



# Repurposing of Kinase Inhibitors for Treatment of COVID-19

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**ABSTRACT** The outbreak of COVID-19, the pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spurred an intense search for treatments by the scientific community. In the absence of a vaccine, the goal is to target the viral life cycle and alleviate the lung-damaging symptoms of infection, which can be life-threatening. There are numerous protein kinases associated with these processes that can be inhibited by FDA-approved drugs, the repurposing of which presents an alluring option as they have been thoroughly vetted for safety and are more readily available for treatment of patients and testing in clinical trials. Here, we characterize more than 30 approved kinase inhibitors in terms of their antiviral potential, due to their measured potency against key kinases required for viral entry, metabolism, or reproduction. We also highlight inhibitors with potential to reverse pulmonary insufficiency because of their anti-inflammatory activity, cytokine suppression, or

antifibrotic activity. Certain agents are projected to be dual-purpose drugs in terms of antiviral activity and alleviation of disease symptoms, however drug combination is also an option for inhibitors with optimal pharmacokinetic properties that allow safe and efficacious co-administration with other drugs, such as antiviral agents, IL-6 blocking agents, or other kinase inhibitors.

**KEY WORDS** Coronavirus · SARS-CoV-2 · SARS-CoV · MERS-CoV · kinase inhibitors · pharmacokinetics · antiviral therapy · COVID-19

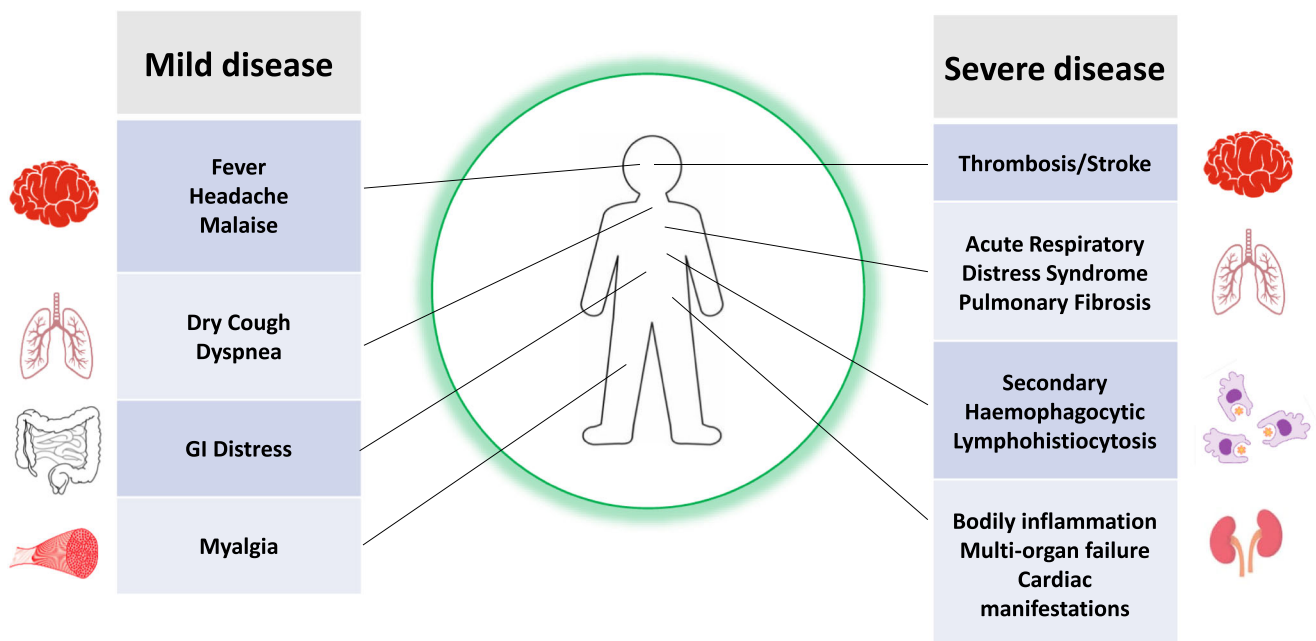
## CLINICAL NEED FOR EFFECTIVE TREATMENTS FOR COVID-19

A novel human coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly named 2019-nCoV), emerged in Wuhan, China. The outbreak in the previously unexposed human population was marked by high morbidity caused by SARS-CoV-2 as a result of the associated disease COVID-19 (**Corona Virus Disease-2019**). There is an urgent need for the development of therapies targeting both direct viral infection and the inflammatory immune response elicited by SARS-CoV-2. While many patients with documented SARS-CoV-2 infections have mild symptomatology, pathology can be severe in a subset of patients (Figure 1). Overall, COVID-19 has milder clinical manifestations and lower fatality than infections by the related viruses, SARS-CoV and MERS-CoV (Figures 1 and 2). However, COVID-19 infection can be fatal. Repurposing of drugs that have pre-existing FDA-approval as treatments for SARS-CoV-2 and related coronaviruses offers an attractive opportunity for the rapid deployment of effective therapeutics in the setting of the current pandemic outbreak, where treatment options are largely limited to supportive and symptomatic care.

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# COVID-19 Symptoms



**Figure 1.** Covid-19 symptoms.

While symptoms associated with SARS-CoV-2 infection initiate with viral infection, the severe and sometimes fatal pathology seen with COVID-19 is primarily due to the onset of a virus-driven hyper-inflammatory response. For example, the first autopsy of a COVID-19 patient demonstrated the

rapid progression of pneumonia and overactivation of T lymphocytes, which failed to establish an effective immune response and resulted in tissue injury, including lung damage and failure of other organs (1) (2). Consequently, while therapy-related suppression of viral infection and replication

Virus species	<i>Middle East respiratory syndrome-related coronavirus</i>	<i>Severe acute respiratory syndrome-related coronavirus</i>	
Individuum	MERS-CoV	SARS-CoV	SARS-CoV-2
First reported	Saudi-Arabia (2012)	China (2002)	China (2019)
Current status	Active	No reports since 2004	Active
Infections	2521+	8098	3,500,000+
Fatality rate	34%	10%	~1%
Preventive/curative treatment	None	None	None

**Figure 2.** Comparison of MERS-CoV, SARS-CoV, and SARS-CoV-2.

is a goal of current treatment approaches, it is posited that judicious suppression of the inflammatory response is also likely to benefit patients with severe COVID-19 disease. (3).

The most common presenting symptoms of SARS-CoV-2 are fever, dyspnea or dry cough, which are consistent with lower respiratory tract infection; other symptoms found to occur in less than 10% of COVID-19 patients analyzed include GI distress (diarrhea, vomiting), headache and weakness (4). Loss of smell and taste have also been reported in a sizable number of patients, including two-thirds of patients in Germany and 30% of patients in South Korea (5). A hallmark feature of COVID-19 infection is a distinct chest tomography pattern of bilateral peripheral ground-glass and consolidative pulmonary opacities (6). These findings can even be seen in patients with minimal symptoms. Potentially fatal sequelae of COVID-19 infection include respiratory failure in the form of acute respiratory distress syndrome (ARDS), which is typified by diffuse alveolar damage in early stages followed by fibroproliferation and fibrosis in prolonged cases. This leads to respiratory failure, requiring intubation and mechanical ventilation as a supportive therapy allowing time for viral clearance and lung healing. Also leading to complications and increased risk of death are pulmonary vascular endothelialitis, thrombosis and angiogenesis, symptoms of which distinguish lung pathobiology of COVID-19 patients from that of severe influenza infection (7).

Additionally, liver, heart and kidney failure, life-threatening coagulopathies, and cases of secondary haemophagocytic lymphohistiocytosis (sHLH) have been reported. Of note, sHLH is a syndrome characterized by systemic inflammation as demonstrated by markedly elevated levels of cytokines, including interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor (GM-CSF), TNF-alpha, interferon-gamma inducible protein 10, macrophage inflammatory protein 1-alpha, and monocyte chemoattractant protein 1, resulting in elevated serum inflammatory markers such as ferritin, cytopenias, and multiorgan failure (8) (3) (9).

The point of entry for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2) is highly expressed in the heart and upregulated in the failing heart (10), and ACE2 receptor levels have been found to be significantly expressed in various organs in the body, such as the esophagus, kidney and bladder (11). These are potential target organs for SARS-CoV-2 and could explain the observed systemic inflammation beyond respiratory issues. In addition, there is evidence for the presence of ACE2 in brain tissue (12), which could explain some of the observed brain manifestations associated with COVID-19.

Long-term or permanent lung damage in the form of pulmonary fibrosis, an epidermal growth factor (EGFR)-mediated process, has been observed in survivors of SARS-CoV and MERS-CoV infections and occurs in up to 64% of patients with ARDS (13). In a study following a SARS-CoV outbreak,

thin-section computed tomographic findings revealed fibrotic changes in 62 % of the patients observed (14).

Pre-existing co-morbidities that appear to worsen the course of SARS-CoV-2 disease include cancer, kidney disease, obesity, diabetes, hypertension, and cardiovascular disease (15). The elderly (>60 years of age) are generally the most vulnerable to the virus with significant increased mortality in patients over the age of 85, with precipitous onset of pneumonia and systemic inflammatory changes (15). Interestingly, unlike influenza, children, who account for 1-5% of COVID-19 cases, and those under the age of 30 are generally spared severe illness (16). The reason for this predilection for older adults is unclear, however may be related to dysregulated immune response in these individuals (17). Still, severe symptoms are observed in up to 6.7% of children, typically those with underlying health issues or who are under the age of 12 months (16).

As reviewed and proposed below, there are three major needs that have yet to be met for effective management of COVID-19 disease: 1) anti-viral therapies that limit viral transmission, cell entry, and replication, 2) therapies that attenuate the non-productive immune response and thus decrease end-organ damage, and 3) therapies that have an anti-fibrotic effect in patients with ARDS and thus decrease long-term sequelae of disease.

## RATIONALE FOR REPURPOSING APPROVED KINASE INHIBITORS

SARS-CoV-2 belongs to the Baltimore Group IV classification of RNA viruses, which also includes hepatitis C virus (HCV), West Nile virus, dengue virus, and rhinoviruses, but it most closely resembles Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (18) (Table 1). SARS-CoV-2, like SARS-CoV and MERS-CoV, is a member of the *Betacoronavirus* genus and shares 80% RNA sequence identity with SARS-CoV (19) (20), and 50% sequence identity with MERS-CoV (20) (Figure 2). While the rates of mortality and transmission differ between SARS-CoV, MERS-CoV, and SARS-CoV-2, there is substantial overlap in the pathogenesis, genetic makeup and clinical features of the diseases caused by these viruses (21). Numerous kinases have been suggested as being important mediators of various viral infections, in particular SARS-CoV and MERS-CoV, and these same proteins are predicted to be involved in mediating infection by SARS-CoV-2, as well.

Protein kinases have become an exceptionally important group of drug targets, accounting for 20-30% of the drug discovery programs of major pharmaceutical companies and are thus an opportune target. Many kinase inhibitors that have pharmacologic effects that may be beneficial in

**Table 1.** Classification of viruses and the kinase inhibitors showing antiviral activity.

Virus	Baltimore classification	Kinase inhibitors showing antiviral activity (potential kinase targets)
SARS-CoV-2	Group IV, positive sense single-stranded RNA virus	imatinib (unpublished; preprint: <a href="https://www.biorxiv.org/content/10.1101/2020.03.25.008482v2.full">https://www.biorxiv.org/content/10.1101/2020.03.25.008482v2.full</a> ) abemaciclib, gilteritinib, osimertinib (unpublished; preprint: <a href="https://www.biorxiv.org/content/10.1101/2020.03.20.999730v3.full.pdf">https://www.biorxiv.org/content/10.1101/2020.03.20.999730v3.full.pdf</a> )
SARS-CoV	Group IV, positive sense single-stranded RNA virus	imatinib, dasatinib, nilotinib (ABL2) (27) (29)
MERS-CoV	Group IV, positive sense single-stranded RNA virus	imatinib, dasatinib (ABL2) (27) saracatinib (LYN, FYN) (33) sorafenib (RAF) (68)
Dengue	Group IV, positive sense single-stranded RNA virus	dasatinib, saracatinib (SRC, FYN) (34) (35) (36) sunitinib, erlotinib (AAK1, GAK, AXL, KIT, RET) (46)
Hepatitis C	Group IV, positive sense single-stranded RNA virus	sunitinib, erlotinib (AAK1, GAK) (41) (42) gefitinib, erlotinib (EGFR) (59) ((56) (57)
West Nile	Group IV, positive sense single-stranded RNA virus	sunitinib, erlotinib (46)
Zika	Group IV, positive sense single-stranded RNA virus	sunitinib, erlotinib (46)
Ebola	Group V, negative sense single-stranded RNA virus	nilotinib (ABL1) (24)
Influenza A	Group V, negative sense single-stranded RNA virus	alvocidib (CDK9)
Human cytomegalovirus	Group I, double-stranded DNA virus	gefitinib, erlotinib (EGFR) (59) (57) (56)
Vaccinia	Group I, double-stranded DNA virus	imatinib (ABL) (25)
Herpes simplex type I	Group I, double-stranded DNA virus	palbociclib (CDK6) (62)

ameliorating the severe and potentially life-threatening symptoms of COVID-19, such as anti-inflammatory activity, cytokine suppression, and antifibrotic activity, are already approved. Ideally, one kinase inhibitor with optimal pharmacokinetic properties could be repurposed as a dual function therapeutic that could reduce infection through direct viral targeting and could also provide clinical benefit by suppressing disease symptoms. Alternatively, kinase inhibitors could be tested in combination with antiviral agents or other targeted therapies that show promise in clinical trials for COVID-19 to achieve greater efficacy than any one agent alone.

