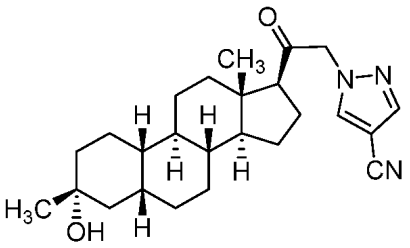
[0006] Accordingly, there is a need for the development of an effective COVID-19 treatment.

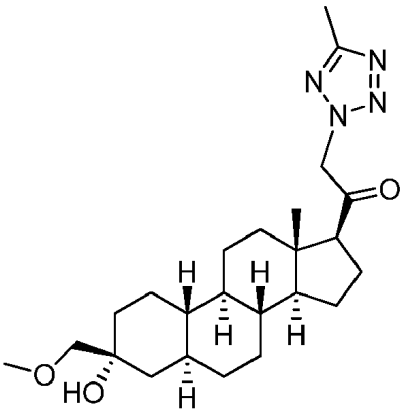
SUMMARY

[0006a] In one aspect of the present disclosure, there is provided a use of a $GABA_A$ PAM, or a pharmaceutically acceptable salt or crystalline form thereof, wherein the $GABA_A$ PAM is selected from the group consisting of **Compound 1**



Compound 1

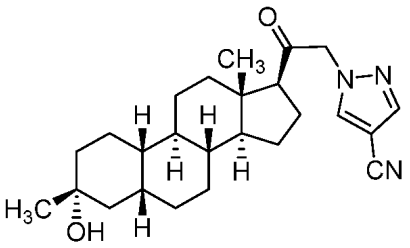
and **Compound 2**



Compound 2

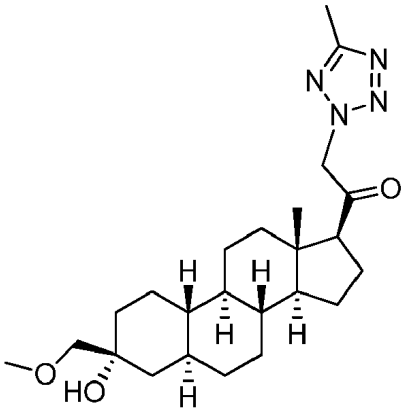
in the manufacture of a medicament for treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a human subject.

[0007] One example of the present disclosure provides a method of treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of an agent selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2,

or a pharmaceutically acceptable salt thereof.

[0008] Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the agent is **Compound 1**. In some examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some examples, the respiratory condition is respiratory distress. In some examples, the respiratory condition is acute respiratory distress syndrome. In some examples, the subject exhibits a symptom of the respiratory condition, wherein the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain. In some examples, the

inflammation of lung tissue is bronchitis or bronchiectasis. In some examples, the inflammation of lung tissue is pneumonia. In some examples, the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia. In some examples, the subject is undergoing or has undergone treatment for an infection, fibrosis, a fibrotic episode, chronic obstructive pulmonary disease, Sarcoidosis (or pulmonary sarcoidosis) or asthma/asthma-related inflammation. In some examples, the subject is undergoing or has undergone treatment for an infection. In some examples, the infection is a viral infection. In some examples, the viral infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus. In some examples, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV. In some examples, the coronavirus is SARS-CoV-2. In some examples, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS. In some examples, the disease is COVID-19. In some examples, the infection is a bacterial infection. In some examples, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae.* In some examples, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*. In some examples, the subject is undergoing or has undergone treatment for fibrosis or a fibrotic episode. In some examples, the fibrosis is cystic fibrosis. In some examples, the subject has been previously administered another agent selected from the group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, an antibody, and an antibacterial. In some examples, the subject has previously been administered the agent described herein and is further administered a second agent selected from a group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, and an antibacterial. In some examples, the subject has the agent co-administered with a second agent selected from a bronchial muscle/airway relaxant, an antiviral, oxygen, and an antibacterial. In some examples, the antiviral is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir. In some examples, the antibody is sarilumab or tocilizumab. In some examples, the antibacterial is azithromycin. In some examples, the subject is being or has been treated with mechanical ventilation. In some examples, the subject is being or has been treated with an oxygen mask. In some examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some

examples, the agent is administered intravenously. In some examples, the agent is administered orally.

[0009] Another example of the disclosure provides a method of treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a subject undergoing or has undergone treatment for an infection, comprising administering an agent selected from the group consisting of **Compound 1** and **Compound 2**, or a pharmaceutically acceptable salt thereof to the subject.

[0010] Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus. In some examples, the virus a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV. In some examples, the coronavirus is SARS-CoV-2. In some examples, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS. In some examples, the disease is COVID-19. In some examples, the infection is a bacterial infection. In some examples, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae.* In some examples, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus.* In some examples, the agent is **Compound 1**. In some examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some examples, the agent is administered intravenously. In some examples, the agent is administered orally.

