METHODS AND REAGENTS FOR THE TREATMENT OF METABOLIC DISORDERS

Background of the Invention

The invention relates to the treatment, prevention, and reduction of metabolic disorders, such as diabetes and obesity.

As the levels of blood glucose rise postprandially, insulin is secreted and stimulates cells of the peripheral tissues (skeletal muscles and fat) to actively take up glucose from the blood as a source of energy. Loss of glucose homeostasis as a result of faulty insulin secretion or action typically results in metabolic disorders such as diabetes, which may be co-triggered or further exacerbated by obesity. Because these conditions are often fatal, strategies to restore adequate glucose clearance from the bloodstream are required.

Although diabetes may arise secondary to any condition that causes extensive damage to the pancreas (e.g., pancreatitis, tumors, administration of certain drugs such as corticosteroids or pentamidine, iron overload (e.g., hemochromatosis), acquired or genetic endocrinopathies, and surgical excision), the most common forms of diabetes typically arise from primary disorders of the insulin signaling system. There are two major types of diabetes, namely type 1 diabetes (also known as insulin dependent diabetes (IDDM)) and type 2 diabetes (also known as insulin independent or non-insulin dependent diabetes (NIDDM)), which share common long-term complications in spite of their different pathogenic mechanisms.

Type 1 diabetes, which accounts for approximately 10% of all cases of primary diabetes, is an organ-specific autoimmune disease characterized by the extensive destruction of the insulin-producing beta cells of the pancreas.

The consequent reduction in insulin production inevitably leads to the deregulation of glucose metabolism. While the administration of insulin provides significant benefits to patients suffering from this condition, the short serum half-life of insulin is a major impediment to the maintenance of normoglycemia. An alternative treatment is islet transplantation, but this strategy has been associated with limited success.

Type 2 diabetes, which affects a larger proportion of the population, is characterized by a deregulation in the secretion of insulin and/or a decreased response of peripheral tissues to insulin, i.e., insulin resistance. While the pathogenesis of type 2 diabetes remains unclear, epidemiologic studies suggest that this form of diabetes results from a collection of multiple genetic defects or polymorphisms, each contributing its own predisposing risks and modified by environmental factors, including excess weight, diet, inactivity, drugs, and excess alcohol consumption. Although various therapeutic treatments are available for the management of type 2 diabetes, they are associated with various debilitating side effects. Accordingly, patients diagnosed with or at risk of having type 2 diabetes are often advised to adopt a healthier lifestyle, including loss of weight, change in diet, exercise, and moderate alcohol intake. Such lifestyle changes, however, are not sufficient to reverse the vascular and organ damages caused by diabetes.

Given that the strategies currently available for the management of diabetes are suboptimal, there is a compelling need for treatments that are more effective and are not associated with such debilitating side-effects.

Summary of the Invention

The present invention features compositions, methods, and kits for treating, preventing, and reducing metabolic disorders. This invention is particularly useful for treating patients having or at risk of having any condition that is characterized

by a state of hyperglycemia, which may be caused, for example, by an alteration in the insulin signaling pathway (e.g., a reduction in insulin production, resistance to insulin, or both). Exemplary disorders amenable to treatment according to this invention are obesity, diabetes (e.g., type 1 diabetes, type 2 diabetes, maturity-onset diabetes of the young (MODY), and gestational diabetes), satiety, endocrine deficiencies of aging, and any of their associated complications (e.g., Syndrome X, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, peripheral vascular disease, hyperlipidemia, hypertension, atherosclerosis, and coronary heart disease).

In a first aspect, the invention features a composition that includes (a) bezafibrate or an analog thereof; and (b) diflunisal or an analog thereof, wherein the bezafibrate and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder (e.g., diabetes or obesity). Exemplary combinations are bezafibrate and diflunisal; bezafibrate and bismuth subsalicylate; bezafibrate and nimosulide; bezafibrate and oxaprozin; bezafibrate and diclofenac; bezafibrate and sundilac; bezafibrate and ibuprofen; clofibrate and diflunisal; clofibrate and bismuth subsalicylate; clofibrate and nimosulide; clofibrate and oxaprozin; clofibrate and diclofenac; clofibrate and sundilac; clofibrate and ibuprofen; clofibrinc acid and diflunisal; clofibric acid and bismuth subsalicylate; clofibric acid and nimosulide; clofibric acid and oxaprozin; clofibric acid and diclofenac; clofibric acid and sundilac; clofibric acid and ibuprofen; clinofibrate and diflunisal; clinofibrate and bismuth subsalicylate; clinofibrate and nimosulide; clinofibrate and oxaprozin; clinofibrate and diclofenac; clinofibrate and sundilac; clinofibrate and ibuprofen; gemfibrozil and diflunisal; gemfibrozil and bismuth subsalicylate; gemfibrozil and nimosulide; gemfibrozil and oxaprozin; gemfibrozil and diclofenac; gemfibrozil and sundilac; and gemfibrozil and ibuprofen.

In a second aspect, the invention features a composition that includes (a) bezafibrate or an analog thereof; and (b) cinnamic acid or an analog thereof, wherein the bezafibrate and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

Exemplary bezafibrate analogs are binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, or gemfibrozil.

In either of the foregoing aspects, the composition may include a third agent selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists, endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors, vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol antagonists, cholesteryl ester transfer protein antagonists, cytokine synthesis inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase

inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

The compositions of the invention may be formulated for oral administration or systemic administration.

The invention also features a method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof by administering to the patient (i) bezafibrate or an analog thereof; and (ii) diflunisal or an analog thereof, wherein the bezafibrate and diflunisal are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder. Exemplary combinations are bezafibrate and diflunisal; bezafibrate and bismuth subsalicylate; bezafibrate and nimosulide; bezafibrate and oxaprozin; bezafibrate and diclofenac; bezafibrate and sundilac; bezafibrate and ibuprofen; clofibrate and diflunisal; clofibrate and bismuth subsalicylate; clofibrate and nimosulide; clofibrate and oxaprozin; clofibrate and diclofenac; clofibrate and sundilac; clofibrate and ibuprofen; clofibrinc acid and diflunisal; clofibric acid and bismuth subsalicylate; clofibric acid and nimosulide; clofibric acid and oxaprozin; clofibric acid and diclofenac; clofibric acid and sundilac; clofibric acid and ibuprofen; clinofibrate

and diflunisal; clinofibrate and bismuth subsalicylate; clinofibrate and nimosulide; clinofibrate and oxaprozin; clinofibrate and diclofenac; clinofibrate and sundilac; clinofibrate and ibuprofen; gemfibrozil and diflunisal; gemfibrozil and bismuth subsalicylate; gemfibrozil and nimosulide; gemfibrozil and oxaprozin; gemfibrozil and diclofenac; gemfibrozil and sundilac; and gemfibrozil and ibuprofen.

The invention also features a method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof by administering to the patient (i) bezafibrate or an analog thereof; and (ii) cinnamic acid or an analog thereof, wherein the bezafibrate and cinnamic acid are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

In either of the foregoing aspects, the patient may also be administered a third agent selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists, endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors, vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol

antagonists, cholesteryl ester transfer protein antagonists, cytokine synthesis inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

The two drugs may be formulated for oral administration or systemic administration. The first and second agents are desirably administered within 10 days of each other, within 7 days of each other, within 24 hours of each other, or within 1 hour of each other.

The invention also features a kit that includes (i) bezafibrate or an analog thereof; and (ii) instructions for administering bezafibrate and cinnamic acid or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) bezafibrate or an analog thereof; and (ii) instructions for administering bezafibrate and diflunisal or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) diflunisal or an analog thereof; and (ii) instructions for administering diflunisal and bezafibrate or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) cinnamic acid or an analog thereof; and (ii) instructions for administering cinnamic acid and bezafibrate or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) a composition containing bezafibrate or an analog thereof and cinnamic acid or an analog thereof; and (ii) instructions for administering the composition to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) a composition containing bezafibrate or an analog thereof and diflunisal or an analog thereof; and (ii) instructions for administering the composition to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) bezafibrate or an analog thereof; (ii) cinnamic acid or an analog thereof; and (iii) instructions for administering bezafibrate and cinnamic acid to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) bezafibrate or an analog thereof; (ii) diflunisal or an analog thereof; and (iii) instructions for administering bezafibrate and diflunisal to a patient having or at risk of having a metabolic disorder.

The invention also features a composition that includes (a) a PPAR agonist; and (b) diflunisal or an analog thereof, wherein the PPAR agonist and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

The invention also features a composition that includes (a) a PPAR agonist; and

(b) cinnamic acid or an analog thereof, wherein the PPAR agonist and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

In either of the foregoing aspects, the patient may also be administered a third agent selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists, endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors, vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol antagonists, cholesteryl ester transfer protein antagonists, cytokine synthesis inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin

synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

The compositions of the invention may be formulated for oral administration or systemic administration.

The invention also features a method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof by administering to the patient (i) a PPAR agonist; and (ii) diflunisal or an analog thereof, wherein the PPARγ agonist and diflunisal are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

The invention also features a method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof by administering to the patient (i) a PPAR agonist; and (ii) cinnamic acid or an analog thereof, wherein the PPARγ agonist and cinnamic acid are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

The invention also features a kit that includes (i) a PPAR agonist; and (ii) instructions for administering the PPAR agonist and cinnamic acid or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention features a kit that includes (i) a PPAR agonist; and (ii) instructions for administering the PPAR agonist and diflunisal or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention features a kit that includes (i) diflunisal or an analog thereof; and (ii) instructions for administering diflunisal and a PPAR agonist or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) cinnamic acid or an analog thereof; and (ii) instructions for administering cinnamic acid and a PPAR agonist or an analog thereof to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) a composition containing a PPAR agonist or an analog thereof and cinnamic acid or an analog thereof; and (ii) instructions for administering the composition to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) a composition containing a PPAR agonist or an analog thereof and diflunisal or an analog thereof; and (ii) instructions for administering the composition to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) a PPAR agonist or an analog thereof; (ii) cinnamic acid or an analog thereof; and (iii) instructions for administering the PPAR agonist and cinnamic acid to a patient having or at risk of having a metabolic disorder.

The invention also features a kit that includes (i) a PPAR agonist or an analog thereof; (ii) diflunisal or an analog thereof; and (iii) instructions for administering the PPAR agonist and diflunisal to a patient having or at risk of having a metabolic disorder.

In any of the foregoing lits, the PPAR agonist is desirably a PPARγ agonist (e.g., balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011, GI262570, GW347845, or FK614).

The invention also features a method of treating a metabolic disorder by administering to a mammal (e.g., human) one or more agents listed in Table 1 in an amount sufficient to treat, prevent, or reduce the metabolic disorder.

For example, the mammal being treated may be administered two agents listed in Table 1 within 28 days of each other in amounts that together are sufficient to treat, prevent, or reduce the metabolic disorder. The two agents are desirably administered within 14 days of each other, more desirably within seven days of each other, and even more desirably within twenty-four hours of each other, or even simultaneously (i.e., concomitantly). If desired, either one of the two agents may be administered in low dosage.

Optionally, the mammal being treated may receive an additional therapeutic regimen. If a therapeutic agent is employed as the additional therapeutic regimen, the agent or agents from Table 1 and the additional agent are present in amounts that, when administered to a mammal, are together sufficient to treat, prevent, or reduce a metabolic disorder. The additional agent may be selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists, endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors,

vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol antagonists, cholesteryl ester transfer protein antagonists, cytokine synthesis inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

If desired, more than one therapeutic agent may be used with any of the agents listed in Table 1.

Table 1

5-10-Dihydro-5-10-Dimethylphenazine	Calcium Chloride	5-Hydroxytryptophan	Indocyanine Green	Mono-Butyl Maleate	Succinylcholine
Acemetacin	Candesartan (e.g., cilexetil salt)	Dopamine (e.g., hydrochloride)	Indomethacin	Nefopam	Sulfaguanidine
Acenocoumarol	Captopril	Doxapram (e.g., hydrochloride salt)	Inulin	Nimesulide	Sulfamethizole
Acetaminophen	Carbamazepine	Doxycycline	Invertase	Nitroxoline	Sulfasomidine
Acetazolamide	Carbinoxamine (e.g., maleate salt)	Doxylamine (e.g., succinate salt)	Iopanoic Acid	Norepinephrine (e.g., bitartrate salt)	Suprofen
Acetohexamide	Carisoprodol	Dyclonine (e.g., hydrochloride salt)	Iophenoxic Acid	Olanzapine	Tadalafil
Acetohydroxamic Acid	Cefamandole (e.g., nafate salt)	Enalaprilat	Iopromide	Oleandomycin	Tannic Acid
Acetrizoate (e.g., sodium salt)	Cefpodoxime Proxetil	Epinephrine (e.g., bitartrate salt)	Isoproterenol (e.g., sulfate salt)	Orphenadrine (e.g., citrate salt)	Telmisartan
Acetylcholine (e.g., chloride salt)	Ciclopirox	Ergoloid Mesylates	Isotretinoin	Oxaprozin	Terbutaline (e.g., sulfate salt)
Acetyldigitoxin	Cinnamic Acid	Ethopropazine (e.g., hydrochloride salt)	Ketoconazole	Oxybutynin (e.g., chloride salt)	Tetrahydrozoline (e.g., hydrochloride salt)
Alachlor	Clenbuterol (e.g., hydrochloride salt)	Etoposide	Ketotifen (e.g., fumarate salt)	Oxymetazoline (e.g., hydrochloride salt)	Tinidazole
Albuterol (Salbutamol) (e.g., sulfate salt)	Clioquinol	Eucalyptol	Lamivudine	Pergolide (e.g., mesylate salt)	Tioconazole
Alprenolol	Copper bis-3,5-diisopropylsalicylate	Evans Blue	Lead Dimethyldithiocarbamate	Phenacemide	Tolazoline (e.g., hydrochloride salt)
Amantadine (e.g., hydrochloride salt)	Cupric Chloride	Exemestane	Leflunomide	Phenindione	Tolfenamic acid
Ametryn	Dexibuprofen	Flunixin (e.g., meglumine salt)	Levocabastine (e.g., hydrochloride salt)	Phensuximide	Tretinoin
Ammonium Chloride	Diacerein	Fumaric Acid Monoethyl Ester	Levonordefrin	Phenylbutazone	Triamterene
Arbutin	Diallyl Maleate	Gemfibrozil	Loxapine (e.g., hydrochloride salt)	Phenylephrine (e.g., hydrochloride salt)	Triflupromazine (e.g., hydrochloride salt)
Artemether	Diatrizoate (e.g., sodium salt)	Genistein	Manganese Sulfate	Phenylpropanolamine (e.g., hydrochloride salt)	Tulobuterol (e.g., hydrochloride salt)
Aspartic Acid Hydroxamate	Diclofenac (e.g., sodium salt)	Geranyl Acetate	Mebhydroline (e.g., 1,5-Naphthalenedisulfonate salt)	Phenytoin	Vincamine
Atrazine	Dicloxacillin (e.g., sodium salt)	Glutamic Acid Hydrochloride	Meclofenoxate	Pilocarpine (e.g., hydrochloride salt)	Warfarin
Azathioprine	Diflunisal	Guaiacol	Mefenamic Acid	Prazosin (e.g., hydrochloride salt)	Xylazine (e.g., hydrochloride salt)
Bamethan	Digitoxin	Guanfacine (e.g., hydrochloride salt)	Meloxicam	Promethazine (e.g., hydrochloride salt)	Zaprinast
Benzbromarone	Dimenhydrinate	Hexylcaine (e.g., hydrochloride salt)	Melphalan	Prostaglandin (e.g., prostaglandin E)	
Bezafibrate	Dimethyl Fumarate	Homatropine Methylbromide	Mercaptoethanol	Pyrilamine (e.g., maleate salt)	
Bismuth Subsalicylate	Diphemanil Methylsufate	Hydroxocobalamin	Metaproterenol (e.g., hemisulfate salt)	Quinacrine	
Bopindolol	Diphenhydramine (e.g., hydrochloride salt)	Hydroxypropyl Cellulose	Methacholine (e.g., chloride or bromide salt)	Ritodrine (e.g., hydrochloride salt)	
Brimonidine	Diphenidol (e.g., hydrochloride salt)	Ibudilast	Methdilazine	RO-20-1724	
Brompheniramine (e.g., maleate salt)	Dipivefrin (e.g., hydrochloride salt)	Ibuprofen	Methyl Linoleate	Rolipram	
Calcitriol	Dirithromycin	Imipramine (e.g., hydrochloride salt)	Methylergonovine (e.g., maleate salt)	Spectinomycin	

If the mammal is administered more than one agent, the different agents may be admixed together in a single formulation. When administered in separate formulations, the agents may be administered simultaneously or within 14 days, 7 days, or 1 day of each other. These agents may or may not be administered by the same route of administration (e.g., oral, intravenous, intramuscular, ophthalmic, topical, dermal, sub-cutaneous, and rectal). Optionally, the additional therapeutic regimen may involve a lifestyle change, including the adoption of a low-fat diet or low-sodium diet, stress management, physical exercise, reduction in alcohol intake, or reduction in smoking.

In a further aspect, the present invention features a kit that includes any one of the agents listed in Table 1 and instructions for its administration to a patient having or at risk of having a metabolic disorder. Optionally, the kit contains two, three, four, or more than four agents from Table 1 that may or may not be admixed in the same formulation. This kit may also contain instructions for administering this agent with a second agent listed in Table 1.

The invention also features a kit that includes (a) one, two, three, or more agents listed in Table 1 and (b) one or more of the following agents: a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, or antioxidant. The kit also includes instructions for administering these agents to a patient having or at risk of having a metabolic disorder.

Alternatively, the kit of the invention may contain one, two, three, or more agent listed in Table 1 or any one of the following agents: a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione,

alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant, as well as instructions for administering these two agents together to a patient having or at risk of having a metabolic disorder.

The invention also features a method of identifying a combination of agents useful for the treatment, prevention, or reduction of a metabolic disorder, involving the steps of: (a) contacting cells with an agent listed in Table 1 and a candidate compound; and (b) determining whether this combination of agents reduces glucose levels relative to cells contacted only with the agent from Table 1 but not contacted with the candidate compound. A reduction in glucose levels identifies the combination as being useful for the treatment, prevention, or reduction of a metabolic disorder. Glucose levels may be reduced, for example, by altering insulin signaling (therefore increasing glucose uptake into cells and subsequent storage or metabolism, for example), altering glucose transporter activity (e.g., increasing GLUT4 expression, translocation, or intrinsic activity), increasing the amount of insulin-sensitive tissue (e.g., by increasing adipocyte or muscle cell differentiation), or altering gene transcription in adipocytes or muscle cells (e.g., altered secretion of factors from adipocytes and expression of metabolic pathway genes).

For example, the screening method for identifying a useful therapeutic combination involves the steps of: (a) contacting cells with an agent listed in Table 1 and a candidate compound; and (b) determining whether this combination of agents alters insulin signaling such that glucose levels are reduced relative to cells contacted with the agent from Table 1 but not contacted with the candidate compound. An alteration in insulin signaling that reduces glucose levels identifies the combination as being useful for the treatment, prevention, or reduction of a metabolic disorder.

Mammalian (e.g., human) cells may be employed in any of the screening methods described herein. Particularly useful cells are muscle cells, intestinal cells, adipocytes, liver cells, and pancreatic cells. Optionally, these cells have an alteration in insulin signaling activity such that glucose levels are increased. Such a reduction in glucose levels may result from an increase in insulin production, an increase in insulin secretion, an increase in glucose uptake by peripheral tissues, a reduction in hepatic glucose production, or a reduction in the absorption of carbohydrates from the intestines.

Analogs of any of the compounds listed in Table 1 may be used in any of the methods, kits, and compositions of the invention. Such analogs include any agent from the same chemical class, mechanistic class, or therapeutic class as those listed in Table 2.

