Kinases as Potential Therapeutic Targets for Anti-coronaviral Therapy

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ABSTRACT: The global coronavirus disease-19 (COVID-19) has affected more than 140 million and killed more than 3 million people worldwide as of April 20, 2021. The novel human severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been identified as an etiological agent for COVID-19. Several kinases have been proposed as possible mediators of multiple viral infections, including life-threatening coronaviruses like SARS-CoV-1, Middle East syndrome coronavirus (MERS-CoV), and SARS-CoV-2. Viral infections hijack abundant cell signaling pathways, resulting in drastic phosphorylation rewiring in the host and viral proteins. Some kinases play a significant role throughout the viral infection cycle (entry, replication, assembly, and egress), and several of them are involved in the virus-induced hyper-inflammatory response that leads to cytokine storm, acute respiratory distress syndrome (ARDS), organ injury, and death. Here, we highlight kinases that are associated with coronavirus infections and their inhibitors with antiviral and potentially anti-inflammatory, cytokine-suppressive, or antifibrotic activity.
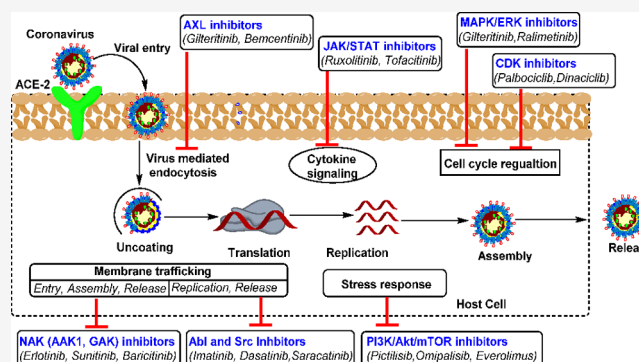
1. INTRODUCTION

The coronavirus disease-19 (COVID-19) pandemic is a potentially fatal respiratory infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1,2] SARS-CoV-2 first appeared in previously unexposed human populations in late 2019 in Wuhan, China, from an undisclosed source. Subsequently, the virus rapidly spread worldwide with a high transmission efficacy.[3,4] According to the latest data, as of April 20, 2021, the virus has affected more than 140 million people, and deaths have surpassed more than 3 million.[5] The unprecedented efforts from health care workers, industry, and academic scientists have resulted in a wide variety of vaccines, several of which have recently been authorized and recommended for use in controlling the SARS-CoV-2 spread around the world. The U.S. Food and Drug Administration (FDA) approved remdesivir in October for use in adult and pediatric patients aged 12 and up with COVID-19 who need hospitalization. However, the World Health Organization (WHO) has not recommended the use of remdesivir irrespective of the seriousness of the disorder, as there is no evidence that it improves survival and other outcomes in hospitalized patients. Moreover, the WHO recommends that seriously ill COVID-19 patients receive systemic corticosteroid medication (e.g., 6 mg dexamethasone daily) for 7−10 days but that nonsevere COVID-19 patients should not receive this treatment. Antibodies like bamlanivimab and etesevimab, which have been approved by the FDA, are only for emergency use in patients

with mild to severe COVID-19. However, they were not approved for patients who are hospitalized or need oxygen therapy due to COVID-19.[6] Monoclonal antibodies can be associated with poorer outcomes in hospitalized COVID-19 patients who require oxygen or mechanical ventilation. As a result, treatment options for human coronavirus (HCoV) diseases are limited, and experts expect that the virus will survive for a longer period.

It is essential to comprehend the coronavirus's basic features and life cycle to develop potential antiviral therapeutics. Coronaviruses are enveloped, positive-sense RNA viruses with the world's largest viral RNA genome ($\sim$26−32 kilobases)[7] that comprises about 30 000 nucleotides. So far, seven human coronaviruses have been discovered, and they are classified into four main genera (α, β, γ, and δ) under the family *Coronaviridae*:[8] α-CoVs are (i) HCoV-229E and (ii) HCoV-OC43, and β-CoVs are (iii) HCoV-HKU1, (iv) HCoV-NL63, (v) SARS-CoV-1, (vi) MERS-CoV, and (vii) SARS-CoV-2 (Figure 1).[9,10] Of the three last-mentioned β-coronaviruses,
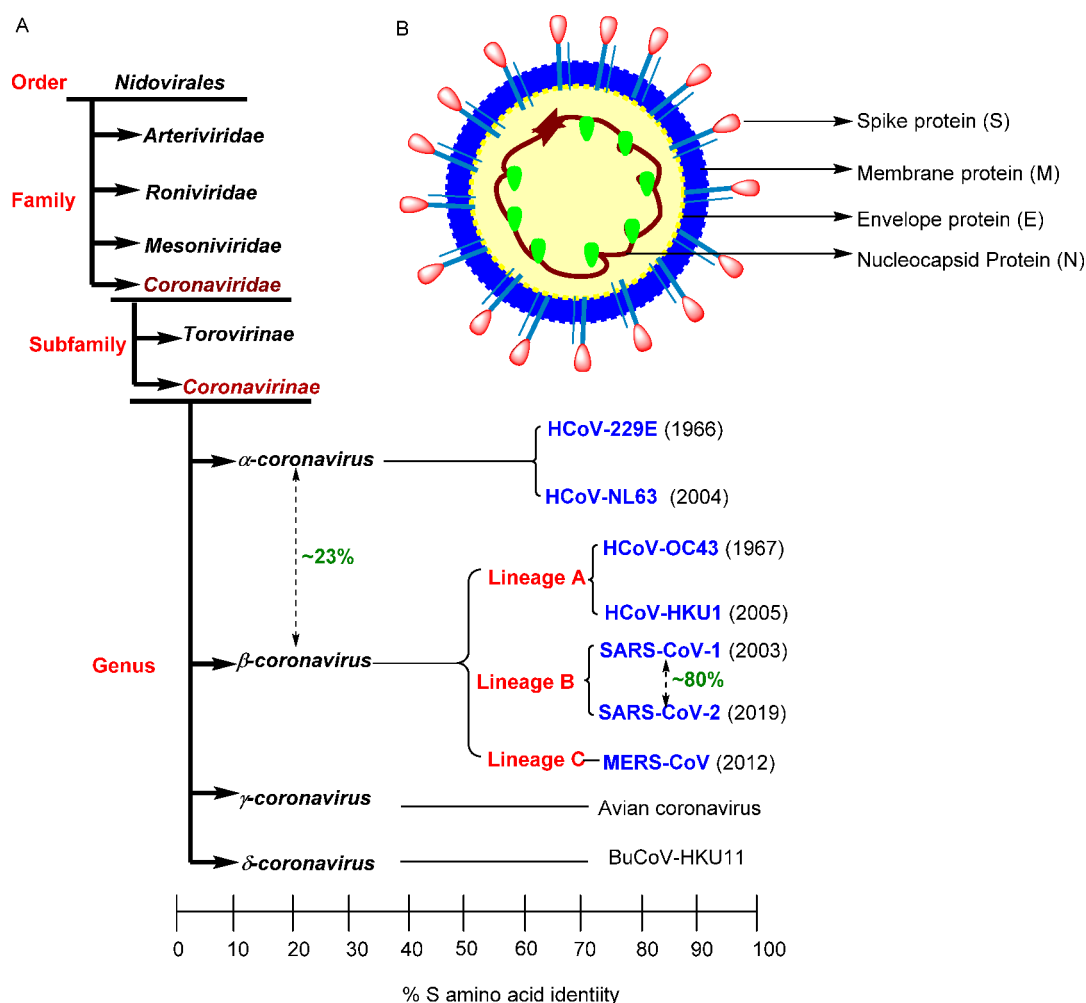
Figure 1. Taxonomy of human coronaviruses depicted schematically. (A) Seven human CoVs assigned to four genera of α, β, γ, and δ are highlighted blue. The discovery of each HCoV is indicated in the brackets. The percent of spike protein (S) amino acid identity between classes is indicated green. (B) Structure of a coronavirus with its functional proteins. Abbreviations: HCoV, human coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; BuCoV, bubaline coronavirus.

SARS-CoV-1 and MERS-CoV are mostly concerned with nosocomial transmission, while SARS-CoV-2 is commonly transmitted in the population. The basic structure of a coronavirus is illustrated in Figure 1. SARS-CoV-1, the etiological agent of SARS that first appeared in 2002-2003, caused 8096 infections with a 10% fatality rate.[11,12] MERS-CoV, which emerged from its zoonotic reservoir in 2012, affected a total of 2574 individuals, including 885 associated deaths (fatality rate = 34.4%) as of March 2021.[13−15] The new SARS-CoV-2 continues to spread incredibly rapidly, and it has had an unprecedented effect on individuals and the global economy, as many governments have imposed travel restrictions, social distancing, and quarantine measurements.

As the name indicates, the genome organization of SARS-CoV-2 shares a high degree of similarity to that of the previously known SARS-CoV-1 (79% genetic similarity),[16] SARS-related CoVs that reside in bats (genetic similarity of up to 98%), and to a lesser extent MERS-CoV (genetic similarity of up to 50%).[16]

Most coronaviruses have a four-step life cycle: entry, replication, assembly, and release (Figure 2).[7,17] At the molecular level, (i) the spike protein-host receptor, which is responsible for the viral entry, (ii) proteases such as the main protease (M^{pro}) and the papain-like protease (PL^{pro}) required

for the proteolytic cleavage of viral proteins, which are required for viral replication and the assembly of the viral particles, and (iii) the RNA-dependent RNA polymerase (RdRp), which is critical for the multiplication of the genome of viral RNA, are considered to be very important biochemical events in the virus life cycle. Targeting any of these processes could become an important therapeutic approach that can directly invade the virus in coronavirus-associated diseases.[18]

2. THE ROLE OF KINASES IN SARS-CoV INFECTION AND THEIR POTENTIAL AS THERAPEUTIC TARGETS

SARS-CoV-2 mainly interacts with the respiratory system and induces dry cough, fever, fatigue, sore throat, and shortness of breath.[19,20] However, in serious circumstances, it can cause acute respiratory distress syndrome (ARDS) (Figure 2), a virus-driven hyperinflammatory reaction that is one of COVID-19's leading causes of mortality. The cytokine storm, which is caused by the release of proinflammatory cytokines, is the most prominent feature of ARDS. Some of the cytokines include interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor (GM-CSF), TNF-α, interferon-γ inducible protein 10, macrophage inflammatory protein 1-α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1).[9,21−25] This virulent
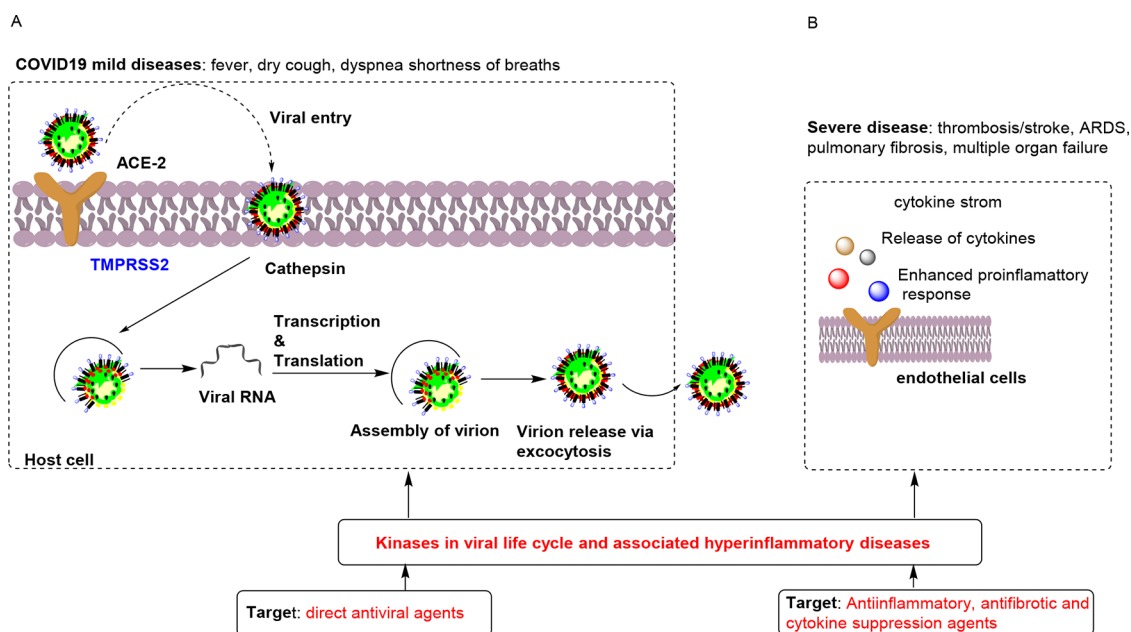
Figure 2. (A) SARS-CoV-2 life cycle as an example: entry, transcription and translation, assembly of virion, and release. (B) Viral infection results in the hyperproduction of proinflammatory cytokines. Kinases involved in both coronavirus viral replication and associated diseases.

Table 1. Kinases as Mediators and Their Roles in Coronavirus Infections

coronavirus	kinases[a]	roles
SARS-CoV-1, SARS-CoV-2	Ca$_2$+/calmodulin-dependent,[36] protein kinase II,[37] ERK1/2/5,[27] EGFR,[27] GSK-3,[38] JAK/STAT,[27] p38 MAPK,[27] NAK, SFK signaling pathway,[27] PI3K/Akt, mTOR,[27] AXL,[39] CDK,[39] CK2,[39] Abl kinases[40]	viral life cycle (entry, replication, assembly, release), hyperimmune activation, proinflammatory cytokine production, cell cycle regulation (pneumonia, inflammation, and fibrosis)
MERS-CoV	Abl kinases,[41,42] p38 MAPK, ERK1/2/5, PI3K/Akt/mTOR,[43] SFK signaling pathway[44]	viral life cycle (entry, replication), symptom associated diseases
HCoV-229E	p38 MAPK,[32] SFK signaling pathway[44]	
HCoV-OC43	receptor-interacting protein kinase 1,[45] mixed lineage kinase domain-like[45]	

[a]Abl, Abelson tyrosine kinase; CDK, cyclin-dependent kinases; CK2, casein kinase 2; EGFR, epidermal growth factor receptor; GSK-3, glycogen synthase kinase 3; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; NAK, numb-associated kinase; PI3K, phosphatidylinositol 3-kinase; PDGFR, platelet-derived growth factor receptors; STAT, signal transducer and activator of transcription; SRPK, serine/threonine-protein kinase.
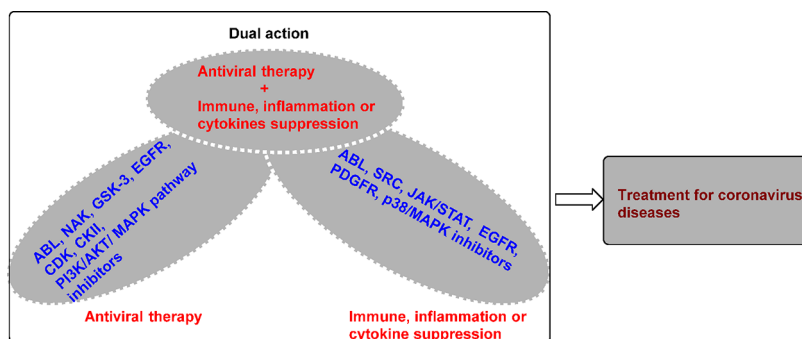

Figure 3. Kinases as potential targets for the management of coronavirus diseases.

inflammatory immune response contributes to ARDS, respiratory failure, organ failure affecting the heart, liver, kidney, and central nervous system (CNS),[26] and death from severe infection.[3]

Of all the host resources, cellular kinases can play a part in various stages of the virus's life cycle. Numerous kinases have been suggested as potential mediators of different virus infections. Several kinases have been suggested as possible mediators of multiple viral infections, including life-threatening coronaviruses like SARS-CoV-1, MERS-CoV, and SARS-CoV-2 (Table 1).[27] SARS-CoV-1 and MERS-CoV fusion with the

endosomal membrane is mediated by Abelson (Abl) kinases.[28,29] For the replication of the murine coronavirus HCoV-229E and other unrelated viruses, activation of p38 MAPK and c-Jun N terminal kinases (JNK1/2) is needed.[30−32] Studies revealed that p38 is implicated in the phosphorylation of the initial translation factor eIF4E, which plays a crucial role in the translation of viral mRNAs and subsequent production of infection of murine CoV (mCoV).[31] The p38 MAPK/ERK signaling pathway has been employed in the entry and production of the influenza A and Ebola viruses.[33−35]
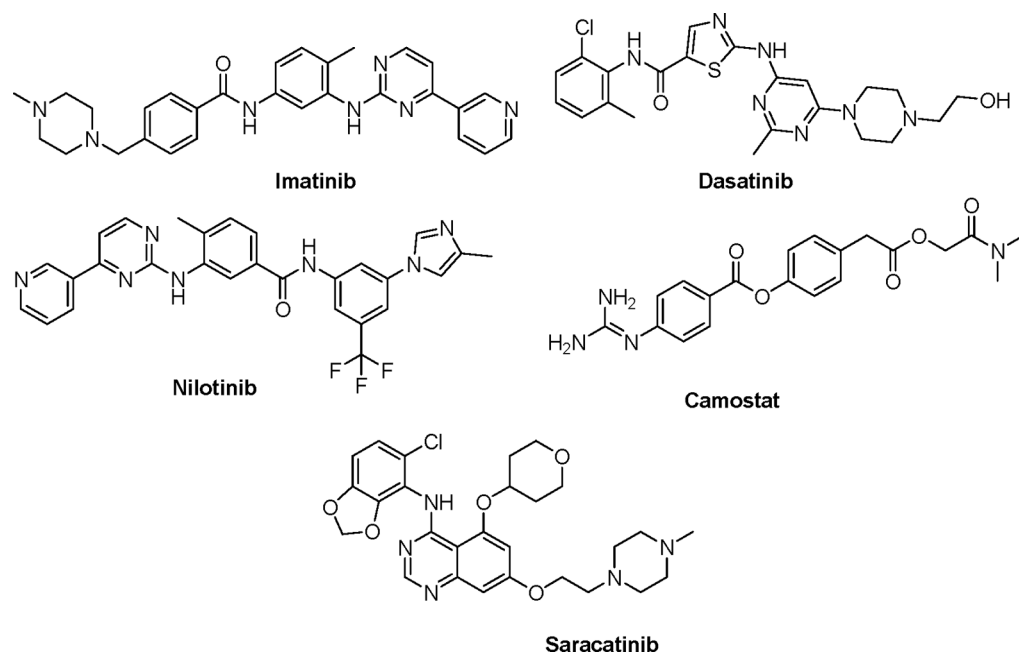
Figure 4. Abl tyrosine kinase and Src kinase inhibitors as antiviral agents (imatinib: SARS-CoV-1, EC$_{50}$ 9.823 μM, MERS-CoV, EC$_{50}$ 2.100 μM;[58] dasatinib: SARS-CoV-1, EC$_{50}$ 17.689 μM, MERS-CoV, EC$_{50}$ 5.468 μM).[58]

Many kinases also play a role in the progression of symptoms like pneumonia, inflammation, and fibrosis that are linked to CoV infections.[27,39,46] Kinases respond to and regulate the synthesis of potentially harmful cytokines (IL-6, IL-10, and TNF) and proteins associated with inflammation and pulmonary fibrosis induction (such as the proinflammatory cytokine TGF-β).[47,48] Therefore, kinase inhibitors can have direct antiviral effects and anti-inflammatory, cytokine-suppressive, and antifibrotic activities, all of which may be useful in the fight against respiratory viral infections (Figure 3). Indeed, several kinase inhibitors are currently being tested in clinical trials for COVID-19 therapy.

Several reviews have been published that illustrate the function of cellular kinases in a variety of viral infections. Raghuvanshi and Bharate discussed how kinase inhibitors have recently been developed to treat various viral infections.[49] They primarily focused on different stages of kinase inhibitors as FDA approved, clinical candidates and on discovery that targeted various virus infections, but they did not discuss kinase inhibitors that target human coronaviruses to date. Several research groups reviewed the critical function of different host kinases in influenza A virus infection.[50−52] Schor and Einav discussed the possibility of repurposing branded kinase inhibitors to have broad antiviral efficacy.[53] Weisberg et al. focused solely on repurposing licensed kinase inhibitors against SARS-CoV-2, the new COVID-19 pandemic's causative agent.[27] However, no systematic review of kinase inhibitors as anticoronaviral agents has been published to date.

In this Perspective, we systematically discuss different kinases associated with coronavirus infections and their inhibitors with antiviral and potential for anti-inflammatory, cytokine-suppressive, or antifibrotic activity.

3. KINASE INHIBITORS AS POTENTIAL ANTIVIRAL AGENTS

3.1. Inhibitors Targeting Abl and Src Kinases. Abl kinases are ubiquitous signaling kinases that play a role in cell proliferation, adhesion, and stress response. They are housekeeping proteins in all cell types. Several experiments have shown that Abl kinases are involved in various stages of the viral life cycle in viruses, including the Ebola virus,[54,55] coxsackievirus,[56] and vaccinia virus.[57] Abl kinases, which are involved in viral entry and replication, have recently been identified as possible therapeutic targets for coronavirus diseases.

Dyall et al. screened approved or experimental drug libraries to identify potential therapeutics against SARS-CoV-1 and MERS-CoV.[58] This led to the development of three kinase signaling pathway inhibitors: imatinib, dasatinib, and nilotinib. Imatinib and dasatinib were active against SARS-CoV-1 and MERS-CoV, while nilotinib was only active against SARS-CoV-1 (Figure 4). Both imatinib (4-[[(4-methylpiperazin-1-yl)-methyl]-N-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]-amino}phenyl)benzamide) and dasatinib (N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide monohydrate) inhibit SARS-CoV-1 and MERS-CoV with EC$_{50}$ values of 2.1−17.6 μM, though SARS-CoV-1 appeared to be sensitive to these kinase inhibitors as well. Dasatinib, for example, inhibited SARS-CoV-1 with a low micromolar EC$_{50}$ of 2.1 μM, while the EC$_{50}$ for inhibiting MERS-CoV was 5.4 μM. Imatinib, instead, needed a high concentration (EC$_{50}$ 9.23 μM) to inhibit SARS-CoV-1, despite having been confirmed to inhibit the Ebola virus, coxsackievirus B, and vaccinia virus with concentrations in the same range.[4,58]

Imatinib is an orally available Abl kinase inhibitor for chronic myeloid leukemia (CML) treatment.[59] Dasatinib is an orally available, second generation Abl kinase inhibitor for CML and acute lymphoblastic leukemia (ALL).[60]

Nilotinib (4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-ylpyrimidin-2-yl)-amino]benzamide), a structural analogy to imatinib, has been used to treat CML. It inhibited the SARS-CoV-1 replication in the micromolar range without compromising cell cytotoxicity but not significantly inhibiting the MERS-CoV (only 39%

inhibition). In Abl-expressing cells, nilotinib, rather than imatinib, effectively blocked Abl activity and proliferation.[41,60−63]

In the subsequent study, imatinib was discovered to be effective in preventing viral infection in its early stages for SARS-CoV-1 and MERS-CoV.[28] It blocked viral entry and replication by preventing virions from fusing at the endosomal membrane. Further insights into mechanistic studies revealed the SARS-CoV-1 and MERS-CoV to rely on Abl2 kinase activity for viral entry but not on Abl1 kinase: inhibition of Abl2 kinase by imatinib blocks viral entry. Imatinib was previously found to inhibit the Ebola virus, poxvirus, and coxsackievirus.[40,54,56]

SH2 and SH3 domains in Abl2 kinase hold the protein in a dormant state.[64] Since the substrate binds to either the SH2 or the SH3 domain, Abl2 may turn from its inactive to active state.[42] Adenosine triphosphate (ATP) binding at the catalytic site and corresponding kinase activity are allowed by Abl2's open, active conformation. It has been proposed that coronavirus infection increases Abl2 substrate binding, allowing Abl2 into an active state and phosphorylate downstream targets.[65] Imatinib inhibited the kinases activity of Abl2 by preventing the phosphorylation of proteins in cells.

Since SARS-CoV-1 and SARS-CoV-2 have a high degree of genome sequence identity (80%), imatinib is predicted to inhibit SARS-CoV-2 as well. Zhao et al. utilized pseudotyped viruses with SARS-CoV-2 spike protein to study imatinib's anti-SARS-CoV-2 activity in Caco-2 cells.[66] At concentrations up to $10 \mu M$, imatinib, on the other hand, did not affect SARS-CoV-2 entry or infection. This result supports the weak activity of imatinib in inhibiting SARS-CoV-1 replication in Vero cells (EC_{50} 9.85 μM).[58]

Severe COVID-19 is characterized by ARDS triggered by enhanced proinflammatory cytokine production. Imatinib has immunomodulatory effects[66,68] and inhibits cytokine receptor signaling (PDGFR, c-Kit, and CSF1R), potentially suppressing cytokine storms. As a result of its immunomodulatory effects, imatinib may display clinical benefits for COVID-19.

In contrast to Zhao et al., a recent preprint reported imatinib to effectively inhibit SARS-CoV-2 replication with an IC_{50} value of 130 nM.[69] However, it was toxic in concentrations between 25 and 3.2 μM. For both SARS-CoV-1 and MERS-CoV virus fusion inhibition, imatinib's antiviral efficacy was the same. Furthermore, imatinib binds to the SARS-CoV-2 spike protein's receptor-binding domain (RBD) with a 2.32 μM affinity, meaning that imatinib did not specifically inhibit the SARS-CoV-2 RBD/ACE2 interaction. As a result, imatinib inhibited both cellular tyrosine kinase and viral fusion, preventing virus replication. Indeed, three clinical trials investigating the therapeutic efficacy of imatinib in COVID-19 patients are currently underway: NCT04394416 (USA), EudraCT2020-001236-10 (The Netherlands), and NCT04357613 (France).

Galimberti et al. reported tyrosine kinase inhibitors (TKIs) to play a protective role against SARS-CoV-2 in patients with Ph+ ALL and CML.[46] In Ph+ ALL and CML Italian cohorts, they found just a few cases of COVID-19. According to the evidence, the use of TKIs may be to account for the low infection rate. It was interesting to see that during treatment of patients with TKIs, such as imatinib or nilotinib, several "proimmune" genes such as CD28 and IFN γ were induced, whereas the expression of anti-immune genes such as ARG-1, CEACAM1, and FUT4 was reduced.

The entry of the virus, which includes receptor binding, S glycoprotein modification, and proteolysis, is the first step in viral replication. Cathepsin L and the transmembrane serine protease 2 (TTSP) TMPRSS2 are playing crucial roles in viral entry. Cathepsin L mediates the proteolysis,[70] while TMPRSS2 helps in the CoV S glycoprotein cleavage to enter the host cells.[71] It was discovered that inhibiting cathepsin L prevented SARS-CoV-1 infection and that using a mixture of EST (a cathepsin inhibitor) and camostat (a serine protease inhibitor, Figure 4) prevented viral entry and replication completely. The study indicated that imatinib inhibits the functionality or action of TMPRSS2.[28] On the other hand, Abl and ARG kinases have been linked to promoting the production of the endosomal protease cathepsin L in cancer cells.[72] Thus, inhibiting cathepsin L in the context of viral replication by targeting these kinases may be a promising strategy.

3.2. Src Family Kinases. Src family kinases (SFKs), crucial modulators of signal transduction, are nonreceptor tyrosine kinases with nine members in the family: Src, Yes, Fyn, Fgr, Lck, Hck, Blk, Lyn, and Yrk. They control a variety of cellular signaling pathways that stimulate cell survival and motility. SFKs are important in the life cycle of a variety of viruses.[73] Src kinases were involved in the vaccinia virus replication via activation of Abl kinases linked to virus actin-based motility. Different SFKs like Fyn, Lyn, c-Src, and Csk (dengue virus,[74−76] hepatitis C virus (HCV)[77]), and c-Yes (West Nile virus (WNV)[78]) were implicated in the replication of the *Flaviviridae* family. De Wispelaere et al. reported that dasatinib and saracatinib (N-(5-chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methyl-1-piperazinyl)-ethoxy]-5-[(tetrahydro-2H-pyran-4-yl)oxy]-4-quinazolin-amine) (Figure 4) inhibited the assembly of the dengue virus.[76] The antiviral activity of these agents contributed to inhibiting SFKs, especially c-Src and Fyn. Saracatinib is a Phase III investigational dual kinase inhibitor that inhibits both Src and Bcr-Abl tyrosine kinases.

