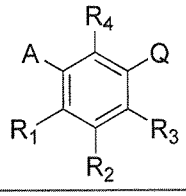
sophisticated approaches of countering cardiac fibrosis like microRNA inhibition (miR-21, for example) are being tested in animal models.

No medication is on the market to prevent or treat cardiac fibrosis and there is a need to develop efficacious pharmaceutical preparation.

SUMMARY OF THE INVENTION

Surprisingly, the inventors have determined that the compounds of the present ~~invention~~ disclosure display *antifibrotic* activity in the lungs, liver, skin and heart. Knowing that the compounds of the present ~~invention~~ disclosure have a good safety profile; the inventors concluded that the compounds of the present disclosure ~~invention~~ are excellent drug candidates for the prevention/treatment of pulmonary fibrosis, liver fibrosis, skin fibrosis and cardiac fibrosis. Cardiac fibrosis and heart fibrosis are interchangeably used herein and are intended to designate the same.

In one aspect, there is provided use of a therapeutically effective amount of 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, OH or F;

R_2 is H, OH, F or CH_2-OH;

R_3 is H, OH, F or CH_2Ph;

R_4 is H, OH or F;

Q is

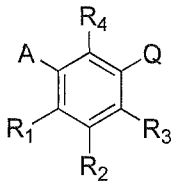
1) $(CH_2)_mC(O)OH$ wherein m is 1 or 2,

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

3) CF_2-C(O)OH, or

4) C(O)-C(O)OH; in the manufacture of a medicament for preventing and/or slowing progression of and/or treating a fibrotic disease in a subject in need thereof, wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis or cardiac fibrosis.

More particularly, the present disclosure ~~invention~~ concerns a method for preventing and/or slowing progression of and/or treating a fibrotic disease in a subject in need thereof. The fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis or cardiac fibrosis. The method comprises the administration of a therapeutically effective amount of 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, OH or F; or is preferably H or OH;

R_2 is H, OH, F or CH_2-OH; or is preferably H, OH or F; or is preferably H or OH;

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

R_4 is H, OH or F; 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) $C(CH_3)_2C(O)OH$,

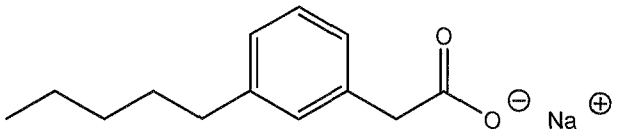
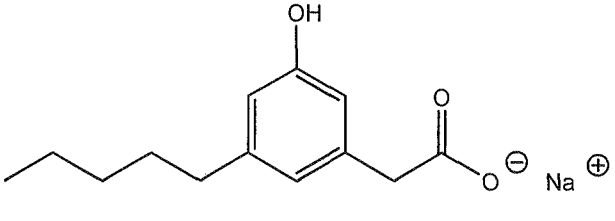
4) CH(F)-C(O)OH,

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.

According to a preferred embodiment of the ~~inventiondisclosure~~, the compound is one of the following compounds:

Compound I	
Compound II	

between about 1 to about 20 mg/kg. The compound is preferably administered orally. The subject is preferably a human. According to a preferred embodiment of the ~~invention~~disclosure, 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, or pulmonary hypertension.

In an embodiment, the fibrotic disease is liver fibrosis. In this embodiment, the therapeutically effective amount is preferably between about 1 to about 50 mg/kg. The compound is preferably administered orally. The subject is preferably human. According to a preferred embodiment of the ~~invention~~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. In this embodiment, the compound is preferably administered topically or orally. When administered topically, the therapeutically effective amount of the compound of the present ~~invention~~ disclosure is preferably between about 0.01 to about 10% (w/w). The subject is preferably human. When administered orally, the therapeutically effective amount of the compound of the present disclosure~~invention~~ is preferably between about 1 to about 50 mg/kg and the subject is human. According to a preferred embodiment of the disclosure~~invention~~, the skin fibrosis is scarring, hypertrophic scarring, keloid scarring, dermal fibrotic disorder, wound healing, delayed wound healing, psoriasis or scleroderma. Said scarring may derived from a burn, a trauma, a surgical injury, a radiation or an ulcer. Said ulcer can be a diabetic foot ulcer, a venous leg ulcer or a pressure ulcer.

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 between about 1 to about 20 mg/kg. The compound is preferably administered orally. The subject is preferably a human.

In addition to the previous embodiments of dosages, for all above mentioned fibrotic diseases, when the compound of the present disclosure~~invention~~ is topically 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~~invention~~ 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 use of a therapeutically effective amount of a compound as described herein, 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, skin or heart. 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 reducing the collagen production in cells, wherein said compound is to be contacted with the cells. According to a preferred embodiment, the ~~invention~~ disclosure also concerns a method for antagonizing collagen secretion or collagen deposition in an organ, such as the lung, the liver, the skin or the heart, of a mammal comprising the administration of a therapeutically effective amount of a compound of the present disclosure~~invention~~ to the mammal that is in need thereof, wherein the organ is lung, liver, skin or heart. The mammal that is in need thereof is a mammal that is subject to an excessive collagen secretion or collagen deposition in an organ such as the lung, the liver, the skin or the heart. Usually, the excessive collagen secretion or collagen deposition in an organ results from an injury or an insult. Such injury and insult are organ-specific and are described herein in details in the background section and in the whole specification. The therapeutically effective amount described hereinabove in detail also applies to the present method for antagonizing collagen secretion or collagen deposition in an organ. The route of administration described herein also applies to the present method. The compound is preferably administered over a sufficient period of time to antagonize the level of collagen deposition in the organ, completely or partially. The term "antagonizing" used herein is intended to mean "decreasing" or "reducing". A sufficient period of time can be during one week, or between 1 week to 1 month, or between 1 to 2 months, or 2 months or more. For chronic condition, the compound of the present disclosure~~invention~~ can be advantageously administered for life time period.

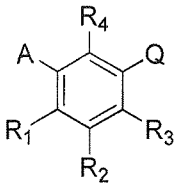
The present disclosure~~invention~~ also concerns a method for reducing the collagen production in cells, which comprises contacting the cells with a therapeutically effective amount of a compound of the present disclosure~~invention~~. The collagen is preferably collagen 1. The collagen production is preferably the collagen mRNA expression or the production of the collagen protein. According to a preferred embodiment, the cells are in culture, are part of an organ or are part of an organ that is entirely part of a live animal, where said animal includes, without limitation, a mouse, a rat or a human. In the case that the cells are part of an organ that is entirely part of a live animal, the step of

contacting the cells with a therapeutically effective amount of a compound of the present disclosure~~invention~~ is equivalent to administering the compound to the animal. In the case that the cells are part of an organ that is entirely part of a live animal and the live animal is a human, the therapeutically effective amount of a compound corresponds to a topical administration of 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), or to an oral administration of 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 the case of cultured cells, the therapeutically effective amount of a compound corresponds to 0,01 to 0,5 mM, and preferably of about 0,2 mM.

In another preferred embodiment, the compound of the present disclosure ~~invention~~ is administered in combination with a therapeutically effective amount of second compound where the second compound is preferably a therapeutic agent known for being effective in preventing or treating or potentially preventing or treating a pulmonary fibrosis, a liver fibrosis or skin fibrosis. In another preferred embodiment, the compound is 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, a lipid receptor modulator, or a thiazolindione.

In a preferred embodiment where the fibrotic disease is pulmonary fibrosis, the compound of the present disclosure~~invention~~ is administered in combination with a therapeutically effective amount of pirfenidone. In this case, the preferred compound is Compound I. In the case that the subject affected by the pulmonary fibrosis is a human, the therapeutically effective amount of Compound I is 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 and the pirfenidone is between about 10 mg/kg to about 40 mg/kg, or between about 1.0 g/day to about 2.5 g/day, when orally administered. The combination of the compound of the present disclosure~~invention~~ and the second therapeutic agent can be administered in a single preparation or in separate preparations.

In another aspect, there is provided a kit for preventing and/or slowing progression of and/or treating fibrotic disease 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, OH or F;

R_2 is H, OH, F or CH_2-OH;

R_3 is H, OH, F or CH_2Ph;

R_4 is H, OH or F;

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;

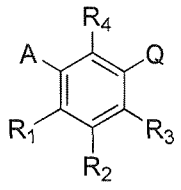
and instructions for administering a therapeutically effective amount of the compound to the subject suffering from said fibrotic disease, wherein the fibrotic disease is pulmonary fibrosis,

liver fibrosis, skin fibrosis or cardiac fibrosis. The present ~~invention~~ disclosure also concerns a kit for preventing and/or slowing progression of and/or treating fibrotic disease in a subject in need thereof. The kit comprises a compound represented by the formula:

When the fibrotic disease is pulmonary fibrosis, heart fibrosis or liver fibrosis, 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. The kit may also comprises instructions for administering any of the above-disclosed therapeutically effective amount of the compound for oral administration.

When the fibrotic disease is skin fibrosis, the kit preferably 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; or instructions for administering between about 1 to about 50 mg/kg of the compound daily and orally to the subject who is a human. The kit may also comprises instructions for administering any of the above-disclosed therapeutically effective amount of the compound for topical administration.

~~The present invention also concerns novel~~In another aspect, there is provided a compound~~s~~ 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, OH or F;

R_2 is H, OH, F or CH_2-OH;

R_3 is CH_2Ph;

R_4 is H, OH or F;

Q is