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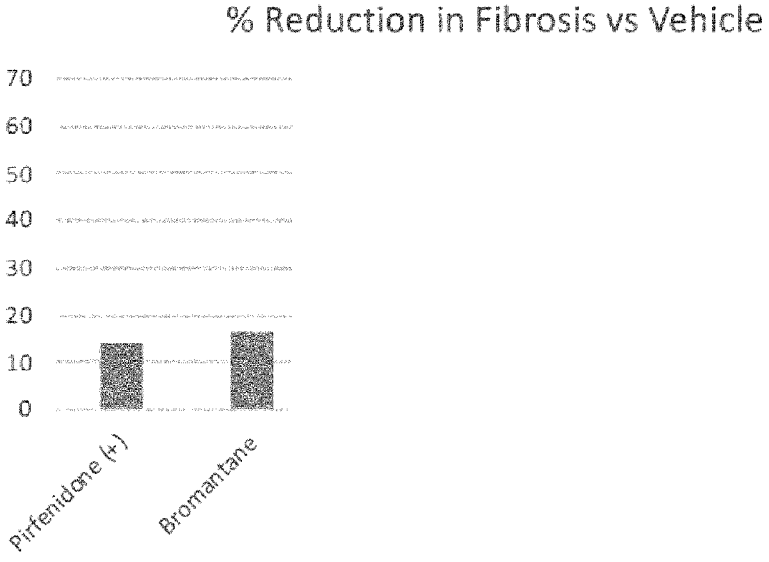
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(54) Title: METHODS AND USES OF BROMANTANE AND DERIVATIVES THEREOF FOR TREATING LUNG DISEASE, FATTY LIVER DISEASE, AND KIDNEY DISORDERS

Figure 3



(57) Abstract: Methods and uses of bromantane and derivatives of the Formula (Ia) or (Ib) for treating fibrotic diseases are taught, and in particular, chronic lung disease, including idiopathic pulmonary fibrosis; non-alcoholic fatty liver disease, and in particular, non-alcoholic fatty liver, and non-alcoholic steatohepatitis; and kidney disorders, and in particular, renal fibrosis and/or chronic kidney disease.

[Continued on next page]

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METHODS AND USES OF BROMANTANE AND DERIVATIVES THEREOF FOR TREATING LUNG DISEASE, FATTY LIVER DISEASE, AND KIDNEY DISORDERS

CROSS-REFERENCE TO RELATED APPLICATION

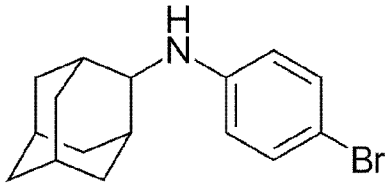
This application claims the benefits of priority to United States Provisional Patent Application No. 62/824,690, filed March 27, 2019, titled METHODS AND USES OF BROMANTANE AND DERIVATIVES THEREOF FOR TREATING LUNG DISEASE, FATTY LIVER DISEASE, AND KIDNEY DISORDERS, the contents of which are hereby expressly incorporated into the present application by reference in their entirety.

TECHNICAL FIELD

[0001] The present invention relates to bromantane and derivatives, methods and uses of bromantane derivatives for treating fibrotic diseases, and in particular, chronic lung disease, including idiopathic pulmonary fibrosis; non-alcoholic fatty liver disease, and in particular, non-alcoholic fatty liver, and non-alcoholic steatohepatitis; and kidney disorders, and in particular, renal fibrosis and/or chronic kidney disease.

BACKGROUND

[01] 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:



[0002] 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.

[0003] 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.

[0004] 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.

[0005] Non-alcoholic fatty liver disease (NAFLD) covers a range of liver conditions characterized by too much fat stored in liver cells. As its name implies, the causes are generally unrelated to alcohol consumption. This is in contrast to alcoholic liver disease, which is caused by heavy alcohol use. Most commonly, NAFLD is either non-alcoholic simple fatty liver or non-alcoholic steatohepatitis (NASH).

[0006] Nonalcoholic fatty liver is a condition where you have fat in your liver but little or no inflammation or liver cell damage. It typically does not progress to cause liver damage or complications.

[0007] NASH includes both a fatty liver and liver inflammation. While those with only nonalcoholic fatty liver are generally asymptomatic, the inflammation and liver cell damage with NASH can cause fibrosis, or scarring, of the liver, and in severe cases, may lead to cirrhosis (advanced scarring) or liver cancer. In that regard, common signs and symptoms of NASH and cirrhosis can include abdominal swelling, enlarged blood vessels just beneath the skin's surface, enlarged breasts in men and jaundice.

[0008] Factors which increase one's risk of NASH include diabetes, obesity, a high fructose diet, genetics and advanced age. While improving one's diet and exercise are an efficient way to manage NAFLD and reduce insulin resistance, there is currently no cure for NAFLD or NASH, and there is no single treatment that works for every individual. Drugs currently used to treat NAFLD and NASH may help to increase fat loss and/or improve biomedical marker levels, but none have been shown to reverse or reduce NAFLD and NASH once liver scarring has begun.

[0009] The murine models of NAFLD and NASH are well-characterized experimental models of metabolically-induced hepatic injury that ultimately lead to spontaneous hepatic steatosis - a common characteristic of many chronic hepatitis disorders. In the dietary models, the progression towards

fatty liver is highly predictable and reproducible, leading to steatosis based on insulin resistance and obesity (Ishii et al, *Female spontaneously diabetic Torii fatty rats develop nonalcoholic steatohepatitis-like hepatic lesions, World J Gastroenterol,* 21(30):9067-78 (2015); Kucera 0 and Cervinkova Z, *Experimental models of non-alcoholic fatty liver disease in rats, World J Gastroenterol,* 20(26):8364-76 (2014); Takahashi et al, *Animal models of nonalcoholic fatty liver diseaselnonalcoholic steatohepatitis, World J Gastroenterol,* 18(19);2300-08 (2012)).

[0010] In one such model (known as the Stelic Animal Model or STAM^{IM}) of NASH-derived hepatocellular carcinoma ("NASH-HCC") in mice, subcutaneous streptozotocin ("STZ") exposure followed by a continuous high-fat diet leads to diabetes, significant steatosis, chronic lobular inflammation, pericellular fibrosis, liver cirrhosis and HCC resembling the *entire* cascade of human NASH-HCC in a relatively short period of 6 to 16 weeks, including moderate increases of transaminases and plasma lipids - major hallmarks of human NASH (Fujii M et al, *A murine model for non-alcoholic steatohepatitis showing evidence of association between diabetes and hepatocellular carcinoma, Med Mol Morphol,* 46(3):141-52 (2013)).

[0011] Chronic kidney disease (CKD) is a form of kidney disease characterized by damage to the kidneys that worsens over time, often as result of renal fibrosis. This causes gradual loss of kidney functions, so that excess fluid and waste from the blood remain in the body and may cause other health problems.

[0012] Early on, an individual with CKD is generally asymptomatic. As the disease progresses, however, symptoms can include muscle cramps, nausea and vomiting, loss of appetite, swelling in your feet and ankles, and tiredness. Symptoms of acute kidney failure include abdominal and back pain, diarrhea, vomiting, and fever.

[0013] Factors which increase the risk of CKD include diabetes, high blood pressure, heart disease, advanced age and a family history of the condition. Blood tests checking for glomerular filtration rate and urine tests to check for albumin (albumin being a protein that can pass into the urine when the kidneys are damaged) can be used to diagnose CKD.

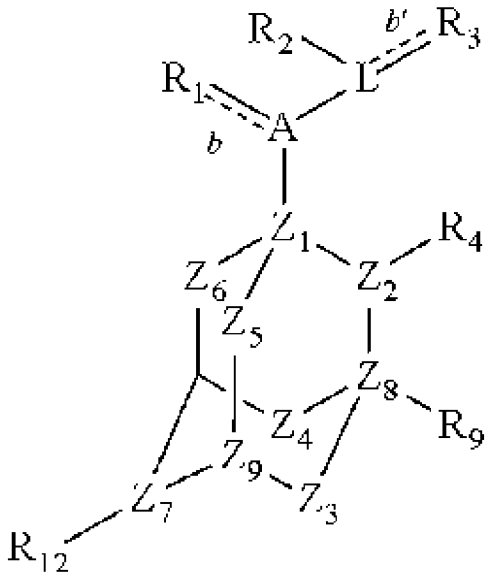
[0014] There is currently no cure for renal fibrosis or CKD. Treatment of CKD generally focus on controlling the risk factors, the goal of therapy is simply to slow down or halt the progression of CKD.

[0015] The murine model of UUO surgical intervention is a well-characterized experimental model of renal injury that ultimately leads to tubulointerstitial fibrosis, depending on the duration of obstruction. In this model, the progression of renal fibrosis is highly predictable and reproducible, leading to significant fibrosis and nephron loss in a relatively short period of 7 to 14 days (Eddy et al., *Investigating mechanisms of chronic kidney disease in mouse models, Pediatr Nephrol.* 2012 August; 27(8):1233-47; Grande M T and Lopez-Novoa J M, *Fibroblast activation and myofibroblast generation in obstructive nephropathy, Nat Rev Nephrol.*, 2009 June; 5(6):319-28).

[0016] There is a need for compounds, compositions, methods and/or use of bromantane and derivatives thereof, for treating lung diseases, and in particular, chronic lung disease, including idiopathic pulmonary fibrosis; non-alcoholic fatty liver disease, and in particular, non-alcoholic fatty liver disease, non-alcoholic fatty liver, and non-alcoholic steatohepatitis; and kidney disorders, and in particular, renal fibrosis and/or chronic kidney disease.

SUMMARY OF THE INVENTION:

[0017] It is an embodiment of the present invention to provide uses of compound of Formula (Ia):



(Ia)

wherein

A is H, C_{1-3} alkylene or a bond between L and the atom at position Z_1;

L is nitrogen;

R_1 is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b′ may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is —(X)(Y);

R_4 is —(R_5)(R_6), halo, is absent, or is —$NR_{13}R_{14}$;

R_5 is nitrogen or oxygen;

R_6 is hydrogen or —(R_7)(R_8)

R_7 is alkylene, —CH(R_{7a})—, —$(CH_2)_{0-6}$CH(OH)—, or represents a bond between R_5 and R_8;

R_{7a} is alkyl;

R_8 is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is —(R_{10})(R_{11}) or is absent;

R_{10} is oxygen, nitrogen, alkyl, —CF_3, or alkylene;

R_{11} is hydrogen, halo, or is absent;

R_{12} is absent, alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, —CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, —CH(Q)-, carbonyl, or a bond;

Q is alkyl, —C(=O)O$(CH_2)_{1-3}CH_3$, or —$(CH_2)_{0-3}$OH;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_1 and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

(i) if A is a bond and R2 is H or absent, except if X is alkynyl, then:
Y is not unsubstituted phenyl, pyridinyl, furanyl, thiopheneyl, pyrrolyl, or benzodioxolyl;
if Y is mono-substituted furanyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, acetylamino, nitro, bromo, chloro, or fluoro;
if Y is mono-substituted phenyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, unsubstituted phenyl, methoxybenzloxy, acetylamino, nitro, bromo, chloro, or fluoro
if Y is mono-substituted thiopheneyl, then the substituent on Y is not methyl, ethyl, chloro, or bromo;
if Y is mono-substituted oxadiazolyl, then the substituent on Y is not methoxyphenyl;
if Y is mono-substituted thiazolyl, then the substituent on Y is not methyl;
if Y is mono-substituted naphthyl, then the substituent on Y is not 1-hydroxyl; and,
if Y is di-substituted phenyl, then the substituents on Y may not both be alkoxy, and,

(ii) if A is C1 alkyl, R1 is NH, and Y is mono-substituted phenyl, then the substituent is not hydroxyl;

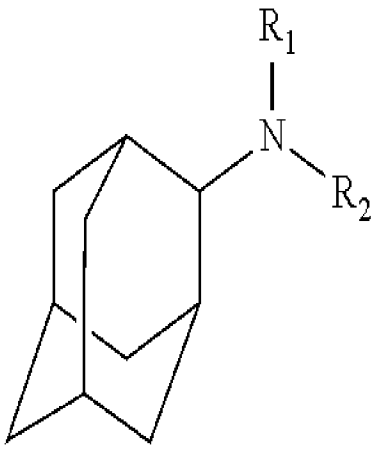
R_{13} together with R_{14} and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system, or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof; or
R_{13} is hydrogen; and
R_{14} is a mono-, di-, or tricyclic ring system bearing one or more optional substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl; or

R_{14} is —(R_{15})(R_{16}), wherein R_{15} is alkyl and R_{16} is an optionally substituted mono-, di-, or tricyclic ring system;

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt or prodrug thereof.

[0018] It is an embodiment of the present invention to provide uses of compound of Formula (Ib):

(Ib)



wherein
R_1 is hydrogen; and,
R_2 is —(R_3)($R_{4'}$);
R_3 is alkyl; and,
$R_{4'}$ is a substituted mono-, di-, or tricyclic ring system, or,
R_1 together with R_2 and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system,
or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

[0019] In some embodiments, $R_{4'}$ is a substituted monocyclic ring. In one preferred embodiment, $R_{4'}$ is a substituted five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl. Preferably, $R_{4'}$ is a halo-substituted six-membered carbocyclic ring. In another preferred embodiment, $R_{4'}$ is a bromine-substituted six-membered carbocyclic ring.

[0020] It is an embodiment of the present invention to provide a method of treating one or more of fibrotic diseases, and in particular, chronic lung disease, including idiopathic pulmonary fibrosis; non-alcoholic fatty liver disease, and in particular, non-alcoholic fatty liver disease, non-alcoholic fatty liver, and non-alcoholic steatohepatitis; and kidney disorders, and in particular, renal fibrosis and/or chronic kidney disease, the method comprising administering a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof to a subject in need thereof.

[0021] It is an embodiment of the present invention to provide a use of a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof, to treat one or more of fibrotic diseases, and in particular, chronic lung disease, including idiopathic pulmonary fibrosis; non-alcoholic fatty liver disease, and in particular, the use of particular test compounds for treating non-alcoholic fatty liver disease, non-alcoholic fatty liver, and non-alcoholic steatohepatitis; and kidney disorders, and in particular, renal fibrosis and/or chronic kidney disease.

[0022] It is an embodiment of the present invention to provide a compound of Formula (Ia) or (Ib) or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt or prodrug thereof.

[0023] In one aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof. The interstitial lung disease may be idiopathic pulmonary fibrosis (IPF), among others.

[0024] In an embodiment, the amount of compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof, used is between 0.8 and 5 mg per kg of the subject per day. In a preferred embodiment, the amount of compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof used is between 1.7 to 3.3 mg per kg of the subject per day. In a further preferred embodiment, the amount of compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof used is about 1.7 mg per kg of the subject per day.

[0025] The compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof, may be administered to the subject orally, intravenously or in a manner known in the art. The compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof, or pharmaceutically acceptable variation thereof, may also be administered with one or more pharmaceutically acceptable excipients.

[0026] In another aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof and one or more of Ifenoprodil, Radiprodil, and Bemithyl. In another aspect, the present invention provides a use and method of treatment or prophylaxis of idiopathic pulmonary fibrosis in a subject with the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof and one or more of

Ifenoprodil, Radiprodil, Bemithyl, Dexamethasone, pirfenidone and nintedanib.

[0027] In another aspect, the present invention provides a use and method of treatment or prophylaxis of NASH or NASH-HCC in a subject with the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof and one or more of Cepharanthine, Repirinast, Ifenoprodil Hemitartrate, Suplatast Tosylate, Actarit, Lobenzarit, Irsogladine, Istradefylline and Trapadil in combination. In another aspect, the present invention provides a use and method of treatment or prophylaxis of NASH or NASH-HCC in a subject with with the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof and one or more of Cepharanthine, Repirinast, Ifenoprodil Hemitartrate, Suplatast Tosylate, Actarit, Lobenzarit, Irsogladine, Istradefylline, Trapadil, a cholesterol lowering drug, a diabetes drug, an antihypertension drug, and Vitamin E.

[0028] In another aspect, the present invention provides a use and method of treatment or prophylaxis of chronic kidney disease in a subject with the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof and one or more of Iguratimod, Repirinast, Lobenzarit, Actarit, Ifenprodil, Bemithyl, Emoxypine, Udenafil, Istradefyllne, and Suplatast Tosylate. In another aspect, the present invention provides a use and method of treatment or prophylaxis of chronic kidney disease in a subject with the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt or prodrug thereof and one or more of Iguratimod, Repirinast, Lobenzarit, Actarit, Ifenprodil, Bemithyl, Emoxypine, Udenafil, Istradefyllne, Suplatast Tosylate, Cenicriviroc, telmisartan, a cholesterol lowering drug, an antihypertension drug, and erythropoietin.

[0029] Examples of cholesterol lowering drugs for use in combinations include Atorvastatin (Lipitor), Fluvastatin (Lescol), Lovastatin, Pitavastatin (Livalo), Pravastatin (Pravachol), Rosuvastatin calcium (Crestor),

Simvastatin (Zocor) and niacin, Alirocumab (Praluent), Evolocumab (Repatha), Alirocumab (Praluent), and Evolocumab (Repatha). Examples of diabetes drugs for use in combinations include insulin. Examples of antihypertension drugs for use in combinations include antihypertensives, calcium channel blockers, ACE inhibitors angiotensin II receptor blockers, diuretics, and beta blockers. Examples of known angiotensin II receptor antagonists include both angiotensin I receptor subtype antagonists and angiotensin II receptor subtype antagonists. Suitable angiotensin II receptor antagonists include losartan and valsartan. Suitable calcium channel blockers include, for example, verapamil, diltiazem, nicardipine, nifedipine, amlodipine, felodipine, nimodipine, and bepridil. Diuretics include, for example, furosemide, diuril, amiloride, and hydrodiuril. Losartan, candesartan, telmisartan, valsartan, olmesartan, irbesartan, and the like can be used as a hypotensive agent.

BRIEF DESCRIPTION OF THE FIGURES

[0030] 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 compound Bromantane compared to the Normal (no BLM) control group, the BLM-Vehicle control group, and the Pirfenidone positive control group;

[0031] Figure 2 is a column graph comparing the mean Trichrome Score data, for the experimental treatment groups of mice, using test compound Bromantane compared to the Normal (no BLM) control group, the BLM-Vehicle control group, and the Pirfenidone positive control group;

[0032] Figure 3 is a column graph comparing the percent reduction in fibrosis for the experimental treatment groups of mice, using test compound Bromantane compared to the BLM-Vehicle control group and the Pirfenidone positive control group;

[0033] FIG. 4 shows an evaluation of liver function and disease progression consisting of the Plasma Alanine Aminotransferases (ALT) in units/L for each of the study groups in a first study of C57BL/6 mice consisting of the "Vehicle" control group and treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test.

[0034] FIGS. 5a, 5b, and 5c show representative photomicrographs of HE-stained liver sections for each of the the study groups of C57BL/6 mice consisting of the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Upper panels are taken at x50 magnification. Lower panels are x200 magnification. The identity of each study group is listed above the upper panel in each pair of panels.

[0035] FIG. 6 shows the NAFLD activity score for each of the 12 study groups of C57BL/6 mice consisting of the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test.

[0036] FIG. 7 shows the steatosis score for each of the study groups of C57BL/6 mice consisting of the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test.

[0037] FIG. 8 shows the lobular inflammation score for each of the study groups of C57BL/6 mice consisting of the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test.

[0038] FIG. 9 shows the hepatocellular ballooning score for each of the study groups of C57BL/6 mice consisting of the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test.

[0039] FIG. 10 shows representative photomicrographs of Sirius red-stained liver sections for study groups of C57BL/6 mice consisting of the "Vehicle" control group and the Bromantane group including the positive control treatment group, Telmisartan. The panels are taken at x200 magnification. The identity of each study group is listed above the upper panel in each pair of panels.

[0040] FIG. 11 shows the Sirius red-positive area for the study groups of C57BL/6 mice consisting of the "Vehicle" control group and the Bromantane treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test.

[0041] Figure 12 shows an evaluation of liver function and disease progression consisting of the Plasma Alanine Aminotransferases (ALT) in units/L for the study groups in a second study of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test;

[0042] Figures 13a, 13b, and 13c show representative photomicrographs of HE-stained liver sections for each of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Upper panels are taken at x50 magnification.

Lower panels are x200 magnification. The identity of each study group is listed above the upper panel in each pair of panels;

[0043] Figure 14 shows the NAFLD activity score for each of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test;

[0044] Figure 15 shows the steatosis score for each of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test;

[0045] Figure 16 shows the lobular inflammation score for each of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test;

[0046] Figure 17 shows the hepatocellular ballooning score for each of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test;

[0047] Figures 18a and 18b shows representative photomicrographs of Sirius red-stained liver sections for each of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and the treatment groups including the positive control treatment group,

Telmisartan. The panels are taken at x200 magnification. The identity of each study group is listed above the upper panel in each pair of panels;

[0048] Figure 19 shows an evaluation of liver function and disease progression consisting of the Fibrosis area, i.e. Sirius red-positive area in percentage of the study groups of C57BL/6 mice consisting of the Normal (no NASH) group, the "Vehicle" control group and the treatment groups including the positive control treatment group, Telmisartan. Mean is indicated ± SD as determined using the Bonferroni multiple comparison test;

[0049] Figure 20 shows a comparison of the change in mean body weight in grams for each of the study groups of C57BL/6 mice a first example consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group, Telmisartan;

[0050] Figure 21 shows an evaluation of renal function consisting of the plasma urea nitrogen (BUN) in mg/dL for each of the study groups of C57BL/6 mice consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group;

[0051] Figure 22 shows an evaluation of renal function consisting of the Creatinine in mg/dL for each of the study groups of C57BL/6 mice consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group;

[0052] Figure 23 shows a comparison of the mean weight difference between the left (ligated UUO) and right (non-ligated) kidneys in grams for each of the study groups of C7BL/6 mice consisting of the sham surgery

control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group, Telmisartan;

[0053] Figure 24 shows an evaluation of renal fibrosis and interstitial damage with the level of fibrosis indicated by Histology Scores of 0 (normal), 1 (light), 2 (moderate) or 3(severe) in three randomly selected fields of renal cross-sections stained with Sirius Red at x20 magnification for each of the study groups of C57BL/6 mice consisting of the sham surgery control group, the surgery vehicle control group, and the treatment groups including the positive control treatment group;

[0054] Figure 25 shows the reduction in renal fibrosis for each the study groups of C57BL/6 mice consisting of the sham surgery control group, the surgery vehicle control group, and the treatment groups including the positive control treatment group;

[0055] Figure 26 shows a comparison of the change in mean body weight in grams for each of the study groups of C57BL/6 mice from a second example consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group, Telmisartan;

[0056] Figure 27 shows an evaluation of renal function consisting of the plasma urea nitrogen (BUN) in mg/dL for each of the study groups of C57BL/6 mice consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group;

[0057] Figure 28 shows an evaluation of renal function consisting of the Creatinine in mg/dL for each of the study groups of C57BL/6 mice

consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group;

[0058] Figure 29 shows the weight of the right kidney in grams for each of the 1 study groups of C57BL/6 mice consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group, Telmisartan;

[0059] Figure 30 shows the weight of the left kidney in grams for each of the study groups of C57BL/6 mice consisting of the sham surgery control group "Sham + Vehicle (Control)", the surgery vehicle control group "Vehicle (Control)", and the treatment groups including the positive control treatment group, Telmisartan;

[0060] Figure 31 shows an evaluation of renal fibrosis and interstitial damage with the level of fibrosis indicated by Histology Scores of 0 (normal), 1 (light), 2 (moderate) or 3(severe) in three randomly selected fields of renal cross-sections stained with Sirius Red at x20 magnification for each of the study groups of C57BL/6 mice consisting of the sham surgery control group, the surgery vehicle control group, and the treatment groups including the positive control treatment group; and

[0061] Figure 32 shows the reduction in renal fibrosis for each the study groups of C57BL/6 mice consisting of the sham surgery control group, the surgery vehicle control group, and the treatment groups including the positive control treatment group.

DETAILED DESCRIPTION

[0062] Without being limited to any particular theory, the inventors believe that compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof act as an actoprotector, has antihypoxic effects, and downregulates HIF1 alpha.

[0063] Adaptation to hypoxia is regulated by hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor consisting of an oxygen-regulated alpha subunit and a constitutively expressed beta subunit. HIF-1 is regulated mainly by oxygen tension through the oxygen-dependent degradation of it's A subunit. Oxygen deprivation initiates a wide range of responses to restore oxygen homeostasis in the affected tissues. These adaptive responses are aimed to increase oxygen supply and compensate for the loss of energy. The transcription factor HIF-1 helps to restore oxygen homeostasis at a cellular, local, and systemic level. HIF-1 functions by regulating many of the genes involved in angiogenesis, erythropoiesis, glycolysis, iron metabolism, and cell survival. In addition to its role in oxygen homeostasis, HIF-1 has been implicated as a critical factor in the pathogenesis of tumor vascularization, and ischemia. Under normoxic conditions, HIF-1a is degraded. Under hypoxic conditions, HIF-1a protein is stabilized and initiates a multistep pathway of activation (Stroka et al., The FASEB Journal, Vol 15, Nov 2001, 2445-2453).

[0064] As employed above and throughout the disclosure, the following terms and abbreviations, unless otherwise indicated, shall be understood to have the following meanings.

[0065] In the present disclosure the singular forms "a," "an," and "the" include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to "a compound" is a reference to

one or more of such compounds and equivalents thereof known to those skilled in the art, and so forth. Furthermore, when indicating that a certain chemical moiety "may be" X, Y, or Z, it is not intended by such usage to exclude in all instances other choices for the moiety; for example, a statement to the effect that R_1 "may be alkyl, aryl, or amino" does not necessarily exclude other choices for R_1, such as halo, aralkyl, and the like.

[0066] When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. As used herein, "about X" (where X is a numerical value) preferably refers to ±10% of the recited value, inclusive. For example, the phrase "about 8" refers to a value of 7.2 to 8.8, inclusive; as another example, the phrase "about 8%" refers to a value of 7.2% to 8.8%, inclusive. Where present, all ranges are inclusive and combinable. For example, when a range of "1 to 5" is recited, the recited range should be construed as including ranges "1 to 4", "1 to 3", "1-2", "1-2 & 4-5", "1-3 & 5", and the like. In addition, when a list of alternatives is positively provided, such listing can be interpreted to mean that any of the alternatives may be excluded, e.g., by a negative limitation in the claims. For example, when a range of "1 to 5" is recited, the recited range may be construed as including situations whereby any of 1, 2, 3, 4, or 5 are negatively excluded; thus, a recitation of "1 to 5" may be construed as "1 and 3-5, but not 2", or simply "wherein 2 is not included." In another example, when a listing of possible substituents including "hydrogen, alkyl, and aryl" is provided, the recited listing may be construed as including situations whereby any of "hydrogen, alkyl, and aryl" is negatively excluded; thus, a recitation of "hydrogen, alkyl, and aryl" may be construed as "hydrogen and aryl, but not alkyl", or simply "wherein the substituent is not alkyl".

[0067] As used herein, the terms "component," "composition of compounds," "compound," "drug," "pharmacologically active agent," "active agent," "therapeutic," "therapy," "treatment," or "medicament" are used

interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action.

[0068] The abbreviations in the specification correspond to units of measure, techniques, properties, or compounds as follows: "min" means minute(s), "g" means gram(s), "mg" means milligram(s), "µg" means microgram(s), "eq" means equivalent(s), "h" means hour(s), "µL" means microliter(s), "mL" means milliliter(s), "mM" means millimolar, "M" means molar, "mmol" or "mmole" means millimole(s), "cm" means centimeters, "SEM" means standard error of the mean, and "IU" means International Units. "IC_{50} value" or "IC_{50}" means dose of the compound which results in 50% alleviation or inhibition of the observed condition or effect.

[0069] As used herein, "alkyl" refers to an optionally substituted, saturated straight, or branched, hydrocarbon radical having from about 1 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein). Where appropriate, "alkyl" can mean "alkylene"; for example, if X is $—R_1R_2$, and R_1 is said to be "alkyl", then "alkyl" may correctly be interpreted to mean "alkylene".

[0070] "Amino" refers to $—NH_2$ and may include one or more substituents that replace hydrogen. "Amino" is used interchangeably with amine and is also intended to include any pharmaceutically acceptable amine salts. For example, amino may refer to $—NH^+(X)(Y)Cl^-$, wherein X and Y are preferably and independently hydrogen or alkyl, wherein alkyl may include one or more halo substitutions.

[0071] As used herein, "aryl", "arene", and "aromatic" each refer to an optionally substituted, saturated or unsaturated, monocyclic, polycyclic, or other homo-, carbo- or heterocyclic aromatic ring system having from about

3 to about 50 ring members (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 5 to about 10 ring atom members being preferred. Such moieties encompass (include) "heteroaryl" and "heteroarene" as defined infra. Where appropriate, "aryl" can mean "arene"; for example, if X is —R_1R_2, and R_1 is said to be "aryl", then "aryl" may correctly be interpreted to mean "arene".

[0072] As used herein, "alkenyl" refers to an alkyl radical having from about 2 to about 20 carbon atoms and one or more double bonds (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein alkyl is as previously defined. In some embodiments, it is preferred that the alkenyl groups have from about 2 to about 6 carbon atoms. Alkenyl groups may be optionally substituted.

[0073] As used herein, "aralkyl" refers to alkyl radicals bearing one or more aryl substituents and having from about 4 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein aryl and alkyl are as previously defined. In some preferred embodiments, the alkyl moieties of the aralkyl groups have from about 1 to about 4 carbon atoms. In other preferred embodiments, the alkyl moieties have from about 1 to about 3 carbon atoms. Aralkyl groups may be optionally substituted.

[0074] "Alkylamino" signifies alkyl-(NH)—, wherein alkyl is as previously described and NH is defined in accordance with the provided definition of amino. "Arylamino" represents aryl-(NH)—, wherein aryl is as defined herein and NH is defined in accordance with the provided definition of amino. Likewise, "aralkylamino" is used to denote aralkyl-(NH)—, wherein aralkyl is as previously defined and NH is defined in accordance with the provided definition of amino. "Alkylamido" refers to alkyl-CH(=O)NH—, wherein alkyl is as previously described. "Alkoxy" as used herein refers to the group R—O— where R is an alkyl group, and alkyl is as previously

described. "Aralkoxy" stands for R—O—, wherein R is an aralkyl group as previously defined. "Alkylsulfonyl" means alkyl-SO_2—, wherein alkyl is as previously defined. "Aminooxy" as used herein refers to the group amino-(O)—, wherein amino is defined as above. "Aralkylaminooxy" as used herein is used to denote aryl-akyl-aminooxy-, wherein aryl, alkyl, and aminooxy are respectively defined as provided previously.

