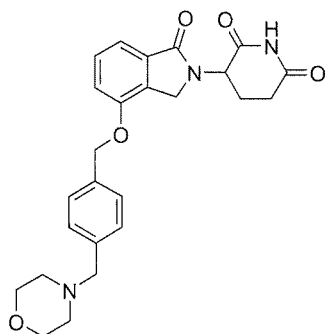


MA, Teirstein AS, Moller DR, Lower EE. Thalidomide for chronic sarcoidosis. Chest. 2002 Jul;122(1):227-32).

[0009] There remains a need for prophylactic or therapeutic drugs that can be used to treat or prevent immune-related and inflammatory diseases, including lupus, scleroderma, lupus pernio, sarcoidosis, Sjögren syndrome, ANCA-induced vasculitis, anti-phospholipid syndrome and myasthenia gravis.

5. SUMMARY

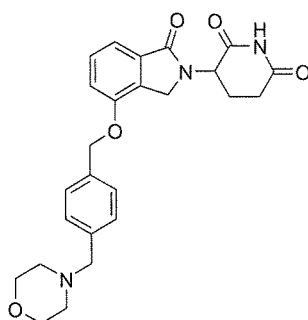
[0010] Provided herein are methods of treating, managing, ameliorating and/or preventing diseases, disorders and/or conditions associated with immune-related and inflammatory diseases comprising administering a therapeutically effective amount of a compound of formula I



Compound I,

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer or racemic mixtures thereof.

[0010a] In one aspect, there is provided use of a compound in the manufacture of a medicament for use in the treatment, prevention or management of an immune-related disease or an inflammatory disease, wherein the compound corresponds to is a compound of formula I

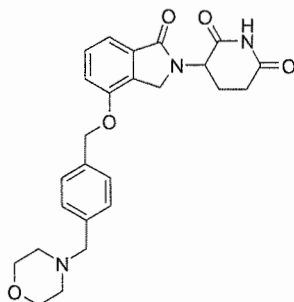


I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof, wherein the disease is lupus, scleroderma, lupus pernio, sarcoidosis, Sjögren syndrome, ANCA-induced vasculitis, anti-phospholipid syndrome, or myasthenia gravis.

[0010b] In another aspect, there is provided use of a compound for the manufacture of a medicament use in for the reduction, inhibition or prevention of a symptom of systemic lupus erythematosus, wherein the symptom is selected from the group consisting of joint pain, joint swelling, arthritis, chest pain

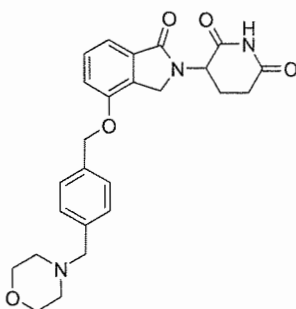
when taking a deep breath, fatigue, fever with no other cause, general discomfort, uneasiness, hair loss, mouth sores, swollen lymph nodes, sensitivity to sunlight, skin rash, headaches, numbness, tingling, seizures, vision problems, personality changes, abdominal pain, nausea, vomiting, abnormal heart rhythms, coughing up blood and difficulty breathing, patchy skin color and Raynaud's phenomenon, and wherein the compound is a compound of~~corresponds to~~ formula I



I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof.

