a dose-dependent manner in Vero cells, and pretreatment of merimepodib significantly reduced viral titers (over 1 log) at a concentration of 3.3 μM, offering the potential to treat COVID-19.[171]

Mizoribine (**21**, MZB) is an immunosuppressive drug of an imidazole nucleoside that has been used in renal transplantation, lupus nephritis, and rheumatoid arthritis (RA).[172] MZB is a prodrug which is phosphorylated by adenosine kinase in cells into mizoribine 5′-monophosphate. This active monophosphate form blocks the de novo synthesis of GMP from IMP via inhibiting both IMPDH and GMP-synthetase.[173] It arrests DNA synthesis in the S stage of the cell cycle without incorporation into nucleotides and suppresses lymphocyte proliferation.[174] MZB inhibits SARS-CoV replication in a plaque assay with EC_{50} values of 3.5 μg/ml for strain Frankfurt-1 and 16 μg/ml for strain HKU39849. Meanwhile, it reduces the infectious SARS-CoV titers to one-tenth or less at the concentration of 10 μg/ml in a reduction assay.[100]

Gemcitabine (**22**, dFdC) is a cytosine arabinoside analogue which was used as a first-line treatment in various types of solid tumor such as pancreatic cancer and non-small-cell lung cancer.[175] Gemcitabine is absorbed via nucleoside transporters and first phosphorylated intracellularly by deoxycytidine kinase to yield gemcitabine monophosphate (dFdCMP) as a rate-limiting step.[176] The monophosphate form is then converted to active gemcitabine diphosphate (dFdCDP) and triphosphate (dFdCTP) catalyzed by other kinases. dFdCTP is a DNA polymerase inhibitor and can be incorporated into DNA, resulting in masked chain termination while dFdCDP inhibits ribonucleoside reductase and depletes the deoxyribonucleotide pools necessary for DNA synthesis, subsequently potentiating the effects of dFdCTP.[177] Gemcitabine hydrochloride inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 replication with low toxicity and EC_{50}s of 4.96, 1.22, and 1.24 μM, respectively.[178,179] Notably, dFdCTP could also be incorporated into RNA.[180] These findings together suggest gemcitabine has therapeutic potential to combat COVID-19.

3.3 | Other virus-based inhibitors

Oseltamivir (**23**, Figure 7), brand name Tamiflu, is an orally administered antiviral medication that was used to treat and prevent influenza A and influenza B. It inhibits influenza's neuraminidase enzyme with high selectivity and prevents the release of progeny virions from the infected host cells.[181] Oseltamivir is administered in a prodrug form of

oseltamivir phosphate that is quickly metabolized into the active oseltamivir carboxylate with high bioavailability.[181] Oseltamivir can reduce the severity and duration of the symptoms of influenza and the risk of associated complications when administered within 48 h of the onset of infection.[182–184] A case was reported that a 52-year-old woman with SARS-CoV-2 infection and a history of type 2 diabetes in Taiwan began to receive supportive therapy with oseltamivir and levofloxacin (a broad-spectrum antibiotic of fluoroquinolones) on Day 3 of hospitalization, and on Day 15 her vital signs were stable without oxygen therapy need.[185] Despite the lack of in vitro and in vivo data, several clinical trials have been launched to evaluate the efficacy of oseltamivir as a monotherapy or in combination with other antivirals such as chloroquine and ASC09F for the treatment of COVID-19.

Umifenovir (**24**), brand name Arbidol, is an antiviral drug, which was approved in Russia and China to treat influenza infections.[186,187] It inhibits membrane fusion between virus and targets host cells, blocking viral entry.[188] Arbidol is effective against a wide range of pH-dependent viruses such as EBOV, RSV, and HCV.[189–191] It was reported that arbidol can efficiently inhibit SARS-CoV-2 replication at a concentration of 10–30 μM.[192] Currently, arbidol is undergoing several clinical trials to evaluate its efficacy for COVID-19 treatment. A retrospective cohort study revealed that the combination group (n = 16) treated with arbidol and LPV/r showed more favorable clinical response compared to the control group (n = 17) with only LPV/r treatment.[193] Another retrospective cohort analysis showed that patients with COVID-19 in the arbidol group (n = 16) had a short duration of positive RNA test in comparison with those in the LPV/r group (n = 34).[194] In addition, as mentioned in favipiravir section (Section 3.2), in a randomized clinical trial, no significant difference was observed in clinical recovery rate of Day 7 between arbidol-treated group (62/120) and favipiravir-treated group (71/116).[140] However, a retrospective study including 81 patients with mild COVID-19 indicated that treatment of arbidol (n = 45) did not improve the prognosis or accelerate the clearance of SARS-COV-2 compared to the control with standard care (n = 36).[195]

Rimantadine (**25**) is an orally available antiviral medication of a cyclic primary amine that is used to treat influenza A infection.[196,197] It suppresses the activity of influenza A/M2 ion channel and blocks viral entry, resulting in the inhibition of viral replication.[198–200] Rimantadine also has some NMDA antagonistic activities like amantadine, possessing therapeutic potential to treat Parkinson's disease.[201] Rimantadine inhibits SARS-CoV (HKU39849) replication (EC_{50} = 8–16 μg/ml) in Vero E6 cells,[63] but has no documented in vitro activity against other CoVs.

Resveratrol (**26**) is a natural polyphenol whose food sources mainly include the skin of grapes, blueberries, raspberries, and mulberries.[202] It is a phytoalexin produced by several plants in response to environmental stress such as injury and pathogen infections.[202] Resveratrol displays various pharmacological and physiological properties including anticancer, anti-inflammation, antioxidant, antiviral, and so forth.[203,204] Currently, numerous clinical trials have been conducted to evaluate its efficacy to treat different human conditions. Resveratrol was found to significantly inhibit MER-CoV infection, prolong cellular survival after virus infection, and decrease the expression of nucleocapsid protein.

[204] Recently, resveratrol was also reported to inhibit SARS-CoV-2 infection in Vero E6 cells with an EC_{50} of ~66 μM.[205]

4 | HOST-BASED SMALL MOLECULE DRUGS FOR CORONAVIRUS

4.1 | Protein synthesis inhibitors

Compound **27**–**29** (Figure 8) are protein synthesis inhibitors that target the eukaryotic ribosome. These compounds were found associated with mRNA and transfer RNA (tRNA) binding sits; anisomycin (**27**) and homoharringtonine (**29**) bind to A-site of the peptidyl transferase center while emetine (**28**) interacts with the ribosomal E-site.[206–209] Anisomycin is an antibiotic isolated from cultures of various *Streptomyces* which prevents the release of nascent peptide from the polyribosome, without affecting the formation of aminoacyl transfer ribonucleic acid. Partial inhibition of DNA synthesis is also observed at the presence of anisomycin, likely due to the inhibitory effect on essential protein for DNA synthesis.[210] At low concentration, anisomycin can activate p38-MAPK and c-Jun N-terminal kinase (JNK) signaling pathways.[211] Anisomycin effectively inhibits SARS-CoV and MERS-CoV infection with EC_{50}s of 0.191 and 0.003 μM, respectively.[178]

Emetine is antiprotozoal drug of a natural alkaloid that is also used to induce vomiting.[212] Emetine displays broad-spectrum antiviral activities, effective against Zika virus (ZIKV), EBOV, CoV, HIV-1, and so forth.[213] Emetine significantly inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 infection with EC_{50}s of 0.051, 0.014, and 0.46 μM, respectively.[178,214] However, its potential cardiotoxicity may hamper its further clinical use in the treatment of CoV infections.[215] Homoharringtonine is a natural plant alkaloid derived from *Cephalotaxus fortunei* which was approved by FDA to treat chronic myeloid leukemia (CML).[216] It inhibits the first cycle of the elongation phase of eukaryotic translation via blocking aminoacyl-tRNA binding and peptide bond formation.[217] Homoharringtonine, like other protein synthesis inhibitors, showed potency against CoVs as well, with EC_{50}s of 0.072 μM for MERS-CoV and 2.55 μM for SARS-CoV-2.[178,214]

4.2 | Drugs targeting host signaling pathways

4.2.1 | Cyclophilin inhibitors—Cyclosporine (**30**, cyclosporin A, CsA, Figure 9) is a natural product used as an immunosuppressive drug to prevent rejection in organ transplants and treat various immune-related diseases.[218] CsA first forms complex with cyclophilins of lymphocytes, especially of T cells, and then binds to calcineurin to inhibit its activity. Calcineurin is a calcium-calmodulin-activated serine/threonine-specific phosphatase which activates nuclear factor of activated T cells (NFAT) via dephosphorylation. Inhibition of calcineurin function blocks the translocation of NFAT from the cytosol into the nucleus, subsequently suppressing the transcription of genes for interleukin 2 (IL-2) and other related cytokines.[219,220] SARS-CoV nsp1 and full replicating SARS-CoV were found to indirectly activate the calcineurin/NFAT pathway and enhance the induction of IL-2, which is likely to play an important role in virus replication. Nsp1 significantly increases the stimulatory effect of phorbol 12-myristate 13-acetate and ionomycin on NFAT activation, whereas CsA can block the increase of NFAT activity.[221,222] CsA inhibits the replication of SARS-CoV (EC_{50} = 3.3 μM), HCoV-NL63 (EC_{50} = 2.3 μM), and HCoV-229E (EC_{50} = 2.3 μM), possibly

acting on genome replication and/or transcription.[221,223] In addition, CsA suppresses MERS-CoV-induced CPE in Vero cells at the concentration of 9 μM while treatment with a combination of CsA and IFN-α was more effective than either agent used alone against MERS-CoV replication.[224] Recently, CsA was found to inhibit SARS-CoV-2 replication with an EC_{50} of 5.82 μM as well.[70]

Alisporivir (**31**, Debio 025) is a synthetic cyclophilin inhibitor with no immunosuppressive activity derived from the parent compound CsA.[225] It has been widely investigated for its therapeutic potential to treat HCV infections.[226,227] The structural changes of alisporivir, compared with CsA, enhanced the binding affinity with cyclophilins and abolished the binding of the formed alisporivir-cyclophilin complex to calcineurin, thus decreasing its immunosuppressive activity.[228] Alisporivir inhibits the replication of SARS-CoV and MERS-CoV with low micromolar EC_{50} values (Table 2).[229] Treatment with alisporivir plus ribavirin primarily showed an additive effect on in vitro antiviral activity; however, this combination treatment was not found to improve the outcome in a mouse model of SARS-CoV infection.[229] Recently, alisporivir was found to inhibit SARS-CoV-2 replication in Vero E6 cells (EC_{50} = 0.46 μM), likely suppressing a postentry step of the SARS-CoV-2 life cycle.[230] Considering the nonimmunosuppressive property of alisporivir and their similar EC_{50} values against CoVs, CsA and alisporivir may exert their anti-CoV activities via preventing those cyclophilin functions essential for viral replication, independent from the calcineurin/NFAT pathway.

4.2.2 | Inhibitors targeting kinase signaling pathways—Imatinib (**32**, Figure 10) is a small-molecule Abl kinase inhibitor which is highly effective to treat early-phase CML.[231] Imatinib mesylate inhibits the replication of SARS-CoV, MERS-CoV, and SARS-CoV-2 with EC_{50}s of 9.82, 17.69, and 5.32 μM, respectively.[178,232] Imatinib was found to target Abelson tyrosine-protein kinase 2 (Abl2) that was required for efficient SARS-CoV and MERS-CoV replication. Imatinib specifically blocks viral fusion with the endosomal membrane and cell-cell fusion via inhibiting Abl kinase activity.[233,234] Currently, several clinical trials are ongoing to evaluate the efficacy of imatinib in COVID-19 treatment. Dasatinib (**33**) and saracatinib (**34**, AZD-0530) are dual Abl kinase and Src inhibitors.[235,236] Dasatinib was approved to treat CML and acute lymphoblastic leukemia[237] while saracatinib, due to the insufficient efficacy in cancer patients, has subsequently been investigated to treat other human conditions such as Parkinson's disease and pulmonary fibrosis.[238–240] Dasatinib was also found to be effective against SARS-CoV (EC_{50} = 2.10 μM) and MERS-CoV (EC_{50} = 5.47 μM).[178] Saracatinib significantly inhibits MERS-CoV, HCoV-229E, and HCoV-OC43 at the early stages of the viral life cycle in Huh-7 cells with EC_{50}s of 2.9, 2.4, and 5.1 μM, respectively.[241] Moreover, treatment of saracatinib in combination with gemcitabine exhibited a synergistic inhibitory effect against MERS-CoV infection with minimal cytotoxic effect in Huh-7 cells. It was demonstrated that multiple Src kinases, often together with Abl kinase, play an important role in the life cycle of various viruses.[242–245] Knockdown of Src kinases, Fyn or Lyn, led to an obvious reduction in MERS-CoV titers.[241] Thus, these two dual inhibitors, dasatinib and saracatinib, may exert their anti-CoV activities via inhibition of both multiple members of Src family and Abl kinase.

A kinome analysis of human hepatocytes infected with MERS-CoV suggested that extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and phosphoinositol 3-kinase (PI3K)/serine-threonine kinase (AKT)/mammalian target of rapamycin (mTOR) signaling responses are selectively modulated in the host, which are essential for MERS-CoV infection.[246] Rapamycin (**35**, Sirolimus), an mTOR inhibitor, suppressed MERS-CoV infection via both pre- and postinfection treatment with inhibition of ~60% at 10 μM.[246] Selumetinib (**36**) and trametinib (**37**) are MEK1/2 inhibitors which affect the ERK/MAPK pathway by inhibiting the activity of MAPK kinase.[247] Selumetinib showed potent antiviral activity against MERS-CoV with inhibition of ~70% at 1 μM when added before infection.[246] Pretreatment with trametinib significantly inhibited MERS-CoV replication with a percentage of ~90% at 0.1 μM. More importantly, trametinib also showed potency against MERS-CoV with inhibition of ~70% at 1 μM via postinfection treatment, indicating its great therapeutic potential for MERS.[246] These data together provide strong evidence for critical roles of mTOR and MEK1/2 in MERS-CoV infection.

Cytokine storm (CS) involves excessive and uncontrolled release of inflammatory cytokines which is comparatively common in severe cases of COVID-19.[248,249] It has become a major cause of lung damage and often leads to the aggravation, even mortality. Thus, combining antiviral and anti-inflammatory treatments may help to prevent further injury.[250] Compounds **38**–**40** are Janus kinase (JAK) inhibitors that can suppress JAK-mediated cytokine release.[251] Clinical trials have been initiated to evaluate the safety and efficacy of these JAK inhibitors combined with antivirals in COVID-19. Among them, baricitinib (**38**) is particularly attractive. Besides its anti-inflammatory property, baricitinib binds with high affinity and inhibits the AP2-associated protein kinase 1 (AAK1) which is an important modulator of clathrin-mediated endocytosis for SARS-CoV-2.[250] Moreover, the plasma concentration of baricitinib is sufficient to inhibit AAK1 when dosing 2 or 4 mg once daily, indicating its therapeutic potential for COVID-19.[252] However, it is worth noting that anti-inflammatory therapy may delay the clearance of virus and increase the chance of secondary infection. Besides, JAK inhibitors also inhibits IFN-α production which is important in eliminating virus. Thus, it remains a critical concern as how to balance the risk and benefit ratio of anti-inflammatory therapy for COVID-19.

Abemaciclib (**41**) is a selective CDK4/6 inhibitor used to treat advanced or metastatic breast cancers[253] while gilteritinib (**42**) is a dual FLT3 and AXL inhibitor which was approved by FDA for treatment of patients with relapsed or refractory acute myeloid leukemia.[254] These two drugs were found to inhibit SARS-CoV-2 replication with a similar EC_{50} value of ~6.7 μM,[70] although their exact mechanisms of antiviral action require further investigations.

4.3 | Inhibitors targeting host proteases

4.3.1 | The endosomal protease inhibitors—The pH-sensitive endosomal proteases cathepsins involve endosomal viral entry and activate CoV membrane fusion via proteolysis of viral S glycoprotein following receptor binding and induced conformational changes in S glycoprotein.[48,49] This proteolytic activation can be blocked by cathepsin inhibitors such as K11777 (**43**, Figure 11) and E-64-d (**44**, EST).[38,255,256] K11777 is an irreversible cysteine protease inhibitor and potently inhibits SARS-CoV replication with IC_{50} of <0.05 μM for

strains Urbani and Toronto-2 in Vero 76 cells in a CPE assay. Meanwhile, it displays low IC_{90}s of 0.35 and 1.04 μM against strains Urbani and Toronto-2, respectively, in a virus reduction assay.[255] K11777 also possesses acceptable safety and PK profiles in rodent, dogs, and primates, offering the potential to treat CoV infections including COVID-19.[257]

E-64-d is an ester prodrug of an epoxide which is rapidly hydrolyzed in the gut to afford the acid form E-64-c (**45**).[258] This series of compounds inhibit cysteine proteases by covalently modifying the cysteine residue of its active site.[259] E-64-d was originally developed to treat muscular dystrophy in the 1980s and failed in phase 3 clinical trials due to the lack of sufficient efficacy.[260] However, these trials have established its safety and PK profiles.[261–263] E-64-d significantly inhibits SARS-CoV and MERS-CoV replication with EC_{50}s of 0.76 and 1.28 μM, respectively. Recently, E-64-d was also reported to inhibit SARS-CoV-2 entry via blocking cathepsin L-mediated S glycoprotein activation.[38] These data together suggest cathepsin inhibitor, E-64-d is also a promising candidate to be developed for COVID-19 treatment.

4.3.2 | The surface protease inhibitors—The surface serine protease TMPRSS2 mediates cell surface nonendosomal virus entry at the plasma membrane via cleavages and activation of the S protein.[51,52,264] Camostat (**46**, Figure 12) is a serine protease inhibitor which was approved in Japan to treat chronic pancreatitis.[265,266] Camostat, as a TMPRSS2 inhibitor, partially blocks the entry of SARS-CoV, MERS-CoV, and SARS-CoV-2 into TMPRSS2-expressing cells while simultaneous treatment of camostat and E-64-d can completely inhibit viral entry, mainly due to the dual blockade of the cell surface and endosomal entry pathways.[41,50,53] Camostat also completely blocks syncytium formation and reduces the infection of SARS-CoV, MERS-CoV, and SARS-CoV-2 in the lung cell line Calu-3.[41,50,53] In addition, camostat treatment effectively protected mice against death induced by SARS-CoV infection when dosed orally at 30 mg/kg twice daily for 9 days.[255]

Nafamostat (**47**) is a broad-spectrum serine protease inhibitor that is mainly used to treat pancreatitis and disseminated intravascular coagulation.[267,268] Nafamostat was screened out as a potent inhibitor of S-mediated membrane fusion, possibly through the inhibition of TMPRSS2 like camostat.[269] Nafamostat is more effective than camostat in reducing the entry and replication of MERS-CoV in Calu-3 cells.[270] It was also found to inhibit SARS-CoV-2 replication with an EC_{50} of 22.5 μM.[110] Currently, several clinical trials are underway to evaluate the efficacy of both camostat and nafamostat as a monotherapy or combined with hydroxychloroquine in COVID-19 treatment. Three cases were reported that treatment with nafamostat improved COVID-19 associated pneumonia of elderly patients who were receiving antiviral drugs and supplementary oxygen therapy.[271] While accumulated studies showed the TMPRSS2-mediated cell surface route is essential for viral entry into primary target cells and viral spread in the infected host,[41,53,255,272] it was also found that simultaneous treatment with camostat and E-64-d displays more potent inhibitory activity against SARS-CoV infection in Calu-3 cells compared to either agent used alone.[53] Thus, combination use of cathepsin and TMPRSS2 inhibitors may be a promising strategy to efficiently block CoV infections.

4.4 | Inhibitors targeting CoV entry into host cell

4.4.1 | The quinoline derivatives targeting endosomal acidification—

Chloroquine (**48**, Figure 13) is a synthetic medication of a 4-aminoquinoline derivative which was discovered in 1934 and specifically used as an antimalarial agent.[273] Besides its antimalarial effect, chloroquine was subsequently found to possess anti-inflammatory and immunomodulatory properties which have encouraged its new uses to treat autoimmune diseases such as RA and systemic lupus erythematosus (SLE).[274] In addition, chloroquine is also effective against a series of pH-dependent viruses, including HIV, dengue virus (DENV), HCV, influenza A virus, EBOV, CoV, and so forth.[275] It was reported to block viral entry mainly by suppressing glycosylation of host receptors and endosomal acidification.[274–276] Due to its anti-inflammatory property, chloroquine inhibits the production of various proinflammatory cytokines and the activation of macrophages induced by viral infection and may improve the clinical symptoms of infected patients.[273,275] Chloroquine inhibits the replication of SARS-CoV, MERS-CoV and SARS-CoV-2 with EC_{50}s of 6.54, 6.28, and 1.13 μM, respectively.[110,178] Different research groups have reported that chloroquine functions at both entry and postentry stages of SARS-CoV and SARS-CoV-2 infections[110,276,277] whereas it inhibits an early step in the replicative cycle of MERS-CoV.[62] However, chloroquine was ineffective to reduce lung virus titers when administered by the intraperitoneal (IP) route in a mouse model of SARS-CoV infection, likely due to the insufficient blockade of viral entry pathways.[278]

Hydroxychloroquine (**49**) is a chloroquine derivative which shares high similarities with chloroquine in chemical structure, mechanisms of action, and therapeutic applications.[274] Hydroxychloroquine has an *N*-hydroxyethyl side chain and thus less tissue accumulation and toxicity than chloroquine.[279,280] As expected, hydroxychloroquine displays antiviral activities against SARS-CoV, MERS-CoV, and SARS-CoV-2 with similar EC_{50} values to those of chloroquine.[178,281,282] Considering its in vitro anti-CoV and anti-inflammatory properties, established clinical safety and PK profiles, and the low cost, chloroquine, and hydroxychloroquine have been fast advanced into numerous clinical trials to evaluate their efficacy in COVID-19 treatment.