[0011] Another example of the disclosure provides a method of treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a subject comprising administering an agent selected from the group consisting of **Compound 1** and **Compound 2**, or a pharmaceutically acceptable salt thereof to the subject, wherein the subject has been treated with or is being treated with mechanical ventilation.

[0012] Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the subject has acute respiratory distress syndrome. In some examples, the agent is **Compound 1**. In some examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some examples, the agent is

Compound 2 or a pharmaceutically acceptable salt thereof. In some examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some examples, the agent is administered intravenously. In some examples, the agent is administered orally. In some examples, the subject is undergoing or has undergone treatment for an infection, comprising administering to the subject an agent selected from the group consisting of **Compound 1** and **Compound 2**, or a pharmaceutically acceptable salt thereof. In some examples, the infection is a viral infection comprising an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus. In some examples, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV. In some examples, the coronavirus is SARS-CoV-2. In some examples, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS. In some examples, the disease is COVID-19.

[0013] Another example of the disclosure provides a method of treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a subject comprising administering an agent selected from the group consisting of **Compound 1** and **Compound 2**, or a pharmaceutically acceptable salt thereof to the subject, wherein the subject has been or is being treated for a disease or condition, wherein the disease or condition is selected from the group consisting of cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, pulmonary sarcoidosis, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus- Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's

disease, several polyglutamine neurological disorders such as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease.

[0014] Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the agent is **Compound 1**. In some examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some examples, the agent is administered intravenously. In some examples, the agent is administered orally. In some examples, the agent is administered at a rate of 90-160 μg/kg per hour for a therapeutically sufficient duration. In some examples, the agent is administered at a rate of 90-150 μg/kg/hour. In some examples, the agent is administered at a rate of 130-150 μg/kg/hour. In some examples, the agent is administered at a rate of 140-150 μg/kg/hour. In some examples, the agent is administered at a rate of about 150 μg/kg/hour. In some examples, the agent is administered at a rate of about 140 μg/kg/hour. In some examples, the agent is administered at a rate of about 120 μg/kg/hour. In some examples, the agent is administered at a rate of about 100 μg/kg/hour. In some examples, the agent is administered at a rate of 10-100 μg/kg/hour. In some examples, the agent is administered at a rate of 30-80 μg/kg/hour. In some examples, the agent is administered at a rate of 35-70 μg/kg/hour. In some examples, the agent is administered at a rate of 70 μg/kg/hour. In some examples, the agent is administered at a rate of 35 μg/kg/hour. In some examples, the agent is administered at a rate of 60-80 μg/kg/hour. In some examples, the therapeutically sufficient duration is at least 24 hours. In some examples, the therapeutically sufficient duration is at least 48 hours. In some examples, the therapeutically sufficient duration is at least 60 hours. In some examples, the therapeutically sufficient duration is at least 3 days. In some examples, the therapeutically sufficient duration is at least 4 days. In some examples, the therapeutically sufficient duration is at least 5 days. In some examples, the therapeutically sufficient duration is at least 6 days. In some examples, the subject is being treated or has been treated with mechanical ventilation. In some examples, the agent is administered to a subject until the subject is no longer being treated with mechanical ventilation.

[0015] Another example of the disclosure provides a method of treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a subject comprising administering an agent selected from the group consisting of **Compound 1** and **Compound 2**, or a pharmaceutically acceptable salt thereof to the subject, wherein the subject has a disease associated with a coronavirus.

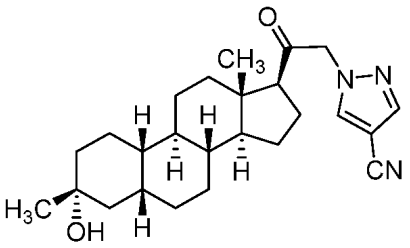
[0016] Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the disease is selected from SARS, MERS and COVID-19. In some examples, wherein the disease is COVID-19. In some examples, the subject suffers from respiratory distress. In some examples, the respiratory distress is acute respiratory distress syndrome. In some examples, the subject exhibits a symptom selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain. In some examples, the inflammation of lung tissue is bronchitis or bronchiectasis. In some examples, the inflammation of lung tissue is pneumonia. In some examples, the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia. In some examples, the subject is being or has been treated with mechanical ventilation or oxygen treatment. In some examples, the subject is being or has been treated with mechanical ventilation. In some examples, the agent is **Compound 1**. In some examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some examples, the agent is administered intravenously. In some examples, the agent is administered orally.