[0075] As used herein, "alkylene" refers to an optionally branched or substituted bivalent alkyl radical having the general formula —$(CH_2)_n$—, where n is 1 to 10. Non-limiting examples include methylene, trimethylene, pentamethylene, and hexamethylene.

[0076] "Alkyleneamino" refers to —$(CH_2)_n$—NH—, where n is 1 to 10 and wherein the bivalent alkyl radical may be optionally branched or substituted, and the amino group may include one or more substituents that replace hydrogen.

[0077] As used herein, "heteroaryl" or "heteroarene" refers to an aryl radical wherein in at least one of the rings, one or more of the carbon atom ring members is independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH, wherein aryl is as previously defined. Heteroaryl/heteroarene groups having a total of from about 3 to about 14 carbon atom ring members and heteroatom ring members are preferred. Likewise, a "heterocyclic ring" is an aryl radical wherein one or more of the carbon atom ring members may be (but are not necessarily) independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH. Heterocyclic rings having a total from about 3 to 14 ring members and heteroatom ring members are preferred, but not necessarily present; for example, "heterocyclohexyl" may be a six-membered aryl radical with or without a heteroatom group.

[0078] "Halo" and "halogen" each refers to a fluoro, chloro, bromo, or iodo moiety, with fluoro, chloro, or bromo being preferred.

[0079] "Haloalkyl" signifies halo-alkyl- wherein alkyl and halo, respectively, are as previously described.

[0080] The phrase reading "[moiety] is absent" may mean that the substituents to which the moiety is attached are directly attached to each other.

[0081] Typically, substituted chemical moieties include one or more substituents that replace hydrogen. As used herein, a "substituent" or "substitution" refers to halo (e.g., F, Cl, Br, I), alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aralkyl, aryl, heteroaryl, heteroaralkyl, spiroalkyl, heterocycloalkyl, hydroxyl (—OH), nitro ($—NO_2$), cyano (—CN), amino ($—NH_2$), —N-substituted amino (—NHR″), —N,N-disubstituted amino (—N(R″)R″), oxo (=O), carboxy (—COOH), —O—C(=O)R″, —C(=O)R″, —OR″, —C(=O)OR″, -(alkylene)-C(=O)—OR″, —NHC(=O)R″, aminocarbonyl ($—C(=O)NH_2$), —N-substituted aminocarbonyl (—C(=O)NHR″), —N,N-disubstituted aminocarbonyl (—C(=O)N(R″)R″), thiol, thiolato (—SR″), sulfonic acid ($—SO_3H$), phosphonic acid ($—PO_3H$), —P(=O)(OR″)OR″, —S(=O)R″, $—S(=O)_2R″$, $—S(=O)_2NH_2$, $—S(=O)_2$ NHR″, $S(=O)_2NR″R″$, $—NHS(=O)_2R″$, $—NR″S(=O)_2R″$, $—CF_3$, $—CF_2CF_3$, —NHC(=O)NHR″, —NHC(=O)NR″R″, —NR″C(=O)NHR″, —NR″C(=O)NR″R″, or —NR″C(=O)R″. In relation to the aforementioned substituents/substitutions, each moiety R″ can be, independently, any of H, alkyl, cycloalkyl, alkenyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl, for example.

[0082] As used herein, the terms "treatment" or "therapy" (as well as different word forms thereof) includes preventative (e.g., prophylactic), curative or palliative treatment.

[0083] As employed above and throughout the disclosure the term "effective amount" refers to an amount effective, at dosages, and for periods of time necessary, to achieve the desired result with respect to the treatment of the relevant disorder, condition, or side effect. It will be appreciated that the effective amount of components of the present invention will vary from patient to patient not only with the particular compound, component or composition selected, the route of administration, and the ability of the components to elicit a desired response in the individual, but also with factors such as the disease state or severity of the condition to be alleviated, hormone levels, age, sex, weight of the individual, the state of being of the patient, and the severity of the pathological condition being treated, concurrent medication or special diets then being followed by the particular patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. Dosage regimens may be adjusted to provide the improved therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the components are outweighed by the therapeutically beneficial effects. As an example, the compounds useful in the methods of the present invention are administered at a dosage and for a time such that the level of activation and adhesion activity of platelets is reduced as compared to the level of activity before the start of treatment.

[0084] "Pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio.

[0085] Within the present invention, the disclosed compounds may be prepared in the form of pharmaceutically acceptable salts. "Pharmaceutically

acceptable salts" refer to derivatives of the disclosed compounds 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 those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. These physiologically acceptable salts are prepared by methods known in the art, e.g., by dissolving the free amine bases with an excess of the acid in aqueous alcohol, or neutralizing a free carboxylic acid with an alkali metal base such as a hydroxide, or with an amine.

[0086] Compounds described herein throughout, can be used or prepared in alternate forms. For example, many amino-containing compounds can be used or prepared as an acid addition salt. Often such salts improve isolation and handling properties of the compound. For example, depending on the reagents, reaction conditions and the like, compounds as described herein can be used or prepared, for example, as their hydrochloride or tosylate salts. Isomorphic crystalline forms, all chiral and racemic forms, N-oxide, hydrates, solvates, and acid salt hydrates, are also contemplated to be within the scope of the present invention.

[0087] Certain acidic or basic compounds of the present invention may exist as zwitterions. All forms of the compounds, including free acid, free

base and zwitterions, are contemplated to be within the scope of the present invention. It is well known in art that compounds containing both amino and carboxy groups often exist in equilibrium with their zwitterionic forms. Thus, any of the compounds described herein throughout that contain, for example, both amino and carboxy groups, also include reference to their corresponding zwitterions.

[0088] "Hydrate" refers to a compound of the present invention which is associated with water in the molecular form, i.e., in which the H—OH bond is not split, and may be represented, for example, by the formula $R.H_2O$, where R is a compound of the invention. A given compound may form more than one hydrate including, for example, monohydrates ($R.H_2O$) or polyhydrates ($R.nH_2O$ wherein n is an integer >1) including, for example, dihydrates ($R.2H_2O$), trihydrates ($R.3H_2O$), and the like, or hemihydrates, such as, for example, $R.n_{/2}H_2O$, $R.n_{/3}H_2O$, $R.n_{/4}H_2O$ and the like wherein n is an integer.

[0089] "Solvate" refers to a compound of the present invention which is associated with solvent in the molecular form, i.e., in which the solvent is coordinatively bound, and may be represented, for example, by the formula R.(solvent), where R is a compound of the invention. A given compound may form more than one solvate including, for example, monosolvates (R.(solvent)) or polysolvates (R.n(solvent)) wherein n is an integer >1) including, for example, disolvates (R.2(solvent)), trisolvates (R.3(solvent)), and the like, or hemisolvates, such as, for example, $R.n_{/2}$(solvent), $R.n_{/3}$(solvent), $R.n_{/4}$(solvent) and the like wherein n is an integer. Solvents herein include mixed solvents, for example, methanol/water, and as such, the solvates may incorporate one or more solvents within the solvate.

[0090] "Acid hydrate" refers to a complex that may be formed through association of a compound having one or more base moieties with at least one compound having one or more acid moieties or through association of a

compound having one or more acid moieties with at least one compound having one or more base moieties, said complex being further associated with water molecules so as to form a hydrate, wherein said hydrate is as previously defined and R represents the complex herein described above.

[0091] The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ as regards the arrangement of the atoms or groups in space.

[0092] "Racemic" means having the capacity for resolution into forms of opposed optical activity.

[0093] As used herein, the term "partial stereoisomer" refers to stereoisomers having two or more chiral centers wherein at least one of the chiral centers has defined stereochemistry (i.e., R or S) and at least one has undefined stereochemistry (i.e., R or S). When the term "partial stereoisomers thereof" is used herein, it refers to any compound within the described genus whose configuration at chiral centers with defined stereochemistry centers is maintained and the configuration of each undefined chiral center is independently selected from R or S. For example, if a stereoisomer has three chiral centers and the stereochemical configuration of the first center is defined as having "S" stereochemistry, the term "or partial stereoisomer thereof" refers to stereoisomers having SRR, SRS, SSR, or SSS configurations at the three chiral centers, and mixtures thereof.

[0094] An "isotopically substituted analogue" is a compound of the present disclosure in which one or more atoms have been replaced with an isotope of that atom. For example, hydrogen (protium) may be substituted with deuterium or tritium. Other atoms that may be replaced with an isotope thereof in order to form an isotopically substituted analogue thereof include, for example, carbon (replaced with C^{13}), nitrogen (replaced with N^{15}), iodine (replaced with I^{131}), fluorine (replaced with F^{18}), or sulfur (replaced with S^{31}).

Any available isotope may be used to form an isotopically substituted analogue thereof, and those of ordinary skill in the art will recognize available techniques for forming such analogues from a given compound.

[0095] "Prodrug" refers to compounds which are themselves inactive or minimally active for the activity desired, but through biotransformation can be converted into biologically active metabolites. For example, a prodrug of the present invention would include, inter alia, any compound which is convertible in vivo by metabolic means to a compound claimed or described in the present disclosure.

[0096] "N-oxide" refers to compounds wherein the basic nitrogen atom of either a heteroaromatic ring or tertiary amine is oxidized to give a quaternary nitrogen bearing a positive formal charge and an attached oxygen atom bearing a negative formal charge.

[0097] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0098] The term "administering" means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the body.

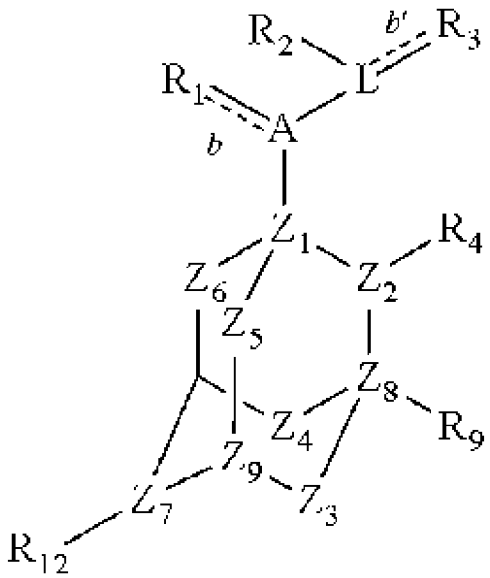
[0099] "Dosage unit" refers to physically discrete units suited as unitary dosages for the particular individual to be treated. Each unit may contain a predetermined quantity of active compound(s) calculated to produce the desired therapeutic effect(s) in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the

invention may be dictated by (a) the unique characteristics of the active compound(s) and the particular therapeutic effect(s) to be achieved, and (b) the limitations inherent in the art of compounding such active compound(s).

[00100] "Subject" or "patient" refers to an embryonic, immature, or adult animal, including the human species, that is treatable with the compositions, and/or methods of the present invention.

[00101] Where any of the groups in the active compounds above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, such groups will be unsubstituted, or substituted by one or two substituents.

[00102] In one embodiment, there a compound:



(Ia)

wherein

A is H, C_{1-3} alkylene or a bond between L and the atom at position Z_1;

L is nitrogen;

R_1 is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b' may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is —(X)(Y);

R_4 is —(R_5)(R_6), halo, is absent, or is —$NR_{13}R_{14}$;

R_5 is nitrogen or oxygen;

R_6 is hydrogen or —(R_7)(R_8)

R_7 is alkylene, —CH(R_{7a})—, —$(CH_2)_{0-6}$CH(OH)—, or represents a bond between R_5 and R_8;

R_{7a} is alkyl;

R_8 is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is —(R_{10})(R_{11}) or is absent;

R_{10} is oxygen, nitrogen, alkyl, —CF_3, or alkylene;

R_{11} is hydrogen, halo, or is absent;

R_{12} is absent, alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, —CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, —CH(Q)-, carbonyl, or a bond;

Q is alkyl, —C(=O)O(CH_2)$_{1-3}$$CH_3$, or —($CH_2$)$_{0-3}$OH;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_1 and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

(i) if A is a bond and R2 is H or absent, except if X is alkynyl, then:
Y is not unsubstituted phenyl, pyridinyl, furanyl, thiopheneyl, pyrrolyl, or benzodioxolyl;
if Y is mono-substituted furanyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, acetylamino, nitro, bromo, chloro, or fluoro;
if Y is mono-substituted phenyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, unsubstituted phenyl, methoxybenzloxy, acetylamino, nitro, bromo, chloro, or fluoro
if Y is mono-substituted thiopheneyl, then the substituent on Y is not methyl, ethyl, chloro, or bromo;
if Y is mono-substituted oxadiazolyl, then the substituent on Y is not methoxyphenyl;
if Y is mono-substituted thiazolyl, then the substituent on Y is not methyl;
if Y is mono-substituted naphthyl, then the substituent on Y is not 1-hydroxyl; and,
if Y is di-substituted phenyl, then the substituents on Y may not both be alkoxy, and,

(ii) if A is C1 alkyl, R1 is NH, and Y is mono-substituted phenyl, then the substituent is not hydroxyl;

R_{13} together with R_{14} and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system, or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof; or
R_{13} is hydrogen; and
R_{14} is a mono-, di-, or tricyclic ring system bearing one or more optional substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl; or

R_{14} is —(R_{15})(R_{16}), wherein R_{15} is alkyl and R_{16} is an optionally substituted mono-, di-, or tricyclic ring system;

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt or prodrug thereof.

[00103] In one embodiment, A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and Y is a carbocyclic ring optionally substituted with one or more substituents independently selected from alkoxy, halo, alkyl, cycloalkyl, hydroxyl, aryl, trifluoromethoxy, trifluoromethyl, alkylsilanyl, alkylsulfanyl, aryloxy, aralkoxy, and hydroxyalkyl.

[00104] In one embodiment, wherein Y is substituted with aryl, aryloxy, or aralkoxy in which the aryl moiety thereof is optionally substituted phenyl, pyrrolidinyl, furanyl, thiopheneyl, oxazolyl, imidazolyl, pyridinyl, naphthyl. isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, thiazolyl, triazolyl, tetrazolyl, morpholinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, cyclopropyl, cyclopentyl, or cyclohexyl.

[00105] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and Y is an unsubstituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[00106] In one embodiment, wherein Y is a six-membered carbocyclic ring that is ortho-fused with a six-membered heterocyclic ring; a six membered heterocyclic ring that is ortho-fused with a six-membered heterocyclic ring; a six membered heterocyclic ring that is ortho-fused with a five-membered heterocyclic ring; a six membered heterocyclic ring that is ortho-fused with a five-membered carbocyclic ring; a six-membered carbocyclic ring that is ortho-fused with a five-membered heterocyclic ring; a pair of ortho-fused five-membered heterocyclic rings; a pair of ortho-fused five-membered carbocyclic rings; or, a single three- to seven-membered carbo- or heterocyclic ring.

[00107] In one embodiment, wherein Y is a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring; a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring; an unsaturated, partly-saturated, or fully-saturated thiophene ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiophene, pyrrole, furan, imidazole, thiazole, or oxazole ring, an unsaturated, partly-saturated, or fully-saturated furan ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiazole or oxazole ring; an unsaturated, partly-saturated, or fully-saturated pyrrole ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiazole or oxazole ring; or, a phenyl ring that is ortho-fused to an unsaturated, partly-saturated, or fully-saturated thiophene, pyridine, imidazole, or furan ring.

[00108] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and Y is a substituted mono-, di-, or tricyclic ring

system that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur.

[00109] In one embodiment, wherein Y is a single three- to seven-membered heterocyclic ring; a single unsaturated, partially saturated, or fully saturated six-membered carbo- or heterocyclic ring; a single unsaturated, partially saturated, or fully saturated five-membered carbo- or heterocyclic ring; a pair of ortho-fused five-membered heterocyclic rings, wherein at least one of said rings is substituted; a pair of ortho-fused six-membered heterocyclic rings, wherein at least one of said rings is substituted; a six-membered heterocyclic ring that is ortho-fused with a six-membered carbocyclic ring, wherein at least one of said rings is substituted; a five-membered heterocyclic ring that is ortho-fused with a five-membered carbocyclic ring, wherein at least one of said rings is substituted; a five-membered heterocyclic ring that is ortho-fused with a six-membered carbocyclic ring, wherein at least one of said rings is substituted; or, a five-membered carbocyclic ring that is ortho-fused with a six-membered heterocyclic ring, wherein at least one of said rings is substituted.

[00110] In one embodiment, wherein said substitutions are independently selected from oxo, hydroxyl, halo, nitro, alkyl, alkoxyalkyl, trifluoromethyl, trifluoromethoxy, cycloalkyl, alkoxy, alkylamino, di-alkylamino, alkoxycarbonylalkyl(alkyl)amino, alkylsulfanyl, alkylsulfanylalkyl, trifluoromethylsulfanyl, cyano, amino, aralkyl, and aryl.

[00111] In one embodiment, wherein Y is substituted with aryl or cycloalkyl, and the aryl or cycloalkyl is isoxazolyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, phenyl, morpholinyl, pyridinyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiopheneyl, furanyl, pyrrolyl, pyrrolidinyl, cyclopropyl, cyclopentyl, or cyclohexyl.

[00112] In one embodiment, wherein Y is a single 5- or 6-membered ring that includes one or more heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein said ring is substituted with one or more of halo, thiopheneyl, alkylthiopheneyl, alkoxythiopheneyl, imidazolyl, imidazolyl substituted with one or both of methyl and trifluoromethyl, tetrahydrofuranyl, furanyl, alkylfuranyl, phenyl, pyridinyl, morpholinomethyl, cyclopropyl, cyclopentyl, cyclohexyl, alkoxy, alkoxyalkyl, alkyl, alkylsulfanyl, alkylsulfanylalkyl, alkylsilanyl, cyano, amino, alkylamino, di-alkylamino, alkoxycarbonylalkyl(alkyl)amino, nitro, alkoxyphenyl, alkylsulfanylphenyl, halophenyl, trifluoromethyl, trifluoromethylphenyl, trifluoromethoxyphenyl, thiazolyl substituted with one or both of methyl and trifluoromethyl, isoxazolyl optionally substituted with methyl, isoxazolinyl, isothiazolyl, isothiazolinyl, oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, morpholinyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, piperadinyl pyrazinyl, or pyrrolyl.

[00113] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and R_9 is —(R_{10})(R_{11}).

[00114] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and R_4 is —(R_5)(R_6).

[00115] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and R_2 is -(D)(E).

[00116] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and Z_7 is alkylene that is substituted with alkyl, hydroxyl, or halo.

[00117] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and Z_7 is alkylene of which one or more carbon atoms is replaced with N, O, or S.

[00118] In one embodiment, wherein A is a bond, R_1 is absent, X is alkylene or —CH(Q)-, and one or more of Z_2-Z_7 is N, O, or S.

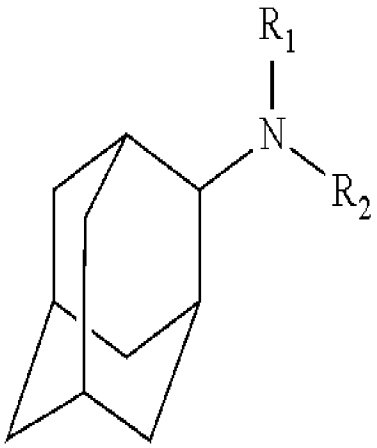
[00119] In one embodiment, wherein A is a bond, R_1 is absent, X is alkenylene or alkynylene, and Y is optionally substituted aryl.

[00120] In some embodiments, R_{14} is a substituted monocyclic ring. In one preferred embodiment, R_{14} is a substituted five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl. Preferably, R_{14} is a halo-substituted six-membered carbocyclic ring. In another preferred embodiment, R_{14} is a bromine-substituted six-membered carbocyclic ring.

[00121] In one embodiment, the compound of formula (Ia) is N-(4-bromophenyl)adamantan-2-amine.

[00122] It is an embodiment of the present invention to provide uses of compound of Formula (Ib):

(Ib)

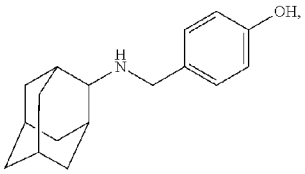


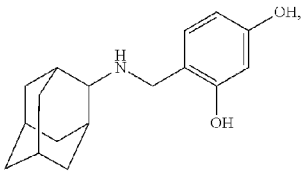
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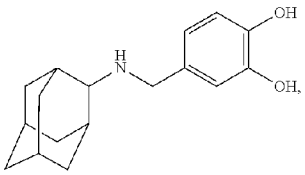
R_1 is hydrogen; and,
R_2 is —(R_3)($R_{4'}$);
R_3 is alkyl or absent; and,
$R_{4'}$ is a substituted mono-, di-, or tricyclic ring system, or,
R_1 together with R_2 and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system,
or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

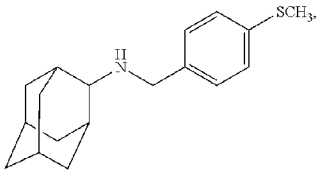
[00123] In some embodiments, $R_{4'}$ is a substituted monocyclic ring. In one preferred embodiment, $R_{4'}$ is a substituted five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl. Preferably, $R_{4'}$ is a halo-substituted six-membered carbocyclic ring. In another preferred embodiment, $R_{4'}$ is a bromine-substituted six-membered carbocyclic ring.

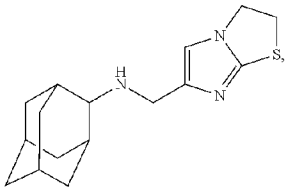
[00124] In one embodiment, the compounds of formula (Ib) include:

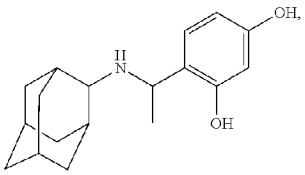


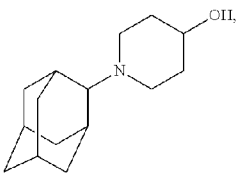


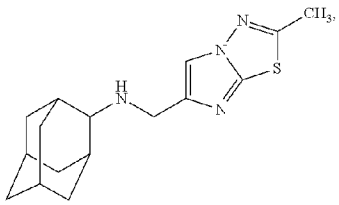












[00125]

[00126] In one embodiment, the compounds of formula (Ia) and (Ib) include compounds as disclosed in US 20150191439 (now patent No. 9884832) which is incorporated by reference in its entirety.

[00127] It has presently been discovered that certain adamantane variants in accordance with the present invention are beneficial in the treatment and/or prevention of various human ailments. These ailments include lung disease, and in particular, chronic lung disease, including idiopathic pulmonary fibrosis; non-alcoholic fatty liver disease, and in particular, non-alcoholic fatty liver disease, non-alcoholic fatty liver, and non-alcoholic steatohepatitis; and kidney disorders, and in particular, renal fibrosis and/or chronic kidney disease.

[00128] The active compounds disclosed herein can, as noted above, be prepared in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

[00129] In one embodiment, the pharmaceutically acceptable salt is selected from the group consisting of Na, K, Li, Ca and Mg salts.

[00130] In one embodiment, a pharmaceutically acceptable prodrug is selected from the group consisting of esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxy derivatives and amino acid conjugates.

[00131] The active compounds described above may be formulated for administration in a pharmaceutical carrier in accordance with known techniques. See, e.g., *Remington, The Science And Practice of Pharmacy* (9th Ed. 1995). In the manufacture of a pharmaceutical formulation according to the invention, the active compound (including the physiologically acceptable salts thereof) is typically admixed with, inter alia, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.01 or 0.5% to 95% or 99% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

[00132] The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), vaginal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), topical (i.e., both skin and mucosal surfaces, including airway surfaces) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

[00133] Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

[00134] Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[00135] When in an orally administered form, the pharmaceutical composition of this invention may comprise conventional excipients such as binders, fillers, thinners, tableting agents, lubricants, disintegrants, coloring agents, flavoring agents and wetting agents. Tablets can be coated when necessary.

[00136] Suitable fillers comprise cellulose, mannitol, lactose, and other similar fillers. Suitable disintegrants comprise starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycolate. Suitable lubricants comprise magnesium stearate. Suitable pharmaceutically acceptable wetting agents comprise sodium lauryl sulfate.

[00137] Orally administered compositions in solid form can be prepared by conventional methods comprising mixing, filling, tableting, etc. Repeated mixing can distribute the active substances throughout those compositions that use large amounts of fillers.

[00138] The orally administered liquid forms can be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or can be a dried product to be reconstituted with water or other suitable carriers before administration. The liquid forms can contain conventional additives, such as suspending agents like sorbitol, syrup, methyl cellulose, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel, or hydrogenated edible fat; emulsifiers like lecithin, sorbitan monooleate or acacia; non-aqueous carriers (which may include edible oils) like almond oil, fractionated coconut oil; oil esters such as esters of glycerol, propylene glycol or ethanol; preservatives such as methyl p-hydroxybenzoate, propyl p-hydroxybenzoate or sorbic acid, and if necessary, may contain conventional flavoring or coloring agents.

[00139] Formulations of the present invention suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The formulations may be presented in unit\dose or multi-dose containers, for

example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. For example, in one aspect of the present invention, there is provided an injectable, stable, sterile composition comprising a compound of Formula (Ia) or (Ib), or a salt thereof, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for injection thereof into a subject. The unit dosage form typically comprises from about 10 mg to about 10 grams of the compound or salt. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent which is physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidyl choline.

[00140] Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[00141] Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

[00142] Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations

suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis\tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

[00143] Further, the present invention provides liposomal formulations of the compounds disclosed herein and salts thereof. The technology for forming liposomal suspensions is well known in the art. When the compound or salt thereof is an aqueous-soluble salt, using conventional liposome technology, the same may be incorporated into lipid vesicles. In such an instance, due to the water solubility of the compound or salt, the compound or salt will be substantially entrained within the hydrophilic center or core of the liposomes. The lipid layer employed may be of any conventional composition and may either contain cholesterol or may be cholesterol-free. When the compound or salt of interest is water-insoluble, again employing conventional liposome formation technology, the salt may be substantially entrained within the hydrophobic lipid bilayer which forms the structure of the liposome. In either instance, the liposomes which are produced may be reduced in size, as through the use of standard sonication and homogenization techniques. Liposomal formulations containing the compounds disclosed herein or salts thereof, may be lyophilized to produce a lyophilizate which may be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension.

[00144] Other pharmaceutical compositions may be prepared from the water-insoluble compounds disclosed herein, or salts thereof, such as aqueous base emulsions. In such an instance, the composition will contain a sufficient amount of pharmaceutically acceptable emulsifying agent to emulsify the desired amount of the compound or salt thereof. Particularly useful emulsifying agents include phosphatidyl cholines, and lecithin.

[00145] In addition to the active compounds, the pharmaceutical compositions may contain other additives, such as pH-adjusting additives. In particular, useful pH-adjusting agents include acids, such as hydrochloric acid, bases or buffers, such as sodium lactate, sodium acetate, sodium phosphate, sodium citrate, sodium borate, or sodium gluconate. Further, the compositions may contain microbial preservatives. Useful microbial preservatives include methylparaben, propylparaben, and benzyl alcohol. The microbial preservative is typically employed when the formulation is placed in a vial designed for multidose use. Of course, as indicated, the pharmaceutical compositions of the present invention may be lyophilized using techniques well known in the art.

[00146] In an embodiment, the amount of compound of Formula (Ia) or (Ib) or a pharmaceutically acceptable salt or prodrug thereof, used is between 0.5 to 200 mg per kg of the subject per day. In a preferred embodiment, the amount of Formula (Ia) or (Ib) or a pharmaceutically acceptable salt or prodrug thereof, used is between 1 to 30 mg per kg of the subject per day. In a further preferred embodiment, the amount of Formula (Ia) or (Ib) or a pharmaceutically acceptable salt or prodrug thereof, used is between 4 to 25 mg per kg of the subject per day. In a yet further preferred embodiment, the amount of Formula (Ia) or (Ib) or a pharmaceutically acceptable salt or prodrug thereof, used is between 8 to 17 mg per kg of the subject per day. In a still further preferred embodiment, the amount of Formula (Ia) or (Ib) or a pharmaceutically acceptable salt or prodrug thereof, used is about 17 mg per kg of the subject per day.

[00147] 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.

[00148] 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.

[00149] The embodiments of the present application described above are intended to be examples only. Those of skill in the art may effect alterations, modifications and variations to the particular embodiments without departing from the intended scope of the present application. In particular, features from one or more of the above-described embodiments may be selected to create alternate embodiments comprised of a subcombination of features which may not be explicitly described above. In addition, features from one or more of the above-described embodiments may be selected and combined to create alternate embodiments comprised of a combination of features which may not be explicitly described above. Features suitable for such combinations and subcombinations would be readily apparent to persons skilled in the art upon review of the present application as a whole. Any dimensions provided in the drawings are provided for illustrative purposes only and are not intended to be limiting on the scope of the invention. The subject matter described herein and in the recited claims intends to cover and embrace all suitable changes in technology.

[00150] **Example 1 – fibrotic lung disease**

[00151] The mouse species or strain is Mouse/C57BL/6, the mice being 8-10 week old males. Nine groups of 10 mice each will be obtained from Charles River Laboratories. Each group will be randomized based on body weight. Bleomycin (BLM) was obtained from Euroasias.

[00152] The mice will be 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 will be provided with TEKLAD 2018-Global 18% diet and Arrowhead drinking water ad libitium.

[00153] The mice will be anesthetized with isoflurane/O2 mixture. Bleomycin (BLM) will then be administered to the mice intratracheally (PennCentury) - single bolus, at 2.5U/kg body weight in 50µl sterile saline.

[00154] Seven days after the bleomycin is administered, and fibroblasts have generally proliferated, groups of IT bleomycin challenged mice will be dosed orally (p.o.) once a day with the active compounds at specified amounts per kg of body weight (mg/kg) daily for 14 consecutive days. The vehicle to used is 0.5% carboxymethyl cellulose (CMC). Vehicle and no-BLM control groups will receive 0.5% CMC orally for 14 consecutive days.

[00155] On day 21 of the study, 4 hours after the last dose, the mice will be 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 will be excised, weighed and fixed in formalin. Gomori's Trichrome stain, a histological stain, will be used to determine collagen content.

[00156] The dose selected for the animal studies will be 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.

[00157] The following measurements and assessments will be taken for each mouse.

[00158] Body Weight: The body weights will be measured over 21 days using a laboratory balance.

[00159] 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.

