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(54) METHODS AND COMPOSITIONSFOR TREATING VIRAL INFECTIONS

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A61K 9/20	(2006.01)

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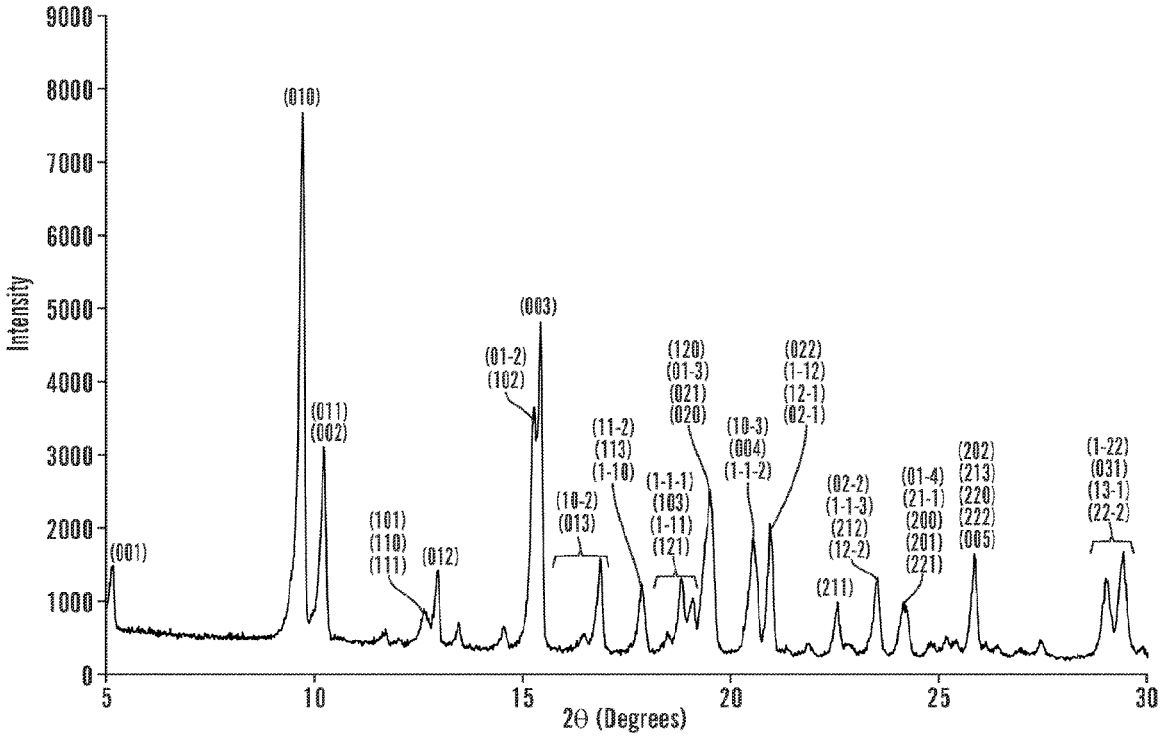
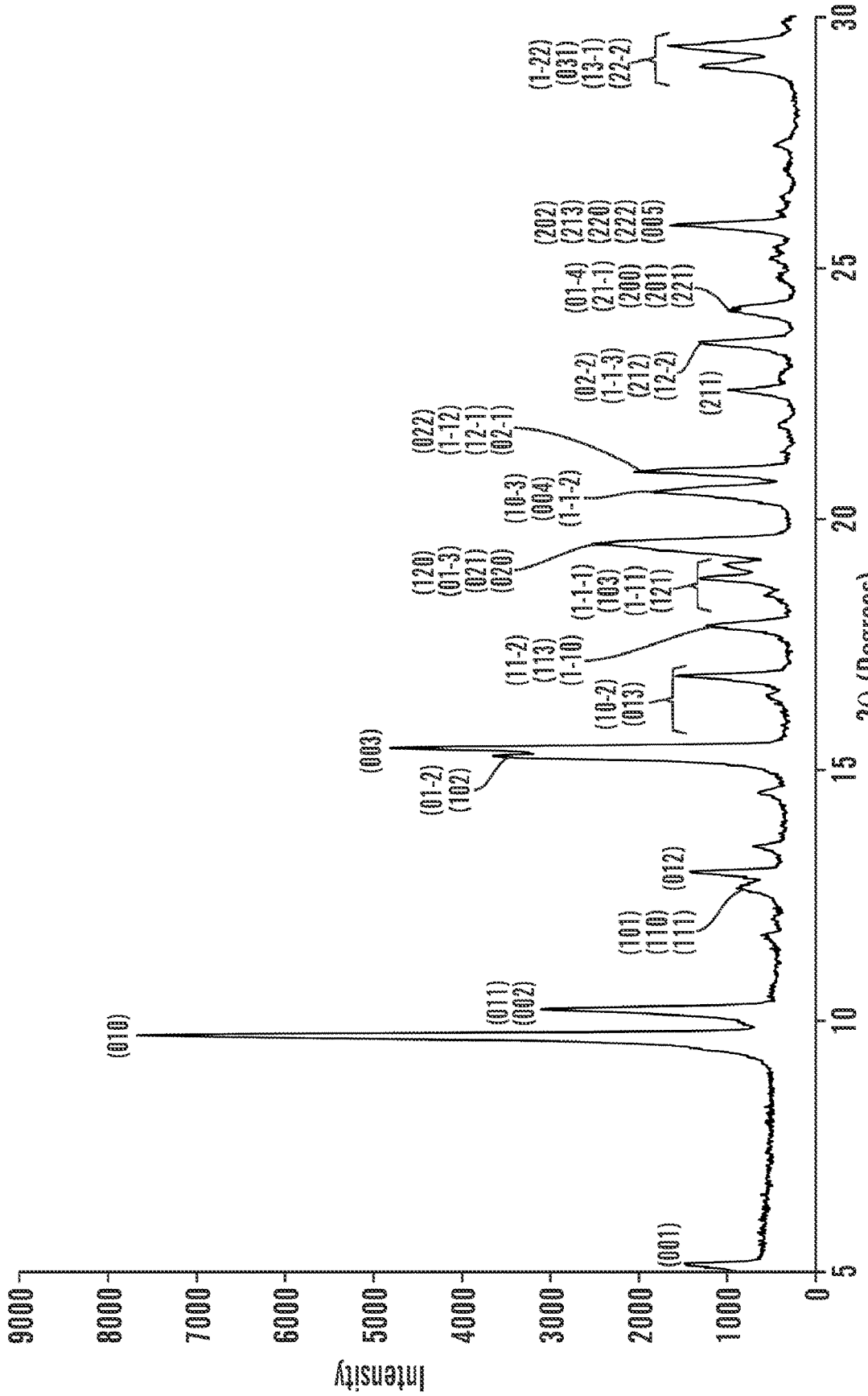
(57) **ABSTRACT**

Compositions and methods that may be useful for the treatment of a viral infection as well as for treating infection induced cytokine release syndrome (CRS) or acute respiratory distress syndrome (ARDS) are described herein. For example, pharmaceutical compositions containing Compound I as disclosed herein may be used to treat infection by a coronavirus, such as SARS-CoV-2 ("COVID-19").




Intensity
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
2Θ (Degrees)
(001)
(010)
(011)
(002)
(101)
(110)
(111)
(012)
(01-2)
(102)
(003)
(11-2)
(113)
(1-10)
(10-2)
(013)
(1-1-1)
(103)
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(212)
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(01-4)
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(201)
(221)
(202)
(213)
(220)
(222)
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(1-22)
(031)
(13-1)
(22-2)

FIG. 1

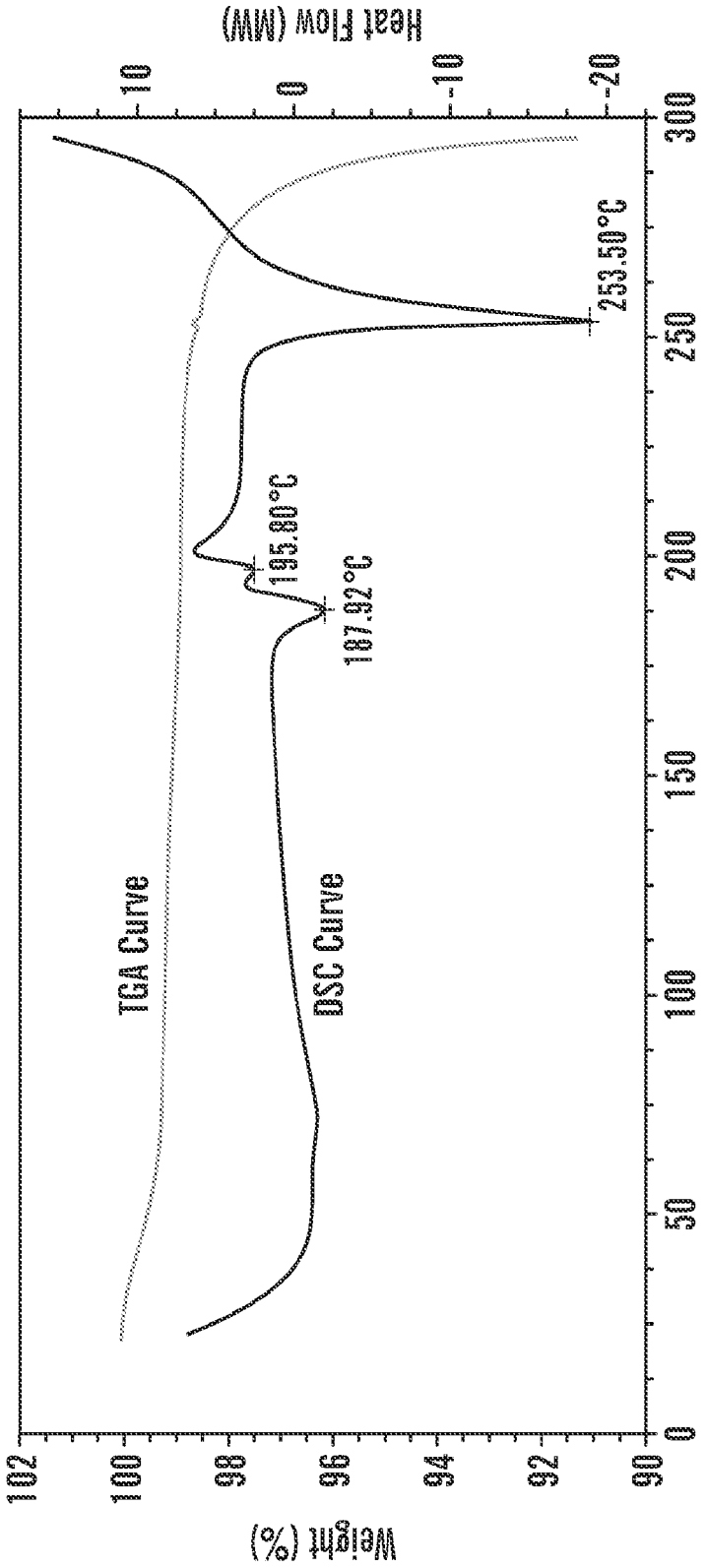

Heat Flow (MW)
10
0
-10
-20
300
250
200
150
100
50
0
Temperature (°C)
253.50°C
195.80°C
187.92°C
TGA Curve
DSC Curve
102
100
98
96
94
92
90
Weight (%)

FIG. 2

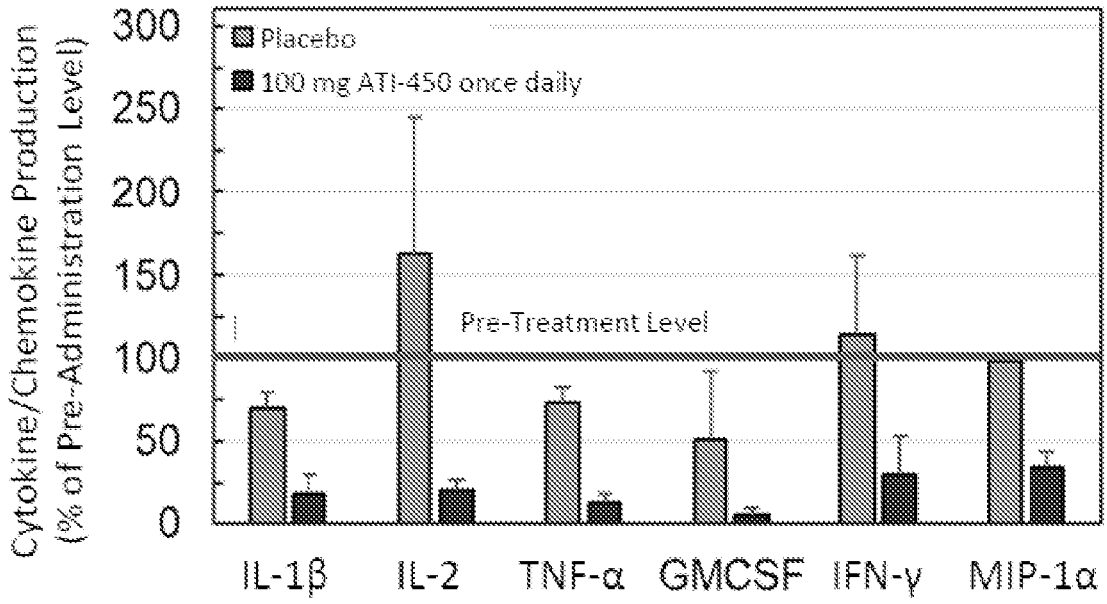

Cytokine/Chemokine Production
(% of Pre-Administration Level)
300
250
200
150
100
50
0
Placebo
100 mg ATI-450 once daily
Pre-Treatment Level
IL-1β
IL-2
TNF-α
GMCSF
IFN-γ
MIP-1α

FIG. 4A

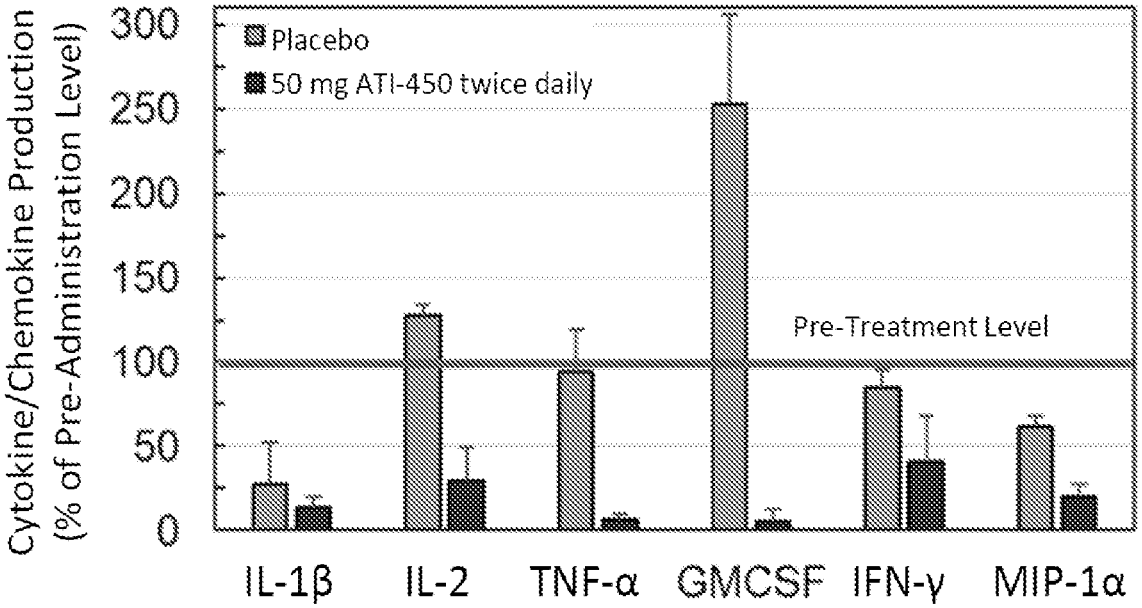

Cytokine/Chemokine Production
(% of Pre-Administration Level)
300
250
200
150
100
50
0
Placebo
50 mg ATI-450 twice daily
Pre-Treatment Level
IL-1β
IL-2
TNF-α
GMCSF
IFN-γ
MIP-1α

