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TITLE OF THE INVENTION (280 characters max)

C-ARYL GLUCOSIDE SGLT2 INHIBITORS AND METHOD

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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- ☐ Drawings - sheets
- ☒ Other (specify): Power of Attorney and Assignment

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C-ARYL GLUCOSIDE SGLT2 INHIBITORS AND METHOD

Field of the Invention

The present invention relates to C-aryl glucosides which are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2) and to a method for treating diabetes, especially type II diabetes, as well as hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis and related diseases, employing such C-aryl glucosides alone or in combination with one, two or more other type antidiabetic agent and/or one, two or more other type therapeutic agents such as hypolipidemic agents.

Background of the Invention

Approximately 100 million people worldwide suffer from type II diabetes (NIDDM), which is characterized by hyperglycemia due to excessive hepatic glucose production and peripheral insulin resistance, the root causes for which are as yet unknown. Hyperglycemia is considered to be the major risk factor for the development of diabetic complications, and is likely to contribute directly to the impairment of insulin secretion seen in advanced NIDDM. Normalization of plasma glucose in NIDDM patients would be predicted to improve insulin action, and to offset the development of diabetic complications. An inhibitor of the sodium-dependent glucose transporter SGLT2 in the kidney would be expected to aid in the normalization of plasma glucose levels, and perhaps body weight, by enhancing glucose excretion.

The development of novel, safe, and orally active antidiabetic agents is also desired in order to complement existing therapies, including the sulfonylureas, thiazolidinediones, metformin, and insulin, and to avoid the potential side effects associated with the use of these other agents.

Hyperglycemia is a hallmark of type II diabetes (NIDDM); consistent control of plasma glucose levels in diabetes can offset the development of diabetic complications and beta cell failure seen in advanced disease. Plasma glucose is normally filtered in the kidney in the glomerulus and actively reabsorbed in the proximal tubule. SGLT2 appears to be the major transporter responsible for the reuptake of glucose at this site. The SGLT specific inhibitor phlorizin or closely related analogs inhibit this reuptake process in diabetic rodents and dogs resulting in normalization of plasma glucose levels by promoting glucose excretion without hypoglycemic side effects. Long term (6 month) treatment of Zucker diabetic rats with an SGLT2 inhibitor has been reported to improve insulin response to glycemia, improve insulin sensitivity, and delay the onset of nephropathy and neuropathy in these animals, with no detectable pathology in the kidney and no electrolyte imbalance in plasma. Selective inhibition of SGLT2 in diabetic patients would be expected to normalize plasma glucose by enhancing the excretion of glucose in the urine, thereby improving insulin sensitivity, and delaying the development of diabetic complications.

Ninety percent of glucose reuptake in the kidney occurs in the epithelial cells of the early S1 segment of the renal cortical proximal tubule, and SGLT2 is likely to be the major transporter responsible for this reuptake. SGLT2 is a 672 amino acid protein containing 14 membrane-spanning segments that is predominantly expressed in the early S1 segment of the renal proximal tubules. The substrate specificity, sodium dependence, and localization of SGLT2 are consistent with the properties of the high capacity, low affinity, sodium-dependent glucose transporter previously characterized in human cortical kidney proximal tubules. In addition, hybrid depletion studies implicate SGLT2 as the predominant Na^+/glucose cotransporter in the S1 segment of the proximal tubule, since virtually all Na-dependent glucose transport activity encoded in mRNA from rat kidney cortex is inhibited by an antisense oligonucleotide specific to rat SGLT2. SGLT2 is a candidate gene for some forms of familial glucosuria, a genetic abnormality in which renal glucose reabsorption is impaired to varying degrees. None of these syndromes investigated to date map to the SGLT2 locus on chromosome 16. However, the studies of highly homologous rodent SGLTs strongly implicate SGLT2 as the major renal sodium-dependent transporter of glucose and suggest that the glucosuria locus that has been mapped encodes an SGLT2 regulator. Inhibition of SGLT2 would be predicted to reduce plasma glucose levels via enhanced glucose excretion in diabetic patients.