[00160] Formalin fixed lung samples will be submitted to affiliated histopathology laboratory for histopathological analysis subjected Gomori's Trichrome stain, a histological stain, which will be used to determine collagen content.

[00161] Each lung will be divided into ten sections. All ten sections were stained and evaluated. A board certified veterinarian pathologist will assess 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.

[00162] Mortality Rate: the mortality rate in each group was also observed over 21 days.

[00163] **Example 2 – non-alcoholic steatohepatitis**

[00164] Male newborn C57BL/6 mice will be used. All mice will be born from pathogen-free 14 day-pregnant mice obtained from Japan SLC, Inc. (Hamamatsu, Japan) prior to the start of the study.

[00165] The murine STAM™ model of NASH-HCC will be performed according to previously described methods known in the art (Takakura et al,

Characterization of non-alcoholic steatohepatitis, *Anticancer Res*, 34(9):4849-55 (2014); Fujii et al, (2013)). NASH will be induced in male mice by a single subcutaneous injection of 200 µg of streptozotocin (STZ, Sigma, MO, USA) at 2 days after birth and continuous feeding after 4 weeks of age (day 28 ± 2) with a high fat diet (CLEA Japan Inc, Tokyo, Japan) given *ad libitum*.

[00166] Following induction of NASH, the mice will be randomized study groups of 8 mice each at 6 weeks of age (day 42 ± 2) based on body weight, the day before the start of treatment.

[00167] One day following randomization, the mice will be administered a once-daily oral treatment from 6 weeks of age plus one day (day 43 ± 2, treatment Day 1) to 9 weeks of age (hereinafter known as the "treatment period"). Telmisartan will be used as the positive control. The pharmaceutically acceptable vehicle in all groups was 0.5% carboxymethyl cellulose (CMC). The mice in the remaining study group (hereafter known as the "vehicle control group") will be treated individually with the same pharmaceutically acceptable vehicle with no active ingredient. Individual body weight will be measured daily during the treatment period. Survival, clinical signs and behavior of mice will be also monitored daily.

[00168] In each case, a volume of 10 mL/kg of 0.5% CMC will be administered orally with (or without) the active ingredient as noted in Table 3 from 6 to 9 weeks of age. All mice will then be sacrificed at 9 weeks of age. Blood samples were collected from all mice and the liver from each mouse will be removed for analysis.

[00169] The dose selected for the animal studies will be determined by taking the maximum known human daily dose, dividing by the average weight of an adult (~60-70 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.

[00170] The following measurements and assessments will be taken for each mouse.

[00171] Body weight: The body weight of all mice will be measured daily throughout the treatment period.

[00172] Blood Sample Collection and Biochemical Analysis: Blood will be collected from all sacrificed mice and frozen for further analyses or shipping.

[00173] Plasma Alanine Aminotransferase (ALT): The plasma from each blood sample will be analyzed by FUJI DRI CHEM (Fujifilm, Japan) for alanine aminotransferase (ALT) as an indicator of liver function and disease progression.

[00174] Liver Sample Collection, Biochemical Analysis, and Histological Analysis: The liver will be removed from all sacrificed mice and frozen for further analyses or shipping.

[00175] Liver Weight: Following removal, the livers from all sacrificed mice will be weighed in grams.

[00176] Liver Histopathology: The removed livers will be fixed in formalin and embedded in paraffin, and cross sections (4μm) were then prepared.

[00177] Assessment of Steatohepatitis: Liver cross-sections will be subjected to hematoxylin and eosin (H&E) staining using standard techniques for histological assessment of hepatic steatosis, lobular inflammation and hepatocellular ballooning. The level of steatohepatitis

severity in each liver cross-section will be indicated by NAFLD Activity Scores of: 0 (normal), 1-2 (NAFLD), 3-4 (borderline) or at least 5 (NASH) in 3 randomly selected fields of H&E-stained liver cross-sections of 4µm thickness at x50 magnification for evaluation of steatosis and x200 magnification each for evaluation of inflammation and evaluation of ballooning. The NAFLD Activity Score is the unweighted sum of the following: 1) hepatic steatosis score (0-3); 2) lobular inflammation score (0-2); 3) hepatocellular ballooning score (0-2).

[00178] The liver cross-sections of the Vehicle group, and the treated groups will also be subjected to Sirius-red staining using standard techniques for histological estimation of the percentage of fibrosis area. For quantitative analysis of fibrosis area, bright field images of Sirius red-stained sections were captured around the central vein using a digital camera (DFC295; Leica, Germany) at 200-fold magnification, and the positive areas in 5 fields/section will be measured using ImageJ software (National Institute of Health, USA).

[00179] Statistically significant decreases in the fibrosis area compared with the Vehicle group will be determined by Sirius red-positive areas.

[00180] **Example 3 – fibrotic kidney disease**

[00181] Male 9-12 week old C57BL/6 mice of 23-25 grams body weight were used. All mice (Sirius red-positive area) acclimated for a minimum of 5 days prior to the start of the study and housed individually in microisolators throughout the study in a 12:12 light-dark cycle on a standard maintenance mouse chow diet (Harlan Teklad 2018) with food and water given *ad libitum*. Prior to surgery, all mice (Sirius red-positive area) weighed for baseline body weight.

[00182] The UUO surgical intervention (Sirius red-positive area) performed according to previously described methods known in the art (Le Meur Y et al., *Macrophage accumulation at a site of renal inflammation is dependent on the M-CSF/c-fms pathway*, *J Leukocyte Biol.*, 72:530-537; 2002).

[00183] All mice will be first anesthetized by intraperitoneal injection with a rodent cocktail (ketamine 10mg/mL and Xyaline 1mg/mL) in normal saline (10µL/g body weight). Pedal reflex and movement of the vibrissae will be used to determine the state of unconsciousness. A state of unconsciousness was confirmed after a period of about 5 minutes in all animals. All mice will then be shaved on the left side of the abdomen. The shaved area will be first swabbed with iodine and then swabbed with alcohol. A vertical incision will be made through the skin with a #22 scalpel and the skin will then be retracted. A further incision of about 2.5cm was then made through the peritoneum avoiding any major blood vessels. The peritoneum will be then retracted and the left kidney was exposed.

[00184] The left kidney will be then brought to the surface by hooking the ureter directly beneath the kidney with sterile forceps and gently manipulating the kidney upward. The ureter will be ligated at two points directly below the kidney with 5-0 surgical silk with excess suture cut away and discarded post-ligation. The kidney will be then gently placed back to its correct anatomical position and the abdomen was lavaged with 1mL sterile saline to replenish fluid loss. The peritoneum and then skin will be sutured with 5-0 Mersilene, and the incision site was gently wiped with iodine. All mice will then be placed individually in clean cages that were set on top of a thermal blanket until recovery at about 30-60 minutes later. In some examples, sham surgery will be performed as a control by following all steps of the UUO surgical intervention procedure except ligation.

[00185] Following surgery, the mice will be divided into study groups of 8 mice each and, following post-surgical recovery, administered a once-daily oral treatment for 14 days. The mice in the study groups (hereafter known as "treatment groups") will all receive the UUO surgical ligation and will be treated individually with active compound. The pharmaceutically acceptable vehicle in all groups was 0.5% carboxymethyl cellulose (CMC). All mice will be sacrificed with CO2 on post-surgical day 15.

[00186] The dose selected for the animal studies will be determined by taking the maximum known human daily dose, dividing by the average weight of an adult (~60-70 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.

[00187] The following measurements and assessments will be taken for each mouse.

[00188] Body weight: The body weights will be measured on days 1, 2, 5, 8, 10 and 14 using a laboratory balance.

[00189] Serum collection: A blood sample will be collected from all mice and plasma analyzed for urea nitrogen and creatinine. Plasma was stored at -80 °C for possible future analysis.

[00190] Kidney weight: The UUO will be examined in situ to ensure that the surgical ligation ties remained patent. Both the ligated (UUO) and non-ligated kidneys were removed for analysis. Weights of both kidneys will be measured using a laboratory balance.

[00191] Histopathology: Formalin-fixed kidney cross-section samples will be subjected histopathological scoring with Sirius Red staining, and

imaged at a magnification of x20, using standard techniques. All three sections were stained and evaluated. The analysis was performed by a board-certified veterinarian pathologist. The presence of interstitial damage and severity score was assessed according to the following criteria: 0= normal, 1= light, 2= moderate, 3= severe.

[00192] **Results – Bromantane treatment and fibrotic lung disease**

[00193] Dosing

[00194] Table 1

	Groups	Once daily oral dosing mg/kg
1	Normal (no BLM)	N/A
2	Prifenidone (+)	300 (as per BMC Pulm Med. 2017 Apr 18;17(1):63)
3	Vehicle (-)	N/A
4	Bromantane	20

[00195] 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.

[00196] 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.

[00197] The following measurements and assessments were taken for each mouse.

[00198] Body Weight: The body weights were measured over 21 days using a laboratory balance.

[00199] 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.

[00200] 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.

[00201] 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.

[00202] Mortality Rate: the mortality rate in each group was also observed over 21 days.

[00203] Body Weight

[00204] The changes in body weights are presented in Figure 1, Tables 2 and 3 and Appendix A. The decrease in body weight (grams) were observed from day 1 till day 5 and then started recovering. Bromantane (20 mg/kg) showed improvement beginning Day 5, with the exception of Day 15 as compared to the BLM-vehicle group. Unexpectedly, the Pirfenidone group (300 mg/kg) showed significant deterioration in body weight throughout the trial.

[00205] Table 2 Body Weight (g)

	Normal (no BLM)	Pirfenidone (+)	Vehicle (-)	Bromantane
7-Nov	23.6	24	25.1	24.8
8-Nov	24	24.2	24.2	24.7
9-Nov	24	23.5	23.3	24
12-Nov	24.5	21.7	22.9	23.1
14-Nov	25.1	21	23	23.7
16-Nov	25.3	20.8	22.8	23.3
20-Nov	25.9	20.3	23	22.9
22-Nov	26.9	21.1	23.9	23.2
26-Nov	27.6	20.9	24.1	23.8
28-Nov	27.8	20.7	24.3	25.2

[00206] Table 3 Percent Change in Body Weight

	Normal (no BLM)	Pirfenidone (+)	Vehicle (-)	Bromantane
7-Nov	0	0	0	0
8-Nov	0.3	0.3	-1	-0.1
9-Nov	0.3	-0.5	-1.8	-0.8
12-Nov	0.8	-2.2	-2.2	-1.8
14-Nov	1.4	-2.9	-2.1	-1.1

16-Nov	1.7	-3.2	-2.3	-1.5
20-Nov	2.3	-3.7	-2.2	-1.9
22-Nov	3.3	-2.9	-1.2	-1.6
26-Nov	4	-3.1	-1	-1
28-Nov	4.1	-3.2	-0.8	0.4

[00207] Trichrome Score

[00208] The Trichrome score data are presented in Figure 2, Table 4 and Appendix B.

[00209] Table 4: 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

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

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

[00210] Percent Survival

[00211] Mortality is an important endpoint for IPF patients. The percent survival data is presented in Table 5.

[00212] Table 5: Survival Data

	Fatality Number	Percent Fatality
Normal (no BLM)	0/10	0
Pirfenidone (+)	2/10	20%
Vehicle (-)	2/10	20%
Bromantane	3/10	30%

[00213] Overall

[00214] The fibrosis percent reduction analysis is presented in Figure 3 and Appendix C.

[00215] In conclusion, oral administration of Bromantane showed improvement in lung fibrosis as well as in the loss of body weight and Trichrome score as compared to BLM-vehicle.

[00216] 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.

[00217] **Results – Bromantane treatment and non-alcoholic steatohepatitis – experiment 1**

[00218] Male newborn C57BL/6 mice were used. All mice were born from pathogen-free 14 day-pregnant mice obtained from Japan SLC, Inc. (Hamamatsu, Japan) prior to the start of the study.

[00219] The murine STAM™ model of NASH-HCC was performed according to previously described methods known in the art (Takakura et al, *Characterization of non-alcoholic steatohepatitis*, *Anticancer Res*, 34(9):4849-55 (2014); Fujii et al, (2013)). NASH was induced in male mice by a single subcutaneous injection of 200 µg of streptozotocin (STZ, Sigma, MO, USA) at 2 days after birth and continuous feeding after 4 weeks of age (day 28 ± 2) with a high fat diet (CLEA Japan Inc, Tokyo, Japan) given *ad libitum*.

[00220] Following induction of NASH, the mice were randomized into individual study groups of 8 mice each at 6 weeks of age (day 42 ± 2) based on body weight, the day before the start of treatment.

[00221] One day following randomization, the mice were administered a once-daily oral treatment from 6 weeks of age plus one day (day 43 ± 2, treatment Day 1) to 9 weeks of age (hereinafter known as the "treatment period". The mice in "treatment groups" were treated individually with a distinct pharmacologic compound formulated with a pharmaceutically acceptable vehicle. The pharmacologic compound were either test agents or Telmisartan as the positive control. The pharmaceutically acceptable vehicle in all groups was 0.5% carboxymethyl cellulose (CMC). The mice in the remaining study group (hereafter known as the "vehicle control group") were treated individually with the same pharmaceutically acceptable vehicle with no active ingredient. Individual body weight was measured daily during the treatment period. Survival, clinical signs and behavior of mice were also monitored daily.

[00222] Dosing

[00223] Table 6a

	Groups	**Once daily oral dosing mg/kg**
1	Normal (no NASH)	N/A
2	Telmisartan (+)	10
3	Vehicle (-)	N/A
4	Bromantane	20

[00224] In each case, a volume of 10 mL/kg of 0.5% CMC was administered orally with (or without) the active ingredient as noted in Table 6a from 6 to 9 weeks of age until sacrifice. All mice were then sacrificed at 9 weeks of age. Blood samples were collected from all mice and the liver from each mouse was removed for analysis.

[00225] 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 (~60-70 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.

[00226] The following measurements and assessments were taken for each mouse.

[00227] Body weight: The body weight of all mice were measured daily throughout the treatment period.

[00228] Blood Sample Collection and Biochemical Analysis: Blood was collected from all sacrificed mice and frozen for further analyses or shipping.

[00229] Plasma Alanine Aminotransferase (ALT): The plasma from each blood sample was analyzed by FUJI DRI CHEM (Fujifilm, Japan) for alanine aminotransferase (ALT) as an indicator of liver function and disease progression.

[00230] Liver Sample Collection, Biochemical Analysis, and Histological Analysis: The liver was removed from all sacrificed mice and frozen for further analyses or shipping.

[00231] Liver Weight: Following removal, the livers from all sacrificed mice were weighed in grams.

[00232] Liver Histopathology: The removed livers were fixed in formalin and embedded in paraffin, and cross sections (4μm) were then prepared.

[00233] Assessment of Steatohepatitis: Liver cross-sections were subjected to hematoxylin and eosin (H&E) staining using standard techniques for histological assessment of hepatic steatosis, lobular inflammation and hepatocellular ballooning. The level of steatohepatitis severity in each liver cross-section was indicated by NAFLD Activity Scores of: 0 (normal), 1-2 (NAFLD), 3-4 (borderline) or at least 5 (NASH) in 3 randomly selected fields of H&E-stained liver cross-sections of 4μm thickness at x50 magnification for evaluation of steatosis and x200 magnification each for evaluation of inflammation and evaluation of ballooning. The NAFLD Activity Score is the unweighted sum of the following: 1) hepatic steatosis score (0-3); 2) lobular inflammation score (0-2); 3) hepatocellular ballooning score (0-2).

[00234] The liver cross-sections were also subjected to Sirius-red staining using standard techniques for histological estimation of the percentage of fibrosis area. For quantitative analysis of fibrosis area, bright field images of Sirius red-stained sections were captured around the central

vein using a digital camera (DFC295; Leica, Germany) at 200-fold magnification, and the positive areas in 5 fields/section were measured using ImageJ software (National Institute of Health, USA).

[00235] Statistical Analysis

[00236] Values are arithmetic means. Comparison between the study group and positive control group was performed using a two-tailed, heteroscedastic (two-sample unequal variance) Student's T-Test. A *P*-value of < 0.05 was considered statistically significant following a Bonferroni post-hoc statistical correction analysis for multiple groups (Bonferroni Multiple Comparison Test). In this case, the correction factor was 12, corresponding to the number of study groups. Following the usual convention, the *P*-value classification and statistical significance levels chosen are shown in Table 2 alongside their corresponding classification scores.

[00237] Results

[00238] Liver Function Evaluation: Liver function and disease progression was evaluated by Plasma ALT as previously described. Results are shown in FIG. 4 and Appendix D.

[00239] Steatohepatitis Evaluation: Steatohepatitis and disease progression was evaluated by H&E-staining of liver cross-sections as previously described. Representative photomicrographs of HE-stained liver sections for each of the 12 study groups are shown in FIGS. 5a-5c.

[00240] The NAFLD Activity Score of each study group consisted of the NAFLD Activity Score average of all mice in each study group. Scores were determined based on the steatosis score, lobular inflammation score and hepatocellular ballooning score for each animal. Results are shown in FIGS. 6-9 and Appendix "E".

[00241] Steatohepatitis and disease progression was also evaluated by Sirius-red staining of liver cross-sections as previously described. Representative photomicrographs of Sirius red-stained liver sections for Vehicle, Bromantane, and Telmisartan study groups are shown in Figure 10. Results are shown in FIG. 11.

[00242] Statistically significant reductions in NAFLD activity score relative to Vehicle control were observed for the Bromantane treatment group, as well as for the Telmisartan positive control. Statistically significant reductions in hepatocellular ballooning score relative to Vehicle control were observed for the Bromantane treatment group.

[00243] The Bromantane group showed significant decreases in the fibrosis area (Sirius red-positive area) compared with the Vehicle group. The fibrosis area in the Telmisartan group tended to decrease compared with the Vehicle group. Liver sections from the Vehicle group showed increased collagen deposition in the pericentral region of liver lobule.

[00244] The statistically significant and clinically relevant composite reduction in NAFLD Activity Scores for Bromantane suggest this compound could be useful in preventing and/or treating NASH and its sequelae.

[00245] **Results – Bromantane treatment and non-alcoholic steatohepatitis – experiment 2**

[00246] As before, male newborn C57BL/6 mice were used. All mice were born from pathogen-free 14 day-pregnant mice obtained from Japan SLC, Inc. (Hamamatsu, Japan) prior to the start of the study.

[00247] The murine STAM™ model of NASH-HCC was performed according to previously described. NASH was induced in male mice by a single subcutaneous injection of 200 μg of streptozotocin (STZ, Sigma, MO,

USA) at 2 days after birth and continuous feeding after 4 weeks of age (day 28 ± 2) with a high fat diet (CLEA Japan Inc, Tokyo, Japan) given *ad libitum*.

[00248] Following induction of NASH, the mice were randomized into individual study groups of 8 mice each at 6 weeks of age (day 42 ± 2) based on their body weight, the day before the start of treatment.

[00249] One day following randomization, the mice were administered a once-daily oral treatment from 6 weeks of age plus one day (day 43 ± 2, treatment Day 1) to 9 weeks of age. The mice in study groups were treated individually with a therapeutic amount of a pharmacologic compound formulated with a pharmaceutically acceptable vehicle. The pharmacologic compound that each of these groups received were either test agents or Telmisartan as the positive control. The pharmaceutically acceptable vehicle in all groups was 0.5% CMC. The mice in the remaining study group, the vehicle control group, were treated individually with the same pharmaceutically acceptable vehicle with no active ingredient. Individual body weight was measured daily during the treatment period. Survival, clinical signs and behavior of mice were also monitored daily.

[00250] Dosing

[00251] Table 6b

	Groups	**Once daily oral dosing mg/kg**
1	Normal (no NASH)	N/A
2	Telmisartan (+)	10
3	Vehicle (-)	N/A
4	Bromantane	20
5	Bromantane	40

[00252] In each case, a volume of 10 mL/kg of 0.5% CMC was administered orally with (or without) the active ingredient as noted in Table 6b from 6 to 9 weeks of age. All mice were then sacrificed at 9 weeks of age. Blood samples were collected from all mice and the liver from each mouse was removed for analysis. Measurements and assessments were taken for each mouse as described above.

[00253] Results

[00254] Liver Function Evaluation: Liver function and disease progression was evaluated by Plasma ALT as previously described. Results are shown in Figure 12 and Appendix F.

[00255] Steatohepatitis Evaluation: Steatohepatitis and disease progression was evaluated by H&E-staining of liver cross-sections as previously described. Representative photomicrographs of HE-stained liver sections for each of the study groups are shown in Figures 13a, 13b, and 13c.

[00256] The NAFLD Activity Score of each study group consisted of the NAFLD Activity Score average of all mice in each study group. Scores were determined based on the steatosis score, lobular inflammation score and hepatocellular ballooning score for each animal. Results are shown in Figures 14-17 and Appendix G.

[00257] Statistically significant reductions in NAFLD activity score relative to Vehicle control were observed for the Bromantane high group, as well as for the Telmisartan positive control. Statistically significant reductions in steatosis score relative to Vehicle control were observed for the

Bromantane high treatment group, as well as for the Telmisartan positive control.

[00258] Significantly, all of the study groups, including the Bromantane low, Bromantane high, showed statistically significant decreases in the fibrosis area (Sirius red-positive area) compared with the Vehicle group. The fibrosis area in the Telmisartan group also tended to decrease compared with the Vehicle group. Results are shown in FIGS 18a and 18b, and 19.

[00259] In conclusion, administration of bromantane showed improvement in reducing the NAFLD Activity Scores, hepatic steatosis, lobular inflammation and hepatocellular ballooning and may be useful in the prophylaxis and/or treatment of NASH.

[00260] **Results – Bromantane treatment and fibrotic kidney disease – experiment 1**

[00261] Dosing

[00262] Table 7

Group	Description	N	ROA	Dose mg/kg	Dosing Volume	Dosing Frequency
1	Sham + vehicle (0.5% CMC)	8	PO	xxxx	10 ml/kg	QD Days 1-14
2	Surgery + Vehicle	8	PO	xxxx	10 ml/kg	QD Days 1-14
3	Surgery + Telmisartan	8	PO	5	10 ml/kg	QD Days 1-14
4	Surgery + Bromantane	8	PO	20	10 ml/kg	QD Days 1-14

[00263] 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 (~60-70 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.

[00264] The following measurements and assessments were taken for each mouse.

[00265] Body weight: The body weights were measured on days 1, 2, 5, 8, 10 and 14 using a laboratory balance.

[00266] Serum collection: A blood sample was then collected from all mice and plasma analyzed for urea nitrogen and creatinine. Plasma was stored at -80 °C for possible future analysis.

[00267] Kidney weight: The UUO was then examined in situ to ensure that the surgical ligation ties remained patent. Both the ligated (UUO) and non-ligated kidneys were removed for analysis. Weights of both kidneys were measured using a laboratory balance.

[00268] Histopathology: Formalin-fixed kidney cross-section samples were subjected histopathological scoring with Sirius Red staining, and imaged at a magnification of x20, using standard techniques. All three sections were stained and evaluated. The analysis was performed by a board-certified veterinarian pathologist. The presence of interstitial damage and severity score was assessed according to the following criteria: 0= normal, 1= light, 2= moderate, 3= severe.

[00269] Values are arithmetic means. Comparison between the study group and positive control group was performed using a two-tailed,

heteroscedastic (two-sample unequal variance) Student's T-Test. A p-value of <0.05 was considered statistically significant.

[00270] Results

[00271] **Body Weight Evaluation:** Results of the evaluation of mean body weight change are shown in Figure 20 and Table 8. Body weights were measured on post-surgical days 1, 2, 5, 8, 10 and 14 as previously described. The mean body weight change of each study group was calculated using the body weight average of all mice in each study group.

[00272] Table 8. Mean Body Weight Change Following Surgery (g)

	Days Post Surgery					
	1	2	5	8	10	14
Sham + Vehicle	0	-0.86	-0.14	-0.02	0.60	1.44
Vehicle	0	-0.71	-1.68	-0.07	0.32	0.90
Telmisartan 5mg/kg (Positive Control)	0	-1.09	-1.96	-0.80	-0.64	-0.13
Bromantane 20mg/kg	0	-0.45	0.06	0.01	0.60	0.89

[00273] Bromantane treatment showed an initial decrease in mean body weight change followed by an increase in mean body weight change until sacrifice. The mean body weight change on post-surgical day 14 with bromantane treatment showed a more positive value than the positive control treatment group (Telmisartan). See FIG 20.

[00274] **Renal Function Evaluation**: Renal function and disease progression was evaluated by BUN (blood urea nitrogen) as previously

described. The BUN of each study group consisted of the BUN average of all mice in each study group. Results are shown in Figures 21 and 22 and Table 9.

[00275] Table 9

Treatment	**BUN mg/dL**	**Creatinine mg/dL**
Sham + Vehicle	19.125	0.20
Vehicle	25.425	0.25
Telmisartan 5mg/kg (Positive Control)	20.9	0.20
Bromantane 200mg/kg	16.2*#	0.20
Note. Table 9 and in Table 11: * - $p < 0.05$ compared to vehicle (Bonferroni post-test); # - $p < 0.05$ compared to vehicle (Tamhane post-test)		

[00276] The BUN was decreased in comparison to the surgery vehicle control group and the positive control treatment group. This indicated that bromantane had less renal dysfunction and disease progression than the positive control treatment with Telmisartan, the current gold standard for treatment of renal fibrosis.

[00277] The BUN for treatment bromantane was decreased in comparison to the sham surgery control group. This indicated that treatment resulted in an improved renal function as compared to the study group that did not receive any surgical ligation (UUO). In particular, bromantane (20 mg/kg) showed significant reductions in the levels of BUN compared to vehicle ($p < 0.05$, Tamhane post-test). The positive control, Telmisartan (5

mg/kg), did not show a significant reduction compared to the vehicle. See FIG 21.

[00278] Serum creatinine was also reduced by bromantane treatment as compared to vehicle. See FIG 22.

[00279] **Kidney Weight Evaluation:** Kidney weight indicating, which indicates functional and pathological changes in the kidney, was evaluated by measuring the weight of both the ligated (UUO) and non-ligated kidneys as previously described. The ligated and non-ligated kidney weights of each study group consisted of the respective kidney weight averages of all mice in each study group. Results are shown in Table 10 and Figure 23.

[00280] Table 10

	L-kidney	R-kidney	Difference (L – R), g	Reduction
Sham + Vehicle	0.129	0.136	-0.007	-
Vehicle	0.520	0.146	0.374	-
Telmisartan 5mg/kg (Positive Control)	0.265	0.128	0.137	63%
Bromantane 20mg/kg	0.501	0.141	0.359	4%

[00281] The ligated kidney weights for the bromantane treatment and surgery vehicle control group were increased in comparison to the sham surgery control group. The increase in weight of the ligated kidney in comparison to the non-ligated kidney was greater as compared to the positive control treatment group. In particular, the positive control Telmisartan (5 mg/kg) showed the greatest numerical reduction in the disparity between the two kidneys.

[00282] **Renal Fibrosis Evaluation:** Renal fibrosis and interstitial damage was evaluated by histochemical staining of renal cross-sections with Sirius Red as previously described. The Histology Score of each study group consisted of the histology score average of all mice in each study group. Results are shown in Table 11 and Figures 24 and 25.

[00283] Table 11

	Histology Score	% Reduction Fibrosis (vs vehicle)
Sham + Vehicle	0.00	100%
Vehicle	2.27	0%
Telmisartan 5mg/kg (Positive Control)	1.31	42%
Bromantane 20mg/kg	1.88	17%

[00284] The p-values of all treatment groups were statistically significant.

[00285] The Histology Scores for the Bromantane (20 mg/kg) treatment group was significantly decreased in comparison to the positive control treatment group Telmisartan.

[00286] Oral administration of Bromantane at 20 mg/kg showed significant reductions in BUN compared to vehicle,

[00287] **Results – Bromantane treatment and fibrotic kidney disease – experiment 2**

[00288] In this example, healthy young female C57BL/6 mice were used for the study. At the commencement of the study, mice were between 9-12

weeks of age, weighing 23-25g. All the mice were obtained from Charles River Laboratories.

[00289] The mice were maintained in a controlled environment with a temp 70-72° F, humidity 30-70 %, with a photo cycle of 12 hours of light and 12 hours of dark. They were provided with Harlan Teklad 2018 standard maintenance mouse chow diet and drinking water *ad libitium*.

[00290] After five days of acclimatization, the mice were grouped according to their body weight. Ten mice were in each study group and each underwent UUO as described above and ten mice underwent a sham procedure to serve as a no-surgery control.

[00291] Following surgery, the mice were divided into individual study groups of 10 mice each and, following post-surgical recovery, administered a once-daily oral treatment for 14 days. The mice in the study groups had all received the UUO surgical ligation and were treated individually with a distinct pharmacologic compound as set out in Table 12. The mice in 2 of the study groups were treated individually with a pharmaceutically acceptable vehicle with no active ingredient. The pharmaceutically acceptable vehicle in all groups was 0.5% carboxymethyl cellulose (CMC). All mice were sacrificed with CO2 on post-surgical day 15.

[00292] Dosing

[00293] Table 12

Group	Description	N	ROA	Dose mg/kg	Dosing Volume	Dosing Frequency
1	Sham + vehicle (0.5% CMC)	10	PO	xxxx	10 ml/kg	QD Days 1-14
2	Surgery + Vehicle	10	PO	xxxx	10 ml/kg	QD Days 1-14
3	Surgery + Telmisartan	10	PO	3	10 ml/kg	QD Days 1-14
4	Surgery + Bromantane	10	PO	40	10 ml/kg	QD Days 1-14

[00294] 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 (~60-70 kg) to get a human mg/kg dose. 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.

[00295] Measurements

[00296] The following measurements and assessments were taken for each mouse.

[00297] Body weight: The body weights were measured on days 1, 4, 7, 10 and 14 using a laboratory balance.

[00298] Serum collection: A blood sample was then collected from all mice and plasma analyzed for urea nitrogen and creatinine. Plasma was stored at -80 °C for possible future analysis.

[00299] Kidney weight: The UUO was then examined in situ to ensure that the surgical ligation ties remained patent. Both the ligated (UUO) and non-ligated kidneys were removed for analysis. Weights of both kidneys were measured using a laboratory balance.

[00300] Histopathology: Formalin-fixed kidney cross-section samples were subjected histopathological scoring with Sirius Red staining, and imaged at a magnification of x20, using standard techniques. All three sections were stained and evaluated. The analysis was performed by a board-certified veterinarian pathologist. The presence of interstitial damage and severity score was assessed according to the following criteria: 0= normal; 1= light; 2= moderate; 3= severe.