FIG. 4B

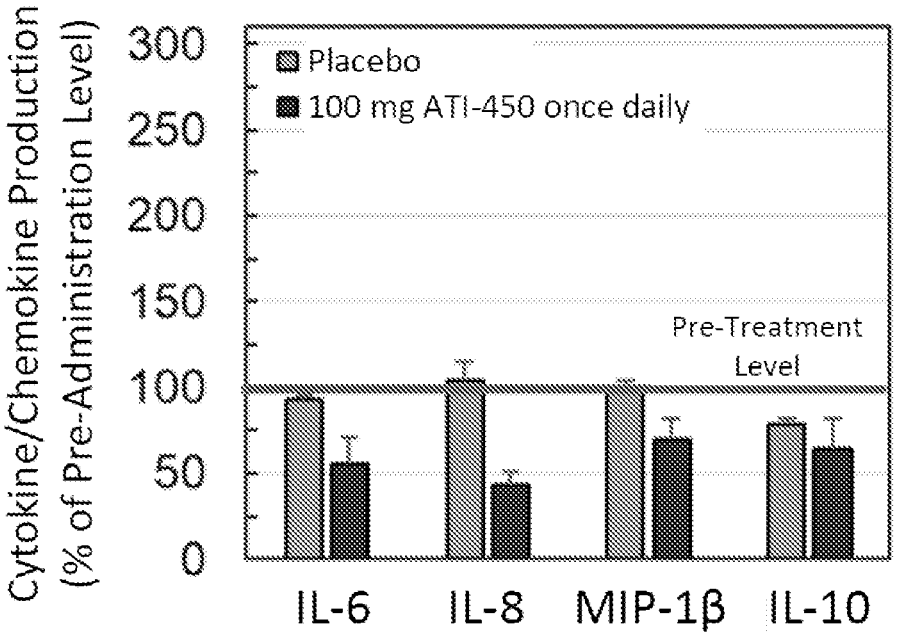

Cytokine/Chemokine Production
(% of Pre-Administration Level)
300
250
200
150
100
50
0
Placebo
100 mg ATI-450 once daily
Pre-Treatment
Level
IL-6
IL-8
MIP-1β
IL-10

FIG. 5A

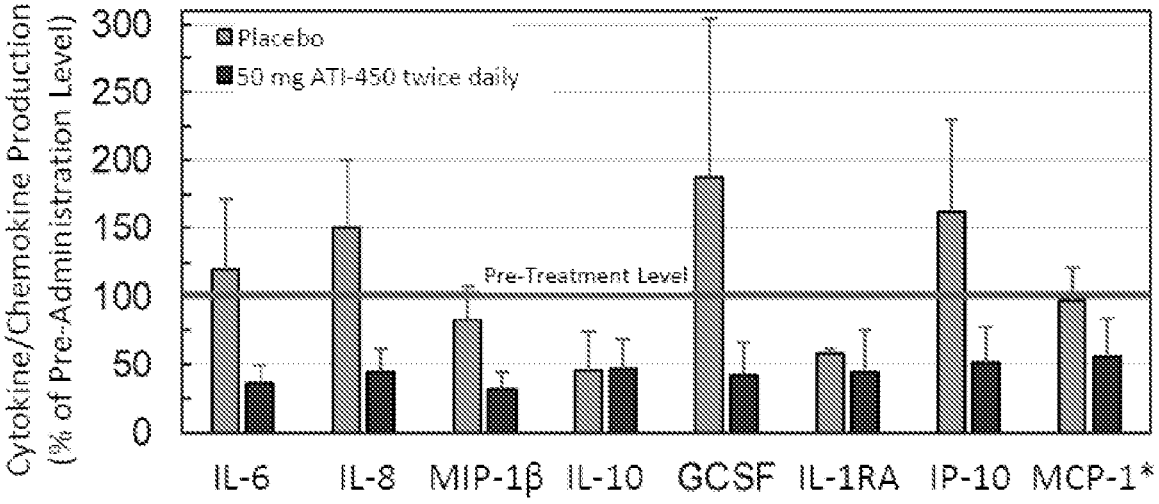

Cytokine/Chemokine Production
(% of Pre-Administration Level)
300
250
200
150
100
50
0
Placebo
50 mg ATI-450 twice daily
Pre-Treatment Level
IL-6
IL-8
MIP-1β
IL-10
GCSF
IL-1RA
IP-10
MCP-1*

FIG. 5B

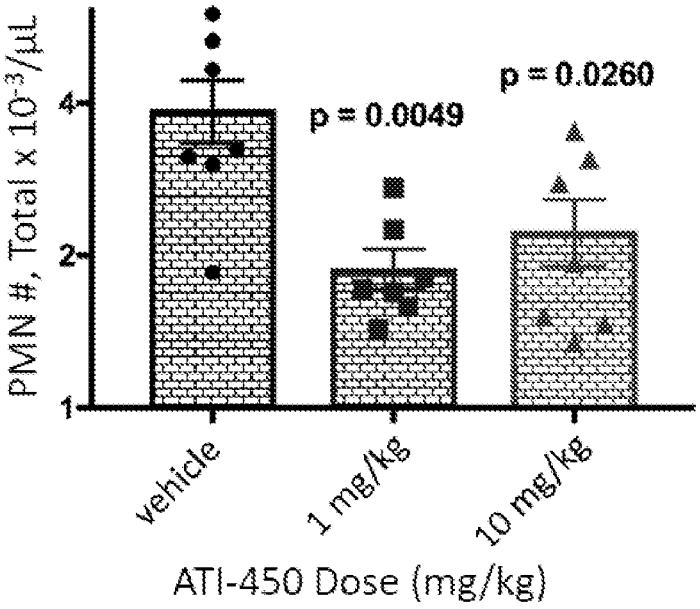

PMN #, Total x 10-3/µL
4
2
1
p = 0.0049
p = 0.0260
vehicle
1 mg/kg
10 mg/kg
ATI-450 Dose (mg/kg)

FIG. 6

METHODS AND COMPOSITIONSFOR TREATING VIRAL INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Ser. No. 63/000,746, filed on Mar. 27, 2020; Ser. No. 63/015,241, filed on Apr. 24, 2020; Ser. No. 63/018,954, filed on May 1, 2020; Ser. No. 63/022,301, filed on May 8, 2020; Ser. No. 63/022,298, filed on May 8, 2020; Ser. No. 63/024,160, filed on May 13, 2020; Ser. No. 63/053,903, filed on Jul. 20, 2020; Ser. No. 63/076,689, filed on Sep. 10, 2020; Ser. No. 63/126,173, filed on Dec. 16, 2020; Ser. No. 63/128,523, filed on Dec. 21, 2020; Ser. No. 63/136,080, filed on Jan. 11, 2021; Ser. No. 63/136,967, filed on Jan. 13, 2021; Ser. No. 63/138,672, filed on Jan. 18, 2021; Ser. No. 63/140,116, filed on Jan. 21, 2021; and Ser. No. 63/149,230, filed on Feb. 13, 2021, each of which is hereby incorporated by reference in its entirety.

FIELD

[0002] This application relates generally to compositions for treating viral infections and more particularly to methods for treating coronaviral infections and its related diseases and symptoms.

BACKGROUND

[0003] Coronaviruses are a large family of viruses that typically circulate among animals including camels, cats, and bats. Rarely, these viruses cross-over into a different species. However, one type, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), recently emerged as a coronavirus strain that was previously restricted to animals but has now jumped and has effectively infected and proliferated in humans. SARS-CoV-2 causes coronavirus disease 2019 ("COVID-19") in humans, where small droplets and aerosols containing the virus can spread from an infected person to another person in close contact. SARS-CoV-2 is closely related to SARS-CoV which emerged in 2002 and caused an outbreak of SARS. SARS was highly lethal but faded after intense public mitigation efforts. MERS-CoV emerged in 2012 as another highly lethal coronavirus causing MERS.

[0004] It has recently been demonstrated that the SARS-CoV-2 virus is a potent inducer of inflammatory cytokines and chemokines, such as IL-1β, IL-1RA, IL-2, IL-4, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF (Huang et al., Lancet, 395(10223):497-506 (2020)). The spectrum of clinical presentations of COVID-19 have ranged from asymptomatic infection to severe respiratory failure. The predominant symptoms of COVID-19 include fever, shortness of breath, fatigue, myalgia, cough, and loss of smell and/or taste. Pneumonia is present in most SARS-CoV-2 infected patients. Less common symptoms include sputum production, headache, hemoptysis, nausea, and diarrhea.

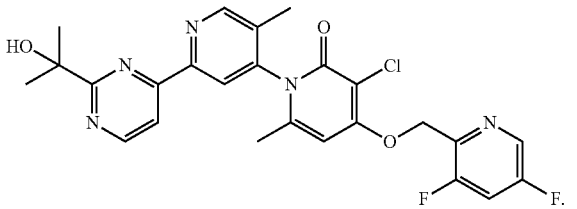
[0005] Respiratory failure from ARDS is the leading cause of mortality in COVID-19 patients. Cytokine storm syndrome has been implicated in a subgroup of patients with severe (and critical) COVID-19. Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyper inflammatory syndrome characterized by a severe and sudden onset of hypercytokinaemia resulting in multi-organ failure and eventual fatality. The cytokine profile of sHLH is characterized by elevated levels of IL-2, IL-7, GCSF, IFN-γ, IP-10, MCP-1, MIP-1α, and TNFα and is associated with COVID-19 disease severity. A recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China indicated that elevated ferritin and IL-6 are predictors of COVID-19 mortality, suggesting that the mortality might be due to SARS-CoV-2-driven hyper inflammation.

[0006] The SARS-CoV-2 virus and related COVID-19 disease represents a challenging and unique threat to public health. There exists a need for new and improved treatments and compositions for preventing and/or treating the SARS-CoV-2 infection and the resulting COVID-19 disease.

SUMMARY

[0007] One aspect of the disclosure is directed to a method of treating a viral infection in a subject in need thereof. The method comprises administering orally, to a subject having a viral infection, a therapeutically effective amount of Compound I or a derivative thereof to treat the viral infection

(I)



[0008] Another aspect of the disclosure is directed to a method of treating infection induced Cytokine Release Syndrome (CRS) or acute respiratory distress syndrome (ARDS) associated with viral infection in a subject. The method comprises administering orally, to a subject having an infection, a therapeutically effective amount of Compound I or a derivative thereof, thereby treating the CRS or ARDS.

[0009] Another aspect of the present disclosure is directed to a method of reducing at least one pro-inflammatory cytokine in the lungs of a subject following viral infection. The method comprises administering orally, to a subject having a viral infection, a therapeutically effective amount of Compound I or a derivative thereof, thereby reducing levels of at least on pro-inflammatory cytokine in the lungs of the subject.

[0010] As described herein the, recitation of "Compound I" throughout this disclosure is intended to encompasses atropisomer compounds (P)-I and (M)-I of Compound I as described herein, where compounds (P)-I and (M)-I are present in any molar ratio from 4:1 ((P)-I:(M)-I) to 999:1 or where Compound (P)-I is substantially free from Compound (M)-I, where Compounds (P)-I and (M)-I are in any form (e.g., free base, crystalline form, etc.) as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1** depicts a PXRD diffractogram obtained from a sample of crystalline form A of (P)-ATI-450.

[0012] FIG. **2** depicts a TGA curve (top curve) and DSC curve (bottom curve) obtained from a sample of crystalline for A of (P)-I.

[0013] FIG. **3** shows modulation of ex vivo lipopolysaccharide (LPS)-stimulated cytokine/chemokine production in whole blood samples from subjects administered ATI-450 (100 mg once daily or 50 mg twice daily). The data is shown as a percent of pre-administration blood level.

[0014] FIG. **4**A and FIG. **4**B illustrate a reduction of at least about 70% of LPS-stimulated GM-CSF, IFNγ, IL-2, and MIP-1α release in subjects administered 100 mg ATI-450 once daily (FIG. **4**A) and 50 mg ATI-450 twice daily (FIG. **4**B).

[0015] FIG. **5**A shows a reduction of LPS-stimulated IL-6, IL-8, and MIP-1β release in blood samples from subjects administered 100 mg ATI-450 once daily.

[0016] FIG. **5**B shows a reduction of LPS-stimulated IL-6, IL-8, MIP-1β, G-CSF, IL-1RA, IP-10, and MCP-1 levels in blood samples from subjects administered 50 mg ATI-450 twice daily. No significant reduction in the anti-inflammatory cytokine IL-1β or IL-1RA was not observed.

[0017] FIG. **6** provides data relating to the number of polymorphonuclear neutrophils (PMN) as an indicator of inflammatory response after administration of ATI-450 as compared to vehicle-treated animals.

DETAILED DESCRIPTION

Definitions

[0018] Before the present compositions and methods are described, it is to be understood that this invention is not limited to the particular processes, formulations, compositions, or methodologies described, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of embodiments herein which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments herein, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated by reference in their entirety. Nothing herein is to be construed as an admission that embodiments herein are not entitled to antedate such disclosure by virtue of prior invention.

[0019] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to a "MK2 inhibitor" is a reference to one or more MK2 inhibitors and equivalents thereof known to those skilled in the art, and so forth.

[0020] The transitional term "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, non-recited elements or method steps. By contrast, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. The compositions and methods of the present disclosure can comprise, consist essentially of, or consist of, the components or steps disclosed.

[0021] As used herein, the term "about" means plus or minus 10% of the numerical value of the number with which it is being used. Therefore, about 50% means in the range of 45%-55%.

[0022] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term "administering", when used in conjunction with a MK2 inhibitor compound, can include, but is not limited to, providing a MK2 inhibitor compound into or onto the target tissue; providing a MK2 inhibitor compound systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue.

[0023] As used herein, the term "a derivative thereof" refers to a salt thereof, a pharmaceutically acceptable salt thereof, an ester thereof, a free acid form thereof, a free base form thereof, a solvate thereof, a deuterated derivative thereof, a hydrate thereof, an N-oxide thereof, a clathrate thereof, a prodrug thereof, a polymorph thereof, a stereoisomer thereof, a geometric isomer thereof, a tautomer thereof, a mixture of tautomers thereof, an enantiomer thereof, a diastereomer thereof, a racemate thereof, a mixture of stereoisomers thereof, an isotope thereof (e.g., tritium, deuterium), or a combination thereof.

[0024] The term "substantially free" as used herein, alone or in combination, refers to the absence of isomers within the limits of detection of analytical methods such as nuclear magnetic resonance (NMR), gas chromatography/mass spectroscopy (GC/MS), high performance liquid chromatography (HPLC), or liquid chromatography/mass spectroscopy (LC/MS).

[0025] The term "condition" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder," "syndrome," and "disease", in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0026] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0027] "MK2 inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to mitogen-activated protein kinase-activated protein kinase 2 ("MK2") activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the MK2 enzyme assays. IC_{50} is the concentration of inhibitor which reduces the activity of an enzyme (e.g., MK2) to half-maximal level. Compounds disclosed herein have been discovered to exhibit inhibition against MK2. In some embodiments, the compounds will exhibit an IC_{50} with respect to MK2 of no

more than about 1 nM. In some embodiments, the compounds will exhibit an IC_{50} with respect to MK2 of no more than about 1 μM. In some embodiments, the compounds will exhibit an IC_{50} with respect to MK2 of about 1 μM to about 50 μM. In certain embodiments, compounds will exhibit an IC_{50} with respect to MK2 of no more than about 10 μM; in further embodiments, compounds will exhibit an IC_{50} with respect to MK2 of no more than about 5 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to MK2 of not more than about 1 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to MK2 of not more than about 300 nM, as measured in the MK2 assay described herein.

[0028] As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

[0029] Suitable pharmaceutically acceptable acid addition salts of the compounds of embodiments herein may be prepared from an inorganic acid or an organic acid. All of these salts may be prepared by conventional means from the corresponding compound of embodiments herein by treating, e.g., the compound with the appropriate acid or base.

[0030] Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, phosphoric and diphosphoric acid; and organic acids, for example formic, acetic, trifluoroacetic, propionic, succinic, glycolic, embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, malonic, galactic, galacturonic, citric, fumaric, gluconic, glutamic, lactic, maleic, malic, mandelic, mucic, ascorbic, oxalic, pantothenic, succinic, tartaric, benzoic, acetic, xinafoic (1-hydroxy-2-naphthoic acid), napadisilic (1,5-naphthalenedisulfonic acid) and the like.

[0031] Salts derived from pharmaceutically-acceptable inorganic bases suitable for the formulations as described herein include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including alkyl amines, arylalkyl amines, heterocyclyl amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, chloroprocaine, diethanolamine, N-methylglucamine, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[0032] Other preferred salts according to embodiments herein are quaternary ammonium compounds wherein an equivalent of an anion (X—) is associated with the positive charge of the N atom. X— may be an anion of various mineral acids (e.g., chloride, bromide, iodide, sulfate, nitrate, phosphate), or an anion of an organic acid (e.g., acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulfonate, p-toluenesulfonate). X— is preferably an anion selected from chloride, bromide, iodide, sulfate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X— is chloride, bromide, trifluoroacetate or methanesulfonate.

[0033] The compounds of embodiments herein may exist in both non-solvated and solvated forms. The term solvate is used herein to describe a molecular complex comprising a compound of embodiments herein and an amount of one or more pharmaceutically acceptable solvent molecules. The term hydrate is employed when said solvent is water. Examples of solvate forms include, but are not limited to, compounds of embodiments herein in association with water, acetone, dichloromethane, 2-propanol, ethanol, methanol, dimethyl sulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in embodiments herein one solvent molecule can be associated with one molecule of the compounds of embodiments herein, such as a hydrate.