Shin et al. discovered that saracatinib inhibited MERS-CoV in Huh-7 cells at an early stage of its life cycle (EC_{50} of 2.9 M, CC_{50} of >50 μM).[44] The authors hypothesized that saracatinib could inhibit MERS-CoV by inhibiting SFK signaling pathways. In a subsequent study, they identified the targets of saracatinib as Lyn and Fyn through a siRNA knock-down study. The study also showed that knocking out Lyn and Fyn resulted in a substantial reduction in viral load, implying that these kinases are needed for effective MERS-CoV replication. In Huh-7 cells, however, knockdown of Yes had little effect on MERS-CoV replication. The coadministration of saracatinib with gemcitabine (Figure 4), a chemotherapy medication for different types of cancers, showed a synergistic effect. Saracatinib also demonstrated broad antiviral activity against HCoV-229E and HCoV-OC43, with EC_{50} values of 2.4 and 5.1 μM, respectively.[44]

Src family kinases have also been shown to be potential molecular targets for HCV[77] and dengue virus infection and replication. Kumar et al. discovered that the Src kinase (Csk) is a critical host kinase in dengue virus replication.[75] Dengue virus RNA levels were suppressed when Csk expression was knocked down by siRNA or inhibitor, and dengue infection was greatly reduced when cells lacked Src kinases (Fyn, Src, and Yes). This data indicates that Src kinases are crucial players in dengue virus replication and assembly. Csk was identified to be hyper-phosphorylated during virus infection, and inhibiting protein kinase A (PKA) prevented viral replication, implying that PKA phosphorylation of Csk is involved in the dengue virus life cycle.

Chu and Yang discovered that the inhibition of Csk by dasatinib exhibits a potent inhibitory effect on dengue virus

replication.[74] Mechanistic studies demonstrated that dasatinib prevents the formation of infectious virus particles. Saracatinib and dasatinib were identified as effective agents against the dengue virus, and both of them targeted Fyn for RNA replication.[76] The genetic knock-down study of Yes was shown to inhibit the West Nile virus titer through the virus replication cycle.[78]

3.3. Numb-Associated Kinase (NAK) Family and AXL Kinase Inhibitors. The numb-associated family of Ser/Ther kinases plays a crucial role in the replication of many unrelated viruses.[26] Four human homologues are in the family: (i) AK1 adaptor protein-associated kinase 1 (AAK1), (ii) BMP-2-inducible kinase (BIKE/BMP2K), (iii) cyclin G-associated kinase (GAK), and (iv) myristoylated and palmitoylated serine/threonine kinase 1 (MPSK1). Two of these homologues, AAK1 and GAK, have been linked to the entry, assembly, and release of viruses such as dengue, HCV, Ebola, SARS-CoV-1 and -2, and MERS-CoV.[79−86]

Sunitinib (*N*-(2-diethylaminoethyl)-5-[(*Z*)-(5-fluoro-2-oxo-1*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide) and erlotinib (*N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine) (for structures, see Figure 5) potentially suppressed AAK1 and GAK and showed antiviral
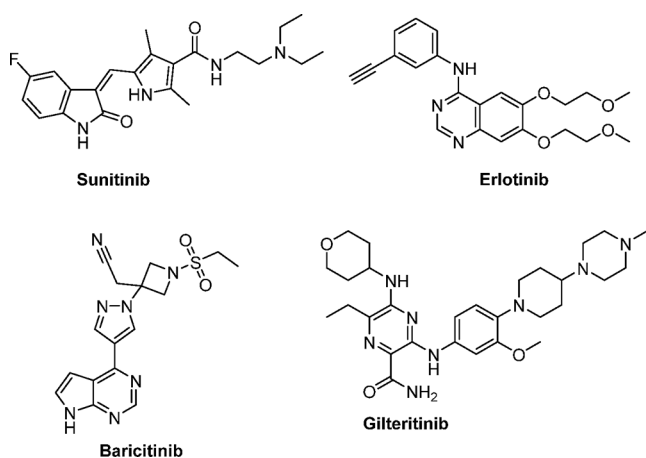
Figure 5. NAK family inhibitors (sunitinib,[86] erlotinib,[86] and baricitinib[44,86]) and AXL kinase inhibitor (gilteritinib: SARS-CoV-2, IC$_{50}$ of 0.807 μM)[39] for the treatment of coronavirus infection.

action against dengue and ebolaviruses in cultured cells.[78,87] The gene silencing of AAK1 and GAK demonstrated their crucial role in viral entry and infection.[83] Sunitinib and erlotinib were found to prevent viral infection through inhibiting AP-mediated intracellular membrane trafficking by AAK1 and GAK at the molecular level.[87] In murine models of dengue and ebolaviruses, the drug combination sunitinib/erlotinib has been shown to minimize morbidity and mortality.[7] However, the dosage required for inhibiting AAK1 and GAK by sunitinib and erlotinib would be much higher in COVID-19 patients.[86]

Sunitinib is an approved multitargeted kinase inhibitor used for renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) treatment. Erlotinib is an EGFR tyrosine kinase inhibitor, which has been licensed by the FDA for the treatment of metastatic non-small cell lung cancer (NSCLC) and pancreatic cancer. Erlotinib is one of the World Health Organization's Essential Medicines.

Baricitinib (2-[1-ethylsulfonyl-3-[4-(7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetonitrile) has re-

cently been suggested as a promising inhibitor of SARS-CoV-2 activity (Figure 5).[86] Indeed, baricitinib showed a promising result for ARDS in COVID-19. In November 2020, the FDA approved baricitinib for emergency use authorization (EUA) status for COVID-19 care in hospitalized patients in combination with remdesivir.[88] Baricitinib is an inhibitor of Janus kinase-1 (JAK-1) and JAK-2, and it has been licensed for treating rheumatoid arthritis and myelofibrosis.[86]

ACE2 has several regulators, among which AAK1 and G-associated kinase (GAK) are known for clathrin-mediated endocytosis. The mode of action of baricitinib on viral entry and controlling ARDS are indicated in Figure 6. Baricitinib not only reduced the ARDS in patients but also interrupted the passage and intracellular assembly of SARS-CoV-2 into the target cells by inhibiting the AAK1 signaling. Furthermore, the clinical dose of baricitinib (2 or 4 mg once daily) rendered it superior as an antiviral agent. In vitro studies demonstrated baricitinib's antiviral properties, and therapy with baricitinib boosted the clinical results of COVID-19 patients. Baricitinib reduced the SARS-CoV-2 viral load by 30−40% in primary human liver spheroids at 400 and 500 nM concentrations, indicating antiviral activity.[89] In human clinical trials with effectiveness in rheumatoid arthritis (RA) patients, baricitinib had a high oral bioavailability (79%) and was well tolerated.[90] Furthermore, baricitinib is a unique candidate for the treatment of COVID-19 because of its favorable side-effect profile, low plasma protein binding, and negligible involvement with CYP enzymes.

Baricitinib's possible role in the treatment of COVID-19 patients has recently been highlighted. The study examined the safety and effectiveness of baricitinib in COVID-19 patients and found that it provided substantial clinical improvement with no infections or side effects 2 weeks after treatment. These findings indicated that using baricitinib for a brief period (1−2 weeks) was the best way to mitigate viral replication and an abnormal host inflammatory response when on the therapeutic dosage.

Another study demonstrated baricitinib as a potential drug to reduce systematic inflammation caused by SARS-CoV-2 infection in rhesus macaques.[92] Inflammation was minimized in animals given baricitinib. More specifically, baricitinib-treated animals had a rapid and potent inhibition of inflammation-related cytokines and chemokines. These data indicated the beneficial role of baricitinib as a potential candidate for the management of inflammation induced by SARS-CoV-2 infection.

The antiviral effect of baricitinib is being studied in several clinical trials either alone or combined with other antivirals for COVID-19 (https://clinicaltrials.gov/ct2/results?cond=Baricitinib) (see Table 2). The anti-SARS-CoV actions of baricitinib in conjunction with remdesivir are being studied in the Adaptive COVID-19 Treatment Trial (ACTT-2; NCT04401579). The FDA approved this combination in November 2020 for emergency use in hospitalized COVID/19 patients who need oxygen.[93] Baricitinib is being studied as a monotherapy in the COV-BARRIER trial (NCT04421027). Also, baricitinib is proposed to interrupt the passage and intracellular assembly of SARS-CoV-2 into the target cells mediated by the ACE2 receptor.[94]

3.4. AXL Kinase Inhibitors. AXL, a tyrosine kinase on the cell surface, controls cell replication, growth, differentiation, and immunity.[95−98] Upon activation by its ligands such as vitamin-K-dependent protein growth-arrest-specific gene 6 (GAS 6), AXL stimulates various downstream signaling pathways that
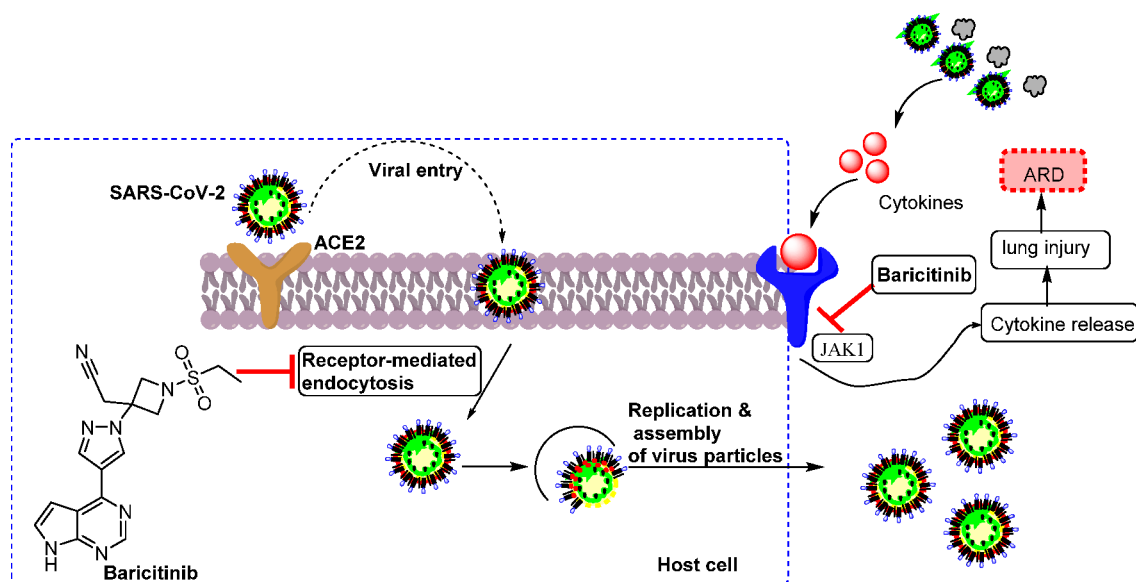
Figure 6. Baricitinib inhibits JAK1 and thereby prevents SARS-CoV-2 entry and ARD.

Table 2. List of Baricitinib Clinical Trials for the Treatment of COVID-19

| clinical trial identifier and use	primary end point
NCT04345289, Phase III: Baricitinib, sarilumab, hydroxychloroquine (HQ), convalescent plasma, intravenous and subcutaneous placebo, or oral placebo were both included in this study	mortality due to any cause or the need for intrusive respiratory support
NCT04390464, Phase IV: baricitinib and ravulizumab	composite end point's time to occurrence: death, artificial breathing, ECMO, cardiovascular organ support, or renal failure
NCT04401579, Phase III: baricitinib + remdesivir compared with remdesivir alone	time to recovery
NCT04321993; (i) lopinavir/ritonavir; (ii) HQ; (iii) baricitinib; and (iv) sarilumab are the four arms of the study	clinical status of subject at day 15
NCT04362943, Observational: baricitinib or anakinra	mortality for all causes
NCT04365764, Observational: specific therapies, such as baricitinib, but not limited to it	respiratory support and mortality as a composite
NCT04320277, Phase III: baricitinib	percent of patients who need ICU admission
NCT04346147, HQ in combination with baricitinib, imatinib, or lopinavir/ritonavir in the early stages	time to clinical improvement
NCT04346147, Phase II: baricitinib + HQ + imatinib, or lopinavir/ritonavir	time to clinical improvement
NCT04366206, Observational: relevant treatments, such as baricitinib, although not limited to it	composite of death and mechanical ventilation
NCT04393051, Phase II: baricitinib	need of invasive mechanical ventilation
NCT04340232, Phase II/III: baricitinib	Baricitinib's safety (Phase II) and effectiveness (Phase II and III)
NCT04373044, Phase II: baricitinib	percentage of patients who need intrusive mechanical ventilation or who die
NCT04399798, Phase II: baricitinib	response to treatment: absence of moderate to severe oxygenation impairment
NCT04358614, Phase II/III: baricitinib + lopinavir/ritonavir	the aim of this study was to determine the efficacy of baricitinib in combination with an antiviral (lopinavir-ritonavir) in terms of the rate of serious and nonserious adverse effects

include RAS/ERK, PI3K-AKT-mTOR, MEK-ERK, NF-κB, JAK/STAT, and p38.[99−101]

For the Zika virus[102] and the Ebola virus,[103] AXL has been confirmed to serve as a viral entry factor/immune modulator. AXL a has crucial role in the relationship between the virus and the host. AXL facilitated virus entry and modulated the antiviral state of human Sertoli cells during Zika virus infection.[7] AXL inhibition led to decreased suppressor of the cytokine signaling-1 (SOCS1) and SOCS3 proteins, increased expression of IFNγ, and reduced replication. In a recently published study, the authors discovered that AXL interacts with the SARS-CoV-2 S glycoprotein on the host cell membrane, allowing the virus to enter the cell.[104] SARS-CoV-2 virus entry into pulmonary and bronchial epithelial cells was substantially reduced when AXL

was knocked down in H1299 and A549 cells, indicating that AXL is needed for SARS-CoV-2 virus entry.

Recently, gilteritinib (6-ethyl-3-[3-methoxy-4-[4-(4-methyl-piperazin-1-yl)piperidin-1-yl]anilino]-5-(oxan-4-ylamino)-pyrazine-2-carboxamide) (Figure 5) was reported to inhibit the replication of SARS-CoV-2 with an IC_{50} value of 0.807 μM in cellular assays.[39] The inhibition of AXL kinase, which is upstream of p38, led to gilteritinib's anti-SARS-CoV-2 replication function. The use of bemcentinib, an AXL inhibitor, in the RECOVERY COVID-19 trial in the United Kingdom, backs up this argument. Gilteritinib is a tyrosine kinase inhibitor105 that has been licensed for the treatment of AML.

3.5. EGFR Signaling Pathway Inhibitors. The epidermal growth factor receptor (EGFR) is a prototypical tyrosine kinase (RTK) receptor. Activation of the EGFR signaling pathway
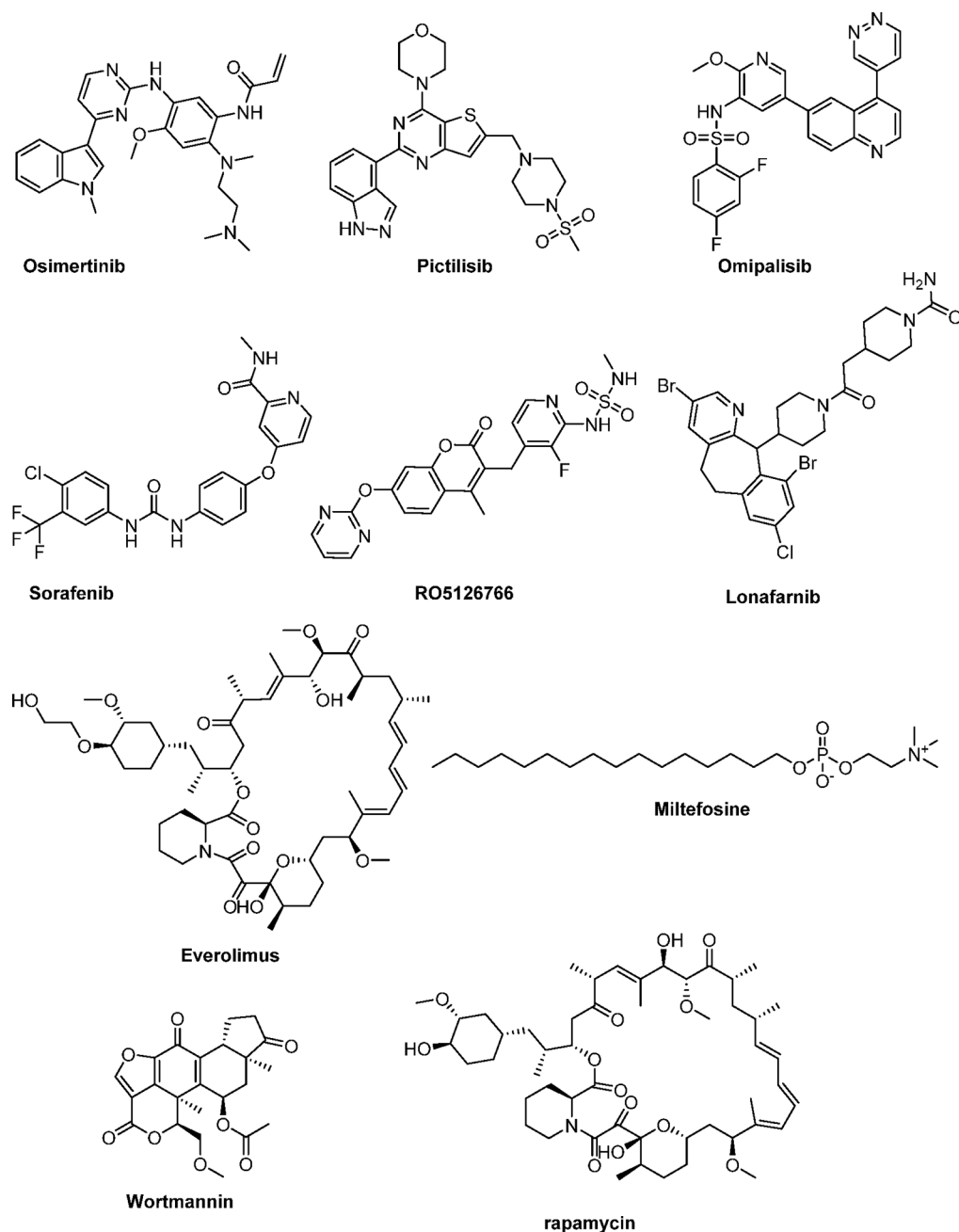
Figure 7. Inhibitors of SARS-CoV-2 and MERS-CoV replication that target EGFR and its downstream signaling pathways. Osimertinib, SARS-CoV-2 S: IC$_{50}$ 3.98 μM;[113] pictilisib: SARS-CoV-2, IC$_{50}$ 2.58 μM;[115] omipalisib: SARS-CoV-2, IC$_{50}$ 0.014 μM;[115] sorafenib: SARS-CoV-2, IC$_{50}$ 4.85 μM[115] RO5126766: SARS-CoV-2, IC$_{50}$ 0.6 μM;[115] lonafarnib: SARS-CoV-2, IC$_{50}$ 4.99 μM;[115] everolimus: 56 or 59% MERS-CoV inhibition;[43] miltefosine: 28% MERS-CoV inhibition;[43] wortmannin: 40% MERS-CoV inhibition;[43] rapamycin: 40% MERS-CoV inhibition.[43]

influences a range of cell functions, including cell proliferation, survival, growth, and development.[106] The EGFR signaling pathway has been identified as one of the crucial players in cancer pathogenesis and has also been linked to various viruses,[107−109] such as the spread and mortality of the vaccinia virus and the process of entry for influenza A, HCV, and Epstein−Barr viruses.[110,111]

EGFR is a cofactor for HCV entry into human host cells. Activation of EGFR signaling leads to suppressed interferon signaling in respiratory virus diseases (influenza and rhinovirus).[112] A loss of functional STAT1 has been associated with the upregulation of EGFR, which may indirectly activate STAT3 constitutively. As a result, targeting EGFR as an approach to

managing COVID-19 could be a viable option. A synergized antiviral reaction against HCV was observed when a possible EGFR inhibitor, erlotinib, was combined with IFN-1 therapy. The reduction of IFN1-induced STAT3 by enhancing SOCS3 expression was the mode of the action of erlotinib.[111]

Osimertinib (N-(2-{[2-(dimethylamino)ethyl](methyl)-amino}-4-methoxy-5-{[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide) was reported to be an effective inhibitor of SARS-CoV-2 S protein (EC$_{50}$ 3.98 μM) (Figure 7).[113] It rescued 60% of the SARS-CoV-2 cytopathogenic effect (CPE), though cytotoxicity limited the therapeutic window.[113] Osimertinib is an EGFR inhibitor that has been approved for the treatment of NSCLC.[114]
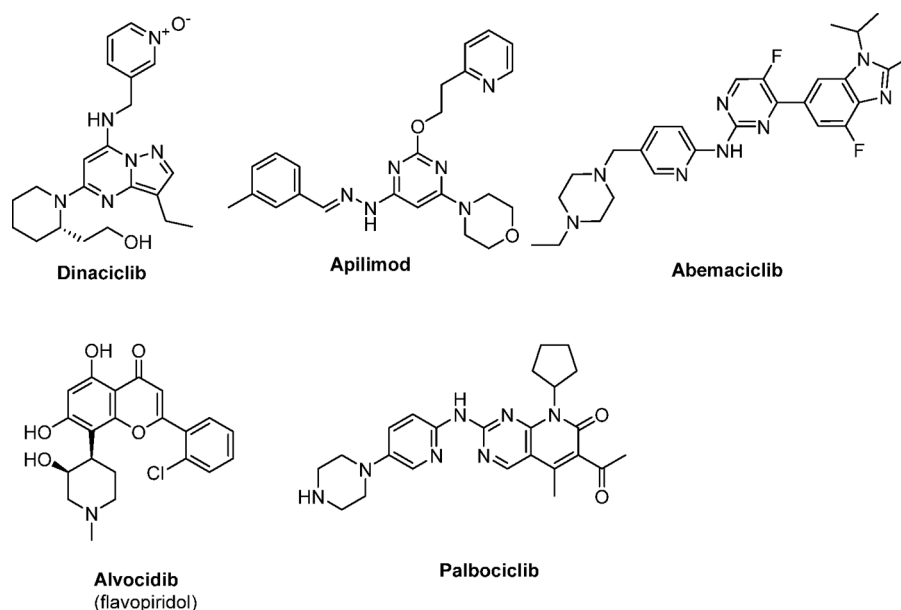
Figure 8. CDK inhibitors as antiviral agents. Dinaciclib: SARS-CoV-2, IC_{50} 0.127 μM (Vero E6), IC_{50} 0.032 μM (A549-ACE2);[39] apilimod: SARS-CoV-2, IC_{50} < 0.08 μM (Vero E6), IC_{50}0.007 μM (A549-ACE2);[39] abemaciclib, SARS-CoV-2: EC_{50} 2.16 μM.[113]

3.6. PI3K/Akt/mTOR Pathway Inhibitors. GFRs integrate and regulate several signaling processes inside the cell. GFR signaling (1) activates the RAF/MEK/ERK MAPK signaling cascade and (2) incorporates (via phosphatidylinositol 3-kinase [PI3K] protein kinase B [AKT]) into mTORC1 signaling to control proliferation.

Klann et al. recently confirmed that many EGFR inhibitors inhibited the replication of SARS-CoV-2.[115] They used the colon epithelial cell line Caco-2, which is extremely permissive for the virus, to create a SARS-CoV-2-infected in vitro cell culture model.[116,117] The cellular phosphoprotein networks revealed extensive cellular signaling pathway rearrangements after infection with SARS-CoV-2, especially GFR signaling. Pictilisib (IC_{50} 2.58 μM), a PI3K inhibitor, and omipalisib (IC_{50} 0.014 μM), a dual PI3K/mTOR inhibitor, inhibited viral replication in cells[115] (Figure 7).

Sorafenib (IC_{50} 4.85 μM) and RO5126766 (IC_{50} 0.6 μM), a dual RAF/MEK inhibitor, both blocked viral replication (Figure 7). During infection and viral replication, both compounds blocked cytopathic effects. Lonafarnib, a RAS inhibitor, inhibited the replication of SARS-CoV-2 (IC_{50} value of 4.99 μM) (Figure 7). Antiviral activity of these drugs was reported in UKF-RC-2 cells infected with SARS-CoV-2 at clinically achievable concentrations,[118−123] highlighting the importance of GFR signaling during SARS-CoV-2 infection. Before the MERS-CoV infection, cells treated with sorafenib, a RAF kinase inhibitor approved for primary kidney cancer treatment, demonstrated good inhibition of the early phases of replication.

EGFR-mediated STAT3 activation is controlled by the RAS/RAF/MAPK and PI3K pathways, and inhibition of these pathways will potentiate IFN-1 and anti-SARS-CoV-2 activity in a synergistic manner. GFR signaling is also implicated in SARS-CoV-1-induced fibrosis.[107,109,115,116,124,125] An inhibitor, omipalisib, has been shown to slow fibrosis development in patients with idiopathic pulmonary fibrosis, which may be related to the deregulation of GFR signaling pathways in coronavirus patients' lung fibrosis.[126]

Several unrelated viruses activate the PI3K/Akt/mTOR pathway to enhance their replication.[127] For example,

HCV[124,129] and WNV utilize this pathway in their life cycle and control apoptosis. Everolimus (dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone) (Figure 7), an approved mTOR inhibitor, showed moderate inhibitory activity (56 or 59% inhibition at 10 μM) against MERS-CoV based on whether it was added pre- or postinfection. Miltefosine (Figure 7), an approved Akt inhibitor for leishmanial infection, had minimal (28%) or no activity against MERS-CoV at the highest concentration tested when added preor postinfectionally.[143] Teriflunomide, an active metabolite of leflunomide, on the other hand, demonstrated good anti-HCV activity in both in vitro and in vivo studies.[130] Leflunomide, a drug that inhibits Akt phosphorylation, has been approved for rheumatoid arthritis.

AXL is known to control various signaling pathways including PI3K, Ras/ERK, and p38. Therefore, the inhibition of AXL may contribute to the downregulation of p38 signaling. PI3K/Akt/mTOR activation has been demonstrated in the growth and replication of various unrelated viruses such as HCV, WNV, and influenza A virus.[128,129] Wortmannin (Figure 7), a covalent inhibitor of PI3Ks, had a 40% inhibitory effect on MERS-CoV. At a concentration of 10 μM, the mTOR inhibitor rapamycin (Figure 7) inhibited MERS-CoV replication in virus-infected cells by 61%.[43] Rapamycin is a macrolide compound and has an immunosuppressant function in humans.

3.7. Cyclin Dependent Kinases (CDKs) Inhibitors. CDKs are kinases that control the cell cycle and have been targeted for anticancer drugs. CDKs are also used in infectious diseases, where the virus alters the expression and function of host CDKs to influence cell cycle progression.[115] For example, several viruses, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), Zika virus, and herpes simplex virus (HSV) have been linked to CDKs.[131] CDK4 and CD6 have been validated as potential targets for the inhibition of HIV-1 infection,[132,133] and CDK9 for herpes simplex virus type 1 (HSV-1) infection.[134] An adenovirus promotes progression into the late G1/S process by increasing CDK2 phosphorylation.[135] HBV infection increases
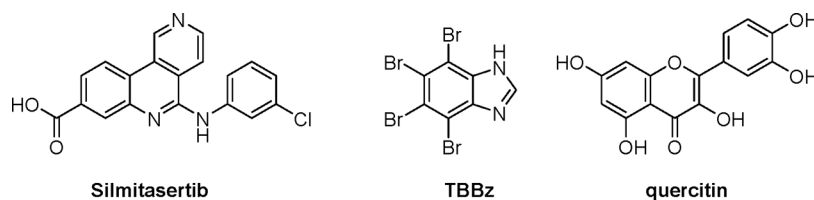
Figure 9. CK2 inhibitors for SARS-CoV-2 (silmitasertib: IC$_{50}$ 1.28 μM),[39] vaccinia virus (4,5,6,7-tetrabromo-1H-benzimidazole (TBBz)),[155] and quercetin.

the activity of the G1-phase CDK4.[136] Several CDK inhibitors such as dinaciclib (an inhibitor of CDK1/2/5/9, Phase III), seliciclib (an inhibitor of CDK2/5, Phase II), alvocidip (an inhibitor of CDK9, Phase II), and PHA-690509 (CDK2 inhibitor, Phase I) displayed a broad spectral antiviral activity against HIV-1,[137,138] influenza A virus,[139] and Zika (for structures, see Figure 8).[140]

Alvocidib (2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone) (Figure 8), a flavonoid alkaloid CDK9 kinase inhibitor and commonly known as flavopiridol, showed activity against influenza A virus, in which CDK9 mediated the activity of RdRP.[138] Palbociclib (6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(1-piperazinyl)-2-pyridinyl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one) (Figure 8), a licensed inhibitor of CDK4/6, was able to inhibit HSV-1, and HSV-1 replication in vitro, possibly through a blockade of cellular protein phosphorylation.[141]

SARS-CoV-2 significantly reduced CDK1/2 behaviors during infection, resulting in an S/G2 phase arrest, close to infectious bronchitis virus (IBV),[142,143] and other RNA viruses,[144,145] according to a recent report. This indicates that the SARS-CoV-2 virus can control the cell cycle to boost the viral life cycle.[146] Dinaciclib is being tested in clinical studies for different types of variety of cancer. Recently, dinaciclib has shown strong anti-SARS-CoV-2 activity.[39] The antiviral activity of dinaciclib in two cell lines (Vero E6 and A549-ACE2 cells) infected with SARS-CoV-2 showed IC$_{50}$ 0.127 μM and IC$_{50}$ 0.032 μM, respectively.[39] The phosphatidylinositol enzyme activities of PIK3CQ, PLCB3, and PIKFYVE were also highlighted in the same study showing that the required balance of phosphatidyl-linositol species may play a role.

The pharmacological inhibition of PIKFYVE, an FYVE finger-containing phosphoinositide kinase, by its inhibitor apilimod (N-[(E)-(3-methylphenyl)methylideneamino]-6-morpholin-4-yl-2-(2-pyridin-2-ylethoxy)pyrimidin-4-amine) (Figure 8) exhibited strong anti-SARS-CoV-2 activity in two cell lines (Vero E6, IC$_{50}$ < 0.08 μM; A549-ACE2, IC$_{50}$ 0.007 μM). Apilimod was first discovered as an inhibitor of IL-12 and IL-23, but it was recently repurposed for Ebola and Lassa virus fever.[147−149]

Interestingly, abemaciclib (N-[5-[(4-ethyl-1-piperazinyl)-methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-meth-ylethyl)-1H-benzimidazol-6-yl]-2-pyrimidinamine) (Figure 8) showed specific inhibition of SARS-CoV-2 S (EC$_{50}$ in Calu3 cell lines).[113] The SARS-CoV-2 CPE was reduced by 60% using this compound.[113] Abemaciclib is a selective CDK4/6 inhibitor that has been used for the treatment of metastatic breast cancer.[150,151] In general, CDK inhibitors block viral genome replication in host cells as part of their antiviral mechanism of action.[1] Abemaciclib, on the other hand, inhibits coronavirus CPE by blocking cell entry, meaning that this compound may be optimized as an active SARS-CoV-2 entry inhibitor.

3.8. Casein Kinase 2 Inhibitors. Casein kinase 2 (CK2/CSNK2) regulates various cellular processes and is essential for

the life cycle of several unrelated viruses such as vesicular stomatitis virus (VCV), HIV, HCV, human papillomavirus (HPV), and HSV-1.[152,153] Recent shreds of evidence suggest that CK2 is involved in various mechanisms to downregulate the potential of cells to generate IFN-1 in response to viral infection.[154] Thus, the pharmacological intervention of CK2 has been considered a potential strategy for antiviral treatment. CK2 is involved in the development of actin tails during vaccinia infection, which allows the virus to travel efficiently from cell to cell.[155] The inhibition of CK2 by its selective inhibitor TBBz (at 8.0 μM concentration) impaired the vaccinia virus spread and actin tail formation. According to a recent analysis, the SARS-CoV-2 nucleocapsid (N) directly targets CK2, and they both colocalize at the filopodia protrusions, which may be essential for virus egress and rapid cell-to-cell spread.[39]

The inhibition of CK2 by silmitasertib (5-[(3-chlorophenyl)-amino]benzo[c][2,6]naphthyridine-8-carboxylic acid) displayed robust antiviral activity (IC$_{50}$ 1.28 μM) (Figure 9), suggesting the significant role of CK2 in the life cycle of SARS-CoV-2. Silmitasertib is being tested in clinical and preclinical trials to treat cholangiocarcinoma and other cancers. Recently, Phase II clinical studies of silmitasertib have been initiated for the management of COVID-19 (https://www.scienceboard.net/index.aspx?sec=sup&sub=can&pag=dis&ItemID=1645).

The recent clinical trial of intravenous CIGB-325 (formerly known as CIGB-300), a peptidic inhibitor of CK2, in patients with COVID-19 (https://covid-19.cochrane.org/studies/crs-13844822, code: IG/CIGB300I/CV/2001) investigated the function of CK2 in coronavirus infection.[156] Twenty patients were randomly allocated to receive either CIGB-325 (2.5 mg/kg/day for 5 days) plus standard-of-care (10 patients) or standard-of-care alone (10 patients). In COVID-19 patients with pneumonia on day 7 received a mixture of CIGB-325 and standard-of-care enhanced chest computed tomography (CT). This study proposed that inhibiting CK2 could be a good way to treat COVID-19.

For the treatment of COVID-19, a significant number of CK2 inhibitors must be investigated. For example, quercetin and enzymatically modified isoquercitrin (EMIQ) have been suggested as potential candidates.[154,157]

4. KINASE PATHWAY INHIBITORS AS ANTI-INFLAMMATORY, CYTOKINE-SUPPRESSIVE, OR ANTIFIBROTIC AGENTS IN COVID-19

4.1. Inhibitors of the p38 MAPK Signaling Pathway. The p38 MAPK signaling pathway is activated by various factors, such as environmental stress, pathogenic infection, and proinflammatory cytokines, and is involved in cell differentiation, apoptosis, and autophagy. Several pathogenic viruses, including SARS-CoV-1, DENV, and IBA activate the p38 MAPK, which results in unregulated inflammatory responses linked to serious diseases. Therefore, the p38 MAPK pathway
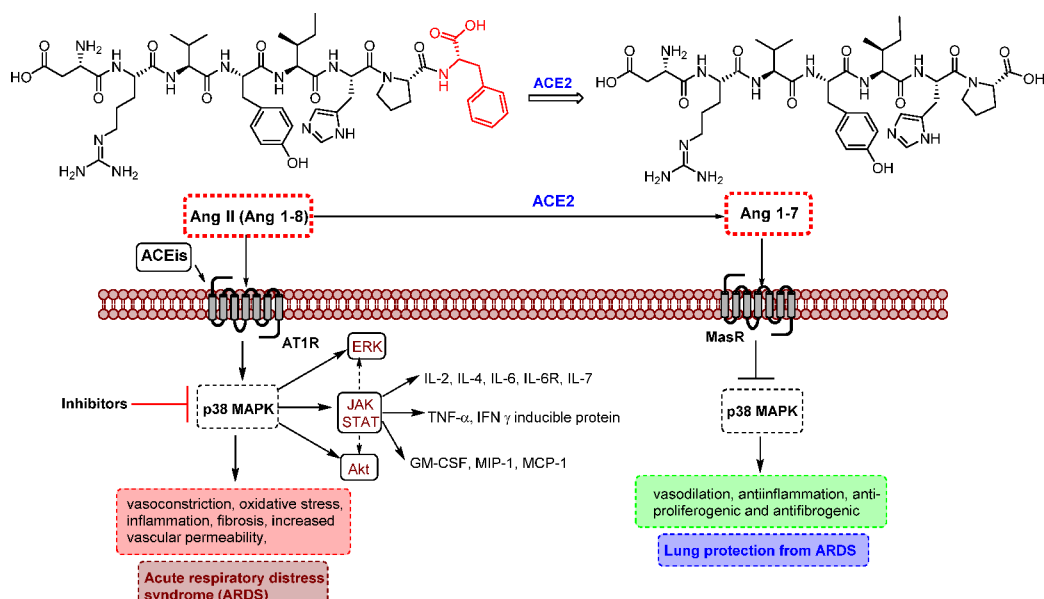
Figure 10. Role of p38 MAPK, as well as its interactions with other signaling pathways and inflammatory cytokines.[167−170] GM-CSF, granulocyte macrophage-colony stimulating factor; IL, interleukin; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; TNF, tumor necrosis factor.
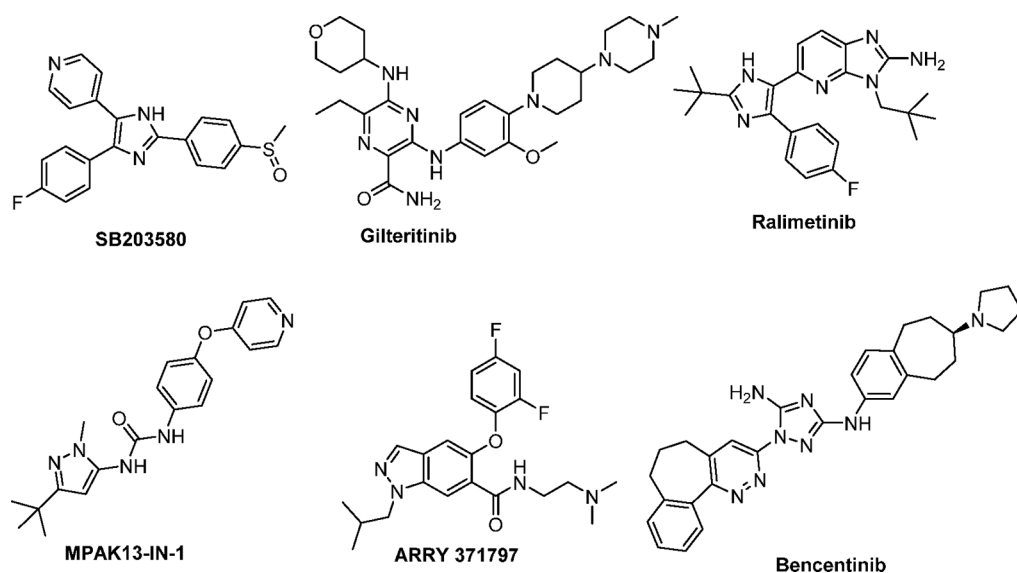
Figure 11. Inhibitors of the p38 MAPK pathway for the treatment of COVID-19 (Gilteritinib: SARS-CoV-2, IC$_{50}$ 0.807 μM;[39] ralimetinib: SARS-CoV-2, IC$_{50}$ 0.873 μM;[39] MPAK13-IN-1: SARS-CoV-2, IC$_{50}$4.63 μM;[39] ARRY 371797: SARS-CoV-2, IC$_{50}$ 0.913 μM).[39]

could be used to regulate proinflammatory cytokine production caused by multiple viral infections.[158−160]

The reason for death in COVID-19 patients mainly occurs due to the overwhelming inflammatory effect that leads to ARDS and myocarditis.[161] The p38 MAPK pathway has previously been linked to the inflammatory response in animal models of acute lung injury and myocarditis.[162,163] The p38 MAPK pathway is activated, which enhances the synthesis of cytokines including IL-6, TNF-α, and β.[164] Therefore, it has been proposed that the upregulation of the p38 MAPK pathway may be one of the causes of inflammatory injury in SARS-CoV-2 patients.

SARS-CoV-2 uses ACE2 to enter host cells, much as SARS-CoV-1 did.[165] Studies revealed that, following SARS-Co-1 infection, ACE2 expression is reduced in lungs, leading to

disruption of the renin-angiotensin system.[166] ACE2 transforms angiotensin II (Ang1−8) to angiotensin I (Ang1−7), which activates the Mas receptor and induces the anti-inflammatory, antiproliferogenic, antifibrogenic, and vasodilation effects by downregulation of p38 MAPK activation (Figure 10).[167] Angiotensin II activation of p38 MAPK, on the other hand, indicates proinflammatory, provasoconstrictive, and prothrombotic action. The p38 MAPK network is complicated, and it interacts with several signaling pathways and proinflammatory cytokines that cause ARDS and organ damage in SARS-CoV-1 and SARS-CoV-2 patients.[168−170]

It has been proposed that the viral entry suppresses the ACE2 activity to produce Ang1−7, leading to an increased expression of inflammatory responses by activating the p38 MAPK pathway in the lungs and heart. Additionally, p38 MAPK activation
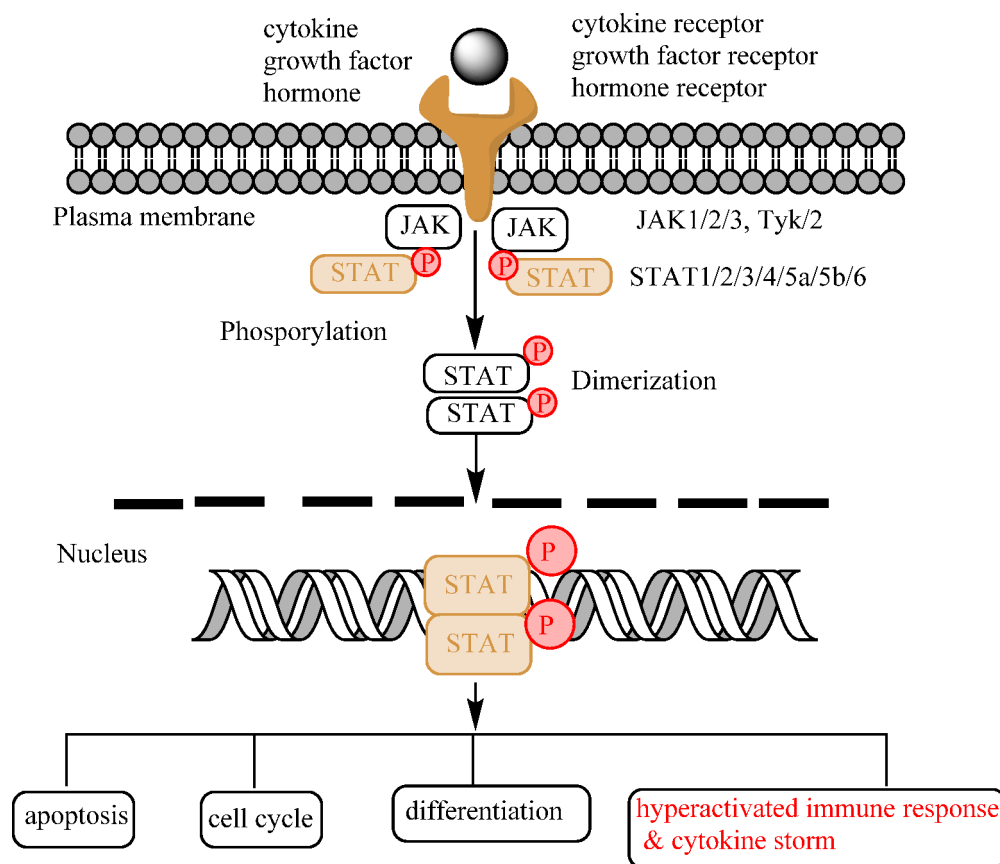
Figure 12. Hyperactivation of the immune response and cytokine storm through the JAK-STAT signaling pathway.