[00301] The data are presented as the mean obtained from Microsoft Excel or GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA). Data were analyzed using two-way ANOVA using Bonferroni and Tamhane post-tests. Differences between groups were considered significant at $p < 0.05$.

[00302] Results

[00303] **Body Weight Evaluation:** Results of the evaluation of mean body weight change are shown in Figure 18 and Table 13. Body weights were measured on post-surgical days 1, 4, 7, 10 and 14 as previously described. The mean body weight change of each study group was calculated using the body weight average of all mice in each study group.

[00304] Table 13. Mean Body Weight Change Following Surgery (g)

Group	Treatment	Change in body weight				
		Day 1	Day 4	Day 7	Day 10	Day 14
1	Sham + Vehicle	0	0.16	0.22	0.59	0.88
2	Vehicle	0	-0.41	0.46	0.68	0.86
3	Telmisartan (3 mg/kg)	0	-0.24	0.39	0.45	0.58
4	Bromantane (40 mg/kg)	0	0.11	0.36	0.15	0.55

[00305] A decrease in body weight gains was observed for the first 4 days in the vehicle group, after which these gains began to recover. With Bromantane (40 mg/kg) there was no initial decrease in body weight, and weight gain continued for the duration of the experiment.

[00306] **Renal Function Evaluation**: Renal function and disease progression was evaluated by BUN (blood urea nitrogen) as previously described. The BUN of each study group consisted of the BUN average of all mice in each study group. Results are shown in Figure 27 and Table 14.

[00307] Table 14. Results of Renal Function Evaluation.

Group	Treatment	BUN	Creatinine
1	Sham + Vehicle	19.4	0.20
2	Vehicle	23.3	0.21
3	Telmisartan (3 mg/kg)	23.5	0.20
4	Bromantane (40 mg/kg)	17.3*#	0.20

[00308] For Table 14: * - significantly different from vehicle following a Bonferroni post-hoc test; # - following a Tamhane post-hoc test ($p < 0.05$)

[00309] The urea nitrogen (BUN) and creatinine data are presented in Figures 27 & 28 and Table 14, respectively. Administration of Bromantane (40 mg/kg) led to significant reductions in the level of BUN compared to vehicle. The positive control Telmisartan did not reduce levels of BUN, and when combined with Bromantane appeared to mitigate the ability of these agents to reduce BUN levels. Bromantane was found to be superior to Telmisartan. There were no differences in the levels of serum creatinine in any of the groups tested.

[00310] **Kidney Weight Evaluation:** Kidney weight, which indicates functional and pathological changes in the kidney, was evaluated by measuring the weight of both the ligated (UUO) and non-ligated kidneys as previously described. The ligated and non-ligated kidney weights of each study group consisted of the respective kidney weight averages of all mice in each study group. Results are shown in Table 15 and Figures 29 and 30.

[00311] Table 15. Kidney Weights for Study Groups.

Gp	Treatment	Excised Left Kidney (g)	Drained Left Kidney (g)	Right Kidney (g)
1	Sham + Vehicle	0.106	0.106	0.1116
2	Vehicle	0.5054	0.2325	0.1888
3	Telmisartan (3 mg/kg)	0.411	0.1853*	0.1263*
4	Bromantane (40 mg/kg)	0.3995	0.1775	0.143*

[00312] For Table 15: * - significantly different from vehicle following a Bonferroni post-hoc test.

[00313] The weight of the left (ligated) kidney in the vehicle group was greatly increased. Bromantane (40 mg/kg) effected numerical reductions in the weight of the left kidney. During the experiment, the vehicle group also saw a significant increase in the weight of the right (unligated) kidney. All of the treatments tested were able to significantly reduce the weight of this organ.

[00314] **Renal Fibrosis Evaluation:** Renal fibrosis and interstitial damage was evaluated by histochemical staining of renal cross-sections with Sirius Red as previously described. The Histology Score of each study group consisted of the histology score average of all mice in each study group. Results are shown in Table 16 and Figures 31 and 32.

[00315] Table 16. Histology

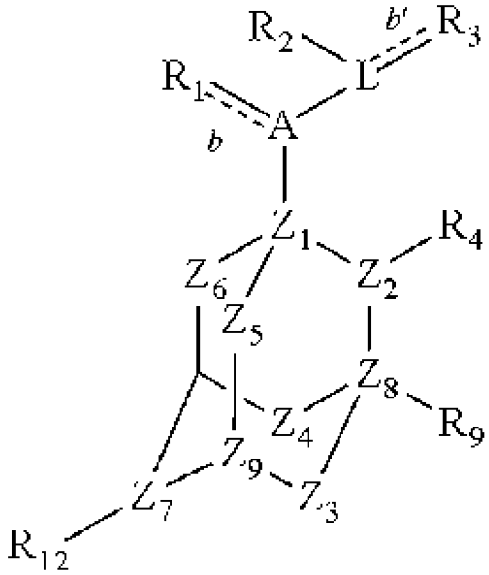
Group	Treatment	Histology Score	Reduction of fibrosis (%) (versus vehicle)
1	Sham + Vehicle	0.00	100%
2	Vehicle	2.40	0%
3	Telmisartan (3 mg/kg)	1.62*#	33%
4	Bromantane (40 mg/kg)	1.02*#	58%

[00316] Bromantane (40 mg/kg) was able to significantly reduce the level of kidney fibrosis compared to vehicle and BUN compared to vehicle, and appeared to reverse the negative effects of UUO on body weight gain.

[00317] Oral administration of Telmisartan at 3 mg/kg did not show significant reductions in BUN levels or fibrosis.

CLAIMS

1. Use of a compound of formula (Ia) for treating one or more of lung disease; non-alcoholic fatty liver disease; and kidney disorder:



(Ia)

wherein

A is H, C_{1-3} alkylene, or a bond between L and the atom at position Z_1;

L is nitrogen;

R_1 is NH, NH_2, alkyl, or, if A is a bond, is absent;

dashed lines b and b′ may independently represent a double bond;

R_2 is H, alkyl, -(D)(E), or is absent;

R_3 is —(X)(Y);

R_4 is —(R_5)(R_6), halo, is absent, or is —$NR_{13}R_{14}$;

R_5 is nitrogen or oxygen;

R_6 is hydrogen or —(R_7)(R_8)

R_7 is alkylene, —$CH(R_{7a})$—, —$(CH_2)_{0-6}CH(OH)$—, or represents a bond between R_5 and R_8;

R_{7a} is alkyl;

R_8 is optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

R_9 is —(R_{10})(R_{11}) or is absent;

R_{10} is oxygen, nitrogen, alkyl, —CF_3, or alkylene;

R_{11} is hydrogen, halo, or is absent;

R_{12} is absent, alkyl, alkoxy, halo, oxo, or hydroxyl;

D is alkylene, alkenylene, alkynylene, —CH(Q)-, carbonyl, or a bond;

E is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

X is alkylene, alkenylene, alkynylene, —CH(Q)-, carbonyl, or a bond;

Q is alkyl, —$C(=O)O(CH_2)_{1-3}CH_3$, or —$(CH_2)_{0-3}OH$;

Y is an optionally substituted mono-, di-, or tricyclic ring system that optionally includes one or more heteroatoms;

Z_2 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_1 and Z_8;

Z_3 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S, or represents a bond between Z_8 and Z_9;

Z_4, Z_5, and Z_6 are independently alkylene, N, O, or S;

Z_7 is optionally substituted alkylene of which one or more carbon atoms is optionally replaced with N, O, or S;

(i) if A is a bond and R2 is H or absent, except if X is alkynyl, then:

Y is not unsubstituted phenyl, pyridinyl, furanyl, thiopheneyl, pyrrolyl, or benzodioxolyl;

if Y is mono-substituted furanyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, acetylamino, nitro, bromo, chloro, or fluoro;

if Y is mono-substituted phenyl, then the substituent on Y is not methyl, hydroxyl, methanolyl, alkoxy, unsubstituted phenyl, methoxybenzloxy, acetylamino, nitro, bromo, chloro, or fluoro

if Y is mono-substituted thiopheneyl, then the substituent on Y is not methyl, ethyl, chloro, or bromo;

if Y is mono-substituted oxadiazolyl, then the substituent on Y is not methoxyphenyl;

if Y is mono-substituted thiazolyl, then the substituent on Y is not methyl;

if Y is mono-substituted naphthyl, then the substituent on Y is not 1-hydroxyl; and,

if Y is di-substituted phenyl, then the substituents on Y may not both be alkoxy, and,

(ii) if A is C1 alkyl, R1 is NH, and Y is mono-substituted phenyl, then the substituent is not hydroxyl;

R_{13} together with R_{14} and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system, or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof; or

R_{13} is hydrogen; and

R_{14} is a mono-, di-, or tricyclic ring system bearing one or more optional substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl; or

R_{14} is —(R_{15})(R_{16}), wherein R_{15} is alkyl and R_{16} is an optionally substituted mono-, di-, or tricyclic ring system;

or a stereoisomer, isotopically substituted analogue, or pharmaceutically acceptable salt or prodrug thereof.

2. The use of the compound of claim 1 wherein R_{13} is hydrogen and R_{14} is a substituted five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl.

3. The use of the compound of claim 1 or 2 wherein R_{14} is a halo-substituted six-membered carbocyclic ring, and preferably, R_{14} is a bromine-substituted six-membered carbocyclic ring.

4. The use of any one of claims 1 to 3 wherein the compound of formula (Ib) is N-(4-bromophenyl)adamantan-2-amine.

5. The use of the compound of any one of claims 1 to 4 further comprising one or more pharmaceutical carriers.

6. A method of treating one or more of lung disease; non-alcoholic fatty liver disease; and kidney disorder, the method comprising administering a therapeutically effective amount of the compound of any one of claims 1 to 5 to a subject in need thereof.

7. The method of claim 6 wherein the lung disease is chronic lung disease, and preferably idiopathic pulmonary fibrosis; the non-alcoholic fatty liver disease is non-alcoholic fatty liver disease, non-alcoholic fatty liver, or non-alcoholic steatohepatitis; and the kidney disorder is renal fibrosis and/or chronic kidney disease.

8. The method of claim 7, wherein the amount is between 0.5 to 200 mg per kg of the subject.

9. The method of claim 8, wherein the amount is between 5 to 50 mg per kg of the subject.

10. The method of claim 9, wherein the amount is between 5 to 30 mg per kg of the subject.

11. The method of claim 10, wherein the amount is between 8 to 17 mg per kg of the subject.

12. The method of claim 11, wherein the amount is about 17 mg per kg of the subject.

13. Use of the compound of any one of claims 1 to 5 in the preparation of a medicament to treat one or more of lung disease; non-alcoholic fatty liver disease; and kidney disorder.

14. The use of claim 13, wherein the use is between 0.5 to 200 mg per kg of the subject.

15. The use of claim 14, wherein the use is between 5 to 50 mg per kg of the subject.

16. The use of claim 15, wherein the use is between 5 to 30 mg per kg of the subject.

17. The use of claim 16, wherein the use is between 8 to 17 mg per kg of the subject.

18. The method of claim 17, wherein the use is about 17 mg per kg of the subject.

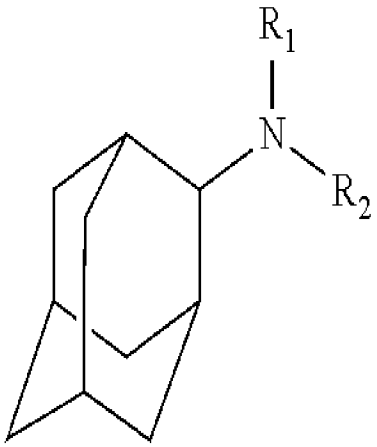
19. The use of any one of claims 13 to 18wherein the lung disease is chronic lung disease, and preferably idiopathic pulmonary fibrosis; the non-alcoholic fatty liver disease is non-alcoholic fatty liver disease, non-alcoholic fatty liver, or non-alcoholic steatohepatitis; and the kidney disorder is renal fibrosis and/or chronic kidney disease.

20. The use of claim 19, wherein the non-alcoholic fatty liver disease is non-alcoholic steatohepatitis.

21. The use of claim 20, wherein the non-alcoholic fatty liver disease is non-alcoholic steatohepatitis-derived hepatocellular carcinoma.

22. A use of a compound of formula (Ib) for treating one or more of lung disease; non-alcoholic fatty liver disease; and kidney disorder

(Ib)



wherein
R_1 is hydrogen; and,
R_2 is —(R_3)($R_{4'}$);
R_3 is alkyl or is a bond; and,
$R_{4'}$ is a substituted mono-, di-, or tricyclic ring system, or,
R_1 together with R_2 and the atom to which they are both attached form an optionally substituted mono-, di-, or tricyclic ring system,
or a stereoisomer, partial stereoisomer, isotopically substituted analogue, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid hydrate, or N-oxide thereof.

23. The use of the compound of claim 22 wherein $R_{4'}$ is a substituted five- or six-membered carbocyclic or heterocyclic ring bearing one or more substituents independently selected from hydroxyl, halo, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, alkylsulfanyl, cycloalkyl, and aryl,

preferably, $R_{4'}$ is a halo-substituted six-membered carbocyclic ring, more prerably $R_{4'}$ is a bromine-substituted six-membered carbocyclic ring.

24. The use of the compound of claim 22 or 23 further comprising one or more pharmaceutical carriers.

25. A method of treating one or more of lung disease; non-alcoholic fatty liver disease; and kidney disorder, the method comprising administering a therapeutically effective amount of the compound of any one of claims 22 to 24 to a subject in need thereof.

26. The method of claim 35 wherein the lung disease is chronic lung disease, and preferably idiopathic pulmonary fibrosis; the non-alcoholic fatty liver disease is non-alcoholic fatty liver disease, non-alcoholic fatty liver, or non-alcoholic steatohepatitis; and the kidney disorder is renal fibrosis and/or chronic kidney disease.

27. The method of claim 26, wherein the amount is between 0.5 to 200 mg per kg of the subject.

28. The method of claim 27, wherein the amount is between 5 to 50 mg per kg of the subject.

29. The method of claim 28, wherein the amount is between 5 to 30 mg per kg of the subject.

30. The method of claim 29, wherein the amount is between 8 to 17 mg per kg of the subject.

31. The method of claim 30, wherein the amount is about 17 mg per kg of the subject.

32. Use of the compound of any one of claims 22 to 24 in the preparation of a medicament to treat one or more of lung disease; non-alcoholic fatty liver disease; and kidney disorder.

33. The use of claim 32, wherein the use is between 0.5 to 200 mg per kg of the subject.

34. The use of claim 32, wherein the use is between 5 to 50 mg per kg of the subject.

35. The use of claim 34, wherein the use is between 5 to 30 mg per kg of the subject.

36. The use of claim 35, wherein the use is between 8 to 17 mg per kg of the subject.

37. The method of claim 36, wherein the use is about 17 mg per kg of the subject.

38. The method of any one of claims 25 to 37 wherein the lung disease is chronic lung disease, and preferably idiopathic pulmonary fibrosis; the non-alcoholic fatty liver disease is non-alcoholic fatty liver disease, non-alcoholic fatty liver, or non-alcoholic steatohepatitis; and the kidney disorder is renal fibrosis and/or chronic kidney disease.

39. The method of claim 38, wherein the non-alcoholic fatty liver disease is non-alcoholic steatohepatitis.

40. The method of claim 39, wherein the non-alcoholic fatty liver disease is non-alcoholic steatohepatitis-derived hepatocellular carcinoma.

Figure 1

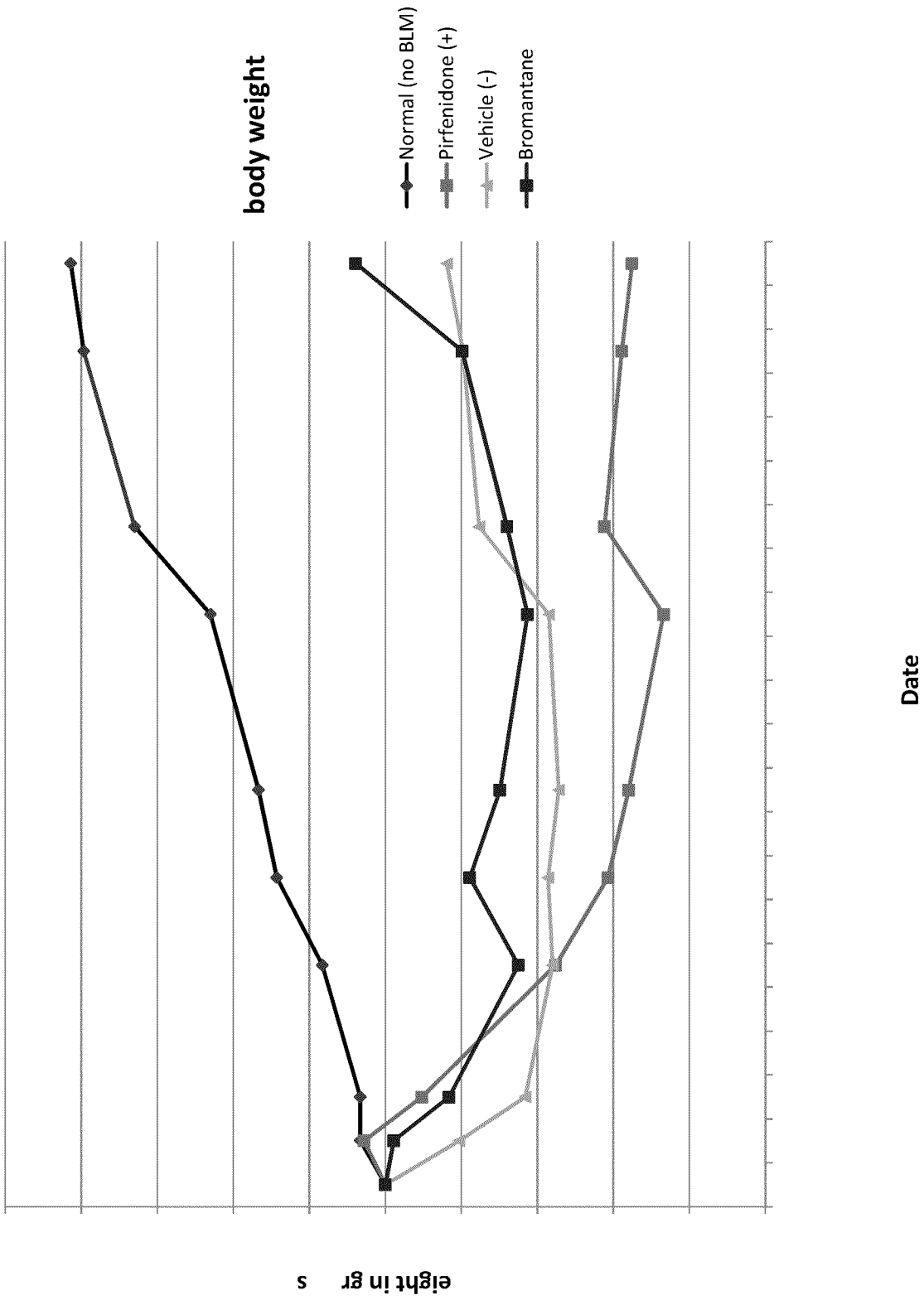

body weight
Normal (no BLM)
Pirfenidone (+)
Vehicle (-)
Bromantane
eight in gr s
Date

Figure 2

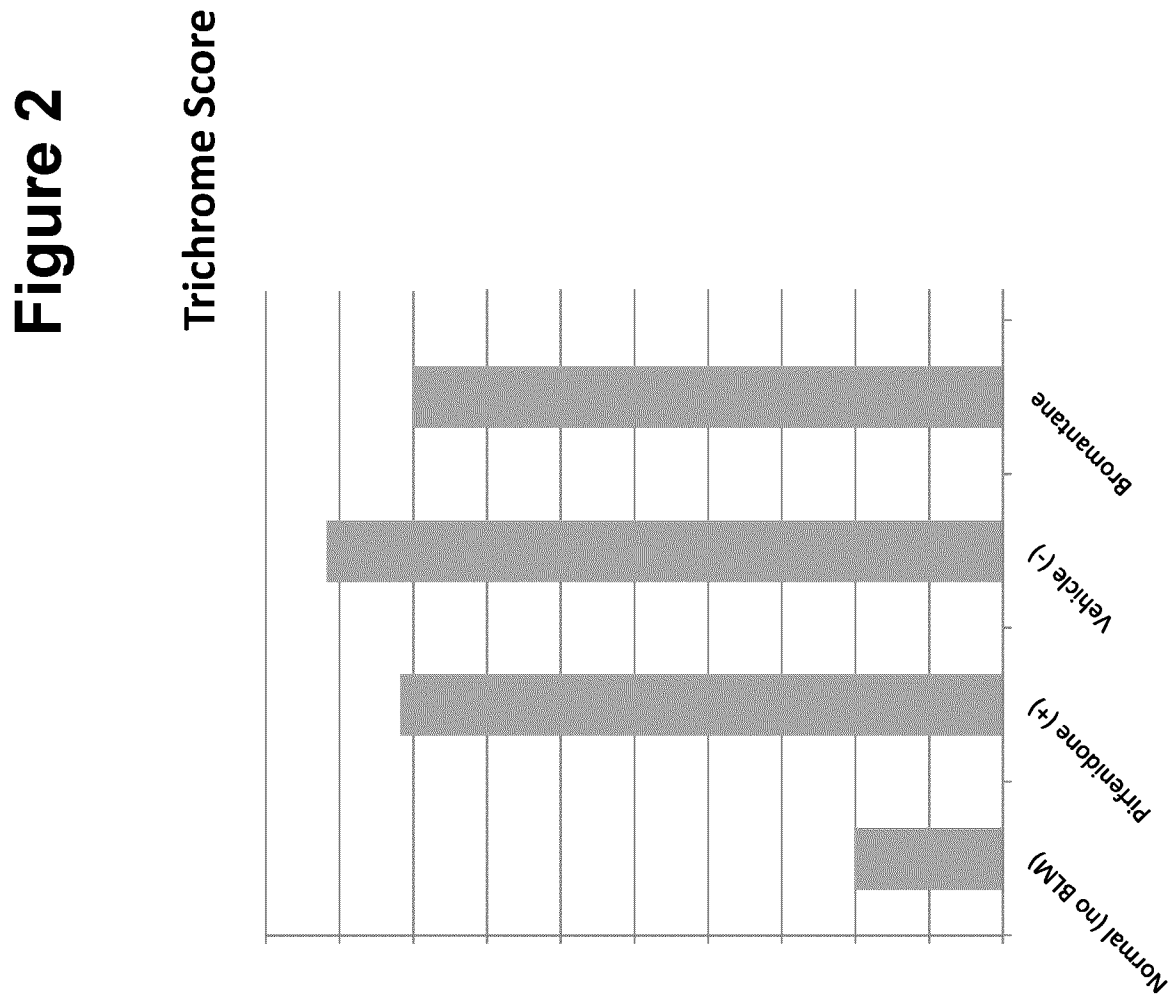
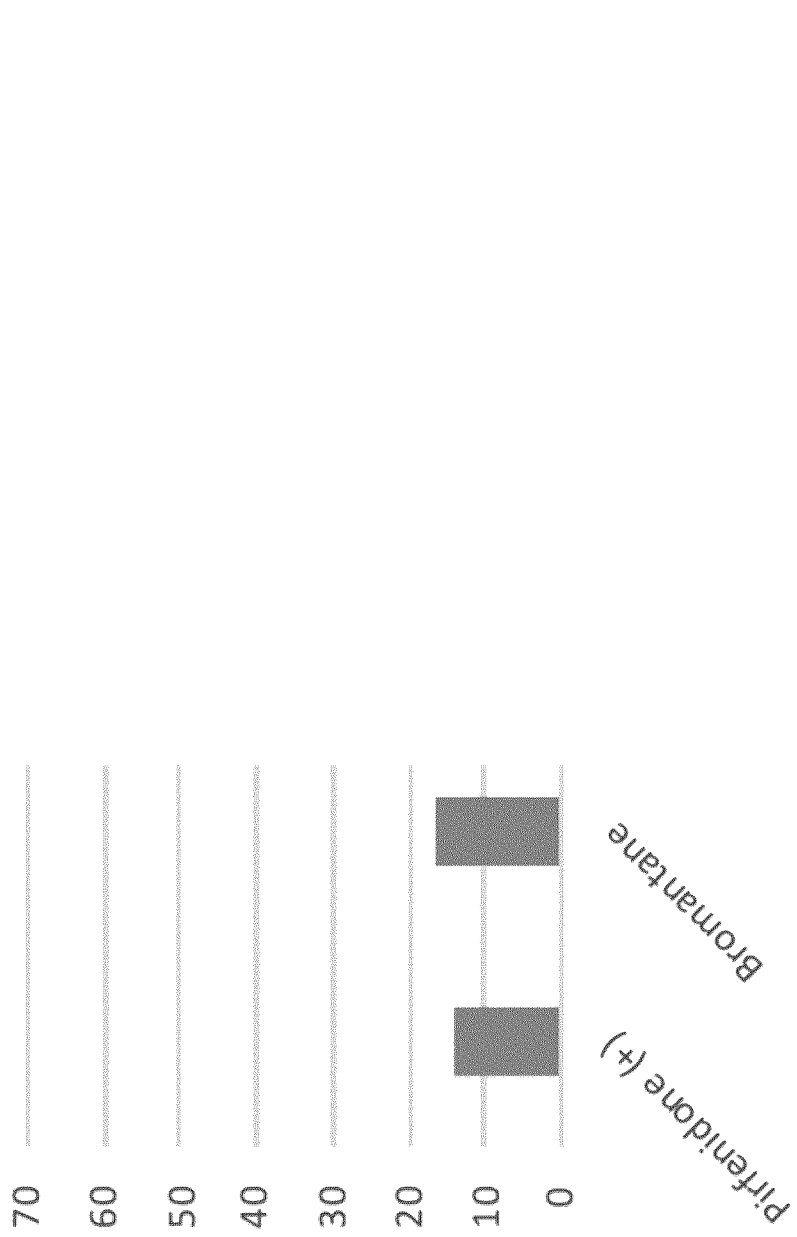

Trichrome Score
trichrome score
Normal (no BLM)
Pirfenidone (+)
Vehicle (-)
Bromantane

Figure 3


% Reduction in Fibrosis vs Vehicle
70
60
50
40
30
20
10
0
Pirfenidone (+)
Bromantane

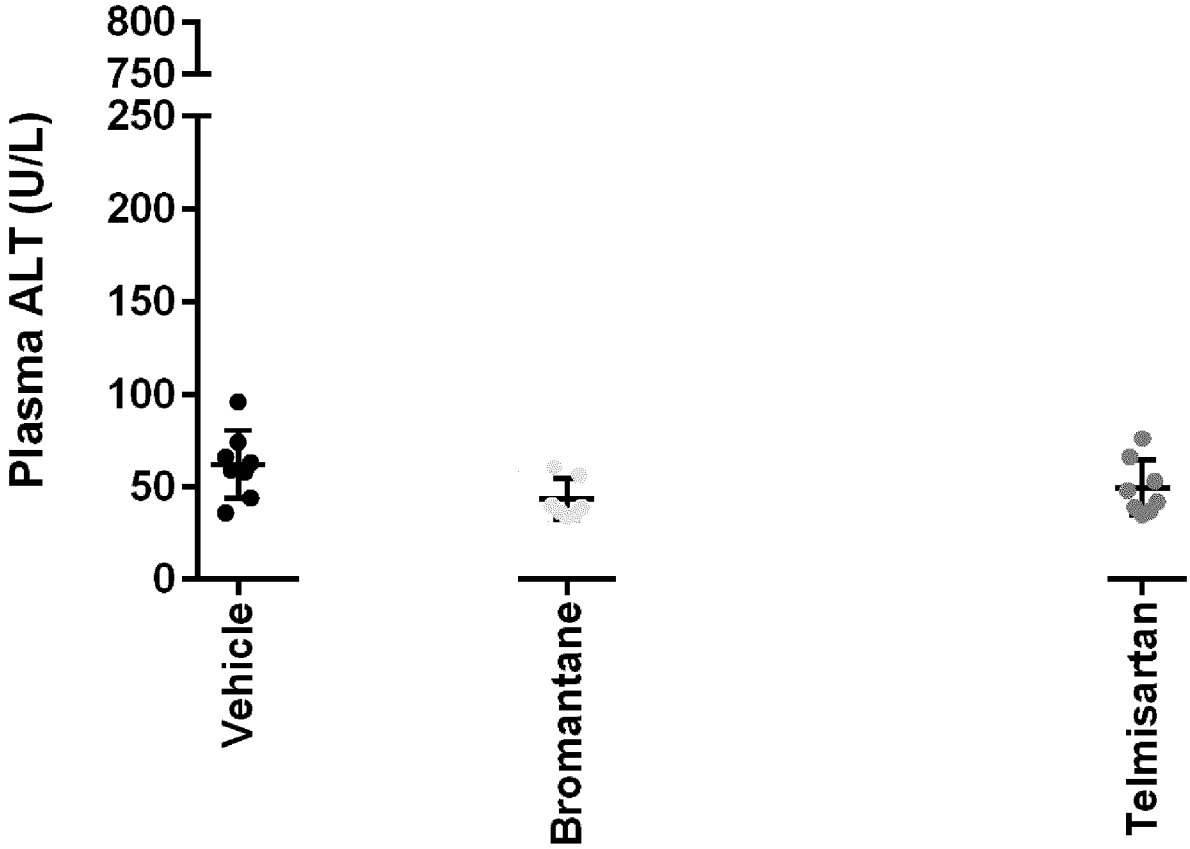

Plasma ALT (U/L)
800
750
250
200
150
100
50
0
Vehicle
Bromantane
Telmisartan

Figure 4

Figure 5a

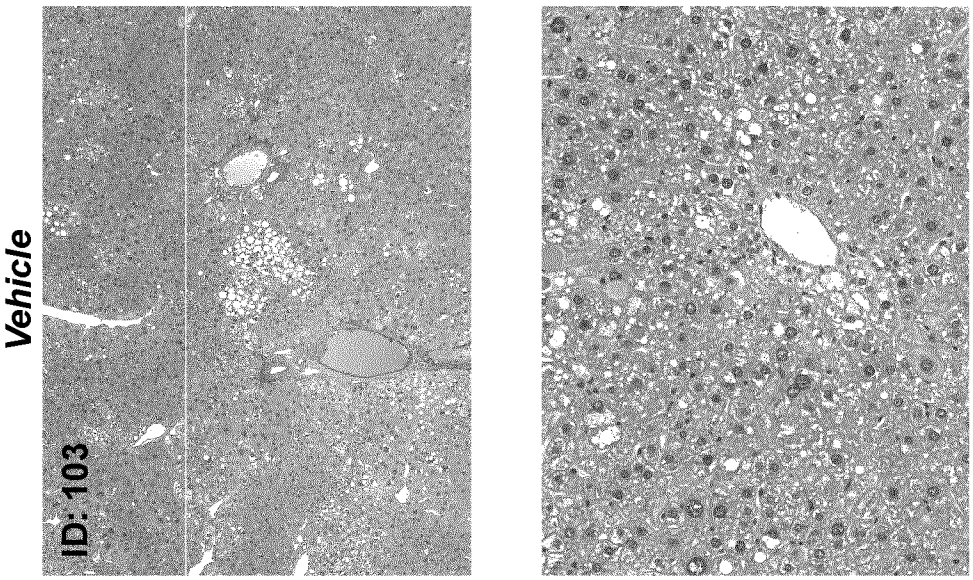
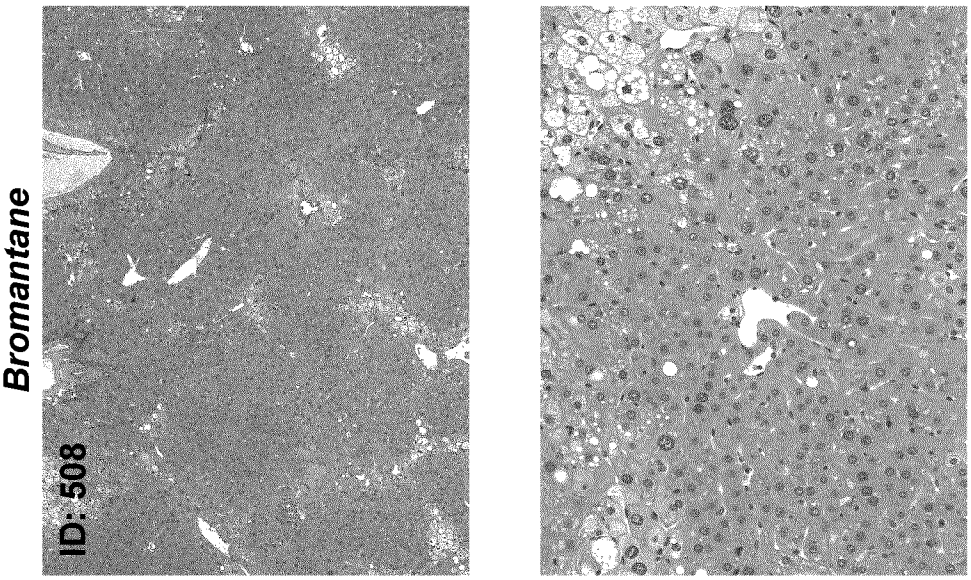