## KINASE INHIBITORS AS POTENTIAL ANTIVIRAL THERAPEUTICS

The fact that treatments for respiratory viral infections like those caused by SARS-CoV, MERS-CoV, and SARS-CoV-2 are restricted to medications designed to treat only symptoms of pulmonary disease justifies the repurposing of drugs, preferably FDA-approved drugs already investigated in patients for tolerance and toxicity, with the dual ability to target the root causes of infection and to mitigate symptoms of respiratory distress caused by the infection. It would thus be beneficial to find and identify multi-targeted drugs in clinical

use that encompass both properties. Such drugs would ideally also be able to potentiate the effectiveness of other more targeted antiviral agents or supportive therapies approved for severe or potentially fatal respiratory diseases.

A number of approved antiviral treatments are designed to inhibit enzymes such as polymerases or proteases through a “one drug, one bug” line of attack, which has been deemed inadequate due to the inefficiency of these treatments in working against multiple viruses, as well as failure to treat emerging new strains with accumulating mutations that are drug-resistant. The high cost and lengthy timeline for development of a novel agent are additional factors that dramatically limit the efficiency of this approach for covering a wide range of existing viruses as well as newly emerging ones or those that have developed resistance to current therapies. A different strategy involves targeting integral host cell proteins that are required by a broad spectrum of pathogens, including those that are emerging and novel and for which no effective treatment exists. An advantage of targeting host cellular proteins is that they do not undergo the same mutation rates that are seen for genomes of viruses.

There is a difference between developing drug therapies for a chronic virus, such as human immunodeficiency virus (HIV) or HCV, which the immune system cannot clear, versus developing drug therapies for acute viruses, such as influenza or SARS-CoV-2, which the immune system eventually does clear. For acute viruses, given the correlation of viral burden

with disease severity, the goal may be to lower viral replication to prevent severe disease (flatten the curve of viral replication/burden). The potential drawback to direct-acting antiviral agents that do not have near sterilizing potency (or that cannot be used as a combination to suppress replication to near sterilizing levels), is that allowing the virus to replicate leads to resistance. Inhibiting a host target is unlikely ever to have the potency one can achieve with, as an example, an inhibitor of the viral RNA-dependent RNA polymerase (RdRp). However, host-targeted antiviral drugs exploit the dependence of the virus on specific host proteins and pathways during replication. Resistance may be less likely to develop against these agents because a single point mutation in the viral genome is unlikely to enable the virus to replicate independently of the targeted host factor. Another challenge in making antiviral agents against acute viral pathogens is that there is a narrow window in which the antiviral can have an effect (as an example influenza drugs). This raises the challenge of being able to diagnose and treat early in the disease course in order for the drug to provide clinical benefit.

Many FDA-approved, small molecule kinase inhibitors have multiple protein targets, including those identified in the host cell as being necessary or required for viral life cycle, replication, and infection of multiple virus types. This property could potentially be applied toward a more broad-spectrum antiviral therapy. The fact that approved therapies are well-characterized in terms of safety and pharmacokinetics and thus could be readily repurposed would reduce the cost and time involved for drug development and increase drug availability to patients.

## ABL AND SRC INHIBITORS

ABL kinase inhibitors have been demonstrated to inhibit replication of several unrelated viruses at different stages of their life cycle, including the coxsackie virus and dengue, Ebola, and vaccinia, in *in vitro* cell-based studies (Table 1) (22) (23) (24) (25) (26). For the coxsackie virus, ABL is activated following attachment of the virus to the glycosylphosphatidylinositol (GPI)-anchored protein decay-accelerating factor (DAF) on the apical cell surface; the ABL activation in turn triggers Rac-dependent actin reassembly that allows delivery of the virus to the tight junction (22). FYN kinase is also activated in response to viral attachment to DAF, and this leads to phosphorylation of the plasma membrane protein, caveolin, and viral transport into the cell through caveolin-containing vesicles (22). Activation of ABL by the coxsackie virus and the role ABL plays in viral infection are independent of SRC kinases (22), whereas in contrast ABL kinases partner with SRC family kinases to stimulate the actin-based movement of vaccinia virus (23). In the case of Ebola virus, regulation of viral replication by ABL1 was demonstrated by ABL1-

specific siRNA inhibition of the release of virus-like particles in a cell culture co-transfection system; nilotinib also showed antiviral activity in this assay, at  $\mu\text{M}$  concentrations that were not cytotoxic (24). *In vivo* antiviral efficacy of imatinib was shown in a model of vaccinia virus; testing of imatinib in this model was based on the demonstrated involvement of ABL in release of cell-associated enveloped virions from the host cell (25). In this study, a dose of 200 mg/kg/day of imatinib was able to reduce the number of viral genome copies by around 4 logs (25). Lack of efficacy of dasatinib in the same model was attributed to immunotoxicity due to Src inhibition, however it is believed that dasatinib could still be a candidate coronavirus treatment with a dosing regimen that effectively blocks viral dissemination while exhibiting minimal Src-related immunotoxicity (27).

The ABL inhibitors, imatinib and dasatinib, were identified in a screen as inhibitors of both SARS-CoV and MERS-CoV replication, and nilotinib was identified as an inhibitor of only SARS-CoV, *in vitro* (27). Investigation of the mechanism for imatinib against SARS-CoV and MERS-CoV revealed inhibition of the early stages of the virus life cycle, and inhibition of viral replication through blocking the fusion of the coronavirus virion with the endosomal membrane (28) (29). Importantly, authors show that targeted knockdown of ABL2, however not ABL1, significantly inhibited SARS-CoV and MERS-CoV replication/entry *in vitro* (29). The relatively high, albeit minimally toxic,  $\mu\text{M}$  range concentrations of imatinib and dasatinib required to inhibit SARS-CoV and MERS-CoV in the aforementioned cell-based studies may be attributable to experimental factors such as drug resistance of the cell lines used as tools for propagating the viruses (27) (29), and thus *in vivo* testing would be needed to determine optimal dosing. It is worth noting that in many cell-based assays measuring drug effects on virus titer, the antiviral activity is cell-type dependent, and there is also variability depending on which virus strain is used. Recent, unpublished results, reported as a preprint, suggest that imatinib inhibits SARS-CoV-2 *in vitro*, among 17 other FDA-approved drugs with IC50 values similar to those observed for SARS-CoV and MERS-CoV; concentrations showing antiviral activity were not cytotoxic (BioRxiv, 2020, <https://doi.org/10.1101/2020.03.25.008482>)

As discussed above, infection by SARS-CoV is the result of several steps, including receptor binding, S glycoprotein conformational alterations, and proteolysis within endosomes that is mediated by cathepsin L (30). SARS-CoV infection has been shown to be blocked by targeted inhibitors of cathepsin L (30). On a related note, it has been shown that complete inhibition of viral entry and replication can result from treatment of cells with a cathepsin inhibitor as well as treatment with the serine protease inhibitor, camostat, which blocks activity of the type II transmembrane serine protease (TTSP)

TMPRSS2, a surface-expressed serine protease that cleaves the coronavirus S protein and is involved in viral entry into a host cell (31). It has been proposed that imatinib may inhibit the function, localization or activity of TMPRSS2 (29). This suggests that this may be a promising drug:target match that could be further explored as a potential treatment for SARS-CoV-2 infection, since SARS-CoV-2 uses the SARS-CoV receptor ACE2 and the protease TMPRSS2 to enter host cells. In addition, ABL and ARG kinases have been found, in cancer cells, to promote secretion of the endosomal protease cathepsin L (30) (32). Thus, the testing of the ability of ABL inhibitors to inhibit cathepsin L in the context of viral infection may be warranted. It may generally be worthwhile to evaluate each of these targets with respect to what is known about SARS-CoV-2 infection and conduct further studies to elucidate potential therapeutic approaches involving ABL inhibition.

Several of the SRC family kinases have been implicated in replication of viruses, including those related to SARS-CoV-2, as well as unrelated viruses. The ABL/SRC inhibitor, saracatinib, has been shown to inhibit MERS-CoV at early stages of the viral life cycle, at  $\mu\text{M}$  range concentrations (33). In this study, siRNA knockdown of SRC family proteins, LYN and FYN, the latter implicated in coxsackievirus entry through epithelial tight junctions (22), led to significant reductions in MERS-CoV titer, suggesting these proteins may be important for MERS-CoV replication (33). Saracatinib was also shown to synergize with gemcitabine, which also exhibits anti-MERS-CoV activity (33). SRC has been shown, through siRNA knockdown, to be important for replication of dengue virus; dasatinib inhibited dengue infection by preventing infectious virus particle formation within the virus replication complex (34) (35). Saracatinib and dasatinib were shown to exhibit activity against dengue virus *in vitro*, with FYN implicated as a target for RNA replication (36). YES was demonstrated, through genetic knockdown, to reduce West Nile virus titers through effects on the viral replication cycle and to attenuate viral assembly and egress (37). Finally, siRNA library screenings focused on identifying host factors required for replication of HCV and dengue revealed c-terminal SRC kinase (Csk) as being important (38) (35).

## NAK INHIBITORS

Important virus-associated protein targets include those associated with intracellular membrane trafficking, a cellular process vulnerable to “hijacking” by a broad range of unrelated viruses. Two host cell kinases that have been found to play an integral role in viral infection and life cycles are members of the numb-associated kinase (NAK) family: (1) AP2-associated protein kinase 1 (AAK1), which promotes endocytosis, and (2) cyclin G-associated kinase (GAK), which mediates

endocytosis (39) (40). AAK1 and GAK are reported to be exploited by a variety of viruses, including HCV and dengue virus, which fall into the same Group IV Baltimore classification as SARS-CoV, MERS-CoV and SARS-CoV-2, and also the Ebola virus, which belongs to a different group (Table 1) (18) (41) (42) (43) (44) (45). The importance of AAK1 and GAK for HCV and dengue virus infection *in vitro* was shown via genetic (siRNA) silencing of AAK1 and GAK, which inhibited viral entry and infectious virus production (42) (46). Genetic (siRNA) silencing of AAK1 and GAK also decreased infection by Ebola virus (46).

Several kinase inhibitors have been proposed to exhibit antiviral activity based on their ability to potently target AAK1 and GAK. One drug, the FDA-approved janus kinase (JAK) inhibitor, baricitinib, was identified in response to the SARS-CoV-2 outbreak as a possible treatment for COVID-19 by investigators from BenevolentAI and Imperial College London (45). Baricitinib was proposed to potentially reduce infection, based on the drug's ability to inhibit AAK1 and bind to GAK (45). It has been argued that the therapeutic dosing and low plasma protein binding of baricitinib, in contrast to the JAK kinase inhibitors, ruxolitinib and fedratinib, may make baricitinib more likely to inhibit AAK1 at therapeutically effective and tolerated doses and potentially reduce viral infectivity in patients than the other inhibitors (45) (47). AAK1 and GAK binding potency for these inhibitors is shown in Table 2.

The multi-targeted kinase inhibitor sunitinib and the EGFR tyrosine kinase inhibitor erlotinib, which potently bind to AAK1 and GAK (dissociation constant [ $K_D$ ] of 11 and 3.1 nM, respectively) (48), were shown to block HCV assembly and inhibit HCV entry with overexpression of AAK1 or GAK effectively reversing their antiviral activity (41) (42). Sunitinib and erlotinib also exhibited broad spectrum activity against dengue, West Nile virus and Zika virus infection *in vitro* at  $\mu\text{M}$  concentrations that were nontoxic to cells (46). To confirm antiviral activity of sunitinib and erlotinib, levels of phospho-AP2, a substrate of AAK1 and GAK, were measured and were found to be reduced in a dose-dependent fashion (46). Genetic (siRNA) depletion of AXL, KIT, and RET, out of a total of 27 protein targets of sunitinib and erlotinib, were found to inhibit dengue infection in a cell-based assay (46). This suggests that these three proteins are potential host targets mediating antiviral effects of the two drugs. Synergy between sunitinib and erlotinib was observed in a murine model of dengue, with 30-60 mg/kg of the drugs administered (doses chosen were at or near the approved human dose) (46). Sunitinib showed some efficacy in this model as a single agent (46). The protective effects of the combination of sunitinib and erlotinib observed in this murine model suggest it is plausible to utilize tolerable drug

**Table 2.** FDA approved kinase inhibitors: Kinase targets and respiratory benefits

Kinase Inhibitor (brand name) (indication; main therapeutic targets)	Selected Kinase Target Affinity (antiviral and pulmonary benefit) KINOMEScan ( $k_d < 100$ nM)	Anti-inflammatory activity, cytokine suppression, antifibrotic activity
Midostaurin (Rydapt) (acute myeloid leukemia, systemic mastocytosis; multi-targeted; FLT3-ITD, D816V-c-KIT)	AAK1, JAK2, JAK3, $K_d$ KIT (220nM), $K_d$ RET (350nM) (48)	Anti-inflammatory and cytokine suppression (107)
Lestaurtinib (orphan drug status, acute myeloid leukemia; multi-targeted; FLT3, JAK2, TrkA, TrkB, TrkC)	AAK1, AXL, FYN, GAK, JAK1, JAK2, JAK3, RET $K_d$ KIT (150nM)*	Anti-inflammatory and cytokine suppression (107)
Gilteritinib (Xospata) (acute myeloid leukemia; FLT3-ITD; AXL)	AXL $IC_{50}$ (41 nM) (49)**	
Dasatinib (Sprycel) (chronic myeloid leukemia, Ph+acute lymphoblastic leukemia; multi-targeted; BCR-ABL, SRC)	ABL1, ABL2, CSK, FYN, GAK, KIT, LYN, SRC, YES	Anti-inflammatory, cytokine suppression, antifibrotic (100) (99) (102) (103) (104) (101)
Imatinib Mesylate (Gleevec (US)/Glivec (Europe/Australia)) (chronic myeloid leukemia, Ph+acute lymphoblastic leukemia, gastrointestinal stromal tumor; chronic eosinophilic leukemia, hypereosinophilic syndrome, systemic mastocytosis; myelodysplastic syndrome; BCR-ABL, KIT, FIP1L1-PDGFRalpha)	ABL1, ABL2, KIT	Anti-inflammatory, cytokine suppression/immunomodulatory, antifibrotic (91) (92) (90) (79) (94) (95) (96) (93) (77)
Nilotinib (Tasigna) (chronic myeloid leukemia; BCR-ABL)	ABL1, ABL2, KIT	Antifibrotic ((80) (81) (82) (83) (84) (85) (86)
Ponatinib (Idusig) (chronic myeloid leukemia, Ph+ acute lymphoblastic leukemia; BCR-ABL)	ABL1, ABL2, KIT, RET, SRC	Cytokine suppression (78)
Saracatinib (orphan drug status, idiopathic pulmonary fibrosis; ABL, SRC, LCK, FGR, BLK)	ABL1 FYN, LYN, SRC, YES1 $IC_{50}$ v-ABL (30 nM); $IC_{50}$ FYN (10 nM); $IC_{50}$ LYN (5 nM) (isolated protein kinase assay) (186)**	Antifibrotic (100) (99) (105)
Bosutinib (Bosulif) (chronic myeloid leukemia; ABL, SRC)	ABL1, ABL2, AXL, CSK, EGFR, FYN, GAK, LYN, SRC, YES	Anti-inflammatory, cytokine suppression, and antifibrotic (104) (87) (88)
Baricitinib (Olumiant) (rheumatoid arthritis; JAK1, JAK2)	JAK1, JAK2, TYK2 $K_d$ AAK1 (17 nM); $K_d$ GAK (136 nM) (cell-free assay) (47)**	Anti-inflammatory and cytokine suppression (106) (107) (108)
Ruxolitinib (Jakafi) (myelofibrosis, polycythemia vera; JAK1, JAK2)	GAK, JAK1, JAK2, JAK3, TYK2 $K_d$ AAK1 (100 nM); $K_d$ GAK (120 nM) (cell-free assay) (47)**	Anti-inflammatory and cytokine suppression, antifibrotic (107)
Fedratinib (Inrebic) (myelofibrosis; JAK2)	AAK1, ABL1, FYN, GAK, JAK2, SRC $K_d$ AAK1 32 nM; $K_d$ GAK 1 nM (cell-free assay) (47)**	Anti-inflammatory and cytokine suppression, (107) (115)
Tofacitinib (XELJANZ XR) (ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis; JAK1, JAK3)	JAK1, JAK2, JAK3, TYK2 No AAK1 inhibitory activity (47)	Anti-inflammatory and cytokine suppression (109) (110) (107) (111)
Gefitinib (Iressa) (non-small cell lung cancer; EGFR)	EGFR, GAK	Antifibrotic (119) (116) (178) (118)
Afatinib (Gilotrif) (non-small cell lung cancer, advanced squamous cell carcinoma; Her2/EGFR)	EGFR, GAK	Anti-inflammatory, antifibrotic (116) (178) (179)
Lapatinib (Tykerb and Tyverb) (breast cancer; Erb1/Erb2, EGFR)	EGFR	Antifibrotic (116) (178)
Osimertinib (Tagrisso) (non-small cell lung cancer; EGFR)	EGFR (60)**	AZ5104, active metabolite of osimertinib, downregulates Th17-related cytokine production via inhibition of SRC-ERK-STAT3 (127)

**Table 2. (continued)**

Kinase Inhibitor (brand name) (indication; main therapeutic targets)	Selected Kinase Target Affinity (antiviral and pulmonary benefit) KINOMEScan (kd < 100 nM)	Anti-inflammatory activity, cytokine suppression, antifibrotic activity
Erlotinib (Tarceva) (non-small cell lung cancer, pancreatic cancer; Erb B, EGFR)	EGFR, GAK Kd ABL1 (310nM) (48)	Antifibrotic (116) (178)
Neratinib (Nerlynx) (breast cancer; Her2/EGFR)	EGFR	
Pazopanib (Votrient) (renal cell carcinoma, advanced soft tissue sarcoma; multi-targeted; c-KIT, FGFR, PDGFR, VEGFR)	KIT	Anti-inflammatory potential, antifibrotic (136)
Sorafenib (Nexavar) (renal cell carcinoma, hepatocellular carcinoma, thyroid cancer; multi-targeted; PDGFR, VEGFR, RAF)	KIT, RET	Antifibrotic (125) (126) (187)
Sunitinib malate (Sutent) (renal cell carcinoma, gastrointestinal stromal tumor; multi-targeted; PDGFR, VEGFR)	AAK1, AXL, GAK, JAK1, KIT, RET	Anti-inflammatory potential, cytokine suppression, antifibrotic (137) (135) (107)
Axitinib (Inlyta) (renal cell carcinoma; c-KIT, PDGFR, VEGFR1, VEGFR2, VEGFR3)	ABL1, ABL2, KIT	Anti-inflammatory and cytokine suppression (128)
Vandetanib (Caprelsa) (medullary thyroid carcinoma; EGFR, RET, VEGFR)	ABL2, EGFR, GAK, RET, SRC Kd ABL1 (270nM) (48)	
Regorafenib (Stivarga) (colorectal cancer, gastrointestinal stromal tumor, hepatocellular cancer; PDGFR $\beta$ , Raf-1, TIE2, VEGFR1/2/3)	KIT, RET	
Ibrutinib (Imbruvica) (mantel cell lymphoma, Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, Small lymphocytic lymphoma, marginal zone lymphoma; BTK)	EGFR, RET	Anti-inflammatory (132) (133)
Palbociclib (Ibrance) (breast cancer; CDK4, CDK6)	CDK6	
Abemaciclib (Verzenio and Verzenios) (breast cancer; CDK4,CDK6)	CDK6 IC <sub>50</sub> (10 nmol/L) CDK9 IC <sub>50</sub> (57 nmol/L) (188)**	Abemaciclib in combination with anastrozole led to increased cytokine signaling and immune activation (189)
Alvociclib (orphan drug status, acute myeloid leukemia; CDK1, CDK2, CDK4, CDK9)	CDK9	Anti-inflammatory (134)
Ceritinib (Zykadia) (non-small cell lung cancer; ALK, IGF1R, InsR, STK22D)		
Crizotinib (Xalkori) (non-small cell lung cancer; ALK/ROS1)	ABL1, AXL	
Masitinib (Masivet) (orphan drug status, potential amyotrophic lateral sclerosis drug; FAK, FGFR3, KIT, LCK, PDGFR)	ABL1, KIT, LYN	
Nintedanib (Ofev and Vargatef) (idiopathic pulmonary fibrosis, non-small cell lung cancer; FGFR, PDGFR, VEGFR)	AAK1, ABL1, AXL, JAK2, JAK3, KIT, RET, YES1	Anti-inflammatory, cytokine suppression, antifibrotic (129) (130) (131)

Left Column: Drug names and disease indication, and main therapeutic targets. Middle Column: Potency (based on KINOMEScan data) against key proteins associated with respiratory function and proteins involved in viral replication/life span/infection- believed to be necessary for a wide variety of viruses, including SARS-CoV and MERS-CoV and SARS-CoV-2. Right column: Anti-inflammatory activity, cytokine suppression, and antifibrotic activity of the kinase inhibitors.

\*These values were derived from ChEMBL database: <https://www.ebi.ac.uk/chembl/>.

\*\*These values were not derived from KINOMEScan; References are cited.



dosages with the potential to inhibit viral replication (46). It has been suggested, however, that side effects associated with these agents at doses required to inhibit AAK1 may not be tolerated by patients infected with SARS-CoV-2 (45).

Gilteritinib is a potent inhibitor of AXL (49), which is one of the targets of sunitinib and erlotinib identified to be important for dengue infection (46). Gilteritinib was reported (unpublished results; preprint) to be one of 24 FDA-approved drugs to show *in vitro* activity against SARS-CoV-2 (0.1  $\mu\text{M}$  < IC<sub>50</sub> < 10  $\mu\text{M}$ ) (BioRxiv. <https://doi.org/10.1101/2020.03.20.999730>) (Table 1). Gilteritinib has been approved for adult patients with mutant FLT3-positive refractory/relapsed AML (Table 2).

## EGFR INHIBITORS

Epidermal growth factor receptor (EGFR) has been implicated in infection by a wide range of unrelated viruses (50), including the spread and motility of vaccinia virus (51) and the processes of endocytosis (for influenza A and HCV), and entry and/or post-entry events (for human cytomegalovirus (HCMV) and adeno-associated virus serotype A (AAV6) (Table 1) (52) (53) (54) (55) (56) (57). In fact, among the first studies to show that tyrosine kinase inhibitors can have significant antiviral activity was one identifying EGFR as a co-factor for entry of HCV into human host cells (56). EGFR is also used by different viruses, including many respiratory viruses, to evade the host immune response (58). Activity against HCMV and HCV *in vitro* and *in vivo* has been demonstrated by the EGFR-targeting inhibitors, gefitinib and erlotinib (59) (56) (57).

Osimertinib is a potent inhibitor of EGFR (60). Osimertinib was reported (unpublished results; preprint) to be one of 24 FDA-approved drugs to show *in vitro* activity against SARS-CoV-2 (0.1  $\mu\text{M}$  < IC<sub>50</sub> < 10  $\mu\text{M}$ ) (BioRxiv. <https://doi.org/10.1101/2020.03.20.999730>) (Table 1). Osimertinib has been approved for non-small cell lung carcinoma (Table 2).

## CYCLIN-DEPENDENT KINASE INHIBITORS

Cell cycle progression of host cells can be modulated by viruses through influences on host cell cyclin-dependent kinases (CDKs). As an example, CDK9 has been implicated in infection by herpes simplex virus type 1 (HSV-1) (Table 1) (61). Specifically, CDK9 was shown for HSV-1 to be involved in expression of genes controlled by the viral regulatory protein, ICP22, and through binding to ICP22 leads to phosphorylation of RNA polymerase II (61). Palbociclib, at least partly through inhibition of CDK6, inhibited HSV-1 replication *in vitro* (62), likely through blockade of cellular protein

phosphorylation (62). CDK9-targeting alvocidib showed activity against influenza A (Table 1) (63). CDK9 has been found to mediate the activity of RdRp of the influenza virus; cells lacking CDK9 showed impairment of viral replication (64).

The CDK4/6 inhibitor, abemaciclib, was identified as one of 24 FDA-approved drugs to display *in vitro* activity against SARS-CoV-2 (0.1  $\mu\text{M}$  < IC<sub>50</sub> < 10  $\mu\text{M}$ ); these results are unpublished and are reported as a preprint (BioRxiv. <https://doi.org/10.1101/2020.03.20.999730>) (Table 1). Abemaciclib has been approved for advanced or metastatic breast cancer (Table 2).

## PI3K/AKT/MTOR AND ERK/MAPK INHIBITORS

Activation of the phosphatidylinositol 3'-kinase-Akt-mammalian target of rapamycin (PI3K/Akt/mTOR) pathway has been implicated in growth and replication of numerous viruses, including HCV, West Nile virus, and influenza A virus (65) (66) (67). Pathway overrepresentation analysis and functional network analysis employed to identify cell signaling changes occurring during MERS-CoV infection (68) revealed members of the PI3K/AKT/mTOR signaling pathway, including AKT, target of rapamycin (mTOR), RPS6KB1, PDK1, PIK3R1, and PIK3R2, and members of the Ras/Raf/MEK/ERK signaling pathway signaling pathway, including MAP2K1, MAPK3 and MAPK14, to be upregulated (68). At a concentration of 10  $\mu\text{M}$ , the mTOR inhibitor, rapamycin, caused significant (61%) inhibition of MERS-CoV infection (correlated with decreased viral titers) in MERS-CoV-infected cells (68). Treatment of cells prior to MERS-CoV infection with sorafenib, which targets RAF, strongly inhibited infection (93%) (68). The inhibitory activity was diminished when sorafenib was added post-infection, suggesting a possible role for RAF early in the viral life cycle. Genetic knockdown studies, focusing on mTOR and RAF and other signaling molecules shown to be overrepresented during MERS-CoV infection, are warranted to validate the role of these proteins in this process.

