wherein

A is straight chain C_5 alkyl, straight chain C_6 alkyl, straight chain C_5 alkenyl, straight chain C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4; or is preferably C_5 alkyl, C_5 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3; or is preferably C_6 alkyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 4;

R_1 is H, F or OH; or is preferably H or OH;

R_2 is straight chain C_5 alkyl, straight chain C_6 alkyl, straight chain C_5 alkenyl, straight chain C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4; or is preferably C_5 alkyl, C_5 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3; or is preferably C_6 alkyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 4;

R_3 is H, F, OH or CH_2Ph; or is preferably H, F or OH; or is preferably H or OH;

R_4 is H, F or OH; or is preferably H or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,

2) $CH(CH_3)C(O)OH$,

3) $C(CH_3)_2C(O)OH$,

4) CH(F)-C(O)OH,

5) CF_2-C(O)OH, or

6) C(O)-C(O)OH.

In a preferred embodiment, the pharmaceutically acceptable salt of the compound is sodium, potassium, lithium, ammonium, calcium, magnesium, manganese, zinc, iron, or copper. The preferred pharmaceutically acceptable salt of the compound is sodium.

A preferred compound according to the present disclosure is one of the following compounds:

5) CF_2-C(O)OH, or

6) C(O)-C(O)OH;

in the manufacture of a medicament for preventing and/or slowing progression of and/or treating ~~a fibrotic disease~~fibrosis in a subject in need thereof. In yet another aspect, there is provided use of a therapeutically effective amount of a compound as described herein; in the manufacture of a medicament for preventing and/or slowing progression of and/or treating ~~a fibrotic disease~~fibrosis in a subject in need thereof. In a preferred embodiment of the disclosure, the subject has a fibrotic disease ~~is~~ selected from the group consisting of pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, pancreas fibrosis, systemic sclerosis, cardiac fibrosis ~~or~~ and macular degeneration.

The compound is preferably administered orally. The subject is preferably a human. When compound is administered orally and the subject is a human, the therapeutically effective amount is preferably between about 1 to about 50 mg/kg, or between about 1 to about 25 mg/kg or between about 5 to about 25 mg/kg, or between about 1 to about 20 mg/kg, or between about 1 to about 10 mg/kg, or between about 10 to 20 mg/kg.

According to a preferred embodiment of the disclosure, the fibrotic disease is pulmonary fibrosis. The pulmonary fibrosis is preferably idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension.

In an embodiment, the fibrotic disease is liver fibrosis. According to a preferred embodiment of the disclosure, the liver fibrosis is resulting from a chronic liver disease, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, alcoholic liver disease or non-alcoholic steatohepatitis, obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1 -antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins.

In an embodiment, the fibrotic disease is skin fibrosis. According to a preferred embodiment of the disclosure, the skin fibrosis is scarring, hypertrophic scarring, keloid scarring, dermal fibrotic disorder, wound healing, delayed wound healing, psoriasis or scleroderma. Said scarring may

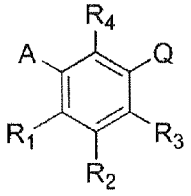
condition, the compound of the present disclosure can be advantageously administered for life time period.

In an embodiment, the fibrotic disease is cardiac fibrosis. In this embodiment, the therapeutically effective amount is preferably between about 1 to about 50 mg/kg, and preferably or between about 1 to 25 mg/kg, or between about 1 to about 10 mg/kg, between about 5 to about 25 mg/kg, between about 5 to about 20 mg/kg, or between about 10 to about 20 mg/kg. The compound is preferably administered orally. The subject is preferably a human.

In another preferred embodiment, the compound of the present disclosure can be administered in combination with a therapeutically effective amount of second compound where the second compound is preferably a therapeutic agent know for being effective in preventing or treating or potentially preventing or treating a fibrotic disease. According to an embodiment of the present disclosure, the compound can be administered in combination with a therapeutically effective amount of second compound, the second compound is an immunosuppressive drug, an anti-inflammatory drug, a cytokine, a monoclonal antibody, a multiple receptor tyrosine kinase inhibitor, an antioxidant, an enzyme inhibitor, an integrin inhibitor, an hypertensive inhibitor, a lipid receptor modulator or a thiazolindione.

In addition to the previous embodiments of dosages, for all above mentioned fibrotic diseases, when the compound of the present disclosure is orally administered to a human, the therapeutically effective amount of a compound corresponds to preferably between about 0.01 to about 10% (w/w), or between about 0.1 to 10% (w/w), or between about 1.0 to about 10% (w/w), between about 0.1 to about 5% (w/w), or between about 1.0 to about 5% (w/w). In all above mentioned fibrotic diseases, when the compound of the present disclosure is orally administered to a human, the therapeutically effective amount of a compound corresponds preferably between about 1 to about 50 mg/kg, or between about 1 to 25 mg/kg, or between about 1 to about 10 mg/kg, between about 5 to about 25 mg/kg, or between about 10 to about 20 mg/kg.