SGLT1, another Na-dependent glucose cotransporter that is 60% identical to SGLT2 at the amino acid level, is expressed in the small intestine and in the more distal S3 segment of the renal proximal tubule. Despite their sequence similarities, human SGLT1 and SGLT2 are biochemically distinguishable. For SGLT1, the molar ratio of Na^+ to glucose transported is 2:1, whereas for SGLT2, the ratio is 1:1. The K_m for Na^+ is 32 and 250-300 mM for SGLT1 and SGLT2, respectively. K_m values for uptake of glucose and the nonmetabolizable glucose analog α-methyl-D-glucopyranoside (AMG) are similar for SGLT1 and SGLT2, i.e. 0.8 and 1.6 mM (glucose) and 0.4 and 1.6 mM (AMG) for SGLT1 and SGLT2 transporters, respectively.

However, the two transporters do vary in their substrate specificities for sugars such as galactose, which is a substrate for SGLT1 only.

Administration of phlorizin, a specific inhibitor of SGLT activity, provided proof of concept *in vivo* by promoting glucose excretion, lowering fasting and fed plasma glucose, and promoting glucose utilization without hypoglycemic side effects in several diabetic rodent models and in one canine diabetes model. No adverse effects on plasma ion balance, renal function or renal morphology have been observed as a consequence of phlorizin treatment for as long as two weeks. In addition, no hypoglycemic or other adverse effects have been observed when phlorizin is administered to normal animals, despite the presence of glycosuria. Administration of an inhibitor of renal SGLTs for a 6-month period (Tanabe Seiyaku) was reported to improve fasting and fed plasma glucose, improve insulin secretion and utilization in obese NIDDM rat models, and offset the development of nephropathy and neuropathy in the absence of hypoglycemic or renal side effects.

Phlorizin itself is unattractive as an oral drug since it is a nonspecific SGLT1/SGLT2 inhibitor that is hydrolyzed in the gut to its aglycone phloretin, which is a potent inhibitor of facilitated glucose transport. Concurrent inhibition of facilitative glucose transporters (GLUTs) is undesirable since such inhibitors would be predicted to exacerbate peripheral insulin resistance as well as promote hypoglycemia in the CNS. Inhibition of SGLT1 could also have serious adverse consequences as is illustrated by the hereditary syndrome glucose/galactose malabsorption (GGM), in which mutations in the SGLT1 cotransporter result in impaired glucose uptake in the intestine, and life-threatening diarrhea and dehydration. The biochemical differences between

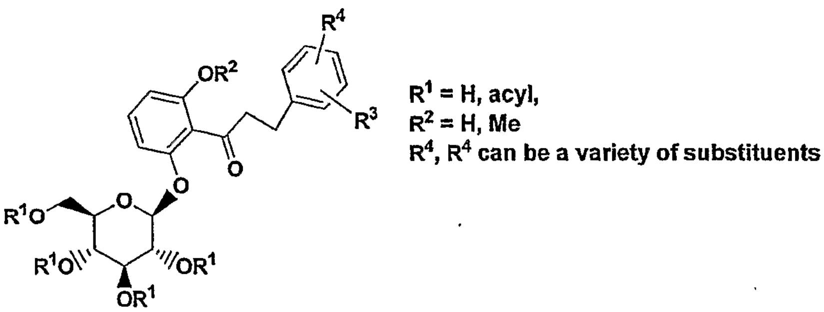
SGLT2 and SGLT1, as well as the degree of sequence divergence between them, allow for identification of selective SGLT2 inhibitors.

The familial glycosuria syndromes are conditions in which intestinal glucose transport, and renal transport of other ions and amino acids, are normal. Familial glycosuria patients appear to develop normally, have normal plasma glucose levels, and appear to suffer no major health deficits as a consequence of their disorder, despite sometimes quite high (110-114 g/daily) levels of glucose excreted. The major symptoms evident in these patients include polyphagia, polyuria and polydipsia, and the kidneys appear to be normal in structure and function. Thus, from the evidence available thus far, defects in renal reuptake of glucose appear to have minimal long term negative consequences in otherwise normal individuals.

The following references disclose O-aryl glucosides SGLT2 inhibitors for treating diabetes.

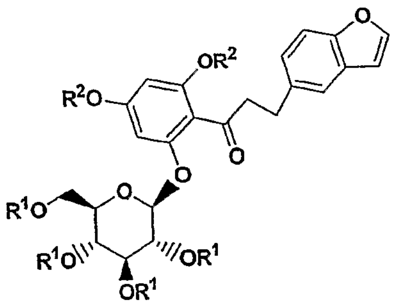
EP 598359A1 (also JP 035988) (Tanabe Seiyaku)discloses compounds of the following structure <u>**A**</u>

<u>**A**</u>



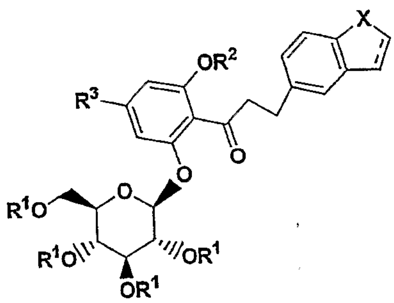
EP 0850948A1 discloses structures of the following genus <u>**B**</u>

B



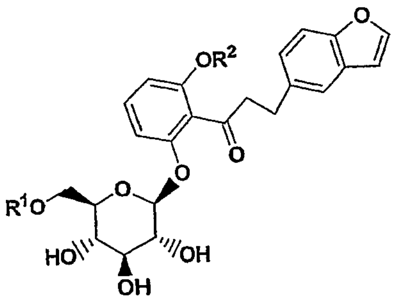
R^1 = H, acyl, CO(OAlkyl)
R^2 = H, allyl
R^3 = H or Me

JP 09188625A expands upon structure B to include examples of B where R3 is H and where the 5 membered ring is saturated as well as the counterparts of benzothiophenes (O = S) and indenes (O = CH2)



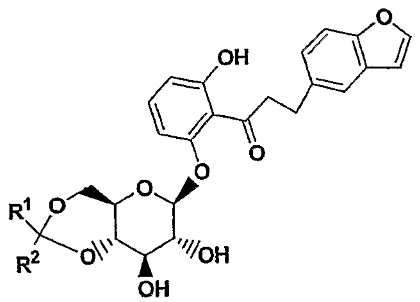
R^1 = H, acyl, CO(OAlkyl)
R^2 = H, allyl
R^3 = H or Me

JP 09124685A expands upon structure B for R3 = H to include derivatives of mono acylated C6 hydroxyl where the acyl group is a substituted benzoic or pyridyl carboxylic acid or a urethane generated from the corresponding phenol.



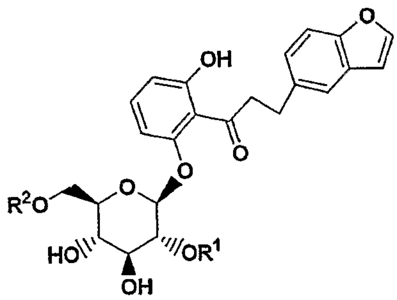
R^1 = H, acylaryll, CO(OAryl)
R^2 = H

JP 09124684 discloses derivatives of structure B



R^1, R^2 = H, alkyl, alkoxy, aryl or together oxo)

EP 773226-A1 discloses derivatives of structure **B**



R^1 = alkanoyl if R^2 = H
R^2 = alkoxycarbonyl if R^1 =H

JP 08027006-A discloses derivatives of structure **A** where various combinations of the glucose hydroxyl are acylated and appears to be similar to EP 598359A1

EP 684254-A1 appears to encompass derivatives of structure **B** disclosed in JP 09188625A.

Other disclosures and publications which disclose SGLT2 inhibitors are as following:

K. Tsujihara, et al, Chem. *Pharm. Bull.* **44**, 1174-1180 (1996)

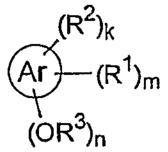
M. Hongu et al, Chem. *Pharm. Bull.* **46**, 22-33 (1998)

M. Hongu et al, Chem. *Pharm. Bull.* **46**, 1545-1555 (1998)

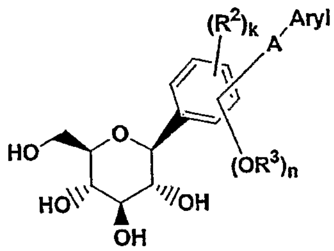
A.Oku et al, *Diabetes*,**48**, 1794-1800 (1999)

JP 10245391 (Dainippon) discloses 500 structures as hypoglycemic agents for treatment of diabetes. These are O-glucosides of hydroxylated coumarins.

WO 98/31697 disclosed compounds of the structure



Where Ar includes, among others, phenyl, biphenyl, diphenylmethane, diphenylethane, and diphenylether, and R^1 is a glycoside, R^2 is H, OH, amino, halogen, carboxy, alkyl, cycloalkyl, or carboxamido and R^3 is hydrogen, alkyl, or acyl, and k,m,and n are independently 1 - 4. A subset of compounds disclosed in WO 98/31697 contains compounds of the following structures

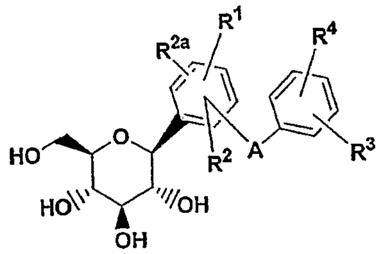


A is O or $(CH_2)_x$ where x = 0-3
R^3 is hydrogen, alkyl or acyl group where n is 1-4
R^2 is hydrogen, alkyl, OH, NH_2, halogen, CO_2H or carboximide where k is 1-4

which are disclosed for use in the treatment or prevention of inflammatory diseases, autoimmune diseases, infections, cancer, and cancer metastasis, reperfusion disorders, thrombosis, ulcer, wounds, osteoporosis, diabetes mellitus, atherosclerosis, among others.

Description of the Invention

In accordance with the present invention, C-aryl glucoside compounds are provided which have the structure I.



wherein

R^1, R^2 and R^{2a} are independently hydrogen, OH, OR^5, lower alkyl, CF_3, $OCHF_2$, OCF_3, or halogen, or two of R^1, R^2 and R^{2a} together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^3 and R^4 are independently hydrogen, OH, OR^{5a}, OAryl, OCH_2Aryl, lower alkyl, cycloalkyl, CF_3, $-OCHF_2$, $-OCF_3$, halogen, -CN, $-CO_2R^{5b}$, $-CO_2H$, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $-CONR^6R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2$Aryl, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2$Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2, or R^3 and R^4 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^5, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} and R^{5h} are independently lower alkyl;

R^6, R^{6a}, R^{6b}, R^{6c} and R^{6d} are independently hydrogen, alkyl,aryl, alkylaryl or cycloalkyl, or R^6 and R^{6a} together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

A is O, S, NH, or $(CH_2)_n$ where n is 0 – 3, and a pharmaceutically acceptable salt thereof, all stereoisomers thereof, and all prodrug esters thereof.

The compounds of formula I of the invention as defined above also include the proviso that where A is $(CH_2)_n$ where n is 0,1,2, or 3 or A is O, and at least one of R^1, R^2, and R^{2a} is OH or OR^5, then at least one of R^1,

R^2, and R^{2a} is CF_3, OCF_3, or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3, $-OCHF_2$, $-OCF_3$, $CH(OR^{5h})R^{6d}$, $CH(OH)R^{6c}$, COR^{6b}, -CN, $-CO_2R^{5b}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$.

Preferred compounds of formula I as defined above include the proviso that where A is $(CH_2)_n$ where n is 0,1,2, or 3 or A is O, and at least one of R^1, R^2, R^{2a}, R^3 and R^4 is OH or OR^5, then at least one of R^1, R^2, and R^{2a} is CF_3, OCF_3, or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3, $-OCHF_2$, $-OCF_3$, -CN, $-CO_2R^{5b}$, $CH(OR^{5h})R^{6d}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$.

The compounds of formula I possess activity as inhibitors of the sodium dependent glucose transporters found in the intestine and kidney of mammals and are useful in the treatment of diabetes and the micro- and macrovascular complications of diabetes such as retinopathy, neuropathy, nephropathy, and wound healing.

