SUBSTITUTED FUSED HETEROCYCLIC C-GLYCOSIDES

FIELD OF THE INVENTION

This invention relates to substituted fused heterocyclic C-glycosides, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of diabetes and Syndrome X.

BACKGROUND OF THE INVENTION

Diabetes is a chronic disorder affecting carbohydrate, fat and protein metabolism in animals.

Type I diabetes mellitus, which comprises approximately 10% of all diabetes cases, was previously referred to as insulin-dependent diabetes mellitus ("IDDM") or juvenile-onset diabetes. This disease is characterized by a progressive loss of insulin secretory function by beta cells of the pancreas. This characteristic is also shared by non-idiopathic, or "secondary", diabetes having its origins in pancreatic disease. Type I diabetes mellitus is associated with the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia; polyuria; polydipsia and/or hyperphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension which can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

Type II diabetes mellitus (non-insulin-dependent diabetes mellitus or NIDDM) is a metabolic disorder involving the dysregulation of glucose metabolism and impaired insulin sensitivity. Type II diabetes mellitus usually develops in adulthood and is associated with the body's inability to utilize or make sufficient insulin. In addition to the insulin resistance observed in the target tissues, patients suffering from type II diabetes mellitus have a relative insulin deficiency -- that is, patients have lower than predicted insulin levels for a given plasma glucose concentration. Type II diabetes mellitus is

characterized by the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia; polyuria; polydipsia and/or hyperphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension which can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

Syndrome X, also termed Insulin Resistance Syndrome (IRS), Metabolic Syndrome, or Metabolic Syndrome X, is recognized in some 2% of diagnostic coronary catheterizations. Often disabling, it presents symptoms or risk factors for the development of Type II diabetes mellitus and cardiovascular disease, including impaired glucose tolerance (IGT), impaired fasting glucose (IFG), hyperinsulinemia, insulin resistance, dyslipidemia (e.g., high triglycerides, low HDL), hypertension and obesity.

Therapy for IDDM patients has consistently focused on administration of exogenous insulin, which may be derived from various sources (e.g., human, bovine, porcine insulin). The use of heterologous species material gives rise to formation of anti-insulin antibodies which have activity-limiting effects and result in progressive requirements for larger doses in order to achieve desired hypoglycemic effects.

Typical treatment of Type II diabetes mellitus focuses on maintaining the blood glucose level as near to normal as possible with lifestyle modification relating to diet and exercise, and when necessary, the treatment with anti-diabetic agents, insulin or a combination thereof. NIDDM that cannot be controlled by dietary management is treated with oral antidiabetic agents.

Although insulin resistance is not always treated in all Syndrome X patients, those who exhibit a prediabetic state (e.g., IGT, IFG), where fasting glucose levels may be higher than normal but not at the diabetes diagnostic criterion, is treated in some countries (e.g., Germany) with metformin to prevent diabetes. The anti-diabetic agents may be combined with

pharmacological agents for the treatment of the concomitant co-morbidities (e.g., antihypertensives for hypertension, hypolipidemic agents for lipidemia).

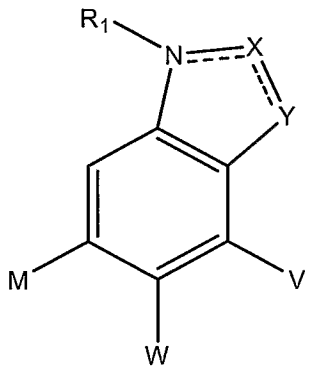
First-line therapies typically include metformin and sulfonylureas as well as thiazolidinediones. Metformin monotherapy is a first line choice, particularly for treating type II diabetic patients who are also obese and/or dyslipidemic. Lack of an appropriate response to metformin is often followed by treatment with metformin in combination with sulfonylureas, thiazolidinediones, or insulin. Sulfonylurea monotherapy (including all generations of drugs) is also a common first line treatment option. Another first line therapy choice may be thiazolidinediones. Alpha glucosidase inhibitors are also used as first and second line therapies. Patients who do not respond appropriately to oral anti-diabetic monotherapy, are given combinations of the above-mentioned agents. When glycemic control cannot be maintained with oral antidiabetics alone, insulin therapy is used either as a monotherapy, or in combination with oral antidiabetic agents.

One recent development in treating hyperglycemia is focused on excretion of excessive glucose directly into urine. Specific inhibitors of SGLTs have been shown to increase the excretion of glucose in urine and lower blood glucose levels in rodent models of IDDM and NIDDM.

SUMMARY OF THE INVENTION

One aspect of the present invention is directed to methods and compositions for the treatment or prophylaxis of diabetes, Syndrome X, or associated symptoms or complications. More specifically, this invention is directed to a novel method of treating diabetes or Syndrome X, or associated symptoms or complications thereof, in a subject afflicted with such a condition, said method comprising administering one or more glucose reabsorption inhibitors and administering one or more antidiabetic agent(s) for the treatment of diabetes or Syndrome X, or associated symptoms or complications thereof.

Another aspect of the invention features compounds of formula (IV)

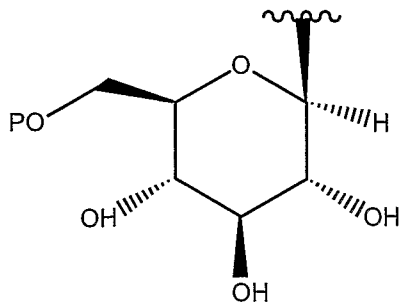


(IV)

wherein:

one of the dashed lines between NR_1 and X or between X and Y is present, or both are absent;

two of V, M, and W are H and the third is



R_1 is H, or C_{1-4} alkyl; or R_1 is absent where the dashed line between NR^1 and X is present,

X is N, C=O, CH, or C-Q-Z;

Y is N-Q-Z or C-Q-Z, where X is N, C=O, or CH;
Y is CH, where X is C-Q-Z;

Q = $-(CH_2)_n-$ where n = 1 or 2;

Z is substituted or unsubstituted, and is selected from C_{3-7} cycloalkyl, phenyl, a 5- or 6- membered heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, a biaryl, a 9- or 10-membered fused bicyclyl (such as naphthyl), and a fused heterobicyclyl, wherein said fused heterobicyclyl has between 1 and 4 heteroatoms (and preferably between 1 and 3 or between 1 and 2 heteroatoms) independently selected from N, O, and S;

P = H, C_{1-7} acyl, or (C_{1-6} alkoxy)carbonyl;

or a pharmaceutically acceptable salt, thereof.

One aspect of the invention features a pharmaceutical composition comprising a glucose reabsorption inhibitor, at least one additional antidiabetic agent, and a pharmaceutically acceptable carrier. The invention also provides a process for formulating a pharmaceutical composition, comprising formulating together a glucose reabsorption inhibitor, one or more antidiabetic agent(s), and a pharmaceutically acceptable carrier.

An embodiment of the invention is a method for treating diabetes or Syndrome X, or associated symptoms or complications thereof in a subject, said method comprising administering to said subject a jointly effective amount of a glucose reabsorption inhibitor and administering to said subject a jointly

effective amount of at least one antidiabetic agent, said combined administration providing the desired therapeutic effect.

Another embodiment of the invention is a method for inhibiting the onset of diabetes or Syndrome X, or associated symptoms or complications thereof in a subject, said method comprising administering to said subject a jointly effective dose of a glucose reabsorption inhibitor and administering to said subject a jointly effective amount of one or more anti-diabetic agent(s), said combined administration providing the desired prophylactic effect.

In the disclosed methods, the diabetes or Syndrome X, or associated symptoms or complications thereof, is selected from IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts.

Also included in the invention is the use of one or more glucose reabsorption inhibitors in combination with one or more antidiabetic agents for the preparation of a medicament for treating a condition selected from IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome or polycystic ovarian syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts.

DETAILED DESCRIPTION OF THE INVENTION

All diabetics, regardless of their genetic and environmental backgrounds, have in common an apparent lack of insulin or inadequate insulin function. Because transfer of glucose from the blood into muscle and fatty tissue is insulin dependent, diabetics lack the ability to utilize glucose adequately, which leads to undesired accumulation of glucose in the blood (hyperglycemia). Chronic hyperglycemia leads to decrease in insulin secretion and contributes to increased insulin resistance, and as a result, the blood glucose concentration is increased so that diabetes is self-exacerbated (Diabetologia, 1985, "Hyperglycaemia as an inducer as well as a consequence of impaired isle cell function and insulin resistance: implications for the management of diabetes", Vol. 28, p. 119); Diabetes Cares, 1990, Vol. 13, No. 6, "Glucose Toxicity", pp. 610-630). Therefore, by treating hyperglycemia, the aforementioned self-exacerbating cycle is interrupted so that the prophylaxis or treatment of diabetes is made possible.

US Patent NO. 6,153,632 to R. Rieveley discloses a method and composition stated to be for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II), which incorporates a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus.

According to one aspect, the invention features the combination of a PPAR modulator, preferably a PPAR δ agonist, and an SGLT inhibitor, preferably an SGLT 2 inhibitor or a selective SGLT 2 inhibitor.

A. Terms

Some terms are defined below and by their usage throughout this disclosure.

Unless otherwise noted, "alkyl" and "alkoxy" as used herein, whether used alone or as part of a substituent group, include straight, cyclic, and branched-chain alkyl having 1 to 8 carbon atoms, or any number within this range. For example, alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, 2-butenyl, 2-butynyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. The alkyl and alkoxy group may be independently substituted with one to five, preferably one to three groups selected from halogen (F, Cl, Br, I), oxo, OH, amino, carboxyl, and alkoxy. The alkyl and alkoxy group may also be independently linked to one or more PEG radicals (polyethylene glycol).

The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having a carbonyl group linked to hydrocarbyl group having 1 to 7 carbon atoms (branched or straight chain or cyclic) derived from an organic acid by removal of the hydroxyl group. For example C_4 acyl can include $(CO)CH_2CH_2CH_2CH_3$ and $(CO)(CH_2\ (CH)\ (CH_3)_2$; similarly, C_6 acyl includes both $(CO)(C_6H_{13})$ and $(CO)(C_6H_5)$. The term "Ac" as used herein, whether used alone or as part of a substituent group, means acetyl.

"Aryl" is a carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2- naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, OH, CN, mercapto, nitro, amino, cyano, optionally substituted C_1-C_8-alkyl, optionally substituted alkoxy, alkylthio, alkylsulfinyl,

alkylsulfonyl, alkyl-amino, di(C_1-C_8-alkyl)amino, formyl, carboxyl, alkoxycarbonyl, alkoxycarbonyloxy, alkanoyloxy, phenyl, carbamoyl, carboxamide, di-lower alkylcarbamoyloxy, phenoxycarbonyloxy group, lower alkylenedioxy, benzoyloxy, alkyl-CO-O-, alkyl-O-CO-, -$CONH_2$, alkyl-O-CO-O-, or alkyl-CO-NH-. Illustrative aryl radicals include, for example, phenyl, naphthyl, biphenyl, indene ( ), indane ( ), fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl, dimethylcarbamylphenyl and the like. “Ph” or “PH” denotes phenyl.