[0017] In some examples, the agent is administered at a rate of 90-160 μg/kg per hour for a therapeutically sufficient duration. In some examples, the agent is administered at a rate of 90-150 μg/kg/hour. In some examples, the agent is administered at a rate of 130-150 μg/kg/hour. In some examples, the agent is administered at a rate of 140-150 μg/kg/hour. In some examples, the agent is administered at a rate of about 150 μg/kg/hour. In some examples, the agent is administered at a rate of about 140 μg/kg/hour. In some examples, the agent is administered at a rate of about 120 μg/kg/hour. In some examples, the agent is administered at a rate of about 100 μg/kg/hour. In some examples, the agent is administered at a rate of 10-100 μg/kg/hour. In some examples, the agent is administered at a rate of 30-80 μg/kg/hour. In some examples, the agent is administered at a rate of 35-70 μg/kg/hour. In some examples,

the agent is administered at a rate of 70 µg/kg/hour. In some examples, the agent is administered at a rate of 35 µg/kg/hour. In some examples, the agent is administered at a rate of 60-80 µg/kg/hour. In some examples, the therapeutically sufficient duration is at least 24 hours. In some examples, the therapeutically sufficient duration is at least 48 hours. In some examples, the therapeutically sufficient duration is at least 60 hours. In some examples, the therapeutically sufficient duration is at least 3 days. In some examples, the therapeutically sufficient duration is at least 4 days. In some examples, the therapeutically sufficient duration is at least 5 days. In some examples, the therapeutically sufficient duration is at least 6 days. In some examples, the subject is being treated or has been treated with mechanical ventilation. In some examples, the agent is administered to a subject until the subject is no longer being treated with mechanical ventilation. In some examples, the patient has acute respiratory distress syndrome. In some examples, the patient is intubated. In some examples, the patient is under 70 years of age.

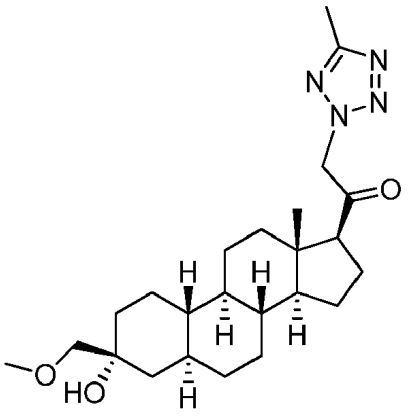
[0018] In some examples, the patient is 70 years of age or older in any one example of the present disclosure.

[0019] In one example, the disclosure includes a method of treating a subject with a respiratory condition, comprising administering an agent selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2,

or a pharmaceutically acceptable salt thereof.

[0020] In one example of this example, the agent is **Compound 1**.

[0021] In another example, the agent is a pharmaceutically acceptable salt of **Compound 1**.

[0022] In one example, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof.

[0023] In one example, the respiratory condition is respiratory distress.

[0024] In a further example, the respiratory condition is acute respiratory distress syndrome.

[0025] In one example, the subject exhibits a symptom of the respiratory condition, wherein the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

[0026] In another example, the inflammation of lung tissue is bronchitis or bronchiectasis.

[0027] In a further example, the inflammation of lung tissue is pneumonia.

[0028] In still a further example, the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia.

[0029] In one example, the subject is undergoing or has undergone treatment for an infection, fibrosis, a fibrotic episode, chronic obstructive pulmonary disease, Sarcoidosis (or pulmonary sarcoidosis) or asthma/asthma-related inflammation.

[0030] In one example, the subject is undergoing or has undergone treatment for an infection.

[0031] In another example, the infection is a viral infection.

[0032] In one example, the viral infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus.

[0033] In a further example, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

[0034] In still a further example, the coronavirus is SARS-CoV-2.

[0035] In one example, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS.

[0036] In a further example, the disease is COVID-19.

[0037] In one example, the infection is a bacterial infection.

[0038] In a further example, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae.*

[0039] In still a further example, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*.

[0040] In one example, the subject is undergoing or has undergone treatment for fibrosis or a fibrotic episode.

[0041] In a further example, the fibrosis is cystic fibrosis.

[0042] In one example, the subject has been previously administered an agent selected from the group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, an antibody, and an antibacterial.

[0043] In one example, the subject has previously been administered the agent, further comprising administering to the subject a second agent selected from a group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, and an antibacterial.

[0044] In one example, the subject has the agent co-administered with an agent selected from a bronchial muscle/airway relaxant, an antiviral, oxygen, and an antibacterial.

[0045] In another example, the antiviral is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir.

[0046] In another example, the antibody is sarilumab or tocilizumab.

[0047] In another example, the antibacterial is azithromycin.

[0048] In one example, the subject is being or has been treated with mechanical ventilation.

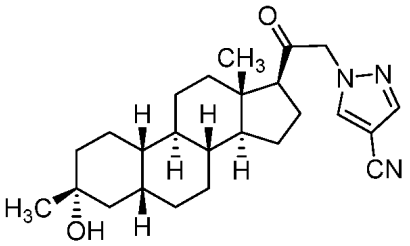
[0049] In one example, the subject is being or has been treated with an oxygen mask.

[0050] In one example, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally.

[0051] In a further example, the agent is administered intravenously.

