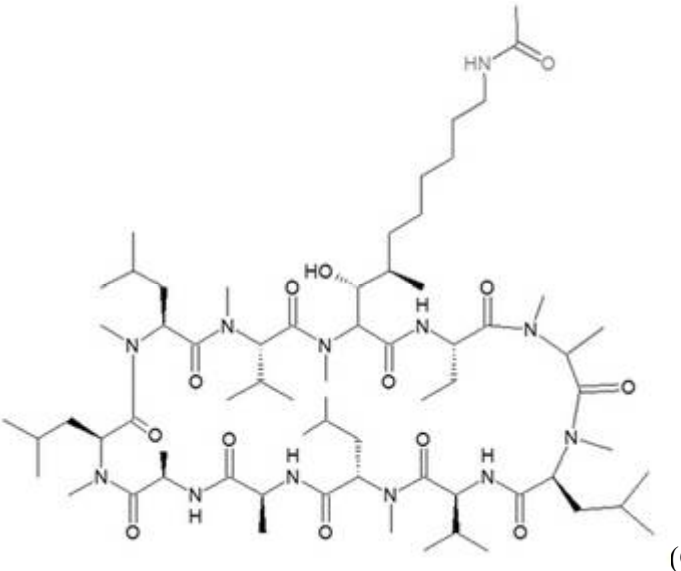


(CRV431).

[0023] In some embodiments, the pharmaceutical composition is for intravenous administration, oral administration, or parenteral administration. In some embodiments, the pharmaceutical composition is in the form of powder, pill, tablet, microtablet, pellet, micropellet, capsule, capsule containing microtablets, liquid, aerosols, or nanoparticles.

[0024] Disclosed herein include a kit, comprising

a pharmaceutical composition disclosed herein; and

a label, wherein the label indicating one or more of:

(a) the kit is for preventing or treating fibrosis,

(b) the kit is for reducing or inhibiting fibrosis formation,,

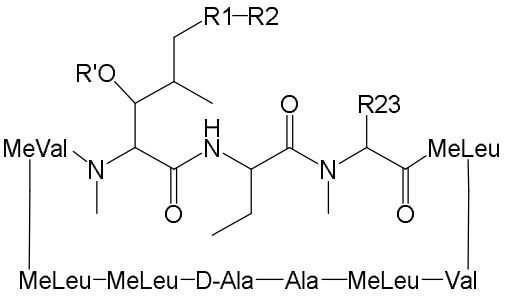
(c) the kit is for reversing fibrosis,

(d) the kit is for reducing the amount of fibrosis, and

(e) the kit is for delaying the onset of fibrosis.

[0025] In some embodiments, the kit further comprises instructions for identifying a subject at risk of development fibrosis, instructions for identifying a subject suffering from fibrosis, or both

[0025a] In one aspect, disclosed herein is a use of a composition comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, in the manufacture of a medicament for treating non-liver fibrosis, for reducing fibrosis or reversing fibrosis, for preventing or treating fibrosis, for preventing or reducing fibrosis formation, for reducing the amount of fibrosis, and/or for delaying the onset of fibrosis, in a subject in need thereof,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

[0025b] In another aspect, disclosed herein is a kit, comprising a pharmaceutical composition; and a label, wherein the label indicating one or more of:

(a) the kit is for preventing or treating fibrosis,

(b) the kit is for reducing or inhibiting fibrosis formation,

(c) the kit is for reversing fibrosis,

(d) the kit is for reducing the amount of fibrosis, and

(e) the kit is for delaying the onset of fibrosis.

BRIEF DESCRIPTION OF THE DRAWINGS

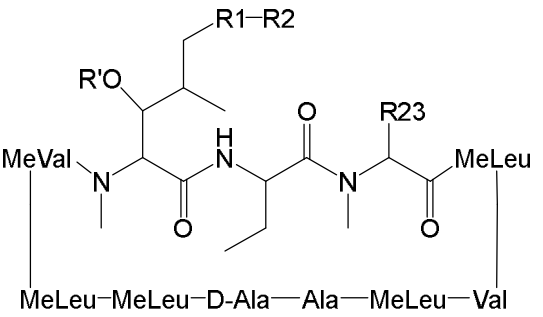
[0026] FIGS. 1A-B are histograms showing dose-dependent decreases in the abundance of procollagen and fibronectin caused by CRV431 treatment in human LX-2 hepatic stellate cell culture.

[0027] FIGS. 2A-B are histograms showing dose-dependent decreases in the abundance of procollagen and fibronectin caused by CRV431 treatment in human IPF lung fibroblast culture.

[0028] FIGS. 3A-B are histograms showing dose-dependent decreases in the

WHAT IS CLAIMED IS:

1. Use of a composition comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, in the manufacture of a medicament for treating non-liver fibrosis, for reducing fibrosis or reversing fibrosis, for preventing or treating fibrosis, for preventing or reducing fibrosis formation, for reducing the amount of fibrosis, and/or for delaying the onset of fibrosis, in a subject in need thereof,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

2. The use of claim 1, wherein the subject in need thereof is a subject suffering from non-liver fibrosis.

3. The use of any one of claims 1-2, wherein the amount of non-liver fibrosis in the subject is reduced, and optionally wherein the amount of non-liver fibrosis in the subject is reduced by 5%, 10%, 20%, or more, and/or wherein the formation of non-liver fibrosis in the subject is reduced, and optionally wherein the formation of non-liver fibrosis in the subject is reduced by 5%, 10%, 20%, or more.

4. The use of any one of claims 1-**Error! Reference source not found.**, wherein the non-liver fibrosis comprises fibrosis in lung, kidney, heart, skin, eye, gastrointestinal tract, peritoneum, bone marrow, muscle, blood vessel, vasculature, or any combination thereof, and/or wherein the subject in need thereof is a subject suffering from a fibrotic disorder selected from the group consisting of idiopathic pulmonary fibrosis (IPF), cardiac fibrosis, dermal fibrosis, renal fibrosis, or a combination thereof.

5. The use of claim 1, wherein the subject in need thereof is a subject at a risk of developing fibrosis.

6. The use of claim 5, wherein the subject in need thereof is a subject having no fibrosis progression.

7. The use of any one of claims 5-6, wherein the risk of developing fibrosis in the subject is reduced by at least 5%, 10%, 20% or more as compared to untreated subjects.

8. The use of any one of claims 1-7, wherein the onset of fibrosis is delayed in the subject by at least a month, a year, or more, and/or wherein the fibrosis formation is reduced in the subject by at least a month, a year, or more as compared to untreated subjects.

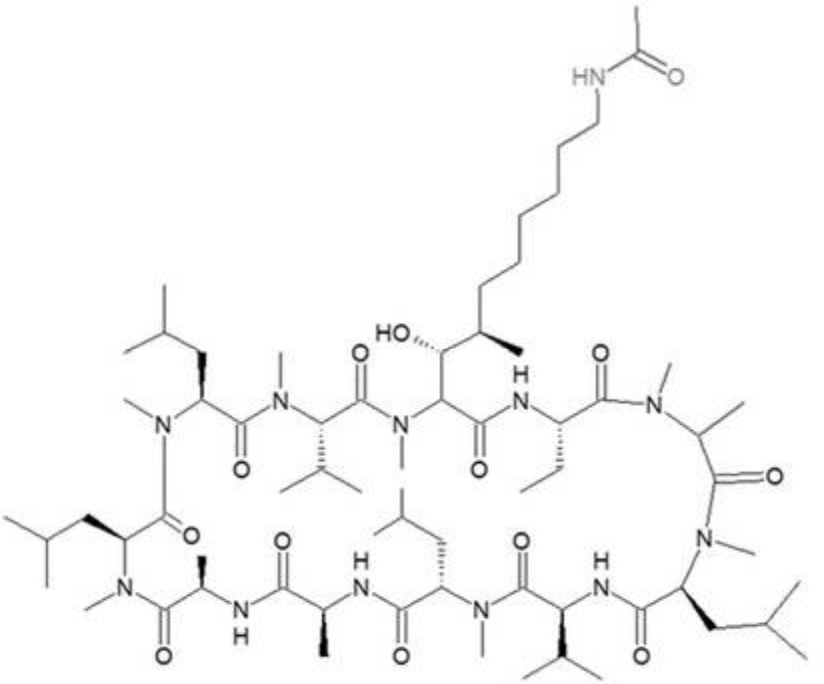
9. The use of claim 1, wherein the subject in need thereof is a subject suffering from fibrosis.

10. The use of any one of claims 1-9, wherein fibrosis formation is inhibited in the subject.

11. The use of any one of claims 1-10, wherein the fibrosis is non-liver fibrosis.

12. The use of any one of claims **Error! Reference source not found.** and 5-10, wherein the fibrosis is liver fibrosis, optionally wherein the liver fibrosis is cirrhosis, and optionally wherein the cirrhosis is associated with viral hepatitis, schistosomiasis and chronic alcoholism.