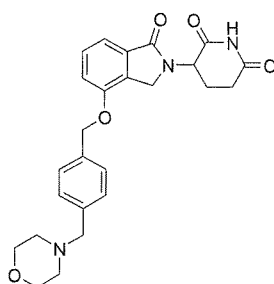
[0010c] In another aspect, there is provided use of a compound in the manufacture of a medicament for the use in reductioning, inhibitiong or preventiong of a symptom of scleroderma, wherein the symptom is selected from the group consisting of (i) gradual hardening, thickening, and tightening of the skin; (ii) skin discoloration; (iii) numbness of extremities; (iv) shiny skin; (v) small white lumps under the surface of the skin that erupt into a chalky white fluid; (vi) Raynaud's esophageal dysfunction; (vii) telangiectasia; (viii) pain and/or stiffness of the joints; (ix) swelling of the hands and feet; (x) itching of the skin; (xi) stiffening and curling of the fingers; (xii) ulcers on the outside of ~~certain joints, such as knuckles and elbows~~; (xiii) ~~digestive problems, such as heartburn, difficulty in swallowing, diarrhea, irritable bowel, and constipation~~; (xiv) fatigue and weakness; (xv) shortness of breath; (xvi) arthritis; (xvii) hair loss; (xviii) internal organ problems; (xix) digital ulcers; and (xx) digital auto-amputation, and wherein the compound is a compound of~~corresponds to~~ formula I



I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof.

[0010d] In another aspect, there is provided use of a compound in the manufacture of a medicament for use in improvementing of the modified Rodnan skin score, reductioning or improvementing of the skin thickness, reductioning or improvementing of skin induration, improvementing of the pulmonary function, improvementing of the dermatology quality of life index, improvementing of the carbon monoxide diffusing capacity, improvementing of the Mahler Dyspnea index, improvementing of the Saint George's Respiratory Questionnaire score, improvementing of the UCLA scleroderma clinical trial consortium gastrointestinal tract score, improvementing of flow-mediated dilatation or improvementing or increaseing of the six minute walk distance of a patient having scleroderma, wherein the compound ~~corresponds to~~ is a compound ~~having of~~ formula I:



I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof.

[0010e] In another aspect, there is provided use of a compound for the manufacture of a medicament for use in modulating activity of a B cell comprising contacting the cell with an effective amount of the compound, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-isoindo-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solid form, solvate, hydrate, tautomer, stereoisomer or racemate thereof.

[0010f] In another aspect, there is provided use of a compound for the manufacture of a medicament for use in modulating activity of a T cell comprising contacting the cell with an effective amount of the compound, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-isoindo-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solid form, solvate, hydrate, tautomer, stereoisomer or racemate thereof.

[0010g] ~~In another aspect, there is provided a method of identifying a subject who is likely to be responsive to a treatment of a disease, disorder, or condition with a treatment compound, comprising:~~

a) ~~determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof; and~~

b) comparing the level of the biomarker in the biological sample from the subject to a reference level of the biomarker;

wherein the subject is likely to be responsive to the treatment if the level of the biomarker in the biological sample obtained from the subject is altered as compared to the reference level of the biomarker.

[0010h] In another aspect, there is provided a method of identifying a subject who is likely to be responsive to a treatment of a disease, disorder, or condition with a treatment compound, comprising:

- a) determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof;
- b) determining the level of the biomarker in a control sample; and
- c) comparing the level of the biomarker in the biological sample from the subject to the level of the biomarker in the control sample;

wherein the subject is likely to be responsive to the treatment if the level of the biomarker in the biological sample from the subject is altered as compared to the level of the biomarker in the control sample.

[0010i] In another aspect, there is provided a method of predicting the responsiveness of a subject to a treatment of a disease, disorder, or condition with a treatment compound, comprising:

- a) determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof; and
- b) comparing the level of the biomarker in the biological sample to a reference level of the biomarker;

wherein the difference between the level of the biomarker in the biological sample from the subject and the reference level of the biomarker correlates with the responsiveness of the subject to the treatment.

[0010j] In another aspect, there is provided a method of predicting the responsiveness of a subject to a treatment of a disease, disorder, or condition with a treatment compound, comprising:

- a) determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof;
- b) determining the level of the biomarker in a control sample; and
- c) comparing the level of the biomarker in the biological sample from the subject to the level of the biomarker in the control sample;

wherein the difference between the level of the biomarker in the biological sample from the subject and the level of the biomarker in the control sample correlates with the responsiveness of the subject to the treatment.

[0010k] In another aspect, there is provided a method of monitoring the efficacy of a treatment of a disease, disorder, or condition in a subject treated with a treatment compound, comprising:

- a) determining the level of a biomarker in a first biological sample that had been obtained from the subject, wherein the biomarker is the CD44, CD83 or combination thereof;
- b) determining the level of the biomarker in a second biological sample that had been obtained from the subject after administration of the treatment compound, and
- e) comparing the levels of the biomarker in the first and second biological samples; wherein the subject is responsive to the treatment if the level of the biomarker in the second biological sample of the subject is altered as compared to the level of the biomarker in the first biological sample of the subject.

[0010l] In another aspect, there is provided a method of monitoring the compliance of a subject with a treatment of a disease, disorder, or condition with a treatment compound, comprising:

- a) determining the level of a biomarker in a biological sample that had been obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof; and
 - b) comparing the level of the biomarker with the level of the biomarker in a control untreated sample from the subject;
- wherein the change in the level of the biomarker in the biological sample in comparison with the level of the biomarker in the control sample indicates the compliance of the subject with the treatment.

[0011] In one embodiment, the compound is 3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione.

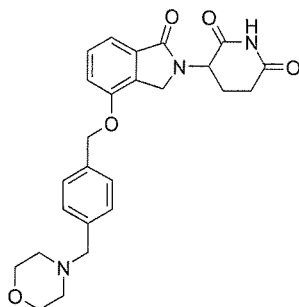
[0012] In one embodiment, the compound is a pharmaceutically acceptable salt of 3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione.

[0013] In one embodiment, the compound is 3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione hydrochloride.

[0014] In one embodiment, the compound is (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione, having the following structure:

What is claimed is:

1. ~~A-Use of a compound for use in the manufacture of a medicament for the treating,~~
~~prevention or management of an immune-related disease or an inflammatory disease,~~
wherein the compound ~~corresponds to~~ is a compound of formula I

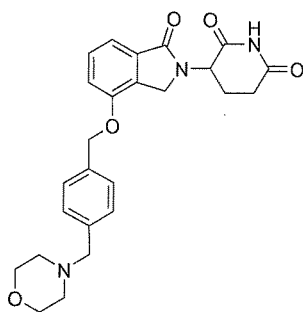


I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof, wherein the disease is lupus, scleroderma, lupus pernio, sarcoidosis, Sjögren syndrome, ANCA-induced vasculitis, anti-phospholipid syndrome, or myasthenia gravis.

2. ~~The compound use of claim 1, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-indol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solid form, solvate, hydrate, or tautomer, stereoisomer or racemate thereof.~~
3. ~~The compound use of claim 1, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-indol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione.~~
4. ~~The compound use of claim 1, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-indol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione hydrochloride.~~
5. ~~The compound use of any of claims 1-4, wherein the disease is systemic lupus erythematosus, scleroderma, lupus pernio, or sarcoidosis, Sjögren syndrome, ANCA-induced vasculitis, anti-phospholipid syndrome or myasthenia gravis.~~
6. ~~The compound use of any of claims 1-5~~ claim 5, wherein the disease is systemic lupus erythematosus.
7. ~~The compound use of any of claims 1-6~~ claim 6, wherein the disease is severe systemic lupus erythematosus.
8. ~~The compound use of any of claims 1-4~~ claim 5, wherein the disease is scleroderma.
9. ~~The compound use of claim 8, wherein the scleroderma is localized, systemic, limited or diffuse scleroderma.~~
10. ~~The compound use of claim 9, wherein the systemic scleroderma comprises CREST syndrome.~~

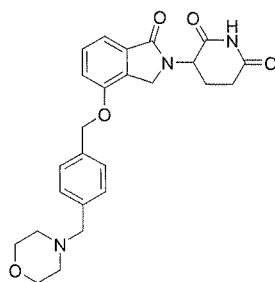
11. ~~A Use of a compound for use in the manufacture of a medicament for the reductioning, inhibitionng or preventionng of~~ a symptom of systemic lupus erythematosus, wherein the symptom is selected from the group consisting of joint pain, joint swelling, arthritis, chest pain when taking a deep breath, fatigue, fever with no other cause, general discomfort, uneasiness, hair loss, mouth sores, swollen lymph nodes, sensitivity to sunlight, skin rash, headaches, numbness, tingling, seizures, vision problems, personality changes, abdominal pain, nausea, vomiting, abnormal heart rhythms, coughing up blood and difficulty breathing, patchy skin color and Raynaud's phenomenon, and wherein the compound ~~corresponds to~~ is a compound of formula I



I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof.

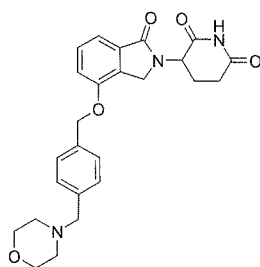
12. ~~A Use of a compound for use in the manufacture of a medicament for the reductioning, inhibitionng or preventionng of~~ a symptom of scleroderma, wherein the symptom is selected from the group consisting of (i) gradual hardening, thickening, and tightening of the skin; (ii) skin discoloration; (iii) numbness of extremities; (iv) shiny skin; (v) small white lumps under the surface of the skin that erupt into a chalky white fluid; (vi) Raynaud's esophageal dysfunction; (vii) telangiectasia; (viii) pain and/or stiffness of the joints; (ix) swelling of the hands and feet; (x) itching of the skin; (xi) stiffening and curling of the fingers; (xii) ulcers on the outside of certain joints, ~~such as~~ knuckles and elbows; (xiii) ~~digestive problems, such as~~ heartburn, difficulty in swallowing, diarrhea, irritable bowel, and constipation; (xiv) fatigue and weakness; (xv) shortness of breath; (xvi) arthritis; (xvii) hair loss; (xviii) internal organ problems; (xix) digital ulcers; and (xx) digital auto-amputation, and wherein the compound ~~corresponds to~~ is a compound of formula I



I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof.

13. ~~A Use of a compound for use in the manufacture of a medicament for improving of~~ the modified Rodnan skin score, ~~reducing or improving of~~ the skin thickness, ~~reducing or improving of~~ skin induration, ~~improving of~~ the pulmonary function, ~~improving of~~ the dermatology quality of life index, ~~improving of~~ the carbon monoxide diffusing capacity, ~~improving of~~ the Mahler Dyspnea index, ~~improving of~~ the Saint George's Respiratory Questionnaire score, ~~improving of~~ the UCLA scleroderma clinical trial consortium gastrointestinal tract score, ~~improving of~~ flow-mediated dilatation or ~~improving or increasing of~~ the six minute walk distance of a patient having scleroderma, wherein the compound corresponds to compound I having formula is a compound of formula I:



I,

or a pharmaceutically acceptable salt, solid form, solvate, hydrate, stereoisomer, tautomer or racemic mixture thereof.

14. ~~The compound use of any one of claims 11-13, wherein the compound is~~ (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-indol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solid form, solvate, hydrate, or tautomer, ~~stereoisomer or racemate~~ thereof.

15. ~~The compound use of any one of claims 11-13, wherein compound is~~ (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-indol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione.

16. ~~The compound use of any one of claims 11-13, wherein compound is~~ (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-indol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione hydrochloride.

17. ~~The compound use of any one of claims 1-16 further comprising, wherein the medicament is to be administered in combination with a second active agent, which is an anti-inflammatory or immunomodulatory compound.~~
18. ~~The compound use of any one of claims 1-17, wherein the effective amount of the compound I is about 0.005 mg/kg to about 10 mg/kg of the patient's body weight.~~
19. ~~A Use of a compound for use in the manufacture of a medicament for modulating activity of a B cell comprising contacting the cell with an effective amount of the compound, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solid form, solvate, hydrate, tautomer, stereoisomer or racemate thereof.~~
20. ~~A Use of a compound for use in the manufacture of a medicament for modulating activity of a T cell comprising contacting the cell with an effective amount of the compound, wherein the compound is (S)-3-[4-(4-morpholin-4-ylmethylbenzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]piperidine-2,6-dione (S)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione or a pharmaceutically acceptable salt, solid form, solvate, hydrate, tautomer, stereoisomer or racemate thereof.~~
21. ~~A method of identifying a subject who is likely to be responsive to a treatment of a disease, disorder, or condition with a treatment compound, comprising:~~
- ~~a) — determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof; and~~
 - ~~b) — comparing the level of the biomarker in the biological sample from the subject to a reference level of the biomarker;~~
- ~~wherein the subject is likely to be responsive to the treatment if the level of the biomarker in the biological sample obtained from the subject is altered as compared to the reference level of the biomarker.~~
22. ~~A method of identifying a subject who is likely to be responsive to a treatment of a disease, disorder, or condition with a treatment compound, comprising:~~
- ~~—— a) — determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof;~~
 - ~~—— b) — determining the level of the biomarker in a control sample; and~~
 - ~~—— c) — comparing the level of the biomarker in the biological sample from the subject to the level of the biomarker in the control sample;~~
- ~~—— wherein the subject is likely to be responsive to the treatment if the level of the biomarker in the biological sample from the subject is altered as compared to the level of the biomarker in the control sample.~~
23. ~~A method of predicting the responsiveness of a subject to a treatment of a disease, disorder, or condition with a treatment compound, comprising:~~
- ~~—— a) — determining the level of a biomarker in a biological sample obtained from the subject;~~

wherein the biomarker is CD44, CD83 or combination thereof; and

_____ b) _____ comparing the level of the biomarker in the biological sample to a reference level of the biomarker;

_____ wherein the difference between the level of the biomarker in the biological sample from the subject and the reference level of the biomarker correlates with the responsiveness of the subject to the treatment.

24. _____ A method of predicting the responsiveness of a subject to a treatment of a disease, disorder, or condition with a treatment compound, comprising:

_____ a) _____ determining the level of a biomarker in a biological sample obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof;

_____ b) _____ determining the level of the biomarker in a control sample; and

_____ c) _____ comparing the level of the biomarker in the biological sample from the subject to the level of the biomarker in the control sample;

_____ wherein the difference between the level of the biomarker in the biological sample from the subject and the level of the biomarker in the control sample correlates with the responsiveness of the subject to the treatment.

25. _____ A method of monitoring the efficacy of a treatment of a disease, disorder, or condition in a subject treated with a treatment compound, comprising:

_____ a) _____ determining the level of a biomarker in a first biological sample that had been obtained from the subject, wherein the biomarker is the CD44, CD83 or combination thereof;

_____ b) _____ determining the level of the biomarker in a second biological sample that had been obtained from the subject after administration of the treatment compound; and

_____ c) _____ comparing the levels of the biomarker in the first and second biological samples;

_____ wherein the subject is responsive to the treatment if the level of the biomarker in the second biological sample of the subject is altered as compared to the level of the biomarker in the first biological sample of the subject.

26. _____ A method of monitoring the compliance of a subject with a treatment of a disease, disorder, or condition with a treatment compound, comprising:

_____ a) _____ determining the level of a biomarker in a biological sample that had been obtained from the subject, wherein the biomarker is CD44, CD83 or combination thereof; and

- _____b)_____comparing the level of the biomarker with the level of the biomarker in a control untreated sample from the subject;
- _____wherein the change in the level of the biomarker in the biological sample in comparison with the level of the biomarker in the control sample indicates the compliance of the subject with the treatment.
- 27._____The method of any of claims 21 to 36, wherein the treatment compound is an immunomodulatory compound.
- 28._____The method of claim 27, wherein the treatment compound is (S)-3-(4-(4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione.
- 29._____The method of claim 28, wherein the treatment compound is (S)-3-(4-(4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride.