

**FUROSTAN-3-OL DERIVATIVES
FOR THE TREATMENT OF OBESITY AND DIABETES**

CROSS REFERENCE TO RELATED APPLICATIONS

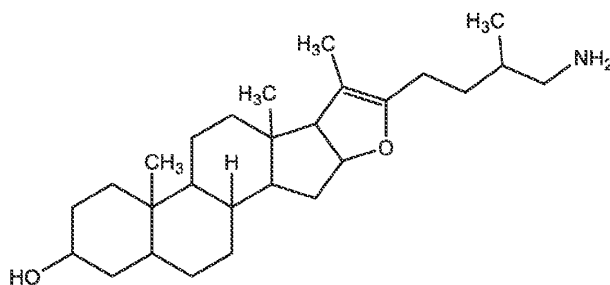
[0001] This application claims priority of US provisional Provisional Application 63/592,627, filed October 24, 2023, and U.S. Provisional Application 63/557,269, filed February 23, 2024, the disclosures of both of which are hereby incorporated herein by reference in their entirety.

FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with Government support under contract R44AR069400 awarded by the National Institutes of Health. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The invention relates to the use of furostan-3-ol derivatives, in particular the compound of Formula I, i.e. 10-(4-amino-3-methylbutyl)-6a,8a,9-trimethyl-2,2a,3,4,5,6,6a,6b,7,8,8a,8b,11a,12,12a,12b-hexadecahydro-1H-naphtho[2',1':4,5]indeno[2,1-b]furan-4-ol:



Formula 1

[0004] The compound and its salts, e.g. those described below, are useful for treating obesity and diabetes.

BACKGROUND

[0005] Diabetes is a major worldwide health problem. Diabetes facts and figures show the growing global burden for individuals, families, and countries. The International Diabetes Federation (IDF) Diabetes Atlas for 2021 reports that 10.5% of the adult population (20-79 years) has diabetes, with almost half unaware that they are living with the condition. By 2045, IDF projections show that 1 in 8 adults, approximately 783 million, will be living with diabetes, an increase of 46%. Over 90% of people with diabetes have type 2 diabetes, which is driven by socio-economic, demographic, environmental, and genetic factors. Approximately 537 million adults (20-79 years) are living with diabetes at present and the total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045. Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus, is now internationally recognized as one of the major threats to human health in the 21st century. Those that suffer from type 2 diabetes, if left untreated, can experience life-threatening complications, including blindness, kidney failure, and heart disease. The key contributors to the rise in type 2 diabetes include: urbanization, an ageing population, decreasing levels of physical activity, increasing overweight and obesity prevalence.

[0006] Obesity is a significant public health issue, presenting a yearly increasing prevalence worldwide, reaching pandemic proportions that imply economic and personal costs. The latest data by the World Health Organization (WHO) show that the prevalence of obesity has tripled since 1975, with over 650 million people worldwide being obese in 2016. Obesity is typically defined by a body mass index (BMI) of $\geq 30 \text{ kg/m}^2$, although a lower cutoff point of $\geq 27.5 \text{ kg/m}^2$ is used in Asian populations.

[0007] In 1973, the term “diabesity” was first used by Sims et al. to describe the pathophysiological connection between excess weight and type 2 diabetes. Diabesity management is challenging because several types of glucose-lowering medications that are used in diabetes management, such as sulfonylureas, meglitinides, thiazolidinediones, and insulin (including insulin analogs), could cause weight gain. Increasing physical activity and following a calorie restriction diet are the main pillars for weight reduction. Weight loss of at least 5% of baseline level in obese patients is clinically significant and improves several obesity-related cardio-metabolic complications, such as arterial hypertension, dyslipidemia, and impaired glucose metabolism (including prediabetes and type 2 diabetes).

[0008] Pharmacological treatment is generally recommended in patients who do not present significant improvement after lifestyle modifications and BMI ≥ 30 kg/m² or ≥ 27.5 kg/m², with excess weight-associated comorbidities. Currently approved anti-obesity drugs include orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide. The GLP-1 (glucagon-like peptide-1) agonists, including semaglutide and liraglutide, and the dual GLP-1/GIP agonist tirzepatide are highly effective weight loss agents. But they are also expensive and can have untoward side effects, including but not limited to skeletal muscle atrophy and weakness.

[0009] For type 2 diabetes, many patients require more than one pharmacologic agent for effective management, and multiple classes of pharmacologic agents are available, but no existing agents reliably protect against dysfunction of insulin-producing pancreatic beta cells, one of the most important pathogenic deficits in type 2 diabetes. Moreover, many patients suffer from obesity and type 2 diabetes at the same time, and in those patients, obesity-related insulin resistance often plays an important role in the pathogenesis of their diabetes.

[0010] Most existing classes of pharmacologic agents for type 2 diabetes do not promote weight loss, and pharmacologic agents for type 2 diabetes that also promote weight loss have side effect profiles that can be intolerable or unsafe for some patients. Thus, there is still a very large unmet need for additional pharmacologic agents for obesity and type 2 diabetes, especially agents that promote weight loss without muscle loss and that protect against dysfunction of pancreatic beta cells.

[0011] For obesity, existing pharmacologic agents such as GLP-1 receptor agonists (e.g. semaglutide/ Ozempic/Wegovy) or the dual GLP-1/GIP agonist tirzepatide/Mounjaro/Zepbound can promote dramatic caloric restriction and weight loss, leading to a wide range of important health benefits for patients. However, that weight loss is frequently accompanied by significant muscle loss and weakness, which can have deleterious short-term and long-term effects. Indeed, when weight loss is achieved through caloric restriction (via current pharmacologic agents, bariatric surgery, or dieting), 15-40% of the weight loss is due to loss of lean mass. Most of the reduction in lean mass is due to a loss of skeletal muscle mass, which typically represents 40% of overall body weight and plays a major role in resting energy expenditure, activity, and systemic metabolism. Loss of skeletal muscle during weight loss can cause important functional deficits, and it also significantly reduces energy expenditure, which impairs both weight loss and maintenance of weight loss. Furthermore, after weight loss, many patients eventually regain weight over time, and the

weight that is regained is mostly if not entirely fat. [See Christoffersen et al. "Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss." *Obesity* (Silver Spring). Apr 2022;30(4):841-57. Epub 2022/03/26.] This is especially problematic in older adults, who often have baseline sarcopenia and suffer from age-related impairments in recovery of muscle mass. Thus, there is an increasing focus on the quality of weight loss (reducing fat mass while preserving muscle mass) and maintenance of weight loss (via protection of muscle mass and energy expenditure), as well as increasing recognition that weight loss and maintenance of weight loss may require different therapeutic strategies.

[0012] Most existing classes of pharmacologic agents for type 2 diabetes are either weight-neutral (e.g., metformin, DPP-4 inhibitors) or promote weight gain (e.g., insulin, sulfonylureas, meglitinides, thiazolidinediones). Classes of pharmacologic agents for type 2 diabetes that also promote weight loss (GLP-1 receptor agonists, tirzepatide, and to a lesser extent, SGLT2 inhibitors) have side effect profiles that can be unsafe or intolerable for some patients, and they also reduce muscle mass as discussed above.

[0013] The furostanol scaffold of the compounds described below is found primarily in the aglycone portion of plant saponins. The plant saponins are frequently associated in the literature with various biological activities, but therapeutic properties are not commonly ascribed to the unglycosylated furostanol sapogenins. For example, US published application 2007/0254847 describes a class of saponins obtained from *Dioscorea panthaica* and *Dioscorea nipponica* which are said to possess utility in treating cerebrovascular and coronary heart diseases. Although the glycosides share a furostanol core, it is the glycoside saponin, not the furostanol aglycone to which the utility is ascribed. The synthesis of the furostanols below is described in US patent 10,662,219 and its continuation 11,136,348; these two patents also describe the utility of the furostanol compounds for treating muscle atrophy and as muscle hypertrophic agents.

SUMMARY OF THE INVENTION

[0014] In one aspect, the present invention provides a method of treating a human afflicted with diabetes, pre-diabetes, and/or obesity. The treatment comprises administering to humans a therapeutically effective amount of the compound of formula I. Particular metabolic disorders are type 2 diabetes and obesity.

[0015] In a second aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and the compound of formula I in the form of its mesylate salt.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] In the accompanying drawings the drawings are not necessarily complete when viewed without reference to the text, emphasis instead being placed upon illustrating the principles of the invention.

[0017] FIG. 1 presents a graph of body weight in grams as a function of time in weeks.

[0018] FIG. 2 presents a graph of blood glucose in mg/dL as a function of time in minutes.

[0019] FIG. 3 presents a graph of blood glucose in mg/dL as a function of time in weeks.

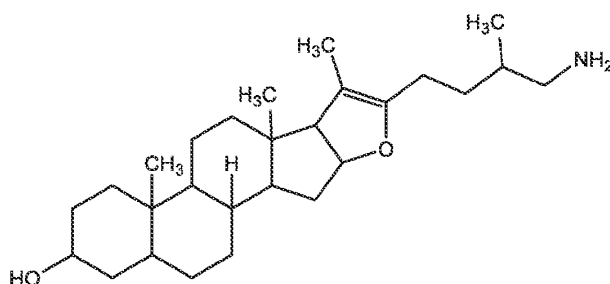
[0020] FIG. 4 presents a graph of blood glucose in mg/dL as a function of time in minutes.

[0021] FIG. 5 presents a graph of blood glucose in mg/dL as a function of time in weeks. The curves compare the compound of example 3 with control and with tomatidine.

[0022] FIG. 6 presents a graph of blood glucose in mg/dL as a function of time in minutes. The curves compare the compound of example 3 with control and with tomatidine.

DETAILED DESCRIPTION OF THE INVENTION

[0023] In the first aspect, the invention relates to the use of compounds of formula I



I

to treat adiposity and metabolic disorders such as obesity and diabetes, particularly type-2 diabetes.

[0024] In another aspect, the invention relates to particular salts of the amines of formula I and to pharmaceutical formulations containing them.

[0025] It has been found that the compound of Formula I demonstrates excellent oral bioavailability, pharmacokinetics, and safety in rodent models, as well as strong efficacy towards obesity and type 2 diabetes. Importantly, in obese mice, the compound of Formula I preserved muscle mass and improved functional capacity while generating striking reductions in body weight, adiposity, and glucose intolerance. Furthermore, in a mouse model of type 2 diabetes with pancreatic beta cell failure, the compound of Formula I protected pancreatic beta cell mass and significantly improved insulin secretion and glycemic control. Studies *in vitro* indicated that the compound of Formula I directly acts upon both skeletal muscle (where it promotes protein accretion, which is important for maintenance of muscle mass and strength) and on pancreatic islets from humans (where it reduces beta cell dysfunction and improves glucose-stimulated insulin secretion). Based on these results, the compound of Formula I represents an exciting new class of potential pharmaceuticals for obesity and type 2 diabetes that promotes weight loss without muscle loss and that protects pancreatic beta cells.

[0026] As used herein, and as would be understood by the person of skill in the art, the recitation of a “compound” - unless expressly further limited - is intended to include salts, solvates and inclusion complexes of that compound as well as any stereoisomeric form, or a mixture of any such forms of that compound in any ratio.

[0027] In methods of the invention, the term “subject” refers to the target of administration, e.g. an animal. Thus the subject of the herein disclosed methods can be a

vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. More specifically, the subject of the herein disclosed methods can be a human, a non-human primate, a dog, or a cat. A patient refers to a subject afflicted with a disease or disorder, e.g. diabetes. The term “patient” includes human and veterinary subjects.

[0028] As used herein, the term “treatment” refers to the medical management of a patient with the intent to cure, ameliorate, palliate, stabilize, or forestall a disease, pathological condition, or disorder. This term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; treatment directed to minimizing or partially or completely inhibiting the development of the associated disease and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease. Aspects of the invention include the use for aesthetic and self-improvement purposes rather than for curing, ameliorating, or forestalling a disease. For example, such uses include, but are not limited to, the administration of the disclosed compound in nutraceuticals, medicinal foods, functional foods, energy bars, energy drinks, sports drinks, protein bars, protein powders, tea, coffee, milk, milk products, cereal, oatmeal, infant formulas, supplements (such as multivitamins) or chewing gum.

