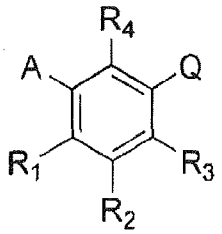
inflammation. Disruption of the highly ordered tissue architecture in the eye caused by vascular leakage, hemorrhage, and concomitant fibrosis can lead to mechanical disruption of the visual axis and/or biological malfunctioning. The CNS is highly specialized in many ways, including the types of inflammatory and wound-healing cells present. Since the retina is part of the CNS, its response to injury utilizes mechanisms very similar to those observed in the rest of the brain; this is true not only for the wound-healing response but also for utilization of migratory cues functional during development of the neuronal and vascular component of this highly organized tissue (Friedlander M.; Fibrosis and diseases of the eye, J. Clin. Invest. 2007). As discussed below, the response of the anterior segment of the eye to wound healing more closely resembles the response of non-CNS tissues than do such events in the posterior segment or the eye. Therefore, I refer to such wound-healing events in the anterior segment as fibrosis, whereas comparable events in the retina are referred to as gliosis. Although such distinction is somewhat artificial, it does serve to differentiate between the fibroblasts and glial cells that effect the wound-healing and scar-formation events. An increased understanding of inflammation, wound healing, and angiogenesis has led to the development of drugs effective in modulating these biological processes and, in certain circumstances, the preservation of vision. Unfortunately, such pharmacological interventions often are too little, too late, and progression of vision loss frequently occurs. There is need to prevent or treat each fibrotic disease with a safe and efficacious drug.

SUMMARY OF THE INVENTION

More particularly, the present ~~invention~~ disclosure concerns novel substituted aromatic compounds as defined by the formula herein below. Compared to known aromatic compounds, the present compounds have a longer chain at position R_2; and this particularity of the present compounds has shown to have favorable and surprising impact on the activity. Therefore, ~~the present invention~~in one aspect, there is provided ~~concerns~~ a pharmaceutically acceptable salt of the compound defined 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_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) $C(CH_3)_2C(O)OH$,

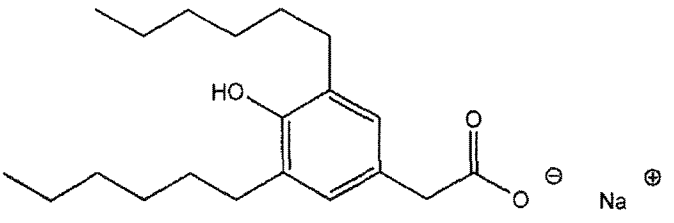
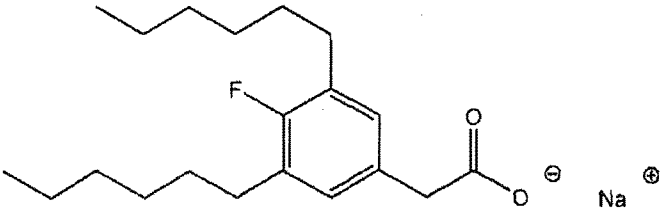
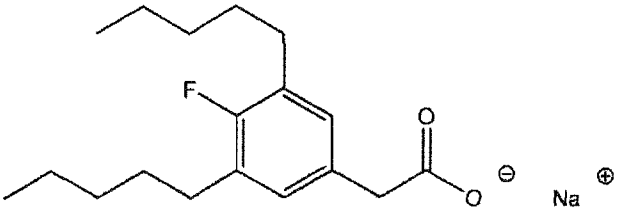
4) CH(F)-C(O)OH,

5) CF_2-C(O)OH, or

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

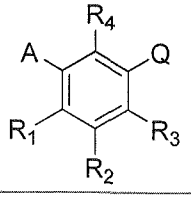
In a preferred embodiment, the pharmaceutically acceptable salt of the compound is sodium, potassium, lithium, ammonium, calcium, magnesium, manganese, zinc, iron, or copper. The preferred pharmaceutically acceptable salt of the compound is sodium.

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

Compound 6	
Compound 7	
Compound 8	

In another aspect, there is provided a compound which is a free acid form or a pharmaceutically acceptable salt of one of the above compounds.

The present ~~invention~~ disclosure also concerns a method for reducing the collagen production in cells, comprising contacting the cells with a therapeutically effective amount of a compound of the present ~~invention~~disclosure. In yet another 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, 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

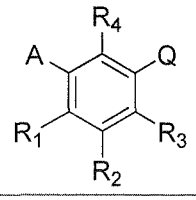
6) $C(O)-C(O)OH$;

in the manufacture of a medicament for reducing collagen production in cells, wherein said compound is contacted with the cells. 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 reducing collagen production in cells, wherein said compound is contacted with the cells. The collagen is preferably collagen 1. The collagen production is preferably the collagen mRNA expression and 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 ~~invention~~ disclosure 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.

The present ~~invention~~ disclosure further concerns a method for preventing and/or slowing progression of and/or treating a fibrotic disease in a subject in need thereof, comprising the administration of a therapeutically effective amount of the compound of the present ~~invention~~disclosure. In another 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, 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 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 in a subject in need thereof. In a preferred embodiment of the ~~invention~~disclosure, the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, pancreas fibrosis, systemic sclerosis, cardiac fibrosis or 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 ~~invention~~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 ~~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.

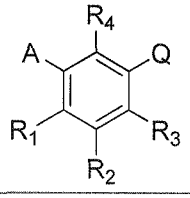
In an embodiment, the fibrotic disease is skin fibrosis. According to a preferred embodiment of the ~~invention~~disclosure, the skin fibrosis is scarring, hypertrophic scarring, keloid scarring, dermal fibrotic disorder, wound healing, delayed wound healing, psoriasis or scleroderma. Said scarring may

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.

When the fibrotic disease is a skin fibrosis, the compound is preferably administered topically or orally. When the compound is administered topically and the subject is human, the therapeutically effective amount of the compound of the present ~~invention~~ disclosure is 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),. When administered orally, the therapeutically effective amount of the compound of the present ~~invention~~ disclosure is 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, and the subject is human.

In an embodiment, the fibrotic disease is kidney fibrosis. According to a preferred embodiment of the ~~invention~~disclosure, the kidney fibrosis is resulting from dialysis following kidney failure, catheter placement, a nephropathy, glomerulosclerosis, glomerulonephritis, chronic renal insufficiency, acute kidney injury, end stage renal disease or renal failure.

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 ~~invention~~ disclosure to the mammal that is in need thereof, wherein the organ is kidney, lung, liver, skin or heart. In another aspect, there is provided use of a therapeutically effective amount of a compound to the mammal in need thereof, wherein the organ is lung, liver, kidney, pancreas, skin or heart, wherein the compound is 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;

in the manufacture of a medicament for antagonizing collagen secretion or collagen deposition in an organ of a mammal. 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 antagonizing collagen secretion or collagen deposition in an organ of a mammal, wherein the organ is lung, liver, kidney, pancreas, 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 kidney, 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

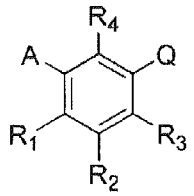
condition, the compound of the present ~~invention~~ disclosure can be advantageously administered for life time period.

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 ~~invention~~ 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~~invention~~, 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 ~~invention~~ 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 ~~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~~The present invention 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:



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. In a preferred embodiment of the ~~invention~~disclosure, the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, pancreas fibrosis,

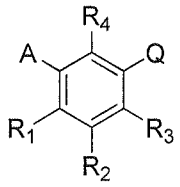
5) CF_2-C(O)OH, or

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 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;