In another aspect, there is provided a kit for preventing and/or slowing progression of and/or treating ~~fibrotic disease~~fibrosis in a subject in need thereof. The kit comprises a compound represented by the formula:



or a pharmaceutically acceptable salt thereof, wherein

A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4; or is preferably C_5 alkyl, C_5 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3; or is preferably C_6 alkyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 4;

R_1 is H, F or OH; or is preferably H or OH;

R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4; or is preferably C_5 alkyl, C_5 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3; or is preferably C_6 alkyl, C_6alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 4;

R_3 is H, F, OH or CH_2Ph; or is preferably H, F or OH; or is preferably H or OH;

R_4 is H, F or OH; or is preferably H or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,

2) $CH(CH_3)C(O)OH$,

3) $C(CH_3)_2C(O)OH$,

4) CH(F)-C(O)OH,

5) CF_2-C(O)OH, or

6) C(O)-C(O)OH;

and instructions for administering a therapeutically effective amount of the compound to the subject suffering from said ~~fibrotic disease~~fibrosis. In a preferred embodiment of the disclosure, the subject has a fibrotic disease ~~is~~ selected from the group consisting of pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, pancreas fibrosis,

systemic sclerosis, cardiac fibrosis ~~or~~ and macular degeneration. The kit may also comprises instructions for administering any of the above-disclosed therapeutically effective amount of the compound for oral administration.

For all fibrotic diseases, the kit preferably further comprises instructions for administering between about 1 to about 50 mg/kg of the compound daily and orally to the subject who is a human.

When the fibrotic disease is skin fibrosis, the kit preferably further comprises instructions suggesting administering topically and daily between about 0.01 to about 10 % (w/w) of the compound to the subject who is a human; or instructions suggesting administering orally and daily between about 1 to about 50 mg/kg of the compound to the subject who is a human.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the glomerular filtration rate (GFR) function in db/db diabetic mouse compared to C57BL/6 mice (control mice), and in db/db diabetic mouse following oral treatment with Compound 1 at a dose of 10 and 50 mg/kg.

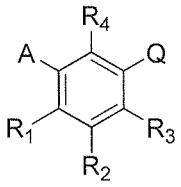
DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "alkyl" is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups having five or six carbon atoms. Examples of alkyl defined above include, but are not limited to, n-pentyl, n-hexyl, isopentyl, isohexyl, t-pentyl and t-hexyl. Similarly, as used herein, the term "alkenyl" is intended to include unsaturated straight or branched chain hydrocarbon groups having five or six carbon atoms, and in which at least two carbon atoms are bonded to each other by a double bond, and having E or Z regiochemistry and combinations thereof. Examples of alkenyl defined above include, but are not limited to, 1-pentenyl, 2-pentenyl, 1 -hexenyl and 2-hexenyl.

The compounds of the present invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centers, chiral axes and chiral planes, and may thus give rise to enantiomers, diastereomers and other stereoisomeric forms and subsequently may be defined in terms of absolute stereochemistry such as (R)- or (S)-. The present invention is therefore intended to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L); isomers may be prepared using chiral synthons or chiral reagents or resolved using conventional techniques, such as reverse phase

CLAIMS

1. A pharmaceutically acceptable salt of a compound represented by the formula:



wherein

A is straight chain C_5 alkyl, straight chain C_6 alkyl, straight chain C_5 alkenyl, straight chain C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_1 is H, F or OH;

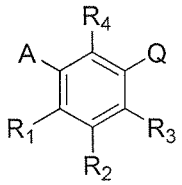
R_2 is straight chain C_5 alkyl, straight chain C_6 alkyl, straight chain C_5 alkenyl, straight chain C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_3 is H, F, OH or CH_2Ph;

R_4 is H, F or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,
2) $CH(CH_3)C(O)OH$,
3) $C(CH_3)_2C(O)OH$,
4) $CH(F)-C(O)OH$,
5) $CF_2-C(O)OH$, or
6) $C(O)-C(O)OH$.



or a pharmaceutically acceptable salt thereof, wherein

A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_1 is H, F or OH;

R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, $C(O)-(CH_2)_n-CH_3$ or $CH(OH)-(CH_2)_n-CH_3$ wherein n is 3 or 4;

R_3 is H, F, OH or CH_2Ph;

R_4 is H, F or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,

2) $CH(CH_3)C(O)OH$,

3) $C(CH_3)_2C(O)OH$,

4) CH(F)-C(O)OH,

5) CF_2-C(O)OH, or

6) C(O)-C(O)OH; in the manufacture of a medicament for preventing and/or slowing progression of and/or treating ~~a fibrotic disease~~fibrosis in a subject in need thereof.

9. Use of a therapeutically effective amount of a compound as defined in any one of claims 1 to 5; in the manufacture of a medicament for preventing and/or slowing progression of and/or treating ~~a fibrotic disease~~fibrosis in a subject in need thereof.

10. The use of claim 8 or 9, wherein the subject has a fibrotic disease that is selected from the group consisting of pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, pancreas fibrosis, systemic sclerosis, cardiac fibrosis ~~or~~ and macular degeneration.

11. The use of claim 9 or 10, wherein the therapeutically effective amount is ~~between~~ about 1 ~~to~~ about 50 mg/kg, the compound is administered orally, and the subject is human.

12. The use of claim 11, wherein the therapeutically effective amount is between about 1 to about 20 mg/kg.

13. The use according to claim 10, wherein the pulmonary fibrosis is idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, pulmonary hypertension or chronic obstructive pulmonary disease.

14. The use according to claim 10, wherein the liver fibrosis is resulting from a chronic liver disease, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, alcoholic liver disease or non-alcoholic steatohepatitis, obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins.

15. The use according to claim 10, wherein the skin fibrosis is scarring, hypertrophic scarring, keloid scarring, dermal fibrotic disorder, wound healing, delayed wound healing, psoriasis or scleroderma.

16. The use of claim 15, wherein said scarring derives from a burn, a trauma, a surgical injury, a radiation or an ulcer.

17. The use of claim 16, wherein said ulcer is diabetic foot ulcer, venous leg ulcer or pressure ulcer.

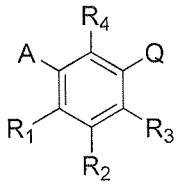
5) CF_2-C(O)OH, or

6) C(O)-C(O)OH; in the manufacture of a medicament for antagonizing collagen secretion or collagen deposition in an organ of a mammal.

20. Use of a therapeutically effective amount of a compound as defined in any one of claims 1 to 5, in the manufacture of a medicament for antagonizing collagen secretion or collagen deposition in an organ of a mammal, wherein the organ is lung, liver, kidney, pancreas, skin or heart.

21. The use according to any one of claims 6 to 20, wherein the compound is to be administered in combination with a therapeutically effective amount of second compound, the second compound is an immunosuppressive drug, an anti-inflammatory drug, a cytokine, a monoclonal antibody, a multiple receptor tyrosine kinase inhibitor, an antioxidant, an enzyme inhibitor, an integrin inhibitor, an hypertensive inhibitor, a lipid receptor modulator or an anti-diabetic drug.

22. A kit for preventing and/or slowing progression of and/or treating ~~fibrotic disease~~fibrosis in a subject in need thereof, comprising a compound represented by the formula:



or a pharmaceutically acceptable salt thereof, wherein

A is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, C(O)-$(CH_2)_n$-CH_3 or CH(OH)-$(CH_2)_n$-CH_3 wherein n is 3 or 4;

R_1 is H, F or OH;

R_2 is C_5 alkyl, C_6 alkyl, C_5 alkenyl, C_6 alkenyl, C(O)-$(CH_2)_n$-CH_3 or CH(OH)-$(CH_2)_n$-CH_3 wherein n is 3 or 4;

R_3 is H, F, OH or CH_2Ph;

R_4 is H, F or OH;

Q is

1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,

2) $CH(CH_3)C(O)OH$,

3) $C(CH_3)_2C(O)OH$,

4) CH(F)-C(O)OH,

5) CF_2-C(O)OH, or

6) C(O)-C(O)OH;

and instructions for administering a therapeutically effective amount of the compound to the subject suffering from said ~~fibrotic disease~~fibrosis.

23. The kit of claim 22, wherein the subject has a fibrotic disease that is selected from the group consisting of pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, pancreas fibrosis, systemic sclerosis, cardiac fibrosis ~~or~~ and macular degeneration.

24. The kit of claim 22 or 23, further comprises instructions for administering between about 1 to about 50 mg/kg of the compound daily and orally to the subject who is a human.

25. The kit of claim 23, further comprises instructions for administering between about 0.01 to about 10 % (w/w) of the compound daily and topically to the subject who is a human, and wherein the fibrotic disease is skin fibrosis.

26. The kit of any one of claims 22 to 25, wherein the compound is one of the following compounds: