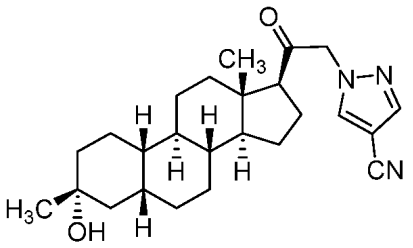
[0006] Accordingly, there is a need for the development of an effective COVID-19 treatment.

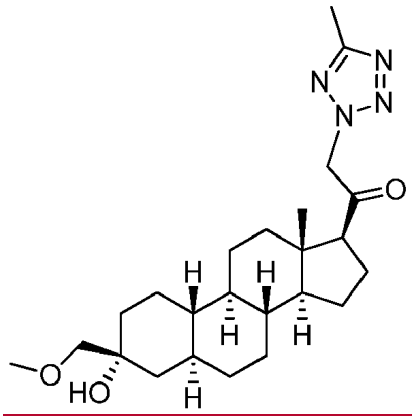
SUMMARY

[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

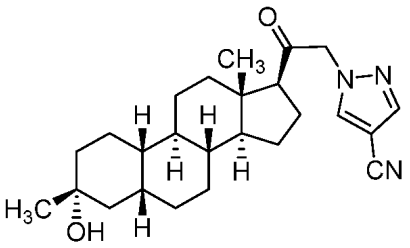
and **Compound 2**



Compound 2

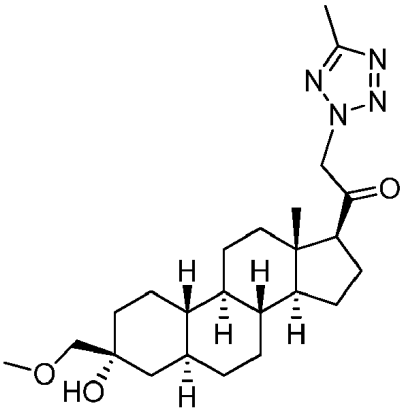
in the manufacture of a medicament for treating a respiratory disease or condition, or a symptom of a respiratory disease or condition in a human subject.

[0007] One ~~aspect~~example of the present ~~invention~~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] ~~Embodiment~~Examples of this ~~aspect~~example of the ~~invention~~disclosure may include one or more of the following optional features. In some ~~embodiment~~examples, the agent is **Compound 1**. In some ~~embodiment~~examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some ~~embodiment~~examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the respiratory condition is respiratory distress. In some ~~embodiment~~examples, the respiratory condition is acute respiratory distress syndrome. In some ~~embodiment~~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 ~~embodiment~~examples, the

inflammation of lung tissue is bronchitis or bronchiectasis. In some ~~embodiment~~examples, the inflammation of lung tissue is pneumonia. In some ~~embodiment~~examples, the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia. In some ~~embodiment~~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 ~~embodiment~~examples, the subject is undergoing or has undergone treatment for an infection. In some ~~embodiment~~examples, the infection is a viral infection. In some ~~embodiment~~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 ~~embodiment~~examples, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV. In some ~~embodiment~~examples, the coronavirus is SARS-CoV-2. In some ~~embodiment~~examples, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS. In some ~~embodiment~~examples, the disease is COVID-19. In some ~~embodiment~~examples, the infection is a bacterial infection. In some ~~embodiment~~examples, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae.* In some ~~embodiment~~examples, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*. In some ~~embodiment~~examples, the subject is undergoing or has undergone treatment for fibrosis or a fibrotic episode. In some ~~embodiment~~examples, the fibrosis is cystic fibrosis. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the antiviral is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir. In some ~~embodiment~~examples, the antibody is sarilumab or tocilizumab. In some ~~embodiment~~examples, the antibacterial is azithromycin. In some ~~embodiment~~examples, the subject is being or has been treated with mechanical ventilation. In some ~~embodiment~~examples, the subject is being or has been treated with an oxygen mask. In some ~~embodiment~~examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some