[0034] In some embodiments herein one solvent molecule can be associated with one molecule of the compound described herein, such as a hydrate. In some embodiments, more than one solvent molecule may be associated with one molecule of the compound described herein, such as a dihydrate. Additionally, in some embodiments herein less than one solvent molecule may be associated with one molecule of the compound described herein, such as a hemihydrate. Furthermore, solvates of embodiments herein are contemplated as solvates of the compound described herein that retain the biological effectiveness of the non-solvate form of the compounds.

[0035] Embodiments herein also includes isotopically-labeled compounds of embodiments herein, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of embodiments herein include isotopes of hydrogen, such as ^{2}H and ^{3}H carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{31}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Certain isotopically-labeled compounds of embodiments herein, e.g., those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, ^{3}H, and carbon-14, ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, e.g., increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0036] Isotopically-labeled compounds of embodiments herein can generally be prepared by conventional techniques

known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[0037] Preferred isotopically-labeled compounds include deuterated derivatives of the compounds of embodiments herein. As used herein, the term deuterated derivative embraces compounds of embodiments herein where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium (D or ^{2}H) is a stable isotope of hydrogen which is present at a natural abundance of 0.015 molar %.

[0038] Hydrogen deuterium exchange (deuterium incorporation) is a chemical reaction in which a covalently bonded hydrogen atom is replaced by a deuterium atom. Said exchange (incorporation) reaction can be total or partial.

[0039] Typically, a deuterated derivative of a compound of embodiments herein has an isotopic enrichment factor (ratio between the isotopic abundance and the natural abundance of that isotope (the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen) for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 3500 (52.5% deuterium incorporation).

[0040] In some embodiments, the isotopic enrichment factor is at least 5000 (75% deuterium). In some embodiments, the isotopic enrichment factor is at least 6333.3 (95% deuterium incorporation). In some embodiments, the isotopic enrichment factor is at least 6633.3 (99.5% deuterium incorporation). It is understood that the isotopic enrichment factor of each deuterium present at a site designated as a site of deuteration is independent from the other deuteration sites.

[0041] The term "subject" as used herein and interchangeably with "patient", includes, but is not limited to, humans and non-human vertebrates such as wild, domestic, and farm animals. In certain embodiments, the subject described herein is an animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

[0042] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder or on the effecting of a clinical endpoint.

[0043] The term "therapeutically acceptable" refers to those compounds, and a derivative thereof, which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0044] The terms "treat," "treated," "treating", or "treatment" as used herein refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total, whether induction of or maintenance of), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. Treatment may also be preemptive in nature, i.e., it may include prevention of disease. Prevention of a disease may involve complete protection from disease, for example as in the case of prevention of infection with a pathogen, or may involve prevention of disease progression. For example, prevention of a disease may not mean complete foreclosure of any effect related to the diseases at any level, but instead may mean prevention of the symptoms of a disease to a clinically significant or detectable level. Prevention of diseases may also mean prevention of progression of a disease to a later stage of the disease and prolonging disease-free survival as compared to disease-free survival if not receiving treatment and prolonging disease-free survival as compared to disease-free survival if not receiving treatment.

[0045] Also provided are embodiments wherein any embodiment herein be combined with any one or more of these embodiments, provided the combination is not mutually exclusive.

[0046] Oral Compositions for Treating a Viral Infection

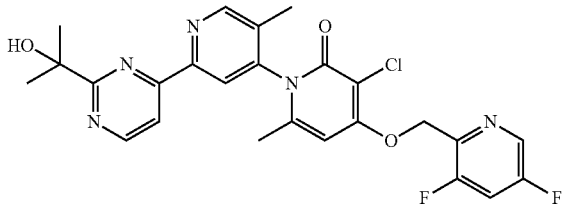
[0047] Embodiments herein are directed to oral pharmaceutical compositions that inhibit MK2 activity and methods of treatment that involve administering to a subject in need thereof an oral dose of the MK2 inhibitor compound. Some embodiments include methods for the treatment of viral infections in a subject by orally administering the MK2 inhibitor compound described herein. Some embodiments include methods for treating infection induced cytokine release syndrome or acute respiratory distress syndrome in a subject by orally administering the MK2 inhibitor compound described herein.

[0048] The oral compositions disclosed herein possess a specific MK2 inhibitor which prevents p38 MAP Kinase mediated inflammatory signaling, and thus, can be used in the treatment or prophylaxis of a viral infection in which p38 MAP Kinase signaling plays an active role. Thus, embodiments provide oral pharmaceutical compositions comprising the MK2 inhibitor disclosed herein together with a pharmaceutically acceptable carrier, as well as methods for using the compounds and compositions. Certain embodiments

provide methods for inhibiting p38 MAP kinase using compounds of embodiments herein. Also provided is the use of the specific MK2 inhibitor disclosed herein for use in the manufacture of a medicament for the treatment of a viral infection ameliorated by the inhibition of p38 MAP Kinase.

[0049] The oral pharmaceutical composition disclosed herein comprises a therapeutically effective amount of Compound (I) as shown below.

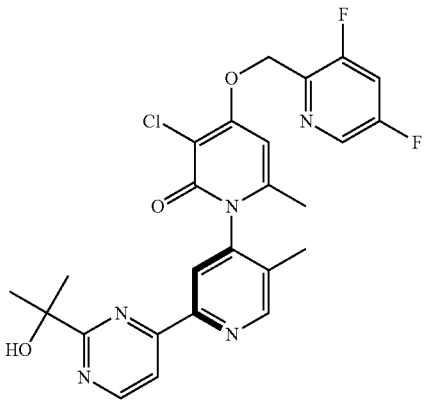
(I)



[0050] Compound I is chemically known as 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and may be prepared according to the methods described in U.S. Pat. No. 9,115,089, which is hereby incorporated by reference in its entirety. 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one is manufactured by and commercially available from Aclaris Therapeutics, Inc. (640 Lee Road, Suite 200, Wayne, Pa. 19087, USA).

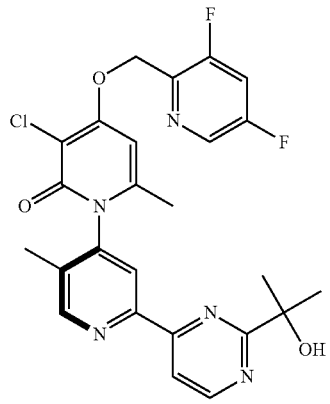
[0051] There are two atropisomers of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (Compound I), which are depicted below as Compounds (P)-I ((P)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one) and (M)-I (M)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one).

(*P*)-I



-continued

(*M*)-I



[0052] The term "atropisomerism" refers to a type of isomerism resulting from hindered rotation around a single bond due to steric strain of the substituents. This phenomenon creates stereoisomers which display axial chirality. Atropisomers may be separated (resolved) via supercritical fluid chromatography using a mobile phase of carbon dioxide and ethanol/methanol. As used throughout this disclosure, recitation of "Compound I" encompasses atropisomer compounds (P)-I and (M)-I as depicted above in any molar ratio from 4:1 ((P)-I:(M)-I) to 999:1 or Compound (P)-I substantially free from Compound (M)-I, where Compounds (P)-I and (M)-I are in any form (e.g., free base, crystalline form, etc.) as described herein.

[0053] In any embodiment, Compound I of the oral composition as disclosed herein comprises Compound (P)-I and Compound (M)-I in a molar ratio of about 4:1 ((P)-I:(M)-I) to about 999:1. In any embodiment, the molar ratio of (P)-I to (M)-I is about 4.3:1, about 4.6:1, about 4.9:1, about 5.25:1, about 5.7:1, about 6.1:1, about 6.7:1, about 7.3:1, about 8.1:1, about 9:1, about 10:1, about 11.5:1, about 13.3:1, about 15.7:1, about 19:1, about 24:1, about 32.3:1, about 49:1, about 91:1, about 110.1:1, about 124:1, about 141.9:1, about 165.7:1, about 199:1, about 249:1, about 332.3:1, about 399:1, about 499:1, and about 999:1. In a preferred embodiment, the molar ratio of (P)-I to (M)-I is about 399:1.

[0054] Said another way, Compound I of the oral composition as disclosed herein comprises at least 80 mol % of Compound (P)-I. In any embodiment the oral composition as disclosed herein comprises at least 81 mol % of Compound (P)-I, at least 82 mol % of Compound (P)-I, at least 83 mol % of Compound (P)-I, at least 84 mol % of Compound (P)-I, at least 85 mol % of Compound (P)-I, at least 86 mol % of Compound (P)-I, at least 87 mol % of Compound (P)-I, at least 88 mol % of Compound (P)-I, at least 89 mol % of Compound (P)-I, at least 90 mol % of Compound (P)-I, at least 91 mol % of Compound (P)-I, at least 92 mol % of Compound (P)-I, at least 93 mol % of Compound (P)-I, at least 94 mol % of Compound (P)-I, at least 95 mol % of Compound (P)-I, at least 96 mol % of Compound (P)-I, at least 97 mol % of Compound (P)-I, at least 98 mol % of Compound (P)-I, at least 99 mol % of Compound (P)-I, at least 99.1 mol % of Compound (P)-I, at least 99.2 mol % of Compound (P)-I, at least 99.3 mol % of Compound (P)-I, at least 99.4 mol % of Compound (P)-I, at least 99.5 mol % of Compound (P)-I, at least 99.6 mol % of

Compound (P)-I, at least 99.7 mol % of Compound (P)-I, at least 99.8 mol % of Compound (P)-I, at least 99.9 mol % of Compound (P)-I. In any embodiment the oral composition as disclosed herein comprises at least 99.75 mol % of Compound (P)-I. In a preferred embodiment the oral composition as disclosed herein comprises at least 99.75 mol % of Compound (P)-I. In any embodiment, Compound I of the oral composition as disclosed herein comprises Compound (P)-I substantially free from Compound (M)-I.

[0055] In any embodiment, the oral pharmaceutical composition disclosed herein comprises 10 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 40 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 50 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 60 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 80 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 100 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 120 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 160 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 200 mg of Compound I. In any embodiment, the oral pharmaceutical composition disclosed herein comprises 240 mg of Compound I.

[0056] In any embodiment, the oral pharmaceutical compositions described herein comprise Compound I in an amount of about 5 mg to about 200 mg. In any embodiment, Compound I is present in the pharmaceutical composition as described herein in an amount of about 5 mg to about 300 mg, about 7.5 mg to about 300 mg, about 10 mg to about 300 mg, about 12.5 mg to about 300 mg, about 15 mg to about 300 mg, about 17.5 mg to about 300 mg, about 20 mg to about 300 mg, about 22.5 mg to about 300 mg, about 25 mg to about 300 mg, about 27.5 mg to about 300 mg, about 30 mg to about 300 mg, about 32.5 mg to about 300 mg, about 35 mg to about 300 mg, about 37.5 mg to about 300 mg, about 40 mg to about 300 mg, about 42.5 mg to about 300 mg, about 45 mg to about 300 mg, about 47.5 mg to about 300 mg, about 50 mg to about 300 mg, about 50 mg to about 290 mg, about 50 mg to about 280 mg, about 50 mg to about 270 mg, about 50 mg to about 260 mg, about 50 mg to about 250 mg, about 50 mg to about 240 mg, about 50 mg to about 230 mg, about 50 mg to about 220 mg, about 50 mg to about 210 mg, about 50 mg to about 200 mg about 50 mg to about 190 mg, about 50 mg to about 180 mg, about 50 mg to about 170 mg, about 50 mg to about 160 mg, about 50 mg to about 150 mg, about 50 mg to about 140 mg, about 50 mg to about 130 mg, about 50 mg to about 120 mg, about 50 mg to about 110 mg, about 50 mg to about 100 mg, about 50 mg to about 90 mg, about 50 mg to about 80 mg, about 50 mg to about 70 mg, about 50 mg to about 60 mg, about 40 mg to about 50 mg, about 30 mg to about 60 mg, about 20 mg to about 70 mg, about 15 mg to about 80 mg, about 10 mg to about 90 mg, about 5 mg to about 100 mg, or any amount in between. In a preferred embodiment, the oral pharmaceutical compositions described herein comprise Compound I in an amount of about 50 mg to about 240 mg.

[0057] In any embodiment, Compound I is present in the pharmaceutical composition as described herein in an amount of about 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 42.5 mg, 45 mg, 47.5 mg, 50 mg, 52.5 mg, 55 mg, 57.5 mg, 60 mg, 62.5 mg, 65 mg, 67.5 mg, 70 mg, 72.5 mg, 75 mg, 77.5 mg, 80 mg, 82.5 mg, 85 mg, 87.5 mg, 90 mg, 92.5 mg, 95 mg, 97.5 mg, 100 mg, 105 mg, 107.5 mg, 110 mg, 112.5 mg, 115 mg, 117.5 mg, 120 mg, 122.5 mg, 125 mg, 127.5 mg, 130 mg, 132.5 mg, 135 mg, 137.5 mg, 140 mg, 142.5 mg, 145 mg, 147.5 mg, 150 mg, 152.5 mg, 155 mg, 157.5 mg, 160 mg, 162.5 mg, 165 mg, 167.5 mg, 170 mg, 172.5 mg, 175 mg, 177.5 mg, 180 mg, 182.5 mg, 185 mg, 187.5 mg, 190 mg, 192.5 mg, 195 mg, 197.5 mg, 200 mg, 200 mg, 205 mg, 207.5 mg, 210 mg, 212.5 mg, 215 mg, 217.5 mg, 220 mg, 222.5 mg, 225 mg, 227.5 mg, 230 mg, 232.5 mg, 235 mg, 237.5 mg, 240 mg, 242.5 mg, 245 mg, 247.5 mg, 250 mg, 252.5 mg, 255 mg, 257.5 mg, 260 mg, 262.5 mg, 265 mg, 267.5 mg, 270 mg, 272.5 mg, 275 mg, 277.5 mg, 280 mg, 282.5 mg, 285 mg, 287.5 mg, 290 mg, 292.5 mg, 295 mg, 297.5 mg, or 300 mg. In preferred embodiments, Compound I is present in the pharmaceutical composition as described herein in an amount of 50 mg, 80 mg, 100 mg, 120 mg, 160 mg, or 240 mg.

[0058] In any embodiment, Compound I of the oral composition as disclosed herein comprises a free base. In any embodiment, Compound I of the oral composition as disclosed herein comprises a pharmaceutically acceptable salt.

[0059] In any embodiment, Compound I of the oral composition comprises Compound (P)-I and Compound (M)-I as disclosed herein in the free base form. In any embodiment, Compound I of the oral composition comprises Compound (P)-I and Compound (M)-I as disclosed herein in form of pharmaceutically acceptable salts, as described supra.

[0060] In any embodiment, Compound I of the oral compositions is a non-solvated form or in a solvated form. In any embodiment herein one solvent molecule can be associated with one molecule of Compound I described herein, such as a hydrate. In some embodiments, more than one solvent molecule may be associated with one molecule of Compound I as described herein, such as a dihydrate. Additionally, in some embodiments herein less than one solvent molecule may be associated with one molecule of Compound I described herein, such as a hemihydrate. Furthermore, solvates of embodiments herein are contemplated as solvates of Compound I as described herein that retain the biological effectiveness of the non-solvate form of Compound I.

[0061] In any embodiment, Compound 1 of the oral composition is a deuterated derivative. As used herein, the term deuterated derivative embraces compounds of embodiments herein where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium (D or ^{2}H) is a stable isotope of hydrogen which is present at a natural abundance of 0.015 molar %.

[0062] In any embodiment, Compound I of the oral composition as disclosed herein comprises Compound (P)-I (free base) in a crystalline form. In any embodiment, the crystalline form of Compound (P)-I is crystalline Form A as disclosed and characterized herein.

[0063] Compound I or a derivative thereof may be used according to the methods herein in any crystalline or amorphous form. Crystalline forms may be characterized by one or more of powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis

(TGA), Raman spectroscopy, infrared (IR) spectroscopy, solid-state NMR, and the like.

[0064] For example, the crystalline form A of Compound (P)-I of the oral composition may be characterized by its PXRD pattern. Thus, in any embodiment, the crystalline Form A of Compound (P)-I is characterized by an PXRD pattern having a peak expressed in degrees 2θ at about 9.78±0.2. In any embodiment, the crystalline Form A of Compound (P)-I is characterized by an PXRD pattern having peaks expressed in degrees 2θ at 9.78±0.2 and 15.51±0.2. In any embodiment, the crystalline Form A of Compound (P)-I is characterized by an PXRD pattern having peaks expressed in degrees 2θ at 9.78±0.2, 15.51±0.2, 19.6±0.2, and 25.92±0.2. In any embodiment, the crystalline Form A of Compound (P)-I is characterized by an PXRD pattern having peaks expressed in degrees 2θ at 9.78±0.2, 15.34±0.2, 15.51±0.2, 19.6±0.2, 20.57±0.2, 21.01±0.2, 25.92±0.2, 29.05±0.2, and 29.48±0.2. Alternatively, crystalline form A of (P)-I may be characterized by a PXRD pattern shown in FIG. **1**. The diffractogram of FIG. **1** was acquired on a PANalytical X'Pert Pro diffractometer using Ni-filtered Cu Ka (45 kV/40 mA) radiation and a step size of 0.02° 2θ and X'celerator™ RTMS (Real Time Multi-Strip) detector. Configuration on the incidental beam side: fixed divergence slit (0.25°), 0.04 rad Soller slits, anti-scatter slit (0.25°), and 10 mm beam mask. Configuration on the diffracted beam side: fixed divergence slit (0.25°) and 0.04 rad Soller slit. Samples were mounted flat on zero-background Si wafers.