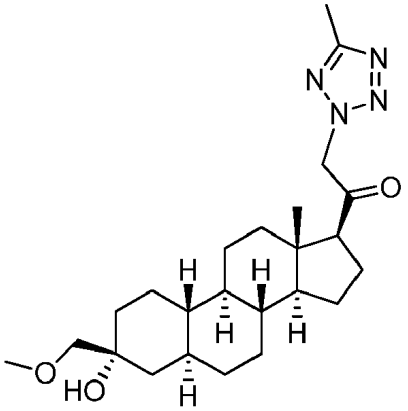
[0052] In another example, the agent is administered orally.

[0053] In another example, the disclosure includes a method of treating a subject undergoing or has undergone treatment for an infection, comprising administering an agent selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2,

or a pharmaceutically acceptable salt thereof to the subject.

[0054] In one example of this example, the infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus.

[0055] In another example, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

[0056] In a further example, the coronavirus is SARS-CoV-2.

[0057] In one example, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS.

[0058] In a further example, the disease is COVID-19.

[0059] In one example, the infection is a bacterial infection.

[0060] In a further example, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae.*

[0061] In still a further example, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus.*

[0062] In one example, the agent is **Compound 1**.

[0063] In another example, the agent is a pharmaceutically acceptable salt of **Compound 1**.

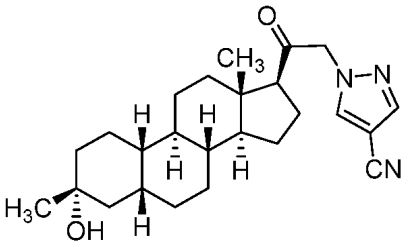
[0064] In another example, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof.

[0065] In one example, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally.

[0066] In one example, the agent is administered intravenously.

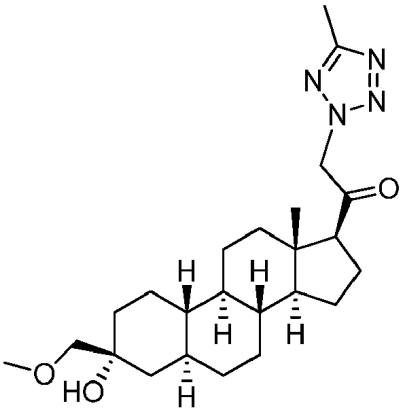
[0067] In another example, the agent is administered orally.

[0068] In another example, the disclosure includes a method of treating a subject comprising administering an agent selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2,

or a pharmaceutically acceptable salt thereof to the subject, wherein the subject has been treated with or is being treated with mechanical ventilation.

[0069] In one example, the subject has acute respiratory distress syndrome.

[0070] In one example, the agent is **Compound 1**.

[0071] In another example, the agent is a pharmaceutically acceptable salt of **Compound 1**.

[0072] In another example, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof.

[0073] In one example, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally.

[0074] In one example, the agent is administered intravenously.

[0075] In another example, the agent is administered orally.

[0076] In one example, the subject is undergoing or has undergone treatment for an infection, the treatment comprising administering to the subject an agent selected from the group consisting of **Compound 1** and **Compound 2**, or a pharmaceutically acceptable salt thereof.

[0077] In one example, the infection is a viral infection comprising an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus.

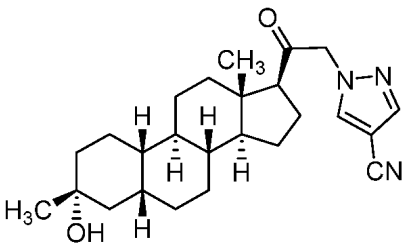
[0078] In one example, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

[0079] In a further example, the coronavirus is SARS-CoV-2.

[0080] In another example, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS.

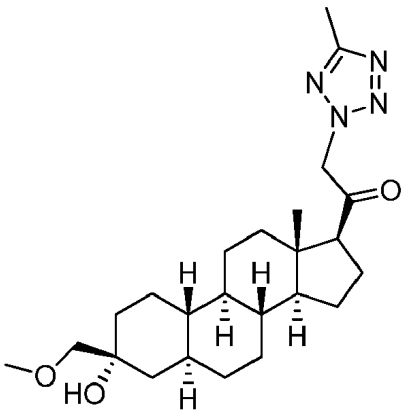
[0081] In a further example, the disease is COVID-19.

[0082] In another example, the disclosure includes a method of treating a subject comprising administering an agent selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2,

or a pharmaceutically acceptable salt thereof to the subject, wherein the subject has been or is being treated for a disease or condition,

wherein the disease or condition is selected from the group consisting of cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, pulmonary sarcoidosis, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus- Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease.

[0083] In one example, the agent is **Compound 1**.

[0084] In another example, the agent is a pharmaceutically acceptable salt of **Compound 1**.

[0085] In another example, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof.

[0086] In one example, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally.

[0087] In one example, the agent is administered intravenously.

[0088] In another example, the agent is administered orally.

[0089] In one example, the agent is administered at a rate of 90-160 µg/kg per hour for a therapeutically sufficient duration.

[0090] In a further example, the agent is administered at a rate of 90-150 µg/kg/hour.

[0091] In a further example, the agent is administered at a rate of 130-150 µg/kg/hour.

[0092] In a further example, the agent is administered at a rate of 140-150 µg/kg/hour.

[0093] In a further example, the agent is administered at a rate of about 150 µg/kg/hour.

[0094] In a further example, the agent is administered at a rate of about 140 µg/kg/hour.

[0095] In a further example, the agent is administered at a rate of about 120 µg/kg/hour.

[0096] In a further example, the agent is administered at a rate of about 100 µg/kg/hour.

[0097] In one example, the agent is administered at a rate of 10-100 µg/kg/hour.

[0098] In a further example, the agent is administered at a rate of 30-80 µg/kg/hour.

[0099] In a further example, the agent is administered at a rate of 35-70 µg/kg/hour.

[00100] In a further example, the agent is administered at a rate of 70 µg/kg/hour.

[00101] In a further example, the agent is administered at a rate of 35 µg/kg/hour.

[00102] In a further example, the agent is administered at a rate of 60-80 µg/kg/hour.

[00103] In one example, the therapeutically sufficient duration is at least 24 hours.

[00104] In a further example, the therapeutically sufficient duration is at least 48 hours.

[00105] In a further example, the therapeutically sufficient duration is at least 60 hours.

[00106] In a further example, the therapeutically sufficient duration is at least 3 days.

[00107] In a further example, the therapeutically sufficient duration is at least 4 days.

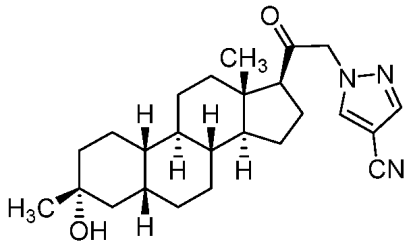
[00108] In a further example, the therapeutically sufficient duration is at least 5 days.

[00109] In a further example, the therapeutically sufficient duration is at least 6 days.

[00110] In a further example, the subject is being treated or has been treated with mechanical ventilation.

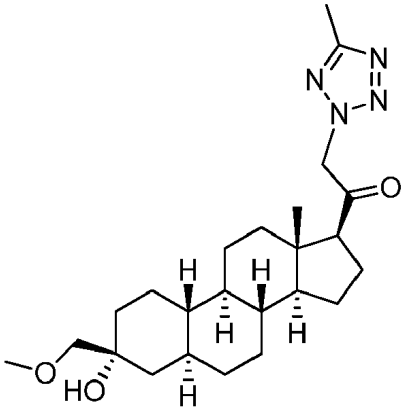
[00111] In a further example, the agent is administered to a subject until the subject is no longer being treated with mechanical ventilation.

[00112] In another example, the disclosure includes a method of treating a subject comprising administering an agent selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2,

or a pharmaceutically acceptable salt thereof to the subject, wherein the subject has a disease associated with a coronavirus.

[00113] In one example, the disease is selected from SARS, MERS and COVID-19.

[00114] In a further example, the disease is COVID-19.

[00115] In one example, the subject suffers from respiratory distress.

[00116] In one example, the respiratory distress is acute respiratory distress syndrome.

[00117] In one example, the subject exhibits a symptom selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

[00118] In one example, the inflammation of lung tissue is bronchitis or bronchiectasis.

[00119] In another example, the inflammation of lung tissue is pneumonia.

[00120] In a further example, the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia.

[00121] In one example, the subject is being or has been treated with mechanical ventilation or oxygen treatment.

[00122] In a further example, the subject is being or has been treated with mechanical ventilation.

[00123] In one example, the agent is **Compound 1**.

[00124] In another example, the agent is a pharmaceutically acceptable salt of **Compound 1**.

[00125] In another example, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof.

[00126] In one example, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally.

[00127] In one example, the agent is administered intravenously.

[00128] In another example, the agent is administered orally.

[00129] In one example, the agent is administered at a rate of 90-160 μg/kg per hour for a therapeutically sufficient duration.

[00130] In a further example, the agent is administered at a rate of 90-150 μg/kg/hour.

[00131] In a further example, the agent is administered at a rate of 130-150 μg/kg/hour.

[00132] In a further example, the agent is administered at a rate of 140-150 μg/kg/hour.

[00133] In a further example, the agent is administered at a rate of about 150 μg/kg/hour.

[00134] In a further example, the agent is administered at a rate of about 140 μg/kg/hour.

[00135] In a further example, the agent is administered at a rate of about 120 μg/kg/hour.

[00136] In a further example, the agent is administered at a rate of about 100 μg/kg/hour.

[00137] In one example, the agent is administered at a rate of 10-100 μg/kg/hour.

[00138] In a further example, the agent is administered at a rate of 30-80 μg/kg/hour.

[00139] In a further example, the agent is administered at a rate of 35-70 μg/kg/hour.

[00140] In a further example, the agent is administered at a rate of 70 μg/kg/hour.

[00141] In a further example, the agent is administered at a rate of 35 μg/kg/hour.

[00142] In a further example, the agent is administered at a rate of 60-80 μg/kg/hour.

[00143] In one example, the previous claims, wherein the therapeutically sufficient duration is at least 24 hours.

[00144] In a further example, the therapeutically sufficient duration is at least 48 hours.

[00145] In a further example, the therapeutically sufficient duration is at least 60 hours.

[00146] In a further example, the therapeutically sufficient duration is at least 3 days.

[00147] In a further example, the therapeutically sufficient duration is at least 4 days.

[00148] In a further example, the therapeutically sufficient duration is at least 5 days.

[00149] In a further example, the therapeutically sufficient duration is at least 6 days.

[00150] In one example, the subject is being treated or has been treated with mechanical ventilation.

[00151] In a further example, the agent is administered to a subject until the subject is no longer being treated with mechanical ventilation.

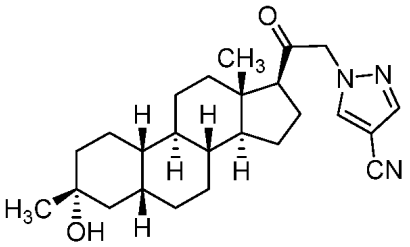
[00152] In one example, the patient has acute respiratory distress syndrome.

[00153] In another example, the patient is intubated.

[00154] In one example, the patient is under 70 years of age.

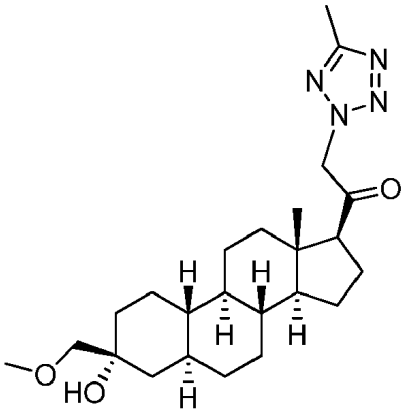
[00155] In another example, the patient is 70 years of age or older.

[00156] In another example, the disclosure includes a method of treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a subject in a subject, comprising administering to said subject a therapeutically effective amount of a $GABA_A$ PAM, or a pharmaceutically acceptable salt or crystalline form thereof, wherein the $GABA_A$ PAM is selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2.

[00157] In one example, the respiratory condition is respiratory distress.

[00158] In a further example, the respiratory condition is acute respiratory distress syndrome.

[00159] In one example, the subject exhibits a symptom of the respiratory condition, wherein the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

[00160] In another example, the inflammation of lung tissue is bronchitis or bronchiectasis.

[00161] In one example, the inflammation of lung tissue is pneumonia.

[00162] In a further example, the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia.

[00163] In one example, the subject is undergoing or has undergone treatment for an infection, fibrosis, a fibrotic episode, chronic obstructive pulmonary disease, Sarcoidosis (or pulmonary sarcoidosis) or asthma/asthma-related inflammation.

[00164] In one example, the subject is undergoing or has undergone treatment for an infection.

[00165] In a further example, the infection is a viral infection.

[00166] In another example, the viral infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus.

[00167] In a further example, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

[00168] In still a further example, the coronavirus is SARS-CoV-2.

[00169] In one example, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS.

[00170] In a further example, the disease is COVID-19.

[00171] In one example, the infection is a bacterial infection.

[00172] In another example, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae.*

[00173] In a further example, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*.

[00174] In one example, the subject is undergoing or has undergone treatment for fibrosis or a fibrotic episode.

[00175] In a further example, the fibrosis is cystic fibrosis.

[00176] In one example, the method further comprises administering to the subject one or more additional agents selected from a group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, an antibody, and an antibacterial.

[00177] In one example, the one or more additional agents are administered to the subject prior to, after, or concurrently with the $GABA_A$ PAM.

[00178] In one example, the antiviral agent is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir.

[00179] In another example, the antibody is sarilumab or tocilizumab.

[00180] In another example, the antibacterial is azithromycin.

[00181] In one example, the subject is being treated, or has been treated with an oxygen mask.

[00182] In another example, the subject is being treated, or has been treated with mechanical ventilation.

[00183] In a further example, the $GABA_A$ PAM is administered to a subject until the subject is no longer being treated with mechanical ventilation.

[00184] In one example, the subject has been or is being treated for a disease or condition selected from the group consisting of cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, pulmonary sarcoidosis, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus- Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

[00185] In one example, the $GABA_A$ PAM is administered via inhalation, intravenously, intramuscularly, subcutaneously, or orally.

[00186] In another example, the $GABA_A$ PAM is administered orally.

[00187] In another example, the $GABA_A$ PAM is administered intravenously.

[00188] In a further example, the $GABA_A$ PAM is administered by continuous intravenous infusion.

[00189] In one example, the $GABA_A$ PAM is administered at a rate of 90-160 μg/kg per hour for a therapeutically effective duration.

[00190] In a further example, the $GABA_A$ PAM is administered at a rate of 90-150 μg/kg/hour.

[00191] In a further example, the $GABA_A$ PAM is administered at a rate of 130-150 μg/kg/hour.

[00192] In a further example, the $GABA_A$ PAM is administered at a rate of 140-150 μg/kg/hour.

[00193] In a further example, the $GABA_A$ PAM is administered at a rate of about 150 μg/kg/hour.

[00194] In a further example, the $GABA_A$ PAM is administered at a rate of about 140 μg/kg/hour.

[00195] In a further example, the $GABA_A$ PAM is administered at a rate of about 120 μg/kg/hour.

[00196] In a further example, the $GABA_A$ PAM is administered at a rate of about 100 μg/kg/hour.

[00197] In another example, the $GABA_A$ PAM is administered at a rate of 10-100 μg/kg/hour, for a therapeutically effective duration.

[00198] In a further example, the $GABA_A$ PAM is administered at a rate of 30-80 μg/kg/hour.

[00199] In a further example, the $GABA_A$ PAM is administered at a rate of 35-70 μg/kg/hour.

[00200] In a further example, the $GABA_A$ PAM is administered at a rate of 70 μg/kg/hour.

[00201] In a further example, the $GABA_A$ PAM is administered at a rate of 35 μg/kg/hour.

[00202] In a further example, the $GABA_A$ PAM is administered at a rate of 60-80 μg/kg/hour.

[00203] In one example, the therapeutically effective duration is at least 24 hours.

[00204] In a further example, the therapeutically effective duration is at least 48 hours.

[00205] In a further example, the therapeutically effective duration is at least 60 hours.

[00206] In a further example, the therapeutically effective duration is at least 3 days.

[00207] In a further example, the therapeutically effective duration is at least 4 days.

[00208] In a further example, the therapeutically effective duration is at least 5 days.

[00209] In a further example, the therapeutically effective duration is at least 6 days.

[00210] In one example, the $GABA_A$ PAM is administered at a rate of 150 μg/kg/h for about 140 hours.

[00211] In one example, the method further comprises the steps of:

a. decreasing the administration rate to about 120 μg/kg/h for one hour;

b. further decreasing the administration rate to about 90 μg/kg/h for one hour;

c. further decreasing the administration rate to about 60 μg/kg/h for one hour; and

d. further decreasing the administration rate to about 30 μg/kg/h for one hour.

[00212] In another example, the $GABA_A$ PAM is administered at a rate of 70 μg/kg/h for about 58 hours.

[00213] In one example, the method further comprises decreasing the rate of administration of the $GABA_A$ PAM to about 35 μg/kg/h for about 2 hours.

[00214] In one example, treating a respiratory disease or condition in a subject comprises ameliorating one or more symptoms of the respiratory disease or condition.

[00215] In another example, the method comprises ameliorating one or more symptoms of acute respiratory distress syndrome in a subject.

[00216] In another example, the method comprises ameliorating one or more symptoms of COVID-19 in a subject.

[00217] In one example, the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

[00218] In another example, the $GABA_A$ PAM is administered to the subject in an amount sufficient to increase oxygen saturation in the blood of the subject.

[00219] In a further example, the oxygen saturation in the blood of the subject is measured using pulse oximetry.

[00220] In one example, the subject is also experiencing a cytokine storm (also known as cytokine release syndrome).

[00221] In a further example, the patient has an inflammation resulting from cytokine release syndrome.

[00222] In still a further example, the inflammation is a lung inflammation.

[00223] In one example, the patient has acute respiratory distress syndrome.

[00224] In one example, the patient is intubated.

[00225] In one example, the patient is under 70 years of age.

[00226] In another example, the patient is 70 years of age or older.

[00227] In one example, the $GABA_A$ PAM is Compound 1, wherein the Compound 1 is a free base.

[00228] In another example, the $GABA_A$ PAM is a pharmaceutically acceptable salt of Compound 1.

[00229] In one example, the $GABA_A$ PAM is Compound 2, wherein the Compound 2 is a free base.

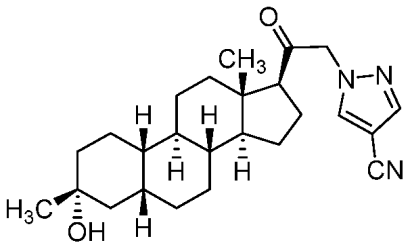
[00230] In another example, the $GABA_A$ PAM is a pharmaceutically acceptable salt of Compound 2.

[00231] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[00232] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION

[00233] Described herein are methods of ameliorating one or more symptoms of a respiratory condition in a subject, comprising administering to the subject a therapeutically effective amount of an agent selected from the group consisting of **Compound 1**

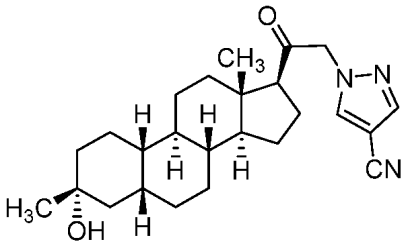


Compound 1

and **Compound 2**

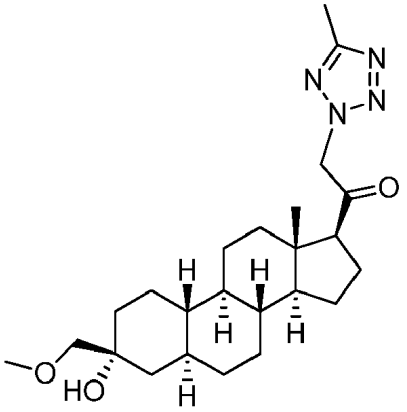
WHAT IS CLAIMED IS:

1. Use of a $GABA_A$ PAM, or a pharmaceutically acceptable salt or crystalline form thereof, wherein the $GABA_A$ PAM is selected from the group consisting of **Compound 1**



Compound 1

and **Compound 2**



Compound 2

in the manufacture of a medicament for treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a human subject.

2. The use of claim 1, wherein the respiratory condition is respiratory distress or acute respiratory distress syndrome.

3. The use of claim 1 or 2, wherein the subject exhibits a symptom of the respiratory condition, wherein the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

4. The use of claim 3, wherein the inflammation of lung tissue is bronchitis, bronchiectasis, or pneumonia; optionally wherein the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia.

5. The use of any one of claims 1-4, wherein the subject is undergoing or has undergone treatment for an infection, fibrosis, a fibrotic episode, chronic obstructive pulmonary disease, Sarcoidosis (or pulmonary sarcoidosis) or asthma/asthma-related inflammation; optionally wherein the fibrosis is cystic fibrosis.

6. The use of claim 5, wherein the infection is a viral infection or a bacterial infection.

7. The use of claim 6, wherein

a) the viral infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus; optionally,

i) wherein the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV; and/or

ii) wherein the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS; or

b) wherein the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*, optionally; optionally,

i) wherein the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*.

8. The use of any one of claims 1-7, wherein the subject is to be administered one or more additional agents selected from a group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, an antibody, and an antibacterial; optionally, wherein the one or more additional agents are to be administered to the subject prior to, after, or concurrently with the $GABA_A$ PAM.

9. The use of claim 8, wherein

a) the antiviral agent is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir; and/or

b) the antibody is sarilumab or tocilizumab; and/or

c) the antibacterial is azithromycin.

10. The use of any one of claims 1-9, wherein the subject is being treated, or has been treated with an oxygen mask or with mechanical ventilation; optionally, wherein the $GABA_A$ PAM is to be administered to a subject until the subject is no longer being treated with mechanical ventilation.

11. The use of any one of claims 1-10, wherein the subject has been or is being treated for a disease or condition selected from the group consisting of cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, pulmonary sarcoidosis, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus- Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion

protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

12. The use of any one of claims 1-11, wherein the $GABA_A$ PAM is to be administered via inhalation, intravenously, intramuscularly, subcutaneously, orally, or by a continuous intravenous infusion.

13. The use of claim 12, wherein the $GABA_A$ PAM is to be administered by continuous intravenous infusion, and is to be administered:

A) at a rate of 90-160, 90-150, 130-150, 140-150, 150, 140, 120, or 100 μg/kg per hour for a therapeutically effective duration; or

B) at a rate of 10-100, 30-80, 35-70, 60-80, 35, or 70 μg/kg/hour, for a therapeutically effective duration;

optionally, wherein the therapeutically effective duration is at least 24 hours, at least 48 hours, at least 60 hours, at least 3 days, at least 4 days, at least 5 days, or at least 6 days.

14. The use of any one of claims 1-13, wherein treating a respiratory disease or condition in a subject comprises ameliorating one or more symptoms of the respiratory disease or condition,

(i) optionally, wherein the respiratory disease or condition is acute respiratory distress syndrome or COVID-19; and/or

(ii) optionally, wherein the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

15. The use of any one of claims 1-14, wherein the $GABA_A$ PAM is to be administered to the subject in an amount sufficient to increase oxygen saturation in the blood of the subject, optionally wherein the oxygen saturation in the blood of the subject is measured using pulse oximetry.

16. The use of any one of claims 1-15, wherein the subject is also experiencing a cytokine storm (also known as cytokine release syndrome); optionally, wherein the patient has an inflammation resulting from cytokine release syndrome; optionally, wherein the inflammation is a lung inflammation; and/or optionally, wherein the patient has acute respiratory distress syndrome.

17. The use of any one of claims 1-16, wherein

a) the patient is intubated; and/or

b) (i) the patient is under 70 years of age or (ii) patient is 70 years of age or older.

18. The use of any one of claims 1-17, wherein the $GABA_A$ PAM is

a) Compound 1, wherein the Compound 1 is a free base;

b) a pharmaceutically acceptable salt of Compound 1;

c) Compound 2, wherein the Compound 2 is a free base; or

d) a pharmaceutically acceptable salt of Compound 2.