According to the early clinical results from more than 100 inpatients with COVID-19 in China, chloroquine phosphate treatment might be associated with improved radiological findings, enhanced viral elimination and delayed disease progression.[283] Two French studies reported that hydroxychloroquine could reduce viral load in patients with COVID-19, especially used in combination with azithromycin (an antibiotic of a macrolide used to treat diverse bacterial infections, see Section 4.5, **75**).[284,285] However, the result from another study revealed that no clinical benefit was observed for combination treatment of hydroxychloroquine and azithromycin in critically ill patients with COVID-19.[286] In addition, a randomized parallel-group study enrolling 62 patients with mild COVID-19 indicated that hydroxychloroquine treatment was associated with shortened clinical recovery time (temperature and cough) and improved pneumonia compared to placebo.[287] In a multicenter retrospective observational study involving 2541 patients with COVID-19, treatment with hydroxychloroquine alone (162/1202, 12.5%) and in combination with azithromycin (157/783, 20.1%) was associated with reduction in in-hospital mortality while

groups treating with azithromycin alone or neither drug showed death rates of 22.4% (33/147) and 26.4% (108/409), respectively.[288] However, these clinical data on chloroquine and hydroxychloroquine are far from convincing and several limitations exist such as a small cohort, absence of randomization, and no control arm.[289,290] Very recently, a retrospective multicenter cohort study involving 1438 patients revealed that treatment with hydroxychloroquine (54/271), azithromycin (21/211), or both (189/735), compared with neither treatment (28/221), was not associated with significant differences in in-hospital fatality.[291] Another randomized clinical trial indicated that the group (n = 1542) treating with hydroxychloroquine showed no statistically significant difference in 28-day mortality (26.8% vs. 25.0%) compared to the control receiving usual care (n = 3132).[292] Moreover, although chloroquine and hydroxychloroquine were demonstrated to be relatively well tolerated in patients with malaria and SLE, they can cause QTc prolongation and arrhythmia, with an increased risk especially used in combination with other medications such as azithromycin known to prolong QT interval.[274,293]

Mefloquine (**50**) and amodiaquine (**51**) are antimalarial medications of the quinoline class that exhibit similar anti-CoV activities to chloroquine. Mefloquine displays EC_{50}s of 15.5, 7.42, and 4.33 μM for SARS-CoV, MERS-CoV, and SARS-CoV-2, respectively, while amodiaquine effectively inhibits the replication of these three CoVs with EC_{50} values of 1.27–6.21 μM.[70,178] Like chloroquine, amodiaquine failed to reduce lung virus titers via IP administration in a SARS-CoV-infected mouse model.[278]

4.4.2 | The phenothiazine derivatives targeting clathrin-mediated endocytosis—Compounds **52**–**57** (Figure 14) are phenothiazine derivatives which act as antagonists on different postsynaptic and presynaptic receptors such as dopamine receptors, serotonin receptors and histamine receptors. Compounds **52**–**55** are antipsychotic medications while promethazine (**56**) and thiethylperazine (**57**) are used as an antihistamine and an antiemetic, respectively. These medications were found to inhibit SARS-CoV, MERS-CoV, and SARS-CoV-2 replication with EC_{50} values ranging from 4.03 to 21.4 μM.[178,232] They block clathrin-dependent entry (IC_{50} = 3.23–7.48 μM) via preventing the assembly of clathrin-coated pits at the plasma membrane.[294–296] In addition, chlorpromazine (**52**) was reported to suppress MERS-CoV replication at both an early and a postentry stage, suggesting that it has other antiviral mechanism beside blocking clathrin-mediated endocytosis.[62] Chlorpromazine was also reported to block the entry of HCV,[297] alphaviruses,[298] infectious bronchitis virus,[299] and mouse hepatitis virus type 2 (MHV-2) by targeting clathrin-mediated endocytosis.[300] Based on its in vitro anti-SARS-CoV-2 activity (EC_{50} = 4.03 μM),[232] two clinical trials have been initiated to evaluate the efficacy of chlorpromazine in COVID-19 treatment.

4.4.3 | The cardiotonic steroids that inhibit CoV entry into host cell via targeting ATP1A1-mediated Src signaling—Compounds **58**–**61** (Figure 15) are medications of cardiotonic steroids that can increase the force of myocardium contraction and cardiac output by inhibiting the Na/K-ATPase, also known as the sodium-potassium ion pump.[301] The ATP1A1 α subunit was found to be critical for CoV infection, and cardiotonic steroids, ouabain (**58**) and bufalin (**59**), inhibit CoV infection at low concentrations by

targeting ATP1A1 without affecting the transport function of Na^+/K^+-ATPase.[302] However, these antiviral effects can be relieved by different Src kinase inhibitors, indicating the crucial role of ATP1A1-mediated Src signaling in the inhibition of CoV infection. Ouabain blocks viral entry at an early stage before the formation of early endosomes, but it remains to be elucidated how ATP1A1-mediated Src signaling could affect clathrin-mediated entry.[302] Ouabain significantly inhibit SARS-CoV-2 infection (EC_{50} < 0.097 μM) while proscillaridin (**60**), digoxin (**61**), and digitoxin (**62**) show potency against SARS-CoV-2 with EC_{50}s of 2.01, 0.19, and 0.23 μM, respectively.[70] However, the potential cardiotoxicity of cardiotonic steroids may hamper their further clinical use in patients with CoV infections.

4.4.4 | Other drugs that inhibit CoV entry into host cell—

Clomipramine (**63**, Figure 16) is a tricyclic antidepressant which blocks the reuptake of serotonin and norepinephrine back into neurons, resulting in increased serotonergic and noradrenergic neurotransmission.[303] Its hydrochloride was reported to inhibit SARS-CoV (EC_{50} = 13.24 μM), MERS-CoV (EC_{50} = 9.33 μM), and SARS-CoV-2 (EC_{50} = 7.59 μM) infections while it blocks MERS-CoV entry with an IC_{50} of 8.79 μM.[178,232,294] Tamoxifen (**64**) and toremifene (**65**) are selective estrogen receptor modulators which are used to treat breast cancer. Tamoxifen citrate and toremifene citrate exhibit similar potency against MERS-CoV (EC_{50} = 10.12 and 12.92 μM, respectively) and SARS-CoV-2 (EC_{50} = 8.98 and 11.30 μM, respectively), and varied antiviral activities against SARS-CoV (EC_{50} = 92.89 and 11.97 μM, respectively).[178,232] Astemizole (**66**) and chlorphenoxamine (**67**) are antihistamine and anticholinergic medications. Astemizole significantly inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 infections with EC_{50}s of 5.59, 4.88, and ~1.1 μM, respectively, while chlorphenoxamine displays relatively low potency against SARS-CoV (EC_{50} = 20.03 μM) and MERS-CoV (EC_{50} = 12.65 μM).[178,304] Tamoxifen and astemizole suppress clathrin-dependent entry with IC_{50}s of 7.46 and 3.48 μM, respectively, and the anti-CoV activities of toremifene and chlorphenoxamine possibly attribute to this mechanism as well due to their highly similar structures.[294]

4.5 | Other Host-based inhibitors

Niclosamide (**68**, Figure 17) is an FDA-approved anthelmintic drug that has been widely used in human to treat tapeworm infections by inhibiting oxidative phosphorylation.[305] It was found to regulate multiple signaling pathways and biological processes and effective against various viral infections such as CoVs, ZIKV, and EBOV.[9,306] Niclosamide inhibits SARS-CoV and SARS-CoV-2 replication with EC_{50}s of <0.1 and 0.28 μM, respectively.[70,307,308] It also suppresses MERS-CoV infection by up to 1000-fold at 48 h post infection (PI) at a concentration of 10 μM likely through S-phase kinase-associated protein 2 (SKP2) inhibition.[309] These data suggest that niclosamide, an inexpensive and well-tolerated drug, has great potential being repurposed to treat CoV infections. However, it should be mentioned that niclosamide has limited aqueous solubility and relatively low oral bioavailability and developing nano-based formulations of niclosamide or new optimized analogues may be a fast and useful approach to improving its PK properties and maximizing its therapeutic potential.[9] More comprehensive understanding of niclosamide as a broad spectrum antiviral agent and its therapeutic potential for COVID-19 was recently reviewed by us,[9] and more effective analogues with lower cytotoxic effects were also reported.[310,311]

Nitazoxanide (**69**) is a thiazolide medication which was initially developed as an oral antiparasitic agent and approved by FDA to treat diarrhea caused by *Cryptosporidium parvum* and *Giardia intestinalis* in adults and children at least 12 months old.[312] Nitazoxanide was subsequently found as a broad antiviral agent and numerous clinical trials have been conducted to evaluate its efficacy for the treatment of influenza, viral gastroenteritis caused by rotavirus and norovirus, HBV, HCV, and HIV infections.[312] Nitazoxanide was reported to induce the host innate immune response via enhancing the production of type 1 IFN-α and IFN-β, activating protein kinase R, and so forth.[312–315] Nitazoxanide is rapidly metabolized into its active circulating form tizoxanide (**70**) in plasma and peak and trough serum concentrations of tizoxanide were 17.3 μM (4.6 μg/ml) and 3.0 μM (0.8 μg/ml), respectively, when treating patients with nitazoxanide controlled release tablets twice daily in a phase 2b/3 clinical trial.[316] Moreover, the maximum plasma concentration of tizoxanide can reach as high as 37 μM (10 μg/ml) after oral administration of one 500 mg nitazoxanide tablet with food.[317,318] Nitazoxanide significantly inhibits SARS-CoV-2 replication with an EC_{50} of 2.12 μM, which is far below its maximum serum concentration, indicating its great potential to treat SARS-CoV-2 infection.[110] Given its in vitro evidence and immunomodulatory effect as well as the favorable in vivo PK and safety profiles, several clinical trials have been initiated to investigate the efficacy of nitazoxanide in COVID-19 treatment.

Hexachlorophene (**71**) is an organochlorine compound that is often used in soaps and toothpaste as an anti-infective and antibacterial agent. It strongly inhibits MHV and SARS-CoV-2 replication with EC_{50}s of 1.2 and 0.9 μM, respectively.[70,319] Tilorone (**72**) is a synthetic, orally bioavailable small molecule which displays antiviral activities associated with inducing IFN.[320] It has been approved in Russia for the treatment of several viral infections such as influenza and acute respiratory viral infection.[321] Tilorone is effective against a broad range of CoVs, displaying EC_{50}s of 10.56 μM for MERS-CoV and 4.09 μM for SARS-CoV-2, respectively.[70,322] Terconazole (**73**) is a broad antifungal drug of a triazole derivative which is often used to treat vaginal yeast infection as a lotion or a suppository.[323] It binds to the cytochrome P450 enzyme of fungi and inhibits 14α-desmethyl sterol synthesis, consequently resulting in the accumulation of 14-methylsterols in the membrane.[324,325] Terconazole suppresses SARS-CoV, MERS-CoV and SARS-CoV-2 infection with EC_{50}s ranging from 11.92 to 16.14 μM.[178,232]

Azithromycin (**74**, Figure 18) is a macrolide that is effective against a broad range of Gram-positive and Gram-negative bacteria and used to treat diverse bacterial infections such as middle ear infections and pneumonia.[326] It inhibits bacterial protein synthesis via binding to its ribosome and thus preventing mRNA translation.[327] Azithromycin possesses high tissue penetration and anti-inflammatory properties, unrelated to its antimicrobial activity.[328,329] Due to these properties, azithromycin is also used to treat many chronic lung diseases including chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, and so forth.[330–332] Considering its clinical benefit in lung disease, numerous clinical trials have been initiated to test the efficacy of azithromycin in conjunction with hydroxychloroquine in COVID-19 patients. However, as mentioned in the discussion of hydroxychloroquine (see Section 4.4.1), the clinical benefit of azithromycin for COVID-19 patients remains

controversial, and the combination use of azithromycin and hydroxychloroquine may cause additive cardiac toxicity, especially to those who have cardiac-related comorbidities.

Salinomycin (**75**) is a polyether ionophore antibiotic isolated from *Streptomyces albus*.[333] It is highly effective against Gram-positive bacteria and used as a coccidiostat for poultry. It disturbs the natural Na^+/K^+ cations balance, changes the intracellular pH, and finally results in cell death.[334] In addition, salinomycin was shown to inhibit cancer stem cells in different types of human cancers.[335] Salinomycin sodium potently inhibits SARS-CoV-2 and MERS-CoV infection with EC_{50}s of 0.24 and 5.49 μM, respectively.[70,322] Nevertheless, the severe toxicity of salinomycin may limit its potential use as an antiviral agent. Ivermectin (**76**) is an FDA-approved antiparasitic drug that also displays broad antiviral activities, effective against DENV, HIV, chikungunya virus (CHIKV), and so forth.[336–338] Ivermectin inhibits SARS-CoV-2 replication with an EC_{50} of ~2.0 μM and results in a ~5000-fold reduction in viral RNA at 48 h when treated 2 h PI at a concentration of 5 μM, warranting further investigation for possible benefits in humans.[336] Anidulafungin (**77**, LY303366) is a semisynthetic echinocandin which is used to treat fungal infections.[339] It inhibits the synthesis of 1,3-β-D-glucan, a major fungal cell wall component.[340] Anidulafungin undergoes slow chemical degradation to its inactive forms under physiological conditions, not through hepatic enzymatic metabolism or renal elimination.[341] Anidulafungin was found to suppress SARS-CoV-2 infection with an EC_{50} of 4.64 μM.[70]

Benztropine (**78**, Figure 19) is an anticholinergic drug which blocks the activity of the muscarinic acetylcholine receptor. Its mesylate inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 with micromolar EC_{50} values ranging from 13.8 to 21.6 μM.[178,232] Fluspirilene (**79**) is an antipsychotic drug of the diphenylbutylpiperidine class used to treat schizophrenia.[342] It was found effective against SARS-CoV and MERS-CoV (EC_{50} = 5.96 and 7.48 μM, respectively).[178] Bazedoxifene (**80**) is a third-generation selective estrogen receptor modulator that is used to treat postmenopausal osteoporosis.[343] Bazedoxifene suppresses SARS-CoV-2 infection with an EC_{50} of 3.44 μM.[70] Loperamide (**81**) is a medication used to treat diarrhea. As an opioid-receptor agonist, it targets μ-opioid receptors in the myenteric plexus and decreases its activity.[344] Loperamide inhibits SARS-CoV, MERS-CoV, and SARS-CoV-2 infection with EC_{50}s of 8.8, 4.9, and 9.27 μM, respectively.[62,70] It possibly acts at an early step in viral replicative cycle.[62] Compounds **82**–**84** are bis-benzylisoquinoline alkaloids that possess anti-inflammatory effect.[345–347] Cepharanthine (**82**), berbamine (**83**), and tetrandrine (**84**) show potency against SARS-CoV-2 with EC_{50}s of 4.47, 7.87, and 3.00 μM, respectively.[70] Reserpine (**85**), a well-known antihypertensive drug, was found to inhibit SARS-CoV replication with an EC_{50} of 3.4 μM.[348]

Ivacaftor (**86**, Figure 20), a drug used to treat cystic fibrosis, displays antiviral activity against SARS-CoV-2 (EC_{50} = 6.57 μM).[70,349] ESI-09 (**87**) is an exchange protein directly activated by cAMP (EPAC) inhibitor, and ESI-09 treatment was reported effective in protecting cell cultures against MERS-CoV and SARS-CoV at the concentration of 10 μM, resulting in about 2log and 4log reduction in virus titer, respectively.[350] Eltrombopag (**88**) is a small molecule agonist of the thrombopoietin (c-mpl) receptor that was developed for certain conditions associated with thrombocytopenia.[351] Eltrombopag inhibits SARS-CoV-2 replication with an EC_{50} of 8.27 μM.[70] In addition, platelets were reported to play an

important role in innate immunology in the lung such as the defense against various respiratory viral infections.[352] These findings together indicate that eltrombopag may have potential to combat the severe COVID-19. Hydroxyprogesterone caproate (**89**, OHPC) is an agonist of the progesterone receptor which is used to prevent preterm birth in pregnant women and to treat gynecological disorders.[353] OHPC shows micromolar potency against SARS-CoV-2 (EC_{50} = 6.30 μM).[70] Ciclesonide (**90**) is an inhaled corticosteroid used to treat asthma and allergic rhinitis.[354] It inhibits SARS-CoV-2 replication (EC_{50} = 4.33 μM), and mutants in nsp3 and nsp4 of SARS-CoV-2 showed resistance against ciclesonide.[70,355] Cases were also reported that ciclesonide inhalation treatment was associated with clinical improvement in three COVID-19 patients.[356] These data, together with its antiviral and anti-inflammatory properties, warrant further studies for the clinical benefit of ciclesonide in COVID-19 treatment.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Given the urgent unmet medical need in combating the COVID-19 pandemic, numerous human clinical trials have currently been launched to evaluate potential treatments for COVID-19 including biologicals such as vaccines, convalescent plasma, mAb, antiviral agents, immunomodulatory agents (supporting agents), and other miscellaneous agents with known or unknown mechanism of CoV inhibition. The representative small molecule compounds, which are undergoing clinical trials for COVID-19 with recruiting participants, were summarized in Table 3. Most of them are repurposed agents previously designed for other human conditions. Hydroxychloroquine and chloroquine were once granted emergency authorization by FDA for use in COVID-19 treatment; however, their clinical efficacy remains controversial and their use may be associated with potential severe side effects for some patients.[357] Very recently, FDA revoked the Emergency Use Authorization of hydroxychloroquine and chloroquine for emergency use to treat COVID-19.[358] Among these molecules, remdesivir, an RdRp inhibitor, seems to be most promising candidate which was reported to reduce the duration of recovery in a human phase 3 trial and has been authorized for emergency use in the U.S.[124,359] On October 22, 2020, FDA approved Veklury (remdesivir), the first antiviral drug approved to treat COVID-19, for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kg (about 88 pounds) requiring hospitalization.[360] As inflammatory CS is comparatively common in COVID-19 patients,[250] a large number of adjunctive therapies have also been investigated in clinical trials including corticosteroids and immunomodulatory agents such as JAK inhibitors and fingolimod. A controlled, open-label trial revealed that the use of dexamethasone (a common corticosteroid medication) resulted in lower 28-day mortality among hospitalized patients with COVID-19 who were receiving respiratory support, but no benefit was observed for those with less severe symptoms.[361] Although use of ACE inhibitor (ACEI)/angiotensin receptor blocker (ARB) was reported to lower all-cause mortality compared with ACEI/ARB nonusers among COVID-19 inpatients with hypertension, the rationality of ACEI/ARB for treating COVID-19 remains disputed.[362,363]

Although many virus-based and host-based small molecule drugs were reported with potent in vitro efficacy against CoVs, only a few are likely to be advanced into clinical trials to unravel their potential. Most of them possess one or several drawbacks including high

EC_{50}/C_{max} values at clinically relevant dosages, severe side effects, immunosuppression, poor PK profiles or the lack of efficient drug delivery method. These limitations hamper their further clinical development as anti-CoV agents. Developing nano-based formulations and new delivery methods are rapid and promising strategies to improve the PK properties of some existing drugs and maximize their therapeutic potential for clinical applications. Another useful approach is combinational use of anti-CoV agents targeting different processes or proteins involved in virus life cycle that may slow the development of drug resistance and reduce the effective concentration of individual drugs and thus the potential side effects. Alternatively, these drugs can also serve as lead compounds to develop more effective, safer, and more specific anti-CoV drugs along the pipeline through medicinal chemistry optimization and drug development efforts. In the long run, it is imperative to develop more effective and broad-spectrum anti-CoV drugs such as RdRp inhibitors and $3CL^{pro}$ inhibitors to ultimately fight the circulating and emerging CoV infections of the future.

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Abbreviations:

3CL^{pro}	3C-like protease
AAK1	AP2-associated protein kinase 1
ACE2	angiotensin-converting enzyme 2

ACEI	ACE inhibitor
AIDS	acquired immunodeficiency syndrome
AKT	protein kinase B
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ARB	angiotensin receptor blocker
ASC09F	ASC09/ritonavir
CC_{50}	cytotoxic concentration 50%
CHIKV	chikungunya virus
C_{max}	the maximum serum concentration
CML	chronic myeloid leukemia
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	coronavirus disease 2019
CPE	cytopathic effect
CRAC	Ca^{2+} release-activated Ca^{2+}
CS	cytokine storm
CSCs	cancer stem cells
CTD	C-terminal domain
DENV	dengue virus
DPP4	dipeptidyl peptidase 4
E	envelop
EBOV	Ebola virus
EC_{50}	half maximal effective concentration
EMCV	encephalomyocarditis virus
EPAC	exchange protein directly activated by cAMP
ER	endoplasmic reticulum
ERGIC	endoplasmic reticulum-Golgi intermediate compartment
ERK	extracellular signal-regulated kinase

EUA	Emergency Use Authorization
EVD	EBOV disease
EV-A71	enterovirus A71
GMP	guanosine-5′-monophosphate
HAE	human airway epithelial
HBV	hepatitis B virus
HCoV	Human coronavirus
HCV	hepatitis C virus
HCMV	human cytomegalovirus
HIV	human immunodeficiency virus
HTS	high-throughput screening
IC_{50}	half maximal inhibitory concentration
IFN	interferon
IL-2	interleukin 2
IMP	inosine-5′-monophosphate
IMPDH	inosine-5′-monophosphate dehydrogenase
JAK	Janus kinase
JNKc	Jun N-terminal kinase
LPV	rlopinavir/ritonavir
M	membrane
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MARV	Marburg virus
MERS-CoV	Middle East respiratory syndrome coronavirus
MHV-2	mouse hepatitis virus type 2
mTOR	mammalian target of rapamycin
N	nucleocapsid
NFAT	nuclear factor of activated T cells
nsp	nonstructural protein

NTD	N-terminal domain
ORF	open reading frame
PDE5	cGMP-specific phosphodiesterase type 5
PI	post infection
PI3K	phosphoinositol 3-kinase
PK	pharmacokinetic
PKR	protein kinase R
PL^{pro}	papain-like protease
RA	rheumatoid arthritis
RBD	receptor binding domain
RdRp	RNA-dependent RNA polymerase
RSV	respiratory syncytial virus
RTC	replicase-transcriptase complex
S	spike
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SGLT2	sodium-glucose transport protein 2
SKP2	S-phase kinase-associated protein 2
SLE	systemic lupus erythematosus
TMPRSS2	transmembrane protease serine 2
WHO	World Health Organization
ZIKV	Zika virus

REFERENCES

1. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. Coronaviruses—drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327–347. [PubMed: 26868298]
2. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA. 2020;323(8): 707–708. [PubMed: 31971553]
3. Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J. 2005;24(11 Suppl): S223–S227. [PubMed: 16378050]
4. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273. [PubMed: 32015507]
5. Anthony SJ, Gilardi K, Menachery VD, et al. Further evidence for bats as the evolutionary source of Middle East respiratory syndrome coronavirus. mBio. 2017;8(2):e00373–17. [PubMed: 28377531]

6. Hu B, Ge X, Wang L-F, Shi Z. Bat origin of human coronaviruses. Virol J. 2015;12(1):221. [PubMed: 26689940]
7. Huynh J, Li S, Yount B, et al. Evidence supporting a zoonotic origin of human coronavirus strain NL63. J Virol. 2012; 86(23):12816–12825. [PubMed: 22993147]
8. Osman EEA, Toogood PL, Neamati N. COVID-19: living through another pandemic. ACS Infect Dis. 2020; 6:1548–1552. 10.1021/acsinfecdis.0c00224 [PubMed: 32388976]
9. Xu J, Shi PY, Li H, Zhou J. Broad spectrum antiviral agent niclosamide and its therapeutic potential. ACS Infect Dis. 2020;6(5):909–915. [PubMed: 32125140]
10. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. 12 31, 2003. https://www.who.int/csr/sars/country/table2004_04_21/en/. Accessed May 26, 2020.
11. Reusken CB, Haagmans BL, Müller MA, Gutierrez C, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. Lancet Infect Dis. 2013;13(10): 859–866. [PubMed: 23933067]
12. Haagmans BL, Al Dhahiry SHS, Reusken CBEM, et al. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. Lancet Infect Dis. 2014;14(2):140–145. [PubMed: 24355866]
13. Azhar EI, El-Kafrawy SA, Farraj SA, et al. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med. 2014;370(26):2499–2505. [PubMed: 24896817]
14. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet. 2015;386(9997):995–1007. [PubMed: 26049252]
15. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). 1, 2020. https://www.who.int/emergencies/mers-cov/en/. Accessed May 26, 2020.
16. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan China: a descriptive study. Lancet 2020;395(10223):507–513. [PubMed: 32007143]
17. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514–523. [PubMed: 31986261]
18. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020;382(13):1199–1207. [PubMed: 31995857]
19. World Health Organization. 2020, 3 19. Getting your workplace ready for COVID-19: how COVID-19 spreadsGeneva: World Health Organization.
20. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323(13):1239–1242. [PubMed: 32091533]
21. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. N Engl J Med. 2020;382(13):1278–1280. [PubMed: 32069388]
22. Gates B Responding to Covid-19—a once-in-a-century pandemic? N Engl J Med. 2020;382(18):1677–1679. [PubMed: 32109012]
23. World Health Organization. Coronavirus disease (COVID-2019) situation reports. Weekly Epidemiological and Operational updates 12 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed December 2, 2020.
24. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1):41–58. [PubMed: 30310233]
25. Woo PCY, Huang Y, Lau SKP, Yuen K-Y. Coronavirus genomics and bioinformatics analysis. Viruses. 2010;2(8): 1804–1820. [PubMed: 21994708]
26. Fehr AR, Perlman S. Coronaviruses: An Overview of their Replication and Pathogenesis. In: Maier HJ, Bickerton E, Britton P eds. Coronaviruses: Methods and Protocols. New York, NY: Springer New York; 2015:1–23.
27. Cheng VCC, Lau SKP, Woo PCY, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660–694. [PubMed: 17934078]

28. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev. 2015;28(2):465–522. [PubMed: 25810418]
29. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020; 92(4):418–423. [PubMed: 31967327]
30. van Boheemen S, de Graaf M, Lauber C, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. mBio. 2012;3(6):e00473–12. [PubMed: 23170002]
31. Woo PC, Lau SK, Li KS, Tsang AK, Yuen KY. Genetic relatedness of the novel human group C betacoronavirus to *Tylonycteris* bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5. Emerg Microbes Infect. 2012;1(11):e35. [PubMed: 26038405]
32. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181(2):281–292. [PubMed: 32155444]
33. Tortorici MA, Veesler D. Chapter Four—Structural Insights into Coronavirus Entry. In: Rey FA, ed. Advances in Virus Research. Vol 105. Academic Press; 2019:93–116. [PubMed: 31522710]
34. Singh Tomar PP, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. Biochem Biophys Res Commun. 2020;530(1):10–14. [PubMed: 32828269]
35. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019;16(1):69. [PubMed: 31133031]
36. McBride R, van Zyl M, Fielding BC. The coronavirus nucleocapsid is a multifunctional protein. Viruses. 2014;6(8): 2991–3018. [PubMed: 25105276]
37. Dyall J, Gross R, Kindrachuk J, et al. Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. Drugs. 2017;77(18):1935–1966. [PubMed: 29143192]
38. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020;11(1):1620. [PubMed: 32221306]
39. Tortorici MA, Veesler D. Structural insights into coronavirus entry. Adv Virus Res. 2019;105:93–116. [PubMed: 31522710]
40. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–454. [PubMed: 14647384]
41. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280. [PubMed: 32142651]
42. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495(7440):251–254. [PubMed: 23486063]
43. Lu L, Liu Q, Zhu Y, et al. Structure-based discovery of Middle East respiratory syndrome coronavirus fusion inhibitor. Nat Commun. 2014;5(1):3067. [PubMed: 24473083]
44. Bosch BJ, van der Zee R, de Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77(16):8801–8811. [PubMed: 12885899]
45. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci USA. 2009;106(14):5871–5876. [PubMed: 19321428]
46. Peeples L News feature: avoiding pitfalls in the pursuit of a COVID-19 vaccine. Proc Natl Acad Sci USA. 2020; 117(15):8218–8221. [PubMed: 32229574]
47. Gierer S, Bertram S, Kaup F, et al. The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. J Virol. 2013;87(10): 5502–5511. [PubMed: 23468491]
48. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci USA. 2005;102(33):11876–11881. [PubMed: 16081529]

49. Bosch BJ, Bartelink W, Rottier PJ. Cathepsin L functionally cleaves the severe acute respiratory syndrome coronavirus class I fusion protein upstream of rather than adjacent to the fusion peptide. J Virol. 2008;82(17): 8887–8890. [PubMed: 18562523]
50. Shirato K, Kawase M, Matsuyama S. Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2. J Virol. 2013;87(23):12552–12561. [PubMed: 24027332]
51. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol. 2010;84(24): 12658–12664. [PubMed: 20926566]
52. Shulla A, Heald-Sargent T, Subramanya G, Zhao J, Perlman S, Gallagher T. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J Virol. 2011;85(2): 873–882. [PubMed: 21068237]
53. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol. 2012;86(12):6537–6545. [PubMed: 22496216]
54. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583:459–468. 10.1038/s41586-020-2286-9 [PubMed: 32353859]
55. Gil C, Ginex T, Maestro I, et al. COVID-19: drug targets and potential treatments. J Med Chem. 2020;63: 12359–12386. 10.1021/acs.jmedchem.0c00606 [PubMed: 32511912]
56. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung S-H. An overview of severe acute respiratory syndrome–coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J Med Chem. 2016;59(14):6595–6628. [PubMed: 26878082]
57. Huang J, Song W, Huang H, Sun Q. Pharmacological therapeutics targeting RNA-dependent RNA polymerase, proteinase and spike protein: from mechanistic studies to clinical trials for COVID-19. J Clin Med. 2020;9(4):1131.
58. Dai W, Zhang B, Jiang XM, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science. 2020;368(6497):1331–1335. [PubMed: 32321856]
59. Jin Z, Du X, Xu Y, et al. Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors. Nature. 2020;582(7811): 289–293. [PubMed: 32272481]
60. Yin W, Mao C, Luan X, et al. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. Science. 2020;368(6498):1499–1504. [PubMed: 32358203]
61. Cvetkovic RS, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. Drugs. 2003; 63(8):769–802. [PubMed: 12662125]
62. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother. 2014;58(8):4875–4884. [PubMed: 24841269]
63. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004;31(1):69–75. [PubMed: 15288617]
64. López Aspiroz E, Santos Buelga D, Cabrera Figueroa S, et al. Population pharmacokinetics of lopinavir/ritonavir (Kaletra) in HIV-infected patients. Ther Drug Monit. 2011;33(5):573–582. [PubMed: 21912331]
65. Nukoolkarn V, Lee VS, Malaisree M, Aruksakulwong O, Hannongbua S. Molecular dynamic simulations analysis of ritronavir and lopinavir as SARS-CoV $3CL^{pro}$ inhibitors. J Theor Biol. 2008;254(4):861–867. [PubMed: 18706430]
66. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J. 2003;9(6):399–406. [PubMed: 14660806]
67. Chu CM. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59(3):252–256. [PubMed: 14985565]

68. Chan JFW, Yao Y, Yeung ML, et al. Treatment with lopinavir/ritonavir or interferon-beta1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis. 2015;212(12):1904–1913. [PubMed: 26198719]
69. Arabi YM, Asiri AY, Assiri AM, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. Trials. 2020;21(1):8. [PubMed: 31900204]
70. Jeon S, Ko M, Lee J, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother. 2020;64(7):e00819–20. [PubMed: 32366720]
71. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787–1799. [PubMed: 32187464]
72. Yamamoto N, Yang R, Yoshinaka Y, et al. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. Biochem Biophys Res Commun. 2004;318(3):719–725. [PubMed: 15144898]
73. Xu Z, Yao H, Shen J, et al. Nelfinavir is active against SARS-CoV-2 in Vero E6 cells. ChemRxiv. 2020. 10.26434/chemrxiv.12039888.v1
74. Driessen C, Kraus M, Joerger M, et al. Treatment with the HIV protease inhibitor nelfinavir triggers the unfolded protein response and may overcome proteasome inhibitor resistance of multiple myeloma in combination with bortezomib: a phase I trial (SAKK 65/08). Haematologica. 2016;101(3):346–355. [PubMed: 26659919]
75. Fintelman-Rodrigues N, Sacramento CQ, Lima CR, et al. Atazanavir inhibits SARS-CoV-2 replication and proinflammatory cytokine production. bioRxiv. 2020. 10.1101/2020.04.04.020925
76. Chen J, Xia L, Liu L, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. Open Forum Infect Dis. 2020;7(7):ofaa241. [PubMed: 32671131]
77. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020; 19(3):149–150. [PubMed: 32127666]
78. Njoroge FG, Chen KX, Shih N-Y, Piwinski JJ. Challenges in modern drug discovery: a case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. Acc Chem Res. 2008;41(1):50–59. [PubMed: 18193821]
79. Ma C, Sacco MD, Hurst B, et al. Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. Cell Res. 2020;30:678–692. 10.1038/s41422-020-0356-z [PubMed: 32541865]
80. Krampe H, Ehrenreich H. Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. Curr Pharm Des. 2010;16(19):2076–2090. [PubMed: 20482514]
81. Lipsky JJ, Shen ML, Naylor S. In vivo inhibition of aldehyde dehydrogenase by disulfiram. Chem-Biol Interact. 2001: 130–132.
82. Lin M-H, Moses DC, Hsieh C-H, et al. Disulfiram can inhibit MERS and SARS coronavirus papain-like proteases via different modes. Antivir Res. 2018;150:155–163. [PubMed: 29289665]
83. Schewe T Molecular actions of Ebselen—an antiinflammatory antioxidant. Gen Pharmacol. 1995;26(6):1153–1169. [PubMed: 7590103]
84. Marshall AC, Kidd SE, Lamont-Friedrich SJ, et al. Structure, mechanism, and inhibition of *Aspergillus fumigatus* thioredoxin reductase. Antimicrob Agents Chemother. 2019;63(3):e02281–18. [PubMed: 30642940]
85. Parnham M, Sies H. Ebselen: prospective therapy for cerebral ischaemia. Expert Opin Invest Drugs. 2000;9(3): 607–619.
86. Kil J, Lobarinas E, Spankovich C, et al. Safety and efficacy of ebselen for the prevention of noise-induced hearing loss: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2017;390(10098):969–979. [PubMed: 28716314]
87. Neuman RS, Zebrowska G. Serotonin (5-HT2) receptor mediated enhancement of cortical unit activity. Can J Physiol Pharmacol. 1992;70(12):1604–1609. [PubMed: 1301238]
88. Chen L, Gui C, Luo X, et al. Cinanserin is an inhibitor of the 3C-Like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro. J Virol. 2005;79(11):7095–7103. [PubMed: 15890949]

89. Itil TM, Polvan N, Holden JM. Clinical and electroencephalographic effects of cinanserin in schizophrenic and manic patients. Dis Nerv Syst. 1971;32(3):193–200. [PubMed: 4929084]

90. Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK. Broad-spectrum antiviral activity of Virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. Science. 1972;177(4050):705–706. [PubMed: 4340949]

91. Graci JD, Cameron CE. Mechanisms of action of ribavirin against distinct viruses. Rev Med Virol. 2006;16(1):37–48. [PubMed: 16287208]

92. Hall CB, Walsh EE, Hruska JF, Betts RF, Hall WJ. Ribavirin treatment of experimental respiratory syncytial viral infection: a controlled double-blind study in young adults. JAMA. 1983;249(19):2666–2670. [PubMed: 6341640]

93. Reichard O, Yun Z-B, Sönnerborg A, Weiland O. Hepatitis C viral RNA titers in serum prior to, during, and after oral treatment with ribavirin for chronic hepatitis C. J Med Virol. 1993;41(2):99–102. [PubMed: 8283183]

94. Paeshuyse J, Dallmeier K, Neyts J. Ribavirin for the treatment of chronic hepatitis C virus infection: a review of the proposed mechanisms of action. Curr Opin Virol. 2011;1(6):590–598. [PubMed: 22440916]

95. Ascioglu S, Leblebicioglu H, Vahaboglu H, Chan KA. Ribavirin for patients with Crimean-Congo haemorrhagic fever: a systematic review and meta-analysis. J Antimicrob Chemother. 2011;66(6):1215–1222. [PubMed: 21482564]

96. Bausch DG, Hadi CM, Khan SH, Lertora JJ. Review of the literature and proposed guidelines for the use of oral ribavirin as postexposure prophylaxis for Lassa fever. Clin Infect Dis. 2010;51(12):1435–1441. [PubMed: 21058912]

97. Soares-Weiser K, Thomas S, Garner GGT. Ribavirin for for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis. BMC Infect Dis. 2010;10(1):207. [PubMed: 20626907]

98. Eriksson B, Helgstrand E, Johansson NG, et al. Inhibition of influenza virus ribonucleic acid polymerase by ribavirin triphosphate. Antimicrob Agents Chemother. 1977;11(6):946–951. [PubMed: 879760]

99. Olschlager S, Neyts J, Gunther S. Depletion of GTP pool is not the predominant mechanism by which ribavirin exerts its antiviral effect on Lassa virus. Antiviral Res. 2011;91(2):89–93. [PubMed: 21616094]

100. Saijo M, Morikawa S, Fukushi S, et al. Inhibitory effect of mizoribine and ribavirin on the replication of severe acute respiratory syndrome (SARS)-associated coronavirus. Antiviral Res. 2005;66(2–3):159–163. [PubMed: 15911031]

101. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel beta coronavirus replication by a combination of interferon-alpha2b and ribavirin. Sci Rep. 2013;3:1686. [PubMed: 23594967]

102. Cheng VC, Chan JF, To KK, Yuen KY. Clinical management and infection control of SARS: lessons learned. Antiviral Res. 2013;100(2):407–419. [PubMed: 23994190]

103. Leong HN, Ang B, Earnest A, Teoh C, Xu W, Leo YS. Investigational use of ribavirin in the treatment of severe acute respiratory syndrome, Singapore, 2003. Trop Med Int Health. 2004;9(8):923–927. [PubMed: 15303999]

104. So LKY, Lau AC, Yam LY, et al. Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet. 2003;361(9369):1615–1617. [PubMed: 12747883]

105. Booth CM. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA. 2003;289(21):2801–2809. [PubMed: 12734147]

106. Falzarano D, de Wit E, Rasmussen AL, et al. Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med. 2013;19(10):1313–1317. [PubMed: 24013700]

107. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis. 2014;14(11):1090–1095. [PubMed: 25278221]

108. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis. 2014;20:42–46. [PubMed: 24406736]

109. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. J Antimicrob Chemother. 2015;70(7): 2129–2132. [PubMed: 25900158]
110. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–271. [PubMed: 32020029]
111. Lo MK, Jordan R, Arvey A, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci Rep. 2017;7(1):43395. [PubMed: 28262699]
112. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9(396):eaal3653. [PubMed: 28659436]
113. Tchesnokov EP, Feng JY, Porter DP, Gotte M. Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses. 2019;11(4):326.
114. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio. 2018;9(2):e00221–18. [PubMed: 29511076]
115. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature. 2016;531(7594):381–385. [PubMed: 26934220]
116. Siegel D, Hui HC, Doerffler E, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-*f*] [triazin-4-amino] adenine *C*-nucleoside (GS-5734) for the treatment of ebola and emerging viruses. J Med Chem. 2017;60(5):1648–1661. [PubMed: 28124907]
117. Mulangu S, Dodd LE, Davey RT, et al. A randomized, controlled trial of ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293–2303. [PubMed: 31774950]
118. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222. [PubMed: 31924756]
119. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA. 2020;117(12):6771–6776. [PubMed: 32054787]
120. Shannon A, Le NT-T, Selisko B, et al. Remdesivir and SARS-CoV-2: structural requirements at both nsp12 RdRp and nsp14 Exonuclease active-sites. Antivir Res. 2020;178:104793. [PubMed: 32283108]
121. Gordon CJ, Tchesnokov EP, Woolner E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020; 295(20):6785–6797. [PubMed: 32284326]
122. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382(24):2327–2336. [PubMed: 32275812]
123. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–1578. [PubMed: 32423584]
124. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19—final report. N Engl J Med. 2020; 383:1813–1826. 10.1056/NEJMoa2007764 [PubMed: 32445440]
125. Gilead. Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19 [press release]. 2020, 7 10.
126. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020;324(11):1048–1057. [PubMed: 32821939]
127. Yoon J-J, Toots M, Lee S, et al. Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses. Antimicrob Agents Chemother. 2018;62(8):e00766–18. [PubMed: 29891600]
128. Toots M, Yoon J-J, Cox RM, et al. Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. Sci Transl Med. 2019;11(515):eaax5866. [PubMed: 31645453]

129. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020;12(541):eabb5883. [PubMed: 32253226]
130. Furuta Y, Takahashi K, Fukuda Y, et al. In vitro and in vivo activities of anti-influenza virus compound T-705. Antimicrob Agents Chemother. 2002;46(4):977–981. [PubMed: 11897578]
131. Zaraket H, Saito R. Japanese surveillance systems and treatment for influenza. Curr Treat Options Infect Dis. 2016; 8(4):311–328. [PubMed: 28035195]
132. Baranovich T, Wong S-S, Armstrong J, et al. T-705 (Favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses *in vivo*. J Virol. 2013;87(7):3741–3751. [PubMed: 23325689]
133. Furuta Y, Takahashi K, Kuno-Maekawa M, et al. Mechanism of action of T-705 against influenza virus. Antimicrob Agents Chemother. 2005;49(3):981–986. [PubMed: 15728892]
134. Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J. The ambiguous base-pairing and high substrate efficiency of T-705 (Favipiravir) Ribofuranosyl 5'-triphosphate towards influenza A virus polymerase. PLOS One. 2013;8(7): e68347. [PubMed: 23874596]
135. Goldhill DH, Te Velthuis AJW, Fletcher RA, et al. The mechanism of resistance to favipiravir in influenza. Proc Natl Acad Sci USA. 2018;115(45):11613–11618. [PubMed: 30352857]
136. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449–463.
137. Furuta Y, Takahashi K, Shiraki K, et al. T-705 (favipiravir) and related compounds: novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res. 2009;82(3):95–102. [PubMed: 19428599]
138. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020;209:107512. [PubMed: 32097670]
139. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020. 10.1016/j.eng.2020.03.007
140. Chen C, Zhang Y, Huang J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020. 10.1101/2020.03.17.20037432
141. Warren TK, Wells J, Panchal RG, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature. 2014;508(7496):402–405. [PubMed: 24590073]
142. Julander JG, Siddharthan V, Evans J, et al. Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model. Antivir Res. 2017;137:14–22. [PubMed: 27838352]
143. Westover JB, Mathis A, Taylor R, et al. Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. Antivir Res. 2018;156:38–45. [PubMed: 29864447]
144. Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci. 2020;253:117592. [PubMed: 32222463]
145. Shiraki K Antiviral Drugs Against Alphaherpesvirus. In: Kawaguchi Y, Mori Y, Kimura H eds., Human Herpesviruses. Singapore: Springer; 2018:103–122.
146. Sacks SL, Wilson B. Famciclovir/penciclovir. Adv Exp Med Biol. 1999;458:135–147. [PubMed: 10549386]
147. Randolph B Penciclovir for the treatment of herpes simplex labialis: a review. ASDC J Dent Child. 2001;68(3): 189–190. [PubMed: 11693011]
148. Shiraki K Antiviral drugs against alphaherpesvirus. Adv Exp Med Biol. 2018;1045:103–122. [PubMed: 29896665]
149. Fickert P, Hinterleitner TA, Wenzl HH, Aichbichler BW, Petritsch W. Mycophenolate mofetil in patients with Crohn's disease. Am J Gastroenterol. 1998;93(12):2529–2532. [PubMed: 9860419]
150. Silverman Kitchin JE, Pomeranz MK, Pak G, Washenik K, Shupack JL. Rediscovering mycophenolic acid: a review of its mechanism, side effects, and potential uses. J Am Acad Dermatol. 1997;37(3):445–449. [PubMed: 9308561]
151. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2–3): 85–118. [PubMed: 10878285]

152. Morrey JD, Smee DF, Sidwell RW, Tseng C. Identification of active antiviral compounds against a New York isolate of West Nile virus. Antivir Res. 2002;55(1):107–116. [PubMed: 12076755]
153. Sebastian L, Sebastian L, Madhusudana SN, Ravi V, Desai A. Mycophenolic acid inhibits replication of Japanese encephalitis virus. Chemotherapy. 2011;57(1):56–61. [PubMed: 21282947]
154. Leyssen P, Balzarini J, De Clercq E, Neyts J. The predominant mechanism by which ribavirin exerts its antiviral activity in vitro against flaviviruses and paramyxoviruses is mediated by inhibition of IMP dehydrogenase. J Virol. 2005;79(3):1943–1947. [PubMed: 15650220]
155. Diamond MS, Zachariah M, Harris E. Mycophenolic acid inhibits dengue virus infection by preventing replication of viral RNA. Virology. 2002;304(2):211–221. [PubMed: 12504563]
156. Khan M, Dhanwani R, Patro IK, Rao PVL, Parida MM. Cellular IMPDH enzyme activity is a potential target for the inhibition of Chikungunya virus replication and virus induced apoptosis in cultured mammalian cells. Antivir Res. 2011;89(1):1–8. [PubMed: 21070810]
157. Pan Q, de Ruiter PE, Metselaar HJ, et al. Mycophenolic acid augments interferon-stimulated gene expression and inhibits hepatitis C Virus infection in vitro and in vivo. Hepatology. 2012;55(6):1673–1683. [PubMed: 22213147]
158. Ye L, Li J, Zhang T, et al. Mycophenolate mofetil inhibits hepatitis C virus replication in human hepatic cells. Virus Res. 2012;168(1):33–40. [PubMed: 22728816]
159. Chan JFW, Chan KH, Kao RYT, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect. 2013;67(6):606–616. [PubMed: 24096239]
160. Hart BJ, Dyall J, Postnikova E, et al. Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. J Gen Virol. 2014;95(Pt 3):571–577. [PubMed: 24323636]
161. Chan JFW, Yao Y, Yeung ML, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis. 2015;212(12):1904–1913. [PubMed: 26198719]
162. Barnard DL, Day CW, Bailey K, et al. Enhancement of the infectivity of SARS-CoV in BALB/c mice by IMP dehydrogenase inhibitors, including ribavirin. Antiviral Res. 2006;71(1):53–63. [PubMed: 16621037]
163. Faure E, Poissy J, Goffard A, et al. Distinct immune response in two MERS-CoV-infected patients: can we go from bench to bedside? PLOS One. 2014;9(2):e88716. [PubMed: 24551142]
164. AlGhamdi M, Mushtaq F, Awn N, Shalhoub S. MERS CoV infection in two renal transplant recipients: case report. Am J Transplant. 2015;15(4):1101–1104. [PubMed: 25716741]
165. Kato F, Matsuyama S, Kawase M, Hishiki T, Katoh H, Takeda M. Antiviral activities of mycophenolic acid and IMD-0354 against SARS-CoV-2. Microbiol Immunol. 2020;64(9):635–639. [PubMed: 32579258]
166. Jain J, Almquist SJ, Shlyakhter D, Harding MW. VX-497: a novel, selective IMPDH inhibitor and immunosuppressive agent. J Pharm Sci. 2001;90(5):625–637. [PubMed: 11288107]
167. Markland W, McQuaid TJ, Jain J, Kwong AD. Broad-spectrum antiviral activity of the IMP dehydrogenase inhibitor VX-497: a comparison with ribavirin and demonstration of antiviral additivity with alpha interferon. Antimicrob Agents Chemother. 2000;44(4):859–866. [PubMed: 10722482]
168. Tong X, Smith J, Bukreyeva N, et al. Merimepodib, an IMPDH inhibitor, suppresses replication of Zika virus and other emerging viral pathogens. Antiviral Res. 2018;149:34–40. [PubMed: 29126899]
169. Li S-F, Gong M-J, Shao J-J, Sun Y-F, Zhang Y-G, Chang H-Y. Antiviral activity of merimepodib against foot and mouth disease virus in vitro and in vivo. Mol Immunol. 2019;114:226–232. [PubMed: 31386979]
170. Marcellin P, Horsmans Y, Nevens F, et al. Phase 2 study of the combination of merimepodib with peginterferon-α2b, and ribavirin in nonresponders to previous therapy for chronic hepatitis C. J Hepatol. 2007;47(4):476–483. [PubMed: 17629590]
171. Bukreyeva N, Mantlo EK, Sattler RA, Huang C, Paessler S, Zeldis J. The IMPDH inhibitor merimepodib suppresses SARS-CoV-2 replication in vitro. bioRxiv. 2020. 10.1101/2020.04.07.028589

172. Tsuzuki K Role of mizoribine in renal transplantation. Pediatr Int. 2002;44(2):224–231. [PubMed: 11896891]

173. Kawasaki Y Mizoribine: a new approach in the treatment of renal disease. Clin Dev Immunol. 2009;2009:681482. [PubMed: 20052390]

174. Yokota S Mizoribine: mode of action and effects in clinical use. Pediatr Int. 2002;44(2):196–198. [PubMed: 11896886]

175. Alvarellos ML, Lamba J, Sangkuhl K, et al. PharmGKB summary: gemcitabine pathway. Pharmacogenet Genom. 2014; 24(11):564–574.

176. Wong A, Soo RA, Yong W-P, Innocenti F. Clinical pharmacology and pharmacogenetics of gemcitabine. Drug Metab Rev. 2009;41(2):77–88. [PubMed: 19514966]

177. Mini E, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. Ann Oncol. 2006;17(Suppl 5): v7–v12. [PubMed: 16807468]

178. Dyall J, Coleman CM, Hart BJ, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother. 2014;58(8):4885–4893. [PubMed: 24841273]

179. Zhang Y-N, Zhang Q-Y, Li X-D, et al. Gemcitabine, lycorine and oxysophoridine inhibit novel coronavirus (SARS-CoV-2) in cell culture. Emerg Microbes Infect. 2020;9(1):1170–1173. [PubMed: 32432977]

180. Ruiz van Haperen VWT, Veerman G, Vermorken JB, Peters GJ. 2′,2′-Difluoro-deoxycytidine (gemcitabine) incorporation into RNA and DNA of tumour cell lines. Biochem Pharmacol. 1993;46(4):762–766. [PubMed: 8363650]

181. Davies BE. Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations. J Antimicrob Chemother. 2010;65(suppl_2):5–10.

182. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545. [PubMed: 24811411]

183. Heneghan CJ, Onakpoya I, Jones MA, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(42):1–242.

184. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015;385(9979):1729–1737. [PubMed: 25640810]

185. Liu Y-C, Liao C-H, Chang C-F, Chou C-C, Lin Y-R. A locally transmitted case of SARS-CoV-2 infection in Taiwan. N Engl J Med. 2020;382(11):1070–1072. [PubMed: 32050059]

186. Leneva IA, Russell RJ, Boriskin YS, Hay AJ. Characteristics of arbidol-resistant mutants of influenza virus: implications for the mechanism of anti-influenza action of arbidol. Antiviral Res. 2009;81(2):132–140. [PubMed: 19028526]

187. Leneva IA, Burtseva EI, Yatsyshina SB, et al. Virus susceptibility and clinical effectiveness of anti-influenza drugs during the 2010–2011 influenza season in Russia. Int J Infect Dis. 2016;43:77–84. [PubMed: 26775570]

188. Boriskin YS, Leneva IA, Pecheur EI, Polyak SJ. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem. 2008;15(10):997–1005. [PubMed: 18393857]

189. Pécheur EI, Borisevich V, Halfmann P, et al. The synthetic antiviral drug arbidol inhibits globally prevalent pathogenic viruses. J Virol. 2016;90(6):3086–3092. [PubMed: 26739045]

190. Boriskin YS, Pécheur E-I, Polyak SJ. Arbidol: a broad-spectrum antiviral that inhibits acute and chronic HCV infection. Virol J. 2006;3(1):56. [PubMed: 16854226]

191. Blaising J, Polyak SJ, Pécheur E-I. Arbidol as a broad-spectrum antiviral: an update. Antivir Res. 2014;107:84–94. [PubMed: 24769245]

192. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1): 58–60. [PubMed: 32147628]

193. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against corona virus disease 2019: a retrospective cohort study. J Infect. 2020;81(1):e1–e5.

194. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020; 81(1):e21–e23. [PubMed: 32283143]

195. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clin Microbiol Infect. 2020;26(7):917–921. [PubMed: 32344167]

196. Wintermeyer SM, Nahata MC. Rimantadine: a clinical perspective. Ann Pharmacother. 1995;29(3):299–310. [PubMed: 7606077]

197. Govorkova EA, Fang HB, Tan M, Webster RG. Neuraminidase inhibitor-rimantadine combinations exert additive and synergistic anti-influenza virus effects in MDCK cells. Antimicrob Agents Chemother. 2004;48(12):4855–4863. [PubMed: 15561867]

198. Jing X, Ma C, Ohigashi Y, et al. Functional studies indicate amantadine binds to the pore of the influenza A virus M2 proton-selective ion channel. Proc Natl Acad Sci USA. 2008;105(31):10967–10972. [PubMed: 18669647]

199. Wang C, Takeuchi K, Pinto LH, Lamb RA. Ion channel activity of influenza A virus M2 protein: characterization of the amantadine block. J Virol. 1993;67(9):5585–5594. [PubMed: 7688826]

200. Belshe RB, Smith MH, Hall CB, Betts R, Hay AJ. Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. J Virol. 1988;62(5):1508–1512. [PubMed: 3282079]

201. Evidente VG, Adler CH, Caviness JN, Gwinn-Hardy K. A pilot study on the motor effects of rimantadine in Parkinson's disease. Clin Neuropharmacol. 1999;22(1):30–32. [PubMed: 10047931]

202. Jasiński M, Jasińska L, Ogrodowczyk M. Resveratrol in prostate diseases—a short review. Cent European J Urol. 2013;66(2):144–149.

203. Vang O, Ahmad N, Baile CA, et al. What is new for an old molecule? Systematic review and recommendations on the use of resveratrol. PLoS One. 2011;6(6):e19881. [PubMed: 21698226]

204. Lin S-C, Ho C-T, Chuo W-H, Li S, Wang TT, Lin C-C. Effective inhibition of MERS-CoV infection by resveratrol. BMC Infect Dis. 2017;17(1):144. [PubMed: 28193191]

205. Ellen ter BM, Dinesh Kumar N, Bouma EM, et al. Resveratrol and pterostilbene potently inhibit SARS-CoV-2 infection in vitro. bioRxiv. 2020. 10.1101/2020.09.24.285940

206. Garreau de Loubresse N, Prokhorova I, Holtkamp W, Rodnina MV, Yusupova G, Yusupov M. Structural basis for the inhibition of the eukaryotic ribosome. Nature. 2014;513(7519):517–522. [PubMed: 25209664]

207. Jimenez A, Carrasco L, Vazquez D. Enzymic and nonenzymic translocation by yeast polysomes. Site of action of a number of inhibitors. Biochemistry. 1977;16(21):4727–4730. [PubMed: 334249]

208. Grollman AP. Structural basis for inhibition of protein synthesis by emetine and cycloheximide based on an analogy between ipecac alkaloids and glutarimide antibiotics. Proc Natl Acad Sci USA. 1966;56(6):1867–1874. [PubMed: 16591432]

209. Wong W, Bai X, Brown A, et al. Cryo-EM structure of the Plasmodium falciparum 80S ribosome bound to the anti-protozoan drug emetine. eLife. 2014;3:e03080.

210. Grollman AP. Inhibitors of protein biosynthesis. II. Mode of action of anisomycin. J Biol Chem. 1967;242(13): 3226–3233. [PubMed: 6027796]

211. Liu Y, Ge J, Li Q, et al. Low-dose anisomycin sensitizes glucocorticoid-resistant T-acute lymphoblastic leukemia CEM-C1 cells to dexamethasone-induced apoptosis through activation of glucocorticoid receptor and p38-MAPK/JNK. Leuk Lymphoma. 2014;55(9):2179–2188. [PubMed: 24597985]

212. Khandelwal N, Chander Y, Rawat KD, et al. Emetine inhibits replication of RNA and DNA viruses without generating drug-resistant virus variants. Antivir Res. 2017;144:196–204. [PubMed: 28624461]

213. Andersen PI, Krpina K, Ianevski A, et al. Novel antiviral activities of obatoclax, emetine, niclosamide, brequinar, and homoharringtonine. Viruses. 2019;11(10):964.

214. Choy K-T, Wong AY-L, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antivir Res. 2020;178:104786. [PubMed: 32251767]

215. Ho PC, Dweik R, Cohen MC. Rapidly reversible cardiomyopathy associated with chronic ipecac ingestion. Clin Cardiol. 1998;21(10):780–783. [PubMed: 9789704]
216. Gilles A, Frechin L, Natchiar K, et al. Targeting the human 80S ribosome in cancer: from structure to function and drug design for innovative adjuvant therapeutic strategies. Cells. 2020;9(3):629.
217. Fresno M, Jiménez A, Vázquez D. Inhibition of translation in eukaryotic systems by harringtonine. Eur J Biochem. 1977;72(2):323–330. [PubMed: 319998]
218. Fahr A Cyclosporin clinical pharmacokinetics. Clin Pharmacokinet. 1993;24(6):472–495. [PubMed: 8513650]
219. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology. 2000;47(2):119–125. [PubMed: 10878286]
220. Handschumacher RE, Harding MW, Rice J, Drugge RJ, Speicher DW. Cyclophilin: a specific cytosolic binding protein for cyclosporin A. Science. 1984;226(4674):544–547. [PubMed: 6238408]
221. Pfefferle S, Schöpf J, Kögl M, et al. The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. PLoS Pathog. 2011;7(10):e1002331. [PubMed: 22046132]
222. Tanaka Y, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. Viruses. 2013;5(5): 1250–1260. [PubMed: 23698397]
223. de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol. 2011;92(Pt 11):2542–2548. [PubMed: 21752960]
224. de Wilde AH, Raj VS, Oudshoorn D, et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol. 2013;94(Pt 8):1749–1760. [PubMed: 23620378]
225. Gallay PA, Lin K. Profile of alisporivir and its potential in the treatment of hepatitis C. Drug Des Devel Ther. 2013; 7:105–115.
226. Paeshuyse J, Kaul A, De Clercq E, et al. The nonimmunosuppressive cyclosporin DEBIO-025 is a potent inhibitor of hepatitis C virus replication in vitro. Hepatology. 2006;43(4):761–770. [PubMed: 16557546]
227. Coelmont L, Kaptein S, Paeshuyse J, et al. Debio 025, a cyclophilin binding molecule, is highly efficient in clearing hepatitis C virus (HCV) replicon-containing cells when used alone or in combination with specifically targeted antiviral therapy for HCV (STAT-C) inhibitors. Antimicrob Agents Chemother. 2009;53(3):967–976. [PubMed: 19104013]
228. Ptak RG, Gallay PA, Jochmans D, et al. Inhibition of human immunodeficiency virus type 1 replication in human cells by Debio-025, a novel cyclophilin binding agent. Antimicrob Agents Chemother. 2008;52(4):1302–1317. [PubMed: 18212100]
229. de Wilde AH, Falzarano D, Zevenhoven-Dobbe JC, et al. Alisporivir inhibits MERS- and SARS-coronavirus replication in cell culture, but not SARS-coronavirus infection in a mouse model. Virus Res. 2017;228:7–13. [PubMed: 27840112]
230. Softic L, Brillet R, Berry F, et al. Inhibition of SARS-CoV-2 infection by the cyclophilin inhibitor alisporivir (Debio 025). Antimicrob Agents Chemother. 2020;64(7):e00876–20. [PubMed: 32376613]
231. Weisberg E, Manley PW, Cowan-Jacob SW, Hochhaus A, Griffin JD. Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia. Nat Rev Cancer. 2007;7(5):345–356. [PubMed: 17457302]
232. Weston S, Haupt R, Logue J, Matthews K, Frieman MB. FDA approved drugs with broad anti-coronaviral activity inhibit SARS-CoV-2 in vitro. bioRxiv. 2020. 10.1101/2020.03.25.008482
233. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB. Abelson kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus fusion. J Virol. 2016;90(19):8924–8933. [PubMed: 27466418]
234. Sisk JM, Frieman MB, Machamer CE. Coronavirus S protein-induced fusion is blocked prior to hemifusion by Abl kinase inhibitors. J Gen Virol. 2018;99(5):619–630. [PubMed: 29557770]

235. Das J, Chen P, Norris D, et al. 2-Aminothiazole as a novel kinase inhibitor template. structure–activity relationship studies toward the discovery of N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl)]-2-methyl-4-pyrimidinyl]amino)]-1,3-thiazole-5-carboxamide (Dasatinib, BMS-354825) as a potent pan-Src kinase inhibitor. J Med Chem. 2006;49(23):6819–6832. [PubMed: 17154512]

236. Hennequin LF, Allen J, Breed J, et al. N-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a novel, highly selective, orally available, dual-specific c-Src/Abl kinase inhibitor. J Med Chem. 2006;49(22):6465–6488. [PubMed: 17064066]

237. Keating GM. Dasatinib: a review in chronic myeloid leukaemia and Ph+acute lymphoblastic leukaemia. Drugs. 2017; 77(1):85–96. [PubMed: 28032244]

238. Reddy SM, Kopetz S, Morris J, et al. Phase II study of saracatinib (AZD0530) in patients with previously treated metastatic colorectal cancer. Invest New Drugs. 2015;33(4):977–984. [PubMed: 26062928]

239. Sanz-Blasco S, Bordone MP, Damianich A, et al. The kinase Fyn as a novel intermediate in L-DOPA-induced dyskinesia in Parkinson's disease. Mol Neurobiol. 2018;55(6):5125–5136. [PubMed: 28840468]

240. Hu M, Che P, Han X, et al. Therapeutic targeting of SRC kinase in myofibroblast differentiation and pulmonary fibrosis. J Pharmacol Exp Ther. 2014;351(1):87–95. [PubMed: 25047515]

241. Shin JS, Jung E, Kim M, Baric RS, Go YY. Saracatinib inhibits middle east respiratory syndrome-coronavirus replication in vitro. Viruses. 2018;10(6):283.

242. Coyne CB, Bergelson JM. Virus-induced Abl and Fyn kinase signals permit coxsackievirus entry through epithelial tight junctions. Cell. 2006;124(1):119–131. [PubMed: 16413486]

243. de Wispelaere M, LaCroix AJ, Yang PL. The small molecules AZD0530 and dasatinib inhibit dengue virus RNA replication via Fyn kinase. J Virol. 2013;87(13):7367–7381. [PubMed: 23616652]

244. Kumar R, Agrawal T, Khan NA, Nakayama Y, Medigeshi GR. Identification and characterization of the role of c-terminal Src kinase in dengue virus replication. Sci Rep. 2016;6:30490. [PubMed: 27457684]

245. Newsome TP, Weisswange I, Frischknecht F, Way M. Abl collaborates with Src family kinases to stimulate actin-based motility of vaccinia virus. Cell Microbiol. 2006;8(2):233–241. [PubMed: 16441434]

246. Kindrachuk J, Ork B, Hart BJ, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. Antimicrob Agents Chemother. 2015;59(2):1088–1099. [PubMed: 25487801]

247. Miller CR, Oliver KE, Farley JH. MEK1/2 inhibitors in the treatment of gynecologic malignancies. Gynecol Oncol. 2014;133(1):128–137. [PubMed: 24434059]

248. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020; 214:108393. [PubMed: 32222466]

249. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. [PubMed: 31986264]

250. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400–402. [PubMed: 32113509]

251. Pesu M, Laurence A, Kishore N, Zwillich SH, Chan G, O'Shea JJ. Therapeutic targeting of Janus kinases. Immunol Rev. 2008;223(1):132–142. [PubMed: 18613833]

252. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30–e31. [PubMed: 32032529]

253. Lu J Palbociclib: a first-in-class CDK4/CDK6 inhibitor for the treatment of hormone-receptor positive advanced breast cancer. J Hematol Oncol. 2015;8(1):98. [PubMed: 26264704]

254. Park I-K, Mishra A, Chandler J, Whitman SP, Marcucci G, Caligiuri MA. Inhibition of the receptor tyrosine kinase Axl impedes activation of the FLT3 internal tandem duplication in

human acute myeloid leukemia: implications for Axl as a potential therapeutic target. Blood. 2013;121(11):2064–2073. [PubMed: 23321254]

255. Zhou Y, Vedantham P, Lu K, et al. Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res. 2015; 116:76–84. [PubMed: 25666761]
256. Park J-E, Li K, Barlan A, et al. Proteolytic processing of Middle East respiratory syndrome coronavirus spikes expands virus tropism. Proc Natl Acad Sci USA. 2016;113(43):12262–12267. [PubMed: 27791014]
257. Abdulla M-H, Lim K-C, Sajid M, McKerrow JH, Caffrey CR. Schistosomiasis mansoni: novel chemotherapy using a cysteine protease inhibitor. PLOS Med. 2007;4(1):e14. [PubMed: 17214506]
258. Tamai M, Matsumoto K, Omura S, Koyama I, Ozawa Y, Hanada K. In vitro and in vivo inhibition of cysteine proteinases by EST, a new analog of E-64. J Pharmacobiodyn. 1986;9(8):672–677. [PubMed: 3023601]
259. Hook G, Hook V, Kindy M. The cysteine protease inhibitor, E64d, reduces brain amyloid-beta and improves memory deficits in Alzheimer's disease animal models by inhibiting cathepsin B, but not BACE1, beta-secretase activity. J Alzheimers Dis. 2011;26(2):387–408. [PubMed: 21613740]
260. Satoyoshi E Therapeutic trials on progressive muscular dystrophy. Intern Med. 1992;31(7):841–846. [PubMed: 1450492]
261. Imahori K, Sugita H, Miyatake T, Ishihara T, Miyatani N, Kuwabara T. Pharmacokinetics and safety of EST, a new thiol protease inhibitor in patients with muscle diseases. Rinsho yakuri/ Japanese J Clin Pharmacol Ther. 1985;16(4): 749–757.
262. Miyahara T, Shimojo S, Toyohara K, et al. Phase I study of EST, a new thiol protease inhibitor. the 1st report: safety and pharmacokinetics at single administration. Rinsho yakuri/Japanese J Clin Pharmacol Ther. 1985;16(2):357–365.
263. Miyahara T, Shimojo S, Toyohara K, et al. Phase I study of EST, a new thiol protease inhibitor. the 2nd report: safety and pharmacokinetics in continuous administration. Rinsho yakuri/ Japanese J Clin Pharmacol Ther. 1985;16(3): 537–546.
264. Glowacka I, Bertram S, Muller MA, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122–4134. [PubMed: 21325420]
265. Talukdar R, Tandon RK. Pancreatic stellate cells: new target in the treatment of chronic pancreatitis. J Gastroenterol Hepatol. 2008;23(1):34–41. [PubMed: 17995943]
266. Sai JK, Suyama M, Kubokawa Y, Matsumura Y, Inami K, Watanabe S. Efficacy of camostat mesilate against dyspepsia associated with non-alcoholic mild pancreatic disease. J Gastroenterol. 2010;45(3):335–341. [PubMed: 19876587]
267. Chen X, Xu Z, Zeng S, et al. The molecular aspect of antitumor effects of protease inhibitor nafamostat mesylate and its role in potential clinical applications. Front Oncol. 2019;9:852. [PubMed: 31552177]
268. Al-Horani RA, Desai UR. Recent advances on plasmin inhibitors for the treatment of fibrinolysis-related disorders. Med Res Rev. 2014;34(6):1168–1216. [PubMed: 24659483]
269. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrob Agents Chemother. 2020;64(6): e00754–20. [PubMed: 32312781]
270. Yamamoto M, Matsuyama S, Li X, et al. Identification of nafamostat as a potent inhibitor of Middle East respiratory syndrome coronavirus S protein-mediated membrane fusion using the split-protein-based cell-cell fusion assay. Antimicrob Agents Chemother. 2016;60(11):6532–6539. [PubMed: 27550352]
271. Jang S, Rhee J-Y. Three cases of treatment with nafamostat in elderly patients with COVID-19 pneumonia who need oxygen therapy. Int J Infect Dis. 2020;96:500–502. [PubMed: 32470602]
272. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J Virol. 2019;93(6): e01815–18. [PubMed: 30626688]

273. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722–727. [PubMed: 14592603]

274. Pastick KA, Okafor EC, Wang F, et al. Review: hydroxychloroquine and chloroquine for treatment of SARS-CoV-2 (COVID-19). Open Forum Infect Dis. 2020;7(4):ofaa130. [PubMed: 32363212]

275. Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect. 2017;5(1): e00293. [PubMed: 28596841]

276. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2(1):69. [PubMed: 16115318]

277. Keyaerts E, Vijgen L, Maes P, Neyts J, Van, Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004;323(1):264–268. [PubMed: 15351731]

278. Barnard DL, Day CW, Bailey K, et al. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir Chem Chemother. 2006;17(5):275–284. [PubMed: 17176632]

279. Shippey EA, Wagler VD, Collamer AN. Hydroxychloroquine: an old drug with new relevance. Cleve Clin J Med. 2018; 85(6):459–467. [PubMed: 29883308]

280. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16(3):155–166. [PubMed: 32034323]

281. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6(1):16.

282. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71:732–739. 10.1093/cid/ciaa237 [PubMed: 32150618]

283. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72–73. [PubMed: 32074550]

284. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial. Int J Antimicrob Agents. 2020;56:105949. [PubMed: 32205204]

285. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis. 2020;34:101663. [PubMed: 32289548]

286. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020;50(4):384. [PubMed: 32240719]

287. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial medRxiv. 2020. 10.1101/2020.03.22.20040758

288. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis. 2020;97:396–403. [PubMed: 32623082]

289. Taccone FS, Gorham J, Vincent J-L. Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. Lancet Respir Med. 2020;8(6):539–541. [PubMed: 32304640]

290. White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, Tarning J. COVID-19 prevention and treatment: a critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLOS Med. 2020;17(9): e1003252. [PubMed: 32881895]

291. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA. 2020;323(24):2493–2502. [PubMed: 32392282]

292. Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multi-centre, randomized, controlled trial. medRxiv. 2020.

293. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;323(18):1824–1836. [PubMed: 32282022]
294. Liu Q, Xia S, Sun Z, et al. Testing of Middle East respiratory syndrome coronavirus replication inhibitors for the ability to block viral entry. Antimicrob Agents Chemother. 2015;59(1):742–744. [PubMed: 25331705]
295. Inoue Y, Tanaka N, Tanaka Y, et al. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. J Virol. 2007;81(16):8722–8729. [PubMed: 17522231]
296. Wang LH, Rothberg KG, Anderson RG. Mis-assembly of clathrin lattices on endosomes reveals a regulatory switch for coated pit formation. J Cell Biol. 1993;123(5):1107–1117. [PubMed: 8245121]
297. Blanchard E, Belouzard S, Goueslain L, et al. Hepatitis C virus entry depends on clathrin-mediated endocytosis. J Virol. 2006;80(14):6964–6972. [PubMed: 16809302]
298. Pohjala L, Utt A, Varjak M, et al. Inhibitors of alphavirus entry and replication identified with a stable chikungunya replicon cell line and virus-based assays. PLOS One. 2011;6(12):e28923. [PubMed: 22205980]
299. Chu VC, McElroy LJ, Ferguson AD, Bauman BE, Whittaker GR. Avian infectious bronchitis virus enters cells via the endocytic pathway. Adv Exp Med Biol. 2006;581:309–312. [PubMed: 17037550]
300. Pu Y, Zhang X. Mouse hepatitis virus type 2 enters cells through a clathrin-mediated endocytic pathway independent of Eps15. J Virol. 2008;82(16):8112–8123. [PubMed: 18550663]
301. Patel S Plant-derived cardiac glycosides: role in heart ailments and cancer management. Biomed Pharmacother. 2016;84:1036–1041. [PubMed: 27780131]
302. Burkard C, Verheije MH, Haagmans BL, et al. ATP1A1-mediated Src signaling inhibits coronavirus entry into host cells. J Virol. 2015;89(8):4434–4448. [PubMed: 25653449]
303. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol. 1997;340(2):249–258. [PubMed: 9537821]
304. Riva L, Yuan S, Yin X, et al. Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. Nature. 2020;586:113–119. 10.1038/s41586-020-2577-1 [PubMed: 32707573]
305. Chen W, Mook RA, Premont RT, Wang J. Niclosamide: beyond an antihelminthic drug. Cell Signal. 2018;41:89–96. [PubMed: 28389414]
306. Li Y, Li P-K, Roberts MJ, Arend RC, Samant RS, Buchsbaum DJ. Multi-targeted therapy of cancer by niclosamide: a new application for an old drug. Cancer Lett. 2014;349(1):8–14. [PubMed: 24732808]
307. Wu C-J, Jan J-T, Chen C-M, et al. Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother. 2004;48(7):2693–2696. [PubMed: 15215127]
308. Wen C-C, Kuo Y-H, Jan J-T, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem. 2007;50(17):4087–4095. [PubMed: 17663539]
309. Gassen NC, Niemeyer D, Muth D, et al. SKP2 attenuates autophagy through Beclin1-ubiquitination and its inhibition reduces MERS-Coronavirus infection. Nat Commun. 2019;10(1):5770. [PubMed: 31852899]
310. Xu J, Berastegui-Cabrera J, Chen H, Pachón J, Zhou J, Sánchez-Céspedes J. Structure–activity relationship studies on diversified salicylamide derivatives as potent inhibitors of human adenovirus infection. J Med Chem. 2020;63(6): 3142–3160. [PubMed: 32045239]
311. Li Z, Xu J, Lang Y, et al. JMX0207, a niclosamide derivative with improved pharmacokinetics, suppresses Zika virus infection both *in vitro* and *in vivo*. ACS Infect Dis. ACS Infect Dis 2020;6:2616–2628. 10.1021/acsinfecdis.0c00217 [PubMed: 32866370]
312. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. Antiviral Res. 2014;110:94–103. [PubMed: 25108173]

313. Clerici M, Trabattoni D, Pacei M, Biasin M, Rossignol J-F. The anti-infective nitazoxanide shows strong immumodulating effects (155.21). J Immunol. 2011;186(1 Suppl):155.21.

314. Elazar M, Liu M, McKenna SA, et al. The anti-hepatitis C agent nitazoxanide induces phosphorylation of eukaryotic initiation factor 2α via protein kinase activated by double-stranded RNA activation. Gastroenterology. 2009;137(5): 1827–1835. [PubMed: 19664635]

315. Jasenosky LD, Cadena C, Mire CE, et al. The FDA-approved oral drug nitazoxanide amplifies host antiviral responses and inhibits Ebola virus. iScience. 2019;19:1279–1290. [PubMed: 31402258]

316. Haffizulla J, Hartman A, Hoppers M, et al. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. Lancet Infect Dis. 2014;14(7):609–618. [PubMed: 24852376]

317. Galan-Herrera JF, Poo JL, Rosales-Sanchez O, et al. Bioavailability of two oral formulations of a single dose of levofloxacin 500 mg: an open-label, randomized, two-period crossover comparison in healthy Mexican volunteers. Clin Ther. 2009;31(8):1796–1803. [PubMed: 19808138]

318. Korba BE, Montero AB, Farrar K, et al. Nitazoxanide, tizoxanide and other thiazolides are potent inhibitors of hepatitis B virus and hepatitis C virus replication. Antiviral Res. 2008;77(1):56–63. [PubMed: 17888524]

319. Cao J, Forrest JC, Zhang X. A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs. Antiviral Res. 2015;114:1–10. [PubMed: 25451075]

320. Stringfellow DA, Glasgow LA. Tilorone hydrochloride: an oral interferon-inducing agent. Antimicrob Agents Chemother. 1972;2(2):73–78. [PubMed: 4670490]

321. Ekins S, Lane TR, Madrid PB. Tilorone: a broad-spectrum antiviral invented in the USA and commercialized in Russia and beyond. Pharm Res. 2020;37(4):71. [PubMed: 32215760]

322. Shen L, Niu J, Wang C, et al. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. J Virol. 2019;93(12):e00023–19. [PubMed: 30918074]

323. Tolman EL, Isaacson DM, Rosenthale ME, et al. Anticandidal activities of terconazole, a broad-spectrum antimycotic. Antimicrob Agents Chemother. 1986;29(6):986–991. [PubMed: 3729366]

324. Isaacson DM, Tolman EL, Tobia AJ, et al. Selective inhibition of 14 alpha-desmethyl sterol synthesis in Candida albicans by terconazole, a new triazole antimycotic. J Antimicrob Chemother. 1988;21(3):333–343. [PubMed: 3129389]

325. Yoshida Y Cytochrome P450 of Fungi: Primary Target for Azole Antifungal Agents. In: McGinnis MR ed., Current Topics in Medical Mycology. New York, NY. New York: Springer; 1988:388–418.

326. Peters DH, Friedel HA, McTavish D. Azithromycin. Drugs 1992;44(5):750–799. [PubMed: 1280567]

327. Parnham MJ, Haber VE, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther. 2014;143(2):225–245. [PubMed: 24631273]

328. Steel HC, Theron AJ, Cockeran R, Anderson R, Feldman C. Pathogen- and host-directed anti-inflammatory activities of macrolide antibiotics. Mediat Inflamm. 2012;2012:584262–17.

329. Feola DJ, Garvy BA, Cory TJ, et al. Azithromycin alters macrophage phenotype and pulmonary compartmentalization during lung infection with pseudomonas. Antimicrob Agents Chemother. 2010;54(6):2437–2447. [PubMed: 20231397]

330. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non–cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA. 2013; 309(12):1251–1259. [PubMed: 23532241]

331. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. Eur J Clin Pharmacol. 2012;68(5):479–503. [PubMed: 22105373]

332. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. Chest. 2004;125(2):52–61.

333. Antoszczak M, Huczyński A. Salinomycin and its derivatives—a new class of multiple-targeted “magic bullets”. Eur J Med Chem. 2019;176:208–227. [PubMed: 31103901]

334. Antoszczak M A comprehensive review of salinomycin derivatives as potent anticancer and anti-CSCs agents. Eur J Med Chem. 2019;166:48–64. [PubMed: 30684870]
335. Naujokat C, Steinhart R. Salinomycin as a drug for targeting human cancer stem cells. J Biomed Biotechnol. 2012; 2012:950658–17. [PubMed: 23251084]
336. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antivir Res. 2020;178:104787. [PubMed: 32251768]
337. Varghese FS, Kaukinen P, Gläsker S, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antivir Res. 2016;126:117–124. [PubMed: 26752081]
338. Tay MYF, Fraser JE, Chan WKK, et al. Nuclear localization of dengue virus (DENV) 1–4 nonstructural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antivir Res. 2013;99(3):301–306. [PubMed: 23769930]
339. Denning DW. Echinocandins: a new class of antifungal. J Antimicrob Chemother. 2002;49(6):889–891. [PubMed: 12039879]
340. Gobernado M, Canton E. Anidulafungin. Rev Esp Quimioter. 2008;21(2):99–114. [PubMed: 18509769]
341. Damle BD, Dowell JA, Walsky RL, Weber GL, Stogniew M, Inskeep PB. In vitro and in vivo studies to characterize the clearance mechanism and potential cytochrome P450 interactions of anidulafungin. Antimicrob Agents Chemother. 2009;53(3):1149–1156. [PubMed: 19029327]
342. Abhijnhan A, Adams CE, David A, Ozbilen M. Depot fluspirilene for schizophrenia. Cochrane Database Syst Rev. 2007; (1):CD001718. 10.1002/14651858.CD001718.pub2 [PubMed: 17253464]
343. Yavropoulou MP, Makras P, Anastasilakis AD. Bazedoxifene for the treatment of osteoporosis. Expert Opin Pharmacother. 2019;20(10):1201–1210. [PubMed: 31091133]
344. Wade P, Palmer J, McKenney S, et al. Modulation of gastrointestinal function by MuDelta, a mixed μ opioid receptor agonist/μ opioid receptor antagonist. Br J Pharmacol. 2012;167(5):1111–1125. [PubMed: 22671931]
345. Toyama M, Hamasaki T, Uto T, et al. Synergistic inhibition of HTLV-1-infected cell proliferation by combination of cepharanthine and a tetramethylnaphthalene derivative. Anticancer Res. 2012;32(7):2639–2645. [PubMed: 22753721]
346. Li Z, Geng Y-N, Jiang J-D, Kong W-J. Antioxidant and anti-inflammatory activities of berberine in the treatment of diabetes mellitus. Evid Based Complement Alternat Med. 2014;2014:289264–12. [PubMed: 24669227]
347. Kwan CY, Achike FI. Tetrandrine and related bis-benzylisoquinoline alkaloids from medicinal herbs: cardiovascular effects and mechanisms of action. Acta Pharmacol Sin. 2002;23(12):1057–1068. [PubMed: 12466042]
348. Wu C-Y, Jan J-T, Ma S-H, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci USA. 2004;101(27):10012–10017. [PubMed: 15226499]
349. McPhail GL, Clancy JP. Ivacaftor: the first therapy acting on the primary cause of cystic fibrosis. Drugs Today (Barc). 2013;49(4):253–260. [PubMed: 23616952]
350. Tao X, Mei F, Agrawal A, et al. Blocking of exchange proteins directly activated by cAMP leads to reduced replication of Middle East respiratory syndrome coronavirus. J Virol. 2014;88(7):3902–3910. [PubMed: 24453361]
351. Kim TO, Despotovic J, Lambert MP. Eltrombopag for use in children with immune thrombocytopenia. Blood Adv. 2018;2(4):454–461. [PubMed: 29487060]
352. Qiu J, Ma J, Zhang S, Han J, Liu S. Promoting platelets is a therapeutic option to combat severe viral infection of the lung. Blood Adv. 2020;4(8):1640–1642. [PubMed: 32315397]
353. Hines M, Lyseng-Williamson KA, Deeks ED. 17 α-Hydroxyprogesterone Caproate (Makena®). Clin Drug Investig. 2013;33(3):223–227.
354. Schaffner TJ, Skoner DP. Ciclesonide: a safe and effective inhaled corticosteroid for the treatment of asthma. J Asthma Allergy. 2009;2:25–32. [PubMed: 21437141]

355. Matsuyama S, Kawase M, Nao N, et al. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting viral replication-transcription complex in culture cells. J Virol. 2020. 10.1128/JVI.01648-20

356. Iwabuchi K, Yoshie K, Kurakami Y, Takahashi K, Kato Y, Morishima T. Therapeutic potential of ciclesonide inahalation for COVID-19 pneumonia: report of three cases. J Infect Chemother. 2020;26(6):625–632. [PubMed: 32362440]

357. Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. Can Med Assoc J. 2020;192(17):E450–E453. [PubMed: 32269021]

358. U.S. Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. 6 15, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and. Accessed June 15, 2020.

359. U.S. Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment. 5 01, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Accessed May 28, 2020.

360. U.S. Food and Drug Administration (FDA). FDA's approval of Veklury (remdesivir) for the treatment of COVID-19—The Science of Safety and Effectiveness. 10 22, 2020. Accessed November 2, 2020.

361. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med. 2020. 10.1056/NEJMoa2021436

362. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Resp Med. 2020;8(4):e21.

363. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020; 126(12):1671–1681. [PubMed: 32302265]

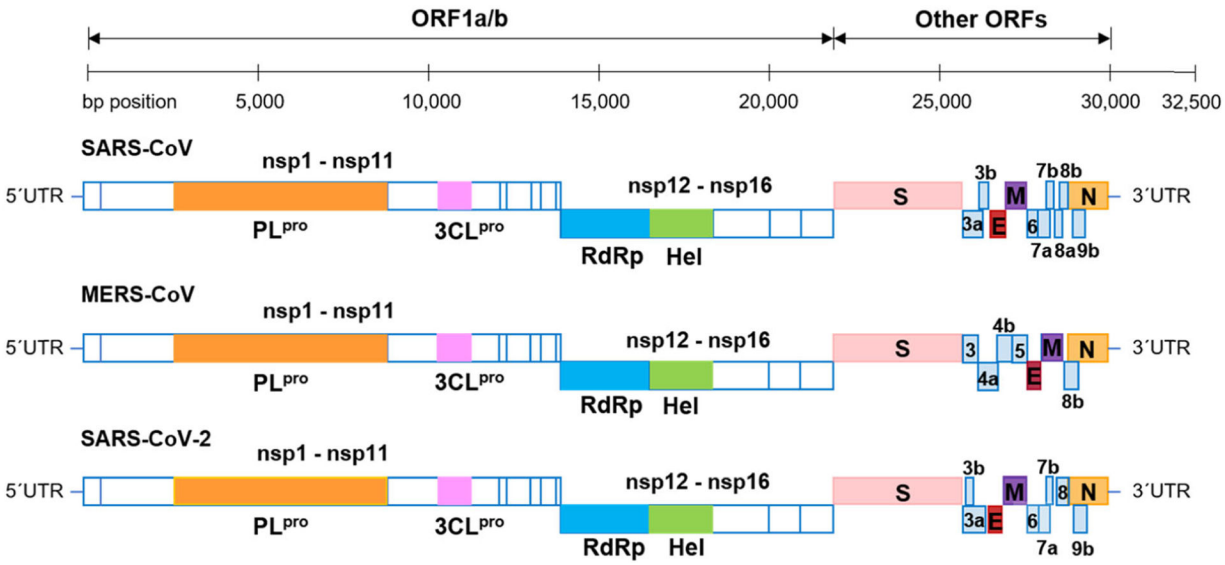


FIGURE 1.

The genome organization of SARS-CoV, MERS-CoV, and SARS-CoV-2. The ORFs 1a/b encode 16 nsps. Other ORFs encode structural proteins including S, E, M, and N proteins as well as accessory proteins. E, envelop; M, membrane; MERS-CoV, Middle East respiratory syndrome coronavirus; N, nucleocapsid; nsp, nonstructural protein; ORF, open reading frame; S, spike; SARS-CoV, severe acute respiratory syndrome coronavirus

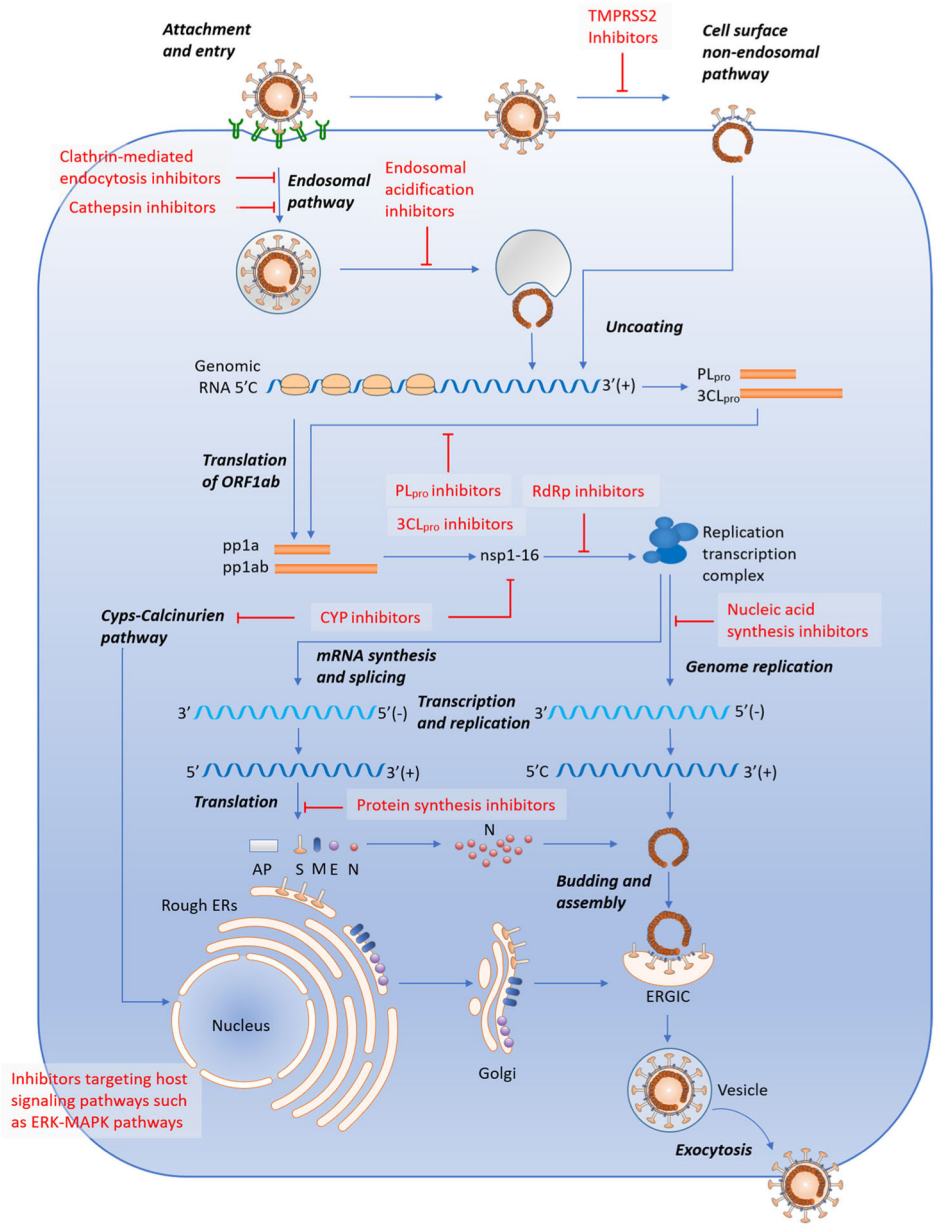


FIGURE 2.

Candidate drugs for CoV infections targeting different processes of the CoV life cycle. Adapted with permission from Ref. 28, American Society for Microbiology. AKT, protein kinase B; AP, accessory protein; $3CL^{pro}$, 3C-like protease; Cyps, cyclophilins; E, envelope; ER, endoplasmic reticulum; ERGIC, endoplasmic reticulum-Golgi intermediate compartment; ERK, extracellular signal-regulated kinases; M, membrane; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; N, nucleocapsid; NFAT, nuclear factor of activated T cells; nsp, nonstructural protein; ORF, open reading frame; PI3K, phosphoinositol 3-kinase; PL^{pro}, papain-like protease; RdRp, RNA-dependent RNA polymerase; S, spike; TMPRSS2, transmembrane protease serine 2

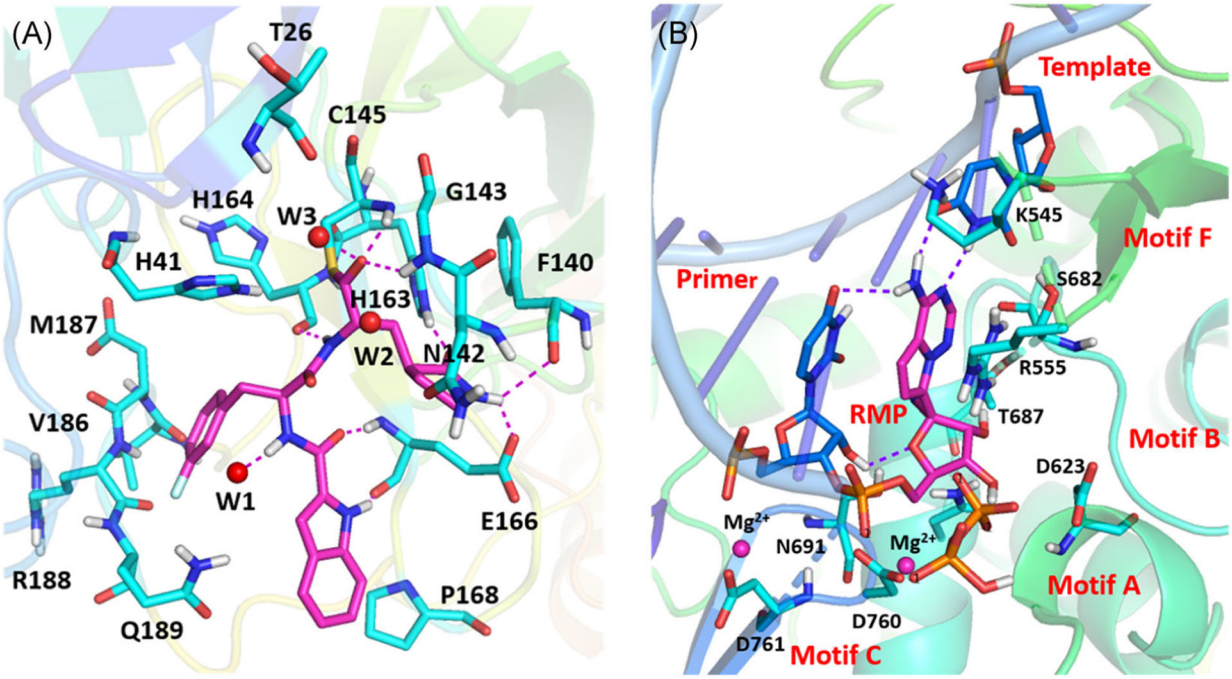


FIGURE 3.

The determination of SARS-CoV-2 3CL^{pro} and RdRp crystal structures facilitates the design and development of SARS-CoV-2 inhibitors. (A) The crystal structure of SARS-CoV-2 3CL^{pro} in complex with a peptide-aldehyde inhibitor (PDB: 6M0K). (B) The cryo-EM structure of SARS-CoV-2 RdRp in complex with a template-primer RNA and remdesivir (PDB: 7BV2). 3CL^{pro}, 3C-like protease; cryo-EM, cryogenic electron microscopy; RdRp, RNA-dependent RNA polymerase; SARS-CoV, severe acute respiratory syndrome coronavirus

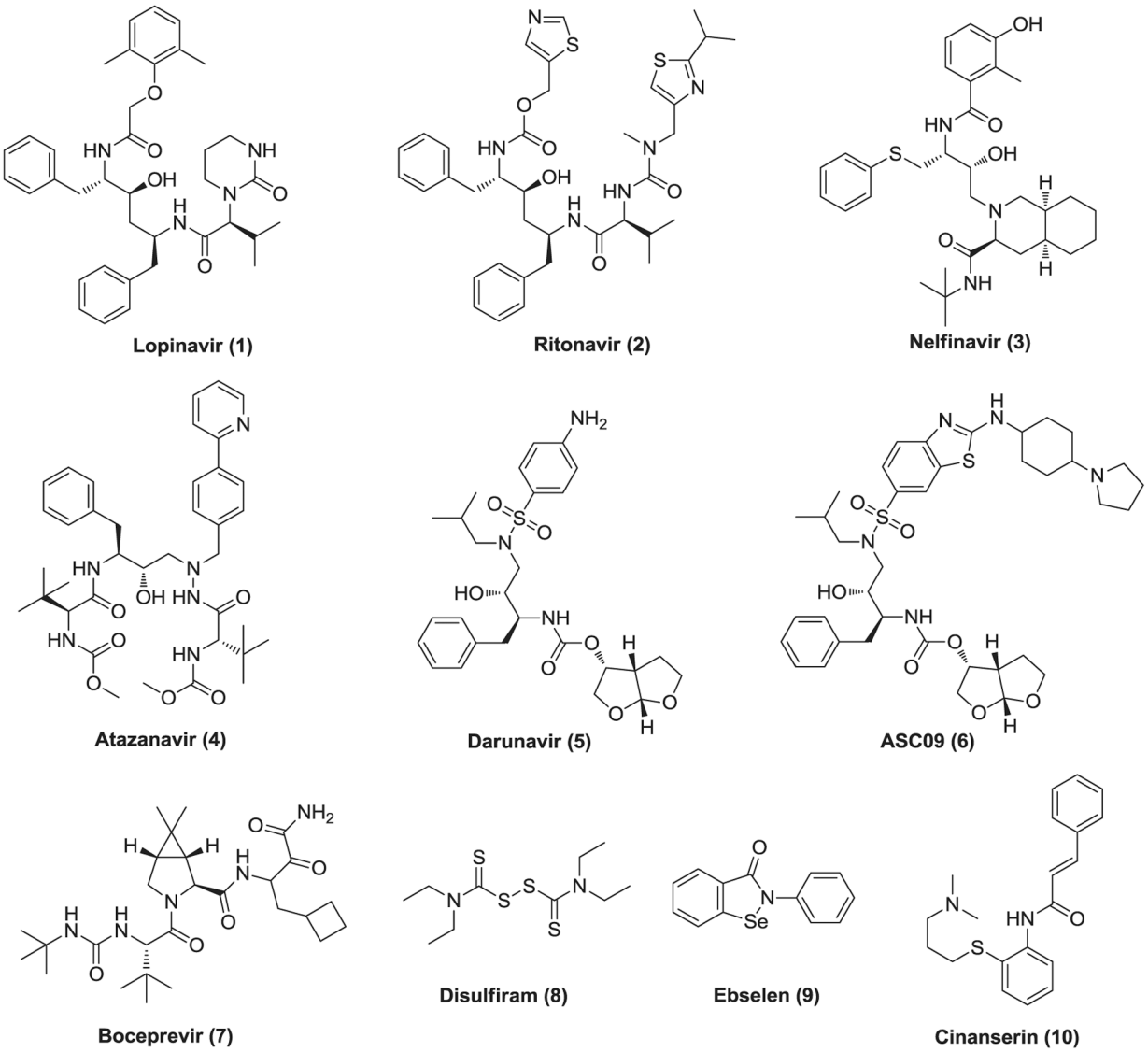


FIGURE 4.
The potential drugs targeting coronavirus proteases

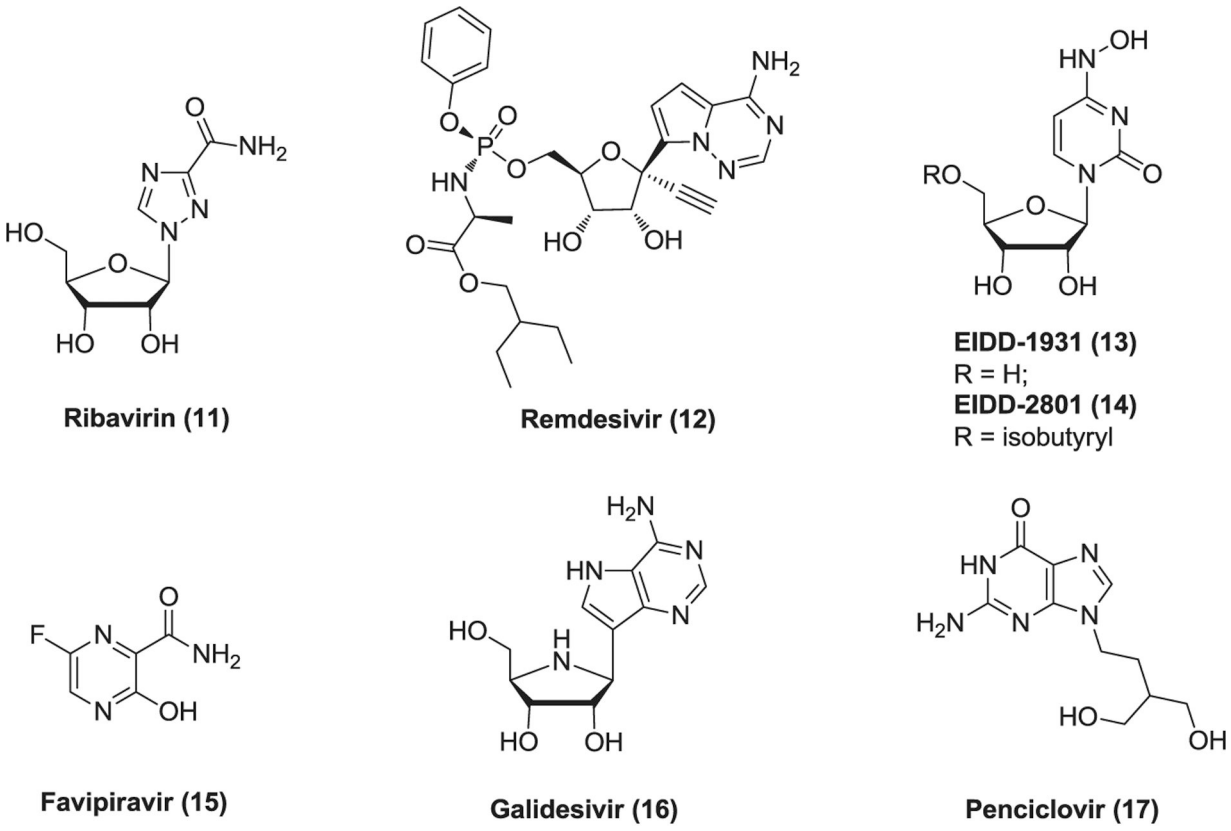


FIGURE 5.
The potential RNA-dependent RNA polymerase inhibitors against coronaviruses

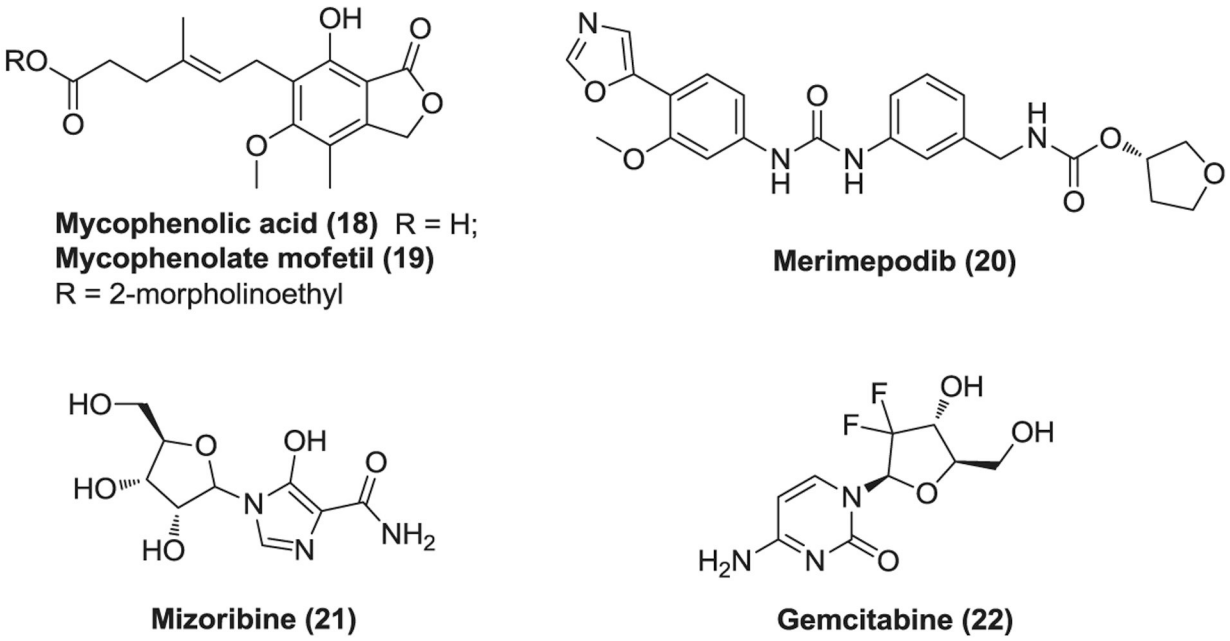


FIGURE 6.
The inhibitors against the nucleic acid synthesis of coronaviruses

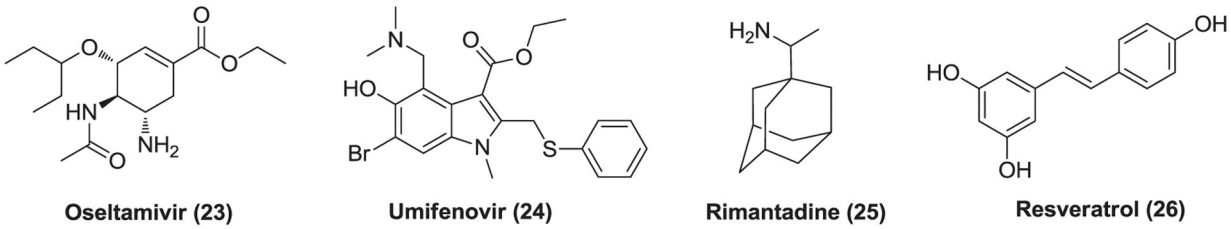


FIGURE 7.
Other virus-based drugs effective against coronaviruses

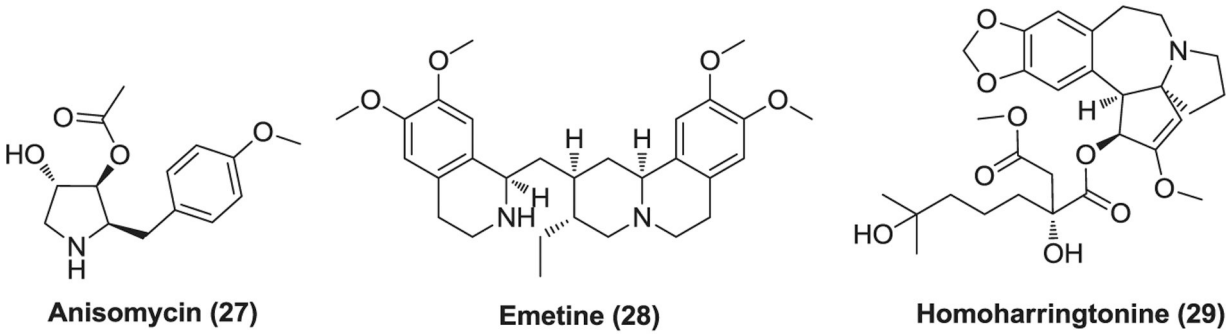
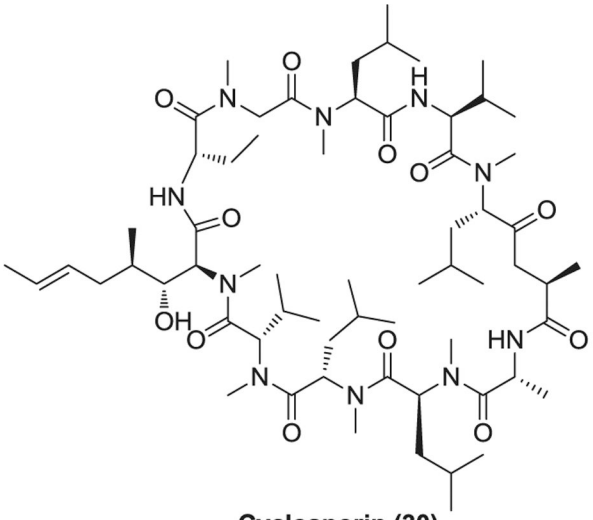


FIGURE 8.
The inhibitors against protein synthesis of coronaviruses



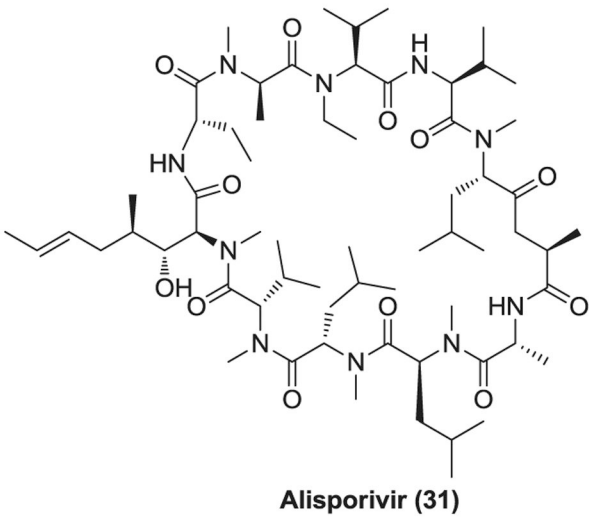


FIGURE 9.
The cyclophilin inhibitors

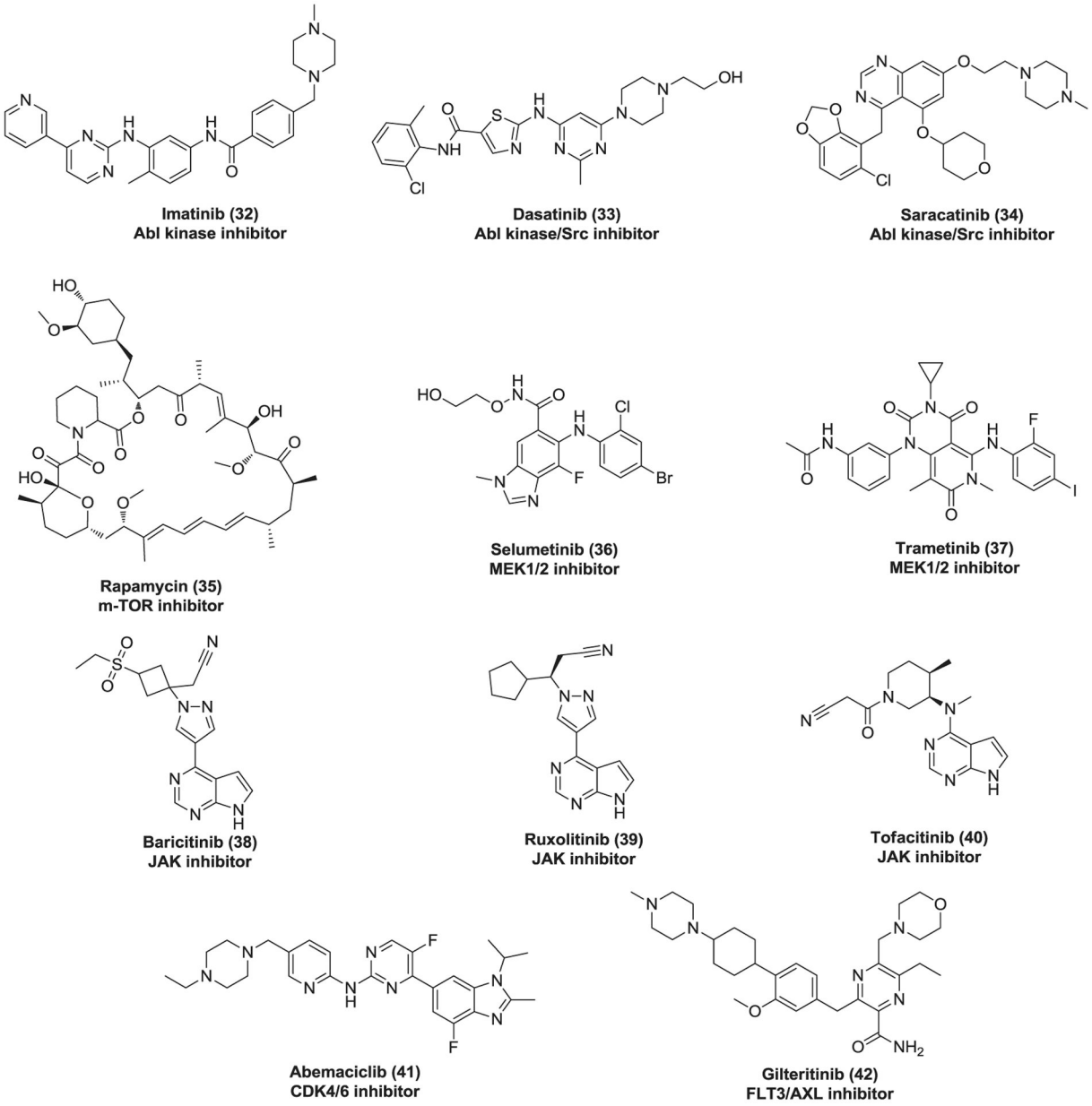
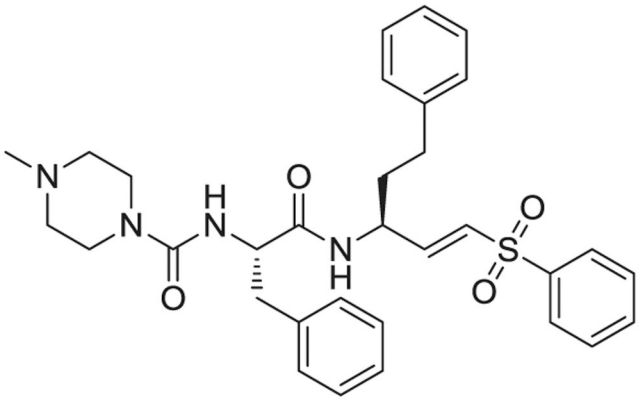
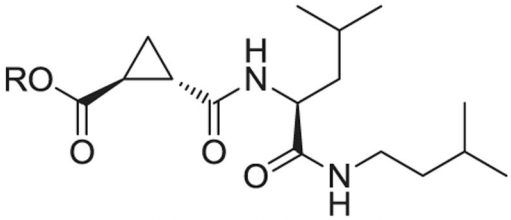


FIGURE 10.

The inhibitors targeting kinase signaling pathways against coronaviruses



K11777 (43)



E-64-d (44) R = Et
E-64-c (45) R = H

FIGURE 11.
The endosomal protease (cathepsin) inhibitors

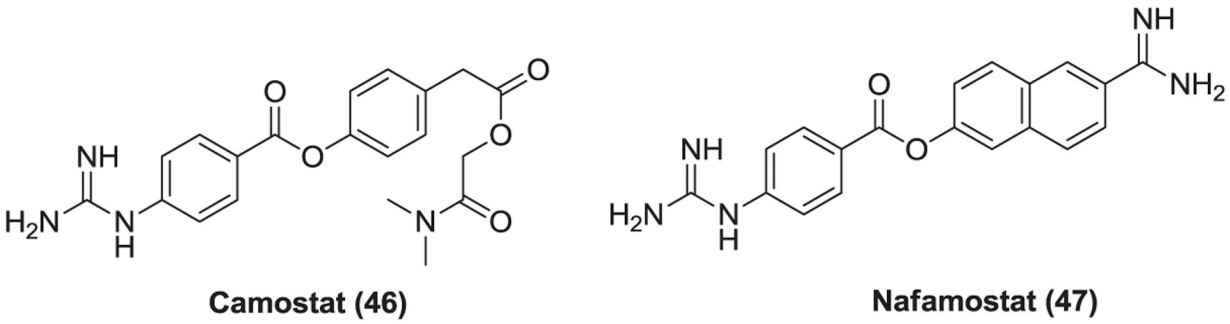


FIGURE 12.
The surface protease (TMPRSS2) inhibitors. TMPRSS2, transmembrane protease serine 2

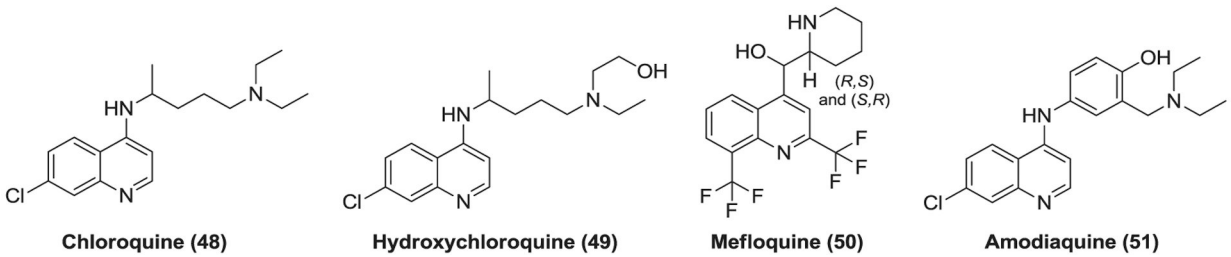


FIGURE 13.

