AUTOTAXIN INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/167,216 filed on May 27, 2015, which is herein incoporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are methods of using autotaxin inhibitors, and pharmaceutical compositions and medicaments thereof, in the treatment of conditions, diseases, or disorders associated with autotaxin activity.

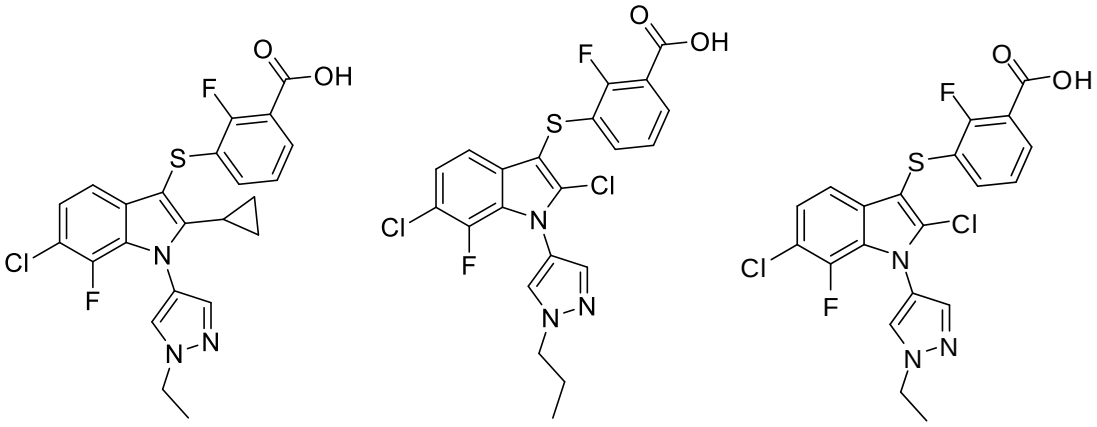
BACKGROUND OF THE INVENTION

[0003] Autotaxin (ATX), also known as ectonucleotide pyrophosphatase/phosphodiesterase family member 2 or ENNP2, is an adipocyte secreted lysophospholipase D that catalyzes the formation of the lipid mediator, lysophosphatidic acid (LPA). Autotaxin expression is enhanced in individuals with certain conditions or diseases.

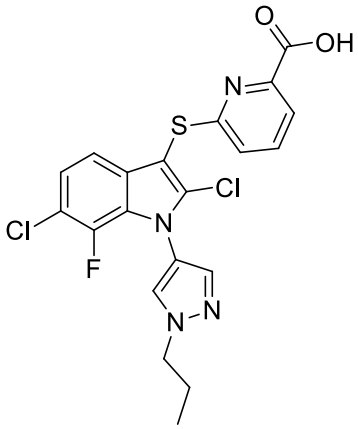
SUMMARY

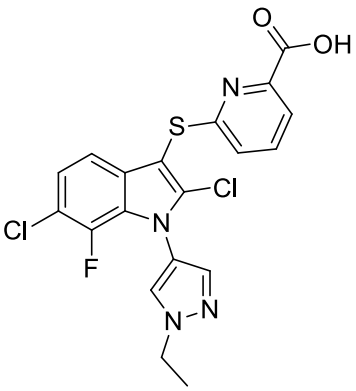
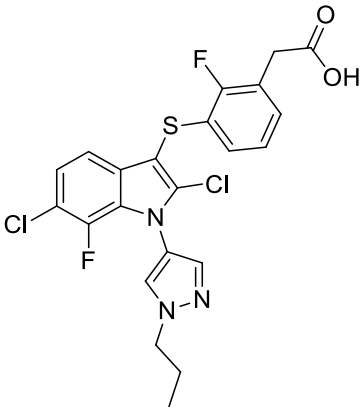
[0004] The autotaxin-lysophosphatidic acid signaling pathway has been implicated in a variety of signaling pathways involved in cell migration, proliferation, and survival. Due to its role in these pathways, autotaxin has been explored as a drug discovery target for the treatment of chronic inflammation, neuropathic pain, fibrotic disease, and various cancers. Intensive efforts have focused on identifying autotaxin inhibitors in the treatment of these disorders.

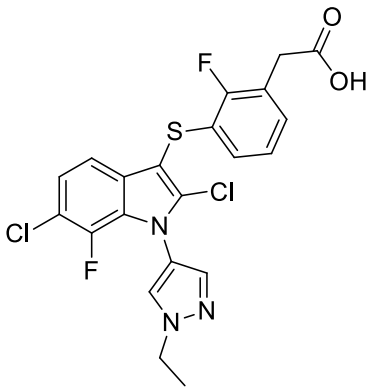
[0004a] In an aspect, there is provided a use of an autotaxin inhibitor in the manufacture of a medicament for treating fibrosis, pruritis, inflammatory disease or conditions, cancer, obesity, or a combination thereof in a mammal, wherein the autotaxin inhibitor has the following structure:



Compound A , Compound B , Compound E



Compound F ,  Compound G ,  Compound H

or 

Compound I

or a pharmaceutically acceptable salt, or solvate thereof.

[0005] In one example, provided herein are methods of using one or more autotaxin inhibitors for the treatment or prevention of diseases or conditions in which autotaxin and/or LPA participates, is involved in the etiology or pathology of the disease, or is otherwise associated with at least one symptom or complication of the disease. Inhibition of the physiological activity of autotaxin and/or LPA is useful in a variety of diseases or conditions. The autotaxin-LPA signaling pathway has been implicated in fibrotic diseases, colitis, cancer, pruritus, angiogenesis, inflammation, autoimmune diseases, reproduction, neurological diseases, and tumor progression.

[0006] In one example, the methods described herein involve the use of one or more autotaxin inhibitor compounds for the treatment of diseases or conditions in which autotaxin activity contributes to the symptomology or progression of the disease, disorder or condition. These diseases, disorders, or conditions may arise from one or more of a genetic, iatrogenic, immunological, infectious, metabolic, oncological, toxic, surgical, and/or traumatic etiology. In one example, the methods, compounds, pharmaceutical compositions, and medicaments described herein comprise autotaxin inhibitors.

[0007] In one example, the autotaxin inhibitors are useful for the treatment of diseases or conditions such as, but not limited to, fibrosis, colitis, cell proliferative disease, inflammatory disease, autoimmune diseases, reproductive diseases, abnormal angiogenesis-associated disease, scleroderma, brain or heart reperfusion injury, neurodegenerative disease, neuropathic pain, peripheral neuropathy, ocular disease, diabetic retinopathy, proliferative vitreoretinopathy, cicatricial pemphigoid, metabolic disorder, and glaucoma.

[0008] In one example, provided herein are pharmaceutical compositions comprising one or more autotaxin inhibitors, pharmaceutically acceptable salts, or solvates thereof useful for the treatment or prevention of one or more diseases or conditions. In some examples, the pharmaceutical composition attenuates or reverses one or more signs or symptoms associated with the one or more disease or conditions. In some examples, the pharmaceutical composition prevents the onset of one or more complications associated with the one or more diseases or conditions. In some examples, the pharmaceutical composition comprises autotaxin inhibitor A. In some examples, the pharmaceutical composition comprises autotaxin inhibitor B. In some examples, the pharmaceutical composition comprises autotaxin inhibitor C. In some examples, the pharmaceutical composition comprises autotaxin inhibitor D. In some examples, the pharmaceutical composition comprises autotaxin inhibitor E. In some examples, the pharmaceutical composition comprises autotaxin inhibitor F. In some examples, the pharmaceutical composition comprises autotaxin inhibitor G. In some examples, the pharmaceutical composition comprises autotaxin inhibitor H. In some examples, the pharmaceutical composition comprises autotaxin inhibitor I. In some examples, the pharmaceutical composition further comprises an additional therapeutic agent. In some examples, the pharmaceutical composition is administered in combination with one or more additional treatments for a disease, disorder or condition. In some examples, the pharmaceutical composition comprises at least one pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[0009] In one example, described herein is a method of treating or preventing any one of the diseases or conditions described herein comprising administering a therapeutically effective

amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to a mammal in need thereof.

[0010] In one example, described herein is a method of treating or preventing any one of the diseases or conditions described herein comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to a mammal in need thereof; wherein the autotaxin inhibitor, or the pharmaceutically acceptable salt or solvate thereof, does not cause hepatobiliary damage in the mammal.

[0011] In one example, described herein is a method of treating or preventing any one of the diseases or conditions described herein comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to a mammal in need thereof; wherein one or more liver proteins are not significantly elevated in the subject after the administration of the autotaxin inhibitor, or the pharmaceutically acceptable salt or solvate thereof. In some examples, a significant elevation in the concentration of a liver protein is at least a 50%, 100%, 200% or 500% increase in the concentration of the liver protein. In some examples, the liver protein is aspartate transaminase. In some examples, the liver protein is alkaline phosphatase. In some examples, the liver protein is bilirubin.

[0012] In another example, described herein is a method for treating or preventing fibrosis, pruritus, colitis, cancer, an inflammatory disease or condition, an airway disease or condition, an autoimmune disease or condition, a neurological disease or condition, obesity, intraocular pressure, neuropathic pain, or combinations thereof in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the administration of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof attenuates at least one symptom of fibrosis, pruritus, colitis, cancer, an inflammatory disease or condition, an airway disease or condition, an autoimmune disease or condition, neurological disease or condition, obesity, intraocular pressure, neuropathic pain, or combinations thereof.

[0013] In one example, described herein is a method for treating or preventing a disease, disorder or condition described herein, the method comprising administering an autotaxin inhibitor to a mammal in need thereof; wherein following the administration of the autotaxin inhibitor, blood lysophosphatidic acid levels in the mammal decrease by at least about 5%, 10%, 20%, 30%, 40% or 50%.

[0014] In one example, described herein is a method for treating or preventing a disease, disorder or condition described herein, the method comprising administering an autotaxin inhibitor to a mammal in need thereof; wherein following the administration of the autotaxin inhibitor, blood autotaxin levels in the mammal decrease by at least about 5%, 10%, 20%, 30%, 40% or 50%.

[0015] In one example, described herein is a method for treating or preventing a disease, disorder or condition described herein, the method comprising administering an autotaxin inhibitor, or a

pharmaceutically acceptable salt or solvate thereof, wherein the autotaxin inhibitor is formulated for administration to a mammal in need thereof by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration.

[0016] In one example, described herein is a method for treating or preventing a disease, disorder or condition described herein, the method comprising administering an autotaxin inhibitor, or a pharmaceutically acceptable salt or solvate thereof, wherein the autotaxin inhibitor is in a pharmaceutical composition having the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[0017] In one example, described herein is a method for the treatment or prevention of fibrosis in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, accumulation of extracellular matrix or the rate of accumulation of extracellular matrix in a tissue having fibrosis is reduced following administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof. In some examples, the fibrosis comprises peritoneal fibrosis, lung fibrosis, liver fibrosis, kidney fibrosis, ocular fibrosis or cutaneous fibrosis. As an example, the method comprises administering an autotaxin inhibitor to a mammal having liver fibrosis. In some instances, the onset of cirrhosis or liver failure is delayed or prevented following administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof. In some instances, the accumulation of fibrogenic cells and/or the deposition of extracellular matrix proteins within the liver is attenuated or prevented following administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof. In one example, the method comprises administering an autotaxin inhibitor to a mammal having kidney fibrosis. In some instances, administration of an autotaxin inhibitor to the mammal prevents renal failure. As another example, the method comprises administering an autotaxin inhibitor to a mammal having peritoneal fibrosis. As a further example, the method comprises administering an autotaxin inhibitor to a mammal having skin fibrosis. In some instances, dermal thickness of a skin sample having fibrosis is decreased by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% following administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof.

[0018] In one example, described herein is a method for the treatment or prevention of fibrosis in a mammal comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and a second therapeutic agent. In some examples, the second therapeutic agent

comprises an angiotensin inhibitor, colchicine, corticosteroid, an endothelin inhibitor, interferon-alpha, interleukin 10, an

antioxidant, a hepatic stellate cell (HSC) inhibitor, an ACE inhibitor, an ADAM inhibitor, a metalloenzyme, pirfenidone, tranilast, fluorofenidone, an anti-inflammatory agent, an immunosuppressant, or a combination thereof.

[0019] In one example, described herein is a method for the treatment or prevention of colitis in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In one example, described herein is a method for the treatment or prevention of inflammatory bowel disease in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some instances, the colitis is acute colitis. In some instances, the colitis is chronic colitis. In some examples, the colitis is autoimmune colitis, idiopathic colitis, latrogenic colitis, vascular disease or infectious colitis.

[0020] In one example, described herein is a method for the treatment or prevention of ulcerative colitis in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, reduces ulcer size in ulcerative colitis by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% following the administration.

[0021] In some examples, one or more signs or symptoms of colitis are reduced in the mammal following administration of the autotaxin inhibitor. Signs or symptoms include, without limitation, abdominal pain, diarrhea, mucus in stool, cramping, abdominal tenderness, fever, bloody stool, distension, colonic mucosal erythema and ulcers.

[0022] In one example, described herein is a method for the treatment or prevention of colitis in a mammal comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and a second therapeutic agent. In some examples, the second therapeutic agent comprises a steroid, an anti-inflammatory agent, an immunosuppressant, or a combination thereof. In one example, provided herein is a method for the treatment or prevention of colitis in a mammal, the method comprising the administration of an autotaxin inhibitor and cyclosporine A. In one example, provided herein is a method for the treatment or prevention of colitis in a mammal, the method comprising the administration of an autotaxin inhibitor and sulfasalazine.

[0023] In one example, described herein is a method for the treatment or prevention of a neurological disease or disorder in a mammal comprising administering a therapeutically

effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In one example, described herein is a method for the treatment or

prevention of multiple sclerosis in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, attenuates, reverses, or inhibits demyelination in the mammal. In some examples, administration of the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof to a mammal having multiple sclerosis, decreases the frequency, severity and/or duration of a relapse of multiple sclerosis symptoms in the mammal. Multiple sclerosis symptoms include, without limitation, numbness or weakness in a limb, partial or complete loss of vision, double vision, blurring of vision, tingling sensation, tremors, lack of coordination, unsteady gait, slurred speech, fatigue and dizziness.

[0024] In one example, described herein is a method for the treatment or prevention of a neurological disease in a mammal, the method comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and a second therapeutic agent. In some examples, the second therapeutic agent comprises a corticosteroid, a beta interferon, glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide, natalizumab, mitoxantrone, a muscle relaxant, or a combination thereof. In some instances, the neurological disease is multiple sclerosis.

[0025] In one example, described herein is a method for treating or preventing pruritus in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the pruritus is associated with dermatitis herpetiformis, dermatomyositis, pemphigoid, Sjögren's syndrome, Darier's disease, Hailey-Hailey disease, Ichthyoses, Sjögren-Larsson syndrome, dermatophytosis, folliculitis, impetigo and other bacterial infections, insect bites, pediculosis, scabies, viral infection, asteatosis, atopic eczema, contact dermatitis, drug reaction, lichen planus, lichen simplex chronicus, mastocytosis (urticaria pigmentosa), miliaria, psoriasis, scar(s), urticaria, cutaneous T-cell lymphoma or mycosis fungoides, cutaneous B-cell lymphoma, leukemia cutis, pemphigoid gestationis, polymorphic eruption of pregnancy or prurigo gestationis. In one example, described herein is a method for treating or preventing cholestatic pruritus in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal in need thereof. In some examples, following administration of the autotaxin inhibitor, the number of scratch movements exhibited by a mammal having pruritus decreases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In one example, described herein is a

method for the treatment or prevention of a pruritus in a mammal, the method comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a

pharmaceutically acceptable salt, or solvate thereof and a second therapeutic agent. In some examples, the second therapeutic agent comprises topical capsaicin.

[0026] In one example, described herein is a method for treating or preventing cancer in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the cancer is a solid tumor. In some examples, the cancer is bladder cancer, colon cancer, brain cancer, breast cancer, endometrial cancer, heart cancer, kidney cancer, lung cancer, liver cancer, uterine cancer, blood and lymphatic cancer, ovarian cancer, pancreatic cancer, prostate cancer, thyroid cancer, or skin cancer. In some examples, the cancer is a sarcoma, carcinoma, or lymphoma. In some examples, the cancer is amenable to treatment with an autotaxin inhibitor. In some examples, the method further comprises administering a second therapeutic agent to the mammal in addition to the autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof. In one example, described herein is a method for the treatment or prevention of cancer in a mammal, the method comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and a second anti-cancer agent or therapy.

[0027] In one example, described herein is a method of reducing or inhibiting angiogenesis in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, reducing or inhibiting angiogenesis in the mammal treats atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, or diabetic retinopathy. In one example, described herein is a method for the reduction or inhibition of angiogenesis in a mammal, the method comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and a second therapeutic agent or therapy. In some instances, the second therapeutic agent comprises an angiogenesis inhibitor, for example, a VEGF inhibitor (bevacizumab), sorafenib, sunitinib, pazopanib, everolimus, or a combination thereof.

[0028] In another example, described herein is a method of treating or preventing an inflammatory disease or condition in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the inflammatory disease or condition is psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial

cystitis, scleroderma, eczema, lupus erythematosus, dermatomyositis, Sjogren's syndrome, thyroiditis, myasthenia

gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, allergic conjunctivitis or atopic dermatitis. In one example, described herein is a method for treating or preventing an inflammatory disease or condition in a mammal, the method comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and an anti-inflammatory drug. In some examples, the anti-inflammatory drug comprises a non-steroidal anti-inflammatory drug.

[0029] In another example, described herein is a method of treating or preventing an autoimmune disease or condition in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In one example, described herein is a method for treating or preventing an autoimmune disease or condition in a mammal comprising administering to the mammal a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof and an immunosuppressant. In some examples, the immunosuppressant comprises a glucocorticoid, cytostatic, antibody, drug, or a combination thereof.

[0030] In another example, described herein is a method of treating or preventing an airway disease or condition in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the airway disease is chronic obstructive pulmonary disease, cystic fibrosis or asthma.

[0031] In another example, described herein is a method of treating or preventing intraocular pressure in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the intraocular pressure is associated with glaucoma.

[0032] In another example, described herein is a method of treating or preventing neuropathic pain in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal. In some examples, the neuropathic pain is the result of a nerve injury.

[0033] In one example, described herein is a method of treating or preventing a metabolic disorder, and/or one or more conditions associated with a metabolic disorder, the method comprising administering an autotaxin inhibitor to a mammal in need thereof. In another example, described herein is a method for preventing or delaying the onset of at least one metabolic disorder in a mammal at risk for developing a metabolic disorder, comprising

administering to the mammal an autotaxin inhibitor. In some examples, the metabolic disorder is treated by reducing blood glucose levels. In some instances, blood glucose levels decrease in the subject by

at least bout 10% following administration of the autotaxin inhibitor. In some examples, the metabolic disorder is treated by reducing plasma lysophosphatidic acid levels. In some examples, the metabolic disorder is treated by improving insulin sensitivity. In some examples, the metabolic disorder is treated by increasing insulin secretion. In some examples, the metabolic disorder is treated by improving glucose tolerance. In some examples, the metabolic disorder is treated by decreasing adipose tissue expansion. In some examples, the metabolic disorder does not induce hypoglycemia. In some examples, the metabolic disorder is selected from the group consisting of: metabolic syndrome, elevated blood glucose levels, insulin resistance, glucose intolerance, type 2 diabetes, type 1 diabetes, pre-diabetes, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), obesity, or a combination thereof. In some examples, the mammal has a body mass index of at least 25 kg/m2 and at least one or more of the diabetes risk factors selected from the group consisting of: physical inactivity, a first-degree relative with diabetes, a high-risk race or ethnicity, a woman that delivered a baby weighing more than 9 pounds, a woman previously diagnosed with gestational diabetes, hypertensive, HDL cholesterol levels lower than at least 0.9 mmol/L (35 mg/dL), triglyceride levels at least 2.82 mmol/L (250 mg/dL) or greater, a woman with polycystic ovarian syndrome, severe obesity, acanthosis nigrican, and cardiovascular disease.

[0034] In another example, described herein is a method of treating or preventing obesity in a mammal comprising administering a therapeutically effective amount of an autotaxin inhibitor, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal.

[0035] In one example, described herein is a method for reducing blood glucose levels of a mammal comprising administering to the mammal an autotaxin inhibitor, thereby decreasing the blood glucose levels of the mammal. Further provided is a method for preventing or delaying the onset of an elevated blood glucose level in a mammal at risk for developing an elevated glucose level, the method comprising administering to the mammal an autotaxin inhibitor. In some examples, the mammal has an elevated blood glucose level. In certain examples, the method comprises measuring the blood glucose level of the mammal. In certain examples, the method comprises selecting a mammal having an elevated blood glucose level. The measured blood glucose level is inclusive of fasted blood glucose level, post-prandial blood glucose level, whole blood glucose level and plasma blood glucose level. In some examples, the blood glucose level is reduced to below 200 mg/dL, 175 mg/dL, 150 mg/dL, 125 mg/dL, 120 mg/dL, 115 mg/dL, 110 mg/dL, 105 mg/dL, or 100 mg/dL after treatment with an autotaxin inhibitor.

[0036] In one example, described herein is a method for reducing plasma lysophosphatidic acid levels of a mammal comprising administering to the mammal an autotaxin inhibitor; and thereby decreasing plasma lysophosphatidic acid levels of the mammal. In some examples, the mammal has an elevated blood glucose level. In some examplesthe mammal is insulin resistant.

[0037] In one example, described herein is a method for improving insulin sensitivity, delaying the onset of insulin resistance, and/or increasing insulin secretion in a mammal comprising administering to the mammal an autotaxin inhibitor; and thereby improving insulin resistance in the mammal.

[0038] In one example, described herein is a method for improving glucose tolerance in a mammal comprising administering to the mammal an autotaxin inhibitor; and thereby improving glucose tolerance.

[0039] In one example, described herein is a method for decreasing adipose tissue expansion in a mammal comprising administering to the mammal an autotaxin inhibitor; and thereby decreasing adipose tissue expansion in the mammal. In some examples, the mammal has an elevated blood glucose level. In some examples, the mammal is insulin resistant.

[0040] In any of the aforementioned examplesare further examplesin which the effective amount of the autotaxin inhibitor, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by inhalation; and/or (e) administered by nasal administration; or and/or (f) administered by injection to the mammal; and/or (g) administered topically to the mammal; and/or (h) administered by ophthalmic administration; and/or (i) administered rectally to the mammal; and/or (j) administered non-systemically or locally to the mammal.

[0041] In any of the aforementioned examplesare further examplescomprising single administrations of the effective amount of the autotaxin inhibitor, including further examplesin which the autotaxin inhibitor is administered once a day to the mammal or the autotaxin inhibitor is administered to the mammal multiple times over the span of one day. In some examples, the autotaxin inhibitor is administered on a continuous dosing schedule. In some examples, the autotaxin inhibitor is administered on a continuous daily dosing schedule.

[0042] In any of the aforementioned examplesinvolving the treatment of autotaxin dependent diseases or conditions are further embodiments comprising administering at least one additional agent in addition to the administration of an autotaxin inhibitor, or a pharmaceutically

acceptable salt thereof. In various examples, each agent is administered in any order, including simultaneously.

[0043] In any of the examplesdisclosed herein, the mammal is a human.

[0044] In some examples, autotaxin inhibitors provided herein are administered to a human.

[0045] In some examples, autotaxin inhibitors provided herein are orally administered.

[0046] Articles of manufacture, which include packaging material, an autotaxin inhibitor, or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that the autotaxin inhibitor or composition, or pharmaceutically acceptable salt, tautomers, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of autotaxin, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from inhibition of the activity of autotaxin, are provided.

[0047] Other objects, features and advantages of the autotaxin inhibitors, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0048] **Fig. 1** provides hydroxyproline levels in skin biopsies from PBS-injected or bleomycin-injected mice treated with an autotaxin inhibitor. Cmpd A attenuates skin fibrosis when dosed prophylactically (pro) or therapeutically (ther) in a mouse subcutaneous bleomycin model.

[0049] **Fig. 2** provides hydroxyproline levels in non-ligated and ligated kidneys from UUO-mice after prophylactic (A) or therapeutic (B) treatment with an autotaxin inhibitor. Cmpd A attenuates renal fibrosis when dosed prophylactically (A) or therapeutically (B) in a mouse UUO model.

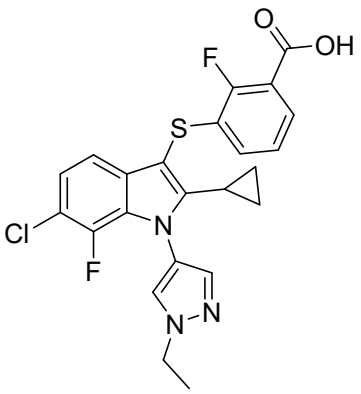
[0050] **Fig. 3** provides hydroxyproline levels in mice peritoneum from vehicle or chlorhexidine gluconate injected mice treated with an autotaxin inhibitor. Cmpd A attenuates peritoneal fibrosis when dosed prophylactically in a mouse chlorhexidine gluconate model.

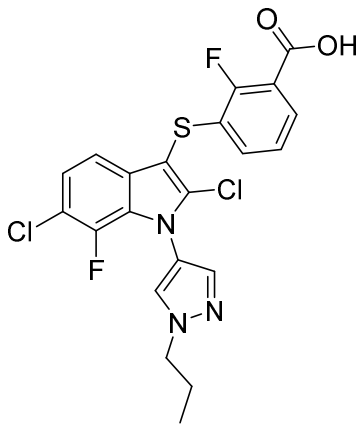
[0051] **Fig. 4** provides percent PSR positive area in the livers from CDAA/HFD fed mice treated therapeutically with vehicle or autotaxin inhibitors. Cmpd A and cmpd B attenuate hepatic fibrosis when dosed therapeutically in a mouse CDAA/HFD model.

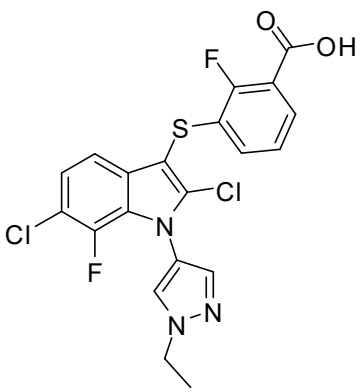
CLAIMS

WHAT IS CLAIMED IS:

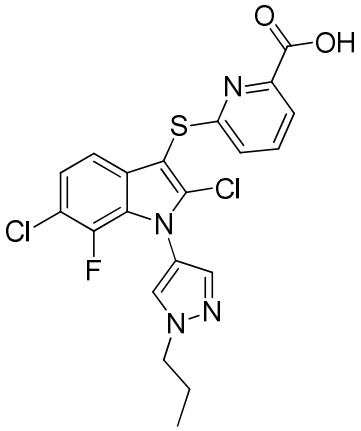
1. Use of an autotaxin inhibitor in the manufacture of a medicament for treating fibrosis, pruritus, inflammatory disease or conditions, cancer, obesity, or a combination thereof in a mammal, wherein the autotaxin inhibitor has the following structure:

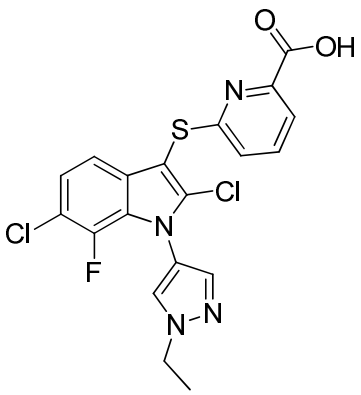


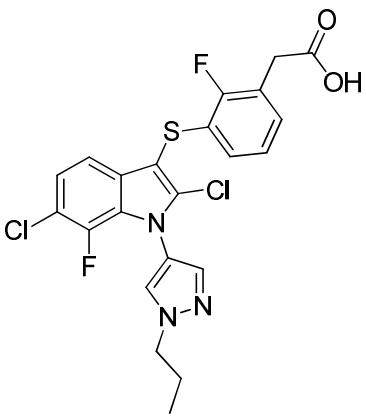
Compound A , 

Compound B , 

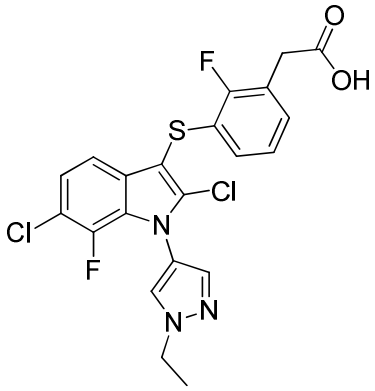
Compound E



Compound F , 

Compound G , 

Compound H

or 

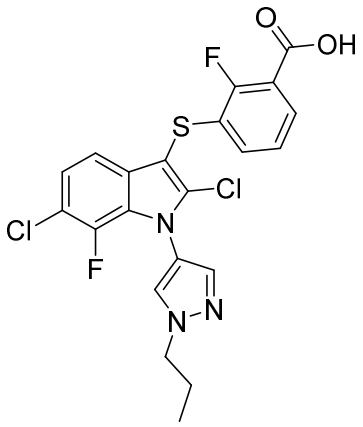
Compound I

or a pharmaceutically acceptable salt, or solvate thereof.

2. The use according to claim 1, wherein Compound A, Compound B, Compound E, Compound F, Compound G, Compound H, or Compound I is to be administered in the form of a pharmaceutically acceptable salt.

3. The use according to claim 2, wherein Compound A, Compound B, Compound E, Compound F, Compound G, Compound H, or Compound I is to be administered in the form of a sodium salt.

4. The use according to claim 1, wherein the autotaxin inhibitor has the structure of Compound B, with the following structure:



Compound B

or a pharmaceutically acceptable salt thereof.

5. The use according to claim 4, wherein compound B is to be administered in the form of a pharmaceutically acceptable salt.

6. The use according to claim 4, wherein compound B is to be administered in the form of a sodium salt.

7. The use according to any one of claims 1 to 6, wherein the medicament is for treating fibrosis in the mammal.

8. The use according to claim 7, wherein the fibrosis is suitable for treatment with an autotaxin inhibitor.

9. The use according to claim 7, wherein the fibrosis is pulmonary fibrosis, hepatic fibrosis, renal fibrosis, ocular fibrosis, peritoneal fibrosis, skin fibrosis, or a combination thereof.

10. The use according to claim 7, wherein the fibrosis is a fibrotic disease of the liver.

11. The use according to claim 10, wherein the fibrotic disease of the liver includes fatty liver disease, steatosis, cholestatic liver disease, cirrhosis, alcohol-induced liver fibrosis, bile duct injury, bile duct fibrosis, or cholangiopathy.

12. The use according to claim 10, wherein the fibrotic disease of the liver includes nonalcoholic steatohepatitis (NASH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), or nonalcoholic fatty liver disease (NAFLD).

13. The use according to claim 7, wherein the fibrosis is a pulmonary fibrotic disease.

14. The use according to claim 13, wherein the pulmonary fibrotic disease includes pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonia (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiolitis obliterans, or bronchiectasis.

15. The use according to claim 7, wherein the fibrosis is a fibrotic disease of the skin.

16. The use according to claim 15, wherein the fibrotic disease of the skin includes dermal fibrosis, scleroderma, nephrogenic systemic fibrosis, scarring, or keloids.

17. The use according to claim 7, wherein the autotaxin inhibitor inhibits or reduces the rate of accumulation of fibrogenic cells and deposition of extracellular matrix proteins in the tissue of the mammal.

18. The use according to any one of claims 1 to 6, wherein the medicament is for treating pruritus in the mammal.

19. The use according to claim 18, wherein the pruritus is associated with dermatitis herpetiformis, dermatomyositis, pemphigoid, Sjögren's syndrome, Darier's disease, Hailey-Hailey disease, Ichthyoses, Sjögren-Larsson syndrome, dermatophytosis, folliculitis, impetigo and other bacterial infections, insect bites, pediculosis, scabies, viral infection, asteatosis, atopic eczema, contact dermatitis, drug reaction, lichen planus, lichen simplex, mastocytosis (urticaria pigmentosa), miliaria, psoriasis, scarring, urticaria, cutaneous T-cell lymphoma or mycosis fungoides, cutaneous B-cell lymphoma, leukemia cutis, pemphigoid gestationis, polymorphic eruption of pregnancy, or prurigo gestationis.

20. The use according to claim 18, wherein the pruritus is cholestatic pruritus.

21. The use according to any one of claims 1 to 6, wherein the medicament is for treating an inflammatory disease or condition in the mammal.

22. The use according to claim 21, wherein the inflammatory disease or condition is psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, eczema, lupus erythematosus, dermatomyositis, Sjogren's syndrome, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, allergic conjunctivitis or atopic dermatitis.

23. The use according to claim 21, wherein the inflammatory disease or condition is inflammatory bowel disease.

24. The use according to claim 23, wherein the inflammatory bowel disease is colitis.

25. The use according to claim 24, wherein the colitis is acute colitis.

26. The use according to claim 24, wherein the colitis is chronic colitis.

27. The use according to claim 24, wherein the colitis is idiopathic colitis, iatrogenic colitis, vascular disease, or infectious colitis.

28. The use according to claim 24, wherein the colitis is ulcerative colitis.

29. The use according to claim 21, wherein the inflammatory disease or condition is multiple sclerosis.

30. The use according to claim 29, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis, relapsing multiple sclerosis, primary-progressive multiple sclerosis, or secondary-progressive multiple sclerosis.

31. The use of claim 30, wherein the autotaxin inhibtior decreases the frequency, severity and/or duration of a relapse of one or more multiple sclerosis symptoms.

32. The use according to claim 31, wherein the symptoms of multiple sclerosis include numbness or weakness in a limb, partial or complete loss of vision, double vision, blurring of vision, tingling, tremors, lack of coordination, unsteady gait, slurred speech, fatigue, dizziness, or a combination thereof.

33. The use according to claim 1-6, wherein the medicament is for treating cancer in the mammal.

34. The use according to claim 33, wherein the cancer is a solid tumor.

35. The use according to claim 33, wherein the cancer is bladder cancer, colon cancer, brain cancer, breast cancer, endometrial cancer, heart cancer, kidney cancer, lung cancer, liver cancer, uterine cancer, blood and lymphatic cancer, ovarian cancer, pancreatic cancer, prostate cancer, thyroid cancer, or skin cancer.

36. The use according to claim 33, wherein the cancer is a sarcoma, carcinoma, or lymphoma.

37. The use according to any one of claims 1 to 36, wherein the medicament is to be administered topically, orally or parenterally to the mammal.

38. The use according to any one of claims 1 to 36, wherein the medicament is to be administered systemically to the mammal.

39. The use according to any one of claims 1 to 36, wherein the medicament is to be administered orally to the mammal.

40. The use according to claim 39, wherein the medicament is to be administered to the mammal in the form of an oral solution, oral suspension, powder, pill, tablet, or capsule.

41. The use according to any one of claims 1 to 36, wherein the medicament is to be administered to the mammal by injection or intravenously.

42. The use according to any one of claims 1 to 41, furthering comprising at least one addtional therapy to be administered to the mammal.

43. The use according to any one of claims 1 to 42, wherein the mammal is a human.