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

In addition, in accordance with the present invention, a method is provided for treating diabetes, especially type II diabetes, including complications of diabetes, including retinopathy, neuropathy, nephropathy and wound healing, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis and hypertension, and for increasing high density lipoprotein levels, wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I and another type antidiabetic agent and/or hypolipidemic agent is administered to a human patient in need of treatment.

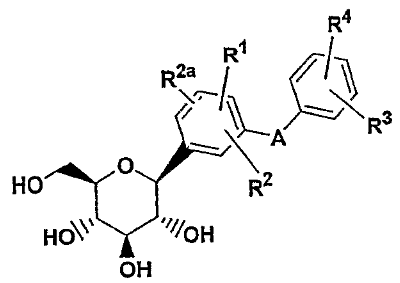
The conditions, diseases, and maladies collectively referred to as "Syndrome X" (also known as Metabolic Syndrome) are detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

The term "other type of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than SGLT2 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents (including anti-atherosclerosis agents).

In the above method of the invention, the compound of structure I of the invention will be employed in a weight ratio to the one, two or more antidiabetic agent and/or one, two or more other type therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 300:1, preferably from about 0.1:1 to about 10:1.

Preferred are compounds of formula IA

IA



wherein A is CH_2 or O or S and is linked meta to the glucoside;

R^1, R^2 and R^{2a} are independently selected from H, alkyl or $OCHF_2$ or two of R^1, R^2 and R^{2a} are H and the other is $OCHF_2$;

R^3 and R^4 are independently selected from alkyl, alkoxy, CHF_2O, $R^{5e}S$, OH, $R^{5a}O$, CO_2R^{5b}, -3,4-(OCH_2O)-, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, CF_3, $R^{5c}-C(=O)-NH-$, $R^{5f}SO_2$, aryl, arylSO_2NH-, $R^{5d}SO_2NH$-, COOH, thiadiazole, tetrazole, aryl-CH_2O-, CF_3O, aryloxy, or H.

More preferred are compounds of formula I where A is CH_2;

R^1 is hydrogen or alkyl;

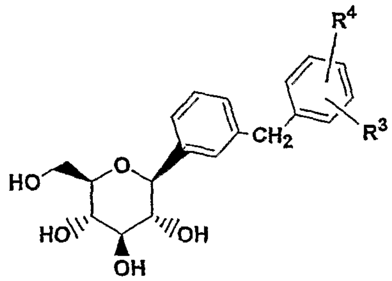
R^2 and R^{2a} are each H;

R^3 is H;

R^4 is alkyl, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $R^{5a}O$, CHF_2O, CF_3O or $R^{5e}S$. It is preferred that the R^4 substituent be linked at the para position.

Most preferred are compounds of formula I of the structure IB

IB



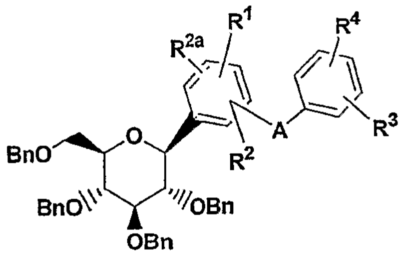
where one of R^3 and R^4 is alkyl and the other is H.

Detailed Description of the Invention

The compounds of formula I of the invention can be prepared as shown in the following reaction schemes and description thereof wherein temperatures are expressed in degrees Centigrade.

Compounds of formula I where A is O or NH or $(CH_2)_n$ can be prepared as shown in Scheme 1 by treatment of compounds of formula II

II

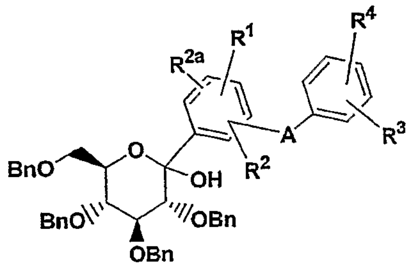


(where Bn = benzyl)

with H_2 in the presence of a catalyst such as 1) Pd/C employing a solvent such as MeOH or EtOH or 2) preferably $Pd(OH)_2$ using a solvent such as EtOAc. Alternatively, compounds of formula I can be prepared by treatment of compounds of formula II with a Lewis acid such BBr_3, BCl_3, or $BCl_3 \cdot Me_2S$ in a solvent such as CH_2Cl_2 at −78°.