The quinoline derivatives targeting endosomal acidification

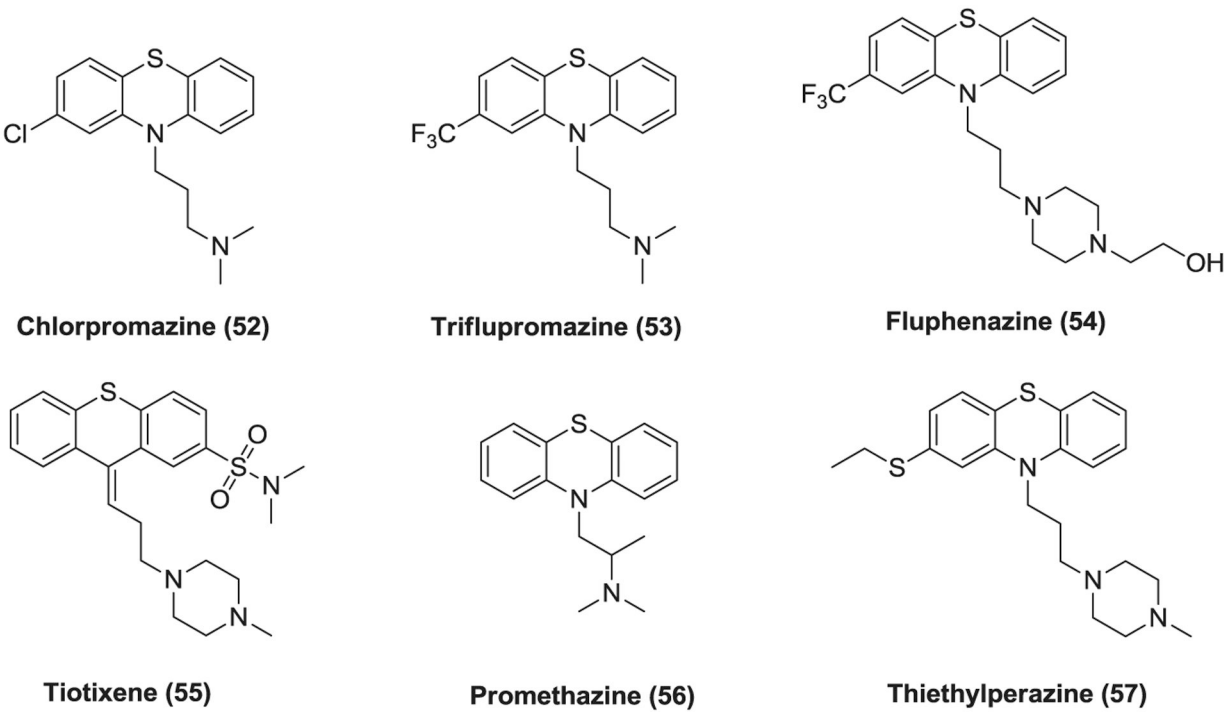


FIGURE 14.
The phenothiazine derivatives targeting clathrin-mediated endocytosis

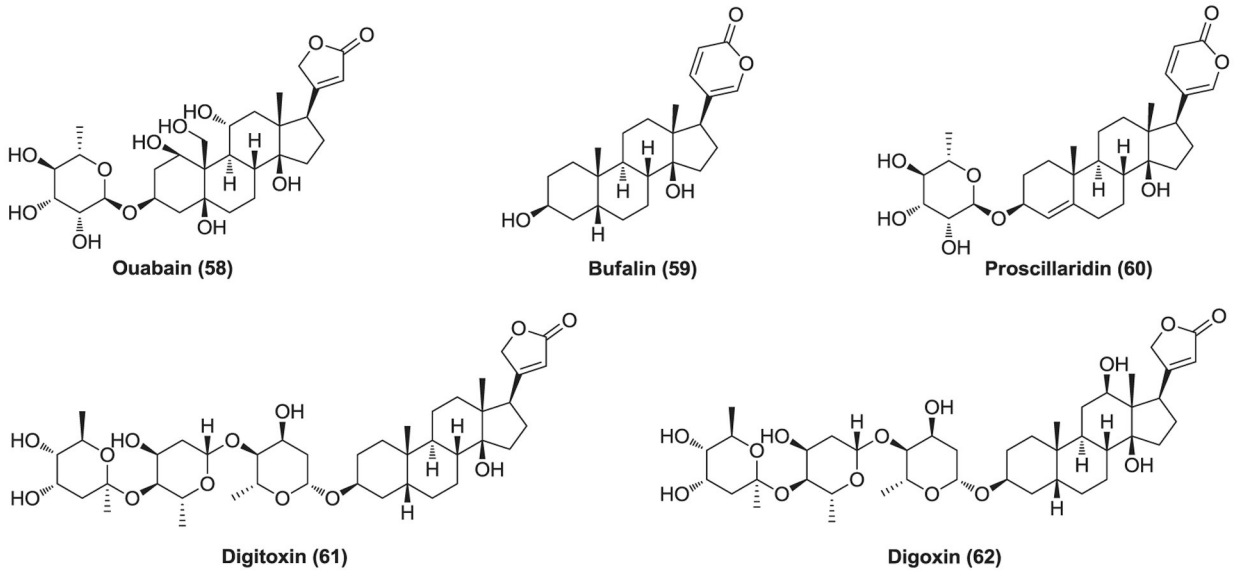


FIGURE 15.

The cardiotonic steroids that inhibit coronavirus entry into host cell via targeting ATP1A1-mediated Src signaling

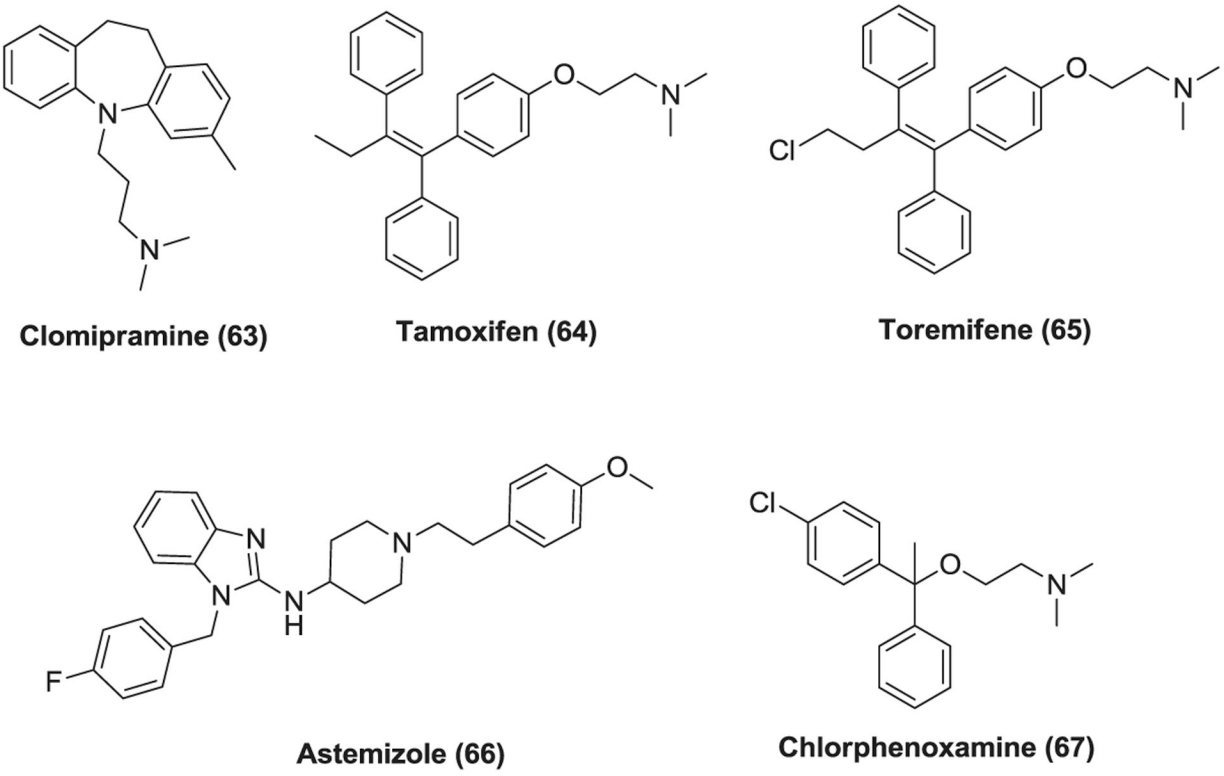


FIGURE 16.
Other drugs that inhibit coronavirus entry into host cell

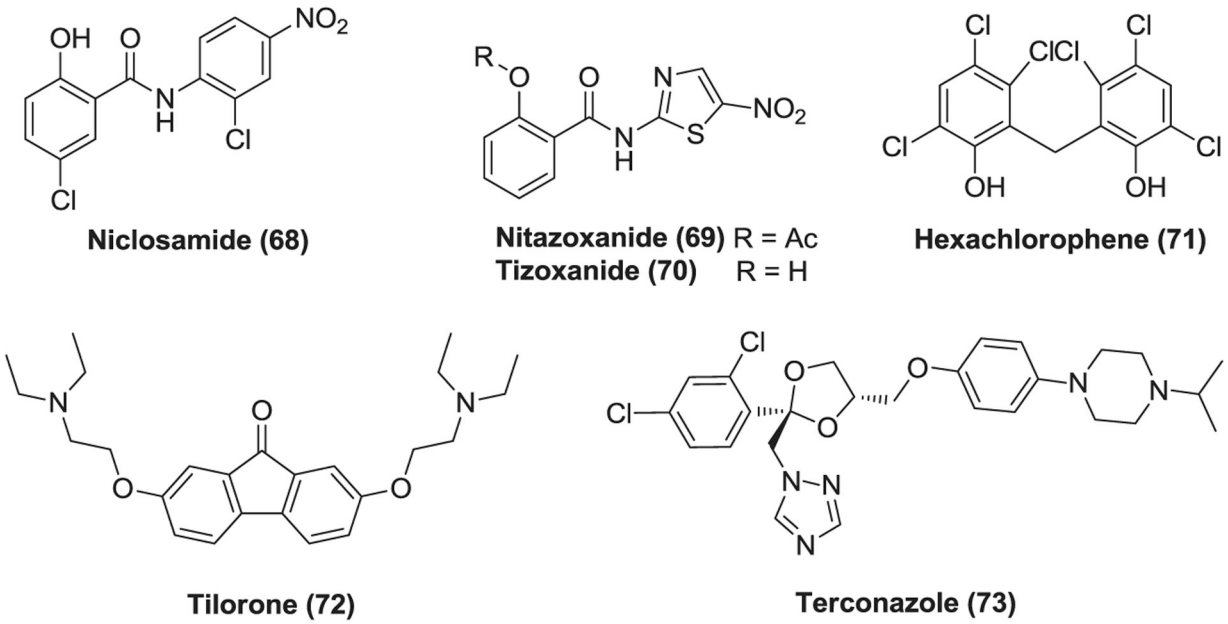


FIGURE 17.
Other host-based inhibitors (**68**–**73**) against coronaviruses

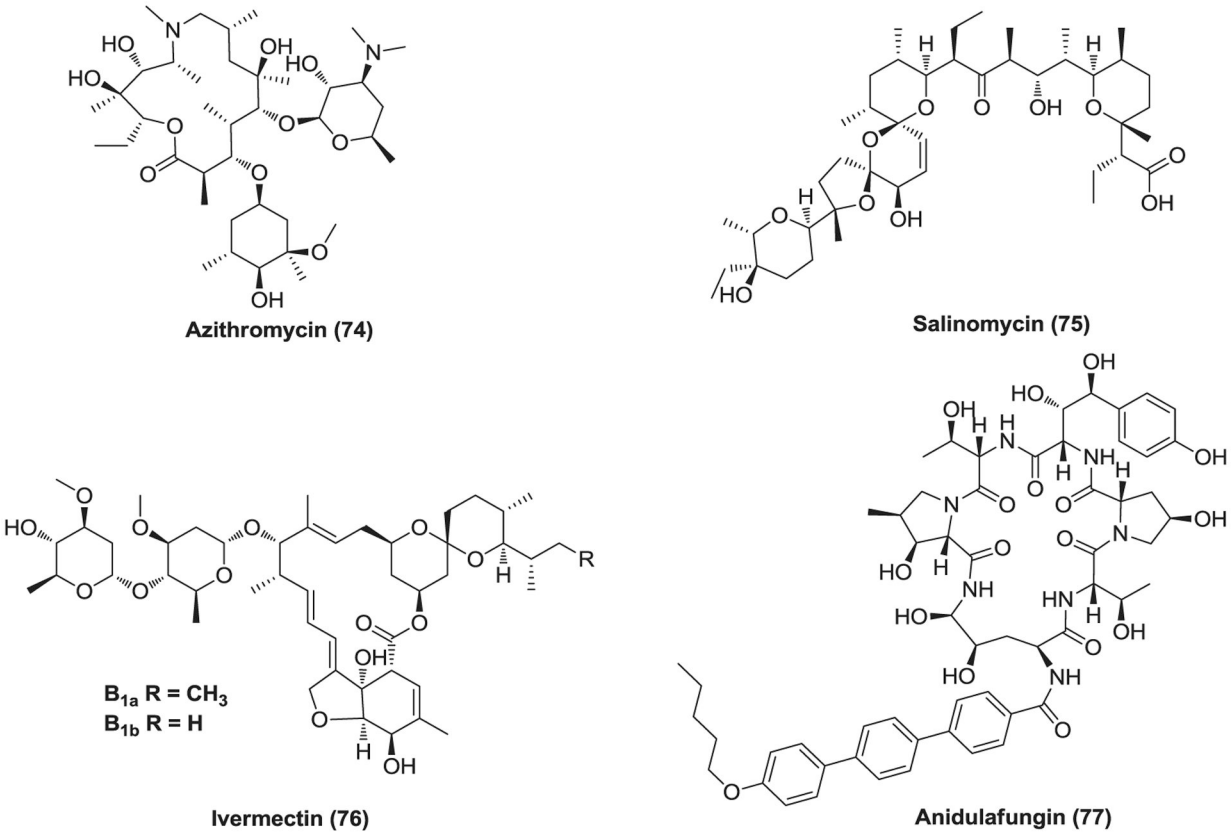


FIGURE 18.
Other host-based inhibitors (**74**–**77**) against coronaviruses

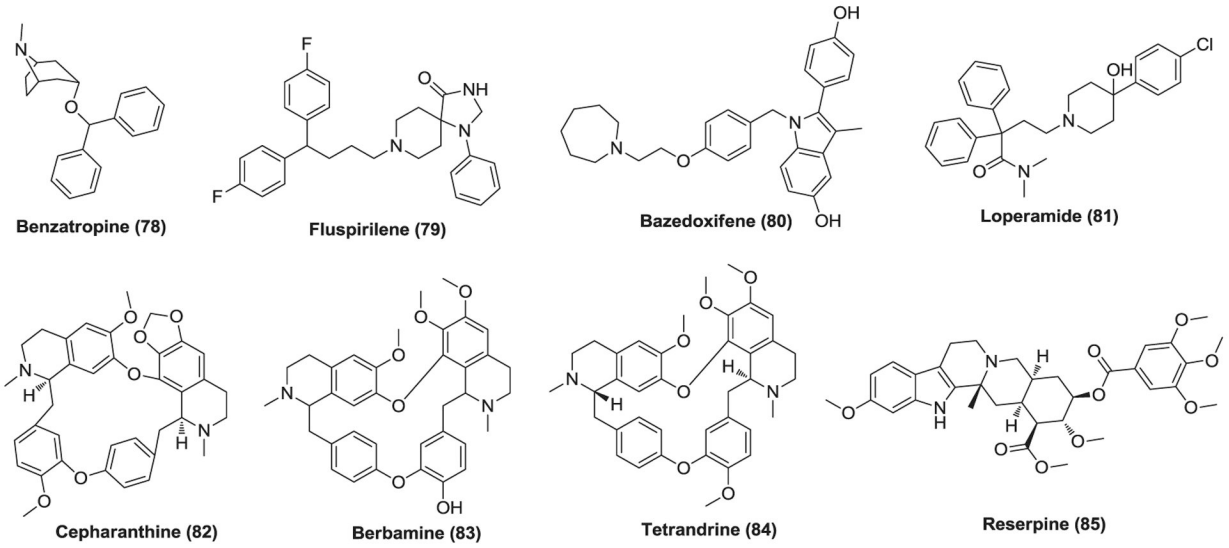


FIGURE 19.

Other host-based inhibitors (**78**–**85**) against coronaviruses

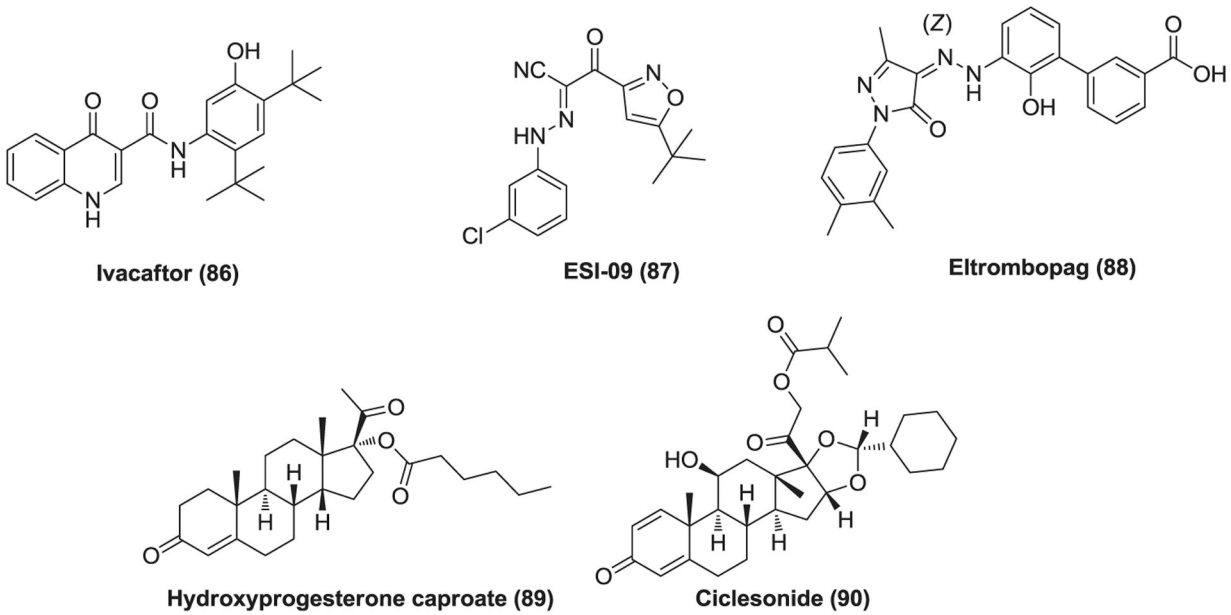


FIGURE 20.
Other host-based inhibitors (**86**–**90**) against coronaviruses

TABLE 1

The virus-based small molecule drugs with therapeutic potentials for CoVs

Antiviral agent	Drug class and/or targets	Activity against coronaviruses (cells/virus strain)	Ref.
Lopinavir (**1**)	$3CL^{pro}$ inhibitor	SARS-CoV: EC_{50} = 17.1 μM, CC_{50} > 32 μM (Vero E6/Frankfurt-1) EC_{50} at 48 h = 4–8 μg/ml (Vero E6/HKU39849) MERS-CoV: EC_{50} = 8.0 μM, CC_{50} = 24.4 μM (Huh7/EMC/2012) SARS-CoV-2: EC_{50} = 9.12 μM, CC_{50} > 50 μM (Vero)	62,63,70
Nelfinavir (**3**)	$3CL^{pro}$ inhibitor	SARS-CoV: EC_{50} = 0.048 μM, CC_{50} = 14.75 μM (Vero E6/FFM-1) SARS-CoV-2: EC_{50} = 9.12 μM, CC_{50} = 51.75 μM (Vero E6)	72,73
Atazanavir (**4**)	$3CL^{pro}$ inhibitor	SARS-CoV-2: EC_{50} = 2.0 μM, CC_{50} = 312 μM (Vero) EC_{50} = 0.22 μM (A549)	75
darunavir (**5**)	$3CL^{pro}$ inhibitor	Not reported	
ASC09 (**6**)	$3CL^{pro}$ inhibitor	Not reported	
Boceprevir (**7**)	$3CL^{pro}$ inhibitor	SARS-CoV-2: EC_{50} = 1.9 μM, CC_{50} > 100 μM (Vero 76)	79
Disulfiram (**8**)	PL^{pro} inhibitor	SARS-CoV-2 3CLpro: IC_{50} = 9.35 μM	59
Ebselen (**9**)	$3CL^{pro}$ inhibitor	SARS-CoV-2: EC_{50} = 4.6 μM (Vero E6)	59
Cinanserin (**10**)	$3CL^{pro}$ inhibitor	SARS-CoV: decreased viral replication by more than 1000-fold at 50 μg/ml with no toxic effect SARS-CoV-2: EC_{50} = 20.61 μM, CC_{50} > 200 μM (Vero E6)	59,88
Ribavirin (**11**)	RdRp inhibitor	SARS-CoV: EC_{50} = 80 μg/ml, CC_{50} > 200 μg/ml (Vero E6/HKU39849) MERS-CoV: EC_{50} = 41.4 μg/ml (Vero RML6/hCoV-EMC/2012) SARS-CoV-2: EC_{50} = 109.5 μM, CC_{50} > 400 μM (Vero E6)	100,101,110
Remdesivir (**12**)	RdRp inhibitor	SARS-CoV: EC_{50} = 0.069 μM, CC_{50} > 10 μM (HAE) MERS-CoV: EC_{50} = 0.074 μM, CC_{50} > 10 μM (HAE) SARS-CoV-2: EC_{50} = 0.77 μM, CC_{50} > 100 μM (Vero E6) Reduced lung viral load and improved clinical signs and respiratory functions in a mouse (or rhesus macaque) models of SARS-CoV or MERS-CoV infection	110,112,114,118,119
EIDD-1931 (**13**)	RdRp inhibitor	SARS-CoV: EC_{50} = 0.14 μM (HAE) MERS-CoV: EC_{50} = 0.024 μM (HAE); EC_{50} = 0.15 μM, CC_{50} > 10 μM (Calu-3) SARS-CoV-2: EC_{50} = 0.30 μM, CC_{50} > 10 μM (Vero E6); EC_{50} = 0.08 μM (Calu-3) Reduced viral load and improved pulmonary function in a mouse model of SARS-CoV or MERS-CoV infection	129
Favipiravir (**15**)	RdRp inhibitor	SARS-CoV-2: EC_{50} = 22.50 μM, CC_{50} > 100 μM (Vero E6)	110
Galidesivir (**16**)	RdRp inhibitor	SARS-CoV: EC_{50} = 57.7 μM, CC_{50} > 296 μM (Vero 76/Urbani) MERS-CoV: EC_{50} = 68.4 μM, CC_{50} > 100 μM (Vero E6/Jordan N3)	141
Penciclovir (**17**)	RdRp inhibitor	SARS-CoV-2: EC_{50} = 95.96 μM, CC_{50} > 400 μM (Vero E6)	110
Mycophenolic acid (**18**)	IMPDH inhibitor; noncompetitive PL^{pro} inhibitor	MERS-CoV: EC_{50} = 0.17 μg/ml, CC_{50} > 32 μg/ml (Vero); EC_{50} = 2.87 μM, CC_{50} > 70 μM (Vero E6) Its prodrug MMF (**19**) treatment resulted in a worse outcome in a marmoset model of MERS-CoV infection. SARS-CoV-2: EC_{50} = 0.87 μM, CC_{50} > 128 μM (Vero E6/Wk521)	159–161,165
Merimepodib (**20**)	Noncompetitive IMPDH inhibitor	SARS-CoV-2: decreased viral titers by over 10-fold at 3.3 μM	171
Mizoribine (**21**)	IMPDH and GMP-synthetase inhibitor	SARS-CoV: EC_{50} = 3.5 μg/ml, CC_{50} > 200 μg/ml (Vero E6/Frankfurt-1); EC_{50} = 16 μg/ml (Vero E6/HKU39849)	100
Gemcitabine hydrochloride (**22**)	Nucleic acid synthesis inhibitors	SARS-CoV: EC_{50} = 4.96 μM, CC_{50} > 10 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 1.22 μM, CC_{50} > 10 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 1.24 μM, CC_{50} >40 μM (Vero E6)	178,179

Antiviral agent	Drug class and/or targets	Activity against coronaviruses (cells/virus strain)	Ref.
Oseltamivir (**23**)	Neuraminidase inhibitor	Not reported	
Umifenovir (**24**)	S protein/ACE2, membrane fusion inhibitor	Inhibited SARS-CoV-2 replication at 10–30 μM	192
Rimantadine (**25**)	Influenza M2 protein inhibitor	SARS-CoV: EC_{50} at 48 h = 8–16 μg/ml (Vero E6/HKU39849); EC_{50} at 48 h = 8–16 μg/ml (fRhK4 cells/10 strains), CC_{50} = 64 μg/ml	63
Resveratrol (**26**)	Nucleocapsid protein	Significantly reduced MERS-CoV titers at 150 μM at 48 h postinfection SARS-CoV-2: EC_{50} = ~66 μM, CC_{50} > 250 μM (Vero E6)	204,205

Abbreviations: $3CL^{pro}$, 3C-like protease; ACE2, angiotensin-converting enzyme 2; CC_{50}, cytotoxic concentration 50%; EC_{50}, half-maximal effective concentration; GMP, guanosine-5′-monophosphate; IMPDH, inosine-5′-monophosphate dehydrogenase; MERS-CoV, Middle East respiratory syndrome coronavirus; PL^{pro}, papain-like protease; RdRp, RNA-dependent RNA polymerase; SARS-CoV, severe acute respiratory syndrome coronavirus.

