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Canadian Intellectual Property Office

CA 3101853 C 2022/06/14

(11)(21) 3 101 853

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2020/02/14
(87) Date publication PCT/PCT Publication Date: 2020/08/20
(45) Date de délivrance/Issue Date: 2022/06/14
(85) Entrée phase nationale/National Entry: 2020/11/27
(86) N° demande PCT/PCT Application No.: CA 2020/050199
(87) N° publication PCT/PCT Publication No.: 2020/163966
(30) Priorités/Priorities: 2019/02/14 (US62/805,755); 2019/07/12 (US62/873,723)

(51) Cl.Int./Int.Cl. *A61K 31/445* (2006.01), *A61K 31/454* (2006.01), *A61P 11/00* (2006.01)

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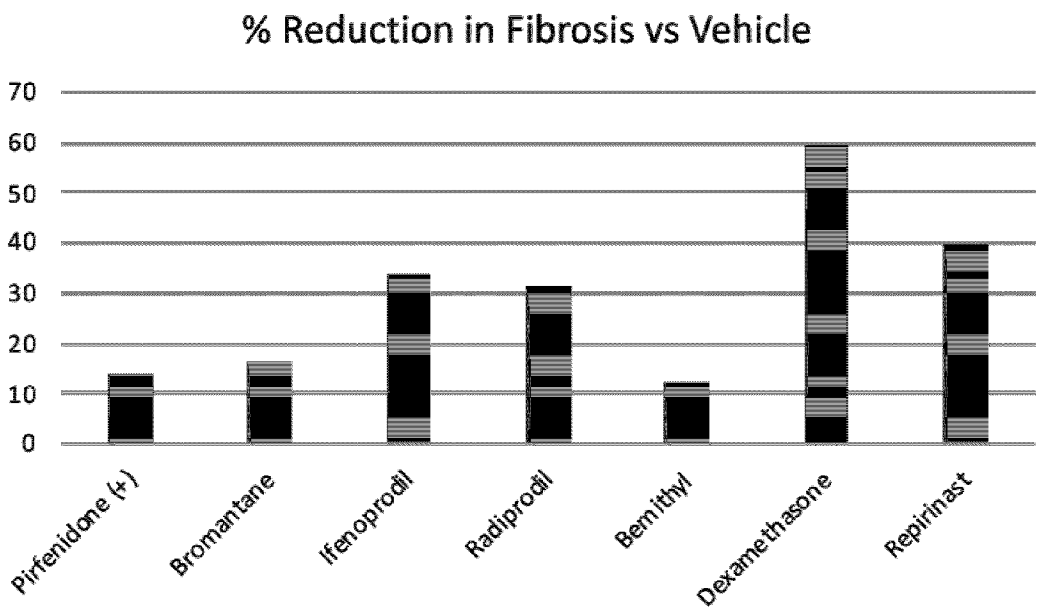
(54) Titre : COMPOSITIONS ET METHODES DE TRAITEMENT DE FIBROSE PULMONAIRE IDIOPATHIQUE
(54) Title: COMPOSITIONS AND METHODS FOR TREATING IDIOPATHIC PULMONARY FIBROSIS



(57) Abrégé/Abstract:
The use of pharmaceutically active compounds for treating chronic lung diseases including idiopathic pulmonary fibrosis is disclosed. The compounds include NMDA receptor antagonists, glutamate 2b receptor antagonists and sigma receptor agonists. In particular, the use of bromantane, ifenprodil, radiprodil, bemithyl and repirinast are effective in treating idiopathic pulmonary fibrosis. Methods of use thereof are also disclosed.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 August 2020 (20.08.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/163966 A1

(51) International Patent Classification:
A61K 31/4741 (2006.01) *C07C 211/52* (2006.01)
A61K 31/136 (2006.01) *C07D 211/22* (2006.01)
A61K 31/4184 (2006.01) *C07D 235/28* (2006.01)
A61K 31/445 (2006.01) *C07D 413/12* (2006.01)
A61K 31/454 (2006.01) *C07D 491/052* (2006.01)
A61P 11/00 (2006.01)

(21) International Application Number:
PCT/CA2020/050199

(22) International Filing Date:
14 February 2020 (14.02.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/805,755 14 February 2019 (14.02.2019) US
62/873,723 12 July 2019 (12.07.2019) US

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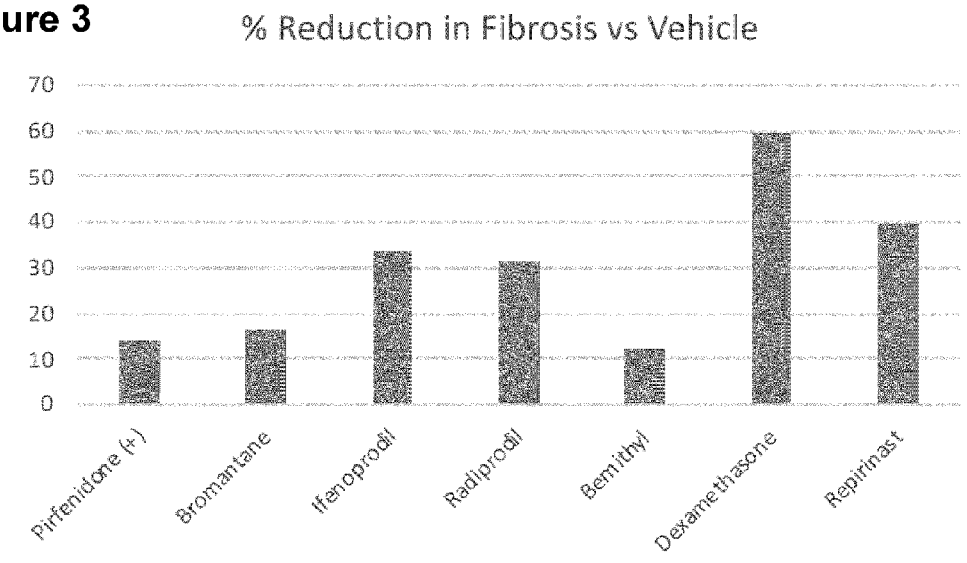
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: COMPOSITIONS AND METHODS FOR TREATING IDIOPATHIC PULMONARY FIBROSIS

Figure 3



(57) **Abstract:** The use of pharmaceutically active compounds for treating chronic lung diseases including idiopathic pulmonary fibrosis is disclosed. The compounds include NMDA receptor antagonists, glutamate 2b receptor antagonists and sigma receptor agonists. In particular, the use of bromantane, ifenprodil, radiprodil, bemithyl and repirinast are effective in treating idiopathic pulmonary fibrosis. Methods of use thereof are also disclosed.

WO 2020/163966 A1

[Continued on next page]

WO 2020/163966 A1

Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

Title: COMPOSITIONS AND METHODS FOR TREATING IDIOPATHIC PULMONARY FIBROSIS

Reference to Related Applications

[0001] The present application claims priority from US provisional application no. 62/805,755 filed February 14, 2019 and US provisional application no. 62/873,723 filed July 12, 2019, the contents of which are hereby incorporated by reference.

Field of Invention

[0002] The present invention relates to the use of compounds for treating fibrosis in the lungs, and in particular, the use of Bromantane, Ifenprodil, Radiprodil, Bemithyl, and/or Repirinast for treating chronic lung disease, including idiopathic pulmonary fibrosis.

Background

[0003] Idiopathic pulmonary fibrosis (IPF) is a form of interstitial lung disease that is characterized by scarring (fibrosis) of the lungs. This results in progressive and irreversible decline in lung operation, including breathing. Symptoms typically include gradual onset of shortness of breath and a dry, chronic cough. Other symptoms include chest pain and fatigue. The causes of IPF is not completely understood. However, factors which increase the risk of IPF include cigarette smoking, acid reflux, and a family history of the condition.

[0004] There is currently no cure for IPF and no procedures or medications that can remove the scarring from the lungs. Conventional treatment of IPF tends to focus on slowing the progression of the lung scarring. Such treatment includes pulmonary rehabilitation, supplemental oxygen, and/or use of medications like pirfenidone or nintedanib. Lung transplantation is also an option in severe cases.

Date reçue / Date received 2021-11-22

[0005] The bleomycin (BLM) murine models is probably the most accepted model of pulmonary fibrosis. Intratracheal administration of bleomycin effectively mimics the chronic aspect of pulmonary fibrosis, as well as other characteristics including the presence of hyperplastic alveolar epithelial cells. (Mouratis et al., *Modeling pulmonary fibrosis with bleomycin, Current Opinion in Pulmonary Medicine:* September 2011, Vol 17(5):355–361). In one such model, BLM is initially and directly introduced to the alveolar epithelial cells, to develop neutrophilia and lymphocytes and BLM-induced fibrosis develops after about seven days. In this model, only a single instillation is needed, the disease develops in a short time frame and it has high reproducibility. BLM-induced fibrosis in mice constitutes an animal model of IPF with high degree of similarity to the histopathological characteristics and distribution of lung fibrosis described in human idiopathic pulmonary fibrosis.

[0006] The present invention provides a novel use of existing drugs, typically studied and used as potential therapies for other pathologies, for the treatment and/or alleviation of IPF.

Summary of Invention

[0007] In one aspect, the present invention provides methods and uses of Bromantane for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject.

[0008] In another aspect, the present invention provides methods and uses of Ifenoprodil for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject.

[0009] In another aspect, the present invention provides methods and uses of Radiprodil for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject.

Date reçue / Date received 2021-11-22

[00010] In another aspect, the present invention provides methods and uses of Bemithyl for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject.

[00011] In another aspect, the present invention provides methods and uses of Repirinast for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject.

[00012] In an embodiment of the invention, a glutamate 2b receptor (Glut2B or GluN2B) antagonist for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject. The Glut2B antagonist may be one or more of Ifenprodil, Radiprodil, Traxoprodil, Rislenmdaz, Eliprodil, Ro-25-6981, and BMT-108908, EVT-101, CP101-606, MK-0657, EVT-103, and AZD 6765 (Annual Reports in Medicinal Chemistry (2012) Volume 47: 94-103).

Brief Description of the Figures

[00013] Exemplary embodiments are illustrated in referenced figures of the drawings. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[00014] Figure 1 is a line graph comparing the mean percentage change in body weights in grams for the experimental treatment groups of mice, using test compounds Bromantane, Ifenoprodil, Radiprodil, Bemithyl, Dexamethasone, and Repirinast, compared to the Normal (no BLM) control group, the BLM-Vehicle control group, and the Pirfenidone positive control group.

[00015] Figure 2 is a column graph comparing the mean Trichrome Score data, for the experimental treatment groups of mice, using test compounds Bromantane, Ifenoprodil, Radiprodil, Bemithyl, Dexamethasone, and Repirinast, compared to the Normal (no BLM) control group, the BLM-Vehicle control group, and the Pirfenidone positive control group.

[00016] Figure 3 is a column graph comparing the percent reduction in fibrosis for the experimental treatment groups of mice, using test compounds

Date reçue / Date received 2021-11-22

Bromantane, Ifenoprodil, Radiprodil, Bemithyl, Dexamethasone, and Repirinast, compared to the BLM-Vehicle control group and the Pirfenidone positive control group.

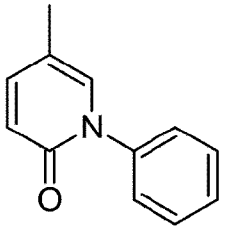
Detailed Description

[00017] The inventor has found certain pharmacologic compounds approved for use in other pathologies are useful in inhibiting or alleviating fibrosis in the lungs and appear useful in the prophylaxis and/or treatment of interstitial lung disease.

[00018] It was found that in BLM-induced fibrosis, the level of pulmonary inflammation is inhibited or alleviated. Based on the experimental results described herein, it is shown that the compounds described are useful in the prophylaxis and/or treatment of interstitial lung disease or idiopathic pulmonary fibrosis.

[00019] The currently used therapy for lung fibrosis and idiopathic pulmonary fibrosis is administering the pharmacologic compound Pirfenidone, which was used as a positive control in the experimental examples described herein.

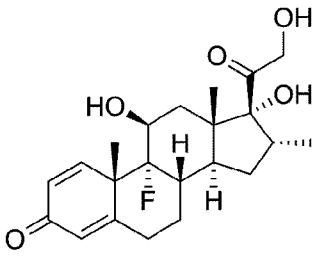
[00020] Pirfenidone, 5-methyl-1-phenylpyridin-2(1H)-one, is an orally active synthetic antifibrotic agent known in the art for inhibiting collagen formation used to treat idiopathic pulmonary fibrosis. The chemical structure of Pirfenidone is:



Dexamethasone, NaN_3 or $C_{22}H_{29}FO_5$, is an orally active synthetic anti-inflammatory agent known in the art for inhibiting inflammation and used

Date reçue / Date received 2021-11-22

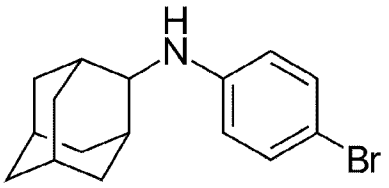
as a positive control in idiopathic pulmonary fibrosis models. The chemical structure of Dexamethasone is:



[00021] The examples and data below show the effects of inhibiting or alleviating lung fibrosis by administering a therapeutically effective amount of Bromantane, Ifenoprodil, Radiprodil, Bemithyl, and Repirinast. These compounds described herein are existing drugs, typically known for treatment of non-pulmonary related conditions.

Use of Bromantane

[00022] Bromantane, N-(4-bromophenyl)adamantan-2-amine, is known in the art as a psychostimulant and anxiolytic drug of the adamantane family. The chemical structure of Bromantane is:



[00023] In one aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with Bromantane or a pharmaceutically acceptable variation thereof. The interstitial lung disease may be idiopathic pulmonary fibrosis (IPF), among others.

[00024] In an embodiment, the amount of Bromantane used is between 0.8 and 5 mg per kg of the subject per day. In a preferred embodiment, the

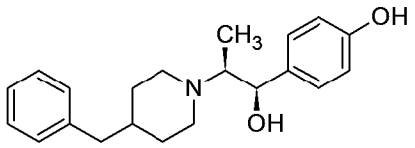
Date reçue / Date received 2021-11-22

amount of Bromantane used is between 1.7 to 3.3 mg per kg of the subject per day. In a further preferred embodiment, the amount of Bromantane used is about 1.7 mg per kg of the subject per day.

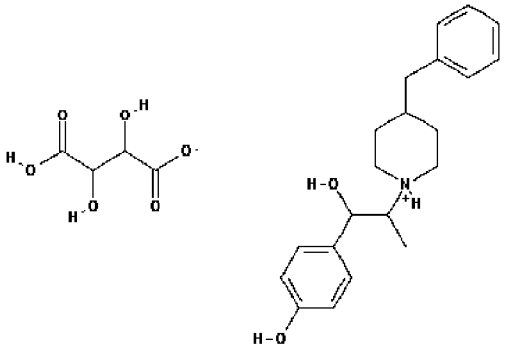
[00025] The Bromantane, or pharmaceutically acceptable variation thereof, may be administered to the subject orally, intravenously or in a manner known in the art. The Bromantane, or pharmaceutically acceptable variation thereof, may also be administered with one or more pharmaceutically acceptable excipients.

Use of Ifenoprodil

[00026] Ifenprodil, 4-[2-(4-benzylpiperidin-1-ium-1-yl)-1-hydroxypropyl] phenol; 2,3,4-trihydroxy-4-oxobutanoate, is known in the art as a selective NMDA receptor (glutamate) antagonist. Ifenprodil was originally (in the early 1970's) developed as a vasodilator. Ifenprodil is currently being studied for treatment of adolescent PTSD. The chemical structure is:



[00027] In some embodiments tested in the examples herein, Ifenprodil hemitartrate having the following structure was used:



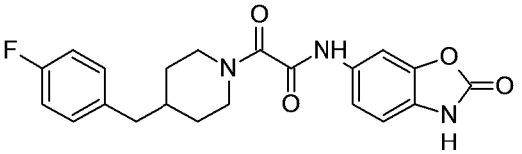
[00028] In one aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with Ifenoprodil or a pharmaceutically acceptable variation thereof. The interstitial lung disease may be idiopathic pulmonary fibrosis (IPF), among others.

[00029] In an embodiment, the amount of Ifenoprodil used is between 0.6 and 5 mg per kg of the subject per day. In a preferred embodiment, the amount of Ifenoprodil used is between 0.8 to 3 mg per kg of the subject per day. In a further preferred embodiment, the amount of Ifenoprodil used is about 1 mg per kg of the subject per day.

[00030] The Ifenoprodil, or pharmaceutically acceptable variation thereof, may be administered to the subject orally, intravenously or in a manner known in the art. The Ifenoprodil, or pharmaceutically acceptable variation thereof, may also be administered with one or more pharmaceutically acceptable excipients.

Use of Radiprodil

[00031] Radiprodil, 2-[4-[(4-fluorophenyl)methyl]piperidin-1-yl]-2-oxo-N-(2-oxo-3H-1,3-benzoxazol-6-yl)acetamide, is known in the art as an NMDA receptor antagonist. It has been used in trials studying the treatment of Infantile Spasms (IS) and Diabetic Peripheral Neuropathic Pain. The chemical structure of Radiprodil is:



[00032] In one aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with Radiprodil or a pharmaceutically acceptable variation thereof. The interstitial lung disease may be idiopathic pulmonary fibrosis (IPF), among others.

[00033] In an embodiment, the amount of Radiprodil used is between 1.6 and 3.3 mg per kg of the subject per day. In a preferred embodiment, the amount of Radiprodil used is about 2.5 mg per kg of the subject per day. In a

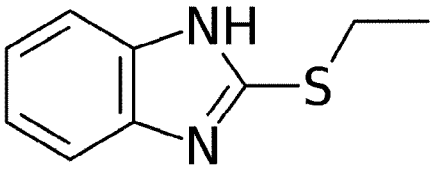
Date reçue / Date received 2021-11-22

further preferred embodiment, the amount of Radiprodil used is about 2.25 mg per kg of the subject par day.

[00034] The Radiprodil, or pharmaceutically acceptable variation thereof, may be administered to the subject orally, intravenously or in a manner known in the art. The Radiprodil, or pharmaceutically acceptable variation thereof, may also be administered with one or more pharmaceutically acceptable excipients.

Use of Bemithyl

[00035] Bemithyl, 2-Ethylsulfanyl-1H-benzoimidazole, is known in the art as a synthetic actoprotector, antioxidant, and antimutagenic, and is often used to increase physical performance. The chemical structure of Bemithyl is:



[00036] In one aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with Bemithyl or a pharmaceutically acceptable variation thereof. The interstitial lung disease may be idiopathic pulmonary fibrosis (IPF), among others.

[00037] In an embodiment, the amount of Bemithyl used is between 0.5 to 50 mg per kg of the subject per day. In a preferred embodiment, the amount of Bemithyl used is between 1 to 30 mg per kg of the subject per day. In a further preferred embodiment, the amount of Bemithyl used is between 4 to 25 mg per kg of the subject per day. In a yet further preferred embodiment, the amount of Bemithyl used is between 8 to 17 mg per kg of the subject per day. In a still further preferred embodiment, the amount of Bemithyl used is about 17 mg per kg of the subject per day.

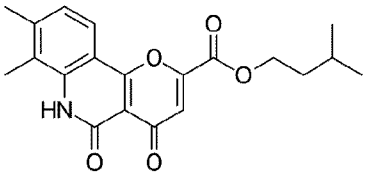
[00038] The Bemithyl, or pharmaceutically acceptable variation thereof, may be administered to the subject orally, intravenously or in a manner known

Date reçue / Date received 2021-11-22

in the art. The Bemithyl, or pharmaceutically acceptable variation thereof, may also be administered with one or more pharmaceutically acceptable excipients.

Use of Repirinast

[00039] Repirinast, Isopentyl 7,8-dimethyl-4,5-dioxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-2-carboxylate, is known in the art as an is an antihistamine. The chemical structure of Repirinast is:



[00040] In one aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with Repirinast or a pharmaceutically acceptable variation thereof. The interstitial lung disease may be idiopathic pulmonary fibrosis (IPF), among others.

[00041] In an embodiment, the amount of Repirinast used is between 1 to 50 mg per kg of the subject per day. In a preferred embodiment, the amount of Repirinast used is between 2.5 to 10 mg per kg of the subject per day. In a further preferred embodiment, the amount of Repirinast used is about 7.5 mg per kg of the subject per day.

[00042] The Repirinast, or pharmaceutically acceptable variation thereof, may be administered to the subject orally, intravenously or in a manner known in the art. The Repirinast, or pharmaceutically acceptable variation thereof, may also be administered with one or more pharmaceutically acceptable excipients.

[00043] In an embodiment of the invention, there is provided a glutamate 2b receptor (Glut2B or GluN2B) antagonist for the treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject. The Glut2B antagonist may be one or more of Ifenprodil, Radiprodil, Traxoprodil, Rislenmdaz, Eliprodil, Ro-25-6981, and BMT-108908, EVT-101, CP101-606, MK-0657, EVT-103, and AZD 6765 (Annual Reports in Medicinal Chemistry (2012) Volume 47: 94-103).

Date reçue / Date received 2021-11-22

[00044] In another aspect of the invention, ifenprodil is known to exhibit NDMA receptor antagonism (GluN1 and more specifically GlunN2B subunits) and sigma receptor agonist (more specifically subtype 1) activity. Sigma receptors are intracellular chaperones that reside in the endoplasmic reticulum of a cell. Thus molecules with similar activity have anti-fibrotic effects and treat IPF. Representative sigma receptor agonists include selective serotonin reuptake inhibitors (SSRI) such as fluvoxamine, fluoxetine, excitalpram and donepezil (J. Pharmacological Sciences (2015) 127:6-9).

Use in Combination

[00045] In another aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with one or more of Bromantane, Ifenoprodil, Radiprodil, Bemithyl, Traxoprodil, Rislenmdaz, Eliprodil, Ro-25-6981, and BMT-108908, EVT-101, CP101-606, MK-0657, EVT-103, and AZD 6765, in combination. In another aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with one or more of Bromantane, Ifenoprodil, Radiprodil, Bemithyl, and Dexamethasone in combination with one or more of Dexamethasone, pirfenidone and nintedanib.

[00046] A further aspect provides a use or method of treatment or prophyliaxis of idiopathic pulmonary fibrosis in a subject with repirinast in combination with one or more of: anti-inflammatory drugs, immune system suppressors, antibiotics, anti-diarrheals, pain relievers, iron supplements, vitamin B-12 shots, and calcium and vitamin D supplements.

[00047] The term "therapeutically effective amount" used herein refers to the amount of an active ingredient sufficient to confer a desired prophylactic or therapeutic effect in a treated subject. In some embodiments, the effective amount is determined, for example, based on the administration route and frequency, body weight and species of the subject receiving the pharmacologic compound.

Date reçue / Date received 2021-11-22

[00048] In some embodiments, an effective amount of the pharmacologic compound is formulated with a pharmaceutically acceptable vehicle and administered to the subject. The term "pharmaceutically acceptable" used herein means that the vehicle is known in the art as compatible with the pharmacologic compound while also being safe to the subject receiving the treatment. In some embodiments, the pharmaceutically acceptable vehicle is determined by persons skilled in the art evaluating, for example, the solubility of the pharmacologic compound in said vehicle.

[00049] Embodiments of the present invention are further described with reference to the following examples, which are intended to be illustrative and not limiting in nature.

Example – Materials and Methods

[00050] The mouse species or strain was Mouse/C57BL/6, the mice being 8-10 week old males. Nine groups of 10 mice each were obtained from Charles River Laboratories. Each group was randomized based on body weight. Bleomycin (BLM) was obtained from Euroasias.

[00051] The mice were maintained in a controlled environment with a temperature of 70-72° F, humidity 30-70%, with a photocycle of 12 hours of light and 12 hours of dark. They were provided with TEKLAD 2018-Global 18% diet and Arrowhead drinking water ad libitium.

[00052] The mice were anesthetized with isoflurane/O2 mixture. Bleomycin (BLM) was then administered to the mice intratracheally (PennCentury) - single bolus, at 2.5U/kg body weight in 50µl sterile saline.

[00053] Seven days after the bleomycin is administered, and fibroblasts have generally proliferated, six of the nine groups of IT bleomycin challenged mice were be dosed orally (p.o.) once a day with Bromantane, Ifenoprodil, Radiprodil, Bemithyl, Dexamethasone, or Repirinast at specified amounts per kg of body weight (mg/kg) daily for 14 consecutive days. The amounts are set out

Date reçue / Date received 2021-11-22

in Table 1 below. The vehicle used was 0.5% carboxymethyl cellulose (CMC). Pirfenidone was also prepared in 0.5% CMC and administrated orally once a day to one of the nine IT bleomycin challenged mice groups beginning for 14 consecutive days. Vehicle and no-BLM control groups received 0.5% CMC orally for 14 consecutive days.

[00054] Table 1

	Groups	**Once daily oral dosing mg/kg**
1	Normal (no BLM)	N/A
2	Pirfenidone (+)	300 (as per BMC Pulm Med. 2017 Apr 18;17(1):63)
3	Vehicle (-)	N/A
4	Bromantane	20
5	Ifenprodil	30
6	Radiprodil	30
7	Bemithyl	200
8	Dexamethasone	0.25
9	Repirinast	90

[00055] On day 21 of the study, 4 hours after the last dose, the mice were sacrificed and plasma was collected and frozen for cytokine analysis (testing for IL-6, IL-12, TGFβ, IL-13 proteins, or fibrosis markers). Brochoalveolar lavage fluid (BALF) was collected and frozen for optional cytokine analyses and cell counts pending the initial data. The lungs were then excised, weighed and fixed in formalin. Gomori's Trichrome stain, a histological stain, was used to determine collagen content.

[00056] The dose selected for the animal studies was determined by taking the maximum known human daily dose, dividing by the average weight of an adult (~60 kg) to get a human mg/kg dose. Then that number was multiplied by 12 to convert to a mouse dose based on conventional dosing tables. See Nair and Jacob, *J Basic Clin Pharm* March 2016-May 2016, 7(2):27-31.

Date reçue / Date received 2021-11-22

[00057] For example:

Daily dose of Radiprodil = 45 mg three times a day (TID) for diabetic neuropathy = 135 mg/day

Max daily human dose = 135/60 = 2.25 mg/kg

Mouse dose = 2.25 x 12 = 27 mg/kg/day (increased to 30 to match Ifenprodil)

[00058] The following measurements and assessments were taken for each mouse.

[00059] Body Weight: The body weights were measured over 21 days using a laboratory balance.

[00060] Trichrome Score: A trichrome score measures the level of scarring to the lungs caused by the disease. The greater the trichrome score, the greater the scarring.

[00061] Formalin fixed lung samples were submitted to affiliated histopathology laboratory for histopathological analysis subjected Gomori's Trichrome stain, a histological stain, which was used to determine collagen content.

[00062] Each lung was divided into ten sections. All ten sections were stained and evaluated. A board certified veterinarian pathologist assessed the presence of lung fibrosis and severity score - The expression of collagen (associated with fibrosis) is determined from the ratio of the stained area versus the total area of the lung section.

[00063] Mortality Rate: the mortality rate in each group was also observed over 21 days.

Results

[00064] Body Weight

Date reçue / Date received 2021-11-22

[00065] The changes in body weights are presented in Figure 1 and Tables 4 and 5. The decrease in body weight were observed from day 1 till day 5 and then started recovering. Differences were observed with the groups treated with Ifenprodil (30 mg/kg)] Radiprodil (30 mg/kg), Bemithyl (200 mg/kg), and Dexamethasone (0.25 mg/kg). They showed improvement beginning on Day 5 as compared to the BLM-vehicle group. Bromantane (20 mg/kg) also showed improvement beginning Day 5, with the exception of Day 15 as compared to the BLM-vehicle group. No significant differences were observed between treatment group Repirinast and BLM-vehicle group. Unexpectedly, the Pirfenidone group (300 mg/kg) showed significant deterioration in body weight throughout the trial.

[00066] Trichrome Score

[00067] The Trichrome score data are presented in Figure 2 and Table 2. The Trichrome score measured the level of scarring to the lungs caused by the disease. No significant differences were observed between treatment groups and BLM-vehicle group though the response was better with Dexamethasone (0.25 mg/kg) and Repirinast (90 mg/kg), followed by Ifenprodil (30 mg/kg), and Radiprodil (30 mg/kg) treated groups.

[00068] Table 2: Trichrome Score Average

	Trichrome score	% reduction in fibrosis
Normal (no BLM)	1.00	N/A
Pirfenidone (+)	4.09	13.9
Vehicle (-)	4.59	0
Bromantane	4.00	16.4
Ifenoprodil	3.37	34.0
Radiprodil	3.45	31.8
Bemithyl	4.14	12.5
Dexamethasone	2.45	59.6
Repirinast	3.16	39.8

An example of how reduction in fibrosis for Pirfenidone was calculated is as follows:

Date reçue / Date received 2021-11-22

% reduction = 100 - (trichrome score Pirfenidone – trichrome score normal) divided by (trichrome score vehicle – trichrome score normal)

[00069] Percent Survival

[00070] Mortality is an important endpoint for IPF patients. The percent survival data is presented in Table 3. The percent survival was higher with the treatment group treated with Dexamethasone (0.25 mg/kg) and Repirinast (90 mg/kg), followed by Ifenprodil (30 mg/kg), and Radiprodil (30 mg/kg).

[00071] Table 3: Survival Data

	Fatality Number	Percent Fatality
Normal (no BLM)	0/10	0
Pirfenidone (+)	2/10	20%
Vehicle (-)	2/10	20%
Bromantane	3/10	30%
Ifenoprodil	0/10	0
Radiprodil	2/10	20%
Bemithyl	1/10	10%
Dexamethasone	2/10	20%
Repirinast	1/10	10%

[00072] Overall

[00073] The fibrosis percent reduction analysis is presented in Figure 3. The percent reduction in lung fibrosis in comparison to the BLM-vehicle group was higher with the treatment group treated with Dexamethasone (0.25 mg/kg) and Repirinast (90 mg/kg), followed by Ifenprodil (30 mg/kg), and Radiprodil (30 mg/kg).

Conclusions

[00074] In conclusion, oral administration of Dexamethasone at 0.25 mg/kg, Repirinast at 90 mg/kg, Ifenproodil at 30 mg/kg and Rediprodil at 30 mg/kg showed improvement in lung fibrosis as well as in the loss of body weight, Trichrome score and mortality as compared to BLM-vehicle. The

Date reçue / Date received 2021-11-22

improvement was generally most pronounced with the groups treated with Dexamethasone and Repirinast.

[00075] Oral administration of Pirfenidone at 300 mg/kg showed minimal improvement in the loss of body weight and trichrome index as compared to BLM-vehicle.

[00076] Throughout the following description, specific details are set forth in order to provide a more thorough understanding to persons skilled in the art. However, well known elements may not have been shown or described in detail to avoid unnecessarily obscuring the disclosure. Accordingly, the description and drawings are to be regarded in an illustrative, rather than a restrictive, sense.

[00077] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are consistent with the broadest interpretation of the specification as a whole.

Date reçue / Date received 2021-11-22

Table 4: Body Weight (g)

	7-Nov	8-Nov	9-Nov	12-Nov	14-Nov	16-Nov	20-Nov	22-Nov	26-Nov	28-Nov
Normal (no BLM)	23.6	24.0	24.0	24.5	25.1	25.3	25.9	26.9	27.6	27.8
Pirfenidone (+)	24.0	24.2	23.5	21.7	21.0	20.8	20.3	21.1	20.9	20.7
Vehicle (-)	25.1	24.2	23.3	22.9	23.0	22.8	23.0	23.9	24.1	24.3
Bromantane	24.8	24.7	24.0	23.1	23.7	23.3	22.9	23.2	23.8	25.2
Ifenoprodil	24.4	24.3	24.1	22.4	23.1	23.6	24.1	24.9	24.6	25.1
Radiprodil	23.6	23.6	23.2	21.3	21.8	22.6	22.4	23.3	24.0	24.0
Bemithyl	24.6	24.7	24.1	23.0	23.5	22.9	23.1	24.0	23.7	24.3
Dexamethasone	24.3	24.1	23.7	22.4	22.7	23.4	22.7	24.2	24.5	25.0
Repirinast	23.5	23.7	23.2	21.5	21.8	21.1	21.4	22.3	21.9	22.3

Table 5: Percent Change in Body Weight

	7-Nov	8-Nov	9-Nov	12-Nov	14-Nov	16-Nov	20-Nov	22-Nov	26-Nov	28-Nov
Normal (no BLM)	0.0	0.3	0.3	0.8	1.4	1.7	2.3	3.3	4.0	4.1
Pirfenidone (+)	0.0	0.3	-0.5	-2.2	-2.9	-3.2	-3.7	-2.9	-3.1	-3.2
Vehicle (-)	0.0	-1.0	-1.8	-2.2	-2.1	-2.3	-2.2	-1.2	-1.0	-0.8
Bromantane	0.0	-0.1	-0.8	-1.8	-1.1	-1.5	-1.9	-1.6	-1.0	0.4
Ifenoprodil	0.0	-0.1	-0.3	-2.0	-1.3	-0.8	-0.3	0.5	0.2	0.7
Radiprodil	0.0	0.0	-0.4	-2.3	-1.8	-1.0	-1.2	-0.3	0.3	0.4
Bemithyl	0.0	0.0	-0.6	-1.6	-1.1	-1.7	-1.6	-0.6	-0.9	-0.3
Dexamethasone	0.0	-0.2	-0.6	-1.9	-1.6	-0.9	-1.5	-0.1	0.3	0.7
Repirinast	0.0	0.2	-0.3	-2.0	-1.8	-2.5	-2.2	-1.3	-1.6	-1.3

What is claimed is:

1. Use of Ifenprodil for the treatment of interstitial lung disease in a subject.

2. The use of claim 1, wherein the amount of Ifenprodil is between 0.1 to 5 mg per kg of the subject.

3. The use of claim 2, wherein the amount of Ifenprodil is between 0.5 to 3 mg per kg of the subject.

4. The use of claim 3, wherein the amount of Ifenprodil is about 1 mg per kg of the subject.

5. The use of claim 3, wherein the amount of Ifenprodil is about 2 mg per kg of the subject.

6. The use of claim 3, wherein the amount of Ifenprodil is about 3 mg per kg of the subject.

7. Use of Radiprodil for the treatment of interstitial lung disease in a subject.

8. The use of claim 7, wherein the amount of Radiprodil is between 1 to 5 mg per kg of the subject.

9. The use of claim 8, wherein the amount of Radiprodil is about 1 mg per kg of the subject.

10. The use of claim 8, wherein the amount of Radiprodil is about 2 mg per kg of the subject.

11. The use of claim 8, wherein the amount of Radiprodil is about 3 mg per kg of the subject.

12. The use of claim 8, wherein the amount of Radiprodil is about 4 mg per kg of the subject.

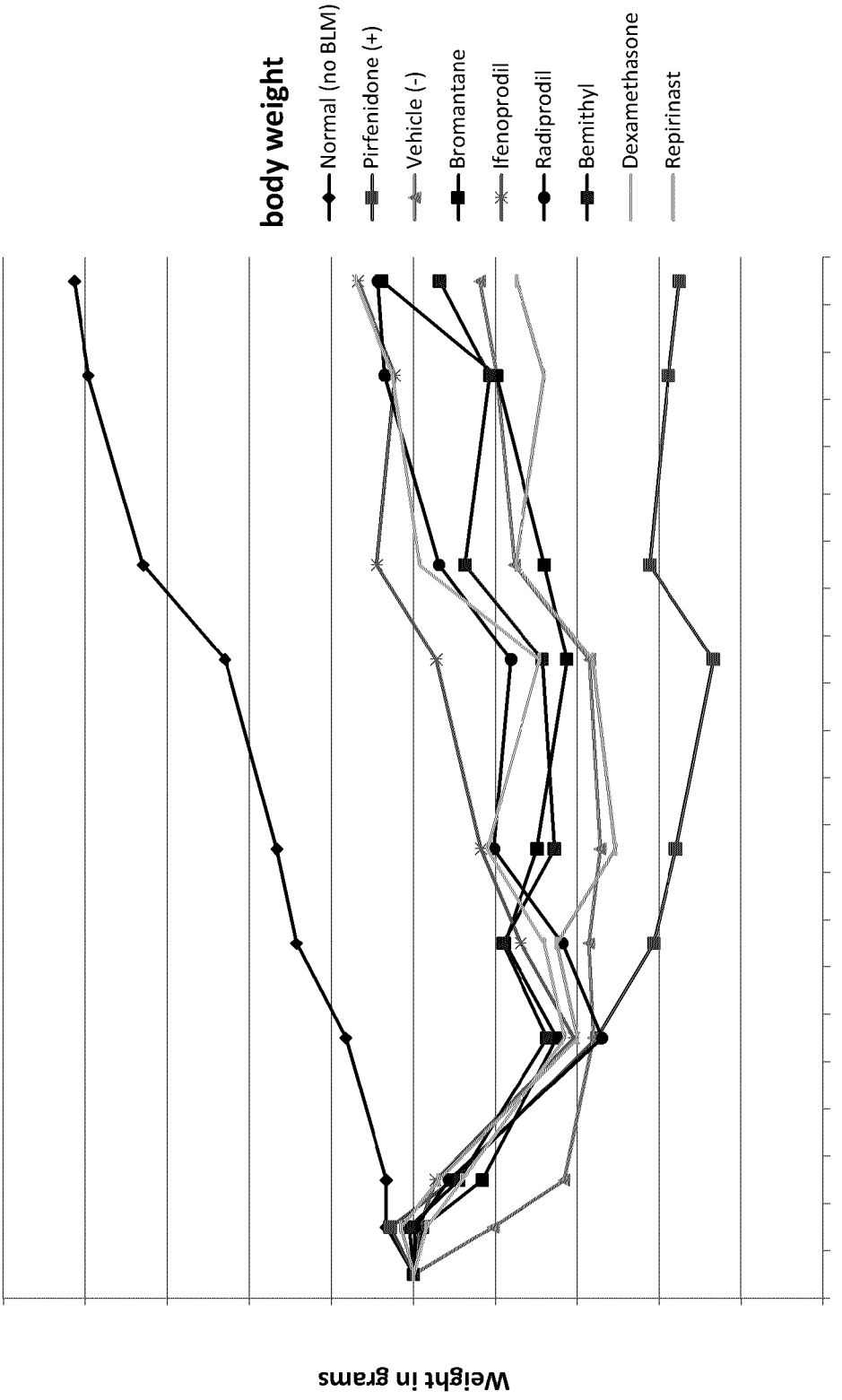
Date reçue / Date received 2021-11-22

13. The use of claim 8, wherein the amount of Radiprodil is about 5 mg per kg of the subject.

14. The use of any one of claims 1-13, wherein the interstitial lung disease is idiopathic pulmonary fibrosis.

Date reçue / Date received 2021-11-22

Figure 1



Date reçue / Date received 2021-11-22

Figure 2

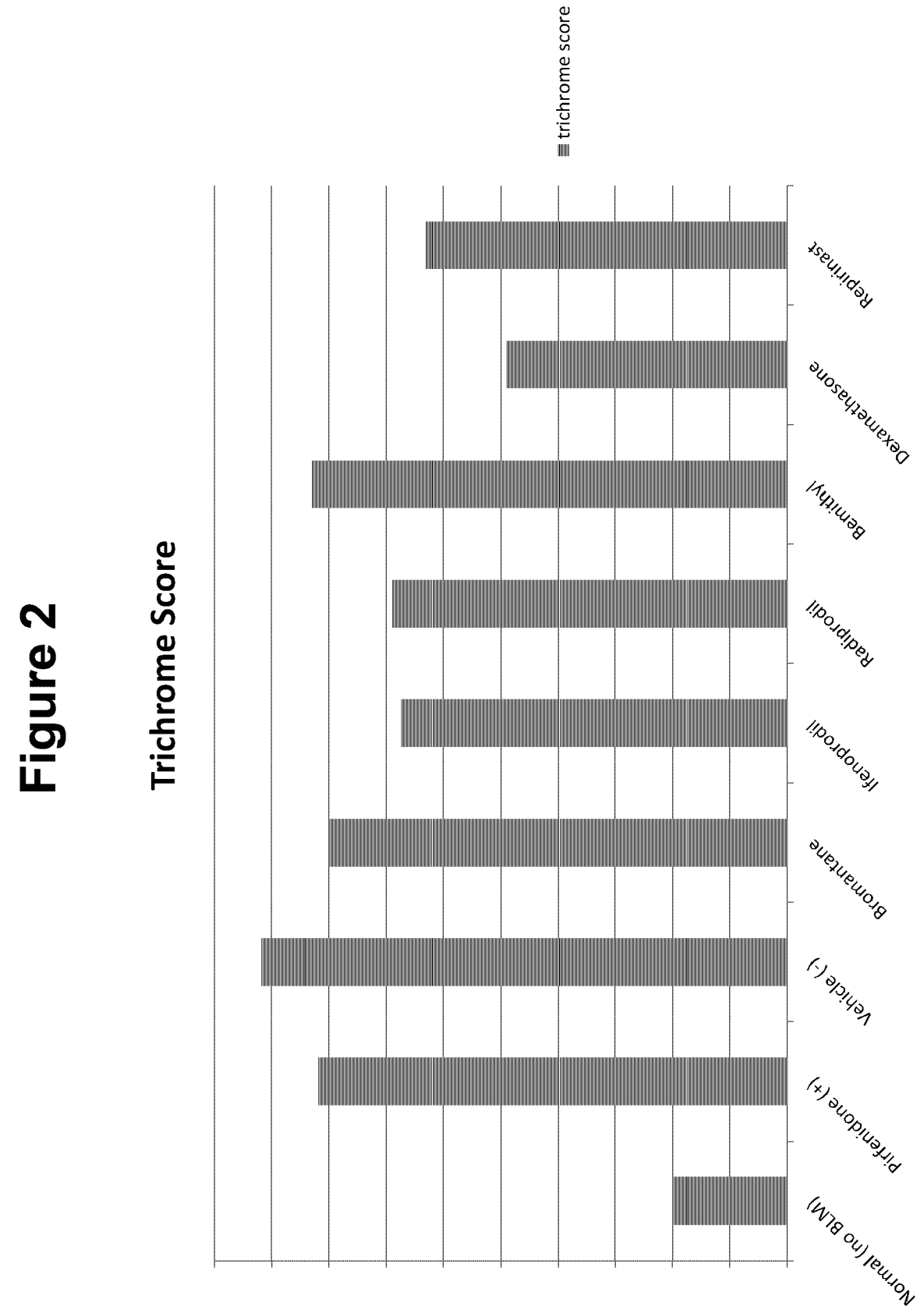
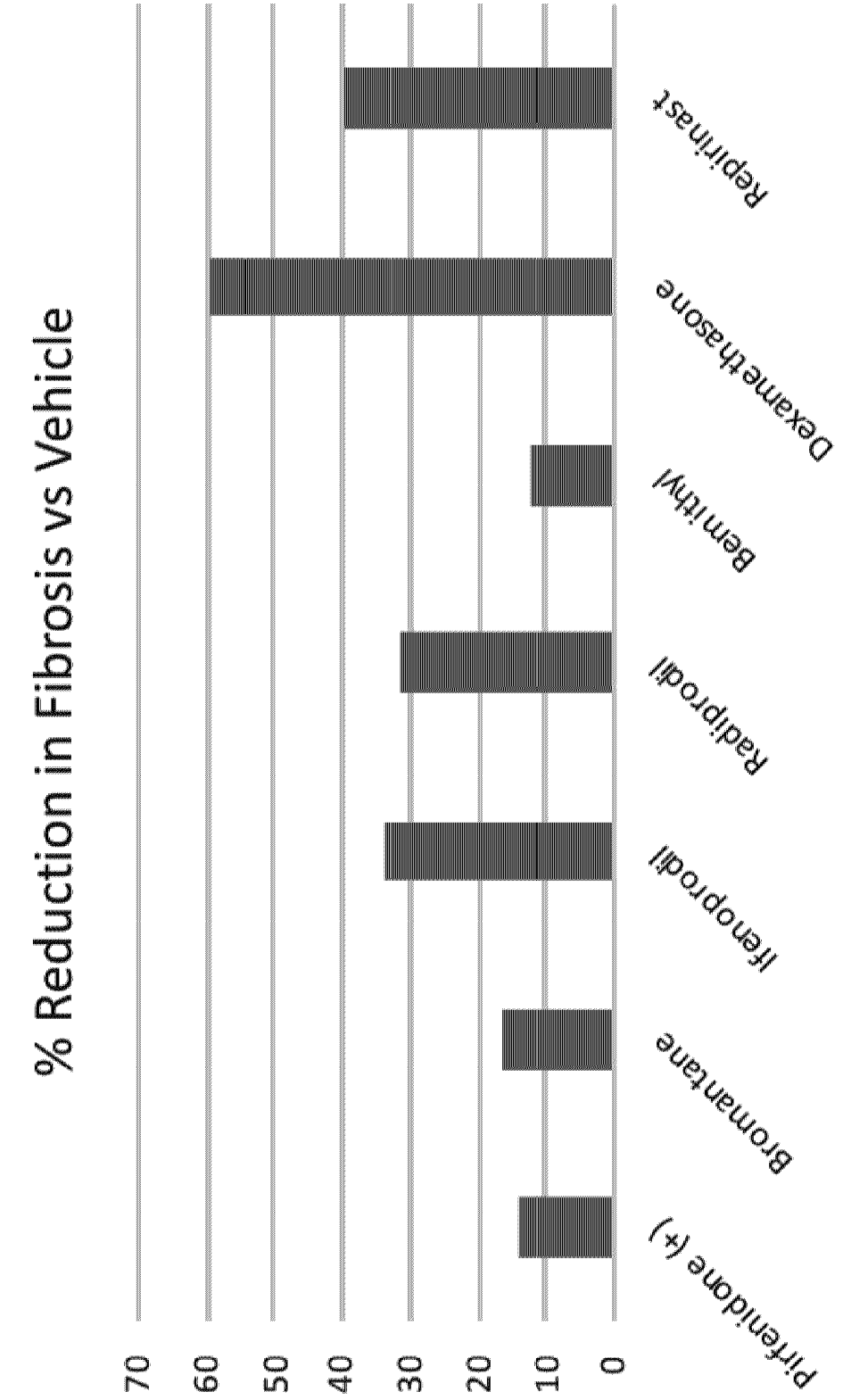
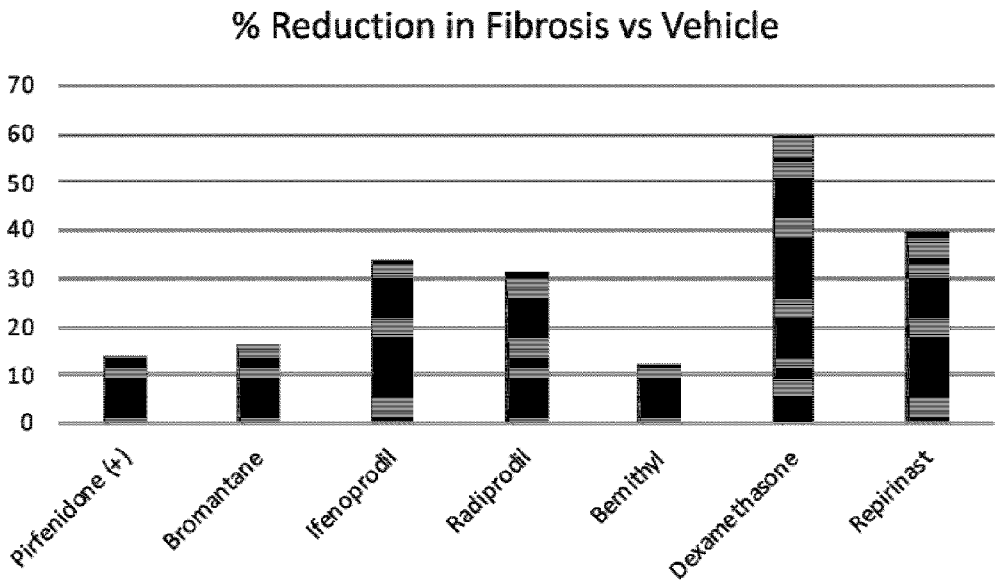

Trichrome Score
trichrome score
Normal (no BLM)
Pirfenidone (+)
Vehicle (-)
Bromantane
Ifenoprodil
Raditprodil
Bemnitiv
Dexamethasone
Reprinast

Figure 3



Date reçue / Date received 2021-11-22


% Reduction in Fibrosis vs Vehicle
70
60
50
40
30
20
10
0
Pirfenidone (+)
Bromantane
Ifenoprodil
Radiprodil
Bemithyl
Dexamethasone
Repirinast