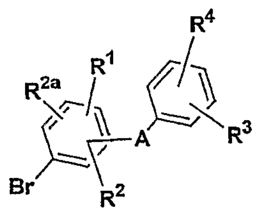
Compounds of formula II (which are novel intermediates) can be prepared by treatment of compounds of formula III with silanes such as Et_3SiH in a solvent such as MeCN containing a Lewis acid such as $BF_3 \cdot Et_2O$ at −30°.

III



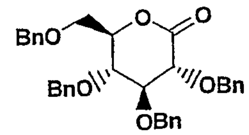
Compounds of formula III (which are novel intermediates) can be prepared by coupling of a compound of formula IV

IV



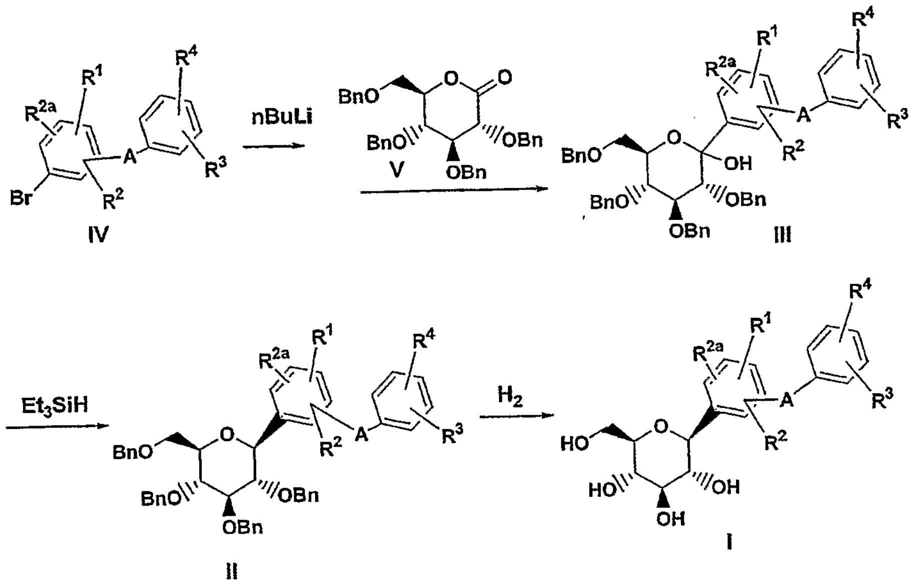
with compound V.

V



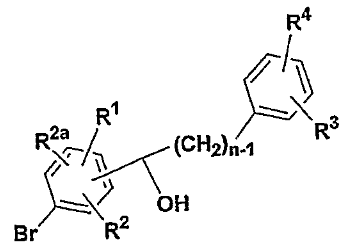
Compounds of formula IV are activated for coupling by treatment with *n*-BuLi or *t*-BuLi at -78° in a solvent such as THF prior to addition of lactone V. Preparation of lactone V is described in. R. Benhaddou, S Czernecki, et al., *Carbohydr. Res.*, **260** (1994), 243-250.

Scheme 1



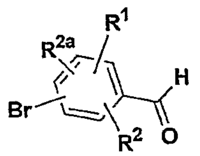
Compounds of formula IV where A is $(CH_2)_n$ where n = 1-3 can be prepared as shown in Scheme 2 by treatment of compounds of formula VI

VI



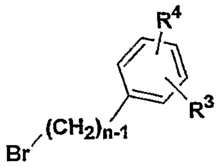
with silanes such as iPr_3SiH or Et_3SiH in a solvent such as MeCN or CH_2Cl_2 containing a Lewis acid such as $BF_3 \cdot Et_2O$ or TFA at -30° to +20°.

