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(54) Title: COMPOSITIONS AND METHODS FOR TREATING LUNG DISEASES

(57) Abstract: Provided are methods of treating or preventing lung diseases (e.g., idiopathic pulmonary fibrosis (IPF) or radiation-induced pulmonary fibrosis (RIPF)) using Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions and pharmaceutical kits suitable for the treatment of prevention.

COMPOSITIONS AND METHODS FOR TREATING LUNG DISEASES

BACKGROUND

[001] Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by progressive lung scarring and the histological picture of usual interstitial pneumonia (UIP). It is associated with increasing cough and dyspnoea and impaired quality of life. IPF affects ~3 million people worldwide, with incidence increasing dramatically with age (Nat. Rev. Dis. Primers 3;17074 (2017)).

[002] Radiation-induced pulmonary fibrosis (RIPF) is a common complication in patients with lung cancer and breast cancer after receiving thoracic radiotherapy. The average incidence of RIPF is 16%-28% after radiotherapy. RIPF includes a heterogeneous group of lung disorders characterized by progressive and irreversible destruction of lung architecture and disruption of gas exchange (Translational Oncology 12; 162–169 (2019)). There is thus a need for novel methods of treating or preventing lung diseases (e.g., idiopathic pulmonary fibrosis (IPF) or radiation-induced pulmonary fibrosis (RIPF)). The present disclosure addresses the need.

SUMMARY

[003] In some aspects, the present disclosure provides a method of treating or preventing a lung disease in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[004] In some aspects, the present disclosure provides Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing a lung disease in a subject.

[005] In some aspects, the present disclosure provides use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a lung disease in a subject.

[006] In some aspects, the present disclosure provides a pharmaceutical composition for treating or preventing a lung disease, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[007] In some aspects, the present disclosure provides a pharmaceutical kit for treating or preventing a lung disease, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[008] 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 disclosure belongs. 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 disclosure, 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 the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[009] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

BRIEF DESCRIPTIONS OF FIGURES

[010] FIGS. 1A and 1B are a set of graphs showing that Compound No. 1 and Compound No. 2 significantly improved the body weight loss and survival of mice with idiopathic pulmonary fibrosis.

[011] FIGS. 2A and 2B are a set of graphs showing that Compound No. 1 and Compound No. 2 significantly improved lung fibrosis and inflammatory score of mice with idiopathic pulmonary fibrosis.

[012] FIG. 3 is a graph showing that Compound No. 1 significantly reduced collagen deposition in the lung of mice with idiopathic pulmonary fibrosis.

[013] FIG. 4 is a graph showing that Compound No. 1 and Compound No. 2 significantly reduced the number of SA-β-galactosidase-positive cell in the lung of mice with idiopathic pulmonary fibrosis.

[014] FIG. 5 is a graph showing that Compound No. 1 and Compound No. 2 significantly reduced the mRNA level of p16 gene in the lung of mice with idiopathic pulmonary fibrosis.

[015] FIGS. 6A and 6B are a set of graphs showing that Bleomycin challenge significantly increased the mRNA level of BCL-xL gene in mouse lung.

[016] FIGs. 7A-7F is a graph showing that Compound No. 1 and Compound No. 2 significantly reduced the mRNA level of SASP-related genes in the lung of mice with idiopathic pulmonary fibrosis.

[017] FIGS. 8A and 8B are a set of graphs showing the expression level of BCL-xL protein was significantly increased in lung of mice after bleomycin challenge as compared with naïve mice.

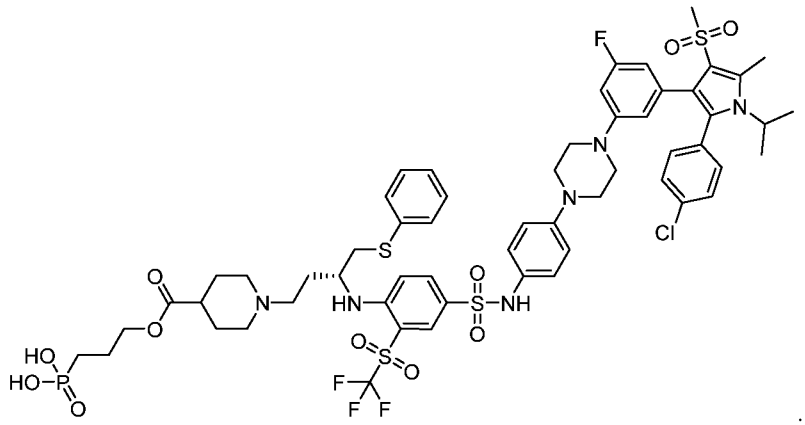
[018] FIG. 9 is a graph showing Compound No. 1 and Compound No. 2 significantly improved the survival proportion of mice with radiation-induced pulmonary fibrosis.

[019] FIG. 10 is a graph showing Compound No. 1 and Compound No. 2 significantly reduced the lung size of mice with radiation-induced pulmonary fibrosis.

[020] FIG. 11 is a graph showing Compound No. 2 significantly reduced the number of senescent cells in the lung of mice with radiation-induced pulmonary fibrosis.

DETAILED DESCRIPTION

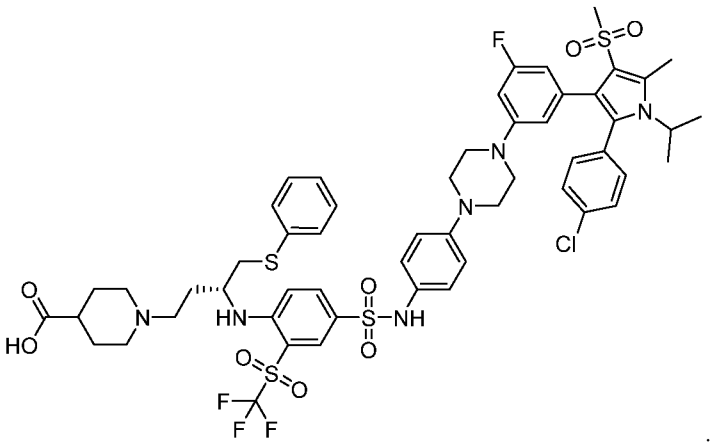
[021] It is understood that the term "Compound No. 1," as used herein, refers to a compound having the following structure:



(Compound No. 1)

[022] Compound No. 1 may be identified by the IUPAC name of (3R)-1-(3-(4-(4-(4-(3-(2-(4-chlorophenyl)-1-isopropyl-4-methylsulfonyl-5-methyl-1H-pyrrol-3-yl)-5-fluorophenyl)piperazin-1-yl)-phenylaminosulfonyl)-2-trifluoromethylsulfonyl-anilino)-4-phenylthio-butyl)-piperidine-4-carboxylic acid 3-phosphonopropyl ester.

[023] It is understood that the term "Compound No. 2," as used herein, refers to a compound having the following structure:



(Compound No. 2)

[024] Compound No. 2 may be identified by the IUPAC name of (R)-1-(3-((4-(N-(4-(4-(3-(2-(4-chlorophenyl)-1-isopropyl-5-methyl-4-(methylsulfonyl)-1H-pyrrol-3-yl)-5-fluorophenyl)-piperazin-1-yl)phenyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)-butyl)piperidine-4-carboxylic acid.

Methods and Uses of the Present Disclosure

[025] In some aspects, the present disclosure provides a method of treating or preventing a lung disease in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[026] In some aspects, the present disclosure provides a method of treating or preventing a lung disease in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1 or a pharmaceutically acceptable salt thereof.

[027] In some aspects, the present disclosure provides a method of treating or preventing a lung disease in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 2 or a pharmaceutically acceptable salt thereof.

[028] In some aspects, the present disclosure provides Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing a lung disease in a subject.

[029] In some aspects, the present disclosure provides Compound No. 1, or a pharmaceutically acceptable salt thereof, for treating or preventing a lung disease in a subject.

[030] In some aspects, the present disclosure provides Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing a lung disease in a subject.

[031] In some aspects, the present disclosure provides use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a lung disease in a subject.

[032] In some aspects, the present disclosure provides use of Compound No. 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a lung disease in a subject.

[033] In some aspects, the present disclosure provides use of Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a lung disease in a subject.