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

[0009] Another ~~aspect~~example of the ~~invention~~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] ~~Embodiment~~Examples of this ~~aspect~~example of the ~~invention~~disclosure may include one or more of the following optional features. In some ~~embodiment~~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 ~~embodiment~~examples, the virus a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV. In some ~~embodiment~~examples, the coronavirus is SARS-CoV-2. In some ~~embodiment~~examples, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS. In some ~~embodiment~~examples, the disease is COVID-19. In some ~~embodiment~~examples, the infection is a bacterial infection. In some ~~embodiment~~examples, the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae.* In some ~~embodiment~~examples, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus.* In some ~~embodiment~~examples, the agent is **Compound 1**. In some ~~embodiment~~examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some ~~embodiment~~examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some ~~embodiment~~examples, the agent is administered intravenously. In some ~~embodiment~~examples, the agent is administered orally.

[0011] Another ~~aspect~~example of the ~~invention~~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] ~~Embodiment~~Examples of this ~~aspect~~example of the ~~invention~~disclosure may include one or more of the following optional features. In some ~~embodiment~~examples, the subject has acute respiratory distress syndrome. In some ~~embodiment~~examples, the agent is **Compound 1**. In some ~~embodiment~~examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some ~~embodiment~~examples, the agent is

Compound 2 or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some ~~embodiment~~examples, the agent is administered intravenously. In some ~~embodiment~~examples, the agent is administered orally. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV. In some ~~embodiment~~examples, the coronavirus is SARS-CoV-2. In some ~~embodiment~~examples, the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS. In some ~~embodiment~~examples, the disease is COVID-19.

[0013] Another ~~aspect~~example of the ~~invention~~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] ~~Embodiment~~Examples of this ~~aspect~~example of the ~~invention~~disclosure may include one or more of the following optional features. In some ~~embodiment~~examples, the agent is **Compound 1**. In some ~~embodiment~~examples, the agent is a pharmaceutically acceptable salt of **Compound 1**. In some ~~embodiment~~examples, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the agent is administered via inhalation, intravenously, by injection (e.g. intramuscularly), subcutaneously, or orally. In some ~~embodiment~~examples, the agent is administered intravenously. In some ~~embodiment~~examples, the agent is administered orally. In some ~~embodiment~~examples, the agent is administered at a rate of 90-160 µg/kg per hour for a therapeutically sufficient duration. In some ~~embodiment~~examples, the agent is administered at a rate of 90-150 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 130-150 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 140-150 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of about 150 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of about 140 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of about 120 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of about 100 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 10-100 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 30-80 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 35-70 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 70 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 35 µg/kg/hour. In some ~~embodiment~~examples, the agent is administered at a rate of 60-80 µg/kg/hour. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 24 hours. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 48 hours. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 60 hours. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 3 days. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 4 days. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 5 days. In some ~~embodiment~~examples, the therapeutically sufficient duration is at least 6 days. In some ~~embodiment~~examples, the subject is being treated or has been treated with mechanical ventilation. In some ~~embodiment~~examples, the agent is administered to a subject until the subject is no longer being treated with mechanical ventilation.

[0015] Another ~~aspect~~example of the ~~invention~~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.

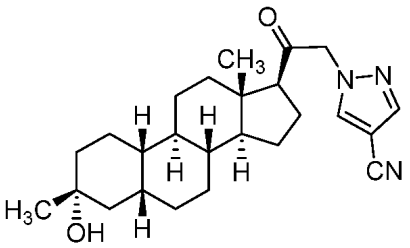
[0016] ~~Embodiment~~Examples of this ~~aspect~~example of the ~~invention~~disclosure may include one or more of the following optional features. In some ~~embodiment~~examples, the disease is selected from SARS, MERS and COVID-19. In some ~~embodiment~~examples, wherein the disease is COVID-19. In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

