and symptoms associated with activation of MCR, especially MC1R, and the documents also describe systemic sclerosis as a target disease. However, no effect is known for interstitial lung disease, or for a disease or symptom accompanied by systemic sclerosis, such as skin fibrosis, flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, or renal crisis.

Prior Art Documents

[Patent Documents]

[0005]

[Patent Document 1] WO 2015/182723

[Patent Document 2] WO 2020/138481

SUMMARY

[0005a]

In an aspect of the present disclosure, there is provided a use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof in the manufacture of a medicament for the treatment or prevention of interstitial lung disease in a subject.

[0005b]

In another aspect of the present disclosure, there is provided a use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof in the manufacture of a medicament for the treatment or prevention of a disease or symptom accompanied by systemic sclerosis in a subject, the disease or symptom being at least one selected from skin fibrosis,

flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, and renal crisis.

[0005c]

In a further aspect of the present disclosure, there is provided a use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof, in the manufacture of a medicament for decreasing the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a subject.

[0005d]

In another aspect of the present disclosure, there is provided a use of an MC1R agonist such as α-MSH or an analog thereof, in the manufacture of a medicament for the treatment or prevention of a disease or symptom accompanied by systemic sclerosis, the disease or symptom being a disease or symptom selected from the group consisting of Raynaud phenomenon, digital ulcers, pulmonary hypertension, renal crisis, interstitial lung disease, skin fibrosis, flexion contracture, gastroesophageal reflux disease, and dysphagia.

[0005e]

In a further aspect of the present disclosure, there is provided a method of judging therapeutic effectiveness of an MC1R agonist for a patient with systemic sclerosis, the method comprising the step of measuring the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a sample from the patient with systemic sclerosis.

[0005f]

In another aspect of the present disclosure, there is provided a method of judging whether or not an MC1R agonist can be administered to a patient with systemic sclerosis, the method comprising the step of measuring the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a sample from the patient with systemic sclerosis.

[0006]

An object of the present disclosure is to provide a medicament for treatment and/or prevention of interstitial lung disease, or of a disease or symptom accompanied by systemic sclerosis, selected from skin fibrosis, flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, and renal crisis.

[0007]

In order to solve the above problems, the present inventors intensively studied. As a result, the present inventors discovered that, by administering Compound A, which is an MC1R agonist, or a pharmaceutically acceptable salt or co-crystal thereof (hereinafter referred to as “Compound A or the like”) to a systemic sclerosis model animal, the expression levels of disease-related markers such as P-selectin, osteoprotegerin, cystatin C, GDF-15 (growth and differentiation factor-15), ET-1 (endothelin-1), IL-6, CCL2 (chemokine (C-C motif) ligand 2) (another name, MCP-1: monocyte chemoattractant protein 1), TNFR (tumor necrosis factor receptor) I,

TNFRII, SP-D (surfactant protein D), S100A9 (S100 calcium binding protein A9), adiponectin, MMP (matrix metalloproteinase)-2, MMP-3, TIMP-1 (tissue inhibitor of metalloproteinases-1), collagen, and α-SMA (alpha smooth muscle actin, encoded by the *Acta2* gene) can be decreased. Thereby, MC1R agonists such as Compound A were found to be effective for treatment and prevention of interstitial lung disease, and of diseases and symptoms accompanied by systemic sclerosis, selected from skin fibrosis, flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, and renal crisis, thereby completed the present disclosure.

[0008]

The following is an outline of the present disclosure.

[1] A medicament for treatment or prevention of interstitial lung disease (ILD) in a subject, the medicament comprising, as an effective ingredient, 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof.

[1-1] 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof for use in treatment or prevention of interstitial lung disease in a subject.

[1-2] Use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof in manufacture of a medicament for treatment or prevention of interstitial lung disease in a subject.

[1-3] A method of treating or preventing interstitial lung disease in a subject,

at least one disease or symptom selected from the group consisting of Raynaud phenomenon, digital ulcers, pulmonary hypertension, renal crisis, interstitial lung disease, skin fibrosis, flexion contracture, gastroesophageal reflux disease, and dysphagia.

[17] The method according to [15] or [16], wherein the MC1R agonist is 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof.

[18] A method of judging whether or not an MC1R agonist can be administered to a patient with systemic sclerosis, the method comprising the step of measuring the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a sample from the patient with systemic sclerosis.

[19] The method according to [18], wherein the patient with systemic sclerosis has at least one disease or symptom selected from the group consisting of Raynaud phenomenon, digital ulcers, pulmonary hypertension, renal crisis, interstitial lung disease, skin fibrosis, flexion contracture, gastroesophageal reflux disease, and dysphagia.

[20] The method according to [18] or [19], wherein the MC1R agonist is 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof.

[0009]

The medicament of the present disclosure enables effective treatment or

prevention of interstitial lung disease, for example, idiopathic interstitial pneumonia, connective tissue disease-associated interstitial lung disease, or systemic sclerosis-associated interstitial lung disease. The medicament of the present disclosure also enables effective treatment or prevention of skin fibrosis, flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, or renal crisis that occur in patients with systemic sclerosis. In particular, since Compound A is a low molecular weight compound, a medicament which can be produced at low cost, which is stable, and which can be easily taken, can be provided therewith.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010]

Fig. 1 shows the effect of Compound A on skin fibrosis and lung inflammation in a bleomycin (BLM)-induced systemic sclerosis (SSc) model: prevention evaluation. On day 0 to day 25, BLM was administered daily to the same area of the back skin of mice. For 29 days (day 0 to day 28), Compound A or a vehicle was orally administered to the mice once daily. Each sample was collected on day 29. A: Experimental schedule. B: Changes in the body weight of the mice during the experimental period. C: Collagen content in the skin. D: Wet weight of the left lung. E: Serum level of surfactant protein-D (SP-D). F and G: Expression of chemokine Ccl2 (another name, Mcp-1) and interleukin-6 (Il-6) mRNAs (calculated as relative values to hypoxanthine phosphoribosyltransferase 1 (Hprt)) in lung. H: Serum concentration of endothelin-1 (ET-1). B to H: Each bar represents the mean ± SEM (n=10 in all groups except 0.03 mg/kg Compound A treatment group (n=9)). ## $p<0.01$, BLM vs. PBS (according to Student's t-test); ** $p<0.005$, BLM vs. Compound A (according to Williams' test).

Fig. 2 shows the effect of Compound A on skin fibrosis in a BLM-induced SSc model: treatment evaluation. BLM was injected to the same area of the back

What is claimed is:

1. Use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof in the manufacture of a medicament for the treatment or prevention of interstitial lung disease in a subject.

2. The use according to claim 1, wherein the interstitial lung disease is idiopathic interstitial pneumonia, or connective tissue disease-associated interstitial lung disease.

3. The use according to claim 1, wherein the interstitial lung disease is systemic sclerosis-associated interstitial lung disease.

4. The use according to claim 3, wherein the systemic sclerosis is diffuse cutaneous systemic sclerosis.

5. The use according to any one of claims 1 to 4, wherein the subject is a patient whose expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA is increased compared to the expression level in a healthy individual.

6. Use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof in the manufacture of a medicament for the treatment or prevention of a disease or symptom accompanied by systemic sclerosis in a subject, the disease or symptom being at least one selected from skin fibrosis, flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, and renal crisis.

7. The use according to claim 6, wherein the subject is a patient with diffuse

cutaneous systemic sclerosis.

8. The use according to claim 6 or 7, wherein the subject is a patient whose expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA is increased compared to the expression level in a healthy individual.

9. Use of 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof, in the manufacture of a medicament for decreasing the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a subject.

10. The use according to claim 9, wherein the subject is a subject having interstitial lung disease.

11. The use according to claim 10, wherein the interstitial lung disease is idiopathic interstitial pneumonia, or connective tissue disease-associated interstitial lung disease.

12. The use according to claim 10, wherein the interstitial lung disease is systemic sclerosis-associated interstitial lung disease.

13. The use according to claim 9, wherein the subject is a subject having a disease or symptom accompanied by systemic sclerosis, the disease or symptom being at least one selected from skin fibrosis, flexion contracture, gastroesophageal reflux disease, dysphagia, Raynaud phenomenon, digital ulcers, pulmonary hypertension, and renal crisis.

14. Use of an MC1R agonist such as α-MSH or an analog thereof, in the

manufacture of a medicament for the treatment or prevention of a disease or symptom accompanied by systemic sclerosis, the disease or symptom being a disease or symptom selected from the group consisting of Raynaud phenomenon, digital ulcers, pulmonary hypertension, renal crisis, interstitial lung disease, skin fibrosis, flexion contracture, gastroesophageal reflux disease, and dysphagia.

15. A method of judging therapeutic effectiveness of an MC1R agonist for a patient with systemic sclerosis, the method comprising the step of measuring the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a sample from the patient with systemic sclerosis.

16. The method according to claim 15, wherein the patient with systemic sclerosis has at least one disease or symptom selected from the group consisting of Raynaud phenomenon, digital ulcers, pulmonary hypertension, renal crisis, interstitial lung disease, skin fibrosis, flexion contracture, gastroesophageal reflux disease, and dysphagia.

17. The method according to claim 15 or 16, wherein the MC1R agonist is 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof.

18. A method of judging whether or not an MC1R agonist can be administered to a patient with systemic sclerosis, the method comprising the step of measuring the expression level of at least one marker selected from P-selectin, osteoprotegerin, cystatin C, GDF-15, ET-1, IL-6, CCL2 (MCP-1), TNFRI, TNFRII, SP-D, S100A9, adiponectin, MMP-2, MMP-3, TIMP-1, collagen, and α-SMA in a sample from the patient with systemic sclerosis.

19. The method according to claim 18, wherein the patient with systemic sclerosis has at least one disease or symptom selected from the group consisting of Raynaud phenomenon, digital ulcers, pulmonary hypertension, renal crisis, interstitial lung disease, skin fibrosis, flexion contracture, gastroesophageal reflux disease, and dysphagia.

20. The method according to claim 18 or 19, wherein the MC1R agonist is 1-{2-[(3*S*,4*R*)-1-{[(3*R*,4*R*)-1-cyclopentyl-3-fluoro-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-4-(methoxymethyl)pyrrolidin-3-yl]-5-(trifluoromethyl)phenyl}piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt or co-crystal thereof.