Exemplary Embodiments of the Methods and Uses

[034] In some aspects, the present disclosure provides a method of treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[035] In some aspects, the present disclosure provides a method of treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1 or a pharmaceutically acceptable salt thereof.

[036] In some aspects, the present disclosure provides a method of treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 2 or a pharmaceutically acceptable salt thereof.

[037] In some aspects, the present disclosure provides Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

[038] In some aspects, the present disclosure provides Compound No. 1, or a pharmaceutically acceptable salt thereof, for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

[039] In some aspects, the present disclosure provides Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

[040] In some aspects, the present disclosure provides use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

[041] In some aspects, the present disclosure provides use of Compound No. 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

[042] In some aspects, the present disclosure provides use of Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

[043] In some aspects, the present disclosure provides a method of treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[044] In some aspects, the present disclosure provides a method of treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1 or a pharmaceutically acceptable salt thereof.

[045] In some aspects, the present disclosure provides a method of treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 2 or a pharmaceutically acceptable salt thereof.

[046] In some aspects, the present disclosure provides Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

[047] In some aspects, the present disclosure provides Compound No. 1, or a pharmaceutically acceptable salt thereof, for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

[048] In some aspects, the present disclosure provides Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

[049] In some aspects, the present disclosure provides use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

[050] In some aspects, the present disclosure provides use of Compound No. 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

[051] In some aspects, the present disclosure provides use of Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

Suitable Subjects and Diseases

[052] In some embodiments, the subject is a mammal.

[053] In some embodiments, the subject is a mouse.

[054] In some embodiments, the subject is a human.

[055] In some embodiments, the lung disease is an interstitial lung disease.

[056] In some embodiments, the lung disease is a pulmonary fibrosis.

[057] In some embodiments, the lung disease is idiopathic pulmonary fibrosis (IPF).

[058] In some embodiments, the lung disease is a radiation-induced lung disease.

[059] In some embodiments, the lung disease is a radiation-induced interstitial lung disease.

[060] In some embodiments, the lung disease is a radiation-induced pulmonary fibrosis (RIPF).

Administrations of Compound No. 1

[061] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by enternal administration.

[062] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by oral administration.

[063] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by parenteral administration.

[064] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by intravenous administration.

[065] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by intratracheal instillation.

[066] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered once daily.

[067] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered twice daily.

[068] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered three or more times daily.

[069] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered once weekly.

[070] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered twice weekly.

[071] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered three or more times weekly.

[072] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered with one or more drug holidays.

[073] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered without any drug holiday.

[074] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered for about one week, about two weeks, or about three weeks.

[075] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered for about three weeks.

[076] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered twice (e.g., at day 1 and day 4) weekly for a bout three weeks.

[077] In some embodiments, Compound No. 1 or the pharmaceutically acceptable salt thereof is administered once daily for about three weeks.

Administrations of Compound No. 2

[078] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by enternal administration.

[079] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by oral administration.

[080] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by parenteral administration.

[081] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by intravenous administration.

[082] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by intratracheal instillation.

[083] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered once daily.

[084] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered twice daily.

[085] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered three or more times daily.

[086] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered once weekly.

[087] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered twice weekly.

[088] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered three or more times weekly.

[089] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered with one or more drug holidays.

[090] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered without any drug holiday.

[091] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered for about one week, about two weeks, or about three weeks.

[092] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered for about three weeks.

[093] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered twice (e.g., at day 1 and day 4) weekly for a bout three weeks.

[094] In some embodiments, Compound No. 2 or the pharmaceutically acceptable salt thereof is administered once daily for about three weeks.

Pharmaceutical Compositions and Kits

[095] In some aspects, the present disclosure provides a pharmaceutical composition for treating or preventing a lung disease, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[096] In some aspects, the present disclosure provides a pharmaceutical composition for treating or preventing idiopathic pulmonary fibrosis (IPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[097] In some aspects, the present disclosure provides a pharmaceutical composition for treating or preventing radiation-induced pulmonary fibrosis (RIPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[098] In some embodiments, the pharmaceutical composition comprises Compound No. 1 or a pharmaceutically acceptable salt thereof.

[099] In some embodiments, the pharmaceutical composition comprises Compound No. 2 or a pharmaceutically acceptable salt thereof.

[0100] In some aspects, the present disclosure provides a pharmaceutical kit for treating or preventing a lung disease, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[0101] In some aspects, the present disclosure provides a pharmaceutical kit for treating or preventing idiopathic pulmonary fibrosis (IPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[0102] In some aspects, the present disclosure provides a pharmaceutical kit for treating or preventing radiation-induced pulmonary fibrosis (RIPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[0103] In some embodiments, the pharmaceutical kit comprises Compound No. 1 or a pharmaceutically acceptable salt thereof.

[0104] In some embodiments, the pharmaceutical kit comprises Compound No. 2 or a pharmaceutically acceptable salt thereof.

[0105] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries

that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0106] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0107] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0108] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with

excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0109] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0110] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0111] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0112] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers

to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0113] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease and also preferably causing complete regression of the disease.

[0114] It is understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Definitions

[0115] As used herein, the term "about" refers to a range covering any normal fluctuations appreciated by one of ordinary skill in the relevant art. In some embodiments, the term "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0116] As used herein, the term "pharmaceutically acceptable salt" refers to a derivative of the compound of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic,

hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc. Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3. It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0117] It is understood that the compounds described herein include the compounds themselves, as well as their pharmaceutically acceptable salts, and their solvates, if applicable. A pharmaceutically acceptable salt, for example, can be formed between an pharmaceutically acceptable anion and a positively charged group (e.g., amino) on a substituted benzene compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate).

[0118] As used herein, the term “pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a substituted benzene compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The substituted benzene compounds also include those salts containing quaternary nitrogen atoms.

[0119] It is understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates and dihydrates. Nonlimiting examples of solvates include ethanol solvates and acetone solvates.

[0120] As used herein, the expressions "one or more of A, B, or C," "one or more A, B, or C," "one or more of A, B, and C," "one or more A, B, and C," "selected from the group consisting of A, B, and C", "selected from A, B, and C", and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0121] It is understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0122] It is understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art

[0123] As used herein, the term "subject" is interchangeable with the term "subject in need thereof", both of which refer to a subject having a disease or having an increased risk of developing the disease. A "subject" includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the mammal is a human.

[0124] As used herein, the term "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model.

[0125] It is understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0126] As used herein, the term "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0127] As used herein, the term "pharmaceutical composition" is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is

mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0128] As used herein, the term "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0129] As used herein, the term "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0130] As used herein, the term "pharmaceutically effective amount", refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Pharmaceutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0131] It is understood that, for the compounds of the present disclosure beingcapable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0132] As used herein, the term "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. In some embodiments, the pharmaceutically acceptable salt of a compound is also a prodrug of the compound. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene

sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0133] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0134] It is understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0135] As used herein, the term “prodrug” refers to any agent which, when administered to a mammal, is converted in whole or in part to a targeted compound. In some embodiments, the prodrug of a compound is also a pharmaceutically acceptable salt of the compound.

[0136] It is understood that the compounds of the present disclosure can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, acetate, propionate or other ester.

[0137] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0138] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0139] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0140] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0141] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

EXAMPLES

Example 1. Study of Compound No. 1 and Compound No. 2 in Mouse Model of Idiopathic Pulmonary Fibrosis.

[0142] **Mouse model of idiopathic pulmonary fibrosis.** All animal experiments were approved by Shanghai ChemPartner Co., Ltd. (Shanghai, China). Male C57BL/6 mice (6-8 weeks, 18-20 g) were randomized into the following four groups: (1) naïve group, (2) model + vehicle group, (3) Compound No. 1 group, and (4) Compound No. 2 group. Mice in the naïve group were intratracheally instilled with 50 μL 0.9% saline and left untreated until sacrifice. Mice in the rest three groups were intratracheally instilled with 50 μL bleomycin at the dose of 1 unit/kg, and then treated with vehicle (Compound No. 1 vehicle, iv, biw_D1/4×3w), Compound No. 1 (50 mg/kg, iv, biw_D1/4×3w) or Compound No. 2 (10 mg/kg, ip, qd×3w) starting from the day of bleomycin challenge. Mice were sacrificed under anesthesia on the 22nd day.

[0143] The body weight and survival proportion of mice were recorded daily. As seen in FIGS. 1A and 1B, intratracheal bleomycin instillation caused continuous weight loss and death of the mice. The average body weight of mice decreased from 23.3±0.3 g before bleomycin challenging to 18.8±1.4 g at the end of the study, and the survival proportion was 80%. On the other hand, no obvious body weight loss was observed in the mice treated with Compound No. 1 and Compound No. 2, with the survival proportions of 100% and 90% at the end of the study.

[0144] **Histopathology.** The left lungs of mice were fixed with 10% neutral-buffered formalin for 48 hours at room temperature, then subjected to paraffin embedding and sliced into 4 μm sections. After dewaxing, the lung sections were subjected to hematoxylin and eosin (H&E) and Masson's trichrome staining. Specimen with H&E staining were used to evaluate tissue inflammation based on the extent of inflammatory cell infiltration (0 for no visible lesion, 1 for minimal, 2 for mild, 3 for moderate, and 4 for marked). Specimen with Masson's trichrome staining were used to evaluate fibrosis according to an eight-tier, modified Ashcroft scale. All the assessments were conducted in a blinded fashion.

[0145] As seen in FIGS. 2A and 2B, intratracheal bleomycin instillation induced severe lung fibrosis and inflammation, which was indicated by the pathological score of 6.5±0.1 and 3.7±0.2, respectively. The unchallenged naïve C57BL/6 mice showed no sign of lung fibrosis and inflammation. Treatment with Compound No. 1 and Compound No. 2 significantly reduced the pathological score both in fibrosis and inflammation. Fifty mg/kg Compound No. 1 reduced the fibrosis and inflammation scores to 4.1±0.2 and 1.5±0.2 respectively ($p < 0.0001$, vs Model-vehicle); 10 mg/kg Compound No. 2 reduced the fibrosis and inflammation scores to 5.6±0.2 ($p < 0.01$, vs Model-vehicle) and 2.2±0.1 ($p < 0.0001$, vs Model-vehicle) respectively.

[0146] **Collagen assay.** A portion of the right lungs were used for collagen assay. The harvested lung tissue were added with 6 M HCl at the ratio of 1 : 10 (mg tissue : μL 6 M HCl), and incubated at 95 °C for 20 hours in a calibrated oven. After cooling back to room temperature, the samples were centrifuged at 13,000 g for 10 minutes. The obtained supernatants were diluted appropriately and subjected to collagen content assay using a total collagen assay kit (QuickZyme, Netherland). The data were presented as micrograms of collagen per right lung.

[0147] As seen in FIG. 3, the lung of mice challenged with bleomycin showed significantly higher collagen deposition than that of the naïve mice (12.7±1.1 vs 3.0±0.1 μg/right lung, $p < 0.0001$), suggesting the formation of fibrosis. Treatment with 50 mg/kg Compound No. 1 significantly reduced the collagen content to 5.6±0.5 μg/right lung ($p < 0.0001$, vs model-vehicle), which was in agreement with the reduced fibrosis score.

[0148] **SA-β-Gal staining.** Frozen sections were prepared using half of the right lungs. SA-β-Gal staining was conducted using Senescence β-Galactosidase Staining Kit (Solarbio Life Science, Beijing, China) following the manufacturer's protocol. Images were acquired using a Nikon Eclipse 90i microscope, and the number of SA-β-galactosidase-positive cells, i.e. senescent cells, was counted in six random microscopic fields per sample.

[0149] As seen in FIG. 4, intratracheal bleomycin instillation resulted in a significant increase of the number of senescent cells in the lung of mice ($p < 0.0001$ vs naïve), reaching 10.4±1.2 per field. Treatment with 50 mg/kg Compound No. 1 and 10 mg/kg Compound No. 2 significantly reduced the number of senescent cells to 6.2±0.6 ($p < 0.01$, vs Model-vehicle) and 3.9±0.6 ($p < 0.0001$, vs Model-vehicle) per field respectively.

[0150] **Gene expression analysis by quantitative RT-PCR.** Total RNA was extracted from a portion of the right lung using RNeasy mini kits (Qiagen, CA, USA) following manufacturer's instructions. After quantification by NanoDrop2000, the extracted RNA was subjected to reverse transcription using High-Capacity cDNA Reverse Transcription Kits (Applied Biosystems, CA, USA). qPCR was performed using ViiA™ 7 Real-Time PCR System (Applied Biosystems, CA, USA) following the instruction of "ABI Taqman gene expression master mix protocol". Hprt mRNA was used as housekeeping genes, and quantification was performed using the ΔΔ Ct method. Transcriptional levels of SASP-related genes were normalized to Hprt mRNA. All the Taqman probes were purchased from Applied Biosystems (CA, USA). Transcriptional levels of

BCL-2 and *BCL-xL* genes which might contribute to the survival of senescent cells were also determined using quantitative RT-PCR, where *GAPDH* gene was used as the house-keeping gene.

[0151] As seen in FIG. 5, the mRNA level of senescence marker *p16* was significantly increased in lung of mice after bleomycin challenge as compared with naïve mice ($p < 0.0001$), indicating the induction of cellular senescence *in vivo*. Consistent with the reduction of SA-β-Gal positive cell, the mRNA level of *p16* gene was also significantly reduced after Compound No. 1 treatment ($p < 0.0001$, vs model-vehicle).

[0152] As shown in FIGS. 6A and 6B, the mRNA level of *BCL-xL* gene in lung of mice challenged with bleomycin was 1.8-fold that of naïve mice, suggesting that the survival of cells in the lung of mice with idiopathic pulmonary fibrosis was dependent on BCL-xL, which was in agreement with the efficacy of BCL-xL inhibitors, e.g. Compound No. 1 and Compound No. 2, in this mice model of idiopathic pulmonary fibrosis.

[0153] FIG. 7 showed the change of the transcriptional level of SASP-related genes in the lung of mice with idiopathic pulmonary fibrosis after treatment with Compound No. 1 and Compound No. 2. The mRNA levels of pro-inflammatory (*Mcp1*, *Mmp10* and *Il-6*) and pro-fibrotic (*Pai-1*, *Il-11* and *Tgfb*) SASP factors were significantly increased after bleomycin challenge, but was significantly reduced after treatment with Compound No. 1 and Compound No. 2. These results were in agreement with the reduced senescence level in the lung (reduced number of SA-β-galactosidase-positive cell and reduced mRNA level of *p16* gene) and overall efficacy in fibrosis (reduced collagen content in the lung and reduced fibrosis score).

[0154] **Immunohistochemistry.**The lungs of mice were fixed with 10% neutral-buffered formalin for 48 hours at room remperature, then subjected to paraffin embedding and sliced into 4μm sections. After dewaxing, the lung sections were subjected to IHC staining to detect the expression of BCL-2 and BCL-xL proteins in the lung of mice. Three representative regions were selected from each slide, and then analyzed by ImageJ software to obtain the percentage of positively stained area.

[0155] As seen in FIG.8A and 8B, the BCL-2 protein expression was slightly increased in lung of mice after bleomycin challenge as compared with naïve mice ($p > 0.05$, t-test). On the other hand, the expression level of BCL-xL protein was significantly increased in lung of mice after bleomycin challenge as compared with naïve mice ($p < 0.05$, t-test).

Example 2. Study of Compound No. 1 and Compound No. 2 in Mouse Model of Radiation-Induced Pulmonary Fibrosis.

[0156] **Mouse model of radiation-induced pulmonary fibrosis.** All animal experiments were approved by the Institutional Animal Care and Use Committee at Institute of Radiation Medicine, Peking Union Medical College and Chinese Academy of Medical Sciences. Male C57BL/6 mice (23-25 g) were randomized into the following four groups: (1) naïve group, (2) model + vehicle group, (3) Compound No. 1 group, and (4) Compound No. 2 group. Mice in the naïve group were untreated until sacrifice. Mice in the rest three groups were exposed to a single dose of 17 Gy of radiation on the right side of the thorax, and 16 weeks after irradiation, the mice were treated with with vehicle (Compound No. 1 vehicle, iv, biw_D1/4×3w), Compound No. 1 (50 mg/kg, iv, biw_D1/4×3w) or Compound No. 2 (10 mg/kg, ip, qd×3w) for another 6 weeks.

[0157] As seen in FIG. 9, all the mice remained alive in the naïve group with irradiation, while irradiation caused animal death during the experiment, with 70% of survival proportion at the end of study. Treatment with Compound No. 1 and Compound No. 2 improved the survival of mice to 100% and 90%, suggesting their efficacy in radiation-induced pulmonary fibrosis. The lung tissues were collected and imaged after the mice were sacrificed. As seen in FIG.10, irradiation obviously increased the lung size, which might be due to the inflammation and fibrosis. Drug treatment with Compound No. 1 and Compound No. 2 reduced the lung size almost to the normal level, suggesting the improvement in inflammation and fibrosis.

[0158] **Histopathology.** The left lungs of mice were fixed with 10% neutral-buffered formalin for 48 hours at room temperature, then subjected to paraffin embedding and sliced into 4 μm sections. After dewaxing, the lung sections were subjected to hematoxylin and eosin (H&E) and Masson's trichrome staining. Specimen with H&E staining were used to evaluate tissue inflammation based on the extent of inflammatory cell infiltration (0 for no visible lesion, 1 for minimal, 2 for mild, 3 for moderate, and 4 for marked). Specimen with Masson's trichrome staining were used to evaluate fibrosis according to an eight-tier, modified Ashcroft scale. All the assessments were conducted in a blinded fashion.

[0159] **SA-β-Gal staining.** Frozen sections were prepared using half of the right lungs. SA-β-Gal staining was conducted using Senescence β-Galactosidase Staining Kit (Solarbio Life Science, Beijing, China) following the manufacturer's protocol. Images were acquired using a Nikon Eclipse 90i microscope, and the number of SA-β-galactosidase-positive cells, i.e. senescent cells, was counted in six random microscopic fields per sample.

[0160] As seen in FIG. 11, comparing with naïve group, thoracic irradiation resulted in a significant increase of the number of senescent cells in the lung of mice (44.0±4.7 vs 8.7±2.1, $p <$ 0.0001). Treatment with 50 mg/kg Compound No. 1 and 10 mg/kg Compound No. 2 reduced the number of senescent cells to 42.9±2.5 and 32.4±2.6 respectively. Significant difference were observed for Compound No. 2 group ($p < 0.05$, vs Model-vehicle), suggesting clearance of senescent cell might be responsible for the efficacy in radiation-induced pulmonary fibrosis.

EQUIVALENTS

[0161] It is understood that the invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A method of treating or preventing a lung disease in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

2. Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing a lung disease in a subject.

3. Use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a lung disease in a subject.

4. A method of treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

5. Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

6. Use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing idiopathic pulmonary fibrosis (IPF) in a subject.

7. A method of treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

8. Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

9. Use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing radiation-induced pulmonary fibrosis (RIPF) in a subject.

10. A pharmaceutical composition for treating or preventing a lung disease, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition for treating or preventing idiopathic pulmonary fibrosis (IPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition for treating or preventing radiation-induced pulmonary fibrosis (RIPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical kit for treating or preventing a lung disease, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical kit for treating or preventing idiopathic pulmonary fibrosis (IPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical kit for treating or preventing radiation-induced pulmonary fibrosis (RIPF), comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

16. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein the subject is a mammal.

17. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein the subject is a human.

18. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein the lung disease is idiopathic pulmonary fibrosis (IPF).

19. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein the lung disease is a radiation-induced pulmonary fibrosis (RIPF).

20. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by enternal administration.

21. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by oral administration.

22. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by parenteral administration.

23. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by intravenous administration.

24. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered by intratracheal instillation.

25. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered once daily.

26. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered twice daily.

27. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered three or more times daily.

28. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered once weekly.

29. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered twice weekly.

30. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered three or more times weekly.

31. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered about three weeks.

32. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered twice weekly for a bout three weeks.

33. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered once daily for about three weeks.

34. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by enternal administration.

35. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by oral administration.

36. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by parenteral administration.

37. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by intravenous administration.

38. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered by intratracheal instillation.

39. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered once daily.

40. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered twice daily.

41. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered three or more times daily.

42. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered once weekly.

43. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered twice weekly.

44. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered three or more times weekly.

45. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered with one or more drug holidays.

46. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered without any drug holiday.

47. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered for about one week, about two weeks, or about three weeks.

48. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered for about three weeks.

49. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered twice weekly for a bout three weeks.

50. The method, compound, use, pharmaceutical composition, or pharmaceutical kit of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered once daily for about three weeks.

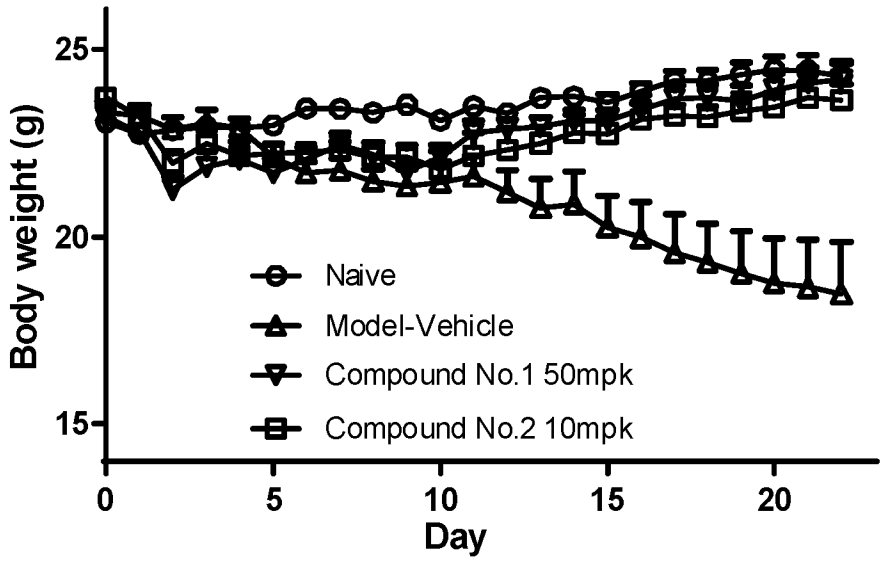

Body weight (g)
25
20
15
0
5
10
15
20
Day
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 1A

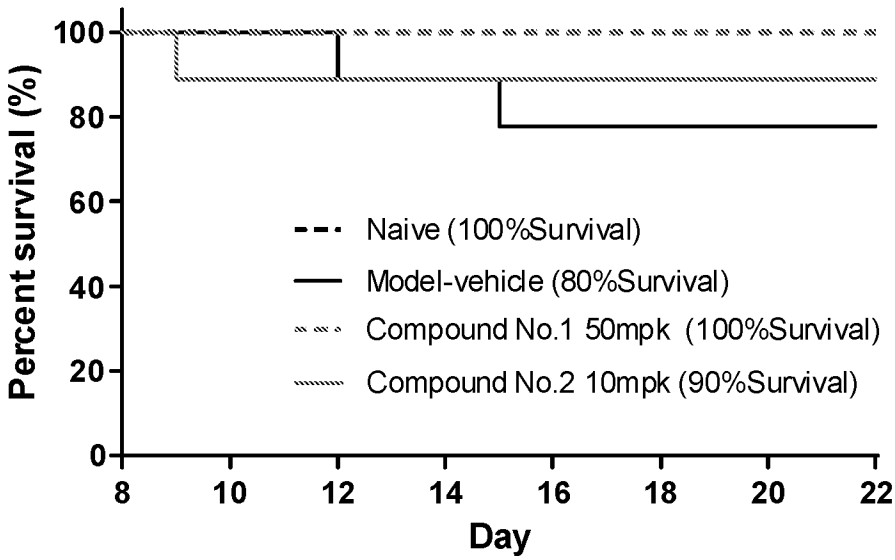

Percent survival (%)
100
80
60
40
20
0
8
10
12
14
16
18
20
22
Day
Naive (100%Survival)
Model-vehicle (80%Survival)
Compound No.1 50mpk (100%Survival)
Compound No.2 10mpk (90%Survival)

FIG. 1B

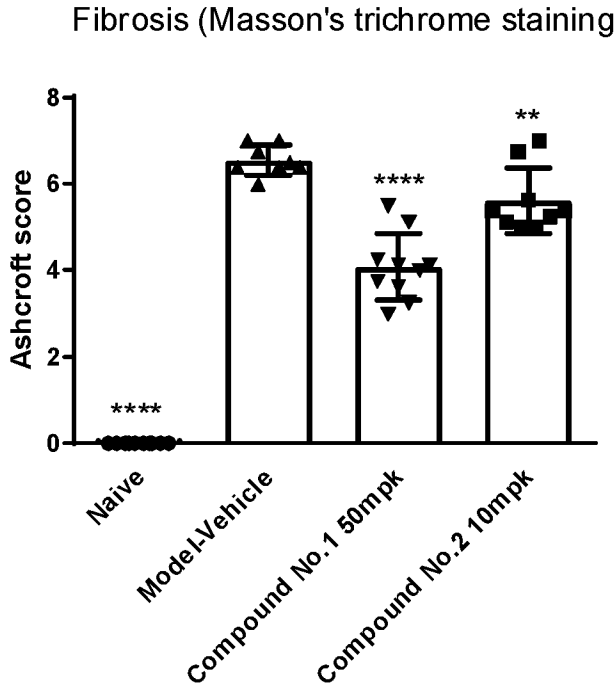

Fibrosis (Masson's trichrome staining)
Ashcroft score
8
6
4
2
0
****
****
**
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 2A

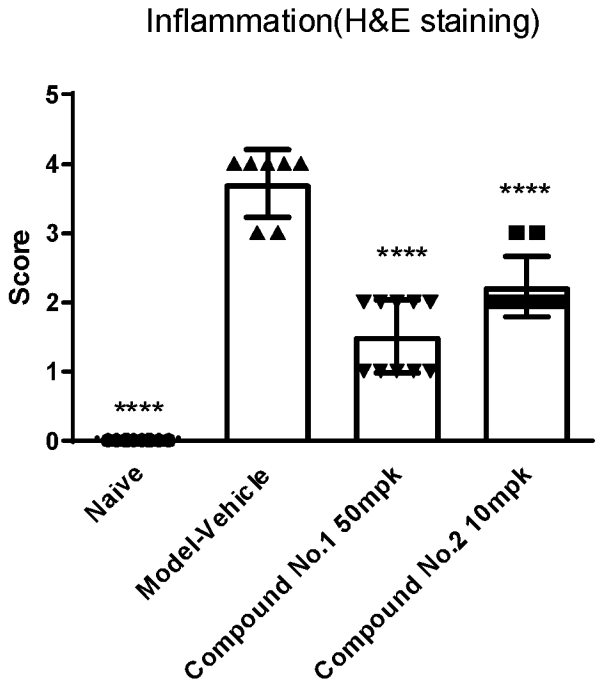

Inflammation(H&E staining)
Score
5
4
3
2
1
0
****
****
****
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 2B

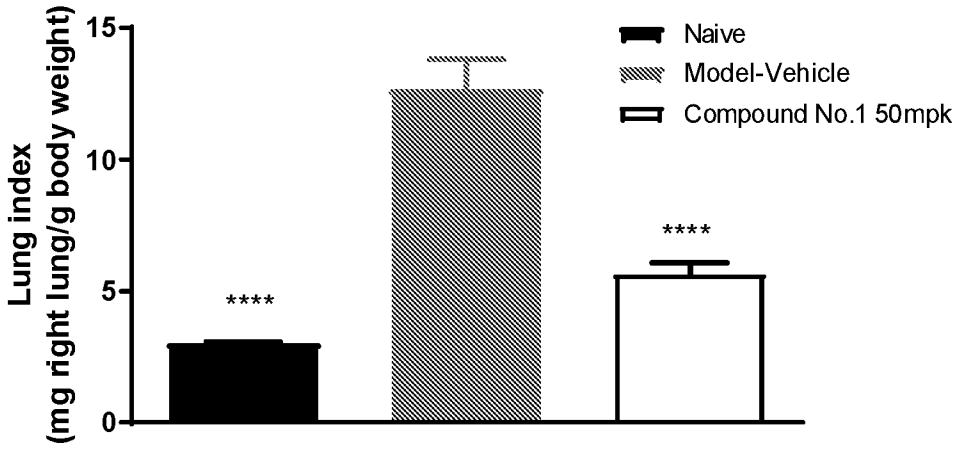

Lung index
(mg right lung/g body weight)
15
10
5
0
****
****
Naive
Model-Vehicle
Compound No.1 50mpk

FIG. 3

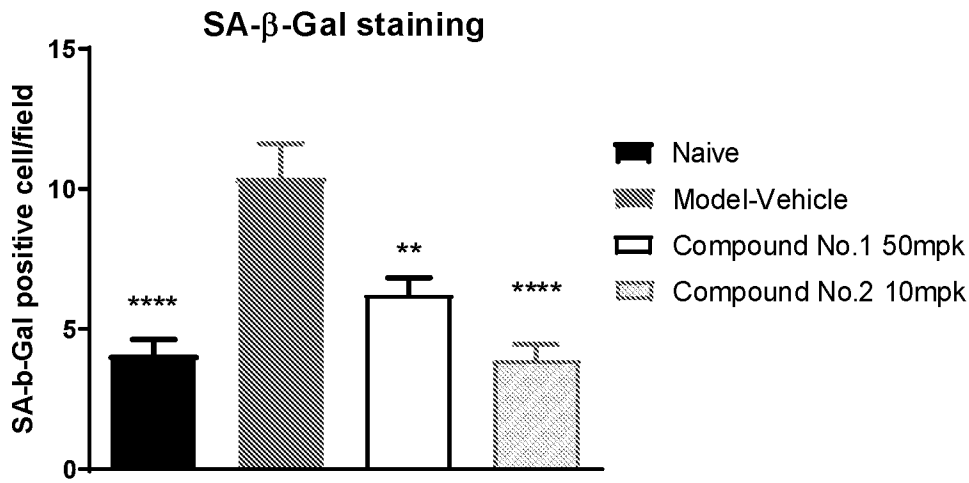

SA-β-Gal staining
SA-b-Gal positive cell/field
15
10
5
0
****
**
****
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 4

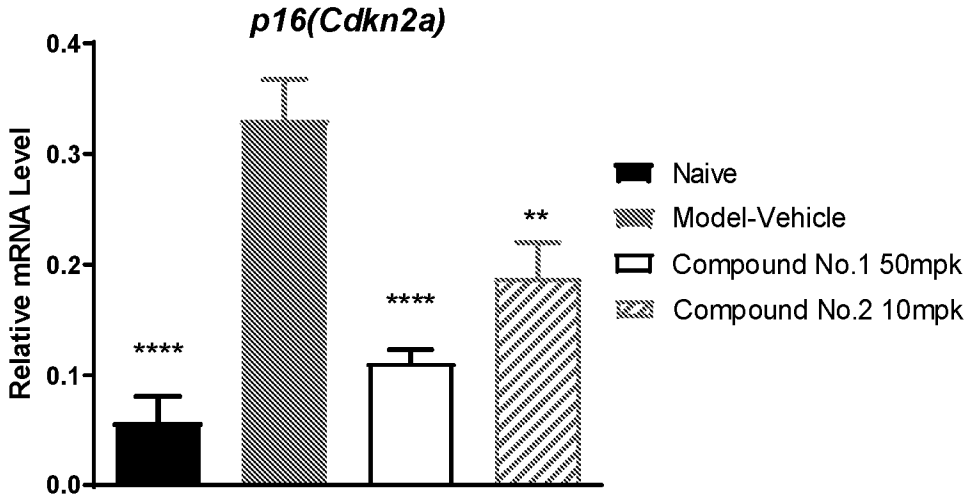


FIG. 5

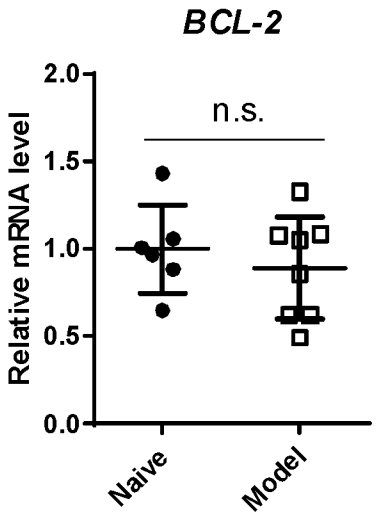


FIG. 6A

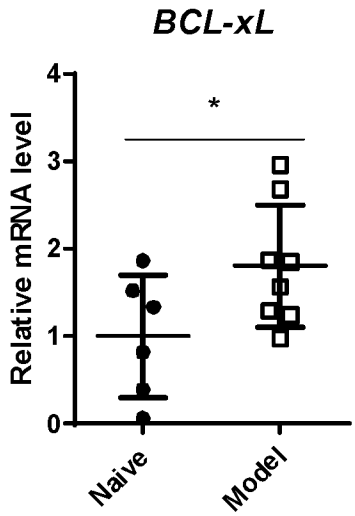


FIG. 6B

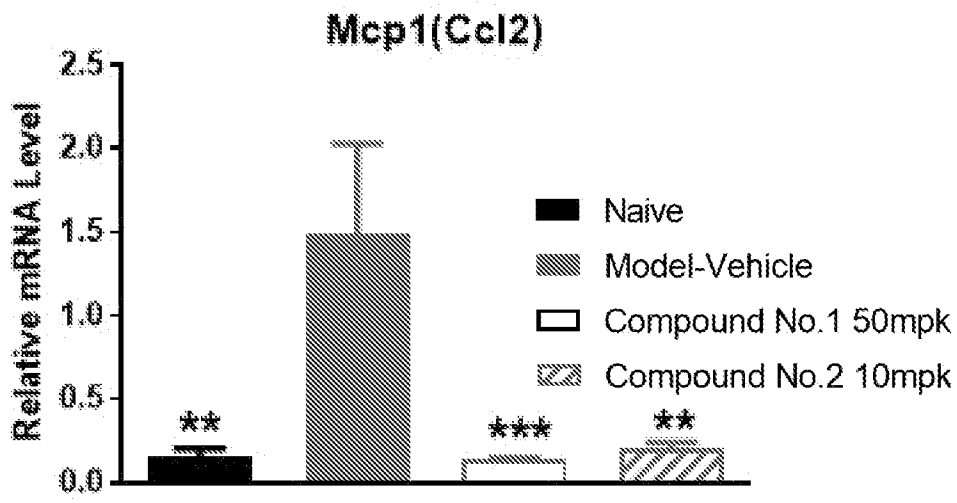

Mcp1(Ccl2)
Relative mRNA Level
2.5
2.0
1.5
1.0
0.5
0.0
**
***
**
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 7A

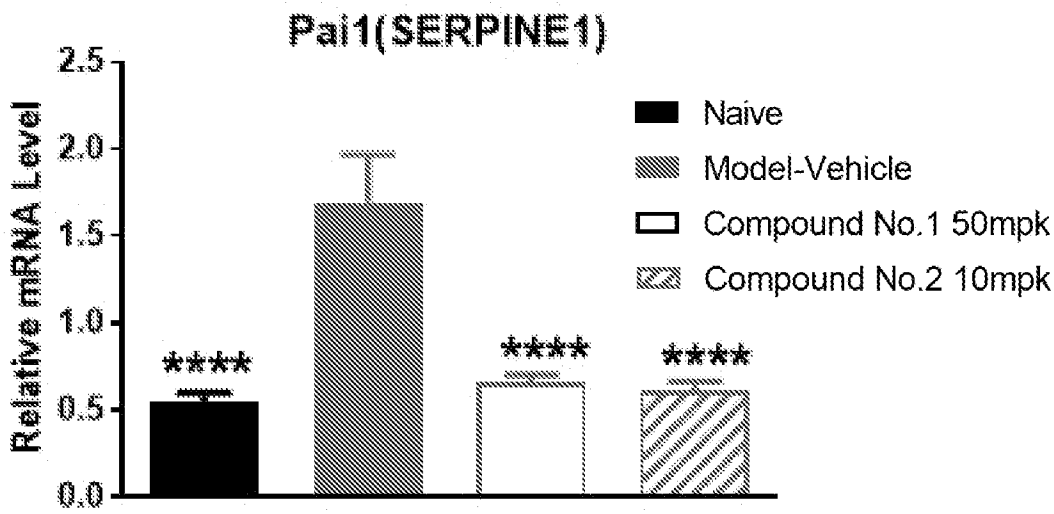

Pai1(SERPINE1)
Relative mRNA Level
2.5
2.0
1.5
1.0
0.5
0.0
****
****
****
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 7B

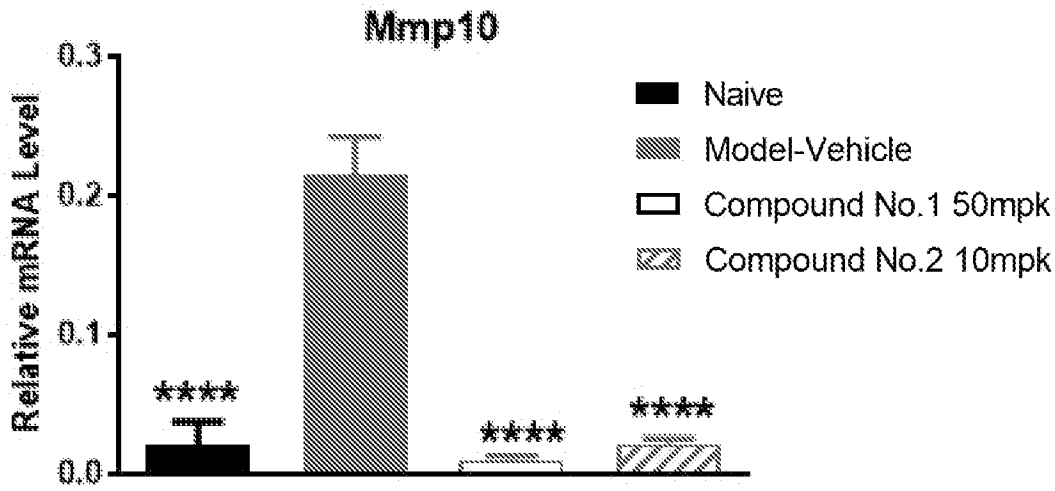

Mmp10
Relative mRNA Level
0.3
0.2
0.1
0.0
****
****
****
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 7C

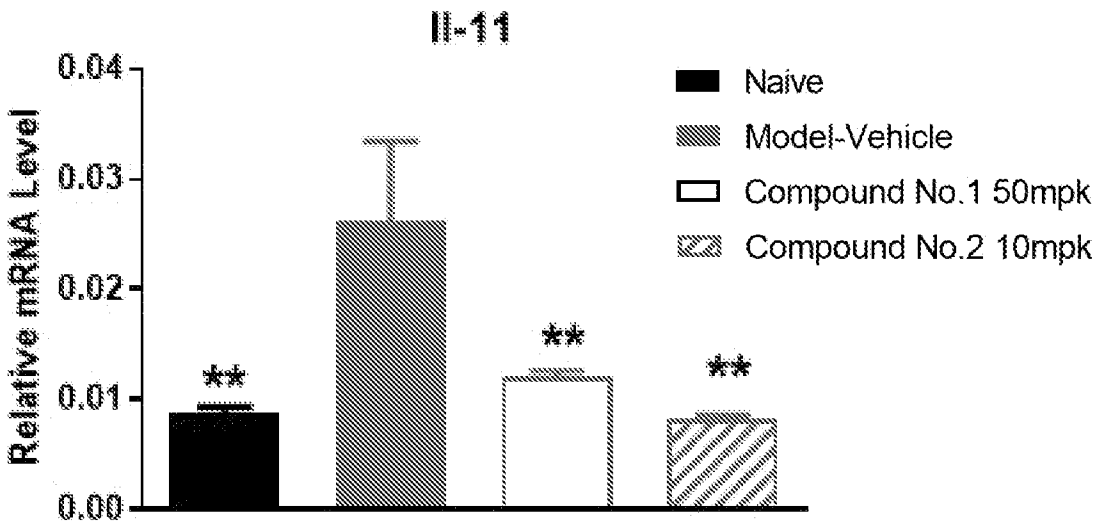

Il-11
Relative mRNA Level
0.04
0.03
0.02
0.01
0.00
**
**
**
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 7D

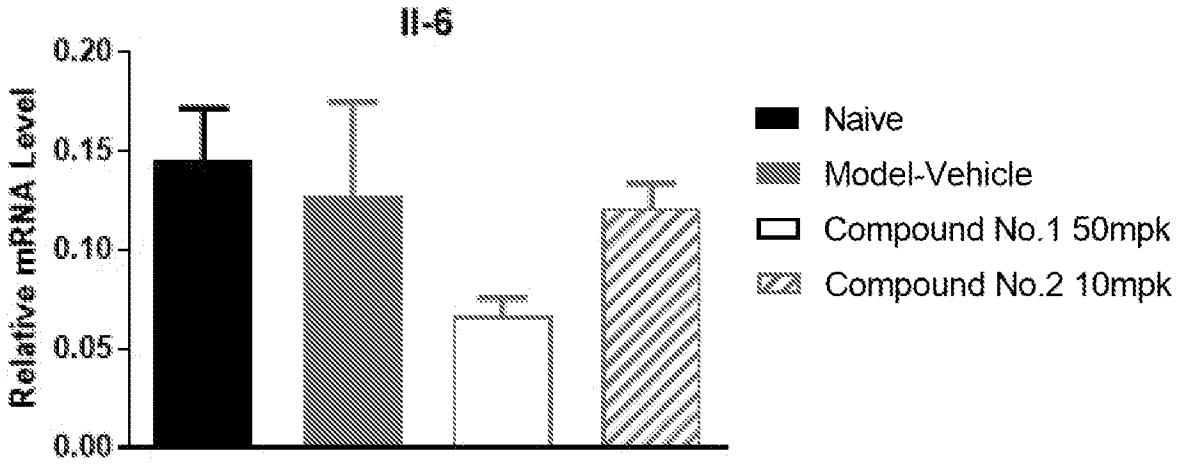

Il-6
Relative mRNA Level
0.20
0.15
0.10
0.05
0.00
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 7E

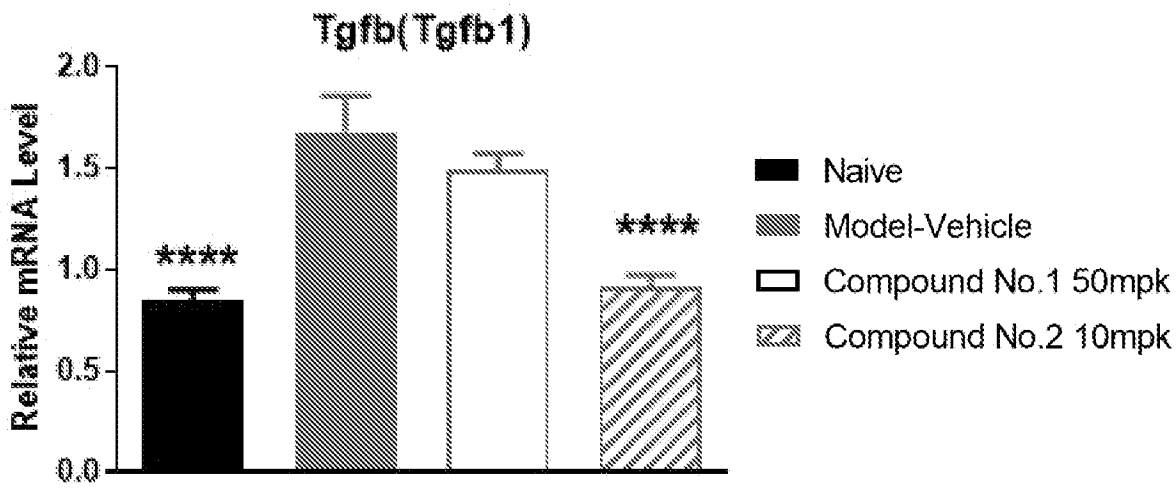

Tgfb(Tgfb1)
Relative mRNA Level
2.0
1.5
1.0
0.5
0.0
****
****
Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 7F

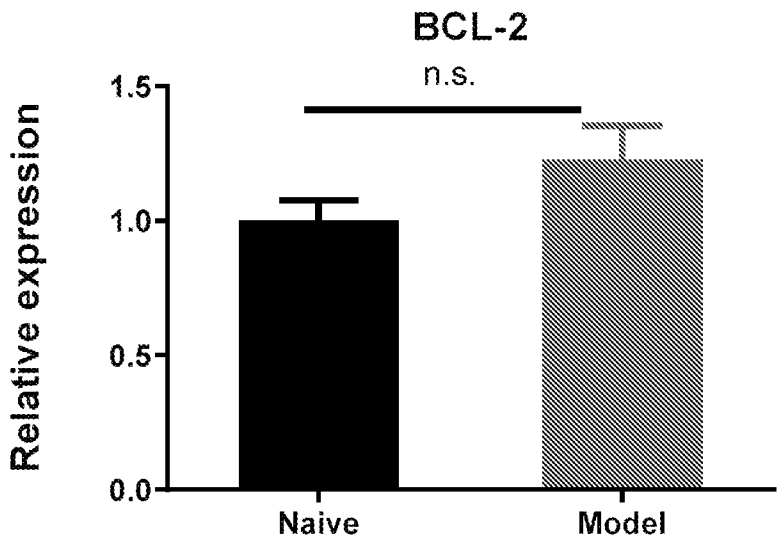

BCL-2
n.s.
Relative expression
1.5
1.0
0.5
0.0
Naive
Model

FIG. 8A

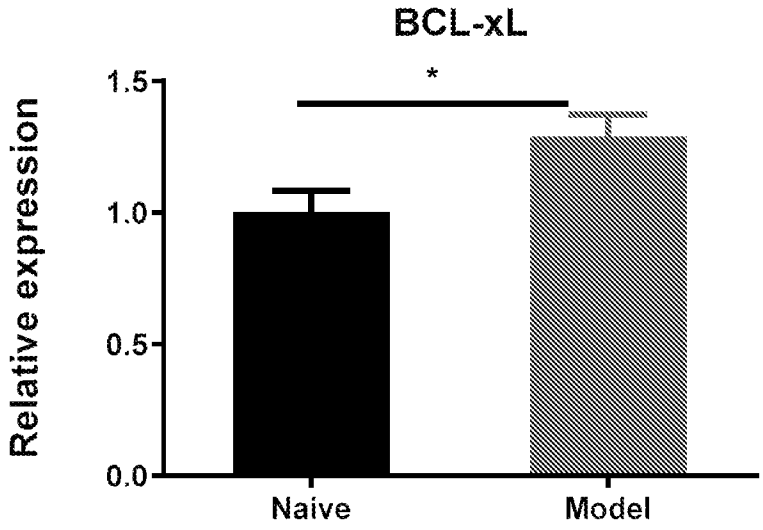

BCL-xL
*
Relative expression
1.5
1.0
0.5
0.0
Naive
Model

FIG. 8B

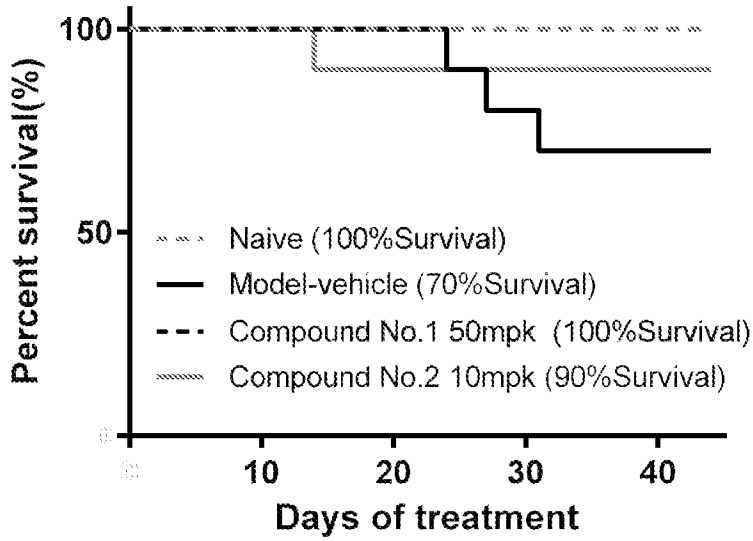

100
50
0
Percent survival(%)
Naive (100%Survival)
Model-vehicle (70%Survival)
Compound No.1 50mpk (100%Survival)
Compound No.2 10mpk (90%Survival)
10
20
30
40
Days of treatment

FIG. 9

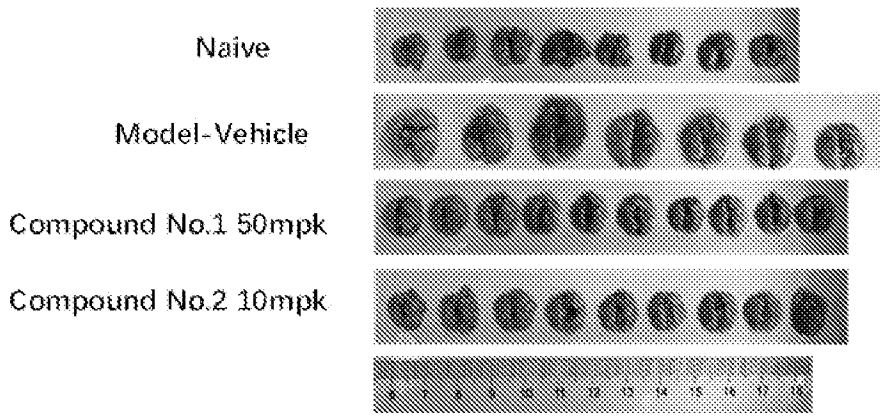

Naive
Model-Vehicle
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 10

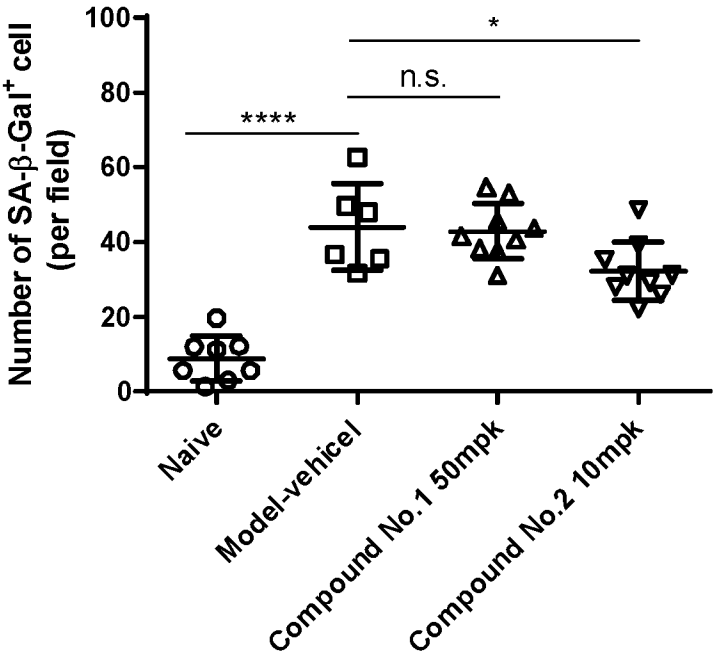

Number of SA-β-Gal+ cell (per field)
100
80
60
40
20
0
****
n.s.
*
Naive
Model-vehicel
Compound No.1 50mpk
Compound No.2 10mpk

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2021/109800

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/496(2006.01)i; A61K 31/675(2006.01)i; C07D 401/14(2006.01)i; A61P 11/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K,C07D,A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI,SIPOABS,CNABS,CNMED,CNTXT,CNKI,REGISTRY,CAPLUS,MEDLINE, VEN, ISI-WEB OF SCIENCE, PubMed, Lung disease, pneumonia, UIP, nonsmall-cell lung cancer, NSCLC,idiopathic pulmonary fibrosis, IPF, radiation-induced pulmonary fibrosis, RIPF

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 108025006 A (BUCK AGEING INST) 11 May 2018 (2018-05-11) see claims 22, 53, 64	1-6, 8, 10-50
A	CN 108025006 A (BUCK AGEING INST) 11 May 2018 (2018-05-11) see claims 22, 53, 64	7, 9
X	CN 110960537 A (ASCE-N ASCENTAGE PHARMA SUZHOU CO., LTD) 07 April 2020 (2020-04-07) see claims 3、11, compound 15, 26, paragraphs 0196-0200	1-3, 5, 8, 10-50
A	CN 110960537 A (ASCE-N ASCENTAGE PHARMA SUZHOU CO., LTD) 07 April 2020 (2020-04-07) see claims 3、11, compound 15, 26, paragraphs 0196-0200	4, 6, 7, 9
X	CN 105246882 A (UNIV MICHIGAN REGNTS) 13 January 2016 (2016-01-13) see claim17, paragraph 0063, compound11, 15, paragraphs 0069, 0073, 0076	1-3, 5, 8, 10-50
A	CN 105246882 A (UNIV MICHIGAN REGNTS) 13 January 2016 (2016-01-13) see claim17, paragraph 0063, compound11, 15, paragraphs 0069, 0073, 0076	4, 6, 7, 9

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2021	**04 November 2021**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **LI,Gang** Telephone No. **62411207**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2021/109800

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **1,4,7,16-50**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 1,4,7,16-50 relate to a treating method. They are not required to carry out an international search (Rule 39.1 (iv) PCT). The international search report is made based on the assumption that claims 24-25 are uses in the manufacture of medicaments.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2021/109800

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
CN 108025006 A	11 May 2018	US 20200338097 A1	29 October 2020
		AU 2016215035 A1	28 September 2017
		EP 3253387 A4	19 December 2018
		US 20200338094 A1	29 October 2020
		WO 2016127135 A1	11 August 2016
		CA 2981753 A1	11 August 2016
		EP 3253387 A1	13 December 2017
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		US 2018110787 A1	26 April 2018
		JP 2018508569 A	29 March 2018
		HK 1249030 A0	26 October 2018
		US 2018000816 A1	04 January 2018
		US 2019175623 A1	13 June 2019
CN 110960537 A	07 April 2020	US 2020297743 A1	24 September 2020
		TW 202019421 A	01 June 2020
		CN 110960537 B	06 April 2021
		AU 2019315550 A1	09 April 2020
		EP 3829593 A1	09 June 2021
		WO 2020024976 A1	06 February 2020
		HK 40016287 A0	11 September 2020
		US 2021060039 A1	04 March 2021
		CN 113018446 A	25 June 2021
CN 105246882 A	13 January 2016	SG 11201505525 A1	28 August 2015
		JP 2016506916 A	07 March 2016
		ZA 201504902 A	27 July 2016
		US 2014199234 A1	17 July 2014
		AU 2014207716 A1	23 July 2015
		AU 2014207716B B2	27 July 2017
		JP 6347793 B2	27 June 2018
		HK 40008278 A0	12 June 2020
		IN 201504906 P4	01 July 2016
		IN 345082 B	28 August 2020
		KR 102210316B B1	29 January 2021
		CN 110302205 A	08 October 2019
		CN 110305162 A	08 October 2019
		CN 110302205 B	09 June 2020
		CA 2897055 C	20 April 2021
		EP 2945940 A1	25 November 2015
		HK 1219734 A0	13 April 2017
		HK 40008279 A0	12 June 2020
		ES 2819232T T3	15 April 2021
		US 9096625 B2	04 August 2015
		KR 20150104631 A	15 September 2015
		CA 2897055 A1	24 July 2014
		NZ 709635 A	25 October 2019
		EP 2945940 B1	15 July 2020
		KR 20210002126 A	06 January 2021
		WO 2014113413 A1	24 July 2014
		SG 11201505525 B	09 May 2018
		EP 3689886 A1	05 August 2020