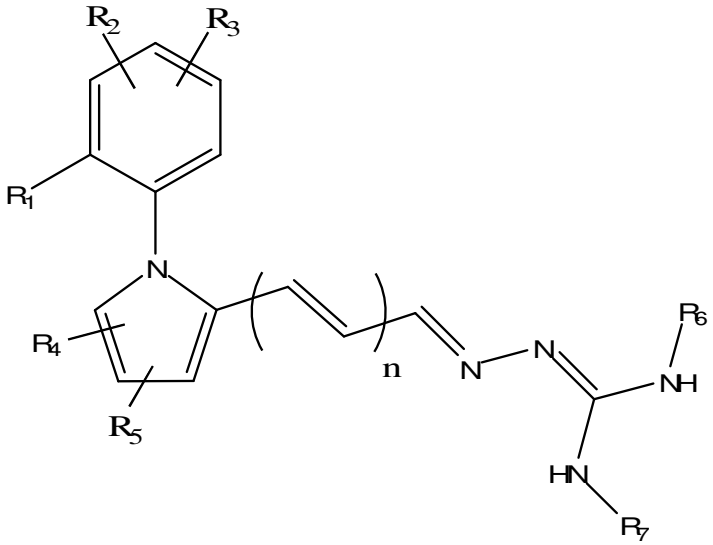
and endogenous antagonists. The biological functions of melanocortin system are mediated by the five melanocortin receptors (MCRs), which have distinct tissue distribution, convey different signalling and exert varying biological activities in different organ systems.

Phenyl pyrrole aminoguanidine derivatives with activity on the melanocortin receptors are disclosed in WO 2007/141343. One example of such compound is the anti-inflammatory AP1189 (*(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium acetate) which was first shown to bind the MC1R (WO 2007/141343) and later was identified as a biased dual agonist at receptors MC1R and MC3R that does not provoke canonical cAMP generation. The mechanism of action of AP1189 is to promote resolution of inflammation through melanocortin receptor activation directly on macrophages, thereby reducing the pro-inflammatory activity of macrophages and stimulating macrophage efferocytosis, a specific ability to clear inflammatory cells (Montero-Melendez et al. 2015). This effect has shown to be effective in disease models of inflammatory and autoimmune diseases and the clinical potential of the approach is currently tested in a clinical phase 2 study in patients with active Rheumatoid Arthritis

Summary

In one aspect, the present disclosure relates to use of a composition comprising a compound of formula (I):



formula (I)

including tautomeric and stereoisomeric forms thereof; wherein n is 1;
R1 is CF_3, CCl_3, F, Cl, NO_2 or CN, and R2, R3, R4, R5, R6, and R7 is hydrogen; or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for treatment, amelioration, and/or alleviation of viral diseases or disorders.

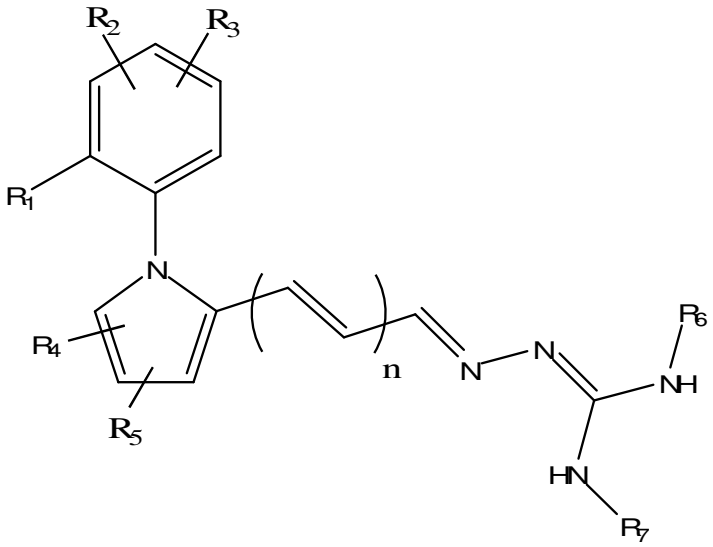
The present inventors have found that the phenyl pyrrole aminoguanidine derivative AP1189 (*(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium acetate) reduces the levels of pro-inflammatory cytokines IL-1 and IL-1β, and reduces neutrophil accumulation, as compared to vehicle. This implies that AP1189 and related compounds are candidates for the treatment of symptomatic COVID-19.

Samples from patients with COVID-19 pneumonia have shown that macrophages make up to 80% of total cells in the lung alveoli and play a key role for the hyperinflammation associated with the devastating effects of COVID-19 infections.

Clinical trial data has now demonstrated that in patients with COVID-19 induced pulmonary insufficiency receiving AP1189, none of them developed a need for more intensive pulmonary support and patients were discharged between day 3 and 9 of treatment.

AP1189 and related compounds are thus promising candidates for the treatment of viral diseases and disorders, via its capabilities to control or dampen inflammation, including the inopportune over-activation of the immune system and resulting hyper-inflammation, while rendering the immune system fully capable of fighting the underlying viral infection, in some instances even stimulating the immune system. This is called resolution therapy.

It is an example of the present disclosure to provide a composition comprising a compound of formula (I):



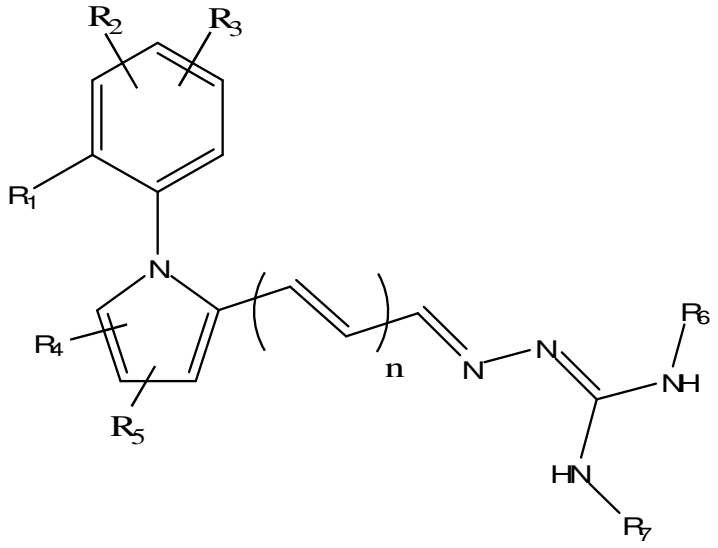
formula (I)

including tautomeric and stereoisomeric forms thereof;

wherein n is 1; and R1 is CF3, CCl3, F, Cl, NO2 or CN, and R2, R3, R4, R5, R6, and R7 are hydrogen; or a pharmaceutically acceptable derivative thereof,

for use in the treatment of viral diseases and disorders, such as symptomatic viral diseases and disorders, such as symptomatic viral diseases and disorders with respiratory symptoms including respiratory failure and ARDS.

It is an example of the present disclosure to provide a composition comprising a compound of formula (I):



formula (I)

including tautomeric and stereoisomeric forms thereof;
wherein n is 1; and R_1 is CF_3, CCl_3, F, Cl, NO_2 or CN, and R_2, R_3, R_4, R_5, R_6, and R_7 are hydrogen; or a pharmaceutically acceptable derivative thereof,
for use in the treatment of symptomatic COVID-19, such as symptomatic COVID-19 with respiratory symptoms including respiratory failure and ARDS.

In one example said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium, and pharmaceutically acceptable salts thereof.

In one example said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate (AP1189).

Description of Drawings

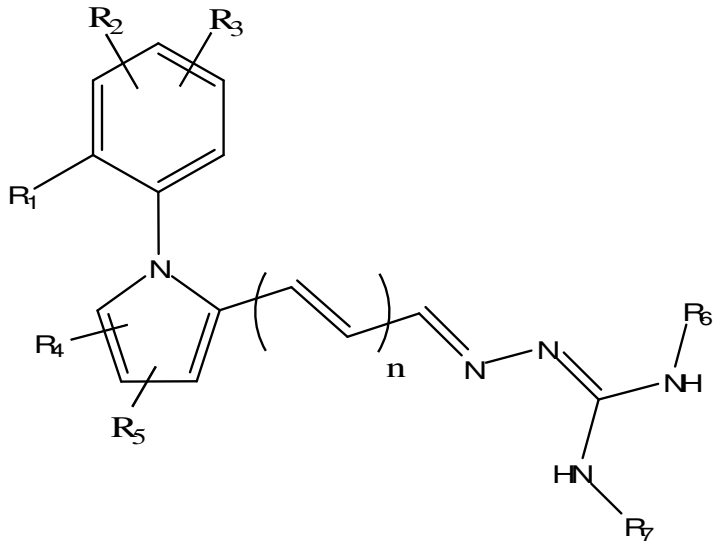
Test Item A = AP1189 *(E)-N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium acetate.

Figure 1: Pre-treatment with AP1189 reduces the levels of the pro-inflammatory cytokines IL-1β compared to pretreatment with vehicle by 37%.

Figure 2: Pre-treatment with AP1189 reduces the levels of the pro-inflammatory cytokines IL-6 compared to pretreatment with vehicle by 59%.

Claims

1. Use of a composition comprising a compound of formula (I):



formula (I)

including tautomeric and stereoisomeric forms thereof; wherein n is 1; R1 is CF_3, CCl_3, F, Cl, NO_2 or CN, and R2, R3, R4, R5, R6, and R7 is hydrogen; or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for treatment, amelioration, and/or alleviation of viral diseases or disorders.

2. The use according to any of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof.

3. The use according to any of the preceding claims, wherein said pharmaceutically acceptable derivative thereof is a pharmaceutically acceptable salt thereof, such as a pharmaceutically acceptable salt of an inorganic acid or an organic acid; such as wherein said inorganic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulphuric acid and nitric acid; such as wherein said organic acid is selected from the group consisting of: formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, propionic acid, benzoic acid, cinnamic acid, citric acid,

fumaric acid, glycolic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, oxalic acid, picric acid, pyruvic acid, salicylic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, tartaric acid, ascorbic acid, pamoic acid, bismethylene salicylic acid, ethanedisulfonic acid, gluconic acid, citraconic acid, aspartic acid, stearic acid, palmitic acid, EDTA, glycolic acid, p-aminobenzoic acid, glutamic acid, benzenesulfonic acid and p-toluenesulfonic acid.

4. The use according to any of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate (AP1189).

5. The use according to any of the preceding claims, wherein said compound:
   i) is an agonist of one or more MC receptors,
   ii) is an agonist of the MC1R and MC3R, and/or
   iii) is a biased agonist of the MC1R and MC3R.

6. The use according to any of the preceding claims, wherein said viral diseases or disorders is symptomatic viral diseases and disorders.

7. The use according to any of the preceding claims, wherein said viral disease or disorder is symptomatic COVID-19, such as
   a. wherein said symptomatic COVID-19 comprise one or more respiratory symptoms,
   b. wherein said symptomatic COVID-19 comprise one or more respiratory symptoms selected from the group consisting of cough, dry cough, dyspnea, respiratory illness, respiratory dysfunction, respiratory failure, respiratory syndrome and 2019-nCoV acute respiratory disease (2019-nCoV ARD),
   c. comprise viral pneumonia, including mild pneumonia, pneumonia, pneumonia with abnormal findings and novel coronavirus pneumonia (NCP),
   d. wherein said symptomatic COVID-19 is severe disease,
   e. wherein said symptomatic COVID-19 is critical disease,

f. wherein said symptomatic COVID-19 present with elevated levels of one or more pro-inflammatory cytokines, such as IL-6 and/or IL-1β,
g. wherein said symptomatic COVID-19 is COVID-19 with respiratory failure,
h. wherein said symptomatic COVID-19 is COVID-19 with acute respiratory distress syndrome (ARDS),
i. wherein said symptomatic COVID-19 is COVID-19 with systemic inflammatory distress syndrome (SIDS),
j. wherein said symptomatic COVID-19 require mechanical ventilation, or
k. wherein said symptomatic COVID-19 is COVID-19 induced pulmonary insufficiency, such as wherein said COVID-19 induced pulmonary insufficiency is defined as a need for supplementary oxygen to maintain normal saturation or wherein said COVID-19 induced pulmonary insufficiency is defined as SaPO2 lower than 93% on spontaneous respiration.

8. The use according to any of the preceding claims, wherein said viral diseases or disorders:
    a. are inflammatory viral diseases or disorders, such as virally induced inflammatory conditions, such as virally induced inflammation, such as virally induced hyperinflammation,
    b. is virally induced inflammation in one or more organs, such as virally induced hyperinflammation in one or more organs, such as wherein said hyperinflammation is characterized as C-reactive protein (CRP) >100 mg/l or ferritin 900 ng/ml, or
    c. is viral diseases or disorders with local inflammation or with a local inflammatory condition, such as a local inflammatory condition in one or more organs,

    such as wherein said one or more organs are selected from the group consisting of lungs, the respiratory tract, kidney, liver, pancreas, spleen, exocrine glands, endocrine glands, lymph nodes, brain, heart, muscles, bone marrow, skin, skeleton, bladder, reproduction organs including the phallopian tubes, eye, ear, vascular system, the gastroinstestinal tract including small intestines, colon, rectum, canalis analis and the prostate gland.

9. The use according to any of the preceding claims, wherein said viral diseases or disorders is viral diseases or disorders:

    a. with inflammation in the respiratory system, such as in the lungs and/or respiratory tract, or

    b. with one or more respiratory symptoms, such as wherein said one or more respiratory symptoms are selected from the group consisting of cough, dry cough, dyspnea, impaired oxygenation, respiratory illness, respiratory dysfunction, respiratory failure, respiratory syndrome and acute respiratory disease (ARD), such as wherein said respiratory symptom is selected from the group consisting of respiratory failure type 1, respiratory failure type 2, acute respiratory failure and chronic respiratory failure.

10. The use according to any of the preceding claims, wherein said viral diseases or disorders:

    a. is acute respiratory distress syndrome (ARDS),

    b. is severe disease, such as wherein said severe disease present with one or more of dyspnoea, increased respiratory frequency, reduced blood oxygen saturation and/or lung infiltrates,

    c. is critical disease, such as wherein said critical disease present with one or more of respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or multiple organ failure (MOF),

    d. is viral bronchiolitis,

    e. is viral pneumonia, such as wherein said viral pneumonia is selected from the group consisting of mild pneumonia, pneumonia, and pneumonia with abnormal findings,

    f. is pulmonary insufficiency, such as wherein said pulmonary insufficiency is defined as a need for supplementary oxygen to maintain normal saturation, such as wherein said pulmonary insufficiency is defined as $SaPO_2$ lower than 93% on spontaneous respiration,

    g. require mechanical ventilation, such as wherein said mechanical ventilation include protective mechanical ventilation, high-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV),

    h. is viral diseases or disorders with systemic inflammation,

    i. is systemic inflammatory distress syndrome (SIDS), or

j. is acute respiratory distress syndrome (ARDS) and systemic inflammatory distress syndrome (SIDS).

11. The use according to any of the preceding claims, wherein said treatment reduces the time to recovery.

12. The use according to any of the preceding claims, wherein said treatment:
    a. promotes inflammatory resolution,
    b. reduce the risk of development of severe inflammation,
    c. reduces the risk of development of severe acute respiratory distress syndrome (ARDS),
    d. reduces the requirement for supplementary oxygen to maintain normal saturation,
    e. reduces the risk of developing a need for more intensive pulmonary support.

13. The use according to any of the preceding claims, wherein said viral diseases or disorders:
    a. have elevated levels of one or more cytokines, such as one or more pro-inflammatory cytokines, such as IL-6 and/or IL-1β, or
    b. is treated with oxygen on nasal catheter, such as oxygen on nasal catheter with flow between 2-5 LO_2/min, and/or mechanical ventilation.

14. The use according to any of the preceding claims, wherein said viral diseases or disorders is viral diseases or disorders:
    a. with a cytokine storm (hypercytokinemia),
    b. with multisystem organ failure caused by viral hypercytokinemia,
    c. with cytokine release syndrome (CRS),
    d. with renal inflammation and/or renal dysfunction,
    e. with acute renal failure or chronic renal failure, or
    f. with end-stage renal disease,

    such as wherein said viral diseases or disorders are selected from the group consisting of viral kidney infection (pyelonephritis), viral urinary tract infection (UTI) and/or viral kidney inflammation (nephritis).

15. The use according to any of the preceding claims, wherein said viral diseases or disorders is viral diseases or disorders:
    a. with bladder infection and/or bladder inflammation (cystitis), such as severe haemorrhagic cystitis or urinary obstruction,
    b. with liver infection and/or liver inflammation (hepatitis), such as acute hepatitis and chronic hepatitis, and liver cirrhosis,
    c. with pancreas infection and/or pancreas inflammation (pancreatitis),
    d. with intestinal infection and/or intestinal inflammation, such as of the small intestine and/or of the large intestine, such as wherein said intestinal inflammation is colitis or enteritis,
    e. with brain infection and/or brain inflammation, such as wherein said brain inflammation is encephalitis; progressive multifocal leukoencephalopathy (PML); or inflammation of the white matter of the brain at one or multiple locations, or
    f. with eye infection and/or eye inflammation, such as wherein said eye inflammation is retinitis.

16. The use according to any of the preceding claims, wherein the viral diseases or disorders is virally-induced:
    a. spleen enlargement/atrophy, or
    b. diffuse lymphoid organ atrophy.

17. The use according to any of the preceding claims, wherein said viral diseases or disorders are caused by:
    a. viral infection, such as a viral infection selected from the group consisting of Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), SARS-CoV, MERS-CoV, the dengue virus and influenza virus (including Type A, Type B and Type C),
    b. dengue virus, such as wherein said viral diseases or disorders is dengue hemorrhagic fever or dengue shock syndrome,
    c. influenza virus, or
    d. a virus selected from the group consisting of SARS-CoV-2, SARS-CoV and MERS-CoV.

18. The use according to any of the preceding claims, for use in the treatment of viral diseases or disorders is in a subject:
    a. with an immunodeficiency, such as wherein said subject with an immunodeficiency is selected from a subject with a T cell deficiency, including a primary immunodeficiency of T cells such as severe combined immunodeficiency (SCID), Omenn syndrome, and Cartilage–hair hypoplasia, and a secondary immunodeficiency of T cells such as those caused by HIV/AIDS, cancer chemotherapies, lymphoma, and glucocorticoid therapy, or
    b. from a high-risk population, including HSCT patients (Hematopoietic stem-cell transplantation), SOT patients (solid organ transplant), elderly subjects and very young subjects.

19. The use according to any of the preceding claims, wherein said composition:
    a. comprises, separately or together, one or more additional active pharmaceutical ingredients, such as one or more additional active pharmaceutical ingredients used for the treatment of viral diseases or disorders, such as wherein said one or more additional active pharmaceutical ingredients are active pharmaceutical ingredients used for the treatment of symptomatic COVID-19,
    b. is an add-on therapy to one or more additional therapies used for the treatment of viral diseases or disorders, or
    c. is pharmaceutically safe.

20. The use according to any of the preceding claims, wherein said compound:
    a. is administered in an amount of 1 mg to 1000 mg per day, such as 1 to 5 mg, 5 to 10 mg, 10 to 15 mg, 15 to 20 mg, 20 to 30 mg, 30 to 60 mg, 60 to 80 mg, 80 to 100 mg, 100 to 130 mg, 130 to 160 mg, 160 to 200 mg, 200 to 240 mg, 240 to 280 mg, 280 to 320 mg, 320 to 360 mg, 360 to 400 mg, 400 to 440 mg, 440 to 500 mg, 500 to 560 mg, 560 to 620 mg, 620 to 680 mg, 680 to 740 mg, 740 to 800 mg, 800 to 860 mg, 860 to 920 mg, 920 to 980 mg, 980 to 1000 mg, for example 500 to 1000 mg per day,
    b. is administered in an amount of 100 mg once daily, 200 mg once daily, 300 mg once daily, 400 mg once daily, 500 mg once daily, 600 mg once

daily, 700 mg once daily, 800 mg once daily, 900 mg once daily or 100 mg once daily, such as wherein said compound is administered in an amount of 100 mg once daily, 100 mg two times daily (BID) or 100 mg three times daily (TID), such as wherein said compound is administered in an amount of 200 mg two times daily (BID) or 200 mg three times daily (TID), or

c. is administered as a once daily oral dosing of 100 mg AP1189.