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

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

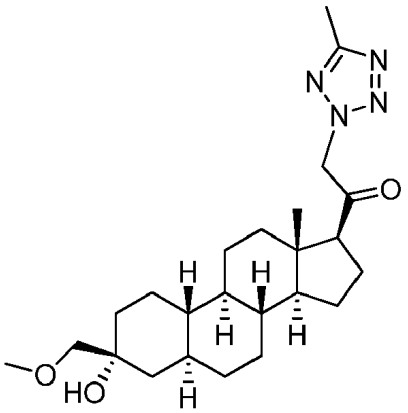
[0018] In some ~~embodiment~~example**s**, the patient is 70 years of age or older in any one ~~aspect~~example of the present ~~invention~~disclosure.

[0019] In one ~~aspect~~example, the ~~invention~~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 ~~embodiment~~example of this ~~aspect~~example, the agent is **Compound 1**.

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

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

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

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

[0025] In one ~~embodiment~~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 ~~embodiment~~example, the inflammation of lung tissue is bronchitis or bronchiectasis.

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

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

[0029] In one ~~embodiment~~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 ~~embodiment~~example, the subject is undergoing or has undergone treatment for an infection.

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

[0032] In one ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the coronavirus is SARS-CoV-2.

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

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

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

[0038] In a further ~~embodiment~~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 ~~embodiment~~example, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*.

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

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

[0042] In one ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the antiviral is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir.

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

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

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

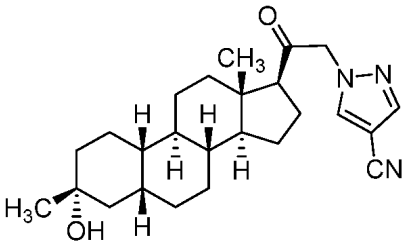
[0049] In one ~~embodiment~~example, the subject is being or has been treated with an oxygen mask.

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

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

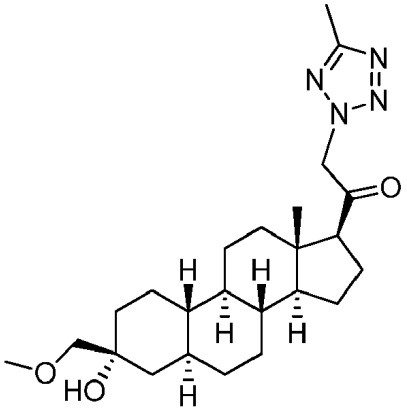
[0052] In another ~~embodiment~~example, the agent is administered orally.

[0053] In another ~~aspect~~example, the ~~invention~~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 ~~embodiment~~example of this ~~aspect~~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 ~~embodiment~~example, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

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

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

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

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

[0060] In a further ~~embodiment~~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 ~~embodiment~~example, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus.*

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

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

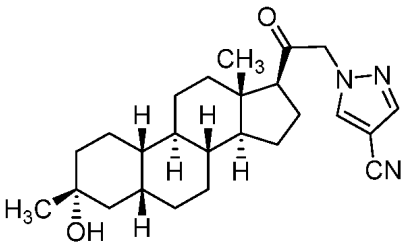
[0064] In another ~~embodiment~~example, the agent is **Compound 2** or a pharmaceutically acceptable salt thereof.

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

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

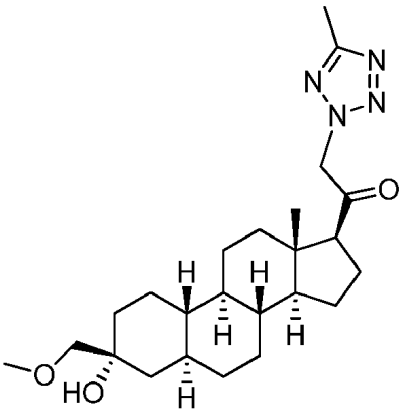
[0067] In another ~~embodiment~~example, the agent is administered orally.