upregulates ADAM17, reducing the supply of ACE2 activity even further.[171] Therefore, ACE2 inhibitors or ACE blockers that balance the renin-angiotensin system may be useful for COVID-19 management.[157] Indeed, proinflammatory AngII levels were linearly correlated with the degree of lung damage and viral load in a recent study of COVID-19 patients, implying a RAS deficiency in the pathogenesis of COVID-19.[172,173]

Bouhaddou et al. recently investigated whether the p38 MAPK pathway was involved in the formation of cytokines in SARS-CoV-2-infected ACE2-A549 cells that were treated with the p38 inhibitor SB203580 (4-(4-fluorophenyl)-2-(4-methyl-sulfinylphenyl)-5-(4-pyridyl)-imidazole, Figure 11).[39] In a dose-dependent way, the inhibitor reduced the mRNA of cytokines such as IL-6, TNF, and others that were elevated during infection. Interestingly, this p38 inhibition led to reducing SARS-CoV-2 replication without significant cellular cytotoxicity. In an ELISA study of supernatant cells, SB203580 inhibited the expression of IL-6, CXCL8, CCL20, and CCL2. An anti-SARS-CoV-2 N protein antibody-based assay confirmed SB203580s inhibitory activity in viral reduction. They also reported that SARS-CoV-2 infection caused cell cycle arrest between the S and G2 phases, implying that p38 activity and cell cycle arrest are systematically related during infection. At a 10 μM concentration, SB203580 prevented MERS-CoV by 45% through p38/MAPK.[32] SB203580 showed antiviral activity against HCoV-229E and, at 4 μM concentration, reduced the viral RNA by ~60%.[32]

In ACE2-A549 cells, the MAPK signaling pathway dependency of SARS-CoV-2 infection was investigated during viral infection. Bouhaddou et al. found that SARS-CoV-2 infection promotes different p38 MAPK signals in ACE2-A549 cells.[39]

Effective viral inhibitory activities were identified for gilteritinib (IC$_{50}$ 0.807 μM), AXL inhibitor;[39] ralimetinib (IC$_{50}$0.873 μM), MAPK11 (p38α) and MAPK14 (p38β) inhibitor,[39] MAPK13-IN-1 (IC$_{50}$ 4.63 μM), MAPK13 (p38-δ) inhibitor;[39] and ARRY-797 (IC$_{50}$0.913 μM),[39] an inhibitor of MAPK14. 20(S)-Ginsenoside is a plant-derived glycoside that inhibits MAPK. It has antiviral activity against mCoV in vitro, with an IC$_{50}$ of 10 μM. 20(S)Ginsenoside inhibits mCoV by suppressing the p38/JNK/MAPK signaling pathway.[174]

The presence of another small molecule AXL inhibitor, bemcentinib, in the RECOVERY COVID-19 Phase II clinical trial COVID-19 patients backed up gilteritinib's antiviral efficacy.[175] Bemcentinib was previously reported to show potent antiviral activity against Ebola and Zika virus in preclinical studies.[176,177] Ralimetinib is being tested in Phase II clinical trials for ovarian cancer,[178] and ARRY-797 is being tested in Phase III clinical trials for cardiomyopathy, a degenerative cardiovascular disease.

Some previous reports revealed that p38 is directly involved in the replication of respiratory viruses like SARS-CoV-1 and H5N1.[179−181] p38 MAPK signaling induces the receptor-mediated endocytosis for the viral entry,[182] and its activation is also employed in the endocytosis of ACE2.[183−185] These findings indicated that SARS-CoV-2 may use a related mechanism to activate p38 MAPK directly. Indeed, SARS-CoV-2 triggered p38 MAPK in vitro, according to a recent report.[186] Treatment of SARS-CoV-1 infected mice with a p38 inhibitor resulted in an 80% survival rate in the treatment community relative to the control group in a preclinical trial (0%).[160]
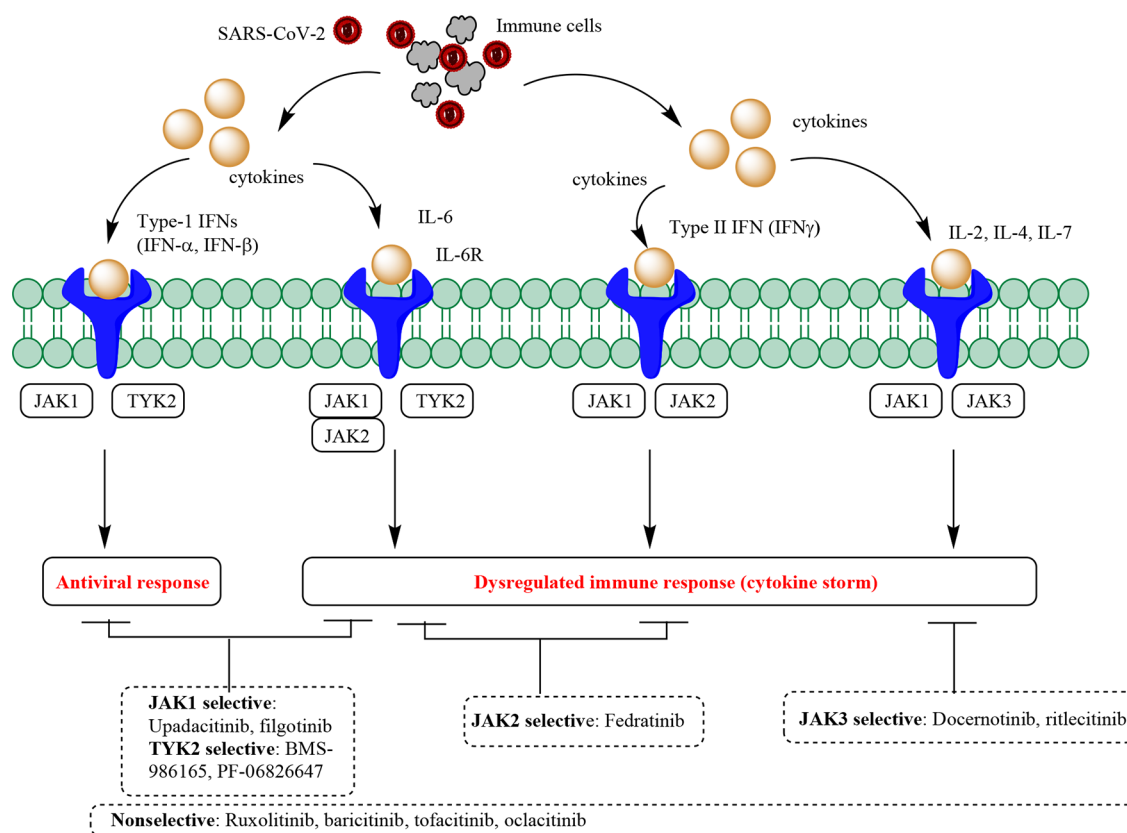
Figure 13. Cytokines and their interaction with JAK signaling pathways in the development of cytokine storm caused by SARS-CoV-2.

4.2. JAK-STAT Signaling Pathway Inhibitors. When cells detect a viral attack, they activate numerous downstream interferon regulatory factors, which cause IFN-1, IFN-II, and IFN-III to be generated.[187] IFNs attach to receptors on nearby cells, signaling them to be on the lookout for a viral threat. This IFN receptor engagement activates various members of Janus kinases and the signal transducers and activators of transcriptions (JAK-STAT) signaling pathway families.

The JAK-STAT signaling pathway is one of the main regulatory cell signaling cascades for many cytokines and growth factors.[188] The nonreceptor JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2) proteins. The STAT family comprises STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. The JAK-STAT signaling cascade regulates cell growth and differentiation, oxidative stress, and immune modulation, among other biological functions (Figure 12).

The JAK-STAT signaling pathway has been unraveled in many DNA and RNA viruses. The interaction of HCV protein with JAK1 through its proline-rich motif is necessary for the development of infectious viruses, indicating that JAK1's function in the HCV life cycle is critical.[189] The JAK-STAT signaling pathway is crucial for the HIV replication via the stimulation of IL-2 by T cells activation in T-lymphocytes. Coronavirus utilizes a variety of mechanisms to hamper IFN production and response.[187] For example, SARS-CoV-1 NSP1 and ORF6 are the main factors that utilize multiplication to measure IFN production and response. As a result, the antiviral JAK1-STAT1 signaling pathway response is inhibited while STAT3 is activated in a compensating manner.[190] STAT3 is a receptor for a harmful IL-6 to stimulate TGF-1β, which may

show a crucial role in pulmonary fibrosis development observed in COVID-19 patients.[191]

Several studies have shown that, in patients with serious COVID-19 infection, the level of cytokines is elevated.[192,193] These include IL-1, IL-2, L-6, IL-7, IL-10, TNF-α, granulocyte colony-stimulating hormone, interferon-inducible protein-1α, MCP-1, and MIP-1α. Cytokines have crucial roles in ARDS development, leading to multiple organ failure and even death in patients with COVID-19. This suggests that blocking the cytokine storm through the JAK-STAT signaling cascade may be a potential approach to enhance COVID-19 clinical management techniques currently in use.[194−197] Indeed, several clinical trials are underway investigating JAK-STAT signaling pathway inhibitors in patients with COVID-19. Inflammation-related disorders such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis are all treated with JAK inhibitors. Selected examples are ruxolitinib,[198] baricitinib,[199] tofacitinib,[200] fedratinib,[201] oclacitinib,[202] and upatacitinib.[203]

The preservation of JAK1-STAT1 function is one of the first considerations in treating SARS-CoV-2 infection (Figure 13). The virus works by delaying an antiviral reaction while hijacking cellular processes for multiplication. If the infection is identified early, however, using IFN-1 to stimulate JAK1 for the antiviral response may be a viable approach.

On the other hand, a delay in IFN-1 treatment would fail to suppress the viral infection and induce cytokines, leading to fatal pneumonia.[187] Since the upper respiratory tract is the main site for viral replication, mucosal therapies of IFN-1 were suggested as a way of preventing SARS-CoV-2. Meng et al. found that using IFN-1 nasal drops in combination with thymosin 1, an immune stimulator, prevented symptoms in over 500 high-risk healthcare
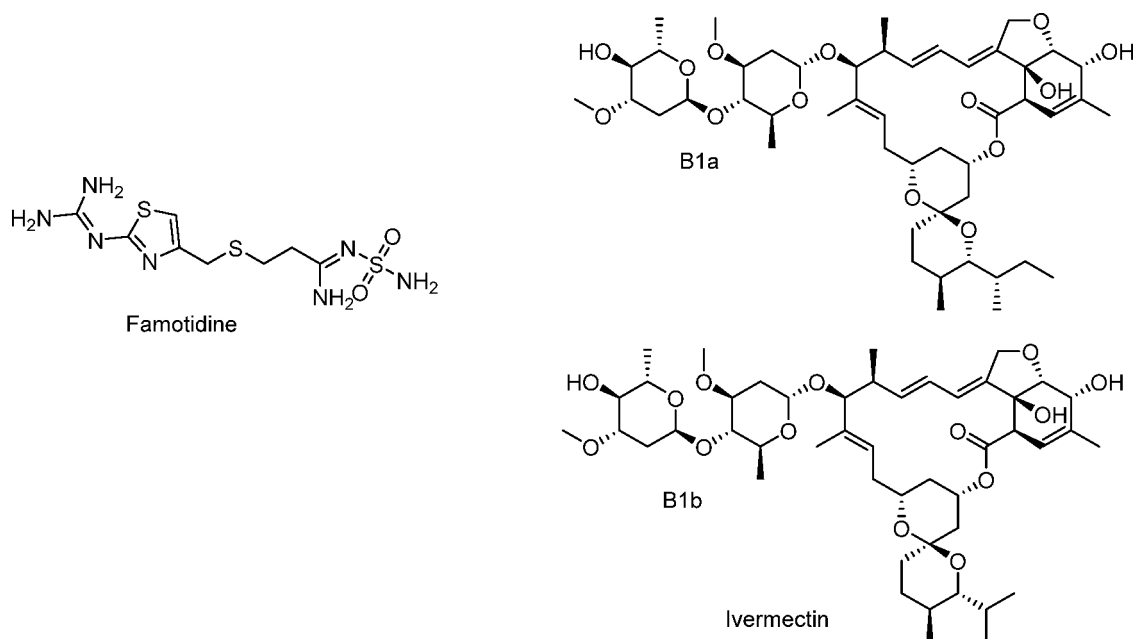
Figure 14. Structure of H2 antagonist famotidine[205] and the broad spectral antiviral agent ivermectin (SARS-CoV-2; IC_{50} 2.2−2.8 μM).[206]
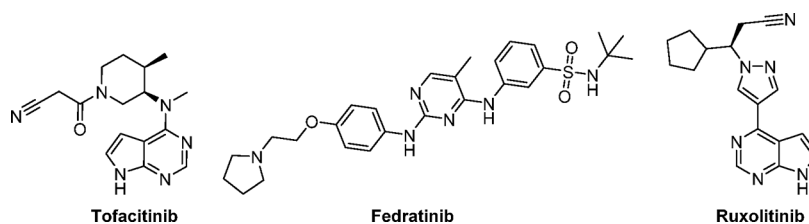
Figure 15. Inhibitors (tofacitinib,[212] fedratinib,[213] and ruxolitinib[223,224]) that target the JAK-STAT pathway.

workers who came into contact with SARS-CoV-2 affected patients with COVID-19 pneumonia.[204]

Some studies have suggested that the H2-mediated antiviral effect could reduce the mortality rate of patients with COVID-19.[205] For example, histamine antagonists may promote the STAT1 activation and IFN response. Indeed, the administration of famotidine (Figure 14), a histamine H2 receptor blocker, was correlated with a 2-fold decrease in clinical worsening leading to intubation or death in COVID-19 patients. However, it did not show any direct antiviral activity in vitro in Vero E6 cells, although computational studies suggested that famotidine could directly bind to the SARS-CoV-2 NSP5.

Ivermectin is an antiparasitic and antiviral drug with a wide range of action. It showed antiviral activity against distinct positive-sense single-strand RNA viruses, which include SARS-CoV-2. With an IC_{50} of 2.2−2.8 μM, ivermectin (Figure 14) inhibited SARS-CoV-2 in the cellular study, making it a possible candidate for the COVID-19 drug repurposing approach.[206] Authors claimed that ivermectin blocked the nuclear transport of viral proteins mediated by KPNA/KPNB1. On the other hand, ivermectin inhibits STAT3 and IL-6 production by inhibiting p21 activated kinase (PAK1), an oncogenic serine-threonine kinase.[207]

Aberrantly activated STAT3 can also be controlled by regulation of endogenous inhibitor PIAS3.[208] Some inhibitors like curcumin and resveratrol have shown to be promising in suppressing the constitutive activity of STAT3[209] through upregulation of PIAS3. However, they did not show any effect in

any randomized, placebo-controlled clinical trials, although both have been widely used for many indications.