[0065] Crystalline form A of (P)-I may be additionally or alternatively characterized by thermogravimetric analysis (TGA). For the purposes of characterization herein, TGA curves were obtained with a TA Instruments Q500 thermogravimetric analyzer under 40 mL/min N_2 purge at 15° C./min in Pt or Al pans. Samples of crystalline form A of (P)-I yielded a TGA curve corresponding substantially to the representative TGA curves (top curve) as depicted in FIG. **2**. FIG. **2** reveals that, in the sample analyzed, negligible weight loss was observed. Weight loss (0.7%) is observed between 25° C. and 256° C. by TGA for freebase crystalline form A of (P)-I, suggesting that crystalline form A of (P)-I is substantially anhydrous.

[0066] The crystalline form A of (P)-I may additionally or alternatively be characterized by differential scanning calorimetry (DSC). Thus, in any embodiment, the crystalline Form A of Compound (P)-I is characterized by a DSC plot (see FIG. **2**) comprising an initial endothermic melting event with an onset temperature of about 188° C., followed by an exothermic recrystallization event at about 196° C., with a final sharp endothermic melting event at about 254° C. For the purposes of characterization herein, DSC analyses were conducted with a TA Instruments Q100 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N_2 purge. DSC thermograms were obtained at 15° C./min in crimped Al pans.

[0067] In any embodiment, the oral composition of the present disclosure comprises Compound I as disclosed herein formulated by admixture with a pharmaceutically acceptable carrier or excipient. In certain embodiments, the pharmaceutical compositions include the therapeutically effective amount of Compound I and a physiologically acceptable diluent or carrier. In certain embodiments, the pharmaceutical composition further includes one or more additional therapeutic components and/or adjuvants.

[0068] In any embodiment, the oral compositions disclosed herein may further comprise pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for preparation and administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, Banker, G. S., & Rhodes, C. T. (2002). *Modern pharmaceutics*. New York: Marcel Dekker.; and Goodman, L. S., Brunton, L. L., Chabner, B., & Knollmann, B. C. (2011). *Goodman & Gilman's pharmacological basis of therapeutics*. New York: McGraw-Hill. can be consulted.

[0069] Methods of Treatment

[0070] Another aspect of the present disclosure relates a method for treating a viral infection in a subject in need thereof. This method comprises orally administering, to a human subject having a viral infection, an oral dose of Compound I, i.e., Compound (P)-I and (M)-I in any molar ratio as described supra and in any form (e.g., free form, crystalline form) as described supra, in an amount that is therapeutically effective to treat the infection.

[0071] Viral infections suitable for treatment in accordance with the methods disclosed herein include any infection caused by or associated with a double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), double-stranded genomic RNA (dsRNA), single-strand positive RNA, and single-strand negative RNA virus. In any embodiment, the viral infection is an infection that causes or is associated with an excessive or uncontrolled release of proinflammatory cytokines (i.e., a cytokine storm). Exemplary viral infections to be treated in accordance with the methods described herein include, without limitation, infection by influenza (e.g., H1N1, H5N1), parainfluenza, paramyxovirus, adenovirus, parvovirus, enterovirus, variola virus, rotavirus, hemorrhagic fever viruses (viruses in the families of Arenaviridae, Bunyaviridae, Filoviridae, Falviviridae, and Togaviridae) hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus (herpes virus), and coronavirus (SARS-CoV, SARS-CoV-2, MERS-CoV).

[0072] In any embodiment, the viral infection to be treated in accordance with the methods and compositions described herein is a coronavirus. These include both human coronaviridae virus (e.g., SARS-CoV-2, SARS-CoV, MERs-CoV, HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1) and animal coronaviridae viruses (e.g., Feline CoV [serotypes I and II], porcine epidemic diarrhea CoV (PEDV), porcine PRCV, porcine TGEV, Dog CCOC, Rabbit RaCoV, etc.). In any embodiment, the viral infection is a SARS-associated coronavirus. In any embodiment, the viral infection is SARS-CoV-2 or a variant thereof.

[0073] In any embodiment, the viral infection to be treated in accordance with the methods and compositions described herein is influenza, e.g., influenza virus A, influenza virus B, influenza virus C, or influenza virus D. In any embodiment, the viral infection to be treated is influenza virus A (e.g., H1N1, H5N1, H3N2).

[0074] Another aspect of the present disclosure relates a method for treating infection induced cytokine release syndrome (CRS) or acute respiratory distress syndrome (ARDS) in a subject. This method involves administering, to a human subject having an infection, an oral dose of Compound I (i.e., Compound (P)-I and (M)-I in any molar

ratio as described supra and in any form (e.g., free form, crystalline form) as described supra, in an amount that is therapeutically effective to treat the infection induced CRS or acute respiratory distress syndrome ARDS.

[0075] CRS is a systemic inflammatory response that can be triggered by a variety of factors, including infections. An immediate onset of the inflammatory response, e.g., in response to infection, is often referred to a cytokine storm. CRS or cytokine storm involves the excessive or uncontrolled release of proinflammatory cytokines, including interferons, interleukins, chemokines, colony stimulating factors (CSFs), and tumor necrosis factor. Inflammation associated with CRS typically begins at a local site and spreads throughout the body via systemic circulation. Infection induced CRS, especially viral or bacterial induced CRS in the lung alveolar environment or in systemic circulation often leads to acute lung injury. Acute lung injury is characterized by acute mononuclear/neutrophilic inflammatory response followed by a chronic fibroproliferative phase marked by progressive collagen deposition in the lung. Acute respiratory distress syndrome (ARDS) is a severe form of acute lung injury associated with pathogen infection

[0076] In any embodiment, the methods of the present disclosure are suitable for treating CRS or ARDS associated with a viral infection, where the viral infection is caused by influenza (e.g., H1N1, H5N1), parainfluenza, paramyxovirus, adenovirus, parvovirus, enterovirus, variola virus, rotavirus, hemorrhagic fever viruses (viruses in the families of Arenaviridae, Bunyaviridae, Filoviridae, Falviviridae, and Togaviridae) hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus (herpes virus), and coronavirus (SARS-CoV, SARS-CoV-2, MERS-CoV).

[0077] In any embodiment, the methods of the present disclosure are suitable for treating CRS or ARDS associated with a bacterial (e.g., streptococcal infection, pneumonia), fungal, or parasitic infection.

[0078] As described supra, the oral composition suitable for administration to a subject in accordance with the methods described herein comprises a therapeutically effective amount of Compound I (i.e., in a molar ratio of Compound (P)-I: Compound (M)-I) of 4:1 to 999:1, in any form as described herein) or an oral pharmaceutical composition comprising the same.

[0079] The specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the viral infection being treated.

[0080] In some embodiments, administration of a therapeutically effective amount of Compound I or an oral composition comprising the same is effective to cause at least partial remission of the symptoms that characterize the viral infection. In some embodiments, administration of a therapeutically effective amount of Compound I or an oral composition comprising the same is effective to cause full remission of the symptoms that characterize the viral infection. Such treatment is effective to inhibit progression of one or more of respiratory distress, low blood oxygen levels, and inflammatory response

[0081] In any embodiment, administration of a therapeutically effective amount of Compound I or an oral composition comprising the same is effective to cause inhibition of p38 MAP kinase-mediated inflammatory signaling. In any embodiments, administration of a therapeutically effective amount of Compound I or an oral composition comprising the same is effective to cause inhibition of MK2 inflammatory signaling. In particular, administration of a therapeutically effective amount of Compound I or an oral composition comprising the same is effective to cause a reduction in the in vivo serum levels of one or more inflammatory cytokines, including, but not limited to TNF-α, IL-1β, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-1α, and IL-1RA as compared to the in vivo serum levels of the corresponding cytokines prior to treatment the composition described herein.

[0082] In any embodiment, the oral compositions of embodiments herein may be administered at a first dose to prevent progression, at a second dose to induce remission, and/or a third dose to prevent the disease and/or maintain remission of the disease. Such doses may be the same dose, a lower dose, or a higher dose. The dose may be administered more frequently, less frequently or at the same frequency. In some embodiments, the dose may be administered in combination with another therapy, a therapeutic, an adjuvant, or the like.

[0083] In any embodiment, a subject can be any mammal or non-mammal. Examples of subjects include a primate, a human, a dog, a cat, a mouse, a rat, a cow, a horse, and a pig. In various embodiments, the subject is a human. The terms "subject," "individual" or "patient" are used interchangeably herein and include human and non-human animals. Non-human animals include all vertebrates, for example, mammals and non-mammals, such as non-human primates, sheep, dogs, rats, cats, cows, horses, chickens, amphibians, and reptiles. Examples of mammals include non-human primates, sheep, dogs, cats, cows, and horses. The various methods of treating a viral infection comprising administering to a subject a therapeutically effective amount of Compound I, as disclosed herein, are suitable for treating humans having a viral infection or disease and may be symptomatic or asymptomatic.

[0084] Dosing Regimen

[0085] Compound I, i.e., Compound (P)-I and (M)-I in any molar ratio as described supra and in any form (e.g., free form, crystalline form) as described supra, or an oral pharmaceutical composition comprising the same is administered in an amount effective to treat a viral infection or infection induced CRS or ARDS in a subject in need thereof. Subjects in need of such therapy are disclosed above. In some embodiments, the subject is one infected with a coronavirus, e.g., SARS-CoV and SARS-CoV-2. In accordance with the methods disclosed herein, a therapeutically effective amount comprises 5 mg/day to 300 mg/day of Compound I. The dosage to be administered to a particular subject will depend on the characteristics of the subject being treated, e.g., the particular subject treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician).

[0086] In any embodiment, 10 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 40 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 50 mg/day of Compound I is administered to the subject to a subject with an infection. In any embodiment, 60 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 80 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 100 mg/day of Compound I is administered to a subject with an infection.

In any embodiment, 120 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 160 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 200 mg/day of Compound I is administered to a subject with an infection. In any embodiment, 240 mg/day of Compound I is administered to a subject with an infection.

[0087] In any embodiment, the therapeutically effective amount of Compound I is 5 mg/day to 300 mg/day, about 7.5 mg/day to about mg/day, about 10 mg/day to about 300 mg/day, about 12.5 mg/day to about 300 mg/day, about 15 mg/day to about 300 mg/day, about 17.5 mg/day to about 300 mg/day, about 20 mg/day to about 300 mg/day, about 22.5 mg/day to about 300 mg/day, about 25 mg/day to about 300 mg/day, about 27.5 mg/day to about 300 mg/day, about 30 mg/day to about 300 mg/day, about 32.5 mg/day to about 300 mg/day, about 35 mg/day to about 300 mg/day, about 37.5 mg/day to about 300 mg/day, about 40 mg/day to about 300 mg/day, about 42.5 mg/day to about 300 mg/day, about 45 mg/day to about 300 mg/day, about 47.5 mg/day to about 300 mg/day, about 50 mg/day to about 300 mg/day, about 50 mg/day to about 290 mg/day, about 50 mg/day to about 280 mg/day, about 50 mg/day to about 270 mg/day, about 50 mg/day to about 260 mg/day, about 50 mg/day to about 250 mg/day, about 50 mg/day to about 240 mg/day, about 50 mg/day to about 230 mg/day, about 50 mg/day to about 220 mg/day, about 50 mg/day to about 210 mg/day, about 50 mg/day to about 200 mg/day, about 50 mg/day to about 190 mg/day, about 50 mg/day to about 180 mg/day, about 50 mg/day to about 170 mg/day, about 50 mg/day to about 160 mg/day, about 50 mg/day to about 150 mg/day, about 50 mg/day to about 140 mg/day, about 50 mg/day to about 130 mg/day, about 50 mg/day to about 120 mg/day, about 50 mg/day to about 110 mg/day, about 50 mg/day to about 100 mg/day, about 50 mg/day to about 90 mg/day, about 50 mg/day to about 80 mg/day, about 50 mg/day to about 70 mg/day, about 50 mg/day to about 60 mg/day, about 40 mg/day to about 50 mg/day, about 30 mg/day to about 60 mg/day, about 20 mg/day to about 70 mg/day, about 15 mg/day to about 80 mg/day, about 10 mg/day to about 90 mg/day, about 5 mg/day to about 100 mg/day, or any amount in between. In a preferred embodiment the therapeutically effective amount of Compound I is about 100 mg/day to about 240 mg/day.

[0088] In any embodiment the therapeutically effective amount of Compound I comprises 5 mg/day, 7.5 mg/day, 10 mg/day, 12.5 mg/day, 15 mg/day 17.5 mg/day, 20 mg/day, 22.5 mg/day, 25 mg/day, 27.5 mg/day, 30 mg/day, 32.5 mg/day, 35 mg/day, 37.5 mg/day, 40 mg/day, 42.5 mg/day, 45 mg/day, 47.5 mg/day, 50 mg/day, 52.5 mg/day, 55 mg/day, 57.5 mg/day, 60 mg/day, 62.5 mg/day, 65 mg/day, 67.5 mg/day, 70 mg/day, 72.5 mg/day, 75 mg/day, 77.5 mg/day, 80 mg/day, 82.5 mg/day, 85 mg/day, 87.5 mg/day, 90 mg/day, 92.5 mg/day, 95 mg/day, 97.5 mg/day, 100 mg/day, 105 mg/day, 107.5 mg/day, 110 mg/day, 112.5 mg/day, 115 mg/day, 117.5 mg/day, 120 mg/day, 122.5 mg/day, 125 mg/day, 127.5 mg/day, 130 mg/day, 132.5 mg/day, 135 mg/day, 137.5 mg/day, 140 mg/day, 142.5 mg/day, 145 mg/day, 147.5 mg/day, 150 mg/day, 152.5 mg/day, 155 mg/day 157.5 mg/day, 160 mg/day, 162.5 mg/day, 165 mg/day, 167.5 mg/day, 170 mg/day, 172.5 mg/day, 175 mg/day, 177.5 mg/day, 180 mg/day, 182.5 mg/day, 185 mg/day, 187.5 mg/day, 190 mg/day, 192.5 mg/day, 195 mg/day, 197.5 mg/day, 200 mg/day, 205 mg/day, 207.5 mg/day, 210 mg/day, 212.5 mg/day, 215 mg/day, 217.5 mg/day, 220 mg/day, 222.5 mg/day, 225 mg/day, 227.5 mg/day, 230 mg/day, 232.5 mg/day, 235 mg/day, 237.5 mg/day, 240 mg/day, 242.5 mg/day, 245 mg/day, 247.5 mg/day, 250 mg/day, 252.5 mg/day, 255 mg/day 257.5 mg/day, 260 mg/day, 262.5 mg/day, 265 mg/day, 267.5 mg/day, 270 mg/day, 272.5 mg/day, 275 mg/day, 277.5 mg/day, 280 mg/day, 282.5 mg/day, 285 mg/day, 287.5 mg/day, 290 mg/day, 292.5 mg/day, 295 mg/day, 297.5 mg/day, or 300 mg/day. In preferred embodiments, the therapeutically effective amount of Compound I comprises 100 mg/day, 160 mg/day, or 240 mg/day.

[0089] In any embodiment, the oral dose of Compound I that is administered to the subject in accordance with the methods disclosed herein comprises Compound (P)-I and Compound (M)-I in a molar ratio of about 4:1 ((P)-I:(M)-I). In any embodiment, the molar ratio of (P)-I to (M)-I is about 4.3:1, about 4.6:1, about 4.9:1, about 5.25:1, about 5.7:1, about 6.1:1, about 6.7:1, about 7.3:1, about 8.1:1, about 9:1, about 10:1, about 11.5:1, about 13.3:1, about 15.7:1, about 19:1, about 24:1, about 32.3:1, about 49:1, about 91:1, about 110.1:1, about 124:1, about 141.9:1, about 165.7:1, about 199:1, about 249:1, about 332.3:1, about 399:1, about 499:1, and about 999:1. In any embodiment, the molar ratio of (P)-I to (M)-I is about 399:1.

[0090] In any embodiment, the oral dose of Compound I that is administered to the subject in accordance with the methods disclosed herein comprises Compound (P)-I substantially free from Compound (M)-I.

[0091] In any embodiment, the oral dose of Compound I that is administered to the subject in accordance with the methods disclosed herein comprises at least 80 mol % of Compound (P)-I. In any embodiment the oral composition as disclosed herein comprises at least 81 mol % of Compound (P)-I, at least 82 mol % of Compound (P)-I, at least 83 mol % of Compound (P)-I, at least 84 mol % of Compound (P)-I, at least 85 mol % of Compound (P)-I, at least 86 mol % of Compound (P)-I, at least 87 mol % of Compound (P)-I, at least 88 mol % of Compound (P)-I, at least 89 mol % of Compound (P)-I, at least 90 mol % of Compound (P)-I, at least 91 mol % of Compound (P)-I, at least 92 mol % of Compound (P)-I, at least 93 mol % of Compound (P)-I, at least 94 mol % of Compound (P)-I, at least 95 mol % of Compound (P)-I, at least 96 mol % of Compound (P)-I, at least 97 mol % of Compound (P)-I, at least 98 mol % of Compound (P)-I, at least 99 mol % of Compound (P)-I, at least 99.1 mol % of Compound (P)-I, at least 99.2 mol % of Compound (P)-I, at least 99.3 mol % of Compound (P)-I, at least 99.4 mol % of Compound (P)-I, at least 99.5 mol % of Compound (P)-I, at least 99.6 mol % of Compound (P)-I, at least 99.7 mol % of Compound (P)-I, at least 99.8 mol % of Compound (P)-I, at least 99.9 mol % of Compound (P)-I. In any embodiment the oral composition as disclosed herein comprises at least 99.75 mol % of Compound (P)-I.

[0092] In any embodiment, a subject having a viral infection is administered orally 5 mg/day to 300 mg/day of Compound I. In some embodiments, the subject having a viral infection is administered an oral composition comprising Compound I once a day. In some embodiments, the subject having a viral infection is administered a composition comprising Compound I twice a day. In some embodiments, the subject having a viral infection is administered an

oral composition comprising 10 mg, 30 mg, 50 mg, 80 mg, 100 mg, 120 mg, 160 mg, 200 mg, or 240 mg of Compound I once daily.

[0093] In any embodiment, a subject having a viral infection is administered orally 5 mg/day to 300 mg/day of Compound I. In some embodiments, the subject having a coronaviral infection is administered an oral composition comprising Compound I once a day. In some embodiments, the subject having a coronaviral infection is administered a composition comprising Compound I twice a day. In some embodiments, the subject having a coronaviral infection is administered an oral composition comprising 10 mg, 30 mg, 50 mg, 80 mg, 100 mg, 120 mg, 160 mg, 200 mg, or 240 mg of Compound I once daily.

[0094] In any embodiment, a subject having a viral infection is administered orally 5 mg/day to 300 mg/day of Compound I. In some embodiments, the subject having a SARS-CoV infection is administered an oral composition comprising Compound I once a day. In some embodiments, the subject having a SARS-CoV infection is administered a composition comprising Compound I twice a day. In some embodiments, the subject having a SARS-CoV infection is administered an oral composition comprising 10 mg, 30 mg, 50 mg, 80 mg, 100 mg, 120 mg, 160 mg, 200 mg, or 240 mg of Compound I once daily.

[0095] In any embodiment, a subject having infection induced CRS or ARDS is administered orally 5 mg/day to 300 mg/day of Compound I. In some embodiments, the subject having an infection induced CRS or ARDS is administered an oral composition comprising Compound I once a day. In some embodiments, the subject having a corona virus infection is administered a composition comprising Compound I twice a day. In some embodiments, the subject having a corona virus infection is administered an oral composition comprising 10 mg, 30 mg, 50 mg, 80 mg, 100 mg, 120 mg, 160 mg, 200 mg, or 240 mg of Compound I once daily.

[0096] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 100 mg of Compound I once daily.

[0097] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 160 mg of Compound I once daily.

[0098] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 200 mg of Compound I once daily.

[0099] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 240 mg of Compound I once daily.

[0100] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 50 mg of Compound I twice daily.

[0101] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 80 mg of Compound I twice daily.

[0102] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 100 mg of Compound I twice daily.

[0103] In any embodiment, the subject having a viral infection or infection induced CRS or ARDS is administered an oral composition comprising 120 mg of Compound I twice daily.

[0104] The dosage administered is a therapeutically effective amount of the composition sufficient to result in amelioration of a symptom or symptoms, and can vary depending upon known factors such as the pharmacodynamic characteristics of the active ingredient and its mode of administration; age, sex, health and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment and the effect desired.

[0105] In some embodiments, the oral composition of embodiments herein can be administered to the subject once (e.g., as a single dose or application). In some embodiments, the oral composition of embodiments herein is administered at least once daily, such as at least two, three or four times daily. In some embodiments, the oral composition of embodiments herein may be administered daily, twice daily, three times daily, weekly, twice weekly, every two weeks, every three weeks, monthly, as needed, or as otherwise directed by a physician. The oral composition of embodiments herein may be administered at any interval to achieve the therapeutically desired effect, e.g., induction or maintenance of remission, prevention or relief of a symptom or symptoms. In some embodiments, the oral composition of embodiments herein may be administered to a subject for a period of 1, 2, 3, 4, 5, 6 days, about a week, about two weeks, about three weeks, about four weeks, about five weeks, about six weeks, about two months, about three months, about four months, about five months, about six months, or a range of any two of these values. In some embodiments, treatment may be continued for at least a week, a month, a year, or as otherwise directed by a physician. In some embodiments, treatment may extend over multiple years, the duration of disease, or the lifetime of the subject. In some embodiments, the oral composition of embodiments herein can be administered once or twice daily to a subject in need thereof for a period of about two to about twenty-eight days, or from about seven to about ten days. The oral composition of embodiments herein can also be administered once, twice, or three times daily to a subject for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 times per year, or a combination thereof.

[0106] In some embodiments the oral composition described herein is administered before, after, or with a meal. In some embodiments the oral composition described herein is administered before, after, or with a high fat meal. In some embodiments, the oral composition described herein is administered before, after, or with a standardized high fat meal. In some embodiments, the high-fat meal is a high-calorie, high-fat meal. In some embodiments, the high fat meal follows the FDA guidance on a high-fat meal. In some embodiments, the high-calorie, high-fat meal follows the FDA guidance on a high-fat and high-calorie meal. In some embodiments, the high-fat meal comprises a fat content of about 50% or greater of total caloric content of the meal. See U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, (2002). Guidance for Industry: Food-Effect

Bioavailability and Fed Bioequivalence Studies. Office of Training and Communications Division of Drug Information, HFD-240. In some embodiments, the high-calorie, high-fat meal comprises a fat content of at least 50% of total caloric content of the meal and a total of about 800 to about 1000 kilocalorie content.

[0107] In some embodiments the oral composition described herein is administered following an overnight fast. In some embodiments, the overnight fast is at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, or at least about 10 hours. For example, the oral composition described herein may be administered following a high-fat meal, high-calorie meal following an overnight fast of at least 10 hours.

[0108] Combination Therapy

[0109] In any embodiment, a method of treating a viral infection in a subject by administering a therapeutically effective amount of Compound I to the subject may further comprise administering to the subject an antiviral agent, for example, as part of a combination therapy. The term "combination therapy" refers to an administration regime comprising the administration of two or more active agents to treat a viral infection, as disclosed herein. Thus, in another aspect, certain embodiments provide methods for treating a viral infection in a human or animal subject in need of such treatment comprising administering to said subject an amount of an oral composition comprising Compound I as disclosed herein in an amount of 5 mg/day to 300 mg/day to reduce or prevent the viral infection or symptoms thereof in the subject, in combination with at least one additional antiviral agent. Examples of suitable antiviral agents include, but are not limited to, oseltamivir (e.g., TAMIFLU™), zanamivir (e.g., RELENZA™), amantadine, rimantadine, remdesivir, chloroquine, ritonavir, lopinavir, ribavirin, penciclovir, nitazoxanide, nafamostat, favipiravir, ivermectin, corticosteroids, and any combination thereof.

[0110] Administration of Compound I in a combination therapy may comprise administering Compound I and substantially simultaneously administering an antiviral agent. Substantially simultaneous administration may comprise administration of a pharmaceutical formulation comprising both Compound I and the antiviral agent, for example, in a single dosage presentation (e.g., a capsule). Alternatively, substantially simultaneous administration may comprise separate administration of separate dosage presentation—one comprising Compound I and one comprising an antiviral agent—within a short period of time, such as within 1 minute, 10 minutes, or 1 hour.

[0111] Combination therapy may alternatively encompass administration of Compound I and an antiviral agent sequentially to the patient, for example, where administration of Compound I is separated from administration from the antiviral agent by about 1 hour to about 24 hours, about 1 to about 7 days, or by 1 or more weeks. In any embodiment, a combination therapy regimen will provide therapeutic effect in treating a viral infection.

[0112] In any embodiment, Compound I may be administered as part of a combination therapy with another immunomodulatory drug. Thus, in another aspect, certain embodiments provide methods for treating a viral infection in a human or animal subject in need of such treatment comprising administering to said subject an amount of an oral composition comprising Compound I as disclosed herein in an amount of 5 mg/day to 300 mg/day to reduce or prevent the viral infection or symptoms thereof in the subject, in combination with at least one additional immunomodulatory agent. Suitable immunomodulatory drugs include, but are not limited to, interleukin-6 inhibitors including, but not limited to, baricitinib (e.g., OLUMIANT®), tocilizumab (e.g., ACTEMRA™); CD20 blockers including, but not limited to, rituximab (e.g., RITUXAN™); Tumor Necrosis Factor (TNF) blockers including, but not limited to, etanercept (e.g., ENBREL™), infliximab (e.g., REMICADE™) and adalimumab (e.g., HUMIRA™); interleukin-1 receptor antagonists including, but not limited to, anakinra (e.g., KINERET™); interleukin-17 inhibitors including, but not limited to, AIN457; Janus kinase inhibitors including, but not limited to, tofacitinib; and syk inhibitors including, but not limited to, fostamatinib. Other known immunomodulatory drugs such as chloroquine and hydroxychloroquine may also optionally be part of a combination therapy with Compound I as described herein.

[0113] A therapeutically effective amount of Compound I may be administered to a subject by any route sufficient to achieve therapeutic systemic circulation levels, for example, orally, intranasally, rectally, topically, transmucosally, intravenously, or other parenteral routes of administration such as subcutaneous, intravenous injection (IV), intramuscular injection (IM), intrathecal injection (IT), or intraperitoneal injection (IP). A therapeutically effective amount of Compound I may be administered in a single dose or in multiple doses at pre-determined intervals over time that when added together provides the therapeutically effective amount.

[0114] Therapeutic Effects in Treating Viral Infections

[0115] Use of the described methods and compositions comprising Compound I result in a reduction or elimination of disease, symptom, virus concentration, or other undesired property in a subject relative to a control population (for example, same or similar viral infection but without treatment by the described methods and materials). A reduction may quantitative or qualitative. For example, a quantitative reduction may be at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, and in an ideal situation, about 100% reduction of an adverse quantifiable state related to the viral infection. A qualitative reduction may be a reduction based on a subject-reported scale (e.g., from 1 to 10) or a subject-reported decrease in adverse symptoms related to the viral infection that are unable to be quantified.

[0116] In any embodiment, the methods of treating a viral infection, for example, a SARS-CoV-2 infection, in a subject in need thereof comprising administering a therapeutically effective amount of Compound I will result in improvement in negative symptoms related to the viral infection. For example, in any embodiment, administration of Compound I may decrease Time to Clinical Improvement (TTCI). TTCI is defined as the time (in days) from initiation of treatment until a decline of at least two categories on a six-category ordinal scale of clinical status. The six-category ordinal scale are (6) Death; (5) ICU, requiring ECMO and/or IMV (invasive mechanical ventilation); (4) ICU/hospitalization, requiring NIV (non-invasive mechanical ventilation)/IFNC (high-flow nasal cannula therapy); (3) hospitalization,

requiring supplemental oxygen (but not NIV/HFNC); (2) hospitalization, not requiring supplemental oxygen; and (1) hospital discharge.

[0117] In any embodiment, administration of a therapeutically effective amount of Compound I to a subject in need thereof may result in one or more of the following: (i) An earlier hospital discharge; (ii) A reduction in NEWS (National Early Warning Score); (iii) Reduced duration on mechanical ventilation; (iv) Reduced duration on extracorporeal membrane oxygenation (ECMO); (v) Reduced duration on supplemental oxygenation; (vi) An earlier negative SARS-CoV-2 RT-PCR test in upper and lower respiratory tract specimens; (vii) A reduction in SARS-CoV-2 viral load in upper and lower respiratory tract specimens as assessed by area under viral load curve; (viii) Reduced frequency of serious adverse events; (ix) Reduced need for endotracheal intubation; (x) Improvement in pulmonary function (PEFR); (xi) Decreased white blood cell and differential count; (xii) Reduced levels of high-sensitivity C-reactive protein (hsCRP); (xiii) Prevention or delay of ARDS; and (xiv) Reduction in levels of serum cytokines IL-1β, IL-10, sIL-2R, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-1α, MIP1β and TNF-α.

[0118] In any embodiment, administration of the pharmaceutical composition disclosed herein to a subject in need thereof reduces at least one pro-inflammatory cytokine in the lung or any other affected organ of a subject following viral infection.

[0119] For example, a method of reducing at least one pro-inflammatory cytokine in the lung of a subject having an infection, e.g., a viral infection, comprises administering to subject in need thereof a pharmaceutical composition comprising an effective amount of Compound I. In some examples, pro-inflammatory cytokines are selected from IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-17, IFNγ, IFN-α, TNF-α, IP-10, MCP-1, MIP-1, RANTES, GM-CSF, and combinations thereof. In some examples, one or more cytokines selected from IL-1β, IL-1RA, IL-6, IL-7, IL-8, IL-9, IL-10, bFGF, GCSF, GMCSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, VEGF, TNFα, ferritin, CRP, and ESR are reduced with treatment. Any of the above-described pharmaceutical compositions can be used in this method. The viral infection can comprise infection by influenza (e.g., H1N1, H5N1), parainfluenza, paramyxovirus, adenovirus, parvovirus, enterovirus, variola virus, rotavirus, hemorrhagic fever viruses (viruses in the families of Arenaviridae, Bunyaviridae, Filoviridae, Falviviridae, and Togaviridae) hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus (herpes virus), and coronavirus (SARS-CoV, SARS-CoV-2, MERS-CoV). In any embodiment, the viral infection comprises infection by SARS-CoV-2 or a variant thereof.

[0120] In other examples, a method of treating a subject having infection induced CRS or ARDS comprises administering a pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises at least an effective amount of Compound I. The infection induced CRS or ARDS can be cause by a viral infection, bacterial infection, or fungal infection. In any embodiment, the CRS or ARDS treated herein is induced by a viral infection with influenza (e.g., H1N1, H5N1), parainfluenza, paramyxovirus, adenovirus, parvovirus, enterovirus, variola virus, rotavirus, hemorrhagic fever viruses (viruses in the families of Arenaviridae, Bunyaviridae, Filoviridae, Falviviridae, and Togaviridae) hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus (herpes virus), or coronavirus (SARS-CoV, SARS-CoV-2, MERS-CoV). In any embodiment, CRS or ARDS in a subject having SARS-CoV-2 is treated according to the methods and composition comprising Compound I as described herein.

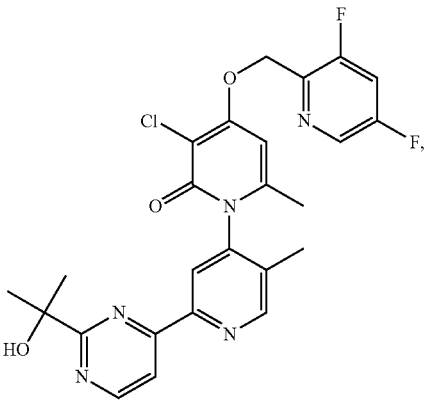
[0121] The present disclosure is not to be limited in terms of the particular embodiments described in this application, which are intended as illustrations of various aspects. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds, compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0122] Various of the above-disclosed and other features and functions, or alternatives thereof, may be combined into many other different systems or applications. Various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art, each of which is also intended to be encompassed by the disclosed embodiments.

EMBODIMENTS OF THE DISCLOSURE

[0123] Embodiment 1 is a method of treating a viral infection in a subject, the method comprising: administering orally, to a subject having a viral infection, a therapeutically effective amount of Compound I

(I)



or a derivative thereof to treat the viral infection.

[0124] Embodiment 2 is a method of treating infection induced cytokine release syndrome (CRS) or acute respiratory distress syndrome (ARDS) in a subject, the method comprising: administering orally, to a subject having an

infection, a therapeutically effective amount of Compound I or a derivative thereof to treat the infection induced CRS or ARDS.

[0125] Embodiment 3 is the method of Embodiment 2, wherein the infection is a viral infection, a bacterial infection, a fungal infection, or a parasitic infection.