Activation of the MAPK/ERK1 pathway has been implicated in influenza A virus production and viral nuclear export of ribonucleoprotein complexes (69). The pathway has also been associated with Ebola virus entry coupled with cellular (glycoprotein-induced) damage and elevated cytokine production (70) (71).

## SUMMARY OF KINASE INHIBITOR ACTIVITY AGAINST VIRUS-ASSOCIATED PROTEINS

Using KINOMEscan biochemical kinase profiling assay data from the Harvard Medical School Library of Integrated Network-based Cellular Signatures (LINCS) (72) and data

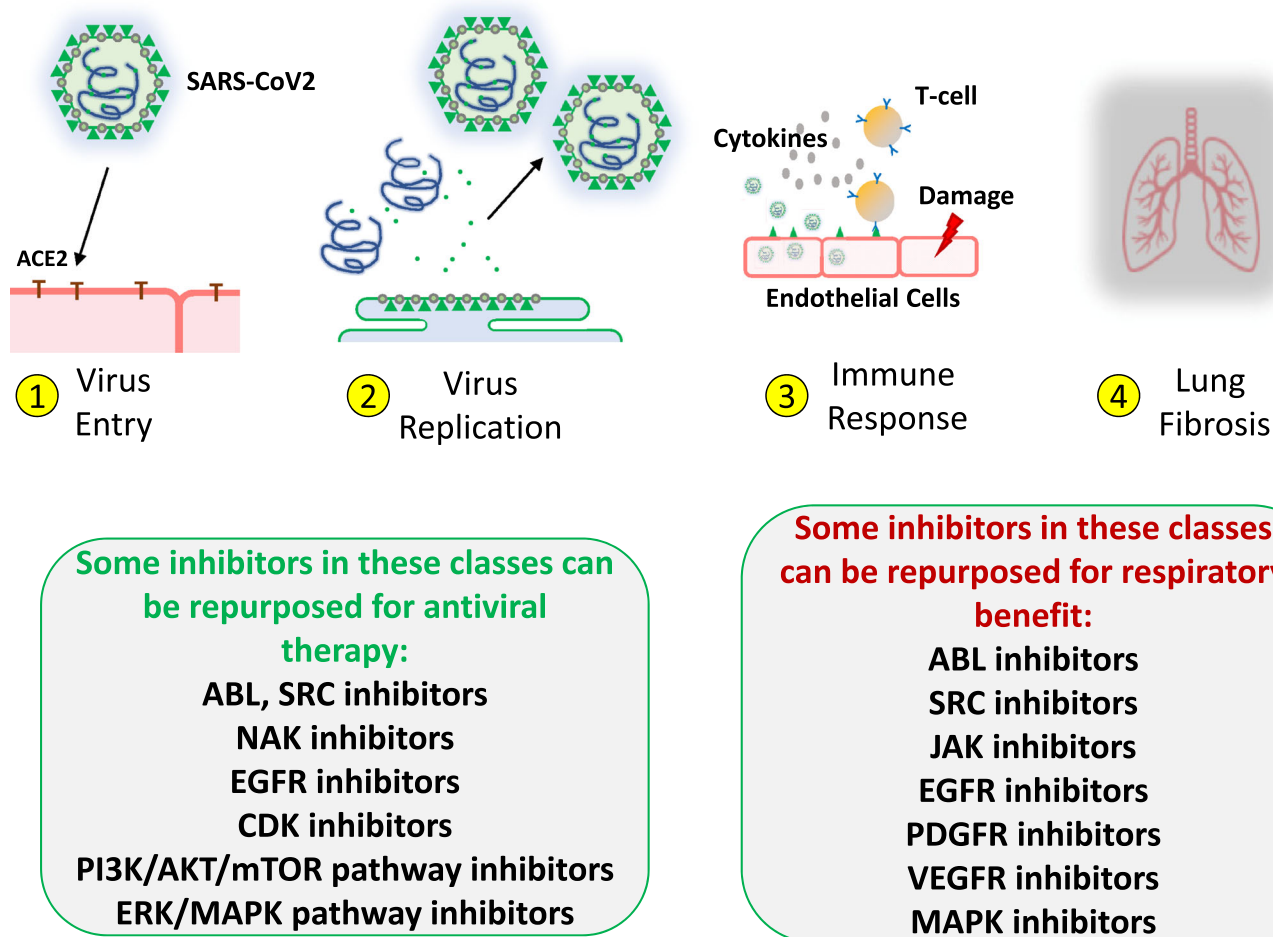
derived from the ChEMBL database, we focused on the ability of a list of FDA-approved kinase inhibitors to target those proteins implicated in SARS-CoV, MERS-CoV and related virus infections, as well as several unrelated viral infections, including ABL proteins, AAK1, AXL, CDK6, CDK9, CSK, EGFR, FYN, GAK, KIT, LYN, RET, SRC, and YES (Table 2, Fig. 3).

## PHARMACOKINETICS OF KINASE INHIBITORS

Kinase inhibitors are significantly metabolized by cytochrome P450 enzymes, and some are either inhibitors or substrates of drug transporters, including P-glycoprotein (P-gp; ABCB1) or Breast Cancer Resistance Protein (BCRP; ABCG2). The extent of plasma protein binding can also affect and in some cases lower drug potency, such as occurs with highly (>99.9% plasma protein bound) midostaurin (73) (74). These factors can lead to differences in the amount of circulating and cellular drug concentrations between patients, and thus the potential a drug has for tissue

distribution/bioavailability may be helpful when considering repurposing a drug based on its anticipated targeted effects. Some drug characteristics are shown in Table 3 (75) (76).

The majority of kinase inhibitors listed are recommended for repurposing for COVID-19 based on the volume of distribution ( $V_d$ ), or the theoretical volume necessary to contain the amount of a dosed drug at the same concentration observed in plasma, the area under the curve (AUC), which defines the variation of a drug concentration in plasma as a function of time (AUC<sub>0-infinity</sub> describes total drug exposure across time), and maximum plasma levels ( $C_{max}$ ), or peak serum concentration achieved by a drug in an identified part of the body following administration of a drug dose. There are several drugs, however, which raise some concerns with respect to pharmacokinetic properties, with limitations that would need to be overcome in order to serve as appropriate therapeutics for SARS-CoV-2 infection. These drugs include nilotinib, ponatinib, saracatinib, tofacitinib, pazopanib, and axitinib (Table 3). For nilotinib, based on the dosage and bioavailability, the drug concentration is adequate, however the volume of distribution (0.55-3.9 L/kg) suggests that



**Figure 3.** Repurposing of kinase inhibitors as antiviral therapies and for respiratory benefit.

nilotinib is mainly distributed in the blood and poorly distributed in tissue. For ponatinib, the  $C_{\max}$  and  $T_{\max}$  of ponatinib were reported as 73 ng/mL and 6 hours, respectively, which suggests that drug absorption is slow and plasma drug concentrations are low. To increase exposure in the blood, ponatinib would need to be taken continuously for a number of days, and this would not be ideal for the rapid treatment necessary for a COVID-19 patient. For saracatinib, both the  $C_{\max}$  (34 ng/mL) and AUC (399 ng\*h/mL) are low, which suggests that dosing continuously for a number of days could potentially increase the blood drug concentration, which is not desirable. For tofacitinib, an oral dose of 5 mg/kg,  $C_{\max}$ =34 ng/mL, AUC=144ng\*h/mL and a half-life of 2.49h would require long-term dosing to achieve optimal drug concentrations and anti-inflammatory effects. Based on this timeline, this would not be ideal for the rapid treatment required for a patient with COVID-19. Pazopanib has been reported clinically to be associated with severe hepatotoxic deaths, and thus there may be potential safety issues for patients. The potential toxicity associated with pazopanib and the volume of distribution (only 11.1 liters) are issues that would need to be addressed for repurposing for COVID-19 treatment. For axitinib, the  $T_{\max}$  (3.2 hrs) and AUC<sub>0-infinity</sub> (160 mg\*h/mL) values were very low, suggesting that multiple doses are necessary. Axitinib is prone to causing elevated blood pressure and arterial thromboembolism events, especially for elderly people, which for an older COVID-19 patient would mean a high risk of death. Lapatinib is more complicated and the following should be taken into consideration prior to using lapatinib as a therapy for COVID-19 patients: The bioavailability is not reported to be high and the recommended dose is considerably high, which are not ideal characteristics. However, the drug is likely to be safe at high doses, meaning that optimal blood concentrations can be reached, with a half-life of 14.8 hours.

### KINASE INHIBITORS AS POTENTIAL THERAPEUTICS FOR COVID-19 RESPIRATORY COMPLICATIONS

Kinase inhibitors that have been approved for treatment of various malignancies have properties, such as anti-inflammatory and cytokine inhibitory activity, which may be able to reduce the likelihood of life-threatening conditions due to lung damage from respiratory virus infections. Numerous small molecule kinase inhibitors target proteins associated with severe respiratory distress, including cytokines (such as IL-6 and TNF-alpha) that contribute to cytokine release syndrome and sHLH, as well as proteins associated with inflammation and induction of pulmonary fibrosis (such as the pro-inflammatory cytokine TGF-beta).

### ABL, PDGFR, AND SRC INHIBITORS

Cytokine inhibition and anti-inflammatory and antifibrotic activity displayed by some inhibitors of Abelson murine leukemia viral oncogene homolog 1 or 2 (ABL1, ABL2), platelet-derived growth factor receptor, and SRC (proto-oncogene encoding a non-receptor tyrosine kinase, similar to the v-Src gene of the Rous sarcoma virus), could potentially provide benefit for SARS-CoV-, MERS-CoV-, or SARS-CoV-2-infected patients (77). For instance, the ABL inhibitor, ponatinib, exhibited cytokine storm suppression in a preclinical model of influenza (78). Imatinib inhibited TNF-alpha production in murine models of acute hepatitis and prevented TNF-alpha-dependent acute liver inflammation in these models (77), and attenuated signaling associated with rheumatoid arthritis, such as KIT-mediated signaling and TNF-alpha release by mast cells, macrophage FMS activation and production of cytokines (79). Nilotinib and bosutinib showed activity against pulmonary fibrosis and other models of fibrosis, through regulation of levels of pro-inflammatory cytokines such as IL-1 and IL-6 (80) (81) (82) (83) (84) (85) (86) (87) (88) (89).

Case study reports and small clinical trial data exist, generally in favor of the anti-inflammatory and antifibrotic effects of imatinib, although results have been variable. Two targets of imatinib are ABL, which is a key downstream mediator of profibrotic TGF-beta signaling, and PDGFR, also associated with fibrotic diseases (90). In chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) patients, imatinib treatment improved rheumatoid arthritis symptoms, suggesting anti-inflammatory activity, and downregulated proinflammatory cytokines, IL-6 and IL-8 (91) (92) (93). Antifibrotic effects of imatinib were demonstrated in two patients with nephrogenic systemic fibrosis, with each patient showing progressive reduction of skin thickening and tethering following the start of imatinib treatment (94), and pulmonary fibrosis improved in a patient treated with imatinib for the 20 weeks the patient was on therapy (95). Antifibrotic activity of imatinib was also demonstrated in a patient with bleomycin interstitial pneumonitis, a condition sharing biochemical and histological features with idiopathic pulmonary fibrosis that is caused by the antibiotic chemotherapy agent bleomycin (96). However, imatinib was not observed to affect lung function or survival in idiopathic pulmonary fibrosis patients followed for 96 weeks in a randomized, placebo-controlled clinical trial (97), and limited success was observed for imatinib in a Hodgkin's lymphoma patient with bleomycin interstitial pneumonitis due to adverse effects including thrombocytopenia with gastrointestinal bleeding (98).

