US6399601B1 20020604 ( US6707590A20000927; US15714899P19990930 ) Bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors - DU BOIS DAISY JOE - PFIZER INC.

This invention relates to compounds of Formula I or stereoisomers, pharmaceutically acceptable salts or prodrugs thereof or a pharmaceutically acceptable salts of the prodrugs. This invention also relates to pharmaceutical compositions comprising a compound of Formula I, and to methods of treatment of diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

Abstract: This invention also relates to pharmaceutical ... a compound of Formula I, and to methods of treatment of diabetes, insulin resistance, diabetic ... atherosclerosis, or tissue ischemia

Description: This invention also relates to the treatment of diabetes, insulin resistance, diabetic ... ischemia, using the bicyclic pyrrolyl amides.

BACKGROUND OF THE INVENTION In spite of the ... insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use ... pioglitazone, as oral hypoglycemic agents, the treatment of diabetes remains less then satisfactory.

Treatment of non-insulin dependent diabetes mellitus (Type ... and in more severe cases, insulin.

Atherosclerosis, a disease of the arteries, is recognized to be the leading ... of death in the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

Epidemiological evidence has firmly established ... a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, ... risk factors in this population. Successful treatment of hyperlipidemia in the general population, and ... is therefore of exceptional medical importance.

Hypertension (or high blood pressure) is a ... as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such ""essential"" hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms ... in the complete absence of any other signs of disease or disorder.

Hypertension can also contribute to the development of atherosclerosis and coronary disease.

The exact cause of essential hypertension is ... are believed to contribute to the onset of the disease.

The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind.

Thus, a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has ... failure, renal failure and brain hemorrhaging.

However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem.

This implies that although high blood pressure is ... essential hypertension is not responding to this treatment.

Hepatic glucose production is an important target for NIDDM therapy.
Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers' disease (glycogen phosphorylase deficiency), display episodic hypoglycemia.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release ... and a new shortened glycogen macromolecule.

These compounds and glycogen phosphorylase ... have been postulated to be of use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.

Also provided are kits for the treatment of diabetes, insulin resistance, diabetic ... comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic ... for containing the first and second compositions.

Also provided are kits for the treatment of diabetes, insulin resistance, diabetic ... comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic ... for containing the first and second compositions.

Also provided are methods of treating diabetes, ... at least one additional compound useful for the treatment of diabetes, insulin resistance, diabetic ... atherosclerosis, or tissue ischemia.

The invention also relates to methods of treatment of diabetes, insulin resistance, diabetic ... salts of the prodrugs of compounds of Formula I.

The term ""therapeutically effective amount"" ... eliminates one or more symptom of a particular disease or condition or prevents or delays the onset of one or more symptom of a particular disease or condition.

The terms ""reaction-inert solvent"" or ""inert ... product The terms ""treatment", ""treat"" or ""treatment"" include preventative (e.g., prophylactic) and palliative treatment.

A patient in need of glycogen phosphorylase inhibition is a patient having a disease or condition in which glycogen phosphorylase plays a role in the disease of condition.

The characteristics of patients at risk of having ... who have a family history of cardiovascular disease, including hypertension and atherosclerosis, ... of high density lipoprotein (HDL), and the like.

The other pharmaceutically active compounds can be intended to treat the same disease or condition as the compounds of the present invention or a different disease or condition.

Since one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of ... separate pharmaceutical compositions in kit form.

The specific dosage and dosage range that can be ... of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered.

Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper active agent in the level animal’s body.

In another aspect, the present invention concerns the treatment of diabetes, including impaired glucose ... (NIDDM or Type II). Also included in the treatment of diabetes are the treatment of the diabetic complications, such as neuropathy, nephropathy, retinopathy or cataracts.

inhaled formulations comprising insulin); GLP-1 ... lithium chloride, CT98014, CT98023; galanin receptor agonists; MTP inhibitors such as those disclosed in U.S.

60/164,803; growth hormone secretagogues such as ... Anorectic agents including 5-HT and 5-HT2C receptor antagonists and/or mimetics: dexfenfluramine, Prozac.RTM., Zoloft.RTM.; CCK receptor agonists: SR-27897B; galanin receptor antagonists; MCR-4 antagonists: HP-228; leptin ... and CRF binding proteins: RU486, urocortin.
In addition to the categories and compounds ... aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors, or sorbitol ... ischemia, particularly myocardial ischemia.

in an article published in Atherosclerosis, 126: ... agents, yet devoid of undesirable cardiac activities.

The disclosure teaches that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial infarction, and angina pectoris.

The term aldose reductase inhibitor refers to ... glucose to sorbitol, which is catalyzed by the enzyme aldose reductase.

The activity of an aldose reductase inhibitor in a tissue can ... and consequently the production of fructose.

The compounds of the present invention can also be used in combination with glucocorticoid receptor antagonists. The glucocorticoid receptor (GR) is present in glucocorticoid responsive ... an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell nucleus where it ... in a glucocorticoid responsive manner.

Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NFkappa-B.

Such interactions result in inhibition of API- ... to be responsible for the anti-inflammatory activity of endogenously administered glucocorticoids.

Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. By definition, glucocorticoid receptor antagonists bind to the receptor and prevent glucocorticoid receptor agonists from binding and eliciting GR mediated events, including transcription.

RU486 is an example of a non-selective glucocorticoid receptor antagonist. GR antagonists can be used in the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body.

As such, they may be used to treat the following: obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, ... enhancement, Cushing’s Syndrome, Addison’s Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, ... immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, ... catabolism and prevention of muscle frailty.

RU486 and 5,728,704 and 5,866,578 disclose compounds and a ... diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

Heathoock, Ed., p 777), metal-halogen exchange of ... of heterocycles of Formula 1 (R""=H) followed by treatment of aryl lithiums of Formula 11 with a formylating agent such as dimethylformamide (Ortiz, J.

For example, with regard to Scheme III, mono- and bis-halide substitution can be accomplished by treatment with an electrophilic halide source such as the ... salts, or elemental halogen (Gale, W.

With regard to Scheme V, the esters of compound A ... catalyst such as concentrated sulfuric add or by treatment with an alkyl halide such as methyl iodide and a base such as potassium carbonate.

The Formula K cyanohydrin can be prepared from the stereochemically pure aldehyde by treatment with sodium or potassium cyanide as described ... to those skilled in the art by crystallization.

BIOLGICAL PROTOCOLS The utility of the ... the present invention as medical agents in the treatment or prevention of diseases (such as are detailed herein) in animals, ... mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in ... Such assays also provide a means whereby the activities of the compounds of his invention can be compared with the activities of other known compounds.
The results of these comparisons are useful for particularly mammals, including humans, for the treatment of such diseases.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 ml), and ... and 0.7 mug/ml concentrations respectively.

containing fractions are pooled following identification by determining enzyme activity described below and visualizing the Mr ... Co., LTD., Tokyo, Japan) and then pooled.

Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... described in Section (A) Activation of GP below.

Determination of GP Enzyme Activity A) Activation of GP: Conversion of GPb to GPa Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... form (designated GPa) by the follow procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel.RTM.

immobilized phosphorylase kinase beads are ... 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).

coli) or the mixture of GPa and GPb obtained from ... (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel.RTM.

The activated sample is removed from the beads ... conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: ... that is noted following conversion of GPb to GPa.

B) GPa Activity Assay The disease/condition treating/preventing activities described herein of the compounds of the present ... effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... by the release of inorganic phosphate.

To measure the GPa enzyme activity in the forward direction, the production of ... coupled general method of Pesce et al.

The compound to be tested is added as 5 mul of ... (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors, e.g., a compound ... of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 mul of 50 mM of the positive control test substance, caffeine.

To measure the GPa enzyme activity in the reverse direction, the conversion of ... general method described by Engers et al3690.

The compound to be tested is added as 5 mul of solution in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors, e.g., a ... of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 mul of 50 mM caffeine.

100: 95-97 (1979)] modified as follows: 150 mul ... green in 1 N HCl is added to 100 mul of the enzyme mix.
The above assays carried out with a range of ... inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

The hypoglycemic activity of the compounds of this invention can be ... vehicle without test compound in male ob/ob mice.

Since the concentration of glucose in blood is closely related to the development of diabetic disorders, the compounds of the present invention, by ... action, prevent, arrest and/or regress diabetic disorders.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

The animals dosed with vehicle maintain ... treated with compounds having hypoglycemic activity at suitable doses have significantly depressed glucose levels. Hypoglycemic activity of the test compounds is determined by ... and vehicle-treated group on day 5. The above assay carried out with a range of doses of a test ... vivo reduction of plasma glucose concentration.

Such activity can be determined by the amount of test compound ... vehicle without test compound in male ob/ob mice.

Since the concentration of cholesterol in blood ... cerebral vascular or peripheral vascular disorders, the compounds of this invention, by virtue of ... prevent, arrest and/or regress atherosclerosis.

Since the concentration of triglycerides in blood ... lowering and/or free fatty acid lowering activity prevent, arrest and/or regress hyperlipidemia.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

The inter assay coefficient of variation is \( \leq 10\% \).

Triglycerides Test reagent system (Abbott ... Division, Irving, Tex.) (lipase-coupled enzyme method; a modification of the method of Sampson, et al, Clinical Chemistry 21: 1983 (1975)).

Cholesterol Test reagent system (cholesterol esterase-coupled enzyme method; a modification of the method of Allain, et al.

Serum free fatty add concentration is determined utilizing a kit from Amano International Enzyme Co., Inc., as adapted for use with the Abbott VP.TM.

The serum insulin, triglycerides, free fatty add and total cholesterol lowering activity of the test compounds are determined by ... group and the vehicle-treated control group

**Claims:** A kit for the treatment of diabetes, insulin resistance, diabetic ... comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic ... for containing the first and second compositions.

A method of treating diabetes, insulin ... at least one additional compound useful for the treatment of diabetes, insulin resistance, diabetic ... atherosclerosis, or tissue ischemia.


Description of US6399601B1 contains 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

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Claims of US6399601B1 contains 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide


Description of US6399601B1 contains 3-Methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic Acid [(1S)-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

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Claims of US6399601B1 contains 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide


Description of US6399601B1 contains 2-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic Acid [(1S)-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

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Description of US6399601B1 contains 4H-1,7-dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

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Description of US6399601B1 contains 6H-Thieno[2,3-b]pyrrole-5-carboxylic Acid [(1S)-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

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Claims of US6399601B1 contains 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-Benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

US2001046956A1 20011129 ( US84127601A20010424; US19995100P20000427 ) Methods of treating obesity using a neurotensin receptor ligand - HADCOCK JOHN R. - HADCOCK JOHN R.

The present invention relates to methods of treating obesity, diabetes, sexual dysfunction, atherosclerosis, insulin resistance, impaired glucose tolerance, hypercholesterolemia or hypertriglyceridemia using a neurotensin receptor ligand. The present invention also relates to pharmaceutical compositions and kits that comprise a neurotensin receptor ligand.

Title: Methods of treating obesity using a neurotensin receptor ligand

Abstract: The present invention relates to methods of ... or hypertriglyceridemia using a neurotensin receptor ligand. The present invention also relates to ... and kits that comprise a neurotensin receptor ligand.

Description: FIELD OF THE INVENTION [0002] The present ... using a compound that is a neurotensin receptor ligand. The present invention also relates to compositions and kits that comprise a neurotensin receptor ligand.

BACKGROUND OF THE INVENTION [0003] Obesity is a devastating disease. Unfortunately, obesity is not well understood, ... to exacerbate the psychological effects of the disease. Because of the impact of obesity on individuals ... success has been achieved in the long-term treatment and/or prevention of obesity.

(The neurotensin-3 receptor is also called sortlin or gp95.) The ... G protein coupled receptors; the neurotensin-3 receptor is not a G protein coupled receptor.
SUMMARY OF THE INVENTION [0006] The present ... amount of a compound that is a neurotensin receptor ligand.

[0007] In a preferred embodiment of the methods, the neurotensin receptor ligand is a neurotensin-1 receptor ligand.

[0008] In another preferred embodiment of the methods, the neurotensin receptor ligand is a neurotensin-2 receptor ligand.

[0009] In another preferred embodiment of the methods, the neurotensin receptor ligand is a neurotensin-3 receptor ligand.

[0012] In another preferred embodiment of the methods, the neurotensin receptor ligand is a neurotensin-1 receptor agonist.

[0013] Also provided are methods of treating ... of a compound that is a selective neurotensin-1 receptor agonist.

[0014] Also provided are pharmaceutical ... [0015] a) a compound that is a neurotensin receptor ligand; and [0016] b) a second compound useful for the treatment of obesity, diabetes, sexual dysfunction, ... hypercholesterolemia or hypertriglyceridemia.

[0017] In a preferred embodiment of the compositions, the neurotensin receptor ligand is a neurotensin-1 receptor agonist.

[0018] In another preferred embodiment of the ... the second compound is a beta3-adrenergic receptor agonist, a cholecystokinin-A agonist, a ... agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a bombesin ... or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, or a ciliary neurotrophic factor.

[0019] Also provided are kits that comprises: ... comprising a compound that is a neurotensin receptor ligand; [0021] b) a second pharmaceutical ... comprising a compound that is useful for the treatment of obesity, diabetes, sexual dysfunction, ... container for the first and second compositions.

[0023] In a preferred embodiment of the kits, the neurotensin receptor ligand is a neurotensin-1 receptor agonist.

[0024] In another preferred embodiment of the ... a compound that is a beta3-adrenergic receptor agonist, a cholecystokinin-A agonist, a ... agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a bombesin ... or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, or a ciliary neurotrophic factor.

[0025] Also provided are methods of treating ... effective amount of a neurotensin receptor ligand.

[0026] In a preferred embodiment of the method, the neurotensin receptor ligand is a neurotensin-1 receptor ligand.

DETAILED DESCRIPTION OF THE INVENTION [0027] The ... using a compound that is a neurotensin receptor ligand.

In addition, the present invention provides ... compositions and kits comprising a neurotensin receptor ligand.

[0028] In accordance with the present invention, ... effective amount of a neurotensin receptor ligand.

In a preferred embodiment of the invention, the neurotensin receptor ligand is a neurotensin-1 receptor ligand.

In a more preferred embodiment of the invention, the neurotensin receptor ligand is a selective neurotensin-1 receptor agonist.
The term "therapeutically effective . . . or combination of compounds that treats a disease; ameliorates, attenuates, or eliminates one or more symptoms of a particular disease; or prevents or delays the onset of one of more symptoms of a disease.

The terms "treating", "treat" or "treatment" include preventative (e.g., prophylactic) and palliative treatment. The phrase "neurotensin receptor ligand" means a compound that binds to a neurotensin receptor, or a stereoisomer of the compound, a . . . pharmaceutically acceptable salt of the prodrug.

It is also contemplated that any additional . . . compound used in combination with a neurotensin receptor ligand can be a stereoisomer of the additional . . . of the prodrug. The phrase "neurotensin receptor agonist" means a neurotensin receptor ligand that activates a neurotensin receptor. The phrase "neurotensin receptor antagonist" means a neurotensin receptor ligand that blocks activation of a neurotensin receptor.

The term "selective" means that a ligand binds with greater affinity to a particular receptor when compared with the binding affinity of the ligand to another receptor.

Preferably, the binding affinity of the ligand for the first receptor is about 50% or greater than the binding affinity for the second receptor.

More preferably, the binding affinity of the ligand to the first receptor is about 75% or greater than the binding affinity to the second receptor.

Most preferably, the binding affinity of the ligand to the first receptor is about 90% or greater than the binding affinity to the second receptor.

Preferred neurotensin receptor ligands of the present invention include . . . that are selective agonists of the neurotensin-1 receptor. Neurotensin receptor ligands can be identified, for example, by screening a compound library.

Specific procedures that can be used to identify neurotensin receptor ligands are presented below. Examples of known neurotensin receptor ligands include hormones such as neurotensin . . . agonists such as those disclosed in U.S. 5,407,916, non-peptide antagonists such as . . . (SR48692), which is a selective neurotensin-1 receptor antagonist, and . . . at neurotensin-1 and neurotensin-2 receptors.

5,250,558 and 5,204,354 disclose neurotensin receptor antagonists, and U.S.

An example of a selective neurotensin-1 receptor agonist is native neurotensin [NT(1-13)], which has a Kd of about 0.3 nM at the neurotensin-1 receptor and about 2-6 nM at the neurotensin-2 receptor. Another example of a selective neurotensin-1 receptor agonist is Trp 11 NT(1-13), which shows a binding affinity of about 1 nM at the neurotensin-1 receptor and about 27 nM at the neurotensin-2 receptor.

A neurotensin receptor ligand is administered to a patient in a therapeutically effective amount. A neurotensin receptor ligand can be administered alone or as part of a pharmaceutically acceptable composition.

A neurotensin receptor ligand can be administered using an immediate . . . release formulation, or combinations thereof.

In addition, a neurotensin receptor ligand can be administered alone, in combination with other neurotensin receptor ligands, or with other pharmaceutically active compounds.

The other pharmaceutically active compounds can be intended to treat the same disease as the neurotensin receptor ligand or a different disease.

Since one aspect of the present invention contemplates the treatment of the diseases referenced with a combination of . . . separate pharmaceutical compositions in kit form.

For example, a kit may comprise two separate . . . compositions comprising: 1) a neurotensin receptor ligand; and 2) a second pharmaceutically active compound.
Also, a daily dose of a neurotensin receptor ligand can consist of one tablet or capsule, ... of several tablets or capsules and vice versa.

[0046] A neurotensin receptor ligand and other pharmaceutically active ... or drops), or as a buccal or nasal spray.

[0055] Compositions for rectal or vaginal administration can be prepared by mixing a neurotensin receptor ligand and any additional compounds with ... or vaginal cavity and release the neurotensin receptor ligand.

[0056] Dosage forms for topical administration of a neurotensin receptor ligand include ointments, powders, sprays and inhalants.

[0057] A neurotensin receptor ligand can be administered to a patient at ... the range of about 0.1 to about 7,000 mg per day.

The specific dosage and dosage range that can be ... of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered.

The administration of a neurotensin receptor ligand can be effected orally or non-orally, for example by injection. An amount of a neurotensin receptor ligand is administered such that a ... between 0.1 and 50 mg/kg of body weight.

Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper active agent level in the animal’s body.

[0071] A neurotensin receptor ligand may contain asymmetric or chiral centers, ... exist in different stereoisomeric forms.

[0073] A neurotensin receptor ligand may exist in unsolvated as well as ... solvents such as water, ethanol, and the like.

[0074] It is also possible that a neurotensin receptor ligand may exist in different tautomeric forms. All tautomers of a neurotensin receptor ligand are contemplated.

Neurotensin receptor ligands, prodrugs thereof, and pharmaceutically ... atoms are within the scope of this invention.

[0078] The present invention relates to the use of neurotensin receptor ligands to treat obesity, diabetes, sexual ... disorders; irritable bowel syndrome; diarrhea; cholic; ... esophagitis; gastroparesis; neurological diseases such as schizophrenia, psychoses, anxiety, manic ... and dysthenias such as Huntington’s disease and Tourett’s syndrome; fungal and viral ... tumors); anorexia; bulimia; asthma; Parkinson’s disease; acute heart failure; hypotension; hypertension; ... prostatic hypertrophy. [0080] The methods of treatment of the present invention can also include ... pharmacologically active compounds useful for the treatment of obesity or other diseases are used in combination with a neurotensin receptor ligand.

[0081] It is known that obese patients have higher incidences of certain diseases such as atherosclerosis, hypercholesterolemia, ... diabetes]; and the diseases associated with diabetes such as nephropathy, ... cataracts, and polycystic ovary syndrome. These diseases can be treated indirectly by treating obesity using a neurotensin receptor ligand or directly by treating the specific disease itself using a neurotensin receptor ligand. These diseases can be treated in the absence of obesity using a neurotensin receptor ligand.

[0082] In one embodiment of the invention, an ... administered a combination of: 1) a neurotensin receptor ligand; and 2) an additional compound useful to ... [including (NIDDM) and the conditions and/or diseases associated with diabetes, such as nephropathy, ... combinations of compounds useful to treat these diseases.
[0083] Sexual dysfunction occurs in males and females and includes hypoactive sexual desire disorder, sexual anhedonia and dyspareunia. Hypoactive sexual desire disorder is a disorder in which sexual fantasies and desire for sexual activity are persistently or recurrently diminished or ... Symptoms and signs of hypoactive sexual desire disorder include the patient complaining of a lack of ... sex, even in ordinarily erotic situations. The disorder is usually associated with infrequent sexual activity, often causing serious conflict between partners.

Sexual anhedonia is decreased or absent pleasure in sexual activity.

Sexual anhedonia is almost always classified under hypoactive sexual desire disorder, because loss of pleasure typically results in loss of desire.

have persons having this condition been offered an oral medicinal treatment.

In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use ... pioglitazone, as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

Treatment of non-insulin dependent diabetes mellitus (Type ... and, in more severe cases, insulin.

[0087] Atherosclerosis, a disease of the arteries, is recognized to be a leading ... of death in the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

[0088] Epidemiological evidence has firmly ... a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, ... risk factors in this population. Successful treatment of hyperlipidemia in the general population, and ... is therefore of exceptional medical importance.

[0089] Hypertension (or high blood pressure) is a ... as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such “essential” hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms ... in the complete absence of any other signs of disease or disorder.

Hypertension can also contribute to the development of atherosclerosis and coronary disease.

[0091] The exact cause of essential hypertension ... are believed to contribute to the onset of the disease.

[0092] The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind.

Thus, a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has ... failure, renal failure and brain hemorrhaging.

[0094] A neurotensin receptor ligand can be used in combination with one or more compounds that are useful to treat obesity.
Additional anti-obesity agents that can be used in combination with a neurotensin receptor ligand include a beta3-adrenergic receptor agonist, a cholecystokinin-A agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanocyte-concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin agonist, a bombesin... or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, and a ciliary neurotrophic factor.

Especially preferred anti-obesity agents that can be used in combination with a neurotensin receptor ligand include compounds selected from the group... y-phenox)acetic acid.

Examples of thyromimetics that can be used in combination with a neurotensin receptor ligand include those disclosed in U.S.

Examples of glucocorticoid receptor ligands that can be used in combination with a neurotensin receptor ligand include those disclosed in U.S.

Examples of neuropeptide-Y antagonists that can be used in combination with a neurotensin receptor ligand include those disclosed in WO 98/23603, U.S.

Additional compounds that can be used to... can be used in combination with a neurotensin receptor ligand include the compounds disclosed in WO 98/46243. can also be used in combination with a neurotensin receptor ligand.

Other compounds that can be used to treat sexual... can be used in combination with a neurotensin receptor ligand include apomorphine and IC351 (ICOS).

In another aspect of the invention, a neurotensin receptor ligand can be administered in combination with a compound that is known to treat hypertension.

Examples of classes of compounds that can be used... ACE inhibitors, diuretics, angiotensin II receptor blockers, beta-blockers, and alpha-adrenergic blockers.

Some examples of specific compounds that can be used in combination with neurotensin receptor ligands include quinapril; amlodipine, including... salt. [0104] In another aspect, a neurotensin receptor ligand can be used in combination with compounds useful for the treatment of diabetes, including impaired glucose... Type 2). Also intended to be encompassed in the treatment of diabetes are the diabetic complications, such... retinopathy, cardiomyopathy or cataracts.

Representative agents that can be used to... can be used in combination with a neurotensin receptor ligand include but are not limited to insulin... those disclosed in WO 96/39385 and WO 96/39384.

Preferred examples of glycogen... invention in combination with a neurotensin receptor ligand include: [0107]... and prodrugs thereof, and salts of the prodrugs.

Commonly assigned PCT published... can be used in combination with a neurotensin receptor ligand.

A neurotensin receptor ligand can also be used in combination with an aldose reductase inhibitor.

The disclosure teaches that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such... include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial infarction, and angina pectoris.

The term aldose reductase inhibitor refers... glucose to sorbitol, which is catalyzed by the enzyme aldose reductase.
Any aldose reductase inhibitor may be used in a combination with a neurotensin receptor ligand.

[0213] The activity of an aldose reductase inhibitor in a tissue can . . . and consequently the production of fructose.

[0245] A neurotensin receptor ligand can also be used in combination with a sorbitol dehydrogenase inhibitor.

5,728,704 and 5,866,578 disclose compounds and . . . diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

The compounds disclosed in these patents and . . . invention in combination with a neurotensin receptor ligand. [0246] A neurotensin receptor ligand can also be used in combination with a glucocorticoid receptor antagonist. The glucocorticoid receptor (GR) is present in glucocorticoid responsive . . . an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell nucleus where it . . . in a glucocorticoid responsive manner.

Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NFkappa-beta.

Such interactions result in inhibition of API- . . . to be responsible for the anti-inflammatory activity of endogenously administered glucocorticoids.

Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. By definition, glucocorticoid receptor antagonists bind to the receptor and prevent glucocorticoid receptor agonists from binding and eliciting GR mediated events, including transcription.

RU486 is an example of a non-selective glucocorticoid receptor antagonist. GR antagonists can be used in the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body.

As such, they may be used to treat the following: obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, . . . enhancement, Cushing’s Syndrome, Addison’s Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, . . . immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, . . . [0247] Examples of preferred glucocorticoid receptor antagonists that can be used in combination with a neurotensin receptor ligand can be found in U.S.

[0248] A neurotensin receptor ligand can also be used in combination with a sodium-hydrogen exchanger type 1 (NHE-1) inhibitor.

Preferred NHE-1 inhibitors that can be used in combination with a neurotensin receptor ligand can be found in PCT publication number WO 99/43663. [0249] In addition, a neurotensin receptor ligand can be used in combination with a thymimetic.

in an article published in Atherosclerosis, 126: . . . agents and are devoid of undesirable cardiac activities. [0250] In addition, a neurotensin receptor ligand can be administered in combination with . . . anti-oxidants and niacin. A neurotensin receptor ligand may also be administered in combination . . . that act to lower plasma cholesterol levels.

The term HMG-CoA reductase inhibitor refers to a . . . A to mevalonic acid as catalyzed by the enzyme HMG-CoA reductase.

The term HMG-CoA synthase inhibitor refers to a . . . A and acetoacetyl-coenzyme A, catalyzed by the enzyme HMG-CoA synthase.

Such inhibitors may either affect transcription . . . the aforementioned attributes by one or more enzymes in the cholesterol biosynthetic cascade or may . . . isoprene metabolite that has the aforementioned activities.

[0255] Any compound having activity as a CETP inhibitor can serve as the second . . . therapy aspect of the instant invention.
5,512,548 discloses certain polypeptide derivatives having activity as CETP inhibitors, while certain ... analogs of cholesteryl ester are disclosed in J.

Other CETP inhibitors that can be used in combination with a neurotensin receptor ligand are disclosed in WO 99/20302, EP 796846, ... DE 19741400, JP 11049743, and JP 09059155.

Preferred CETP inhibitors that can be used in combination with a neurotensin receptor ligand include: [0256] [2R,4S] ... prodrugs thereof, and the salts of the prodrugs.

The term ACAT inhibitor refers to a compound that ... esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase.

5,510,379 discloses certain carboxysulfonates, ... disclose urea derivatives having ACAT inhibitory activity. [0277] Any compound having activity as a squalene synthetase inhibitor can serve as ... therapy aspect of the instant invention.

The term squalene synthetase inhibitor refers to ... squalene, a reaction that is catalyzed by the enzyme squalene synthetase.

European patent application publication number 0 ... synthetase inhibitors and their use in the treatment of hypercholesterolemia and as fungicides.

European patent application publication number 0 ... synthetase inhibitors and their use in the treatment and prevention of hypercholesterolemia and fungal infections.

European patent application publication number 0 ... as squalene synthetase inhibitors useful for the treatment of hypercholesterolemia or coronary sclerosis.

European patent application publication number 0 ... substituted amic acid derivatives useful for the treatment of arteriosclerosis.

European patent application publication number 0 ... plasma cholesterol and triglyceride lowering activities.

These compounds can also be used in combination with a neurotensin receptor ligand.

[0278] It is also contemplated that a neurotensin receptor ligand be administered with a lipase inhibitor ... inhibitor, which are typically used in the treatment of conditions resulting from the presence of ... [0279] In a combination with a neurotensin receptor ligand, any lipase inhibitor or glucosidase inhibitor may be employed.

Under normal physiological conditions, lipolysis ... of an activated serine moiety of the lipase enzyme.

Accordingly, compounds, including lipase ... of ingested fat precursors are useful in the treatment of conditions including obesity, hyperlipidemia, hyperlipoproteinemia, Syndrome X, and the like.

Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions.

Gastric lipolysis of ingested fats is of ... fatty acids needed to trigger pancreatic lipase activity in the intestine and is also of importance for ... associated with pancreatic insufficiency.

The ability of RHC 80267 to inhibit the activity of myocardial lipoprotein lipase is disclosed in Carroll et al., Lipids, 27, pp.

[0293] In combination with a neurotensin receptor ligand, any glucosidase inhibitor may be ... inhibitor comprises an amylase inhibitor.

[0309] In addition, the present invention includes the use of a neurotensin receptor ligand in combination with apo B secretion/MTP inhibitors.
[0320] Additional apo B secretion/MTP inhibitors that can be used in combination with a neurotensin receptor ligand are disclosed in U.S.

[0383] In addition, a neurotensin receptor ligand can be used in combination with one or more additional compounds that are neurotensin receptor ligands such as those set forth above.

2 STOCK FINAL Well + [GTPgamma[35S]] 5 nM H 1, 2 3, 4 200 nM 10 nM [0388] Specific Activity of GTPgamma[35S] is approximately 1250 Ci/m mole.

Set up assay in a 96 well filtering system (Unifilter.RTM).

Ca++ Mobilization Using the FLIPR Assay [0416] Another measure of agonist efficacy and ... the stimulation of intracellular calcium release.

Prepare hepes saline and probenecid solutions fresh for each assay. 1 L of assay buffer is sufficient for a small-scale experiment.

Prepare plate containing compound to be tested, diluting compound to be tested in assay buffer (prepare assay buffer just before use).

Empty media from cell plate and wash with assay buffer on scatron plate washer (if doing large amounts of plates).

Equilibrate cells 10 minutes in assay buffer.

[0438] Assay Buffer (1% probenecid solution in hepes saline) ... in each well is 200 ml. [0443] Specific activity of [125I]NT is 2200 Ci/m mole.

Radioactivity calculators that are well known in the art can be used to calculate the specific activities of the stock solutions.

Set up assay in a 96 well filtering system (Unifilter.RTM).

Set up assay in a 96 well filtering system (Unifilter.RTM).

Agonist-Mediated GTPgamma[35S]Binding Assay [0504] Up to seven compounds can be tested in 7 point competition curves in a 96 well format.

Set up assay in a 96 well filtering system (Unifilter.RTM).

In addition, native neurotensin receptor such as HT29 or SW cells can be used.

For the protein assay dilute 1:5 and measure.

Claims: A method of treating obesity, the method ... amount of a compound that is a neurotensin receptor ligand.

The method of claim 1 wherein the neurotensin receptor ligand is a neurotensin-1 receptor ligand.

The method of claim 1 wherein the neurotensin receptor ligand is a neurotensin-2 receptor ligand.

The method of claim 1 wherein the neurotensin receptor ligand is a neurotensin-3 receptor ligand.

The method of claim 1 wherein the neurotensin receptor ligand is a neurotensin-1 receptor agonist.

A method of treating obesity, the method ... of a compound that is a selective neurotensin-1 receptor agonist.

A pharmaceutical composition comprising: a) a compound that is a neurotensin receptor ligand; and b) a second compound useful for the treatment of obesity, diabetes, sexual dysfunction, ... hypercholesterolemia or hypertriglyceridemia.
The pharmaceutical composition of claim 9 wherein the neurotensin receptor ligand is a neurotensin-1 receptor agonist.

The method of claim 9 wherein the second compound is a beta3-adrenergic receptor agonist, a cholecystokinin-A agonist, a . . . agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a . . . receptor agonist, a galanin antagonist, a bombesin . . . or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, or a ciliary neurotrophic factor.

A kit that comprises: a) a first pharmaceutical . . . comprising a compound that is a neurotensin receptor ligand; b) a second pharmaceutical composition comprising a compound that is useful for the treatment of obesity, diabetes, sexual dysfunction, . . . container for the first and second compositions.

The kit of claim 12 wherein the neurotensin receptor ligand is a neurotensin-1 receptor agonist.

The kit of claim 12 wherein the second . . . a compound that is a beta3-adrenergic receptor agonist, a cholecystokinin-A agonist, a . . . agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a . . . receptor agonist, a galanin antagonist, a bombesin . . . or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, or a ciliary neurotrophic factor.

A method of treating diabetes, sexual . . . effective amount of a neurotensin receptor ligand.

The method of claim 15 wherein the neurotensin receptor ligand is a neurotensin-1 receptor ligand

fulltext score : 69 , cippix score : 204 , hit score : 20
Description of US2001046956A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0206] 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, and the pharmaceutically acceptable salts and prodrugs thereof, and salts of the prodrugs.

Description of US2001046956A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0188] 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0181] 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0201] 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;
Description of US2001046956A1 contains 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0143] 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0122] 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0152] 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 4H-1,7-dithia-4-aza-cyclopenta[a]pentelene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0151] 4H-1,7-dithia-4-aza-cyclopenta[a]pentelene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;
Description of US2001046956A1 contains 3-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide


Description of US2001046956A1 contains 2-fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0133] 2-fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0121] 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;

Description of US2001046956A1 contains 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

[0158] 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide;


Description of US2001046956A1 contains 6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide


Description of US2001046956A1 contains 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide


Description of US2001046956A1 contains 5-chloro-1H-indole-2-carboxylic acid[1-benzyl-2-(3-hydroxy-pyrrolidin-1yl)-2-oxo-ethyl]-amide

The present invention provides methods of treating diabetic cardiomyopathy, the methods comprising administering to a patient having or at risk of having diabetic cardiomyopathy a therapeutically effective amount of a glycogen phosphorylase inhibitor. The present invention also provides methods of treating diabetic cardiomyopathy, the methods comprising administering to a patient having 1) diabetes and 2) having cardiovascular disease, ischemic heart disease, congestive heart failure, congestive heart failure but not having coronary arteriosclerosis, hypertension, diastolic blood pressure abnormalities, microvascular diabetic complications, abnormal left ventricular function, myocardial fibrosis, abnormal cardiac function, pulmonary congestion, small vessel disease, small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing, coagulopathy, cardiac contusion, or having had or at risk of having a myocardial infarction a therapeutically effective amount of a glycogen phosphorylase inhibitor.

Abstract: The present invention also provides methods of ... having 1) diabetes and 2) having cardiovascular disease, ischemic heart disease, congestive heart failure, congestive heart ... function, pulmonary congestion, small vessel disease, small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing, coagulopathy, cardiac ... amount of a glycogen phosphorylase inhibitor

Description: The present invention also relates to methods of ... having 1) diabetes and 2) having cardiovascular disease, ischemic heart disease, congestive heart failure, congestive heart ... function, pulmonary congestion, small vessel disease, small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing, coagulopathy, cardiac ... amount of a glycogen phosphorylase inhibitor.

Background of the Invention: Diabetic cardiomyopathy, a disease of the heart muscle (myocardium), is considered ... entity from either diabetes or cardiovascular disease.

Pathologically, diabetic cardiomyopathy is ... deposition, and varying degrees of small vessel disease.
Diabetic cardiomyopathy differs from ischemic cardiomyopathy because the diseased myocardium and resultant CHF can occur in the coronary atherosclerosis or luminal narrowing.

This suggests that the primary metabolic defects microcirculation itself are responsible for the diseased state and loss of myocardial function in diabetics.

Co-existent hypertension, microvascular fibrinolysis, atherosclerotic cardiovascular disease, and/or myocardial ischemia, which frequently of the underlying diabetic cardiomyopathy.

The microvascular diseases associated with diabetes, e.g. defective cellular metabolism, calcium transport, collagen formation) that are observed in the diseased state of the myocardium in diabetics.

[0006] The major cause of morbidity and mortality in the diabetic population is cardiovascular disease (CVD). Coronary heart disease (CHD), also referred to as coronary artery disease (CAD), the major cause of myocardial infarction and stroke, and peripheral vascular disease (PVD) are all manifestations of CVD.

It is well recognized that diabetics have to the hyperglycemia associated with their disease, independent of other associated co-morbidities, hypertension, atherosclerosis, and dyslipidemia.

patent number 5,990,111 discloses the treatment of diabetic cardiomyopathy using an aldose reductase inhibitor.

[0011] Also provided are methods of treating . . . to a patient having diabetes and cardiovascular disease a therapeutically effective amount of a glycogen phosphorylase inhibitor.

[0012] Also provided are methods of treating . . . to a patient having diabetes and ischemic heart disease a therapeutically effective amount of a glycogen phosphorylase inhibitor.

[0023] Also provided are methods treating . . . to a patient having diabetes and small vessel disease a therapeutically effective amount of a glycogen phosphorylase inhibitor.

[0024] Also provided are methods of treating . . . to a patient having diabetes and small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing a therapeutically effective amount of a glycogen phosphorylase inhibitor.

[0033] Also provided is a method of treating . . . being useful to treat diabetes, cardiovascular disease, ischemic heart disease, congestive heart failure, hypertension, . . . function, pulmonary congestion, small vessel disease, coagulopathy, cardiac contusion, or myocardial infarction.

[0035] In another preferred embodiment, the . . . dehydrogenase inhibitor; a glucocorticoid receptor antagonist; a NHE-1 inhibitor; or a thyromimetic.

The present invention also provides methods of . . . having 1) diabetes and 2) having cardiovascular disease, ischemic heart disease, congestive heart failure, congestive heart . . . function, pulmonary congestion, small vessel disease, small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing, coagulopathy, cardiac . . . amount of a glycogen phosphorylase inhibitor.

[0037] In treating diabetic cardiomyopathy, it . . . diabetes and having an additional condition or disease such as cardiovascular disease, ischemic heart disease, congestive heart failure, congestive heart . . . function, pulmonary congestion, small vessel disease, small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing, coagulopathy, cardiac . . . amount the patient’s heart and cardiovascular system.

[0038] The term "therapeutically effective . . . eliminates one or more symptoms of a particular disease or condition or prevents or delays the onset of one or more symptoms of a particular disease or condition.

[0041] The terms “treating”, “treat” or “treatment” include preventative (e.g., prophylactic) and palliative treatment.
[0045] The phrase “cardiovascular disease” means a disease (or diseases) involving or affecting the heart, blood . . .

[0046] The phrase “ischemic heart disease” (also called myocardial ischemia) means . . . and inadequate removal of metabolites.


[0048] The phrase “microvascular diabetic . . . can lead to renal failure, peripheral arterial disease, or limb amputation.

[0050] The phrase “abnormal cardiac function” means any diseased state or abnormal condition of the heart that . . . normal blood pressure, and normal ECG readings.

Normal blood pressure is nominally defined as . . . National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, NIH publication, 1997).

[0051] The phrase ”small vessel disease” (also referred to as microangiopathy) means a diseased condition of the intramyocardial arteries, . . . namely capillaries, venules, and small veins.

[0052] The phrase “atherosclerotic cardiovascular disease” means a cardiovascular disease that is associated with or secondary to an atherosclerotic condition, e.g. a diseased state of the arteries characterized by an . . . [0053] The phrase “microvascular disease” means a diseased condition of the arterioles and/or the vessels . . . to, the resistance vessels. Microvascular disease may be characterized by an unevenly distributed . . . hormones to the tissues, and/or to remove waste.

Microvascular disease can result in microvascular diabetic complications.

The other pharmaceutically active compounds can be intended to treat the same disease or condition as the glycogen phosphorylase inhibitor or a different disease or condition.

[0092] Since one aspect of the present invention contemplates the treatment of the disclosed diseases/conditions with a combination of . . . separate pharmaceutical compositions in kit form.

The specific dosage and dosage range that can be . . . of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered.

Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper active agent in the level animal’s body.

The disclosure teaches that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial infarction, and angina pectoris.

[0138] The term aldose reductase inhibitor . . . glucose to sorbitol, which is catalyzed by the enzyme aldose reductase.

[0140] The activity of an aldose reductase inhibitor in a tissue can . . . and consequently the production of fructose. patent numbers 5,728,704 and 5,866,578 disclose . . . diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

[0149] A glycogen phosphorylase inhibitor can also be used in combination with a glucocorticoid receptor antagonist. The glucocorticoid receptor (GR) is present in glucocorticoid responsive . . . an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell nucleus where it . . . in a glucocorticoid responsive manner.

Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NF kappa - beta .

Such interactions result in inhibition of API-and . . . to be responsible for the antiinflammatory activity of endogenously administered glucocorticoids.
Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. By definition, glucocorticoid receptor antagonists bind to the receptor and prevent glucocorticoid receptor agonists from binding and eliciting GR mediated events, including transcription.

RU486 is an example of a non-selective glucocorticoid receptor antagonist. GR antagonists can be used in the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body.

As such, they may be used to treat the following: obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, . . . enhancement, Cushing’s Syndrome, Addison’s Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, . . . immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, . . . catabolism and prevention of muscle frailty.

Provisional Patent Application number 60/132,130, . . . [0151] Each of the glucocorticoid receptor antagonists referenced above and other glucocorticoid receptor antagonists can be used in combination with a . . . inhibitor to treat diabetic cardiomyopathy.

in an article published in Atherosclerosis, 126: . . . agents and are devoid of undesirable cardiac activities.

Examples of classes of compounds that can be used . . . ACE inhibitors, diuretics, angiotensin II receptor blockers, beta -blockers, and alpha -adrenergic blockers.

Examples [0158] The utility of the . . . the present invention as medical agents in the treatment or prevention of diseases (such as are detailed herein) in animals, . . . mammals (e.g. humans) is demonstrated by the activity of the compounds in conventional assays and the . . . Such assays also provide a means whereby the activities of the compounds can be compared with the activities of other known compounds.

The results of these comparisons are useful for . . . particularly mammals, including humans, for the treatment of such diseases.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 ml), and . . . and 0.7 mu g/ml concentrations respectively.

GP-containing fractions are pooled following identification by determining enzyme activity described below and visualizing the Mr . . . Co., LTD., Tokyo, Japan) and then pooled.

[0166] Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP [0169] Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . described in Section (A) Activation of GP below.

Determination of GP Enzyme Activity A) Activation of GP: Conversion of GPb to . . . [0171] Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . form (designated GPa) by the following procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel TM . . . and 80 mM CaCl2 at pH 7.4 for 4 hours at 4 DEG C.

Prior to use to convert GPb to GPa, the Affi-Gel . . . 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).
coli) or the mixture of GPa and GPb obtained from ... (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel TM beads.

The activated sample is removed from the beads ... conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: % of total HLGPa = HLGP activity - AMP DIVIDED HLGP activity + AMP [0174] Alternately, the ... that is noted following conversion of GPb to GPa.

B) GPa Activity Assay [0175] The disease/condition treating activities described herein of the compounds of the present ... effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... by the release of inorganic phosphate.

[0176] To measure the GPa enzyme activity in the forward direction, the production of ... coupled general method of Pesce et al.

The compound to be tested is added as 5 mu l of ... (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors, e.g., a compound ... l of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 mu l of 50 mM of the positive control test substance, caffeine.

[0177] To measure the GPa enzyme activity in the reverse direction, the conversion of ... by the general method described by Engers et al.

The compound to be tested is added as 5 mu l of solution in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors, e.g., a ... l of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 mu l of 50 mM caffeine.

100: 95-97 (1979)] modified as follows: 150 mu l ... green in 1 N HCl is added to 100 mu l of the enzyme mix.

[0178] The above assays carried out with a ... of test compound allows the determination of an IC50 value (concentration of test compound required ... inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

Animal Models [0179] Experimental models for the study of the treatment of diabetic cardiomyopathy include the ... as referenced in Nagano, M., and Dhalla, N.

A positive effect of the GPI treatment can be identified by a statistically significant ... between the GPI treated and the untreated group.

In Vivo Experiments [0180] The in vivo ... of glycogen phosphorylase inhibitors in the treatment of human diabetic cardiomyopathy can be ... double-blind, placebo-controlled clinical trial.

Holman, Heart Disease, 3rd Edition, Chapter 11).

[0184] The degree of impairment of cardiac autonomic activity may be shown by a reduction in the normal ... R-R interval, most obviously, during respiration.

The standard deviation of the mean R-R interval ... a measure of parasympathetic nervous system activity.

[0185] A stress thallium test is also ... unequivocal evidence of coronary artery disease.

[0186] The single-blind placebo baseline ... during which patients are randomly assigned to a treatment regimen consisting of either placebo or glycogen phosphorylase inhibitor.

Claims: The inhibitor of claim 1 or use of claim 2 ... patient has 1) diabetes and 2) cardiovascular disease, ischemic heart disease, congestive heart failure, congestive heart ... function, pulmonary congestion, small vessel disease, small vessel disease without atherosclerotic cardiovascular disease or luminal narrowing, coagulopathy or cardiac ... or is at risk of having a myocardial infarction.
An inhibitor or use as claimed in any one of the claims is being useful to treat diabetes, cardiovascular disease, ischemic heart disease, congestive heart failure, hypertension, ... function, pulmonary congestion, small vessel disease, coagulopathy, cardiac contusion, or myocardial infarction.

An inhibitor or use as claimed in claim 11 is ... dehydrogenase inhibitor; a glucocorticoid receptor antagonist; a NHE-1 inhibitor; or a thyromimetic.

**Description of EP1125580A2** contains \((+/\-)\)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([1\text{-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl}]\)-amide\)

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid \([(1\text{S})\text{-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl}]\)-amide; \((+/\-)\)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([1\text{-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl}]\)-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

**Description of EP1125580A2** contains 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([(1\text{S})\text{-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl}]\)-amide

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid \([(1\text{S})\text{-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl}]\)-amide; 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([(1\text{S})\text{-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl}]\)-amide; 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.
Description of EP1125580A2 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0075] Within the above group of especially preferred compounds are the compounds ... acid [(1S)-(2-fluorobenzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-(2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl)-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, ... and 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide.

[0088] Another group of preferred glycogen phosphorylase inhibitors includes: ... acid [(1S)-benzyl-2-(3-hydroxyimino-azetidin-1-yl)-2-oxo-ethyl]-amide; and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, and the pharmaceutically acceptable salts, and prodrugs and salts of the prodrugs.

Description of EP1125580A2 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0075] Within the above group of especially preferred compounds are the compounds ... 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxoethyl]-amide, ... and 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide.

[0088] Another group of preferred glycogen phosphorylase inhibitors includes: ... 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluorobenzyl)-2-(4-hydroxypiperidin-1 ... and the pharmaceutically acceptable salts, and prodrugs and salts of the prodrugs.

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.
Description of EP1125580A2 contains 4H-1,7-dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide\)

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid \([(1S)-benzyl-3-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; 4H-1,7-dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1125580A2 contains 3-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide\)

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid; 3-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 3-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1125580A2 contains 2-fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide\)

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide; 2-fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid \([(1S)-benzyl-2-(((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-cyano-4H-furo[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1 ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1125580A2 contains 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid [(1S)-benzyl-2-morpholin-4-yl-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.
Description of EP1125580A2 contains 6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; 6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1125580A2 contains 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include ... acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1 ...) salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1125580A2 contains 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0088] Another group of preferred glycogen phosphorylase inhibitors includes: ... acid [(1S)-benzyl-3-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid ... and the pharmaceutically acceptable salts, and prodrugs and salts of the prodrugs.
Description of EP1125580A2 contains 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide

[0075] Within the above group of especially preferred compounds are the compounds . . . acid (1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide, and 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide.

Description of EP1125580A2 contains 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0056] Preferred examples of glycogen phosphorylase inhibitors of Formula A include . . . acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-cyano-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1 . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

EP1127882A1 20010829 ( US17798700P20000125 ) Composés tétrazoliques comme ligands du récepteur thyroid; Tetrazole compounds as thyroid receptor ligands; Tetrazolverbindungen als Thyroid-Rezeptor-Liganden - CHIANG, YUAN-CHING PHOEBE; ASPNES, GARY ERIK - PFIZER PRODUCTS INC.

The present invention relates to tetrazole compounds of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs. <CHEM> The invention also relates to compositions comprising the tetrazole compounds and to methods of treating obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, glaucoma, cardiac arrhythmias, congestive heart failure, and osteoporosis using the tetrazole compounds.

Title: Tetrazole compounds as thyroid receptor ligands

Abstract: <CHEM> The invention also relates to compositions . . . atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, . . . and osteoporosis using the tetrazole compounds.

Description: Field of the Invention The present . . . relates to tetrazole compounds that are thyroid receptor ligands.

The invention also relates to compositions and . . . the tetrazole compounds and to methods of treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, . . . and osteoporosis using the tetrazole compounds.

Disorders of the thyroid gland are generally treated by . . . that mimic the effects of thyroid hormones.

Such analogues are called thyromimetics or thyroid receptor ligands.
T3 may be produced directly in the thyroid gland, . . . the removal of the 5' iodine of T4 by deiodinase enzymes. Thyroid receptor ligands can be designed to be structurally similar to T3.

Obesity is a devastating disease.

Unfortunately, obesity is not well understood, . . . to exacerbate the psychological effects of the disease.

Because of the impact of obesity on individuals . . . success has been achieved in the long-term treatment and/or prevention of obesity.

The thyromimetics of the present invention can . . . atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, . . . congestive heart failure, and osteoporosis.

In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use . . . pioglitazone, as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

Treatment of non-insulin dependent diabetes mellitus (Type . . . and, in more severe cases, insulin.

Atherosclerosis, a disease of the arteries, is recognized to be a leading . . . of death in the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

Epidemiological evidence has firmly established . . . a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, . . . risk factors in this population. Successful treatment of hyperlipidemia in the general population, and . . . is therefore of exceptional medical importance.

Hypertension (or high blood pressure) is a . . . as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such "essential" hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms . . . in the complete absence of any other signs of disease or disorder.

Hypertension can also contribute to the development of atherosclerosis and coronary disease.

The exact cause of essential hypertension is . . . are believed to contribute to the onset of the disease.

The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind.

Thus, a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has . . . failure, renal failure and brain hemorrhaging.

Also provided are methods of treating coronary heart disease, the methods comprising the step of . . . having or at risk of having coronary heart disease, a therapeutically effective amount of a . . . acceptable salts of the prodrugs.

Also provided are methods of treating thyroid disease, the methods comprising the step of administering to a patient having or at risk of having thyroid disease, a therapeutically effective amount of a . . . acceptable salts of the prodrugs.
Also provided are kits for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... comprising an additional compound useful for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... for containing the first and second compositions.

Also provided are methods of treating obesity, ... atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... congestive heart failure, or osteoporosis.

Also provided are pharmaceutical compositions ... atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... congestive heart failure, or osteoporosis.

This invention also relates to methods of ... atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... congestive heart failure, and osteoporosis.

The phrase "therapeutically effective amount" ... eliminates one or more symptoms of a particular disease or condition or prevents or delays the onset of one or more symptoms of a particular disease or condition.

The terms "treating", "treat" or "treatment" include preventative (e.g., prophylactic) and palliative treatment.

The characteristics of patients at risk of having ... who have a family history of cardiovascular disease, including hypertension and atherosclerosis, ... patients having low levels of HDL, and the like.

In one aspect, the present invention concerns the treatment of diabetes, including impaired glucose ... (NIDDM or Type II). Also included in the treatment of diabetes are the diabetic complications, such ... nephropathy, retinopathy or cataracts.

In addition, the compounds of the present ... NHE-1 inhibitors and/or glucocorticoid receptor antagonists.

The disclosure teaches that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial infarction, and angina pectoris.

The term aldose reductase inhibitor refers to ... glucose to sorbitol, which is catalyzed by the enzyme aldose reductase.

The activity of an aldose reductase inhibitor in a tissue can ... and consequently the production of fructose).

The compounds of the present invention can also be used in combination with a glucocorticoid receptor antagonist. The glucocorticoid receptor (GR) is present in glucocorticoid responsive ... an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell nucleus where it ... in a glucocorticoid responsive manner.

Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NF kappa - beta.

Such interactions result in inhibition of API-and ... to be responsible for the anti-inflammatory activity of endogenously administered glucocorticoids.

Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. By definition, glucocorticoid receptor antagonists bind to the receptor and prevent glucocorticoid receptor agonists from binding and eliciting GR mediated events, including transcription.
RU486 is an example of a non-selective glucocorticoid receptor antagonist. GR antagonists can be used in the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body.

As such, they may be used to treat the following: obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, ... enhancement, Cushing’s Syndrome, Addison’s Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, ... immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, ... catabolism and prevention of muscle frailty.

Patent numbers 5,728,704 and 5,866,578 disclose ... diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

The term HMG-CoA reductase inhibitor refers to a ... A to mevalonic acid as catalyzed by the enzyme HMG-CoA reductase.

The term HMG-CoA synthase inhibitor refers to a ... A and acetoacetyl-coenzyme A, catalyzed by the enzyme HMG-CoA synthase.

Such inhibitors may either affect transcription ... the aforementioned attributes by one or more enzymes in the cholesterol biosynthetic cascade or may ... isoprene metabolite that has the aforementioned activities.

Any compound having activity as a CETP inhibitor can serve as the second ... therapy aspect of the instant invention.

Patent Number 5,512,548 discloses certain polypeptide derivatives having activity as CETP inhibitors, while certain ... analogs of cholesteryl ester are disclosed in J.

The term ACAT inhibitor refers to a compound that ... esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase.

Patent Number 5,510,379 discloses certain ... disclose urea derivatives having ACAT inhibitory activity. Any compound having activity as a squalene synthetase inhibitor can serve as ... therapy aspect of the instant invention.

The term squalene synthetase inhibitor refers to ... squalene, a reaction that is catalyzed by the enzyme squalene synthetase.

European patent application publication Number 0 ... synthetase inhibitors and their use in the treatment of hypercholesterolemia and as fungicides.

European patent application publication Number 0 ... synthetase inhibitors and their use in the treatment and prevention hypercholesterolemia and fungal infections.

European patent application publication Number 0 ... as squalene synthetase inhibitors useful for the treatment of hypercholesterolemia or coronary sclerosis.

European patent application publication Number 0 ... substituted amic acid derivatives useful for the treatment of arteriosclerosis.

European patent application publication Number 0 ... plasma cholesterol and triglyceride lowering activities.

It is also contemplated that the compounds of the ... inhibitor, which are typically used in the treatment of conditions resulting from the presence of ... hyperlipoproteinemia, Syndrome X, and the like.

Under normal physiological conditions, lipolysis ... of an activated serine moiety of the lipase enzyme.

Accordingly, compounds, including lipase ... of ingested fat precursors are useful in the treatment of conditions including obesity, hyperlipidemia, hyperlipoproteinemia, Syndrome X, and the like.

Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions.
Gastric lipolysis of ingested fats is of . . . fatty acids needed to trigger pancreatic lipase activity in the intestine and is also of importance for . . . associated with pancreatic insufficiency.

The ability of RHC 80267 to inhibit the activity of myocardial lipoprotein lipase is disclosed in Carroll et al., Lipids, 27, pp.

The additional anti-obesity agent is preferably . . . the group consisting of a beta 3-adrenergic receptor agonist, a cholecystokinin-A agonist, a . . . agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin agonist, a leptin receptor agonist, a galanin antagonist, a lipase . . . or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, and a ciliary neurotrophic factor.

Examples of presently marketed products . . . TM, and Plendil TM; angiotensin converting enzyme (ACE) inhibitors, such as Accupril TM, Altace . . . TM, Univasc TM, Vasotec TM and Zestril TM.

The other pharmaceutically active compounds can be intended to treat the same disease or condition as the compounds of the present invention or a different disease or condition.

Since one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of . . . separate pharmaceutical compositions in kit form.

The specific dosage and dosage range that can be . . . of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered.

Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper active agent level in the animal’s body.

Treatment of the compound 1 with neat chlorosulfonic acid . . . gives the 3’-chlorosulfonylated compound 2-1.

Treatment of 1 with hexamethylenetetramine at 65 DEG C in . . . acid (TFA) gives the 3’-aldehyde 3-1.

Treatment of the cyanamide 4-2 with sodium azide in the . . . temperature gives the aminotetrazole 4-3.

Treatment of 5 with arylsulfonic acid in the presence of a . . . at elevated temperature gives the sulfone 8-1.

Treatment of 9-3 with dibromotriphenylphosphorane in acetonitrile gives the benzyl bromide 9-4.

Biological Assays The utility of the compounds of the present invention can be evidenced by activity in at least one of the assays described below. ASSAY 1 Oxygen Consumption As would be . . . animals generally consume more oxygen.

Those skilled in the art understand that . . . of heat may be efficacious with respect to the treatment of, e.g., obesity.

The efficacy endpoints measured are whole body oxygen consumption and the activity of liver mitochondrial alpha-glycerophosphate dehydrogenase (“mGPDH”).

The cardiac endpoints that are measured are heart weight and heart mGPDH activity.

The protocol involves: (a) dosing fatty Zucker . . . of mitochondria and subsequent assaying of enzyme activity thereby.

The rats are placed into the sealed chambers (43 . . . of the Oxymax, the chambers are placed in the activity monitors, and the air flow rate through the . . . set at from about 1.6 l/min to about 1.7 l/min.

The activity monitors have 15 infrared light beams spaced about one inch apart on each axis, and ambulatory activity is recorded when two consecutive beams are . . . Oxygen consumption and ambulatory activity are measured about every 10 minutes for from about 5 hours to about 6.5 hours.
Resting oxygen consumption is calculated on . . . obtained during time periods where ambulatory activity exceeds about 100 counts. ASSAY 2 Binding to Thyroid Hormone Receptors . . . can be demonstrated in the following protocol.

Binding Assay Competition binding assays to measure . . . test thyromimetic compounds with thyroid hormone receptor alpha 1 and beta 1 (TR alpha and TR beta ) are carried out according to the following protocol.

Each compound is serially diluted in an assay buffer (5 mM Tris-HCl, pH 8.0; 50 mM NaCl; 2 mM EDTA; 10 % (v/v) glycerol; 1 mM DTT, "assay buffer") containing 0.4 nM $^{125}$I-T3 (specific activity of about 2200 Ci/mmol) to yield solutions that . . . from about 10 μM to about 0.1 nM.

High Five insect cell nuclear extract containing . . . protein concentration of 0.0075 mg/ml using the assay buffer as diluent.

A one hundred and fifty μl sample of the . . . that has been pre-washed with ice-cold assay buffer.

Each well is washed five times by the addition of 200 μl of ice-cold assay buffer and subsequent vacuum filtration.

Claims: The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of diabetes.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of atherosclerosis.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of hypertension.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of coronary heart disease.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of hypercholesterolaemia.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of hyperlipidaemia.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of thyroid disease.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of hypothyroidism.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of depression.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of obesity.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of osteoporosis.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of thyroid cancer.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of glaucoma.

The use of a compound according to any of Claims . . . for the preparation of a medicament for the treatment of cardiac arrhythmias.
The use of a compound according to any of Claims ... for the preparation of a medicament for the treatment of congestive heart failure.

The use of a compound according to any of Claims ... for the preparation of a medicament for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolaemia, hyperlipidaemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... an additional compound suitable for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolaemia, hyperlipidaemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... failure, or osteoporosis. 34. A kit for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolaemia, hyperlipidaemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... containing said first and second compositions.

The use of a compound according to any of Claims ... which additional compound is suitable for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolaemia, hyperlipidaemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... heart failure, or osteoporosis, for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolaemia, hyperlipidaemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... congestive heart failure, or osteoporosis.

A pharmaceutical composition comprising a ... and an additional compound suitable for the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolaemia, hyperlipidaemia, thyroid disease, thyroid cancer, hypothyroidism, depression, ... and a suitable adjunct, carrier, or diluent


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include ... acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; (+/-)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [1-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include ... acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid ... salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.
Description of EP1127882A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Within the above group of especially preferred compounds are the compounds . . . acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, . . . and 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide.

Another group of preferred glycogen phosphorylase inhibitors includes: . . . acid [(1S)-benzyl-2-(3-hydroxylimino-azetidin-1-yl)-2-oxo-ethyl]-amide; and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, and the pharmaceutically acceptable salts, and prodrugs and salts of the prodrugs.

Description of EP1127882A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Within the above group of especially preferred compounds are the compounds . . . 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, . . . and 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide.

Description of EP1127882A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Another group of preferred glycogen phosphorylase inhibitors includes: . . . 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid . . . and the pharmaceutically acceptable salts, and prodrugs and salts of the prodrugs.

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1127882A1 contains 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.
Description of EP1127882A1 contains 4H-1,7-dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 4H-1,7-dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid; 3-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 3-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-cyano-4H-furo[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-((3R,-4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-morpholin-4-yl-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.


Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-(3S,4R)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.
Description of EP1127882A1 contains 6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; 6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1127882A1 contains 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description of EP1127882A1 contains 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

Another group of preferred glycogen phosphorylase inhibitors includes: . . . acid [(1S)-benzyl-3-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid . . . and the pharmaceutically acceptable salts, and prodrugs and salts of the prodrugs.

Within the above group of especially preferred compounds are the compounds . . . acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide, and 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]amide.

Description of EP1127882A1 contains 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Preferred examples of glycogen phosphorylase inhibitors of Formula AA include . . . acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2,4-dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 2-cyano-6H-thieno[2,3-b]pyrrole-5-carboxylic acid . . . salts and prodrugs of the compounds, and the pharmaceutically acceptable salts of the prodrugs.

Description: Field of the Invention [0001] The . . . phosphorylase inhibitors in the prophylactic treatment of individuals who have not yet presented with . . . an increased risk of developing such condition.

Background of the Invention [0002] The diabetic disease state is characterized by an impaired glucose . . . glucose levels in patients suffering therefrom.

Although hypoglycemic agents such as sulfonylureas have been employed widely in the treatment of NIDDM, this treatment is, in many instances, not completely satisfactory.

Also, many patients gradually lose the ability to respond to treatment with sulfonylureas and are thus gradually forced into insulin treatment.

[0004] Type 2 diabetes is a heterogeneous disorder which appears to be polygenic in nature.

There is great scientific debate about the . . . others in the etiology and progression of the disease from the non-diseased state, and at least one reference suggests that . . . beta-cell and peripheral insulin resistance (Am.)
This progression could then account for ... at any of the three loci, to lead from a non-diseased state, to a state of insulin resistance, and/or ... without full presentation of Type 2 diabetes.

This is called an insulin-resistant state, a ... ovary syndrome, pregnancy, growth hormone disorders, androgen disorders, and the like.

For this reason, it is hypothesized here that treatment of individuals “at risk” for the onset or ... diagnosed Type 2 diabetic state, would be useful.

Therefore, it is stated also here that glycogen ... whom are at increased risk of developing this disease, and/or preventing the disease in patients (people) “at risk” for Type 2 diabetes.

This production of glucose is derived either from ... precursor, a process mediated by the enzyme glucose-6-phosphatase.

Similarly, hepatic glucose production will be increased in Type 1 diabetes if the disease is not properly controlled by insulin treatment.

As the diabetic liver is known to have an ... augmented rate of glucose production, compounds targeting this abnormal activity are highly desirable.

Recently, agents functioning as inhibitors of the hepatic enzyme glucose-6-phosphatase have been disclosed in, ... International Application Publication Nos.

As such, glycogen phosphorylase inhibitors are known to be useful in the treatment of NIDDM by decreasing hepatic glucose production and lowering hypoglycemia.

[0008] Regarding the use of anti-diabetic agents for the prophylactic treatment of certain at-risk individuals, U.S.

Examples of such risk factors may include, but ... or genetic Type 2 diabetes pre-disposing disease state or condition such as a family history of ... a genetic mutation or mutations in the insulin receptor, IRS proteins, glucose transporters, PC-1, glucokinase, UCP-1, beta 3 adrenergic receptor gene, and the like; (vi) risk factors based ... tissue or clinically diagnosed obesity (i.e.

&age; 140 mg/dl, but <200 mg/dl, with normal ... or risk factors associated with eating disorders, including having anorexia nervosa or bulimia, ... lipid parameters, such as hypertension, i.e.

the delivery of offspring having a birthweight of ... syndrome; (xiv) risk factors due to organ disease or dysfunction including liver cirrhosis, or renal disease; (xv) risk factors due to conditions ... (xvi) risk factors due to endocrine disorders or endocrinopathies, such as hyperandrogenism, ... (xviii) risk factors due to immune-mediated disease such as “stiff man” syndrome, production of anti-insulin receptor antibodies, and the like; (xix) risk factors ... nicotinic acid, olanzapine and other serotonin receptor-targeted antipsychotics or antidepressants, vcor, ... porphyria, Prader-Willi Syndrome, Alzheimer’s Disease, and the like; and (xxi) risk factors ... of insulin and/or the presence of ketoacidosis.

Heathcock, Ed., p 777), metal-halogen exchange of ... heterocycles of Formula 1 (R” = H) followed by treatment of heteroaryl lithiums of Formula 11 with a formylating agent such as dimethylformamide (Ortiz, J.

For example, with regard to Scheme III, mono- and bis-halide substitution can be accomplished by treatment with an electrophilic halide source such as the ... salts, or elemental halogen (Gale, W.

With regard to Scheme V, the esters of compound A ... such as concentrated sulfuric acid or by treatment with an alkyl halide such as methyl iodide and a base such as potassium carbonate.

The Formula K cyanohydrin can be prepared from the stereochemically pure aldehyde by treatment with sodium or potassium cyanide as described ... to those skilled in the art by crystallization.

[0239] Generally preferred non-glycogen ... mimetics; PTP1B inhibitors; insulin degrading enzyme inhibitors; glycogen synthase kinase inhibitors; and the like.
Generally preferred anti-obesity agents may comprise, for example, beta-adrenergic receptor agonists, apolipoprotein-B secretion/microsomal . . . bromocriptine), melanocyte-stimulating hormone receptor agonists or mimetics, melanocyte-stimulating . . . concentrating hormone antagonists, cannabinoid receptor antagonists, the OB protein (leptin), a leptin . . . or analogs thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as . . . (referred to hereinafter as AGRP) antagonists.

Particularly preferred anti-obesity . . . of this invention comprise beta-adrenergic receptor agonists, sibutramine, orlistat, fenfluramine, . . . Particularly preferred beta-adrenergic receptor agonists include those substituted . . . PCT International Application Publication No.

Especially preferred beta-adrenergic receptor agonists disclosed therein are selected from the . . . acid.

The dosage of the glycogen . . . of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired.

The dosage of the non-glycogen . . . of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired.

The dosage of the anti-obesity agent . . . of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired.

According to the methods of the . . . agent is administered to the subject in need of treatment therewith, preferably in the form of a pharmaceutical composition.

Rats six weeks of age may be initiated on a daily regimen of treatment employing a glycogen phosphorylase inhibitor, a . . . inhibitor and an anti-obesity agent (p.o. The animals can also be administered a glucose tolerance test after the six week treatment period.

Alternatively, a glucose tolerance test may be administered to the fasted animals after the ten-day treatment period. A reduction in plasma glucose or insulin . . . impaired glucose tolerance by the dexamethasone treatment.

Physiol., 264, E18-23, (1993), the glycogen . . . insulin resistance induced by a cafeteria diet treatment of rats.

Body weight and adipose depot weight are also . . . glucose tolerance induced by the cafeteria diet treatment

Claims: The use according to claim 1 wherein said . . . associated with a Type 2 diabetes pre-disposing disease state or condition.

The use according to claim 2 wherein said risk . . . or genetic Type 2 diabetes pre-disposing disease states or conditions; (iii) risk factors . . . ovary syndrome; (xiv) risk factors due to organ disease or dysfunction; (xv) risk factors due to . . . (xvi) risk factors due to endocrine disorders or endocrinopathies; (xvii) risk factors due to . . . risk factors factors due to immune-mediated disease; (xix) risk factors factors due to . . . of insulin and/or the presence of ketoacidosis.

The use according to claim 3 wherein said risk . . . or genetic Type 2 diabetes pre-disposing disease state or condition comprises a family history of . . . a genetic mutation or mutations in the insulin receptor, IRS proteins, glucose transporters, PC-1, glucokinase, UCP-1, beta 3 adrenergic receptor gene; said risk factor based on the presence of . . . cord injury; said risk factor due to organ disease or dysfunction comprises liver cirrhosis or renal disease; said risk factor due to conditions resulting in . . . ketoacidosis; said risk factor due to endocrine disorders or endocrinopathies comprises hyperandrogenism, . . . trauma; said risk factor due to immune-mediated disease comprises “stiff man” syndrome or the production of anti-insulin receptor antibodies; said risk factor incurred due to drug or chemical exposure comprises treatment with insulin-resistance-inducing or . . . beta -blockers, nicotinic acid, serotonin receptor-targeted antipsychotics or antidepressants, vacor, . . . Prader-Willi Syndrome, and Alzheimer’s Disease.

The use according to claim 14 wherein said . . . mimetic; a PTP1B inhibitor; an insulin degrading enzyme inhibitor; and a glycogen synthase kinase inhibitor.
The use according to claim 17 wherein said . . . from the group consisting of a beta-adrenergic receptor agonist, an apolipoprotein-B . . . agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor antagonist, a cannabionoid receptor antagonist, leptin or an analog thereof, a . . . or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist.

The use according to claim 18 wherein said . . . and pseudoephedrine; said (3-adrenergic receptor agonist is selected from the group consisting of . . . and said anorectic agent is a bombesin agonist.


3-Methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-5-carboxylic acid [1-benzyl-2-((3R,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide]

3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide] the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers and prodrugs.
Claims of EP1136071A2 contains 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs.

13. The use according to claim 12 wherein said compound of formula (IV) is selected from . . . acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; . . . and 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs.

15. The use according to claim 14 wherein said glycogen phosphorylase inhibitor is selected from . . . acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; . . . and 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of said . . . PTP1B inhibitor; an insulin degrading enzyme inhibitor; and a glycogen synthase kinase inhibitor.

18. The use according to claim 17 wherein said glycogen phosphorylase inhibitor is selected from . . . acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; . . . a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist.

Description of EP1136071A2 contains 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0020] A particularly preferred subgroup of formula (II) compounds are those compounds selected . . . 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; . . . thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, and prodrugs.

Claims of EP1136071A2 contains 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

9. The use according to claim 8 wherein said compound of formula (II) is selected from the group . . . 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-thiazolidin-3-yl)-2-oxoethyl]-amide; . . . thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs.

15. The use according to claim 14 wherein said glycogen phosphorylase inhibitor is selected from . . . 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxoethyl]-amide; . . . a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist.

[0236] A preferred subgroup of formula (IV) compounds are those compounds selected from the group . . . acid-[(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hydroxy-3-oxo-propyl]-amide; 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic . . . thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers and prodrugs.


13. The use according to claim 12 wherein said compound of formula (IV) is selected from the group . . . acid-[(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hydroxy-3-oxo-propyl]-amide; 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic . . . thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs.

15. The use according to claim 14 wherein said glycogen phosphorylase inhibitor is selected from . . . acid-[(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hydroxy-3-oxo-propyl]-amide; 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic . . . PTP1B inhibitor; an insulin degrading enzyme inhibitor; and a glycogen synthase kinase inhibitor.

18. The use according to claim 17 wherein said glycogen phosphorylase inhibitor is selected from . . . acid-[(1S)-benzyl-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)hydroxy-3-oxo-propyl]-amide; 2-chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and 3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic . . . a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist.

2-Methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of EP1136071A2 contains 2-Chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

2-Chloro-3-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
Description of EP1136071A2 contains 4H-1,7-Dithia-4-aza-cyclopenta[a]pentalene-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of EP1136071A2 contains 3-Chloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of EP1136071A2 contains 2-Fluoro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide


[0236] A preferred subgroup of formula (IV) compounds are those compounds selected from the group . . . acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic . . . thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers and prodrugs.

2-Bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide


13. The use according to claim 12 wherein said compound of formula (IV) is selected from the group ... acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic ... thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs.

15. The use according to claim 14 wherein said glycogen phosphorylase inhibitor is selected from ... acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic ... PTP1B inhibitor; an insulin degrading enzyme inhibitor; and a glycogen synthase kinase inhibitor.

18. The use according to claim 17 wherein said glycogen phosphorylase inhibitor is selected from ... acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-bromo-4H-thieno[3,2-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic ... a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist.

Description of EP1136071A2 contains 6H-Thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

6H-Thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
Description of EP1136071A2 contains 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of EP1136071A2 contains 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0236] A preferred subgroup of formula (IV) compounds are those compounds selected from the group consisting of: 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; (+/-)-2-bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid... thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers and prodrugs.


13. The use according to claim 12 wherein said compound of formula (IV) is selected from the group consisting of: 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; (+/-)-2-bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid... thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers, and prodrugs.

15. The use according to claim 14 wherein said glycogen phosphorylase inhibitor is selected from... 5-acetyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbamoyl-phenyl)-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; (+/-)-2-bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid... PTP1B inhibitor; an insulin degrading enzyme inhibitor; and a glycogen synthase kinase inhibitor.

18. The use according to claim 17 wherein said glycogen phosphorylase inhibitor is selected from... 5-acetyl-1-ethyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylic acid (3-phenylcarbamoyl-phenyl)-amide; 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid-[(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; (+/-)-2-bromo-4H-furo[3,2-b]pyrrole-5-carboxylic acid... a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and an AGRP antagonist.
Description of EP1136071A2 contains 2,4-Dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

2,4-Dichloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

EP846464A2 19980610 ( US3158496P19961205 ) Verwendung von Glykogen-Phosphorylase-Hemmer zur Verminderung nicht-kardiologischer Gewebeschäden verursacht durch Ischämie; Utilisation d’inhibiteur de la glycogen phosphorylase pour réduire les dommages tissulaires non-cardique résultant d’une ischémie; Use of glycogen phosphorylase inhibitor for reducing non-cardiac tissue damage resulting from ischemia - HOOVER, DENNIS J.; MARTIN, WILLIAM HOLT; TRACEY, WAYNE ROSS; TREADWAY, JUDITH LEE - PFIZER INC.

The use of a glycogen phosphorylase inhibitor for the manufacture of a medicament for reducing non-cardiac tissue damage resulting from ischemia or hypoxia.

Description: BACKGROUND OF THE INVENTION Glycogen … a class of compounds which have use in the treatment of diabetes mellitus.

Commonly assigned PCT applications PCT/IB95/00443 … glycogen phosphorylase inhibitors for the treatment of damage from perioperative myocardial ischemia.

Glycogenolysis in tissues is catalyzed by the enzyme glycogen phosphorylase (GP). In humans, three different isoforms of the enzyme glycogen phosphorylase have been identified to … human brain isoform (herein referred to as HBGP).

263:3850-3857, 1988). Note herein that the term … isoforms of the human glycogen phosphorylase enzyme, any additional human glycogen phosphorylase … all isoforms of mammalian glycogen phosphorylase enzymes in general. GP enzymes cleave the glycogen macromolecule to release … and a new shortened glycogen macromolecule.

1978, 253, 3343-3351 and 9102-9106]. These … been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.

The method comprises administering to a mammal, including a human patient, in need of such treatment an amount of a glycogen phosphorylase inhibitor effective at reducing non-cardiac tissue damage.

The term ”treating” as used herein includes preventative (e.g., prophylactic) and palliative treatment.

Alternatively, Formula I compounds which contain … the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as with … for conversion to the sulfone oxidation state.

Such a mono- or di-alkylation may be conducted by treatment of the R5 aminoalkoxy compound with 1 equivalent … a suitable reducing agent in a suitable solvent.

The Formula XXI cyanohydrin may be prepared from the Formula XX compound by treatment with sodium or potassium cyanide as described … in a mixture of stereoisomers at carbon b.

Formula XXI intermediates of a specific … with retention of this stereochemistry by treatment with an alcohol and a strong acid catalyst, … of water, if necessary, as described above.
For example, Example 24D (contained herein) ... subsequently by an appropriate method, such as treatment with tetrabutylammonium fluoride in ... of Formula XXII with loss of the silyl group).

This reduction is accomplished by treatment of Formula XXX compounds with lithium aluminum ... Syntheses; Wiley: New York, 1990; Collect.

The Formula XLI amino acids may be prepared by ... of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCI3 is ... intermediate R4CH(OH)CCI3, which is converted on treatment with azide and base to an intermediate ... to the desired Formula XLI compound.

The Formula XLI compound is alkylated on oxygen by treatment with an appropriate alkylating agent (e.g., ... 150 DEG C resulting in a Formula LXII compound.

Those Formula III amines wherein R6 contains an ... functionality protected as the t-butyl ester by treatment with anhydrous acid to provide the corresponding ... may be prepared from the Formula XLI compound.

The Formula LXIV compound is reduced to the primary amine by treatment with hydrogen and an appropriate catalyst (e.g., ... or ethanol to give the Formula LXV primary amine.

The Formula LXIII and LXIV compounds wherein n is two are preferably prepared by treatment of the Formula LXI compound with an excess of ... solvent, preferably a polar protic solvent.

Thus a readily available compound of formula ... is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent ... a compound of formula R8R9NH (wherein R8=R9=R).

Alternatively, a formula NH2CONH(OH) amine may be ... nitrogen to give NH2CON(R')(OR'), by successive treatment with the alkylating agents R'X and R"X, ... described by Kreutzkamp and Messinger (Chem.

Alternatively, Formula IA compounds which contain ... the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as ... for conversion to the sulfone oxidation state.

If the protecting group is t-Boc by treatment of the Formula XXV compound with an acid in a suitable, preferably aprotic, solvent.

For example, the Formula XXXIII compound may be ... chloride, or in the case of tert-butanol by treatment of the amino acid with isobutylene and an acid catalyst such as concentrated sulfuric acid or by treatment with an alkyl halide (e.g., methyl iodide) and base (e.g., potassium carbonate).

The Formula XLI amino acids may be prepared by ... of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCI3 is ... intermediate R4CH(OH)CCI3, which is converted on treatment with azide and base to an intermediate ... to the desired Formula XLII compound.

Thus a readily available compound of formula ... is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent ... a compound of formula R8R9NH (wherein R8=R9=R).

Alternatively, N-hydroxyurea (NH2CONH(OH)) may be ... nitrogen to give NH2CON(R')(OR'), by successive treatment with the alkylating agents R'X and R"X, ... described by Kreutzkamp and Messinger (Chem.

The utility of the compounds of the present invention as medical agents in the treatment of metabolic diseases (such as are detailed herein) in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in ... Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.
The results of these comparisons are useful for . . . levels in mammals, including humans, for the treatment of such diseases.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

The sample is then eluted from the column with . . . other bound proteins. Fractions containing the GP activity are pooled (approximately 600 mL), and . . . g/mL and 0.7 μg/mL concentrations respectively.

GP-containing fractions are pooled following identification by determining enzyme (described below) activity and visualizing the Mr approximately 97 kdal GP . . . on ice until use. Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

The Sf9 cell lysates are then cleared by . . . the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . described in Section (A) Activation of GP below.

Determination of GP Activity A) Activation of GP: Conversion of GPb to GPa Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . form (designated GPa) by the follow procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads . . . and 80 mM CaCl2 at pH 7.4 for 4 hours at 4 DEG C.

Prior to use to convert GPb to GPa, the Affi-Gel . . . DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer). coli) or the mixture of GPa and GPb obtained from . . . (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the . . . conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: % of total HLGPa = HLGPa activity - AMP DIVIDED HLGp activity + AMP Alternately, the conversion of GPb to . . . that is noted following conversion of GPb to GPa.

B) GPa Activity Assay The disease/condition treating/preventing activities described herein of the compounds of this . . . effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase . . . by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by . . . by the release of inorganic phosphate.

To measure the GPa enzyme activity in the forward direction, the production of . . . coupled general method of Pesce et al.

20 μl of this stock is added to 80 μl of . . . (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by . . . L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 μL of 50 mM of the positive control test substance, caffeine.

To measure the GPa enzyme activity in the reverse direction, the conversion of . . . by the general method described by Engers et al.

The compounds to be tested are added as 5 μL of solution in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors is determined . . . L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 μL of 50 mM caffeine.

100, 95-97] modified as follows: 150 μL of 10 . . . green in 1 N HCl is added to 100 μL of the enzyme mix.
The above assays carried out with a range of ... of test compound allows the determination of an *IC50* value (concentration of test compound required ... inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

Id=TABLE 1* Columns=3
Head Col 1: Compound Name
Head Col 2: HLGPa IC50 nM
Head Col 3: HMGPa IC50 nM
5-chloro-1H-indole-2-carboxylic acid ... *data are for HLGPa and HMGPa enzyme activity (IC50) as determined by the reverse direction assay.

Cardioprotection, as indicated by ... can be induced pharmacologically using adenosine receptor agonists in isolated, retrogradely perfused ... ischemic preconditioning (Liu et al., Cardiovasc.

Id=TABLE 1 Columns=4
Head Col 1: Treatment
Head Col 2: n
Head Col 3: Infarct Area/ ... of an ischemic event (e.g., arterial embolism).
(prospectively or prophylactically) to blunt or ... (e.g., patients with peripheral vascular disease).

The glycogen phosphorylase inhibitor compounds of ... invention are particularly well suited to the treatment of diabetic patients because of the reduction in ... damage that diabetics are susceptible to.

The compounds of this invention are also well ... procedures or patients with peripheral vascular diseases).

In considering the degree of glycogen phosphorylase inhibitor activity desired, the physician must balance a variety of factors such as the target tissue and severity of the disease/condition age of the patient.

An amount of the glycogen phosphorylase inhibitor of this invention that is effective for the activities of this invention is used.

Generally, the compounds of this invention are ... administration is inappropriate for the instant target or where the patient is unable to ingest the drug (e.g., due to age or surgical state).

fulltext score : 21 , cippix score : 103 , hit score : 7

Description of EP846464A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
Within the above group of especially preferred compounds are the compounds ... acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, ... or 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]amide.
Claims of EP846464A2 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

4. The use of claim 3 wherein said glycogen phosphorylase inhibitor is . . . acid [(1S)-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide; or 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide.

Description of EP846464A2 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide 137 71

Description of EP846464A2 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide 30 97

Claims of EP846464A2 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

4. The use of claim 3 wherein said glycogen phosphorylase inhibitor is . . . 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid . . . acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide.
Description of EP846464A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Within the above group of especially preferred compounds are the compounds . . . 5-Chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, . . . or 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide.

Description of EP846464A2 contains 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide

Within the above group of especially preferred compounds are the compounds . . . acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide, or 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide.

Description of EP846464A2 contains 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide 45 85

Claims of EP846464A2 contains 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

4. The use of claim 3 wherein said glycogen phosphorylase inhibitor is . . . acid [(1S)-benzyl-3-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid . . . acid [(1S)-benzyl-2-((3S,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide.
Use of glycogen phosphorylase inhibitors to inhibit tumor growth; Utilisation d’inhibiteur de la glycogen phosphorylase pour inhiber la croissance de tumeurs; Verwendung von Glykogen-Phosphorylase-Hemmer zur Hemmung des Tumorwachstums - KRASNER, ALAN SETH - PFIZER PRODUCTS INC.

This invention relates to the use of glycogen phosphorylase inhibitors of Formula I or Formula IA: as defined herein, and their pharmaceutically acceptable salts and prodrugs thereof, to inhibit abnormal cell growth in mammals, including humans. The invention also relates to pharmaceutical compositions containing glycogen phosphorylase inhibitors alone or in combination with other glycogen phosphorylase inhibitors or other inhibitors of abnormal cell growth, and to methods of treating cancer, hyperproliferative disorders, or abnormal cell growth in a mammal by administering to a mammal in need thereof the compounds and compositions of the invention.

Abstract: The invention also relates to pharmaceutical ... methods of treating cancer, hyperproliferative disorders, or abnormal cell growth in a mammal by ... the compounds and compositions of the invention.

Description: In humans, three isoforms of this enzyme have been identified: the liver isoform (HLGP), ... isoform (HMGp), and the brain isoform (HBGP).

[0005] Glycogen phosphorylase inhibitors are useful in the treatment of diabetes mellitus.

For example, International Patent publications WO ... amides and derivatives for treatment of diabetes. These compounds are also described as useful in treatment of atherosclerosis, hyperinsulinemia, ... and in prevention of myocardial ischemic injury.

Patent 5,882,885, issued March 16, 1999 refers to ... glycogen phosphorylase as useful in the treatment of otitis media, conjunctivitis, pneumonia, ... sinusitis, pleural empyema and endocarditis.

[0023] The invention also relates to a method ... growth is dependent on glycogen phosphorylase activity.

[0033] The invention also relates to a method ... of 7.5 mM glucose, is characterized by an IC50 having a value less than 100 nanomolar. [0034] The IC50 value is defined as the concentration of the subject compound required to produce an enzyme activity of 50%, compared to 100% enzyme activity in the absence of the compound and 0% activity when the enzyme is fully inhibited, e.g., by caffeine. In this invention, enzyme activity is determined by measurement of the reverse activity of HLGPa, i.e., by measuring the release of ... described hereinbelow. Because the determined IC50 may vary from one experiment to another, it is to be understood that the IC50 value reflects the average value of the IC50 determined from multiple repetitions of ... using a particular compound (e.g., ten or more IC50 determinations wherein the observed maximal and minimum activities are as expected).

Inhibitors of the enzyme that catalyzes this modification, farnesyl ... in which Ras contributes to transformation.

[0038] The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to the ... and a pharmaceutically acceptable carrier.

In one embodiment, said method or pharmaceutical composition is for the treatment of cancer such as lung, squamous cell, gastric, breast or colorectal cancer.

In another embodiment, the method or pharmaceutical composition is for the treatment of cancer of the brain bladder, pancreas, head, ... ovary, cervix, prostate, esophagus, or thyroid.

In another embodiment, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., ... (e.g., benign prostatic hypertrophy (BPH)).

[0039] The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a ... and a pharmaceutically acceptable carrier.

In one embodiment, said method or pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, ... prostate, colon and epidermoid cancer.
0040] The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to ... growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

[0041] Patients that can be treated with a ... the vagina or carcinoma of the vulva), Hodgkin’s disease, cancer of the esophagus, cancer of the small ... brain stem gliomas or pituitary adenomas).

In one embodiment, the chemotherapeutic is ... growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, e.g.

[0044] It is believed that the compounds of ... Ia can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells.

Accordingly, this invention further relates to a ... for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to ... is effective in sensitizing abnormal cells to treatment with radiation.

Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1.

[0049] A compound of Formula I or Formula IA, ... that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF ... growth factor) inhibitors, such as VEGF receptor inhibitors and molecules that can inhibit VEGF; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN TM (Genentech, Inc.

[0052] ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome ... antibodies AR-209 (Aronex Pharmaceuticals Inc.

ErbB2 receptor inhibitors useful in the present invention are ... in United States Provisional Application No.

The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S.

provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the compound of the present invention in accordance with the present invention.

Other cancers which may be treated using a ... the vagina or carcinoma of the vulva), Hodgkin’s Disease, cancer of the esophagus, cancer of the small ... or pituitary adenomas), neoplastic cutaneous diseases (e.g.

[0058] The term “treatment”, as used herein, ... inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, refers to the act of treating, as “treatment” is defined immediately above.

[0059] The terms “therapeutically effective ... eliminates one or more symptoms of a particular disease or condition or prevents or delays the onset of one or more symptoms of a particular disease or condition.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and ... and 0.7 mu g/mL concentrations respectively.

GP-containing fractions are pooled following identification by determining enzyme (described below) activity and visualizing the Mr approximately 97 kdal GP ... Co., LTD., Tokyo, Japan) and then pooled.

[0091] Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic ... is performed as described in the section above.
Activation of GP [0094] Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... procedure described in Activation of GP below.

Determination of GP Enzyme Activity Activation of GP: Conversion of GPb to ... [0096] Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... form (designated GPa) by the follow procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads ... and 80 mM CaCl2 at pH 7.4 for 4 hours at 4 DEG C.

Prior to use to convert GPb to GPa, the Affi-Gel ... 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).

coli) or the mixture of GPa and GPb obtained from ... (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the ... conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percent of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: 

\[
(\text{HLGP activity - AMP)/(HLGP activity + AMP}) \times 100
\]

Alternately, the ... that is noted following conversion of GPb to GPa.

GPa Activity Assay [0100] The effect of the compounds of Formula I or IA on the activity of the activated form of glycogen phosphorylase ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... by the release of inorganic phosphate.

[0101] To measure the GPa enzyme activity in the forward direction, the production of ... coupled general method of Pesce et al.

The compounds to be tested are added as 5 mu L ... (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by ... L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 mu L of 50 mM of the positive control test substance, caffeine.

[0102] To measure the GPa enzyme activity in the reverse direction, the conversion of ... by the general method described by Engers et al.

The compounds to be tested are added as 5 mu L ... in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors is determined ... L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 mu L of 50 mM caffeine.

100, 95-97) modified as follows: 150 mu L of 10 ... green in 1 N HCl is added to 100 mu L of the enzyme mix.

[0103] The above assays can also be used to assess activity of glycogen phosphorylase derived from various pathogenic sources.

[0104] The above assays carried out with a ... of test compound allows the determination of an IC50 value (as defined hereinabove, see e.g., p. 14) for the in vitro inhibition of GPa enzyme activity by that test compound.

Claims: The method of claim 1, wherein the tumor growth is dependent on glycogen phosphorylase activity.
A method of inhibiting tumor growth in a mammal . . . of 7.5 mM glucose, is characterized by an IC50 having a value less than 100 nanomolar.

Description of EP1177791A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0018] In a further embodiment, the method comprises administering to a mammal, including a human, . . . acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, . . . and 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-in-1-yl)-2-oxo-ethyl]amid
Description of EP1177791A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0018] In a further embodiment, the method comprises administering to a mammal, including a human, ... 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, ... and 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide.


[0018] In a further embodiment, the method comprises administering to a mammal, including a human, ... acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide, and 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide.


5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide 45 85

US6107329A 20000822 ( IB9500442W19950606 ) Substituted n-(indole-2-carbonyl)-glycinamides and derivatives as glycogen phosphorylase inhibitors - HOOVER; DENNIS J.; HULIN; BERNARD; MARTIN; WILLIAM H.; PHILLIPS; DOUGLAS; TREADWAY; JUDITH L. - PFIZER, INC.
PCT No. PCT/IB95/00442 Sec. 371 Date Dec. 2, 1997 Sec. 102(e) Date Dec. 2, 1997 PCT Filed Jun. 6, 1995 PCT Pub. No. WO96/39384 PCT Pub. Date Dec. 12, 1996Compounds of Formula (1) wherein R6 is carboxy, (C1-C8)alkoxycarbonyl, benzoxycarbonyl, C(O)NR8R9 or C(O)R12 as glucogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat diabetes, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

Description: In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas (e.g.
Searle) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

**Treatment** of non-insulin dependent diabetes mellitus (Type ... combination of diet, exercise, oral agents, e.g.

Atherosclerosis, a disease of the arteries, is recognized to be the leading ... of death in the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

Epidemiological evidence has firmly established ... a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, ... risk factors in this population. Successful treatment of hyperlipidemia in the general population, and ... is therefore of exceptional medical importance.

Hypertension (or high blood pressure) is a ... as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such “essential” hypertension is often associated with disorders such as obesity, diabetes and hypertriglycerideremia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms ... in the complete absence of any other signs of disease or disorder.

Hypertension can also contribute to the development of atherosclerosis and coronary disease.

The exact cause of essential hypertension is ... are believed to contribute to the onset of the disease.

The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind.

Thus a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has ... failure, renal failure and brain hemorrhaging.

However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem.

This implies that although high blood pressure is ... essential hypertension is not responding to this treatment.

Hepatic glucose production is an important target for NIDDM therapy.

Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers’ disease (glycogen phosphorylase deficiency), display episodic hypoglycemia.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release ... and a new shortened glycogen macromolecule.

These compounds, and glycogen phosphorylase ... been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.

**SUMMARY OF THE INVENTION** This invention is ... inhibitor compound of Formula I useful for the treatment of diabetes, hyperglycemia, ... atherosclerosis and myocardial ischemia.
Yet another aspect of this invention is directed . . . for treating a glycogen phosphorylase dependent disease or condition in a mammal by administering to a . . . from a glycogen phosphorylase dependent disease or condition a glycogen phosphorylase dependent disease or condition treating amount of a Formula I compound.

Included in the treatment of diabetes is the prevention or attenuation of . . . nephropathy, retinopathy or cataracts.

Preferred compositions include pharmaceutical compositions for the treatment of glycogen phosphorylase dependent diseases or conditions in mammals which comprise a glycogen phosphorylase dependent disease or condition treating amount of a compound of Formula I and a pharmaceutically acceptable carrier.

Another aspect of this invention is directed to pharmaceutical compositions for the treatment of diabetes which comprise a therapeutically . . . agents such as insulin and insulin analogs (e.g.

Glycogen phosphorylase dependent diseases or conditions refers to disorders which are mediated, initiated or maintained, in . . . glycogen macromolecule by glycogen phosphorylase enzymes to release glucose-1-phosphate and a new shortened glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity.

The term “”treatment”” as used herein includes preventative (e.g., prophylactic) and palliative treatment.

Alternatively, Formula I compounds which contain . . . the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as . . . at a temperature of about 0°

If the protecting group is t-Boc by treatment of the Formula XXV compound with an acid in a suitable, preferably aprotic, solvent.

For example, the Formula XXXIII compound may be . . . chloride, or in the case of tert-butanol by treatment of the amino acid with isobutylene and an acid catalyst such as concentrated sulfuric acid or by treatment with an alkyl halide (e.g., methyl iodide) and base (e.g., potassium carbonate).

The Formula XLII amino acids may be prepared by . . . of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4 . . . R4 CH(OH)CCI3, which is converted on treatment with azide and base to an intermediate R4 . . . to the desired Formula XLII compound.

Thus a readily available compound of formula . . . CONHOH is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent . . . R9 NH (wherein R8 .dbd.R9 .dbd.R).

Alternatively, N-hydroxyurea (NH2 CONH(OH)) . . . to give NH2 CON(R”')(OR’), by successive treatment with the alkylating agents R’X and R”’X, respectively, in the presence of a suitable base.

The utility of the compounds of the present invention as medical agents in the treatment of metabolic diseases (such as are detailed herein) in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in . . . Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for . . . levels in mammals, including humans, for the treatment of such diseases.

HLGP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in HLGPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the HLGP activity are pooled (approximately 600 mL), and . . . and 0.7 mug/mL concentrations respectively.

HLGP-containing fractions are pooled following identification by determining enzyme (described below) activity and visualizing the M, approximately 97 kdal . . . Co., LTD., Tokyo, Japan) and then pooled.
Determination of HLGP Enzyme Activity

A) Activation of HLGP: Conversion of HLGPb to HLGPa

Prior to the determination of HLGP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads ... mM CaCl2 at pH 7.4 for 4 hours at 4°.

Prior to use to convert HLGPb to HLGPa, the ... 0.3 mM DTT, and 0.3 mM EDTA at pH 7.8 (kinase assay buffer).

The partially purified, inactive HLGPb obtained ... above is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the ... to HLGPa is estimated by determining HLGP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total HLGP enzyme activity due to HLGPa enzyme activity (AMP-independent) is then calculated as follows: EQU1

B) HLGPa Activity Assay

The hypoglycemic activity (also the other disease/condition treating/preventing activities described herein) of the compounds of this ... effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... by the release of inorganic phosphate.

To measure the HLGPa enzyme activity in the forward direction, the production of ... coupled general method of Pesce et al.

The compounds to be tested are added as 5 mul ... (DMSO) prior to the addition of the enzymes. The basal rate of HLGPa enzyme activity in the absence of inhibitors is determined by ... of 14% DMSO and a fully-inhibited rate of HLGPa enzyme activity is obtained by adding 20 mul of 50 mM of the positive control test substance, caffeine.

p To measure HLGPa enzyme activity in the reverse direction, the conversion of ... by the general method described by Engers et al.

The compounds to be tested are added as 5 mul ... in 14% DMSO prior to the addition of the enzyme. The basal rate of HLGPa enzyme activity in the absence of added inhibitors is determined ... of 14% DMSO and a fully-inhibited rate of HLGPa enzyme activity is obtained by adding 20 mul of 50 mM ... measured by the general method of Lanzetta et al.

100, 95-97] modified as follows: 150 muof 10 ... green in 1N HCl is added to 100 mul of the enzyme mix.

The hypoglycemic activity of the compounds of this invention can be ... vehicle without test compound in male ob/ob mice.

Since the concentration of glucose in blood is closely related to the development of diabetic disorders, these compounds by virtue of their hypoglycemic action, prevent, arrest and/or regress diabetic disorders.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

Hypoglycemic activity of the test compounds is determined by ... and vehicle-treated group on day 5. The above assay carried out with a range of doses of test ... vivo reduction of plasma glucose concentration.

Such activity can be determined by the amount of test compound ... vehicle without test compound in male ob/ob mice.

Since the concentration of cholesterol in blood ... cerebral vascular or peripheral vascular disorders, the compounds of this invention by virtue of ... prevent, arrest and/or regress atherosclerosis.

Since the concentration of triglycerides in blood ... by virtue of their triglyceride lowering activity prevent, arrest and/or regress hyperlipidemia.
After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

The inter assay coefficient of variation is .\textless ; 0.10%.

Triglycerides Test reagent system (Abbott ... Division, Irving, Tex.) (lipase-coupled enzyme method; a modification of the method of Sampson, et al., Clinical Chemistry 21, 1983 (1975)).

Cholesterol Test reagent system (cholesterol esterase-coupled enzyme method; a modification of the method of Allain, et al.

The serum insulin, triglycerides, and total cholesterol lowering activity of the test compounds are determined by ... group and the vehicle-treated control group. Activity in providing protection from damage to heart ... along the lines presented in Butwell et al., Am.

The in vivo assay tests the cardioprotection of the test compound ... the control group which receives saline vehicle.

Cardioprotection, as indicated by a reduction in ... using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied ... al., Circulation 84:350-356, 1991). The in vivo assay tests whether compounds can pharmacologically ... administered to intact, anesthetized rabbits.

However, the amount and timing of compound(s) ... will, of course, be dependent on the particular disease/condition being treated, the subject being ... and on the judgment of the prescribing physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the activity (e.g., glucose lowering activity) that the physician considers appropriate for the patient. In considering the degree of activity desired, the physician must balance a variety of ... factors, presence of preexisting disease, and age of the patient and the patient’s motivation. In general an effective dosage for the activities of this invention, for example, the blood glucose, triglycerides, and cholesterol lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the ... and most preferably 0.1 to 15 mg/kg/day.

Generally, the compounds of this invention are ... administration is inappropriate for the instant target or where the patient is unable to ingest the drug.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated, i.e., a glycogen phosphorylase dependent disease/condition.

\textbf{Claims:} A method for treating a glycogen phosphorylase dependent disease or condition in a mammal which comprises ... from a glycogen phosphorylase dependent disease or condition a glycogen phosphorylase dependent disease or condition treating amount of a compound of claim 1.

The pharmaceutical composition as recited in claim 43 for the treatment of glycogen phosphorylase dependent diseases or conditions in mammals which comprises a glycogen phosphorylase dependent disease or condition treating amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
Description of US6107329A contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Claims of US6107329A contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
Description of US6107329A contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide.

Description of US6107329A contains 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide.
aureus (food poisoning and Toxic shock syndrome), ... to infection by Borrelia recurrentis; Lyme disease related to infection by Borrelia burgdorferi; ... Chlamydia trachomatis, Neisseria gonorrhoeae, S. influenzae; disseminated Mycobacterium avium complex (MAC) disease related to infection by Mycobacterium avium, or ... and symptoms of infection by enterotoxigenic E.

Bacterial infections and protozoa infections and disorders related to such infections that may be treated ... include the following: bovine respiratory disease related to infection by Pasteurella haemolyticus, P. multocida, Mycoplasma bovis, or Bordetella spp.; cow enteric disease related to infection by E. dysgalactiae, Klebsiella spp., Corynebacterium, or Enterococcus spp.; swine respiratory disease related to infection by Actinobacillus ... P. multocida, or Mycoplasma spp.; swine enteric disease related to infection by E.

The invention also encompasses treatment of bacteremia, meningitis, pleural empyema, ... river blindness, toxoplasmosis, and endocarditis.

Other bacterial infections and protozoa infections and disorders related to such infections that may be treated ... of the present invention are referred to in J.

These complications include, but are not limited to asthma, and cerebrovascular disease.

[0024] In an alternative embodiment, the ... relates to a pharmaceutical composition for the treatment of bacterial infection comprising an amount of a ... with a pharmaceutically acceptable carrier.

[0030] The term “treating” as used herein ... preventative (e.g., prophylactic) and palliative treatment.

Purification of the enzyme can be accomplished by the procedure of Seok, et al.

Assay of glycogen phosphorylases from different ... conditions following purification of the enzyme activity. The assay can be run in either a forward or reverse manner ... phosphate). [0050] To assess the activity of a compound for general antibacterial activity, those skilled in the art can follow guidelines ... aerobically - 4th Edition; Approved Standard.

Assays for determining antibacterial activity against intracellular pathogens vary according to the proscribed literature for each organism.

Tests for determining activity against other organisms are known in the art.

After the 4-day treatment period, the medium is removed and the monolayers ... solution containing sodium dodecyl sulfate.

Results can be reported as mean numbers of ... per milliliter of macrophage lysate, with each assay performed in triplicate.

et al., Diagnostic Microbiology and Infectious Disease, 1998, 30:37-43).

In vitro activity is defined as the capacity of a compound to inhibit intracellular replication of T.

Compounds are compared by their IC50 values, i.e., the concentration that inhibits ... [0054] Methods for testing of activity against Chlamydia pneumoniae are described in the Examples below.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and ... and 0.7 mu g/mL concentrations respectively.
GP-containing fractions are pooled following identification by determining enzyme (described below) activity and visualizing the Mr approximately 97 kdal GP … Co., LTD., Tokyo, Japan) and then pooled.

[0062] Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates … the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP [0065] Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is … procedure described in Activation of GP below.

Determination of GP Enzyme Activity [0067] Activation of GP: Conversion of … E. coli) or the mixture of GPa and GPb obtained from … (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the … conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percent of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: ((HLGP activity - AMP)/(HLGP activity + AMP)) 100 [0071] Alternately, the … that is noted following conversion of GPb to GPa.

GPa Activity Assay [0072] The effect of the compounds of Formula I or IA on the activity of the activated form of glycogen phosphorylase … by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by … by the release of inorganic phosphate.

[0073] To measure the GPa enzyme activity in the forward direction, the production of … coupled general method of Pesce et al.

The compounds to be tested are added as 5 µL … (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by … L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 µL of 50 mM of the positive control test substance, caffeine.

[0074] To measure the GPa enzyme activity in the reverse direction, the conversion of … by the general method described by Engers et al.

The compounds to be tested are added as 5 µL … in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors is determined … L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 µL of 50 mM caffeine.

100, 95-97) modified as follows: 150 µL of 10 … green in 1 N HCl is added to 100 µL of the enzyme mix.

[0075] The above assays can also be used to assess activity of glycogen phosphorylase derived from various pathogenic sources.

[0076] The above assays carried out with a … of test compound allows the determination of an IC50 value (concentration of test compound required … inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.
As shown in Table 2, both compound 1 and compound 2 exhibited activity against growth of C.

Claims: A compound of formula I or IA, as defined in ... salt or prodrug thereof, for use in the treatment of infection in a mammal.

Description of EP1149580A1 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

Claims of EP1149580A1 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

7. The use according to claim 1 wherein said compound is selected from the group consisting of: ... acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, ... 5-Chloro-1 H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide.

5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide 137 71
Description of EP1149580A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide

[0016] Within the above group of especially preferred compounds are the compounds: ... 5-Chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, ... 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrrolidin-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide.

Claims of EP1149580A1 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide

7. The use according to claim 1 wherein said compound is selected from the group consisting of: ... 5-Chloro-1H-indole-2-carboxylic acid [2-((35,45)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, ... and 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrrolidin-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide.

Description of EP1149580A1 contains 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrrolidin-1-yl)-2-oxo-ethyl]-amide

[0016] Within the above group of especially preferred compounds are the compounds: ... H-indole-2-carboxylic acid [(1S)-benzyl-2-(4-hydroxymino-piperidin-1-yl)-2-oxo-ethyl]-amide, and 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxypyrrrolidin-1-yl)-1H-indole-2-carboxylic acid-2-oxo-ethyl]-amide.

7. The use according to claim 1 wherein said compound is selected from the group consisting of: ... acid [(1S)-benzyl-2-(4-hydroxy-imino piperidin-1-yl)-2-oxo-ethyl]-amide, and 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide.


5-chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide 4585


Processes and intermediates for preparing compounds of Formula (I).

Description: [0002] In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonyleureas (e.g. Searle)) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

Treatment of non-insulin dependent diabetes mellitus (Type ... combination of diet, exercise, oral agents, e.g.

[0003] Atherosclerosis, a disease of the arteries, is recognized to be the leading ... of death In the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

[0004] Epidemiological evidence has firmly ... a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, ... risk factors in this population. Successful treatment of hyperlipidemia in the general population, and ... is therefore of exceptional medical importance.

[0005] Hypertension (or high blood pressure) ... as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such 'essential' hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms ... in the complete absence of any other signs of disease or disorder.

Hypertension can also contribute to the development of atherosclerosis and coronary disease.

[0007] The exact cause of essential ... are believed to contribute to the onset of the disease.
The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind. Thus a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has ... failure, renal failure and brain hemorrhaging.

However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem.

This implies that although high blood pressure is ... essential hypertension is not responding to this treatment.

Hepatic glucose production is an important target for NIDDM therapy.

Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers' disease (glycogen phosphorylase deficiency), display episodic hypoglycemia.

Glycogenolysis is catalyzed in liver, ... and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release ... and a new shortened glycogen macromolecule.

These compounds, and glycogen phosphorylase ... been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.

Summary of the Invention
This ... inhibitor compound of Formula I useful for the treatment of diabetes, hyperglycemia, ... atherosclerosis and myocardial ischemia.

Yet another aspect of this invention is ... for treating a glycogen phosphorylase dependent disease or condition in a mammal by administering to a ... from a glycogen phosphorylase dependent disease or condition a glycogen phosphorylase dependent disease or condition treating amount of a Formula I compound.

Included in the treatment of diabetes is the prevention or attenuation of ... nephropathy, retinopathy or cataracts.

Preferred compositions include pharmaceutical compositions for the treatment of glycogen phosphorylase dependent diseases or conditions in mammals which comprise a glycogen phosphorylase dependent disease or condition treating amount of a compound of Formula I and a pharmaceutically acceptable carrier.

Another aspect of this invention is directed to pharmaceutical compositions for the treatment of diabetes which comprise a therapeutically ... agents such as insulin and insulin analogs (e.g.

Glycogen phosphorylase dependent diseases or conditions refers to disorders which are mediated, initiated or maintained, in ... glycogen macromolecule by glycogen phosphorylase enzymes to release glucose-1-phosphate and a new shortened glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity.

The term “treating” as used herein ... preventative (e.g., prophylactic) and palliative treatment.

Alternatively, Formula I compounds ... the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as ... for conversion to the sulfone oxidation state.

If the protecting group is t-Boc by treatment of the Formula XXV compound with an acid in a suitable, preferably aprotic, solvent.

For example, the Formula XXXIII compound may be ... chloride, or in the case of tert-butanol by treatment of the amino acid with isobutylene and an acid catalyst such as concentrated sulfuric acid or by treatment with an alkyl halide (e.g., methyl iodide) and base (e.g., potassium carbonate).
The Formula XU amino acids may be prepared by treatment of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCl3 is converted on treatment with an appropriate base and alkylating agent to an intermediate R4CH(OH)CCl3, which is converted on treatment with azide and base to an intermediate to the desired Formula XUI compound.

Thus a readily available compound of formula R8R9NH (wherein R8=R9=R) is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent to give NH2CON(R')(OR'), by successive treatment with the alkylating agents R'X and R"X, respectively, in the presence of a suitable base.

[0112] The utility of the compounds of the present invention as medical agents in the treatment of metabolic diseases (such as are detailed herein) in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in ... Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for ... levels in mammals, including humans, for the treatment of such diseases.

HLGP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in HLGP Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the HLGP activity are pooled (approximately 600 mL), and ... and 0.7 μg/mL concentrations respectively.

Determination of HLGP Enzyme Activity: A) Activation of HLGP: Conversion of ... (AMP-independent) is then calculated as follows: % of total HLGP as HLGP enzyme activity in the absence of inhibitors is determined by adding 20 μL of 50 mM of the positive control test substance, caffeine.
The compounds to be tested are added as 5 μL ... of 14% DMSO and a fully-inhibited rate of HLGPa enzyme activity is obtained by adding 20 pL of 50 mM caffeine: ... measured by the general method of Lanzetta et al.

The basal rate of HLGPa enzyme activity in the absence of added inhibitors is determined ... measured by the general method of Lanzetta et al. 

100, 95-97] modified as follows: 150 μL of 10 ... green in 1 N HCl is added to 100 μL of the enzyme mix.

The hypoglycemic activity of the compounds of this invention can be ... vehicle without test compound in male ob/ob mice.

[0125] Since the concentration of glucose in ... closely related to the development of diabetic disorders, these compounds by virtue of their hypoglycemic action, prevent, arrest and/or regress diabetic disorders.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

Hypoglycemic activity of the test compounds is determined by ... and vehicle-treated group on day 5. The above assay carried out with a range of doses of test ... vivo reduction of plasma glucose concentration.

Such activity can be determined by the amount of test compound ... vehicle without test compound in male ob/ob mice.

[0129] Since the concentration of cholesterol ... cerebral vascular or peripheral vascular disorders, the compounds of this invention by virtue of ... prevent, arrest and/or regress atherosclerosis.

[0131] Since the concentration of ... by virtue of their triglyceride lowering activity prevent, arrest and/or regress hyperlipidemia.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

The inter assay coefficient of variation is ≤ 10%.

Serum triglycerides are determined using the ... Diagnostics Division, Irving, TX) (lipase-coupled enzyme method; a modification of the method of Sampson, et al., Clinical Chemistry 21, 1983 (1975)).

Serum total cholesterol levels are determined ... reagent system (cholesterol esterase-coupled enzyme method; a modification of the method of Allain, et al.

The serum insulin, triglycerides, and total cholesterol lowering activity of the test compounds are determined by ... vehicle-treated control group. [0136] Activity in providing protection from damage to heart ... along the lines presented in Butwell et al., Am.

The in vivo assay tests the cardioprotection of the test compound ... the control group which receives saline vehicle.

Cardioprotection, as indicated by a reduction in ... using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied ... al., Circulation 84:350-356, 1991). The in vivo assay tests whether compounds can pharmacologically ... administered to intact, anesthetized rabbits.

[0139] However, the amount and timing of ... will, of course, be dependent on the particular disease/condition being treated, the subject being ... and on the judgment of the prescribing physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the activity (e.g., glucose lowering activity) that the physician considers appropriate for the patient. In considering the degree of activity desired, the physician must balance a variety of ... factors, presence of preexisting disease, and age of the patient and the patient’s motivation.
In general an effective dosage for the activities of this invention, for example, the blood glucose, triglycerides, and cholesterol lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the ... and most preferably 0.1 to 15 mg/kg/day.

Generally, the compounds of this ... administration is inappropriate for the instant target or where the patient is unable to ingest the drug.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated, i.e., a glycogen phosphorylase dependent disease/condition.

Description of EP1134213A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of EP1134213A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Within the above group of especially preferred compounds are the compounds 5-Chloro-1 ... acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1 H-indole-2-carboxylic acid ... acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.
Description of EP1134213A2 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0020] Within the above group of especially preferred compounds are the compounds 5-Chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.

Description of EP1134213A2 contains 5-Chloro-1H-indole-2-carboxylic acid [1-(1-diethylcarbamoyl-2-phenyl-ethyl)-amide]

US6277877B1 20010821 ( US63893800A20000815 ) Substituted n-(indole-2-carbonyl)glycinamides and derivatives as glycogen phosphorylase inhibitors - HOOVER DENNIS J.; HULIN BERNARD; MARTIN WILLIAM H.; PHILLIPS DOUGLAS; TREADWAY JUDITH L. - PFIZER, INC.

Compounds of Formula (I) wherein R6 is carboxy, (C1-C8)alkoxycarbonyl, benzyloxy carbonyl, C(O)NR8R9 or C(O)R12 as glycogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat diabetes, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

Description: In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas (e.g. Searle)) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

Treatment of non-insulin dependent diabetes mellitus (Type 2... combination of diet, exercise, oral agents, e.g.
Atherosclerosis, a disease of the arteries, is recognized to be the leading . . . of death in the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

Epidemiological evidence has firmly established . . . a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, . . . risk factors in this population. Successful treatment of hyperlipidemia in the general population, and . . . is therefore of exceptional medical importance.

Hypertension (or high blood pressure) is a . . . as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such ""essential"" hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms . . . in the complete absence of any other signs of disease or disorder.

Hypertension can also contribute to the development of atherosclerosis and coronary disease.

The exact cause of essential hypertension is . . . are believed to contribute to the onset of the disease.

The treatment of essential hypertension has been undertaken bearing the foregoing factors In mind.

Thus a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has . . . failure, renal failure and brain hemorrhaging.

However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem.

This implies that although high blood pressure is . . . essential hypertension is not responding to this treatment.

Hepatic glucose production is an important target for NIDDM therapy.

Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers’ disease (glycogen phosphorylase deficiency), display episodic hypoglycemia.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release . . . and a new shortened glycogen macromolecule.

These compounds, and glycogen phosphorylase . . . been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.

SUMMARY OF THE INVENTION This invention is . . . Inhibitor compound of Formula I useful for the treatment of diabetes, hyperglycemia, . . . atherosclerosis and myocardial ischemia.

Yet another aspect of this invention is directed . . . for treating a glycogen phosphorylase dependent disease or condition in a mammal by administering to a . . . from a glycogen phosphorylase dependent disease or condition a glycogen phosphorylase dependent disease or condition treating amount of a Formula I compound.

Included in the treatment of diabetes is the prevention or attenuation of . . . nephropathy, retinopathy or cataracts.
Preferred compositions include pharmaceutical compositions for the treatment of glycogen phosphorylase dependent diseases or conditions in mammals which comprise a glycogen phosphorylase dependent disease or condition treating amount of a compound of Formula I and a pharmaceutically acceptable carrier.

Another aspect of this invention is directed to pharmaceutical compositions for the treatment of diabetes which comprise a therapeutically ... agents such as insulin and insulin analogs (e.g.

Glycogen phosphorylase dependent diseases or conditions refers to disorders which are mediated, initiated or maintained, in ... glycogen macromolecule by glycogen phosphorylase enzymes to release glucose-1 -phosphate and a new shortened glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity.

The term ""treating"" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

Alternatively, Formula I compounds which contain ... the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as ... at a temperature of about 0°

If the protecting group is t-Boc by treatment of the Formula XXV compound with an acid in a suitable, preferably aprotic, solvent.

For example, the Formula XXXIII compound may be ... chloride, or in the case of tert-butanol by treatment of the amino acid with isobutylene and an acid catalyst such as concentrated sulfuric acid or by treatment with an alkyl halide (e.g., methyl iodide) and base (e.g., potassium carbonate).

The Formula XL amino acids may be prepared by ... Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4 ... R4 CH(OH)CCl3, which is converted on treatment with azide and base to an Intermediate R4 ... to the desired Formula XLII compound.

Thus a readily available compound of formula ... CONHOH is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent ... R8 R9 NH (wherein R8 =R9 =R).

Alternatively, N-hydroxyurea (NH2 CONH(OH)) ... to give NH2 CON(R”“)(OR'), by successive treatment with the alkylating agents R’X and R””X, respectively, in the presence of a suitable base.

The utility of the compounds of the present invention as medical agents in the treatment of metabolic diseases (such as are detailed herein) in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in ... Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for ... levels in mammals, including humans, for the treatment of such diseases.

HLGP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in HLGPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the HLGP activity are pooled (approximately 600 mL), and ... and 0.7 mg/mL concentrations respectively.

HLGP-containing fractions are pooled following identification by determining enzyme (described below) activity and visualizing the M, approximately 97 kdal ... Co., LTD., Tokyo, Japan) and then pooled.

Determination of HLGP Enzyme Activity A) Activation of HLGP: Conversion of HLGPb to HLGPa Prior to the determination of HLGP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads ... mM CaCl2 at pH 7.4 for 4 hours at 4°
Prior to use to convert HLGPb to HLGPa, the . . . 0.3 mM DTT, and 0.3 mM EDTA at pH 7.8 (kinase assay buffer).

The partially purified, inactive HLGPb obtained . . . above is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the . . . to HLGPa is estimated by determining HLGP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total HLGP enzyme activity due to HLGPa enzyme activity (AMP-independent) is then calculated as follows: EQU1 B) HLGPa Activity Assay. The hypoglycemic activity (also the other disease/condition treating/preventing activities described herein) of the compounds of this . . . effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase . . . by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by . . . by the release of inorganic phosphate.

To measure the HLGPa enzyme activity in the forward direction, the production of . . . coupled general method of Pesce et al.

The compounds to be tested are added as 5 muL . . . (DMSO) prior to the addition of the enzymes. The basal rate of HLGPa enzyme activity in the absence of inhibitors is determined by . . . of 14% DMSO and a fully-inhibited rate of HLGPa enzyme activity is obtained by adding 20 muL of 50 mM of the positive control test substance, caffeine.

To measure HLGPa enzyme activity in the reverse direction, the conversion of . . . by the general method described by Engers et al.

The compounds to be tested are added as 5 muL . . . in 14% DMSO prior to the addition of the enzyme. The basal rate of HLGPa enzyme activity in the absence of added inhibitors is determined . . . of 14% DMSO and a fully-inhibited rate of HLGPa enzyme activity is obtained by adding 20 muL of 50 mM . . . measured by the general method of Lanzetta et al.

100, 95-97] modified as follows: 150 muL of 10 . . . green in 1 N HCl is added to 100 muL of the enzyme mix.

The hypoglycemic activity of the compounds of this invention can be . . . vehicle without test compound in male ob/ob mice.

Since the concentration of glucose in blood is closely related to the development of diabetic disorders, these compounds by virtue of their hypoglycemic action, prevent, arrest and/or regress diabetic disorders.

After a one week acclimation period, the animals . . . from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

Hypoglycemic activity of the test compounds is determined by . . . and vehicle-treated group on day 5. The above assay carried out with a range of doses of test . . . vivo reduction of plasma glucose concentration.

Such activity can be determined by the amount of test compound . . . vehicle without test compound in male ob/ob mice.

Since the concentration of cholesterol in blood . . . cerebral vascular or peripheral vascular disorders, the compounds of this invention by virtue of . . . prevent, arrest and/or regress atherosclerosis.

Since the concentration of triglycerides in blood . . . by virtue of their triglyceride lowering activity prevent, arrest and/or regress hyperlipidemia.

After a one week acclimation period, the animals . . . from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

The inter assay coefficient of variation is .ltoreq.10%.
Triglycerides Test reagent system (Abbott ... Division, Irving, Tex.) (lipase-coupled enzyme method; a modification of the method of Sampson, et al., Clinical Chemistry 21, 1983 (1975)).

Cholesterol Test reagent system (cholesterol esterase-coupled enzyme method; a modification of the method of Allain, et al.

The serum insulin, triglycerides, and total cholesterol lowering activity of the test compounds are determined by ... group and the vehicle-treated control group. Activity in providing protection from damage to heart ... along the lines presented in Butwell et al., Am.

The in vivo assay tests the cardioprotection of the test compound ... the control group which receives saline vehicle.

Cardioprotection, as indicated by a reduction in ... using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied ... al., Circulation 84:350-356, 1991). The in vivo assay tests whether compounds can pharmacologically ... administered to intact, anesthetized rabbits.

However, the amount and timing of compound(s) ... will, of course, be dependent on the particular disease/condition being treated, the subject being ... and on the judgment of the prescribing physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the activity (e.g., glucose lowering activity) that the physician considers appropriate for the patient. In considering the degree of activity desired, the physician must balance a variety of ... factors, presence of preexisting disease, and age of the patient and the patient’s motivation. In general an effective dosage for the activities of this invention, for example, the blood glucose, triglycerides, and cholesterol lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the ... and most preferably 0.1 to 15 mg/kg/day.

Generally, the compounds of this invention are ... administration is inappropriate for the instant target or where the patient is unable to ingest the drug.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated, i.e., a glycogen phosphorylase dependent disease/condition.

fulltext score : 19 , cippix score : 509 , hit score : 5

Description of US6277877B1 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

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5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of US6277877B1 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

Description of US6277877B1 contains 5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-Chloro-1H-indole-2-carboxylic acid [1-benzyl-2-(3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide
Pharmaceutical compositions comprise a glycogen phosphorylase inhibitor and at least one concentration-enhancing polymer. The composition may be a simple physical mixture of glycogen phosphorylase inhibitor and concentration-enhancing polymer or a dispersion of glycogen phosphorylase inhibitor and polymer.:

Description: In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas (e.g., Searle)) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory.

Treatment of non-insulin dependent diabetes mellitus (Type ... combination of diet, exercise, oral agents, e.g. Hepatic glucose production is an important target for NIDDM therapy.

Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers’ disease (glycogen phosphorylase deficiency), display episodic hypoglycemia.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase (GP). This enzyme cleaves the glycogen macromolecule to release ... and a new shortened glycogen macromolecule.

These compounds, and GPIs in general, have been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia [Blundell, T.

Enzyme activity is also controlled by phosphorylation at a single phosphorylation site, Ser 14.

Phosphorylation normally causes an increase in GP activity due to a conformational change in the GP enzyme.

The experimentally determined GP : GPI structures ... occurs upon phosphorylation causing the GP enzyme to adopt the conformation of the “inactive,” unphosphorylated protein.

Such fused ring systems can be considered ... bind to the indole pocket binding site of the GP enzyme.

Accordingly, what is therefore desired is a ... effect the ability of the GPI to bind to the GP enzyme, improves relative bioavailability, and is pharmaceutically acceptable.

The GPI binds to a portion’or all portions of the following residues of a glycogen phosphorylase enzyme: parent secondary structure residue number ... 125-128 strand ss3 129-131 132-133 helix a6.

In another aspect of the invention, a method of treatment of a mammal having an indication due to ... growth inhibition comprises the following steps.

As discussed above in the Background, a new class ... bind to the indole pocket binding site in the GP enzyme.

It is believed that an important part of the ... binds in a hydrophobic pocket within the GP enzyme. In studying the GPI activity, binding mode, and GPI/GP complex structure of a ... that compounds that have good GP inhibition activity at this indole pocket binding site often have a ... low solubilities in aqueous solution (i.
As used herein and in the claims, "bind" means a portion of the GPI binds to the GP enzyme in such a manner that a portion of the GPI is in ... portions of certain residues of the binding site.

In a preferred embodiment, the GPI binds to the GP enzyme with a portion or all portions of the following ... is disclosed more fully in commonly assigned U.

In another aspect, the present invention concerns the treatment of diabetes, including impaired glucose ... mellitus (NIDDM or Type 29. Also included in the treatment of diabetes are the treatment of the diabetic complications, such as neuropathy, nephropathy, retinopathy or cataracts.

In addition to the categories and compounds ... aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors, or sorbitol ... ischemia, particularly myocardial ischemia.

In an article published in Atherosclerosis, 126 : ... agents, yet devoid of undesirable cardiac activities.

The disclosure teaches that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial infarction, and angina pectoris.

The term aldose reductase inhibitor refers to ... glucose to sorbitol, which is catalyzed by the enzyme aldose rea.
sorbitol, which is catalyzed by the enzyme aldose ... ùs’êdli ini : à cdmbhatiohwith/a composition.

The, ""activity-... bf :’an’, ’l’alddte t.

The composition of the present invention can also be used in combination with glucocorticoid receptor antagonists. The glucocorticoid receptor (GR) is present in glucocorticoid responsive ... an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell nucleus where it ... in a glucocorticoid responsive manner.

Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NFK-B.

Such interactions result in inhibition of API-and ... to be responsible for the anti-inflammatory activity of endogenously administered glucocorticoids.

Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. By definition, glucocorticoid receptor antagonists bind to the receptor and prevent glucocorticoid receptor agonists from binding and eliciting GR mediated events, including transcription.

RU486 is an example of a non-selective glucocorticoid receptor antagonist. GR antagonists can be used in the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body.

As such, they may be used to treat the following : obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, glioma, ... enhancement, Cushing’s Syndrome, Addison’s Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, ... immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, ... catabolism and prevention of muscle frailty.

Provisional Patent Application number 60/132, 130.) Each of the glucocorticoid receptor antagonists referenced above and other glucocorticoid receptor antagonists can be used in combination with the ... atherosclerosis, or tissue ischemia.

patent numbers 5, 728, 704 and 5, 866, 578 ... diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

In each case, the targeted tablet weight was 700 mg.

Claims: A pharmaceutical composition comprising a ... following residues of a glycogen phosphorylase enzyme : parent secondary structure residue number ... 277-281 reverse turn 282-289 helix a8 290-304.
The composition of claim 1 wherein a portion of ... residues of said glycogen phosphorylase enzyme in one or both subunits: parent secondary structure residue number ... 248-260 helix a7 261-276 strand llb 277-280 12.

The composition of claim 1 wherein a portion of ... residues of said glycogen phosphorylase enzyme in one or both subunits: residue number 33-39 ... 197 224-226 228-231 238-239 241 245 247 13.

The composition of claim 1 wherein a portion of ... residues of said glycogen phosphorylase enzyme in one or both subunits: residue number 37-39 53 57 60 63-64 184-192 226 229 14.

The composition of any one of claims 2-3 wherein ... following residues of a glycogen phosphorylase enzyme: parent secondary structure residue number ... reverse turn 282-289 helix a8 290-304 15.

The composition of claim 14 wherein a portion of ... residues of said glycogen phosphorylase enzyme in one or both subunits: parent secondary ... 103 helix a4 104-115 116-117 helix a5 118-124 .

The composition of claim 14 wherein a portion of ... residues of said glycogen phosphorylase enzyme in one or both subunits: residue number 33-39 ... 197 224-226 228-231 238-239 241 245 247 17.

The composition of claim 14 wherein a portion of ... residues of said glycogen phosphorylase enzyme in one or both subunits: residue number 37-39 53 57 60 63-64 184-192 226 229 18.

fulltext score: 20, cippix score: 115, hit score: 4

Claims of WO200168055A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl2((3R,4S)-3, 4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

23. The composition of claim 21 wherein said glycogen phosphorylase inhibitor is selected from the ... acid [(1S)-benzyl- 2- (3S, 4S)-3, 4-dihydroxy-pyrrolidin-1-yl]-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl2- ((3R, 4S)-3, 4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [ (1S)- (4-fluoro-benzyl)-2- ... and 5-chloro-1H-indole-2- carboxylic acid [2-(1-oxo-thiazolidin-3-yl)-2-oxo-ethyl]amide.

Description of WO200168055A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2((3R,4- S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl] amide

In another especially preferred embodiment, the GPI is selected from one of the following ... acid [(1S)-benzyl-2((3S, 4S)-3, 4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2 ((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl] amide; 5-chloro-1H-indole-2-carboxylic acid [ (1S)- (4-fluoro- benzyl)-2- ... ; and 5-chloro-1H-indole-2-carboxylic acid [2- (1-oxo- thiazolidin-3-yl)-2-oxo-ethyl]amide.
Claims of WO200168055A1 contains 5-chloro-1H-indole-2-carboxylic acid[(1S)-benzyl-2-((3S,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

23. The composition of claim 21 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide, and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide.

Claims of WO200168055A1 contains 2-Chloro-6H-thieno [2,3-b]pyrrole-5-carboxylic acid[(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide

28. The composition of claim 2 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 2-Chloro-6H-thieno [2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide, 2-Chloro-6H-thieno [2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide, and 2-Chloro-6H-thieno [2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-3-OxO-propyl]-amide.

29. The composition of claim 27 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 2-Chloro-6H-thieno [2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]amide, and 2-Chloro-6H-thieno [2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-3-OxO-propyl]-amide.

EP1032424B9 20041006 (IB9801752W19981102; US6636597P19971121) ZUSAMMENSETZUNGEN WELCHE ALDOSEREDUCTASEHEMMER UND GLYCOGEN PHOSPHORYLASE HEMMER ENTHALTEN; COMBINAISON D’UN INHIBITEUR DE REDUCTASE D’ALDOSE ET D’UN INHIBITEUR DE PHOSPHORYLASE DE GLYCOGENE; COMBINATION OF AN ALDOSE REDUCTASE INHIBITOR AND A GLYCOGEN PHOSPHORYLASE INHIBITOR - MYLARI, BANAVARA, LAKSHMAN; HOOVER, DENNIS, JAY; HULLIN, BERNARD; TREADWAY, JUDITH, LEE - PFIZER PRODUCTS INC.

Description: In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas (e.g.

Treatment of non-insulin dependent diabetes mellitus (Type ... combination of diet, exercise, oral agents, e.g.

Zopolrestat has the structure and, as an aldose reductase inhibitor, is useful in the treatment of the above-mentioned complications arising from diabetes mellitus.

The disclosure notes that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial ... and angina pectoris. Atherosclerosis, a disease of the arteries, is recognized to be the leading ... of death in the United States and Western Europe.
The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

Epidemiological evidence has firmly established . . . a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, . . . risk factors in this population. Successful treatment of hyperlipidemia in the general population, and . . . is therefore of exceptional medical importance.

Hypertension (or high blood pressure) is a . . . as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such ”essential” hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms . . . in the complete absence of any other signs of disease or disorder.

These conditions are capable of causing . . . the development of atherosclerosis and coronary disease.

The exact cause of essential hypertension is . . . are believed to contribute to the onset of the disease.

The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind.

Thus, a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has . . . failure, renal failure and brain hemorrhaging.

However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem.

This implies that although high blood pressure is . . . essential hypertension is not responding to this treatment. Hypertension has been associated with elevated . . . levels, a condition known as hyperinsulinemia.

Hepatic glucose production is an important target for NIDDM therapy.

Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers’ disease (glycogen phosphorylase deficiency), display epidosic hypoglycemia.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release . . . and a new shortened glycogen macromolecule.

These compounds, and glycogen phosphorylase . . . been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.

SUMMARY OF THE INVENTION This invention is . . . in the manufacture of a medicament for the treatment of insulin resistant conditions, including . . . tissue protection) resulting from ischemia.

Preferred insulin resistant conditions taken . . . tissue ischemia and cardiovascular diseases, syndrome X (also referred to as Metabolic . . . growth hormone excess or polycystic ovarian disease.

Especially preferred insulin resistant conditions . . . tissue ischemia, obesity, polycystic ovarian disease, syndrome X and hypertension.

increased free fatty acid, triglyceride, VLDL . . . tissue ischemia, and cardiovascular diseases (Kopelman and Albon, 1997; DeFronzo and Ferrannini, 1991; Reaven, 1991; Malmstrom, et al., 1997).
The term aldose reductase inhibitor refers to . . . of glucose to sorbitol catalyzed by the enzyme aldose reductase.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

The expression "prodrug" refers to compounds that . . . being brought to the physiological pH or through enzyme action is converted to the desired drug form).

The term aldose reductase inhibitor refers to . . . of glucose to sorbitol catalyzed by the enzyme aldose reductase.

The activity of an aldose reductase inhibitor in a tissue can . . . and consequently the production of fructose).

Alternatively, Formula I compounds which contain . . . the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as with . . . for conversion to the sulfone oxidation state.

Such a mono- or di-alkylation may be conducted by treatment of the R5 aminoalkoxy compound with 1 equivalent . . . a suitable reducing agent in a suitable solvent.

The Formula XXI cyanohydrin may be prepared from the Formula XX compound by treatment with sodium or potassium cyanide as described . . . in a mixture of stereoisomers at carbon b.

Formula XXI intermediates of a specific . . . with retention of this stereochemistry by treatment with an alcohol and a strong acid catalyst, . . . of water, if necessary , as described above.

A silyl derivative of a Formula XXI intermediate . . . subsequently by an appropriate method, such as treatment with tetrabutylammonium fluoride in . . . XXI compound to the Formula XXII compound.

This reduction is accomplished by treatment of Formula XXX compounds with lithium aluminum . . . Syntheses; Wiley: New York, 1990; Collect.

The Formula XLII amino acids may be prepared by . . . of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCl3 is . . . intermediate R4CH(OH)CCl3, which is converted on treatment with azide and base to an intermediate . . . to the desired Formula XLII compound.

The Formula LXI compound is alkylated on oxygen by treatment with an appropriate alkylation agent (e.g., . . . about 150 C resulting in a Formula LXII compound.

The corresponding acid may be prepared by . . . functionality protected as the t-butyl ester by treatment with anhydrous acid to provide the corresponding . . . without hydrolyzing the ester at the R6 position.

The Formula LXIV compound is reduced to the primary amine by treatment with hydrogen and an appropriate catalyst (e.g., . . . or ethanol to give the Formula LXV primary amine.

The Formula LXIII and LXIV compounds wherein n is two are preferably prepared by treatment of the Formula LXI compound with an excess of . . . solvent, preferably a polar protic solvent.

Thus a readily available compound of formula . . . is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylation agent . . . a compound of formula R8R9NH (wherein R8=R9=R).

Alternatively, a formula NH2CONH(OH) amine may be . . . nitrogen to give NH2CON(R'(OR')), by successive treatment with the alkylation agents R'X and R"X, respectively , in the presence of a suitable base.

Alternatively, Formula IA compounds which contain . . . the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as . . . for conversion to the sulfone oxidation state.
If the protecting group is t-Boc by treatment of the Formula XXV compound with an acid in a suitable, preferably aprotic, solvent.

For example, the Formula XXXIII compound may be ... chloride, or in the case of tert-butanol by treatment of the amino acid with isobutylene and an acid catalyst such as concentrated sulfuric acid or by treatment with an alkyl halide (e.g., methyl iodide) and base (e.g., potassium carbonate).

The Formula XLI amino acids may be prepared by ... of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCl3 is ... intermediate R4CH(OH)CCl3, which is converted on treatment with azide and base to an intermediate ... to the desired Formula XLII compound.

Thus a readily available compound of formula ... is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent ... a compound of formula R8R9NH (wherein R8=R9=R).

Alternatively, N-hydroxyurea (NH2CONH(OH)) may be ... nitrogen to give NH2CON(R')(OR'), by successive treatment with the alkylating agents R'X and R"X, respectively, in the presence of a suitable base.

The utility of the combinations of the present invention as medical agents in the treatment of diseases such as are detailed herein in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in ... Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for ... levels in mammals, including humans, for the treatment of such diseases.

ALDOSE REDUCTASE INHIBITOR ASSAYS

The assay contains 0.1 ml neutralized 6% perchloric acid nerve extract in a final volume of 1.5 ml.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and ... g/mL and 0.7 g/mL concentrations respectively.

GP-containing fractions are pooled following identification by determining enzyme activity (described below) and visualizing the Mr ... Co., LTD., Tokyo, Japan) and then pooled.

Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

The assay contains 0.1 ml neutralized 6% perchloric acid nerve extract in a final volume of 1.5 ml.

GP in the soluble fraction of the lysates ... the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... described in Section (A) Activation of GP below.

Determination of GP Enzyme Activity A) Activation of GP: Conversion of GPb to GPa Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... form (designated GPa) by the following procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads ... and 80 mM CaCl2 at pH 7.4 for 4 hours at 4 C.

Prior to use to convert GPb to GPa, the Affi-Gel ... 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).
coli) or the mixture of GPa and GPb obtained from ... (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the ... conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GP enzyme activity (AMP-independent) is then calculated as follows: % of total HLGPa = HLGP activity - AMP / (HLGP activity + AMP) Alternately, the conversion of GPb to GPa ... that is noted following conversion of GPb to GPa.

B) GPa Activity Assay The disease/condition treating/preventing activities described herein of the glycogen phosphorylase ... effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... by the release of inorganic phosphate.

To measure the GPa enzyme activity in the forward direction, the production of ... coupled general method of Pesce et al.

The compounds to be tested are added as 5 L of ... (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by ... L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 L of 50 mM of the positive control test substance, caffeine.

To measure the GPa enzyme activity in the reverse direction, the conversion of ... by the general method described by Engers et al.

The compounds to be tested are added as 5 L of solution in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors is determined ... L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 L of 50 mM caffeine.

100, 95-97] modified as follows: 150 L of 10 ... green in 1 N HCl is added to 100 L of the enzyme mix.

The above assays carried out with a range of ... of test compound allows the determination of an IC50 value (concentration of test compound required ... inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

The hypoglycemic activity of the combinations of this invention can be ... vehicle without test compound in male ob/ob mice.

Since the concentration of glucose in blood is closely related to the development of diabetic disorders, these combinations by virtue of their ... action, prevent, arrest and/or regress diabetic disorders.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

Hypoglycemic activity of the test compounds is determined by ... and vehicle-treated group on day 5. The above assay carried out with a range of doses of test ... vivo reduction of plasma glucose concentration.

Such activity can be determined by the amount of test compound ... vehicle without test compound in male ob/ob mice.

Since the concentration of cholesterol in blood ... cerebral vascular or peripheral vascular disorders, the combinations of this invention by virtue of ... prevent, arrest and/or regress atherosclerosis.

Since the concentration of triglycerides and free ... their triglyceride and free fatty add lowering activity prevent, arrest and/or regress hyperlipidemia.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.
The interassay coefficient of variation is 10%.

Serum triglycerides are determined using the ... Diagnostics Division Irving, TX) (lipase-coupled enzyme method; a modification of the method of Sampson, et al., Clinical Chemistry 21, 1983 (1975)).

Serum total cholesterol levels are determined ... reagent system (cholesterol esterase-coupled enzyme method; a modification of the method of Allain, et al.

Serum free fatty add concentration is determined utilizing a kit from Amano International Enzyme Co., Inc., as adapted for use with the Abbott VP ... Spectrum CCX (Abbott Laboratories, Irving, TX).

The serum insulin, triglycerides, free fatty acids and total cholesterol lowering activity of the test compounds are determined by ... along the lines presented in Butwell et al., Am.

The in vivo assay tests the cardioprotection of the test compound ... the control group which receives saline vehicle.

Cardioprotection, as indicated by a reduction in ... using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied ... al., Circulation 84:350-356, 1991). The in vivo assay tests whether compounds can pharmacologically ... administered to intact, anesthetized rabbits.

The effect of the compositions and methods of ... in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate aminotransferase (AST), ... damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several ... Ektachem 500 analyzer reported by Nakano, et al.

The effect of the compositions and methods of ... on a reduction in the release of hepatocellular enzymes immediately following the occlusive period ... in the perfused livers from the rats in the treatment group compared to perfused livers from rats in a placebo-treated control group.

Generally, the compounds of this invention are ... administration is inappropriate for the instant target or where the patient is unable to ingest the drug.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

Thus, because of patient to patient variability, ... titrate doses of the compounds to achieve the treatment (e.g., glucose lowering activity; insulin levels) that the physician considers ... for the patient. In considering the degree of treatment desired, the physician must balance a variety of ... as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention, for example the, triglycerides, and cholesterol lowering activities and hyperinsulinemia reversing activities is used.

In general an effective dosage for the activities of this invention, for example the blood ... free fatty acids and cholesterol lowering activities and hyperinsulinemia reversing activities of the glycogen phosphorylase inhibitor ... and most preferably 0.1 to 15 mg/kg/day.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

Since the present invention has an aspect that relates to the treatment of for example, an insulin resistant condition by treatment with a combination of active ingredients which ... separate pharmaceutical compositions in kit form.

In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas (e.g.
Searle)), alpha-glucosidase inhibitors (e.g., ... agents, there is a continuing need for treatments of diabetes.

**Treatment** of non-insulin dependent diabetes mellitus (Type ... combination of diet, exercise, oral agents, e.g.

Zopolrestat has the structure and, as an aldose reductase inhibitor, is useful in the treatment of the above-mentioned complications arising from diabetes mellitus.

The disclosure notes that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial ... and angina pectoris. Atherosclerosis, a disease of the arteries, is recognized to be the leading ... of death in the United States and Western Europe.

The pathological sequence leading to atherosclerosis and occlusive heart disease is well known.

Epidemiological evidence has firmly established ... a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis.

Cardiovascular disease is especially prevalent among diabetic subjects, ... risk factors in this population. Successful treatment of hyperlipidemia in the general population, and ... is therefore of exceptional medical importance.

Hypertension (or high blood pressure) is a ... as a secondary symptom to various other disorders such as renal artery stenosis, pheochromocytoma or endocrine disorders.

However, hypertension is also evidenced in many patients in whom the causative agent or disorder is unknown.

While such "essential" hypertension is often associated with disorders such as obesity, diabetes and hypertriglyceridemia, the relationship between these disorders has not been elucidated.

Additionally, many patients display the symptoms ... in the complete absence of any other signs of disease or disorder.

These conditions are capable of causing ... the development of atherosclerosis and coronary disease.

The exact cause of essential hypertension is ... are believed to contribute to the onset of the disease.

The treatment of essential hypertension has been undertaken bearing the foregoing factors in mind.

Thus, a broad range of beta-blockers, vasoconstrictors, angiotensin converting enzyme inhibitors and the like have been developed and marketed as antihypertensives. The treatment of hypertension utilizing these compounds has ... failure, renal failure and brain hemorrhaging.

However, the development of atherosclerosis or heart disease due to hypertension over a long period of time remains a problem.

This implies that although high blood pressure is ... essential hypertension is not responding to this treatment. Hypertension has been associated with elevated ... levels, a condition known as hyperinsulinemia.

Hepatic glucose production is an important target for NIDDM therapy.

Glycogenolysis is an important target for interruption of hepatic glucose production.

Second, patients having liver glycogen storage diseases, including Hers' disease (glycogen phosphorylase deficiency), display episodic hypoglycemia.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release ... and a new shortened glycogen macromolecule.

These compounds, and glycogen phosphorylase ... been postulated to be of potential use for the treatment of NIDDM by decreasing hepatic glucose production and lowering glycemia.
SUMMARY OF THE INVENTION This invention is ... in the manufacture of a medicament for the treatment of insulin resistant conditions, including ... tissue protection) resulting from ischemia.

Preferred insulin resistant conditions taken ... tissue ischemia and cardiovascular diseases, syndrome X (also referred to as Metabolic ... growth hormone excess or polycystic ovarian disease.

Especially preferred insulin resistant conditions ... tissue ischemia, obesity, polycystic ovarian disease, syndrome X and hypertension.

increased free fatty acid, triglyceride, VLDL ... tissue ischemia, and cardiovascular diseases (Kopelman and Albon, 1997; DeFronzo and Ferrannini, 1991; Reaven, 1991; Malmstrom, et al., 1997).

The term aldose reductase inhibitor refers to ... of glucose to sorbitol catalyzed by the enzyme aldose reductase.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

The expression “prodrug” refers to compounds that ... being brought to the physiological pH or through enzyme action is converted to the desired drug form).

The term aldose reductase inhibitor refers to ... of glucose to sorbitol catalyzed by the enzyme aldose reductase.

The activity of an aldose reductase inhibitor in a tissue can ... and consequently the production of fructose).

Alternatively, Formula I compounds which contain ... the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as with ... for conversion to the sulfone oxidation state.

Such a mono- or di-alkylation may be conducted by treatment of the R5 aminoalkoxy compound with 1 equivalent ... a suitable reducing agent in a suitable solvent.

The Formula XXI cyanohydrin may be prepared from the Formula XX compound by treatment with sodium or potassium cyanide as described ... in a mixture of stereoisomers at carbon b.

Formula XXI intermediates of a specific ... with retention of this stereochemistry by treatment with an alcohol and a strong acid catalyst, ... of water, if necessary, as described above.

A silyl derivative of a Formula XXI intermediate ... subsequently by an appropriate method, such as treatment with tetrabutylammonium fluoride in ... XXI compound to the Formula XXII compound.

This reduction is accomplished by treatment of Formula XXX compounds with lithium aluminum ... Syntheses; Wiley: New York, 1990; Collect.

The Formula XLI amino acids may be prepared by ... of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCl3 is ... intermediate R4CH(OH)CCl3, which is converted on treatment with azide and base to an intermediate ... to the desired Formula XLI compound.

The Formula LXI compound is alkylated on oxygen by treatment with an appropriate alkylating agent (e.g., ... about 150 C resulting in a Formula LXII compound.

The corresponding acid may be prepared by ... functionality protected as the t-butyler ester by treatment with anhydrous acid to provide the corresponding ... without hydrolyzing the ester at the R6 position.

The Formula LXIV compound is reduced to the primary amine by treatment with hydrogen and an appropriate catalyst (e.g., ... or ethanol to give the Formula LXV primary amine.
The Formula LXIII and LXIV compounds wherein n is two are preferably prepared by treatment of the Formula LXI compound with an excess of . . . solvent, preferably a polar protic solvent.

Thus a readily available compound of formula . . . is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent . . . a compound of formula R8R9NH (wherein R8=R9=R).

Alternatively, a formula NH2CONH(OH) amine may be nitrogen to give NH2CON(R’)(OR’), by successive treatment with the alkylating agents R’X and R”X, respectively, in the presence of a suitable base.

Alternatively, Formula IA compounds which contain . . . the sulfur atom in the unoxidized form, by treatment with a suitable oxidizing agent, such as . . . for conversion to the sulfone oxidation state.

If the protecting group is t-Boc by treatment of the Formula XXV compound with an acid in a suitable, preferably aprotic, solvent.

For example, the Formula XXXIII compound may be . . . chloride, or in the case of tert-butanol by treatment of the amino acid with isobutylene and an acid catalyst such as concentrated sulfuric acid or by treatment with an alkyl halide (e.g., methyl iodide) and base (e.g., potassium carbonate).

The Formula XLI amino acids may be prepared by . . . of the Formula XL protected (PT) amino acids by treatment with an appropriate base and alkylating agent.

Thus, an intermediate of formula R4COCCl3 is . . . intermediate R4CH(OH)CCl3, which is converted on treatment with azide and base to an intermediate . . . to the desired Formula XLII compound.

Thus a readily available compound of formula . . . is dialkylated on nitrogen and oxygen by treatment with base and excess suitable alkylating agent . . . a compound of formula R8R9NH (wherein R8=R9=R).

Alternatively, N-hydroxyurea (NH2CONH(OH)) may be nitrogen to give NH2CON(R’)(OR’), by successive treatment with the alkylating agents R’X and R”X, respectively, in the presence of a suitable base.

The utility of the combinations of the present invention as medical agents in the treatment of diseases such as are detailed herein in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in . . . Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for . . . levels in mammals, including humans, for the treatment of such diseases. ALDOSE REDUCTASE INHIBITOR ASSAYS The activity of an aldose reductase inhibitor can be . . . lower tissue fructose according to the following assay.

The assay contains 0.1 ml neutralized 6% perchloric acid nerve extract in a final volume of 1.5 ml.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and . . . g/mL and 0.7 g/mL concentrations respectively.

GP-containing fractions are pooled following identification by determining enzyme activity (described below) and visualizing the Mr . . . Co., LTD., Tokyo, Japan) and then pooled.

Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . described in Section (A) Activation of GP below.
Determination of GP Enzyme Activity

A) Activation of GP: Conversion of GPb to GPa

Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... form (designated GPa) by the following procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads ... and 80 mM CaCl2 at pH 7.4 for 4 hours at 4 C.

Prior to use to convert GPb to GPa, the Affi-Gel ... 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).

coli) or the mixture of GPa and GPb obtained from ... (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the ... conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: % of total HLGPa = HLGPa activity - AMP / (HLGP activity + AMP) Alternately, the conversion of GPb to GPa ... that is noted following conversion of GPb to GPa.

B) GPa Activity Assay

The disease/condition treating/preventing activities described herein of the glycogen phosphorylase ... effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... the release of inorganic phosphate.

To measure the GPa enzyme activity in the forward direction, the production of ... coupled general method of Pesce et al.

The compounds to be tested are added as 5 L of ... (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by ... L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 L of 50 mM of the positive control test substance, caffeine.

To measure the GPa enzyme activity in the reverse direction, the conversion of ... by the general method described by Engers et al.

The compounds to be tested are added as 5 L of solution in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors is determined ... L of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 L of 50 mM caffeine.

100, 95-97] modified as follows: 150 L of 10 ... green in 1 N HCl is added to 100 L of the enzyme mix.

The above assays carried out with a range of ... of test compound allows the determination of an IC50 value (concentration of test compound required ... inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

The hypoglycemic activity of the combinations of this invention can be ... vehicle without test compound in male ob/ob mice.

Since the concentration of glucose in blood is closely related to the development of diabetic disorders, these combinations by virtue of their ... action, prevent, arrest and/or regress diabetic disorders.

After a one week acclimation period, the animals ... from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

Hypoglycemic activity of the test compounds is determined by ... and vehicle-treated group on day 5. The above assay carried out with a range of doses of test ... vivo reduction of plasma glucose concentration.
Such activity can be determined by the amount of test compound . . . vehicle without test compound in male ob/ob mice.

Since the concentration of cholesterol in blood . . . cerebral vascular or peripheral vascular disorders, the combinations of this invention by virtue of . . . prevent, arrest and/or regress atherosclerosis.

Since the concentration of triglycerides and free . . . their triglyceride and free fatty add lowering activity prevent, arrest and/or regress hyperlipidemia.

After a one week acclimation period, the animals . . . from the retro-orbital sinus prior to any treatment.

Animals are assigned to treatment groups so that each group has a similar mean for plasma glucose concentration.

The inter assay coefficient of variation is 10%.

Serum triglycerides are determined using the . . . Diagnostics Division,Irving, TX) (lipase-coupled enzyme method; a modification of the method of Sampson, et al., Clinical Chemistry 21, 1983 (1975)).

Serum total cholesterol levels are determined . . . reagent system (cholesterol esterase-coupled enzyme method; a modification of the method of Allain, et al.

Serum free fatty add concentration is determined utilizing a kit from Amano International Enzyme Co., Inc., as adapted for use with the Abbott VP . . . Spectrum CCX (Abbott Laboratories, Irving, TX).

The serum insulin, triglycerides, free fatty acids and total cholesterol lowering activity of the test compounds are determined by . . . group and the vehicle-treated control group. Activity in providing protection from ischemia (e.g., . . . along the lines presented in Butwell et al., Am.

The in vivo assay tests the cardioprotection of the test compound . . . the control group which receives saline vehicle.

Cardioprotection, as indicated by a reduction in . . . using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied . . . al., Circulation 84:350-356, 1991). The in vivo assay tests whether compounds can pharmacologically . . . administered to intact, anesthetized rabbits.

The effect of the compositions and methods of . . . in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate amino-transferase (AST), . . . damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several . . . Ektachem 500 analyzer reported by Nakano, et al.

The effect of the compositions and methods of . . . on a reduction in the release of hepatocellular enzymes immediately following the occlusive period . . . in the perfused livers from the rats in the treatment group compared to perfused livers from rats in a placebo-treated control group.

Generally, the compounds of this invention are . . . administration is inappropriate for the instant target or where the patient is unable to ingest the drug.

Topical administration may also be indicated, for . . . the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to . . . organ as determined by the attending physician.

Thus, because of patient to patient variability, . . . titrate doses of the compounds to achieve the treatment (e.g., glucose lowering activity; insulin levels) that the physician considers . . . for the patient. In considering the degree of treatment desired, the physician must balance a variety of . . . as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention, for example the, triglycerides, and cholesterol lowering activities and hyperinsulinemia reversing activities is used.
In general an effective dosage for the activities of this invention, for example the blood . . . free fatty acids and cholesterol lowering activities and hyperinsulinemia reversing activities of the glycogen phosphorylase inhibitor . . . and most preferably 0.1 to 15 mg/kg/day.

In any event, the composition or formulation to . . . invention in an amount effective to treat the disease/condition of the subject being treated.

Since the present invention has an aspect that relates to the treatment of for example, an insulin resistant condition by treatment with a combination of active ingredients which . . . separate pharmaceutical compositions in kit form.

Claims: The use as claimed in claim 7 wherein the insulin . . . atherosclerosis, tissue ischemia, cardiovascular diseases, syndrome X, pregnancy, conditions of infection, . . . growth hormone excess, or polycystic ovarian disease.

Description of EP1032424B9 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide.

Description of EP1032424B9 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide.

Claims of EP1032424B9 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

4. A pharmaceutical composition as recited in any one of claims 1 to 3 wherein the glycogen . . . acid [(1S)-benzyl-3-((cis)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy- 3-oxopropyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; . . . 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide.

13. The use as claimed in any one of claims 7 to 12 wherein the glycogen phosphorylase inhibitor . . . acid [(1S)-benzyl-3-((cis)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy- 3-oxopropyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; . . . 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide.
Description of EP1032424B9 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide.
Another aspect of this invention is directed to a method for treating cardiovascular diseases comprising administering to a mammal (e. g., reopro), aspirin, dipyridamol, potassium chloride, clonidine, prazosin or adenosine A3 receptor agonists.

In the above combination compositions, ... methyl]-. In the methods of treatment as applied to the ... are preferred administration routes, modes etc.

In yet another aspect of this method myocardial ... in a patient with diagnosed coronary heart disease.

The term “treating”, “treat” or “treatment” as used herein includes preventative (e. g., prophylactic) and palliative treatment.

The activity of an aldose reductase inhibitor in a tissue can ... to lower tissue sorbitol (i.

An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention may be used.

In general an effective ... for example the ischemic damage reducing activities of combinations containing the glycogen ... and most preferably 0.1 to 15 mg/kg/day.

The compounds of the present invention inhibit ... as a therapeutic or prophylactic agent for diseases caused or aggravated by the acceleration of the ... transport system, for example, cardiovascular diseases [e.

hemorrhagic shock, endotoxin shock, etc.)], renal diseases (e.

diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion ... g. heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) ... coronary angioplasty (PTCA)], cerebrovascular diseases (e.

ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e. g. disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema.

Preferably, the compounds of this invention can ... in patients with diagnosed coronary heart disease (e.

previous myocardial infarction or unstable ... and two or more risk factors for coronary heart disease).
For this <RTI Measurement of Human NHE-1 Inhibitory Activity> Methodologies for measurement of human NHE-1 activity and inhibitor potency are based on those published by Watson et al., Am.

The potency of human NHE-1 inhibitors is ... pH by 50% (IC50).

Under these conditions reference NHE inhibitors amiioride and HOE-642 had IC50 values for human NHE-1 of 50 M and 0.5 J.

Cardioprotection, as indicated by a reduction in ... can be induced pharmacologically using adenosine receptor agonists in isolated, <RTI ... (Liu et a., Cardiovasc.

The in vivo assay tests the cardioprotection ... the control group which receives saline vehicle.

Cardioprotection, as ... using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied ... Circulation 84: 350-356, 1991). The in vivo assay tests whether compounds can pharmacologically induce cardioprotection, i.

The effect of the compositions and methods of ... in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate aminotransferase (AST), ... damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several ... reported by Nakano, et al.

The effect of the compounds, compositions and ... on a reduction in the release of hepatocellular enzymes immediately following the occlusive period ... livers from the rats in the treatment group compared to perfused <RTI ... ID=86.16>-placebo-treated control group.

The assay contains 0.1 ml neutralized ... fluorescence spectrophotometer.

GP in the soluble fraction of the lysates ... is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and ... and 0.7 ug/mL concentrations respectively.

Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates ... ID=90.12> protein) is purified by monitoring the enzyme activity (as described in GPa Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... (A) Activation of GP below.

Determination of GP Enzyme Activity A) Activation of GP: Conversion of GPb to GPa Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed ... kinase as follows. The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is ... form (designated GPa) by the following procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads ... ester at pH 8.0 for one hour at room temperature.

Prior to use to convert GPb to GPa, the <RTI ... 0.3 mM DTT, and 0.3mMEDTA at pH 7.8 (kinase assay buffer).

The partially purified, inactive GPb obtained ... Sf9 cells) is diluted 1: 10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.
The sample is removed from the beads and the conversion to GPa is estimated by determining enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total enzyme activity due to GPa enzyme activity (AMP-dependent) is then calculated as follows: % of total HLGPa = HLGPa activity - AMP HLGPa activity + AMP

Alternately, the conversion of GPb to GPa is noted following -conversion of GPb to GPa.

B) GPa Activity Assay. The disease/condition treating/preventing activities described herein of the glycogen phosphorylase effect of the compounds of this invention on the activity of the activated form of <RTI ... by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by ... by the release of inorganic phosphate.

To measure the GPa enzyme activity in the forward direction, the production of <RTI ... by the general method described by Engers et al. [Pesce, M. 100,95-97] modified as follows: <RTI ... is added to 100 uL of the enzyme mix.

The above assays carried out with a range of ... ID=94.12>allows the determination of an IC50 value (concentration of test compound required ... ID=94.13>the in vitro inhibition of GPa enzyme activity by that test compound.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of ... as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination ... separate pharmaceutical compositions in kit form.

Microanalyses were performed by <RTI ... was converted to the thioamide by treatment with Lawesson’s reagent (10 g, 25 mmol) in ... mL) at 60 C for 4 hours.

By a similar treatment of the solids that formed in the filtrate from ... was obtained (1.65 g total yield, 73% yield).

Claims: A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment a therapeutically effective amount of a compound ... salt of said compound or of said prodrug.

A method of preventing myocardial ischemic damage ... oral administration to a human in need of such treatment of a therapeutically effective amount of a ... salt of said compound or of said prodrug.

A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment an amount of a first compound, said first ... second compounds result in a therapeutic effect.

A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment an amount of a first compound, said first ... second compounds result in a therapeutic effect.
A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment. ... second compounds result in a therapeutic effect.

A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment an amount of a first compound, said first ... second compounds result in a therapeutic effect.

A pharmaceutical composition as recited in claim ... prazosin or an adenosine A3 receptor agonist.

A method of reducing tissue damage resulting from ... chloride, clonidine, prazosin or an adenosine A3 receptor agonist.

A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment an amount of a first compound, said first ... second compounds result in a therapeutic effect.

A kit as recited in claim 171 wherein the ... chloride, clonidine, prazosin or an adenosine A3 receptor agonist.

fulltext score : 42 , cippix score : 584 , hit score : 3

Description of WO9943663A1 contains 5-chloro-1H-indole-2-carboxylic acid[(1S)-benzyl-2((3S,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3-hydroxyimino- ... acid [(1 S)- (2-fluoro-benzyl)-2- (4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3S, 4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (4-hydroxyimino- piperidin-1-yl)-2-oxo-ethyl]-amide.

Description of WO9943663A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3, 4-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3-hydroxyimino- ... 5-chloro-1 H-indole-2-carboxylic acid [2-((3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3, 4-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [2- (l, 1-dioxo-thiazolidin-3-yl)-2-oxo- ethyl]-amide, ... 5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (4-hydroxyimino- piperidin-1-yl)-2-oxo-ethyl]-amide.
Claims of WO9943663A1 contains 5-chloro-1H-indole-2-carboxylic acid[[(1S)-benzyl-2(cis-3, 4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

-157. A pharmaceutical composition as recited in claim 156 wherein the glycogen phosphorylase . . . H-indole-2-carboxylic acid [2- ( (3S, 4S)- dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1 S)-benzyl-2- (cis-3, 4-dihydroxy-pyrrolidin-1-y1)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [2- (1, 1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; . . . o xo-ethyl]-amide; or a pharmaceutically acceptable salt thereof.

160. A method of reducing tissue damage resulting from ischemia as recited in claim 159 wherein . . . 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1 S)-benzyl-2- (cis-3, 4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [2- (1, 1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; . . . o xo-ethyl]-amide; or a pharmaceutically acceptable salt thereof.

163. A kit as recited in claim 162 wherein the glycogen phosphorylase inhibitor is 5-chloro-1 . . . 5-chloro-1H-indole-2-carboxylic acid [2- (1, 1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; or a pharmaceutically acceptable salt thereof.


A3 agonists having Formula I are described herein as well as methods of using such A3 agonists and pharmaceutical compositions containing such A3 agonists. The A3 agonists are useful for the reduction of tissue damage resulting from tissue ischemia or hypoxia.

**Title:** Compounds for the treatment of ischemia

**Description:** FIELD OF THE INVENTION [0002] The present invention relates to adenosine A-3 receptor agonists, pharmaceutical compositions containing . . . ischemic injury in mammals, including humans.

In addition to reducing myocardial damage and . . . function in patients with ischemic heart disease, cardioprotection would also decrease the . . . 65 years, exercise intolerant, coronary artery disease, diabetes mellitus, hypertension) that require non-cardiac surgery.

5,604,210 discloses the use of certain adenosine type compounds for the prevention or treatment of a brain edema, an intracranial hemorrhage and a cerebral infarction.

5,688,774 discloses A3 selective agonists, . . . groups as agents which activate the A3 receptor.

5,773,423 discloses . . . for the activation of the A3 adenosine receptor.


In particular, 3'-beta-amino compounds were found to have no activity.


The recombinant adenosine receptors can be utilized in an assay to identify and evaluate entities that bind to or enhance binding to adenosine receptors.
Another aspect of this invention are methods of treating a mammal (e.g., human) having a disease or condition mediated by an A3 adenosine receptor by administering a therapeutically effective amount of the compound or the prodrug to the mammal.

One embodiment of the present invention is ... (e.g., a female or male human) in need of such treatment a therapeutically effective amount of a compound ... or hydrate of the compound or the prodrug.

The methods of the present invention may ... or a patient with diagnosed coronary heart disease (e.g., previous myocardial infarction or ... and two or more risk factors for coronary heart disease).

In yet another embodiment of the present ... to a mammal (e.g., human) in need of such treatment of a therapeutically effective amount of a ... or hydrate of the compound or the prodrug.

The present invention is also useful for treating cardiovascular diseases, arteriosclerosis, arrhythmia, angina pectoris, cardiac hypertrophy, renal diseases, diabetetic complications, restenosis, organ ... septic shock and other inflammatory diseases (e.g., septicemia and endotoxemia), cerebro ischemic disorders, myocardial stunning, myocardial dysfunction, and cerebrovascular diseases by administering to a mammal (e.g., a human) a ... or hydrate of the compound or the prodrug.

In yet another aspect of the present ... use by a consumer having or at risk of having a disease or condition resulting from, for example, ischemia or hypoxia is provided.

In the above combination compositions, ... potassium channel openers, adenosine, adenosine receptor agonists, sodium-hydrogen exchanger type 1 ... digoxin, metildigoxin), thrombolytics (e.g. tPA), platelet inhibitors (e.g., ReoPro.TM.), ... biguanides (e.g., metformin) or other adenosine receptor agonists.

Other cardiovascular agents include angiotensin II (All) receptor antagonists, C5a inhibitors, soluble complement receptor type 1 (sCR1) or analogues, partial fatty acid ... protein kinase epsilon), protein kinase delta inhibitors, poly (ADP ribose) synthetase (PARS, ... insulin sensitzers), endothelin converting enzyme (ECE) inhibitors, endothelin ETA receptor antagonists, (thrombin activated fibrinolytic ... TAFI inhibitors and Na/Ca exchanger modulators.

The compositions containing the compounds ... invention described herein are useful in the treatment, reduction and/or prevention of tissue damage ... or which could result from ischemia or hypoxia.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

The term "prodrug" refers to compounds ... being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Typically, the Formula XXXIII compound may be ... conversion to an acid chloride by, for example, treatment with oxalyl chloride in a non-polar aprotic ... formamide, at a temperature of about 0°

The desired Formula XXXIV compound is prepared from the appropriate Formula XXXV compound by treatment with periodic acid which hydrolyzes the ... and cleaves the glycol to furnish the aldehyde.

In combination therapy treatment, both the compounds of this invention and the ... mammals (e.g., humans) by conventional methods.

The term "NHE-1 inhibitor" refers to compounds ... as a therapeutic or prophylactic agent for diseases caused or aggravated by the acceleration of the sodium/proton (Na+/H+) exchange transport system.

Such inhibition is readily determined by those ... cardioprotection assays [see the in vivo assay in Klein, H. et al., Circulation 92:912-917 (1995); the isolated heart assay in Scholz, W.].
The term aldose reductase inhibitor refers to ... of glucose to sorbitol catalyzed by the enzyme aldose reductase.

[0238] The activity of an aldose reductase inhibitor in a tissue can ... and consequently the production of fructose.

[0279] An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention may be used.

[0330] In general an effective dosage for the ... for example the ischemic damage reducing activities of combinations containing the glycogen ... preferably from about 0.1 to about 15 mg/kg/day.

[0332] The compounds of the present invention ... useful as therapeutic or prophylactic agents for diseases caused or aggravated by ischemia or hypoxia, or ischemia/reperfusion for example, cardiovascular diseases [e.g., arteriosclerosis, arrhythmia (e.g. hemorrhagic shock, endotoxin shock, etc.)], renal diseases (e.g. diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.), organ disorders associated with ischemia or ischemic reperfusion ... muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) ... coronary angioplasty (PTCA)], cerebrovascular diseases (e.g., ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e.g., disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema.

[0335] Preferably, the compounds of this ... in patients with diagnosed coronary heart disease (e.g., previous myocardial infarction or ... and two or more risk factors for coronary heart disease).

[0337] The utility of the compounds of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g., ... in patients with diagnosed coronary heart disease, or at risk for coronary heart disease, cardiac dysfunction or myocardial stunning is demonstrated by the activity of the compounds of this invention in ... cardioprotection assays [see the in vivo assay in Klein, H. et al., Circulation 92:912-917 (1995); the isolated heart assay in Tracey, W. et al., Cardiovascular Research 33:410-415 (1997); the antiarrhythmic assay in Yasutake M. Physiol., 36:H2430-H2440 (1994); the NMR assay in Kolke et al., J. Physiol., 36:H2430-H2440 (1994); the antiarrhythmic assay in Yasutake M. Physiol., 36:H2430-H2440 (1994); the NMR assay in Kolke et al., J.

Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for ... levels in mammals, including humans, for the treatment of such diseases. Human Adenosine A1 and A3 Receptor Assays Materials [0338] Full-length human adenosine A1 and A3 receptor cDNA's subcloned into the eukaryotic expression ... from The Garvan Institute, Sydney, Australia.

The A1/A3 adenosine receptor agonist N6-(4-amino-3-[125I]iodobenzyl)adeno- ... by New England Nuclear (Boston, Mass., USA).

Expression of Human Adenosine A1 and A3 Receptors [0339] For stable expression studies, adenosine receptor A1 and A3 expression plasmids (20 ... cell transfection kit (5 Prime-3 Prime).

Receptor Membrane Preparation [0340] Cells stably ... DNAse I (100 mug/ml), ADA (2 U/ml), pH 7.4.

Estimation of Compound Binding Affinity Constants (Ki) [0341] Receptor membranes are resuspended in incubation buffer ... HEPES (10), EDTA (1), MgCl2 (5), pH 7.4.
Assessment of Human Adenosine A3 Receptor Agonist Activity [0342] Adenosine A3 agonist activity is assessed by compound inhibition of isoproterenol-stimulated cAMP levels.

Cardioprotection, as indicated by a reduction in . . . can be induced pharmacologically using adenosine receptor agonists in isolated, retrogradely perfused . . . ischemic preconditioning (Tracey et al. The in vivo assay tests the cardioprotection of the test compound . . . the control group which receives saline vehicle.

Cardioprotection, as indicated by a reduction in . . . using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied . . . al., Circulation 84:350-356, 1991). The in vivo assay tests whether compounds can pharmacologically . . . administered to intact, anesthetized rabbits.

The effect of the compounds, compositions and . . . in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate aminotransferase (AST), . . . damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several . . . Ektachem 500 analyzer reported by Nakano, et al.

The effect of the compounds, compositions and . . . on a reduction in the release of hepatocellular enzymes immediately following the occlusive period . . . in the perfused livers from the rats in the treatment group compared to perfused livers from rats in a placebo-treated control group.

Measurement of Human NHE-1 Inhibitory Activity [0359] Methodologies for measurement of human NHE-1 activity and inhibitor potency are based on those published by Watson et al., Am.

The assay contains 0.1 ml neutralized 6% perchloric acid nerve extract in a final volume of 1.5 ml.

Measurement of SDH Activity [0363] Male Sprague-Dawley rats (350-400 g) are used for these experiments.

Aliquots of tissue extracts are added to an assay system that has final concentrations of reagents . . . and 4 units/ml of sorbitol dehydrogenase.

Aliquots of tissue extracts are added to the assay system, which has final concentrations of . . . dehydrogenase and 0.068% Triton X-100.TM..

[0366] SDH activity is measured by a modification of the method described by U.

Aliquots of sera or urine are added to the assay system, which has final concentrations of . . . and 0.7 units/ml of sorbitol dehydrogenase.

SDH activity is presented as milliOD340 units/minute (OD340 = optical density at 340 nm).

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPA Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and . . . and 0.7 mug/mL concentrations respectively.

GP-containing fractions are pooled following identification by determining enzyme activity (described below) and visualizing the Mr . . . Co., LTD., Tokyo, Japan) and then pooled.

[0375] Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed in E.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPA Activity Assay section, below) from a series of chromatographic steps detailed below.
Activation of GP [0379] Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . described in Section (A) Activation of GP below.

Determination of GP Enzyme Activity [0381] A) Activation of GP: Conversion of GPb to GPa [0382] Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . form (designated GPa) by the following procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads . . . mM CaCl2 at pH 7.4 for 4 hours at 4°C Prior to use to convert GPb to GPa, the Affi-Gel . . . 0.3 mM DTT, and 0.3 mM EDTA at pH 7.8 (kinase assay buffer).

coli) or the mixture of GPa and GPb obtained from . . . (from Sf9 cells) is diluted 1:10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the . . . conversion to GPa is estimated by determining GP enzyme activity in the presence and absence of 3.3 mM AMP. The percentage of total GP enzyme activity due to GPa enzyme activity (AMP-independent) is then calculated as follows: 1 % of total HLGPa = HLP activity - AMP HLP activity + AMP [0385] Alternately, the conversion of GPb . . . that is noted following conversion of GPb to GPa.

[0386] B) GPa Activity Assay [0387] The disease/condition treating/preventing activities described herein of the glycogen phosphorylase . . . effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase . . . by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by . . . by the release of inorganic phosphate.

[0388] To measure the GPa enzyme activity in the forward direction, the production of . . . coupled general method of Pesce et al.

The compounds to be tested are added as 5 muL . . . (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by . . . of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 muL of 50 mM of the positive control test substance, caffeine.

[0389] To measure the GPa enzyme activity in the reverse direction, the conversion of . . . by the general method described by Engers et al.

The compounds to be tested are added as 5 muL . . . in 14% DMSO prior to the addition of the enzyme. The basal rate of GPa enzyme activity in the absence of added inhibitors is determined . . . of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20 muL of 50 mM caffeine.

100, 95-97 (1979)] modified as follows: 150 muL . . . green in 1 N HCl is added to 100 muL of the enzyme mix.

[0390] The above assays carried out with a range . . . inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

Topical administration may also be indicated, for . . . the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to . . . organ as determined by the attending physician.

Thus, because of patient to patient variability, . . . may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of . . . as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

An amount of the compound or the present invention that is effective for ischemic or hypoxic treatment or protection is preferably a dosage from about 0.001 to about 100 mg/kg/day.
In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

[0402] Advantageously, the present invention also ... by a consumer having, or at risk of having, a disease or condition resulting from, for example, ... which can be ameliorated by an A3 agonist.

[0404] Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination ... separate pharmaceutical compositions in kit form.

**Claims:** A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment a therapeutically effective amount of a ... compound or said prodrug according to claim 1.

The pharmaceutical composition of claim 14 ... a potassium channel opener, adenosine, adenosine receptor agonists, an ACE inhibitor, a nitric oxide ... biguanides, NH E-1 inhibitor, angiotensin II receptor antagonists, C5a inhibitors, soluble complement receptor type 1 or analogues thereof, partial fatty acid ... kinase C activators, protein kinase delta inhibitors, poly (ADP ribose) synthetase inhibitors, metformin, endothelin converting enzyme inhibitors, endothelin ET A receptor antagonists, TAFI inhibitors, or a Na/Ca exchanger modulators.

A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment a) an amount of a first compound, said first ... second compounds result in a therapeutic effect.

The method of claim 19 wherein the cardiovascular ... biguanides, NHE-1 inhibitor, angiotensin II receptor antagonists, C5a inhibitors, soluble complement receptor type 1 or analogues, partial fatty acid ... kinase C activators, protein kinase delta inhibitors, poly (ADP ribose) synthetase inhibitors, metformin, endothelin converting enzyme inhibitors, endothelin ET A receptor antagonists, TAFI inhibitors, or a Na/Ca exchanger modulators.

*fulltext score : 40, cippix score : 287, hit score : 3*
Claims of US2003055021A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

16. The pharmaceutical composition of claim 14 wherein the glycogen phosphorylase inhibitor is . . . 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

21. The method of claim 19 wherein the glycogen phosphorylase inhibitor is . . . 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

US2004082614A1 20040429 ( US62303203A20030716; US39696002P20020718 ) Methods of treating infection using antibiotics and glycogen phosphorylase inhibitors - TREADWAY JUDITH L.; SUTCLIFFE JOYCE ANNE - PFIZER INC.

The invention provides methods of treating infection, such as Chlamydia pneumoniae infection, in a mammal comprising administering to a mammal effective amounts of azithromycin and a glycogen phosphorylase inhibitor. The invention also provides methods of treating atherosclerosis by administration of effective amounts of azithromycin and a glycogen phosphorylase inhibitor. Pharmaceutical compositions and kits are also provided.

Description: FIELD OF THE INVENTION [0001] This invention . . . with a glycogen phosphorylase inhibitor for the treatment of infections.

In humans, three isoforms of this enzyme have been identified: the liver isoform (HLGP), . . . into (HBGP).

[0004] Glycogen phosphorylase inhibitors are useful in the treatment of diabetes mellitus.

12. 1996, describe use of substituted N-(indole-2-carbonyl-) amides and derivatives for treatment of diabetes. These compounds are also described as useful treatment of atherosclerosis, hyperinsulinemia, . . . and in prevention of myocardial ischemic injury.

16. 1999 refers to antagonists and agonists of . . . glycogen phosphorylase as useful in the treatment of otitis media, conjunctivitis, pneumonia, . . . sinusitis, pleural emphysema and endocarditis.

SUMMARY OF THE INVENTION [0007] The invention is . . . administering to a mammal in need of such treatment effective amounts of the antibiotic azithromycin and a glycogen phosphorylase inhibitor.

[0008] Another aspect of the invention provides . . . administering to a mammal in need of such treatment effective amounts of azithromycin and a glycogen phosphorylase inhibitor.

[0009] A further aspect of the invention provides . . . administering to a mammal in need of such treatment effective amounts of azithromycin and a glycogen . . . acceptable salt thereof or prodrug thereof.

[0149] The method of the invention is employed to . . . bacterial infections and protozoa infections and disorders related to such infections that include the . . . coagulase-positive staphylococci (i.e., S.
hemolyticus, etc.), Streptococcus pyogenes, ... and cervicitis; and sexually transmitted diseases related to infection by Chlamydia trachomatis, ... urealyticum, or Neisseria gonorrhoeae; toxin diseases related to infection by S. aureus (food poisoning and Toxic shock syndrome), ... to infection by Borrelia burgdorferi; ... Chlamydia trachomatis, Neisseria gonorrhoeae, S.
influenzae; disseminated Mycobacterium avium complex (MAC) disease related to infection by Mycobacterium avium, or ... and symptoms of infection by enterotoxigenic E.

toxic diseases related to infection by S. aureus (food poisoning and Toxic shock syndrome), ... to infection by Borrelia burgdorferi; ... Chlamydia trachomatis, Neisseria gonorrhoeae, S.

[0150] Bacterial infections and protozoa infections and disorders related to such infections that may be treated ... include the following: bovine respiratory disease related to infection by Pasteurella haemolyticus, P. multocida, Mycoplasma bovis, or Bordetella spp.; cow enteric disease related to infection by E. dysgalactiae, Klebsiella spp., Corynebacterium, or Enterococcus spp.; swine respiratory disease related to infection by Actinobacillus ... P. multocida, or Mycoplasma spp.; swine enteric disease related to infection by E coli, Lawsonia ... spp.; cow metritis related to infection by E.

[0151] The invention also encompasses treatment of bacteremia, meningitis, pleural empyema, ... river blindness, toxoplasmosis, and endocarditis.

Other bacterial infections and protozoa infections and disorders related to such infections that may be treated ... of the present invention are referred to in J.

[0152] In a preferred aspect, the methods of the ... are used to treat bacterial infection and disorders related to such infection, more preferably infection by Chlamydia spp and related disorders, most preferably infection by Chlamydia pneumonia and related disorders.

[0153] In another preferred aspect, the invention ... inhibitor to a mammal in need of such treatment.

[0155] Administration of azithromycin with a ... inhibitor could allow more favorable treatment options, reduced dose or frequency of the ... likely to achieve effective MBC concentrations).

[0157] Where used herein, synergistic effective ... or suspected of having, an infection or related disease such as atherosclerosis, are sufficient to ... greater action against the infection or related disease than the sum of the action that would be ... and glycogen phosphorylase inhibitor alone.

[0159] The terms "treating", "treat", "treatment", as used herein, includes curative, preventative (e.g. prophylactic) and palliative treatment.

Generally, the compounds used in this invention ... for treating the infection or related disease, or where patient is unable to ingest the drug.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the activity (e.g., antibacterial and/or antiprotozoan activity) that the physician considers appropriate for the individual patient. In considering the degree of activity desired, the physician must balance a variety of ... weight of the patient and the presence of other diseases.

[0178] Since one aspect of the present invention contemplates the treatment of infection or atherosclerosis with a ... separate pharmaceutical compositions in kit form.

For minimum bacteriocidal concentration (MBC) determination, drugs were removed at 72 h post-treatment, the media was replaced, and cells were maintained for an additional 72 h before termination.

**Claims:** A method of treating a bacterial infection in a ... administering to a mammal in need of such treatment effective amounts of azithromycin and a glycogen phosphorylase inhibitor.
A method of treating a Chlamydia pneumoniae ... administering to a mammal in need of such treatment effective amounts of azithromycin and a glycogen phosphorylase inhibitor.

A method of treating atherosclerosis comprising administering to a mammal in need of such treatment effective amounts of azithromycin and a glycogen ... acceptable salt thereof or prodrug thereof.

Description of US2004082614A1 contains 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

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EP1224179B1 20040714 (IB0001460W20001009; US16237499P19991029) CRISTaux D'INHIBITEURS DE L'ÉCHANGEUR SODIUM-HYDROGÈNE DE TYPE 1; SODIUM-HYDROGEN EXCHANGER TYPE 1 INHIBITORS; TYPE 1 INHIBITORKRISTALLE ALS INHIBITOREN DES NATRIUM-PROTONEN AUSTAUSCHS - BROSTROM, LYLE, ROBINSON; CONNOLLY, TERRENCE, JOSEPH; LI, ZHENG, JANE; ORRILL, SUSAN, L.; SHAH, BHARAT, K. - PFIZER PRODUCTS INC.

Description: In addition to reducing myocardial damage and ... function in patients with ischemic heart disease, cardioprotection would also decrease the ... 65 years, exercise intolerant, coronary artery disease, diabetes mellitus, hypertension) that require non-cardiac surgery.
A variety of publications have disclosed the use of guanidine derivatives as useful for the treatment of, for example, arrhythmias.

The publication further states that "preferred . . . exchange and consequently effective for the treatment of various diseases such as hypertension, arrhythmia, angina . . . arteriosclerosis, and complications of diabetes.

Thus, there is clearly a need and a continuing search in this field of art for compounds for the treatment of perioperative myocardial ischemia and, accordingly, new crystal forms of such compounds.

Another aspect of this invention is the use of a . . . for treating a mammal (e.g., human) having a disease or condition mediated by NHE-1.

Another aspect of this invention is directed to . . . basis in a patient with diagnosed coronary heart disease (e.g., previous myocardial infarction or . . . and two or more risk factors for coronary heart disease).

Another aspect of this invention is directed to . . . oral administration to a mammal in need of such treatment.

Another aspect of this invention is directed to . . . of a medicament for treating cardiovascular diseases in a mammal (e.g., a female or male human).

Another aspect of this invention is directed to . . . preparation of a medicament for treating renal diseases in a mammal (e.g., a female or male human).

Another aspect of this invention is directed to . . . for the preparation of a medicament for treating diseases of cell proliferation in a mammal (e.g., a female or male human).

Another aspect of this invention is directed to . . . of a medicament for treating cancerous diseases in a mammal (e.g., a female or male human).

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In the above combination compositions, . . . chloride, clonidine, prazosin or adenosine A3 receptor agonists.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

The term aldose reductase inhibitor refers to . . . of glucose to sorbitol catalyzed by the enzyme aldose reductase.

An amount of the aldose reductase inhibitor that is effective for the activities of this invention may be used.

In general an effective dosage of the glycogen . . . for example the ischemic damage reducing activities of combinations containing the glycogen . . . and most preferably 0.1 to 15 mg/kg/day.

tPA), platelet inhibitors (e.g., reopro), . . . inhibitors (e.g., zopolrestat) and adenosine A3 receptor agonists may be used in conjunction with the crystals of this invention.

The crystals of the present invention inhibit the . . . as a therapeutic or prophylactic agent for diseases caused by the acceleration of the sodium/proton . . . transport system, for example, cardiovascular diseases [e.g., arteriosclerosis, hypertension, . . . etc.], restenosis after PTCA, shock (e.g.
hemorrhagic shock, endotoxin shock, etc.), renal diseases (e.g., diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion ... heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) ... coronary angioplasty (PTCA), cerebrovascular diseases (e.g., ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e.g., disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema).

Preferably, the crystals of this invention can be ... in patients with diagnosed coronary heart disease (e.g., previous myocardial infarction or ... and two or more risk factors for coronary heart disease).

For this reason, the crystals of this invention are valuable therapeutic agents for use in diseases in which cell proliferation represents a primary ... against diabetic late complications, cancerous diseases, fibrotic diseases such as pulmonary fibrosis, hepatic fibrosis or ... or recurrent stricture after PTCA, or diseases caused by endothelial cell injury.

The utility of the crystals of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g., ... in patients with diagnosed coronary heart disease, is demonstrated by the activity of the crystals of this invention in ... cardioprotection assays [see the in vivo assay in Klein, H. et al., Circulation 92:912-917 (1995); the isolated heart assay in Scholz, W. et al., Cardiovascular Research 29:260-268 (1995); the antiarrhythmic assay in Yasutake M. Physiol., 36:H2430-H2440 (1994); the NMR assay in Kolke et al., J. Such assays also provide a means whereby the activities of the crystals of this invention can be compared with the activities of other known crystals.

The results of these comparisons are useful for ... levels in mammals, including humans, for the treatment of such diseases.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of ... as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

In an especially preferred mode an infusion is ... example about 2 to about 7 days post surgical treatment.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

In addition to reducing myocardial damage and ... function in patients with ischemic heart disease, cardioprotection would also decrease the ... 65 years, exercise intolerant, coronary artery disease, diabetes mellitus, hypertension) that require non-cardiac surgery.

A variety of publications have disclosed the use of guanidine derivatives as useful for the treatment of, for example, arrhythmias.

The publication further states that "preferred ... exchange and consequently effective for the treatment of various diseases such as hypertension, arrhythmia, angina ... arteriosclerosis, and complications of diabetes.

Thus, there is clearly a need and a continuing search in this field of art for compounds for the treatment of perioperative myocardial ischemia and, accordingly, new crystal forms of such compounds.

Another aspect of this invention is the use of a ... for treating a mammal (e.g., human) having a disease or condition mediated by NHE-1.
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The crystals of the present invention inhibit the . . . as a therapeutic or prophylactic agent for diseases caused by the acceleration of the sodium/proton . . . transport system, for example, cardiovascular diseases [e.g., arteriosclerosis, hypertension, . . . etc.), restenosis after PTCA, shock (e.g.

hemorrhagic shock, endotoxin shock, etc.], renal diseases (e.g., diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion . . . heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) . . . coronary angioplasty (PTCA)], cerebrovascular diseases (e.g., ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e.g., disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema).

Preferably, the crystals of this invention can be . . . in patients with diagnosed coronary heart disease (e.g., previous myocardial infarction or . . . and two or more risk factors for coronary heart disease).

For this reason, the crystals of this invention are valuable therapeutic agents for use in diseases in which cell proliferation represents a primary . . . against diabetic late complications, cancerous diseases, fibrotic diseases such as pulmonary fibrosis, hepatic fibrosis or . . . or recurrent stricture after PTCA, or diseases caused by endothelial cell injury.
The utility of the crystals of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g., ... in patients with diagnosed coronary heart disease, is demonstrated by the activity of the crystals of this invention in ... cardioprotection assays [see the in vivo assay in Klein, H. et al., Circulation 92:912-917 (1995); the isolated heart assay in Scholz, W. et al., Cardiovascular Research 29:260-268 (1995); the antiarrhythmic assay in Yasutake M. Physiol., 36:H2430-H2440 (1994); the NMR assay in Kolke et al., J. Such assays also provide a means whereby the activities of the crystals of this invention can be compared with the activities of other known crystals.

The results of these comparisons are useful for ... levels in mammals, including humans, for the treatment of such diseases.

Topical administration may also be indicated, for ... the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of ... as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

In an especially preferred mode an infusion is ... example about 2 to about 7 days post surgical treatment.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

fulltext score : 53 , cippix score : 42 , hit score : 2

Description of EP1224179B1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

BACKGROUND OF INVENTION This invention relates to sodium-hydrogen exchanger type 1 (NHE-1) ... acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, ... temperature at 5 C/min) The X-Ray diffraction d-spacing is provided in the following Table IV

In the above combination compositions, combination methods and kits preferred glycogen ... acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, ... acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.
Description of EP1224179B1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

BACKGROUND OF INVENTION This invention relates to sodium-hydrogen exchanger type 1 (NHE-1) . . . 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, . . . temperature at 5 C/min) The X-Ray diffraction d-spacing is provided in the following Table IV

In the above combination compositions, combination methods and kits preferred glycogen . . . 5-chloro-1H-indole-2-carboxylic acid [2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.

WO200123399A1 20010405 ( US15682899P19990930 ) COMPOSES DESTINES AU TRAITEMENT D’ISCHEMIE; COMPOUNDS FOR THE TREATMENT OF ISCHEMIA - MASAMUNE, HIROKO; DENINNO, MICHAEL, PAUL; SCOTT, ROBERT, WILLIAM - PFIZER PRODUCTS INC.; MASAMUNE, HIROKO; DENINNO, MICHAEL, PAUL; SCOTT, ROBERT, WILLIAM

A3 agonists, methods of using such A3 agonists and pharmaceutical compositions containing such A3 agonists. The A3 agonists are useful for the reduction of tissue damage resulting from tissue ischemia or hypoxia.; La présente invention concerne des agonistes A3, des techniques d’utilisation de ces agonistes et des compositions pharmaceutiques contenant ces antagonistes. Les antagonistes A3 sont utiles pour réduire les dégâts tissulaires résultant d’ischémie ou d’hypoxie tissulaire.

Title: COMPOUNDS FOR THE TREATMENT OF ISCHEMIA

Description: <Desc/Clns Page number 1> COMPOUNDS FOR THE TREATMENT OF ISCHEMIA BACKGROUND OF INVENTION This invention relates to adenosine A-3 receptor agonists, pharmaceutical compositions containing . . . ischemic injury in mammals, including humans.

In addition to reducing myocardial damage and . . . function in patients with ischemic heart disease, cardioprotection would also decrease the . . . intolerant, coronary artery disease, diabetes mellitus, hypertension) that require non-cardiac surgery.

5,604,210 discloses the use of certain adenosine type compounds for the prevention or treatment of a brain edema, an intracranial hemorrhage and a cerebral infarction.

5,688,774 discloses A3 . . . uronamide groups as agents which activate the A3 receptor.

5,773,423 discloses . . . ribosides for the activation of the A3 adenosine receptor.

1994,37,636-646, "Structure-Activity Relationships of N6-<RTI ... ID=0.0>biochemical probes for A3 receptors.

In particular, 3’-p-amino compounds were found to have no activity.

The recombinant adenosine receptors can be utilized in an assay to identify and evaluate entities that bind to or enhance binding to adenosine receptors.

g., human) having a disease or condition mediated by an A3 adenosine receptor by administering a therapeutically effective . . . said compound or of said prodrug to the mammal.

g., a female or male human) in need of such treatment a therapeutically effective . . . salt of said compound or of said prodrug.

Another aspect of this invention is directed to . . . oral administration to a mammal in need of such treatment of a therapeutically effective amount of a . . . salt of said compound or of said prodrug.

Another aspect of this invention is directed to methods for treating cardiovascular diseases comprising administering to a mammal (e.

Another aspect of this invention is directed to methods for treating renal diseases comprising administering to a mammal (e.

Another aspect of this invention is directed to . . . for treating septic shock and other inflammatory diseases (septicemia, endotoxemia) comprising administering to a mammal (e.

Another aspect of this invention is directed to methods for treating cerebro ischemic disorders comprising administering to a mammal (e.

Another aspect of this invention is directed to . . . for treating cerebrovascular diseases comprising administering to a mammal (e.

This invention is also directed to a kit for use by a consumer having or at risk of having a disease or condition resulting from, for example, . . . which may be ameliorated by an A3 agonist.

g., metformin) or other adenosine A3 receptor agonists.

Other cardiovascular agents include angiotensin 11 (All) receptor antagonists, C5a inhibitors, soluble complement receptor type 1 (sCR1) or analogues, partial fatty acid . . . nucleoside inhibitors, anti-apoptotic agents (e.

g., caspase inhibitors), monophosphoryl lipid A . . . sensitizers), endothelin converting enzyme (ECE) inhibitors, endothelin ETA receptor antagonists, (thrombin activated fibrinolytic . . . TAFI inhibitors and Na/Ca exchanger modulators.

In the above combination compositions, . . . methyl]. In the methods of treatment as applied to the combinations described above . . . are preferred administration routes, modes, etc.

In yet another aspect of this inventor myocardial . . . in a patient with diagnosed coronary heart disease.

The term“treatment”, “treat” or” treatment” as used herein includes preventative (e. g., prophylactic) and palliative treatment.

Another prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Typically, the Formula XXXIII compound may be . . . conversion to an acid chloride by, for example, treatment with oxalyl chloride in a non-polar aprotic . . . for about two hours to about eight hours.
The desired Formula XXXIV compound wherein X is ... from the appropriate Formula XXXV compound by treatment with periodic acid which hydrolyzes the <RTI ... and cleaves the glycol to furnish the aldehyde.

The resulting Formula LIX phthalimide is deprotected by treatment with hydrazine hydrate in a protic solvent such ... C for about one to about six hours.

The Formula LV compounds can also be prepared ... Formula LIV compounds by treatment with a boronic acid, preferably <RTI ... one to about twenty-four hours.

In combination therapy treatment, both the compounds of this invention and the other drug therapies are administered to mammals (e.

The term NHE-1 inhibitor refers to compounds ... as a therapeutic or prophylactic agent for diseases caused or aggravated by the acceleration of the sodium/proton (Na+/H+) exchange transport system.

Such inhibition is readily determined by those ... cardioprotection assays [see the in vivo assay in Klein, H.
et al., Circulation 92: 912-917 (1995); the isolated heart assay in Scholz, W.
et al., <RTI ... Research 29: 260-268 (1995); the antiarrhythmic assay in Yasutake M.
Physiol., 36: H2430-H2440 (1994); the NMR assay in Kolke et al., <Desc/Clms Page number 51> J.

The term aldose reductase inhibitor refers to ... of glucose to sorbitol catalyzed by the enzyme aldose reductase.

The activity of an aldose reductase inhibitor in a tissue can ... to lower tissue sorbitol (i.

<Desc/Clms Page number 56> An amount of ... of this invention that is effective for the activities of this invention may be used.

In general an effective dosage ... for example the ischemic damage reducing activities of combinations containing the <RTI ... and most preferably 0.1 to 15 mg/kg/day.

The compounds of the present invention <RTI ... useful as therapeutic or prophylactic agents for diseases caused or aggravated by ischemia or hypoxia, or ischemia/reperfusion for example, cardiovascular diseases [e.

diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion ... g. heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) ... coronary angioplasty (PTCA)], cerebrovascular diseases (e.

g., ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e. g., disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema.

Preferably, the compounds of this invention can ... in patients with diagnosed coronary heart disease (e.

g., age greater than 65 and two or more risk factors for coronary heart disease).

The utility of the compounds of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.

g., humans), for example, myocardial protection ... in patients with diagnosed coronary heart disease, or at risk for coronary heart disease, cardiac dysfunction or myocardial stunning is demonstrated by the activity of the compounds of this invention in ... cardioprotection assays [see the in vivo assay in Klein, H.
et al., Circulation 92: 912-917 (1995) ; the isolated heart assay in Tracey, W.
et al., "RTI . . . Research 33: 410-415 (1997); the antiarrhythmic assay in Yasutake M.

Physiol., 36: H2430-H2440 (1994); the NMR assay in Kolke et al., J.

Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these . . . levels in mammals, including humans, for the treatment of such diseases.

<Desc/Clms Page number 65> Human Adenosine A1 and A3 Receptor Assays Materials Full-length human adenosine Ai and A3 receptor cDNA’s subcloned into the eukaryotic expression . . . from The Garvan Institute, Sydney, Australia.

The A1/A3 adenosine receptor agonist N6- (4-<RTI . . . by New England Nuclear (Boston, MA, USA).

Expression of Human Adenosine A1 and A3 Receptors For stable expression studies adenosine receptor Al and A3 expression <RTI . . . transfection kit (5 Prime-3 Prime).

Receptor Membrane Preparation Cells stably expressing . . . ID=0.0>(100, ug/ml), ADA (2 U/ml), pH 7.4.

Crude cell membranes are . . . Affinity Constants (Kj) Receptor membranes are resuspended in incubation buffer . . . EDTA (1), MgCl2 (5), pH 7.4.

At the concentration of radioligand used in the . . . (10 fold < KD), IC50 = Ki. Assessment of Human Adenosine A3 Receptor Agonist Activity Adenosine A3 agonist activity is assessed by compound inhibition of isoproternol-stimulated cAMP levels.

Cardioprotection, as indicated by a reduction in . . . ID=0.0> pharmacologically using adenosine receptor agonists in isolated, <RTI . . . ischemic preconditioning (Tracey et al.

The in vivo assay tests the cardioprotection of the test compound . . . the control group which receives saline vehicle.

Cardioprotection, as indicated . . . using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied . . . Circulation 84: 350-356,1991). The in vivo assay tests whether compounds can pharmacologically induce cardioprotection, i.

The effect of the compounds, compositions and . . . in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate aminotransferase (AST), . . . damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several . . . Ektachem 500 analyzer reported by Nakano, et al.

The effect of the compounds, compositions and . . . on a reduction in the release of hepatocellular enzymes immediately following the occlusive period . . . in the perfused livers from the rats in the treatment group compared to perfused <RTI . . . placebo-treated control group.

Measurement of Human NHE-1 Inhibitory Activity Methodologies for measurement of human NHE-1 activity and inhibitor potency are based on those published by Watson et al., Am.

The potency of human NHE-1 inhibitors is . . . and HOE-642 had IC50 values for human NHE-1 of 50 liM and 0.

The assay <Desc/Clms Page number 74> . . . acid nerve extract in a final volume of 1.5 mi.

Measurement of SDH Activity Male Sprague-Dawley rats (350-400 g) are used for these experiments.

Aliquots of tissue extracts are added to an assay system which has final concentrations of . . . ID=0.0>units/ml of sorbitol dehydrogenase.
Aliquots of tissue extracts are added to the assay system, which has final concentrations of . . . fructose dehydrogenase and 0.068% Triton X-100.

SDH activity is measured by a modification of the method described by U.

Aliquots of sera or urine are added to the assay system, which has final concentrations of . . . and 0.7 units/ml of sorbitol dehydrogenase.

SDH activity was presented as milliOD340 . . . ID=0.0>(OD340 = optical density at 340 nm).

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPA Activity Assay section, below) from a series of chromatographic steps detailed below.

Fractions containing the GP activity are pooled (approximately 600 mL), and <RTI . . . A are added to obtain 0.3 mM, 0.2 mM, 0.2 mM, 0.

GP-containing fractions are pooled following identification by determining enzyme activity (described below) and visualizing the <RTI . . . Co., LTD., Tokyo, Japan) and then pooled.

Prior to use of the GP enzyme, the enzyme is converted from the inactive form as expressed . . . described in Section (A) Activation of GP below.

GP in the soluble fraction of the lysates . . . the total protein) is purified by monitoring the enzyme activity (as described in GPA Activity Assay section, below) from a series of chromatographic steps detailed below.

Activation of GP Before further chromatography, the fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . (A) Activation of GP below.

Determination of GP Enzyme Activity A) Activation of GP: Conversion of GPb to GPA Prior to the determination of GP enzyme activity, the enzyme is converted from the inactive form as expressed in E.

The fraction of inactive enzyme as expressed in Sf9 cells (designated GPb) is . . . form (designated GPA) by the following procedure.

In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed <RTI . . . ester at pH 8.0 for one hour at room temperature.

Prior to use to convert GPb to GPA, the Affi-Gel . . . 0.3 mM DTT, and 0.3mM EDTA at pH 7.8 (kinase assay buffer).

coli) or the mixture of GPA and GPb obtained from . . . Sf9 cells) is diluted 1: 10 with the kinase assay buffer then mixed with the aforementioned phosphorylase kinase enzyme immobilized on the Affi-Gel beads.

The sample is removed from the beads and the . . . conversion to GPA is estimated by determining GP enzyme activity in the presence and absence of <Desc/Clms . . . 3.3 mM AMP. The percentage of total GP enzyme activity due to GPA enzyme activity (AMP-independent) is then calculated as follows : % of total HLGPa = HLGPa activity-AMP HLGPa activity + AMP Alternately, the conversion of GPb to GPA . . . that is noted following conversion of GPb to GPA.

B) GPA Activity Assay The disease/condition treating/preventing activities described herein of the glycogen phosphor- ylase . . . effect of the compounds of this invention on the activity of the activated form of glycogen phosphorylase . . . by one of two methods; glycogen phosphorylase a activity is measured in the forward direction by . . . phosphate by the release of inorganic phosphate.

To measure the GPA enzyme activity in the forward direction, the production of . . . coupled general method of Pesce et al.
The compounds to be tested are added as <RTI ... (DMSO) prior to the addition of the enzymes. The basal rate of GPa enzyme activity in the absence of inhibitors is determined by ... of 14% DMSO and a fully-inhibited rate of GPa enzyme activity is obtained by adding 20/L of ... of the positive control test substance, caffeine.

To measure the GPa enzyme activity in the reverse direction, the conversion of <RTI ... by the general method described by Engers et al. ... enzyme mix.

The above assays carried out with a range of ... allows the determination of an IC50 value (concentration of test compound ... inhibition) for the in vitro inhibition of GPa enzyme activity by that test compound.

Topical administration may also be indicated, for ... from gastrointestinal disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of ... as age of the patient, presence of preexisting disease, as well as presence of other diseases (e. g., cardiovascular disease).

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

Advantageously, the present ... by a consumer having, or at risk of having, a disease or condition resulting from, for example, ... ameliorated by an A3 agonist.

Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination ... separate pharmaceutical compositions in kit form.

Claims: A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment a therapeutically effective amount of a compound ... salt of said compound or of said prodrug.

A pharmaceutical composition as recited in claim ... Angiotensin II (All) receptor antagonists, C5a inhibitors, soluble complement receptor type 1 (sCR1) or analogues, partial fatty acid ... nucleoside inhibitors, anti-apoptotic agents (e. g., caspase inhibitors), monophosphoryl lipid A ... sensitizers), endothelin coverting enzyme (ECE) inhibitors, endothelin ET A receptor antagonists, TAFI inhibitors, or a Na/Ca exchanger modulators. 41.

A method of reducing tissue damage resulting from ... administering to a mammal in need of such treatment an amount of a first compound, said first ... second compounds result in a therapeutic effect.

A method of reducing tissue damage resulting from ... Angiotensin II (All) receptor antagonists, C5a inhibitors, soluble complement receptor type 1 (sCR1) or analogues, partial fatty acid ... nucleoside inhibitors, anti-apoptotic agents (e. g., caspase inhibitors), monophosphoryl lipid A ... sensitizers), endothelin coverting enzyme (ECE) inhibitors, endothelin ET A receptor antagonists, TAFI inhibitors, or a Na/Ca exchanger modulators.
Description of WO200123399A1 contains 5-chloro-1H-indole-2-carboxylic acid[(1S)-benzyl-2-((3S,4S)-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3-hydroxyimino- ... acid [(1 S)-(2-fluoro-benzyl)-2- (4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3-hydroxy-azetidin-1- ... H-indole-2-carboxylic acid [(1 S)-benzyl-2- (4-hydroxyimino- piperidin-1-yl)-2-oxo-ethyl]-amide.

Description of WO200123399A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxypyrrolidin-1-yl)-2-oxo-ethyl]-amide

5-chloro-1 H-indole-2-carboxylic acid [(1 S)-benzyl-2- (3-hydroxyimino- ... H-indole-2-carboxylic acid [2- (3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3, 4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1 H-indole-2-carboxylic acid [2- (1, 1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, ... H-indole-2-carboxylic acid [(1 S)-benzyl-2- (4-hydroxyimino- piperidin-1-yl)-2-oxo-ethyl]-amide.


NPY antagonists, methods of using such NPY antagonists and pharmaceutical compositions containing such NPY antagonists. The NPY antagonists are useful for the treatment of NPY mediated disease/conditions including obesity.

Title: Compounds for the treatment of obesity

Abstract: The NPY antagonists are useful for the treatment of NPY mediated disease/conditions including obesity

Description: BACKGROUND OF INVENTION [0002] This invention ... to treat, for example, obesity, feeding disorders, as well as other NPY mediated diseases/conditions in mammals, including humans, dogs, cats and horses.

At least 6 NPY receptor subclasses have been identified and cloned to ... and NPY-5, thought to be the most important receptor subtypes modulating food intake and energy expenditure.

The reports clearly indicate that compounds that inhibit the activity of this protein will reduce hypertension and appetite in animals.

[0006] Hence, agents capable of blocking NPY binding at these receptor subtype(s) should have utility in a number of feeding disorders including obesity, anorexia nervosa, bulimia nervosa; obesity-related disorders including but not limited to insulin resistance, ... and hypertension, as well other indications for treatment where blockade of NPY activity is beneficial.
5,576,337 report physiological disorders related to any excess of neuropeptide Y.

[0008] In addition, a variety of publications . . . derivatives for various utilities including the treatment of obesity. WO 99/01128 discloses certain NPY5 receptor mediators useful for treating feeding disorders such as obesity and bulimia as well as certain cardiovascular diseases such as essential hypertension.

4,440,774 and 4,853,383 disclose certain . . . their use as beta-adrenergic blockers for the treatment of, for example, hypertension.

[0035] Another aspect of this invention is a . . . (e.g., human, dogs, cats and horses) having a disease or condition mediated by NPY by administering a . . . prodrug to the mammal. It is preferred that the receptor is the NPY-5 receptor.

[0037] Another aspect of this invention is . . . (e.g., a female or male human) in need of such treatment a therapeutically effective amount of a compound . . . salt of said compound or of said prodrug.

[0038] Another aspect of this invention is directed to a method for treating eating and metabolic disorders such as bulimia and anorexia comprising . . . salt of said compound or of said prodrug.

[0038] Another aspect of this invention is directed to a method for treating diseases related to the heart, blood vessels or renal . . . salt of said compound or of said prodrug.

[0039] Another aspect of this invention is directed to a method for treating peripheral vascular disease comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0039] Another aspect of this invention is related to increased sympathetic nerve activity for example, during or after coronary artery . . . salt of said compound or of said prodrug.

[0040] Another aspect of this invention is directed to a method for treating diseases and diseases related to the central nervous system comprising . . . salt of said compound or of said prodrug.

[0040] Another aspect of this invention is directed to a method for treating Alzheimer’s disease comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0042] Another aspect of this invention is directed to a method for treating attention deficit disorder comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0043] Another aspect of this invention is directed to a method for treating sleep disorders comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0044] Another aspect of this invention is directed to a method for treating seasonal affective disorder comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0045] Another aspect of this invention is directed to a method for treating disorders related to disruption of circadian rhythms . . . salt of said compound or of said prodrug.

[0046] Another aspect of this invention is directed to a method for treating diseases related to abnormal gastrointestinal motility . . . salt of said compound or of said prodrug.

[0048] Another aspect of this invention is directed to a method for treating Crohn’s disease comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0048] Another aspect of this invention is directed to a method for treating inflammatory bowel disease comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

[0049] Another aspect of this invention is directed to a method for treating reproductive disorders comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.
Another aspect of this invention is directed to a method for treating conditions or disorders associated with inflammation comprising salt of said compound or of said prodrug.

Another aspect of this invention is directed to a method for treating respiratory diseases comprising administering to a mammal (e.g., a . . . salt of said compound or of said prodrug.

Another aspect of this invention is directed to a method for treating diseases related to abnormal hormone release comprising salt of said compound or of said prodrug.

In addition to the "direct" effect of the . . . of this invention on the NPY5 subtype there are diseases/conditions that will benefit from the weight . . . hypertension, hyperlipidemia, cardiovascular disease, gall stones, certain cancers, sleep apnea, etc.

This invention is also directed to pharmaceutical compositions for the treatment of obesity which comprise an obesity treating . . . acceptable vehicle, diluent or carrier.

The following are anorectic and/or . . . bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist, a melanin concentrating hormone . . . to as "leptin"), a leptin analog, a leptin receptor agonist, a galanin antagonist or a GI lipase inhibitor or decreaser (such as orlistat).

Other anorectic agents include bombesin agonists, . . . or analogs thereof, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the glyagon-like peptide-1 receptor and ciliary neurotrophic factors such as Axokine.

Another aspect of this invention is a method for treating cardiovascular disease comprising administering to a mammal (e.g., a female or male human) . . . clonidine, prazosin or adenosine A3 receptor agonists.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

The expression "prodrug" refers to . . . being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Furthermore, it will be understood by . . . therapies to treat the conditions and diseases described above.

Thus, the compounds, prodrugs and . . . with other pharmaceutical agents for the treatment of the disease/conditions described herein.

For example, they may be used in combination with . . . hypertension, hyperlipidemia, cardiovascular disease, anxiety, depression, or psychosis. In combination therapy treatment, both the compounds, prodrugs and . . . dogs, cats, horses) by conventional methods.

Compounds which are beta3-receptor agonists have hypoglycemic and/or anti-diabetic activity. Such activity is readily determined by those skilled in the . . . Patent Application, Publication No.

WO 93/16189 (the disclosure of which is . . . discloses the use of selective beta3 receptor agonists in combination with compounds which modify eating behavior for the treatment of obesity.

It is well known to one of ordinary skill in the . . . for a useful therapeutic agent in the treatment of, for example, obesity and related conditions.

Any other NPY receptor antagonists may be used as the second component . . . aspect of this invention. The term NPY receptor antagonist refers to compounds which interact with NPY receptors and inhibit the activity of neuropeptide Y at those receptors and thus are useful in treating disorders associated with neuropeptide Y, such as feeding disorders, including obesity.
In addition, the compounds described and referenced below are NPY receptor antagonists; however, other NPY receptor antagonists will also be known to those skilled in the art.

WO 99/07703 (the disclosure of which is hereby made the disclosure of which is hereby . . . (3,2-d) pyrimidines as neuropeptide Y receptor antagonists.

[0600] For the treatment of Alzheimer's disease, any cholinomimetic drug, such as Donepezil, may . . . aspect of this invention. [0601] For the treatment of anxiety, any antianxiolytic drug, such as a . . . aspect of this invention. [0602] For the treatment of depression, any tricyclic antidepressant such . . . reuptake inhibitor (SSRI's), such as ZOLOFT.RTM.

[0603] For the treatment of psychosis, any typical or atypical . . . aspect of this invention. [0604] For the treatment of for example, diabetes related diseases/conditions any aldose reductase inhibitor may be . . . in the combination aspect of this invention.

The term aldose reductase inhibitor refers to a . . . of glucose to sorbitol catalyzed by the enzyme aldose reductase.

[0605] For the treatment of for example, diabetes related diseases/conditions any glycogen phosphorylase inhibitor . . . in the combination aspect of this invention.

[0606] For the treatment of for example, diabetes related diseases/conditions any sorbitol dehydrogenase inhibitor . . . in the combination aspect of this invention.

The term sorbitol dehydrogenase inhibitor refers to a compound which inhibits the enzyme sorbitol dehydrogenase, which catalyzes the oxidation of sorbitol to fructose.

[0608] Neuropeptide Y (NPY) and related peptides . . . neurons and have a broad array of biological activity mediated through the NPY receptors that exist in a variety of tissues.

Thus NPY antagonists are useful in the treatment of the disease/conditions described above.

Compounds of formula I can additionally be used for the treatment of obese household pets, for example companion animals such as dogs and cats.

[0610] The utility of the compounds of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g. humans) for example, obesity in patients or to induce weight loss or for anorectic activity is demonstrated by the activity of the compounds of this invention in . . . Such assays also provide a means whereby the activities of the compounds of this invention can be compared with the activities of other known compounds.

The results of these comparisons are useful for . . . levels in mammals, including humans, for the treatment of such diseases. Assay for NPY-5 Binding [0611] [125I] peptide YY . . . 5 receptors are harvested at 48 hours. h NPY-Y5 receptor cDNA is cloned using standard cloning techniques.


This assay has been widely used for many GPCR's and offers . . . and Lawler, 1995). GTPgamma35S binding activity is measured using a modification of a previously described method (Wieland and Jacobs, 1994).

Maniatis; Cold Spring Habor Laboratory Press; Cold Spring Habor, N.Y., 1989) receptor and the G-protein subunits alphao, beta1, . . . heat-inactivated fetal bovine serum at 27°

On the day of the assay, thawed membrane homogenates are resuspended in assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM . . . tubes at a concentration of 30 mg/reaction tube.

On the day of the experiment, animals that are . . . the previous night are weighed and assigned to treatment groups.
Assignments are made using a quasi-random method utilizing the body weights to assure that the treatment groups have similar average body weight.

Two hours after test compound treatment, each animal is weighed and placed in a Metabolic Cage.

On the day of the experiment, animals are weighed and assigned to treatment groups.

Assignments are made using a quasi-random method utilizing the body weights to assure that the treatment groups have similar average body weight.

In these studies, animals are administered, on subsequent nights, the same treatment (test compound or 0.5% MC) they had received the first night.

Topical administration may also be indicated, for ... where the patient is suffering from swallowing disorders or whenever the medication is best applied to ... organ as determined by the attending physician.

Thus, because of patient to patient variability, ... may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of ... as age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular disease).

[0649] An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention may be used.

In any event, the composition or formulation to ... invention in an amount effective to treat the disease/condition of the subject being treated.

[0658] Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination ... separate pharmaceutical compositions in kit form.

Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper drug level in the animal’s body.

Claims: A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound ... salt of said compound or of said prodrug.

A pharmaceutical composition for the treatment of obesity which comprises an obesity treating ... acceptable carrier, vehicle or diluent.

A method of treating obesity comprising administering to a mammal in need of such treatment an amount of a first compound, said first ... second compounds result in a therapeutic effect.

fulltext score: 44, cippix score: 286, hit score: 2

Description of US2001039277A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide

[0505] 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide.
The present invention provides novel processes for preparing 3(S)- (5-chloro-1H-indole-2-carbonyl)-amino -2(R)-hydroxy-4-phenyl-butyric acid. Also provided are novel intermediates used in those processes. Further, the 3(S)- (5-chloro-1H-indole-2-carbonyl)-amino -2(R)-hydroxy-4-phenyl-butyric acid prepared by the novel processes can be further reacted to yield known indole 2-carboxamides and derivatives thereof possessing glycogen phosphorylase inhibitory activity, which are useful in the treatment of mammals, especially human beings, having glycogen phosphorylase dependent diseases or conditions.

Abstract: Further, the 3(S)- . . . possessing glycogen phosphorylase inhibitory activity, which are useful in the treatment of mammals, especially human beings, having glycogen phosphorylase dependent diseases or conditions.

Description: FIELD OF THE INVENTION [0001] The . . . which possess glycogen phosphorylase inhibitory activity.

These glycogen phosphorylase inhibitors are useful in the treatment of mammals, especially human beings, having glycogen phosphorylase dependent diseases or conditions including hypercholesterolemia, . . . diabetes and myocardial ischemia.

BACKGROUND OF THE INVENTION [0002] . . . of treating glycogen phosphorylase dependent diseases or conditions by administering such compounds or derivatives.

fulltext score : 12 , cippix score : 31 , hit score : 2

24. The process as defined in claim 23 wherein said substituted N-(indole-2-carbonyl)-amide or ... acid [(1S)-(2-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, ... acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.

Claims of EP1061074A1 contains 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(cis-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide.

24. The process as defined in claim 23 wherein said substituted N-(indole-2-carbonyl)-amide or ... acid [(1S)-benzyl-2-((3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S, 4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, ... acid [(1S)-benzyl-2-(4-hydroxyimino-piperidin-1-yl)-2-oxo-ethyl]-amide.

WO2008127291A2

20081023 ( US85059406P20061010 )


X-ray fluorescence (XRF) spectrometry has been used for detecting binding events and measuring binding selectivities between chemicals and receptors. XRF may also be used for estimating the therapeutic index of a chemical, for estimating the binding selectivity of a chemical versus chemical analogs, for measuring post-translational modifications of proteins, and for drug manufacturing.; Selon l’invention, la spectrométrie à fluorescence de rayons X (SFX) est mise en uvre pour détecter des événements de liaison et mesurer des sélectivités de liaison entre des produits chimiques et des récepteurs. La SFX peut également être mise en uvre pour estimer l’indice thérapeutique d’un produit chimique, pour estimer la sélectivité de liaison d’un produit chimique par rapport à des analogues chimiques, pour mesurer des modifications post-translationnelles de protéines et pour fabriquer des médicaments.

Abstract: X-ray fluorescence (XRF) spectrometry has been used ... binding selectivities between chemicals and receptors.

Description: Combinatorial arrays and high-throughput ... the screening techniques can be used to rapidly assay many biological materials.

An effective binding between the protein, one ... "receptors", and the material that binds to the receptor, referred to herein as "chemical", generally ... that many weak bonds form between the protein receptor and the chemical.

After a receptor array is prepared, it is screened to determine ... have the desirable property or properties.

entitled "Large Scale Photolithographic Solid Phase Synthesis of Polypeptides and Receptor Binding Screening Thereof, which issued ... reference, describes one such screening method.

Small structural changes that accompany even a conformational change of a receptor have been known to affect the binding affinity of the receptor.
Since binding affinities derived using tagged ... be evaluated using the untagged chemical or receptor and not with a tagged surrogate.

drug development, generally involves determining ... that can dissolve into the blood stream) and a receptor (generally a biological material such as an enzyme or non-enzyme protein, DNA, RNA, human cell, plant cell, ... many stages of the drug development process. The receptor may also be a microorganism (e.g.

The drug development process typically involves ... binding affinity and kinetics of binding of a receptor to a chemical to form a complex or the kinetics of release of a bound chemical from a complex.

The binding affinity is defined herein as the ... equilibrium expression: m (chemical) + receptor * chemical-receptor complex The binding affinity, Ka, is defined by equation (1) below. Ka = [chemical-receptor complex]/[receptor][chemical]<m> (1) In equation (1), [chemical-receptor complex] is the concentration in moles per liter of the chemical-receptor complex, [receptor] is the concentration in moles per liter of the receptor, 'm' is the number of molecules of chemical that bind to each molecule of receptor, and [chemical] is the concentration in moles per liter of the chemical.

has a high binding affinity, with a particular receptor.


entitled "Pharmacophore Recombination for the ... identifying a drug lead compound by contacting target biological molecules with cross-linked binding fragments.

entitled "Apparatus for Screening Compound ... and rank members of a library that bind to a target receptor.

The magnitude of a detectable x-ray fluorescence ... whether a binding event between a chemical and a receptor has occurred, and can provide information ... the extent of binding between the chemical and receptor.

The method involves modifying a mixture of ... pharmaceutical chemicals by adding at least one receptor to the mixture.

Effective drugs are selective drugs; they bind to a specific desired receptor, bypassing other receptors, to produce a desired therapeutic effect. This way, they target a specific disease in the body with minimal side effects; ... efficacy without undesirable side effects.

Estimating the therapeutic index of a chemical ... the binding affinity of a chemical to a first receptor, and measuring the binding affinity of the same chemical to a second receptor.

After measuring these binding affinities, the ... of the chemical divided by the amount of first receptor versus the binding affinity of the chemical divided by the amount of the second receptor is determined.

The method includes establishing a baseline X-ray ... for a heavy element in a portion of a first receptor and in a portion of at least one more receptor that may be the same or different from the first receptor, the heavy element being present in a chemical ... to bind to them to form a first chemical-receptor complex and at least one more chemical-receptor complex; measuring the x-ray fluorescence signals due to the heavy element in the first chemical-receptor complex and in the at least one more chemical-receptor complex; subtracting the baseline x-ray fluorescence signal of the first receptor from the measured x-ray fluorescence signal of the of the first chemical-receptor complex to obtain a first net x-ray fluorescence ... ray fluorescence signal of the at least one more receptor from the measured x-ray fluorescence signal of the of the at least one more chemical-receptor complex to obtain at least one more net x-ray ... net x-ray fluorescence signal by the amount of receptor in the portion of the first receptor to obtain a first quotient, dividing the at ... net x-ray fluorescence signal by the amount of receptor in the portion of the at least one more receptor to obtain at least one more quotient, and then ... first quotient to the at least one more quotient.
The method includes establishing a baseline x-ray heavy element in a first portion of a first receptor and in a first portion of a second receptor, the first heavy element being present in a heavy element in a second portion of the first receptor and in a second portion of a second receptor, the second heavy element being present in an analog to bind to them to form a first chemical-receptor complex and a second chemical-receptor complex; measuring the x-ray fluorescence signal heavy element present in the first chemical-receptor complex and in the second chemical-receptor complex; exposing the second portions of the analog to bind to them to form a first analog-receptor complex and a second analog-receptor complex; measuring the x-ray fluorescence signal heavy element present in the first analog-receptor complex and in the second analog-receptor complex; calculating the net x-ray fluorescence to the first heavy element in the first chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the first receptor from the measured x-ray fluorescence signal of the of the first chemical-receptor complex; calculating the net x-ray fluorescence heavy element present in the second chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the second receptor from the measured x-ray fluorescence signal of the second chemical-receptor complex; calculating the net x-ray fluorescence heavy element present in the first analog-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the first receptor from the measured x-ray fluorescence signal of the second chemical-receptor complex; estimating the selectivity of the net x-ray fluorescence of the first chemical-receptor complex by the amount of receptor in the first portion of the first receptor to obtain a first quotient, dividing the net x-ray fluorescence of the second chemical-receptor complex by the amount of receptor in the first portion of the second receptor to obtain a second quotient; estimating the net x-ray fluorescence of the first analog-receptor complex by the amount of receptor in the second portion of the first receptor to obtain a third quotient, dividing the net x-ray fluorescence of the second analog-receptor complex by the amount of receptor in the second portion of the second receptor to obtain a fourth quotient; and comparing first to the third quotient to the fourth quotient.

The method includes establishing a baseline X-ray heavy element in a portion of a first receptor and at least one more chemical-receptor complex and at least one more chemical-receptor complex; measuring the x-ray fluorescence signals due to the heavy element in the first chemical-receptor complex and at least one more chemical-receptor complex; subtracting the baseline x-ray fluorescence signal of the first receptor from the measured x-ray fluorescence signal of the of the first chemical-receptor complex to obtain a first net x-ray fluorescence fluorescence signal of the at least one more receptor from the measured x-ray fluorescence signal of the of the at least one more chemical-receptor complex to obtain at least one more net x-ray net x-ray fluorescence signal by the amount of receptor in the portion of the first receptor to obtain a first quotient, dividing the at net x-ray fluorescence signal by the amount of receptor in the portion of the at least one more receptor to obtain at least one more quotient, and then quotient are different by at least one percent.
The method includes establishing a baseline X-ray heavy element in a first portion of a first receptor and in a first portion of a second receptor, the first heavy element being present in a second heavy element in a second portion of the first receptor and in a second portion of a second receptor, the second heavy element being present in an amount to bind to them to form a first chemical-receptor complex and a second chemical-receptor complex; measuring the x-ray fluorescence signal heavy element present in the first chemical-receptor complex and in the second chemical-receptor complex; exposing the second portions of the... analog to bind to them to form a first analog-receptor complex and a second analog-receptor complex; measuring the x-ray fluorescence signal second heavy element present in the first analog-receptor complex and in the second analog-receptor complex; calculating the net x-ray fluorescence to the first heavy element in the first chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the first receptor from the measured x-ray fluorescence signal of the first chemical-receptor complex; calculating the net x-ray fluorescence heavy element present in the second chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the second receptor from the measured x-ray fluorescence signal of the second chemical-receptor complex; calculating the net x-ray fluorescence... to the second heavy element in the first analog-receptor complex by subtracting the baseline x-ray fluorescence signal of the second portion of the second receptor from the measured x-ray fluorescence signal of the second chemical-receptor complex; estimating the selectivity of the... net x-ray fluorescence of the first chemical-receptor complex by the amount of receptor in the first portion of the first receptor to obtain a first quotient, dividing the net x-ray fluorescence of the second chemical-receptor complex by the amount of receptor in the first portion of the second receptor to obtain a second quotient; estimating the... the net x-ray fluorescence of the first analog-receptor complex by the amount of receptor in the second portion of the first receptor to obtain a third quotient, dividing the net x-ray fluorescence of the second analog-receptor complex by the amount of receptor in the second portion of the second receptor to obtain a fourth quotient; and comparing... one in sufficient quantity for use as a drug.

The invention also includes a method for... solution to bind to a portion of at least one receptor versus the ability of that chemical in a second... to a separate portion of the same at least one receptor.

The method includes establishing a baseline X-ray for a heavy element in a first portion of a receptor and for the heavy element in a separate portion of the receptor, the heavy element being present in a chemical that is being tested for binding to the receptor; exposing the first portion of the receptor to a first solution that includes the chemical, and allowing the chemical to bind to the receptor to form a first chemical-receptor complex; exposing the separate portion of the receptor to a second solution also includes the chemical, and allowing the chemical to bind to the receptor to form a second chemical-receptor complex; measuring the x-ray fluorescence signals due to the heavy element in the first chemical-receptor complex and in the second chemical-receptor complex; calculating the net x-ray fluorescence... due to the heavy element in the first chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of receptor from the measured x-ray fluorescence signal of the first chemical-receptor complex; calculating the net x-ray fluorescence... due to the heavy element in the second chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the separate portion of receptor from the measured x-ray fluorescence signal of the second chemical-receptor complex; and estimating the binding selectivity... x-ray fluorescence signal of the first chemical-receptor complex by the amount of receptor in the first portion of the receptor to obtain a first quotient, dividing the net x-ray fluorescence of the second chemical-receptor complex by the amount of receptor in the separate portion of the receptor to obtain a second quotient, and then comparing the first quotient to the second quotient.
The method includes providing a sample from a . . . a first portion and a second portion of a first receptor and a first portion and a second portion of a second receptor; establishing a baseline X-ray fluorescence . . . heavy element in the first portion of the first receptor and in the first portion of the second receptor, the first heavy element being present in a . . . heavy element in the second portion of the first receptor and in the second portion of the second receptor, the second heavy element being present in a . . . exposing the first portion of the first receptor and the first portion of the second receptor to the first drug and allowing the drug to bind to the first receptor to form a first drug-receptor complex, and to bind to the second receptor to form a second drug-receptor complex; measuring the x-ray fluorescence signal . . . first heavy element present in the first drug-receptor complex and in the second drug-receptor complex; exposing the second portion of the first receptor and the second portion of the second receptor to the second drug and allowing the second drug to bind to the first receptor to form a third drug-receptor complex, and to bind to the second receptor to form a fourth drug-receptor complex; measuring the x-ray fluorescence signal . . . second heavy element present in the third drug-receptor complex and in the fourth drug-receptor complex; calculating a first net x-ray . . . first heavy element present in the first drug-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the first receptor from the measured x-ray fluorescence signal of the of the first drug-receptor complex; calculating a second net x-ray . . . first heavy element present in the second drug-receptor complex by subtracting the baseline x-ray fluorescence signal of the first portion of the second receptor from the measured x-ray fluorescence signal of the fourth drug-receptor complex; calculating binding quotients for the . . . net x-ray fluorescence signal by the amount of receptor in the first portion of the first receptor to obtain a first quotient, dividing the second net x-ray fluorescence signal by the amount of receptor in the first portion of the second receptor to obtain a second quotient; calculating binding . . . net x-ray fluorescence signal by the amount of receptor in the second portion of the first receptor to obtain a third quotient, dividing the fourth net x-ray fluorescence signal by the amount of receptor in the second portion of the second receptor to obtain a fourth quotient; and comparing the . . . of the first drug versus the second drug.

The method involves depositing a portion of a receptor on a substrate; establishing a baseline X-ray . . . signal for a heavy element in the portion of the receptor, the heavy element being present in a chemical being testing for binding to the receptor, exposing the receptor to a solution comprising the chemical at a first . . . and allowing the chemical to bind to the receptor to form a chemical-receptor complex; measuring the x-ray fluorescence signal due to the heavy element in the chemical-receptor complex using excitation photons having an . . . signal due to the heavy element in the chemical-receptor complex by subtracting the baseline x-ray fluorescence signal of the portion of receptor from the measured x-ray fluorescence signal of the chemical-receptor complex, and estimating the binding affinity of the chemical for the receptor by dividing the net x-ray fluorescence signal of the chemical-receptor complex by the amount of the receptor in the portion of the receptor.

Electrospray deposition of matrix (DHB) and analyte (Substance P or reserpine) on a MALDI target plate of varying spray times allowed us to control the thickness of the sample.

Non-porous silicon targets have been used with infrared lasers for . . . interference from low mass background ions.

In this study, we demonstrate the benefits of using untreated silicon targets for matrix-assisted laser desorption ionization (MALDI).

The stainless steel target gave small analyte peaks only at high laser . . . due to ablation of material on the metal target.

It was difficult to obtain signal from the stainless steel target, but highly reproducible mass spectra could be obtained for non-porous silicon substrate.

The silicon target required somewhat higher threshold energy compared to the metal target, but showed somewhat better signal-to-noise . . . small molecule as well as high molecule analyses.

Different target materials and surface imaging techniques are being used to explore ion formation from silicon targets. "Matrix-free Laser Desorption Ionization . . . as one of the key methods for proteomic analysis.
Conventional dried droplet sample preparation was either directly on the stainless steel MALDI target or on the sublayer coated MALDI target.

Special attention was paid to the flatness of the target and its proper electrical ground connection.

Using a cryostat, tissue was sectioned (20μm) and thaw-mounted onto gold-coated MALDI target plates.

The buffer should also preferably be free of at . . . where that chemical element is present in the receptor.

We confirmed that the amount of avidin in each . . . was identical using bicinchoninic acid protein assay kit (Pierce).


X-rays that impinge on the sample may be . . . directly, or indirectly by the excitation of a target by x-rays.

Chemicals which may be used with the present . . . diozone; dinor-n(omega)-hydroxy-l-arginine; disordered solvent; d-isovaline; dcka, . . . L-Tyrosine; L-Valine; Vitamin E; and Vitamin K3.

Proteins that are especially preferable to use . . . Cellobiohydrolase I; 1,4-dihydropyridine Receptor on alphal subunit of L-type voltage sensitive . . . 5'-Fluoro-5'-Deoxyadenosine Synthase; 5-HT-1A Receptor; 5-HT-1B Receptor; 5-HT-1D Receptor; 5-HT-2A Receptor; 5-HT-3 Receptor; 5HT4 receptor; 5-hydroxytryptamine 1E receptor; 5-hydroxytryptamine 1F receptor; 5-hydroxytryptamine 2C receptor; 5-hydroxytryptamine 7 receptor; 5-Methylyctetrahydrofolate S-Homocysteine; . . . Activated Cdc42 Kinase 1; Activator Of; Activin receptor; Activin Receptor Type II; Activa-Orf6 Monoxygenase; . . . Phosphoribosyltransferase 2; Anthrax Toxin Receptor 2; Anti IgE antibody VH domain chain 1; Anti-Platelet Protein; Anti-Sigma F Factor . . . Aspartate Dehydrogenase; Aspartate Transcarbamoylase; . . . Clearance Receptor; Atrial natriuretic peptide receptor A; Atrial Natriuretic Peptide Receptor A; Atrolysin C; Augmenter Of Liver . . . Basic Phospholipase A2; Bba1; Bba5; B-cell receptor; Benzoate 1,2-Dioxygenase Reductase; Benzodiazepine Receptor; Benzoylformate Decarboxylase; Benzyl Alcohol Dehydrogenase; Beta 1 adrenergic receptor; Beta 1.4 Galactosyltransferase; Beta 2 adrenergic receptor; beta chain (FSH); Beta Crystallin B1; Beta Lactamase; Beta platelet-derived growth factor receptor precursor; Beta Trypsin; Beta-(1,3)-glucan . . . Beta3 Alcohol Dehydrogenase; Beta-adrenergic receptor kinase 1; Beta-adrenergic receptor kinase 2; Beta-Agarase A; Beta-Alanine Synthase; . . . Bifunctional Rela/Spot; Bikunin; Bile Acid Receptor; Bile salt export pump; Bile-Salt Activated . . . Dehydrogenase; C Protein Alpha- Antigen; C.
Claims: WHAT IS CLAIMED IS: 1. A method for estimating ... chemical having at least one heavy element to a receptor, comprising: establishing a baseline X-ray fluorescence signal for a heavy element in the first receptor, the heavy element being present in a chemical to be tested for binding to the receptors; exposing the receptor to the chemical and allowing the chemical to bind to them to form a chemical-receptor complex; measuring the x-ray fluorescence signals due to the heavy element in the chemical-receptor complex; subtracting the baseline x-ray fluorescence signal of the receptor from the measured x-ray fluorescence signal of the of the chemical-receptor complex to obtain a net x-ray fluorescence signal; estimating the affinity of the chemical for the receptor by dividing the net x-ray fluorescence signal by the amount of receptor in the portion of the receptor to obtain a quotient of the chemical to the receptor.

2. The method of claim 1, wherein the receptor-chemical complex is deposited on a substrate ... microns.

3. The method of claim 1, wherein the receptor-protein complex is deposited on a substrate ... microns.

4. The method of claim 1, wherein the receptor-chemical complex is deposited on a substrate ... silicon, aluminum, iron, cobalt, and gold.

The method of claim 1, wherein the cross section ... beam is between 25% and 250% of the area of the receptor-chemical complex.

9. The method of claim 1, wherein the protein-receptor complex is exposed to a solution prior to ... anions.

10. The method of claim 1, wherein the receptor-chemical complex is exposed to a solution prior to ... cation.

11. The method of claim 1, wherein the receptor-chemical complex is exposed to a solution prior to ... microns.

12. The method of claim 1, wherein the receptor-chemical complex is purified using gel ... 13. The method of claim 12, wherein the receptor-chemical complex is purified using a ... step.

14. The method of claim 1, wherein the receptor-chemical complex is exposed to a solution prior to ... the solution comprising a matrix modifier.

The method of claim 1, wherein the receptor comprises at least one of the receptors selected from the list of 1, 3, 4, 6, Tetrachloro-1 ... Cellobiohydrolase I; 1, 4-dihydropyridine Receptor on alphasubunit of L-type voltage sensitive ... 5'-Fluoro-5'-Deoxyadenosine Synthase; 5-HT-1A Receptor; 5-HT-1 B Receptor; 5-HT-1 D Receptor; 5-HT-2A Receptor; 5-HT-3 Receptor; 5HT4 receptor; 5'-hydroxytryptamine 1 E receptor; 5'-hydroxytryptamine 1 F receptor; 5'-hydroxytryptamine 2C receptor; 5'-hydroxytryptamine 7 receptor; 5-Methyltetrahydrofolate S-Homocysteine; ... Activated Cdc42 Kinase 1; Activator Of; Activin receptor; Activin Receptor Type II; Actv-a-Orf6 Monooxygenase; Acetylgl; Acylamino-Acid-Releasing Enzyme; Acyl-Coa Dehydrogenase; Acyl-CoA dehydrogenase ... TaqI; Adenosine 2B receptor; Adenosine A1 receptor; Adenosine A3 receptor; Adenosine Deaminase; Adenosine Kinase; ... Lyase; AlgqI; Algq2; 170 ALK tyrosine kinase receptor; Alkaline Phosphatase; Alkaline Phosphatase; ... Ext; Alpha-1 A Adrenergic Receptor; Alphal-Antitrypsin; Alpha-1-Antitrypsin; Alpha-I B adrenergic receptor; Alpha-II adrenergic receptor; Alpha-1-Purothionin; Alpha-2,3/8-Sialyltransferase; Alpha-2A Adrenergic Receptor; 180 Alpha-2B adrenergic receptor; Alpha-2C adrenergic receptor; Alpha-2-Macroglobulin; Alpha-2U-Globulin; ... Ribonucleotide-Triphosphate Reductase; Androgen Receptor; Angiogenin; Angiotatin; Angiotensin Converting Enzyme; Angiotensin-converting enzyme (ACE); Annexin A1; Annexin III; Annexin V; ... 215 Phosphoribosyltransferase 2; Anthrax Toxin Receptor 2; Anti IgE antibody VH domain chain 1; Anti ... 85-C; Anti-H; Anti-Muellerian hormone type II receptor; Anti-Platelet Protein; Anti-Sigma F Factor ... Aspartate Dehydrogenase; Aspartate Receptor; Aspartate Transcarbamoylase; ... Clearance Receptor; Atrial natriuretic peptide receptor A; Atrial Natriuretic Peptide Receptor A; Atr olysin C; Augm enter Of Liver ... Basic Phospholipase A2; Bba1; Bba5; B-cell receptor; Benzoate 1,2-Dioxigenase Reductase; Benzodiazepine Receptor; Benzoylformate Decarboxylase; Benzyl Alcohol Dehydrogenase; Beta 1 adrenergic receptor; 270 Beta 1, 4 Galactosyltransferase; Beta 2 adrenergic receptor; beta chain (FSH); Beta Crystallin B1; Beta Lac tamase; Beta platelet-derived growth factor receptor precursor; Beta Trypsin; Beta-(1,3)-glucan ... Bet a3 Alcohol Dehydrogenase; Beta-adrenergic receptor kinase 1; Beta-adrenergic receptor kinase 2; Beta-Agarase A; Beta-Alanine Synthase; ... Bifunctional Rela/Spot; Bikunin; Bile Acid Receptor; Bile salt export pump; Bile- Salt Activated ... Dehydrogenase; C Protein Alpha-Antigen; C.
pasteurianum Hydrogenase I; C-1027 Apoprotein; C1 ... 4; Calcitonin; Calcitonin Analogue; Calcitonin receptor; Calcium/Calmodulin-Dependent 3',5'-Cycli; ... Phosphodiesterase Pde4D2; Cannabinoid receptor 2; Cannabinoid Receptors; Capsid Protein C; Capsid 345 Protein P40; ... Chea; Chemotaxis Protein Chey; Chemotaxis Receptor Methyltransferase Cher; Chimera Of Glutathione ... Cho Reductase; Cholecystokinin type A receptor; Cholera Toxin; Cholera Toxin B Subunit; ... B; Complement Protein C[delta]Gamma; Complement Receptor Type 2; COMT (catecol-O-methyl-transferase); ... Protein Mth1675; Constitutive Androstane Receptor; Contrysphan-R; Contrysphan-Sm; Contrysphan-Vn, ... 1-beta-dehydrogenase, isozyme 2; Corticotosteroid Receptor; 445 Corticotropin Releasing Hormone; COX-1; ... decarboxylase; Cysteine-Rich Domain Of Mannose Receptor; Cysteinyl leukotriene Receptor 1; Cysteinyl leukotriene receptor 2; Cysteinyl-tRNA Synthetase; Cystic Fibrosis ... Rc557; Cytoglobin; Cytohesin 2; Cytokine Receptor Common Beta Chain; Cytokinin Dehydrogenase 1; ... Valpha Domain; Cytoxin 3; D(1 B) dopamine receptor; D(2) Dopamine Receptor; D(3) Dopamine Receptor; D(4) dopamine receptor; D1 dopamine receptor-interacting protein calcyon; D199S Mutant Of ... Dehydrogenase; Dabd; Dahp Synthetase; D-AlaV.

D-Ala Ligase; D-Alanine Aminotransferase; D- ... Protein Mutl; DNA Nucleotide Excision Repair Enzyme Uvrb; DNA Photolyase; DNA Polymerase; DNA ... Regulator; DNA-directed RNA polymerase (E. coli); DNA-directed RNA polymerase beta chain; ... Dopamine beta hydroxylase; Dopamine D1 Receptor; Dopamine reuptake pump; Dp-Tt2; Dr ... Dutp Pyrophosphatase; D-Xylose 580 Isomerase; E.

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coli ribosomal proteins; Eafp 2; Early Endosomal ... Nitric-Oxide Synthase; Endothelial Protein C Receptor; Endothelin B receptor precursor; Endothelin-1; Endothelin-1 receptor precursor; Endothiapipepsin; Endothiapipepsin ... Neurotoxin; Ep-Cadherin; Ephrin Type-A Receptor 2; Ephrin-A5; Ephrin-B2; Epidermal Growth Factor; Epidermal Growth Factor Receptor; Epidermal Growth Factor receptor precursor; Epidermin Modifying Enzyme Epip; Epididymal Secretory Protein E1; ... Erythrina Crista-Galli Lectin; Erythropoietin receptor; Es1 Histone Acetyltransferase; Es1 Protein; ... Estradiol 17-beta-dehydrogenase 8; Estrogen Receptor; Estrogen Receptor (ER); Estrogen Receptor Alpha; Estrogen Receptor Beta; Estrogen Sulfoxtransferase; Estrogen-Related Receptor Gamma; Eukaryotic Peptide Chain Release Factor ... Gp120; Extracellular calcium-sensing receptor precursor; Extracellular Regulated Kinase 2; ... F-Box Only Protein 2; Fc Fragment; Fc Gamma Receptor 640 FCGR1_HUMAN; Feglymicin; Feline Immunodeficiency Virus Protease; Feline Leukemia Virus Receptor-Binding Domain; Ferredoxin; Ferredoxin II; ... 645 Nadp/Reductase; Ferric Hydroxamate Receptor; Ferric Hydroxamate Uptake Receptor; Ferrichrome-Binding Periplasmic Protein; Ferrichrome-Iron Receptor; Ferrichrome-Iron Receptor Precursor; Ferripoychelin Binding Protein; Ferripoyperidine Receptor; Ferritin heavy chain; Ferritin light chain; ... Fiuoloyl Esterase A; Fez-1 Beta-Lactamase; Fgf Receptor 1; 650 Fiber Protein; Fibrin; Fibrinogin-420; ... Growth Factor 9; Fibroblast Growth Factor Receptor 2; Fibroblast growth factor-4 precursor; ... Cis-Trans Isom; Fksg76; FL cytokine receptor precursor; Flavin reductase; Flavocytchrome B2; ... Fms1 Protein; Focal Adhesion Kinase 1; Folate receptor alpha; Folate receptor beta; Folate receptor gamma; Folate transporter 1; Folic Bifunctional Protein; Follicle Stimulating Hormone Receptor; Folliculin; Folypolyglutamate synthase; ... 665 Oxidoreductase; Formaldehyde-Activating Enzyme Fae; Formate Acetyltransferase 1; Formate ... GABA Transaminase; GABA-A Receptor; GABA-B Receptor; Gag Poly protein; GaHO 680 Bifunctional ... Dehydratase/1; Gamma-aminobutyric-acid receptor alpha-2 subunit precursor; Gamma-aminobutyric-acid receptor alpha-3 subunit precursor; Gamma-aminobutyric-acid receptor alpha-4 subunit precursor; Gamma-aminobutyric-acid receptor alpha-5 subunit 690 precursor; Gamma-aminobutyric-acid receptor alpha-6 subunit precursor; Gamma-aminobutyric-acid receptor rho-1 subunit [Precursor]; Gamma- Glutamyl ... [Includes: Glucose 1-dehydrogenase; Gdnf Family Receptor Alpha 1; GDP-D-Mannose-4,6-695 Dehydratase; ... Globin Lj637; Globin-3; Gipe Protein; Glucagon receptor; Glucan 1,3-Beta-Glucosidase 1/1 I; Glucan 1 ... Glucoamylose; Glucoamylose-471; Glucocorticoid Receptor; Glucokinase; Glucokinase 705 Isomorph 2; ... Decarboxylase A Subunit; Glutamate [NMDA] receptor subunit epsilon 1 precursor; Glutamate [NMDA] receptor subunit epsilon 2 precursor; Glutamate [NMDA] receptor 720 subunit epsilon 3 precursor; Glutamate ... 725 Glutamate Racemase; Glutamate receptor 1 [Precursor]; Glutamate Receptor 2; Glutamate Receptor 2 Precursor; Glutamate receptor 3; Glutamate receptor 4; Glutamate Receptor 6; Glutamate Receptor Subunit 2; Glutamate Receptor, Ionotropic Kainate 1; Glutamate receptor, Ionotropic Kainate 1 precursor; Glutamate Receptor, Ionotropic Kainate 2; Glutamate receptor, Ionotropic Kainate 3; Glutamate receptor, Ionotropic Kainate 5; Glutamate Semialdehyde ... Phosphoribosylpyrophosphate Amidot; Glutamine Receptor 2; Glutamine Synthetase; Glutamyl-Endopeptidase; ... Ribonucleotide Transformase; GLyocine alpha 2 receptor; GLyocine amidinotransferase; GLyocine ... GLyocine Oxidase; GLyocine 765 receptor alpha-1 chain [Precursor]; GLyocine receptor alpha-3 chain; GLyocine receptor beta chain; GLyocine phosphorylase; GLyocine ... Gomesin; Gonadotropin-releasing hormone II receptor; Gonadotropin-releasing hormone receptor; GP41 envelope protein (first heptad repeat); Gp70; GPIIb Receptor; GPIIia Receptor; Gramicidin; Gramicidin A; Gramicidin B; ... 1; Granulocyte colony stimulating factor 780 factor receptor (CD14 antigen); Granulocyte-macrophase colony stimulating factor receptor (GM-CSF-R-alpha or CSF2R); Granulysin; Granzyme ... Growth Differentiation Factor 5; Growth hormone receptor-Bound Protein 2; Growth hormone releasing hormone receptor 785 (GRF receptor); Growth-arrest-specific protein 6; Grp1; Gst2 ... Ribonucleose T1 Precursor; Gurmarin; H-; H.
Pylori rdxA; H+/K+ ATPase (Proton pump); Ha1; ... Activator Precursor; Hepatocyte Growth Factor Receptor; Hepatocyte Growth Factor-Regulated Tyrosine; ... Receptor; High affinity immunoglobulin epsilon receptor alpha-subunit precursor; High affinity immunoglobulin epsilon receptor gamma-subunit precursor; High Affinity Ribose ... High-Molecular-Weight Cytochrome C; Histamine H1 Receptor; Histamine H2 Receptor; Histamine H4 Receptor; Histamine N-Methyltransferase; Histidine 835 ... Dehydrogenase; Homoserine Kinase; Hormone Receptor Alpha 1; Thra1; Horseradish Peroxidase C1A; ... Receptor; Hepatocyte Growth Factor-Regulated Tyrosine; ... Receptor Alpha Chain; Ileal Lipid Binding Protein; ... Synthase Hshf; Immunoglobulin Alpha Fc Receptor; Immunoglobulin Heavy Chain Epsilon-1; ... 5/6-Kinase; Inositol 1,4,5-trisphosphate Receptor Type 1; Inositol Monophosphatase; Inositol-3- ... A; Insecticyanin A Form; Insulin; Insulin receptor; Insulin-Like Growth Factor I; Insulin-Like Growth Factor Receptor 1; Intact Lactose Operon Repressor With ... Adhesion Molecule-2; Interferon gamma receptor including IFNGR1 and IFNGR2 (IFN- gamma binds ... to IFNGR1 and indirectly to IFNGR2); Interferon receptor IFNAR1; Interferon receptor IFNAR2c; Interferon Stimulated Gene 20Kda; ... Interleukin-19; Interleukin-2; Interleukin-2 Receptor alpha chain (IL-2-RA); Interleukin-2 Receptor beta chain (IL-2-RB); Interleukin-3 precursor; ... channel 2; Iols Protein; Ionotropic Glutamate Receptor 5; Iota Toxin Component la; Iota-Carrageenase; ... Dehydrogenase; Ispd/Lspf Bipartional Enzyme; Iswi Protein; Kallikrein; Kallikrein 1; ... Kex1; Killer Cell Immunoglobulin-Like Receptor 2Ds; Kindling Fluorescent Protein; Kinesin; ... acid transporter-2; Low-Density Lipoprotein Receptor; Lq2; L- 1000 Rhamnose Isomerase; L-serine ... Luteinizing Hormone Releasing Hormone (LHRH) Receptor; L-Xyulose Reductase; Lymphocyte ... 1 (CD11a antigen); Lysine 1005 Biosynthesis Enzyme; Lysine hydroxylase; Lysozyme; Lysozyme C; ... Dehydrogenase; M1 muscarinic acetylcholine receptor; M2 muscarinic acetylcholine receptor; Mac-2 Binding 1010 Protein; Macromomycin; ... precursor; Malate Synthase G; Male-B363; Malic Enzyme; Malic Enzyme 2; Malonamidase E2; Malonyl Coa: Acyl Carrier ... Mannanase A; Mannitol Dehydrogenase; Mannose-6-Phosphate Isomerase; Mannose-Binding ... Maspin Precursor; Mast/stem cell growth factor receptor precursor; Matrix Glu-protein; Matrix ... Medium Chain Acyl-Coa Dehydrogenase; Melatonin Receptor; Melatonin receptor type 1 B; Membrane Copper Amine Oxidase; Menb; ... D-Dehydrogenase; Metabolotropic glutamate receptor 1; Metabolotropic Glutamate Receptor Subtype 1; Meta-Cleavage Product Hydrolase; ... Miniaturized Metalloprotei; Mineralocorticoid Receptor; Minor Core Protein Lambda 3; Mitochondrial ... Phosphoryl; MolJd: 1; Molecule: Progesterone Receptor; ... Molecule: Apomyoglobin; Other_Details: Cryst; ... Phosphatase 2; Mre11 Nuclease; Mrna Capping Enzyme; Mrna Decapping Enzyme; Msr3 Protein; 1090 Mta/Sah Nucleosidase; Mu ... transporter; Muscarinic acetylcholine receptor M3; Muscarinic acetylcholine receptor M4; Muscarinic acetylcholine receptor M5; Mutator Mutt Protein; Muth; Mycolic Acid ... Synthase; Myoinositol-11!
1 160 Ferredoxin Oxidoreductase; NADph-Cytochrome c 1; Neuropeptide Y; Neuregulin; Neurotensin receptor type 2; Neurotoxin Bmk M4; Neurotoxin Bmk37; dimethylaminohydrolase 2; Nh; Niacin receptor HM74A; Nickel Responsive Regulator; Nicotinamide ... nicotinic acetylcholine (ganglion) receptor; Nicotinic 1 185 acetylcholine Receptor alpha2/alpha3; Nima-Related Protein; Nine-Haem ... Oxide Reductase; Nitrous-Oxide Reductase; Nk Receptor; NMDA Receptor; N-Methyl-D-Aspartate Receptor Subunit 1; Nmra; Nogalonic Acid Methyl Ester ... Ntphase P4; Nuclear Inclusion Protein A; Nuclear receptor OB1; Nuclear Receptor Ror-1205 Alpha; Nucleoside ... Lush; Odorant-Binding Protein; Old Yellow Enzyme; Offactory Marker Protein; Oligopeptide Abe ... Omegac-Tixi; Omp Synthase; Ompk36; Opioid delta Receptor (OP1); Opioid kappa Receptor (OP2); Opioid mu Receptor (OP3); Opioid sigma 1 Receptor; Opioid sigma Receptor (OP4); Orange Carotenoid Protein; Orc2; Monophosphate Decarboxylase-Orphan Nuclear Receptor Pxz; Osomilarity Sensor Protein; Osmoprotection ... Insensitive NADph Nitroreductase; Oxysterols receptor Lxr-Beta; Oxytocin receptor (Neurophysin 1); P protein ... DNA polymerase; Ribonuclease H); P/nerokinin 1 Receptor; P1 Nuclease; P2 1235 Melvin Protein; P2 Protein; P2Y12 platelet ADP Receptor; P-30 Protein; P300/Cbp Associating Factor; P35; ... precursor; 1270 Peroxiosomal bifunctional enzyme; Peroxiosomal Carnitine O-Octanoyltransferase-1; Peroxiosomal multifunctional enzyme type 2; Peroxiosomal Trans2-Enoyl Coa Reductase; Peroxisome Proliferator Activated Receptor A; Peroxisome 1275 Proliferator Activated Receptor D; Peroxisome Proliferator Activated Receptor G; pH 2.5 Acid Phosphatase; Phage T4 Lysozyme ... decarboxylase proenzyme; Phosphatidylserine receptor; Phospho-2-Dehydro-1295 3-Deoxyoctanote ... Sulfurtransfer; Possible G-T Mismatches Repair Enzyme; Postsynaptic Density Protein; Postsynaptic ... Oxidoredu; Precursor Of Periplasmic 1355 Sugar Receptor; Predicted Amidotransferase; Predicted Cobalamin ... 1375 Hydrolysis; Profilin II; Progesterone Receptor; Progesterone Receptor (PR); Programmed Cell Death Protein 8; Programmed Cell Death Protein 8; Prolactin receptor precursor; Proline Dehydrogenase; Proline ... Subunit; Protacystacin synthase; Prostaglandin D2 receptor; Prostaglandin E2 receptor; EP1 subtype; Prostaglandin E2 receptor; EP2 subtype; Prostaglandin Endoperoxide H ... Prostaglandin F Synthase; Prostaglandin F2-alpha receptor; Prostaglandin G/H Synthase 1 1385 Precursor; ... Prostaglandin H2 Synthase-2; Prostaglandin 9-Reductase; Prostate-specific ... Receptor-Protein-Tyrosine Phosphatase, Non-Receptor; Protein-Tyrosine Phosphatase, Non-Receptor T; Protein-Tyrosine-Phosphatase; Prothrombin; ... Aldehyde Dehydrogenase; Putative Blue Light Receptor; Putative Cellulase; Putative Cellulase Cel6; ... 1425 Binding Core; Putative G-protein coupled receptor 40; Putative Ketoacyl Reductase; Putative Lipase ... I; Rc-Rnase6 Ribonuclease; Reca; Reca Protein; Receive P protein ... Tyrosine Kinase Erbb-3; Receiver-Type Adenylate Cyclase Gresag 4.1; Recombinant ... Restriction Endonuclease Eglii; Reticulon 4 Receptor; Reticulon 4 Receptor; Retinal dehydrogenase 1; Retinal ... Retinoic acid induced 3 protein; Retinoic acid receptor alpha; Retinoic Acid Receptor Beta; Retinoic Acid Receptor Gamma-1; Retinoic Acid Receptor Gamma-2; Retinoic acid receptor responder protein 1; Retinoic acid receptor RXR-alpha; Retinoic acid receptor RXR-beta; Retinoic acid receptor RXR-gamma; Retinoid X Receptor; Beta; Retinoid Binding Protein Complexed With ... Oxidoreductase; Ruvb; Rv3303C-Lpa; Rydanode receptor 1; ... Dockerin Binding Protein A; Scavenger receptor class B member 1; Scavenger Neurophysin; ... 3; SEC14-like protein 4; Sec18P; Secretin receptor; Sedolisin; Seed 1515 Coat Peroxidase; Seed 1515 Coat Peroxidase; tRNA; tRNA Cca-Adding Complex ... 1425 Binding Core; Putative G-protein coupled receptor 40; Putative Ketoacyl Reductase; Putative Lipase ... I; Rc-Rnase6 Ribonuclease; Reca; Reca Protein; Receive P protein...
A system for determining the binding constants of a chemical and a receptor, comprising a process for equilibrating the ... the x-ray fluorescence signal to a concentration.

A system for determining the binding constants of a chemical and a receptor, comprising a process for equilibrating the ... the x-ray fluorescence signal of the chemical.

Description of WO2008127291A2 contains 5-chloro-1h-indole-2-carboxylic acid [1-(4-fluorobenzyl)-2-(4-hydroxyperipederin-1y)]2-oxoethyl]amide
(dimethylarsenic)cysteine; dodecane-trimethylamine; (2s,4s)-alpha-campholinic acid; ... acid; chromophore (met-tyr-gly); i-hydroxyamine-S-cyclohexylpropane; cholic acid; chlorophyll b; glycochenodeoxycholic acid; 3-chloro-4- hydroxyphenylglycine; (3s,8ar)-3-(1 . . . farnesol; forskolin; fosmidomycin; 5-formyl- 5,6,7,8-tetrahydrofolate; f-loop of vitamin b12; [n-

EP1027886B1 20080709 ( US11940199P19990210 ) Pharmazeutische feste Dispersionen; Pharmaceutical solid dispersions; Dispersions pharmaceutiques solides - BABCOCK, WALTER CHRISTIAN; FRIESEN, DWAYNE THOMAS; NIGHTINGALE, JAMES ALAN SCHRIVER; SHANKER, RAVI MYSORE - PFIZER PRODUCTS INC.

Description: A specific advantage of using the high Tg ... to be used while still achieving a given target dispersion Tg and a target level of stability.

Preferred classes of drugs include, but are not ... agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and ... anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, antidepressants, and antiviral agents.

Specific examples of antihypertensives include ... is L-DOPA; specific examples of anti-Alzheimer's Disease agents are THA and donepezil; a specific example ... ypyrrolidin-1-yl)-(2R)-hydroxy-3-oxypropyl]amide.

(This value varies slightly between samples due to small differences in the actual drug assay potency of the samples.) An MFD solution of 1.8 . . . was added to the tube.

A specific advantage of using the high Tg ... to be used while still achieving a given target dispersion Tg and a target level of stability.

Preferred classes of drugs include, but are not ... agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and ... anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, antidepressants, and antiviral agents.

Specific examples of antihypertensives include ... is L-DOPA; specific examples of anti-Alzheimer's Disease agents are THA and donepezil; a specific example ... ypyrrolidin-1-yl)-(2R)-hydroxy-3-oxypropyl]amide.

(This value varies slightly between samples due to small differences in the actual drug assay potency of the samples.) An MFD solution of 1.8 . . . was added to the tube.
Description of EP1027886B1 contains 5-chloro-1H-indole-2-carboxylic acid [(1-benzyl-2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]-amide

Examples 2 through 13 and Comparative Examples C1 through C8 were prepared as in Example 1, except ... ("Drug 3", Pfizer, Inc.), and Examples 12 and 13 and Comparative Example C8 were prepared using 5-chloro-1H-indole-2-carboxylic acid [(1-benzyl-2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]-amide ("Drug 4"). Other variables are noted in Table 1. Table 1Ex. No.Drug Mass (mg)Drug No.Polymer mass ... Examples 2, 5, 8, 10, 11 and 12 are for reference only.

fulltext score: 17, cippix score: 17, hit score: 1

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Description: グリコーゲン生成酵素（glycogenic enzyme）またはグリコーゲンの代謝、表1のIC50値は、およびプロリンなど）(HueL, Gau ssinV. In: AminoAcid.. andT herapy in Health andNutritional Disease (Cynober, L. A., ed) p p. 179－188. CRCPress. Boca Raton, FL. (1995) ) が含まれる。

「処置（treatment）」、

Cell ProliferationBiotrakELISA (Amersham... Assay (Gu ava... LifeSciences Inc. , Boston, MA) が含まれる。

IC50と定義する（Matsumotoetal. , AnalyticalSciences, 18:1 315 (2002) ）。

fulltext score: 5, cippix score: 24, hit score: 1
Description of JP2006508939A5 contains 5-chloro-1H-indol-2-carboxylic acid(1-(4-fluorobenzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxoethyl)amide


fulltext score: 5, cippix score: 22, hit score: 1
Verfahren zur Herstellung von substituierten N-(Indol-2-carbonyl)-glycinamiden - HULIN, BERNARD; HOOVER, DENNIS J.; TREADWAY, JUDITH L.; MARTIN, WILLIAM H.; PHILLIPS, DOUGLAS - PFIZER INC., NEW YORK

Description: Glycogenphosphorylase-abhängige Erkrankungen oder ... durch Glycogenphosphorylase-Enzyme zur Freisetzung von Glucose-1-phosphat und einem ... vermittelt,-gestartet oder beibehalten werden.

Die zu testenden Verbindungen werden als 5 ... 14 % Dimethylsulfoxid (DMSO) vor der Zugabe der Enzyme zugesetzt.

Das vorstehend genannte Assay, ausgeführt mit einem Dosierungsbereich von ... vivo-Verminderung der Plasmaglucosekonzentration.

Das in vivo-Assay testet den Schutz des Herzens durch die ... Kontrollgruppe, die Salzlösungsträger empfängt.

Das in vivo-Assay testet, ob Verbindungen pharmakologisch ... an intakte, anästhesierte Kaninchen verabreicht.

fulltext score : 1, cippix score : 423, hit score : 1