TABLE 2

The host-based small molecule drugs with therapeutic potentials for CoVs

Antiviral agent	Drug class and/or targets	Activity against coronaviruses	Ref.
Anisomycin (**27**)	Protein synthesis inhibitor	SARS-CoV: EC_{50} = 0.191 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 0.003 μM (Vero E6/Jordan N3)	178
Emetine hydrochloride (**28**)	Protein synthesis inhibitor	SARS-CoV: EC_{50} = 0.051 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 0.014 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 0.46 μM, CC_{50} = 56.46 μM (Vero E6)	178,214
Homoharringtonine (**29**)	Protein synthesis inhibitor	MERS-CoV: EC_{50} = 0.072 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 2.55 μM, CC_{50} = 59.75 μM (Vero E6)	178,214
Cyclosporine (**30**)	Inhibitor of cyclophilins and their interaction with nsp1	SARS-CoV: EC_{50} = 3.2 μM, CC_{50} > 17 μM (Vero E6/Frankfurt-1) MERS-CoV: suppressed induced cytopathic effect at 9 μM in Vero cells with no toxic effect SARS-CoV-2: EC_{50} = 5.8 μM, CC_{50} > 50 μM (Vero)	70,221,224
Alisporivir (**31**)	Cyclophilin inhibitor	SARS-CoV: EC_{50} = 8.3 μM, CC_{50} > 50 μM (Vero E6/Frankfurt-1); EC_{50} = 1.3 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 3.6 μM, CC_{50} = 26.4 μM (Vero/EMC/2012); EC_{50} = 3.0 μM (Vero/Jordan N3) SARS-CoV-2: EC_{50} = 0.46 μM, CC_{50} > 20 μM (Vero E6)	229,230
Imatinib mesylate (**32**)	Abl kinase inhibitor	SARS-CoV: EC_{50} = 9.82 μM, CC_{50} > 100 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 17.69 μM, CC_{50} > 100 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 3.24 μM (MOI = 0.004) and 5.32 μM (MOI = 0.01), CC_{50} > 30.86 μM (Vero E6)	178,232
Dasatinib (**33**)	Abl kinase/Src inhibitor	SARS-CoV: EC_{50} = 2.10 μM, CC_{50} > 10 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 5.47 μM, CC_{50} > 10 μM (Vero E6/Jordan N3)	178
Saracatinib (**34**)	Abl kinase/Src inhibitor	MERS-CoV: EC_{50} = 2.9 μM, CC_{50} = 57 μM (Huh-7)	241
Rapamycin (**35**)	mTOR inhibitor	Inhibited MERS-CoV infection by ~60% at 10 μM via both pre- and postinfection treatment	246
Selumetinib (**36**)	MEK1/2 inhibitors	Inhibited MERS-CoV infection by ~70% at 1 μM via preinfection treatment and by ~90% at 10 μM via postinfection treatment	246
Trametinib (**37**)	MEK1/2 inhibitors	Inhibited MERS-CoV infection by ~90% at 0.1 μM via preinfection treatment and by ~70% at 1 μM via postinfection treatment	246
Baricitinib (**38**)	JAK and AAK1 inhibitor	Not reported	
Abemaciclib (**41**)	CDK4/6 inhibitor	SARS-CoV-2: EC_{50} = 6.62 μM, CC_{50} > 50 μM (Vero)	70
Gilteritinib (**42**)	FLT3 and AXL inhibitor	SARS-CoV-2: EC_{50} = 6.76 μM, CC_{50} = 37.16 μM (Vero)	70
K11777 (**43**)	Cathepsin inhibitor	SARS-CoV: IC50 < 0.05 μM, IC90 = 0.35 μM, CC_{50} > 105.6 μM (Vero 76/Urbani); IC50 < 0.05 μM, IC90 = 1.04 μM, CC_{50} = 85.2 μM (Vero 76/Toronto-2); its derivative SMDC256160 showed no in vivo efficacy in a mouse model of SARS-CoV infection	255
E-64-d (**44**)	Cathepsin inhibitor	SARS-CoV: EC_{50} = 0.76 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 1.275 μM (Vero E6/Jordan N3) Inhibited SARS-CoV-2 entry	38,178
Camostat (**46**)	TMPRSS2 inhibitor	Reduced the infection of SARS-CoV, MERS-CoV, and SARS-CoV-2 in Calu-3 cells; showed in vivo efficacy in a mouse model of SARS-CoV infection (30 mg/kg, oral, BID, 9 days)	41,50,53,255
Nafamostat (**47**)	TMPRSS2 inhibitor	MERS-CoV: reduced the entry and replication at 0.1 μM in Calu-3 cells SARS-CoV-2: EC_{50} = 22.50 μM, CC_{50} > 100 μM (Vero E6)	110,270
Chloroquine hydrochloride (**48**)	Antiparasitic/inhibit host receptor glycosylation and endosomal acidification	SARS-CoV: EC_{50} = 6.54 μM (Vero E6/MA15); EC_{50} = 4.0 μM, CC_{50} > 128 μM (Vero E6/Frankfurt-1) MERS-CoV: EC_{50} = 6.28 μM (Vero E6/Jordan N3); EC_{50} = 3.0	62,110,178

Antiviral agent	Drug class and/or targets	Activity against coronaviruses	Ref.
		μM, CC_{50} = 58.1 μM (Huh-7/EMC/2012) SARS-CoV-2: EC_{50} = 1.13 μM, CC_{50} > 100 μM (Vero E6)	
Hydroxychloroquine sulfate (**49**)		SARS-CoV: EC_{50} = 6.54 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 6.28 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 4.51 μM (MOI = 0.01) and 12.96 μM (MOI = 0.8), CC_{50} = 249.5 μM (Vero E6); EC_{50} at 48 h = 0.72 μM (MOI = 0.01) in Vero cells	178,281,282
Mefloquine (**50**)		SARS-CoV: EC_{50} = 15.55 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 7.42 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 4.33 μM, CC_{50} = 13.97 μM (Vero)	70,178
Amodiaquine (**51**)		SARS-CoV: EC_{50} = 1.27 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 6.21 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 5.15 μM, CC_{50} > 50 μM (Vero)	70,178
Chlorpromazine hydrochloride (**52**)	Antipsychotic or antihistamine or antiemetic/phenothiazine/ inhibit clathrin-mediated endocytosis	SARS-CoV: EC_{50} = 12.97 μM, CC_{50} > 100 μM (Vero E6/MA15); EC_{50} = 8.8 μM, CC_{50} = 24.3 μM (Vero E6/Frankfurt-1) MERS-CoV: EC_{50} = 9.51 μM (Vero E6/Jordan N3); EC_{50} = 4.9 μM, CC_{50} = 21.3 μM (Huh-7/EMC/2012) SARS-CoV-2: EC_{50} = 3.14 μM (MOI = 0.004) and 4.03 μM (MOI = 0.01), CC_{50} = 11.88 μM (Vero E6)	62,178,232
Triflupromazine hydrochloride (**53**)		SARS-CoV: EC_{50} = 6.40 μM, CC_{50} > 10 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 5.76 μM (Vero E6/Jordan N3)	178
Fluphenazine hydrochloride (**54**)		SARS-CoV: EC_{50} = 21.43 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 5.87 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 6.36 μM (MOI = 0.004) and 8.98 μM (MOI = 0.01), CC_{50} = 20.02 μM (Vero E6)	178,232
Thiothixene (**55**)		SARS-CoV: EC_{50} = 5.32 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 9.30 μM (Vero E6/Jordan N3)	178
Promethazine hydrochloride (**56**)		SARS-CoV: EC_{50} = 7.55 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 11.80 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 9.21 μM (MOI = 0.004) and 10.44 μM (MOI = 0.01), CC_{50} = 42.59 μM (Vero E6)	178,232
Thiethylperazine maleate (**57**)		MERS-CoV: EC_{50} = 7.87 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 7.09 μM (MOI = 0.004) and 8.02 μM (MOI = 0.01), CC_{50} = 18.37 μM (Vero E6)	178,232
Ouabain (**58**)	Cardiotonic steroids/target ATP1A1 and inhibit CoV entry	Inhibited MERS-CoV infection at 50 nM via preinfection SARS-CoV-2: EC_{50} < 0.097 μM, CC_{50} > 50 μM (Vero)	70,302
Bufalin (**59**)		Inhibited MERS-CoV infection at 10–15 nM via preinfection	302
Proscillaridin (**60**)		SARS-CoV-2: EC_{50} = 2.04 μM, CC_{50} > 50 μM (Vero)	70
Digoxin (**61**)		SARS-CoV-2: EC_{50} = 0.19 μM, CC_{50} > 50 μM (Vero)	70
Digitoxin (**62**)		SARS-CoV-2: EC_{50} = 0.23 μM, CC_{50} > 50 μM (Vero)	70
Clomipramine hydrochloride (**63**)	Tricyclic antidepressant/inhibit clathrin-dependent entry	SARS-CoV: EC_{50} = 13.24 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 9.33 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 5.63 μM (MOI = 0.004) and 7.59 μM (MOI = 0.01), CC_{50} > 29.68 μM (Vero E6)	178,232
Tamoxifen citrate (**64**)	Estrogen receptor modulator/ inhibit CoV entry	SARS-CoV: EC_{50} = 92.89 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 10.12 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 34.12 μM (MOI = 0.004) and 8.98 μM (MOI = 0.01), CC_{50} = 37.96 μM (Vero E6)	178,232
Toremifene citrate (**65**)		SARS-CoV: EC_{50} = 11.97 μM, CC_{50} > 100 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 12.92 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 4.77 μM (MOI = 0.004) and 11.30 μM (MOI = 0.01), CC_{50} = 20.51 μM (Vero E6)	178,232

Antiviral agent	Drug class and/or targets	Activity against coronaviruses	Ref.
Astemizole (**66**)	Antihistamine and anticholinergic/inhibit CoV entry	SARS-CoV: EC_{50} = 5.59 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 4.88 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = ~1.1 μM (Vero E6)	178,304
Chlorphenoxamine (**67**)		SARS-CoV: EC_{50} = 20.03 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 12.65 μM (Vero E6/Jordan N3)	178
Niclosamide (**68**)	Anthelmintic drug/broad antiviral agent	SARS-CoV: EC_{50} < 0.1 μM, CC_{50} = 22.1 μM (Vero E6) SARS-CoV-2: EC_{50} = 0.28 μM, CC_{50} > 50 μM (Vero) Suppressed MERS-CoV infection by ~1000-fold at 48 h at 10 μM	70,308,309
Nitazoxanide (**69**)	Broad antiparasitic and antiviral drug/induce the host innate immune response	SARS-CoV-2: EC_{50} = 2.12 μM, CC_{50} = 35.53 μM (Vero E6)	110,312
Hexachlorophene (**71**)	Disinfectant	SARS-CoV-2: EC_{50} = 0.90 μM, CC_{50} = 19.3 μM (Vero)	70
Tilorone (**72**)	Antiviral drug/interferon inducer	MERS-CoV: EC_{50} = 10.56, CC_{50} > 20 μM (Vero E6) SARS-CoV-2: EC_{50} = 4.09 μM, CC_{50} = 19.67 μM (Vero)	70,322
Terconazole (**73**)	Antifungal drug	SARS-CoV: EC_{50} = 15.33 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 12.20 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 11.92 μM (MOI = 0.004) and 16.14 μM (MOI = 0.01), CC_{50} = 41.46 μM (Vero E6)	178,232
Azithromycin (**74**)	Antibiotic/macrolide	Not reported	
Salinomycin sodium (**75**)	Polyether ionophore antibiotic	MERS-CoV: EC_{50} = 5.49, CC_{50} = 3.84 μM (Vero E6) SARS-CoV-2: EC_{50} = 0.24 μM, CC_{50} > 50 μM (Vero)	70,322
Ivermectin (**76**)	Antiparasitic/broad antiviral agent	SARS-CoV-2: EC_{50} = ~2.0 μM (Vero hSLAM/Australia/VIC01/2020)	336
Anidulafungin (**77**)	Antifungal/semisynthetic echinocandin	SARS-CoV-2: EC_{50} = 4.64 μM, CC_{50} > 50 μM (Vero)	70
Benztropine (**78**)	Anticholinergic	SARS-CoV: EC_{50} = 21.61 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 16.63 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 13.8 μM (MOI = 0.004) and 17.79 μM (MOI = 0.01), CC_{50} » 50 μM (Vero E6)	178,232
Fluspirilene (**79**)	Antipsychotic (diphenylbutylpiperidine)	SARS-CoV: EC_{50} = 5.96 μM (Vero E6/MA15) MERS-CoV: EC_{50} = 7.48 μM (Vero E6/Jordan N3) SARS-CoV-2: EC_{50} = 3.16 μM (MOI = 0.004) and 5.32 μM (MOI = 0.01), CC_{50} = 30.33 μM (Vero E6)	178,232
Bazedoxifene (**80**)	Estrogen receptor modulator	SARS-CoV-2: EC_{50} = 3.44 μM, CC_{50} = 14.97 μM (Vero)	70
Loperamide (**81**)	Antidiarrheals/μ-opioid receptor agonist	SARS-CoV: EC_{50} = 5.9 μM, CC_{50} = 53.8 μM (Vero E6/Frankfurt-1) MERS-CoV: EC_{50} = 4.8 μM, CC_{50} = 15.5 μM (Huh-7/EMC/2012) SARS-CoV-2: EC_{50} = 9.27 μM, CC_{50} = 29.26 μM (Vero)	62,70
Cepharanthine (**82**)	Bis-benzylisoquinoline alkaloids/anti-inflammatory	SARS-CoV-2: EC_{50} = 4.47 μM, CC_{50} > 50 μM (Vero)	70
Berbamine (**83**)		MERS-CoV: EC_{50} = 13.14, CC_{50} > 20 μM (Vero E6) SARS-CoV-2: EC_{50} = 7.87 μM, CC_{50} > 50 μM (Vero)	70,322
Tetrandrine (**84**)		MERS-CoV: EC_{50} = 12.68, CC_{50} > 20 μM (Vero E6) SARS-CoV-2: EC_{50} = 3.00 μM, CC_{50} = 14.92 μM (Vero)	70,322
Reserpine (**85**)	Antihypertensive	SARS-CoV: EC_{50} = 3.4 μM, CC_{50} = 25 μM (Vero E6/H.K. strain)	348
Ivacaftor (**86**)	Potentiator of CFTR/treat cystic fibrosis	SARS-CoV-2: EC_{50} = 6.57 μM, CC_{50} = 12.47 μM (Vero)	70
ESI-09 (**87**)	EPAC inhibitor	Resulted in about 2log and 4log reduction in MERS-CoV and SARS-CoV titer in Vero E6 cells, respectively, at 10 μM	350
Eltrombopag (**88**)	Thrombopoietin (c-mpl) receptor agonist	SARS-CoV-2: EC_{50} = 8.27 μM, CC_{50} > 50 μM (Vero)	70

Antiviral agent	Drug class and/or targets	Activity against coronaviruses	Ref.
Hydroxyprogesterone caproate (**89**)	Progesterone receptor agonist	SARS-CoV-2: EC_{50} = 6.30 μM, CC_{50} > 50 μM (Vero)	70
Ciclesonide (**90**)	Corticosteroid/anti-inflammatory/target nsp15	SARS-CoV-2: EC_{50} = 4.33 μM, CC_{50} > 50 μM (Vero)	70

Abbreviations: AAK1, AP2-associated protein kinase 1; CC_{50}, cytotoxic concentration 50%; EC_{50}, half-maximal effective concentration; EPAC, exchange protein directly activated by cAMP; JAK, Janus kinase; MERS-CoV, Middle East respiratory syndrome coronavirus; MOI, multiplicity of infection; mTOR, mammalian target of rapamycin; SARS-CoV, severe acute respiratory syndrome coronavirus; TMPRSS2, transmembrane protease serine 2.

TABLE 3

Representative small molecule compounds for COVID-19 in human clinical trials with recruiting participants[a]

Agents	Drug class and/or targets	Phase
Lopinavir/ritonavir	HIV protease inhibitor/CYP3A4 inhibitor	Phase 4
Darunavir/cobicistat	HIV protease inhibitor/CYP3A inhibitor	Phase 3
ASC09/ritonavir	HIV protease inhibitor/CYP3A4 inhibitor	Phase 3
Atazanavir	HIV protease inhibitor	Phase 2/3
Ribavirin	Broad antiviral agent/RdRp inhibitor	Phase 2 (completed)
Remdesivir	RdRp inhibitor	Approved
EIDD-2801	RdRp inhibitor	Phase 1/2
Favipiravir	RdRp inhibitor	Phase 2/3
Galidesivir	RdRp inhibitor	Phase 1
Oseltamivir	Influenza neuraminidase inhibitor	Phase 4
Arbidol	Broad antiviral agent/inhibit membrane fusion	N/A
Danoprevir	HCV NS3/4A protease inhibitor	Phase 4
Clevudine	Anti-HBV/nucleoside analog	Phase 2
Emtricitabine	HIV nucleoside reverse-transcriptase inhibitor	Phase 3
Tenofovir disoproxil	HIV nucleoside reverse-transcriptase inhibitor	Phase 3
Merimepodib	Noncompetitive IMPDH inhibitor	Phase 2
Cyclosporine	Immunosuppressive/cyclophilin inhibitors	Phase 4
Imatinib	Abl kinase inhibitor	Phase 2
Sirolimus	mTOR inhibitor	Phase 1/2
Acalabrutinib	Bruton′s tyrosine kinase inhibitor	Phase 2
Tacrolimus	Immunosuppressive	Phase 3
Baricitinib	JAK inhibitor	Phase 2/3
Ruxolitinib	JAK inhibitor	Phase 2/3
Tofacitinib	JAK inhibitor	Phase 2
TD-0903	JAK inhibitor	Phase 1/2
Camostat	Serine protease (TMPRSS2) inhibitor	Phase 2/3
Nafamostat	Serine protease (TMPRSS2) inhibitor	Phase 2/3
Chloroquine	Antimalarial/immunomodulatory	Phase 1–4
Hydroxychloroquine	Antimalarial/immunomodulatory	Phase 1–4
Amodiaquine	Antimalarial/immunomodulatory	Phase 2
GNS651	Chloroquine analog	Phase 2
Atovaquone	Antipneumocystis/antimalarial	Phase 2
Fingolimod	Immunomodulatory	Phase 2
Colchicine	Immunomodulatory	Phase 2
CM-4620	Inhibitor of CRAC channels/immunomodulatory	Phase 2
Azithromycin	Macrolide antibiotic/immunomodulatory	Phase 1–4
Methylprednisolone	Corticosteroid	Phase 3
Dexamethasone	Corticosteroid	Phase 3/4
Hydrocortisone	Corticosteroid	Phase 3/4

Agents	Drug class and/or targets	Phase
Budesonide	Corticosteroid	Phase 2–4
Prednisone	Corticosteroid	Phase 2
Ciclesonide	Corticosteroid	Phase 3
Aescin	Mixture of saponins/anti-inflammatory	Phase 2/3
N-Acetylcysteine	Replenish glutathione stores/anti-inflammatory	Phase 2
Aspirin	Inhibit cyclooxygenase (COX) enzyme	N/A
Ibuprofen	Nonsteroidal anti-inflammatory drug	Phase 4
Naproxen	Nonsteroidal anti-inflammatory drug	N/A
BLD-2260	Inhibitor of calpain 1, 2, and 9	Phase 2
Levamisole	Anthelmintic	Phase 2
Nitazoxanide	Antiprotozoal/broad antiviral agent	Phase 4
Niclosamide	Anthelmintic/broad antiviral agent	Phase 2/3
Ivermectin	Anthelmintic	Phase 2/3
Icosapent ethyl	Prodrug of eicosapentaenoic acid	Phase 2/4
Selinexor	Exportin 1 inhibitor	Phase 2
Spironolactone	Potassium-sparing diuretics	Phase 3
Triiodothyronine	A thyroid hormone	N/A
Tranexamic acid	Antifibrinolytic/lysine analog	Phase 2
Verapamil	Calcium channel blockers	Phase 2/3
Amiodarone	Class III antiarrhythmic agent	Phase 2/3
Valsartan	Angiotensin receptor blocker/antihypertensive	Phase 4
Losartan	Angiotensin receptor blocker/antihypertensive	Phase 2–4
Candesartan	Angiotensin receptor blocker/antihypertensive	Phase 2/3
Linagliptin	Inhibitor of dipeptidyl peptidase 4	Phase 3
Sildenafil	Inhibitor of PDE5	Phase 3
Simvastatin	HMG-CoA reductase inhibitor	Phase 2
Dapagliflozin	SGLT2 inhibitor/antidiabetic	Phase 3
Rivaroxaban	Factor Xa inhibitor	N/A
Clopidogrel	Antiplatelet/inhibit ADP $P2Y_{12}$ receptor	N/A
Fluvoxamine	Serotonin reuptake inhibitor	Phase 2
Deferoxamine	Iron and aluminum chelator	Phase 1/2
Formoterol	β2 agonist/bronchodilator	Phase 2/3

Abbreviations: CRAC, Ca^{2+} release-activated Ca^{2+}; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMPDH, inosine-5′-monophosphate dehydrogenase; JAK, Janus kinase; mTOR, mammalian target of rapamycin; N/A, not applicable; PDE5, cGMP-specific phosphodiesterase type 5; RdRp, RNA-dependent RNA polymerase; SGLT2, sodium-glucose transport protein 2; TMPRSS2, transmembrane protease serine 2.

[a]Data were collected from https://clinicaltrials.gov/ when searching COVID-19 and SARS-CoV-2 for condition or disease. Access date: November 3, 2020. These compounds may be used as single treatment or combination use.