13. The use of any one of claims 1-12, wherein the cyclosporine analogue of Formula L is CRV431:



(CRV431).

14. The use of any one of claims 1-13, wherein the composition comprises a therapeutically or prophylactically effective amount of the cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof.

15. The use of any one of claims 1-14, wherein the non-liver fibrosis or fibrosis is induced by a therapeutic agent, an injury, or a combination thereof, wherein the non-liver fibrosis or fibrosis is associated with the accumulation of extracellular matrix constituents that occurs following trauma, inflammation, tissue repair, immunological reactions, cellular hyperplasia, neoplasia, or a combination thereof, wherein the non-liver fibrosis or fibrosis is associated with major organ diseases, fibroproliferative disorders, scarring associated with trauma, or a combination thereof, and/or wherein the fibrosis is associated with interstitial lung disease, liver cirrhosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, kidney disease, heart or vascular disease, diseases of the eye, systemic and local scleroderma, keloids, hypertrophic scars, atherosclerosis, restenosis, Dupuytren's contracture, surgical complications, chemotherapeutics drug-induced fibrosis, radiation-induced fibrosis, accidental injury and burns, retroperitoneal fibrosis, peritoneal fibrosis/peritoneal scarring,

or a combination thereof, and optionally wherein the fibrosis associated with interstitial lung disease is sarcoidosis, silicosis, drug reactions, infections, collagen vascular diseases, rheumatoid arthritis, systemic sclerosis, scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis, usual interstitial pneumonitis, interstitial lung disease, cryptogenic fibrosing alveolitis, bronchiolitis obliterans, bronchiectasis, or a combination thereof.

16. The use of any one of claims 1-15, wherein fibrosis formation is reduced in the subject by at least 5%, 10%, 20%, 50%, 70%, 90%, or more as compared to untreated subjects, and/or wherein fibrosis formation is delayed in the subject as compared to untreated subjects.

17. The use of any one of claims 1-16, wherein the subject is a mammal, and optionally wherein the subject is a human.

18. The use of any one of claims 1-17, wherein the composition comprises one or more pharmaceutically acceptable excipients, and/or wherein the composition comprises one or more additional therapeutic agents.

19. The use of any one of claims 1-18, wherein the composition is formulated to be administered to the subject and further comprises one or more additional therapeutic agents.

20. The use of claim 18 or 19, wherein the one or more additional therapeutic agents comprise an additional antifibrotic agent, and/or wherein the one or more additional therapeutic agents comprises Type II interferon receptor agonists, pirfenidone and pirfenidone analogs, nintedanib and nintedanib analogs, anti-angiogenic agents, anti-inflammatory agents, IL-1 antagonists, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers and aldosterone antagonists, mitomycin C (MMC), 5-fluorouracil (5-FU), adenylyl cyclase activators, β-adenoreceptor agonists, flavonoids, mast cell stabilizers, phosphodiesterase inhibitors, procyanidins, or a combination thereof.

21. The use of any one of claims 18-**Error! Reference source not found.**, wherein at least one of the one or more additional therapeutic agents is formulated to be co-administered to the subject with the composition.

22. The use of any one of claims 18-**Error! Reference source not found.**, wherein at least one of the one or more additional therapeutic agents is formulated to be administered to the subject before the administration of the composition, after the administration of the composition, or both.

23. The use of any one of claims 1-22, wherein the composition is formulated to be administered to the subject by intravenous administration, oral administration, or parenteral

administration, and/or wherein the composition is in the form of powder, pill, tablet, microtablet, pellet, micropellet, capsule, capsule containing microtablets, liquid, aerosols, or nanoparticles.

24. The use of any one of claims 1-**Error! Reference source not found.**, wherein the composition is formulated to be administered to the subject at an effective daily dose of the cyclosporine analogue or a pharmaceutically acceptable salt, solvate, stereoisomer thereof at from 10 mg to 250 mg.

25. The use of any one of claims 1-24, wherein the composition is a pharmaceutical composition.

26. A kit, comprising

a pharmaceutical composition of claim 25; and

a label, wherein the label indicating one or more of:

(a) the kit is for preventing or treating fibrosis,

(b) the kit is for reducing or inhibiting fibrosis formation,

(c) the kit is for reversing fibrosis,

(d) the kit is for reducing the amount of fibrosis, and

(e) the kit is for delaying the onset of fibrosis.

27. The kit of claim 26, further comprising instructions for identifying a subject at risk of development fibrosis, instructions for identifying a subject suffering from fibrosis, or both.