[00034] Figure 19 is a plot indicating the effect of OCA on mRNA expression of PKG1 in the control and test groups on days 7 and 28.

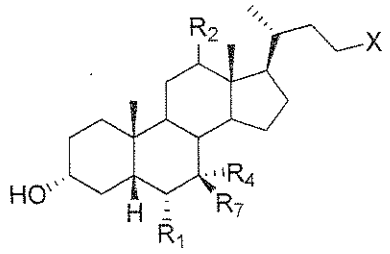
[00035] Figure 20 is a plot indicating the effect of OCA on mRNA expression of GCla3 in the control and test groups on days 7 and 28.

[00036] Figure 21 is a plot indicating the effect of OCA on mRNA expression of PDE5 in the control and test groups on days 7 and 28.

[00037] Figure 22 is a graph depicting univariate analysis of survival in untreated or treated rats over time (days).

SUMMARY ~~OF THE INVENTION~~

[00037a] In one aspect of the present disclosure, there is provided a use of a compound of formula A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating, reducing the risk of, preventing, or alleviating a pulmonary disease or condition in a subject,



(A),

wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

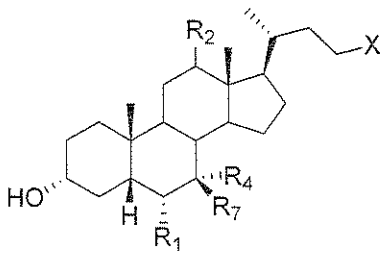
R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is an integer 1, 2, or 3; and

n is an integer 1, 2, or 3.

[00037b] In another aspect of the present disclosure, there is provided a use of a compound of formula A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for reducing or suppressing inflammation in the lung in a subject



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

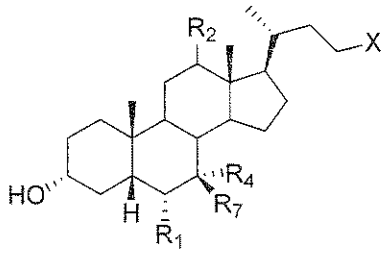
R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is 1, 2, or 3; and

n is 1, 2, or 3.

[00037c] In a further aspect of the present disclosure, there is provided a use of a compound of formula A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for promoting lung repair in a subject,



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

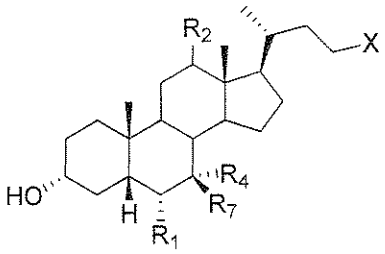
R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is 1, 2, or 3; and

n is 1, 2, or 3.

[00038] The ~~invention~~ present disclosure relates to a method of treating, reducing the risk of, preventing, or alleviating a symptom of a pulmonary disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula A:



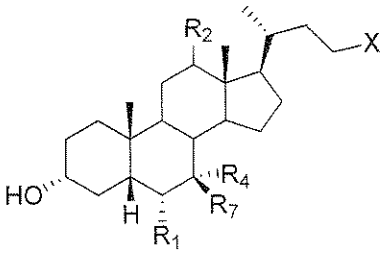
(A),

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00039] The ~~invention~~present disclosure also relates to use of a compound of formula A or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, reducing the risk of, prevention, or alleviation of a symptom of a pulmonary disease or condition in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00040] The ~~invention~~ present disclosure also relates to a compound of formula A or a pharmaceutically acceptable salt thereof, for the treatment, reducing the risk of, prevention, or alleviation of a symptom of a pulmonary disease or condition in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00041] The ~~invention~~ present disclosure further relates to a method of reducing or suppressing inflammation in the lung in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula A:



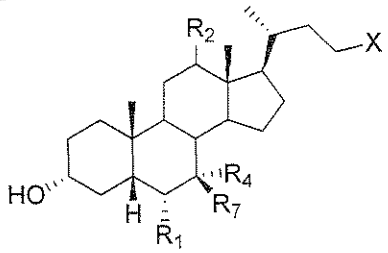
(A),

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00042] The ~~invention~~ present disclosure also relates to use of a compound of formula A or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing or suppressing inflammation in the lung in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00043] The ~~invention~~ present disclousre also relates to a compound of formula A or a pharmaceutically acceptable salt thereof, for reducing or suppressing inflammation in the lung in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00044] The ~~invention~~ present disclosure further relates to a method of promoting lung repair in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula A:



(A),

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00045] The ~~invention~~ present disclosure also relates to use of a compound of formula A or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for promoting lung repair in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00046] The ~~invention~~ present disclosure also relates to a compound of formula A or a pharmaceutically acceptable salt thereof, for promoting lung repair in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00047] The ~~invention~~ present disclosure further relates to a pharmaceutical composition comprising a compound of formula A or a pharmaceutically acceptable salt thereof, and

a pharmaceutically acceptable carrier or excipient for the for treating, reducing the risk of, preventing, or alleviating a symptom of a pulmonary disease or condition, or for reducing or suppressing inflammation in the lung, or for promoting lung repair in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00048] The ~~invention~~ present disclosure further relates to a kit comprising a compound of the invention for use in a method of treating, reducing the risk of, preventing, or alleviating a symptom of a pulmonary disease or condition, or of reducing or suppressing inflammation in the lung, or of promoting lung repair in a subject, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

[00049] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present specification, including definitions, will control. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

[00050] Other features and advantages of the ~~invention~~ present disclosure will be apparent from the following detailed description and claims.

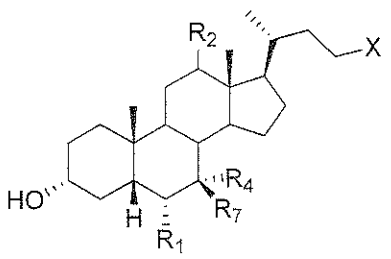
DETAILED DESCRIPTION OF THE INVENTION

[00051] The invention relates to a method of treating, reducing the risk of, preventing, or alleviating a symptom of a pulmonary disease or condition, a method of reducing or suppressing inflammation in the lung, and a method of promoting lung repair by administering an FXR agonist to a subject in need thereof.

[00052] Specifically, the invention relates to a method of treating, reducing the risk of, preventing, or alleviating a symptom of a pulmonary disease or condition, comprising administering to a subject in need thereof a compound of formula A:

CLAIMS

1. Use of a compound of formula A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating, reducing the risk of, preventing, or alleviating a pulmonary disease or condition in a subject,



(A),

wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is an integer 1, 2, or 3; and

n is an integer 1, 2, or 3.

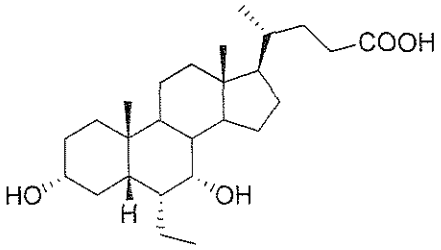
2. The use of claim 1, wherein R_1 is unsubstituted C_1-C_6 alkyl.

3. The use of claim 2, wherein R_1 is methyl, ethyl, or propyl.

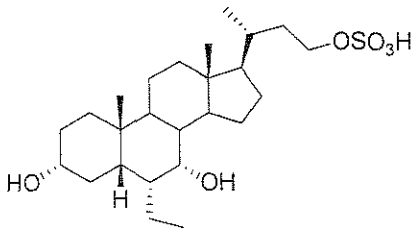
4. The use of claim 3, wherein R_1 is ethyl.

5. The use of claim 1, wherein R_1 is selected from methyl, ethyl and propyl; R_4 is OH; R_7 is H; and R_2 is H.

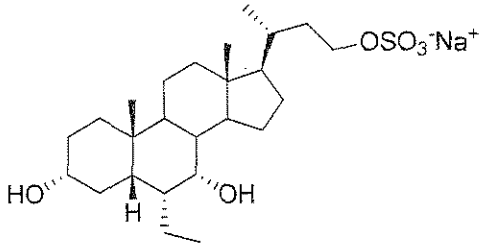
6. The use of claim 1, wherein the compound is selected from



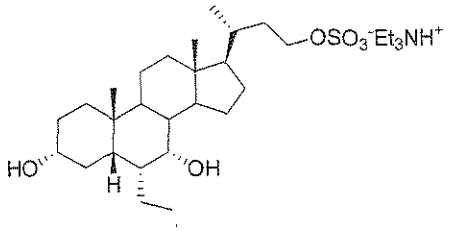
(1),



(2)



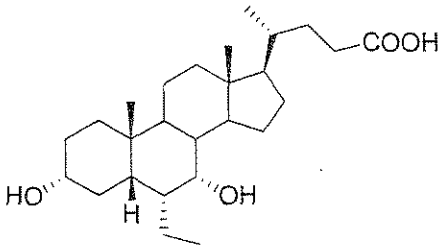
(3), and



(4),

or a pharmaceutically acceptable salt thereof.

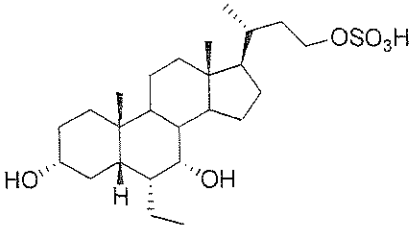
7. The use of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

8. The use of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

9. The use of claim 1, wherein the compound is a pharmaceutically acceptable salt.

10. The use of claim 9, wherein the salt is sodium salt or a triethylammonium salt.

11. The use of claim 1, wherein the pulmonary disease or condition is selected from obstructive pulmonary disease (COPD), emphysema, asthma, idiopathic pulmonary fibrosis, pneumonia, tuberculosis, cystic fibrosis, bronchitis, pulmonary hypertension (*e.g.*, Idiopathic Pulmonary Arterial Hypertension (IPAH) (also known as Primary Pulmonary Hypertension (PPH)) and Secondary Pulmonary Hypertension (SPH)), interstitial lung disease, and lung cancer.

12. The use of claim 11, wherein the pulmonary disease or condition is selected from COPD, emphysema, asthma, cystic fibrosis, and pulmonary hypertension.

13. The use of claim 12, wherein the pulmonary disease or condition is pulmonary hypertension.

14. The use of claim 13, wherein the pulmonary hypertension is IPAH or SPH.

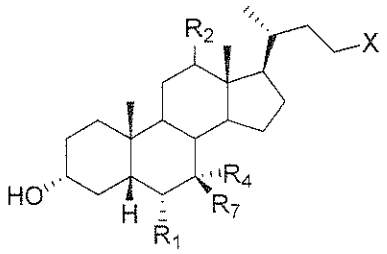
15. The use of claim 1, wherein the pulmonary disease or condition is caused by inflammation, autoimmune disease, scleroderma, rheumatoid arthritis, Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), birth defect of the heart, blood clot in the lungs (pulmonary embolism), congestive heart failure, heart valve disease, HIV infection, extended periods of low oxygen levels in the blood, medication, substance of abuse, or obstructive sleep apnea.

16. The use of claim 15, wherein the pulmonary disease or condition is caused by inflammation.

17. The use of claim 1, wherein the subject is a human.

18. The use of claim 1, wherein the compound is to be administered systemically, orally, intravenously, intramuscularly, intraperitoneally, or by inhalation.

19. Use of a compound of formula A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for reducing or suppressing inflammation in the lung in a subject



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

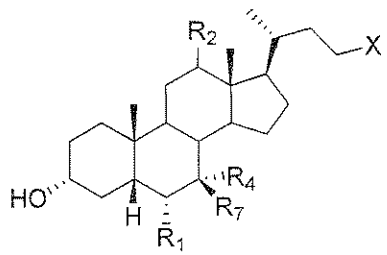
R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is 1, 2, or 3; and

n is 1, 2, or 3.

20. Use of a compound of formula A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for promoting lung repair in a subject,



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

R_4 is hydroxyl or hydrogen;

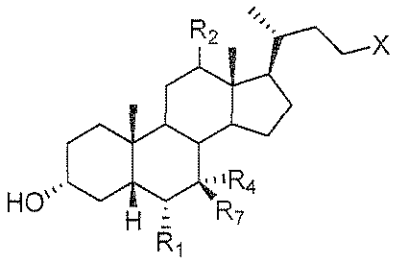
R_7 is hydroxyl or hydrogen;

m is 1, 2, or 3; and

n is 1, 2, or 3.

CLAIMS

1. A method of treating, reducing the risk of, preventing, or alleviating a pulmonary disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula A:



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is an integer 1, 2, or 3; and

n is an integer 1, 2, or 3.

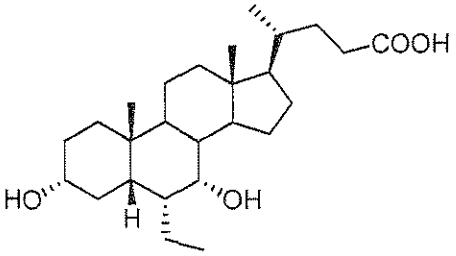
2. The method of claim 1, wherein R_1 is unsubstituted C_1-C_6 alkyl.

3. The method of claim 2, wherein R_1 is methyl, ethyl, or propyl.

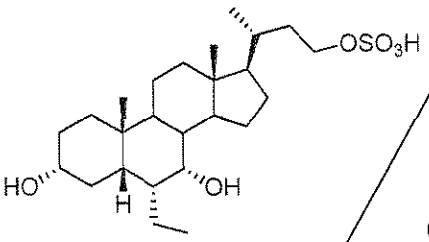
4. The method of claim 3, wherein R_1 is ethyl.

5. The method of claim 1, wherein R_1 is selected from methyl, ethyl and propyl; R_4 is OH; R_7 is H; and R_2 is H.

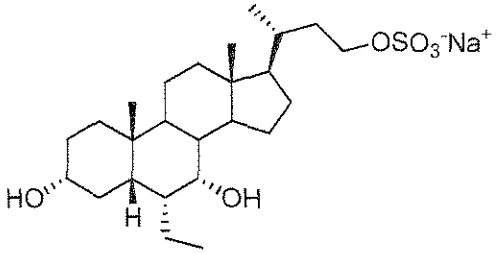
6. The method of claim 1, wherein the compound is selected from



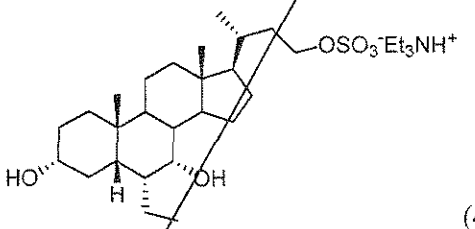
(1),



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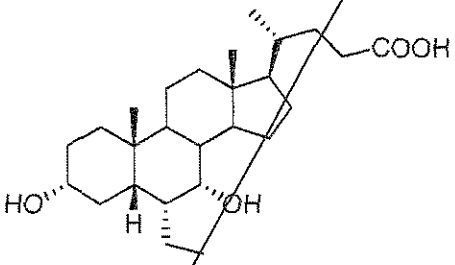
(3), and



(4),

or a pharmaceutically acceptable salt thereof.

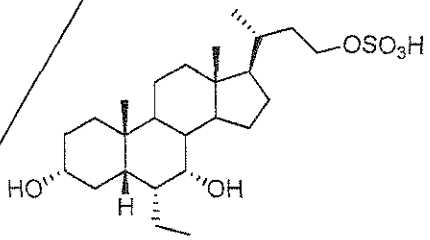
7. The method of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

8. The method of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

9. The method of claim 1, wherein the compound is a pharmaceutically acceptable salt.

10. The method of claim 9, wherein the salt is sodium salt or a triethylammonium salt.

11. The method of claim 1, wherein the pulmonary disease or condition is selected from obstructive pulmonary disease (COPD), emphysema, asthma, idiopathic pulmonary fibrosis, pneumonia, tuberculosis, cystic fibrosis, bronchitis, pulmonary hypertension (*e.g.*, Idiopathic Pulmonary Arterial Hypertension (IPAH) (also known as Primary Pulmonary Hypertension (PPH)) and Secondary Pulmonary Hypertension (SPH)), interstitial lung disease, and lung cancer.

12. The method of claim 11, wherein the pulmonary disease or condition is selected from COPD, emphysema, asthma, cystic fibrosis, and pulmonary hypertension.

13. The method of claim 12, wherein the pulmonary disease or condition is pulmonary hypertension.

14. The method of claim 13, wherein the pulmonary hypertension is IPAH or SPH.

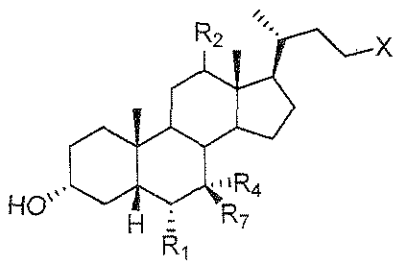
15. The method of claim 1, wherein the pulmonary disease or condition is caused by inflammation, autoimmune disease, scleroderma, rheumatoid arthritis, Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), birth defect of the heart, blood clot in the lungs (pulmonary embolism), congestive heart failure, heart valve disease, HIV infection, extended periods of low oxygen levels in the blood, medication, substance of abuse, or obstructive sleep apnea.

16. The method of claim 15, wherein the pulmonary disease or condition is caused by inflammation.

17. The method of claim 1, wherein the subject is a human.

18. The method of claim 1, wherein the compound is administered systemically, orally, intravenously, intramuscularly, intraperitoneally, or by inhalation.

19. A method of reducing or suppressing inflammation in the lung in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula A:



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

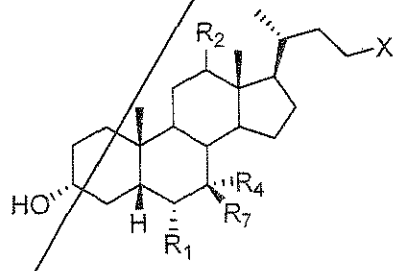
R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is 1, 2, or 3; and

n is 1, 2, or 3.

20. A method of promoting lung repair in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula A:



(A),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is 1, 2, or 3; and

n is 1, 2, or 3.