[0068] In another ~~aspect~~example, the ~~invention~~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 ~~embodiment~~example, the subject has acute respiratory distress syndrome.

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

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

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

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

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

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

[0076] In one ~~embodiment~~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 ~~embodiment~~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.

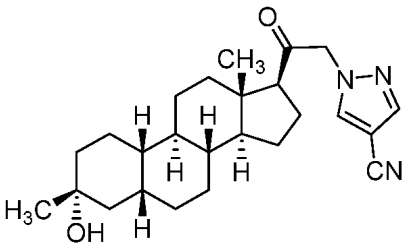
[0078] In one ~~embodiment~~example, the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

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

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

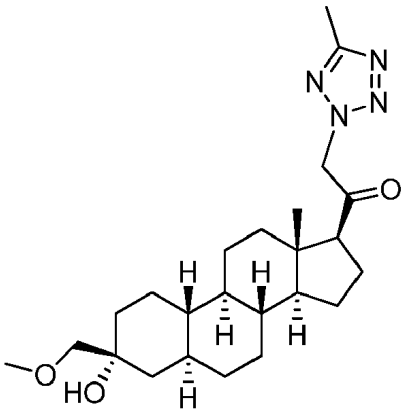
[0081] In a further ~~embodiment~~example, the disease is COVID-19.

[0082] In another ~~aspect~~example, the ~~invention~~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 ~~embodiment~~example, the agent is **Compound 1**.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

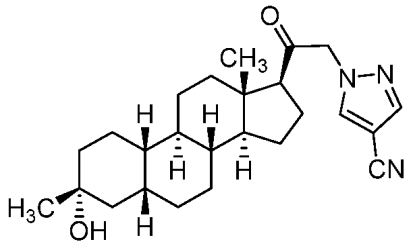
[00108] In a further ~~embodiment~~example, the therapeutically sufficient duration is at least 5 days.

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

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

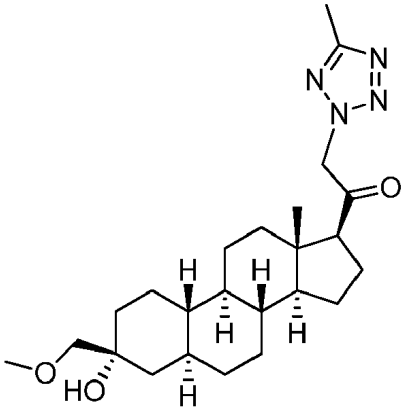
[00111] In a further ~~embodiment~~example, the agent is administered to a subject until the subject is no longer being treated with mechanical ventilation.

[00112] In another ~~aspect~~example, the ~~invention~~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 ~~embodiment~~example, the disease is selected from SARS, MERS and COVID-19.

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

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

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

[00117] In one ~~embodiment~~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 ~~embodiment~~example, the inflammation of lung tissue is bronchitis or bronchiectasis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

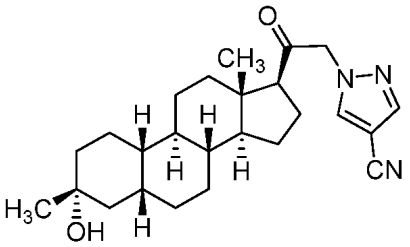
[00152] In one ~~embodiment~~example, the patient has acute respiratory distress syndrome.

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

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

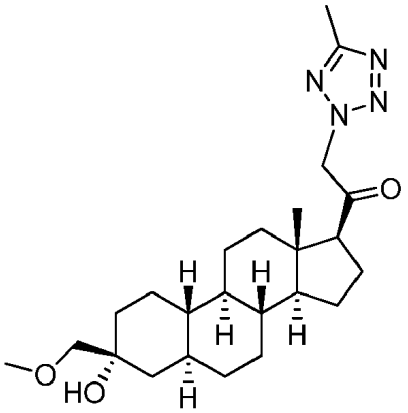
[00155] In another ~~embodiment~~example, the patient is 70 years of age or older.

[00156] In another ~~aspect~~example, the ~~invention~~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 ~~embodiment~~example, the respiratory condition is respiratory distress.

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

[00159] In one ~~embodiment~~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 ~~embodiment~~example, the inflammation of lung tissue is bronchitis or bronchiectasis.

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

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

[00163] In one ~~embodiment~~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 ~~embodiment~~example, the subject is undergoing or has undergone treatment for an infection.

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

[00166] In another ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the coronavirus is SARS-CoV-2.

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

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

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

[00172] In another ~~embodiment~~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 ~~embodiment~~example, the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*.

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

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

[00176] In one ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the antiviral agent is selected from the group consisting of remdesivir, kaletra, lopinavir, and ritonavir.

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

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

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

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

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

[00184] In one ~~embodiment~~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 ~~embodiment~~example, the $GABA_A$ PAM is administered via inhalation, intravenously, intramuscularly, subcutaneously, or orally.

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

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

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

[00189] In one ~~embodiment~~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 ~~embodiment~~example, the $GABA_A$ PAM is administered at a rate of 90-150 µg/kg/hour.

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

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

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

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

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

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

[00197] In another ~~embodiment~~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 ~~embodiment~~example, the $GABA_A$ PAM is administered at a rate of 30-80 µg/kg/hour.

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

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

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

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

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

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

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

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

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

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

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

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

[00211] In one ~~embodiment~~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 ~~embodiment~~example, the $GABA_A$ PAM is administered at a rate of 70 μg/kg/h for about 58 hours.

[00213] In one ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the method comprises ameliorating one or more symptoms of acute respiratory distress syndrome in a subject.

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

[00217] In one ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the oxygen saturation in the blood of the subject is measured using pulse oximetry.

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

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

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

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

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

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

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

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

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

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

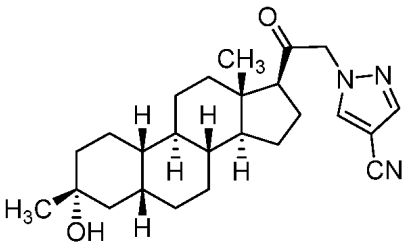
[00230] In another ~~embodiment~~example, the $GABA_A$ PAM is a pharmaceutically acceptable salt of Compound 2.

[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 ~~invention~~disclosure belongs. Methods and materials are described herein for use in the present ~~invention~~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 ~~invention~~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**

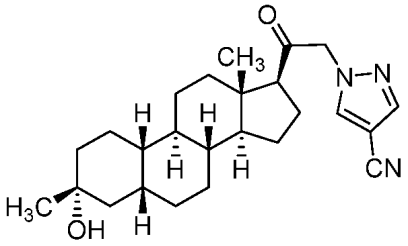


Compound 1

and **Compound 2**

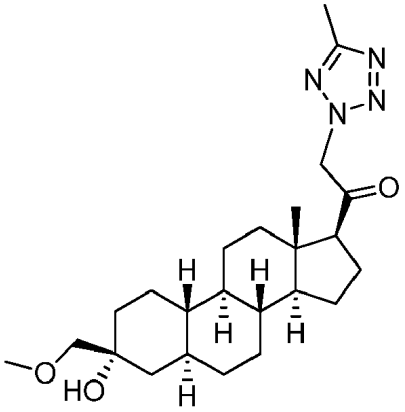
WHAT IS CLAIMED IS:

1. Use~~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~~.~~

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~~method~~ of claim 1, wherein the respiratory condition is respiratory distress or acute respiratory distress syndrome.

~~3. The method of claim 1 or claim 2, wherein the respiratory condition is acute respiratory distress syndrome.~~

~~4.~~3. The use~~method~~ of claim~~any one of clams~~ 1 or 2~~-3~~, 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.

