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(54) Title: RAS INHIBITORS FOR TREATING DISEASES OR PATHOLOGICAL CONDITIONS CHARACTERIZED INSULIN RESISTANCE

(57) Abstract: Disclosed herein are compositions, kits and methods for treating a disease or pathological condition that is characterized, caused or mediated by insulin resistance, including, for example, Type 2 diabetes, and which employ, as an active ingredient, S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with Formula (I).



RAS INHIBITORS FOR TREATING DISEASES OR PATHOLOGICAL CONDITIONS CHARACTERIZED BY INSULIN RESISTANCE

BACKGROUND OF THE INVENTION

[0001] Diabetes mellitus is a metabolic disorder in humans with a prevalence of approximately one percent in the general population (Foster, D. W., *Harrison's Principles of Internal Medicine*, Chap. 114, pp. 661-678, 10th Ed., McGraw-Hill, New York). The disease manifests itself as a series of hormone-induced metabolic abnormalities that eventually lead to serious, long-term and debilitating complications involving several organ systems including the eyes, kidneys, nerves, and blood vessels. Pathologically, the disease is characterized by lesions of the basement membranes, demonstrable under electron microscopy. Diabetes mellitus can be divided into two clinical syndromes, Type 1 and Type 2 diabetes mellitus. Type 1, or insulin-dependent diabetes mellitus (IDDM), also referred to as the juvenile onset form, is a chronic autoimmune disease characterized by the extensive loss of beta cells in the pancreatic Islets of Langerhans, which produce insulin. As these cells are progressively destroyed, the amount of secreted insulin decreases, eventually leading to hyperglycemia (abnormally high level of glucose in the blood) when the amount of secreted insulin drops below the normally required blood glucose levels.

[0002] Type 2 diabetes (also referred to as non-insulin dependent diabetes mellitus (NIDDM), maturity onset form, adult onset form) develops when muscle, fat and liver cells fail to respond normally to insulin. This failure to respond (called insulin resistance) may be due to reduced numbers of insulin receptors on these cells, or a dysfunction of signaling pathways within the cells, or both. The beta cells initially compensate for this insulin resistance by increasing insulin output. Over time, these cells become unable to

produce enough insulin to maintain normal glucose levels, indicating progression to Type 2 diabetes. Insulin resistance, particularly in skeletal muscle cells, is strongly correlated with and is generally regarded as a hallmark of the development of Type 2 diabetes.

[0003] Multiple intracellular defects in insulin action, including decreased glucose transport and phosphorylation, reduced glycogen synthesis, and impaired glycolysis and glucose oxidation, all contribute to the insulin resistance [1]. It is well-established that obesity is the main contributor to the disease onset. However, the exact mechanism as to how obesity promotes insulin resistance is not clearly understood [2]. Studies demonstrated that the accumulation of lipids in adipose tissue and the expansion of the fat mass lead to the initiation of an inflammatory process. This may be initiated through the production of proinflammatory cytokines and chemokines by the adipocytes, including TNF- α , IL-6, leptin, resistin, and MCP-1. Endothelial cells respond through the increased expression of adhesion molecules, which along with the chemokines serve to recruit immune cells, including monocyte-derived macrophages, to the adipose tissue. Together, the adipocyte, immune cell, and endothelial cell-derived substances create an inflammatory milieu that promotes insulin resistance locally [3].

[0004] Currently, there are at least 6 different therapeutic approaches, which are in use both individually and in combination, for the treatment of Type 2 diabetes (Scheen *et al.*, Diabetes Care, 22(9):1568-1577, 1999). They act via different modes of action. For example, sulfonylureas (e.g., glimepiride, glisentide, sulfonylurea, AY31637) essentially stimulate insulin secretion. Biguanides (e.g., metformin) act by promoting glucose utilization, reducing hepatic glucose production and diminishing intestinal glucose output. Alpha-glucosidase inhibitors (e.g., acarbose, miglitol) slow

down carbohydrate digestion and consequently absorption from the gut, and reduce postprandial hyperglycemia. Thiazolidinediones (e.g., troglitazone, pioglitazone, rosiglitazone, glipizide, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, AD 5075, T 174, YM 268, R 102380, NC 2100, NIP 223, NIP 221, MK 0767, ciglitazone, adaglitazone, CLX 0921, darglitazone, CP 92768, BM 152054) enhance insulin action, thus promoting glucose utilization in peripheral tissues. Glucagon-like-peptides including DPP4 inhibitors (e.g., sitagliptin), and insulin each stimulates tissue glucose utilization and inhibits hepatic glucose output. However, each approach has its limitations and adverse effects. Over time, a large percentage of Type 2 diabetic subjects lose their response to these agents. Insulin treatment is typically instituted after diet, exercise, and oral medications have failed to adequately control blood glucose. The drawbacks of insulin treatment are the need for drug injection, the potential for hypoglycemia, and weight gain.

[0005] In view of the problems with current treatments, new therapies to treat Type 2 diabetes and other pathological conditions characterized or mediated by insulin resistance are needed to replace or complement available pharmaceutical approaches.

BRIEF SUMMARY OF THE INVENTION

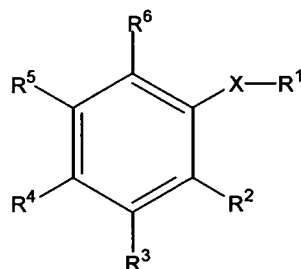
[0006] The results of Applicants' experimental work demonstrate that FTS disrupts the interactions of active Ras with the muscle and fat cell membranes induced glucose uptake *in vitro*, and reduces the level of circulating insulin, and attenuates the incidence of type 2 diabetes in a mouse model of a high-fat diet. Ras proteins bind and become anchored to the inner leaflets of cell membranes where they alternate between inactive and active states. Ras is crucially involved

in the proper activity of the immune system and in the regulation of cell growth, differentiation, survival, migration and death.

[0007] Herein, Applicants provide compounds of formula (I) which exert a therapeutically beneficial effect on humans with a disease or pathological condition characterized, caused or mediated by insulin resistance by down-regulating the activation of protein kinase C (PKC, kinases that regulate a wide variety of cellular functions and are important downstream signaling effector proteins of Ras). Without intending to be bound by any particular theory, it is believed that such a mechanism causes an increase in the expression of I κ B, which in turn inhibits nuclear factor kappa beta (NF- κ B).

[0008] NF- κ B is a transcription factor and regulates expression of genes that plays important roles in the immune system. In normal states, I κ B inhibits NF- κ B activity, but activity of this transcriptional factor can be induced by the presence of a diverse range of stimuli, including, for example, pathogen-derived substances. Pathological dysregulation of NF κ B is linked to inflammatory and autoimmune diseases as well as cancer. This means that Ras-dependent activation of PKC, which positively regulates insulin resistance, can be overcome by blocking Ras.

[0009] Thus, in one of its aspects the present invention provides a method of treating a mammalian subject afflicted with a disease or pathological condition characterized, caused or mediated by insulin resistance, comprising administering to the subject a pharmaceutical composition comprising an effective amount of S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with the compound of formula (I):



wherein X represents S; R¹ represents farnesyl, or geranyl-geranyl; R² is COOR⁷, CONR⁷R⁸, or COOCHR⁹OR¹⁰, wherein R⁷ and R⁸ are each independently hydrogen, alkyl, or alkenyl; wherein R⁹ represents H or alkyl; and wherein R¹⁰ represents alkyl; and wherein R³, R⁴, R⁵ and R⁶ are each independently hydrogen, alkyl, alkenyl, alkoxy, halo, trifluoromethyl, trifluoromethoxy, or alkylmercapto, and a pharmaceutically acceptable carrier.

In some embodiments, the mammalian subject is a human.

In other embodiments, the disease or pathological condition is Type 2 diabetes.

In still other embodiments, the disease or pathological condition is pre-diabetes.

In still yet other embodiments, the disease or pathological condition is metabolic syndrome.

In some embodiments, the compound of formula (I), as defined herein, is FTS.

In some other embodiments, the compound of formula (I), as defined herein, is 5-fluoro-FTS.

In still other embodiments, the compound of formula (I), as defined herein, is administered orally.

In some embodiments, the pharmaceutical composition, as defined herein, is in the form of a tablet.

In other embodiments, the pharmaceutical composition, as defined herein, is in the form of a capsule.

In some embodiments, the compound of formula (I), as defined herein, is administered parenterally.

In some other embodiments, the compound of formula (I), as defined herein, is administered transdermally.

In still other embodiments, the compound of formula (I), as defined herein, is administered in the form of an aerosol.

In still yet other embodiments, the method of the invention further comprises administration of an effective amount of at least one other active ingredient.

In some embodiments, the at least one other active ingredient, as defined herein, is selected from the group consisting of 1) sulfonylureas; 2) biguanides; 3) alpha-glucosidase inhibitors; 4) thiazolidinediones; 5) glucagon-like-peptides including GLP-1 and DPPIIV inhibitors; and 6) insulin and its analogs, and combinations of two or more thereof.

In another one of its aspects the present invention provides an article of manufacture comprising a container, and a pharmaceutical composition within the container comprising the compound of formula (I) and a pharmaceutically acceptable carrier, and a package insert containing instructions to administer the composition to a mammalian subject in need of treatment for a disease or pathological condition characterized by insulin resistance. In some embodiments the composition further comprises a second active agent that is effective in the treatment of a disease or pathological condition characterized or mediated by insulin resistance.

In still another one of its aspects the present invention provides a kit, comprising the container, as defined herein, and a label attached to or packaged with the container that describes the contents of the container and provides indications and/or instructions regarding administration of contents of the container to a mammalian subject in need of treatment for a disease or pathological condition

characterized, caused or mediated by insulin resistance. In some embodiments, the kit, as defined herein, comprises another container that contains a second active agent effective in the treatment of a disease or pathological condition characterized or mediated by insulin resistance.

In still yet another one of its aspects the present invention provides a use of S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with the compound of formula (I), as defined herein, and a pharmaceutically acceptable carrier, in the preparation of a medicament for treating a mammalian subject afflicted with a disease or pathological condition characterized, caused or mediated by insulin resistance.

The compound of formula (I), as defined herein, is one that is suitable for oral, parenteral, transdermal administration and is also suitable for administration in the form of an aerosol.

In some embodiments, the medicament of the invention further comprises at least one other active ingredient, as defined herein.

The present invention also provides a composition comprising an effective amount of S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with the compound of formula (I), as defined herein, and a pharmaceutically acceptable carrier, for use in treating a mammalian subject afflicted with a disease or pathological condition characterized, caused or mediated by insulin resistance.

In some embodiments, the composition of the invention further comprises at least one other active ingredient, as defined herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Fig. 1A** is a graph that shows percent weight gain of fat-induced diabetic mice as a result of administration with embodiments of the present invention compared to positive controls PBS and CMC; **Fig. 1B** is a graph that shows attenuation of experimental type 2 diabetes in mice using methods of the present invention versus control; and **Fig. 1C** shows attenuation of experimental type 2 diabetes in mice using embodiments of the inventive method versus control.

[0011] **Fig. 2** is a bar graph showing comparative decreases in serum insulin levels in mice using embodiments of the present method administered orally and intraperitoneally versus controls.

[0012] **Fig. 3** is a bar graph showing comparative increases in glucose uptake in muscle and liver cells obtained from experimental type 2 diabetic mice after administration of an embodiment of the present invention versus a control.

[0013] **Figs. 4A, B, and C** are bar graphs that show increased expression of *I κ B* (A) and decreased expression of *NF κ B* and *PKC* (B and C) in muscle and fat cells obtained from fat-induced diabetic mice, following administration of an embodiment of the present invention versus a control.

[0014] **Fig. 5A** includes light microscopy photos showing differences between C2 and C12 non-differentiated and differentiated (to myotubes) following overnight incubation in the presence or absence of an embodiment of the present invention; **Fig. 5B** is a bar graph showing that treatment of the myotubes with an embodiment of the present invention increases glucose uptake *in vitro*, relative to a control; **Fig. 5C** is a bar graph showing that an embodiment of the present invention increases glut4 mRNA expression *in vitro*, in myotubes relative to a control; **Fig. 5D** includes bar graphs showing that treatment of myotubes with an embodiment of the present invention decreases *NF κ B* expression; and **Fig. 5E** shows

the increase of *IκB* expression *in vitro*, relative to a control.

DETAILED DESCRIPTION

[0015] The methods of the present invention are useful in the treatment of Type 2 diabetes and other diseases or pathological conditions characterized, caused or mediated by insulin resistance. As used herein, the term "insulin resistance" refers to a non-autoimmune disease or condition in which a normal amount of insulin is unable to produce a normal physiological or molecular response. Insulin resistance is associated with a number of disease states and conditions and is present in approximately 30-40% of non-diabetic individuals. These disease states and conditions include pre-diabetes and metabolic syndrome (also referred to as insulin resistance syndrome).

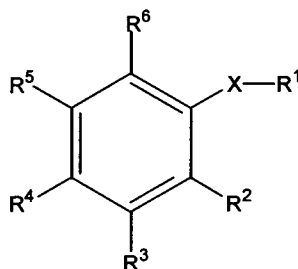
[0016] Pre-diabetes is a state of abnormal glucose tolerance characterized by either impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). Patients with pre-diabetes are insulin resistant and are at high risk for future progression to overt Type 2 diabetes.

[0017] Metabolic syndrome is an associated cluster of traits that include hyperinsulinemia, abnormal glucose tolerance, obesity, redistribution of fat to the abdominal or upper body compartment, hypertension, dysfibrinolysis, and a dyslipidemia characterized by high triglycerides, low HDL-cholesterol, and small dense LDL particles. Insulin resistance has been linked to each of the traits, suggesting metabolic syndrome and insulin resistance are intimately related to one another. The diagnosis of metabolic syndrome is a powerful risk factor for future development of Type 2 diabetes, as well as accelerated atherosclerosis resulting in heart attacks, strokes, and peripheral vascular disease. Obesity is a chronic disease that is highly prevalent and is

associated not only with a social stigma, but also with decreased life span and numerous medical problems including adverse psychological development, dermatological disorders such as infections, varicose veins, exercise intolerance, diabetes mellitus, insulin resistance, hypertension, hypercholesterolemia, and coronary heart disease (Rissanen *et al.*, British Medical Journal 301:835-837 (1990)).

[0018] Obesity is highly correlated with insulin resistance and diabetes in experimental animals and humans. Indeed, obesity and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia, or both, are hallmarks of Type 2 diabetes. Diagnosis of such diseases or conditions in patients, or alternatively the risk for developing such diseases or conditions may be according to standard medical practices known in art.

[0019] FTS and its structural analogs useful in the methods of the present invention may be collectively represented by the formula (I) :



wherein X represents S; wherein R¹ represents farnesyl or geranyl-geranyl; R² is COOR⁷, CONR⁷R⁸, or COOCHR⁹OR¹⁰, wherein R⁷ and R⁸ are each independently hydrogen, alkyl, or alkenyl, including linear and branched alkyl or alkenyl, which in some embodiments includes C1-C4 alkyl or alkenyl; wherein R⁹ represents H or alkyl; and wherein R¹⁰ represents alkyl, including linear and branched alkyl and which in some embodiments represents C1-C4 alkyl; and wherein R³, R⁴, R⁵ and R⁶ are each independently hydrogen, alkyl, alkenyl, alkoxy (including linear and branched alkyl, alkenyl or alkoxy and

which in some embodiments represents C1-C4 alkyl, alkenyl or alkoxy), halo, trifluoromethyl, trifluoromethoxy, or alkylmercapto. In embodiments wherein any of R^7 , R^8 , R^9 and R^{10} represents alkyl, it is preferably methyl or ethyl.

[0020] Thus, aside from FTS (e.g., the isomer S-trans,trans-farnesylthiosalicylic acid, wherein R^1 is farnesyl, R^2 is COOR^7 , and R^7 is hydrogen), in some embodiments, the FTS analog is halogenated, e.g., 5-chloro-FTS (wherein R^1 is farnesyl, R^2 is COOR^7 , R^4 is chloro, and R^7 is hydrogen), and 5-fluoro-FTS (F-FTS) (wherein R^1 is farnesyl, R^2 is COOR^7 , R^4 is fluoro, and R^7 is hydrogen).

[0021] In other embodiments, the FTS analog is FTS-methyl ester (wherein R^1 represents farnesyl, R^2 represents COOR^7 , and R^7 represents methyl).

[0022] In yet other embodiments, the Ras antagonist is an alkoxyalkyl S-prenylthiosalicylate or an FTS-alkoxyalkyl ester (wherein R^2 represents $\text{COOCHR}^9\text{OR}^{10}$). Representative, non-limiting, examples include methoxymethyl S-farnesylthiosalicylate (wherein R^1 is farnesyl, R^9 is H, and R^{10} is methyl); methoxymethyl S-geranylgeranylthiosalicylate (wherein R^1 is geranylgeranyl, R^9 is H, and R^{10} is methyl); methoxymethyl 5-fluoro-S-farnesylthiosalicylate (wherein R^1 is farnesyl, R^5 is fluoro, R^9 is H, and R^{10} is methyl); and ethoxymethyl S-farnesylthiosalicylate (wherein R^1 is farnesyl, R^9 is methyl and R^{10} is ethyl). In each of the embodiments described above, unless otherwise specifically indicated, each of R^3 , R^4 , R^5 and R^6 represents hydrogen.

[0023] In yet other embodiments, the FTS analog is FTS-amide (wherein R^1 represents farnesyl, R^2 represents CONR^7R^8 , and R^7 and R^8 both represent hydrogen); FTS-methylamide (wherein R^1 represents farnesyl, R^2 represents CONR^7R^8 , R^7 represents hydrogen and R^8 represents methyl); or FTS-dimethylamide (wherein R^1 represents farnesyl, R^2 represents CONR^7R^8 , and R^7 and R^8 each represents methyl).

[0024] The term "pharmaceutical composition" as used herein, refers to a combination or mixture of the compound of formula (I) (also referred to hereinafter as the active ingredient) and a pharmaceutically acceptable carrier, and optionally, a pharmaceutically acceptable excipient, which as known in the art include substances or ingredients that are non-toxic, physiologically inert and do not adversely interact with the active ingredient (and any other additional active agent(s) that may be present in the composition). Carriers facilitate formulation and/or administration of the active agent(s).

[0025] Oral compositions suitable for use in the present invention may be prepared by bringing the active ingredient into association with (e.g., mixing with) the carrier, the selection of which is based on the mode of administration. Carriers are generally solid or liquid. In some cases, compositions may contain solid and liquid carriers. Compositions suitable for oral administration that contain the active ingredient are preferably in solid dosage forms such as tablets (e.g., including film-coated, sugar-coated, controlled or sustained release), capsules, e.g., hard gelatin capsules (including controlled or sustained release) and soft gelatin capsules, powders and granules. The compositions, however, may be contained in other carriers that enable administration to a patient in other oral forms, e.g., a liquid or gel. Regardless of the form, the composition is divided into individual or combined doses containing predetermined quantities of the active ingredient.

[0026] Oral dosage forms may be prepared by mixing the active ingredient, typically in the form of an active pharmaceutical ingredient with one or more appropriate carriers (optionally with one or more other pharmaceutically acceptable excipients), and then formulating the composition into the desired dosage form e.g., compressing the composition

into a tablet or filling the composition into a capsule (e.g., a hard or soft gelatin capsule) or a pouch. Typical carriers and excipients include bulking agents or diluents, binders, buffers or pH adjusting agents, disintegrants (including crosslinked and super disintegrants such as croscarmellose), glidants, and/or lubricants, including lactose, starch, mannitol, microcrystalline cellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, dibasic calcium phosphate, acacia, gelatin, stearic acid, magnesium stearate, corn oil, vegetable oils, and polyethylene glycols. Coating agents such as sugar, shellac, and synthetic polymers may be employed, as well as colorants and preservatives. See, *Remington's Pharmaceutical Sciences, The Science and Practice of Pharmacy*, 20th Edition, (2000).

[0027] Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active agent(s), for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent (and mixtures thereof), and/or pharmaceutically acceptable oils or fats. Examples of liquid carriers for oral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably in suspension in sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycerin and non-toxic glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). The liquid composition can contain other suitable pharmaceutical excipients such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colorants, viscosity regulators, stabilizers and osmoregulators.

[0028] Carriers suitable for preparation of compositions for parenteral administration include Sterile Water for

Injection, Bacteriostatic Water for Injection, Sodium Chloride Injection (0.45%, 0.9%), Dextrose Injection (2.5%, 5%, 10%), Lactated Ringer's Injection, and the like. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof, and in oils. Compositions may also contain tonicity agents (e.g., sodium chloride and mannitol), antioxidants (e.g., sodium bisulfite, sodium metabisulfite and ascorbic acid) and preservatives (e.g., benzyl alcohol, methyl paraben, propyl paraben and combinations of methyl and propyl parabens).

[0029] Transdermal (e.g., topical) compositions may take a variety of forms such as gels, creams, lotions, aerosols and emulsions. Representative carriers thus include lubricants, wetting agents, emulsifying and suspending agents, preservatives, anti-irritants, emulsion stabilizers, film formers, gel formers, odor masking agents, resins, hydrocolloids, solvents, solubilizers, neutralizing agents, permeation accelerators, pigments, quaternary ammonium compounds, refatting and superfatting agents, ointment, cream or oil base materials, silicone derivatives, stabilizers, sterilizing agents, propellants, drying agents, opacifiers, thickeners, waxes, emollients, and white oils. In addition, the topical preparations of the present invention can be applied and then covered with a bandage, or patch, or some other occlusive barrier, or may be provided as part of a pre-made, ready-to-use topical device, such as a bandage, pad, patch (e.g., transdermal patch of the matrix or reservoir type) or the like. Thus, the composition containing the active ingredient of formula (I) may be applied to a gauze, pad, swab, cotton ball, batting, bandage, patch or occlusive barrier, or in a well or reservoir or as part of a unitary adhesive or nonadhesive mixture, or sandwiched between a peelable or removable layer and a backing layer, which often forms the reservoir, which is occlusive.

[0030] Carriers for aerosol formulation, in which the active ingredient may be present in finely divided or micronized form, include lactose and propellants such as hydrocarbons (HCF) (propane and n-butane), ether-based propellants such as dimethyl ether and methyl ethyl ether, and hydrofluoroalkanes (HFC) such as HFA 134a and HFA 227. Excipients may also be present, e.g., for such purposes as to improve drug delivery, shelf life and patient acceptance. Examples of excipients include wetting agents (e.g., surfactants), dispersing agents, coloring agents, taste masking agents, buffers, antioxidants and chemical stabilizers.

[0031] The terms "treatment", "treat" and "treating" as used herein refers a course of action which includes administering a compound of formula (I) initiated after the onset of a clinical symptom of a disease or pathological condition characterized, caused or mediated by insulin resistance, so as to eliminate, reduce, suppress or ameliorate, either temporarily or permanently, a clinical manifestation or progression of the disease state or condition. Such treating need not be absolute to be useful.

[0032] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of the active ingredient to the desired site of biological action. Medically acceptable administration techniques suitable for use in the present invention are known in the art. See, e.g., Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa. In some embodiments, the active ingredient is administered orally. In other embodiments, the active ingredient is administered parenterally (which for purposes of the present invention, includes intravenous, subcutaneous, intraperitoneal,

intramuscular, intravascular and infusion). In yet other embodiments, the active ingredient is administered transdermally (e.g., topically). As used herein, topical administration refers to non-enteral and non-parenteral modes of administration, and thus includes direct or indirect application to the skin, as well as inhalational (e.g., via aerosol) and ocular (e.g., eye drops or eardrops) administration.

[0033] The terms "in need of treatment" and "in need thereof" as used herein refer to a judgment made by a medical caregiver that a patient requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of the caregiver's expertise, but that includes the knowledge that the patient is ill as the result of a disease or pathological condition characterized or mediated by insulin resistance treatable by a method using a compound of formula (I).

[0034] The term "therapeutically effective amount" as used herein refers to an amount of a compound of formula (I) that is capable of having any detectable, positive effect on any symptom, aspect, or characteristics of a disease or pathological condition characterized or mediated by insulin resistance when administered to a patient (e.g., as one or more doses). The therapeutically effective amount of the compound of formula (I) may also decrease the incidence or severity, or stabilize, complications or conditions associated with the disease or pathological condition (which for example in the case of Type 2 diabetes, includes retinopathy, renal failure, cardiovascular disease (e.g., atherosclerosis, peripheral vascular disease), and wound healing (e.g., diabetic ulcer). Such effect need not be absolute to be beneficial. Appropriate "effective" amounts for any subject can be determined using techniques, such as a dose escalation study. Specific dose levels for any particular subject will

depend on several factors such as the potency of the active ingredient, the age, weight, and general health of the subject, and the severity of the disorder. The average daily dose of the active ingredient generally ranges from about 200 mg to about 2000 mg, in some embodiments from about 400 to about 1600 mg, and some other embodiments from about 600 to about 1200 mg, and in yet other embodiments, from about 800 mg to about 1200 mg.

[0035] In general, treatment regimens may be designed and optimized by those skilled in the art. For example, the active may be administered until demonstrable symptoms of the inflammatory condition have substantially diminished or the condition is substantially alleviated or healed. Methods of treating a disease or pathological condition characterized or mediated by insulin resistance in accordance with the present invention may use a pre-determined or "routine" schedule for administration of the compound of formula (I). As used herein a routine schedule refers to a predetermined designated period of time between dose administrations. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. Any particular combination would be covered by the routine schedule as long as it is determined ahead of time that the appropriate schedule involves administration on a certain day.

[0036] Alternatively, the inventive methods may use a schedule for administration of the compound of formula (I) that is based upon the presence of disease symptoms and/or changes in any of the following assessments, namely HbA1c, fasting blood sugar levels, OGTT, glucose/insulin C-peptide AUC, use of diabetes medication, insulin sensitivity, serum cytokine levels, CRP levels, quality of life measurements and BMI improvement, as a means to determine when to administer one or more subsequent doses. Similar, this approach may be used as a means to determine whether a subsequent dose should

be increased or decreased, based upon the effect of a previous dose.

[0037] The methods of the present invention may include administration of one or more additional active agents (e.g., which may act via different modes of action). Representative examples of additional active agents suitable for use in treating diseases and pathological conditions characterized or mediated by insulin resistance include the following: 1) sulfonylureas (e.g., chlorpropamide, tolazamide, acetohexamide, tolbutamide, glyburide, glimepiride, glipizide) and/or meglitinides (e.g., repaglinide, nateglinide) which act by essentially stimulating insulin secretion; 2) biguanides (e.g., metformin) which act by promoting glucose utilization, reducing hepatic glucose production and diminishing intestinal glucose output; 3) alpha-glucosidase inhibitors (e.g., acarbose, miglitol) which act by slowing down carbohydrate digestion and consequently absorption from the gut and reduce postprandial hyperglycemia; 4) thiazolidinediones (e.g., troglitazone, pioglitazone, rosiglitazone, glipizide, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, AD 5075, T 174, YM 268, R 102380, NC 2100, NIP 223, NIP 221, MK 0767, ciglitazone, adaglitazone, CLX 0921, darglitazone, CP 92768, BM 152054) which act by enhancing insulin action, thus promoting glucose utilization in peripheral tissues; 5) glucagon-like-peptides including GLP-1 and DPP-IV inhibitors (e.g., sitagliptin); and 6) insulin and its analogs, which act by stimulating tissue glucose utilization and inhibits hepatic glucose output. Yet other active agents that may be useful in the present invention are described in e.g., Nathan, N. Engl. J. Med. 355:2477-2480 (2006); Kahn, et al., N. Engl. J. Med. 355:2427-2443 (2006).

[0038] Combined therapy involving the compound of formula (I) and the other active agent may involve

administration together (in the same composition) or separately, and such separate administrations may be performed at the same point or different points in time, such as for example the same or different days. Administration of the other active agent may be according to standard medical practices known in the art, or the administration may be modified (e.g., longer intervals, smaller dosages, delayed initiation) when used in conjunction with administration of the compound of formula (I). Thus, in some embodiments, treatment with the other active agent is maintained, or reduced or discontinued (e.g., when the subject is stable), while treatment with the compound of formula (I) is maintained at a constant dosing regimen. In other embodiments, treatment with the other active agent is reduced or discontinued (e.g., when the subject is stable), and treatment with the compound of formula (I) is reduced (e.g., lower dose, less frequent dosing, shorter treatment regimen). In other embodiments, treatment with the other active agent is reduced or discontinued (e.g., when the subject is stable), and treatment with the compound of formula (I) is increased (e.g., higher dose, more frequent dosing, longer treatment regimen). In yet other embodiments, treatment with the other active agent is maintained and treatment with the compound of formula (I) is reduced or discontinued (e.g., lower dose, less frequent dosing, shorter treatment regimen).

[0039] Following administration of a compound of formula (I), clinical assessments for a treatment or preventative effect on the aforementioned diseases and conditions are well known in the art and may be used as a means to monitor the effectiveness of methods of the invention.

[0040] For example, response to treatment of Type 2 diabetes may be assessed based on a primary efficacy endpoint of improvement in hemoglobin A1c (HbA1c, see for example

Reynolds et al., BMJ 333(7568):586-589 (2006)). Improvements in HbA1c that are indicative of therapeutic efficacy may vary depending on the initial baseline measurement in a patient, with a larger decrease often corresponding to a higher initial baseline and a smaller decrease often corresponding to a lower initial baseline. In one aspect of the invention, the method should result in an HbA1c decrease of at least about 0.5% (e.g., at least about 0.5%, at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, at least about 3%, at least about 3.5%, at least about 4% or more) compared with pre-dose levels.

[0041] One or more of the following secondary endpoints also may be determined in order to assess efficacy of the treatment, such as for example fasting blood sugar (e.g., glucose) levels (e.g., decrease to ≤ 130 , ≤ 125 , ≤ 120 , ≤ 115 , ≤ 110 , ≤ 105 , ≤ 100 ; alternatively decrease of $>20\%$, $>30\%$, $>40\%$, $>50\%$, $>60\%$, $>70\%$, $>80\%$, $>90\%$, $>95\%$ compared to pre-dose levels), 120 minute oral glucose tolerance test (OGTT) (e.g., ≤ 200 , ≤ 190 , ≤ 180 , ≤ 170 , ≤ 160 , ≤ 150 , ≤ 140), glucose/insulin C-peptide AUC (e.g., $>25\%$, $>50\%$, $>60\%$, $>70\%$, $>80\%$, $>90\%$, $>100\%$ increase from pre-treatment), reduction in diabetes medication (e.g., insulin, oral hypoglycemic agent), improvement in insulin sensitivity, serum cytokine levels (e.g., normalization), CRP levels (e.g., decrease of ≥ 0.2 , ≥ 0.4 , ≥ 0.6 , ≥ 0.8 , ≥ 1.0 , ≥ 1.4 , ≥ 1.8 , ≥ 2.2 , ≥ 2.6 , ≥ 3.0 mg/L; alternatively a decrease of $>20\%$, $>30\%$, $>40\%$, $>50\%$, $>60\%$, $>70\%$, $>80\%$, $>90\%$, $>95\%$ from pre-treatment) quality of life measurements, BMI improvement (reduction of 1%, 3%, 5%), pharmacokinetics, and the like (Saudek, et al., JAMA, 295:1688-97 (2006); Pflutzner et al., Diabetes Technol. Ther. 8:28-36 (2006); Norberg, et al., J Intern Med. 260:263-71 (2006)).

[0042] Similarly, assessment of efficacy for other diseases or conditions may use one or more of the aforementioned

endpoints and/or others known in the art. For example, the effect on hyperglycemia can be assessed by measuring fasting blood sugar (*i.e.*, glucose) levels, the effect on hyperinsulinemia may be assessed by measuring insulin levels and/or C-peptide levels, the effect on obesity may be assessed by measuring weight and/or BMI, and the effect on insulin resistance may be assessed by OGTT.

[0043] Alternatively, or in addition, subjects treated in accordance with the invention may experience a decrease in the triglyceride level in the blood of the subject of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or more from the pre-treatment level. Alternatively, or in addition, subjects treated in accordance with the invention may experience a decrease in the level of free fatty acids of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, or more from the pre-treatment level.

[0044] The pharmaceutical composition containing the compound of formula (I), and optionally another active agent, may be stored in a container or separate containers which may contain a package insert, and be packaged and sold in the form of a kit. For example, the composition containing the compound of formula (I) might be in the form of one or more oral dosage forms such as tablets or capsules. The kit may also contain written instructions for carrying out the inventive methods as described herein.

[0045] The present invention will now be described in terms of the following non-limiting working examples.

Examples

***In vivo* studies**

[0046] To study the effect of F-FTS on type 2 diabetes, we injected 6 week-old male C57/Bl mice with F-FTS (20 mg/kg body weight; *i.p.*, *n* = 30), F-FTS (30 mg/kg body weight; *p.o.*, *n* = 10), FTS (60 mg/kg body weight; *p.o.*, *n* = 10), CMC (*p.o.*,

$n = 10$) or PBS (i.p. $n = 30$) daily for 13 weeks. In order to reproduce a model for type 2 diabetes, the mice were fed with high fat diet (TD.06415, Jackson Laboratory). Blood glucose levels in all injected mice were detected after 13 weeks. Mice were considered diabetic after detection of two consecutive values testing >200 mg/dl glucose.

ELISA for insulin

[0047] Serum insulin levels were detected using an Elisa kit according to the manufacturer's instructions.

Induction of insulin resistance in cell culture

[0048] Mouse C2C12 myoblasts (generously provided by prof. David Yaffe) were maintained in DMEM supplemented with 10% fetal bovine serum, 50 U/ml penicillin, and 50 μ g/ml streptomycin. When cells reached confluence, the medium was switched to the differentiation medium containing DMEM and 2% horse serum, which was changed every other day. After 4 additional days, the differentiated C2C12 cells had fused into myotubes. Lipid-containing media were prepared by conjugation of free fatty acid (FFA) with FFA-free BSA. Palmitate was dissolved in 0.1M NaOH and diluted in DMEM containing 2% (wt/vol) fatty acid-free BSA. Myotubes were incubated for 16 h in serum-free DMEM containing 2% BSA in either the presence or absence of palmitate.

Determination of glucose uptake by C2C12 skeletal muscle cells

[0049] Following insulin resistance induction, all culture media was removed from each well and replaced with 1ml of culture medium in the absence or presence of 10 μ M fluorescent 2-NBDG. 2-NBDG (Molecular Probes) is a new fluorescent derivative of glucose modified with a 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino group at the C-2 position.

[0050] Plates were incubated at 37 °C with 5% CO₂ for 1 hour. Following incubation, cells were washed twice with cold

PBS and collected for flow cytometric measurement (excitation at 485nm; emission at 535nm).

Determination of glucose uptake *in vivo*

[0051] 500ug of 2-NBDG was injected *i.v.* into 5 diet induced diabetic mice treated with either oral 30mg/kg F-FTS or CMC. 2 hour post injection, muscle and liver tissues were removed and single cell suspension was tested for the presence of 2-NBDG by FACS.

Western blotting

[0052] Muscle and fat lysates from fat induced mice were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis followed by western blotting, as described [4], with one of the following antibodies (Abs): I kappa B, NF kappa B, PKC δ (Santa Cruz Biotechnology, CA, USA) or anti-tubulin Ab (eBioScience, San Diego, CA). Protein bands were visualized with an enhanced chemiluminescence kit (Amersham Pharmacia Biotech, Arlington Heights, IL) and quantified by densitometry with Image EZQuant-Gel software[®].

Glut-4 Expression determined by reverse transcription-polymerase chain reaction

[0053] RNA was extracted from 10⁶ C2C12 using an RNeasy Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Reverse transcription-polymerase chain reaction (RT-PCR) was performed according to the protocol of Reverse-iT First Strand synthesis kit (ABgene, UK). GlycerAldehyde-3-Phosphate Dehydrogenase (GAPDH) was analyzed using the following primers: GAPDH forward 5'-ACCACAGTCCATGCCATCAC-3' and GAPDH reverse 5'-TCCACCACCCTGTTGCTGTA-3'.

[0054] PCR was carried out with Readymix PCR mastermix (ABgene, UK) on programmable thermal controller (PTC) device (MJ Research inc) at gene specific conditions. Primer sequences for glut4 were: glut4 forward:

5'-GATGCCGTCGGGTTTCCAGCA -3' and glut4 reverse:
5'-TGAGGGTGCCTTGTGGGATGG -3'.

[0055] The PCR products were subjected to electrophoresis on 2% agarose gel stained with ethidium bromide.

Results:

[0056] We first examined the ability of F-FTS to attenuate the development of diabetes in the high fat diet model. Six weeks old C57Bl mice fed with high fat diet were treated daily with either 20 mg/kg F-FTS (n=30) or PBS (n=30) for 13 weeks (**Fig. 1**). Day zero represents the first day of F-FTS injection. The high fat diet caused a significant increase, as expected [5] in body weight ($34.4 \% \pm 0.73$, n=30) which was not changed upon F-FTS treatment ($33.5 \% \pm 0.66$, n=30) (**Fig. 1A**). The treatment, however, resulted in a significant decrease in the incidence of diabetes (60% of the mice in the PBS-treated group had diabetes, compared to 20% in the F-FTS treated group) (**Fig. 1B**). An additional experiment testing the influence of oral administration of 30mg/kg F-FTS or 60mg/kg FTS was performed. Oral administration of F-FTS and FTS resulted in a major decrease in diabetes incidence compared to the vehicle carboxymethyl cellulose (CMC) treatment; 18% and 30% of the F-FTS and FTS treated mice developed diabetes (respectively) compared to 72% of the CMC treated mice (**Fig. 1C**). The increase in the mice body weight didn't differ between the groups (**Fig. 1A**). Kaplan-Meier curves of the incidence of diabetic mice are shown in **Figs. 1A** and **1B** ($p < 0.05$).

[0057] Next, we compared the circulating levels of insulin in the control PBS-treated mice (n=20) with the i.p F-FTS-treated mice (n=20). Serum insulin was determined by ELISA. Results of the experiments showed a clear and significant decrease of 70% in circulating insulin levels (**Fig. 2**) ($**P < 0.01$). When administrated per os, we observed a significant reduction of 53% and 46% in insulin

concentration in the FTS and F-FTS treated groups, respectively, compared to the control treated group (**Fig. 2**) (**P < 0.01).

[0058] To peruse the question whether the reduction in diabetes incidence is correlated with differences in glucose uptake, we injected i.v a fluorescent derivative of D-glucose, 2-NBDG, which was previously developed for the evaluation of glucose uptake activity by living cells [6]. Two hours post injection we removed the livers and the muscles tissues and evaluated the percentage of fluorescent glucose uptake by FACS. We observed a significant increase of 35% and 44% in glucose uptake within the livers and muscle tissue, respectively (**Fig. 3**) (*P < 0.05).

[0059] Fat and muscle tissue were removed from fat induced diabetic mice treated with either F-FTS p.o or CMC. Protein levels of I κ B, NF κ B and PKC were determined within the organs to investigate a potential cell signaling mechanism.

[0060] A decrease of 30% and 37% in NF κ B expression was demonstrated in muscle and fat tissues treated with F-FTS, respectively, compared with CMC treated group (**Fig. 4A**). This reduction was accompanied with an increase in I κ B expression (158% and 184% in muscle and fat tissues, respectively) (**Fig. 4B**). In addition, PKC expression also exhibited a significant decrease of 12% and 36% in muscle and fat tissues, respectively (**Fig. 4C**).

[0061] Next, we examined the impact of F-FTS on insulin resistance *in vitro*. C2C12 Myotubes in 6-well plates were incubated overnight in the absence or presence 0.75 mM palmitate and 50 μ M F-FTS as detailed in Materials and Methods. The cells differentiated to myotubes as expected (**Fig. 5A**). We used the fluorescent derivative of D-glucose, 2-NBDG to determine the levels of 2-NBDG in the absence and in the presence of F-FTS. Results of a typical experiment (**Fig. 5B**) indicated a significant increase of 36% in glucose

uptake in the F-FTS treated cells as compared with the controls. This increase detected in cells which were induced to insulin resistance ($*P < 0.05$) suggested that F-FTS increases glucose uptake, most likely due to the reduction in insulin resistance. Additional evidence in support of the influence of F-FTS on glucose uptake relies on the increased expression of mRNA of the glucose transporter 4 (glut-4) due to F-FTS treatment. C2C12 myocytes treated with palmitate and F-FTS showed a significant increase of 146% in glut-4 expression compared to palmitate treatment alone ($*P < 0.05$) (**Fig. 5C**).

[0062] When tested for biochemical differences, insulin resistant C2C12 treated with F-FTS, exhibited a significant reduction of 56% in the proinflammatory transcription factor NFkB which was accompanied by a significant increase of 160% in its inhibitor, IkB, as compared to control treated group ($*P < 0.05$) (**Fig. 5D-5E**).

[0063] The results demonstrate that Ras can control insulin resistance in mice. We found that the Ras inhibitor F-FTS, disrupted the interactions of active Ras with the cell membrane blocking its function, induced glucose uptake *in vitro*, reduced the levels of circulating insulin, and attenuated the incidence of type 2 diabetes in the high-fat diet model. These results suggest that insulin resistance is controlled also by Ras and its downstream signaling.

[0064] To our knowledge the actions of F-FTS as well as of FTS are primarily on active Ras proteins and are mimicked by dominant negative Ras or by shRNAs to Ras [4, 7]. Without intending to be bound by any particular theory of operation, Applicants believe that the present invention exerts its therapeutic effect by down-regulating the activation of PKC, and therefore increasing the expression of IkB, the NFkB inhibitor. This means that Ras-dependent activation of PKC

positively regulates insulin resistance which can overcome by blocking Ras.

Citations of the Referenced Publications:

1. DeFronzo, R.A., Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*, 2009. 58(4):773-95.
2. Shoelson, S.E., J. Lee, and A.B. Goldfine, Inflammation and insulin resistance. *Journal of Clinical Investigations*, 2006. 116(7):1793-801.
3. Das, U.N., Obesity, metabolic syndrome X, and inflammation. *Nutrition*, 2002. 18(5):430-2.
4. Mor, A., et al., N-Ras or K-Ras inhibition increases the number and enhances the function of Foxp3 regulatory T cells. *European Journal of Immunology*, 2008. 38(6):1493-502.
5. Surwit, R.S., et al., Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. *Metabolism*, 1995. 44(5):645-51.
6. Zou, C., Y. Wang, and Z. Shen, 2-NBDG as a fluorescent indicator for direct glucose uptake measurement. *Journal of Biochemical and Biophysical Methods*, 2005. 64(3):207-15.
7. Shalom-Feuerstein, R., et al., Galectin-3 regulates RasGRP4-mediated activation of N-Ras and H-Ras. *Biochim Biophys Acta*, 2008.

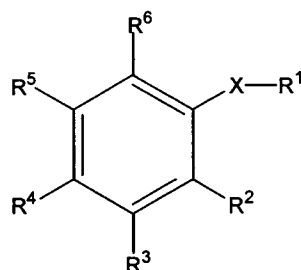
[0065] All patent publications and non-patent publications are indicative of the level of skill of those skilled in the art to which this invention pertains. All these publications are herein incorporated by reference to the same extent as if each individual publication were specifically and individually indicated as being incorporated by reference.

[0066] Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of

the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

CLAIMS

1. A pharmaceutical composition comprising an effective amount of S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with the compound of formula (I) :



wherein X represents S; R^1 represents farnesyl, or geranyl-geranyl; R^2 is COOR^7 , CONR^7R^8 , or $\text{COOCHR}^9\text{OR}^{10}$, wherein R^7 and R^8 are each independently hydrogen, alkyl, or alkenyl; wherein R^9 represents H or alkyl; and wherein R^{10} represents alkyl; and wherein R^3 , R^4 , R^5 and R^6 are each independently hydrogen, alkyl, alkenyl, alkoxy, halo, trifluoromethyl, trifluoromethoxy, or alkylmercapto, and a pharmaceutically acceptable carrier, for use in treating a mammalian subject afflicted with a disease or pathological condition characterized, caused or mediated by insulin resistance.

2. The composition of claim 1, wherein the mammalian subject is a human.

3. The composition of claim 1, wherein the disease or pathological condition is Type 2 diabetes.

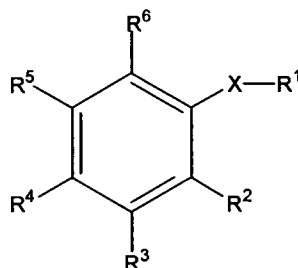
4. The composition of claim 1, wherein the disease or pathological condition is pre-diabetes.

5. The composition of claim 1, wherein the disease or pathological condition is metabolic syndrome.

6. The composition according to any one of claims 1 to 5, wherein the compound of formula (I) is FTS.

7. The composition according to any one of claims 1 to 5, wherein the compound of formula (I) is 5-fluoro-FTS.

8. The composition according to any one of claims 1 to 5, wherein the compound of formula (I) is suitable for oral administration.
9. The composition of claim 8, wherein the pharmaceutical composition is in the form of a tablet.
10. The composition of claim 8, wherein the pharmaceutical composition is in the form of a capsule.
11. The composition according to any one of claims 1 to 7, wherein the compound of formula (I) is suitable for parenteral administration.
12. The composition according to any one of claims 1 to 7, wherein the compound of formula (I) is suitable for transdermal administration.
13. The composition according to any one of claims 1 to 7, wherein the compound of formula (I) is suitable for administration in the form of an aerosol.
14. The composition according to any one of claims 1 to 13, said composition further comprising at least one other active ingredient.
15. The composition of claim 14, wherein the at least one other active ingredient is selected from the group consisting of 1) sulfonylureas; 2) biguanides; 3) alpha-glucosidase inhibitors; 4) thiazolidinediones; 5) glucagon-like-peptides including GLP-1 and DPPPIV inhibitors; and 6) insulin and its analogs, and combinations of two or more thereof.
16. A method of treating a mammalian subject afflicted with a disease or pathological condition characterized, caused or mediated by insulin resistance, comprising administering to the subject a pharmaceutical composition comprising an effective amount of S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with the compound of formula (I) :



wherein X represents S; R¹ represents farnesyl, or geranyl-geranyl; R² is COOR⁷, CONR⁷R⁸, or COOCHR⁹OR¹⁰, wherein R⁷ and R⁸ are each independently hydrogen, alkyl, or alkenyl; wherein R⁹ represents H or alkyl; and wherein R¹⁰ represents alkyl; and wherein R³, R⁴, R⁵ and R⁶ are each independently hydrogen, alkyl, alkenyl, alkoxy, halo, trifluoromethyl, trifluoromethoxy, or alkylmercapto, and a pharmaceutically acceptable carrier.

17. The method of claim 16, wherein the mammalian subject is a human.

18. The method of claim 16, wherein the disease or pathological condition is Type 2 diabetes.

19. The method of claim 16, wherein the disease or pathological condition is pre-diabetes.

20. The method of claim 16, wherein the disease or pathological condition is metabolic syndrome.

21. The method according to any one of claims 16 to 20, wherein the compound of formula (I) is FTS.

22. The method according to any one of claims 16 to 20, wherein the compound of formula (I) is 5-fluoro-FTS.

23. The method according to any one of claims 16 to 22, wherein the compound of formula (I) is administered orally.

24. The method of claim 23, wherein the pharmaceutical composition is in the form of a tablet.

25. The method of claim 23, wherein the pharmaceutical composition is in the form of a capsule.

26. The method according to any one of claims 16 to 22, wherein the compound of formula (I) is administered parenterally.

27. The method according to any one of claims 16 to 22, wherein the compound of formula (I) administered transdermally.

28. The method according to any one of claims 16 to 22, wherein the compound of formula (I) is administered in the form of an aerosol.

29. The method according to any one of claims 16 to 28, further comprising administration of an effective amount of at least one other active ingredient.

30. The method of claim 29, wherein the at least one other active ingredient is selected from the group consisting of 1) sulfonylureas; 2) biguanides; 3) alpha-glucosidase inhibitors; 4) thiazolidinediones; 5) glucagon-like-peptides including GLP-1 and DPPIIIV inhibitors; and 6) insulin and its analogs, and combinations of two or more thereof.

31. An article of manufacture comprising a container, and a pharmaceutical composition within the container comprising the compound of formula (I) and a pharmaceutically acceptable carrier, and a package insert containing instructions to administer the composition to a mammalian subject in need of treatment for a disease or pathological condition characterized by insulin resistance.

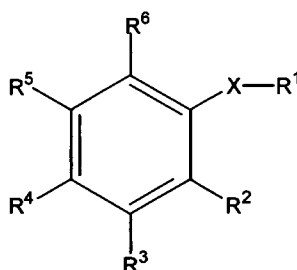
32. The article of manufacture of claim 31, wherein the composition further comprises a second active agent that is effective in the treatment of a disease or pathological condition characterized or mediated by insulin resistance.

33. A kit, comprising the container of claim 31 and a label attached to or packaged with the container that describes the contents of the container and provides indications and/or instructions regarding administration of contents of the container to a mammalian subject in need of treatment for a

disease or pathological condition characterized, caused or mediated by insulin resistance.

34. The kit of claim 33, said kit comprising another container that contains a second active agent effective in the treatment of a disease or pathological condition characterized or mediated by insulin resistance.

35. Use of S-farnesylthiosalicylic acid (FTS) or a structural analog thereof, collectively defined in accordance with the compound of formula (I):



wherein X represents S; R¹ represents farnesyl, or geranyl-geranyl; R² is COOR⁷, CONR⁷R⁸, or COOCHR⁹OR¹⁰, wherein R⁷ and R⁸ are each independently hydrogen, alkyl, or alkenyl; wherein R⁹ represents H or alkyl; and wherein R¹⁰ represents alkyl; and wherein R³, R⁴, R⁵ and R⁶ are each independently hydrogen, alkyl, alkenyl, alkoxy, halo, trifluoromethyl, trifluoromethoxy, or alkylmercapto, and a pharmaceutically acceptable carrier, in the preparation of a pharmaceutical composition for treating a mammalian subject afflicted with a disease or pathological condition characterized, caused or mediated by insulin resistance.

36. The use of claim 35, wherein the mammalian subject is a human.

37. The use of claim 35, wherein the disease or pathological condition is Type 2 diabetes.

38. The use of claim 35, wherein the disease or pathological condition is pre-diabetes.

39. The use of claim 35, wherein the disease or pathological condition is metabolic syndrome.

- 40.** The use according to any one of claims 35 to 39, wherein the compound of formula (I) is FTS.
- 41.** The use according to any one of claims 35 to 39, wherein the compound of formula (I) is 5-fluoro-FTS.
- 42.** The use according to any one of claims 35 to 39, wherein the compound of formula (I) is suitable for oral administration.
- 43.** The use of claim 42, wherein the pharmaceutical composition is in the form of a tablet.
- 44.** The use of claim 42, wherein the pharmaceutical composition is in the form of a capsule.
- 45.** The use according to any one of claims 35 to 41, wherein the compound of formula (I) is suitable for parenteral administration.
- 46.** The use according to any one of claims 35 to 41, wherein the compound of formula (I) is suitable for transdermal administration.
- 47.** The use according to any one of claims 35 to 41, wherein the compound of formula (I) is suitable for administration in the form of an aerosol.
- 48.** The use according to any one of claims 35 to 47, wherein the pharmaceutical composition further comprises at least one other active ingredient.
- 49.** The use of claim 48, wherein the at least one other active ingredient is selected from the group consisting of 1) sulfonylureas; 2) biguanides; 3) alpha-glucosidase inhibitors; 4) thiazolidinediones; 5) glucagon-like-peptides including GLP-1 and DPP-IV inhibitors; and 6) insulin and its analogs, and combinations of two or more thereof.

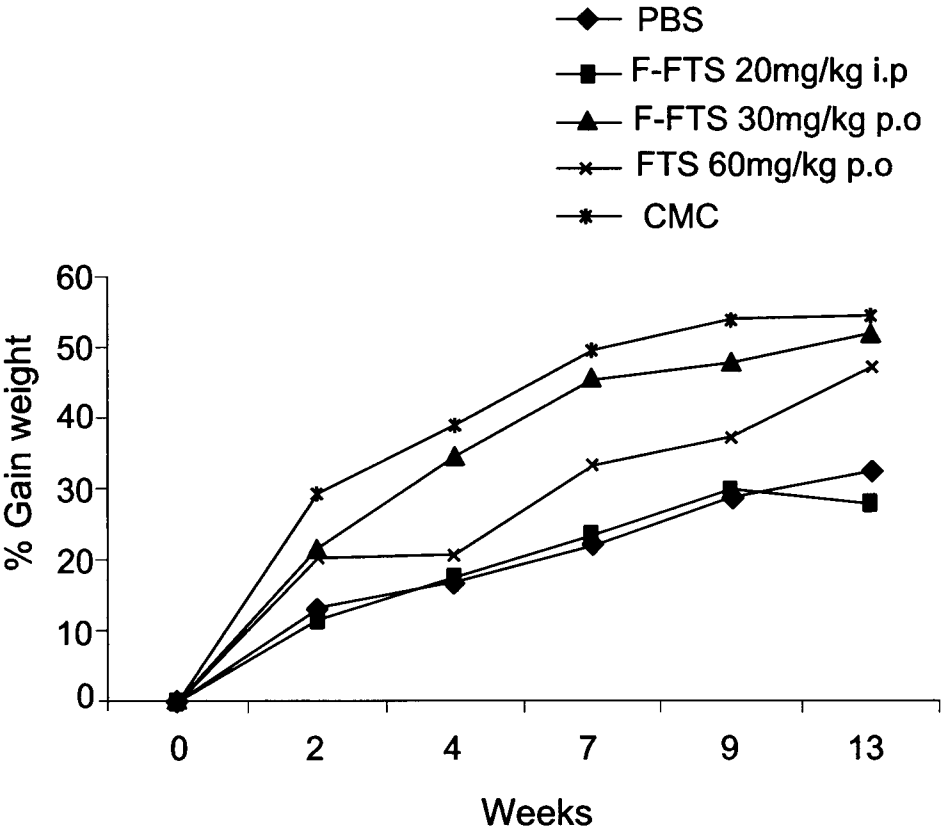


Figure 1A

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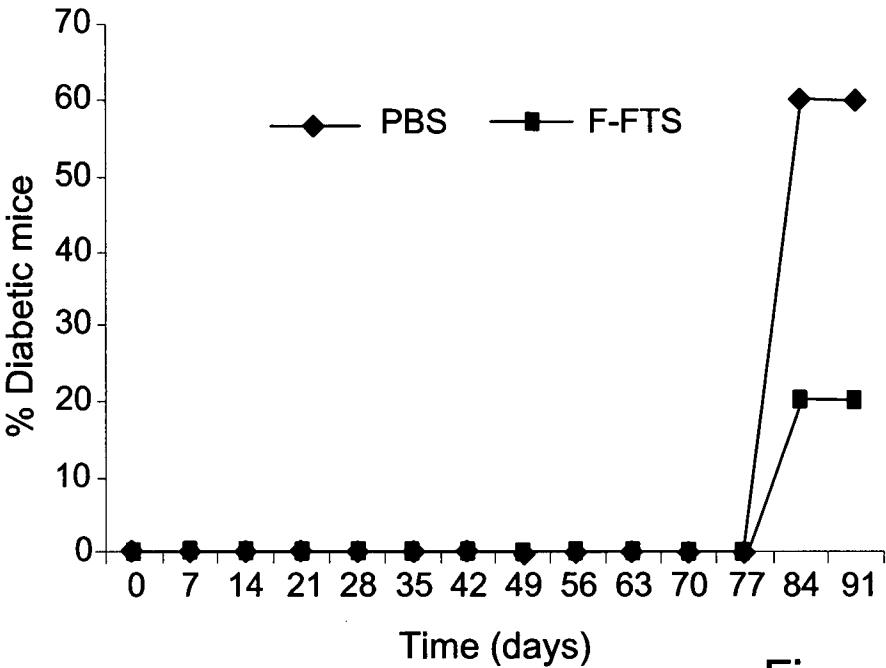


Figure 1B

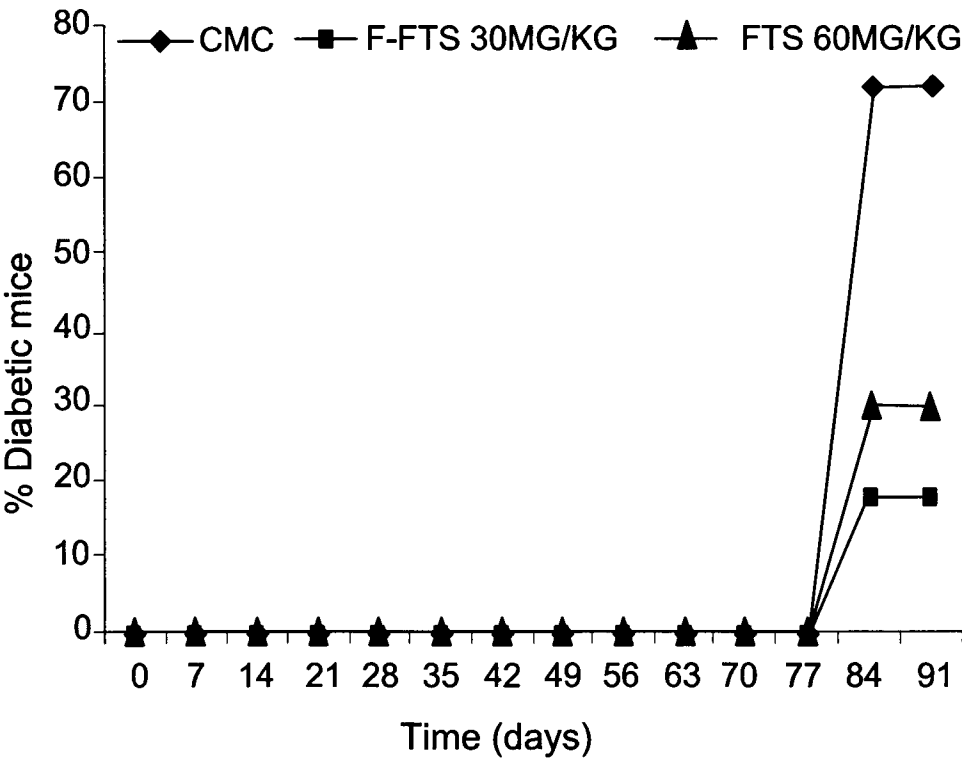


Figure 1C

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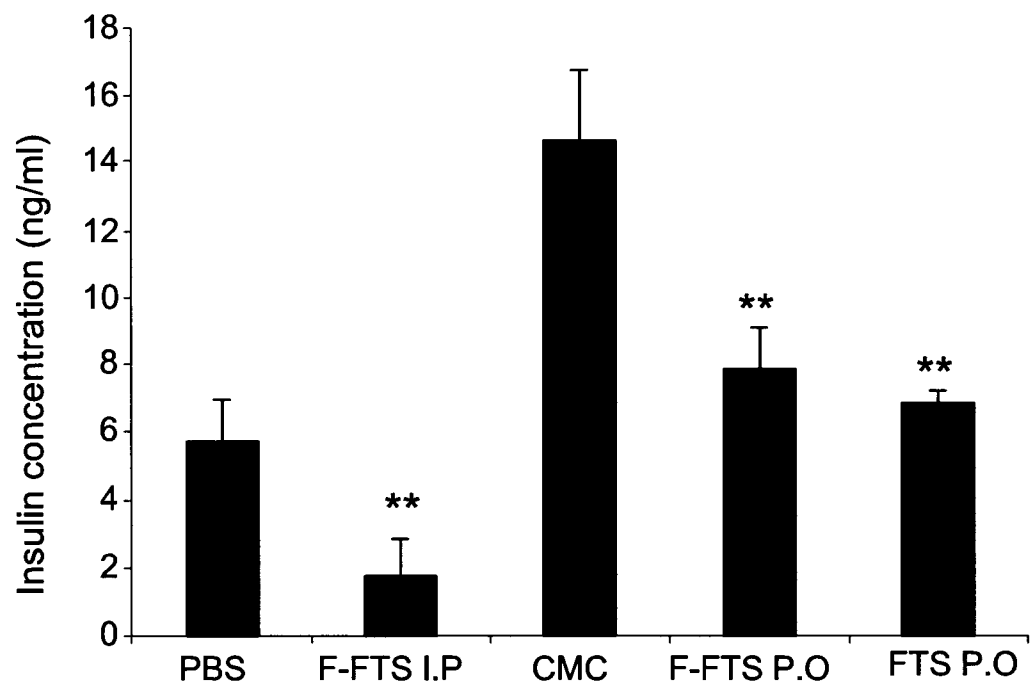


Figure 2

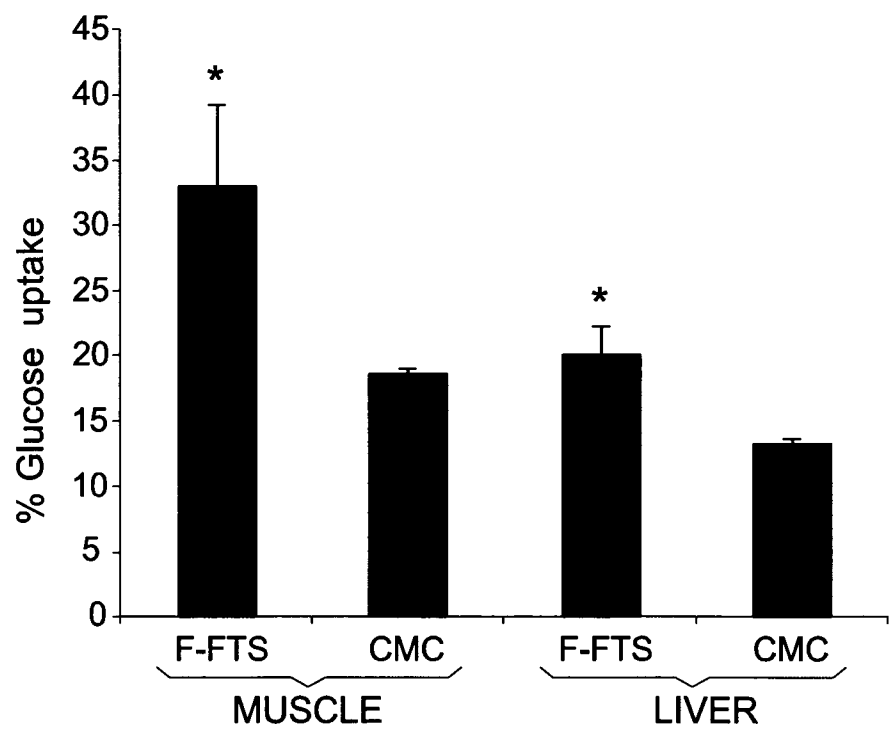


Figure 3

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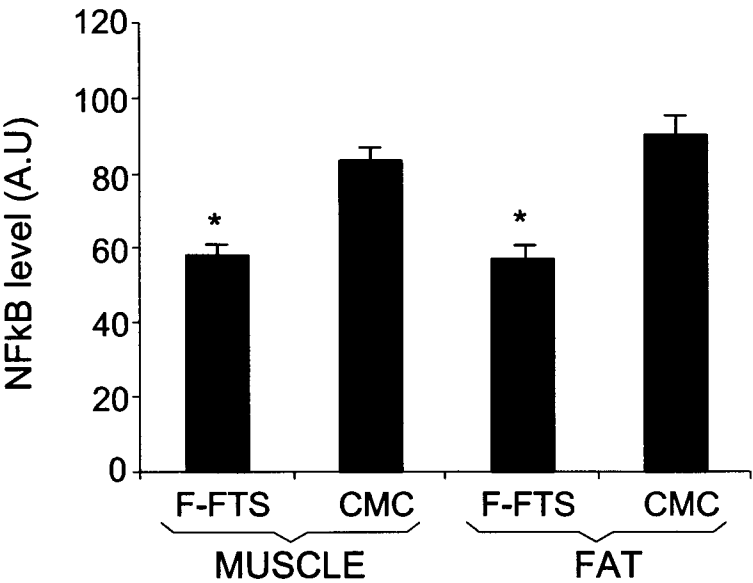


Figure 4A

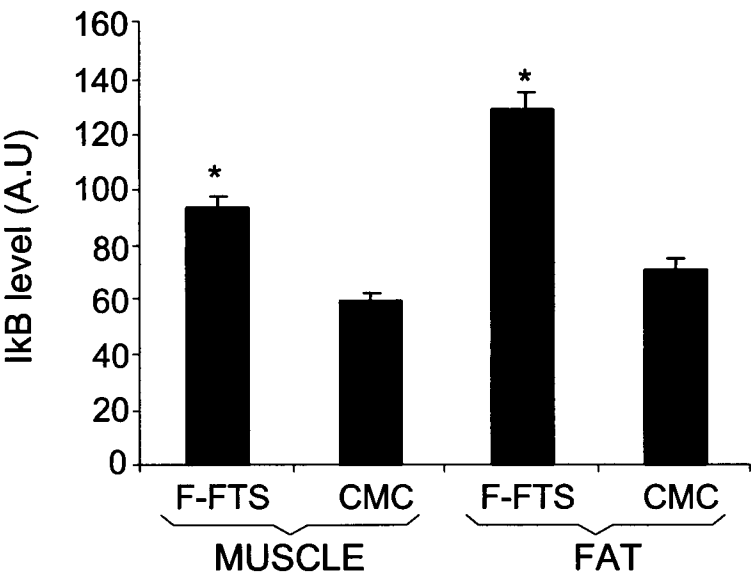


Figure 4B

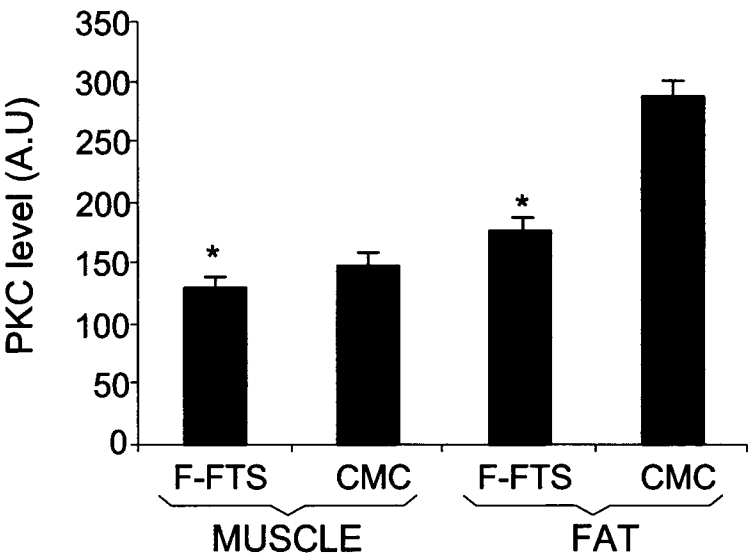


Figure 4C

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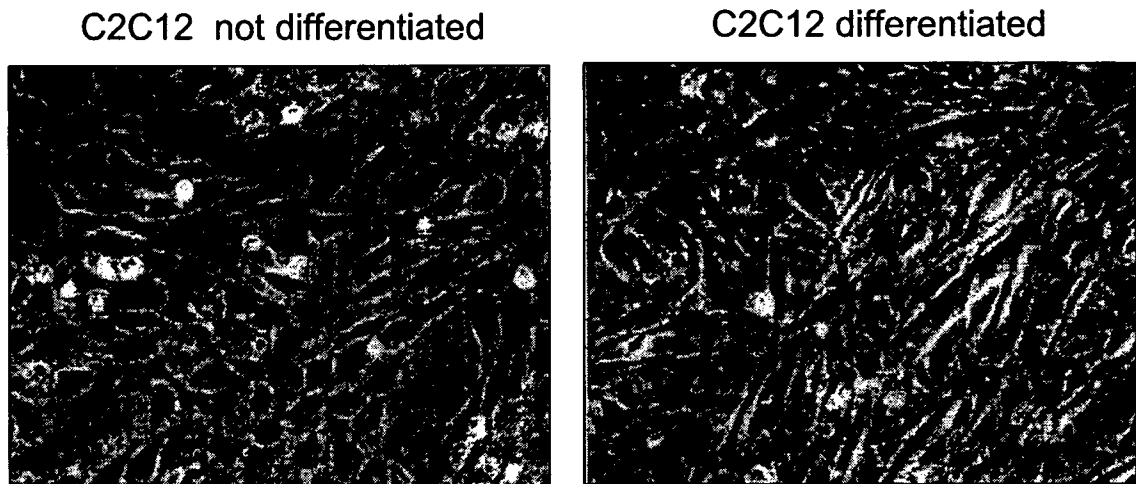


Figure 5A

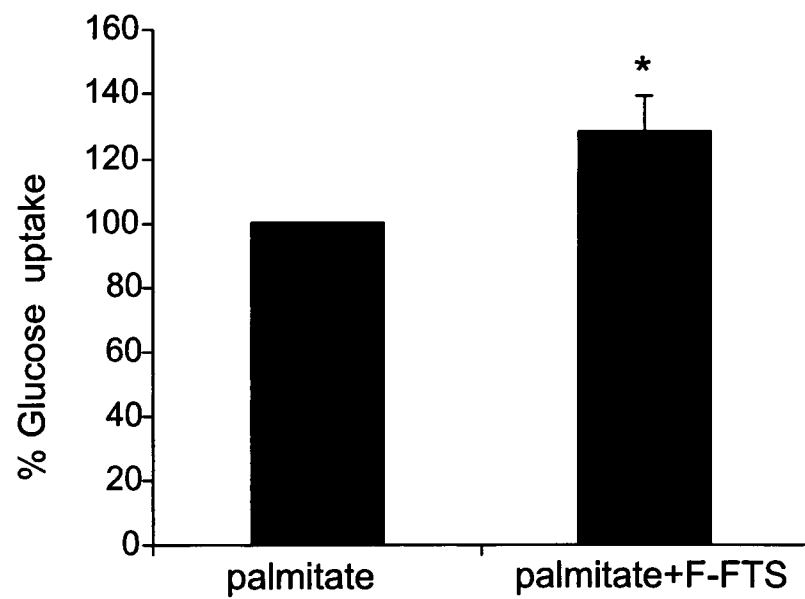


Figure 5B

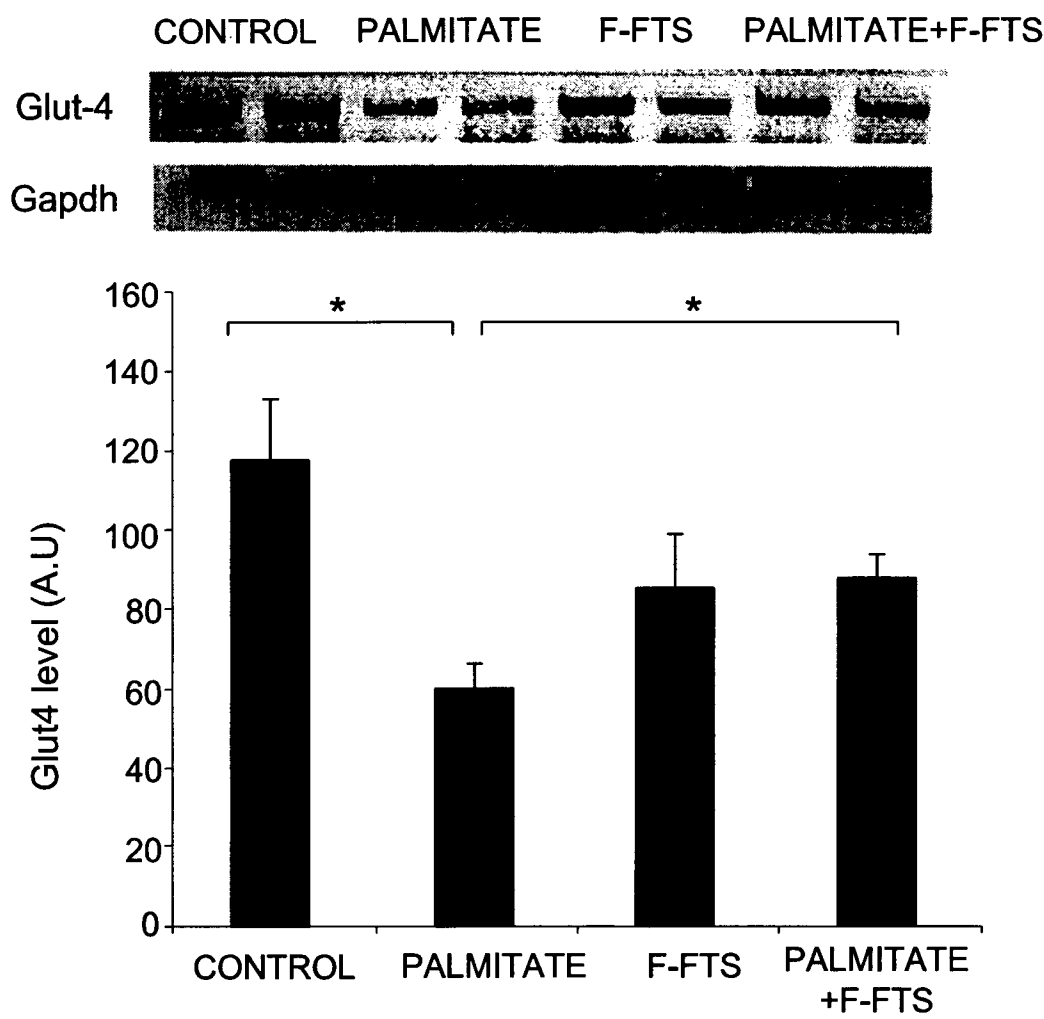


Figure 5C

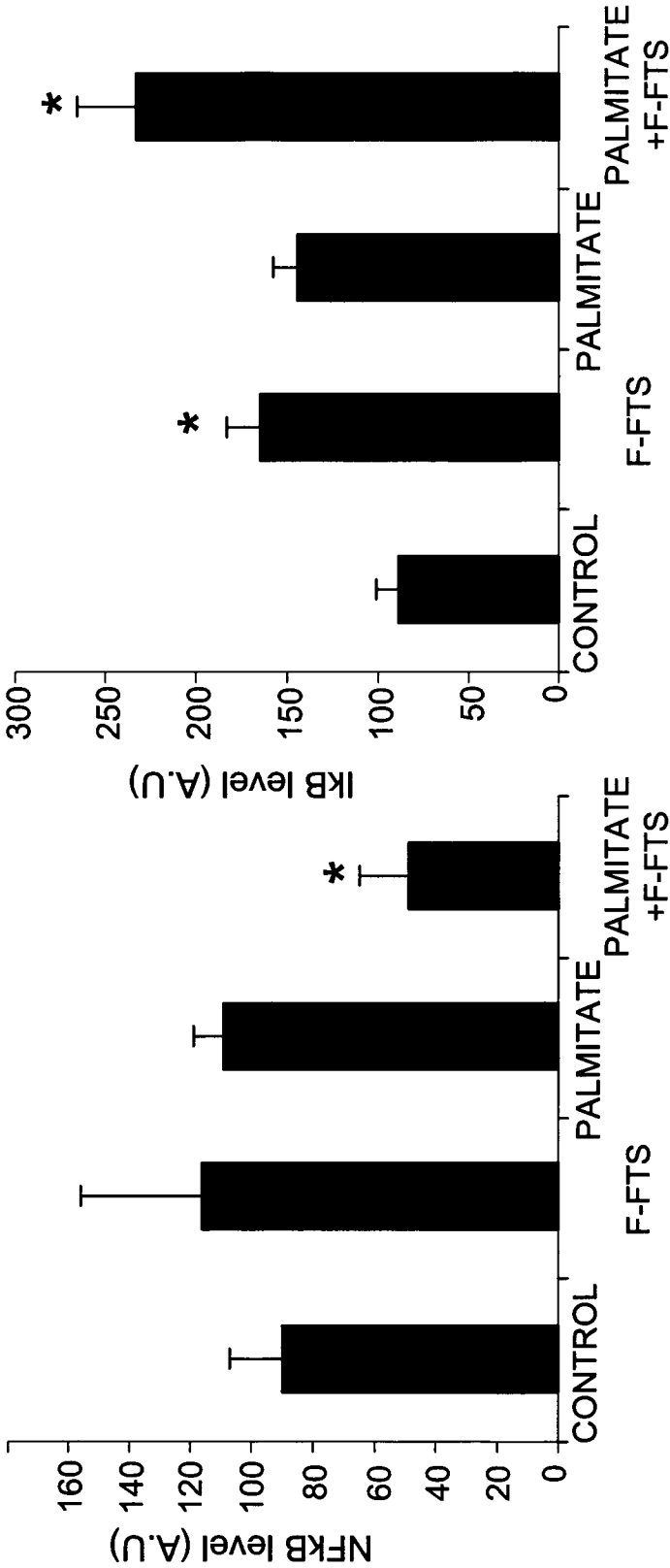
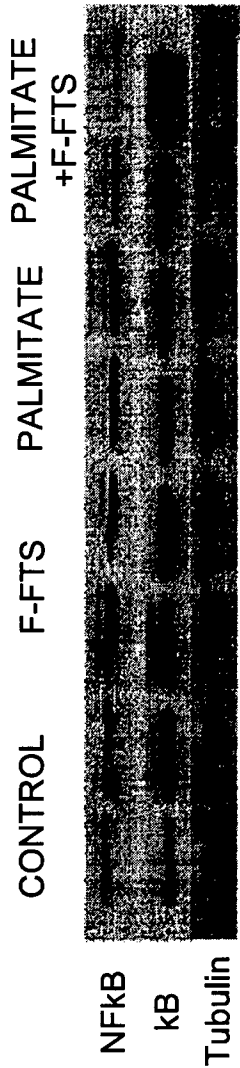


Figure 5D

Figure 5E

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2012/050005

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/166 A61K31/192 A61K31/216 A61K31/235 A61K45/06 A61P3/10 A61P5/50 ADD. 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 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	MOR ADI ET AL: "Ras inhibition induces insulin sensitivity and glucose uptake.", PLOS ONE, vol. 6, no. 6, E21712, 29 June 2011 (2011-06-29), pages 1-11, XP002672251, ISSN: 1932-6203 the whole document ----- -/--	1-49
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document 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 26 March 2012		Date of mailing of the international search report 18/04/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Hoff, Philippe

INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2012/050005

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AIZMAN ELIZABETA ET AL: "Ras inhibition attenuates pancreatic cell death and experimental type 1 diabetes: Possible role of regulatory T cells", EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 643, no. 1, September 2010 (2010-09), pages 139-144, XP002672252, ISSN: 0014-2999	31-34
A	the whole document	1-30, 35-49
X	----- MOR A ET AL: "Ras inhibition increases the frequency and function of regulatory T cells and attenuates type-1 diabetes in non-obese diabetic mice", EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 616, no. 1-3, 15 August 2009 (2009-08-15), pages 301-305, XP026391843, ELSEVIER SCIENCE, NL ISSN: 0014-2999 [retrieved on 2009-06-13]	31-34
A	the whole document	1-30, 35-49
X	----- US 6 462 086 B1 (KLOOG YOEL [IL] ET AL) 8 October 2002 (2002-10-08)	31-34
A	column 2, line 51 - line 60 column 5, line 25 - line 44 column 6, line 54 - column 7, line 45 column 8, line 30 - column 9, line 50 claims 1,2,7,10-12,20; examples -----	1-30, 35-49

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IL2012/050005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 6462086	B1	08-10-2002	US 6462086 B1	08-10-2002
			US 2002115696 A1	22-08-2002