[0126] Embodiment 4 is the method of any one of Embodiments 1-3, wherein the infection is a viral infection, and the viral infection comprises infection by influenza, parainfluenza, paramyxovirus, adenovirus, parvovirus, variola virus, enterovirus, rotavirus, a hemorrhagic fever virus, hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus, or coronavirus.

[0127] Embodiment 5 is the method of Embodiment 4, wherein the subject has a coronavirus infection selected from SARS-CoV-2, SARS-CoV, MERS-CoV, and HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1.

[0128] Embodiment 6 is the method of Embodiment 5, wherein the viral infection comprises infection by SARS-CoV-2 or a variant thereof.

[0129] Embodiment 7 is the method of any one of Embodiments 1-6, wherein 50 mg/day of Compound I is administered to said subject.

[0130] Embodiment 8 is the method of any one of Embodiments 1-6, wherein 100 mg/day of Compound I is administered to said subject.

[0131] Embodiment 9 is the method of any one of Embodiments 1-6, wherein 160 mg/day of Compound I is administered to said subject.

[0132] Embodiment 10 is the method of any one of Embodiments 1-6, wherein 200 mg/day of Compound I is administered to said subject.

[0133] Embodiment 11 is the method of any one of Embodiments 1-6, wherein 240 mg/day of Compound I is administered to said subject.

[0134] Embodiment 12 is the method of any one of Embodiments 1-11, wherein Compound I is administered once a day.

[0135] Embodiment 13 is the method of any one of Embodiments 1-11, wherein Compound I is administered twice a day.

[0136] Embodiment 14 is the method of any one of Embodiments 1-6 wherein 50 mg of Compound I is administered to the subject twice daily.

[0137] Embodiment 15 is the method of any one of Embodiments 1-6, wherein 50 mg of Compound I is administered to a subject infected with a coronavirus twice daily.

[0138] Embodiment 16 is the method of any one of Embodiments 1-6, wherein 80 mg of Compound I is administered to the subject twice daily.

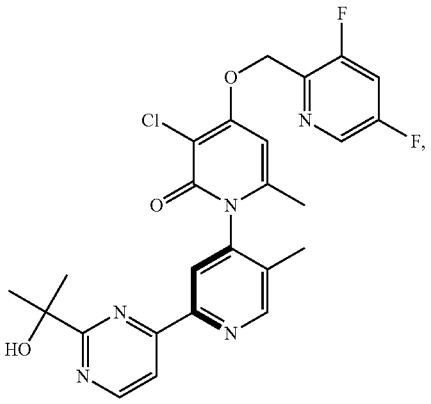
[0139] Embodiment 17 is the method of any one of Embodiments 1-6, wherein 100 mg of Compound I is administered to the subject twice daily.

[0140] Embodiment 18 is the method of any one of Embodiments 1-6, wherein 120 mg of Compound I is administered to the subject twice daily.

[0141] Embodiment 19 is the method of any one of Embodiments 1-18, wherein Compound I is deuterated.

[0142] Embodiment 20 is the method of any one of Embodiments claims **1-19**, wherein Compound I comprises the Compound (P)-I

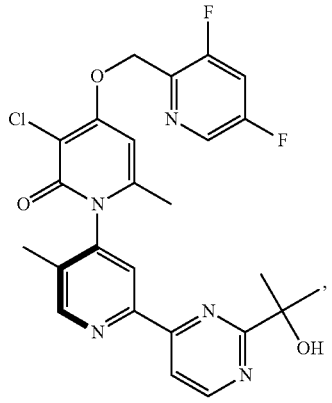
(*P*)-I



and the Compound (M)-I (M)-I

[0143]

(*M*)-I



in a molar ratio of (P)-I to (M)-I of about 4:1.

[0144] Embodiment 21 is the method of Embodiment 20, wherein the molar ratio of (P)-I to (M)-I is about 9:1.

[0145] Embodiment 22 is the method of Embodiment 20, wherein the molar ratio of (P)-I to (M)-I is about 99:1.

[0146] Embodiment 23 is the method of Embodiment 20, wherein the molar ratio of (P)-I to (M)-I is about 199:1.

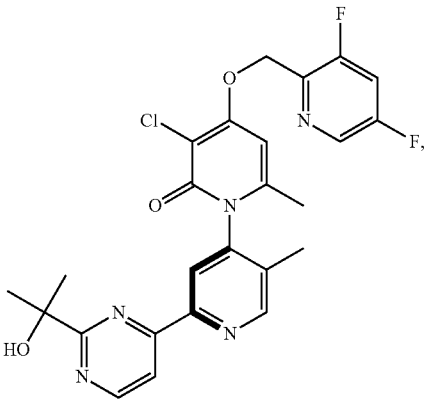
[0147] Embodiment 24 is the method of Embodiment 20, wherein the molar ratio of (P)-I to (M)-I is about 399:1.

[0148] Embodiment 25 is the method of Embodiment 20, wherein the molar ratio of (P)-I to (M)-I is about 999:1.

[0149] Embodiment 26 is the method of any one of claims **1-19**, wherein Compound I comprises the Compound (P)-I substantially free of Compound (M)-I.

[0150] Embodiment 27 is the method of any one of Embodiments claims **1-19**, wherein Compound I comprises at least 80 mol % of Compound (P)-I

(*P*)-I



[0151] Embodiment 28 is the method of Embodiment 27, wherein Compound I comprises at least 90 mol % of Compound (P)-I.

[0152] Embodiment 29 is the method of Embodiment 28, wherein Compound I comprises at least 95 mol % of Compound (P)-I.

[0153] Embodiment 30 is the method of Embodiment 29, wherein Compound I comprises at least 99 mol % of Compound (P)-I.

[0154] Embodiment 31 is the method of any one of Embodiments 1-30, wherein Compound (P)-I is a free base.

[0155] Embodiment 32 is the method of any one of Embodiments 1-30, wherein Compound (P)-I is a pharmaceutically acceptable salt.

[0156] Embodiment 33 is the method of any one of Embodiments 1-30, wherein Compound (P)-I is crystalline form.

[0157] Embodiment 34 is the method of Embodiment 33, wherein the crystalline form of Compound (P)-I is crystalline Form A characterized by an PXRD pattern having a peak expressed in degrees 2θ at about 9.78±0.2.

[0158] Embodiment 35 is the method of Embodiment 33, wherein the crystalline form of Compound (P)-I is the crystalline Form A characterized by an PXRD pattern having peaks expressed in degrees 2θ at 9.78±0.2 and 15.51±0.2.

[0159] Embodiment 36 is the method of Embodiment 33, wherein the crystalline form of Compound (P)-I is the crystalline Form A characterized by an PXRD pattern having peaks expressed in degrees 2θ at 9.78±0.2, 15.51±0.2, 19.6±0.2, and 25.92±0.2.

[0160] Embodiment 37 is the method of Embodiment 33, wherein the crystalline form of Compound (P)-I is the crystalline Form A characterized by an PXRD pattern having peaks expressed in degrees 2θ at 9.78±0.2, 15.34±0.2, 15.51±0.2, 19.6±0.2, 20.57±0.2, 21.01±0.2, 25.92±0.2, 29.05±0.2, and 29.48±0.2,

[0161] Embodiment 38 is the method of any one of Embodiments 1-37, wherein the method further comprises administering at least one additional antiviral agent to the subject.

[0162] Embodiment 39 is the method of any one of embodiments 1-37, wherein the method further comprises administering at least one additional immunomodulatory agent to the subject.

[0163] Embodiment 40 is the method of any one of Embodiments 1-39, wherein Compound 1 is formulated as a solid dosage form selected from a tablet, a capsule, a lozenge, a sachet, a powder, granules, and orally dispersible film.

[0164] Embodiment 41 is the method of any one of Embodiments 1-40, wherein said administering is carried out under conditions effective to significantly reduce in vivo serum levels of one or more inflammatory cytokines.

[0165] Embodiment 42 is the method of Embodiment 41, wherein the one or more inflammatory cytokines is selected from the group consisting of TNF-α, IL-1β, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-1α, and IL-1RA.

Examples

[0166] As described in detail above, 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (i.e., Compound I) exists as a P atropisomer and a M atropisomer. In the Examples and Figures of this disclosure, "ATI-450" refers to the aforementioned compound containing about 99.75 mol % of the P atropisomer and about 0.25 mol % of the M atropisomer, i.e., in a ratio of (P)-I to (M)-I of 399:1.

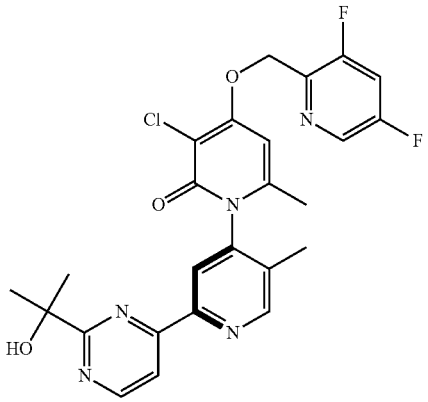
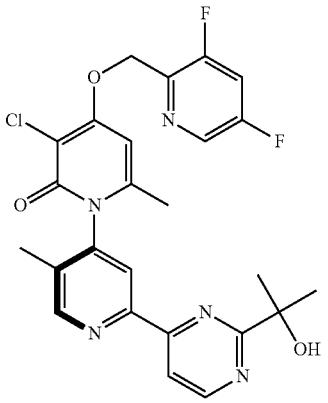
Example 1: p38 Inhibitory Potency and p38/MK2 Substrate Selectivity

[0167] Inhibition of MK2 and PRAK by Compound (P)-I and (M)-I, respectively, was investigated to understand how Compound (P)-I and/or Compound (M)-I may help in reducing inflammatory response, such and as that which occurs as a response to SARS-CoV-2 infection. Compound (P)-I and (M)-I were evaluated in enzyme assays that compared inhibitor potency in blocking p38/MK2 versus p38/PRAK-induced phosphorylation of an HSP-27-derived peptide substrate. The ability of Compound (P)-I and (M)-I to inhibit activated phospho-p38α was evaluated using a p38α/MK2 and a p38α/PRAK cascade assay format. The kinase activity of p38α was determined by its ability to phosphorylate GST-MK2 or GST-PRAK. Activation of MK2 or PRAK by p38α was quantitated by measuring the phosphorylation of a fluorescently-labeled, MK2/PRAK specific peptide substrate, Hsp27 peptide. The phosphorylation of the Hsp27 peptide was quantified using IMAP technology (Molecular Devices, Sunnyvale Calif.). Kinase reactions were carried out in a 384-well plate (Greiner, 781280) in 20 mM HEPES pH 7.5, 10 mM $MgCl_2$, 0.01% Triton X-100, 0.01% BSA, 1 mM DTT, and 2% DMSO. The concentration of inhibitor in the assays was varied between 0.02 nM to 30,000 nM, while the Hsp27 peptide substrate and MgATP were held constant at 1 μM and 10 μM, respectively. Activated p38α was added to a final concentration of 30 μM for reactions with non-phosphorylated 1 nM GST-MK2 in the cascade reaction. For the p38α/PRAK cascade, the concentration of non-activated GST-PRAK was held constant at 10 nM while p38α was added to a final concentration of 200 μM. Kinase reactions were incubated at room temperature and quenched after 120 minutes by the addition of IMAP Binding Solution. Under these conditions, approximately 2000 of the substrate Hsp27 peptide was phosphorylated. Reactions were initiated by the addition of activated p38α except for pre-incubation experiments, where reactions were initiated by the addition of Hsp27 peptide and MgATP. Pre-incubation of p38α with inhibitor or p38α with non-activated GST-MK2 or non-activated GST-PRAK and inhibitor were performed at 2×fi-

nal assay concentrations at room temperature 240 minutes prior to adding ATP and Hsp27 peptide to initiate catalysis. The inhibitory potency of Compounds (P)-I and (M)-I was quantitated from dose-response IC_{50} values or K_i values from p38α/MK2 cascade assays while the substrate selectivity was calculated as a ratio of p38α/PRAK:p38α/MK2 IC_{50} values.

[0168] Compound (P)-I and Compound (M)-I were tested in accordance with the above described assay, yielding IC_{50} values described in Table 1 below:

TABLE 1

Compound	Structure	p38/MK2 IC_{50} (μM)	p38/PRAK IC_{50} (μM)	Selectivity Ratio
(P)-I		0.021	8.1	385x
(M)-I		3.48	12.5	3.6

Example 2: Cytokine Regulation in Human Monocytes

[0169] The p38 pathway has been shown to be critical for the biosynthesis of a number of pro-inflammatory cytokines including TNFα~, IL-1β and IL-6. Therefore, inhibition of the p38 MAP Kinase pathway will lower the inflammatory response by decreasing biosynthesis of pro-inflammatory cytokines. This study shows the amount of Compound (P)-I and Compound (M)-I necessary to inhibit biosynthesis of TNFα, IL-6, and IL-1β (pro-inflammatory cytokines) by half, demonstrating the effectiveness of each compound in helping to lower inflammation, an effect which helps treat many diseases, including viral infections (e.g., Covid-19 infection) and infection relate CRS and ARDS. Evaluation of the potency and efficacy of Compound (P)-I and Compound (M)-I to block cytokine production were carried out using the human U937 cell line. The U937 human pre-monocytic cell line was obtained from the American Type Culture Collection (Rockville, Md.). These cells were differentiated to a monocytic/macrophage phenotype as described by Burnette (Burnette et al, (2009). SD0006: a potent, selective and orally available inhibitor of p38 MAP Kinase, Pharmacology 84(1):42-60). Differentiated U937 cells (human peripheral blood mononuclear cells (hPBMC)) were seeded into 96-well tissue culture plates (200,000 cells/well) in complete media. After 24 hours, the cells were pretreated for 60 minutes in the presence or absence of Compound (P)-I and Compound (M)-I and then stimulated with LPS (0.1 μg/mL) for 4 hours. Culture media was then collected for determination of TNFα, IL-6 or IL-1β levels by ELISA. Cytokine concentrations were extrapolated from recombinant protein standard curves using a four-parameter logistic model and solving for IC_{50} after iterating to the best least-squares fit.

[0170] Both atropisomers of ATI-450 (Compounds (M)-I and (P)-I) were tested in accordance with the above described assay, yielding IC_{50} values described in Table 2 below:

TABLE 2

Compound	hPBMC TNFα IC_{50} (μM)	hPBMC IL-1β IC_{50} (μM)	hPBMC IL-6 IC_{50} (μM)
(P)-ATI-450	0.004	0.012	0.145
(M)-ATI-450	>10,000	>10,000	>10,000

Example 3: Phosphoprotein Analysis in Human Monocytes

[0171] This study shows the effectiveness and selectivity of Compound (P)-I in inhibiting the JNK pathway. The JNK pathway leads to increased inflammation by boosting production of inflammatory cytokines. Inhibition of this pathway will lead to less inflammation and therefore will treat many diseases, including viral infections, including those caused by SARS-CoV-2. Evaluation of the impact of Compound (P)-I on p38 and JNK pathway regulation was carried out using phospho-HSP27 and phosphor-JNK for the two pathways, respectively. Evaluation of the potency and efficacy of Compound (P)-I to impact phosphoprotein levels was carried out using the human U937 cell line. The U937 human pre-monocytic cell line was obtained from the American Type Culture Collection (Rockville, Md.). These cells were differentiated to a monocytic/macrophage phenotype as described by Burnette (Burnette et al, (2009). SD0006: a potent, selective and orally available inhibitor of p38 MAP Kinase, *Pharmacology* 84(1):42-60). Suspension cells (approximately 0.5 million per milliliter in T75 cm^2 tissue culture flasks) were grown in RPMI containing 10% fetal bovine serum (FBS) plus antibiotics. On day one, phorbol 12-myristate 13-acetate (PMA, 20 ng/mL) was added to the culture flask and the cells were incubated overnight at 37° C./5% CO_2. The cells were washed on day two by centrifuging and re-suspended in fresh media without PMA. Adherent cells were harvested on day three by scraping, centrifuged and re-suspended in fresh media at a density of 1 million per milliliter. The PMA-differentiated U937 cells were then distributed into each well of a 96-well flat bottom tissue culture plate (100 mL/well) and the 100,000 cells/well were allowed to recover, incubated, overnight. On the day of the assay, fresh media (50 mL/well) were added to the plates followed by the addition of Compound (P)-I (25 mL/well, concentration response) for 1 hour. The cells were stimulated with LPS (100 ng/mL) in a final assay volume of 100 mL. After 30 minutes, complete lysis buffer (50 mL/well MSD Tris lysis buffer, supplemented with protease inhibitors and phosphatase inhibitors) was added and the plate was placed on a shaker at 4° C. for 30 minutes before being stored frozen at −20° C. The cellular lysate (25 mL/well) was thawed and transferred from the assay plate to Meso Scale detection plates for determination of phospho-Hsp27/total Hsp27 or phospho-JNK/total JNK.

[0172] Compound (P)-I was tested in accordance with the above described assay, yielding IC_{50} and EC_{50} values described in Table 3 below:

TABLE 3

Compound	pHSP27/Total HSP27 IC_{50} (nM)	pJNK/Total JNK EC_{50} (nM)	Selectivity Ratio
(P)-ATI-450	1.15×	117×	102×

Example 4: Endotoxin-Induced Cytokine Production from Human Whole Blood

[0173] Human whole blood (HWB; 25-45 mL) was collected from an NSAID-free donor into vacutainer collection tubes containing sodium heparin (10 mL, 158 USP units), pooled and rocked gently before being distributed into each well of a 96-well round bottom tissue culture plate (180 mL/well). Compound (P)-I (10 mL/well, concentration response) was added and mixed gently for 15-20 seconds using a disposable 96 polypropylene pin tool before the plates were incubated at 37° C./5% CO_2 for 1 hour. The HWB was stimulated with LPS (100 ng/mL) in a final assay volume of 200 mL. After 3 hours, the plates were spun at 240×g for 5 minutes to pellet the red cells. The plasma was carefully transferred to another 96-well round bottom plate and diluted 2-fold with assay media (DMEM containing 10% fetal bovine serum (FBS) plus antibiotics). Finally, the diluted plasma (25 mL/well) were transferred to Meso Scale detection plates for determination of IL-1, IL-6 or TNFα.

[0174] Compound (P)-I was tested in accordance with the above described assay, yielding IC_{50} and EC_{50} values described in Table 4 below:

TABLE 4

Compound	HWB TNF-α IC50 (μM)	HWB IL-1β IC50 (μM)	HWB IL-6 IC50 (μM)
(P)-ATI-450	0.013	0.006	0.035

Example 5: An Open-Label Assessment of the Safety and Efficacy of ATI-450 in the Treatment of COVID-19-Related Cytokine Release Syndrome

[0175] ATI-450 is a small molecule inhibitor of MK2 that inhibits production of multiple cytokines such as TNFα, IL-1β, IL-6 and IL-8. In Phase 1 clinical trials, ATI-450 was well tolerated by test subjects and exhibit a good PK/PD profile. Demonstration of the efficacy and safety of ATI-450 in treating viral infections, for example, of the SARS-CoV-2 virus, represents a pathway to improvement in clinical symptoms in such patients infected with the SARS-CoV-2 virus and therefore a reduction in healthcare utilization, for example, preventing a subject's progression to critical care.

[0176] The safety, tolerability, and pharmacodynamics (PD) effect of ATI-450 was tested in subjects having symptoms related to COVID-19-related CRS. After a 2-day screening period, subjects were administered ATI-450 as part of a 14-day treatment period after which the subject was monitored for a 2-week follow-up period. Subjects were orally administered one tablet comprising 50 mg of ATI-450 twice daily. Subjects undergoing treatment are identified as:

[0177] male or non-pregnant female adult ≥18 years of age;

[0178] having laboratory-confirmed SARS-CoV-2 coronavirus infection as determined by polymerase

chain reaction (PCR), or other commercial or public health assay in oropharyngeal or nasal testing within 72 hours prior to hospitalization;

[0179] requiring hospitalization as a result of symptoms related to the COVID-19 infection;

[0180] involvement of the lungs as confirmed with chest imaging; exhibiting a SaO2/SpO2≤93% on room air or a PaO_2/FiO_2 ratio <300 mmHg within 14 days of illness onset;

[0181] exhibiting symptoms of CRS as indicated an elevation in blood serum levels of at least one of IL-6 and IFNγ that is greater than or equal to 3 times the upper limit of a normal range;

[0182] an hsCRP of at least 5 mg/L;

[0183] an active fever greater than 38° C.; and

[0184] not receiving critical care in an ICU.

[0185] A primary objective of this study is to assess the efficacy of ATI-450 in patients with COVID-19 related cytokine release syndrome. This objective will be assessed determining the proportion of subjects with normalization of fever and oxygen saturation through day 14 of treatment. This is a composite outcome measure that requires (i) a temperature of less than 36.6° C. (armpit) or less than 37.2° C. (oral) sustained for at least 72 hours and (ii) peripheral capillary oxygen saturation (SpO2) greater than 94% for at least 72 hours.

[0186] This objective will also be assessed by determining the following secondary endpoints: Change of oxygen saturation greater than three percentage points or greater than 10% or decrease in FiO_2 need or reduction of at least 30% in pulmonary consolidations evidenced by HR CT-scan; need for endo-tracheal intubation; all-cause mortality; length of hospital stay (days); entry into ICR for critical care management; Improvement in pulmonary function (PEFR); proportion of participants with normalization of fever through day 14; Change from baseline in white blood cell and differential count; Time to SARS-CoV-2 RT-PCR negativity in oropharyngeal or nasal testing; Change from baseline in high-sensitivity C-reactive protein (hsCRP); Development of new ARDS.

[0187] Safety of ATI-450 in patient with COVID-29 cytokine release syndrome will be assessed by determining the number and percent of adverse events and serious adverse events, mean change from baseline in laboratory values, vital signs, and ECGs.

[0188] Exploratory endpoints include an assessment of the pharmacodynamics of ATI-450 in patient with COVID-19 related cytokine release syndrome. This endpoint will be assessed by determining: change from baseline in serum cytokines IL-1β, IL-10, sIL-2R, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-1β, IL-1α, IL-1RA and TNF-α; change from baseline in proportion of CD4+ CD3/CD8+CD3 T cells; mean change from pre-dose in ex vivo stimulated cytokine levels (e.g., TNF-α, IL-β, IL-6, IL-8 IFNγ, IL-17, IL-18, IL-10, IL-1RA- and IL-1α); ex vivo stimulated phosphoprotein modulation.

Example 6: Effect of Oral ATI-450 on Plasma Cytokine and Chemokine Profile

[0189] The effect of orally administered ATI-450 on the production of ex vivo lipopolysaccharide (TLR4)-stimulated cytokines and chemokine in humans was measured using multiplex technology. Lipopolysaccharide (TLR4)-stimulated cytokine and chemokine production was assessed in blood samples obtained after oral administration of ATI-450 in the following subject cohorts:

[0190] Cohort 1: Single-ascending dose (SAD) subjects were administered a single oral dose of 100 mg of ATI-450 in the morning after fasting overnight. Blood samples were collected pre-administration and 1-hour post-administration from 2 subjects administered a placebo and 6 subjects administered ATI-450; and

[0191] Cohort 2: Multiple-ascending dose (MAD) subjects were administered a twice daily oral dose of 50 mg ATI-450 for seven days. Blood samples were collected pre-administration on day 1 and 4-hour post-administration on day 7 from 2 subjects administered a placebo and 8 subjects administered ATI-450.

[0192] Data were collected following stimulation by a lipopolysaccharide (LPS) at a single time point (5 hours) in each isolated ex vivo human whole blood sample collected. cohorts. Cytokines evaluated include: IL-1b, IL-1RA, IL-2, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF.

[0193] FIG. **3** depicts lipopolysaccharide-stimulated cytokine/chemokine production as a percent of pre-administration blood concentrations in samples obtained from both Cohort 1 and Cohort 2. Absolute values (in pg/mL) and increase (fold) stimulation of each chemokine/cytokine analyzed in samples from Cohorts 1 and 2 are reported in Table 5 below.

TABLE 5

	Cohort 1 (SAD) (100 mg ATI-450 once daily) (pg/mL analyte)			Cohort 2 (MAD) (50 mg ATI-450 twice daily) (pg/mL analyte)		
	Not Stimulated	Stimulated	Fold Increase	Not Stimulated	Stimulated	Fold Increase
IFNγ	12.54	57.72	4.60	33.45	57.81	1.73
IL-1β	1.86	776.88	417.52	2.25	381.38	169.82
IL-2	0.65	30.06	46.07	2.86	14.18	4.96
IL-6	15.28	8700.41	569.22	5.70	9359.59	1640.89
IL-8	1564.00	24421.33	15.61	3853.03	30259.47	7.85
IL-10	22.57	752.46	33.33	2.05	108.90	53.21
TNFα	8.57	5270.06	614.99	13.44	6402.98	476.54
GMCSF	0.46	25.12	54.38	0.21	19.15	92.39
IL-7	8.79	8.04	0.92	7.40	6.87	0.93
VEGF	186.34	231.92	1.24	202.39	191.77	0.95
IL-1RA	974.42	7169.95	7.36	893.81	13830.24	15.47

TABLE 5-continued

	Cohort 1 (SAD) (100 mg ATI-450 once daily) (pg/mL analyte)			Cohort 2 (MAD) (50 mg ATI-450 twice daily) (pg/mL analyte)		
	Not Stimulated	Stimulated	Fold Increase	Not Stimulated	Stimulated	Fold Increase
IL-9	0.00	0.00	0.00	3.10	2.77	0.89
MIP-1β	504.74	49549.56	98.17	806.79	89906.73	111.44
IP-10	288.07	1487.58	5.16	474.58	1513.02	3.19
MIP-1α	105.22	32722.63	310.99	193.51	38207.05	197.44
MCP-1	1026.37	1215.21	1.28	728.09	1124.80	1.54
bFGF	29.69	28.63	0.96	25.04	24.50	0.98
GCSF	25.01	232.34	9.29	16.33	292.44	17.91

[0194] Table 5 illustrates that chemokines/cytokine expression was induced to varying levels under human whole blood assay conditions. Cytokine production, rank order, and fold stimulations are comparable across samples collected from Cohort 1 and Cohort 2 when comparisons were performed by heat map analysis.

[0195] FIGS. **4**A and **4**B illustrates that inflammatory cytokines/chemokines GM-CSF, IFNγ, IL-2, and MIP-1α were inhibited by ATI-450 by at least about 70% across both cohorts compared to placebo-administered subjects. Anti-inflammatory mediators such as IL-10 and IL-1RA were inhibited by ATI-450 but to a lesser extent (about 30%) as shown in FIG. **5**A (Cohort 1) and FIG. **5**B (Cohort 2).

[0196] Together this data, showing that oral administration of ATI-450 decreases concentrations of various inflammatory cytokines measured in the LPS-stimulated whole blood samples, indicates that ATI-450 may be effective in treating infection induced cytokine release syndrome, such as observed in subjects infected with the SARS-CoV-2 virus

Example 7: ATI-450 Blocks Lung Neutrophilia in a Rat Model of Pulmonary Inflammation

[0197] The ability of ATI-450 to suppress pulmonary inflammation was investigated in Sprague-Dawley rats orally administered 1 mg/kg or 10 mg/kg of ATI-450. One hour after administration, animals were placed in an aerosol chamber containing 60 μg/mL lipopolysaccharide (LPS) for 40 minutes and then removed to room air. Four hours after LPS exposure, lungs of the animals were lavaged with cold D-PBS/EDTA solution and the total number of polymorphonuclear neutrophils (PMN) in the solution were counted as an indicator of the inflammatory response. FIG. **6** illustrates collected the data, demonstrating that total lung PMNs were significantly reduced in the rats administered ATI-450 when compared to vehicle-treated animals. This suggests that ATI-450 may effectively inhibit lung neutrophilia in vivo.

Example 8: A Double-Blinded, Randomized Placebo-Controlled Trial of MAPKAPK2 Inhibition by ATI-450 in Moderate-to-Severe COVID-19 Pneumonia

[0198] Inflammation and inflammatory diseases, conditions, and disorders propagate primarily through the MAPK signal pathway. Activation of p38α is important for regulating inflammation. Aberrant p38α activation is associated in the pathobiology of diseases such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease and tissue fibrosis. The MAPKAPK2 (MK2) protein is one downstream target of p38α and is responsible for the transcriptional production of pro-inflammatory cytokines, including the same cytokines observed as elevated in COVID-19-related inflammation. Other severe viral illnesses (i.e., Dengue fever, influenza, cytomegalovirus) exhibit activation of the p38-MK2 signaling axis in mediating inflammation. Therefore, it is predicted that COVID-19-mediated inflammatory cytokine production may likewise signal through the p38αMK2 axis. As such, MK2 pathway blockade may suppress inflammation. However, it remains unknown whether reducing inflammation can improve COVID-19 patient outcomes, particularly in those with pre-existing conditions.

[0199] Twenty hospitalized COVID-19-positive subjects exhibiting pulmonary signs and symptoms of moderate-to-severe hypoxic respiratory distress were administered ATI-450 or a placebo twice-daily for up to 14 days.

Example 9: Separation of Compound (P)-I

[0200] Racemic 3-chloro-4-((3,5-difluoropyridin-2-yl) methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5', 6-dimethyl-2H-[1,4'-bipyridin]-2-one (250 mg, 0.49 mmol) may be prepared according to the methods described in U.S. Pat. No. 9,115,089, which is hereby incorporated by reference in its entirety. Chiral resolution of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one to obtain the P atropisomer, i.e., Compound (P)-I as disclosed herein, is carried out as described below.

[0201] Racemic 3-chloro-4-((3,5-difluoropyridin-2-yl) methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5', 6-dimethyl-2H-[1,4'-bipyridin]-2-one (250 mg, 0.49 mmol) was separated using supercritical fluid chromatography (Thar 80, preparative SFC, ChiralCel OD-H, 250×30 mm ID column) with a mobile phase of carbon dioxide and ethanol. The separation method used an isocratic method of 40% ethanol with a flow rate of 50 mL/min and a cycle time of 10 min. Optical rotation was determined using a WZZ-2S polarimeter.

[0202] The faster isomer eluted at 1.77 minutes yielded 115 mg of (−)-3-chloro-4-((3,5-difluoropyridin-2-yl) methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5', 6-dimethyl-2H-[1,4'-bipyridin]-2-one (Compound (P)-I) in ethylene glycol: $[\alpha]_D^{20}$ −46° (CH_3OH); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (d, J=5.09 Hz, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.24 (d, J=5.08 Hz, 1H), 8.10 (t, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 5.26 (s, 1H), 2.11 (s, 3H), 1.98 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H); MS (ES) m/e 514 (M+H).

[0203] The slower isomer eluted at 3.68 minutes yielded 112 mg of (+)-3-chloro-4-((3,5-difluoropyridin-2-yl)

methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5', 6-dimethyl-2H-[1,4'-bipyridin]-2-one (Compound (M)-I) in ethylene glycol: $[\alpha]_D^{20}$ +45° (CH_3OH); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (d, J=5.09 Hz, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.24 (d, J=5.08 Hz, 1H), 8.10 (t, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 5.26 (s, 1H), 2.11 (s, 3H), 1.98 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H); MS (ES) m e 514 (M+H).

Example 10: Crystal Form Screen of Compound (P)-I

[0204] The crystal-form screening study involved a total of 48 neat and binary solvent systems which addressed the moderate solubility of the input material and provided a diverse set of polarities, dielectric constants, dipole moments, and hydrogen-bond donor/acceptor attributes. Water-containing solvents with a variety of water activities (a_w)[1] were also included to probe for the formation of hydrates. Temperatures ranging between 40° C. to −20° C.

[0205] The screening studies were comprised of the following crystallization modes:

[0206] Temperature-cycled ripening of API slurries between 5-40° C. for four days (TC)

[0207] Rapid cooling clarified saturated solutions from 40 to −20° C. and holding at −20° C. for three days (RC)

[0208] Slow evaporation of clarified solutions at RT over 14 days. Rapid evaporation of solvents under reduced pressure from solutions that did not produce solids during slow evaporation after 14 days (EV).

[0209] A summary of the outcomes of the screening study are shown in Table 6.

TABLE 6

#	Solvent	TC	RC	EV	Water Activity
1	Water	Form A			1.00
2	Methanol			Form A	
3	2-Methoxyethanol:Isopropyl ether (20:80)	Form A		Form A	
4	1-Propanol			Form A	
5	Nitromethane	Form A	Form A	Form A	
6	Acetonitrile	Form A	Form A	Form A	
7	Dimethylsulfoxide:t-Butyl methyl ether (20:80)			Form A	
8	Acetone			Form A	
9	2-Butanone			Form A	
10	Dichloromethane			Form A	
11	Methyl acetate:Heptane (20:80)	Form A			
12	4-Methyl-2-pentanone	Form A		Form A	
13	Chloroform				
14	Ethyl acetate			Form A	
15	Chlorobenzene:Cyclohexane (20:80)	Form A			
16	Tetrahydrofuran			Form A	
17	1,4-Dioxane			Form A	
18	Isopropyl ether	Form A			
19	Toluene	Form A		Form A	
20	Cyclohexane	Form A			
21	Heptane	Form A			
22	1-Butanol	Form A			
23	2-Propanol	Form A		Form A	
24	Trifluoroethanol:Isopropyl ether (20:80)	Form A			
25	Dimethyl carbonate	Form A		Form A	
26	t-Butyl methyl ether	Form A			
27	Isopropyl acetate	Form A		Form A	
28	Ethanol			Form A	
29	1-Methoxy-2-propanol:Isopropyl ether (20:80)	Form A			
30	Cyclohexanone				
31	N,N-Dimethylformamide:Water (20:80)	Form A			0.95
32	2-Methoxyethyl ether:Heptane (20:80)	Form A			
33	Methanol:Water (95:5)	Form A		Form A	0.20
34	Acetonitrile:Water (95:5)	Form A			0.94
35	Acetone:Water (20:80)	Form A		Form A	0.96
36	Tetrahydrofuran::Water (20:80)	Form A		Form A	0.82
37	2-propanol:Water (95:5)	Form A		Form A	0.55
38	Methanol:Water (90:10)	Form A	Form A	Form A	0.33
39	Acetonitrile:Water (90:10)	Form A		Form A	0.76
40	Acetone:Water (90:10)			Form A	0.70
41	Tetrahydrofuran:Water (90:10)			Form A	0.83
42	1,4-Dioxane:Water (90:10)			Form A	0.70
43	2-propanol:Water (90:10)		Form A	Form A	0.65
44	Acetone:Water (80:20)		Form A	Form A	0.77
45	Ethanol:Water (20:80)	Form A			0.93
46	Ethyl acetate:Cyclohexane (20:80)	Form A			
47	Acetonitrile:Isopropyl ethyl ether (20:80)	Form A			
48	4-Methyl-2-pentanone:Heptane (20:80)	Form A			

Example 11: Single Crystal Structure Determination of Compound (P)-I (Form A)

[0210] The crystalline form of Compound (P)-I has been characterized relative to the absolute stereochemical configuration of the spatial arrangement of the atoms using

single crystal X-ray diffraction. A detailed description of structure determination by X-ray diffraction is provided in Stout & Jensen, X-Ray Structure Determination: A Practical Guide, Macmillan Co., New York (1968), Chapter 3, which is herein incorporated by reference. Alternatively, the unique spatial arrangements of atoms in three dimensions within the crystalline lattice may be characterized by X-ray powder diffraction analysis. A detailed description of X-ray powder diffraction is provided in Cullity, B. D. Elements of X-ray Diffraction. Addison-Wesley, (1978) ISBN 0-201-01174-3 Chapter 14), which is herein incorporated by reference. PXRD data consists of experimentally determined values of the two-theta position, the intensity values of multiple crystallographic reflections, also known as Bragg reflections, and their peak shape. The PXRD data may be analyzed computational, including by the method of Rietveld refinement. A detailed description of Rietveld refinement of X-ray powder diffraction data is provided in Pecharsky, Vitalij K.; Zavalij, Peter Y. (2009) Fundamentals of powder diffraction and structural characterization of materials (2nd ed.). New York: Springer. ISBN 978-0-387-09579-0. OCLC 314182615, which is herein incorporated by reference.

[0211] PXRD data may be collected at various temperatures or pressures in order to facilitate Rietveld refinement. The experimental PXRD data including 2-theta values, d-spacing, Bragg reflections and intensity values may be compared to a simulated PXRD pattern derived from the single crystal structure determination which represents an idealized pure powder, using a computational method such as described in Macrae, Clare F., et al. "Mercury 4.0: from visualization to analysis, design and prediction." Journal of Applied Crystallography vol. 53, 226-235. 1 Feb. 2020, doi:10.1107/S1600576719014092.

[0212] One of ordinary skill in the art will appreciate that an X-ray powder diffraction pattern may be obtained with a measurement error that is dependent upon the measurement conditions employed in the data collection. It is generally accepted that the peak shape, intensity values and two-theta positions derived from an X-ray powder diffraction pattern can fluctuate depending upon the type of instrument used, the measurement conditions and the method of computational analysis performed. It should be further understood that that the two-theta values and their relative intensities may also vary and accordingly, the exact order of intensity values should not be taken into account.

[0213] Additionally, the experimental error for diffraction angle measurements for a conventional X-ray powder diffraction pattern is typically about 5% or less. Assessment of the extent of measurement error should be taken into account when describing the position of the two-theta diffraction peaks. Consequently, it is to be understood that the crystal forms described in this invention are not limited to the crystal forms that provide X-ray powder diffraction patterns completely identical to the X-ray powder diffraction patterns depicted in the accompanying Figures disclosed herein. Any crystal forms that provide X-ray powder diffraction patterns substantially identical to those disclosed in the accompanying Figures fall within the scope of the present invention. The ability to ascertain substantial identities of X-ray diffraction patterns is within the purview of one of ordinary skill in the art. Likewise, it is to be understood that any crystal forms that provide differential scanning calorimetry (DSC) and/or thermogravimetric analysis (TGA) substantially identical to those disclosed in the accompanying Figures fall within the scope of the present invention. The ability to ascertain substantial identities of these patterns is within the purview of one of ordinary skill in the art.

[0214] Crystalline Form A of Compound (P)-I is anhydrous and was obtained from crystallization conditions described in Example 4 utilizing various organic solvents and organic/water solvent systems.

[0215] X-Ray Powder Diffraction (PXRD) diffractograms were acquired on PANalytical X'Pert Pro diffractometer using Ni-filtered Cu Ka (45 kV/40 mA) radiation and a step size of 0.02° 2θ and X'celerator™ RTMS (Real Time Multi-Strip) detector. Configuration on the incidental beam side: fixed divergence slit (0.25°), 0.04 rad Soller slits, anti-scatter slit (0.25°), and 10 mm beam mask. Configuration on the diffracted beam side: fixed divergence slit (0.25°) and 0.04 rad Soller slit. Samples were mounted flat on zero-background Si wafers.

[0216] Values of significant Bragg reflections, their 2-theta positions and d-spacing values, as compared to results from simulated PXRD data of crystalline Form A of Compound (P)-I are shown in Table 7 and the PXRD spectrum is shown in FIG. **1**.

TABLE 7

Experimental PXRD		Simulated PXRD				
		Bragg Reflections			2-Theta	
2-Theta Angles (°)	d (Å)	h	k	l	Angles (°)	d (Å)
5.21	16.946	0	0	1	5.20	17.2385
9.78	9.0362	0	1	0	9.80	8.99183
10.27	8.6059	0	1	1	10.26	8.48713
13.00	6.8073	0	1	2	13.16	6.92863
15.34	5.7705	0	1	−2	15.22	5.81934
15.51	5.7099	0	0	3	15.41	5.74618
16.92	5.2351	0	1	3	17.07	5.33869
17.92	4.9473	1	1	−2	17.91	4.94901
18.86	4.7017	1	−1	1	18.85	4.70444
19.60	4.5254	0	2	1	19.66	4.58616
20.57	4.3147	1	−1	−2	20.65	4.30016
21.01	4.2259	0	2	2	20.92	4.24356
23.60	3.7675	0	2	−2	23.58	3.77065
24.29	3.6608	0	1	4	24.13	3.65807
25.92	3.4341	2	2	2	25.70	3.46431
29.05	3.0712	1	−1	2	29.19	3.0598
29.48	3.0275	0	3	1	29.48	3.02715

[0217] Differential Scanning Calorimetry (DSC) was conducted with a TA Instruments Q100 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N_2 purge. DSC thermograms were obtained at 15° C./min in crimped Al pans.

[0218] Thermogravimetric Analysis (TGA) thermograms were obtained with a TA Instruments Q500 thermogravimetric analyzer under 40 mL/min N2 purge at 15° C./min in Pt or Al pans.

[0219] DSC analysis indicates crystalline Form A of Compound (P)-I exhibits a melting/racemization event at 187.92° C., followed by a recrystallization event at 195.8° C., and finally a sharp endotherm at 253.5° C. (melt of racemate). Negligible weight loss (0.7%) is observed between 25-256° C. by TGA. DSC and TGS thermograms are shown in FIG. **2** Fourier Transform Infrared Spectroscopy (FT-IR): Char

acteristic spectral absorbance data from FT-IR of Form A of Compound (P)-I showing the location of significant IR-active regions and their functional group assignments is shown in Table 8.

TABLE 8

Wavenumber (cm−1)	Functional Group Assignment
3486	—OH stretch
3072	C—H (aromatic) stretch
2982	C—H (CH3) stretch
1656	C═O stretch
1605	C═N stretch
1592	C═N stretch
1571	C═C stretch
1546	C═N stretch
1525	C═C stretch
1476	C—H (CH2) bend
1457	CH2 scissor
1429	C—H (CH3) bend
1385	C—H (gem dimethyl) bend
1380	—O—H bend
1350	C—N(pyridone) stretch
1296	C—F stretch
1237	C—O (conjugated, alkyl ether) stretch
1214	C—H (aromatic) bend
1184	C—O (tertiary alcohol) stretch
1130	C—F stretch
1103	C—H (aromatic) bend
1051	C—F stretch
1044	C—F stretch
1005	C—H (aromatic) bend
978	C—H (aromatic) bend
964	C—H (aromatic) bend
860	C—H (aromatic) bend
840	C—H (aromatic) bend
810	C—H (aromatic) bend
793	C—H (aromatic) bend
781	C—H (aromatic) bend
755	C—Cl stretch
741	C—H (aromatic) bend
703	C—H (aromatic) bend
669	N—C═O bend

Example 12: Formulations of ATI-450 Tablets

[0220] The compositions of the tablets comprising ATI-450 and tablets comprising placebo used in the Examples herein are provided in Table 9 below. The excipients used in the drug tables and their function are provided in Table 10 below.

TABLE 9

	10 mg strength		Placebo		50 mg strength		Placebo	
Component	% w/w	mg/tab	% w/w	mg/tab	% w/w	mg/tab	% w/w	mg/tab
ATI-450	12.5	10	—	—	12.5	50	—	—
Silicified microcrystalline cellulose	71	56.8	83.5	66.8	71	284	83.5	334
Mannitol	10	8	10	8	10	40	10	40
Crospovidone	5	4	5	4	5	20	5	20
Hydrophilic fumed silica	0.75	0.6	0.75	0.6	0.75	3	0.75	3
Magnesium stearate	0.75	0.6	0.75	0.6	0.75	3	0.75	3
Total	100	80	100	80	100	400	100	400

TABLE 10

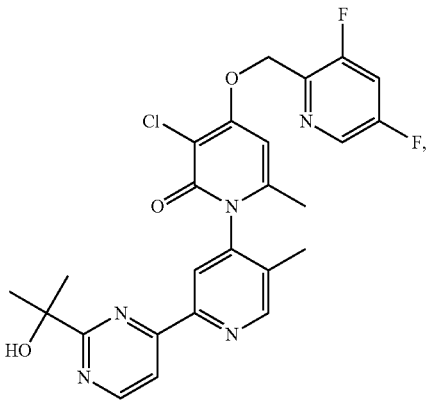
Excipient	Chemical Name	Function	Quality Standard
ProSolv HD 90	Silicified microcrystalline cellulose	Filler/Binder	NF/EP/JP
Perlitol 200 SD	Mannitol	Diluent	USP/EP
Polyplasdone XL	Crospovidone	Disintegrant	NF/EP/JP
Aerosil 200	Colloidal silicone dioxide	Glidant	NF/EP/JP
Magnesium stearate	Magnesium stearate	Lubricant	NF/EP/JP

[0221] Although embodiments herein have been described in considerable detail with reference to certain preferred embodiments thereof, other versions are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description and the preferred versions contained within this specification.

1. A method of treating a viral infection in a subject, the method comprising:

administering orally, to a subject having a viral infection, a therapeutically effective amount of Compound I

(I)



or a derivative thereof to treat the viral infection.

2. The method of claim **1**, wherein the viral infection comprises infection by influenza, parainfluenza, paramyxovirus, adenovirus, parvovirus, variola virus, enterovirus,

rotavirus, hemorrhagic fever virus, hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus, or coronavirus.

3. The method of claim **2**, wherein the subject has a coronavirus infection selected from SARS-CoV-2, SARS-CoV, MERS-CoV, and HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1.

4. The method of claim **1** or claim **2**, wherein the viral infection comprises infection by SARS-CoV-2 or a variant thereof.

5. The method of any one of claims **1-4**, wherein 50 mg/day of Compound I is administered to said subject.

6. The method of any one of claims **1-4**, wherein 100 mg/day of Compound I is administered to said subject.

7. The method of any one of claims **1-4**, wherein 160 mg/day of Compound I is administered to said subject.

8. The method of any one of claims **1-4**, wherein 200 mg/day of Compound I is administered to said subject.

9. The method of any one of claims **1-4**, wherein 240 mg/day of Compound I is administered to said subject.

10. The method of any one of claims **1-9**, wherein Compound I is administered once a day.

11. The method of any one of claims **1-9**, wherein Compound I is administered twice a day.

12. The method of any one of claims **1-4**, wherein 50 mg of Compound I is administered to the subject twice daily.

13. The method of any one of claim **1-4**, wherein 50 mg of Compound I is administered to a subject infected with a coronavirus twice daily.

14. The method of any one of claims **1-4**, wherein 80 mg of Compound I is administered to the subject twice daily.

15. The method of any one of claims **1-4**, wherein 100 mg of Compound I is administered to the subject twice daily.

16. The method of any one of claims **1-4**, wherein 120 mg of Compound I is administered to the subject twice daily.

17. The method of any one of claims **1-16**, wherein the method further comprises administering at least one additional antiviral agent to the subject.

18. The method of any one of claims **1-16**, wherein the method further comprises administering at least one additional immunomodulatory agent to the subject.

19. The method of any one of claims **1-18**, wherein Compound 1 is formulated as a solid dosage form selected from a tablet, a capsule, a lozenge, a sachet, a powder, granules, and orally dispersible film.

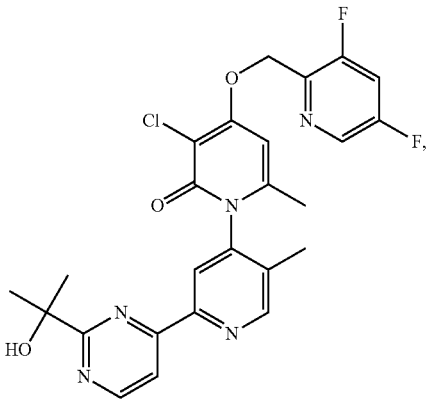
20. The method of any one of claims **1-19**, wherein said administering is carried out under conditions effective to significantly reduce in vivo serum levels of one or more inflammatory cytokines.

21. The method of claim **20**, wherein the one or more inflammatory cytokines is selected from the group consisting of TNF-α, IL-1β, IL-6, IL-8, IFNγ, IL-17, IL-18, IL-1α, and IL-1RA.

22. A method of treating infection induced cytokine release syndrome (CRS) or acute respiratory distress syndrome (ARDS) in a subject, the method comprising:

administering orally, to a subject having an infection, a therapeutically effective amount of Compound I

(I)



or a derivative thereof to treat the CRS or ARDS.

23. The method of claim **22**, wherein the subject has a viral infection or a bacterial infection.

24. The method of claim **23**, wherein the subject has a viral infection caused by influenza, parainfluenza, paramyxovirus, adenovirus, parvovirus, variola virus, enterovirus, rotavirus, hemorrhagic fever viruses hepatitis virus, parechovirus, human T-lymphotrophic virus, Epstein-Barr virus, or coronavirus.

25. The method of claim **24**, wherein the subject has a coronavirus infection selected from SARS-CoV-2, SARS-CoV, MERS-CoV, and HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1.

26. The method of claim **25**, wherein the subject is infected with SARS-CoV-2.

27. The method of any one of claims **22-26**, wherein 50 mg/day of Compound I is administered to said subject.

28. The method of any one of claims **22-26**, wherein 100 mg/day of Compound I is administered to said subject.

29. The method of any one of claims **22-26**, wherein 160 mg/day of Compound I is administered to said subject.

30. The method of any one of claims **22-26**, wherein 200 mg/day of Compound I is administered to said subject.

31. The method of any one of claims **22-26**, wherein 240 mg/day of Compound I is administered to said subject.

32. The method of any one of claims **22-31**, wherein Compound I is administered once a day.

33. The method of any one of claims **22-31**, wherein Compound I is administered twice a day.

34. The method of any one of claims **22-26**, wherein 50 mg of Compound I is administered to the subject twice daily.

35. The method of any one of claim **22-26**, wherein 50 mg of Compound I is administered to a subject infected with a coronavirus twice daily.

36. The method of any one of claims **22-26**, wherein 80 mg of Compound I is administered to the subject twice daily.

37. The method of any one of claims **22-26**, wherein 100 mg of Compound I is administered to the subject twice daily.

38. The method of any one of claims **22-26**, wherein 120 mg of Compound I is administered to the subject twice daily.

39. The method of any one of claims **1-16**, wherein the method further comprises administering at least one additional antiviral agent to the subject.

40. The method of any one of claims **1-16**, wherein the method further comprises administering at least one additional immunomodulatory agent to the subject.

41. The method of any one of claims **1-39**, wherein the subject is a human.

42. The method of any one of claims **1-39**, wherein the subject is a human.

* * * * *