Table 2

name	chemical class	mechanistic class	therapeutic class
5-10-dihydro-5-10-dimethylphenazine	phenothiazine		
5-hydroxytryptophan (e.g., dl form)		intermediate metabolite of lt in the production of serotonin	anti-depressant
acemetacin	indomethacin derivative	cyclooxegynase inhibitor	anti-inflammatory agents non-steroidal
acenocoumarol	heterocyclic coumarin	anticoagulant	thromboembolism atrial fibrillation pulmonary embolism
acetaminophen	sodium sulfate	blocks cyclooxygenase (prostaglandin formation)	NSAID
acetazolamide	sulfa-based	carbonic anhydrase inhibitor	anti-epileptic
acetohexamide	sulfonylureas	stimulate beta cell insulin secretion	oral hypoglycemic drugs
acetohydroxamic acid		specific inhibitor of urease	antibacterial
acetrizoate (e.g., sodium salt)	acetrizoic acid	iodinated radiographic contrast medium used in hysterosalpingography	
acetylcholine (e.g., chloride salt)		mixed cholinergic agonist	neurotransmitter
acetyldigitoxin		sodium potassium atpase	inotropic congestive heart failure
alachlor	acetamide		herbicide

albuterol (salbutamol) sulfate	ethanolamine	beta agonist	bronchodilator
alprenolol	proponalamine	andrenergic beta antagonist	antihypertensive, anti-anginal, and anti-arrhythmic agent
amantadine (e.g., hydrochloride salt)			antiparkinson
ametryn	triazine		herbicide
ammonium chloride	ammonia derivative		diuretics, expectorants
arbutin		tyrosinase inhibitor	dermatological
artemether	artemisinins		anti-malarial
aspartic acid hydroxamate	asperigine		antineoplastic agents antiviral agents

name	chemical class	mechanistic class	therapeutic class
Atrazine	triazine	selective triazine herbicide	herbicide
azathioprine	heterocyclic		immunosuppressive
bamethan			vasodilator
benzbromarone	benzofuran	acts by increasing uric acid clearance	antigout
bezafibrate	butyrate	lowers cholesterol and triglycerides	antilipemic, cholesterol lowering
bismuth subsalicylate	bismuth salt	increases intracellular Ca2+, MAP-kinase activity, and cell proliferation in normal human gastric mucous epithelial cells	anti-diarrheal
bopindolol	beta antagonist - antihypertensive		
brimonidine		alpha-adrenergic receptor agonist	anti-glaucoma
brompheniramine maleate	pheniramine	histamine H1 antagonist	anti-allergic agent
calcitriol	vitamin D analog	calcium channel agonists	dermatological
calcium chloride			dietary supplyment
candesartan (e.g., cilexetil salt)	benzimidazole	TL-type angiotensin II receptor antagonist	antihypertensive
captopril	mercaptan	angiotensin-converting enzyme inhibitors	antihypertensive
carbamazepine	iminostilbene derivative		anticonvulsant
carbinoxamine (e.g., maleate salt)		histamine H1 antagonist	antihistamine
carisoprodol	carbamic acid		sedative/ muscle relaxent
cefamandole (e.g., nafate salt)	cephalosporins	cell wall synthesis inhibitor	antibiotic
cefpodoxime proxetil	cephalosporins		antibiotic
ciclopirox	hydroxypyridone	fungicide	topical antifungal
cinnamic acid	cinnamate		flavoring, coloring
clenbuterol hydrochloride	beta-2-symphatomimetic	beta agonist	anticatabolic
clioquinol	8-hydroxyquinoline derivative		antifungal, amoebicides
copper bis-3,5-diisopropylsalicylate	salicyclic acid		antineoplastic, hypoglycemic agent
cupric chloride	mineral		antifungal
dexibuprofen	single-enantiomer form of ibuprofen	inhibits prostaglandin synthesis	NSAID
diacerein	anthraquinones		NSAID
diallyl maleate	mallic acid		plastics additive
diatrizoate (e.g., sodium salt)			x-ray contrast medium
diclofenac sodium	benzeneacetic acid		NSAID

name	chemical class	mechanistic class	therapeutic class
dicloxacillin (e.g., sodium salt)	penicillin derivative/ beta-lactam	inhibits bacterial cell wall synthesis	antibiotic
diflunisal	salicylate derivative	cyclooxygenase inhibitors	NSAID
digitoxin	cardiac glycoside	inhibits Na+/K+ ATPase cell membrane transport complex	inotropic cardiovascular agent, congestive heart failure
dimenhydrinate	diphenhydramine and chlorotheophylline	histamine H1 antagonists	vertigo agent
dimethyl fumarate	fumarate		anti-psoriatic
diphemanil methylsufate	synthetic quaternary ammonium compound	anti-muscarinic agent	
diphenhydramine (e.g., hydrochloride salt)	ethanolamine	histamine H1 receptor antagonist	antihistamine
diphenidol (e.g., hydrochloride salt)		muscarinic antagonist	anti-nausea, vomiting, dizziness
dipivefrin hydrochloride	prodrug of epinephrine	bronchodialator	anti-glaucoma
dirithromycin		inhibits bacterial protein synthesis at the 50s ribosome (macrolide)	antibacterial
dopamine (e.g., hydrochloride)		neurotransmitter	antidepressant
doxapram (e.g., hydrochloride salt)		respiratory stimulant	acute hypercapnic respiratory failure
doxycycline	tetracycline derivative	protein-synthesis-inhibitor	antibiotic
doxylamine (e.g., succinate salt)	butanedioic acid	antihistamine-H1/serotonin-secretion-inhibitor	allergic rhinitis
dyclonine (e.g., hydrochloride salt)		nerve sodium-permeability-inhibitor	pain reliever
enalaprilat	oligopeptide	ACE inhibitor	antihypertensive
epinephrine bitartrate	hormone	induces cyclic AMP	stimulant, asthma
ergoloid mesylates	dihydroergotoxine	adrenergic alpha-antagonists	Alzheimer's disease
ethopropazine (e.g., hydrochloride salt)	phenothiazine	Antidyskinetic	Parkinson's disease
etoposide	glucoside	topoisomerase II inhibitor	antineoplastic agent, phytogenic
eucalyptol	cyclohexanols		local anti-infective agent
evans blue	azo dye		diagnostic for blood volume determination
exemestane	androstadiene	aromatase antagonist/inhibitor	antineoplastic agent
flunixin meglumine	clinixin derivative	prostaglandin antagonist	NSAID
fumaric acid monoethyl ester	fumarate		anti-psoriatic

name	chemical class	mechanistic class	therapeutic class
gemfibrozil	pentonoic acid	lowers elevated serum lipids primarily by decreasing serum triglycerides	lipid lowering
genistein	isoflavone		angiogenesis blocker
geranyl acetate	isoflavone		antineoplastic agent
glutamic acid hydrochloride	amino acid	amino acid	
guaiacol	phenol		disinfectant, expectorant
guanfacine (e.g., hydrochloride salt)	acetamide	α2-adrenoceptor agonist	antihypertensive
hexylcaine (e.g., hydrochloride salt)	benzoic acid derivitive		topical anesthetic
homatropine methylbromide	tropine ester of mandelic acid		antispasmodic and inhibitor of secretions
hydroxocobalamin	vitamin B12	inhibits vitamin B12 deficiency	synthetic vitamin B12
hydroxypropyl cellulose	cellulose	Mechanical	topical artificial tear
ibudilast	pyridine	phosphodiesterase iv inhibitor	anti-asthma
ibuprofen	phenylpropionates	cyclooxygenase inhibitor	NSAID
imipramine (e.g., hydrochloride salt)	dibenzazepine	blocks ne uptake at adrenergic nerve endings	antidepressant
indocyanine green	tricarbocyanine	infrared absorbance	diagnostic for angiography
indomethacin	indole	cyclooxygenase inhibitor	NSAID
inulin	oligosaccharide		diagnostic for kidney health; probiotic; dietary fiber
invertase	beta-fructofuranosidase	hydrolysis of the terminal nonreducing beta-fructofuranoside residues in beta-fructofuranosides	enzyme
iopanoic acid		radiopaque compound	antihyperthyroid agent; x-ray contrast medium
iophenoxic acid		radiopaque compound	x-ray contrast medium
iopromide	benzoic acid derivitive		
isoproterenol (e.g., sulfate salt)	amine	beta adrenergic agonist	inotropic agent
isoproterenol sulfate	analog of epinephrine	sympathomimetic, direct-acting	beta agonist
isotretinoin	retinoid		acne vulgaris
ketoconazole	azole		antifungal
ketotifen fumarate	cycloheptathiophene	H1 receptor antagonist	asthma, rhinitis, skin allergies, and anaphylaxis.
lamivudine	deoxyribonucleoside	reverse transcriptase inhibitor	anti-HIV treatment
lead dimethyldithiocar-bamate	carbamic acid		rubber accelerator

name	chemical class	mechanistic class	therapeutic class
leflunomide	oxazole	inhibits dihydroorotate dehydrogenase	DMARD
levocabastine (e.g., hydrochloride salt)		antihistaminic, H1-receptor; ophthalmic	antiallergic; opthalmic
levonordefrin	norepinephrine derivative	stimulates alpha- and beta-adrenergic systems	vasoconstrictor, local anesthetic for dentistry
loxapine (e.g., hydrochloride salt)	tricyclic dibenzoxazepine		antipsychotic agent
manganese sulfate	sulfate		
mebhydroline (e.g., 1,5-naphthalenedisulfonate salt)	aralkylamine carboline	histamine H1 antagonists	antihistamine
mebhydroline 1,5-naphthalenedisulfonate salt	naphthalenesulfonates		
meclofenoxate	aminoalcohol		stimulant
mefenamic acid	anthranilic acid	cyclooxygenase inhibitor	NSAID
meloxicam	oxicam derivative	cyclooxygenase inhibitor	NSAID
melphalan	nitrogen mustard compound	alkylating antineoplastic not completely understood	antineoplastic
mercaptoethanol	sulfhydryl compound	reducing agent	biochem reagent
metaproterenol (e.g., hemisulfate salt)	ethanolamine	beta-adrenergic agonist	treatment of asthma and bronchospams
metaproterenol hemisulfate salt	synthetic sympathomimetic amine	beta agonist	bronchodilator
methacholine (e.g., bromide salt)	quarternary ammonium	muscarinic agonist	parasympathomimetic bronchoconstrictor agent
methacholine (e.g., chloride salt)	quarternary ammonium	muscarinic agonist	parasympathomimetic bronchoconstrictor agent
methdilazine	phenothiazine	antihistamine h1receptor agonist	allergies, antipsychotic
methyl linoleate	linoleic acid	antioxidant	flavoring agent
methylergonovine (e.g., maleate salt)	ergot alkyloid homolog	oxytocic	obstetrics, to induce labor
mono-butyl maleate	maleate ester	fumarate sar	anti-inflammatory
nefopam	oxazocine		analgesic
nimesulide	sulfonanilide	COX-2 inhibitor	NSAID
nitroxoline	chelating agent	bactericidal chelation	antibacterial, antifungal
norepinephrine bitartrate	catecholamine	alpha adrenergic agonist	vasoconstrictor

name	chemical class	mechanistic class	therapeutic class
olanzapine	benzodiazepine	antiemetic	anti-nausea
oleandomycin	macrolide	binds to 23s rrna or 50s subunit inhibits translocation or trna, inhibits peptidyl transferase interfere w/ formation of 50s unit inhibit protein synthesis	antibiotic
orphenadrine (e.g., citrate salt)	ethylamine	muscarinic antagonist	drug-induced parkinsonism
oxaprozin	propionic acid derivative	prostaglandin inhibitor	NSAID
oxybutynin (e.g., chloride salt)	mandelic acid	competitive antagonist of acetylcholine at postganglionic muscarinic receptors,	antispasmodic, urinary tract
oxymetazoline (e.g., hydrochloride salt)	imidazole	adrenergic alpha-agonists, direct acting sympathomimetic	vasoconstrictor to relieve nasal congestion
pergolide (e.g., mesylate salt)	ergoline	dopamine agonist	Parkinson's disease
phenacemide	urea deriviative		anti-epileptic drug
phenindione	indandione derivative	anti-vitamin K agent	anticoagulent
phensuximide	succinimide		anticonvulsant
phenylbutazone	pyrazole	cyclooxegenase inhibitor	ankylosing spondylitis, rheumatoid arthritis
phenylephrine (e.g., hydrochloride salt)	ethanolamine	alpha-adrenergic agonist	ophthalmic examinations
phenylpropanolamine (e.g., hydrochloride salt)	propanolamine	adrenergic alpha-agonists	nasal vasoconstrictor and an appetite depressant.
phenytoin	barbiturates		anticonvulsant
pilocarpine (e.g., hydrochloride salt)	lactone imdiazole	acetylcholine agonist	antiglaucoma agent
prazosin (e.g., hydrochloride salt)	quinazoline piperazine	alpha-adrenergic receptor antagonist	antihypertensive
promethazine (e.g., hydrochloride salt)	phenathiazine	histamine H1 receptor antagonists	antihistamine
prostaglandin e	carboxylic acid	prostaglandin	vasodilator
pyrilamine (e.g., maleate salt)		histamine H1 receptor antagonists	antihistamine
quinacrine		phospholipase inhibitor	anti-malarial
ritodrine hydrochloride	catecholamine	beta agonist	relaxant
RO-20-1724	polyphenyl imidazole	camp phosphodiesterase inhibitor	NSAID
rolipram	polyphenyl pyrrole	phosphodiesterase IV inhibitor	NSAID, antidepressant, anti-parkinsonian, tranquilizer
spectinomycin		antibiotic	bacterial infection
succinylcholine		acetylcholine agonist	muscle relaxant

name	chemical class	mechanistic class	therapeutic class
sulfaguanidine	sulfonamide derivative	anti-bacterial agent	antibiotic
sulfamethizole	sulfa drug	antibiotic	urinary-tract infections
sulfasomidine	sulfa drug	antibiotic	urinary-tract infections
suprofen	thiopene ketoacid	Prostaglandin-antagonist/nsaid	analgesics
tadalafil	PDEi	phosphodiesterase inhibitor	vasodilator
tannic acid	glycoside		astringent
telmisartan	carboxylic acid	ACE inhibitor	antihypertensive (angio 2 receptor antagonist)
terbutaline (e.g., sulfate salt)		bronchodilator	asthma
tetrahydrozoline (e.g., hydrochloride salt)	naphthalene imidazole	HMG-coA reductase inhibitor/sympathomimetics-alpha	conjunctival congestion
tinidazole	imidazole		antiprotozoal
tioconazole	imidazole	phenolic antioxitant	antifungal
tolazoline (e.g., hydrochloride salt)	imidazole	vasodilator	peripheral vascular-disorders
tolfenamic acid	anthranillic acid	calcium channel blocker	NSAID
tretinoin	trans-retinoic acid	lysosomal labilization	keratolytic
triamterene	triaminopteridine	aldosterone receptor antagonist	diuretic
triflupromazine (e.g., hydrochloride salt)	phenathiazine	dopamine receptor antagonist	antipsychotic
tulobuterol hydrochloride	benzyl alcohol	beta agonist	bronchiodilator
vincamine		vasodialator	tinnitus anti-ischemic
warfarin	coumarin derivative	anti-vitamin k agent	anticoagulant
xylazine (e.g., hydrochloride salt)	thaizine	alpha-2-adrenergic agonist	analgesic
zaprinast	cyclic amidine	phosphodiesterase v inhibitor	vasodilator

By "treating, reducing, or preventing a metabolic disorder" is meant ameliorating such a condition before or after it has occurred. As compared with an equivalent untreated control, such reduction or degree of prevention is at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, or 100% as measured by any standard technique.

A patient who is being treated for a metabolic disorder is one who a medical practitioner has diagnosed as having such a condition. Diagnosis may be performed by any suitable means, such as those described herein. A patient in whom the development of diabetes or obesity is being prevented may or may not have received such a diagnosis. One in the art will understand that patients of the invention may have been subjected to standard tests or may have been identified, without examination, as one at high risk due to the presence of one or more risk factors, such as family history, obesity, particular ethnicity (e.g., African Americans and Hispanic Americans), gestational diabetes or delivering a baby that weighs more than nine pounds, hypertension, having a pathological condition predisposing to obesity or diabetes, high blood levels of triglycerides, high blood levels of cholesterol, presence of molecular markers (e.g., presence of autoantibodies), and age (over 45 years of age). An individual is considered obese when their weight is 20% (25% in women) or more over the maximum weight desirable for their height. An adult who is more than 100 pounds overweight, is considered to be morbidly obese. Obesity is also defined as a body mass index (BMI) over 30 kg/m^2.

By "a metabolic disorder" is meant any pathological condition resulting from an alteration in a patient's metabolism. Such disorders include those resulting from an alteration in glucose homeostasis resulting, for example, in hyperglycemia. According to this invention, an alteration in glucose levels is typically an increase in glucose levels by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or even 100% relative to such levels in a healthy individual. Metabolic disorders include obesity and diabetes (e.g., diabetes type I, diabetes type II, MODY, and gestational diabetes), satiety, and endocrine deficiencies of aging.

By "reducing glucose levels" is meant reducing the level of glucose by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% relative to

an untreated control. Desirably, glucose levels are reduced to normoglycemic levels, i.e., between 150 to 60 mg/dL, between 140 to 70 mg/dL, between 130 to 70 mg/dL, between 125 to 80 mg/dL, and preferably between 120 to 80 mg/dL. Such reduction in glucose levels may be obtained by increasing any one of the biological activities associated with the clearance of glucose from the blood. Accordingly, an agent having the ability to reduce glucose levels may increase insulin production, secretion, or action. Insulin action may be increased, for example, by increasing glucose uptake by peripheral tissues and/or by reducing hepatic glucose production. Alternatively, the agent of the invention may reduce the absorption of carbohydrates from the intestines, alter glucose transporter activity (e.g., by increasing GLUT4 expression, intrinsic activity, or translocation), increase the amount of insulin-sensitive tissue (e.g., by increasing muscle cell or adipocyte cell differentiation), or alter gene transcription in adipocytes or muscle cells (e.g., altered secretion of factors from adipocytes expression of metabolic pathway genes). Desirably, the agent of the invention increases more than one of the activities associated with the clearance of glucose.

By "alter insulin signaling pathway such that glucose levels are reduced" is meant to alter (by increasing or reducing) any one of the activities involved in insulin signaling such that the overall result is an increase in the clearance of glucose from plasma. For example, the agent of the invention alters the insulin signaling pathway causing an increase in insulin production, secretion, or action, an increase in glucose uptake by peripheral tissues, a reduction in hepatic glucose production, or a reduction in the absorption of carbohydrates from the intestines.

By "patient" is meant any animal (e.g., a human), including horses, dogs, cats, pigs, goats, rabbits, hamsters, monkeys, guinea pigs, rats, mice, lizards, snakes, sheep, cattle, fish, and birds.

By "an amount sufficient" is meant the amount of a compound, alone or in combination with another therapeutic regimen, required to treat, prevent, or reduce

a metabolic disorder such as diabetes in a clinically relevant manner. A sufficient amount of an active compound used to practice the present invention for therapeutic treatment of conditions caused by or contributing to diabetes varies depending upon the manner of administration, the age, body weight, and general health of the mammal or patient. Ultimately, the prescribers will decide the appropriate amount and dosage regimen. Additionally, an effective amount may be an amount of compound in the combination of the invention that is safe and efficacious in the treatment of a patient having a metabolic disorder such as diabetes over each agent alone as determined and approved by a regulatory authority (such as the U.S. Food and Drug Administration).

By "more effective" is meant that a treatment exhibits greater efficacy, or is less toxic, safer, more convenient, or less expensive than another treatment with which it is being compared. Efficacy may be measured by a skilled practitioner using any standard method that is appropriate for a given indication.

By a "low dosage" is meant at least 5% less (e.g., at least 10%, 20%, 50%, 80%, 90%, or even 95%) than the lowest standard recommended dosage of a particular compound formulated for a given route of administration for treatment of any human disease or condition. For example, a low dosage of an agent that reduces glucose levels and that is formulated for administration by inhalation will differ from a low dosage of the same agent formulated for oral administration.

By a "high dosage" is meant at least 5% (e.g., at least 10%, 20%, 50%, 100%, 200%, or even 300%) more than the highest standard recommended dosage of a particular compound for treatment of any human disease or condition.

Compounds useful in the invention include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, esters, solvates, and polymorphs thereof, as well as racemic mixtures and pure isomers of the compounds described herein.

By "corticosteroid" is meant any naturally occurring or synthetic compound characterized by a hydrogenated cyclopentanoperhydrophenanthrene ring system and having immunosuppressive and/or anti-inflammatory activity. Naturally occurring corticosteroids are generally produced by the adrenal cortex. Synthetic corticosteroids may be halogenated. Exemplary corticosteroids are provided herein.

By "non-steroidal immunophilin-dependent immunosuppressant" or "NsIDI" is meant any non-steroidal agent that decreases proinflammatory cytokine production or secretion, binds an immunophilin, or causes a down regulation of the proinflammatory reaction. NsIDIs include calcineurin inhibitors, such as cyclosporine, tacrolimus, ascomycin, pimecrolimus, as well as other agents (peptides, peptide fragments, chemically modified peptides, or peptide mimetics) that inhibit the phosphatase activity of calcineurin. NsIDIs also include rapamycin (sirolimus) and everolimus, which bind to an FK506-binding protein, FKBP-12, and block antigen-induced proliferation of white blood cells and cytokine secretion.

By "small molecule immunomodulator" is meant a non-steroidal, non-NsIDI compound that decreases proinflammatory cytokine production or secretion, causes a down regulation of the proinflammatory reaction, or otherwise modulates the immune system in an immunophilin-independent manner.

In the generic descriptions of compounds of this invention, the number of atoms of a particular type in a substituent group is generally given as a range, e.g., an alkyl group containing from 1 to 4 carbon atoms or C_{1-4} alkyl. Reference to such a range is intended to include specific references to groups having each of the integer number of atoms within the specified range. For example, an alkyl group from 1 to 4 carbon atoms includes each of C_1, C_2, C_3, and C_4. A C_{1-12} heteroalkyl, for example, includes from 1 to 12 carbon atoms in addition to one or more

heteroatoms. Other numbers of atoms and other types of atoms may be indicated in a similar manner.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 6 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

By "C_{1-4} alkyl" is meant a branched or unbranched hydrocarbon group having from 1 to 4 carbon atoms. A C_{1-4} alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{1-4} alkyls include, without limitation, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and cyclobutyl.

By "halogen" is meant bromine, chlorine, iodine, or fluorine.

By "alkoxy" is meant a chemical substituent of the formula -OR, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

Other features and advantages of the invention will be apparent from the detailed description and from the claims.

Brief Description of the Drawings

FIG 1 is a graph showing insulin sensitivity in male Sprague Dawley rats, as determined using the homeostasis model assessment (HOMA). Insulin resistance was induced by four weeks of high fat feeding (60% of calories derived from fat). Drug treatment began one week after initiation of high fat diet. Drugs were administered daily, by oral gavage for a three week period.

Following the three weeks of treatment, animals were fasted for five hours and anesthetized, and blood collected from the inferior vena cava for determination of serum glucose and insulin levels. Insulin sensitivity was determined using HOMA.

$$\text{HOMA} = \frac{\text{fasting serum glucose X fasting serum insulin}}{22.5}$$

Pio=pioglitazone; Bez-bezafibrate; DF=diflunisal; HF=high fat.

FIG 2 is a graph showing blood glucose levels in male Sprague Dawley rats. Insulin resistance was induced by four weeks of high fat feeding (60% of calories derived from fat). Drug treatment began one week after initiation of high fat diet. Drugs were administered daily, by oral gavage for a three week period. Following the three weeks of treatment, animals were fasted for five hours and anesthetized, and blood collected from the inferior vena cava.

FIG 3 is a graph showing blood serum insulin levels in male Sprague Dawley rats. Insulin resistance was induced by four weeks of high fat feeding (60% of calories derived from fat). Drug treatment began one week after initiation of high fat diet. Drugs were administered daily, by oral gavage for a three week period. Following the three weeks of treatment, animals were fasted for five hours and anesthetized, and blood collected from the inferior vena cava.

Detailed Description

We have discovered compounds that the certain bezafibrate-containing combinations have in vitro and in vivo activities that suggest that these combinations may be useful for treating a patient that has been diagnosed with or is at risk of having a metabolic disorder. Optionally, analogs of these agents may be employed. In the case of diabetes and obesity, for example, such administration may reduce the levels of glucose, reduce levels of LDL-cholesterol, increase the levels of HDL-cholesterol, result in a more favorable ratio between

LDL-cholesterol and HDL-cholesterol, reduce the triglyceride values, or reduce serum levels of CRP (C-reactive protein). The ability of the agent to cause the clearance of glucose may be attributed, for example, to its ability to increase insulin production, secretion, or action (e.g., stimulation of glucose uptake by peripheral tissues and/or reduction in hepatic glucose production), reduce the absorption of carbohydrates from the intestines, alter glucose transporter activity (e.g., by increasing GLUT4 expression, intrinsic activity, or translocation), increase the level of insulin-sensitive tissue (e.g., by increasing adipocyte or muscle cell differentiation), or alter gene transcription in adipocytes or muscle cells (e.g., altered secretion of factors from adipocytes and expression of metabolic pathway genes).

In one example, we propose that the administration of bezafibrate and cinnamic acid to a patient having a metabolic disorder such as diabetes within 14 days of each other will treat, prevent, or reduce the metabolic disorder. In another example, the administration of bezafibrate and diflunisal to the patient within 14 days of each other will also treat, prevent, or reduce the metabolic disorder. The two agents are desirably administered within 10 days of each other, more desirably within seven days of each other, and even more desirably within twenty-four hours of each other, one hour of each other, or even simultaneously (i.e., concomitantly). If desired, either one of the two agents may be administered in low dosage.

In view of this discovery, the aforementioned combinations of drugs can be used in a variety of compositions, methods, and kits, as described herein. Additionally, if desired, structural or functional analogs may be used in place of one or more of the drugs in a combination. Such analogs are described below.

We have also discovered compounds that, alone or in combination, are effective in the treatment, reduction, or prevention of metabolic disorders such as diabetes and obesity. Accordingly, a mammal that has been diagnosed with or is at risk of having a metabolic disorder is administered one, two, three, or more

agents from Table 1. Optionally, analogs of these agents may be employed. In the case of diabetes and obesity, for example, such administration may reduce the levels of glucose, reduce levels of LDL-cholesterol, increase the levels of HDL-cholesterol, result in a more favorable ratio between LDL-cholesterol and HDL-cholesterol, reduce the triglyceride values, or reduce serum levels of CRP (C-reactive protein). The ability of the agent to cause the clearance of glucose may be attributed, for example, to its ability to increase insulin production, secretion, or action (e.g., stimulation of glucose uptake by peripheral tissues and/or reduction in hepatic glucose production), reduce the absorption of carbohydrates from the intestines, alter glucose transporter activity (e.g., by increasing GLUT4 expression, intrinsic activity, or translocation), increase the level of insulin-sensitive tissue (e.g., by increasing adipocyte or muscle cell differentiation), or alter gene transcription in adipocytes or muscle cells (e.g., altered secretion of factors from adipocytes and expression of metabolic pathway genes). Optionally, the mammal may also receive other therapeutic regimens.

In one particular example, the mammal being treated is administered two agents listed in Table 1 within 28 days of each other in amounts that together are sufficient to treat, prevent, or reduce the metabolic disorder. The two agents are desirably administered within 14 days of each other, more desirably within seven days of each other, and even more desirably within twenty-four hours of each other, or even simultaneously (i.e., concomitantly). If desired, either one of the two agents may be administered in low dosage.

Diagnosis of metabolic disorders

The methods and compositions of the present invention are useful for treating any patient that has been diagnosed with or is at risk of having a metabolic disorder, such as diabetes. A patient in whom the development of a metabolic disorder (e.g., diabetes or obesity) is being prevented may or may not have

received such a diagnosis. One in the art will understand that patients of the invention may have been subjected to standard tests or may have been identified, without examination, as one at high risk due to the presence of one or more risk factors.

Diagnosis of metabolic disorders may be performed using any standard method known in the art, such as those described herein. Methods for diagnosing diabetes are described, for example, in U.S. Patent No. 6,537,806, hereby incorporated by reference. Diabetes may be diagnosed and monitored using, for example, urine tests (urinalysis) that measure glucose and ketone levels (products of the breakdown of fat); tests that measure the levels of glucose in blood; glucose tolerance tests; and assays that detect molecular markers characteristic of a metabolic disorder in a biological sample (e.g., blood, serum, or urine) collected from the mammal (e.g., measurements of Hemoglobin A1c (HbA1c) levels in the case of diabetes).

Patients may be diagnosed as being at risk or as having diabetes if a random plasma glucose test (taken at any time of the day) indicates a value of 200 mg/dL or more, if a fasting plasma glucose test indicates a value of 126 mg/dL or more (after 8 hours), or if an oral glucose tolerance test (OGTT) indicates a plasma glucose value of 200 mg/dL or more in a blood sample taken two hours after a person has consumed a drink containing 75 grams of glucose dissolved in water. The OGTT measures plasma glucose at timed intervals over a 3-hour period. Desirably, the level of plasma glucose in a diabetic patient that has been treated according to the invention ranges between 160 to 60 mg/dL, between 150 to 70 mg/dL, between 140 to 70 mg/dL, between 135 to 80 mg/dL, and preferably between 120 to 80 mg/dL.

Optionally, a hemoglobin A1c (HbA1c) test, which assesses the average blood glucose levels during the previous two and three months, may be employed. A person without diabetes typically has an HbA1c value that ranges between 4%

and 6%. For every 1% increase in HbA1c, blood glucose levels increases by approximately 30 mg/dL and the risk of complications increases. Preferably, the HbA1c value of a patient being treated according to the present invention is reduced to less than 9%, less than 7%, less than 6%, and most preferably to around 5%. Thus, the HbA1c levels of the patient being treated are preferably lowered by 10%, 20%, 30%, 40%, 50%, or more relative to such levels prior to treatment.

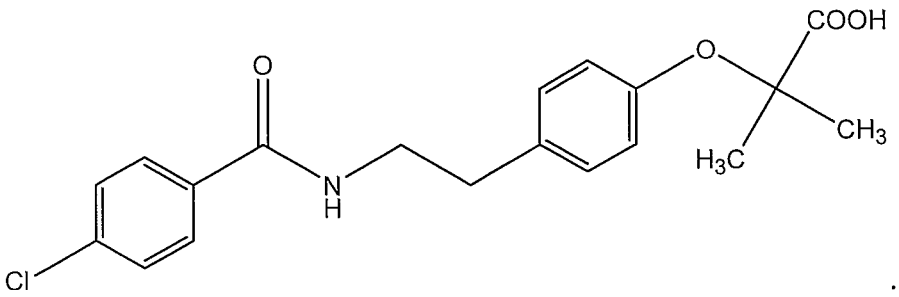
Gestational diabetes is typically diagnosed based on plasma glucose values measured during the OGTT. Since glucose levels are normally lower during pregnancy, the threshold values for the diagnosis of diabetes in pregnancy are lower than in the same person prior to pregnancy. If a woman has two plasma glucose readings that meet or exceed any of the following numbers, she has gestational diabetes: a fasting plasma glucose level of 95 mg/dL, a 1-hour level of 180 mg/dL, a 2-hour level of 155 mg/dL, or a 3-hour level of 140 mg/dL.

Ketone testing may also be employed to diagnose type 1diabetes. Because ketones build up in the blood when there is not enough insulin, they eventually accumulate in the urine. High levels of blood ketones may result in a serious condition called ketoacidosis.

The use of any of the above tests or any other tests known in the art may be used to monitor the efficacy of the present treatment. Since the measurements of hemoglobin A1c (HbA1c) levels is an indication of average blood glucose during the previous two to three months, this test may be used to monitor a patient's response to diabetes treatment.

Bezafibrate

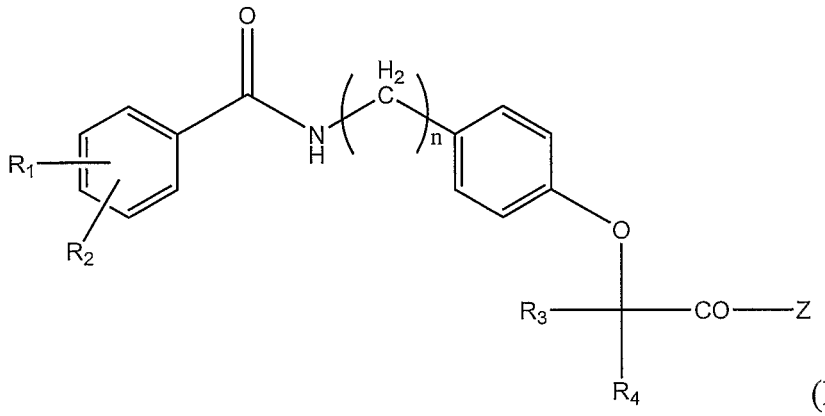
Bezafibrate (2-[4-2-[(4-chlorobenzoyl)amino]-ethyl]phenozy]-2-methylpropanoic acid) has the following structure:



The synthesis of bezafibrate is described in U.S. Patent No. 3,781,328.

Bezafibrate analogs

Bezafibrate analogs include binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil. Other bezafibrate analogs are described by formula (I).



(I).

In this formula, each of R_1 and R_2 is, independently, hydrogen, halogen, C_{1-4} alkyl, and C_{1-4} alkoxy, each of R_3 and R_4 is, independently, hydrogen and C_{1-4} alkyl, n is 1, 2, and 3, and Z is hydroxyl and C_{1-4} alkyl.

Specific bezafibrate analogs of formula (I) are alpha-[4-(2-methoxy-5-chlorobenzoylaminoethyl)-phenoxy-]isobutyric acid, alpha-[4-(4-methylbenzoylaminomethyl)-phenoxy]-isobutyric acid, alpha-[4-(2-methylbenzoylaminoethyl)-phenoxy]-isobutyric acid, and alpha-[4-(4-chlorobenzoylaminoethyl)-phenoxy]-proprionic acid.

Bezafibrate analogs are also described in U.S. Patent Nos. 3,262,850; 3,674,836; 3,716,583; 3,723,446, 3,948,973; 4,010,279; 4,026,896; 4,042,711;

4,058,552; 4,151,303; 4,153,728; 4238,506; 4,318,923; and 4,409,240, each of which is hereby incorporated by reference.

PPAR agonists

PPARs (Peroxisome Proliferator-Activated receptors) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. Three different PPARs have been identified to date (PPARα, PPARβ and PPARγ) each displaying distinct tissue distribution pattern. PPARs are activated by natural ligands such as fatty acids and eicosanoids (leukotrienes, prostaglandins) and by pharmacological agonists such as fibrates, binding to PPARα and glitazones, binding to PPARγ. Upon ligand activation, PPARs regulate the transcription of several genes. Activated PPARs heterodimerize with another nuclear receptor, the retinoid X receptor, and modify the transcription of target genes after binding to specific peroxisome proliferator response elements (PPRE).

Bezafibrate is a fibrate and thus a PPARα agonist. Because of the interaction between PPARα and PPARγ, PPARγ agonists may nonetheless be used in place of bezafibrate in the compositions, methods, and kits of the invention. For example, glitazones (e.g., balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, and CS-011), also referred to as thiazolidinediones, can be used in combination with cinnamic acid, diflunisal, or an analog thereof, for treating a patient having a metabolic disorder. Similarly, tyrosine-based PPARγ modulators (e.g., GI262570; [(S)-2-(2-benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyl-2-oxazol-4-yl)ethoxy]phenyl]propionic acid, and GW347845 (Cobb et al., J Med Chem. 41:5055-5069, 1998)) can also be substituted for bezafibrate, as can other PPARγ

agonists (e.g., 3-(2,4-dichlorobenzyl)-2-methyl-N-(pentylsulfonyl)-3 H-benzimidazole-5-carboxamide (FK614)).

Other PPAR agonists that may be used in lieu of bezafibrate in the compositions, methods, and kits of the invention are AA-10090, AD-5075, AMG-131, ARH-049020, AVE-0847, AVE-8134, AY-31637, BAY-549801, bexarotene, BM-131246, BM-501050, CLX-0921, CLX-0940, DRF-10945, DRF-4832, E-3030, farglitazar, fenofibrate/metformin, GW-0072, GW-1929, GW-2570, GW-409544, GW-409890, GW-501516, GW-5393, GW-590735, GW-7282, GW-9578, KRP-101, KT-6207, L-764406, LF-200337, LG-101506, LR-90, LY-465608, LY-510929, LY-518674, MBX-102, MK-0767, muraglitazar, naveglitazar, NC-2100, NS-220, ONO-5129, oxeglitazar, PD-72953, R-119702, ragaglitazar, reglitazar, SB-219994, tesaglitazar, 641597, and TY-51501.

Statins

Statins or statin-containing drug combinations may be used in lieu of bezafibrate in the compositions, methods, and kits of the invention. Exemplary statins and statin-containing combinations are acitemate, amlodipine/atorvastatin, atorvastatin, atorvastatin/torcetrapib, BAY102987, BAY X 2678, BB476, bervastatin, BMY21950, BMY22089, cerivastatin, colestolone, CP83101, crilvastatin, dalvastatin, DMP565, ezetimibe/simvastatin, fluvastatin, glenvastatin, L659699, L669262, mevastatin, nicotinic acid/lovastatin, nicotinic acid/simvastatin, P882222, P882284, PD134965, PD135022, pitavastatin, rosuvastatin, RP61969, S2468, SC37111, SC45355, simvastatin, SQ33600, SR12813, SR45023A, U20685, and U88156.

NSAIDs

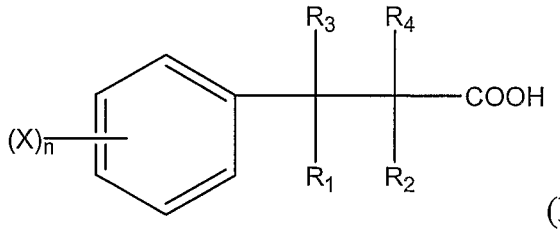
NSAIDs may also be used in lieu of bezafibrate in the combinations, methods, and kits of the invention. Suitable NSAIDs include A183827, ABT963,

aceclofenac, acemetacin, acetyl salicylic acid, AHR10037, alclofenac, alminoprofen, ampiroxicam, amtolmetin guacil, apazone, aspirin, atliprofen methyl ester, AU8001, benoxaprofen, benzydamine flufenamate, bermoprofen, bezpiperylon, BF388, BF389, BIRL790, BMS347070, bromfenac, bucloxic acid, butibufen, BW755C, C53, C73, C85, carprofen, CBS1108, celecoxib, CHF2003, chlorobiphenyl, choline magnesium trisalicylate, CHX108, cimicoxib, cinnoxicam, clidanac, CLX1205, COX-2 inhibitor (PharmaVU/Vanderbilt University), CP331, CS502, CS706, D1367, darbufelone, deracoxib, dexibuprofen, dexibuprofen lysine, dexketoprofen, DFP, DFU, diclofenac (e.g., diclofenac potassium, diclofenac sodium), diflunisal, DP155, DRF4367, E5110, E6087, eltenac, ER34122, esflurbiprofen, etoricoxib, F025, felbinac ethyl, fenbufen, fenclofenac, fenclozic acid, fenclozine, fenoprofen, fentiazac, feprazone, filenadol, flobufen, florifenine, flosulide, flubichin methanesulfonate, flufenamic acid, fluprofen, flurbiprofen, FPL62064, FR122047, FR123826, FR140423, FR188582, FS205397, furofenac, GR253035, GW406381, HAI105, HAI106, HCT2035, HCT6015, HGP12, HN3392, HP977, HX0835. HYAL AT2101, ibufenac, ibuprofen, ibuproxam-beta-cyclodextrin, icodulinum, IDEA070, iguratimod, imrecoxib, indomethacin, indoprofen, IP751, isoxepac, isoxicam, KC764, ketoprofen, L652343, L745337, L748731, L752860, L761066, L768277, L776967, L783003, L784520, L791456, L804600, L818571, LAS33815, LAS34475, licofelone, LM 4108, lobuprofen, lornoxicam, lumiracoxib, mabuprofen, meclofenamic acid, meclofenamate sodium, mefenamic acid, meloxicam, mercaptoethylguanidine, mesoporphyrin, metoxibutropate, miroprofen, mofebutazone, mofezolac, MX1094, nabumetone, naproxen sodium, naproxen-sodium/metoclopramide, NCX1101, NCX284, NCX285, NCX4016, NCX4215, NCX530, niflumic acid, nitric oxide-based COX-2 inhibitors and NSAIDs (NitroMed), nitrofenac, nitroflurbiprofen, nitronaproxen, NS398, ocimum sanctum oil, ONO3144, orpanoxin, oxaprozin, oxindanac, oxpinac,

oxycodone/ibuprofen, oxyphenbutazone, P10294, P54, P8892, pamicogrel, parcetasal, parecoxib, PD138387, PD145246, PD164387, pelubiprofen, pemedolac, phenylbutazone, pirazolac, piroxicam, piroxicam beta-cyclodextrin, piroxicam pivalate, pirprofen, pranoprofen, resveratrol, R-ketoprofen, R-ketorolac, rofecoxib, RP66364, RU43526, RU54808, RWJ63556, S19812, S2474, S33516, salicylsalicylic acid, satigrel, SC236, SC57666, SC58125, SC58451, SFPP, SKF105809, SKF86002, sodium salicylate, sudoxicam, sulfasalazine, sulindac, suprofen, SVT2016, T3788, TA60, talmetacin, talniflumate, tazofelone, tebufelone, tenidap, tenoxican, tepoxalin, tiaprofenic acid, tilmacoxib, tilnoprofen arbamel, tinoridine, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, triflusal, tropesin, TY10222, TY10246, TY10474, UR8962, ursolic acid, valdecoxib, WAY120739, WY28342, WY41770, ximoprofen, YS134, zaltoprofen, zidometacin, and zomepirac.

Cinnamic acid and analogs thereof

Cinnamic acid (3-phenyl-2-propenoic acid) has the structure $C_6H_5CH=CHCOOH$. Cinnamic acid analogs are described by formula (II):



(II).

In formula (II), R_1 and R_2 each represent a hydrogen atom or a C_{1-4} alkyl group; R_3 and R_4 each represent a hydrogen atom or may be combined together to form an additional chemical bond; X represents a hydroxyl group, a halogen atom, a straight or branched chain saturated or unsaturated C_{1-4} alkyl group, a straight or branched chain saturated or unsaturated C_{1-4} alkoxy group, a C_{1-4} acyloxy group, or a C_{3-6} cycloalkyl group; n is zero or an integer from 1 to 3, with the proviso that

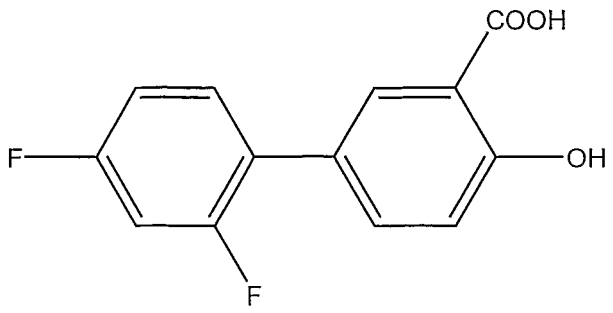
when n is 2 or 3, each X may be the same or different and that when two X's are commonly the alkyl or alkoxy group, both X's may be combined together to form a ring.

Specific cinnamic acid analogs of formula (II) are hydrocinnamic acid, 2-, 3- and 4-methylhydrocinnamic acid, 2-, 3- and 4-ethylhydrocinnamic acid, 2-, 3- and 4-propylhydrocinnamic acid, 2-, 3- and 4-hydroxyhydrocinnamic acid, 2-, 3- and 4-methoxyhydrocinnamic acid, 2-, 3- and 4-ethoxyhydrocinnamic acid, 2-, 3- and 4-chlorohydrocinnamic acid, 2-, 3- and 4-bromohydrocinnamic acid, 2-, 3- and 4-fluorohydrocinnamic acid, 2, 4-, 2,5- and 3,4-dimethylhydrocinnamic acid, 2,4-diethylhydrocinnamic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihydroxyhydrocimmamic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyhydrocinnamic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyhydrocinnamic acid, 2,3-, 2,4- and 3,4-dipropoxyhydrocinnamic acid, 2-hydroxy-3-methoxyhydrocinnamic acid, 3-hydroxy-4-methoxyhydrocinnamic acid, 4-hydroxy-3-methoxyhydrocinnamic acid, 3-ethoxy-4-methoxyhydrocinnamic acid, 4-hydroxy-3-methoxyhydrocinnamic acid, 2-ethoxy-3-methoxyhydrocinnamic acid, 3-ethoxy-4-methoxyhydrocinnamic acid, 4-ethoxy-3-methoxyhydrocinnamic acid, 3-methoxy-2-propoxyhydrocinnamic acid, 3-methoxy-4-propoxyhydrocinnamic acid, 3,4-methylenedioxyhydrocinnamic acid, 2,4-, 2,6- and 3,4-dichlorohydrocinnamic acid, 2,3,4-, 2,4,5- and 3,4,5-trimethoxyhydrocinnamic acid, 2-bromo-4-hydroxy-5-methoxyhydrocinnamic acid, 4-isopropylhydrocinnamic acid, 3- and 4-isopropoxyhydrocinnamic acid, 3- and 4-isobutoxyhydrocinnamic acid, 3- and 4-sec-butoxyhydrocinnamic acid, 3-methoxy-4-isopropoxyhydrocinnamic acid, 2-, 3- and 4-allyloxyhydrocinnamic acid, 2-, 3- and 4-methallyloxyhydrocinnamic acid, 3-methoxy-4-allyloxyhydrocinnamic acid, 3-methoxy-4-methallyloxyhydrocinnamic acid, 2-, 3- and 4-acetoxyhydrocinnamic acid, 3,4-trimethylenehydrocinnamic acid, and α- and/or β-alkyl-substituted hydrocinnamic acids carrying substituents the same as

those mentioned in the case of the above-mentioned hydrocinnamic acids; and aromatic unsaturated carboxylic acids such as 2-, 3- and 4-methylcinnamic acid, 2-, 3- and 4-ethylcinnamic acid, 2-, 3- and 4-propylcinnamic acid, 2-, 3- and 4-hydroxycinnamic acid, 2-, 3- and 4-methoxycinnamic acid, 2-, 3- and 4-ethoxycinnamic acid, 2-, 3- and 4-propoxycinnamic acid, 2-, 3- and 4-butoxycinnamic acid, 2-, 3- and 4-fluorocinnamic acid, 2-, 3- and 4-chlorocinnamic acid, 2-, 3- and 4-bromocinnamic acid, 2,4- and 2,5 and 3,4-dimethylcinnamic acid, 2,4-diethylcinnamic acid, 2,3-, 2,4-, 2,5- 2,6-, 3,4- and 3,5-dihydroxycinnamic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxycinnamic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxycinnamic acid, 2,3-, 2,4- and 3,4-dipropoxycinnamic acid, 2-hydroxy-3-methoxycinnamic acid, 3-hydroxy-4-methoxycinnamic acid, 4-hydroxy-3-methoxycinnamic acid, 2-ethoxy-3-methoxycinnamic acid, 3-ethoxy-4-methoxycinnamic acid, 4-ethoxy-3-methoxycinnamic acid, 3-methoxy-2-propoxycinnamic acid, 3-methoxy-4-propoxycinnamic acid, 3,4-methylenedioxycinnamic acid, 2,4-, 2,6- and 3,4-dichlorocinnamic acid, 2,3,4-, 2,4,5- and 3,4,5-trimethoxycinnamic acid, 2-bromo-4-hydroxy-5-methoxycinnamic acid, 4-isopropylcinnamic acid, 3- and 4-isopropoxycinnamic acid, 3- and 4-isobutoxycinnamic acid, 3- and 4-sec-butoxycinnamic acid, 3-methoxy-4-isoproxycinnamic acid, 2-, 3- and 4-allyloxycinnamic acid, 2-, 3- and 4-methallyloxycinnamic acid, 3-methoxy-4-allyloxycinnamic acid, 3-methoxy-4-methallyloxycinnamic acid, 2-, 3- and 4-acetoxycinnamic acid, 3,4-trimethylenecinnamic acid, and α- and/or β -alkylsubstituted cinnamic acids carrying substituents the same as those mentioned in the case of the above-mentioned cinnamic acids.

Diflunisal

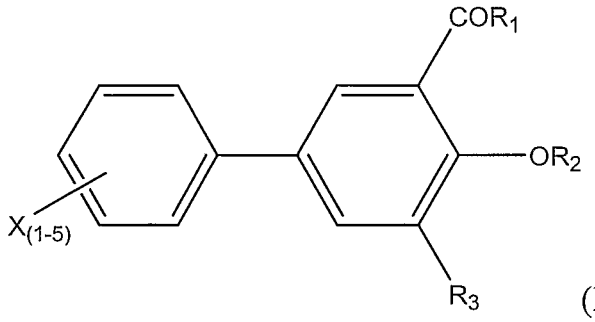
Diflunisal (2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid) is an NSAID having the structure:



Methods of making diflunisal are described in U.S. Patent No. 3,714,226.

Diflunisal analogs

Diflunisal analogs are described by formula (III):



(III)

wherein each X is, independently, a halogen atom; R_1 is selected from the group consisting of hydroxy, phenoxy, di(C_1-C_4)alkylamino, di(C_1-C_4)alkylamino (C_1-C_4)alkoxy; R_2 is selected from the group consisting of hydrogen and (C_1-C_4)alkanoyl (such as acetyl, propionyl and butyryl); and R_3 is selected from the group consisting of hydrogen and methyl.

Other diflunisal analogs are flufenisal, 2-hydroxy-5-(4'-fluorophenyl)benzoic acid; 2-acetoxy-5-(4'-fluorophenyl)benzoic acid; 2-hydroxy-5-(2'-fluorophenyl)benzoic acid; 2-hydroxy-5-(3'-fluorophenyl)benzoic acid; 2-hydroxy-5-pentafluorophenyl benzoic acid; 2-hydroxy-3-methyl-5-(4'-fluorophenyl)benzoic acid; 2-hydroxy-5-(4'-chlorophenyl)benzoic acid; N,N-dimethyl-5-(4'-fluorophenyl)salicylamide; β-diethylaminoethyl-5-(4'-fluorophenyl)salicylate; phenyl-5-(4'-fluorophenyl)salicylate; aluminum-2-acetoxy-5-(4'-fluorophenyl)-benzoate salt; aluminum-2-hydroxy-5-(4'-

fluorophenyl)-benzoate salt; choline-2-acetoxy-5-(4'-fluorophenyl)-benzoate salt; choline-2-hydroxy-5-(4'-fluorophenyl)-benzoate salt; sodium-2-acetoxy-5-(4'-fluorophenyl)-benzoate salt; sodium-2-hydroxy-5-(4'-fluorophenyl)-benzoate salt; 2-hydroxy-5-(pentafluorophenyl)-benzoic acid; 2-acetoxy-5-(pentafluorophenyl)-benzoic acid; β-diethylaminoethyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate; β-diethylaminoethyl-2-acetoxy-5-(4'-fluorophenyl)-benzoate; 2-hydroxy-5-(4'-fluorophenyl)-benzamide; 2-hydroxy-5-(4'-fluorophenyl)-3-methyl benzamide; 2-acetoxy-5-(4'-fluorophenyl)-benzamide; 2-acetoxy-5-(4'-fluorophenyl)-benzmorpholide; 2-hydroxy-5-(4'-fluoro-2'-methoxyphenyl)benzoic acid; 2-acetoxy-5-(4'-fluoro-2'-methoxyphenyl)benzoic acid; 2-hydroxy-5-(4'-fluoro-2'-methylphenyl)benzoic acid; 2-acetoxy-5-(4'-fluoro-3'-methylphenyl)benzoic acid;2-hydroxy-3-allyl-5-(4'-fluorophenyl)benzoic acid; 2-hydroxy-3-propyl-5-(4'-fluorophenyl)benzoic acid; and the compounds described in U.S. Patent Nos. 3,674,870, 3,681,445, 3,692,821, 3,714,226, 4,044,049, 4,542,158, and 6,593,365.

If desired, other NSAIDs can be used in place diflunisal. Suitable NSAIDs include A183827, ABT963, aceclofenac, acemetacin, acetyl salicylic acid, AHR10037, alclofenac, alminoprofen, ampiroxicam, amtolmetin guacil, apazone, aspirin, atliprofen methyl ester, AU8001, benoxaprofen, benzydamine flufenamate, bermoprofen, bezpiperylon, BF388, BF389, BIRL790, BMS347070, bromfenac, bucloxic acid, butibufen, BW755C, C53, C73, C85, carprofen, CBS1108, celecoxib, CHF2003, chlorobiphenyl, choline magnesium trisalicylate, CHX108, cimicoxib, cinnoxicam, clidanac, CLX1205, COX-2 inhibitor (PharmaVU/Vanderbilt University), CP331, CS502, CS706, D1367, darbufelone, deracoxib, dexibuprofen, dexibuprofen lysine, dexketoprofen, DFP, DFU, diclofenac (e.g., diclofenac potassium, diclofenac sodium), diflunisal, DP155, DRF4367, E5110, E6087, eltenac, ER34122, esflurbiprofen, etoricoxib, F025, felbinac ethyl, fenbufen, fenclofenac, fenclozic acid, fenclozine, fenoprofen, fentiazac, feprazone, filenadol, flobufen, florifenine, flosulide, flubichin

methanesulfonate, flufenamic acid, fluprofen, flurbiprofen, FPL62064, FR122047, FR123826, FR140423, FR188582, FS205397, furofenac, GR253035, GW406381, HAI105, HAI106, HCT2035, HCT6015, HGP12, HN3392, HP977, HX0835. HYAL AT2101, ibufenac, ibuprofen, ibuproxam-beta-cyclodextrin, icodulinum, IDEA070, iguratimod, imrecoxib, indomethacin, indoprofen, IP751, isoxepac, isoxicam, KC764, ketoprofen, L652343, L745337, L748731, L752860, L761066, L768277, L776967, L783003, L784520, L791456, L804600, L818571, LAS33815, LAS34475, licofelone, LM 4108, lobuprofen, lornoxicam, lumiracoxib, mabuprofen, meclofenamic acid, meclofenamate sodium, mefenamic acid, meloxicam, mercaptoethylguanidine, mesoporphyrin, metoxibutropate, miroprofen, mofebutazone, mofezolac, MX1094, nabumetone, naproxen sodium, naproxen-sodium/metoclopramide, NCX1101, NCX284, NCX285, NCX4016, NCX4215, NCX530, niflumic acid, nitric oxide-based COX-2 inhibitors and NSAIDs (NitroMed), nitrofenac, nitroflurbiprofen, nitronaproxen, NS398, ocimum sanctum oil, ONO3144, orpanoxin, oxaprozin, oxindanac, oxpinac, oxycodone/ibuprofen, oxyphenbutazone, P10294, P54, P8892, pamicogrel, parcetasal, parecoxib, PD138387, PD145246, PD164387, pelubiprofen, pemedolac, phenylbutazone, pirazolac, piroxicam, piroxicam beta-cyclodextrin, piroxicam pivalate, pirprofen, pranoprofen, resveratrol, R-ketoprofen, R-ketorolac, rofecoxib, RP66364, RU43526, RU54808, RWJ63556, S19812, S2474, S33516, salicylsalicylic acid, satigrel, SC236, SC57666, SC58125, SC58451, SFPP, SKF105809, SKF86002, sodium salicylate, sudoxicam, sulfasalazine, sulindac, suprofen, SVT2016, T3788, TA60, talmetacin, talniflumate, tazofelone, tebufelone, tenidap, tenoxican, tepoxalin, tiaprofenic acid, tilmacoxib, tilnoprofen arbamel, tinoridine, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, triflusal, tropesin, TY10222, TY10246, TY10474, UR8962, ursolic acid, valdecoxib, WAY120739, WY28342, WY41770, ximoprofen, YS134, zaltoprofen, zidometacin, and zomepirac.

Additional therapeutic agents

The present invention involves the administration of an effective amount of one, two, three, four, or more agents listed in Table 1 to a mammal at risk of having or having a metabolic disorder, thereby treating, preventing, and reducing such a disorder.

In the case of diabetes, the agent of the invention increases the clearance of glucose from the plasma by any mechanism thereby reducing glucose levels to normoglycemic levels. For example, a combination of the invention may alter the insulin signaling pathway, reduce the absorption of carbohydrates from the intestines, alter glucose transporter activity (e.g., by increasing GLUT4 expression, intrinsic activity, or translocation), increase the level of insulin-sensitive tissue (e.g., by increasing adipocyte or muscle cell differentiation), or alter gene transcription in adipocytes or muscle cells (e.g., altered secretion of factors from adipocytes expression of metabolic pathway genes). Given that plasma glucose levels prior to eating typically range between 80 and 120 mg/dL and that postprandial blood levels range between 100 to 140 mg/dL, the plasma glucose levels of the patient being treated according to the invention is stabilized such that glucose levels range between 60 and 150 mg/dL, between 70 and 140 mg/dL, between 80 and 130 mg/dL, and preferably between 80 and 120 mg/dL prior to a meal and between 90 mg/dL to 160 mg/dL, between 90 mg/dL to 150 mg/dL, and preferably between 90 to 140 mg/dL two hours after eating. A particularly desirable result of treatment is a reduction of any of the symptoms associated with the metabolic disorder.

Analogs of any of the compounds listed in Table 1 may be used in any of the methods, kits, and compositions of the invention. Analogs are known in the art (e.g., as described herein). Acemetacin analogs are described in German patent DE 2234651 and U.S.P.N. 3,910952. Acenocoumarol analogs are described in

U.S.P.N. 2,648,682. Acetaminophen analogs are described in U.S.P.N. 2,998,450 and German patent DE 453577. Acetazolamide analogs are described in U.S.P.N. 2,554,816. Acetohexamide analogs are described in GB 912789. Acetyldigitoxin analogs are described in U.S.P.N. 2,776,963. Alachlor analogs are described in NL 6602564. Albuterol (Salbutamol) analogs are described in ZA 67 05591 and U.S.P.N. 3,644,353. Alprenolol analogs are described in NL 6605692 and NL 6612958. Ametryn analogs are described in CH 337019 and U.S.P.N. 3,558,622. Atrazine analogs are described in CH 342784, CH 342785, HU 149189, and FR 1317812. Azathioprine analogs are described in U.S.P.N. 3,056,785 and benzbromarone analogs are described in BE 553621 and U.S.P.N. 3,012,042. Bezafibrate analogs are described in DE 2149070 and U.S.P.N. 3,781,328. Bopindolol analogs are described in U.S.P.N. 4,340,541 and DE 2635209. Brimonidine analogs are described in U.S.P.N. 3,890,319 and German patent DE 2309160. Brompheniramine (e.g., maleate salt) analogs are described in U.S.P.N. 2,567,245, U.S.P.N. 2,676,964, and U.S.P.N. 3,061,517. Candesartan (e.g., cilexetil salt) analogs are described in EP 459136 and U.S.P.N. 5,196,444, captopril analogs are described in DE 2703828, U.S.P.N. 4,046,889, and U.S.P.N. 4,105,776, and carbamazepine analogs are described in U.S.P.N. 2,948,718. Carbinoxamine (e.g., maleate salt) analogs are described in U.S.P.N. 2,606,195, U.S.P.N. 2,800,485, and GB 905993. Carisoprodol analogs are described in U.S.P.N. 2,937,119 and cefamandole (e.g., nafate salt) analogs are described in German patents DE 2018600 and DE 2312997, as well as U.S.P.N. 3,641,021 and U.S.P.N. 3,840,531. Cefpodoxime Proxetil analogs are described in EP 49118 and U.S.P.N. 4,486,425. Ciclopirox analogs are described in ZA 69 06039 and U.S.P.N. 3,883,545. Clenbuterol analogs are described in ZA 67 05692 and U.S.P.N. 3,536,712. Diacerein analogs are described in German patent DE 2711493, Japanese Patent JP Kokai 83 225015, U.S.P.N. 4,244,968, and U.S.P.N. 4,346,103. Diclofenac (e.g., sodium salt) analogs are described in U.S.P.N.

3,558,690 and NL 6604752. Dicloxacillin (e.g., sodium salt) analogs are described in GB 978299 and U.S.P.N. 3,239,507. Diflunisal analogs are described in ZA 67 01021, FR 1522570, and U.S.P.N. 3,714,226. Dimenhydrinate analogs are described in U.S.P.N. 2,499,058 and U.S.P.N. 2,534,813. Diphemanil Methylsufate analogs are described in U.S.P.N. 2,739,968. Diphenhydramine (e.g., hydrochloride salt) analogs are described in U.S.P.N. 2,421,714, U.S.P.N. 2,427,878, and U.S.P.N. 2,397,799 as well as Japanese patent JP 64 243. Diphenidol (e.g., hydrochloride salt) analogs are described in U.S.P.N. 2,411,664 and GB 683950. Dipivefrin (e.g., hydrochloride salt) analogs are described in German patents DE 2152058 and DE 2343657 as well as U.S.P.N. 4,085,270, U.S.P.N. 3,809,714, and U.S.P.N. 3,839,584. Dirithromycin analogs are described in BE 840431 and U.S.P.N. 4,048,306. 5-Hydroxytryptophan (e.g., DL form) analogs are described in CA 619472 and GB 845034. Doxapram (e.g., hydrochloride salt) analogs are described in BE 613734 and U.S.P.N. 3,192,206. Doxycycline analogs are described in U.S.P.N. 3,019,260 and U.S.P.N. 3,200,149. Enalaprilat analogs are described in EP 12401 and U.S.P.N. 4,374,829. Ethopropazine (e.g., hydrochloride salt) analogs are described in U.S.P.N. 2,607,773. Etoposide analogs are described in U.S.P.N. 3,524,844. Evans Blue analogs are described in German patents DE 35341, DE 38802, DE 3949, DE 57327, and DE 75469. Exemestane analogs are described in U.S.P.N. 4,808,616 and German patent DE 3622841. Flunixin (e.g., meglumine salt) analogs are described in BE 679271, BE 812772, as well as U.S.P.N. 3,337,570 and U.S.P.N. 3,839,344. Gemfibrozil analogs are described in DE 1925423 and U.S.P.N. 3,674,836 and U.S.P.N. 4,126,637. Indocyanine Green analogs are described in U.S.P.N. 2,895,955. Indomethacin analogs are described in U.S.P.N. 3,161,654 and BE 679678. Iopanoic Acid analogs are described in U.S.P.N. 2,705,726. Iophenoxic Acid analogs are described in GB 726987. Iopromide analogs are described in DE 2909439 and U.S.P.N. 4,364,921. Isoproterenol (e.g., sulfate salt)

analogs are described in German patent DE 723278 and U.S.P.N. 2,308,232 and 2,715,141. Isotretinoin analogs are described in EP 111325 and U.S.P.N. 4,556,518. Ketoconazole analogs are described in German patent DE 2804096, U.S.P.N. 4,144,346, and U.S.P.N. 4,223,036. Ketotifen (e.g., fumarate salt) analogs are described in German patent DE 2111071 and U.S.P.N. 3,682,930. Lamivudine analogs are described in PCT WO 91/17159. Leflunomide analogs are described in German patent DE 2854439 and U.S.P.N. 4,284,786. Levocabastine (e.g., hydrochloride salt) analogs are described in EP 34415 and U.S.P.N. 4,369,184. Loxapine (e.g., hydrochloride salt) analogs are described in NL 6406089 and U.S.P.N. 3,546,226 and U.S.P.N. 3,412,193. Mebhydroline (e.g., 1,5-Naphthalenedisulfonate salt) analogs are described in U.S.P.N. 2,786,059. Meclofenoxate analogs are described in FR M398. Mefenamic Acid analogs are described in BE 605302 and U.S.P.N. 3,138,636. Meloxicam analogs are described in U.S.P.N. 4,233,299. Melphalan analogs are described in U.S.P.N. 3,032,584 and U.S.P.N. 3,032,585. Mercaptoethanol analogs are described in U.S.P.N. 2,402,665 and U.S.P.N. 3,394,192. Metaproterenol (e.g., hemisulfate salt) analogs are described in U.S.P.N. 3,341,594 and BE 611502. Methacholine analogs are described in U.S.P.N. 2,040,146. Methdilazine analogs are described in U.S.P.N. 2,945,855. Methylergonovine (e.g., maleate salt) analogs are described in U.S.P.N. 2,265,207. Nateglinide analogs are described in EP 196222 and U.S.P.N. 4,816,484. Nefopam analogs are described in NL 6606390 and U.S.P.N. 3,830,803. Nimesulide analogs are described in BE 801812 and U.S.P.N. 3,840,597. Norepinephrine (e.g., bitartrate salt) analogs are described in U.S.P.N. 2,774,789. Olanzapine analogs are described in EP 454436 and U.S.P.N. 5,229,382. Oleandomycin analogs are described in U.S.P.N. 2,757,123 and U.S.P.N. 2,842,481. Orphenadrine (e.g., citrate salt) analogs are described in U.S.P.N. 2,567,351and U.S.P.N. 2,991,225. Oxaprozin analogs are described in FR 2001036, GB 1206403, and U.S.P.N. 3,578,671. Oxybutynin (e.g., chloride

salt) analogs are described in GB 940540. Oxymetazoline (e.g., hydrochloride salt) analogs are described in German patent DE 1117588. Pergolide (e.g., mesylate salt) analogs are described in U.S.P.N. 4,166,182. Phenacemide analogs are described in U.S.P.N. 2,887,513. Phensuximide analogs are described in U.S.P.N. 2,643,258. Phenylbutazone analogs are described in U.S.P.N. 2,562,830 and GB 812449. Phenylephrine analogs are described in U.S.P.N. 1,932,347 and U.S.P.N. 1,954,389. Phenytoin analogs are described in U.S.P.N. 2,409,754. Prazosin (e.g., hydrochloride salt) analogs are described in GB 1156973, U.S.P.N. 3,511,836, and NL 7206067. Promethazine (e.g., hydrochloride salt) analogs are described in U.S.P.N. 2,530,451 and U.S.P.N. 2,607,773. Prostaglandin (e.g., Prostaglandin E) analogs are described in GB 851827, U.S.P.N. 3,598,858, NL 6505799, DE 2126127, U.S.P.N. 3,657,327, U.S.P.N. 3,069,322, and U.S.P.N. 3,598,858. Pyrilamine (e.g., maleate salt) analogs are described in U.S.P.N. 2,502,151. Quinacrine analogs are described in German patents DE 553072, DE 571499, U.S.P.N. 2,113,357, U.S.P.N. 1,782,727, and U.S.P.N. 1,889,704. Ritodrine (e.g., hydrochloride salt) analogs are described in BE 660244 and U.S.P.N. 3,410,944. Rolipram analogs are described in BE 826923 and U.S.P.N. 4,193,926. Succinylcholine analogs are described in AT 171411. Sulfaguanidine analogs are described in U.S.P.N. 2,218,490, U.S.P.N. 2,229,784, U.S.P.N. 2,233,569, and GB 551524. Sulfamethizole analogs are described in U.S.P.N. 2,447,702. Suprofen analogs are described in U.S.P.N. 4,035,376. Telmisartan analogs are described in EP 502314. Terbutaline (e.g., sulfate salt) analogs are described in BE 704932 and U.S.P.N. 3,937,838. Tetrahydrozoline (e.g., hydrochloride salt) analogs are described in U.S.P.N. 2,731,471 and U.S.P.N. 2,842,478. Tinidazole analogs are described in U.S.P.N. 3,376,311. Tioconazole analogs are described in BE 841309 and U.S.P.N. 4,062,966. Tolazoline (e.g., hydrochloride salt) analogs are described in U.S.P.N. 2,161,938. Tolfenamic acid analogs are described in NL 6600251 and U.S.P.N. 3,313,848.

Triamterene analogs are described in U.S.P.N. 3,081,230. Trifluprομazine (e.g., hydrochloride salt) analogs are described in GB 813861. Tulobuterol (e.g., hydrochloride salt) analogs are described in German patent DE 2244737. Vincamine analogs are described in German patent DE 2115718 and U.S.P.N. 3,770,724. Warfarin analogs are described in U.S.P.N. 2,427,578, U.S.P.N. 2,765,321, U.S.P.N. 2,777,859, and U.S.P.N. 3,239,529. Xylazine (e.g., hydrochloride salt) analogs are described in BE 634552, DE 1173475, and U.S.P.N. 3,235,550. All of these references are hereby incorporated by reference.

If desired, the patient may also receive additional therapeutic regimens. For example, therapeutic agents may be administered with the agent or agents described herein at concentrations known to be effective for such therapeutic agents. Particularly useful agents include those that reduce glucose levels or those used to treat, prevent, or reduce metabolic disorders. Such agents include those that alter the insulin signaling pathway, such as agents that increase the insulin supply, reduce insulin resistance, increase the effectiveness of insulin, reduce hepatic glucose output, control blood glucose and triglyceride levels, and reduce the absorption of carbohydrates from the intestine. Exemplary agents are sulfonylureas (e.g., acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, and glyburide), non-sulfonylurea secretagogues (e.g., nateglinide and repaglinide), insulin, insulin analogs (e.g., insulin lispro, insulin aspart, insulin glarginine, NPH, lente insulin, ultralente insulin, humulin, novolin), glucagon-like peptides (e.g., GLP-1), exendin-4 (e.g., AAC2993), beta-3 adrenergic receptor agonists (e.g., YM178), PPAR gamma agonists (e.g., FK614), dipeptidyl peptidase IV inhibitors, biguanides (e.g., metformin and metformin/glyburide), thiazalidinediones (e.g., troglitazone, pioglitazone and rosiglitazone), alpha-glucosidase inhibitors (e.g., acarbose and miglitol), immunosuppressants or immmunomodulators (e.g., glucocorticoids, cyclophosphamide, cyclosporine A, rapamycin, FK506 cytokines such as IL-4 and

-IL-10, OK-432, LZ-8, BCG, and CFA, angiotensin converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril), angiotensin II receptor blockers (e.g., candesartan, eprosartan, irbesarten, losartin, telmisartan, and valsartan), antioxidants(e.g., nicotinamide, vitamin E, probucol, MDL29311 and U78518F), and combinations thereof.

It may also be desirable to administer to the patient therapeutic compounds, such as corticosteroids, NSAIDs (e.g., naproxen sodium, diclofenac sodium, diclofenac potassium, aspirin, sulindac, diflunisal, piroxicam, indomethacin, ibuprofen, nabumetone, choline magnesium trisalicylate, sodium salicylate, salicylsalicylic acid, fenoprofen, flurbiprofen, ketoprofen, meclofenamate sodium, meloxicam, oxaprozin, sulindac, and tolmetin), COX-2 inhibitors (e.g., rofecoxib, celecoxib, valdecoxib, and lumiracoxib), DMARD, anti-cytokine agents or agents that modulate the immune response to positively effect disease, such as agents that influence cell adhesion, or biologics (i.e., agents that block the action of IL-6, IL-1, IL-2, IL-12, IL-15 or TNFα (e.g., etanercept, adelimumab, infliximab, or CDP-870).

If more than one agent is employed, therapeutic agents may be delivered separately or may be admixed into a single formulation. When agents are present in different pharmaceutical compositions, different routes of administration may be employed. Routes of administration for the various embodiments include, but are not limited to, topical, transdermal, and systemic administration (such as, intravenous, intramuscular, subcutaneous, inhalation, rectal, buccal, vaginal, intraperitoneal, intraarticular, ophthalmic or oral administration). As used herein, "systemic administration" refers to all nondermal routes of administration, and specifically excludes topical and transdermal routes of administration. Desirably, the agent of the invention and additional therapeutic agents are administered within at least 1, 2, 4, 6, 10, 12, 18, 24 hours, 3 days, 7 days, or 14 days apart.

The dosage and frequency of administration of each component of the combination can be controlled independently. For example, one compound may be administered three times per day, while the second compound may be administered once per day. Combination therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to recover from any as yet unforeseen side effects. The compounds may also be formulated together such that one administration delivers both compounds. Optionally, any of the agents of the combination may be administered in a low dosage or in a high dosage, each of which is defined herein.

The therapeutic agents of the invention may be admixed with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers. A pharmaceutical carrier can be any compatible, non-toxic substance suitable for the administration of the compositions of the present invention to a mammal. Pharmaceutically acceptable carriers include, for example, water, saline, buffers and other compounds described for example in the Merck Index, Merck & Co., Rahway, New Jersey. Slow release formulation or a slow release apparatus may be also be used for continuous administration.

In addition to the administration of therapeutic agents, the second therapeutic regimen may involve transplantation of insulin-producing cells, tissues, or organs (e.g., pancreatic cells, beta pancreatic cells, or pancreas) or a modification to the lifestyle of the patient being treated. Such lifestyle changes may be helpful to control glucose levels and include weight loss, physical exercise, diet control, reduction in alcohol intake, or reduction in smoking.

Corticosteroids

A corticosteroid may be formulated in the composition of the invention or administered to the mammal being treated according to the invention. Suitable corticosteroids include 11-alpha,17-alpha,21-trihydroxypregn-4-ene-3,20-dione;

11-beta,16-alpha,17,21-tetrahydroxypregn-4-ene-3,20-dione; 11-beta,16-alpha,17,21-tetrahydroxypregn-1,4-diene-3,20-dione; 11-beta,17-alpha,21-trihydroxy-6-alpha-methylpregn-4-ene-3,20-dione; 11-dehydrocorticosterone; 11-deoxycortisol; 11-hydroxy-1,4-androstadiene-3,17-dione; 11-ketotestosterone; 14-hydroxyandrost-4-ene-3,6,17-trione; 15,17-dihydroxyprogesterone; 16-methylhydrocortisone; 17,21-dihydroxy-16-alpha-methylpregna-1,4,9(11)-triene-3,20-dione; 17-alpha-hydroxypregn-4-ene-3,20-dione; 17-alpha-hydroxypregnenolone; 17-hydroxy-16-beta-methyl-5-beta-pregn-9(11)-ene-3,20-dione; 17-hydroxy-4,6,8(14)-pregnatriene-3,20-dione; 17-hydroxypregna-4,9(11)-diene-3,20-dione; 18-hydroxycorticosterone; 18-hydroxycortisone; 18-oxocortisol; 21-deoxyaldosterone; 21-deoxycortisone; 2-deoxyecdysone; 2-methylcortisone; 3-dehydroecdysone; 4-pregnene-17-alpha,20-beta, 21-triol-3,11-dione; 6,17,20-trihydroxypregn-4-ene-3-one; 6-alpha-hydroxycortisol; 6-alpha-fluoroprednisolone, 6-alpha-methylprednisolone, 6-alpha-methylprednisolone 21-acetate, 6-alpha-methylprednisolone 21-hemisuccinate sodium salt, 6-beta-hydroxycortisol, 6-alpha, 9-alpha-difluoroprednisolone 21-acetate 17-butyrate, 6-hydroxycorticosterone; 6-hydroxydexamethasone; 6-hydroxyprednisolone; 9-fluorocortisone; alclometasone dipropionate; aldosterone; algestone; alphaderm; amadinone; amcinonide; anagestone; androstenedione; anecortave acetate; beclomethasone; beclomethasone dipropionate; beclomethasone dipropionate monohydrate; betamethasone 17-valerate; betamethasone sodium acetate; betamethasone sodium phosphate; betamethasone valerate; bolasterone; budesonide; calusterone; chlormadinone; chloroprednisone; chloroprednisone acetate; cholesterol; clobetasol; clobetasol propionate; clobetasone; clocortolone; clocortolone pivalate; clogestone; cloprednol; corticosterone; cortisol; cortisol acetate; cortisol butyrate; cortisol cypionate; cortisol octanoate; cortisol sodium phosphate; cortisol sodium succinate; cortisol valerate; cortisone; cortisone acetate; cortodoxone; daturaolone; deflazacort, 21-deoxycortisol,

dehydroepiandrosterone; delmadinone; deoxycorticosterone; deprodone; descinolone; desonide; desoximethasone; dexafen; dexamethasone; dexamethasone 21-acetate; dexamethasone acetate; dexamethasone sodium phosphate; dichlorisone; diflorasone; diflorasone diacetate; diflucortolone; dihydroelatericin a; domoprednate; doxibetasol; ecdysone; ecdysterone; endrysone; enoxolone; flucinolone; fludrocortisone; fludrocortisone acetate; flugestone; flumethasone; flumethasone pivalate; flumoxonide; flunisolide; fluocinolone; fluocinolone acetonide; fluocinonide; 9-fluorocortisone; fluocortolone; fluorohydroxyandrostenedione; fluorometholone; fluorometholone acetate; fluoxymesterone; fluprednidene; fluprednisolone; flurandrenolide; fluticasone; fluticasone propionate; formebolone; formestane; formocortal; gestonorone; glyderinine; halcinonide; hyrcanoside; halometasone; halopredone; haloprogesterone; hydrocortiosone cypionate; hydrocortisone; hydrocortisone 21-butyrate; hydrocortisone aceponate; hydrocortisone acetate; hydrocortisone buteprate; hydrocortisone butyrate; hydrocortisone cypionate; hydrocortisone hemisuccinate; hydrocortisone probutate; hydrocortisone sodium phosphate; hydrocortisone sodium succinate; hydrocortisone valerate; hydroxyprogesterone; inokosterone; isoflupredone; isoflupredone acetate; isoprednidene; meclorisone; mecortolon; medrogestone; medroxyprogesterone; medrysone; megestrol; megestrol acetate; melengestrol; meprednisone; methandrostenolone; methylprednisolone; methylprednisolone aceponate; methylprednisolone acetate; methylprednisolone hemisuccinate; methylprednisolone sodium succinate; methyltestosterone; metribolone; mometasone; mometasone furoate; mometasone furoate monohydrate; nisone; nomegestrol; norgestomet; norvinisterone; oxymesterone; paramethasone; paramethasone acetate; ponasterone; prednisolamate; prednisolone; prednisolone 21-hemisuccinate; prednisolone acetate; prednisolone farnesylate; prednisolone hemisuccinate; prednisolone-21(beta-D-glucuronide); prednisolone metasulphobenzoate; prednisolone sodium

phosphate; prednisolone steaglate; prednisolone tebutate; prednisolone tetrahydrophthalate; prednisone; prednival; prednylidene; pregnenolone; procinonide; tralonide; progesterone; promegestone; rhapontisterone; rimexolone; roxibolone; rubrosterone; stizophyllin; tixocortol; topterone; triamcinolone; triamcinolone acetonide; triamcinolone acetonide 21-palmitate; triamcinolone diacetate; triamcinolone hexacetonide; trimegestone; turkesterone; and wortmannin.

Standard recommended dosages for corticosteroids are provided, e.g., in the Merck Manual of Diagnosis & Therapy (17th Ed. MH Beers et al., Merck & Co.) and Physicians' Desk Reference 2003 (57th Ed. Medical Economics Staff et al., Medical Economics Co., 2002). In one embodiment, the dosage of corticosteroid administered is a dosage equivalent to a prednisolone dosage, as defined herein. For example, a low dosage of a corticosteroid may be considered as the dosage equivalent to a low dosage of prednisolone.

Other compounds that may be used as a substitute for or in addition to a corticosteroid in the methods, compositions, and kits of the invention A-348441 (Karo Bio), adrenal cortex extract (GlaxoSmithKline), alsactide (Aventis), amebucort (Schering AG), amelometasone (Taisho), ATSA (Pfizer), bitolterol (Elan), CBP-2011 (InKine Pharmaceutical), cebaracetam (Novartis) CGP-13774 (Kissei), ciclesonide (Altana), ciclometasone (Aventis), clobetasone butyrate (GlaxoSmithKline), cloprednol (Hoffmann-La Roche), collismycin A (Kirin), cucurbitacin E (NIH), deflazacort (Aventis), deprodone propionate (SSP), dexamethasone acefurate (Schering-Plough), dexamethasone linoleate (GlaxoSmithKline), dexamethasone valerate (Abbott), difluprednate (Pfizer), domoprednate (Hoffmann-La Roche), ebiratide (Aventis), etiprednol dicloacetate (IVAX), fluazacort (Vicuron), flumoxonide (Hoffmann-La Roche), fluocortin butyl (Schering AG), fluocortolone monohydrate (Schering AG), GR-250495X (GlaxoSmithKline), halometasone (Novartis), halopredone (Dainippon), HYC-141

(Fidia), icomethasone enbutate (Hovione), itrocinonide (AstraZeneca), L-6485 (Vicuron), Lipocort (Draxis Health), locicortone (Aventis), meclorisone (Schering-Plough), naflocort (Bristol-Myers Squibb), NCX-1015 (NicOx), NCX-1020 (NicOx), NCX-1022 (NicOx), nicocortonide (Yamanouchi), NIK-236 (Nikken Chemicals), NS-126 (SSP), Org-2766 (Akzo Nobel), Org-6632 (Akzo Nobel), P16CM, propylmesterolone (Schering AG), RGH-1113 (Gedeon Richter), rofleponide (AstraZeneca), rofleponide palmitate (AstraZeneca), RPR-106541 (Aventis), RU-26559 (Aventis), Sch-19457 (Schering-Plough), T25 (Matrix Therapeutics), TBI-PAB (Sigma-Tau), ticabesone propionate (Hoffmann-La Roche), tifluadom (Solvay), timobesone (Hoffmann-La Roche), TSC-5 (Takeda), and ZK-73634 (Schering AG).

Non-steroidal immunophilin-dependent immunosuppressants

The present invention may also involve the administration of a non-steroidal immunophilin-dependent immunosuppressant (NsIDI). In healthy individuals the immune system uses cellular effectors, such as B-cells and T-cells, to target infectious microbes and abnormal cell types while leaving normal cells intact. In individuals with an autoimmune disorder (e.g., diabetes), activated T-cells damage healthy tissues. Calcineurin inhibitors (e.g., cyclosporines, tacrolimus, pimecrolimus), and rapamycin target many types of immunoregulatory cells, including T-cells, and suppress the immune response in autoimmune disorders. Immunosuppressants are particularly useful if the mammal is also receiving an organ, tissue, or cellular implant. Exemplary immunosuppressants are provided below.

Cyclosporines

The cyclosporines are fungal metabolites that comprise a class of cyclic oligopeptides that act as immunosuppressants. Cyclosporine A, and its deuterated

analogue ISAtx247, is a hydrophobic cyclic polypeptide consisting of eleven amino acids. Cyclosporine A binds and forms a complex with the intracellular receptor cyclophilin. The cyclosporine/cyclophilin complex binds to and inhibits calcineurin, a Ca^{2+}-calmodulin-dependent serine-threonine-specific protein phosphatase. Calcineurin mediates signal transduction events required for T-cell activation (reviewed in Schreiber et al., Cell 70:365-368, 1991). Cyclosporines and their functional and structural analogs suppress the T-cell-dependent immune response by inhibiting antigen-triggered signal transduction. This inhibition decreases the expression of proinflammatory cytokines, such as IL-2.

Many cyclosporines (e.g., cyclosporine A, B, C, D, E, F, G, H, and I) are produced by fungi. Cyclosporine A is a commercially available under the trade name NEORAL from Novartis. Cyclosporine A structural and functional analogs include cyclosporines having one or more fluorinated amino acids (described, e.g., in U.S. Patent No. 5,227,467); cyclosporines having modified amino acids (described, e.g., in U.S. Patent Nos. 5,122,511 and 4,798,823); and deuterated cyclosporines, such as ISAtx247 (described in U.S. Patent Publication No. 20020132763). Additional cyclosporine analogs are described in U.S. Patent Nos. 6,136,357, 4,384,996, 5,284,826, and 5,709,797. Cyclosporine analogs include, but are not limited to, D-Sar $(\alpha\text{-SMe})^3$ Val^2-DH-Cs (209-825), Allo-Thr-2-Cs, Norvaline-2-Cs, D-Ala (3-acetylamino)-8-Cs, Thr-2-Cs, and D-MeSer-3-Cs, D-Ser ($O\text{-}CH_2CH_2\text{-}OH$)-8-Cs, and D-Ser-8-Cs, which are described in Cruz et al. (Antimicrob. Agents Chemother. 44:143-149, 2000).

Cyclosporines are highly hydrophobic and readily precipitate in the presence of water (e.g., on contact with body fluids). Methods of providing cyclosporine formulations with improved bioavailability are described in U.S. Patent Nos. 4,388,307, 6,468,968, 5,051,402, 5,342,625, 5,977,066, and

6,022,852. Cyclosporine microemulsion compositions are described in U.S. Patent Nos. 5,866,159, 5,916,589, 5,962,014, 5,962,017, 6,007,840, and 6,024,978.

Cyclosporines can be administered either intravenously or orally, but oral administration is preferred. To counteract the hydrophobicity of cyclosporine A, an intravenous cyclosporine A is usually provided in an ethanol-polyoxyethylated castor oil vehicle that must be diluted prior to administration. Cyclosporine A may be provided, e.g., as a microemulsion in a 25 mg or 100 mg tablets, or in a 100 mg/ml oral solution (NEORAL™).

Typically, patient dosage of an oral cyclosporine varies according to the patient's condition, but some standard recommended dosages in prior art treatment regimens are provided herein. Patients undergoing organ transplant (e.g., pancreatic islet transplantation) typically receive an initial dose of oral cyclosporine A in amounts between 12 and 15 mg/kg/day. Dosage is then gradually decreased by 5% per week until a 7-12 mg/kg/day maintenance dose is reached. For intravenous administration, 2-6 mg/kg/day is preferred for most patients. Often cyclosporines are administered in combination with other immunosuppressive agents, such as glucocorticoids. Additional information is provided in Table 3.

Table 3—NsIDIs

Compound	Transplant
Cyclosporine A (NEORAL)	~7-12 mg/kg/day
Tacrolimus	0.1-0.2 mg/kg/day (oral)
Pimecrolimus	40-120 mg/day (oral)

Tacrolimus

Tacrolimus (PROGRAF, Fujisawa), also known as FK506, is an immunosuppressive agent that targets T-cell intracellular signal transduction pathways. Tacrolimus binds to an intracellular protein FK506 binding protein (FKBP-12) that is not structurally related to cyclophilin (Harding et al. Nature 341:758-7601, 1989; Siekienka et al. Nature 341:755-757, 1989; and Soltoff et al., J. Biol. Chem. 267:17472-17477, 1992). The FKBP/FK506 complex binds to calcineurin and inhibits calcineurin's phosphatase activity. This inhibition prevents the dephosphorylation and nuclear translocation of NFAT, a nuclear component that initiates gene transcription required for lymphokine (e.g., IL-2, gamma interferon) production and T-cell activation. Thus, tacrolimus inhibits T-cell activation.

Tacrolimus is a macrolide antibiotic that is produced by *Streptomyces tsukubaensis*. It suppresses the immune system and prolongs the survival of transplanted organs. It is currently available in oral and injectable formulations. Tacrolimus capsules contain 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus within a gelatin capsule shell. The injectable formulation contains 5 mg anhydrous tacrolimus in castor oil and alcohol that is diluted with 9% sodium chloride or 5% dextrose prior to injection. While oral administration is preferred, patients unable to take oral capsules may receive injectable tacrolimus. The initial dose should be administered no sooner than six hours after transplant by continuous intravenous infusion.

Tacrolimus and tacrolimus analogs are described by Tanaka et al., (J. Am. Chem. Soc., 109:5031, 1987), and in U.S. Patent Nos. 4,894,366, 4,929,611, and 4,956,352. FK506-related compounds, including FR-900520, FR-900523, and FR-900525, are described in U.S. Patent No. 5,254,562; O-aryl, O-alkyl, O-alkenyl, and O-alkynylmacrolides are described in U.S. Patent Nos. 5,250,678, 532,248, 5,693,648; amino O-aryl macrolides are described in U.S. Patent No.

5,262,533; alkylidene macrolides are described in U.S. Patent No. 5,284,840; N-heteroaryl, N-alkylheteroaryl, N-alkenylheteroaryl, and N-alkynylheteroaryl macrolides are described in U.S. Patent No. 5,208,241; aminomacrolides and derivatives thereof are described in U.S. Patent No. 5,208,228; fluoromacrolides are described in U.S. Patent No. 5,189,042; amino O-alkyl, O-alkenyl, and O-alkynylmacrolides are described in U.S. Patent No. 5,162,334; and halomacrolides are described in U.S. Patent No. 5,143,918.

While suggested dosages will vary with a patient's condition, standard recommended dosages used in prior art treatment regimens are provided below. Patients having a transplanted organ typically receive doses of 0.1-0.2 mg/kg/day of oral tacrolimus. Patients being treated for rheumatoid arthritis typically receive 1-3 mg/day oral tacrolimus. For the treatment of psoriasis, 0.01-0.15 mg/kg/day of oral tacrolimus is administered to a patient. Patients receiving oral tacrolimus capsules typically receive the first dose no sooner than six hours after transplant, or eight to twelve hours after intravenous tacrolimus infusion was discontinued. Thus, suggested tacrolimus dosages include 0.005-0.01 mg/kg/day, 0.01-0.03 mg/kg/day, 0.03-0.05 mg/kg/day, 0.05-0.07 mg/kg/day, 0.07-0.10 mg/kg/day, 0.10-0.25 mg/kg/day, or 0.25-0.5 mg/kg/day.

Tacrolimus is extensively metabolized by the mixed-function oxidase system, in particular, by the cytochrome P-450 system. The primary mechanism of metabolism is demethylation and hydroxylation. While various tacrolimus metabolites are likely to exhibit immunosuppressive biological activity, the 13-demethyl metabolite is reported to have the same activity as tacrolimus.

Pimecrolimus and ascomycin derivatives

Ascomycin is a close structural analog of FK506 and is a potent immunosuppressant. It binds to FKBP-12 and suppresses its proline rotamase

activity. The ascomycin-FKBP complex inhibits calcineurin, a type 2B phosphatase.

Pimecrolimus (also known as SDZ ASM-981) is an 33-epi-chloro derivative of the ascomycin. It is produced by the strain *Streptomyces hygroscopicus var. ascomyceitus*. Like tacrolimus, pimecrolimus (ELIDEL™, Novartis) binds FKBP-12, inhibits calcineurin phosphatase activity, and inhibits T-cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits IL-2 production and the release of other proinflammatory cytokines.

Pimecrolimus structural and functional analogs are described in U.S. Patent No. 6,384,073. Pimecrolimus is particularly useful for the treatment of atopic dermatitis. Pimecrolimus is currently available as a 1% cream. While individual dosing will vary with the patient's condition, some standard recommended dosages are provided below. Patients having an organ transplant can be administered 160-240 mg/day of pimecrolimus. Thus, useful dosages of pimecrolimus range between 0.5-5 mg/day, between 5-10 mg/day, between 10-30 mg/day, between 40-80 mg/day, between 80-120 mg/day, or even between 120-200 mg/day.

Rapamycin

Rapamycin (Rapamune® sirolimus, Wyeth) is a cyclic lactone produced by *Steptomyces hygroscopicus*. Rapamycin is an immunosuppressive agent that inhibits T-lymphocyte activation and proliferation. Like cyclosporines, tacrolimus, and pimecrolimus, rapamycin forms a complex with the immunophilin FKBP-12, but the rapamycin-FKBP-12 complex does not inhibit calcineurin phosphatase activity. The rapamycin-immunophilin complex binds to and inhibits the mammalian target of rapamycin (mTOR), a kinase that is required for cell

cycle progression. Inhibition of mTOR kinase activity blocks T-lymphocyte proliferation and lymphokine secretion.

Rapamycin structural and functional analogs include mono- and diacylated rapamycin derivatives (U.S. Patent No. 4,316,885); rapamycin water-soluble prodrugs (U.S. Patent No. 4,650,803); carboxylic acid esters (PCT Publication No. WO 92/05179); carbamates (U.S. Patent No. 5,118,678); amide esters (U.S. Patent No. 5,118,678); biotin esters (U.S. Patent No. 5,504,091); fluorinated esters (U.S. Patent No. 5,100,883); acetals (U.S. Patent No. 5,151,413); silyl ethers (U.S. Patent No. 5,120,842); bicyclic derivatives (U.S. Patent No. 5,120,725); rapamycin dimers (U.S. Patent No. 5,120,727); O-aryl, O-alkyl, O-alkyenyl and O-alkynyl derivatives (U.S. Patent No. 5,258,389); and deuterated rapamycin (U.S. Patent No. 6,503,921). Additional rapamycin analogs are described in U.S. Patent Nos. 5,202,332 and 5,169,851.

Everolimus (40-O-(2-hydroxyethyl)rapamycin; CERTICAN^{TM}; Novartis) is an immunosuppressive macrolide that is structurally related to rapamycin, and has been found to be particularly effective at preventing acute rejection of organ transplant when given in combination with cyclosporin A.

Rapamycin is currently available for oral administration in liquid and tablet formulations. RAPAMUNE^{TM} liquid contains 1 mg/mL rapamycin that is diluted in water or orange juice prior to administration. Tablets containing 1 or 2 mg of rapamycin are also available. Rapamycin is preferably given once daily as soon as possible after transplantation. It is absorbed rapidly and completely after oral administration. Typically, patient dosage of rapamycin varies according to the patient's condition, but some standard recommended dosages are provided below. The initial loading dose for rapamycin is 6 mg. Subsequent maintenance doses of 2 mg/day are typical. Alternatively, a loading dose of 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, or 25 mg can be used with a 1 mg, 3 mg, 5 mg, 7 mg, or 10 mg per day maintenance dose. In patients weighing less than 40 kg, rapamycin dosages are

typically adjusted based on body surface area; generally a 3 mg/m^2/day loading dose and a 1-mg/m^2/day maintenance dose is used.

Conjugates

If desired, the drugs used in any of the combinations described herein may be covalently attached to one another to form a conjugate of formula XXX.

(A)-(L)-(B) (XXX)

In formula XXX, (A) is a drug listed on Table 1 covalently tethered via a linker (L) to (B), a sulfonylurea, a non-sulfonylurea secretagogue, insulin, an insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, a dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, an alpha-glucosidase inhibitor, an immunosuppressant, an immmunomodulator, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker, an antioxidant, or a second drug listed on Table 1.

Conjugates of the invention can be administered to a subject by any route and for the treatment of any disease described herein.

The conjugates of the invention can be prodrugs, releasing drug (A) and drug (B) upon, for example, cleavage of the conjugate by intracellular and extracellular enzymes (e.g., amidases, esterases, and phosphatases). The conjugates of the invention can also be designed to largely remain intact in vivo, resisting cleavage by intracellular and extracellular enzymes. The degradation of the conjugate in vivo can be controlled by the design of linker (L) and the covalent bonds formed with drug (A) and drug (B) during the synthesis of the conjugate.

Conjugates can be prepared using techniques familiar to those skilled in the art. For example, the conjugates can be prepared using the methods disclosed in G. Hermanson, Bioconjugate Techniques, Academic Press, Inc., 1996.

The synthesis of conjugates may involve the selective protection and deprotection of alcohols, amines, ketones, sulfhydryls or carboxyl functional groups of drug (A), the linker, and/or drug (B). For example, commonly used protecting groups for amines include carbamates, such as *tert*-butyl, benzyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 9-fluorenylmethyl, allyl, and m-nitrophenyl. Other commonly used protecting groups for amines include amides, such as formamides, acetamides, trifluoroacetamides, sulfonamides, trifluoromethanesulfonyl amides, trimethylsilylethanesulfonamides, and *tert*-butylsulfonyl amides. Examples of commonly used protecting groups for carboxyls include esters, such as methyl, ethyl, *tert*-butyl, 9-fluorenylmethyl, 2-(trimethylsilyl)ethoxy methyl, benzyl, diphenylmethyl, O-nitrobenzyl, ortho-esters, and halo-esters. Examples of commonly used protecting groups for alcohols include ethers, such as methyl, methoxymethyl, methoxyethoxymethyl, methylthiomethyl, benzyloxymethyl, tetrahydropyranyl, ethoxyethyl, benzyl, 2-napthylmethyl, O-nitrobenzyl, P-nitrobenzyl, P-methoxybenzyl, 9-phenylxanthyl, trityl (including methoxy-trityls), and silyl ethers. Examples of commonly used protecting groups for sulfhydryls include many of the same protecting groups used for hydroxyls. In addition, sulfhydryls can be protected in a reduced form (e.g., as disulfides) or an oxidized form (e.g., as sulfonic acids, sulfonic esters, or sulfonic amides). Protecting groups can be chosen such that selective conditions (e.g., acidic conditions, basic conditions, catalysis by a nucleophile, catalysis by a lewis acid, or hydrogenation) are required to remove each, exclusive of other protecting groups in a molecule. The conditions required for the addition of protecting groups to amine, alcohol, sulfhydryl, and carboxyl functionalities and the conditions required for their removal are provided in detail in T.W. Green and P.G.M. Wuts, Protective Groups in Organic Synthesis (2^{nd} Ed.), John Wiley & Sons, 1991 and P.J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994. Additional synthetic details are provided below.

Linkers

The linker component of the invention is, at its simplest, a bond between drug (A) and drug (B), but typically provides a linear, cyclic, or branched molecular skeleton having pendant groups covalently linking drug (A) to drug (B).

Thus, linking of drug (A) to drug (B) is achieved by covalent means, involving bond formation with one or more functional groups located on drug (A) and drug (B). Examples of chemically reactive functional groups which may be employed for this purpose include, without limitation, amino, hydroxyl, sulfhydryl, carboxyl, carbonyl, carbohydrate groups, vicinal diols, thioethers, 2-aminoalcohols, 2-aminothiols, guanidinyl, imidazolyl, and phenolic groups.

The covalent linking of drug (A) and drug (B) may be effected using a linker which contains reactive moieties capable of reaction with such functional groups present in drug (A) and drug (B). For example, an amine group of drug (A) may react with a carboxyl group of the linker, or an activated derivative thereof, resulting in the formation of an amide linking the two.

Examples of moieties capable of reaction with sulfhydryl groups include α-haloacetyl compounds of the type XCH_2CO- (where X=Br, Cl or I), which show particular reactivity for sulfhydryl groups, but which can also be used to modify imidazolyl, thioether, phenol, and amino groups as described by Gurd, *Methods Enzymol.* 11:532 (1967). N-Maleimide derivatives are also considered selective towards sulfhydryl groups, but may additionally be useful in coupling to amino groups under certain conditions. Reagents such as 2-iminothiolane (Traut et al., *Biochemistry* 12:3266 (1973)), which introduce a thiol group through conversion of an amino group, may be considered as sulfhydryl reagents if linking occurs through the formation of disulphide bridges.

Examples of reactive moieties capable of reaction with amino groups include, for example, alkylating and acylating agents. Representative alkylating agents include:

(i) α-haloacetyl compounds, which show specificity towards amino groups in the absence of reactive thiol groups and are of the type XCH_2CO- (where X=Cl, Br or I), for example, as described by Wong *Biochemistry* 24:5337 (1979);

(ii) N-maleimide derivatives, which may react with amino groups either through a Michael type reaction or through acylation by addition to the ring carbonyl group, for example, as described by Smyth et al., *J. Am. Chem. Soc.* 82:4600 (1960) and *Biochem. J.* 91:589 (1964);

(iii) aryl halides such as reactive nitrohaloaromatic compounds;

(iv) alkyl halides, as described, for example, by McKenzie et al., *J. Protein Chem.* 7:581 (1988);

(v) aldehydes and ketones capable of Schiff's base formation with amino groups, the adducts formed usually being stabilized through reduction to give a stable amine;

(vi) epoxide derivatives such as epichlorohydrin and bisoxiranes, which may react with amino, sulfhydryl, or phenolic hydroxyl groups;

(vii) chlorine-containing derivatives of s-triazines, which are very reactive towards nucleophiles such as amino, sufhydryl, and hydroxyl groups;

(viii) aziridines based on s-triazine compounds detailed above, e.g., as described by Ross, *J. Adv. Cancer Res.* 2:1 (1954), which react with nucleophiles such as amino groups by ring opening;

(ix) squaric acid diethyl esters as described by Tietze, *Chem. Ber.* 124:1215 (1991); and

(x) α-haloalkyl ethers, which are more reactive alkylating agents than normal alkyl halides because of the activation caused by the ether oxygen atom, as described by Benneche et al., *Eur. J. Med. Chem.* 28:463 (1993).

Representative amino-reactive acylating agents include:

(i) isocyanates and isothiocyanates, particularly aromatic derivatives, which form stable urea and thiourea derivatives respectively;

(ii) sulfonyl chlorides, which have been described by Herzig et al., *Biopolymers* 2:349 (1964);

(iii) acid halides;

(iv) active esters such as nitrophenylesters or N-hydroxysuccinimidyl esters;

(v) acid anhydrides such as mixed, symmetrical, or N-carboxyanhydrides;

(vi) other useful reagents for amide bond formation, for example, as described by M. Bodansky, Principles of Peptide Synthesis, Springer-Verlag, 1984;

(vii) acylazides, e.g. wherein the azide group is generated from a preformed hydrazide derivative using sodium nitrite, as described by Wetz et al., *Anal. Biochem.* 58:347 (1974); and

(viii) imidoesters, which form stable amidines on reaction with amino groups, for example, as described by Hunter and Ludwig, *J. Am. Chem. Soc.* 84:3491 (1962).

Aldehydes and ketones may be reacted with amines to form Schiff's bases, which may advantageously be stabilized through reductive amination. Alkoxylamino moieties readily react with ketones and aldehydes to produce stable alkoxamines, for example, as described by Webb et al., in *Bioconjugate Chem.* 1:96 (1990).

Examples of reactive moieties capable of reaction with carboxyl groups include diazo compounds such as diazoacetate esters and diazoacetamides, which react with high specificity to generate ester groups, for example, as described by Herriot, *Adv. Protein Chem.* 3:169 (1947). Carboxyl modifying reagents such as carbodiimides, which react through O-acylurea formation followed by amide bond formation, may also be employed.

It will be appreciated that functional groups in drug (A) and/or drug (B) may, if desired, be converted to other functional groups prior to reaction, for

example, to confer additional reactivity or selectivity. Examples of methods useful for this purpose include conversion of amines to carboxyls using reagents such as dicarboxylic anhydrides; conversion of amines to thiols using reagents such as N-acetylhomocysteine thiolactone, S-acetylmercaptosuccinic anhydride, 2-iminothiolane, or thiol-containing succinimidyl derivatives; conversion of thiols to carboxyls using reagents such as α -haloacetates; conversion of thiols to amines using reagents such as ethylenimine or 2-bromoethylamine; conversion of carboxyls to amines using reagents such as carbodiimides followed by diamines; and conversion of alcohols to thiols using reagents such as tosyl chloride followed by transesterification with thioacetate and hydrolysis to the thiol with sodium acetate.

So-called zero-length linkers, involving direct covalent joining of a reactive chemical group of drug (A) with a reactive chemical group of drug (B) without introducing additional linking material may, if desired, be used in accordance with the invention.

Most commonly, however, the linker will include two or more reactive moieties, as described above, connected by a spacer element. The presence of such a spacer permits bifunctional linkers to react with specific functional groups within drug (A) and drug (B), resulting in a covalent linkage between the two. The reactive moieties in a linker may be the same (homobifunctional linker) or different (heterobifunctional linker, or, where several dissimilar reactive moieties are present, heteromultifunctional linker), providing a diversity of potential reagents that may bring about covalent attachment between drug (A) and drug (B).

Spacer elements in the linker typically consist of linear or branched chains and may include a C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-10} heteroalkyl.

In some instances, the linker is described by formula (XXXI):

$$G^1\text{-}(Z^1)_o\text{-}(Y^1)_u\text{-}(Z^2)_s\text{-}(R_{30})\text{-}(Z^3)_t\text{-}(Y^2)_v\text{-}(Z^4)_p\text{–}G^2 \quad \text{(XXXI)}$$

In formula (XXXI), G^1 is a bond between drug (A) and the linker; G^2 is a bond between the linker and drug (B); Z^1, Z^2, Z^3, and Z^4 each, independently, is selected from O, S, and NR_{31}; R_{31} is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; Y^1 and Y^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

o, p, s, t, u, and v are each, independently, 0 or 1; and R_{30} is a C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-10} heteroalkyl, or a chemical bond linking $G^1\text{-}(Z^1)_o\text{-}(Y^1)_u\text{-}(Z^2)_s$- to -$(Z^3)_t\text{-}(Y^2)_v\text{-}(Z^4)_p\text{–}G^2$.

Examples of homobifunctional linkers useful in the preparation of conjugates of the invention include, without limitation, diamines and diols selected from ethylenediamine, propylenediamine and hexamethylenediamine, ethylene glycol, diethylene glycol, propylene glycol, 1,4-butanediol, 1,6-hexanediol, cyclohexanediol, and polycaprolactone diol.

Formulation

Any of the agents employed according to the present invention may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for the oral, parenteral (e.g., intravenously, intramuscularly), rectal, cutaneous, nasal, vaginal, inhalant, skin (patch), or ocular administration route. Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders,

granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy, 20th edition, 2000, ed. A.R. Gennaro, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

If more than one agent is employed, each agent may be formulated in a variety of ways that are known in the art. Desirably, the agents are formulated together for the simultaneous or near simultaneous administration of the agents. Such co-formulated compositions can include the two agents formulated together in the same pill, capsule, liquid, etc. It is to be understood that, when referring to the formulation of such combinations, the formulation technology employed is also useful for the formulation of the individual agents of the combination, as well as other combinations of the invention. By using different formulation strategies for different agents, the pharmacokinetic profiles for each agent can be suitably matched.

The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include kits that contain, e.g., two pills, a pill and a powder, a suppository and a liquid in a vial, two topical creams, etc. The kit can include optional components that aid in the administration of the unit dose to patients, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, inhalers, etc. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions. The kit may be manufactured as a single use unit dose for one patient, multiple uses for a particular patient (at a constant dose or in which the individual compounds may vary in potency as therapy progresses); or the kit may contain multiple doses

suitable for administration to multiple patients ("bulk packaging"). The kit components may be assembled in cartons, blister packs, bottles, tubes, and the like.

Dosages

Generally, when administered to a human, the dosage of any of the agents of the combination of the invention will depend on the nature of the agent, and can readily be determined by one skilled in the art. Typically, such dosage is normally about 0.001 mg to 2000 mg per day, desirably about 1 mg to 1000 mg per day, and more desirably about 5 mg to 500 mg per day. Dosages up to 200 mg per day may be necessary.

Administration of each drug in the combination can, independently, be one to four times daily for one day to one year, and may even be for the life of the patient. Chronic, long-term administration will be indicated in many cases.

Additional applications

If desired, the compounds of the invention may be employed in mechanistic assays to determine whether other combinations, or single agents, are as effective as the combination in treating, reducing, or preventing metabolic disorders (e.g., diabetes or any of its associated conditions) using assays generally known in the art, examples of which are described herein. For example, candidate compounds may be tested, alone or in combination (e.g., with an agent that reduces glucose levels, such as those described herein) and applied to adipocytes or muscle cells in the presence of insulin and glucose. After a suitable time, these cells are examined for glucose uptake. An increase in glucose uptake identifies a candidate compound or combination of agents as an effective agent to treat, prevent, or reduce a metabolic disorder.

The agents of the invention are also useful tools in elucidating mechanistic information about the biological pathways involved in glucose transport and glucose utilization. Such information can lead to the development of new combinations or single agents for treating, preventing, or reducing diabetes. Methods known in the art to determine biological pathways can be used to determine the pathway, or network of pathways affected by contacting cells (e.g., adipocytes, muscle cells, or any cells that utilizes glucose as a source of energy) in the presence of insulin and glucose or by contacting pancreatic cells (any cell that has the ability to produce insulin) with the compounds of the invention. Such methods can include, analyzing cellular constituents that are expressed or repressed after contact with the compounds of the invention as compared to untreated, positive or negative control compounds, and/or new single agents and combinations, or analyzing some other metabolic activity of the cell such as enzyme activity, nutrient uptake, and proliferation. Cellular components analyzed can include gene transcripts, and protein expression. Suitable methods can include standard biochemistry techniques, radiolabeling the compounds of the invention (e.g., ^{14}C or ^{3}H labeling), and observing the compounds binding to proteins, e.g. using 2D gels, gene expression profiling. Once identified, such compounds can be used in *in vivo* models (e.g., NOD mice) to further validate the tool or develop new agents or strategies to treat, prevent, or reduce metabolic disorders.

As indicated above, the methods of this invention may also be used prophylactically, in patients who are an increased risk of developing diabetes or a condition associated with diabetes. Risk factors include for example, family history of diabetes or obesity conditions, quality of nutrition, level of physical activity, presence of molecular markers of diabetes, age, race, or sex. Patients affected with other non-related disorders may also be predisposed to secondary diabetes.

Exemplary candidate compounds

Peptide moieties

Peptides, peptide mimetics, and peptide fragments (whether natural, synthetic or chemically modified) are suitable for use in practicing the invention. Exemplary inhibitors include compounds that reduce the amount of target protein or RNA levels (e.g., antisense compounds, dsRNA, ribozymes) and compounds that compete with endogenous mitotic kinesins or protein tyrosine phosphatases for binding partners (e.g., dominant negative proteins or polynucleotides encoding the same).

Antisense compounds

The biological activity of any enzyme that increases blood glucose concentration can be reduced through the use of an antisense compound directed to RNA encoding the target protein. Antisense compounds that reduce expression of signaling molecules can be identified using standard techniques. For example, accessible regions of the target the mRNA of the target enzyme can be predicted using an RNA secondary structure folding program such as MFOLD (M. Zuker, D. H. Mathews & D. H. Turner, Algorithms and Thermodynamics for RNA Secondary Structure Prediction: A Practical Guide. In: RNA Biochemistry and Biotechnology, J. Barciszewski & B. F. C. Clark, eds., NATO ASI Series, Kluwer Academic Publishers, (1999)). Sub-optimal folds with a free energy value within 5% of the predicted most stable fold of the mRNA are predicted using a window of 200 bases within which a residue can find a complimentary base to form a base pair bond. Open regions that do not form a base pair are summed together with each suboptimal fold and areas that are predicted as open are considered more accessible to the binding to antisense nucleobase oligomers. Other methods for antisense design are described, for example, in U.S. Patent No. 6,472,521,

Antisense Nucleic Acid Drug Dev. 1997 7:439-444, Nucleic Acids Research 28:2597-2604, 2000, and Nucleic Acids Research 31:4989-4994, 2003.

RNA interference

The biological activity of a signaling molecule can be reduced through the use of RNA interference (RNAi), employing, e.g., a double stranded RNA (dsRNA) or small interfering RNA (siRNA) directed to the signaling molecule in question (see, e.g., Miyamoto et al., Prog. Cell Cycle Res. 5:349-360, 2003; U.S. Patent Application Publication No. 20030157030). Methods for designing such interfering RNAs are known in the art. For example, software for designing interfering RNA is available from Oligoengine (Seattle, WA).

Dominant negative proteins

One skilled in the art would know how to make dominant negative proteins to the signaling molecules to be targeted. Such dominant negative proteins are described, for example, in Gupta et al., J. Exp. Med., 186:473-478, 1997; Maegawa et al., J. Biol. Chem. 274:30236-30243, 1999; Woodford-Thomas et al., J. Cell Biol. 117:401-414, 1992).

Example 1: An increase in insulin-stimulated glucose uptake in vitro

Differentiated mouse adipocytes were employed to identify combinations of agents that have the ability to increase glucose uptake upon insulin stimulation, as detected by scintillation counting of radiolabelled glucose (using, for example, the Perkin Elmer 1450 Microbeta JET reader). These assays were conducted as follows.

Materials and methods

Prees media

Complete media, also referred to as "Prees" media, was prepared as follows. Dulbecco's Modified Eagle's Medium (DMEM) was supplemented with L-glutamine, penicillin-G and streptomycin (pen/strep), and heat-inactivated fetal bovine serum (FBS) (heat inactivated at 65°C for 30 minutes). Because serum can affect the growth, adherence, and differentiation of cells, any new lot of serum was first tested prior to use. Media was equilibrated in the incubator (5% CO_2) until the pH was within the proper range (~7), as indicated by the red/orange color of the indicator dye. If the media became pink (indicating a high pH), we discarded the media as basic conditions can affect cells and denature the insulin used in the differentiation medium-1 (DM1) and the differentiation medium-2 (DM2).

Differentiation medias

Differentiation media-1 (DM1) was prepared by supplementing DMEM with 10% FBS, L-glutamine, pen/strep, IBMX (375 μM), insulin (120 nM), and dexamethasone (188 nM). Differentiation media-2 (DM2) was prepared by supplementing DMEM with 10% FBS, L-glutamine, pen/strep, and insulin (120 nM).

Preparation of gelatinized plates

Cell culture plates were gelatinized as follows. Gelatin (1%w/v in distilled water) was autoclaved and stored at room temperature. The bottom of each cell culture well was covered uniformly in the gelatin solution, ensuring that no bubbles were formed. This solution was removed leaving behind a thin film of gelatin. These plates were left to dry under the tissue culture hood. Plates were next washed with PBS, after which a 0.5% glutaric dialdehyde solution (glutaraldehyde in distilled water) was added to the cell culture wells. After ten

minutes, wells were washed twice with DMEM containing pen-strep. Each washing step should last for approximately five minutes.

Cell culture

3T3-L1 pre-adipocyte cells were split approximately every 2-3 days or upon reaching a confluence of approximately 60%. Overconfluency may affect the ability of these cells to differentiate into adipocytes.

Other reagents

D-(+)-glucose ("cold" glucose, not radiolabeled) was added to DPBS mix to a final concentration of 10 mM.

Lysis buffer, a mixture of a base (e.g., sodium hydroxide at a final concentration of 0.5N) and a detergent (e.g., sodium dodecyl sulphate (SDS) diluted to a final concentration of 0.1% w/v) was freshly prepared each time (within one to two hours of use). Prior to use, lysis buffer was warmed up to a temperature exceeding that of room temperature for a period of approximately 30 minutes to avoid precipitation of the buffer.

Determination of glucose uptake

Pre-adipocyte 3T3-L1 cells were plated at a density of approximately 5000 cells/well (in black NUNC 96 well plate). These cells were differentiated into adipocytes in two separate steps. Initially, cells were cultured in differentiation medium-1 (DM1) (day 1 of adipocyte differentation) for a period of two to three days. DM1 prevents proliferation and induces the expression of adipocyte-specific genes. Cells were next cultured in differentiation medium-2 (DM2) for 3 to 4 days, after which the culture media was replaced by fresh DM2. The glucose uptake assay was performed at day 9-15 of differentiation.

Two days prior to the experiment (at day 7-13 of differentiation), DM2 was removed and replaced with fresh Prees media. Candidate compounds were added

at this time, allowing an incubation period of approximately 48 hours. On the day of the experiment, cells (now at day 9 to 15 of differentiation) were serum starved for three hours in DPBS, magnesium sulfate (0.8 mM), and Hepes (10mM) at pH ~7. After this incubation period, fresh DPBS containing insulin (10 nM) was added to the adipocytes. Fresh DPBS without any insulin were placed on cells that served as a negative control. Following an incubation period of 25 minutes at 37°C, radioactive glucose (labeled with ^{14}C , at a final concentration of 0.04 mM, ~0.26 μCi ^{14}C-glucose in each well) was added to the media for a period of 15 minutes at room temperature. Media was next removed and cells were washed thoroughly and lysed. Upon lysis, cells form a small, cloudy mass, detached from the well bottom. 10% glacial acetic acid was added to each well to neutralize the lysis reaction. Scintillation fluid was next added to the wells and the incorporation of glucose was determined by measuring the amount of radioactivity in each well using the MicroBeta plate reader.

The data are shown in Tables 4 and 5, below.

Table 4

		Diflunisal (μM)			
		36	18	9	0
Bezafibrate (μM)	36	1.69	1.74	1.74	1.57
	18	1.67	1.62	1.57	1.37
	9	1.65	1.42	1.27	1.16
	0	1.52	1.19	1.12	0.99

The average fold increase in insulin-stimulated glucose uptake compared to vehicle treated control was determined. The average of four biological replicates is shown. At all combination doses there is an increase in glucose uptake as compared to the single agents.

Table 5

		Bezafibrate (μM)			
		36	18	9	0
Cinnamic acid (μM)	12	1.46	1.36	1.23	1.10
	6	1.49	1.36	1.17	1.03
	3	1.30	1.26	1.10	0.98
	0	1.15	1.21	0.94	0.88

The average fold increase in insulin-stimulated glucose uptake compared to vehicle treated control was determined. The average of three biological replicates is shown. At all combination doses there is an increase in glucose uptake as compared to the single agents.

Example 2: The combination of bezafibrate and diflunisal reduce insulin sensitivity in a rat model

Insulin resistance was induced in male Sprague Dawley rats by four weeks of high fat feeding (60% of calories derived from fat). Drug treatment began one week after initiation of high fat diet. Drugs were administered daily, by oral gavage for a three week period.

Following the three weeks of treatment, animals were fasted for five hours and anesthetized, and blood collected from the inferior vena cava for determination of serum glucose and insulin levels. Insulin sensitivity was determined using the homeostasis model assessment (HOMA).

$$\text{HOMA} = \frac{\text{fasting serum glucose X fasting serum insulin}}{22.5}$$

The results are shown in Figs. 1-3.

Example 3: Screening assays identify additional agents that increase glucose uptake by adipocytes

Differentiated mouse adipocytes were employed to identify combinations of agents that have the ability to increase glucose uptake upon insulin stimulation, as detected by scintillation counting of radiolabelled glucose (using, for example, the Perkin Elmer 1450 Microbeta JET reader). These assays were conducted as follows.

Materials and methods

Prees media

Complete media, also referred to as "Prees" media, was prepared as follows. Dulbecco's Modified Eagle's Medium (DMEM) was supplemented with L-glutamine, penicillin-G and streptomycin (pen/strep), and heat-inactivated fetal bovine serum (FBS) (heat inactivated at 65°C for 30 minutes). Because serum can affect the growth, adherence, and differentiation of cells, any new lot of serum was first tested prior to use. Media was equilibrated in the incubator (5% CO_2) until the pH was within the proper range (~7), as indicated by the red/orange color of the indicator dye. If the media became pink (indicating a high pH), we discarded the media as basic conditions can affect cells and denature the insulin used in the differentiation medium-1 (DM1) and the differentiation medium-2 (DM2).

Differentiation medias

Differentiation media-1 (DM1) was prepared by supplementing DMEM with 10% FBS, L-glutamine, pen/strep, IBMX (375 μM), insulin (120 nM), and dexamethasone (188 nM). Differentiation media-2 (DM2) was prepared by supplementing DMEM with 10% FBS, L-glutamine, pen/strep, and insulin (120 nM).

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Cell culture

3T3-L1 pre-adipocyte cells were split approximately every 2-3 days or upon reaching a confluence of approximately 60%. Overconfluency may affect the ability of these cells to differentiate into adipocytes.

Other reagents

D-(+)-glucose ("cold" glucose, not radiolabeled) was added to DPBS mix to a final concentration of 10 mM.

Lysis buffer, a mixture of a base (e.g., sodium hydroxide at a final concentration of 0.5N) and a detergent (e.g., sodium dodecyl sulphate (SDS) diluted to a final concentration of 0.1% w/v) was freshly prepared each time (within one to two hours of use). Prior to use, lysis buffer was warmed up to a temperature exceeding that of room temperature for a period of approximately 30 minutes to avoid precipitation of the buffer.

Determination of glucose uptake

Pre-adipocyte 3T3-L1 cells were plated at a density of approximately 5000 cells/well (in black NUNC 96 well plate). These cells were differentiated into adipocytes in two separate steps. Initially, cells were cultured in differentiation medium-1 (DM1) (day 1 of adipocyte differentation) for a period of two to three days. DM1 prevents proliferation and induces the expression of adipocyte-specific genes. Cells were next cultured in differentiation medium-2 (DM2) for 3 to 4 days, after which the culture media was replaced by fresh DM2. The glucose uptake assay was performed at day 9-15 of differentiation.

Two days prior to the experiment (at day 7-13 of differentiation), DM2 was removed and replaced with fresh Prees media. Candidate compounds were added at this time, allowing an incubation period of approximately 48 hours. On the day of the experiment, cells (now at day 9 to 15 of differentiation) were serum starved for three hours in DPBS, magnesium sulfate (0.8 mM), and Hepes (10mM) at pH ~7. After this incubation period, fresh DPBS containing insulin (10 nM) was added to the adipocytes. Fresh DPBS without any insulin were placed on cells that served as a negative control. Following an incubation period of 25 minutes at 37°C, radioactive glucose (labeled with ^{14}C , at a final concentration of 0.04 mM, ~0.26 μCi ^{14}C-glucose in each well) was added to the media for a period of 15 minutes at room temperature. Media was next removed and cells were washed thoroughly and lysed. Upon lysis, cells form a small, cloudy mass, detached from the well bottom. 10% glacial acetic acid was added to each well to neutralize the lysis reaction. Scintillation fluid was next added to the wells and the incorporation of glucose was determined by measuring the amount of radioactivity in each well using the MicroBeta plate reader. Compounds that exhibited glucose uptake activity are shown in Table 4. Table 4 shows glucose uptake activity (denoted as F (fold over base) with the standard deviation (sF)) of each of the compounds at various concentrations. S/N denotes the signal over noise ratio.

In another set of experiments, human skeletal myoblasts obtained by the conditional immortalization of cells derived from a non-diabetic subject, were used to screen the effect of a multitude of compounds on glycogen synthesis. For each compound, two doses were tested in triplicate. The vehicle was used as a negative control and insulin was used as a positive control. Prior to treatment, cells were serum-starved for 12 to 18 hours in Ham's F10 medium. Cells were next incubated either with the test compounds or control for a period of two hours in serum-free media containing radiolabeled glucose, after which, glycogen synthesis was measured. The results of these experiments are shown in Table 4 (denoted as Xlsyz).

Table 6

Name	CRx F	CRx sF	CRx S/N	CRx uM	Xlsyz F(L)	Xlsyz sF(L)	Xlsyz S/N (L)	Xlsyz uM(L)	Xlsyz F(H)	Xlsyz sF(H)	Xlsyz S/N (H)	Xlsyz uM(H)
Tetrahydrozoline Hydrochloride	1.0225	0.0755	13.54	39.5477	1.2564	0.039	32.22	4.3938	1.6	0.1451	11.03	43.9375
ISOPROTERENOL SULFATE	1.5553	0.0975	15.95	39.494	1.6714	0.0815	20.51	3.2331	1.5225	0.1165	13.07	32.3311
Acetyldigitoxin	0.8077	0.1165	6.93	11.1535	1.3016	0.0434	29.99	12.3916	1.2593	0.047	26.79	1.2392
NOREPINEPHRINE BITARTRATE	1.7559	0.2784	6.31	27.797	1.3758	0.0924	14.89	3.0882	1.4353	0.1497	9.59	30.8825
Dipivefrin Hydrochloride	1.8856	0.113	16.69	23.2042	1.2562	0.0375	33.50	2.6553	2.6154	0.3631	7.20	26.5532
Brimonidine	1.4251	0.2061	6.91	31.4307	1.6094	0.0966	16.66	3.492	1.2967	0.0784	16.54	34.9195
Epinephrine Bitartrate	1.6511	0.1809	9.13	9.4304	1.511	0.1387	10.89	3.2103	1.7681	0.1006	17.58	32.1032
Terbutaline Sulfate	1.2758	0.0854	14.94	33.7985	1.3013	0.0271	48.02	3.755	1.4059	0.1136	12.38	37.5501
Homatropine Methylbromide	1.0613	0.074	14.34	25.0363	1.3401	0.0401	33.42	2.7815	1.3333	0.1324	10.07	27.8153
Loxapine Hydrochloride	0.9649	0.122	7.91	18.8457	1.4364	0.1353	10.62	2.0938	1.2281	0.0377	32.58	20.9376
Ethopropazine Hydrochloride	0.9375	0.1223	7.67	28.8937	1.395	0.09	15.50	3.2101	0.8406	0.0212	39.65	32.1009
Candesartan Cilexetil	1.33	0.1416	9.39	15.9295	1.7284	0.1165	14.84	1.7698	0.6667	0.0223	29.90	17.6977
Inulin	1.0249	0.0918	11.16	1.4576	1.3377	0.1023	13.08	1.6194	1.0089	0.0339	29.76	0.1619
Metaproterenol Hemisulfate Salt	1.7249	0.2108	8.18	16.8778	1.4052	0.0959	14.65	1.7812	1.1261	0.0292	38.57	17.8116
Invertase	1.2175	0.1785	6.82	1.843	1.3974	0.108	12.94	2.02	0.8561	0.0305	28.07	0.202
Methylergonovine Maleate	0.5265	0.2648	1.99	20.7485	1.2906	0.0823	15.68	2.3052	1.05	0.0271	38.75	23.0516
Prostaglandin E	1.5723	0.1088	14.45	26.0518	1.7037	0.165	10.33	2.8944	1	0.149	6.71	28.9436
Guanfacine Hydrochloride	0.6974	0.2239	3.11	31.8616	1.4264	0.11	12.97	3.5398	1.1364	0.0349	32.56	35.3982
Methacholine Chloride	1.152	0.114	10.11	47.8331	1.3086	0.0698	18.75	5.3143	1.0156	0.0467	21.75	53.1426
Digitoxin	0.8801	0.0449	19.60	11.8851	1.3846	0.1713	8.08	13.2043	1.146	0.0486	23.58	1.3204
Geranyl Acetate	0.9527	0.0694	13.73	45.8528	1.3523	0.1396	9.69	5.0942	0.9	0.0642	14.02	50.9424
Evans Blue	0.9008	0.115	7.83	9.6492	1.3913	0.1889	7.37	10.7202	1.0519	0.0406	25.91	1.072
Xylazine Hydrochloride	1.0978	0.081	13.55	51.1733	1.3401	0.0537	24.96	5.6854	1.0857	0.0521	20.84	56.8536
Oleandomycin	1.1002	0.0811	13.57	11.5675	1.6271	0.2313	7.03	12.8515	0.9744	0.0403	24.18	1.2852
Prazosin Hydrochloride	1.2437	0.1464	8.50	21.4358	1.3333	0.1184	11.26	2.3815	0.7021	0.0264	26.59	23.8152
Tinidazole	1.0177	0.0646	15.75	36.3967	1.2177	0.1579	7.71	4.0437	1.0588	0.066	16.04	40.4367
Enalaprilat	0.992	0.1543	6.43	26.0636	1.2739	0.0814	15.65	2.8957	0.8333	0.0692	12.04	28.9567
Tannic Acid	0.8674	0.0779	11.13	5.2909	1.2949	0.1048	12.36	5.8782	1.0522	0.0219	48.05	0.5878
Azathioprine	1.7493	0.2205	7.93	37.0961	1.2275	0.0948	12.95	3.6062	1.0938	0.0352	31.07	36.062
Ritodrine Hydrochloride	1.5011	0.1595	9.41	27.7977	1.2121	0.0445	27.24	3.0883	1.039	0.0563	18.45	30.8833
Guaiacol	1.0722	0.062	17.29	72.5294	1.2105	0.0801	15.11	5.6529	0.9873	0.028	35.26	56.5291
Eucalyptol	1.1325	0.1543	7.34	4948.67	1.2047	0.1552	7.76	549.797	1.038	0.0387	26.82	5497.97
Promethazine Hydrochloride	0.9391	0.1273	7.38	28.0489	1.2585	0.18	6.99	3.1162	0.5797	0.0416	13.94	31.1624
METHANTHELINE BROMIDE	1.2479	0.1282	9.73	23.0738	1.219	0.1438	8.48	2.5635	1.1136	0.0301	37.00	25.6349
METHDILAZINE	0.9361	0.1008	9.29	31.6248	1.2127	0.0957	12.67	3.5135	0.75	0.0258	29.07	35.1351
Glutamic Acid Hydrochloride	0.964	0.2332	4.13	43.2463	1.2292	0.0384	32.01	4.8047	0.9535	0.0658	14.49	48.0466
Ergoloid Mesylates	1.1518	0.1728	6.67	21.2536	1.2045	0.0227	53.06	1.5158	1.1095	0.0288	38.52	15.1584
QUINACRINE	1.0058	0.1727	5.82	20.5561	1.2378	0.0468	26.45	2.2838	1.046	0.0843	12.41	22.8378
Meclofenoxate	1.1681	0.1143	10.22	34.8777	1.2103	0.0548	22.09	3.8749	1.0625	0.0287	37.02	38.7492
GENISTEIN	0.4522	0.0432	10.47	33.312	1.2013	0.0438	27.43	3.701	0.7857	0.0355	22.13	37.0096
Pergolide Mesylate	1.1326	0.1253	9.04	21.9213	1.2698	0.1331	9.54	2.4355	1.039	0.0425	24.45	24.3546
Triflupromazine Hydrochloride	0.9717	0.1634	5.95	23.1445	1.2443	0.0686	18.14	2.5714	0.2479	0.0202	12.27	25.7136

Name	CRx F	CRx sF	CRx S/N	CRx uM	Xlsyz F(L)	Xlsyz sF(L)	Xlsyz S/N (L)	Xlsyz uM(L)	Xlsyz F(H)	Xlsyz sF(H)	Xlsyz S/N (H)	Xlsyz uM(H)
Levocabastine Hydrochloride	1.2727	0.1069	11.91	19.6956	1.2127	0.0791	15.33	2.1882	0.9667	0.0687	14.07	21.8818
Hydroxypropyl Cellulose	1.0957	0.0531	20.63	1.9082	1.2583	0.1044	12.05	2.12	1.107	0.0519	21.33	0.212
Oxybutynin Chloride	1.0483	0.1851	5.66	23.0734	1.0847	0.0483	22.46	2.5634	1.5652	0.1325	11.81	25.6345
DOXAPRAM HYDROCHLORIDE	1.1028	0.0713	15.47	21.6188	0.9091	0.0375	24.24	2.4018	1.4615	0.2139	6.83	24.0185
Pyrilamine Maleate	1.1294	0.0933	12.11	24.66	1.1603	0.0329	35.27	2.7397	1.3778	0.0901	15.29	27.3973
LEAD DIETHYLDITHIOCARBAMATE	1.524	0.4049	3.76	21.9875	1.064	0.0607	17.53	2.4428	1.2527	0.0391	32.04	24.4281
Dimenhydrinate	1.1102	0.0697	15.93	19.7254	0.9571	0.0366	26.15	2.1915	1.5385	0.1913	8.04	21.9149
Bamethan	1.1895	0.1516	7.85	17.7718	0.9106	0.0412	22.10	1.9744	1.3846	0.1387	9.98	19.7445
Dyclonine Hydrochloride	1.1238	0.1232	9.12	29.5519	0.9339	0.0334	27.96	3.2832	1.9231	0.2533	7.59	32.8322
Dopamine Hydrochloride	1.1203	0.1517	7.38	47.4731	1.0909	0.0756	14.43	5.2743	2	0.2348	8.52	52.7426
Spectinomycin	1.0474	0.1049	9.98	25.0888	1.1245	0.0244	46.09	2.7874	1.2881	0.0819	15.73	27.8737
Acetohexamide	1.0591	0.1317	8.04	27.7463	1.0179	0.0816	12.47	3.0826	1.3939	0.1572	8.87	30.8261
DL-5-Hydroxytryptophan	1.0187	0.0972	10.48	40.876	1.1353	0.0645	17.60	4.5413	1.2903	0.0608	21.22	45.4133
Pioglitazone Hydrochloride	2.1107	0.2432	8.68	7.6519	1.0848	0.0538	20.16	2.5967	1.8586	0.0109	170.51	2.5504
Doxylamine Succinate	1.1094	0.0546	20.32	24.5584	0.9643	0.0367	26.28	2.7284	1.7692	0.2447	7.23	27.2844
Phensuximide	1.1431	0.0842	13.58	48.5249	1	0.0276	36.23	5.3911	1.3333	0.1003	13.29	53.9112
Melphalan	1.398	0.1619	8.63	27.6151	0.9691	0.0714	13.57	3.068	1.2982	0.0324	40.07	30.6803
Phenylpropanolamine Hydrochloride	1.077	0.1579	6.82	49.8718	0.9313	0.0232	40.14	5.5408	1.4222	0.1019	13.96	55.4076
Acetylcholine Chloride	1.0512	0.1161	9.05	50.5279	1.1605	0.0689	16.84	5.6136	1.3305	0.0637	20.89	5.7788
Carbamazepine	0.7464	0.1508	4.95	41.9001	1.0739	0.0482	22.28	4.6551	1.4211	0.1096	12.97	46.551
Doxycycline	0.447	0.1142	3.91	19.0911	1.0579	0.0288	36.73	2.121	1.7692	0.3167	5.59	21.2102
Phenylephrine Hydrochloride	1.2537	0.089	14.09	44.187	1.1789	0.0482	24.46	4.9092	1.6061	0.1069	15.02	49.0918
Diclofenac Sodium	1.3966	0.0673	20.75	30.3169	1.1322	0.0345	32.82	3.458	1.4615	0.1966	7.43	34.5803
Acetaminophen	1.021	0.1744	5.85	60.1251	1.0089	0.0416	24.25	6.6799	1.6154	0.141	11.46	66.7989
Carbinoxamine Maleate	0.7798	0.1566	4.98	21.8995	1	0.0536	18.66	2.433	1.6842	0.1255	13.42	24.3303
Diphenhydramine Hydrochloride	0.931	0.1519	6.13	31.1546	0.9714	0.0331	29.35	3.4613	1.9231	0.4585	4.19	34.6127
Oxymetazoline Hydrochloride	0.8959	0.1035	8.66	35.4664	1.1333	0.0621	18.25	3.4704	1.3623	0.1591	8.56	34.7035
Imipramine Hydrochloride	0.8539	0.0501	17.04	28.403	1.003	0.0839	11.95	3.1556	1.3218	0.0693	19.07	31.5557
Phenacemide	1.0254	0.0733	13.99	53.5407	1	0.0247	40.49	5.9484	1.3333	0.0993	13.43	59.4837
Carisoprodol	1.1305	0.0708	15.97	35.9621	1.0992	0.04	27.48	3.9954	1.3846	0.1515	9.14	39.9539
Pilocarpine Hydrochloride	0.8768	0.1514	5.79	37.8869	1.187	0.0834	14.23	4.2092	1.2889	0.0883	14.60	42.0924
Acetrizoate Sodium	1.2587	0.0957	13.15	15.7065	0.9494	0.0464	20.46	1.745	1.3158	0.115	11.44	17.4499
Hydroxocobalamin	1.1725	0.215	5.45	6.752	1.1068	0.0352	31.44	7.5015	1.2416	0.1306	9.51	0.7501
Calcium Chloride	0.7358	0.2489	2.96	83.8859	1.0714	0.0441	24.29	9.3197	1.2121	0.1806	6.71	93.1973
Cupric Chloride	1.3661	0.0795	17.18	53.3191	1.0643	0.0326	32.65	5.9238	1.25	0.1173	10.66	59.2375
Vincamine	0.8026	0.0952	8.43	25.3976	1.1446	0.0346	33.08	2.8217	1.2619	0.0733	17.22	28.2167
Acetohydroxamic Acid	1.0424	0.083	12.56	130.639	1.0272	0.0446	23.03	14.514	1.3333	0.1459	9.14	145.14
Dirithromycin	1.0697	0.0698	15.33	11.8561	0.9862	0.03	32.87	1.3172	1.2533	0.0543	23.08	13.1721
Sulfamethizole	1.0749	0.0786	13.68	33.9657	1.101	0.0285	38.63	3.7736	1.2	0.0806	14.89	37.7358
Ammonium Chloride	0.8881	0.1503	5.91	173.288	0.8482	0.0444	19.10	19.2523	1.2105	0.0912	13.27	192.523
Tolazoline Hydrochloride	0.967	0.0701	13.79	47.5899	0.9615	0.0324	29.68	5.2872	1.2469	0.0997	12.51	52.8724
Diphenidol Hydrochloride	1.0194	0.1118	9.12	26.2819	0.9781	0.0357	27.40	2.9199	1.3846	0.3815	3.63	29.1992
Bismuth Subsalicylate	1.69	0.1409	11.99	24.8575	1.0089	0.0428	23.57	3.1759	1.2105	0.1328	9.12	31.7592
PHENYTOIN	1.1755	0.1697	6.93	35.6754	0.9796	0.0345	28.39	3.9635	1.2174	0.0874	13.93	39.6354
Dicloxacillin Sodium	1.0042	0.1082	9.28	18.6968	1.0511	0.068	15.46	2.0772	1.3846	0.1962	7.06	20.7721
Indocyanine Green	0.8824	0.1506	5.86	12.0364	1.0603	0.079	13.42	1.3372	1.2	0.0405	29.63	13.3724
HEXYLCAINE HYDROCHLORIDE	1.0422	0.0802	13.00	30.8602	1.1545	0.0663	17.41	3.4286	1.2121	0.0947	12.80	34.2857
AMANTADINE HYDROCHLORIDE	0.618	0.0917	6.74	47.9536	0.8699	0.0666	13.06	5.3276	1.2308	0.1149	10.71	53.2765
Orphenadrine Citrate	0.9749	0.1018	9.58	20.0887	0.9704	0.0683	14.21	2.2318	1.2174	0.0661	18.42	22.3185
Diflunisal	1.5694	0.0744	21.09	36.8314	0.9421	0.0315	29.91	4.0767	1.2308	0.1346	9.14	40.7674
DIPHEMANIL METHYLSULFATE	1.2078	0.0672	17.97	24.5269	0.9708	0.0573	16.94	2.7249	1.2308	0.2763	4.45	27.2494

Acetazolamide	0.8994	0.1774	5.07	41.3183	1.0268	0.0421	24.39	4.5905	1.3077	0.2004	6.53	45.9046
Sulfasomidine	1.1803	0.0729	16.19	32.6659	1.0165	0.0312	32.58	3.6292	1.3077	0.1693	7.72	36.2918
Diatrizoate Sodium	0.9858	0.0493	20.00	16.2778	0.9562	0.0343	27.88	1.8085	1.3077	0.15	8.72	18.0846
Cefamandole Nafate	1.2353	0.0735	16.81	17.914	1.0165	0.0397	25.60	1.9902	1.25	0.109	11.47	19.9024
Arbutin	1.0786	0.1077	10.01	36.6911	1.056	0.0489	21.60	4.0764	1.2045	0.0495	24.33	40.7639
Iopromide	0.8499	0.0662	12.84	11.7205	0.9852	0.0316	31.18	1.3022	1.25	0.0825	15.15	13.0215
Phenylbutazone	1.2098	0.0872	13.87	29.4777	0.9675	0.0642	15.07	3.275	1.2444	0.0894	13.92	32.7497
Name	CRx F	CRx sF	CRx S/N	CRx uM	Xlsyz F(L)	Xlsyz sF(L)	Xlsyz S/N (L)	Xlsyz uM(L)	Xlsyz F(H)	Xlsyz sF(H)	Xlsyz S/N (H)	Xlsyz uM(H)
SUCCINYLCHOLIN E	1.0409	0.1125	9.25	23.7879	0.9577	0.0383	25.01	2.6428	1.2231	0.095	12.87	26.4284
Captopril	0.662	0.3	2.21	44.321	1.0804	0.0503	21.48	4.9241	1.2632	0.109	11.59	49.2407
Iophenoxic Acid	1.0641	0.0986	10.79	16.3681	1.0504	0.0382	27.50	1.8185	1.2119	0.0796	15.22	18.185
OLANZAPINE	1.0506	0.2278	4.61	28.8121	1.0681	0.0595	17.95	3.201	1.2	0.0507	23.67	32.0102
Etoposide	1.037	0.1142	9.08	15.5979	0.7273	0.0491	14.81	1.7329	1.2468	0.0929	13.42	17.3293
Nefopam	0.8859	0.1159	7.64	31.6802	1.1617	0.0329	35.31	3.5197	1.2368	0.0569	21.74	35.1967
Suprofen	1.4298	0.203	7.04	34.5789	1.0962	0.0233	47.05	3.8417	1.2203	0.0788	15.49	38.4172
Iopanoic Acid	1.252	0.0601	20.83	18.7617	0.8708	0.0323	26.96	2.0844	1.2318	0.0871	14.14	20.8443

Other Embodiments

All publications, patent applications, and patents mentioned in this specification are herein incorporated by reference.

Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific desired embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the fields of medicine, immunology, pharmacology, endocrinology, or related fields are intended to be within the scope of the invention.

What is claimed is:

Claims

1. A composition comprising:

(a) bezafibrate or an analog thereof; and

(b) diflunisal or an analog thereof, wherein said bezafibrate and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

2. A composition comprising:

(a) bezafibrate or an analog thereof; and

(b) cinnamic acid or an analog thereof, wherein said bezafibrate and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

3. The composition of claim 1 or 2, wherein said bezafibrate analog is selected from the group consisting of binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil.

4. The composition of claim 1 or 2, further comprising a third agent selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists,

endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors, vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol antagonists, cholesteryl ester transfer protein antagonists, cytokine synthesis inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

5. The composition of claim 4, wherein said sulfonylurea is selected from the group consisting of acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, and glyburide.

6. The composition of claim 4, wherein said non-sulfonylurea secretagogue is nateglinide or repaglinide.

7. The composition of claim 4, wherein said insulin analog is selected from the group consisting of insulin lispro, insulin aspart, insulin glarginine, NPH, lente insulin, ultralente insulin, humulin, and novolin.

8. The composition of claim 4, wherein said PPARγ agonist is selected from the group consisting of balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011, GI262570, GW347845, and FK614.

9. The composition of claim 4, wherein said biguanide is metformin or metformin/glyburide.

10. The composition of claim 4, wherein said alpha-glucosidase inhibitor is acarbose or miglitol.

11. The composition of claim 4, wherein said immmunomodulator is a corticosteroid, cyclophosphamide, or NsIDI.

12. The composition of claim 4, wherein said angiotensin converting enzyme (ACE) inhibitor is selected from the group consisting of benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

13. The composition of claim 4, wherein said angiotensin II receptor blocker is selected from the group consisting of candesartan, eprosartan, irbesarten, losartin, telmisartan, and valsartan.

14. The composition of claim 4, wherein said antioxidant is selected from the group consisting of nicotinamide, vitamin E, probucol, MDL29311, and U78518F.

15. The composition of claim 4, wherein said exendin 4 is AC2993.

16. The composition of claim 4, wherein said glucagon-like peptide is GLP-1.

17. The composition of any one of claims 1-16, wherein said composition is formulated for oral administration.

18. The composition of any one of claims 1-16, wherein said composition is formulated for systemic administration.

19. A method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof, said method comprising administering to said patient

(i) bezafibrate or an analog thereof; and

(ii) diflunisal or an analog thereof,

wherein said bezafibrate and diflunisal are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

20. A method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof, said method comprising administering to said patient

(i) bezafibrate or an analog thereof; and

(ii) cinnamic acid or an analog thereof,

wherein said bezafibrate and cinnamic acid are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

21. The method of claim 19 or 20, wherein said bezafibrate analog is selected from the group consisting of binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil.

22. The method of claim 19 or 20, further comprising administering to said patient a third agent selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists, endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors, vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol antagonists, cholesteryl ester transfer protein

antagonists, cytokine synthesis inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

23. The method of claim 22, wherein said sulfonylurea is selected from the group consisting of acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, and glyburide.

24. The method of claim 22, wherein said non-sulfonylurea secretagogue is nateglinide or repaglinide.

25. The method of claim 22, wherein said insulin analog is selected from the group consisting of insulin lispro, insulin aspart, insulin glarginine, NPH, lente insulin, ultralente insulin, humulin, and novolin.

26. The method of claim 22, wherein said PPARγ agonist is selected from the group consisting of balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011, GI262570, GW347845, and FK614.

27. The method of claim 22, wherein said biguanide is metformin or metformin/glyburide.

28. The method of claim 22, wherein said alpha-glucosidase inhibitor is acarbose or miglitol.

29. The method of claim 22, wherein said immmunomodulator is a corticosteroid, cyclophosphamide, or NsIDI.

30. The method of claim 22, wherein said angiotensin converting enzyme (ACE) inhibitor is selected from the group consisting of benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

31. The method of claim 22, wherein said angiotensin II receptor blocker is selected from the group consisting of candesartan, eprosartan, irbesarten, losartin, telmisartan, and valsartan.

32. The method of claim 22, wherein said antioxidant is selected from the group consisting of nicotinamide, vitamin E, probucol, MDL29311, and U78518F.

33. The method of claim 22, wherein said exendin 4 is AC2993.

34. The method of claim 22, wherein said glucagon-like peptide is GLP-1.

35. The method of any one of claims 19-34, wherein said composition is formulated for oral administration.

36. The method of any one of claims 19-34, wherein said composition is formulated for systemic administration.

37. The method of any one of claims 19-36, wherein said first and second agents are administered within 10 days of each other.

38. The method of claim 37, wherein said first and second agents are administered within 7 days of each other.

39. The method of claim 38, wherein said first and second agents are administered within 24 hours of each other.

40. The method of claim 38, wherein said first and second agents are administered within 1 hour of each other.

41. The method of any one of claims 19-40, wherein said metabolic disorder is diabetes or obesity.

42. A kit comprising:

(i) bezafibrate or an analog thereof; and

(ii) instructions for administering said bezafibrate and cinnamic acid or an analog thereof to a patient having or at risk of having a metabolic disorder.

43. A kit comprising:

(i) bezafibrate or an analog thereof; and

(ii) instructions for administering said bezafibrate and diflunisal or an analog thereof to a patient having or at risk of having a metabolic disorder.

44. A kit comprising:

(i) diflunisal or an analog thereof; and

(ii) instructions for administering said diflunisal and bezafibrate or an analog thereof to a patient having or at risk of having a metabolic disorder.

45. A kit comprising:

(i) cinnamic acid or an analog thereof; and

(ii) instructions for administering said cinnamic acid and bezafibrate or an analog thereof to a patient having or at risk of having a metabolic disorder.

46. A kit comprising:

(i) a composition comprising bezafibrate or an analog thereof and cinnamic acid or an analog thereof; and

(ii) instructions for administering said composition to a patient having or at risk of having a metabolic disorder.

47. A kit comprising:

(i) a composition comprising bezafibrate or an analog thereof and diflunisal or an analog thereof; and

(ii) instructions for administering said composition to a patient having or at risk of having a metabolic disorder.

48. A kit comprising:

(i) bezafibrate or an analog thereof;

(ii) cinnamic acid or an analog thereof; and

(iii) instructions for administering said bezafibrate and said cinnamic acid to a patient having or at risk of having a metabolic disorder.

49. A kit comprising:

(i) bezafibrate or an analog thereof;

(ii) diflunisal or an analog thereof; and

(iii) instructions for administering said bezafibrate and said diflunisal to a patient having or at risk of having a metabolic disorder.

50. The kit of any of claims 42-49, wherein said bezafibrate analog is selected from the group consisting of binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil.

51. A composition comprising:

(a) a PPAR agonist; and

(b) diflunisal or an analog thereof, wherein said PPAR agonist and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

52. A composition comprising:

(a) a PPAR agonist; and

(b) cinnamic acid or an analog thereof, wherein said PPAR agonist and diflunisal are present in amounts that, when administered to a patient, are sufficient to treat, prevent, or reduce a metabolic disorder.

53. The composition of claim 51 or 52, wherein said PPAR agonist is a PPARγ agonist.

54. The composition of claim 53, wherein said PPARγ agonist is selected from the group consisting of balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011, GI262570, GW347845, and FK614.

55. The composition of any of claims 51-54, further comprising a third agent selected from the group consisting of sulfonylureas, non-sulfonylurea secretagogues, insulin, insulin analogs, glucagon-like peptides, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, biguanides, alpha-glucosidase inhibitors, immunomodulators, statins and statin-containing combinations, angiotensin converting enzyme inhibitors, adenosine A1 receptor agonists, adenosine A2 receptor agonists, aldosterone antagonists, alpha 1 adrenoceptor antagonists, alpha 2 adrenoceptor agonists, alpha 2 adrenoceptor agonists, angiotensin receptor antagonists, antioxidants, ATPase inhibitors, atrial peptide agonists, beta adrenoceptor antagonists, calcium channel agonists, calcium channel antagonists, diuretics, dopamine D1 receptor agonists, endopeptidase inhibitors, endothelin receptor antagonists, guanylate cyclase stimulants, phosphodiesterase V inhibitors, protein kinase inhibitors, Cdc2 kinase inhibitors, renin inhibitors, thromboxane synthase inhibitors, vasopeptidase inhibitors, vasopressin I antagonists, vasopressin 2 antagonists, angiogenesis inhibitors, advanced glycation end product inhibitors, bile acid binding agents, bile acid transport inhibitors, bone formation stimulants, apolipoprotein A1 agonists, DNA topoisomerase inhibitors, cholesterol absorption inhibitors, cholesterol antagonists, cholesteryl ester transfer protein antagonists, cytokine synthesis

inhibitors, DNA polymerase inhibitors, dopamine D2 receptor agonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, lipase inhibitors, lipid peroxidation inhibitors, lipoprotein A antagonists, microsomal transport protein inhibitors, microsomal triglyceride transfer protein inhibitors, nitric oxide synthase inhibitors, oxidizing agents, phospholipase A2 inhibitors, radical formation agonists, platelet aggregation antagonists, prostaglandin synthase stimulants, reverse cholesterol transport activators, rho kinase inhibitors, selective estrogen receptor modulators, squalene epoxidase inhibitors, squalene synthase inhibitors, thromboxane A2 antagonists, amylin agonists, cannabinoid receptor antagonists, cholecystokinin A agonists, corticotropin-releasing factor agonists, dopamine uptake inhibitors, G protein-coupled receptor modulators, glutamate antagonists, glucagon-like peptide-1 agonists, insulin sensitizers, lipase inhibitors, melanin-concentrating hormone receptor antagonists, nerve growth factor agonists, neuropeptide Y agonists, neuropeptide Y antagonists, SNRIs, protein tyrosine phosphatase inhibitors, and serotonin 2C receptor agonists.

56. The composition of claim 55, wherein said sulfonylurea is selected from the group consisting of acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, and glyburide.

57. The composition of claim 55, wherein said non-sulfonylurea secretagogue is nateglinide or repaglinide.

58. The composition of claim 55, wherein said insulin analog is selected from the group consisting of insulin lispro, insulin aspart, insulin glarginine, NPH, lente insulin, ultralente insulin, humulin, and novolin.

59. The composition of claim 55, wherein said biguanide is metformin or metformin/glyburide.

60. The composition of claim 55, wherein said alpha-glucosidase inhibitor is acarbose or miglitol.

61. The composition of claim 55, wherein said immmunomodulator is a corticosteroid, cyclophosphamide, or NsIDI.

62. The composition of claim 55, wherein said angiotensin converting enzyme (ACE) inhibitor is selected from the group consisting of benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

63. The composition of claim 55, wherein said angiotensin II receptor blocker is selected from the group consisting of candesartan, eprosartan, irbesarten, losartin, telmisartan, and valsartan.

64. The composition of claim 55, wherein said antioxidant is selected from the group consisting of nicotinamide, vitamin E, probucol, MDL29311, and U78518F.

65. The composition of claim 55, wherein said exendin 4 is AC2993.

66. The composition of claim 55, wherein said glucagon-like peptide is GLP-1.

67. The composition of any one of claims 51-66, wherein said composition is formulated for oral administration.

68. The composition of any one of claims 51-66, wherein said composition is formulated for systemic administration.

69. A method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof, said method comprising administering to said patient

(i) a PPAR agonist; and

(ii) diflunisal or an analog thereof,

wherein said PPARγ agonist and diflunisal are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

70. A method for treating, preventing, or reducing a metabolic disorder in a patient in need thereof, said method comprising administering to said patient

(i) a PPAR agonist; and

(ii) cinnamic acid or an analog thereof,

wherein said PPARγ agonist and cinnamic acid are administered in amounts that together are sufficient to treat, prevent, or reduce a metabolic disorder.

71. The method of claim 69 or 70, wherein said PPAR agonist is a PPARγ agonist.

72. The method of claim 71, wherein said PPARγ agonist is selected from the group consisting of balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011, GI262570, GW347845, and FK614.

73. A kit comprising:

(i) a PPAR agonist; and

(ii) instructions for administering said PPAR agonist and cinnamic acid or an analog thereof to a patient having or at risk of having a metabolic disorder.

74. A kit comprising:

(i) a PPAR agonist; and

(ii) instructions for administering said PPAR agonist and diflunisal or an analog thereof to a patient having or at risk of having a metabolic disorder.

75. A kit comprising:

(i) diflunisal or an analog thereof; and

(ii) instructions for administering said diflunisal and a PPAR agonist or an analog thereof to a patient having or at risk of having a metabolic disorder.

76. A kit comprising:

(i) cinnamic acid or an analog thereof; and

(ii) instructions for administering said cinnamic acid and a PPAR agonist or an analog thereof to a patient having or at risk of having a metabolic disorder.

77. A kit comprising:

(i) a composition comprising a PPAR agonist or an analog thereof and cinnamic acid or an analog thereof; and

(ii) instructions for administering said composition to a patient having or at risk of having a metabolic disorder.

78. A kit comprising:

(i) a composition comprising a PPAR agonist or an analog thereof and diflunisal or an analog thereof; and

(ii) instructions for administering said composition to a patient having or at risk of having a metabolic disorder.

79. A kit comprising:

(i) a PPAR agonist or an analog thereof;

(ii) cinnamic acid or an analog thereof; and

(iii) instructions for administering said PPAR agonist and said cinnamic acid to a patient having or at risk of having a metabolic disorder.

80. A kit comprising:

(i) a PPAR agonist or an analog thereof;

(ii) diflunisal or an analog thereof; and

(iii) instructions for administering said PPAR agonist and said diflunisal to a patient having or at risk of having a metabolic disorder.

81. The kit of any of claims 73-80, wherein said PPAR agonist is a PPARγ agonist.

82. The kit of claim 81, wherein said PPARγ agonist is selected from the group consisting of balaglitazone, troglitazone, pioglitazone, ciglitazone, englitazone, rosiglitazone, darglitazone, englitazone, netoglitazone, KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011, GI262570, GW347845, and FK614.

83. A composition comprising:

(a) a first agent selected from any one of the agents of Table 1; and

(b) a second agent, wherein said second agent is selected from the group consisting of a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant;

wherein said first agent and said second agent are present in amounts that, when administered to a mammal, are sufficient to treat, prevent, or reduce a metabolic disorder.

84. The composition of claim 83, further comprising one or more additional agents selected from Table 1.

85. The composition of claim 83, wherein said sulfonylurea is selected from the group consisting of acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, and glyburide.

86. The composition of claim 83, wherein said non-sulfonylurea secretagogue is nateglinide or repaglinide.

87. The composition of claim 83, wherein said insulin analog is selected from the group consisting of insulin lispro, insulin aspart, insulin glarginine, NPH, lente insulin, ultralente insulin, humulin, and novolin.

88. The composition of claim 83, wherein said biguanide is metformin or metformin/glyburide.

89. The composition of claim 83, wherein said thiazalidinedione is selected from the group consisting of troglitazone, pioglitazone and rosiglitazone.

90. The composition of claim 83, wherein said alpha-glucosidase inhibitor is acarbose or miglitol.

91. The composition of claim 83, wherein said immmunomodulator is a glucocorticoid, cyclophosphamide, cyclosporine A, rapamycin, or FK506 cytokine.

92. The composition of claim 83, wherein said angiotensin converting enzyme (ACE) inhibitor is selected from the group consisting of benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

93. The composition of claim 83, wherein said angiotensin II receptor blocker is selected from the group consisting of candesartan, eprosartan, irbesarten, losartin, telmisartan, and valsartan.

94. The composition of claim 83, wherein said antioxidant is selected from the group consisting of nicotinamide, vitamin E, probucol, MDL29311 and U78518F.

95. The composition of claim 83, wherein said exendin 4 is AC2993.

96. The composition of claim 83, wherein said glucagon-like peptide is GLP-1.

97. The composition of claim 83, further comprising at least one agent selected from the group consisting of a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant.

98. The composition of any one of claims 83-97, wherein said composition is formulated for oral administration.

99. The composition of any one of claims 83-97, wherein said composition is formulated for systemic administration.

100. A method for treating, preventing, or reducing a metabolic disorder, said method comprising administering to a mammal one or more agents selected from any one of the agents of Table 1 in an amount sufficient to treat, prevent, or reduce said metabolic disorder.

101. A method for treating, preventing, or reducing a metabolic disorder, said method comprising administering to a mammal at least two different agents from Table 1, wherein the first and second agents are administered simultaneously or within 28 days of each other, in amounts that together are sufficient to treat, prevent, or reduce said metabolic disorder.

102. The method of claim 101, wherein said first and second agents are administered within 14 days of each other.

103. The method of claim 102, wherein said first and second agents are administered within 7 days of each other.

104. The method of claim 103, wherein said first and second agents are administered within 24 hours of each other.

105. The method of claim 100 or 101, wherein said metabolic disorder is diabetes or obesity.

106. The method of claim 100 or 101, wherein said agent reduces glucose levels in said mammal relative to such levels in a control.

107. The method of claim 100 or 101, wherein said mammal is a human.

108. The method of claim 100 or 101, further comprising an additional therapeutic regimen.

109. The method of claim 108, wherein said additional therapeutic regimen comprises administering to said mammal an additional therapeutic agent, wherein the agent or agents from Table 1 and said additional therapeutic agents are present in amounts that, when administered to a mammal, are sufficient to treat, prevent, or reduce a metabolic disorder.

110. The method of claim 109, wherein said additional therapeutic agent is selected from the group consisting of a sulfonylurea, a non-sulfonylurea secretagogue, insulin, an insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione,

an alpha-glucosidase inhibitor, an immunosuppressant, an immmunomodulator, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker, and an antioxidant.

111. The method of claim 110, wherein said sulfonylurea is selected from the group consisting of acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, and glyburide.

112. The method of claim 110, wherein said non-sulfonylurea secretagogue is nateglinide or repaglinide.

113. The method of claim 110, wherein said insulin analog is selected from the group consisting of insulin lispro, insulin aspart, insulin glarginine, NPH, lente insulin, ultralente insulin, humulin, and novolin.

114. The method of claim 110, wherein said biguanide is metformin or metformin/glyburide.

115. The method of claim 110, wherein said thiazalidinedione is selected from the group consisting of troglitazone, pioglitazone and rosiglitazone.

116. The method of claim 110, wherein said alpha-glucosidase inhibitor is acarbose or miglitol.

117. The method of claim 110, wherein said immmunomodulator is a glucocorticoid, cyclophosphamide, cyclosporine A, rapamycin, or FK506 cytokine.

118. The method of claim 110, wherein said angiotensin converting enzyme (ACE) inhibitor is selected from the group consisting of benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

119. The method of claim 110, wherein said angiotensin II receptor blocker is selected from the group consisting of candesartan, eprosartan, irbesarten, losartin, telmisartan, and valsartan.

120. The method of claim 110, wherein said antioxidant is selected from the group consisting of nicotinamide, vitamin E, probucol, MDL29311 and U78518F.

121. The method of claim 110, wherein said exendin 4 is AC2993.

122. The method of claim 110, wherein said glucagon-like peptide is GLP-

123. The method of claims 100-122, wherein said agent or agents from Table 1 and said additional agent are administered within 14 days of each other.

124. The method of claim 123, wherein said agent or agents from Table 1 and said additional agent are administered within 7 days of each other.

125. The method claim 124, wherein said agent or agents from Table 1 and said additional agent are administered within 1 day of each other.

126. The method of any one of claims 100-122, wherein said agent from Table 1, said additional agent, or both are administered orally or systemically.

127. A kit comprising:

(i) an agent selected from any one of the agents of Table 1; and

(ii) instructions for administering said agent to a patient having or at risk of having a metabolic disorder.

128. A kit comprising:

(i) a composition comprising two agents selected from any one of the agents of Table 1; and

(ii) instructions for administering said composition to a patient having or at risk of having a metabolic disorder.

129. A kit comprising:

(i) a first agent selected from any one of the agents of Table 1;

(ii) a second agent selected from any one of the agents of Table 1; and

(iii) instructions for administering said first and said second agents to a patient having or at risk of having a metabolic disorder.

130. A kit comprising:

(i) an agent selected from any one of the agents of Table 1; and

(ii) instructions for administering said agent with a second agent selected from any one of the agents of Table 1 to a patient having or at risk of having a metabolic disorder, wherein said second agent is not the agent in (i).

131. A kit, comprising:

(i) a composition comprising

(a) a first agent selected from any one of the agents of Table 1; and

(b) a second agent selected from the group consisting of a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant; and

(ii) instructions for administering said composition to a patient having or at risk of having a metabolic disorder.

132. A kit, comprising:

(i) a first agent selected from any one of the agents of Table 1; and

(ii) a second agent selected from the group consisting of a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant; and

(iii) instructions for administering said first and said second agents to a patient having or at risk of having a metabolic disorder.

133. A kit comprising:

(i) an agent selected from any one of the agents of Table 1; and

(ii) instructions for administering said agent and a second agent to a patient having or at risk of having a metabolic disorder, wherein said second agent is selected from the group consisting of a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-

glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant.

134. A kit comprising:

(i) an agent selected from the group consisting of a sulfonylurea, non-sulfonylurea secretagogue, insulin, insulin analog, glucagon-like peptide, exendin-4, YM178, FK614, dipeptidyl peptidase IV inhibitor, biguanide, thiazalidinedione, alpha-glucosidase inhibitor, immunosuppressant, immmunomodulator, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, and antioxidant; and

(ii) instructions for administering said agent from (i) with any agent selected from any one of the agents of Table 1 to a patient having or at risk of having a metabolic disorder.

135. A method of identifying a combination that may be useful for the treatment, prevention, or reduction of a metabolic disorder, said method comprising the steps of:

(a) contacting cells with an agent selected from any one the agents of Table 1 and a candidate compound; and

(b) determining whether the combination of said agent and said candidate compound reduces glucose levels relative to cells contacted with said agent but not contacted with the candidate compound, wherein a reduction in glucose levels identifies the combination as a combination useful for the treatment, prevention, or reduction of a metabolic disorder.

136. The method of claim 135, wherein reduction in glucose levels is the result of altering insulin signaling, altering glucose transporter activity, or increasing adipocyte or muscle cell differentiation, or altering gene transcription in adipocytes or muscle cells.

137. A method of identifying a combination that may be useful for the treatment, reduction, or prevention of a metabolic disorder, said method comprising the steps of:

(a) contacting cells with an agent selected from any one of the agents of Table 1 and a candidate compound; and

(b) determining whether the combination of said agent and said candidate compound alter insulin signaling such that glucose levels are reduced relative to cells contacted with said agent but not contacted with said candidate compound, wherein an alteration resulting in an increase in glucose reduction identifies the combination as a combination useful for the treatment, prevention, or reduction of a metabolic disorder.

138. The method of claim 135 or 137, wherein said cells are mammalian cells.

139. The method of claim 138, wherein said cells are human cells.

140. The method of claim 139, wherein said cells are muscle cells, intestinal cells, adipocytes, liver cells, or pancreatic cells.

141. The method of claim 135 or 137, wherein said cells have an alteration in insulin signaling activity such that glucose levels are increased.

142. The method of claim 135 or 137, wherein a reduction in glucose levels is a result of an increase in insulin production, an increase in insulin secretion, an increase in glucose uptake by peripheral tissues, a reduction in hepatic glucose production, or a reduction in the absorption of carbohydrates from the intestines.