SRC kinases are activated by profibrotic cytokines TGF-beta and PDGF (99), and SRC kinases are important for inflammatory responses (100). Dasatinib has been proposed as an agent for fibrotic diseases, based on its inhibition of

**Table 3** Pharmacokinetics and reports of pulmonary toxicity for kinase inhibitors

Kinase Inhibitor (brand name) (company)	Absorption/bioavailability/peak plasma levels/volume of distribution (adults)	Metabolism (adults)	Recommended daily dose (adults); serum protein matrix binding: human serum $\alpha$ -1 glycoprotein (AAG), human serum albumin (HSA)	Pulmonary Toxicity
Midostaurin (Rydapt)(Novartis)	Time to $T_{max}$ between 1-3 h post dose in fasted state; following 50 mg oral dose, mean $C_{max}$ (total circulating radioactivity, unchanged midostaurin, and metabolites CGP52421 and CGP62221)=2160 ng/mL, 1240 ng/mL, 328 ng/mL and 562 ng/mL, respectively; mean AUC (0-infinity) (total circulating radioactivity, unchanged midostaurin, and metabolites CGP52421 and CGP62221) = 165 x 103 ng Eq* <sup>h</sup> /mL, 15.7 x 103 ng* <sup>h</sup> /mL, 146 x 103 ng* <sup>h</sup> /mL, and 27.1 x 103 ng* <sup>h</sup> /mL, respectively; high oral absorption rate following 50 mg dose (190); rat and dog: bioavailability low to moderate (9.3-48.5%); human oral bioavailability low to moderate (190); $V_d$ = 95.2L (parent drug and metabolites distributed in plasma)	Metabolized by hepatic CYP3A4(Yin et al.,2008);CYP3A4 inhibitors may increase exposure to midostaurin and active metabolites	50 mg orally twice daily; >99.9% binding (AAG)	One case reported of interstitial lung disease while on midostaurin therapy post allogeneic stem cell transplant (191); in phase III trial, 8% of midostaurin-treated patients had grade 3-5 pneumonitis or radiographic pulmonary opacities (192)
Lestaurtinib(Cephalon)	No information available	No information available	80 mg orally twice daily;High protein binding (AAG) (193) 120 mg orally once daily;94% (HSA)	Boxed warning: 3% of patients experienced differentiation syndrome, characterized by symptoms including dyspnea, pleural effusion, pulmonary edema, may be life-threatening or fatal if not treated; Occurred as early as 2 days and up to 75 days following treatment initiation (194)
Gilteritinib (Xospata)(Astellas Pharma)	$C_{max}$ observed 2 h following oral administration; $C_{max}$ =374 ng/mL;AUC=6943 ng/L/mL; $V_d$ = 1092 L (central); $V_d$ = 1100 L (peripheral)	Metabolized mainly by CYP3A4		
Dasatinib (Sprycel)(Bristol-Myers Squibb)	Oral bioavailability ranged from 14% (mouse) to 34% (dog); incomplete bioavailability because of incomplete absorption and high first-pass metabolism; not due to Pgp (195); $V_d$ = 2505 L	Metabolized by CYP3A4; extensively metabolized with 29 metabolites resulting from oxidation; possible inhibitor of CYP3A4 and CYP2C8	140 mg orally once daily;96% (AAG, HSA)	Pleural effusions are more frequently observed in dasatinib-treated patients than imatinib-treated patients; with 10-35 % of dasatinib-treated patients developing pleural effusions (196); reversible pulmonary arterial hypertension has been observed in a small percentage of dasatinib-treated patients (197)
Imatinib Mesylate (Gleevec (US)/Glivec (Europe/Australia)(Novartis)	Well absorbed; absolute bioavailability=98%; maximum plasma levels within 2-4 h of dosing; $V_d$ = 347 L (+/-62)(198)	Metabolized mainly by hepatic CYP3A4 and to a lesser extent by CYP1A2, CYP2D6, CYP2C9, CYP2C19	400 mg orally daily (chronic myeloid leukemia (chronic phase); 600 mg orally daily (chronic myeloid leukemia (accelerated phase);95% binding (AAG, HSA)	Most pulmonary toxicities associated with imatinib are related to fluid retention, with peripheral and periorbital edema more common than pleural or pericardial effusions and pulmonary edema; acute pneumonia and subacute interstitial pneumonitis occur rarely (199) (200) (201)
Nilotinib (Tasigna)(Novartis)	$C_{max}$ 0.5-4 h; moderate bioavailability (17-44%); absolute oral bioavailability predicted to be low (< 25%) (202); $V_d$ = 0.55 to 3.9 l/kg across several species (202); (transported by ABCB1 and ABCG2) (203)	Metabolized mainly by CYP3A4 (203)	400 mg orally twice daily (resistant or intolerant chronic myeloid leukemia (chronic and accelerated phases);300 mg orally twice daily (newly diagnosed chronic myeloid leukemia (chronic phase));98% binding (AAG, HSA)	Lung-related adverse effects are rare in comparison to imatinib and dasatinib; in one clinical trial, pleural effusion was observed in less than 1% of nilotinib-treated patients (204) (141); case report of acute respiratory failure from diffuse alveolar hemorrhage (205)
Ponatinib (Iclusig)(Ariad)	Absolute bioavailability unknown; peak concentrations within 6 h of dosing; following 45 mg dose: $C_{max}$ = 73 ng/mL; AUC = 1253 ng* <sup>h</sup> /mL; $V_d$ = 1223 L (oral administration, 45 mg ponatinib once daily for 28 days)(weak substrate for P-gp and ABCG2)	Metabolized by CYP3A4 and to a lesser extent CYP2C8, CYP2D6, CYP3A5 involved in phase I metabolism <i>in vitro</i> ; esterases and/or amidases	Commence treatment at 45 mg once daily (chronic myeloid leukemia and Ph+ acute lymphoblastic leukemia) (due to severe vascular occlusive events at this dose lower doses are being explored); start at 30 mg once daily (patients taking strong CYP3A inhibitors; patients with hepatic impairment); > 99 % binding	Pulmonary arterial hypertension has been reported for ponatinib (206)

**Table 3 (continued)**

Kinase Inhibitor (brand name) (company)	Absorption/bioavailability/peak plasma levels/volume of distribution (adults)	Metabolism (adults)	Recommended daily dose (adults); serum protein matrix binding: human serum $\alpha$ -1 glycoprotein (AAG), human serum albumin (HSA)	Pulmonary Toxicity
Saracatinib (AstraZeneca)	Linear pharmacokinetic properties with single dose range 50–175 mg/d; following dosing 50 mg/d, $C_{max}$ = 34 ng/mL, and AUC (0–24 h) = 399 ng <sup>h</sup> /mL; slow elimination indicated that multiple administration may result in accumulation. Food increases exposure; following 15 daily doses of bosutinib 500 mg with food: $C_{max}$ = 200 ng/mL; AUC = 3650 ng <sup>h</sup> /mL; compared to initial administration, plasma drug exposure did not increase significantly; following 15 daily doses 400 mg once daily: AUC = 2235 ng <sup>h</sup> /mL; $T_{max}$ = 4 h; Has acceptable exposure; $V_d$ = 6080 ± 1230 L; (substrate of ABCB1)	Metabolized mainly by P4503A4	Information not available	
Bosutinib (Bosulfil) (Pfizer)	Food increases exposure; following 15 daily doses of bosutinib 500 mg with food: $C_{max}$ = 200 ng/mL; AUC = 3650 ng <sup>h</sup> /mL; compared to initial administration, plasma drug exposure did not increase significantly; following 15 daily doses 400 mg once daily: AUC = 2235 ng <sup>h</sup> /mL; $T_{max}$ = 4 h; Has acceptable exposure; $V_d$ = 6080 ± 1230 L; (substrate of ABCB1)	Metabolized mainly by CYP3A4, which can increase AUC and $C_{max}$	500 mg orally once daily (chronic myeloid leukemia (chronic and accelerated phases and blast crisis with resistance/intolerance to prior therapy)); 400 mg orally once daily (newly diagnosed chronic myeloid leukemia (chronic phase)); 94% binding to human plasma proteins <i>in vitro</i> ; 96% bound to human plasma proteins in healthy subjects <i>ex vivo</i>	Plural effusion is the main lung toxicity associated with bosutinib; 8% of patients in one study developed pleural effusions (207)
Baricitinib (Olumiant) (Eli Lilly)	Rapid absorption; oral bioavailability = 79%; median time to peak plasma concentration ( $T_{max}$ ) 1h; food decreases exposure by up to 14% and decreases peak plasma concentration ( $C_{max}$ ) by up to 18% and $T_{max}$ by 0.5 h; $V_d$ = 76 L (IV administration)	Metabolized by CYP3A4; less than 10% of total dose prone to metabolism	2 mg orally once daily; 50% binding	Shown in clinical trials to cause a modest increase in upper respiratory tract infections (47)
Ruxolitinib (Jakafi) (Incyte Corporation)	Rapid absorption; not affected by food; $C_{max}$ , 15 mg, healthy subject = 649 nmol/L; $T_{max}$ , 15 mg, healthy subject = 1.5 h; $V_d$ = 76.6 L	Metabolized by CYP3A4	Starting dose 5–20 mg orally twice daily (depending on platelet count, for myelofibrosis); 97% binding (HSA)	Plural effusion, pulmonary hypertension exacerbations, and acute respiratory distress are extremely rare (208); although rare, mild acute respiratory distress syndrome may occur secondary to ruxolitinib treatment (209)
Fedratinib (Inrebic) (Celgene)	Not affected by high fat breakfast; 400mg oral dose: $C_{max}$ = 1804 ng/mL, AUC = 26,870 ng <sup>h</sup> /mL (210); rapidly absorbed, peak plasma concentration after 3 h after dosing; exposure increased in a greater than dose-proportional manner; $V_d$ = 1770L	Metabolized by CYP3A4, CYP2C19, flavin-containing monooxygenase 3; CYP3A4 inhibitor can increase exposure of tofacitinib in plasma	400 mg orally once daily; reduced dose for patients taking strong CYP3A inhibitors or with severe renal impairment; > 92% binding	
Tofacitinib (Xeljanz XR) (Pfizer)	AUC not affected by fatty meals, but reduction in $C_{max}$ by 32%; rapidly absorbed, plasma concentrations and total radioactivity peaking 1 h after oral dosing; after single oral dose (10 mg), $C_{max}$ = 98.3 ng/mL, $T_{max}$ = 0.5 h; AUC (0–infinity) = 274 ng <sup>h</sup> /mL; $T_{1/2}$ = 2.49 hr; Absolute bioavailability = 74%; oral absorption; No accumulation effect; $V_d$ = 87L (IV administration)	Metabolized mainly by hepatic CYP3A4 and to a lesser extent by CYP2C19	5 mg orally twice daily; extended release 11 mg orally once daily; 40% binding (HSA)	Increased risk of blood clots in the lungs and death when a 10 mg twice daily dose of tofacitinib was used in patients with rheumatoid arthritis. FDA has not approved this 10 mg twice daily dose for RA; this dose is only approved in the dosing regimen for patients with ulcerative colitis (163); pulmonary complications were only described in less than 1% of the patients participating in several clinical trials (211) (110)
Gefitinib (Iressa) (AstraZeneca/Teva)	Bioavailability not affected by food; slowly absorbed following oral administration; mean bioavailability = 60%. Peak plasma levels 3–7 h following dosing; $V_d$ = 1400 L (IV administration)	Metabolized mainly by hepatic CYP3A4	250 mg orally once daily; 90% binding (AAG, HSA)	Associated with increased incidence of interstitial lung disease, which often acts as a precursor to pulmonary fibrosis; approximately 1 percent of patients treated with gefitinib develop pulmonary toxicity, within the first few months of treatment; gefitinib-related interstitial lung disease is generally uncommon (212) (213) (140) (214); shown to exacerbate bleomycin-induced pulmonary fibrosis in preclinical models (215)

**Table 3 (continued)**

Kinase Inhibitor (brand name) (company)	Absorption/bioavailability/peak plasma levels/volume of distribution (adults)	Metabolism (adults)	Recommended daily dose (adults); serum protein matrix binding; human serum $\alpha$ -1 glycoprotein (AAG), human serum albumin (HSA)	Pulmonary Toxicity
Afatimib (Gilotrif)(Boehringer Ingelheim)	High fat meal decreases exposure by 50% ( $C_{max}$ ) and 39% (AUC (0 - infinity)) following oral dosing. $T_{max}$ = 2 to 5 h; $C_{max}$ and AUC (0-infinity) values increased slightly more than dose proportional in range 20 to 50 mg; geometric mean relative bioavailability of 20 mg tablets = 92% compared to oral solution; $V_d$ = 4500 L (suggests potentially high tissue distribution) (216)(P-gp substrate) (181)	Enzyme-catalyzed metabolism plays insignificant role <i>in vivo</i>	40 mg orally once daily; 30 mg orally once daily in patients with severe renal impairment/ <i>in vitro</i> binding to human plasma proteins is around 95%; binds to proteins both non-covalently (traditional binding) and covalently	In an NSCLC clinical trial, among 230 treated patients, there were 3 cases of potential interstitial lung disease (1 %); in another NSCLC clinical trial, of 242 treated patients, 1 developed grade 4 interstitial lung disease however recovered (217) (218)
Lapatinib (Tykerb and Tyverb)(GlaxoSmithKline)	Incomplete/variable absorption after oral dosing; average absolute bioavailability 25% or less; consistent with low absorption/solubility; peak plasma concentrations do not occur until 4 h after dosing; following 25 mg oral dose, the median $T_{max}$ = 3 h; geometric mean (95% CI) values: $C_{max}$ = 349 ng/mL; AUC (0-infinity) = 4410 ng*h/mL; half-life: 14.8 h; absorption limited by first-pass metabolism by CYP3A4/5 and low solubility; transporters possibly involved, although lapatinib not a P-gp substrate (ABCB1) (219)	Metabolized mainly by CYP3A4 and CYP3A5 and to a lesser extent by CYP2C19 and CYP2C8	1, 250 mg orally once daily continuously in combination with capecitabine (for metastatic breast cancer); 1, 500 mg orally once daily in combination with letrozole (for hormone receptor positive HER2 positive metastatic breast cancer); > 99% binding (AAG, HSA)	Unlike gefitinib and erlotinib, pulmonary toxicity due to lapatinib is very rare; only one case of interstitial pneumonitis has been reported for lapatinib (220)
Osimertinib (Tagrisso)(AstraZeneca)	$C_{max}$ = 6 h (median time); $V_d$ = 986 L	Metabolized mainly by CYP3A and metabolized to two pharmacologically active metabolites, AZ7550 and AZ5105	80 mg tablet orally once daily; 95% binding	Interstitial lung disease associated with osimertinib (221) the incidence of interstitial lung disease associated with osimertinib is unclear due to small sample sizes in published reports (222)
Erlotinib (Tarceva)(Genentech, OSI Pharmaceuticals (US), Roche (elsewhere))	Bioavailability significantly enhanced by food to nearly 100%; 60% absorption following oral dosing; peak plasma levels 4 h after dosing; $V_d$ = 232 L	Metabolized mainly by hepatic CYP3A4 and to a lesser extent by CYP1A2 and extrahepatic isoform CYP1A1	150 mg (for non-small cell lung cancer); 100 mg (pancreatic cancer); 95% binding (AAG, HSA)	Interstitial lung disease associated with erlotinib; approximately 1 percent of patients treated with erlotinib develop pulmonary toxicity, within the first few months of treatment (223) (140)
Neratinib (Nerlynx)(Puma Biotechnology)	High fat meal increases $C_{max}$ by 1.7-fold and increases total exposure by 2.2-fold; standard meal increases $C_{max}$ by 1.2-fold, increases total exposure by 1.1-fold; proton pump inhibitors decrease $C_{max}$ by 71% and decrease total exposure by 65%; neratinib/metabolites have a $T_{max}$ = 2-8 h; $V_d$ = 6433 L	Metabolized mainly by CYP3A4	240 mg orally once daily; > 99% binding (AAG, HSA)	In a Phase III study, neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET), interstitial lung disease occurred in two patients in the neratinib group and one patient in the placebo group, pulmonary fibrosis in one and two patients, respectively, and pneumonitis in one patient in each group (224)
Pazopanib (Votrient)(Novartis)	Slow and incomplete absorption and bioavailability; over 50-2000 mg, absorption nonlinear (in cancer patients); substantial accumulation in patients receiving 800 mg once daily (22 days); bioavailability (cancer patient) = 21% for oral tablet 800 mg; $C_{max}$ = 58.1 $\mu$ g/mL; AUC = 1037 $\mu$ g*h/mL; $V_d$ = 11.1 L (IV administration 5 mg)	Metabolized mainly by CYP3A4 and to a lesser extent by CYP1A2, CYP2C8	Not to exceed 800 mg; reduce to 200 mg daily in patients with moderate hepatic impairment; not recommended in patients with severe hepatic impairment; > 99% binding	Pneumothorax was reported in 3%-14% of pazopanib-treated patients in clinical trials (225) (226)
Sorafenib (Nexavar)(Bayer and Onyx Pharmaceuticals)	High fat meal decreases bioavailability by 29%; mean relative bioavailability = 38-49% for tablet form; peak plasma levels achieved 3 h after dosing; $V_d$ = 213 L (suggests potentially high	Metabolized mainly by hepatic CYP3A4; glucuronidation mediated by UGT1A9	400 mg (2x200 mg tablets) orally twice daily; 99.5% binding (AAG, HSA)	There have been several reported cases of sorafenib-induced interstitial lung disease (203); pulmonary toxicity in association with sorafenib has been reported to be uncommon (228)

**Table 3 (continued)**

Kinase Inhibitor (brand name) (company)	Absorption/bioavailability/peak plasma levels/volume of distribution (adults)	Metabolism (adults)	Recommended daily dose (adults); serum protein matrix binding: human serum $\alpha$ -1 glycoprotein (AAG), human serum albumin (HSA)	Pulmonary Toxicity
Sunitinib malate (Sutent)(Pfizer)	tissue distribution despite a high level of plasma protein binding, likely due to high lipophilicity (227) Bioavailability not affected by food after oral dosing, $C_{max}$ observed 6–12 h ( $T_{max}$ ); $V_d = 2230$ L (substrate for ABCB1) (84)	Metabolized mainly by CYP3A4	50 mg orally once daily (4 weeks on, 2 weeks off); 37.5 mg orally (continuous daily dosing); 95% binding for sunitinib, 90% binding for sunitinib's primary metabolite (HSA)	Dyspnea and cough have been reported in association with sunitinib treatment (229); there are no reports of sunitinib treatment-induced pneumonitis.
Axitinib (Inlyta)(Pfizer)	Following 5 mg dose, 2.5–4.1 h to reach $C_{max}$ ; $C_{max} = 32.2$ ng/ml, $T_{max} = 3.2$ h, AUC (0–infinity) = 160 ng $\cdot$ h/ml, $TI/2 = 5.4$ h; $V_d = 275$ L	Metabolized mainly by CYP3A4 and CYP3A5 and to a lesser extent by CYP1A2, CYP2C19, UGT1A1	Starting dose 5 mg orally twice daily; > 99% binding (moderate to AAG; preferential to HSA)	The toxicity profile of axitinib in a Phase II clinical trial was consistent with the one reported with the VEGFR-TKI family with grade 3–4 adverse effects, including dyspnea (14.5%) as a respiratory symptom (230); in clinical trials, fatal pulmonary embolism was reported in 1/359 patients (< 1%) receiving axitinib (Pfizer Labs Patient Information approved by FDA)
Vandetanib (Caprelsa)(Sanofi Genzyme)	Slow absorption; $C_{max}$ reached at median 6 h; $V_d = 7450$ L	Metabolized by CYP3A4, flavin-containing monooxygenase enzymes FMO1 and FMO3	300 mg orally once daily; 90% binding (HSA)	Interstitial lung disease and pneumonitis have been reported more often in patients receiving vandetanib as compared to those receiving placebo; fatal adverse reactions for patients receiving vandetanib (2%) were respiratory failure and arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis (231)
Regorafenib (Stivarga)(Bayer)	$C_{max} = 2.5$ $\mu$ g/ml; $T_{max} = 4$ h; AUC = 70.4 $\mu$ g $\cdot$ h/ml; mean relative bioavailability of tablets = 69% to 83%; $V_d =$ over 24 h dosing, enterohepatic circulation, multiple plasma concentration peaks; (inhibitor of P-gp)	Metabolized by CYP3A4 and UGT1A9 (-232) (metabolites substrates of P-gp)	Starting dose 160 mg orally once daily for three weeks, followed by a one week treatment abstinence; 99.5% binding	Shown to be an irreversible inhibitor of mutant EGFR in NSCLC (234), shown to exacerbate bleomycin-induced pulmonary fibrosis in pre-clinical models (235)
Ibrutinib (Imbruvica)(Pharmaceuticals/Janssen)	Rapid absorption following oral dosing; $C_{max} = 35$ ng/ml; $T_{max} = 1.2$ h; AUC = 953 mg $\cdot$ h/ml; $V_d = 10,000$ L	Metabolized mainly by CYP3A5 and CYP3A4 and to a lesser extent by CYP2D6 (233)	560 mg orally once daily (lymphoma); 420 mg orally once daily (chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Graft versus host disease); irreversible protein binding = 97.3% of administered dose (AAG, HSA)	There is a small risk of potentially severe lung inflammation in palbociclib-treated patients.
Palbociclib (Ibrance)(Pfizer)	$C_{max}$ 6–12 h following oral dosing; oral bioavailability = 46%, steady-state reached after 8 days, median accumulation ratio of 2.4; $V_d = 2583$ L (suggests potentially high tissue distribution) (236)	Metabolized mainly by CYP3A and the sulfotransferase 2A1	125 mg capsule orally once daily for 21 days followed by one week drug abstinence; binding to human plasma proteins accounts = 85% of administered dose	
Abemaciclib (Verzenio and Verzenio)(Eli Lilly)	Following oral dose 200 mg, $C_{max} = 158$ ng/ml (after 6 h); $T_{max} = 4$ –6 h following oral dose 50–275 mg, but could range up to 24 h; Absolute bioavailability = 45%; $V_d = 690.3$ L	Metabolized by CYP3A4	200 mg tablet orally twice daily (as single agent); 95–98% (HSA, AAG)	There is a small risk of potentially severe lung inflammation in abemaciclib-treated patients.
Alvociclib (Tolero Pharmaceuticals)	Dose (infusion dose plus loading dose), mg, 30+ 30. AUC (0–infinity) 14.5 uM $\cdot$ h/mL; Vz value = 367 L	No information available	> 95% binding (HSA)	Alvociclib-related pro-inflammatory syndrome is associated with induction of IL-6 (237)
Ceritinib (Zykadia)(Novartis)	$C_{max}$ after approximately 4 to 6 h following oral dosing; $V_d = 4230$ L (after 750 mg)	Metabolized mainly by CYP3A	450 mg orally once daily; 97% binding	Pulmonary toxicity, such as interstitial lung disease, is a rare side effect associated with ALK inhibitors; most can be managed efficiently by lowering doses or interrupting treatment; in a clinical trial, pneumonitis was reported in 4% of ceritinib-treated patients (238) (239) (240)

**Table 3 (continued)**

Kinase Inhibitor (brand name) (company)	Absorption/bioavailability/peak plasma levels/volume of distribution (adults)	Metabolism (adults)	Recommended daily dose (adults); serum protein matrix binding: human serum $\alpha$ -1 glycoprotein (AAG), human serum albumin (HSA)	Pulmonary Toxicity
Crizotinib (Xalkori)(Pfizer)	High-fat meal decreases $C_{max}$ and AUC; $C_{max}$ 4 to 6 h following oral dosing; $M$ =Mean absolute bioavailability=43% after 250 mg oral dose; $V_d$ = 1772 L (after IV administration 50 mg) (suggests potentially high tissue distribution)	Metabolized by CYP3A4, CYP3A5	250 mg orally twice daily; 91% binding	Pulmonary toxicity, such as interstitial lung disease, is a rare side effect associated with ALK inhibitors; most can be managed efficiently by lowering doses or interrupting treatment; crizotinib was responsible for adverse pulmonary interstitial lung disease and severe pneumonitis in a small percentage of patients (238) (239) (240); associated with ground-glass opacity predominant pattern interstitial lung disease (151)
Masitinib (Masivet)(AB Science)	Absorption: mean $T_{max}$ between 1.7 and 4.7 h; following oral administration of 8.4mg/kg (dog); good absorption/exposure with AUC (0-24 h)=4045 ng <sup>2</sup> h/mL	Phase I metabolic pathways: reduction, demethylation, hydroxylation, oxidative deamination, oxidation and N-oxide formation; phase II metabolic pathways: direct conjugation of masitinib, N-demethyl metabolites and oxidative metabolites with glucuronic acid	Information not available	
Nintedanib (Ofev and Vargatef)(Boehringer Ingelheim)	Fatty meal increased $C_{max}$ 15% and AUC by 20%; following oral dosing, $T_{max}$ after 2 hours in fasted patients, 4 hours in fed patients; absolute bioavailability is low (4.7%), likely due to P-gp transporters and significant first-pass metabolism (241); $V_d$ = 1050 L (IV administration) (suggests potentially high tissue distribution)	CYP3A4 plays a minor role, accounting for 5% metabolism; esterase cleavage accounts for 25% metabolism	150 mg orally twice daily; 100 mg orally twice daily in patients with mild hepatic impairment; 97.8% binding (HSA)	In placebo-controlled INPULSIS® trials, among adverse events leading to permanent treatment discontinuation was pneumonia (0.9%) (242)



TGFβ-induced myofibroblast differentiation through SRC-mediated signaling *in vitro* (101). Dasatinib blocked production of pro-inflammatory cytokines in a model of autoimmune arthritis, including IL-1, TNF-α, and IL-6, and stimulated production of the anti-inflammatory cytokine IL-10 (102) (103), and caused macrophages to change to an anti-inflammatory phenotype marked by high IL-10 production and suppression of levels of pro-inflammatory cytokines (IL-6, TNF-α) (104). Preclinical studies with the SRC/ABL inhibitor, saracatinib, which has orphan drug status for idiopathic pulmonary fibrosis, showed that it decreases collagen deposition and fibroblast activity, which are characteristic of lung fibrosis (105). Specifically, saracatinib, in an *in vitro* lung fibroblast model, inhibited TGF-β-induced SRC activation and consequently inhibited myofibroblast differentiation, supporting the notion that SRC promotes myofibroblast differentiation and lung fibroblast activation (105). Saracatinib also showed efficacy in a mouse model of bleomycin-induced lung fibrosis (105).

## JAK INHIBITORS

Selective JAK inhibitors, such as baricitinib, through targeted inhibition of JAK1 and JAK2, inhibit production of cytokines, including IL-2, IL-6, GM-CSF, and IFN-γ and exhibit significant anti-inflammatory effects in animal models (106) (107). Baricitinib, ruxolitinib, and tofacitinib are anti-inflammatory treatments for rheumatoid arthritis (108) (109) (110), with suppression of inflammatory cytokines associated with rheumatoid arthritis, including TNF-α, IL-6, IL-17, and IFN-γ (111). Ruxolitinib has been observed to normalize the cytokine profile of myelofibrosis patients (112). Due to the JAK inhibitory activity of more multi-targeted agents such as midostaurin (Rydapt; Novartis), lestaurtinib (Cephalon), and sunitinib (Table 2, Fig. 3), each has anti-inflammatory potential as well as potential to combat cytokine release syndrome, which could benefit patients infected with respiratory viruses (107).