Figure 5b



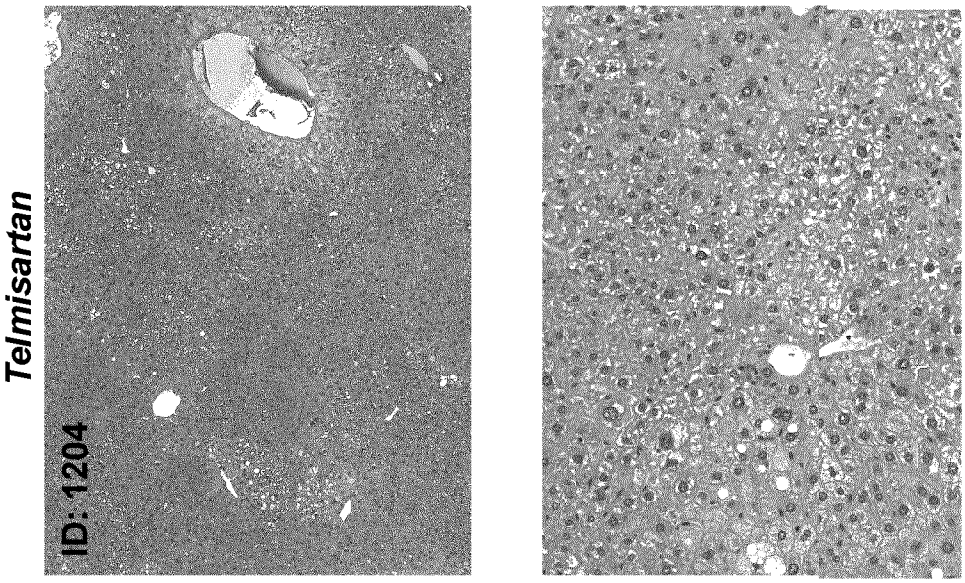
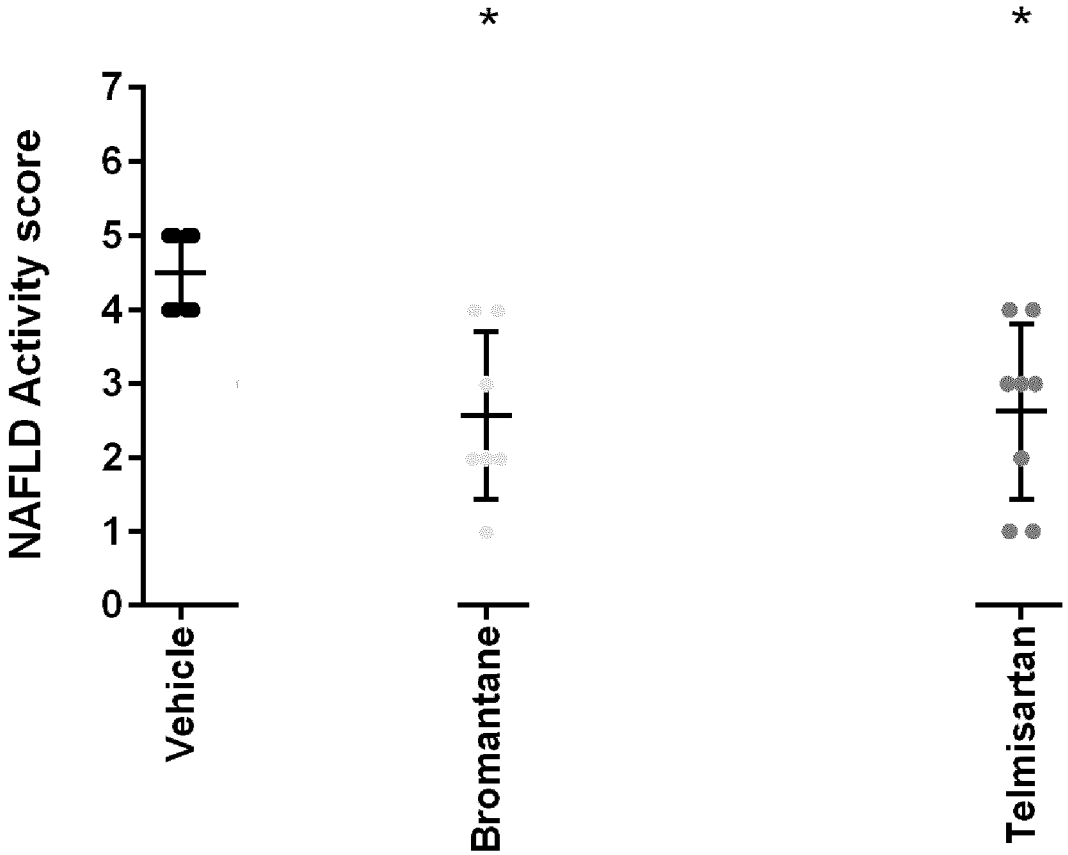


Figure 5c



*; p<0.05, **; p<0.01, ***; p<0.001 (vs Vehicle)

Figure 6

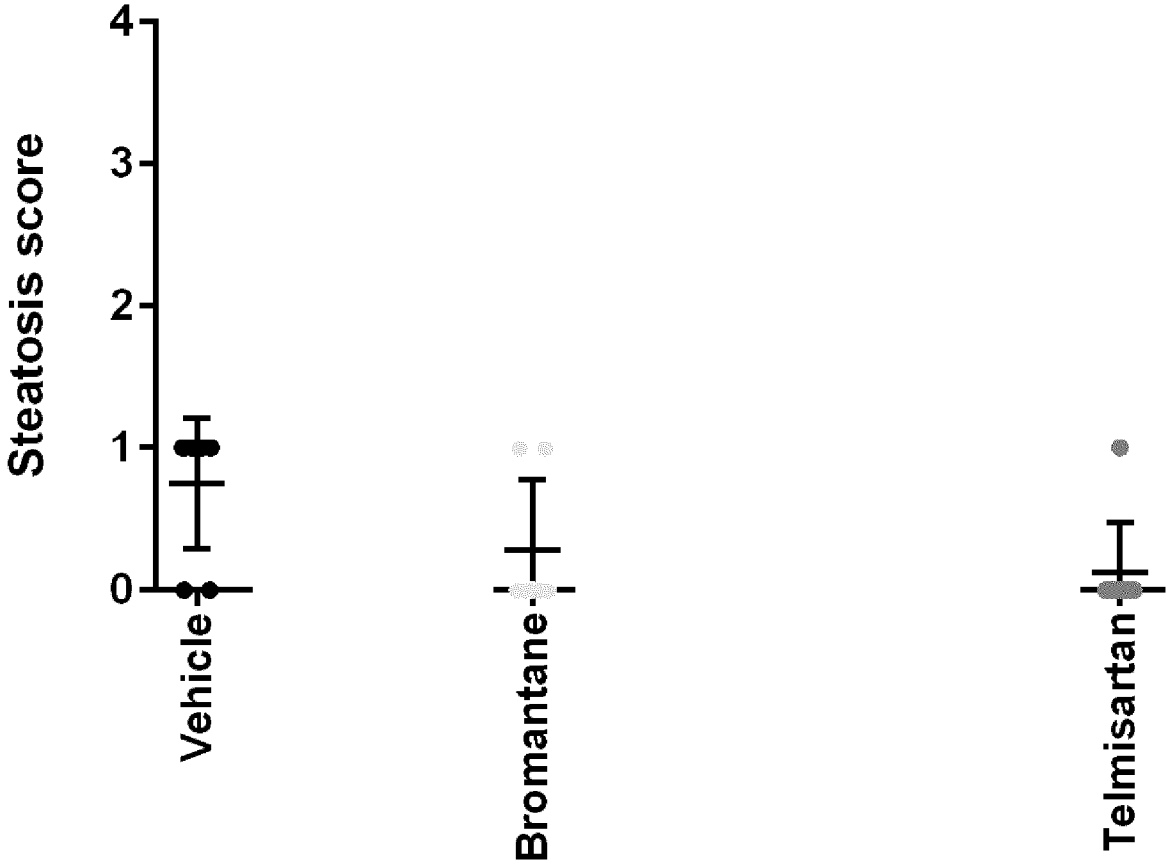


Figure 7

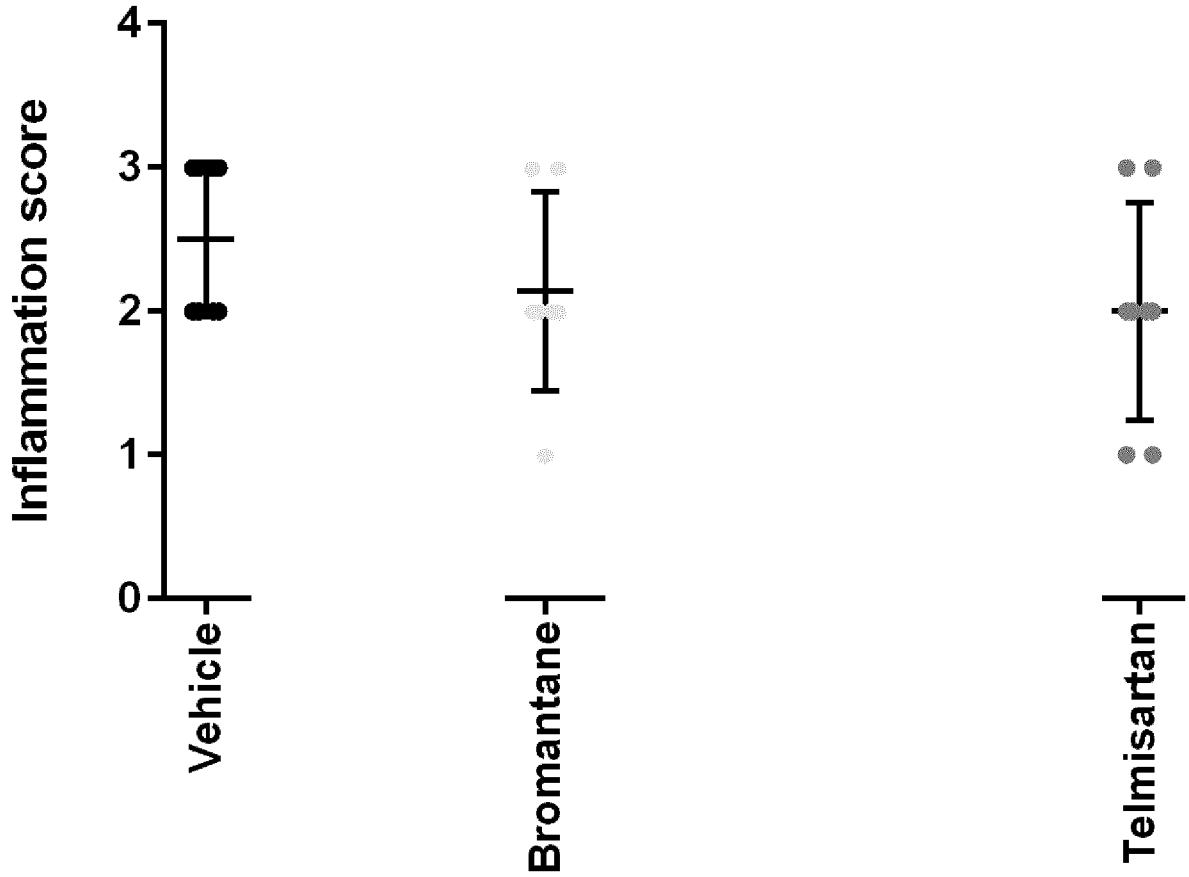
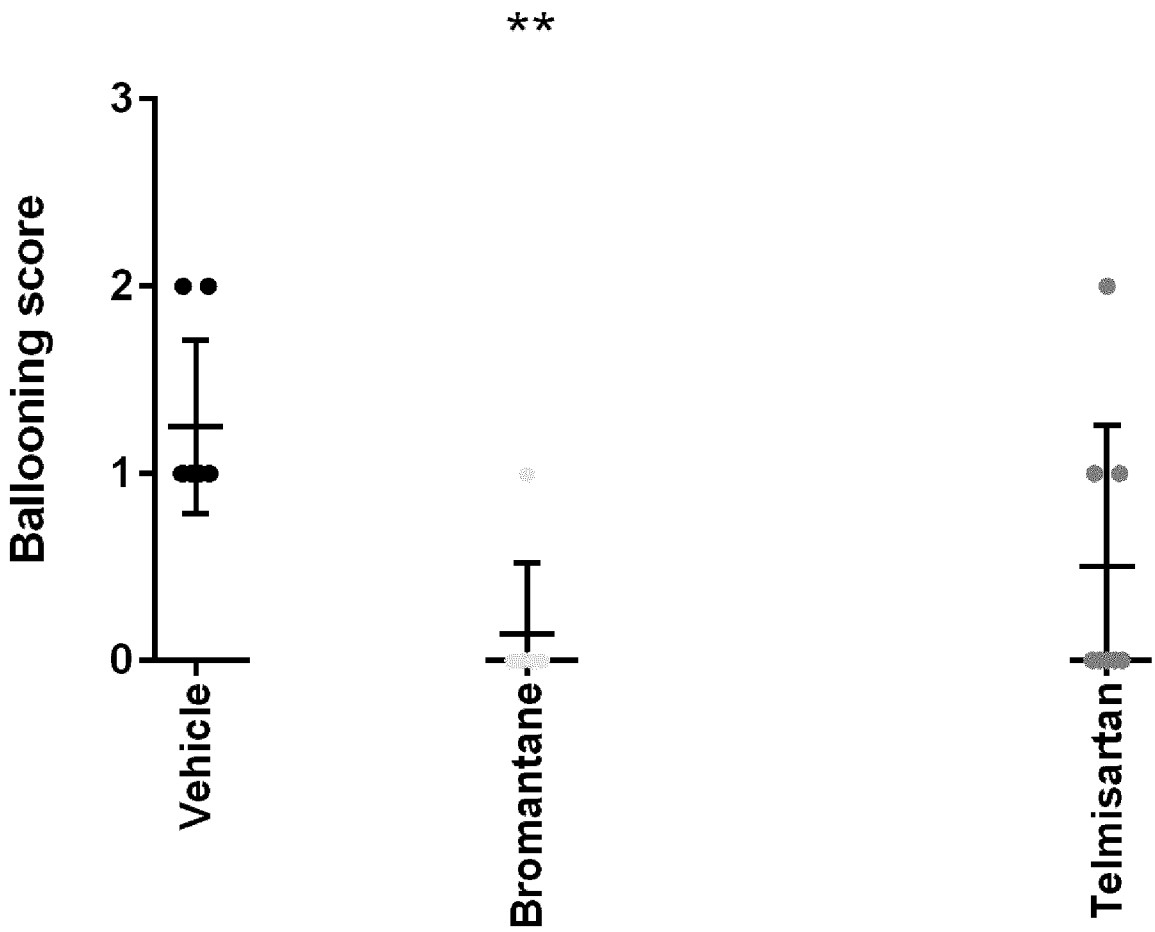

Inflammation score
4
3
2
1
0
Vehicle
Bromantane
Telmisartan

Figure 8



*; p<0.05, **; p<0.01 (vs Vehicle)

Figure 9

Figure 10

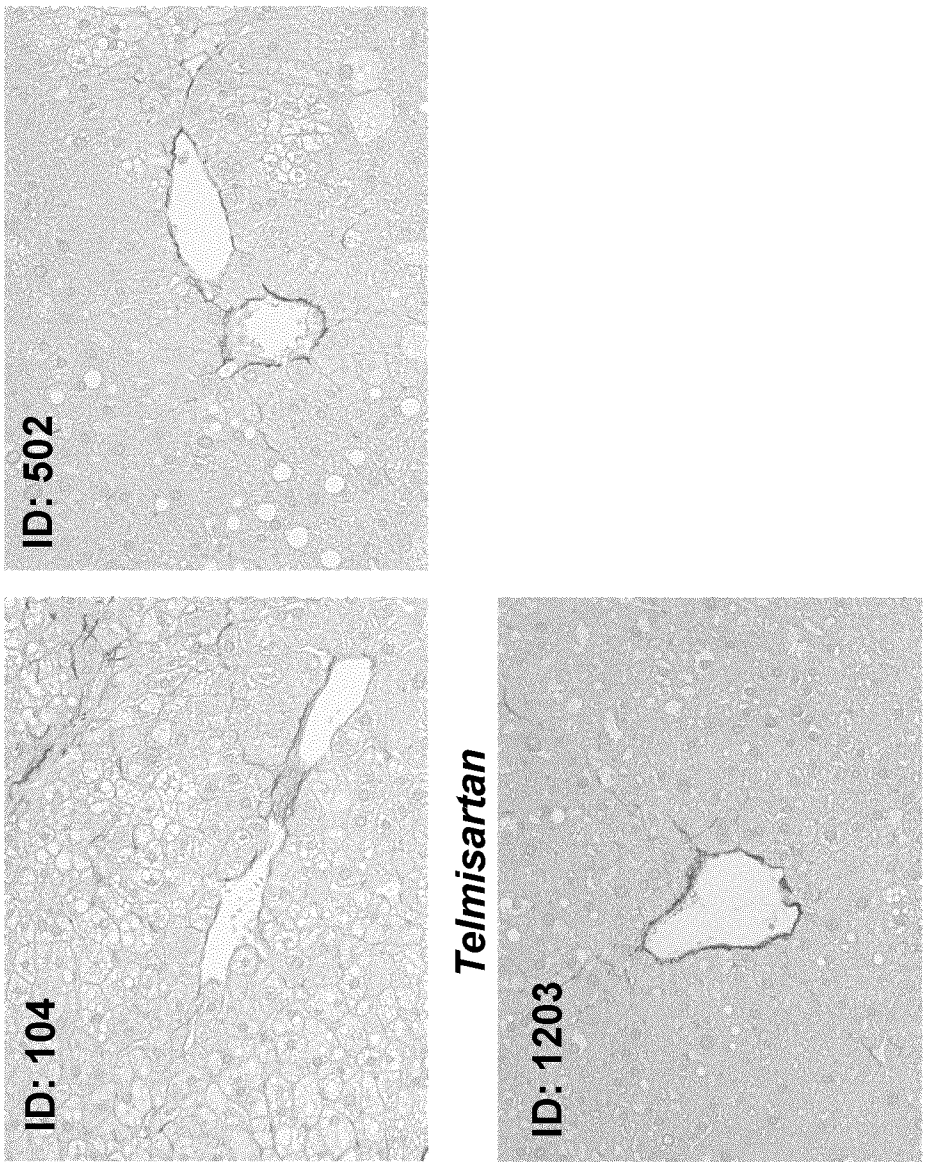


Figure 11

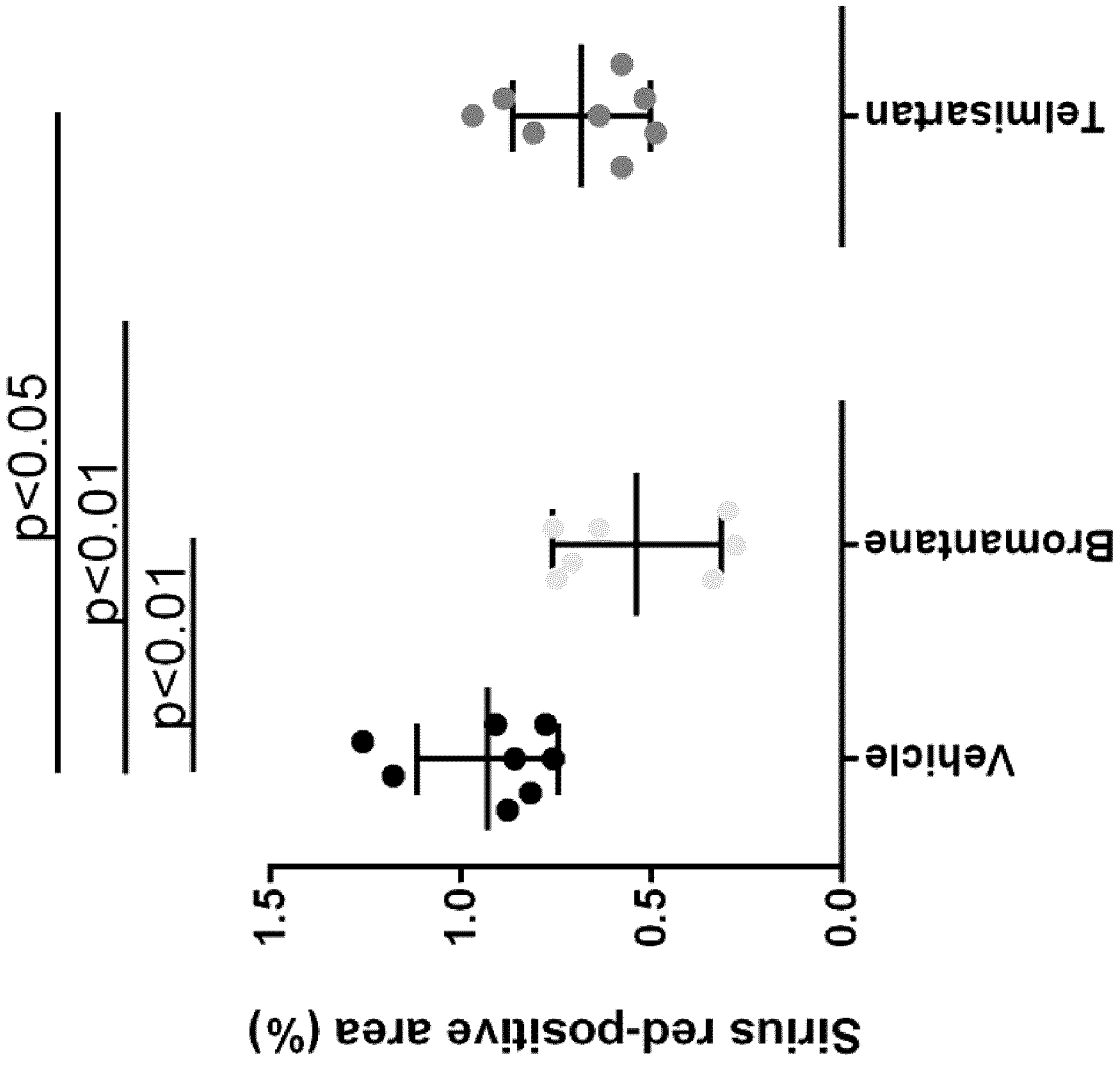

p<0.05
p<0.01
p<0.01
Vehicle
Bromantane
Telmisartan
1.5
1.0
0.5
0.0
Sirius red-positive area (%)

Figure 12

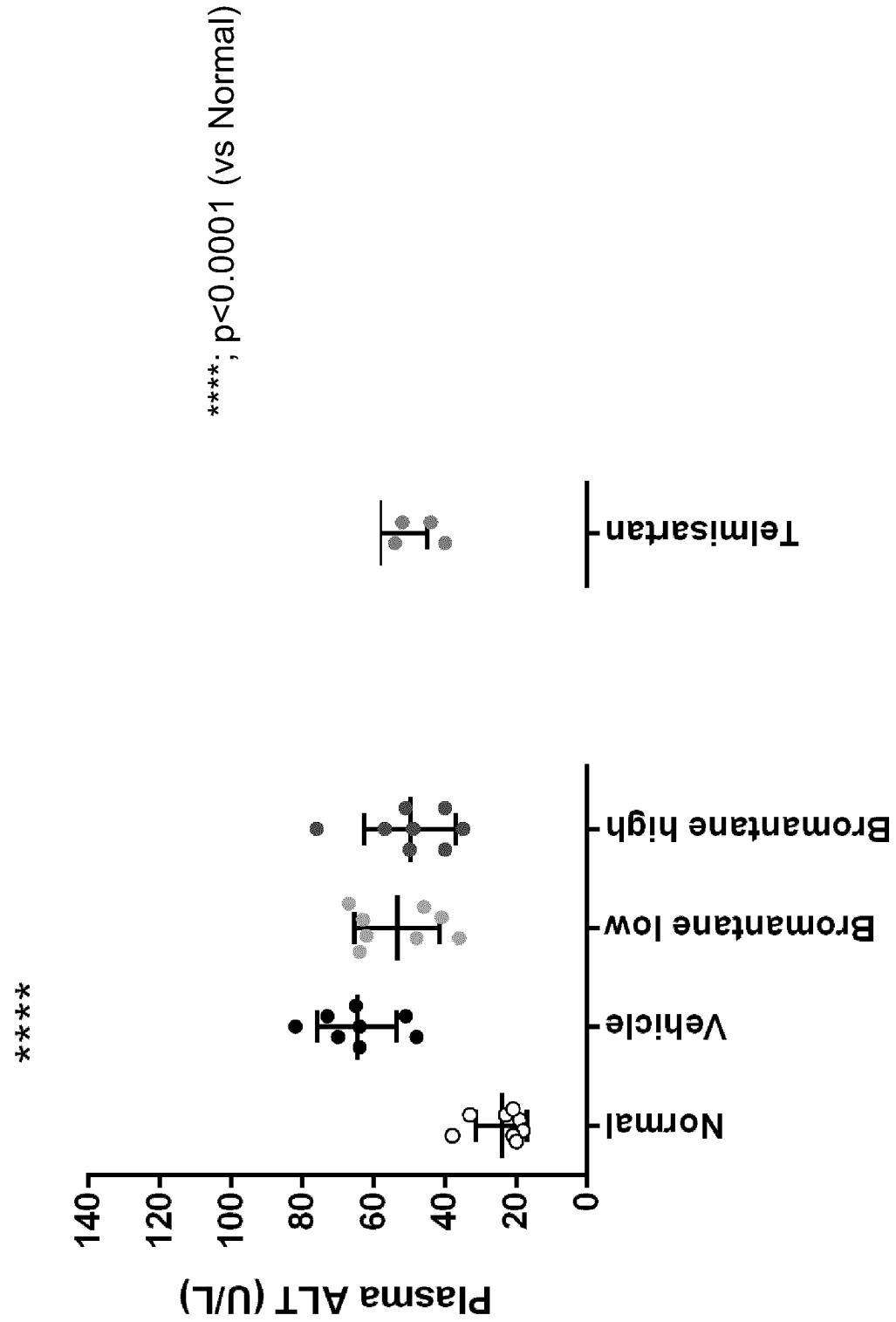

****; p<0.0001 (vs Normal)
Plasma ALT (U/L)
0
20
40
60
80
100
120
140
****
Normal
Vehicle
Bromantane low
Bromantane high
Telmisartan

Figure 13a

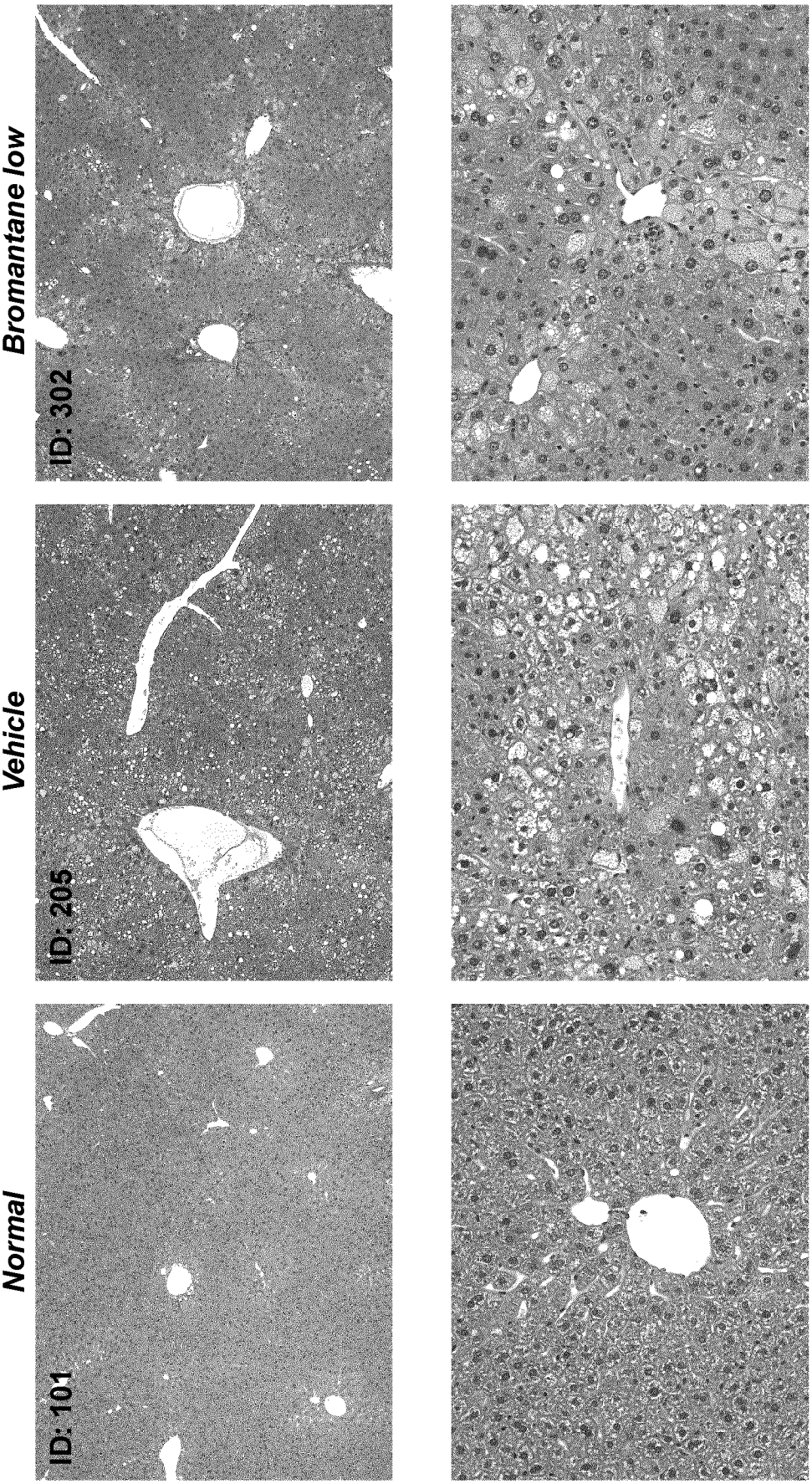


Figure 13b

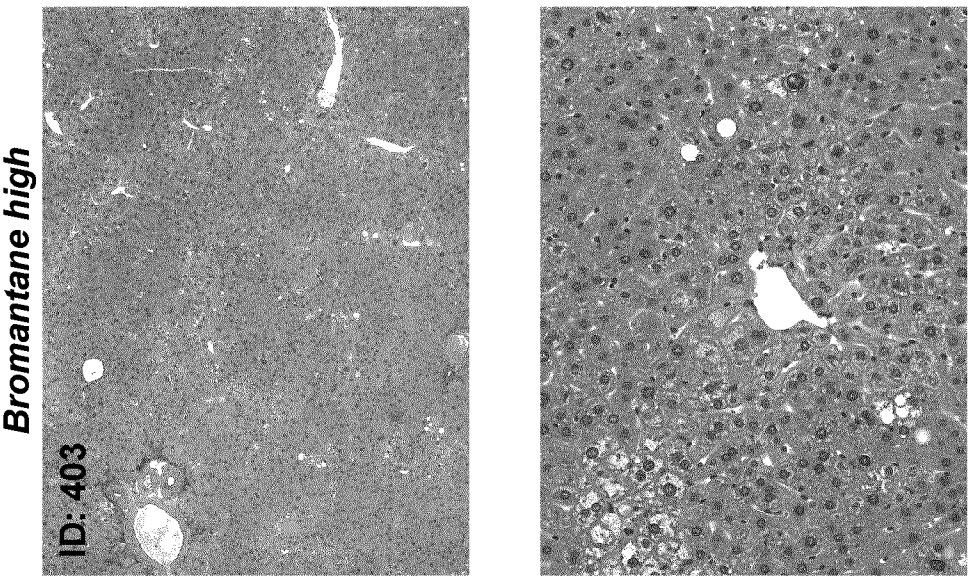


Figure 13c

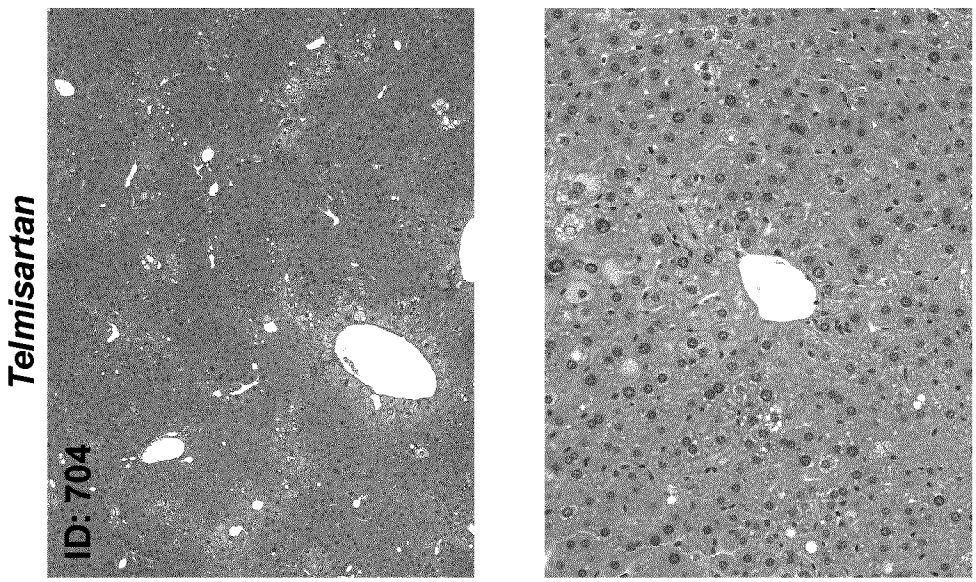


Figure 14

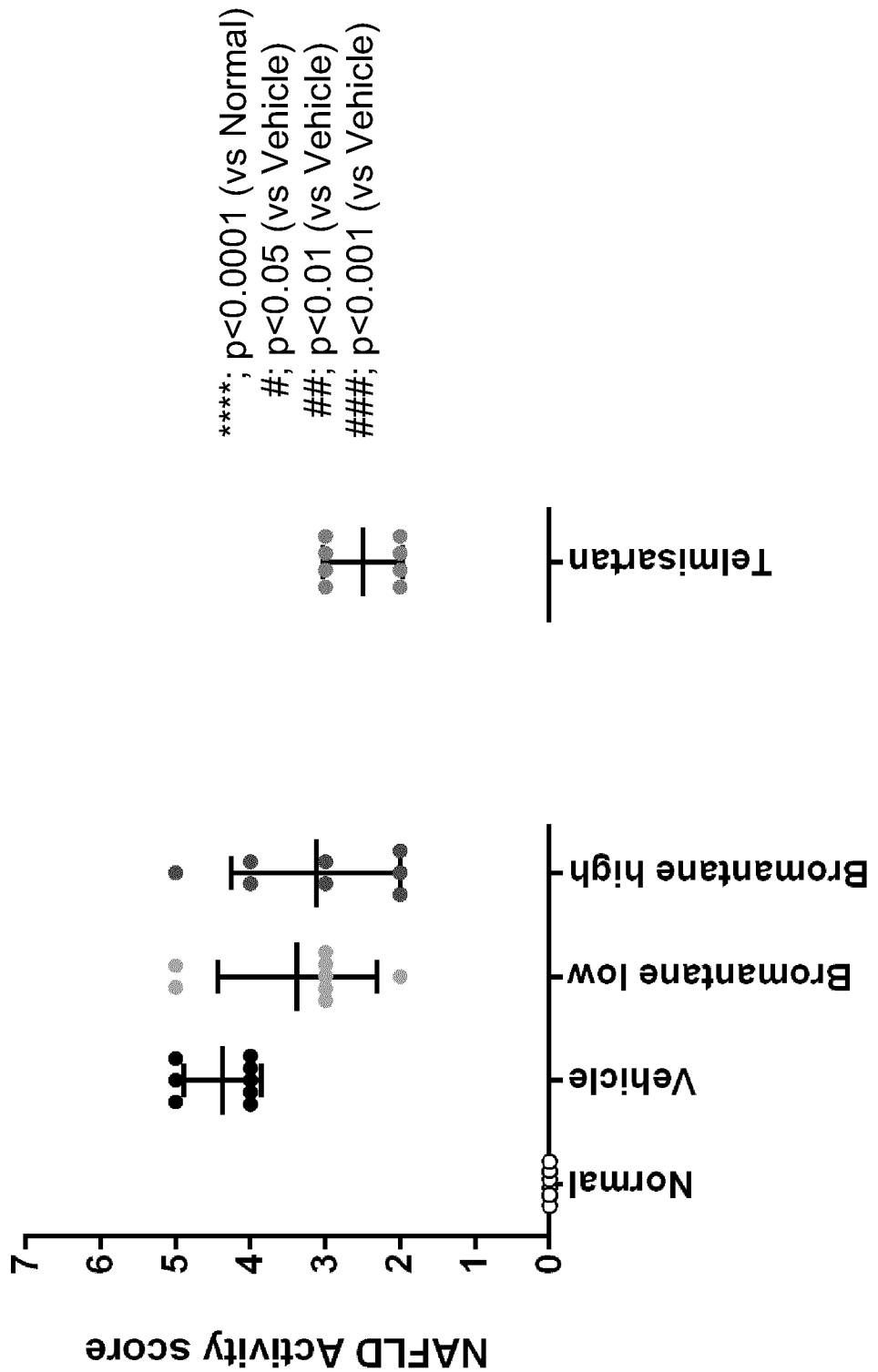

NAFLD Activity score
0
1
2
3
4
5
6
7
Normal
Vehicle
Bromantane low
Bromantane high
Telmisartan
*****
#
###
*****; p<0.0001 (vs Normal)
#; p<0.05 (vs Vehicle)
##; p<0.01 (vs Vehicle)
###; p<0.001 (vs Vehicle)

Figure 15

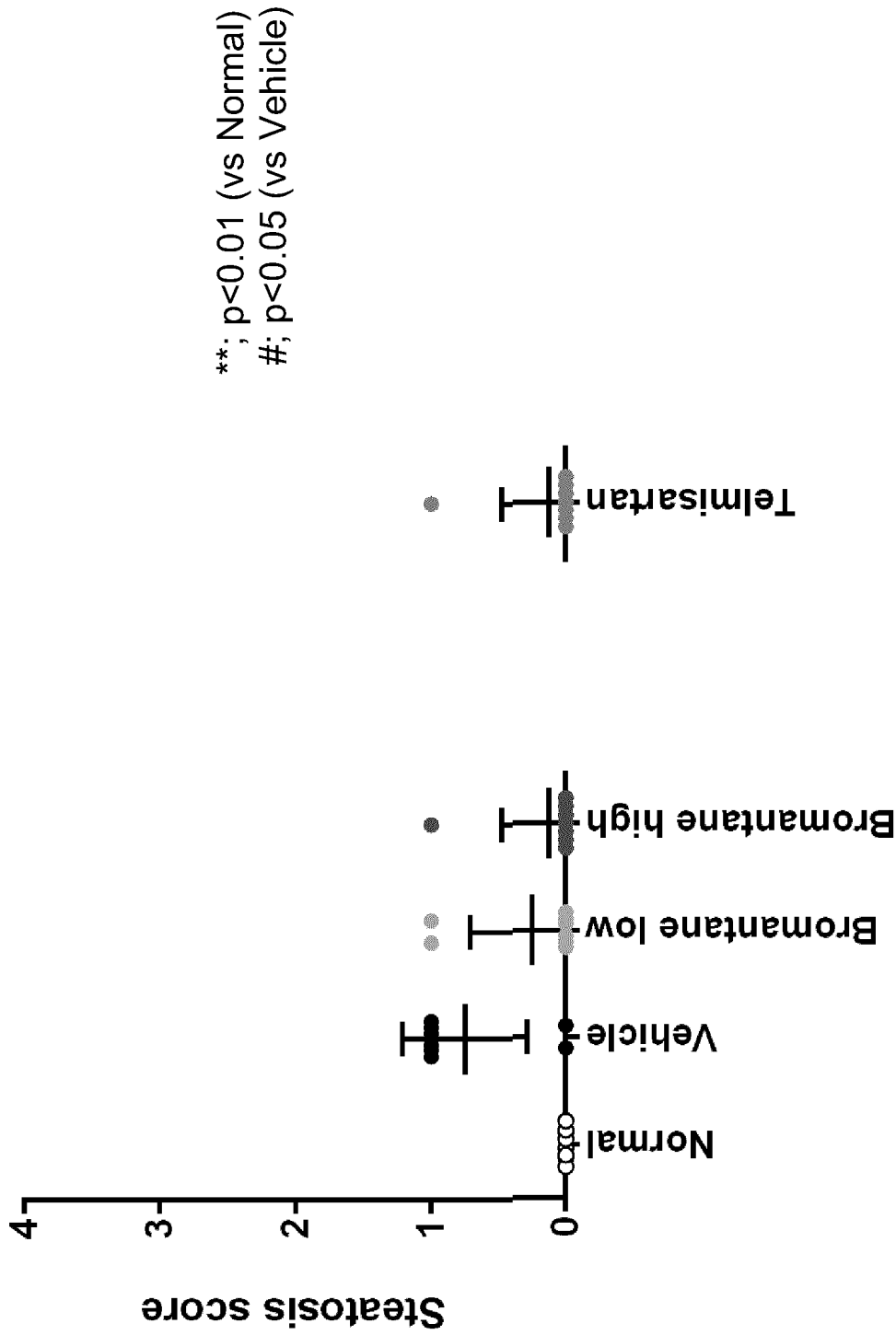

**; p<0.01 (vs Normal)
#; p<0.05 (vs Vehicle)
Steatosis score
0
1
2
3
4
Normal
Vehicle
Bromantane low
Bromantane high
Telmisartan
**
#
#

Figure 16

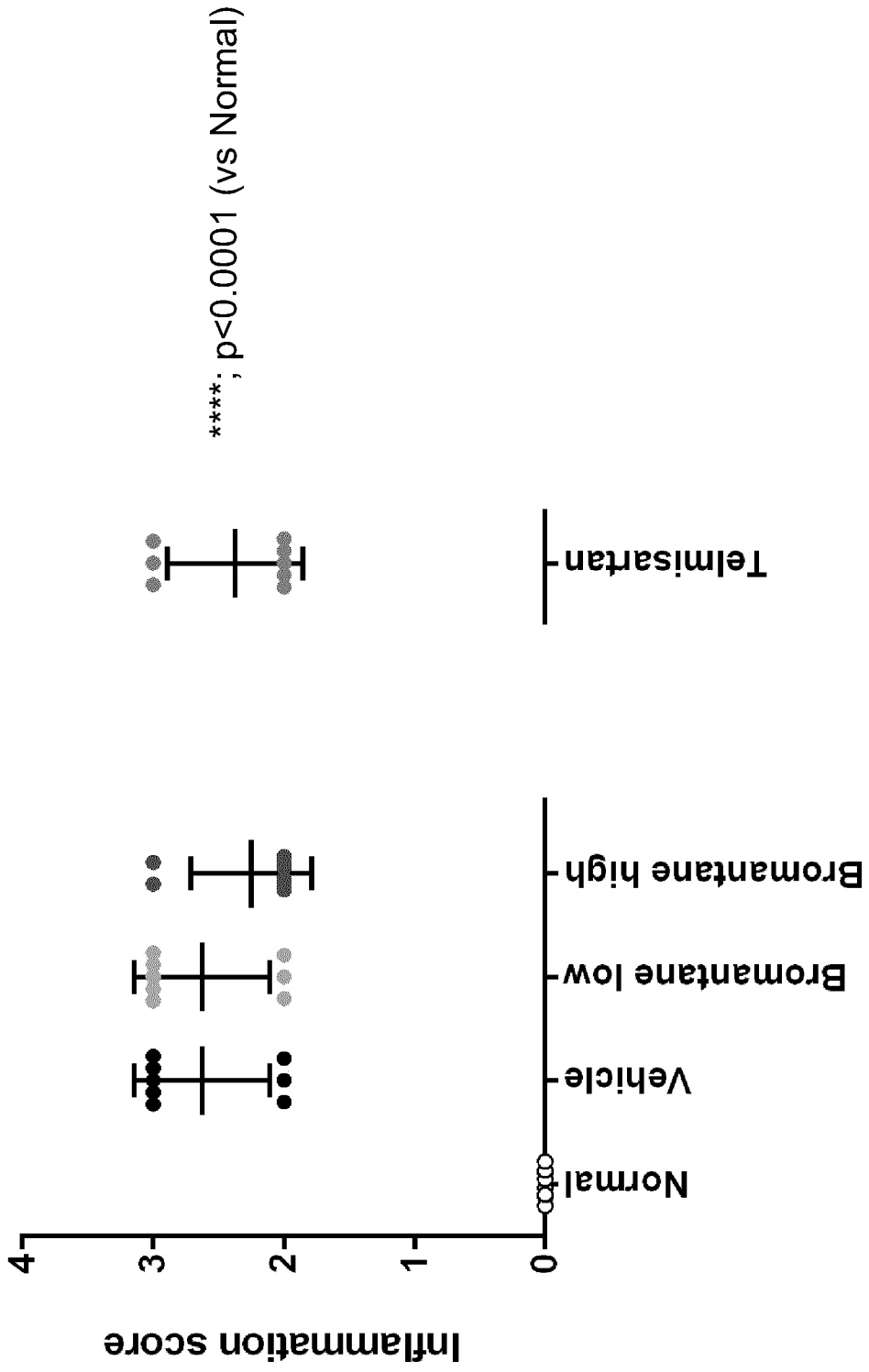

****; p<0.0001 (vs Normal)
****
Inflammation score
0
1
2
3
4
Normal
Vehicle
Bromantane low
Bromantane high
Telmisartan

Figure 17

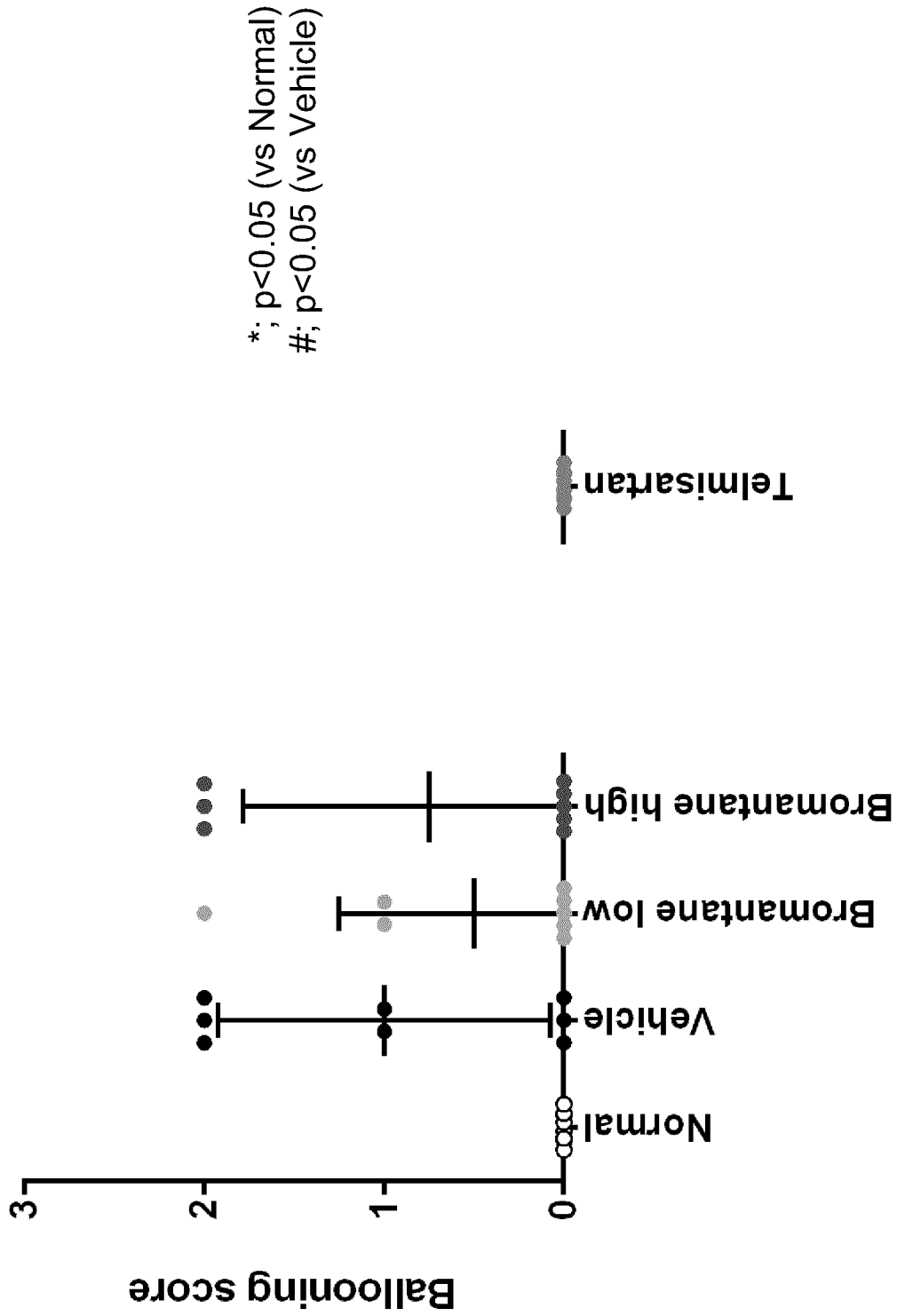

*; p<0.05 (vs Normal)
#; p<0.05 (vs Vehicle)
Ballooning score
0
1
2
3
Normal
Vehicle
Bromantane low
Bromantane high
Telmisartan
*
#

Figure 18a

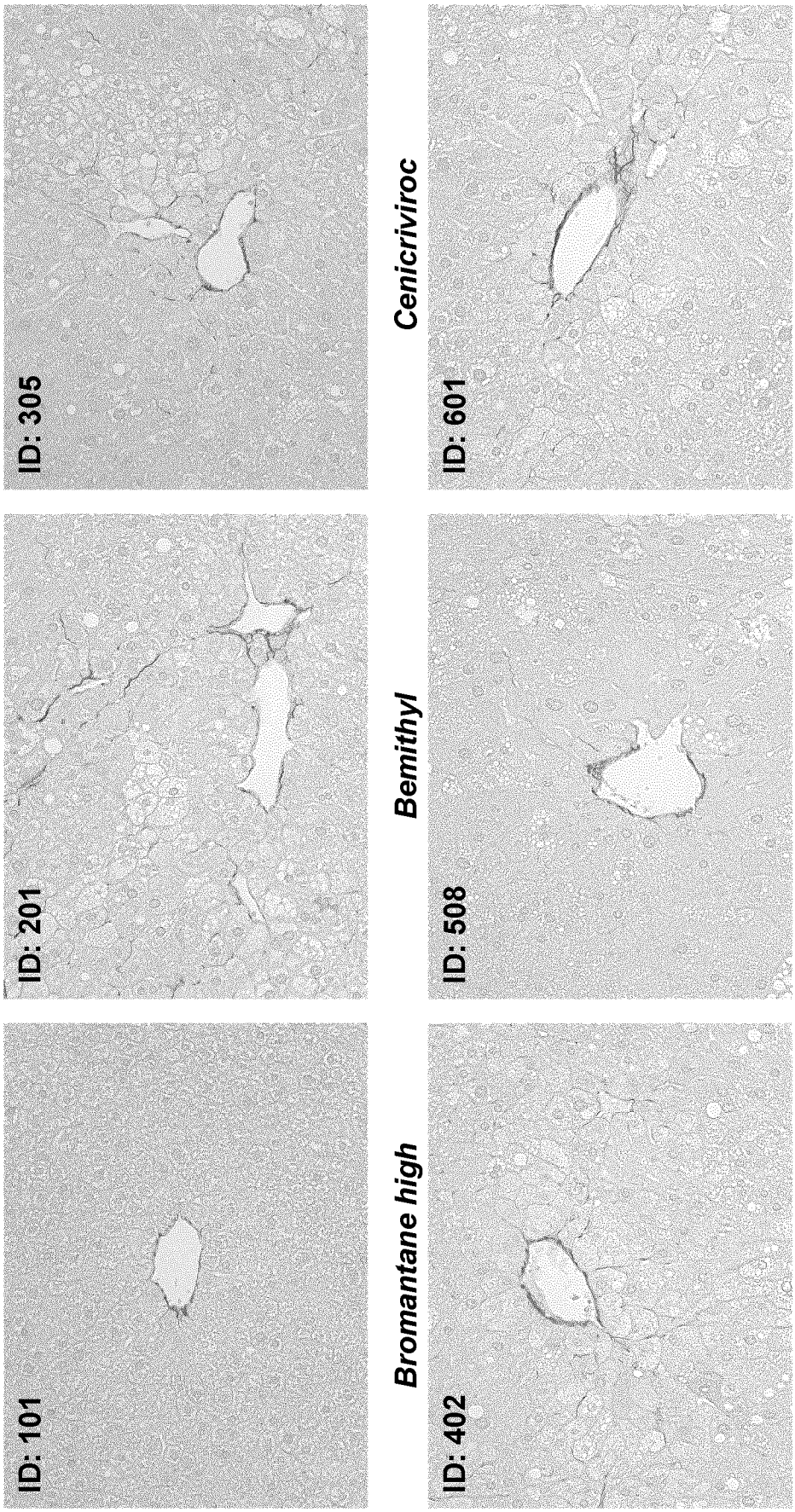

Normal
ID: 101
Vehicle
ID: 201
Bromantane low
ID: 305
Bromantane high
ID: 402
Bemithyl
ID: 508
Cenicriviroc
ID: 601

Figure 18b

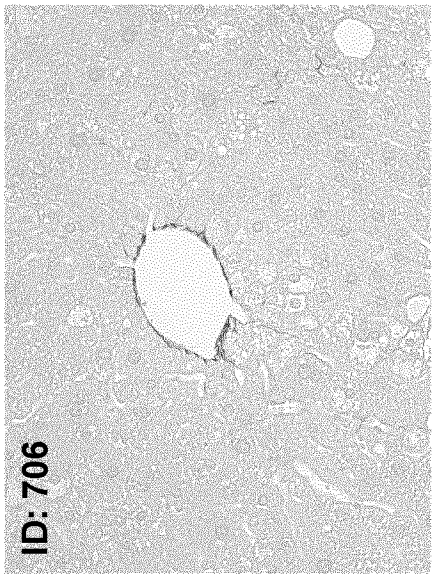


Figure 19

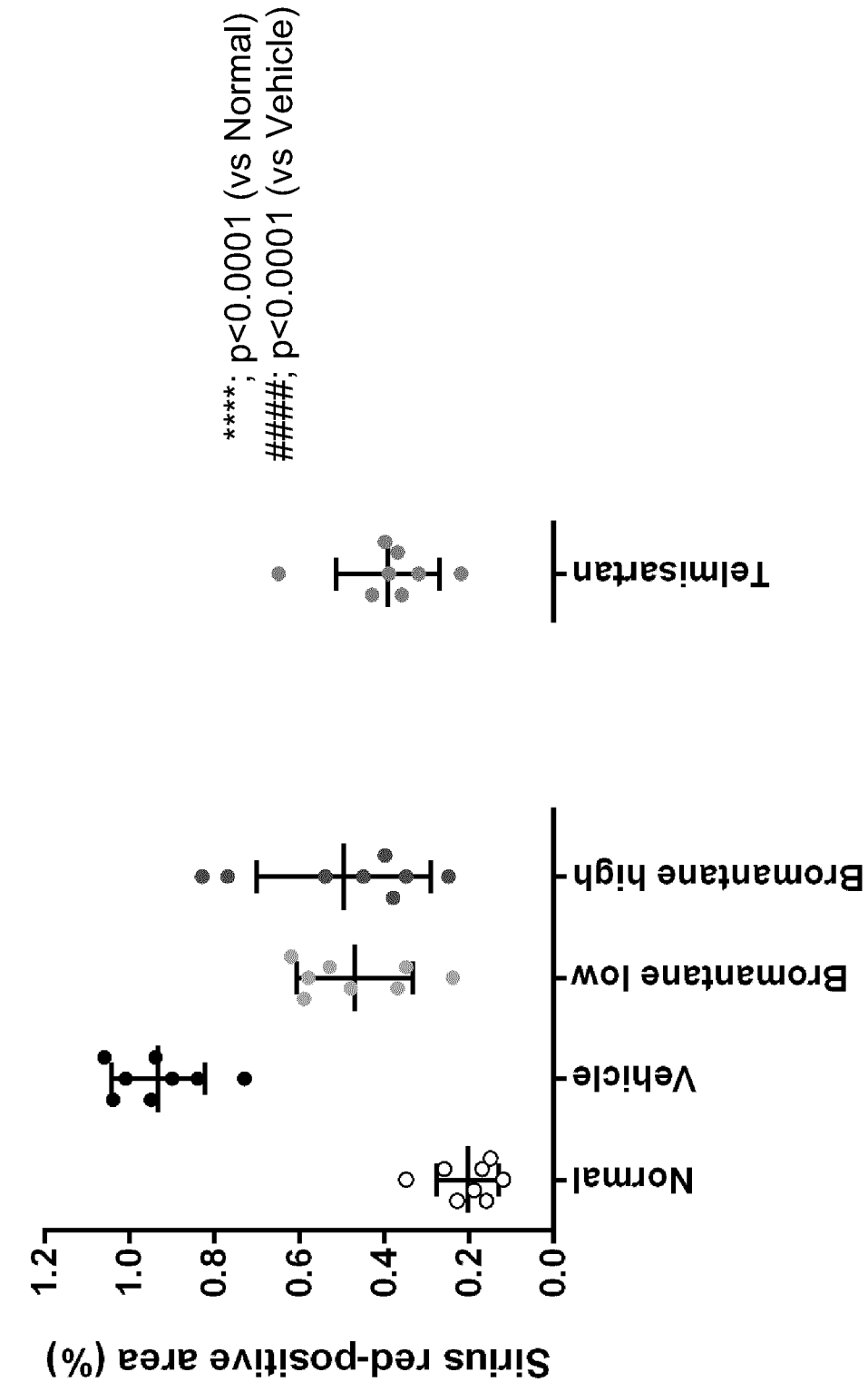

****; p<0.0001 (vs Normal)
####; p<0.0001 (vs Vehicle)
Sirius red-positive area (%)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Normal
Vehicle
Bromantane low
Bromantane high
Telmisartan
****
####
####
####
####