[0029] As used herein, the terms “administering” and “administration” refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration.

[0030] As used herein, the terms “effective amount” and “amount effective” refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a “therapeutically effective amount” refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific

therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications.

[0031] While it may be possible for the compounds of formula (I) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0032] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0033] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Preferred dosage forms would be tablets, capsules and solutions or suspensions. The solutions and suspensions are particularly well suited to incorporate the active ingredient into a foodstuff. For example, one might make a drink using water, a solution of the compound described below, and optionally a sugar substitute, salt, and/or small amounts of flavorings and colors.

[0034] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

[0035] Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Formulations for parenteral administration also include aqueous and non-aqueous sterile suspensions, which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid carrier, for example saline, phosphate-buffered saline (PBS) or the like, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0036] Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient. It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of

formulation in question, for example those suitable for oral administration may include flavoring agents.

[0037] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. The compounds of the present invention being basic, salts may be prepared from pharmaceutically acceptable acids. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, adipic, alginic, ascorbic, aspartic, benzenesulfonic (besylate), benzoic, betulinic, boric, butyric, camphoric, camphorsulfonic, carbonic, citric, ethanedisulfonic, ethanesulfonic, ethylenediaminetetraacetic, formic, fumaric, glucoheptonic, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, laurylsulfonic, maleic, malic, mandelic, methanesulfonic, mucic, naphthylenesulfonic, nitric, oleic, pamoic, pantothenic, phosphoric, pivalic, polygalacturonic, salicylic, stearic, succinic, sulfuric, tannic, tartaric acid, teoclastic, p-toluenesulfonic, ursolic and the like.

[0038] Dosages of these particular medicaments, perhaps more than some other medicaments, are optimally measured in relation to the body weight of the subject. Dosage levels of 4 mg/kg/day for a 60 kg human would be roughly 250 mg per day. A 4 mg/kg dose might go up to something like 750 mg per day for an obese person of about 180 kg. The medicament could be supplied in unit dosage forms of 50, 100, 200, or 150 mg. An appropriate dosage level will generally be about 1 to 10 mg per kg patient body weight per day and can be administered in single or multiple doses. Preferably, the dosage level will be about 2 to about 6 mg/kg per day. For oral administration, the compositions are preferably provided in solution, in suspension, or in the form of tablets containing 50 to 500 milligrams of the active ingredient, particularly 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient.

[0039] The term "optically pure" as used in describing compounds herein means that the compositions contain at least 90% by weight of one enantiomer and 10% by weight or less of the other. In a more preferred embodiment, the term "substantially optically pure" means that the composition contains at least 99% by weight of one enantiomer, and 1% or less of the opposite enantiomer. These percentages are based upon the total amount of 10-(4-amino-3-methylbutyl)-6a,8a,9-trimethyl-2,2a,3,4,5,6,6a,6b,7,8,8a,8b,11a,12,12a,12b-hexadecahydro-

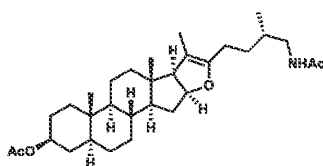
1H-naphtho[2',1':4,5]indeno[2,1-b]furan-4-ol in the composition. The compounds of the examples below will commonly be optically pure as defined above.

[0040] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, and/or methods claimed herein are made and evaluated. They are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[0041] Certain materials, reagents and kits were obtained from specific vendors as indicated below, and as appropriate the vendor catalog, part or other number specifying the item are indicated. Vendors indicated below are as follows: "Pierce" is Pierce Biotechnology, Inc., Milwaukee, Wisconsin, USA, a division of Thermo Fisher Scientific, Inc.; "Roche Diagnostics" is Roche Diagnostics Corporation, Indianapolis, Indiana, USA; and, "Sigma" is Sigma-Aldrich Corporation, Saint Louis, Missouri, USA. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

Compounds of the invention were synthesized as follows:

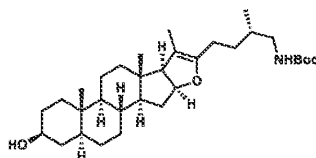
[0042] Example 1. (2a*S*,4*S*,6a*S*,6b*S*,8a*S*,8b*S*,11a*S*,12a*S*,12b*R*)-10-((*S*)-4-acetamido-3-methylbutyl)-6a,8a,9-trimethyl-2,2a,3,4,5,6,6a,6b,7,8,8a,8b,11a,12,12a,12b-hexadecahydro-1H-naphtho[2',1':4,5]indeno[2,1-*b*]furan-4-yl acetate



[0043] Tomatidine hydrochloride (200 mg, 0.44 mmol), pyridine (8 mL), and acetic anhydride (4 mL) were allowed to stir at room temperature for 18 h. The solution was diluted with water and extracted with 3 times with ethyl acetate; the combined extracts were washed

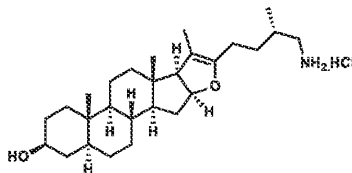
with 3N aq. HCl and dried over anhyd. MgSO₄, concentrated *in vacuo* and the residue purified by flash chromatography eluting with hexanes and ethyl acetate to afford 35 mg of the title compound as an amorphous solid, 16%. ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) were consistent. LC t_r=6.0 min (C-18 column, 5 to 95% acetonitrile/water over 6 min at 1.7 mL/min with detection 210 nm, at 23 °C). ES(pos)MS m/z 500 (M+H calcd for C₃₁H₅₀NO₄ requires 500).

[0044] Example 2. *tert*-Butyl ((*S*)-4-((2*aS*,4*S*,6*aS*,6*bS*,8*aS*,8*bS*,11*aS*,12*aS*,12*bR*)-4-hydroxy-6*a*,8*a*,9-trimethyl-2,2*a*,3,4,5,6,6*a*,6*b*,7,8,8*a*,8*b*,11*a*,12,12*a*,12*b*-hexadecahydro-1*H*-naphtho[2',1':4,5]indeno[2,1-*b*]furan-10-yl)-2-methylbutyl)carbamate



[0045] A solution of tomatidine hydrochloride (250 mg, 0.55 mmol), di-*tert*-butyl dicarbonate (152 μ L, 0.66 mmol), potassium carbonate (182 mg, 1.32 mmol) in 1 mL of 1,4-dioxane were stirred at 50 °C for 18 h. The solution was diluted with water and extracted with 3 times with ether; the combined extracts were washed with water, brine, dried over anhyd. MgSO₄, concentrated *in vacuo*, and the residue purified by flash chromatography eluting with hexanes and ethyl acetate to afford 215 mg of the title compound as a white solid, 76%. ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) were consistent. LC t_r=7.8 min (C-18 column, 5 to 95% acetonitrile/water over 6 min at 1.7 mL/min with detection 210 nm, at 23 °C). ES(pos)MS m/z 516 (M+H calcd for C₃₂H₅₄NO₄ requires 516).

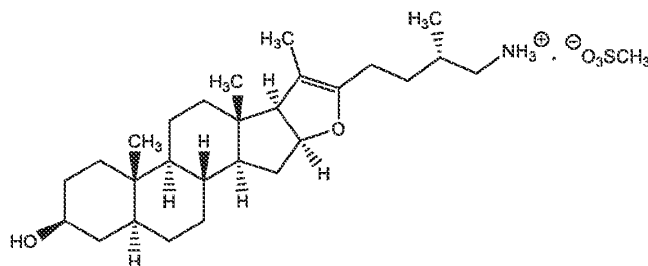
[0046] Example 3. (2*aS*,4*S*,6*aS*,6*bS*,8*aS*,8*bS*,11*aS*,12*aS*,12*bR*)-10-((*S*)-4-Amino-3-methylbutyl)-6*a*,8*a*,9-trimethyl-2,2*a*,3,4,5,6,6*a*,6*b*,7,8,8*a*,8*b*,11*a*,12,12*a*,12*b*-hexadecahydro-1*H*-naphtho[2',1':4,5]indeno[2,1-*b*]furan-4-ol hydrochloride



[0047] A solution of *tert*-butyl ((*S*)-4-((2*aS*,4*S*,6*aS*,6*bS*,8*aS*,8*bS*,11*aS*,12*aS*,12*bR*)-4-hydroxy-6*a*,8*a*,9-trimethyl-2,2*a*,3,4,5,6,6*a*,6*b*,7,8,8*a*,8*b*,11*a*,12,12*a*,12*b*-hexadecahydro-1*H*-

naphtho[2',1':4,5]indeno[2,1-*b*]furan-10-yl)-2-methylbutyl)carbamate (50 mg, 0.10 mmol) and 1 mL of 4M HCl in 1,4-dioxane for 0.5 h. The solution was concentrated and the residue dissolved in acetonitrile whereupon a precipitate formed that was isolated by filtration and dried *in vacuo* to afford 33.7 mg of pure product 75%. ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CD₃OD) consistent. LC t_r=3.7 min (C-18 column, 5 to 95% acetonitrile/water over 6 min at 1.7 mL/min with detection 210 nm, at 23 °C). ES(pos)MS m/z 416 (M+H calcd for C₂₇H₄₆NO₂ requires 416).

[0048] Example 4. Preparation of (((*S*)-4-((2*aS*,4*S*,6*aS*,6*bR*,8*aS*,8*bS*,11*aS*,12*aS*,12*bR*)-4-hydroxy-6*a*,8*a*,9,12*b*-tetramethyl-2,2*a*,3,4,5,6,6*a*,6*b*,7,8,8*a*,8*b*,11*a*,12,12*a*,12*b*-hexadecahydro-1*H*-naphtho[2',1':4,5]indeno[2,1-*b*]furan-10-yl)-2-methylbutyl)ammonio)methanesulfonate.



[0049] The product from Example 2, *tert*-Butyl ((*S*)-4-((2*aS*,4*S*,6*aS*,6*bS*,8*aS*,8*bS*,11*aS*,12*aS*,12*bR*)-4-hydroxy-6*a*,8*a*,9-trimethyl-2,2*a*,3,4,5,6,6*a*,6*b*,7,8,8*a*,8*b*,11*a*,12,12*a*,12*b*-hexadecahydro-1*H*-naphtho[2',1':4,5]indeno[2,1-*b*]furan-10-yl)-2-methylbutyl)carbamate, (250 mg, 0.47 mmol), was dissolved in 1,4-dioxane and treated with methane sulfonic acid, (2 equiv). After stirring at room temperature for 1 h the mixture was concentrated in *vacuo* and the residue dissolved in acetonitrile whereupon a precipitate formed that was isolated by filtration and dried *in vacuo* to afford 210.7 mg of pure product 86%. ¹H NMR (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) were consistent with the desired product. ES (pos) MS m/z 523 (M+H calcd for C₂₉H₄₉NO₅S requires 523).

Results of Biological Testing

In an *in vitro* screen, the compound of Formula I (also referred to as "Formula I") strongly stimulated protein accretion in a dose-dependent manner. The *in vitro* studies demonstrated

that the compound possesses drug-like physicochemical properties, including polarity consistent with drug-like characteristics, excellent stability in plasma and whole blood (half-life > 120 minutes), no inhibitory effects on key cytochrome P450 drug metabolizing enzymes, and excellent membrane transport without any evidence of efflux in bi-directional Caco-2 cell permeability assays. The *in vivo* studies, performed in healthy rats, demonstrated that the compound of Formula I has good oral bioavailability (35.8%), significantly enhanced oral bioavailability relative to a standard, an *in vivo* plasma half-life of 13.5 hours, and no evidence of toxicity.

[0050] Effect on adiposity. Weight-matched cohorts of 8-week-old male C57BL/6 mice were randomized to receive ad libitum access to either standard chow (control) or standard chow supplemented with 0.05% (w/w) of the compound of Example 3. Five weeks later, mice were weighed again, fat mass and lean mass were assessed by NMR, and fat pads (retroperitoneal and epididymal) were dissected and weighed. Data are means $\pm$ SEM from 15-16 mice per cohort. * $P < 0.05$ by unpaired t-test. The compound of Example 3 significantly decreased fat mass ($P = 0.02$) and fat pad weight ($P = 0.03$) and tended to increase % lean mass ($P = 0.07$).

Table 1

	Control	0.05% Example 3
Initial Body Weight (g)	23.0 $\pm$ 0.4	23.1 $\pm$ 0.2
Final Body Weight (g)	28.3 $\pm$ 0.5	27.7 $\pm$ 0.4
Final Fat Mass (g)	3.4 $\pm$ 0.5	2.1 $\pm$ 0.3*
Final Lean Mass (g)	19.1 $\pm$ 0.5	19.4 $\pm$ 0.3
Final % Fat	11.8 $\pm$ 1.6	7.5 $\pm$ 1.1*
Final % Lean	67.5 $\pm$ 1.3	70.2 $\pm$ 1.1
Fat Pad Weight (mg)	966.7 $\pm$ 91.3	743.9 $\pm$ 66.1*

[0051] In a second *in vivo* efficacy study in mouse models, the dose of the compound of Example 3 was molar-matched to 0.05% tomatidine. Weight-matched cohorts of 8-week-old male C57BL/6 mice were randomized to receive ad libitum access to either standard chow (control) or standard chow supplemented with Formula I molar-matched to 0.05% tomatidine. Five weeks later, fat mass and lean mass were assessed by NMR. Similar to 0.05% tomatidine, the compound of Formula I significantly ($P=0.02$) decreased fat mass (as

shown in Table 1 above) and significantly ($P=0.03$) decreased dissected fat pad weight (as shown in Table 1 above) in non-obese mice. However, in contrast to 0.05% tomatidine, the compound of Formula I did not significantly alter skeletal muscle mass (combined weights of bilateral tibialis anterior, gastrocnemius, soleus, quadriceps, and triceps muscles). In addition, in these healthy, normoglycemic animals, the compound of Formula I did not alter glucose levels, insulin levels, or pancreatic beta cell mass. Thus, in healthy mice, the compound of Formula I significantly reduces adiposity, without inducing muscle atrophy, muscle hypertrophy, hyperglycemia, or hypoglycemia.

[0052] Effect on adiposity and weight gain in diet-induced obesity. (Figure 1) Weight-matched cohorts of 8-week-old male C57BL/6 mice were subjected to body composition analysis by NMR (fat mass and lean mass), and then randomized to receive ad libitum access to either high-fat chow (control) or high-fat chow supplemented with 0.05% (w/w) of the compound of Example 3. Nine weeks later, body weight, fat mass, and lean mass were re-assessed, and fat pads (retroperitoneal and epididymal) were dissected and weighed. Data are means $\pm$ SEM from 12 mice per cohort. * $P < 0.0001$ by unpaired t-test. Example 3 significantly decreased final body weight, final fat mass, and fat pad weight, and the compound of Example 3 significantly increased % lean mass ($P < 0.0001$). All other parameters were not significantly different between control and Example 3-treated mice ($P > 0.05$).

Table 2

	Control	0.05% Example 3
Initial Body Weight (g)	22.6 $\pm$ 0.4	22.4 $\pm$ 0.4
Initial Fat Mass (g)	1.2 $\pm$ 0.2	1.2 $\pm$ 0.1
Initial Lean Mass (g)	16.4 $\pm$ 0.4	16.3 $\pm$ 0.3
Initial % Fat	5.4 $\pm$ 0.7	5.6 $\pm$ 0.6
Initial % Lean	72.3 $\pm$ 0.8	72.6 $\pm$ 0.6
Final Body Weight (g)	39.4 $\pm$ 0.9	31.4 $\pm$ 0.8*
Final Fat Mass (g)	14.5 $\pm$ 0.7	6.1 $\pm$ 0.8*
Final Lean Mass (g)	19.9 $\pm$ 0.4	19.6 $\pm$ 0.4
Final % Fat	36.6 $\pm$ 1.2	19.0 $\pm$ 2.2*
Final % Lean	50.7 $\pm$ 0.9	62.7 $\pm$ 1.6*
Fat Pad Weight (mg)	3113 $\pm$ 127	1429 $\pm$ 169*

In this model, the compound of Formula I significantly decreased weight gain and fat mass, unlike a molar-matched dose of tomatidine (additional data not shown). Importantly, despite its dramatic effects on adiposity and weight gain in diet-induced obese mice, the compound of Formula I did not decrease lean mass or skeletal muscle mass, in contrast to current pharmacologic and surgical anti-obesity interventions, which decrease adiposity and body weight by decreasing food intake, and thus, also promote skeletal muscle atrophy and weakness. Thus, on balance, the compound of Formula I decreased the relative amount of fat mass, while increasing the relative amount of lean mass. Moreover, the compound of Formula I significantly ($P=0.0001$) improved grip strength and significantly ($P=0.02$) improved rotarod performance in standard mouse tests, consistent with preservation of skeletal muscle. Furthermore, and consistent with preservation of lean mass and energy expenditure, the compound of Formula I did not decrease food intake, but rather tended to increase food intake (food intake was 3.27 ± 0.86 g/mouse/day in control mice and 4.12 ± 0.67 g/mouse/day in the compound of Formula I -treated mice; $P = 0.42$). The current data indicate that the compound of Formula I does not reduce adiposity and obesity by decreasing food intake, but, rather, suggest that the anti-obesity effects of the compound of Formula I may be mediated by an increase in energy expenditure, possibly related to preservation of skeletal muscle mass, a major determinant of resting energy expenditure, activity, and systemic metabolism. Thus, Formula I is a novel, orally available compound with a favorable safety profile, favorable pharmacologic properties, enhanced anti-obesity effects, and a capacity to induce substantial weight loss and fat loss without loss of skeletal muscle or functional capacity.

[0053] Effect on obesity-related glucose intolerance. (Figure 2) Diet-induced obese mice also exhibit modest elevations in fasting blood glucose and glucose intolerance, similar to prediabetes. Interestingly, in diet-induced obese mice, the compound of Formula I significantly reduced fasting blood glucose and glucose intolerance. Weight-matched cohorts of 8-week-old male C57BL/6 mice were randomized to receive ad libitum access to either high-fat chow (control) or high-fat chow supplemented with 0.05% Example 3. Eight weeks later, mice were fasted for 6 hours and then subjected to glucose tolerance testing by measuring fasting blood glucose, administering an intraperitoneal injection of glucose (2 g / kg body weight), and then measuring blood glucose levels 5, 15, 30, 60, and 120 minutes later. Example 3 significantly reduced fasting blood glucose (163 ± 5 mg/dL in control mice, and 144 ± 8 mg/dL in Example 3-treated mice; $P = 0.03$). Example 3 also significantly reduced

the area under the curve (AUC) in the glucose tolerance test ($35,054 \pm 1,129$ in control mice, and $28,083 \pm 1,249$ in Example 3-treated mice; $P < 0.001$), indicating a reduction in obesity-related glucose intolerance. In contrast, a molar-matched dose of tomatidine, the chemical precursor of the furostanols, did not significantly alter blood glucose in diet-induced obese mice.

[0054] Effect on hyperglycemia in diabetes mellitus. (Figure 3) To test the hypothesis that the compound of Formula I might have efficacy towards type 2 diabetes, we used a well-established mouse model of type 2 diabetes with beta cell failure (Luo et al. "Nongenetic mouse models of non-insulin-dependent diabetes mellitus." *Metabolism*, Jun 1998;47(6):663-8. Epub 1998/06/17). In this model, mice are fed a high-fat diet (HFD; 55% calories from fat) for 4 weeks to induce obesity and glucose intolerance, and then administered a single dose of streptozotocin (STZ; 100 mg/kg) to injure insulin-secreting pancreatic beta cells. The single dose of STZ in combination with HFD induces endoplasmic reticulum (ER stress) in pancreatic beta cells, impairs beta cell function, and ultimately reduces approximately 50% of the total beta cell mass due to cell death and/or dedifferentiation. Following STZ administration, mice are continued on a HFD to generate a type 2 diabetes-like phenotype, with hyperglycemia secondary to a combination of obesity-related insulin resistance and moderate but not absolute insulin deficiency. Weight-matched cohorts of 8-week-old male C57BL/6 mice were provided *ad libitum* access to high-fat chow. Four weeks later, non-fasting blood glucose levels were assessed, and mice were administered an intraperitoneal injection of streptozotocin (100 mg / kg body weight) to induce diabetes mellitus. Mice were then randomized to receive *ad libitum* access to either high-fat chow (control) or high-fat chow supplemented with 0.05% Example 3 for 5 weeks, and non-fasting blood glucose levels were re-assessed each week. During weeks 3-5, Example 3 significantly decreased blood glucose (* $P < 0.03$), indicating a reduction in diabetes-related hyperglycemia. At six weeks, the mice were fasted for 6 hours and then subjected to insulin tolerance tests by measuring fasting glucose, administering insulin (1 unit/kg i.p.), and then reassessing blood glucose. the compound of formula I increased the level of plasma insulin from 500 pM to 950 pM and increased the ratio of plasma insulin to plasma glucose from 2 to 5 ($P < 0.01$)

[0055] Seven weeks after STZ administration, animals were euthanized and pancreata were collected. Pancreatic sections were subjected to immunofluorescence microscopy with antibodies targeting insulin and glucagon, followed by quantification of total islet area and

islet insulin-positive area. Statistically significant ($P=0.02$) increases in total islet area and statistically significant ($P=0.06$) increases in islet insulin-positive area were observed.

[0056] Effect on diabetes-related fasting hyperglycemia and glucose intolerance. (Figure 4) Weight-matched cohorts of 8-week-old male C57BL/6 mice were provided *ad libitum* access to high-fat chow. Four weeks later, mice were administered an intraperitoneal injection of streptozotocin (100 mg / kg body weight) to induce diabetes mellitus. Mice were then randomized to receive *ad libitum* access to either high-fat chow (control) or high-fat chow supplemented with 0.05% Example 3. Five weeks later, mice were fasted for 6 hours and then subjected to glucose tolerance testing by measuring fasting blood glucose, administering an intraperitoneal injection of glucose (2 g / kg body weight), and then measuring blood glucose levels 15, 30, 45, 60, 90, and 120 minutes later. Example 3 significantly reduced fasting blood glucose relative to control mice (250 ± 18 mg/dL in control mice, and 188 ± 10 mg/dL in Example 3-treated mice; $P=0.003$), indicating a reduction in diabetes-related fasting hyperglycemia. Example 3 also significantly reduced the area under the curve (AUC) in the glucose tolerance test ($65,381 \pm 4,612$ in control mice, and $50,751 \pm 4,331$ in Example 3-treated mice; $P=0.02$), indicating a reduction in diabetes-related glucose intolerance.

[0057] Comparison of Example 3 and tomatidine in diabetes mellitus. (Figure 5) Weight-matched cohorts of 8-week-old male C57BL/6 mice were provided *ad libitum* access to high-fat chow. Four weeks later, non-fasting blood glucose levels were assessed, and mice were administered an intraperitoneal injection of streptozotocin (100 mg / kg body weight) to induce diabetes mellitus. Mice were then randomized to receive *ad libitum* access to either high-fat chow (control), high-fat chow supplemented with 0.05% Example 3, or high-fat chow supplemented with 0.05% tomatidine for 5 weeks, and non-fasting blood glucose levels were re-assessed each week. During weeks 1-5, glucose levels in Example 3-treated mice were significantly lower than glucose levels in control mice ($P < 0.02$), indicating alleviation of diabetes-related hyperglycemia. In addition, glucose levels in Example 3-treated mice were significantly lower than glucose levels in tomatidine-treated mice during weeks 1-5 ($P < 0.02$). Glucose levels in control and tomatidine-treated mice were not significantly different ($P > 0.05$).

[0058] Comparison of Example 3 and tomatidine in diabetes-induced fasting hyperglycemia and glucose intolerance. (Figure 6) Weight-matched cohorts of 8-week-old male C57BL/6 mice were provided ad libitum access to high-fat chow. Four weeks later, mice were administered an intraperitoneal injection of streptozotocin (100 mg / kg body weight) to induce diabetes mellitus. Mice were then randomized to receive ad libitum access to either high-fat chow (control), high-fat chow supplemented with 0.05% Example 3, or high-fat chow supplemented with 0.05% tomatidine. Five weeks later, mice were fasted for 6 hours and then subjected to glucose tolerance testing by measuring fasting blood glucose, administering an intraperitoneal injection of glucose (2 g / kg body weight), and then measuring blood glucose levels 15, 30, 45, 60, 90, and 120 minutes later. Example 3 significantly reduced fasting blood glucose relative to control mice (318 ± 34 mg/dL in control mice, and 195 ± 13 mg/dL in Example 3-treated mice; $P < 0.01$). Example 3 also significantly reduced fasting blood glucose relative to tomatidine-treated mice (269 ± 29 mg/dL in tomatidine-treated mice, and 195 ± 13 mg/dL in Example 3-treated mice; $P < 0.05$). In addition, Example 3 significantly reduced the area under the curve (AUC) in the glucose tolerance test relative to control mice ($70,142 \pm 6,609$ in control mice, and $53,299 \pm 4,101$ in Example 3-treated mice; $P < 0.05$). Furthermore, Example 3 significantly reduced AUC in the glucose tolerance test relative to tomatidine-treated mice ($70,497 \pm 4,350$ in tomatidine-treated mice, and $53,299 \pm 4,101$ in Example 3-treated mice; $P < 0.01$).

[0059] To begin to investigate mechanism by which the compound of Formula I protects pancreatic beta cells in diabetic animals, pancreatic islets were isolated and mRNA expression was analyzed in an unbiased manner using whole-genome RNA-sequencing (RNA-Seq). As expected, in the absence of the compound of Formula I, pancreatic islets from diabetic mice exhibited strong induction of endoplasmic reticulum (ER) stress pathways, which are known to drive pancreatic beta cell failure during type 2 diabetes. However, the compound of Formula I significantly repressed ER stress pathways in pancreatic islets from diabetic animals. Although applicants do not wish to be limited by the theory, this would provide a likely explanation for how the compound of Formula I protects beta cells and preserves insulin secretion in the setting of type 2 diabetes. Furthermore, unbiased pathway analyses of the RNA-Seq data indicated that ER stress was the most significantly upregulated cellular process in pancreatic islets from untreated type 2 diabetic animals and the most significantly repressed process in pancreatic islets from type 2 diabetic animals who received the compound of Formula I. Moreover, in other work, it was found

that one of the central mediators of ER stress and the integrated stress response (ISR), the transcription regulator ATF4, promotes skeletal muscle atrophy and weakness (Ebert et al. "Identification and Small Molecule Inhibition of an Activating Transcription Factor 4 (ATF4)-dependent Pathway to Age-related Skeletal Muscle Weakness and Atrophy." *The Journal of Biological Chemistry*. Oct 16 2015;290(42):25497-511), suggesting ER stress and the ISR as a potential common mechanistic target for the compound of Formula I in both pancreatic beta cells and skeletal muscle fibers.

[0060] To test the hypothesis that the compound of Formula I might reduce beta cell dysfunction via direct actions on pancreatic islets, we utilized a well-established *in vitro* model of islet failure in human type 2 diabetes. In this model, cadaveric pancreatic islets from non-diabetic humans (obtained from Prodo Laboratories) are cultured in the presence of a well-defined cytokine mixture (IL-2 β + TNF α + IFN γ) that induces beta cell dysfunction, leading to impaired glucose-stimulated insulin secretion (Nunemaker CS. "Considerations for Defining Cytokine Dose, Duration, and Milieu That Are Appropriate for Modeling Chronic Low-Grade Inflammation in Type 2 Diabetes." *J Diabetes Res*. 2016;2016:2846570. Epub 2016/11/16;33). To determine the effect of the compound of Formula I in this model, we incubated human pancreatic islets with cytokines in the absence and presence of the compound of Formula I. Importantly, in a dose-dependent manner, and with efficacy observed at 300 nM and 1 μ M (the highest dose tested), the compound of Formula I inhibited the deleterious effects of cytokines and significantly improved glucose-stimulated insulin secretion. These data identify pancreatic islets as another direct site of the compound of Formula I action and indicate that the compound of Formula I produces beneficial effects in pancreatic islets from humans.

[0061] The compound of Formula I promotes weight loss and reduces obesity without reducing food intake, and with preferential loss of fat mass and preservation of skeletal muscle mass and function. These pharmacologic endpoints are important for, e.g., persons with overweight or obesity, whether or not those persons also have type 2 diabetes. In addition to its beneficial effects on body composition and weight, the compound of Formula I reduces hyperglycemia in type 2 diabetes by protecting the normal function and survival of insulin-producing pancreatic beta cells in type 2 diabetes. Importantly, however, compound of Formula I does not constitutively raise the circulating level of insulin (like insulin and insulin secretagogues), and thus, compound of Formula I does not induce hypoglycemia. Because the compound of Formula I does not induce hypoglycemia, it could be safely used by persons without diabetes, similar to GLP-1 receptor agonists, tirzepatide, and SGLT2

inhibitors. In addition, because protection of muscle mass during weight loss plays an important role in maintenance of weight loss, the compound of Formula I could facilitate maintenance of weight loss in patients who have successfully completed therapy with current pharmacologic agents for obesity or who have undergone bariatric surgery.

[0062] The solubility and oral bioavailability of the compounds of Examples 3 and 4 were examined.

[0063] Naïve Sprague-Dawley male rats (weighing 275g-375 g) were used for the pharmacokinetic study. Food was withheld from the rats for twelve hours prior to test article administration until four hours post dose, and water was offered ad libitum. For intravenous (IV) delivery, formulations were administered via the tail vein using a 27g needle and syringe with 20% EtOH:Solutol HS 2:1 in normal saline serving as vehicle. For oral delivery, formulations were administered via gavage needle and syringe with 0.5% methylcellulose (400 cp):2% Tween80 in water serving as vehicle. Blood samples were collected 0 minutes, 5 minutes 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours post dosing via the jugular vein, placed into chilled tubes containing sodium heparin, inverted several times to mix, and kept on ice until centrifugation. Blood samples were then centrifuged at 3,500 rpm for 5 minutes at 4°C, plasma collected and transferred into polypropylene 96 well tubes and then frozen on dry ice.

[0064] Standards were prepared in blank male naïve Sprague-Dawley rat plasma and were treated identically to the study samples. Working standard solutions were prepared in 50:50 acetonitrile:water. Working solutions were then added to plasma to make calibration standards to final concentrations of 2000, 1000, 500, 250, 100, 50, 10, 5, 2 and 1 ng/mL. Plasma samples were manually extracted via precipitation with acetonitrile in a 96-well plate by adding 200 µl of acetonitrile containing the internal standard warfarin (250ng/mL) to each blank, standard, or experimental sample and then vortexed. Samples were then centrifuged at 3000 rpm for 5 minutes, and 100µL of supernatant plus 100µL DI water were used in the HPLC detection assay.

[0065] Pharmacokinetic parameters were calculated from the time course of the plasma concentration. Pharmacokinetic parameters were determined with Phoenix WinNonlin (v8.0) software using a non-compartmental analysis model. The maximum plasma concentration

(C_{max}) and the time to reach maximum plasma concentration (t_{max}) after dosing were observed from the data. The area under the time-concentration curve (AUC) was calculated using the linear trapezoidal rule with calculation to the last quantifiable data point (AUC_{0-last}), and with extrapolation to infinity (AUC_∞). Plasma half-life (t_{1/2}) was calculated from 0.693/slope of the terminal elimination phase. Mean residence time, MRT, was calculated by dividing the area under the moment curve (AUMC) by the AUC. Any samples below the limit of quantitation (2.0 ng/mL plasma) were not used in the calculation of mean values.

The results are shown in Table 3:

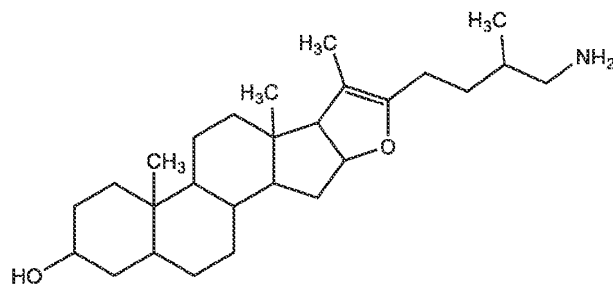
Table 3

Compound	In Vitro Equilibrium Solubility		Oral Bioavailability (%)
	Solubility in Aqueous Buffer pH 1.2 (μM)	Solubility in Aqueous Buffer pH 7.4 (μM)	
Example 3	5.0	2.5	35.8
Example 4	90.2	16.1	46.9

[0066] It can be seen that, while both salts are effective for the intended purpose, the methanesulfonate salt (Example 4) exhibits unexpected advantages over the hydrochloride salt (Example 3), in formulation and in bioavailability.

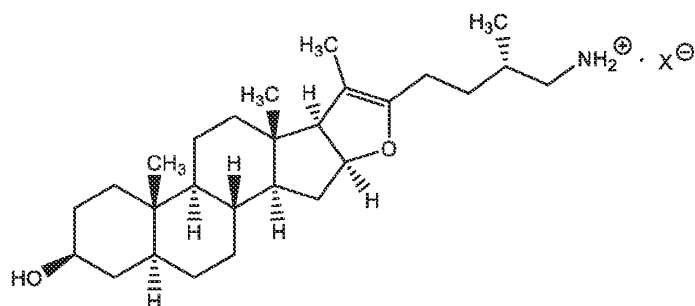
CLAIMS

1. A method for reducing adiposity, treating obesity or treating diabetes in a subject, said method comprising administering to said subject a therapeutically effective amount of a compound of formula I:



I.

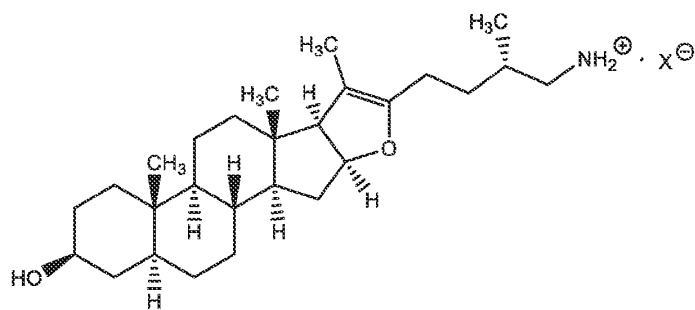
2. The method according to claim 1 wherein said compound is in the form of a salt.
3. The method according to claim 2 wherein the salt is a methanesulfonic acid salt.
4. The method according to claim 1 wherein said subject is a human and said therapeutically effective amount is from 2 to 6 mg/kg/day.
5. The method according to claim 1 wherein said compound is >90% e.e. of the (2a*S*,4*S*,6a*S*,6b*S*,8a*S*,8b*S*,11a*S*,12a*S*,12b*R*) enantiomer.
6. The method according to claim 1 wherein the compound of formula I is administered as a salt having formula Ia:



Ia

wherein X is a pharmaceutically acceptable anion.

7. The method according to claim 6 wherein X is Cl^- or CH_3SO_3^- .
8. The method according to claim 1 for reducing adiposity.
9. The method according to claim 8 for reducing adiposity wherein the subject is suffering from, or at risk of, obesity.
10. The method according to claim 1 wherein the subject is suffering from, or at risk of, diabetes.
11. The method according to claim 10 wherein the diabetes is type 2 diabetes.
12. The method according to any of claims 1 to 11 wherein the compound is administered orally.
13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula Ia.



Ia

wherein X is methanesulfonate.

14. The pharmaceutical composition according to claim 13 wherein the composition is suitable for oral administration.

15. The pharmaceutical composition according to claim 14 in the form of a tablet or capsule.

16. The pharmaceutical composition according to claim 14 in the form of a solution or suspension.