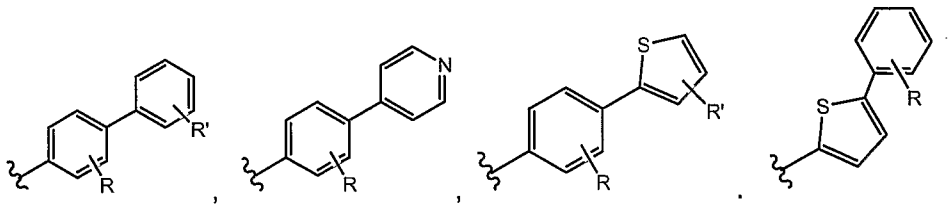
The term "heteroaryl" as used herein represents a stable five or six-membered monocyclic or bicyclic aromatic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O and S. The heteroaryl group may be attached at any heteroatom or carbon atom, which results in the creation of a stable structure. Examples of heteroaryl groups include, but are not limited to benzofuranyl, benzothiophenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, thiophenyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, benzoxazolyl, benzopyrazolyl, indolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl or quinolinyl. Prefered heteroaryl groups include pyridinyl, thiophenyl, furanyl, and quinolinyl. When the heteroaryl group is substituted, the heteroaryl group may have one to three substituents which are independently selected from halogen, OH, CN, mercapto, nitro, amino, cyano, optionally substituted C_1-C_8-alkyl, optionally substituted alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkyl-amino, di(C_1-C_8-alkyl)amino, formyl, carboxyl, alkoxycarbonyl, alkoxycarbonyloxy, alkanoyloxy, phenyl, carbamoyl, carboxamide, di-lower alkylcarbamoyloxy, phenoxycarbonyloxy group, lower alkylenedioxy, benzoyloxy, alkyl-CO-O-, alkyl-O-CO-, -$CONH_2$, alkyl-O-CO-O-, or alkyl-CO-NH-.

The terms "heterocycle," "heterocyclic," and "heterocyclyl" refer to an optionally substituted, fully or partially saturated, aromatic or nonaromatic, cyclic group which is, for example, a 4- to 7-membered monocyclic, 7- to 11-membered (or 9- to 10-membered) bicyclic (or heterobicyclyl), or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, or 3 heteroatoms selected from nitrogen atoms, oxygen atoms, and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The nitrogen atoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl; oxetanyl; pyrazolinyl; imidazolinyl; imidazolidinyl; oxazolyl; oxazolidinyl; isoxazolinyl; thiazolidinyl; isothiazolidinyl; tetrahydrofuryl; piperidinyl; piperazinyl; 2-oxopiperazinyl; 2-oxopiperidinyl; 2-oxopyrrolidinyl; 4-piperidonyl; tetrahydropyranyl; tetrahydrothiopyranyl; tetrahydrothiopyranyl sulfone; morpholinyl; thiomorpholinyl; thiomorpholinyl sulfoxide; thiomorpholinyl sulfone; 1,3-dioxolane; dioxanyl; thietanyl; thiiranyl; and the like. Exemplary bicyclic heterocyclic groups (or heterobicyclyls) include quinuclidinyl; tetrahydroisoquinolinyl; dihydroisoindolyl; dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl); dihydrobenzofuryl; dihydrobenzothienyl; dihydrobenzothiopyranyl; dihydrobenzothiopyranyl sulfone; dihydrobenzopyranyl; indolinyl; isochromanyl; isoindolinyl; benzimidazolyl, benzthiazolyl; piperonyl; tetrahydroquinolinyl; and the like. When the heteroaryl group is substituted, the heterocyclyl may be independently substituted with one to five, preferably one to three groups selected from halogen, OH, CN, mercapto, nitro, amino, cyano, optionally substituted C_1-C_8-alkyl, optionally substituted alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkyl-amino, di(C_1-C_8-alkyl)amino, formyl, carboxyl, alkoxycarbonyl, alkoxycarbonyloxy, alkanoyloxy, phenyl, carbamoyl, carboxamide, di-lower alkylcarbamoyloxy, phenoxycarbonyloxy group, lower alkylenedioxy,

benzoyloxy, alkyl-CO-O-, alkyl-O-CO-, -$CONH_2$, alkyl-O-CO-O-, or alkyl-CO-NH-.

The term "biaryl" includes a heteroaryl linked to a phenyl, a phenyl linked to a heteroaryl (such as furan, pyridine, thiophene), and a phenyl linked to a phenyl. Examples of phenyl-phenyl, heteroaryl-phenyl and phenyl-heteroaryl, include:



The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "combined administration" includes co-administration wherein: 1) the two or more agents are administered to a subject at substantially similar times; and 2) the two or more agents are administered to a subject at different times, at independent intervals which may or may not overlap or coincide.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who is the object of treatment, observation or experiment.

The term "RXR modulator" as used herein, refers to Retinoid-X receptor agonists, partial agonists, or antagonists. Preferably the modulator increases insulin sensitivity. According to one aspect, the modulator is an RXR agonist.

Diabetes, Syndrome X, and associated symptoms or complications include such conditions as IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome,

hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts. Examples of a prediabetic state includes IGT and IFG.

Methods are known in the art for determining effective doses for therapeutic and prophylactic purposes for the disclosed pharmaceutical compositions or the disclosed drug combinations, whether or not formulated in the same composition. For therapeutic purposes, the term "jointly effective amount" as used herein, means that amount of each active compound or pharmaceutical agent, alone or in combination, that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. For prophylactic purposes (i.e., inhibiting the onset or progression of a disorder), the term "jointly effective amount" refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that inhibits in a subject the onset or progression of a disorder as being sought by a researcher, veterinarian, medical doctor or other clinician, the delaying of which disorder is mediated by the modulation of glucose reabsorption activity or other antidiabetic agent activity or both. Thus, the present invention provides combinations of two or more drugs wherein, for example, (a) each drug is administered in an independently therapeutically or prophylactically effective amount; (b) at least one drug in the combination is administered in an amount that is sub-therapeutic or sub-prophylactic if administered alone, but is therapeutic or prophylactic when administered in combination with the second or additional drugs according to the invention; or (c) both drugs are administered in an amount that is sub-therapeutic or sub-prophylactic if administered alone, but are therapeutic or prophylactic when administered together.

The term "protecting groups" refer to those moieties known in the art that are used to mask functional groups; protecting groups may be removed during subsequent synthetic transformations or by metabolic or other in vivo

administration conditions. During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known in the art. Examples of hydroxyl and diol protecting groups are provided below.

Protection for the hydroxyl group includes methyl ethers, substituted methyl ethers, substituted ethyl ethers, substitute benzyl ethers, and silyl ethers.

Substituted Methyl Ethers

Examples of substituted methyl ethers include methyoxymethyl, methylthiomethyl, *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, (4-methoxyphenoxy)methyl, *t*-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl.

Substituted Ethyl Ethers

Examples of substituted ethyl ethers include 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl, and polyethyleneglycol ethers.

Substituted Benzyl Ethers

Examples of substituted benzyl ethers include *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, *p, p′*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4′-bromophenacyloxy)phenyldiphenylmethyl, 4,4′,4″-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4′,4″-tris(levulinoyloxyphenyl)methyl, 4,4′,4″-tris(benzoyloxyphenyl)methyl, 3-(*I*midazol-1-ylmethyl)bis(4 ′,4″-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1′-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido.

Silyl Ethers

Examples of silyl ethers include trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

Esters

In addition to ethers, a hydroxyl group may be protected as an ester. Examples of esters include formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate(levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate(mesitoate), and polyethyleneglycol esters.

Carbonates

Examples of carbonates include methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, methyl dithiocarbonate, and polyethyleneglycol carbonates.

Assisted Cleavage

Examples of assisted cleavage include 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate, 4-(methylthiomethoxy)butyrate, and 2-(methylthiomethoxymethyl)benzoate.

Miscellaneous Esters

Examples of miscellaneous esters include 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate(tigloate), *o*-(methoxycarbonyl)benzoate, *p*-P-benzoate, α-naphthoate, nitrate, alkyl N,N,N′,N′-tetramethylphosphorodiamidate, N-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate

Sulfonates

Examples of sulfonates include sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

PROTECTION FOR 1,2- AND 1,3-DIOLS

Cyclic Acetals and Ketals

Examples of cyclic acetals and ketals include methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl)ethylidene, 2,2,2-

trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

Cyclic Ortho Esters

Examples of cyclic ortho esters include methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidine, 1,2-dimethoxyethylidene, α-methoxybenzylidene, 1-(N,N-dimethylamino)ethylidene derivative, α-(N,N-dimethylamino)benzylidene derivative, and 2-oxacyclopentylidene.

Silyl Derivatives

Examples of silyl derivatives include di- *t*-butylsilylene group, and 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) derivative.

Glucose Reabsorption Inhibitors

One method of treating hyperglycemia is to excrete excessive glucose directly into urine so that the blood glucose concentration is normalized. For example, sodium-glucose cotransporters (SGLTs), primarily found in chorionic membrane of the intestine and the kidney, are a family of proteins actively involved in the normal process of glucose absorption. Among them, SGLT1 is present in intestinal and renal epithelial cells (Lee et al., 1994), whereas SGLT2 is found in the epithelium of the kidney (You et al., 1995, MacKenzie et al., 1994). Glucose absorption in the intestine is primarily mediated by SGLT1, a high-affinity low-capacity transporter with a Na^+:glucose transport ratio of 2:1. SGLT2, also known as SAAT1, transports Na^+ and glucose at a ratio of 1:1 and functions as a low-affinity high-capacity transporter. These SGLTs are characterized in Table 1:

Table 1

ISOFORM	TISSUE	Stoichiometry	Preferred Substrate	K_m * in vitro	TmG** in vitro	K_m * In vivo
SGLT1	Sm. Intestine	2:1	D-glucose D-galactose	0.1	nd	Nd
	Kidney (S1, S3)	2:1	D-glucose D-galactose	0.39	7.9	0.3
SGLT2 (SAAT1)	Kidney (S3)	1:1	D-glucose	1.64	83	6

* (mM) for D-glucose
** Maximal transport rate pmol/min/mm

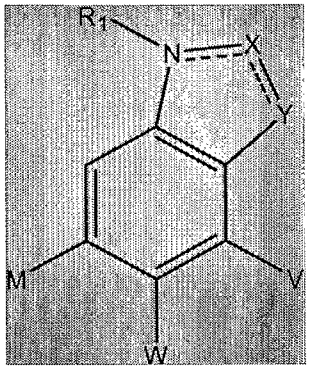
1. Renal reabsorption of glucose is mediated by SGLT1 and SGLT2 (Silverman et al., 1992; Deetjen et al., 1995). Plasma glucose is filtered in the glomerulus and is transepithelially reabsorbed in the proximal tubules. SGLT1 and SGLT2 are located in the apical plasma membranes of the epithelium and derive their energy from the inward sodium gradient created by the Na^+/K^+ ATPase pumps located on the basolateral membrane. Once reabsorbed, the elevated cytosolic glucose is then transported to the interstitial space by facilitated glucose transports (GLUT1 and GLUT2). Therefore, inhibition of SGLTs reduces plasma glucose through suppression of glucose reabsorption

in the kidney. A therapeutically or prophylactically effective amount of an SGLT inhibitor, such as that sufficient to increase urine glucose excretion, or to decrease plasma glucose, in a subject by a desired amount per day, can be readily determined using methods established in the art. Recently, it has been found that phlorizin, a natural glycoside present in barks and stems of *Rosaceae* (e.g., apple, pear, etc.), inhibits Na^+-glucose co-transporters located in chorionic membrane of the intestine and the kidney. By inhibiting Na^+-glucose co-transporter activity, phlorizin inhibits the renal tubular glucose reabsorption and promotes the excretion of glucose so that the glucose level in a plasma is controlled at a normal level for a long time via subcutaneous daily administration (Journal of Clinical Investigation, 1987, Vol. 79, p. 1510).

Other SGLT inhibitors include alkyl- and phenyl-glucosides, 1-5-isoquinolinesulfonyl)-2-methylpiperazine-HCl (indirectly via protein kinase C), p-chloromercuribenzoate (PCMB), N,N'-dicyclohexylcarbodiimide (DCCD), copper and cadmium ions, and trivalent lanthanides.

B. Compounds

The invention features compounds of Formula (IV):

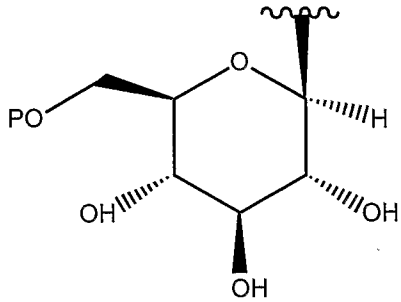


(IV)

wherein:

one of the dashed lines between NR_1 and X or between X and Y is present, or both are absent;

two of V, M, and W are H and the third is



R_1 is H, or C $_{1-4}$ alkyl; or R_1 is absent where the dashed line between NR^1 and X is present,

X is N, C=O, CH, or C-Q-Z;

Y is N-Q-Z or C-Q-Z, where X is N, C=O, or CH;

Y is CH, where X is C-Q-Z;

Q = $-(CH_2)_n-$ where n = 1 or 2;

Z is substituted or unsubstituted, and is selected from C_{3-7} cycloalkyl, phenyl, a 5- or 6- membered heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, a biaryl, a 9- or 10-membered fused bicyclyl (such as naphthyl), and a fused heterobicyclyl, wherein said fused heterobicyclyl has between 1 and 4 heteroatoms (and preferably between 1 and 3 or between 1 and 2 heteroatoms) independently selected from N, O, and S;

P = H, C_{1-7} acyl, or (C_{1-6} alkoxy)carbonyl;

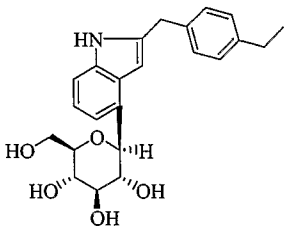
or a pharmaceutically acceptable salt, thereof.

Examples of preferred compounds of Formula (IV) include: (a) R_1 is H or absent; (b) Z is independently substituted with between 1 and 3 substituents independently selected from C_{1-4} alkoxy, phenoxy, C_{1-4} alkyl, C_{3-6} cycloalkyl, halo, hydroxy, cyano, amino, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} aminoalkyl, mono and di C_{1-4} alkylamino, phenyl, C_{1-4} alkylaminosulfonyl (SO_2NHR), amino(C_{1-4} alkylsulfonyl) ($NHSO_2R$), di C_{1-4} alkylaminosulfinyl (SONHRR), C_{1-4} alkylamido (NHCOR), C_{1-4} alkylcarbamido (CONHR), 5-6 membered heterocyclyl containing between 1 and 3 heteroatoms independently selected from N, S, and O; and wherein the substituent(s) on Z can be further independently substituted with between 1 and 3 substituents independently selected from C_{1-4} alkoxy, C_{1-4} alkyl, halo, hydroxy, cyano, amino, mono or di C_{1-4} alkyl amino and C_{1-4} alkylthio; (c) Z is 4-substituted phenyl, 3,4-disubstituted phenyl, benzhydryl, substituted or unsubstituted thienyl, biaryl, benzofuranyl, dihydrobenzofuranyl, 4-substituted pyridyl, benzo[b]thienyl, chromanyl, benzothiophenyl, indanyl, naphthyl, and 2,3-dihydro-benzo[1,4] dioxan; (d) limitations of (c) wherein Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl; (e) Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl, (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl; (f) R_1 is H; (g) n is 1; (h) R_1 is H or absent, and n is 1; (i) Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-imidazole-1-

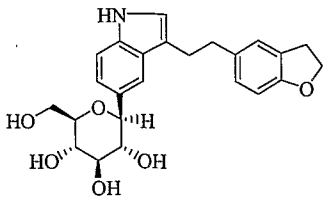
yl)-phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl, (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl; and Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl; (j) limitations of (i) and R_1 is H; (k) limitations of (i) and n is 1; (l) W and M are H; (m) V and M are H; (n) X is CH and Y is C-Q-Z; (o) X is C-Q-Z and Y is CH; (p) and combinations of the above.

Preferred examples of compounds of the invention include: 3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-(4-methoxybenzyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole; and 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole.

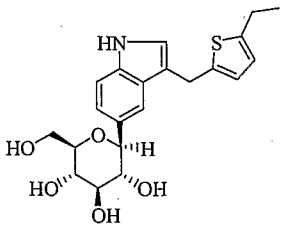
Additional preferred compounds include those selected from 2-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole; 3-[2-(2,3-Dihydro-benzofuran-5-yl)-ethyl]-5-(β-D-glucopyranosyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-(5-ethyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzimidazole; 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1,3-dihydro-benzoimidazol-2-one and 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzotriazole.



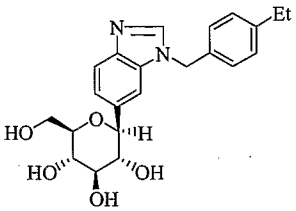
#A#



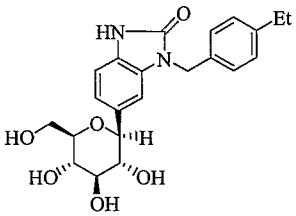
#B#



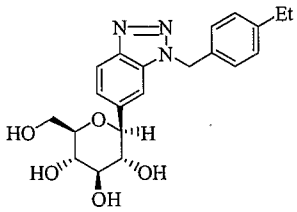
#C#



#D#



#E#



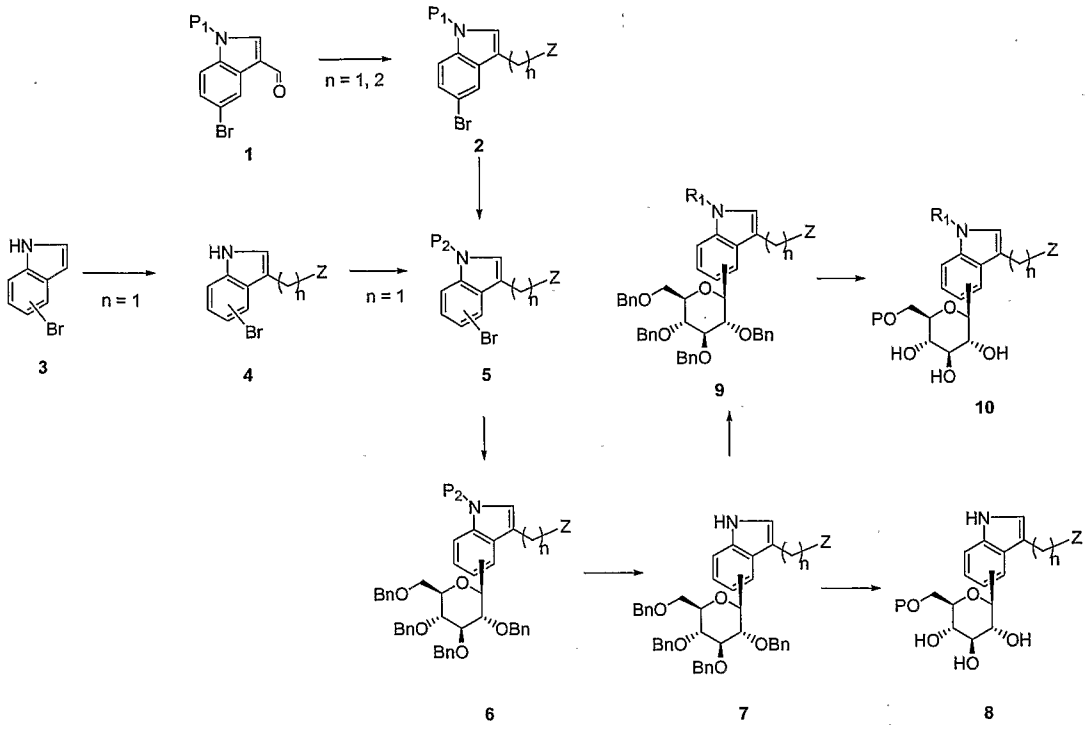
#F#

The most preferred compounds are selected from: 3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole; 2-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-(5-methyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzimidazole and 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzotriazole.

C. Synthetic Methods.

One aspect of the invention features compounds of formula (IV). These compounds can be made according to traditional synthetic organic methods or combinatorial or matrix synthesis methods. The following schemes and chemical Examples 1-4 provide general guidance.

Scheme 1.



Compounds of this invention where X is C-H, Y is C-Q-Z (e.g. 3-alkyl indole) can be prepared as outlined in Scheme 1. Compounds of formula **1** wherein R_3 is H and P_1 is N,N-diethylcarbamyl can be prepared by treatment of the sodium salt of commercially available 5-bromo-1H-indole-3-carboxaldehyde with N,N-diethylcarbamyl chloride in anhydrous THF. The protected indole may be treated with ylides under standard Wittig reaction conditions to provide an E/Z mixture of compounds. Hydrogenation of the alkene over Platinum(IV)oxide (Adam's catalyst) in a chlorinated solvent at 1 atmosphere provides compounds of formula **2**, wherein n is 2. A compound of formula **1** can also be treated with an aryl magnesium bromide in THF to give an indolecarbinol. The crude indolecarbinol can be reduced with triethylsilane and stannic chloride in dichloromethane at -78 °C to provide compounds of formula **2**, wherein n is 1. The indole nitrogen of compounds of formula **2**, where n is 1 or 2, can be deprotected by treatment with an aqueous base such as sodium hydroxide in refluxing ethanol to remove the N,N-diethylcarbamyl group followed by reprotection with *tert*-butlydimethylsilyl (TBDMS) group (P_2) by treatment with *tert*-butyldimethylsilyl chloride using known procedures to yield 5-bromo indole derivative **5**.

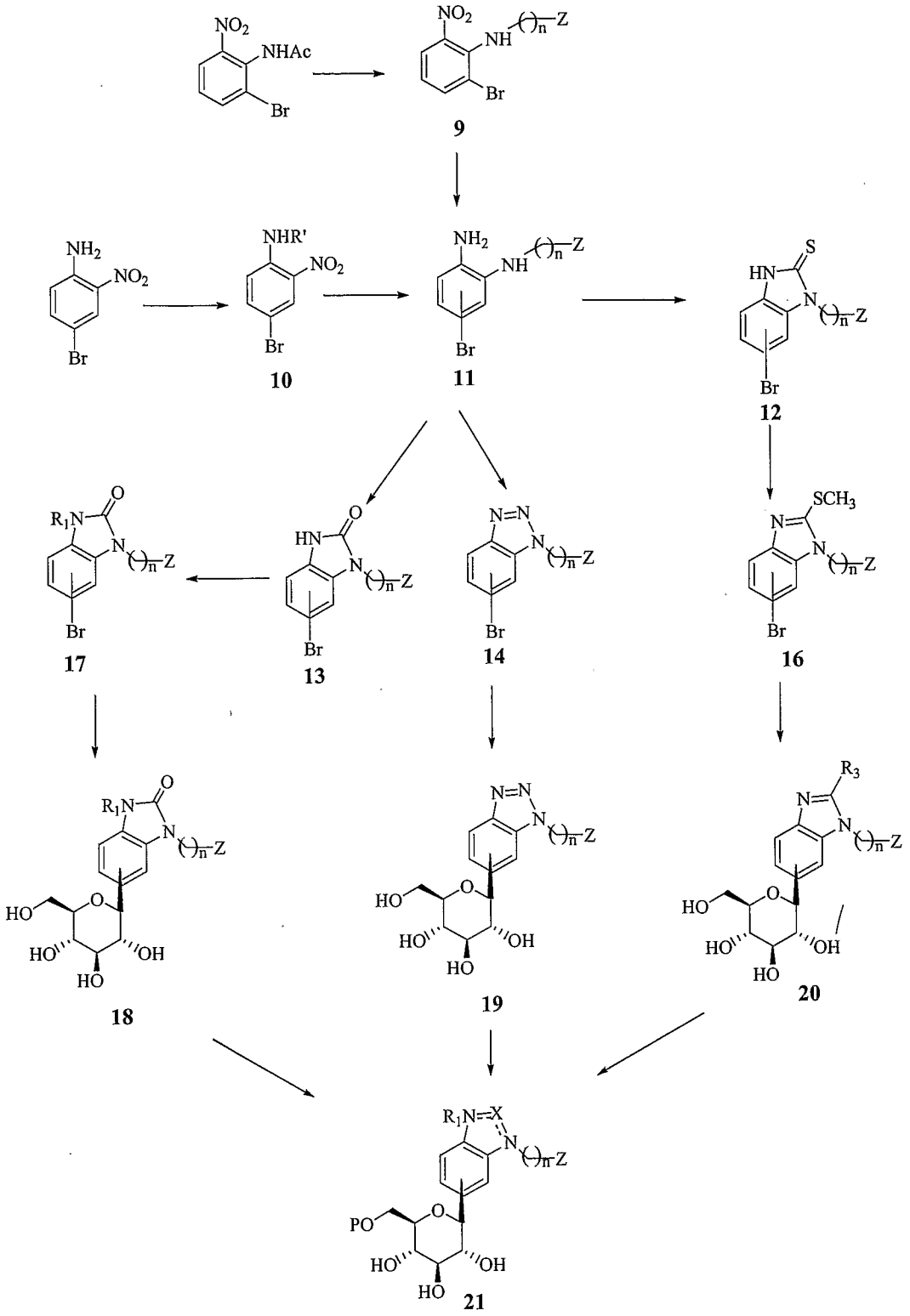
Alternatively, a compound of formula **5**, where n is 1 (either 4-bromoindole derivatives or 5-bromoindole or 6-bromoindole derivatives), can be prepared in three steps from commercial available sources of formula **3**. Friedel-Craft acylation of compounds of formula **3** with substituted benzoyl chlorides using a Lewis Acid, such as aluminum trichloride, in a chlorinated solvent, such as dichloromethane, followed by reduction of the carbonyl group with sodium borohydride to provide compounds of formula **4**. The indole nitrogen of formula **4** can be protected with TBDMS group as described above to give compounds of formula **5**, where n is 1.

Compounds of formula **5** are activated for coupling by treatment with t-BuLi at –78 °C in a solvent such as THF prior to addition of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone as described by Czernecki and Ville [J. Org. Chem. 1989, 53, 610 – 612]. The resulting lactol can be treated with silanes such as triethylsilane in a solvent such as dichloromethane at –30 °C to provide compounds of formula **6**. The TBDMS group can be removed with an aqueous base such as sodium hydroxide in refluxing THF to yield compounds of formula **7**. Hydrogenolysis of glucopyranose **7** over palladium hydroxide (Pearlman's catalyst) at one atmosphere can provide compounds of formula **8** where P is H.

The sodium salt of **7** can be treated with an alkyl halide to give the N-alkylated (R_1) product **9**, which was undergone hydrogenolysis as previously described to provide compound of formula **10** where P is H.

Further treatment of compounds of formula **8** or **10**, where P is H, with one equivalent of alkyl chloroformate or alkanoyl chloride in collidine to selectively acylate the 6-OH group of the glucopyranose can provide compounds of formula **8** or **10**, where P is acyl, or alkoxycarbonyl.

Scheme 2



Compounds of this invention wherein Y is N-Q-Z, X is N, C=O or C-H, and R_1 is as defined in the claims above could be prepared as outlined in Scheme 2

using procedures known in the art for the synthetic transformations described. Commercially available N-(2-Bromo-6-nitro-phenyl)-acetamide could be heated under acidic condition to remove the acetyl group then alkylated with substituted benzyl, aryl or heteroaryl alkyl halides, acylated with benzoyl or phenylacetyl chlorides followed by LAH or borane reduction or reductively aminated with substituted benzaldehydes in the presence of sodium cyanoborohydride to provide compounds of formula **9**. The nitro group could then be reduced using reagents such as tin (II) chloride or iron in acetic acid to obtain compounds of formula **11** wherein the bromine is attached at position V in claim 1.

Alternatively, one could start with commercially available 4-Bromo-2-nitroaniline, introduce the side-chain containing Z as described above to afford compounds of formula **10** where R' is $-(CH_2)_nZ$ then reduce the nitro group to provide compounds of formula **11** wherein the bromine is attached at position M in claim 1.

On the other hand, the aniline nitrogen of commercially available 4-Bromo-2-nitroaniline could be acetylated or alternatively protected with an appropriate protecting group such as toluenesulfonyl or benzenesulfonyl to yield compounds of formula **10** wherein R' is the protecting group. The nitro group could then be reduced to a primary amine with tin (II) chloride and subsequently alkylated by treatment with substituted benzyl, aryl or heteroaryl alkyl halides, under basic conditions or reductively aminated with substituted benzaldehydes in the presence of sodium cyanoborohydride. Alternatively the primary amine could be acylated with benzoyl or phenylacetyl chlorides followed by LAH or borane reduction. Final removal of the nitrogen protecting group using procedures known in the art could provide compounds of formula 11 wherein the bromine is attached at position W in claim 1.

Compounds of formula **11** could be reacted further to form compounds of formula **12**, **13**, and **14**. These transformations can be accomplished by

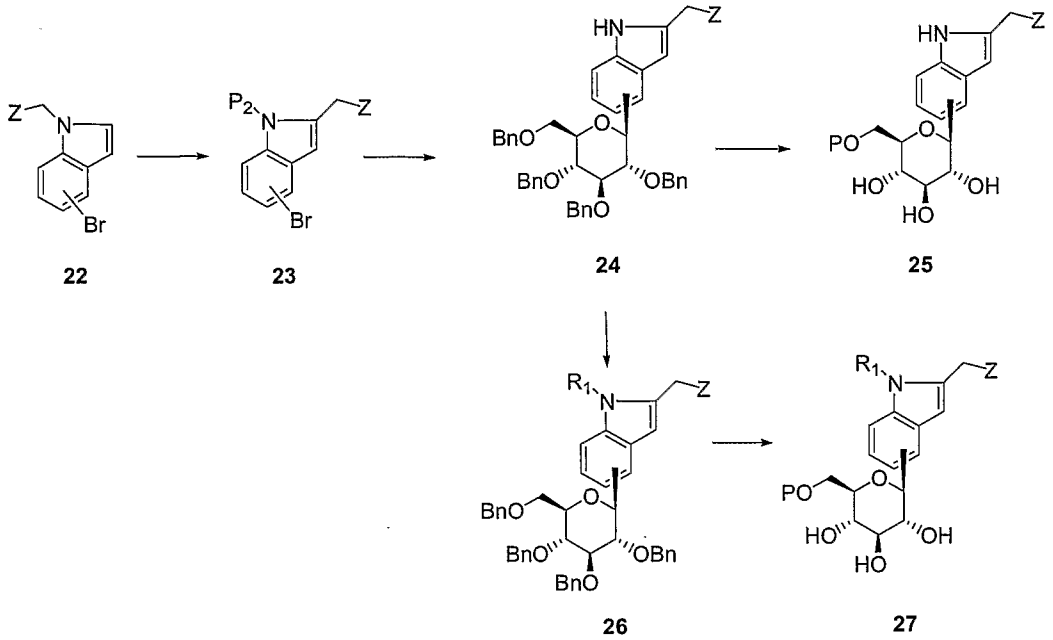
treating the diamine with 1,1'-thiocarbonyldiimidazole or carbon disulfide to provide compound of formula **12** or with triphosgene, urea or carbonyldimidazole to give compounds of formula **13**. Alternatively, the diamine **11** could be treated with sodium nitrate under acidic conditions at cool temperatures to provide compounds of Formula **14**.

Methylation of compounds of formula **12** with iodomethane in the presence of a base can afford compounds of formula **16**. Compounds of formula **13** can be treated with base such as sodium hydride and alkylated with alkyl halides to provide compounds of formula **17** wherein R_1 is alkyl. The unsubstituted nitrogen of compound of formula **13** can also be protected with an alkoxy carbonyl group as described by Meanwell et. al. [J. Org. Chem. **1995**, *60*, 1565 – 1582] to provide compounds of formula **17** wherein R_1 is either an ethoxy carbonyl moiety or a t-butoxycarbonyl group.

Formation of the C-glycosides can be accomplished by treating compounds of formula **14**, **16** or **17** (compound 15 is omitted) with butyllithium at –78 °C prior to the addition of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone followed by reduction of the resulting hemiacetal in the presence of excess triethylsilane and boron trifluoride diethyl etherate in an appropriate solvent such as dichloromethane as described by Czernecki and Ville (J. Org. Chem. 1989, 54, 610 – 612). Compounds of formula **18**, wherein R_1 is H, can be prepared by removing the protection groups under basic condition (for ethoxy carbonyl group) or under acidic condition (for tert-butoxycarbonyl group) followed by debenzylation of the hydroxyl groups using palladium catalysts under hydrogenation conditions. Compounds of formula **18**, wherein R1 is an alkyl group, or formula **19** can be formed by debenzylation of the hydroxyl groups using palladium catalysts under hydrogenation conditions. Compounds of formula **20** wherein R_3 is H can be prepared by a Raney nickel mediated cleavage of the 2-methylthio group as described by Townsend, et. al. (J. Med. Chem. 1994, 37, 2942 – 2949) followed by debenzylation of the hydroxyl groups using palladium catalysts under hydrogenation conditions.

Further treatment with one equivalent of alkyl chloroformate or alkanoyl chloride in collidine to selectively acylate the 6-OH group of the glucopyranose can provide compounds of formula **21** where P is acyl, or alkoxycarbonyl.

Scheme 3.



Compounds of this invention where X is C-Q-Z and Y is CH (e.g. 2-alkyl indole) as defined in the claims above can be prepared as outlined in Scheme 3. Compounds of formula **22** can be prepared by treatment of the sodium salt of commercially available bromoindoles (either 4-bromoindole or 5-bromoindole or 6-bromoindole) with an alkyl halides in anhydrous THF. The resulting N-alkyl indole can be rearranged to 2-alkyl indole at 180 °C in polyphosphoric acid under microwave condition, followed by protection of indole nitrogen with TBDMS group (P_2) to provide compounds of formula **23**.

Formation of the C-glycosides can be accomplished by treating compounds of formula **23** with butyllithium at –78° C prior to the addition of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone as described in Scheme 1. The resulting lactol can be treated with silanes, such as triethylsilane, in a solvent such as dichloromethane at -30 °C, followed by deprotection of the TBDMS group with

an aqueous base, such as sodium hydroxide, in refluxing THF to yield compounds of formula **24**.

Hydrogenolysis of glucopyranose **24** over palladium hydroxide (Pearlman's catalyst) at one atmosphere can provide compounds of formula **25** where P is H. The sodium salt of **24** can be treated with an alkyl halide to give the N-alkylated (R_1) product **26**, followed by hydrogenolysis as previously described to provide compound of formula **27** where P is H.

D. Additional Antidiabetic Agents

Antidiabetic agents that can be used according to the invention, as a second, third, or subsequent antidiabetic agent, in a composition, formulation, or combination method of treatment (dosing regimen) include, but are not limited to the classes and compounds exemplified in Table 2.

Table 2
Combination Therapies with SGLT Inhibitors

Mechanism or Class	Drug/Compound
Biguanide (class)	metformin
	Fortamet (metformin XT)
	metformin GR
	metformin XL
	NN-414
	fenofibrate/metformin combo
Insulin Secretagogue (mech), Sulfonylureas (class)	glimeparide
	glyburide/glibenclamide combo
	glyburide/metformin combo
	glipizide
	glipizide/metformin combo
	gliclazide
	chlorpropamide
	tolbutamide
	tolazamide
Insulin Secretagogue (mech), Meglitinides (class)	repaglinide
	nateglinide
	mitiglinide
Alpha-glucosidase inhibitors (mech)	acarbose
	miglitol
	voglibose

	emiglitate
Insulin and Insulin analogues (class)	insulin lispro
	insulin glargine
	insulin detemir
	insulin glulisine
	insulin aspart
	human insulin (Humulin R)
	human insulin (Novolin R
	human insulin (Novolin BR)
	insulin, zinc suspension (Humulin L)
	insulin NHP (Humulin N)
	insulin, zinc suspension (Novolin L)
	insulin NHP (Novolin N)
	insulin, zinc suspension (Humulin U)
	human insulin, regular and NHP mix (Humulin 50/50)
	human insulin, regular and NHP mix (Humulin 70/30)
	human insulin, regular and NHP mix (Novolin 70/30)
Inhaled insulin (class)	Exubera
	AERx Insulin Diabetes Management System
	AIR inhaled insulin
Oral insulin (class)	Oralin
PPARgamma (mech)	rosiglitazone
	rosiglitazone/metformin combo
	pioglitazone
	isaglitazone (netoglitazone, MCC-555)
	rosiglitazone/sulfonylurea
	ragaglitazar
	balaglitazone (NN-2344)
	R-483
	rivoglitazone (CS-011)
	FK-614
	SCD-DKY
	tesaglitazar
	T131
	CLX0921
	LY-293111 (VML-295)
	MBX 102
	AA10090
	CDDO (TP-155C)
	DRF-2189
	PHT-46
	farglitazar
	GW-7845
	L-764406
	NC-2100
	PN 2022 (PN 2034)
PPARalpha/gamma dual agonists (mech)	MK767/MK0767 (KRP 297)
	muraglitazar (BMS-298585)
	tesaglitazar
	LY-818
	oxeglitazar (EML-4156)
	LY-929

	BVT-142
	DRF-2655
	DRF-4832
	DRF-4158
	LY-465608
	KT6-207
	LSN-862
PPARalpha Agonist (mech)	Fenofibrate
	Gemfibrozil
	Clofibrate
	Ciprofibrate
	Benzafibrate
	K-111
	LY518674 (LY674)
	KRP-101
	NS-220
	GW-9578
	GW-7647
	GW-9820
	LF-200337
	ST-1929
	Wy-14643
PPARdelta Agonist (mech)	GW501516
	GW-1514
	L-165041
	GW 8547
PPARalpha/delta Dual Agonist (mech)	GW-2433
PPARgamma/delta Dual Agonist (mech)	none in the last PPAR CEA
PPARalpha/gamma/delta Modulator (mech)	CLX-0940
RXR Agonist (mech)	
Insulin Seretagogue (mech), GLP-1 analogue (class)	Exanatide injectable
	Exanatide LAR injectable
	Exanantide oral
	Liraglutide
GLP-1 agonist (mech)	exenatide (AC2993)
	liraglutide (NN2211)
	LY-307161
	CJC-113
	ZP10
	GLP-1
	BIM-51077
DPPIV Inhibitor (mech)	LAF-237
	P32/98
	P93/01
	NVP-728
Lipase Inhibitor (mech)	Orlistat
	ATL962
Glucokinase Activator (mech)	Ro 28-1675
	Ro 27-4375
beta-3 Agonist (mech)	LY-337604
	L-796568

	CP-331684
	CP-331679
	CP-114271
	Rafabegron (TAK-677)
	YM-178
	N5984
	GW427353
IBAT Inhibitor (mech)	AZD-7806
	SC-990
	SC-017
	GW-264
HM74a/HM74 Agonist (mech)	Acipimox
Glucocorticoid Antagonist (mech)	A348441
	A362947
	CP394531
	CP409069
	CP472555
Glycogen Phosphorylase a Inhibitor (mech)	NN4201
	Ingliforib (CP368296)
FXR Antagonist (mech)	GW-4064
LXR Agonist (mech)	GW-3965
	T-0901317
	T-0314407
FXR Antagonist (mech)	
GLP-1 Analogue (class)	Albugon
GSK-3beta Inhibitor (mech)	
PTP-1b Inhibitor (mech)	ISIS-113715
	KP102
Amylin Receptor Agonist	Pramlintide (symlin/amylin)
NO Scavenger (mech)	NOX-700
11beta-Hydroxysteroid Dehydrogenase Inhibitor	BVT-3498
Peptide YY hormone	AC162325
Glucagon Antagonist (mech)	NN-2501
PEPCK Inhibitor (mech)	R1438
Somatotropin Release-inhibiting Factor (mech)	SOM230
CPT-1 Inhibitor (mech)	ST1326
Carboxypeptidase Inhibitor (mech)	MLN-4760
Leptin analogue (class)	Metrileptin

E. Combinations

The invention features a combination therapy comprising administering a glucose reabsorption inhibitor, such as an SGLT inhibitor, and one or more antidiabetic agent(s) for the treatment of diabetes or Syndrome X, or associated symptoms or complications thereof. The demonstrated efficacy of SGLT inhibitors in numerous models of NIDDM validates the utility of this drug alone for the treatment of NIDDM in humans. Since glucose reabsorption inhibitors have a mechanism of action distinct from that of other antidiabetic agents, such as RXR modulators, the disclosed combination may have the advantage of reducing the amount of either drug necessary to achieve combined therapeutic or pharmaceutical efficacy, relative to the use of either drug alone, thereby reducing one or more adverse side-effects, which often include weight gain, edema, cardiac hypertrophy, hepatohypertrophy, hypoglycemia, or hepatotoxicity, or any combination thereof.

The invention provides a method for treating diabetes or Syndrome X, or complications thereof in a subject, said method comprising administering to said subject a jointly effective amount of a glucose reabsorption inhibitor in combination with a jointly effective amount of an antidiabetic agent, such as an RXR modulator. In one aspect of the invention, the antidiabetic agent is an RXR agonist or RXR antagonist that increases insulin sensitivity in the subject. For example, an insulin sensitizer can increase glucose tolerance in a subject in an oral glucose tolerance test.

Preferably, the diabetes or Syndrome X, or associated symptoms or complication thereof is selected from IDDM, NIDDM, IGT, and IFG.

This invention also provides a pharmaceutical composition comprising one or more glucose reabsorption inhibitors (alone or in combination with one or more antidiabetic agents), and a pharmaceutically acceptable carrier. In one aspect of the invention, the antidiabetic agent is an RXR agonist or RXR antagonist that increases insulin sensitivity in the subject.

In particular, the glucose reabsorption inhibitor is a SGLT1 and/or SGLT2 inhibitor.

For use in medicine, the salt or salts of the compounds of Formula (IV) refer to non-toxic "pharmaceutically acceptable salt or salts." Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benezenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative basic/cationic salts include, but are not limited to, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, or zinc. The compounds of Formula (IV) or a pharmaceutically acceptable salt thereof, may include an intramolecular salt thereof, or a solvate or hydrate thereof.

F. Administration, Formulation, and Dosages

The utility of the disclosed compounds, compositions, and combinations to treat disorders in glucose and lipid metabolism can be determined according to the procedures well known in the art (see the references listed below), as well as all the procedures described in US PATENT NOs. 5424406, 5731292, 5767094, 5830873, 6048842, WO01/16122 and WO01/16123 which are incorporated herein by reference. The compound may be administered to a patient by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral administration. Preferably, formulations are for oral administration.

The present invention also provides pharmaceutical compositions comprising one or more glucose reabsorption inhibitors and one or more RXR modulators in association with a pharmaceutically acceptable carrier.

The daily dosage of the products may be varied over a wide range from 1 to 1000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 or 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 2 times per day. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly

administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient or ingredients are mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of one or more glucose reabsorption inhibitors and one or more antidiabetic agents, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient or ingredients are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient or ingredients of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include

synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin. The liquid forms in suitably flavored suspending or dispersing agents may also include the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Advantageously, the combinations of one or more glucose reabsorption inhibitors of the present invention, alone or in combination with one or more additional antidiabetic agents, may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, one or more glucose reabsorption inhibitors and/or one or more antidiabetic agents according to the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Wherein the present invention is directed to the administration of a combination, the compounds may be co-administered simultaneously, sequentially, or in a single pharmaceutical composition. Where the compounds are administered separately, the number of dosages of each compound given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

The novel compositions of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of lipids, including but not limited to amphipathic lipids such as phosphatidylcholines, sphingomyelins, phosphatidylethanolamines, phophatidylcholines, cardiolipins, phosphatidylserines, phosphatidylglycerols, phosphatidic acids, phosphatidylinositols, diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, and stearylamine, neutral lipids such as triglycerides, and combinations thereof. They may either contain cholesterol or may be cholesterol-free.

From Formula (IV) and other disclosed formulae it is evident that some compounds in the compositions of the invention may have one or more asymmetric carbon atoms in their structure. It is intended that the present invention include within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure isomeric forms may be obtained by the application of art known principles.

Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereospecific reactions.

Some compounds in the compositions of the present invention may have various individual isomers, such as trans and cis, and various alpha and beta attachments (below and above the plane of the drawing). In addition, where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared as a single stereoisomer or in racemic form as a mixture of some possible stereoisomers. The non-racemic forms may be obtained by either synthesis or resolution. The compounds may, for example, be resolved into their components enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation. The compounds may also be resolved by covalent linkage to a chiral auxiliary, followed by chromatographic separation and/or crystallographic separation, and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using chiral chromatography. Unless otherwise noted, the scope of the present invention is intended to cover all such isomers or stereoisomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

The therapeutic effect of the glucose reabsorption inhibitor administered in combination with one or more antidiabetic agent(s) in treating diabetes, Syndrome X, or associated symptoms or complications can be shown by methods known in the art. The following examples of combination treatment with SGLT inhibitors and other antidiabetic agents such as RXR modulators are intended to illustrate the invention but not to limit it.

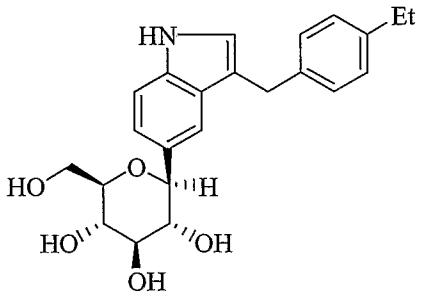
G. Synthetic Chemical Examples.

One aspect of the invention features compounds of formula (IV) as described above in the Summary section, the description, and the appended claims. These disclosed compounds may be made according to traditional synthetic organic chemistry methods or according to matrix or combinatorial chemistry methods. The Schemes and Examples 1-9 below provide general guidance and detailed examples of how the disclosed compounds may be prepared.

^{1}HNMR spectra were measured on a Brucker AC-300 (300 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard.

Example 1

3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole



A. 5-Bromo-3-formyl-indole-1-carboxylic acid diethylamide: To a suspension of sodium hydride (0.93 g, 37 mmol) in anhydrous THF (75 mL) was added dropwise a solution of 5-bromo-1H-indole-3-carbaldehyde (7.5 g, 34 mmol) in anhydrous THF (60 ml) at 0 °C. After stirring at 0 °C for 15 min, N,N-diethylcarbamyl chloride (5.0 g, 37 mmol) was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was crystallized from ether/hexane to give the title compound (8.75 g, 80%) as a white solid.

B. 5-Bromo-3-(4-ethyl-benzyl)-indole-1-carboxylic acid diethylamide: To a solution of Part A (3.3 g, 10 mmol) in 20 mL of anhydrous THF was added dropwise a 0.5 M solution of 4-ethylphenylmagnesium bromide in anhydrous THF (22 mL, 11 mmol) at

0 °C. The reaction mixture was continued stirring at 0° C for 30 min, quenched with a saturated ammonium chloride solution and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated in vacuo. The crude product was used directly in the next step.

To a solution of the crude indolecarbinol in 20 mL of dichloromethane was added triethylsilane (1.16 g, 10.0 mmol) at –78° C, followed by addition of a 1.0 M solution of stannic chloride in dichloromethane (20 mL, 20 mmol). The reaction mixture was continued stirring at -78° C for 20 min, quenched with water and warmed to room temperature. After extraction with dichloromethane, the organic extracts were dried over sodium sulfate, concentrated in vacuo and chromatographed with silica gel eluting with ethyl acetate/hexane (10: 100) to provide the titled compound (3.4 g, yield: 82%) as a white solid.

C. 5-Bromo-3-(4-ethyl-benzyl)-1H-indole: The compound prepared in Part B (3.4 g, 8.2 mmol) was dissolved in ethanol (60 mL) and 25% aqueous sodium hydroxide (20 mL) and the resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (60 mL), concentrated in vacuo to remove most of ethanol, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (2.0 g, 79%) as white needle crystals.

D. 5-Bromo-1-(tert-butyl-dimethyl-silanyl)-3-(4-ethyl-benzyl)-1H-indole: To a suspension of sodium hydride (0.12 g, 4.8 mmol) in anhydrous THF (2 mL) was added dropwise a solution of the compound prepared in Part C (1.28 g, 4.0 mmol) in anhydrous THF (6 ml) at 0° C. After stirring at 0° C for 30 min, a 1.0M solution of tert-butyl-chloro-dimethyl-silane in anhydrous THF (4.5 mL, 4.5 mmol) was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (0.5:100) to provide the title compound (1.75 g, 100%) as a light yellow oil.

E. 3-(4-Ethylbenzyl)-5-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-1-(tert-butyl-dimethyl-silanyl)-1H-indole: To a stired solution of the compound prepared in Part D (1.75 g, 4.0 mmol) in dry THF (2 mL) at –78 °C was added a 1.7 M solution of tert-butyl lithium in heptane (4.7 mL, 8.0 mmol) over a period of 15 min. After stirring 30 min, a solution of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone (4.3 g, 8.0 mmol; prepared as described by Benhaddou, R.; Carbohydrate Research 1994, 260, 243 – 250) in dry THF (10 mL) was added at –78 °C over a period of 15 min. The reaction mixture was stirred at –78° C for 1 hr (reaction progress was monitored by TLC). Upon completion the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), warmed to room temperature and the reaction mixture was diluted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide a mixture of the desired lactol and unreacted 2,3,4,6-tetra-O-benzyl-β-D-glucolactone (2.8 g, ~50% of the desired lactol) as a light brown oil. This mixture was used directly to the next step without further purification.

To a solution of the above mixture (2.8 g) in dichloromethane (20 mL) was added triethylsilane (0.5 mL, 3.2 mmol) at –30 °C, followed by the addition of trifluoroborane diethyl ether (0.2 mL, 1.6 mmol). After siring between –30 to –20° C for 1 hr, when TLC analysis indicated the reaction was completed, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL). The mixture was warmed to room temperature and stirred for 1 hr. The reaction mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (0.68 g, 19% for two steps) as a yellow oil.

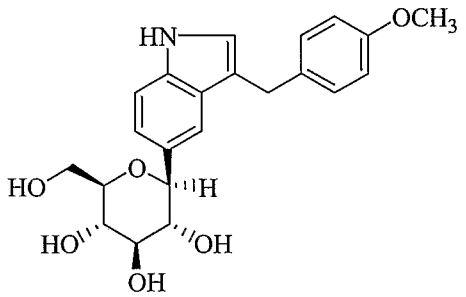
F. 3-(4-Ethylbenzyl)-5-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-1H-indole:Part E (0.68 g, 0.78 mmol) was dissolved in THF (15 mL) and 25% aqueous sodium hydroxide (5 mL) and the resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (30 mL), and extracted with ethyl acetate. The organic extracts were

washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:3) to provide the title compound (0.5 g, 85%) as white solid.

G. 3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole: A solution of Part F (0.30 g, 0.4 mmol) in ethanol (10 mL) and ethyl acetate (20 mL) was hydrogenated over 10% Pearlman's catalyst (0.30 g) under 14 psi of H_2 for 40 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with methanol/chloroform (10:100) to provide the titled compound (0.04 g, 25%) as a white solid. ^{1}HNMR (300MHz, CD_3OD) δ 7.51 (s, 1H), 7.32 (d, J = 8.52Hz, 1H), 7.19 - 7.15 (m, 3H), 7.06 (d, J = 7.87Hz, 2H), 6.95 (s, 1H), 4.18 - 4.15 (m, 1H), 4.04 (s, 2H), 3.87 (d, J = 12.2Hz, 1H), 3.71 – 3.65 (m, 1H), 3.53 - 3.48 (m, 2H), 3.45 – 3.41 (m, 2H), 2.58 (q, J = 7.58Hz, 2H), 1.19 (t, J = 7.65Hz, 3H). MS: m/z (M+Na) 420.

Example 2

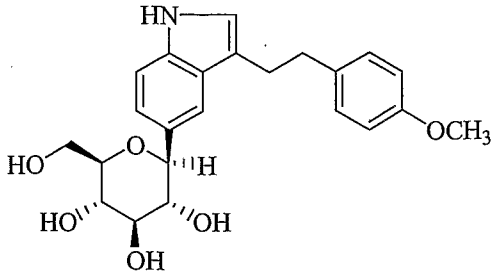
5-(β-D-Glucopyranosyl)-3-(4-methoxybenzyl)-1H-indole



The title compound was prepared as a white solid, from 5-bromo-3-formyl-indole-1-carboxylic acid diethylamide (Example 1, Part A) and 4-methoxyphenyl-magnesium bromide by the same procedure as described in Example 1, Part B to G). ^{1}HNMR (300MHz, CD_3OD) δ 7.49 (s, 1H), 7.32 (d, J = 8.20Hz, 1H), 7.19 - 7.15 (m, 3H), 6.95 (s, 1H), 6.79 (d, J = 8.55Hz, 2H), 4.18 - 4.15 (m, 1H), 4.02 (s, 2H), 3.88 - 3.85 (m, 1H), 3.74 (s, 3H), 3.70 - 3.66 (m, 1H), 3.50 - 3.48 (m, 2H), 3.42 - 3.35 (m, 2H). MS: m/z (M+Na) 422.

Example 3

5-(β-D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole



A. 5-Bromo-3-[2-(4-methoxy-phenyl)-ethyl]-indole-1-carboxylic acid diethylamide:

To a solution of 4-methoxybenzyl triphenyphosphonium chloride (7.5 g, 18 mmol) in anhydrous THF (75 mL) at –78° C was added LDA (9.0 mL, 18 mmol) and the resulting reaction mixture was allowed to stir at –78° C for 1 h. Thereafter, 5-bromo-3-formyl-indole-1-carboxylic acid diethylamide (1.9 g, 6 mmol, Example 1, Part A) was added and the resulting reaction mixture was allowed to stir at –78° C for 1 h and then warmed to room temperature to stir overnight. The reaction mixture was poured onto 1N HCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the mixture of alkenes (2.3 g, 90%, E:Z ~ 1:1) as a brown oil. A solution of the above alkenes (2.3 g, 5.4 mmol) in dichloromethane (100 mL) was hydrogenated over Adam's catalyst (300 mg) under H_2 (15 psi) for 2 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (1.43 g, 62%) as a colorless oil.

B. 5-Bromo-3-[2-(4-methoxy-phenyl)-ethyl]-1H-indole:Part B (1.43 g, 3.3 mmol) was dissolved in ethanol (30 mL) and 25% aqueous sodium hydroxide (10 mL) and the resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (30 mL), concentrated in vacuo to remove most of ethanol, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (1.0 g, 91%) as a light brown oil.

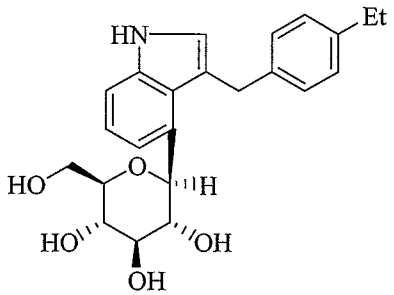
C. 5-Bromo-1-(tert-butyl-dimethyl-silanyl)-3-[2-(4-methoxy-phenyl)-ethyl]-1H-indole: To a suspension of sodium hydride (0.081 g, 4.0 mmol) in anhydrous THF (2 mL) was added dropwise a solution of Part C (0.85 g, 2.7

mmol) in anhydrous THF (3 ml) at 0°C. After stirring at 0°C for 30 min, a 1.0 M solution of tert-butyl-chloro-dimethyl-silane in anhydrous THF (3.2 mL, 3.2 mmol) was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (0.5:100) to provide the title compound (0.92 g, 79%) as a light yellow oil.

D. 5-(β-D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole: The title compound was prepared as a white solid, from Part C by the same procedure as described in Example 1, Part E, F and G. ^{1}HNMR (300MHz, CD_3OD) δ 7.58 (s, 1H), 7.31 (d, J = 8.06Hz, 1H), 7.18 (dd, J = 8.39, 1.59Hz, 1H), 7.10 (dd, J = 6.63, 2.16Hz, 2H), 6.92 (s, 1H), 6.81 - 6.78 (m, 2H), 4.21 (d, J = 8.99Hz, 1H), 3.91 - 3.87 (m, 1H), 3.75 (s, 3H), 3.73 - 3.69 (m, 1H), 3.54 - 3.51 (m, 2H), 3.49 - 3.45 (m, 2H), 3.00 - 2.98 (m, 2H), 2.94 - 2.90 (m, 2H). MS: m/z (M+Na) 436.

Example 4

3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole



A. (4-Bromo-1H-indol-3-yl)-(4-ethyl-phenyl)-methanone: To a suspension of $AlCl_3$ (3.0 g, 22.5 mmol) in dichloromethane (50 mL) was added a solution of 4-bromoindole (2.21 g, 11.3 mmol) in dichloromethane (25 mL) at room temperature over the period of 20 mins, followed by the addition of a solution of 4-ethyl-benzoyl chloride (2.5 mL, 17 mmol) in dichloromethane (25 mL) over the period of 20 mins. The resulting solution was stirred at room temperature overnight, and saturated sodium bicarbonate solution was added in a water-ice

bath to quench the reaction. The aqueous layer was extracted with dichloromethane. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was triturated in diethyl ether to obtain the title compound (1.8 g, 48%) as white solids.

B. (1-Benzenesulfonyl-4-bromo-1H-indol-3-yl)-(4-ethyl-phenyl)-methanone: A mixture of a compound prepared from Part A (1.6 g, 5 mmol), tetrabutylammonium bromide (0.16 g, 0.5 mmol) and benzenesulfonyl chloride (1.3 g, 7.5 mmol) in 25% aqueous sodium hydroxide (10 mL) and benzene (50 mL) was stirred at room temperature overnight. The reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo and chromatographed on silica gel eluting with ethyl acetate/hexane (30:100) to give the title compound (1.80 g, 76%).

C. 1-Benzenesulfonyl-4-bromo-3-(4-ethyl-benzyl)-1H-indole: To a suspended $AlCl_3$ (0.8 g, 6 mmol) in dichloromethane (10 mL) was added borane-tert-butylamine complex (0.52 g, 6 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 mins followed by addition of a solution of a compound from Part B (0.94 g, 2 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature overnight, and NaOH (3M, 20 mL0 was added with crushed ice to quench the reaction. The basic aqueous layer was extracted with dichloromethane. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product (0.90 g, 99%) was pure enough for the next step without further purification.

D. 4-Bromo-3-(4-ethyl-benzyl)-1H-indole: Part C (0.90 g, 2 mmol) was dissolved in 1:1 mixture of ethanol and THF (20 mL) with 50% aqueous sodium hydroxide (2 mL). The resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (20 mL), concentrated in vacuo to remove most of ethanol, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate/hexane (30:100) to give the title compound (0.53 g, 84%) as a colorless oil.

E. 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole: The title compound was prepared as a white solid, from Part D by the same procedure as described in Example 1, Part D, E, F and G. ^{1}HNMR (300MHz, CD_3OD) δ 7.33 (dd, J = 7.42, 1.64 Hz, 1H), 7.18 (d, J = 1.79 Hz, 1H), 7.16 - 7.07 (m, 5H), 6.90 (s, 1H), 4.72 (d, J = 9.64 Hz, 1H), 4.35 (d, J = 16.5 Hz, 1H), 4.26 (d, J = 16.4, 1H), 3.69-3.52 (m, 3H), 3.44 - 3.39 (m, 2H), 2.95 (s, 1H), 2.58 (q, J = 7.58Hz, 2H), 1.19 (t, J = 7.65Hz, 3H). MS: m/z (M+Na) 420.

H. Biological Examples:

EXAMPLE 1

Materials and Methods

Cloning of the human SGLT1 and human SGLT2 cDNAs and construction of the mammalian expression vector: The human SGLT1 cDNA (Genbank M24847) was cloned from human small intestine. Human SGLT2 cDNA (Genbank M95549) was cloned from human kidney. Both full cDNAs were subcloned into pcDNA and sequenced to verify the integrity of the construct.

Generation of CHO-K1 cells stably expressing human SGLT1 or human SGLT2: Transfection of CHO-K1 cells was performed using DMRIE-C reagent (Life Technologies, Gaithersburg, MD). Transfectants were then selected in the presence of the antibiotic G418 (Gibco-BRL, Grand Island, NY) at 400 μg/ml. Individual clones were then characterized using the functional assay described below.

Cell-based assay for sodium-dependent glucose transport: Cell lines stably expressing human SGLT1 or SGLT2 were then used for functional analysis of Na+-dependent glucose uptake. Briefly, cells were plated at a density of 65,000 cells per well in a 96-well plate and allowed to grow for 48 hours. Cells were subsequently washed one time with Assay Buffer (50 mM HEPES pH 7.4, 20 mM Tris, 5 mM KCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$ and 137 mM NaCl) and treated with compound in the absence or presence of NaCl for 15 minutes. Cells were then labeled with ^{14}C -α-methylglucopyranoside (AMG, Sigma, St. Louis, MO) a non-metabolizable glucose analog specific for sodium-dependent glucose transporters as previously described (Peng, H. and Lever J.E. Post-transcriptional regulation of Na^+/glucose cotransporter (SGLT1) gene expression in LLC-PK1 cells. J Biol Chem 1995; 270:20536-20542.). After 2 hours the labelled cells were washed three times with ice-cold PBS. After aspiration, cells were solubilized using Microscint 20 (Packard, Meriden, CT) and Na-dependent ^{14}C-AMG uptake was quantified by measuring radioactivity.

Plates were counted in a TopCount (Packard, Meriden, CT). Results are reported as the % inhibition or IC50 value from a representative experiment. Variability for the functional assay was typically within 20 %.

TABLE 3

Example #	CHOK-SGLT2 IC50 (uM)	CHOK-SGLT1 IC50 (uM)
4	12% Inh at 10 uM	inactive
3	60% Inh at 10 uM	inactive
2	1.395 ± 0.067	inactive
1	0.132 ± 0.024	inactive

EXAMPLE 2

In Vivo Assay for Efficacy

Male Zucker Diabetic Fatty (ZDF) rats (7-8 weeks) were obtained from Charles River. Animals were maintained on a 12-hour light/dark cycle in a temperature-controlled room. Animals were given ad libitum access to food (standard rodent diet Purina 5008) and water. Animals were fasted for 12 hours prior to initiation of the experiment. On the morning of the experiment, animals were administered vehicle (0.5 % methylcellulose) or compound by oral gavage (1ml/kg). After one hour, animals received an oral glucose challenge (4 ml/kg of 50% solution) and were immediately placed in metabolism cages. Animals were given free access to water and urine was collected for 4 hours. Urinary glucose was quantified using the Trinder Reagent (Sigma).

EXAMPLE 3

Effects on Plasma Glucose, Plasma Insulin, Plasma Triglycerides, Plasma Free Fatty Acids, Liver Weight, and Body Weight

To examine the effect of an SGLT inhibitor in combination with an RXR agonist, female db/db mice (6-7 weeks of age/Jackson Labs, ME) are treated daily for 11 days with vehicle (0.5% methylcellulose), an RXR agonist (0.1 –10 mpk (mg/kg)), an SGLT inhibitor (100 mpk), or an RXR agonist plus SGLT inhibitor. Mice (n=8 animals/group) receive the test compounds or vehicle by oral gavage in a volume of 10 ml/kg of body weight. Body weight is recorded on day 1, prior to dosing, and days 4, 8 and 11. Eighteen hours after the final dose, mice are weighed and anesthetized with CO_2/O_2 (70:30). Mice are then bled by retro-orbital sinus puncture into 2 mL heparinized polypropylene tubes on ice. Plasma samples are then assayed for glucose, insulin, triglycerides, and free fatty acids. Livers are excised, weighed and frozen.

The SGLT inhibitors and RXR agonists have distinct mechanisms of action. Improved glycemic control, measured as a decrease in plasma glucose, plasma insulin, plasma free fatty acids, or plasma triglycerides, or a combination thereof, can be observed at lower concentrations of an RXR agonist when given in combination with an SGLT inhibitor. Therefore, a leftward shift in the dose-response curve for effect of an RXR agonist on the above parameters can become apparent. In addition, the weight gain observed following treatment with RXR agonists is less pronounced when given with the SGLT inhibitor, since SGLT inhibitors' promotion of the urinary excretion of glucose and loss of calories from the body is demonstrated by reduction in weight or weight gain. Also, since SGLT inhibitors promote a mild diuresis, the edema (and the edematous weight gain) commonly observed after treatment with RXR agonists can be less pronounced or absent. A reduction in the amount of an RXR agonist such as MX-6054 necessary to achieve efficacy in turn improves the side-effect profile. The decreased side effects can include such conditions as fatty liver, increased liver weight, body weight gain, heart

weight gain, edema, cardiac hypertrophy, hepatohypertrophy, hypoglycemia, and hepatotoxicity, or any combination thereof.

EXAMPLE 4

Effects on plasma Glucose, HbA1c, Hematocrit, Plasma Insulin, Plasma Triglycerides, Plasma Free Fatty Acids, Total Cholesterol, HDL, Plasma Drug Levels, Liver Weight, Heart Weight, Fat Content and Body Weight

To examine the effect of an SGLT inhibitor in combination with an RXR agonist, male ZDF rats (6 weeks of age/GMI) are treated daily for 28 days with vehicle (0.5% methylcellulose), an RXR agonist (0.1 mpk-10mpk), SGLT inhibitor (3-100 mpk), or an RXR agonist plus SGLT inhibitor. Rats (n=8 animals/group) receive the test compounds or vehicle by oral gavage in a volume of 2 ml/kg of body weight. Body weight is recorded on day 1, prior to dosing, and twice a week for the duration of the study. On the day prior to the final dose, animals are fasted overnight. One hour after the final dose, rats are weighed and anesthetized with CO_2/O_2 (70:30). Rats are then bled by retro-orbital sinus puncture into 2 mL heparinized polypropylene tubes on ice. Rats then receive a glucose challenge (2 g/kg p.o) and are placed in metabolism cages for the urine collection (4 hours). Animals are then sacrificed and epididymal fat pads, livers, and hearts are excised, weighed and frozen for histological examination. Plasma samples are then assayed for glucose, HbA1c, insulin, hematocrit, plasma drug levels, total cholesterol, HDL, free fatty acids, and triglycerides. Urine volume and urinary glucose, protein, osmolarity, electrolytes (Na, K, Cl), BUN and creatinine are measured.

The SGLT inhibitors and RXR agonists have distinct mechanisms of action. Improved glycemic control, measured as a decrease in plasma glucose, HbA1c, plasma insulin, or plasma triglycerides, or a combination thereof, can be observed at lower concentrations of RXR agonists when given in combination with an SGLT inhibitor. Therefore, a leftward shift in the dose-

response curve for effect of RXR agonists on the above parameters can become apparent. In addition, the weight gain observed following treatment with RXR agonists is less pronounced when given with the SGLT inhibitor, since SGLT inhibitors' promotion of the urinary excretion of glucose and loss of calories from the body is demonstrated by reduction in weight or weight gain. Also, since SGLT inhibitors promote a mild diuresis, the edema (and the edematous weight gain) commonly observed after treatment with RXR agonists can be less pronounced or absent. This can be demonstrated by a reduction in the RXR agonist-induced increase in heart weight. A reduction in the amount of RXR agonists necessary to achieve efficacy in turn improves the side-effect profile. The decreased side effects can include such conditions as fatty liver, increased liver weight, body weight gain, heart weight gain, edema, cardiac hypertrophy, hepatohypertrophy, hypoglycemia, and hepatotoxicity, or any combination thereof.

The above examples can also show that the oral administration of an SGLT inhibitor in combination with an antidiabetic agents, such as an RXR modulator,improve the status of other markers of diabetes mellitus including glycosylated hemoglobin (Hgb A1C) levels. Particularly, the oral administration of an SGLT inhibitor in combination with one or more RXR modulators can reduce body weight or body weight gain as well as liver weight or liver weight gain, compared to administration of one or more RXR modulators alone.

Thus, for treating diabetes, particularly Type II diabetes mellitus, or Syndrome X, a compound of Formula (IV) in combination with one or more antidiabetic agents, such as an RXR agonist that increases insulin sensitivity, may be employed comprising administering repeated oral doses of the compound of Formula (IV) in the range of about 25 to 1000 mg once or twice daily and repeated doses of the anti-diabetic agent or agents at jointly effective dosages. The jointly effective dosage for antidiabetic agents disclosed herein may be readily determined by those skilled in the art based on standard dosage guidelines. In particular, such combined administration can be

effective to accomplish reduction of body weight, body weight gain, liver weight, or liver weight gain in the subject.

Additionally, a method comprising (a) administering to a subject a jointly effective amount of a glucose reabsorption inhibitor; and (b) administering to the subject a jointly effective amount of an antidiabetic agent such as an RXR modulator can be used to reduce body weight, body weight gain, or liver weight of the subject in need thereof, wherein the combined administration can be in any order and the combined jointly effective amounts provide the desired therapeutic effect.

Also, a method comprising (a) administering to a subject a jointly effective amount of a glucose reabsorption inhibitor; and (b) administering to the subject a jointly effective amount of an antidiabetic agent can be used to control body weight, body weight gain, liver weight, or liver weight gain of the subject having diabetes, Syndrome X, or associated symptoms or complications, wherein the combined administration can be in any order and the combined jointly effective amounts providing the desired therapeutic effect.

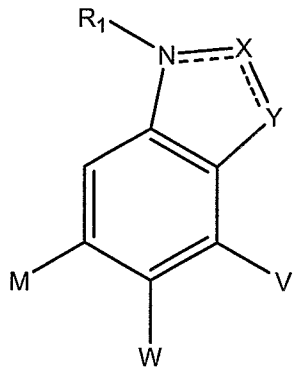
Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, time of administration and concomitant diseases, will result in the need to adjust dosages.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

What is claimed is:

CLAIMS

1. A compound of formula IV:

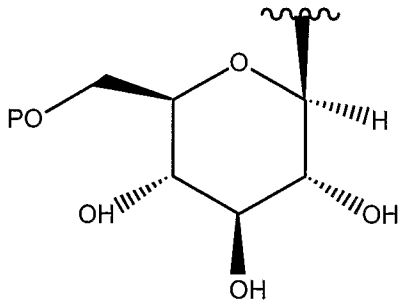


(IV)

wherein:

one of the dashed lines between NR_1 and X or between X and Y is present, or both are absent;

two of V, M, and W are H and the third is



R_1 is H, or C_{1-4} alkyl; or, where the dashed line between NR^1 and X is present, R_1 is absent;

X is N, C=O, CH, or C-Q-Z;

Y is N-Q-Z or C-Q-Z, where X is N, C=O, or CH;
Y is CH, where X is C-Q-Z;

Q = $-(CH_2)_n-$ where n = 1 or 2;

P = H, C_{1-7} acyl, or C_{1-6} alkoxycarbonyl;

Z is substituted or unsubstituted, and is selected from C_{3-7} cycloalkyl, phenyl, a 5- or 6- membered heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, a biaryl, a 9- or 10-membered fused bicyclyl, and a fused heterobicyclyl, wherein said fused heterobicyclyl has between 1 and 4 heteroatoms independently selected from N, O, and S; or a pharmaceutically acceptable salt, thereof.

2. A compound of claim 1, wherein R_1 is H or absent.

3. A compound of claim 1, wherein Z is independently substituted with between 1 and 3 substituents independently selected from C_{1-4} alkoxy, phenoxy, C_{1-4} alkyl, C_{3-6} cycloalkyl, halo, hydroxy, cyano, amino, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfinyl, C_{1-4} aminoalkyl, mono and di C_{1-4} alkylamino, phenyl, C_{1-4} alkylaminosulfonyl (SO_2NHR), amino(C_{1-4} alkylsulfonyl) ($NHSO_2R$), di C_{1-4} alkylaminosulfinyl (SONHRR), C_{1-4} alkylamido (NHCOR), C_{1-4} alkylcarbamido (CONHR), 5-6 membered heterocyclyl containing between 1 and 3 heteroatoms independently selected from N, S, and O; and wherein the substituent(s) on Z can be further independently substituted with between 1 and 3 substitutents independently selected from C_{1-4} alkoxy, C_{1-4} alkyl, halo, hydroxy, cyano, amino, mono or di C_{1-4} alkyl amino and C_{1-4} alkylthio.

4. A compound of claim 1, wherein Z is 4-substituted phenyl, 3,4-disubstituted phenyl, benzhydryl, substituted or unsubstituted thiophenyl, biaryl, benzofuranyl, hydrobenzofuranyl, dihydrobenzofuranyl, 4-substituted pyridyl, ,

benzo[b]thienyl, chromanyl, benzothiophenyl, indanyl, naphthyl, and 2,3-dihydro-benzo[1,4] dioxan.

5. A compound of claim 3, wherein Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl.

6. A compound of claim 1, wherein Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl, (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl.

7. A compound of claim 1 wherein R_1 is H;

8. A compound of claim 1, wherein n is 1.

9. A compound of claim 8, wherein R_1 is H or absent.

10. A compound of claim 1, wherein Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl), (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl; and Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl.

11. A compound of claim 10, wherein n is 1.

12. A compound of claim 10, wherein R is H.

13. A compound of claim 1, wherein M and V are H.

14. A compound of claim 1, wherein M and W are H.

15. A compound of claim 1, wherein X is CH and Y is C-Q-Z.

16. A compound of claim 1, wherein X is C-Q-Z and Y is CH.

17. A compound of claim 15, wherein R_1 is H or absent, and n = 1.

18. A compound of claim 1, selected from examples: 3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-(4-methoxybenzyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole and 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole.

19. A compound of claim 1, selected from 2-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole; 3-[2-(2,3-Dihydro-benzofuran-5-yl)-ethyl]-5-(β-D-glucopyranosyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-(5-methyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzimidazole; 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1,3-dihydro-benzoimidazol-2-one and 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzotriazole.

20. A compound of claim 1, selected from 3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole; 2-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole; 5-(β-D-Glucopyranosyl)-3-(5-methyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzimidazole and 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-3H-benzotriazole.

21. A pharmaceutical composition, comprising a compound of claim 1, 5, 6, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

22. A pharmaceutical composition of claim 21, comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

23. A method for treating diabetes in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.

24. A method of claim 23, wherein said diabetes is type II diabetes.

25. A method for lowering serum glucose in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.

26. A method for treating impaired glucose tolerance in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.

27. A method for treating or inhibiting impaired glucose tolerance in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.

28. A method for reducing the body mass index, body weight, or percentage body fat in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.

29. A method of claim 28, wherein said reduction of body mass index is a method for treating obesity or an overweight condition.

30. A method for inhibiting the sodium glucose transporter in a cell, by exposing said cell to a compound of claim 1 or a metabolite thereof.

31. A method for treating diabetes or Syndrome X, or associated symptoms or complications thereof in a subject, comprising

a) administering to said subject a jointly effective amount of a glucose reabsorption inhibitor of formula (IV); and
b) administering to said subject a jointly effective amount of a second antidiabetic agent,

said co-administration being in any order and the combined jointly effective amounts providing the desired therapeutic effect.

32. The method of claim 31, wherein the second antidiabetic agent is an RXR agonist.

33. The method of claim 31, wherein the diabetes or Syndrome X, or associated symptoms or complications thereof is selected from IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts.

34. The method of claim 31 wherein the diabetes or Syndrome X, or associated symptoms or complication thereof is IDDM.

35. The method of claim 31, wherein the diabetes or Syndrome X, or associated symptoms or complications thereof is NIDDM.

36. The method of claim 31, wherein the diabetes or Syndrome X, or associated symptoms or complications thereof is IGT or IFG.

37. The method of claim 31, further comprising administering to said subject a jointly effective amount of a third antidiabetic agent.

38. The method of claim 37, wherein the third antidiabetic agent is selected from

(aa) insulins,

(bb) insulin analogues;
(cc) insulin secretion modulators, and
(dd) insulin secretagogues.

39. The method of claim 31, wherein the glucose reabsorption inhibitor is an SGLT inhibitor.

40. The method of claim 31, wherein the glucose reabsorption inhibitor is an SGLT1 inhibitor.

41. The method of claim 31, wherein the glucose reabsorption inhibitor is an SGLT2 inhibitor.

42. The method of claim 31, wherein the glucose reabsorption inhibitor is a compound of Formula (IV) or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof.

43. The method of claim 31, wherein the jointly effective amount of an SGLT inhibitor is from about 10 to 1000 mg.

44. The method of claim 31, wherein the jointly effective amount of an SGLT inhibitor is an amount sufficient to reduce the plasma glucose excursion following a meal.

45. A method for inhibiting the onset of diabetes or Syndrome X, or associated symptoms or complications thereof in a subject, said method comprising

(a) administering to said subject a jointly effective amount of a glucose reabsorption inhibitor of formula (IV); and
(b) administering to said subject a jointly effective amount of a second antidiabetic agent,

said co-administration being in any order and the combined jointly effective amounts providing the desired prophylactic effect.

46. The method of claim 45, wherein said onset is from pre-diabetic state to NIDDM.

47. A pharmaceutical composition comprising a glucose reabsorption inhibitor of formula (IV), a second antidiabetic agent, and a pharmaceutically acceptable carrier.

48. The pharmaceutical composition of claim 45, 46, or 47, wherein the glucose reabsorption inhibitor is an SGLT inhibitor.

49. The pharmaceutical composition of claim 45, wherein the glucose reabsorption inhibitor is an SGLT1 inhibitor.

50. The pharmaceutical composition of claim 45, wherein the glucose reabsorption inhibitor is an SGLT2 inhibitor.

51. A process for formulating a pharmaceutical composition, comprising formulating together a glucose reabsorption inhibitor, a second antidiabetic agent, and a pharmaceutically acceptable carrier.

52. A process for making a pharmaceutical composition comprising mixing one or more glucose reabsorption inhibitors in combination with a second antidiabetic agent for the preparation of a medicament for treating a condition selected from IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts.

53. A method for inhibiting the progression of a prediabetic condition in a subject to a diabetic condition, comprising

(a) administering to said subject a jointly effective amount of a glucose reabsorption inhibitor of formula (IV); and
(b) administering to said subject a jointly effective amount of an second diabetic agent,

said co-administration being in any order and the combined jointly effective amounts providing the desired inhibiting effect.

54. The method of claim 53 wherein said condition is IGT or IFG.

55. The method of claim 53 wherein said inhibiting of the progression of a prediabetic condition is prevention of the progression of the prediabetic condition to a diabetic condition.

56. The method of claim 53, wherein the glucose reabsorption inhibitor is a compound of formula (IV), optionally having one or more hydroxyl or diol protecting groups, or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture, ester, prodrug form, or a pharmaceutically acceptable salt thereof.