Figure 20

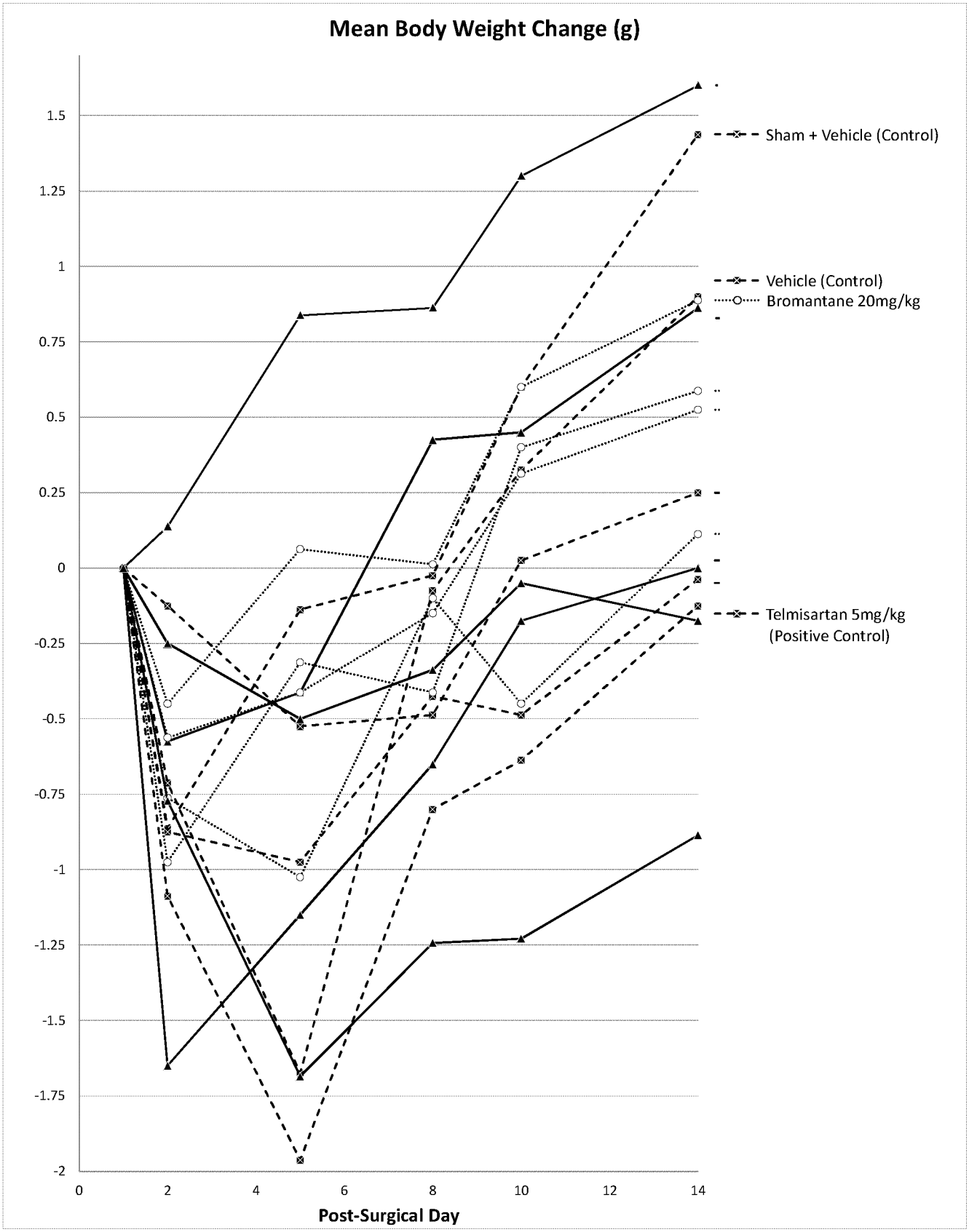

Mean Body Weight Change (g)
1.5
1.25
1
0.75
0.5
0.25
0
-0.25
-0.5
-0.75
-1
-1.25
-1.5
-1.75
-2
0
2
4
6
8
10
12
14
Post-Surgical Day
Sham + Vehicle (Control)
Vehicle (Control)
Bromantane 20mg/kg
Telmisartan 5mg/kg
(Positive Control)

Figure 21

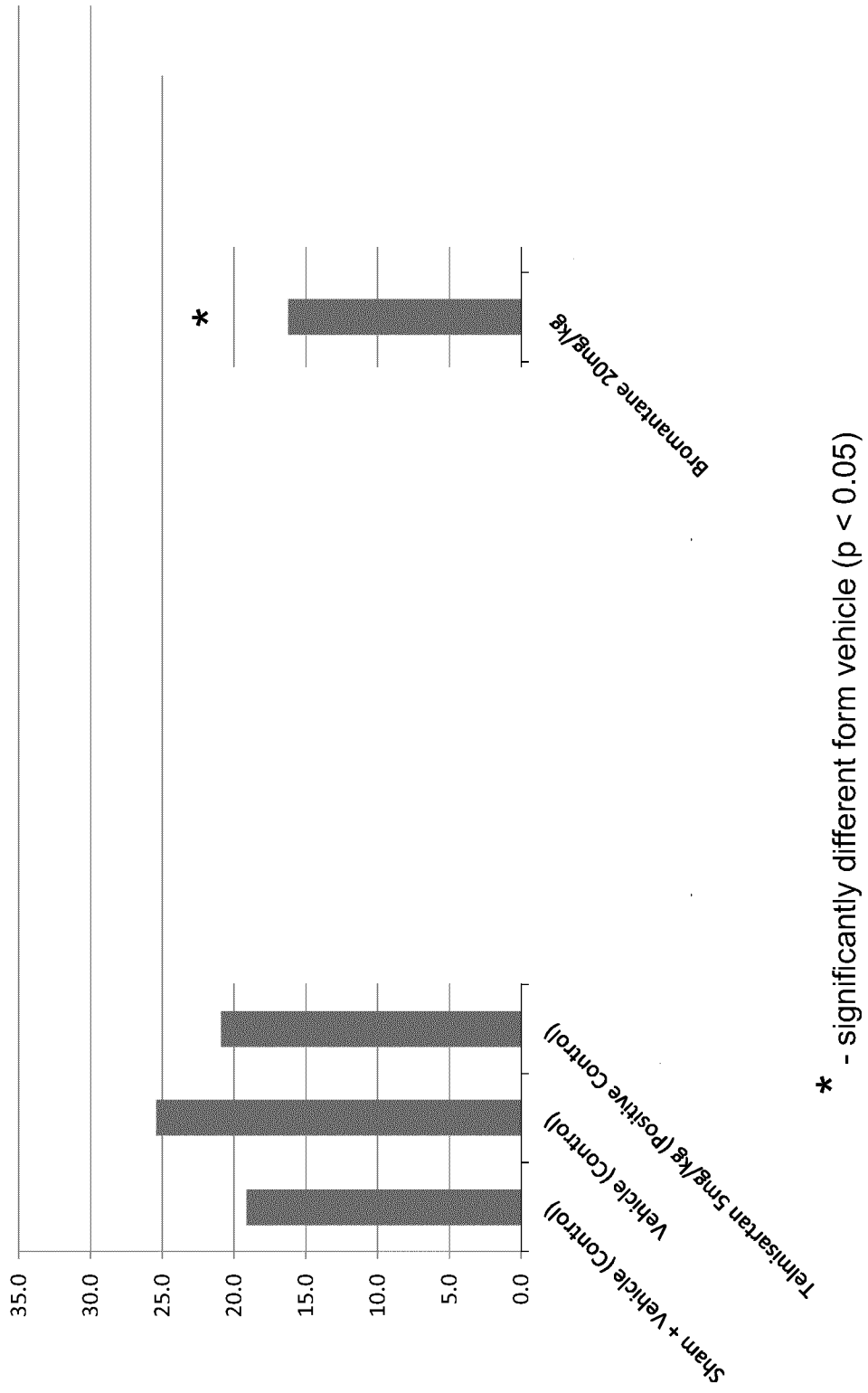

Blood Urea Nitrogen (BUN)
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
*
Sham + Vehicle (Control)
Vehicle (Control)
Telmisartan 5mg/kg (Positive Control)
Bromantane 20mg/kg
* - significantly different form vehicle (p < 0.05)

Figure 22

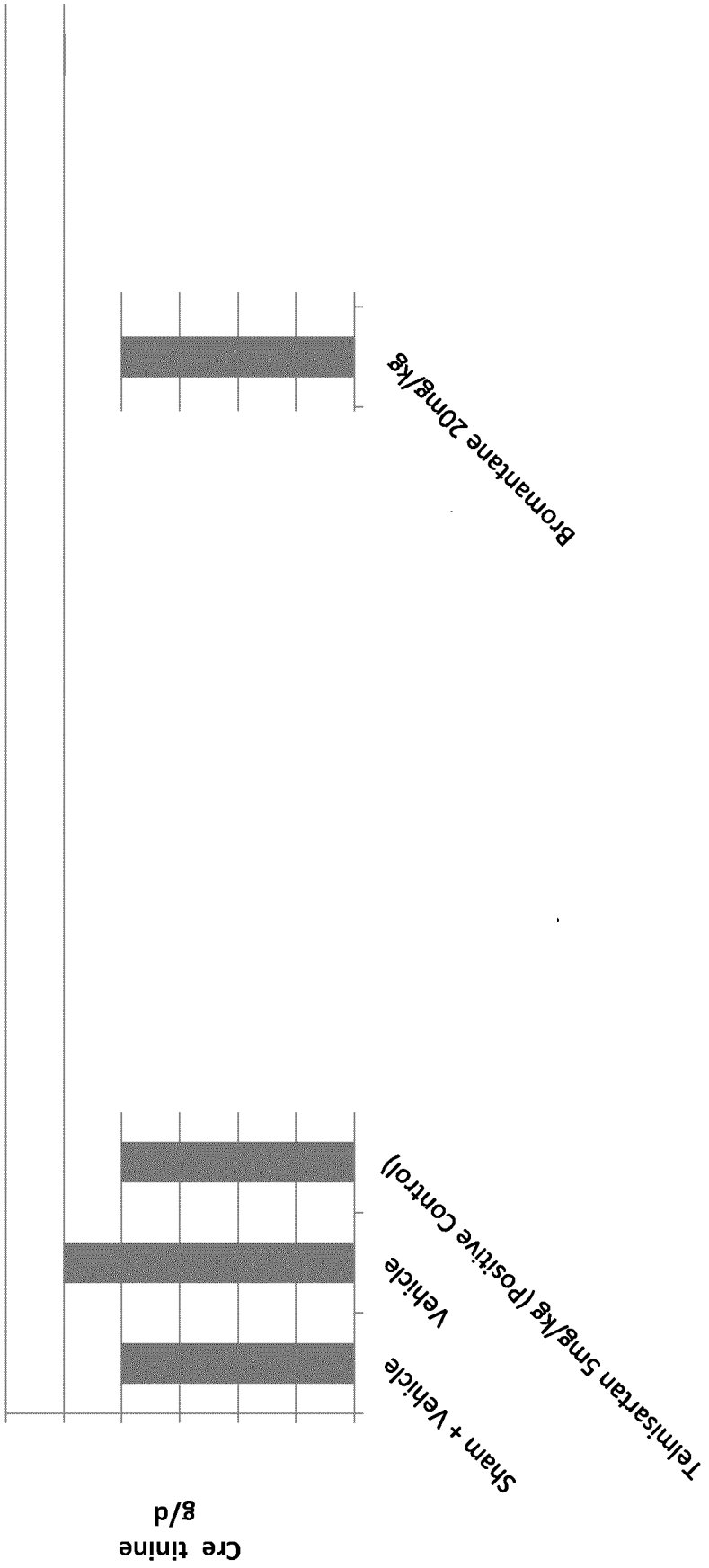

Cre tinine
g/d
Sham + Vehicle
Vehicle
Telmisartan 5mg/kg (Positive Control)
Bromantane 20mg/kg

Figure 23

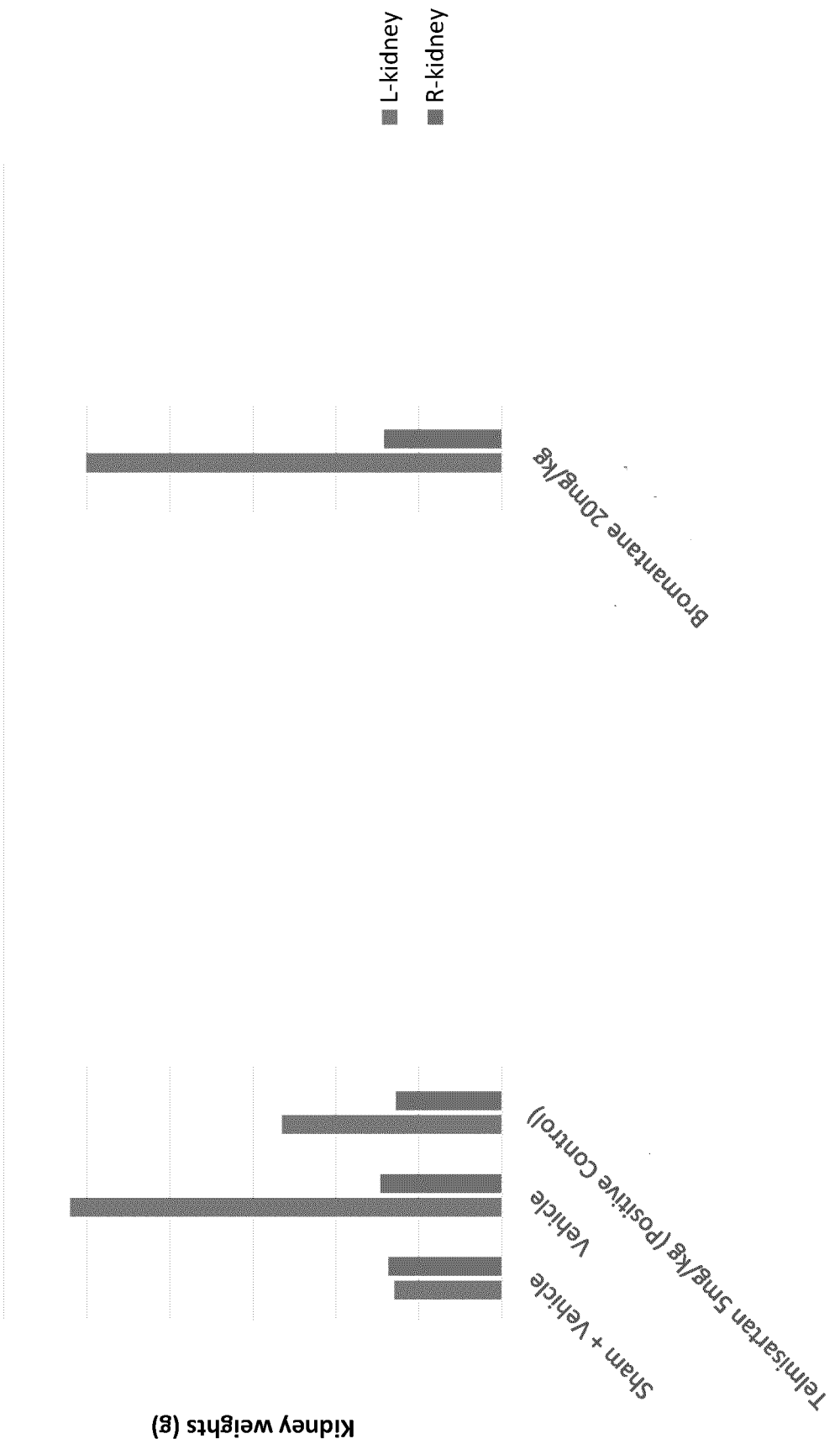

L-kidney
R-kidney
Bromantane 20mg/kg
Telmisartan 5mg/kg (positive Control)
Vehicle
Sham + Vehicle
Kidney weights (g)

Figure 24

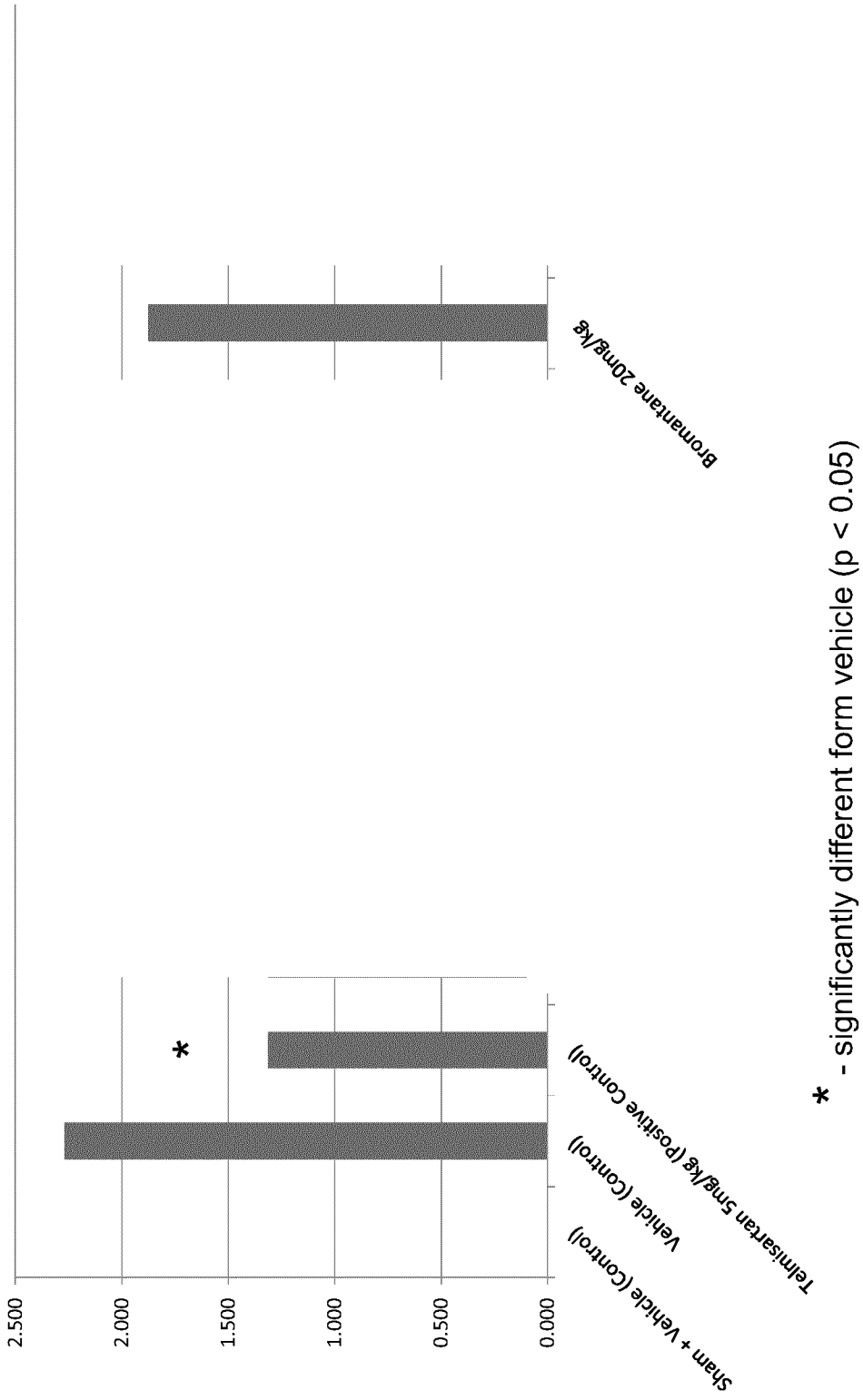

Histology Score
2.500
2.000
1.500
1.000
0.500
0.000
*
Sham + Vehicle (Control)
Vehicle (Control)
Telmisartan 5mg/kg (Positive Control)
Bromantane 20mg/kg
* - significantly different form vehicle (p < 0.05)

Figure 25

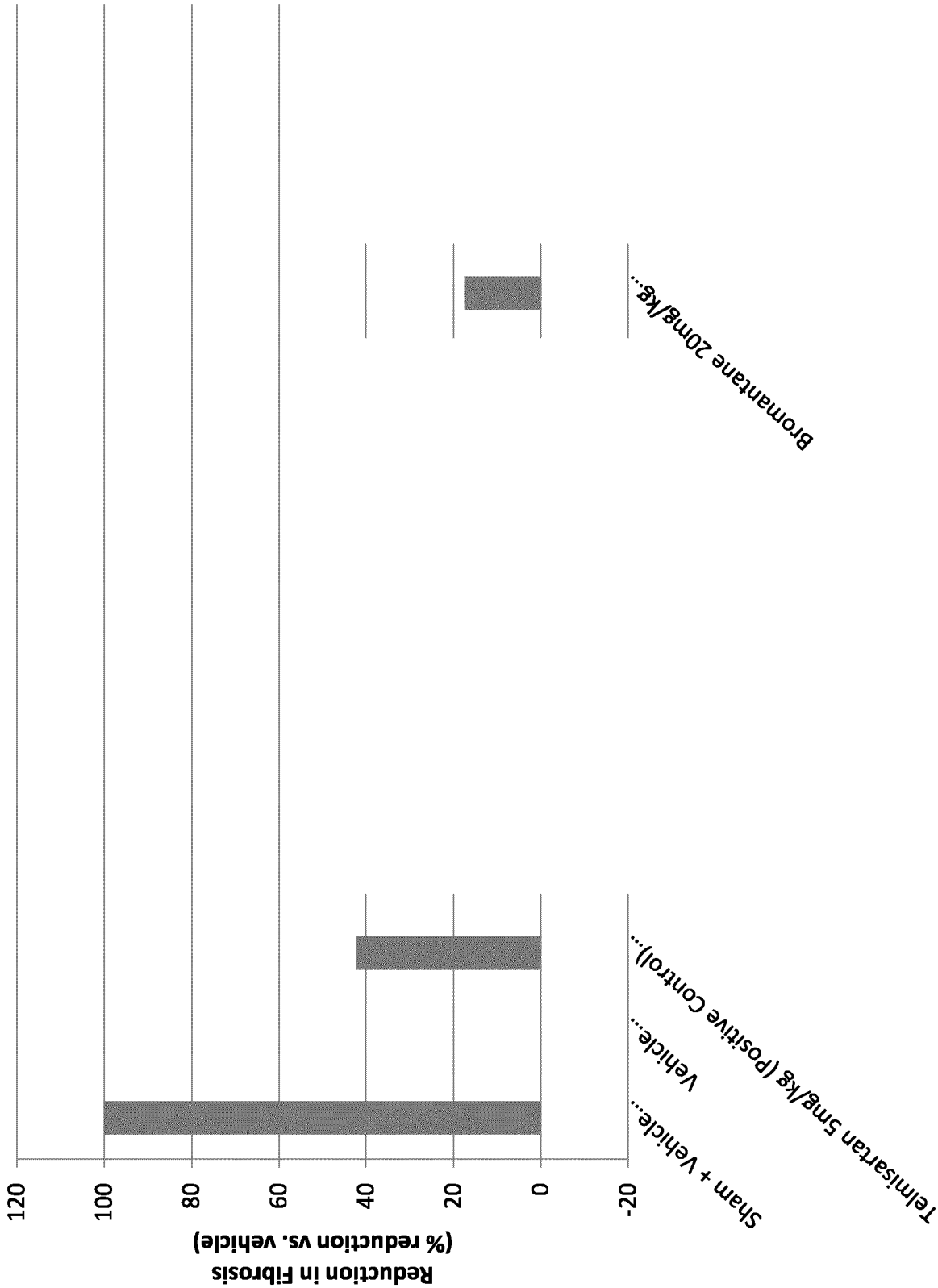

Reduction in Fibrosis
(% reduction vs. vehicle)
120
100
80
60
40
20
0
-20
Sham + Vehicle...
Vehicle...
Telmisartan 5mg/kg (Positive Control)...
Bromantane 20mg/kg...

Figure 26

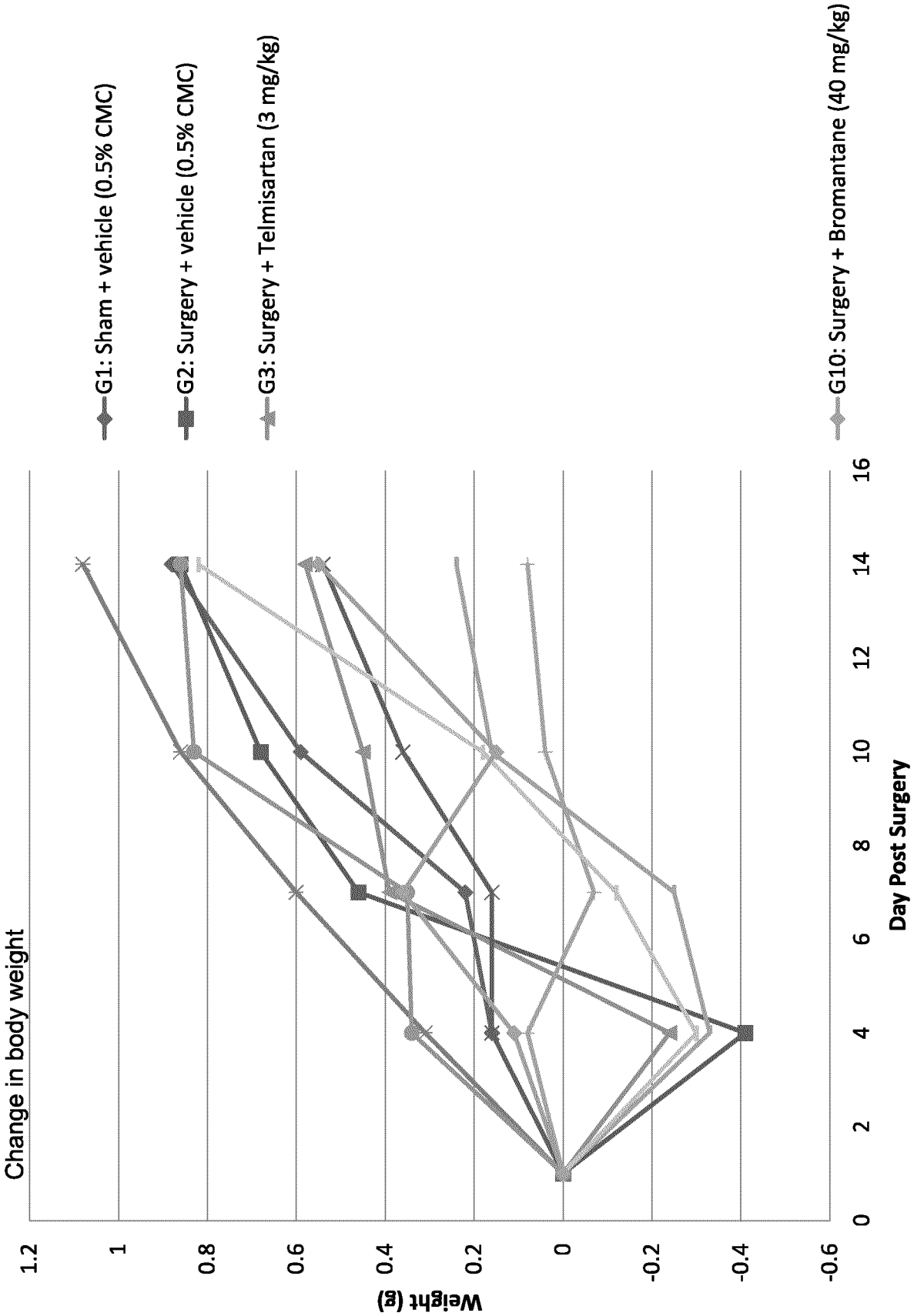

Change in body weight
G1: Sham + vehicle (0.5% CMC)
G2: Surgery + vehicle (0.5% CMC)
G3: Surgery + Telmisartan (3 mg/kg)
G10: Surgery + Bromantane (40 mg/kg)
Weight (g)
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
0
2
4
6
8
10
12
14
16
Day Post Surgery

Figure 27

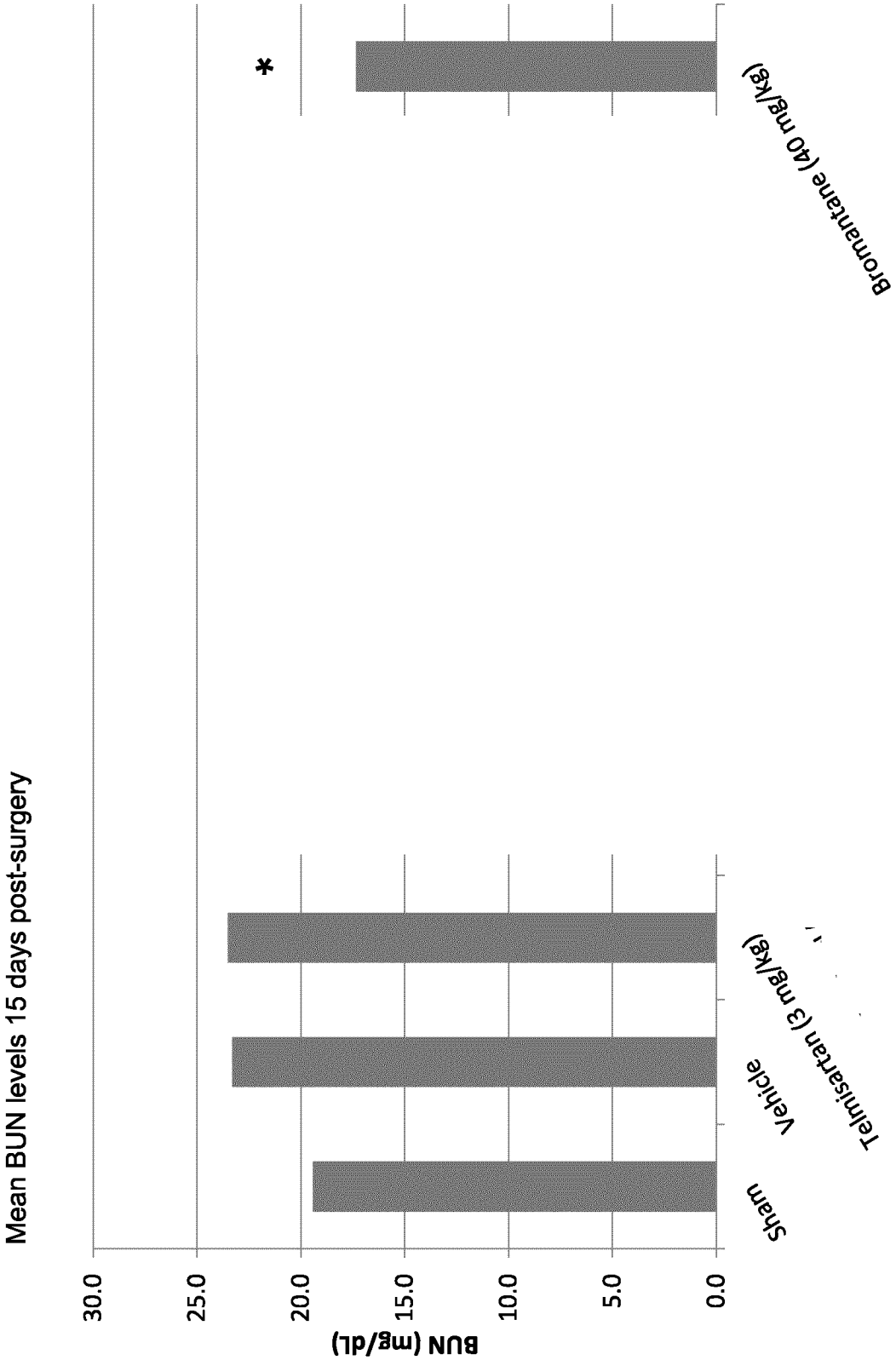

Mean BUN levels 15 days post-surgery
BUN (mg/dL)
30.0
25.0
20.0
15.0
10.0
5.0
0.0
*
Sham
Vehicle
Telmisartan (3 mg/kg)
Bromantane (40 mg/kg)