~~5.~~4. The use~~method~~ of claim 3~~4~~, wherein the inflammation of lung tissue is bronchitis, ~~or~~ bronchiectasis, or pneumonia; optionally wherein the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia.

~~6. The method of claim 5, wherein the inflammation of lung tissue is pneumonia.~~

~~7. The method of claim 6, wherein the pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia.~~

~~8.~~5. The use~~method~~ of any one of claims 1-~~4~~7, 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.

~~9. The method of claim 8, wherein the subject is undergoing or has undergone treatment for an infection.~~

~~10.~~6. The use~~method~~ of claim 5~~9~~, wherein the infection is a viral infection or a bacterial infection.

~~11.~~7. The use~~method~~ of claim 6~~10~~, 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*.

~~12. The method of claim 11, wherein the virus is a coronavirus selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.~~

~~13. The method of claim 12, wherein the coronavirus is SARS-CoV-2.~~

~~14. The method of any one of claims 1-13, wherein the subject has been or is being treated for a disease selected from SARS, COVID-19 or MERS.~~

~~15. The method of claim 14, wherein the disease is COVID-19.~~

~~16. The method of claim 9, wherein the infection is a bacterial infection.~~

~~17. The method of claim 16, wherein the bacterial infection is selected from the group consisting of *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*.~~

~~18. The method of claim 17, wherein the *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus*.~~

~~19. The method of claim 8, wherein the subject is undergoing or has undergone treatment for fibrosis or a fibrotic episode.~~

~~20. The method of claim 19, wherein the fibrosis is cystic fibrosis.~~

~~21.~~8. The use~~method~~ of any one of claims 1-7~~20~~, ~~further comprising administering to~~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.

~~22. The method of claim 21, wherein the one or more additional agents are administered to the subject prior to, after, or concurrently with the $GABA_A$ PAM.~~

~~23.~~9. The use~~method~~ of ~~any of~~ claim~~s~~ 8~~21-22~~, 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.

~~24. The method of any of claims 21-23, wherein the antibody is sarilumab or tocilizumab.~~

~~25. The method of any of claims 21-24, wherein the antibacterial is azithromycin.~~

~~26.~~10. The use~~method~~ of any one of claims 1-9~~25~~, 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.

~~27. The method of any one of claims 1-26, wherein the subject is being treated, or has been treated with mechanical ventilation.~~

~~28. The method of claim 27, wherein the $GABA_A$ PAM is administered to a subject until the subject is no longer being treated with mechanical ventilation.~~

~~29.~~11. The use~~method~~ of any one of claims 1-10~~28~~, 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.

~~30.~~12. The use~~method~~ of any one of claims 1-11~~29~~, wherein the $GABA_A$ PAM is to be administered via inhalation, intravenously, intramuscularly, subcutaneously, ~~or~~ orally, or by a continuous intravenous infusion.

~~31. The method of claim 30, wherein the $GABA_A$ PAM is administered orally.~~

~~32. The method of claim 30, wherein the $GABA_A$ PAM is administered intravenously.~~

~~33. The method of claim 32, wherein the $GABA_A$ PAM is administered by continuous intravenous infusion~~

~~34.~~13. The use~~method~~ of claim 12~~33~~, 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.

~~35. The method of claim 34, wherein the $GABA_A$ PAM is administered at a rate of 90-150 µg/kg/hour.~~

~~36. The method of claim 35, wherein the $GABA_A$ PAM is administered at a rate of 130-150 µg/kg/hour.~~

~~37. The method of claim 36, wherein the $GABA_A$ PAM is administered at a rate of 140-150 µg/kg/hour.~~

~~38. The method of claim 34, wherein the $GABA_A$ PAM is administered at a rate of about 150 µg/kg/hour.~~

~~39. The method of claim 34, wherein the $GABA_A$ PAM is administered at a rate of about 140 µg/kg/hour.~~

