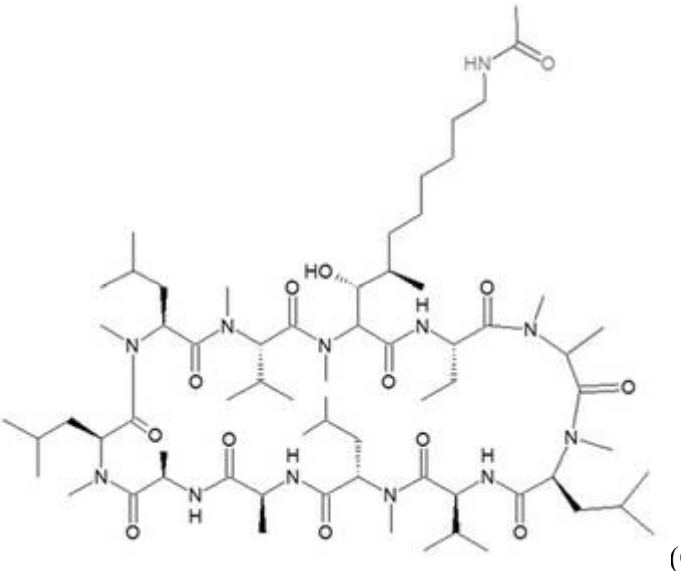


(CRV431).

[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,,

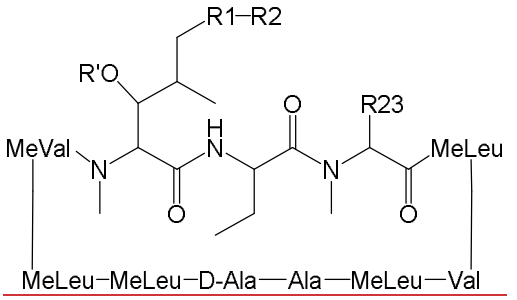
(c) the kit is for reversing fibrosis,

(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

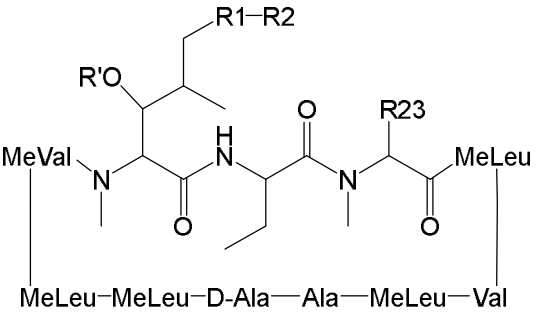
[0026] FIGS. 1A-B are histograms showing dose-dependent decreases in the abundance of procollagen and fibronectin caused by CRV431 treatment in human LX-2 hepatic stellate cell culture.

[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. ~~A method for treating non-liver fibrosis, comprising administering to a subject in need thereof~~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 ~~method~~use of claim 1, wherein the subject in need thereof is a subject suffering from non-liver fibrosis.

~~3.~~ The ~~method~~use of any one of claims 1-2, ~~comprising reducing~~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 method of claim 3, wherein the amount of non-liver fibrosis in the subject is reduced by 5%, 10%, 20%, or more.~~

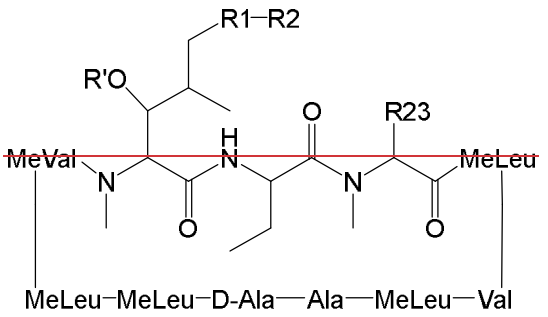
~~5. The method of any one of claims 1-2, comprising reducing formation of non-liver fibrosis in the subject.~~

~~6.~~3. ~~The method of claim 5, wherein the formation of non-liver fibrosis in the subject is reduced by 5%, 10%, 20%, or more.~~

~~7.~~ The ~~method~~use of any one of claims 1-3~~36~~, 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.

~~8.~~4. ~~The method of any one of claims 1-6, 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.~~

~~9. A method for preventing or delaying the onset of fibrosis, comprising administering to a subject in need thereof a composition comprising cyclosporine analogue of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer 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.~~

~~10.~~5. The ~~method~~use of claim ~~9~~1, wherein the subject in need thereof is a subject at a risk of developing fibrosis.

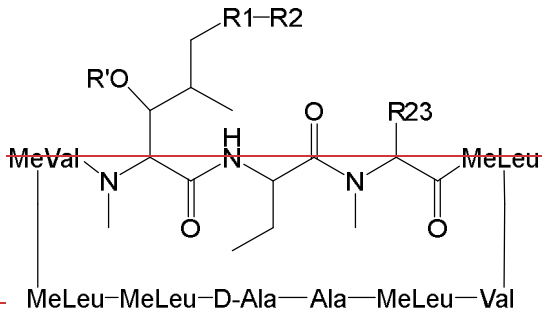
~~11.~~6. The ~~method~~use of ~~any one of claims 9-10~~claim 5, wherein the subject in need thereof is a subject having no fibrosis progression.

~~12.~~7. The ~~method~~use of any one of claims ~~5~~5~~10~~-~~6~~6~~11~~, wherein the risk of developing fibrosis in the subject is reduced by at least 5%, 10%, 20% or more as compared to untreated subjects.

~~13.~~ The ~~method~~use of any one of claims ~~9~~1-~~7~~7~~12~~, 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.

~~14. The method of any one of claims 9-13, comprising reducing fibrosis formation, wherein the fibrosis formation is reduced in the subject by at least a month, a year, or more as compared to untreated subjects.~~

~~15. A method for reducing fibrosis or reversing fibrosis, comprising administering to a subject in need thereof a composition comprising cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer 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

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

16.9. The methoduse of claim 151, wherein the subject in need thereof is a subject suffering from fibrosis.

17.10. The methoduse of any one of claims 91-9916, comprising inhibitingwherein fibrosis formation is inhibited in the subject.

18. The methoduse of any one of claims 91-101017, wherein the fibrosis is non-liver fibrosis.

19. The method of claim 18, 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.

20. The method of any one of claims 9-17, wherein the subject in need thereof is a subject suffering from a fibrotic disorder selected from the group consisting of pulmonary fibrosis, cardiac fibrosis, dermal fibrosis, renal fibrosis, hepatic fibrosis, or a combination thereof.

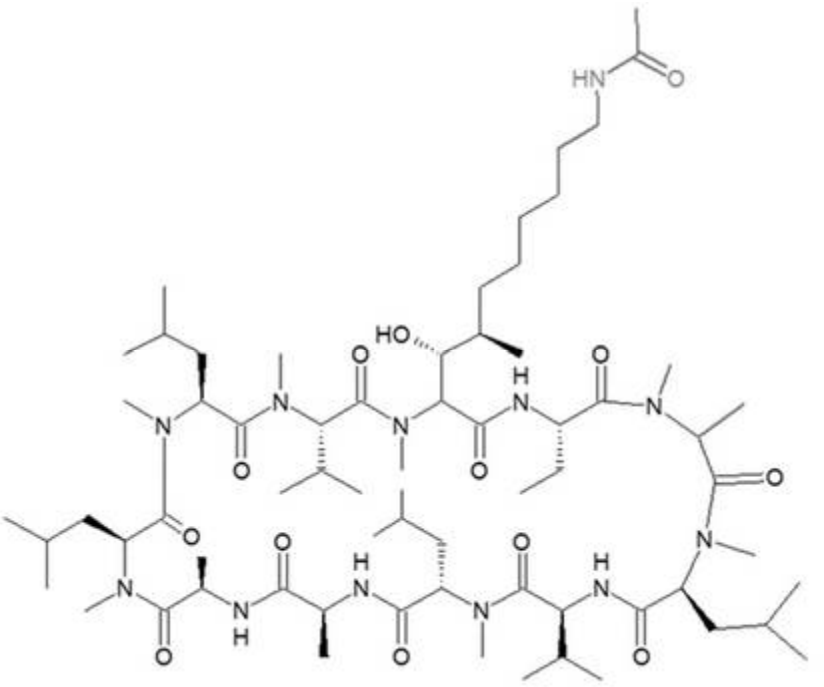
21.11. The method of any one of claims 9-17, wherein the subject in need thereof is a subject suffering from idiopathic pulmonary fibrosis (IPF).

22.12. The methoduse of any one of claims 119 and 5-101017, 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.

23. The method of claim 22, wherein the liver fibrosis is cirrhosis.

24. The method of claim 23, wherein the cirrhosis is associated with viral hepatitis, schistosomiasis and chronic alcoholism.

25.13. The methoduse of any one of claims 1-2412, wherein the cyclosporine analogue of Formula L is CRV431:



(CRV431).

~~26.~~14. The ~~method~~use of any one of claims 1-13~~1325~~, 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.

~~27.~~15. The ~~method~~use of any one of claims 1-14~~1426~~, 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.

~~28. The method of any one of claims 1-26, 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, a combination thereof.~~

~~29. The method of any one of claims 1-26, wherein the non-liver fibrosis or fibrosis is associated with major organ diseases, fibroproliferative disorders, scarring associated with trauma, or a combination thereof.~~

~~30. The method of any one of claims 9-26, 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.~~

~~31. The method of claim 30, 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.~~

~~32.~~16. The ~~method~~use of any one of claims ~~91~~-~~31~~15, ~~comprising reducing~~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.

~~33. The method of any one of claims 9-31, comprising delaying fibrosis formation in the subject as compared to untreated subjects.~~

~~34.~~17. The ~~method~~use of any one of claims 1-16~~33~~, wherein the subject is a mammal, and optionally wherein the subject is a human.

~~35. The method of any one of claims 1-33, wherein the subject is a human.~~

~~36.~~ The ~~method~~use of any one of claims 1-~~35~~17, wherein the composition comprises one or more pharmaceutically acceptable excipients, and/or wherein the composition comprises one or more additional therapeutic agents.

~~37.~~18. ~~The method of any one of claims 1-36, wherein the composition comprises one or more additional therapeutic agents.~~

~~38.~~19. The ~~method~~use of any one of claims 1-~~36~~18, ~~further comprising administering~~wherein the composition is formulated to be administered to the subject ~~in need thereof~~and further comprises one or more additional therapeutic agents.

~~39.~~ The ~~method~~use of claim 18~~18~~37 or 19~~19~~38, 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.

~~40.~~20. ~~The method of claim 37 or 38, 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.~~

~~41.~~21. The ~~method~~use of any one of claims 18~~18~~37-20~~20~~40, wherein at least one of the one or more additional therapeutic agents is formulated to be co-administered to the subject with the composition.

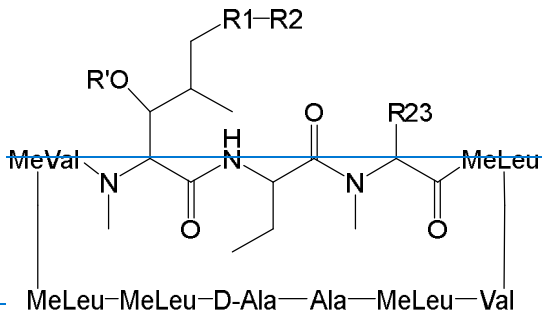
~~42.~~22. The ~~method~~use of any one of claims 18~~18~~37-20~~20~~40, wherein at least one of the one or more additional therapeutic agents is formulated to be administered to the subject before the administration of the composition, after the administration of the composition, or both.

~~43.~~ The ~~method~~use of any one of claims 1-22~~22~~42, 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.

~~44.~~23. ~~The method of any one of claims 1-43, wherein the composition is in the form of powder, pill, tablet, microtablet, pellet, micropellet, capsule, capsule containing microtablets, liquid, aerosols, or nanoparticles.~~

~~45.~~24. The ~~method~~use of any one of claims 1-23~~23~~44, 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.

46. A pharmaceutical composition, comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, for use in preventing or treating fibrosis, or for use in preventing or reducing fibrosis formation, or for use in reversing fibrosis, or for reducing the amount of fibrosis, or for delaying the onset of fibrosis



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;

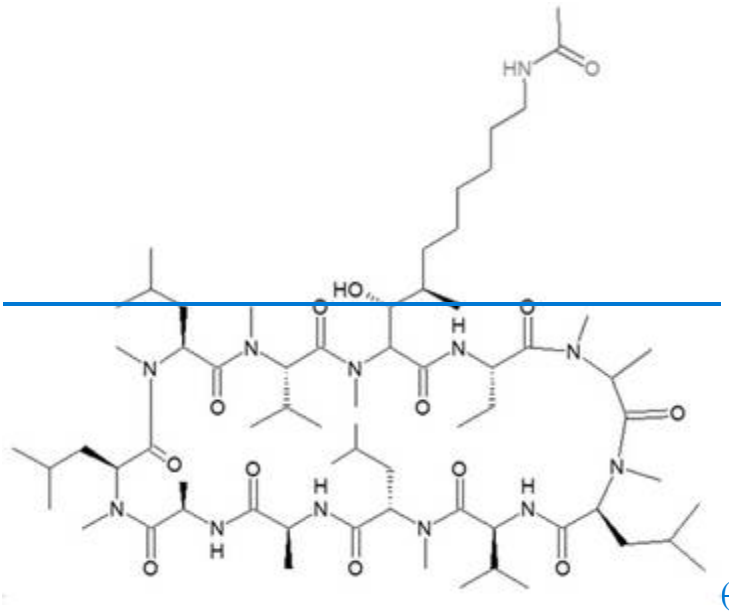
xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

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

25. ~~d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.~~ The use of any one of claims 1-24, wherein the composition is a pharmaceutical composition.

~~47. The pharmaceutically composition of claim 46, wherein the cyclosporine analogue is CRV431:~~



~~(CRV431).~~

~~48. The pharmaceutical composition of claim 46, wherein the pharmaceutical composition is for intravenous administration, oral administration, or parenteral administration.~~

~~49. The pharmaceutical composition of any one of claims 46-48, wherein the pharmaceutical composition is in the form of powder, pill, tablet, microtablet, pellet, micropellet, capsule, capsule containing microtablets, liquid, aerosols, or nanoparticles.~~

~~50.~~26. A kit, comprising

a pharmaceutical composition of ~~any one of~~ claim ~~s 46-49~~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.

~~51.~~27. The kit of claim ~~50~~ 26, further comprising instructions for identifying a subject at risk of development fibrosis, instructions for identifying a subject suffering from fibrosis, or both.