Figure 28

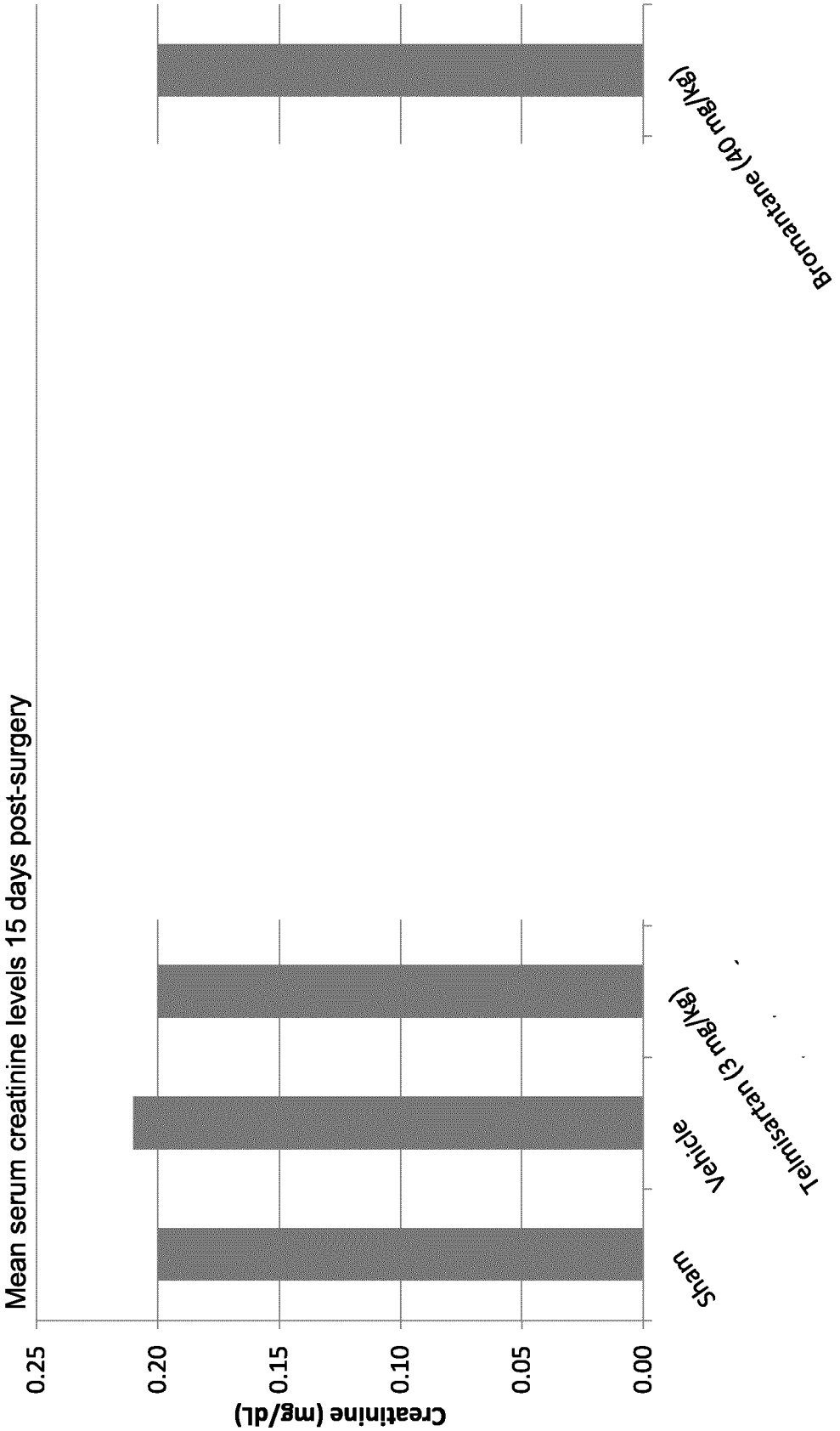
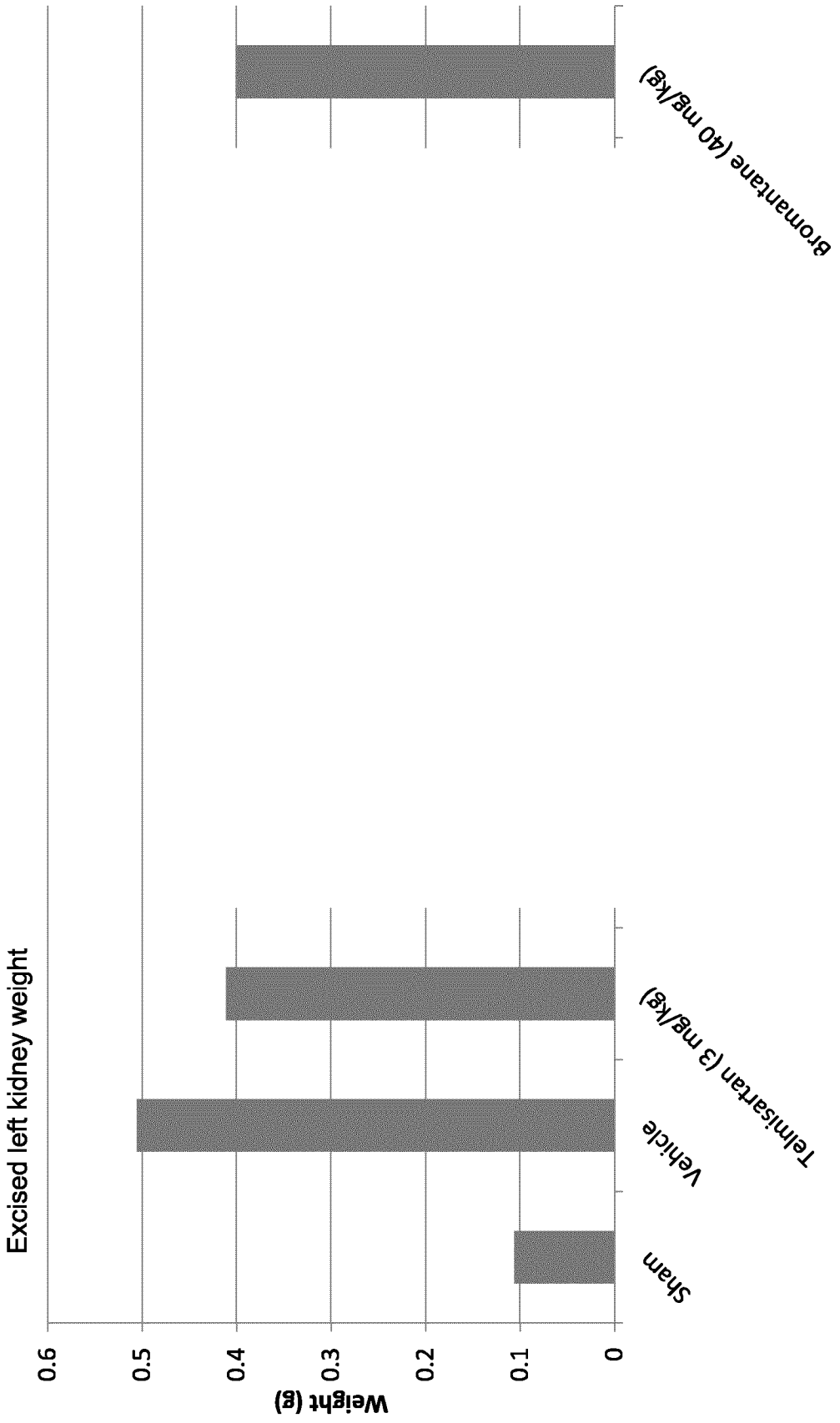
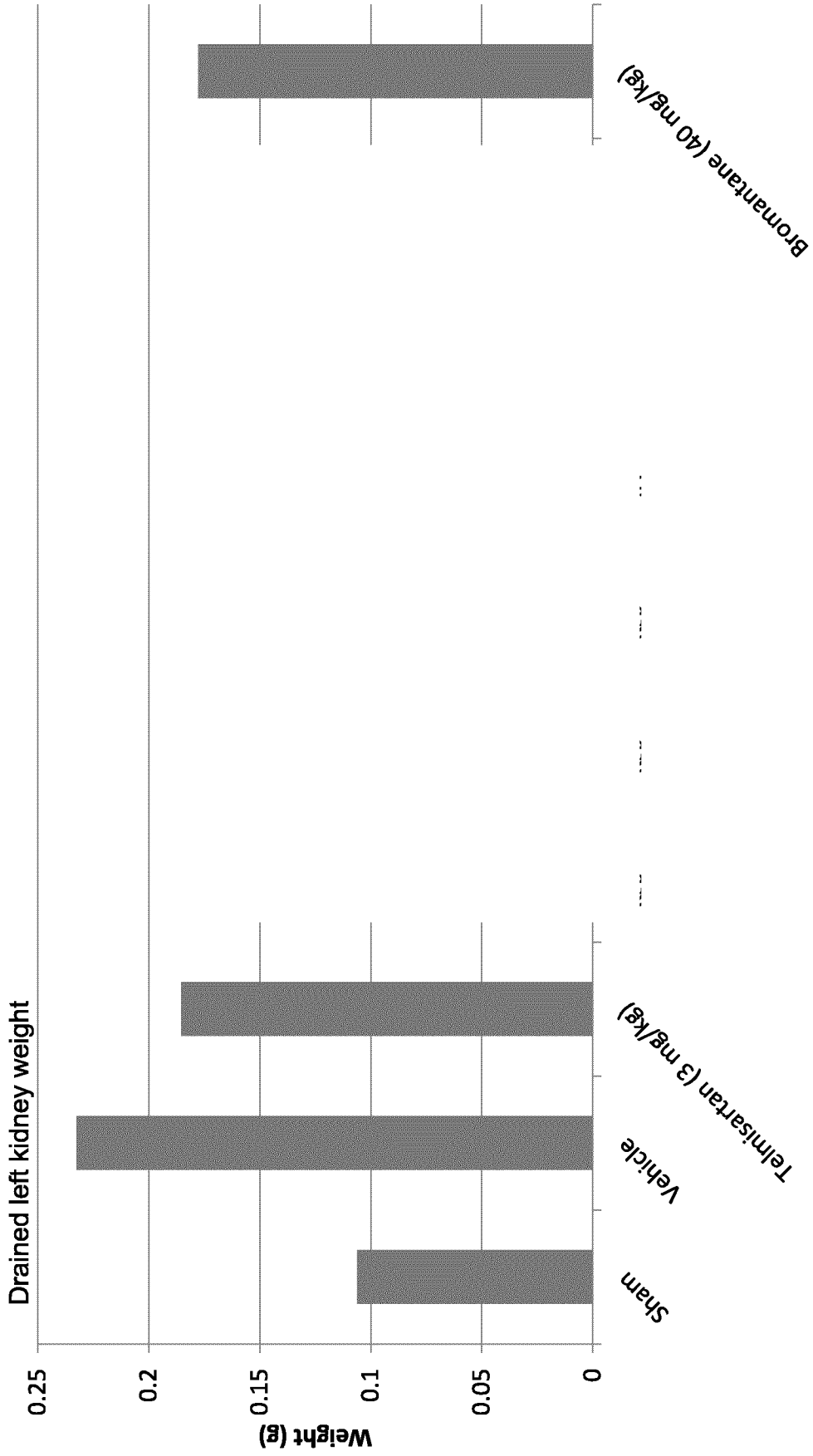

Mean serum creatinine levels 15 days post-surgery
Creatinine (mg/dL)
0.25
0.20
0.15
0.10
0.05
0.00
Sham
Vehicle
Telmisartan (3 mg/kg)
Bromantane (40 mg/kg)

Figure 29



* - significantly different form vehicle ($p < 0.05$)

Figure 30



* - significantly different form vehicle ($p < 0.05$)

Figure 31

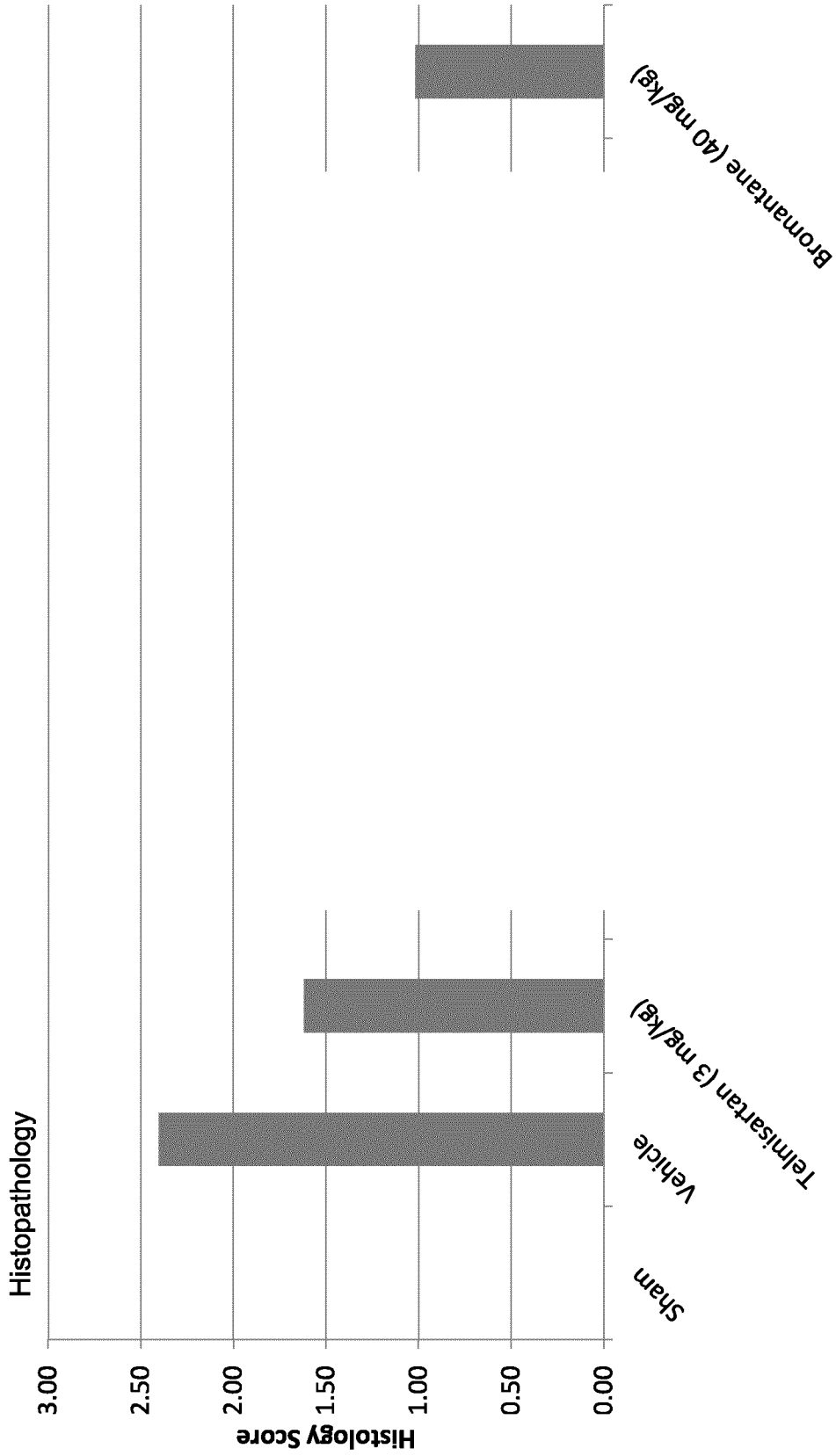
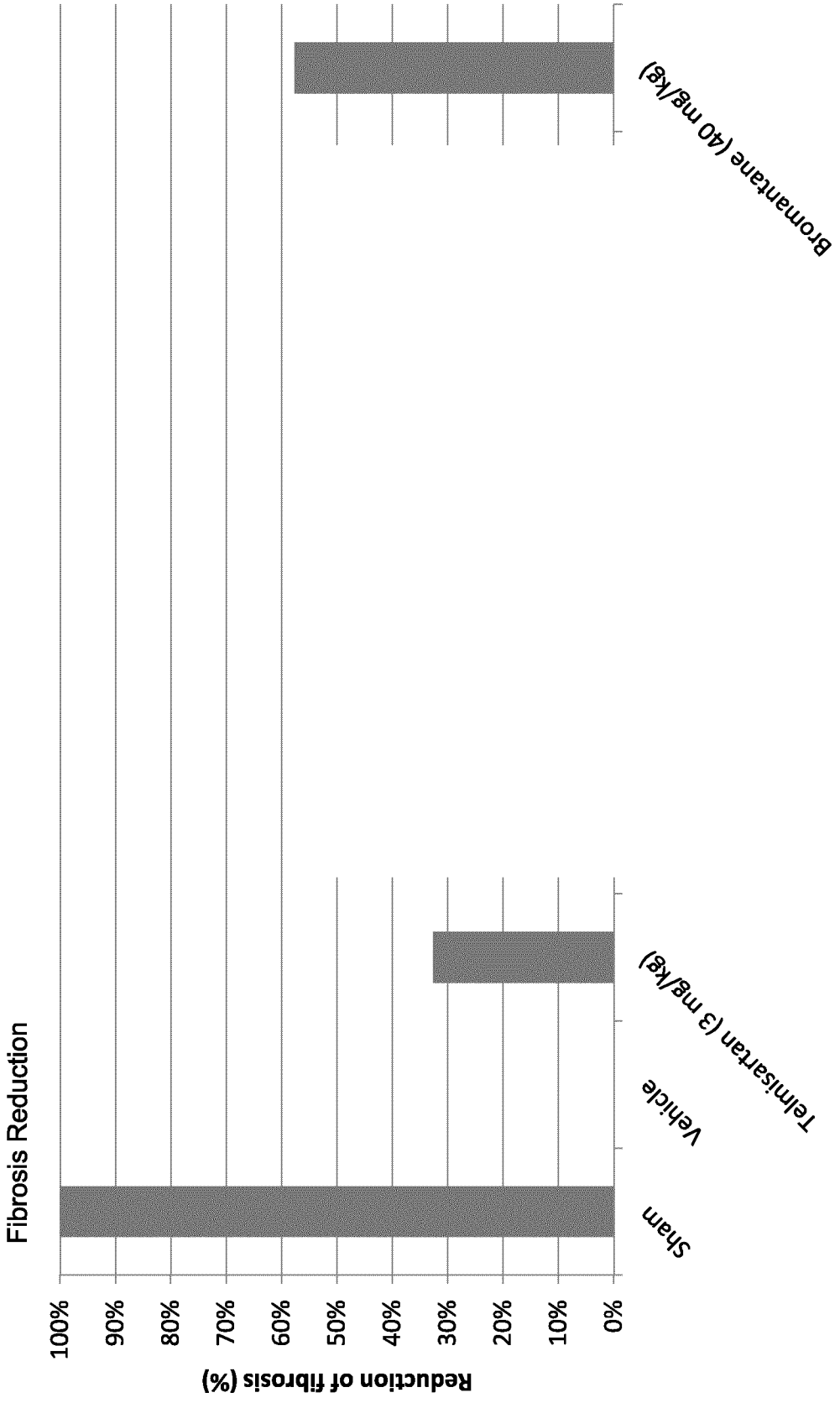

Histopathology
Histology Score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Sham
Vehicle
Telmisartan (3 mg/kg)
Bromantane (40 mg/kg)

Figure 32


Fibrosis Reduction
Reduction of fibrosis (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Sham
Vehicle
Telmisartan (3 mg/kg)
Bromantane (40 mg/kg)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2020/050409

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/136*** (2006.01) , ***A61K 31/429*** (2006.01) , ***A61K 31/433*** (2006.01) , ***A61K 31/451*** (2006.01) , ***A61P 1/16*** (2006.01) , ***A61P 11/00*** (2006.01) (more IPCs on the last page)

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 31/136, A61K 31/429, A61K 31/433, A61K 31/451, A61P 1/16, A61P 11/00, A61P 13/12, C07C 211/52, C07D 211/46, C07D 513/04

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN, Canadian Patent Database, Scopus, Questel-Orbit, Google. Keywords: bromantane, NP-160, NASH, IPF, fibrosis, lung disease, nonalcohol fatty liver, kidney disorder, liver, pulmonary, renal fibrosis, non-alcoholic fatty liver disease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO2020/006631A1 (WILLIAMS, M.) 9 January 2020 (09-01-2020) *abstract; paragraphs [059]-[062]; examples*	1-40
P, X	WO2020/000092A1 (WILLIAMS, M.) 2 January 2020 (02-01-2020) *abstract; paragraphs [065]-[068]; examples*	1-19, 22-38
P, X	WO2019/204813A1 (SANTOS, W. L. et al.) 24 October 2019 (24-10-2019) *abstract; paragraph [0153], compounds 1-81 to 1-85*	1, 5-20, 22, 24-39

☑ 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
"D"	document cited by the applicant in the international application
"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 13 May 2020 (13-05-2020)	Date of mailing of the international search report 02 June 2020 (02-06-2020)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Geneviève Fortier, PhD (819) 639-8658

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☑ Claim Nos.: 1 and 5-21
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:

The claims on file relate to such an extremely large number of possible compounds that a meaningful search over the whole claimed scope is impossible. Consequently, the search has been carried out of those parts of the application which do appear to be concise and supported as follows: (Continuation on page 7)

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

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation from page 3:

CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61P 13/12*** (2006.01) , ***C07C 211/52*** (2006.01) , ***C07D 211/46*** (2006.01) , ***C07D 513/04*** (2006.01)

Continuation from Box No. II:

- fully defined compounds of page 40;
- compounds of formula Ia where "Z_1-Z_9" are carbon atoms, "A" is a hydrogen atom, "R_4" is "$NR_{13}R_{14}$" and "R_9" and "R_{12}" are also hydrogen atoms;
- compounds of formula Ia where "Z_1-Z_9" are carbon atoms, "A" is a hydrogen atom, "R_4" is "$NR_{13}R_{14}$" and "R_{12}" is as defined;
- compounds of formula Ia where "Z_1-Z_9" are carbon atoms, "R_4" is "$NR_{13}R_{14}$", "R_{12}" is as defined and "A" is a hydrogen atom or a C_{1-3} alkyl group, with "R_1", "R_2" and "R_3" undefined; and
- compounds of formula Ib as defined in claim 22.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Repurposed Compounds NP-135 and NP-160 Reduce Fibrosis in a NASH Pre-Clinical Mouse Model" Mark Williams, 2nd Global Nash Congress, February 2019, 1 page https://algernonpharmaceuticals.com/wp-content/uploads/2018/01/Algernon-NASH-Congress-2019.pdf	1-40
L	Agenda, 2nd Global Nash Congress, February 2019, pages 1 and 13 http://www.global-engage.com/wp-content/uploads/2018/08/Global-NASH-Congress-Europe-Agenda-2019.pdf *poster no.14*	1-40
L	Google results for "NP-160" bromantane (publication before 27 March 2019), 1 page https://www.google.ca/search?tbs=cdr%3A1%2Ccd_min%3A01-01-1900%2Ccd_max%3A03-27-2019&ei=4xa8XqCbGI_M_Abr_qmgCA&q=%22NP-160%22+bromantane&oq=%22NP-160%22+bromantane&gs_lcp=CgZwc3ktYWIQDEoGCBoSAjk0SgUIIRIBMVDkmgFYxbABYOS-AWgAcAB4AIABsAGIAbICkgEDMC4ymAEAoAEBqgEHZ3dzLXdpeg&sclient=psy-ab&ved=0ahUKEwjgmP2hmLHpAhUPJt8KHWt_CoQQ4dUDCAs#spf=1589384956338	1-40
X	WO2008/055013A2 (PLAYER, M. R. et al.) 8 May 2008 (08-05-2008) *page 58, lines 14-24; compound 107*	1, 5-19, 22, 24-38
X	PONOMAREV, K. Y. et al.: "Aminoadamantanes containing monoterpene-derived fragments as potent tyrosyl-DNA phosphodiesterase 1 inhibitors" *Bioorganic Chemistry*, Vol. 76, pages 392-399, 2018 *abstract; compound (+)-3C*	1, 5-7, 13, 19
X	CA2905426A1 (HASVOLD, L. A. et al.) 9 October 2014 (09-10-2014) *page 21, lines 31-32; example 72*	1, 2, 5-19, 22-38
X	CA2791505A1 (NAGATA, T. et al.) 22 September 2011 (22-09-2011) *page 33, item (68); paragraph [0211], formula 63*	1, 5-19, 22, 24-38

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2020/050409

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2020006631A1	09 January 2020 (09-01-2020)	None	
WO2020000092A1	02 January 2020 (02-01-2020)	None	
WO2019204813A1	24 October 2019 (24-10-2019)	WO2019204816A1	24 October 2019 (24-10-2019)
		WO2019204819A1	24 October 2019 (24-10-2019)
WO2008055013A2	08 May 2008 (08-05-2008)	WO2008055013A3	22 January 2009 (22-01-2009)
		AR063723A1	11 February 2009 (11-02-2009)
		CL2007003163A1	27 June 2008 (27-06-2008)
		US2008114007A1	15 May 2008 (15-05-2008)
CA2905426A1	09 October 2014 (09-10-2014)	AU2014248647A1	01 October 2015 (01-10-2015)
		BR112015022551A2	18 July 2017 (18-07-2017)
		CN105164113A	16 December 2015 (16-12-2015)
		CN105164113B	02 March 2018 (02-03-2018)
		EP2970193A1	20 January 2016 (20-01-2016)
		EP2970193B1	25 July 2018 (25-07-2018)
		JP2016512542A	28 April 2016 (28-04-2016)
		MX2015012431A	31 May 2016 (31-05-2016)
		US2014275079A1	18 September 2014 (18-09-2014)
		US9493411B2	15 November 2016 (15-11-2016)
		WO2014165127A1	09 October 2014 (09-10-2014)
CA2791505A1	22 September 2011 (22-09-2011)	CA2791505C	07 June 2016 (07-06-2016)
		AU2011228237A1	30 August 2012 (30-08-2012)
		AU2011228237B2	21 April 2016 (21-04-2016)
		BR112012017474A2	19 April 2016 (19-04-2016)
		CN102803226A	28 November 2012 (28-11-2012)
		CN102803226B	04 May 2016 (04-05-2016)
		CN105801489A	27 July 2016 (27-07-2016)
		CN105801489B	10 December 2019 (10-12-2019)
		CO6511269A2	31 August 2012 (31-08-2012)
		CY1119423T1	07 March 2018 (07-03-2018)
		DK2548871T3	06 November 2017 (06-11-2017)
		EP2548871A1	23 January 2013 (23-01-2013)
		EP2548871A4	31 July 2013 (31-07-2013)
		EP2548871B1	19 July 2017 (19-07-2017)
		ES2643132T3	21 November 2017 (21-11-2017)
		HRP20171560T1	01 December 2017 (01-12-2017)
		HUE035072T2	02 May 2018 (02-05-2018)
		IL221903A	31 January 2018 (31-01-2018)
		JPWO2011115064A1	27 June 2013 (27-06-2013)
		JP5807006B2	10 November 2015 (10-11-2015)
		JP2015164972A	17 September 2015 (17-09-2015)
		JP6153971B2	28 June 2017 (28-06-2017)
		JP2017122128A	13 July 2017 (13-07-2017)
		KR20130028705A	19 March 2013 (19-03-2013)
		KR101704095B1	09 February 2017 (09-02-2017)
		KR20160003325A	08 January 2016 (08-01-2016)
		KR101706885B1	14 February 2017 (14-02-2017)
		LT2548871T	25 September 2017 (25-09-2017)
		MX2012008372A	08 August 2012 (08-08-2012)
		MX358628B	28 August 2018 (28-08-2018)
		NZ601658A	29 August 2014 (29-08-2014)
		PL2548871T3	29 December 2017 (29-12-2017)
		PT2548871T	18 October 2017 (18-10-2017)

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
		RS56445B1	31 January 2018 (31-01-2018)
		RU2012144332A	27 April 2014 (27-04-2014)
		RU2572814C2	20 January 2016 (20-01-2016)
		SG182767A1	30 August 2012 (30-08-2012)
		SG10201502026XA	28 May 2015 (28-05-2015)
		SI2548871T1	30 October 2017 (30-10-2017)
		TW201136895A	01 November 2011 (01-11-2011)
		TWI609857B	01 January 2018 (01-01-2018)
		US2013022587A1	24 January 2013 (24-01-2013)
		US2013230501A9	05 September 2013 (05-09-2013)
		US8609710B2	17 December 2013 (17-12-2013)
		US2014178349A1	26 June 2014 (26-06-2014)
		US9340531B2	17 May 2016 (17-05-2016)
		WO2011115064A1	22 September 2011 (22-09-2011)
		ZA201206968B	26 March 2014 (26-03-2014)