~~40. The method of claim 34, wherein the $GABA_A$ PAM is administered at a rate of about 120 µg/kg/hour.~~

~~41. The method of claim 34, wherein the $GABA_A$ PAM is administered at a rate of about 100 µg/kg/hour.~~

~~42. The method of claim 33, wherein the $GABA_A$ PAM is administered at a rate of 10-100 µg/kg/hour, for a therapeutically effective duration.~~

~~43. The method of claim 42, wherein the $GABA_A$ PAM is administered at a rate of 30-80 µg/kg/hour.~~

~~44. The method of claim 43, wherein the $GABA_A$ PAM is administered at a rate of 35-70 µg/kg/hour.~~

45. The method of claim 42, wherein the $GABA_A$ PAM is administered at a rate of 70 µg/kg/hour.

46. The method of claim 42, wherein the $GABA_A$ PAM is administered at a rate of 35 µg/kg/hour.

47. The method of claim 42, wherein the $GABA_A$ PAM is administered at a rate of 60-80 µg/kg/hour.

48. The method of any one of claims 34-47, wherein the therapeutically effective duration is at least 24 hours.

49. The method of claim 48, wherein the therapeutically effective duration is at least 48 hours.

50. The method of claim 49, wherein the therapeutically effective duration is at least 60 hours.

51. The method of claim 50, wherein the therapeutically effective duration is at least 3 days.

52. The method of claim 51, wherein the therapeutically effective duration is at least 4 days.

53. The method of claim 52, wherein the therapeutically effective duration is at least 5 days.

54. The method of claim 53, wherein the therapeutically effective duration is at least 6 days.

55. The method of claim 34, wherein the $GABA_A$ PAM is administered at a rate of 150 µg/kg/h for about 140 hours.

56. The method of claim 58, further comprising 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.~~

~~57. The method of claim 42, wherein the $GABA_A$ PAM is administered at a rate of 70 μg/kg/h for about 58 hours.~~

~~58. The method of claim 57, further comprising decreasing the rate of administration of the $GABA_A$ PAM to about 35 μg/kg/h for about 2 hours.~~

~~59.~~14. The use~~method~~ of any one of claims 1-13~~58~~, 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.

~~60. The method of claim 59, comprising ameliorating one or more symptoms of acute respiratory distress syndrome in a subject.~~

~~61. The method of claim 59, comprising ameliorating one or more symptoms of COVID-19 in a subject.~~

~~62. The method of any of claims 59-61, wherein the symptom is selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.~~

~~63.~~15. The use~~method~~ of any one of claims 1-14~~62~~, 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.

~~64. The method of claim 63, wherein the oxygen saturation in the blood of the subject is measured using pulse oximetry.~~

~~65.~~16. The use~~method~~ of any one of claims 1-15~~64~~, 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.

~~66. The method of claim 65, wherein the patient has an inflammation resulting from cytokine release syndrome.~~

~~67. The method of claim 66, wherein the inflammation is a lung inflammation.~~

~~68. The method of any one of claims 65-67, wherein the patient has acute respiratory distress syndrome.~~

~~69.~~17. The use~~method~~ of any one of claims 1-16~~68~~, 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.

~~70. The method of any one of claims 1-69, wherein the patient is under 70 years of age.~~

~~71. The method of any one of claims 1-69, wherein the patient is 70 years of age or older.~~

~~72.~~18. The use~~method~~ of any one of claims 1-17~~71~~, 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.

~~73. The method of any one of claims 1-71, wherein the $GABA_A$ PAM is a pharmaceutically acceptable salt of Compound 1.~~

~~74. The method of any one of claims 1-71, wherein the $GABA_A$ PAM is Compound 2, wherein the Compound 2 is a free base.~~

~~75. The method of any one of claims 1-71, wherein the $GABA_A$ PAM is a pharmaceutically acceptable salt of Compound 2.~~