Tofacitinib (3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo-[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropaneni-trile) (Figure 15) is an orally available JAK inhibitor that is approved as an anti-inflammatory agent to treat RA, an autoimmune disease. It inhibits JAK3 and TYK2 (Figure 13) with an EC_{50} of less than 5 nM, suppressing inflammatory cytokines like IL-2, IL-4, IL-6, and IL-7 that are linked to RA.[210]

Tofacitinib has a decent pharmacokinetic profile, with 74% oral bioavailability and a half-life of 2.3−3.1 h.[210] In RA patients, tofacitinib showed a consistent safety profile and efficacy. However, there is a risk of herpes zoster, cellulitis infections, and thrombosis with the use of tofacitinib.[211] This drug was demonstrated to be effective in COVID-19 patients who had a 13-year history of ulcerative colitis. All symptoms were resolved without the need for hospitalization after 2 weeks, according to the recent report.[212]

The study suggested that tofacitinib therapy can be continued in patients suffering from SARS-CoV-2, but it was not shown that tofacitinib helped patients recover from COVID-19 in this situation. Several clinical trials have been started to see how it will help with COVID-19 (see, for example, in Table 3).

Another report proposed the selective JAK2 inhibitor fedratinib (N-tert-butyl-3-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfona-mide) (Figures 13 and 15) that has been accepted for myelofibrosis as a possible candidate in COVID-19 manage-ment to suppress TH17-associated cytokine activation.[213]

Table 3. Clinical Trials of Tofacitinib for the Management of COVID-19

clinical trial identifier and use	primary end point
NCT04412252, Phase II: tofacitinib	using an ordinal scale to assess clinical condition
NCT04390061, Phase II: tofacitinib plus hydroxychloroquine versus hydroxychloroquine	mechanical ventilation is needed to prevent serious respiratory failure
NCT04415151, Phase II: tofacitinib	disease severity
NCT04332042, Phase II: tofacitinib	rates of artificial ventilation, ICU entry, mortality, and adverse events in patients

TH17 type responses are mediated by several cytokines linked to extreme COVID-19 patients, and TH17 cells themselves produce IL-17 and GM-CSF. It was found that murine TH17 cells treated with fedratinib showed decreased expression of IL-17, and therefore, this can be promising to prevent the outcomes of TH17-associated cytokine storm in COVID-19 patients.

Ruxolitinib ((3R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]-pyrimidin-4-yl)pyrazol-1-yl]propanenitrile) (Figures 13 and 15), is an orally available medication that suppresses the elevated levels of cytokine production associated with myelofibrosis, polycythemia vera, and acute graft-versus-host disease. Ruxolitinib was demonstrated to inhibit HIV-1 virus replication in lymphocytes and macrophages[214] by suppressing a range of cytokines like IL-β, IL-2, IL-5, IL-6, IL-7, IL-13, IL-15, and IFNG.[215−217] In peripheral blood mononuclear cells, it inhibits the phosphorylation of STAT3 by IL-6 and the development of monocyte chemoattractant protein-1.[218] In animal studies, oral administration of ruxolitinib was found to be involved in cytokine suppression. The antiviral potency of ruxolitinib also proved to be effective against Epstein−Barr (EBV) infection.[219,220] Mechanistically, ruxolitinib inhibited the EBV-infected proliferation and reduced cytokines by inhibition of STAT3.[221,222] Since ruxolitinib is a powerful candidate for the diseases associated with the hyperimmune syndrome, its efficacy has been employed in COVID-19 patients. As a result, when compared to the control group, patients who obtained ruxolitinib plus standard of care had a quicker clinical development and no major side effects.[223] At least 20 clinical trials evaluating the effectiveness of ruxolitinib in patients with COVID-19 are currently underway. Few studies published results revealing its potential to overcome ARD in patients.[224]

COVID-19 patients have been reported to be vulnerable to bacterial infections.[225] Since the JAK-STAT pathway mediates signal transduction of type 1 IFNs[226] and is also a player in suppressing virus replication and infection at the early stages, JAK inhibitors in treating COVID-19 patients may have an elevated risk of bacterial infections.[227,228] Inhibition of the JAK signaling pathway can thus result in suppression of the antiviral responses mediated by type 1 IFNs through the JAK-STAT pathway. Indeed, some experiments demonstrated that patients taking JAK inhibitors have a higher risk of infection.[228,229]

The most frequent side effects identified in patients treated with ruxolitinib[230] and baricitinib,[231] respectively, were urinary tract infections and upper respiratory tract infections. JAK inhibitors have also been linked to an increased risk of viral infections, such as herpes virus reactivation infection.[232] A recent study reported the development of hematologic toxicity in the treatment of ruxolitinib in two patients with COVID-19: one developed soft-tissue infection, and the other one developed an infection associated with herpes labialis. These severe drug reactions led to the suspension of the ruxolitinib treatment in both cases.[233] While type 1 IFNs play an important role in the antibacterial and antiviral responses, their role in coronavirus infections has yet to be fully understood.

In animal models of MERS-CoV infection, type 1 IFNs were shown to be useful during the early stages of infection in some trials. However, it was not advantageous in the later stages because it raised the risk of death.[234] Another research study found that IFNα and type II IFN (TFN) signaling were elevated in patients with SARS-CoV-1 infection who experienced hypoxemia and died but lower in those who survived after a comparatively mild SARS illness.[235]

The SARS-CoV-2 infection resulted in low IFN expression but substantially improved chemotactic and inflammatory responses, including CCL2, CCL8, IL-6, IL-1 β, and IL1RA, according to a recent review. SARS-CoV-2 infection in patients inhibits IFN-mediated immune cell recruitment and promotion of IFN-stimulated genes.[236]

The SARS-CoV-2 entry receptor ACE is also an interferon-stimulated gene (ISG) that is primarily expressed in human airway epithelial cells.[237] All of these findings led to the suggestion that further research is needed to classify IFNs in response to SARS-CoV-2 infection, implying that the COVID-19 control strategy targeting JAK inhibition can still be used. It is also possible that selective JAK2 inhibition (e.g., fedratinib) or JAK2 and JAK3 inhibition (e.g., tofacitinib) will be advantageous since they would not interfere with JAK-type 1 IFN-mediated antiviral and antibacterial immunity.[238,239]

4.3. The Signaling Pathway of Glycogen Synthase Kinase 3 (GSK-3). Glycogen synthase kinase 3 exists in GSK-3α and GSK-3β isoforms. The kinase domains of the isoforms have a high degree of sequence similarity (98%) between them.[240] It plays a role in metabolism, inflammatory reaction, and modulation of innate immunity.[241] Therefore, targeting GSK-3 has been linked to treating various diseases like diabetes, neurodegenerative disorders, different types of cancer, and bipolar disorders.[242]

GSK-3 can mediate the expression of other genes by transcription factors, including c-Jun, CREB, STAT3, C/EBP, NFAT, NF-B, and p53. IL-1, IL-16,[243] IL-17, IL-18,[244] IL-23,[245] IL-12, and IFN-γ,[246] chemokines IL-8,[244] C−C motif chemokine ligands 2,[246] 3, 4 and 12,[247] and C-X-C motif chemokine ligands 1, 2, 5, and 10[248] are all positive regulators of GSK-3.

In comparison to the MAPK, PI3K, PKC, and Wnt/-catenin signaling pathways, GSK 3 is a lesser-known signaling pathway in the virology field. Recent research suggests that GSK-3 can play a crucial role in viral replication, replication, and pathogenesis.[249,250] Also, GSK-3 activation is linked to a reduction in host immunity and antioxidant response. The GSK-3-associated signals have been employed in the entry, replication, and egress of various unrelated viruses.[251] GSK-3 has been reported to be involved in the phosphorylation of occludin at Ser341, which enhances the binding and entry of HCV.[252,253] GSK-3β, a substrate for AKT, has been identified as one of the host factors in influenza virus entry.[254,255] The overexpression of GSK-3β has been associated with HCV entry.[256] In HIV-1 infected T cells and monocytic cell lines, the upregulation of GSK-3β has been identified.[257] Coxsackievirus B3 (CVB3) infection induced GSK-3 expression in HeLa cell lines and a mouse model, resulting in virus-driven cytopathic effects and apoptosis.[258]

GSK-3 has been investigated as a possible mediator of HCV virion assembly and release. As a result, blocking GSK-3

Table 4. Kinase Inhibitors: Targets, Original Use, and Repurposing Benefits in Viral Infections

drug (brand name)	status	kinases as targets	original use	repurposing	benefits
imatinib (Gleevec)	FDA approved	Abl (Abl-1, Abl-2) kinase	chronic myeloid leukemia	SARS-CoV-1,[58] MERS-CoV,[58] SARS-CoV-2, ebolavirus,[54] poxvirus,[56] coxsackievirus[40]	antiviral, anti-inflammatory, immunomodulatory/cytokine suppression, antifibrotic
dasatinib (Sprycel)	FDA approved	Abl (Abl-1, Abl-2) kinase, SFKs (FYN, SRC, YES), CSK	chronic myeloid leukemia	SARS-CoV-1,[58] MERS-CoV,[58] dengue virus[76]	antiviral, anti-inflammatory, cytokine suppression, antifibrotic
nilotinib (Tasigna)	FDA approved	Abl (Abl-1, Abl-2) kinase	chronic myeloid leukemia,	SARS-CoV-1, MERS-CoV,[58]	antiviral, antifibrotic
saracatinib	experimental (Phase III) drug	Abl-1, SFKs (FYN, LYN, SRC, YES)	idiopathic pulmonary fibrosis	dengue virus,[76] MERS-CoV,[44] hCoV-229E,[44] hCoV-OC43[44]	antiviral, antifibrotic
sunitinib (Sutent)	FDA approved	AAK1, AXL, GAK, JAK1, KIT	renal cell carcinoma, gastrointestinal stromal tumor (GIST),	dengue and ebolaviruses	antiviral, anti-inflammatory, cytokine suppression, antifibrotic
erlotinib (Tarceva)	FDA approved	EGFR tyrosine kinase, GAK, Abl1	non-small cell lung cancer (NSCLC) and pancreatic cancer	dengue and ebolaviruses[7]	antiviral, antifibrotic
baricitinib (Olumiant)	FDA approved	JAK1, JAK2, TYK1	rheumatoid arthritis	SARS-CoV-2[44,86]	antiviral, anticytokine, anti-inflammatory
gilteritinib (Xospata)	FDA approved	AXL kinase	acute myeloid leukemia	SARS-CoV-2[39]	antiviral
bemcentinib	experimental (Phase II) drug	AXL kinase	acute myeloid leukemia	SARS-CoV-2,[175] Ebola and Zika viruses[176,177]	antiviral
osimertinib (Tagrisso)	FDA approved	EGFR	NSCLC	SARS-CoV-2[113]	antiviral, anticytokine
pictilisib	experimental (Phase I) drug	PI3K/mTOR	breast cancer, relapsed or refractory chronic lymphocytic leukemia	SARS-CoV-2[115]	antiviral
omipalisib	experimental (Phase III) drug	PI3K/mTOR	cancer and idiopathic pulmonary fibrosis	SARS-CoV-2[115]	antiviral, antifibrotic
sorafenib (Nexavar)	FDA approved	VEGFR, PDGFR, RAF kinases	renal cell carcinoma, hepatocellular carcinoma, thyroid cancer	SARS-CoV-2[115]	antiviral
ROS126766	An experimental (Phase I)drug	RAF/MEK	solid tumors or multiple myeloma	SARS-CoV-2[99]	antiviral
lonafarnib (Zokinvy)	FDA approved	RAS, GFR signaling	Hutchinson-Gilford progeria syndrome	SARS-CoV-2[115]	antiviral
leflunomide (Arava)	FDA approved	Akt	rheumatoid arthritis and psoriatic arthritis.	HCV[115]	antiviral
dinaciclib	experimental (Phase III) drug	CDK1/2/5/9	different types of cancer	influenza A virus,[139] SARS-CoV-2[39]	antiviral
seliciclib	experimental (Phase II) drug	CDK2/5	multiple myeloma	HIV-1, herpes simplex virus	antiviral
alvocidip	experimental (Phase II) drug	CDK9	acute myeloid leukemia	influenza A virus[139]	antiviral, anti-inflammatory
palbociclib (Ibrance)	FDA approved	CDK4/6	breast cancer	SARS-CoV-2[115]	antiviral
PHA-690509	experimental (Phase I) drug	CDK2	cancer	HCV[115]	antiviral
apilimod	experimental (Phase II) drug	PIKfyve	B-cell non-Hodgkin lymphoma	ebolavirus, Lassa virus,[147–149] SARS-CoV-2[39]	antiviral, anti-inflammatory
abemaciclib (Verzenio)	FDA approved	CDK4/6	metastatic breast cancer	SARS-CoV-2[113]	antiviral
TBBz	experimental drug	CK2	cancer	vaccinia virus[155]	antiviral
silmitasertib	orphan drug status by FDA	CK2	cholangiocarcinoma (bile duct cancer)	SARS-CoV-2[39]	antiviral, anti-inflammatory
CIGB-325	experimental drug	CK2	cancer	SARS-CoV-2[156]	antiviral, anti-inflammatory