The peripheral blood of a patient with severe COVID-19 was shown to have a substantially high number of CCR6+ T helper 17 cells (TH17), a subset of pro-inflammatory T helper cells that produce IL-17 (1), and MERS-CoV and SARS-CoV patients also showed increased TH17 responses or IL-17-mediated signaling (113) (114). The TH17 type response is associated with the cytokine storm in SARS-CoV-2 infection that leads to pulmonary edema and lung damage. The JAK2 inhibitor, fedratinib, was observed to suppress production of TH17-related cytokines and is proposed to be potentially useful for patients with COVID-19 suffering from TH17-related cytokine storm (115).

## EGFR INHIBITORS

Studies suggest that inhibiting EGFR signaling might prevent an excessive fibrotic response to SARS-CoV and other respiratory infections (like that characteristic of COVID-19). EGFR plays a role in interstitial lung disease, and interaction between EGF and TGF-β signaling is believed to drive development of fibrosis (116) (117). The role of EGFR signaling in the development of lung fibrosis is complex, though, with data suggesting both profibrotic and antifibrotic roles for EGFR signaling, at least in part seeming to depend on the trigger for fibrosis (13). Gefitinib inhibited TGF-β1 induction of fibrosis *in vivo* (118) and inhibited bleomycin-induced fibrosis in a mouse model (119), and erlotinib was reported to block fibrosis development in a variety of *in vivo* models (13).

TGF-β induces the expression of EGFR ligands, which in turn activate EGFR. Of relevance, TGF-β was one of several pro-inflammatory cytokines that were observed to be highly upregulated in SARS-CoV patients (120) (121) (122), and mouse models of SARS-CoV infection showed interferon, cytokine and lung-associated wound-healing and ARDS-related genes (123). These findings are consistent with TGF-β being profibrotic, as has been demonstrated in animal models (124). The kinase inhibitor, sorafenib, attenuated bleomycin-induced pulmonary fibrosis in a preclinical model (125) and ameliorated fibrosis in liver fibrosis models through STAT3 inhibition and downregulation of TGF-β- and PDGFRβ-mediated pathways of fibrogenesis (126).

The EGFR inhibitor, osimertinib, is metabolized and broken down into two pharmacologically active metabolites (AZ7550 and AZ5104), which circulate at around 10% of the concentration of the parent compound (Table 3). One metabolite, AZ5104, which is more potent than osimertinib, downregulates Th17-related cytokine production via inhibition of SRC-ERK-STAT3 (127) (Table 2).

## OTHER KINASE INHIBITORS

Among numerous other kinase inhibitors with demonstrated therapeutic potential are axitinib, which, through VEGFR-3 (vascular endothelial growth factor receptor-3) inhibition, improved lymphangiogenesis and oxygen saturation in preclinical model of aspiration pneumonia (128). Nintedanib is approved for idiopathic pulmonary fibrosis and displays anti-inflammatory activity through TNF-α and IL-6 inhibition (129) (130) (131). Ibrutinib exerted anti-inflammatory effects in a model of neuroinflammation-related disease (132) and mitigated acute lung inflammation in a model of pneumococcal pneumonia (133). Alvocidib also shows anti-inflammatory activity by blocking leukocyte-endothelial association by inhibiting CDK9 (134). Pazopanib exhibits antifibrotic

activity through modulating inflammatory cytokines, and sunitinib inhibited bleomycin-induced pulmonary fibrosis in mice (135) (136). Sunitinib, believed to primarily work through PDGFR-mediated signaling, was also shown to suppress cytokine storm in a mouse model (137). Finally, sunitinib was shown to synergize with an anti-TNF antibody against lethal dengue infection (138).

## ADVERSE PULMONARY EFFECTS ASSOCIATED WITH KINASE INHIBITORS

Pulmonary toxicity is reportedly a rare event with many targeted treatments. The incidence of lung toxicity with tyrosine kinase inhibitors is relatively low, although there is substantial variability in their occurrence with a reported range from 0.2–10.9% (139). However certain adverse side effects, such as pleural effusions associated with ABL inhibitors dasatinib or imatinib, interstitial lung disease associated with EGFR inhibitors erlotinib and gefitinib, or ALK inhibitors ceritinib or crizotinib, can occur but often reverse quickly with lowering the dose or terminating use (140). The timing of onset of toxicities following initial dosing needs to be considered for patients afflicted with cancer and other diseases, for whom therapy can be implemented for months, versus patients infected with a respiratory virus that require immediate treatment. Reported cases of adverse pulmonary effects for the listed kinase inhibitors are shown in Table 3.

### IMATINIB AND DASATINIB

Respiratory side effects of imatinib include pneumonia (1–10%). Generally, imatinib-induced pulmonary fibrosis and pneumonitis are very infrequently occurring (141) (142), and imatinib-induced pneumonitis develops in a median time of 49 days (143). In dasatinib-treated CML patients, pleural effusion and lung parenchyma changes (ground-glass or alveolar opacities and septal thickening) were described, however resolved after treatment was interrupted (144). The median time between dasatinib treatment initiation and respiratory symptoms was 229 days. In a case study of a dasatinib-treated Japanese patient, pneumonia developed two years after initiation of dasatinib therapy, and drug discontinuation along with corticosteroid therapy greatly improved symptoms (145).

### ERLOTINIB AND GEFITINIB

Pulmonary toxicities associated with erlotinib have been infrequently reported. Two cases were described that developed acute pneumonitis (chest tomography scan showed bilateral

ground-glass infiltrates), 5–6 days following initiation of erlotinib treatment (146). Interstitial lung disease has been observed as a serious adverse side effect for gefitinib (147), with a 0.3% incidence in the U.S. and a 2% incidence in Japan. The median onset of gefitinib-induced interstitial pneumonia in the U.S. was 42 days, and in Japan was 24 days, with around one-third of all cases caused by gefitinib being fatal (148).

### CERITINIB AND CRIZOTINIB

Interstitial lung disease/pneumonitis resulting from ALK inhibitors is relatively rare (1.2–8% of patients) (149) (150) (151). In a case study of a Korean ALK-rearranged metastatic lung adenocarcinoma patient, ceritinib induced organizing pneumonia (152). Treatment was ceased and the patient was treated with antibiotics and recovered. In a study testing crizotinib in Japanese patients with ALK-positive non-small cell lung cancer, the incidence of interstitial lung disease was 5.77%, and interstitial lung disease developed within 4 weeks in 41.9% patients from the start of crizotinib treatment and within 8 weeks in 69.2% of patients (153). In a clinical study of 250 NSCLC patients treated with ALK inhibitors, including crizotinib or ceritinib, the median time from the start of treatment to the development of pneumonitis, which occurred in 11 of the patients, was 5 months (range 0.5–11 months) (154).

### RISK OF INFECTION DUE TO KINASE INHIBITOR TREATMENT

For ABL inhibitors, including imatinib, dasatinib, nilotinib, basutinib, and ponatinib, there is a modest increased risk of overall infection, with a risk of invasive fungal infection, tuberculosis, and cytomegalovirus (especially with dasatinib, particularly after hematopoietic stem cell transplantation), and a risk of hepatitis B virus reactivation (155). For the BTK/EGFR inhibitor, ibrutinib, there is a modest increased risk of overall infection, with a risk of *pneumocystis jirovecii* pneumonia, invasive fungal infection, and progressive multifocal leukoencephalopathy, and a risk of hepatitis B virus reactivation (155). For JAK inhibitors, including ruxolitinib, tofacitinib, baricitinib, there is a major increased risk of overall infection, with a risk of *pneumocystis jirovecii* pneumonia, herpes zoster, tuberculosis, cytomegalovirus, Epstein-Barr virus, and progressive multifocal leukoencephalopathy, as well as a risk of hepatitis B virus reactivation (155).

It should be noted that the overall risk of a COVID-19 patient being treated with JAK inhibitors and afflicted with tuberculosis as a side effect is likely exceptionally low, especially given that for a COVID-19 patient, treatments for many of the trials are carried out for a couple of weeks. The risk of developing serious infections, such as tuberculosis, is higher for

patients that are on medication causing chronic immunosuppression, such as would be the case for a patient with a chronic illness like rheumatologic disorders, or patients with latent tuberculosis. However, with a short course of treatment in the case of a COVID-19 patient, it is unclear whether the period of immunosuppression would be long enough to result in a meaningful risk. In addition, latent tuberculosis can be tested for rather quickly (1-2 days) with a T-spot. TB test. This would normally be carried out for patients treated with JAK inhibitors, although there may be more of a delay than is ideal for patients with high risk COVID-19.

## CLINICAL TRIALS: SINGLE AGENT AND COMBINATION THERAPY APPROACHES

Based on a query of [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), which lists numerous ongoing trials for COVID-19, a number of studies were found that include testing of kinase inhibitors listed in this article. There are currently several COVID-19 clinical studies investigating imatinib as a single agent (NCT04346147, NCT04357613, NCT04356495). COVID-19 trials are ongoing that investigate ruxolitinib as a single agent and in combination with the lipid-lowering medication, simvastatin (NCT04348071, NCT04355793, NCT04354714, NCT04362137, NCT04334044, NCT04366232, NCT04338958, NCT04331665, NCT04337359, NCT04361903, NCT04348695, NCT04359290). Although there is no strong clinical evidence to date that statins are beneficial for COVID-19 patients and the limited evidence is mixed (156) (157), statins are still under consideration due to possible generation of a greater potent adaptive immune response and a decreased mortality rate associated with patients with influenza, pneumonia, and MERS-CoV (158) (159) (160) (161). COVID-19 clinical studies are investigating baricitinib, both as a single agent and in combination with the antiviral drugs, lopinavir-ritonavir (NCT04340232, NCT04362943, NCT04346147, NCT04358614, NCT04320277, NCT04321993, NCT04345289, NCT04366206). Baricitinib does not interact with antiviral agents due to its prevalent renal elimination, and so it is proposed to be suitable for combination therapy (162). There is one study investigating nintedanib, an FGFR (fibroblast growth factor receptor)/PDGFR/VEGFR inhibitor approved for idiopathic pulmonary fibrosis, as a single agent treatment for pulmonary fibrosis in patients with moderate to severe COVID-19 (NCT04338802).

A COVID-19 study is ongoing that investigates tofacitinib as a single agent at 10 mg twice a day for 14 days (NCT04332042). Of note, this dose of tofacitinib administration has been associated with an increased risk of thrombosis and death and the FDA has issued a boxed warning (163) (Table 3). In a clinical study investigating the predisposition

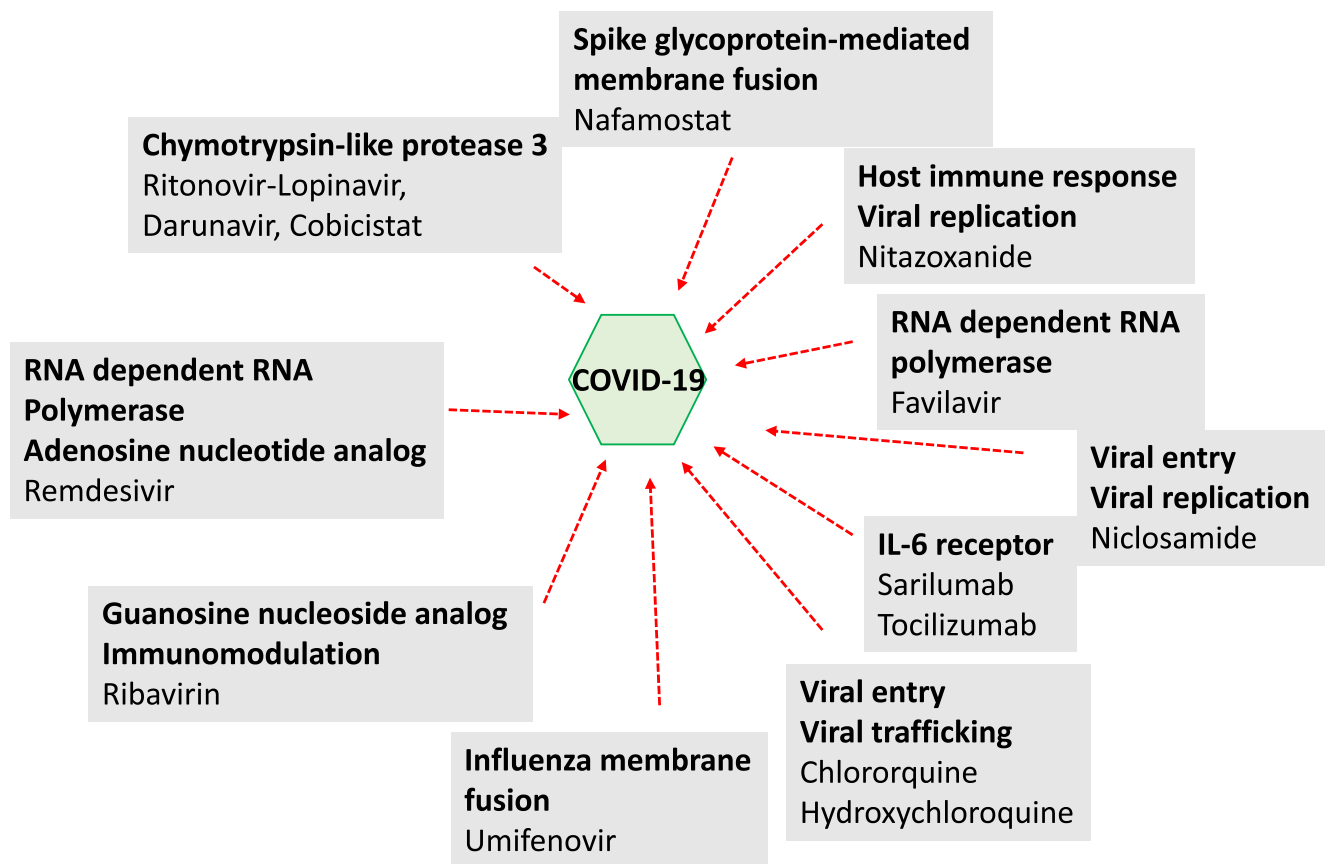
of COVID-19 patients to venous and arterial thromboembolism, a 31% incidence of thrombotic complications, with pulmonary embolism being the most prevalent, was observed in intensive care unit SARS-CoV-2-infected patients (164). The blood clotting risk reported for tofacitinib pertains to patients receiving the drug chronically, and while the increased risk reported for tofacitinib at 10 mg twice daily for 14 days is not known, it is anticipated to be small. It is also general practice as a precaution to place hospital-admitted patients with COVID-19 on blood thinners as DVT/clot prophylaxis (most usually enoxaparin or heparin). This would likely make the risk of blood clots minimal (although not zero percent).

Though not included on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) as a COVID-19 trial, results of a clinical trial with Waldenström's macroglobulinemia patients suggest that ibrutinib might confer protection against lung damage in hypoxic COVID-19 patients, and it may possibly improve respiratory function (165). However, the study was small and involved 6 COVID-positive patients, 5 of whom received ibrutinib at 420 mg and presented with mild symptoms that did not require hospitalization. The 6th patient on a lower dose of ibrutinib had progressive dyspnea and hypoxia and was placed on treatments in addition to ibrutinib at the lower dose, including hydroxychloroquine, azithromycin and tocilizumab. Due to worsening hypoxia, the patient was eventually placed on the higher ibrutinib dose (420 mg) and this was followed by improvement of symptoms (165).

Kinase inhibitors with good safety profiles and desirable pharmacokinetics properties, including minimal association with drug transporters and CYP enzymes, warrant testing in combination with antiviral agents or other targeted agents, to more effectively decrease viral load and potentially more dramatically improve COVID-19 symptoms. There are currently numerous direct antiviral agents that are under consideration for COVID-19 (several prominent investigational drugs are shown in Fig. 4).

Although imatinib is, at the time of the writing of this article, under investigation in COVID-19 patients as a single agent, it may effectively combine with certain antiviral agents and this might be an approach worth considering for COVID-19 trials. For instance, ribavirin has demonstrated synergy *in vitro* with imatinib against leukemia growth (166). Despite proposed lack of efficacy of ribavirin as a single agent against SARS-CoV-2 (167), it is possible that it could synergize with imatinib against SARS-CoV-2 if the drugs are able to be administered at doses that are effective but safe.

The drug-drug interactions between imatinib and a wide variety of antiviral and other agents have been thoroughly assessed. Imatinib displays variable drug-drug interactions and so its potential for effective combination needs to be taken on a case by case basis. For instance, protease inhibitors ritonavir-lopinavir and darunavir increase imatinib exposure, and saquinavir and indinavir decrease imatinib exposure



**Figure 4.** Drug therapies under investigation for COVID-19.

(168). Contrarily, there is no interaction between imatinib and the antiviral/nucleoside analogs acyclovir and valaciclovir, although its intracellular exposure is reduced by ganciclovir and valganciclovir (168). The antimalarial drug, chloroquine, decreases imatinib intracellular exposure (168).

The FDA-approved tapeworm medication, niclosamide, reported as having antiviral activity against SARS-CoV and MERS-CoV is presently under investigation as a SARS-CoV-2 agent (169). Niclosamide has been reported (unpublished results; preprint) to be one of 24 FDA-approved drugs to show *in vitro* activity against SARS-CoV-2, with an IC<sub>50</sub> of 0.28  $\mu$ M (<https://www.biorxiv.org/content/10.1101/2020.03.20.999730v3.full.pdf>). The inhibitory activity of niclosamide against SKP2, which diminishes MERS-CoV replication and augments autophagy (170), is proposed to be the potential mechanism through which niclosamide acts against SARS-CoV-2. Niclosamide was demonstrated to synergize in preclinical studies with imatinib and other kinase inhibitors against different malignancies. For instance, synergy between niclosamide and imatinib, as well as niclosamide and dasatinib or ponatinib, against CML cells was demonstrated (171). Niclosamide was also found to potentiate the effects of erlotinib against head and neck cancer cells

through STAT3 inhibition (172), with erlotinib against human colon cancer lines (173), and with sorafenib against human renal cell cancer cells (174).

EGFR-targeting kinase inhibitors are characterized by extensive tissue distribution, moderate to high plasma protein binding, and a relatively high volume of distribution (>1700 L) (175). Although not currently under investigation for COVID-19 as of this writing, the non-small cell lung cancer drug and EGFR inhibitor, afatinib, has been shown to be safely administered with various antiviral agents in clinical studies (176) (177). In a phase I study in human papillomavirus (HPV)-associated head and neck squamous cell carcinoma, afatinib, with demonstrated anti-inflammatory and antifibrotic activity (116) (178) (179), was tested in combination with ribavirin and standard chemotherapy (176). Afatinib was used because of its targeting of ErbB proteins associated with HPV infection, and ribavirin was chosen due to its targeting of oncogenic eIF4E (180) (176). In this study, there were no dose-limiting toxicities, supporting the safe, clinical use of ribavirin with a kinase inhibitor having key virus-associated protein targets and those with respiratory benefit. Another clinical study showed low potential for interaction between afatinib, a P-gp pump transporter substrate, and the protease inhibitor, ritonavir, a potent inhibitor of P-gp

**Table 4** Chemical structures of kinase inhibitor candidates for COVID-19 treatment. Chemical structures and molecular weights were obtained on chemspider.com

Molecule Name	Structure	SMILES	Molecular weight (g/mol)
Abemaciclib		<chem>CCN1CCN(CC2=CN=C(NC3=NC=C(F)C(=N3)C3=C(C(F)=C4N=C(C)N(C(C)C)C4=C3)C=C2)CC1</chem>	506.61
Afatinib		<chem>CN(C)C=C(C(=O)NC1=CC2=C(C=C1O[C@H]1CCOC1)N=CN=C2N)C1=CC(Cl)=C(F)C=C1</chem>	485.94
Baricitinib		<chem>CCS(=O)(=O)N1C(C(C#N)(C1)N1C=C(C=N1)C1=C2C=CNC2=NC=N1</chem>	371.42
Bosutinib		<chem>COC1=C(C)C=C(C)C(NC2=C(C=N)C3=CC(OCCCN4CCN(C)CC4)=C(O)C)C=C23)C#N)C=C1</chem>	530.45
Erlotinib		<chem>COCOC1=C(OC)C=C(C2C(NC3=CC(=CC=C3)C#C)N=C2=C1)C</chem>	393.44
Fedratinib		<chem>CC1=CN=C(NC2=CC=C(OCCN3CC(C)C=C2)N=C1)NC1=CC(=CC=C1)S(=O)(=O)NC(C)(C)C</chem>	524.68
Gilteritinib		<chem>CCc1nc(C(N)=O)c(Nc2ccc(N3CCC(C)N3)N3CCN(C)C3)c(O)C2)c1NC1CCOCC1</chem>	552.72
Imatinib		<chem>CN1CCN(CC2=C(C=C(C2)C(=O)NC2=CC=C(C)C(NC3=NC=CC(=N3)C3=CC=CN=C3)C=C2)CC1</chem>	493.62

**Table 4 (continued)**

Nintedanib		<chem>COC(=O)C1=CC2=C(C=C(C1)C(=C(NC1=CC=C(C=C1)N(C)C(=O)CN1C)N(C)C1)C1=CC=C(C1)C(=O)N2</chem>	539.64
osimertinib		<chem>COC1=C(NC2=N)C=C(C=C2)C2=C(N(C)C3=C2C=CC=C3)C=C(NC(=O)C=C(C1)N(C)CCN(C)C</chem>	499.62
Sorafenib		<chem>CNC(=O)C1=CC(OCC2=C(C)N(C(=O)N)C3=CC=C(C)C=C3)C(F)(F)F)C=C2=CC=N1</chem>	464.83
Sunitinib		<chem>CCN(CC)CCNC(=O)C1=C(C)NC(\C=C2\C(O)NC3=C2C=C(F)C=C3)C1C</chem>	398.48
Vandetanib		<chem>COC1=CC2=C(N)C3=CC=C(Br)C=C3)N=CN=C2C=C1OCC1CCN(C)CC1</chem>	475.36

(181) (177). This was partially attributed to the fact that afatinib is not a modulator of substrate of cytochrome P450 enzymes. It is possible that the combination of afatinib and antiviral agents, such as ribavirin or ritonavir, which show little activity on their own against COVID-19, may be synergistic in the context of the disease. Alternatively afatinib could potentially be combined with remdesivir, more recently shown to reduce the length of hospital stay for COVID-19 patients and thus exhibiting a degree of activity against SARS-CoV-2 in patients. Or perhaps afatinib could be investigated as a treatment for COVID-19 in combination with several antiviral drugs as part of a cocktail.

Afatinib has also been tested in combination with nintedanib in a Phase I dose-escalation study in patients with advanced solid tumors (182). It was determined that afatinib at 10 mg/day combined with nintedanib at 200 mg twice a day had a manageable safety profile, however the doses were

subtherapeutic. The antifibrotic and anti-inflammatory potential of afatinib and nintedanib, coupled with key virus-associated protein targets for each (Table 2, Fig. 3), warrant investigation of this drug combination for treatment of COVID-19.

Ritonavir is a strong inhibitor of CYP3A4 and it also inhibits ABCB1, and the multi-targeted inhibitor sunitinib is metabolized by CYP3A4 and is a substrate for ABCB1 (183) (184). Consequently, this combination has the potential for reduced efficacy and/or increased toxicity. Sunitinib was investigated in HIV-positive cancer patients treated with ritonavir, and due to toxicities was recommended to be dosed at 37.5mg/day on a 4 week on/2 week off schedule in these patients (185). These results suggest that drug-drug interactions between sunitinib and ritonavir require dosing modifications for sunitinib. Should sunitinib, with key virus-associated targets and anti-inflammatory, cytokine-suppressive and antifibrotic potential, be considered for co-administration with a protease inhibitor like ritonavir for COVID-19, this established dosing regimen would need to be considered to control toxicity.

Table 4 shows the chemical structures and molecular weights of a panel of the most promising kinase inhibitors in terms of their pharmacokinetics, potential antiviral targets and anti-inflammatory, cytokine suppressive, or antifibrotic activity. Also included in Table 4 are those kinase inhibitors with potential to effectively synergize with other agents, including antiviral drugs.

## CONCLUSION

There are many factors to consider when repurposing approved drugs for a new indication, and identification of key protein targets that are potently inhibited offers an attractive option for a new therapeutic application. The urgency of need and constraints of time, however, which come with developing effective therapeutic approaches during a pandemic crisis can make it challenging to conduct well-controlled studies with data that definitively attribute efficacy to a drug. Numerous agents, which show promise based on preclinical studies and anecdotal data, are presently under clinical investigation as single agents or in combination with other therapies. Several kinase inhibitors are under clinical investigation for COVID-19 that target key virus-associated proteins as well as proteins that play a role in development of symptoms associated with COVID-19, including pneumonia, fibrosis and inflammation. For optimal drug repurposing, the pharmacokinetics of agents need to be taken into consideration. For instance, drugs that require long-term dosing to achieve optimal drug concentrations and anti-inflammatory effects, may not easily treat the symptoms of COVID-19 due to the immediacy of treatment requirement for afflicted patients. Similarly, adverse effects

associated with some kinase inhibitors also need to be considered and may present a challenge for treatment of some COVID-19 patients. However, short-term dosing may minimize these risks.

Roads less traveled might also be considered over time as an alternative to the current therapies being tested in COVID-19 clinical trials, such as the combination of IL-6 blocking agents (tocilizumab sarilumab) or antiviral therapies (ribavirin, ritonavir-lopinavir, remdesivir, niclosamide), with kinase inhibitors (imatinib, osimertinib, gilteritinib, abemaciclib, afatinib, sunitinib, sorafenib, erlotinib), or the direct combination of kinase inhibitors with each other that target relevant virus-associated proteins and proteins associated with pulmonary health (sunitinib and erlotinib, or afatinib and nintedanib). As historically drug combinations and cocktails have offered substantial clinical benefit in the context of other life-threatening diseases, such as AIDS caused by HIV, there is reason to believe the same approach with drugs shown to safely combine and that have provided some benefit on their own, warrants testing in the context of the current SARS-CoV-2 pandemic.

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