[0019] Colchicine has a narrow therapeutic index with no clear distinction between nontoxic, toxic, and lethal doses. Metabolically, colchicine is eliminated via P-glycoprotein (P-gp; also known as Multi-Drug Resistance 1 (MDR1) protein). Drug-drug interactions are common with CYP3A4 and P-glycoprotein inhibitors which can increase colchicine blood concentrations to toxic levels leading to colchicine poisoning and death. Life-threatening and fatal toxicities have been observed when colchicine is administered with P-gp or strong CYP3A4 inhibitors even at approved therapeutic doses. Additional serious toxicities including myelosuppression, disseminated intravascular coagulation, and cell damage in renal, hepatic, circulatory, and central nervous systems have been observed with approved therapeutic doses of colchicine. These observed serious adverse events limit the clinical use of colchicine.

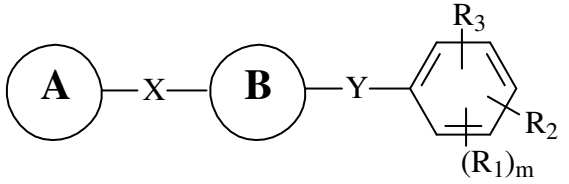
[0020] The antiviral activity of combretastatin, colchicine, and colchicine derivatives and their selected prodrugs against DENV and ZIKV in cell culture was observed at low micromolar and sub-micromolar concentrations. A major problem with taxanes, as with many biologically active natural products, is its lipophilicity and lack of solubility in aqueous systems. This leads to the use of emulsifiers like Cremophor EL and Tween 80 in clinical preparations, which leads to serious hypersensitivity reactions.

[0021] Nocodazole is a synthetic compound identified in a screen for anthelminthic agents. Nocodazole is a microtubule depolymerization agent as it binds to free tubulin heterodimers and prevents them from incorporating into microtubules. It has not been used clinically because of poor bioavailability and high toxicity.

[0022] The cellular and viral solution to master intracellular trafficking is an organized network or filaments including microtubules. Cells require microtubules for long-term normal physiology, and viruses are obligate intracellular parasites that completely depend on the physiology of the host cell. Thus, it is no surprise that most, if not all, viral life cycles require microtubules for efficient replication. The viral binding sites on microtubules might provide new targets for antiviral therapy. The inventions of this application address a novel method of interfering with microtubules of the cytoskeleton to prevent virus intracellular transportation, replication, and egress.

SUMMARY ~~OF THE INVENTION~~

[0023] In one aspect, the present disclosure provides use of a formulation having a therapeutically effective amount of a compound of Formula (I):



(I)

wherein

A is phenyl, indolyl, or indazolyl, optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, OC(O)CF_3, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -C(O)NH_2 or NO_2;

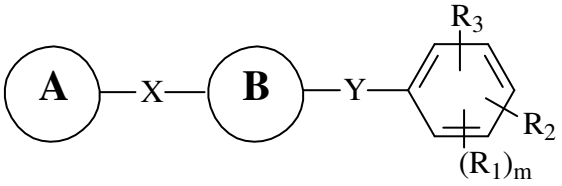
B is an imidazole or benzimidazole, optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-halo(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, hydroxyl, or NO_2;

R_1, R_2 and **R_3** are independently at least one of hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, OC(O)CF_3, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -C(O)NH_2 or NO_2;

X is a bond or NH;

Y is -C=O; and

m is 1-3, or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof, in the manufacture of a medicament for treating a coronavirus infection in a subject in need thereof. One example of ~~The invention~~ the disclosure encompasses methods of treating a coronavirus infection in a subject in need thereof by administering to the subject a formulation having a therapeutically effective amount of a compound of Formula (I)



(I)

wherein

A is phenyl, indolyl, or indazolyl, optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

B is an imidazole or benzimidazole, optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-halo(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, hydroxyl, or NO_2;

R_1, R_2 and **R_3** are independently at least one of hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

X is a bond or NH;

Y is -C=O; and

m is 1-3, or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

[0024] In an ~~embodiment~~example of the ~~invention~~disclosure, the method encompasses compounds of Formula I wherein **A** is phenyl or indolyl, optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

B is an imidazole, optionally substituted with at least one of (C_1-C_4)alkyl;

R_1, R_2 and **R_3** are independently at least one of hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

X is a bond or NH;

Y is -C=O; and

m is 1-3, or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

[0025] In another ~~embodiment~~example of the ~~invention~~disclosure, the method encompasses compounds of Formula I wherein **A** is phenyl, optionally substituted with at least one of $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkylamino, amino$(C_1$-$C_4)$alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-$(C_1$-$C_4)$alkyl, COOH, -C(O)Ph, C(O)O-$(C_1$-$C_4)$alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

B is an imidazole, optionally substituted with at least one of $(C_1$-$C_4)$alkyl;

R_1, R_2 and **R_3** are independently at least one of hydrogen, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkylamino, amino$(C_1$-$C_4)$alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-$(C_1$-$C_4)$alkyl, COOH, -C(O)Ph, C(O)O-$(C_1$-$C_4)$alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

X is a bond or NH;

Y is -C=O; and

m is 1-3, or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

[0026] In yet another ~~embodiment~~example of the ~~invention~~disclosure, the method encompasses compounds of Formula I wherein **A** is indolyl, optionally substituted with at least one of $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkylamino, amino$(C_1$-$C_4)$alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-$(C_1$-$C_4)$alkyl, COOH, -C(O)Ph, C(O)O-$(C_1$-$C_4)$alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

B is an imidazole, optionally substituted with at least one of $(C_1$-$C_4)$alkyl;

R_1, R_2 and **R_3** are independently at least one of hydrogen, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkylamino, amino$(C_1$-$C_4)$alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-$(C_1$-$C_4)$alkyl, COOH, -C(O)Ph, C(O)O-$(C_1$-$C_4)$alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

X is a bond or NH;

Y is -C=O; and

m is 1-3, or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

[0027] An ~~embodiment~~example of the ~~invention~~disclosure, the method encompasses compounds of Formula I wherein **A** is indolyl, optionally substituted with at least one of $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkylamino, amino$(C_1$-$C_4)$alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-$(C_1$-$C_4)$alkyl, COOH, -C(O)Ph, C(O)O-$(C_1$-$C_4)$alkyl, C(O)H, -$C(O)NH_2$ or NO_2;

B is an imidazole, optionally substituted with at least one of $(C_1$-$C_4)$alkyl;

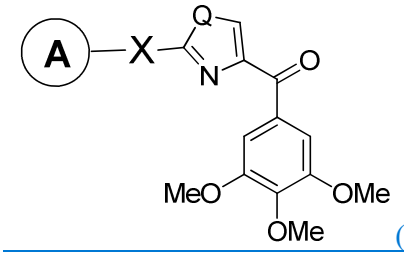
R_1, R_2 and **R_3** are independently at least one of hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, OC(O)CF_3, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -C(O)NH_2 or NO_2;

X is a bond;

Y is -C=O; and

m is 1-3, or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

[0028] In one aspect, the present disclosure provides use of a formulation having a therapeutically effective amount of a compound of the Formula **VII**:



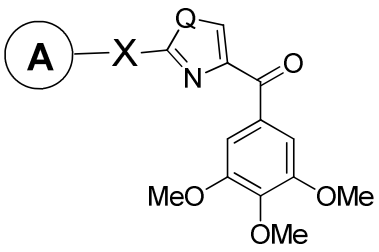
(**VII**)

wherein

X is a bond or NH;

Q is NH and

A is a phenyl, indolyl, or indazolyl ring optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, OC(O)CF_3, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -C(O)NH_2 or NO_2; or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof, in the manufacture of a medicament for treating a coronavirus infection in a subject in need thereof. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating a coronavirus infection in a subject in need thereof by administering to the subject a formulation having a therapeutically effective amount of a compound of the Formula **VII**:



(**VII**)

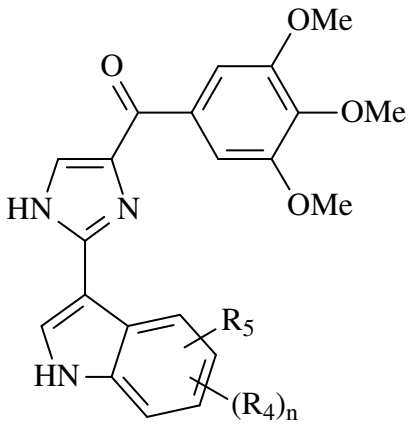
wherein

X is a bond or NH ;

Q is NH; and

A is a phenyl, indolyl, or indazolyl ring optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2; or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof. In another ~~embodiment~~example of the ~~invention~~disclosure, the method encompasses compounds of Formula VII wherein X is NH. In yet another ~~embodiment~~example of the ~~invention~~disclosure, the method encompasses compounds of Formula VII, wherien **X** is a bond; **Q** is NH; and **A** is an indolyl ring optionally substituted with at least one of (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2; or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

[0029] In one aspect, the present disclosure provides use of a formulation having a therapeutically effective amount of a compound of the Formula **VII(c)**:

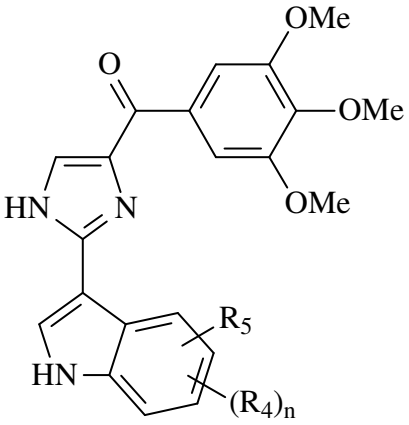


VII(c)

wherein

R4 and **R5** independently hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, OC(O)CF_3, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -C(O)NH_2 or NO_2; and

n is 1-4; or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof, in the manufacture of a medicament for treating a coronavirus infection in a subject in need thereof. An ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating a coronavirus infection in a subject in need thereof by administering to the subject a formulation having a therapeutically effective amount of a compound of the Formula **VII(c)**:



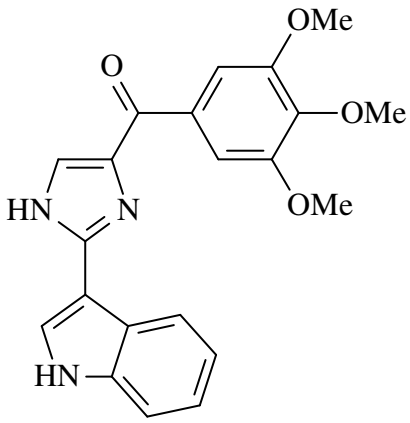
VII(c)

wherein

R_4 and **R_5** independently hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-(C_1-C_4)haloalkyl, (C_1-C_4)alkylamino, amino(C_1-C_4)alkyl, F, Cl, Br, I, CN, -CH_2CN, NH_2, hydroxyl, $OC(O)CF_3$, -OCH_2Ph, -NHCO-(C_1-C_4)alkyl, COOH, -C(O)Ph, C(O)O-(C_1-C_4)alkyl, C(O)H, -$C(O)NH_2$ or NO_2; and

n is 1-4; or a pharmaceutically acceptable salt, hydrate, polymorph, or isomer thereof.

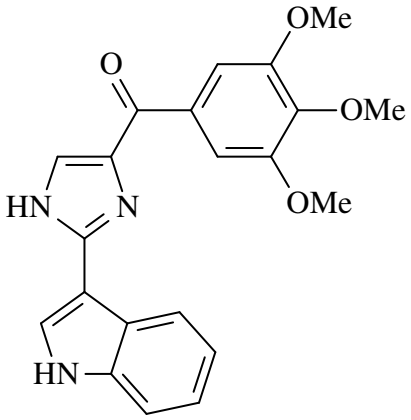
[0030] In one aspect, the present disclosure provides use of a formulation having a therapeutically effective amount of a compound **17ya** represented:



(**17ya**),

in the manufacture of a medicament for treating a coronavirus infection in a subject in need thereof.

Another ~~embodiment~~example of the ~~invention~~disclosure, encompasses methods of treating a coronavirus infection in a subject in need thereof by administering to the subject a formulation having a therapeutically effective amount of a compound **17ya** represented:



(**17ya**).

[0031] Yet another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating viral infections wherein the viral infection is caused by a *Coronaviridae* virus. An ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating coronavirus infections wherein the infection is caused by SARS-CoV,

MERS-CoV, COVID-19 or SARS-CoV-2. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating coronavirus infections wherein the infection is caused by COVID-19.

[0032] An ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating viral infections in which the infection is caused by a coronavirus. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses, methods of treating a coronavirus infection caused by SARS-CoV, MERS-CoV, or SARS-CoV-2. A preferred ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating a subject with SARS-CoV-2 infection. A further ~~embodiment~~example of the ~~invention~~disclosure encompasses methods of treating a subject with SARS-CoV-2 infection at high risk for acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS). Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection reduces respiratory failure and/or mortality. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection at high risk for acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) reduces mortality. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection reduces morbidity. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection at high risk for acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) reduces morbidity. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection reduces respiratory failure, days in ICU, days on mechanical ventilator, or improves WHO Ordinal Scale for Clinical Improvements. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection at high risk for acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) reduces respiratory failure, days in ICU, days on mechanical ventilator, or improves WHO Ordinal Scale for Clinical Improvements. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection reduces mortality or respiratory failure in subjects >60 years of age. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection at high risk for acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) reduces mortality or respiratory failure in subjects >60 years of age. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection reduces mortality or respiratory failure when dosed in combination with remdesivir and/or dexamethasone. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein treating a subject with SARS-CoV-2 infection at high risk for acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) reduces mortality or respiratory failure when dosed in combination

with remdesivir and/or dexamethasone. As used herein, the reduction in mortality, morbidity, or respiratory failure, days in ICU, days on mechanical ventilator, and the like means the reduction is in comparison to a subject (or subject population) treated with placebo. Likewise, any improvement, such as in WHO Ordinal Scale for Clinical Improvements, means an improvement in comparison to a subject (or subject population) treated with placebo.

[0033] Yet another ~~embodiment~~example of the ~~invention~~disclosure, the methods further comprise at least one additional therapy. An ~~embodiment~~example of the method further comprises a second antiviral therapy such as a neuraminidase inhibitor, remdesivir, hydroxychloroquine, azithromycin, or hemagglutinin inhibitor. An ~~embodiment~~example of the method further comprises medications that modulate the immune system or host cell factors such as dexamethasone or another corticosteroid, an IL-6 inhibitor such as tocilizumab, interferons, an IL-1 inhibitor, or a kinase inhibitor such as baricitinib. Yet another ~~embodiment~~example of the ~~invention~~disclosure, the methods further comprise an antibody therapy such as high titer COVID-19 convalescent plasma, intravenous immunoglobulin therapy (IVIG), a monoclonal antibody therapy such as casirivimab plus imdevimab, bamlanivimab, or bamlanivimab plus etesevimab. An ~~embodiment~~example of the method further comprises an additional therapy such as a remdesivir and/or dexamethasone or other corticosteroids. An ~~embodiment~~example of the method further comprises an additional therapy such as tocilizumab. An ~~embodiment~~example of the method further comprises an additional therapy such as baricitinib. An ~~embodiment~~example of the method further comprises an additional therapy such as high title COVID-19 convalescent plasma. An ~~embodiment~~example of the method further comprises an additional therapy such as IVIG. An ~~embodiment~~example of the method further comprises an additional therapy such as casirivimab plus imdevimab. An ~~embodiment~~example of the method further comprises an additional therapy such as bamlanivimab. An ~~embodiment~~example of the method further comprises an additional therapy such as bamlanivimab plus etesevimab. Yet another ~~embodiment~~example of the methods includes a second antiviral therapy that is at least one of favipiravir, lopinavir, ritonavir, remdesivir, janus kinase inhibitors, hydroxychloroquine, azithromycin, amantadine, rimantadine, ribavirin, idoxuridine, trifluridine, vidarabine, acyclovir, ganciclovir, foscarnet, zidovudine, didanosine, peramivir, zalcitabine, stavudine, famciclovir, oseltamivir, zanamivir, or valaciclovir. Yet another ~~embodiment~~example of the methods includes a second therapy that is at least one of vitamins C or D, zinc, famotidine, ivermectin, or angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor binding (ARB) agent.

[0034] An ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein the compound of the ~~invention~~disclosure is administered in an amount of about 1 mg to about 100 mg. Another ~~embodiment~~example of the ~~invention~~disclosure

encompasses methods wherein the compound of the ~~invention~~disclosure is administered in an amount of about 4 to about 90 mg. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein the compound of the ~~invention~~disclosure is administered in an amount of about 9 mg to about 18 mg. Another ~~embodiment~~example of the ~~invention~~disclosure encompasses methods wherein the compound of the ~~invention~~disclosure is administered in an amount of about 4 mg to about 45 mg. In yet another ~~embodiment~~example of the method encompasses at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[0036] **Figure 1** illustrates the mean WHO Ordinal Scale for Clinical Improvement by Day (0=baseline). The area under the mean curve is 153 for the patient group treated with Compound 17ya and 182 for the group treated with placebo.

DETAILED DESCRIPTION OF THE INVENTION

[0037] Microtubule based macromolecule intracellular transport is a critical aspect of viral replication. For viral infection, expression of viral proteins alters the organization of these microtubular networks to serve their need to replicate and spread infectious virion. Microtubules not only facilitate infection, but microtubules are actively manipulated by viruses. Furthermore, cytoskeleton disruptor agents suppress viral infection.

[0038] Not to be limited by theory, the invention is based, in part, on the fact that tubulin interacts with the cytoplasmic domain of *alphacoronavirus* and *betacoronavirus* SARS-CoV spike S proteins. The reduction in infectious virus titer may follow by treatment with a drug that causes microtubule depolymerization, mainly because there is less S protein present at the assembly site due to impaired S protein-microtubule transport and that the incorporation process of S protein itself into virions is tubulin-dependent. Furthermore, disruption of microtubule trafficking impaired the egress out of the cell of these poorly assembled virions with less surface spike S proteins, making them less infectious. A microtubule depolymerizing agent may be effective in treating coronavirus infection by disrupting microtubule trafficking which is critical for the virus replication cycle.

[0039] The present invention is directed to antiviral therapy based upon the cytoskeleton disruptor activity of the claimed compounds that interrupts the intracellular microtubules trafficking network.