Table 4. continued

drug (brand name)	status	kinases as targets	original use	repurposing	benefits
SB203580	experimental drug	p38 MAPK	autoimmune inflammatory diseases	SARS-CoV-2,[39] MERS-CoV[32]	anti-inflammatory, anticytokine
ralimetinib	experimental (Phase II) drug	MAPK11 (p38α) and MAPK14 (p38β),	ovarian cancer	SARS-CoV-2[39]	anti-inflammatory
MAPK13-IN-1	experimental drug	MAPK13 (p38-δ)		SARS-CoV-2[39]	anti-inflammatory
ARRY-797	experimental drug	MAPK14 (p38β),	dilated cardiomyopathy, multiple myeloma	SARS-CoV-2[39]	anti-inflammatory
tofacitinib (Xeljanz)	FDA approved	JAK/TYK	rheumatoid arthritis, ulcerative colitis, psoriatic arthritis	SARS-CoV-2[212]	anti-inflammatory, anticytokine
fedratinib (INREBIC)	FDA approved	JAK2	myelofibrosis	SARS-CoV-2[213]	anti-inflammatory, anticytokine
ruxolitinib (JAKAFI)		JAK1/2	myelofibrosis, polycythemeia vera, and acute graft-versus-host diseases	Ebola,[219] HIV-1,[214] SARS-CoV-2[223,224]	anti-inflammatory, anticytokine, antifibrotic
kenpaullone	experimental drug	GSK-3β	glioblastoma	SARS-CoV-2[266]	antiviral
tideglusib	experimental drug	GSK-3β	Alzheimer's disease and progressive supranuclear palsy, myotonic muscular dystrophy type I	SARS-CoV-2[269]	antiviral

prevented the process.[259] In HIV-1-infected macrophages or cell lines, inhibiting GSK-3 decreased viral replication, according to another study.[260,257] In Huh 7.5 cells, inhibition of GSK-3β led to a reduction of both replication and viral particle production of HCV but for hepatitis E virus (HEV).[261] The increased GSK-3β-Ser9 phosphorylation has been linked to the replication of the HBV,[262,263] indicating a beneficial effect of GSK-3β inhibition for HBV replication. GSK-3 phosphorylation of assembly protein precursor, a protein involved in the organization and maturation of cytomegalovirus, is required.[264,265]

One of the most important structural proteins in coronaviruses, nucleocapsid-protein N, is strongly conserved across organisms. Protein N has a variety of roles in the viral life cycle, the most important of which is packing the virus's genomic RNA into the protective coating. The N protein of SARS-CoV-1 hijacks the host immune system for virus progeny and related diseases to spread. GSK-3 has been linked to SARS-CoV-1 N phosphorylation on a serine residue, which is necessary for viral replication. As a result, it acts as a viral life cycle regulator.[266] The host translational machinery is also inhibited by phosphorylation of N protein, which interferes with antiviral response signaling. Inhibition of GSK 3 in cells infected with SARS-CoV-1 resulted in the prevention of SARS-CoV-1 N phosphorylation, and, as a result, the viral replication was impaired.[66−268]

The GSK-3 selective inhibitors LiCl and kenpaullone (9-bromo-7,12-dihydro-indolo[3,2-d][1]benzazepin-6 (5H)-one) (Figure 16) reduced viral titer and cytopathic effects in Vero E6 cells infected with SARS-CoV-1 without affecting cell viability.[266] According to this study, this kinase's phosphorylation is closely linked to viral replication. The nitro analogue alsterpaullone potently inhibits the replication of HIV-1 with an IC$_{50}$ value of 150 nM in virus-infected cells.[137] Lithium, a GSK-3 inhibitor, has been used to treat mood and bipolar conditions in patients. In porcine cells, lithium chloride therapy helped to cure a transmissible gastroenteritis coronavirus infection. In avian cells, lithium chloride treatment protects against the bronchitis virus by blocking the synthesis of genomic and subgenomic RNA while leaving the host translation pathways unaffected. A recent study showed the potential antiviral activity of thiadiazolidinone tideglusib (Figure 16) against SARS-CoV-2 M^{pro} activity.[269] Tideglusib (NP031112, NP-12) is a non-ATP-competitive, irreversible GSK-3 inhibitor that has recently been shown to have an IC$_{50}$ of 1.5 μM in inhibiting SARS-CoV-2 M^{pro}.[269]

The SARS-CoV-1 N protein has a high degree of resemblance to the SARS-CoV-2 N protein, and both proteins have conserved serine residues (Ser189 and Ser207), according to the sequence analysis.[38] Thus, the serine residues in SARS-CoV-2 are predicted to be phosphorylated by GSK-3 in the same way as they are in SARS-CoV-1. CoV's key protease, which is necessary for viral replication and transcription, is also inhibited by GSK-3 inhibition.[270−272]

T cell proliferation and activity are believed to be negatively regulated by GSK-3.[273,274] Indeed, inhibiting GSK-3 with molecules like SB415286 improved the adaptive CD8+ cytolytic cell (CTL) role significantly.[275,276] This effect is essential for the production of cytolytic effectors such as granzyme B, perforin, and interferon-γ in CD8+ cells.[277,278] GSK-3 has an impact on CD4+ T cells, which are essential for the growth of cytokine release syndrome (CRS) in the more extreme COVID-19 cases.

Inhibiting GSK-3 with small molecules has been shown to cause CD4+ T cells to produce the suppressive cytokine IL-10, which can help to reduce CRS in severe disease.[279] In infections
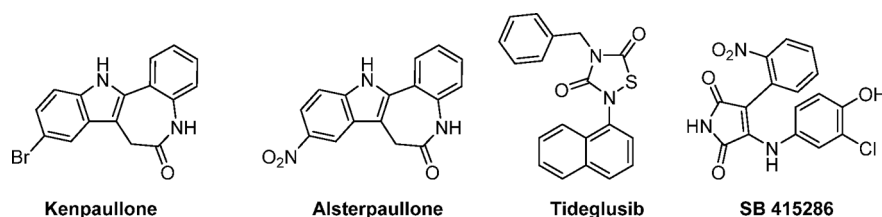
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Figure 16. GSK-3 inhibitors (kenpaullone,[266] alsterpaullone,[137] and tideglusib: SARS-CoV-2, IC$_{50}$ 1.5 μM,[269] SB415286[276,277]).
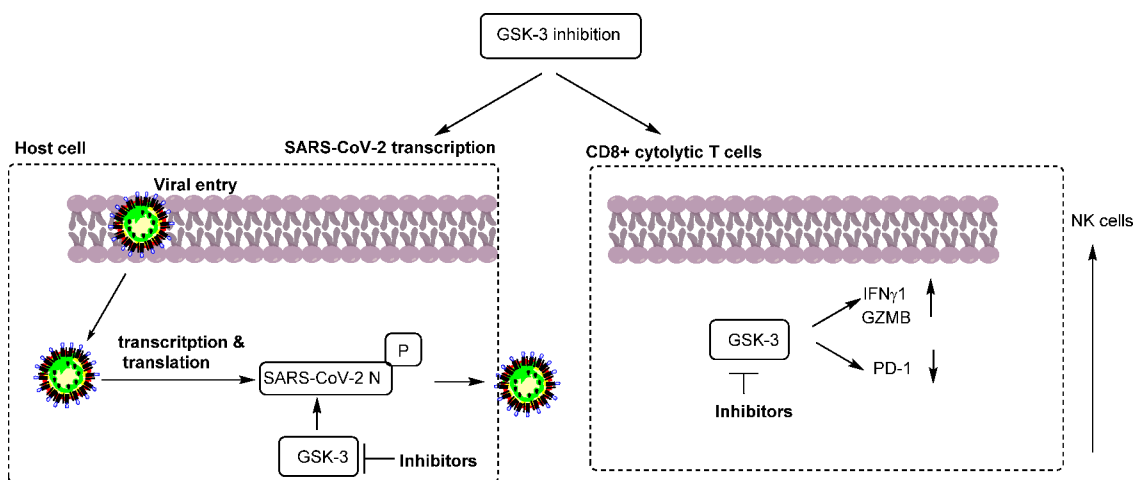

Figure 17. GSK-3 as a possible target for anti-coronaviral treatment, such as anti-SARS-CoV-2 therapy. According to the model, inhibiting GSK-3 will also inhibit SARS-CoV-2 N protein and improve CD8+ T cell resistance to the virus. Left: SARS-CoV-2 N protein and viral replication are assumed to be inhibited by inhibiting GSK-3. Right: Inhibition of GSK 3 improves CD8+ cell responses to viruses. In CD8+ T cells, inhibiting GSK-3 decreases the expression of inhibitory receptors PD-1 and LAG-3 while increasing the expression of GMZB and IFNg1. Inhibition of GSK-3 also escalates natural killer function. PD-1, programmed cell death protein 1; LAG-3, lymphocyte-activation gene 3; GMZB, granzyme B; IFNg1, interferon-gamma.

and autoimmune disorders, IL-10 suppresses the immune response and prevents tissue damage.[280]

In addition, inhibiting GSK-3 stimulates the development of natural killer cells,[281] which are innate immune system effector cells that help to control infection.[282] Based on the findings, inhibiting GSK-3 may be a promising therapeutic strategy for preventing SARS-CoV-2 infection by reducing viral replication and enhancing the immune response to the virus, as seen in Figure 17.

5. CONCLUSIONS AND PERSPECTIVES

The novel human SARS-CoV-2 is a causative agent for COVID-19 that has emerged in the human population. For the treatment of COVID-19, several antiviral agents are being tested in clinical trials as single agents or conjunction with other therapies. Many inhibitors targeting kinases have direct antiviral effects, targeting essential virus-associated proteins and proteins that play a role in the production of COVID-19 symptoms such as pneumonia-like infection, ARDS, cytokine storm, systemic inflammation, and fibrosis.

The summary of kinase inhibitors, their original use, and their repurposing for viral diseases, including COVID-19, are outlined in Table 4. Several of these kinase inhibitors are already approved, and some are being clinically investigated in Phase I—III trials for various diseases. However, adverse effects and pharmacokinetic properties of kinases inhibitors need to be considered, when repurposing them for the treatment of COVID-19. For example, some drugs need long-term dosing to achieve the required pharmacological concentrations and exert their effect, which may not be a suitable option to treat the

symptoms associated with COVID-19 as immediate treatment is required for the affected patients. Likewise, treatment of kinase inhibitors associated with a series of side effects or that could decrease immune responses at the beginning of the viral life cycle (e.g., inhibitors that interrupt type 1 IFNs-JAK1, see section 4.2) would pose a challenge for patients infected with COVID-19.

In a murine model of the vaccinia virus, imatinib, an inhibitor of Abl tyrosine kinase, effectively decreased viral load, dissemination, and mortality. However, it did not protect the mice from the infection.[45] This raises the issue concerning its efficacy in governing the viral infection in vivo. In animal models of other viral infections, such as SARS-CoV-2, it is crucial to investigate the antiviral efficacy and safety profile of drugs that target Abl and Src.

Combination therapy in the context of COVID-19 will have significant therapeutic advantages, as this technique has previously been seen to be effective in the treatment of life-threatening diseases including HIV-related AIDS. As a result, antivirals (ribavirin, ritonavir-lopinavir, remdesivir) combined with kinase inhibitors (sunitinib, erlotinib, sorafenib, imatinib, gilteritinib, gilteritinib, osimertinib) or kinase inhibitors that target both virus-related proteins and proteins associated with pulmonary health would be beneficial.

One of the effective therapeutic techniques in the control of the COVID-19 pandemic may be to target the JAK-STAT signaling pathway. This signaling pathway mediates a hyper-immune activation by proinflammatory cytokines that leads to ARD, organ damage, and ultimately death in COVID-19 patients. Therefore, the approach that allows the repurposing of already FDA-approved and experimental drugs targeting the

JAK-STAT signaling pathway would be potentially beneficial. Additionally, drugs that selectively target JAK2, JAK3, or JAK2/3 would be a potential treatment option concerning the suppression of cytokines, and at the same time, they would not interrupt IFN-JAK1-mediated antiviral and antibacterial immunity in patients infected with COVID-19 (Figure 13). On the other hand, bacterial infections can be a risk factor for using JAK-STAT pathway inhibitors for COVID-19 because JAK inhibitors inhibit IFN type 1 IFNs, which are formed in response to bacterial infections, and thus can prevent viral replication and infection.[227,228] However, selective inhibitors that target JAK2/JAK3 can still be repositioned for COVID-19 treatment as they would not interact with JAK-1.

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Stefan Laufer studied Pharmacy and completed his Ph.D. at Regensburg University. After postdoctoral research in Frankfurt, he took a position in the pharmaceutical industry but maintained lectureships at Frankfurt and later at Mainz University, where he finished his habilitation in 1997. Since 1999, he has been full professor (chair) for pharmaceutical and medicinal chemistry at Tübingen University. He is cofounder/spokesman of ICEPHA (Interfaculty Center for Pharmacogenomics and Pharma Research), TüCAD$_2$ (Tübingen Center for Academic Drug Discovery), and cofounder of the two startups CAIR Biosciences and Heparegenix. Three compounds from his lab made it first into man. His research interests are protein kinase inhibitors and eicosanoid modulators.

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■ ABBREVIATIONS USED

Abl, Abelson tyrosine kinase; ALL, acute lymphoblastic leukemia; ARDS, acute respiratory distress syndrome; AAK1, adaptor protein-associated kinase 1; ACE2, angiotensin-converting enzyme 2; ATP, adenosine triphosphate; BMP2K, BMP-2-inducible kinase; CML, chronic myeloid leukemia; CREB, cAMP response element-binding protein; CDK, cyclin-dependent kinases; CKII, casein kinase 2; CNS, central nervous system; CoV, coronavirus; COVID-19, coronavirus disease-19; CVB, coxsackievirus B; CPE, cytopathic effects; EGFR, epidermal growth factor receptor; GAK, cyclin G-associated kinase; GIST, gastrointestinal stromal tumor; GM-CSF, granulocyte-colony stimulating factor; GAS 6, growth-arrest-specific gene 6; GSK-3, glycogen synthase kinase; herpes simplex virus; HCV, hepatitis C virus; HPV, human papillomavirus; HCoV, human coronavirus; HSV, herpes simplex virus; HKU, Hong Kong University; HIV, human immunodeficiency virus; IL, interleukin; IFN, interferon; IBV, infectious bronchitis virus; JAK, Janus kinase; M^{pro}, main protease; mTORC, mammalian target of rapamycin complex; MERS-COV, Middle East respiratory syndrome; MAPK, mitogen-activated protein kinase; MPSK1, myristoylated and palmitoylated serine/threonine kinase 1; NAK, numb-associated kinase; SARS, severe acute respiratory syndrome; NSCLC, non-small cell lung cancer; NSP, nonstructural protein; NF-κB, nuclear factor "kappa-light-chain-enhancer" of activated B-cell; PL^{pro}, papain-like protease; PI3K, phosphatidylinositol 3-kinase; PDGFR, platelet-derived growth factor receptors; PK, protein kinase; RBD, receptor-binding domain; RNA, ribonucleic acid; RCC, renal cell carcinoma; RdRp, RNA dependent RNA polymerase; STAT, signal transducer and activator of transcription; siRNA, small interfering ribonucleic acid; SOCS, suppressor of the cytokine signaling; SFKs, Src family kinases; TNF, tumor necrosis factor; TKI, tyrosine kinase inhibitors; TTSP, type II transmembrane serine protease; VCV, vesicular stomatitis virus; WHO, World Health Organization

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