Compounds of formula VI can be prepared by coupling commercially available bromobenzaldehydes of formula VII



with either the lithium or magnesium organometalic derivative of compounds of formula VIII

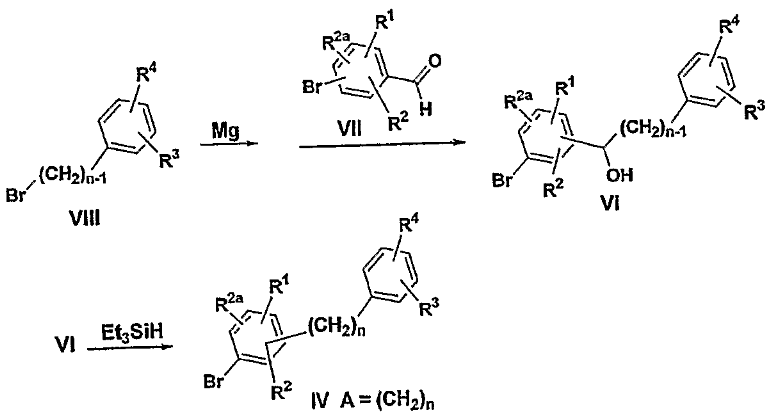
VIII



in a solvent such as Et_2O or THF using conditions familiar to those skilled in the art.

Compounds of formula VIII are either commercially available or readily prepared by standard methods known to those skilled in the art.

Scheme 2



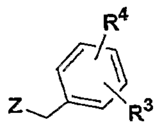
Compounds of formula I where R^4 is $CH(OR^{5h})R^{6d}$ can be prepared by treatment of compounds of formula I where R^4 is COR^{6b} sequentially with 1) an acetylating agent such as Ac_2O in a solvent such as pyridine alone or CH_2Cl_2 containing 1.5 equivalents of a base such as Et_3N, 2) a reducing agent such as $NaBH_4$ in a solvent such as EtOH, 3) an alkylating agent such as $R^{5h}Br$ or $R^{5h}I$ in the presence of a base such as NAH in a solvent such as DMF, and 4) alkaline ester hydrolysis conditions such as LiOH in a 2:3:1 mixture of $THF/MeOH/H_2O$.

Compounds of formula I where R^4 is $CH(OH)R^{6c}$ can be prepared by treatment of compounds of formula I where R^4 is COR^{6b} with a reducing agent such as $NaBH_4$ in a solvent such as EtOH.

Compounds of formula I where R^4 is COR^{6b} can be prepared by treatment of compounds of formula II where R^4 is COR^{6b} with a Lewis acid such as BCl_3 or BBr_3 at -78° in a solvent such as CH_2Cl_2.

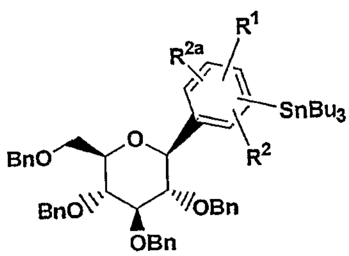
Compounds of formula II where A is CH_2 and R^4 is $-COR^{6b}$ can be prepared as shown in Scheme 3 by coupling commercially available or readily accessible compounds of formula IX

IX



where Z is Br or Cl with compounds of formula X

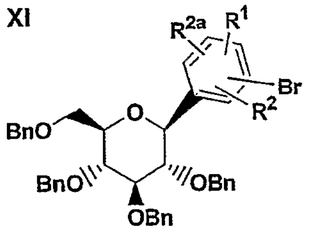
X



by heating the two components in a solvent such as PhMe in the presence of a catalyst such as $Pd(PPh_3)_4$.

Compounds of formula X (which are novel intermediates) can be prepared from compounds of formula XI

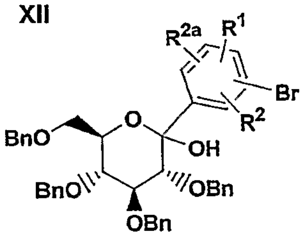
XI



by treatment with $(Bu_3Sn)_2$ and a catalyst such as $Pd(Ph_3P)_4$ in a solvent such as toluene.

Compounds of formula XI (which are novel intermediates) can be prepared from compounds of formula XII

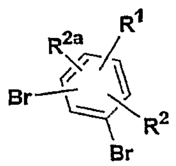
XII



by treatment with silanes such as $i Pr_3SiH$ or Et_3SiH in a solvent such as MeCN containing a Lewis acid such as $BF_3 \cdot Et_2O$ at −30°.

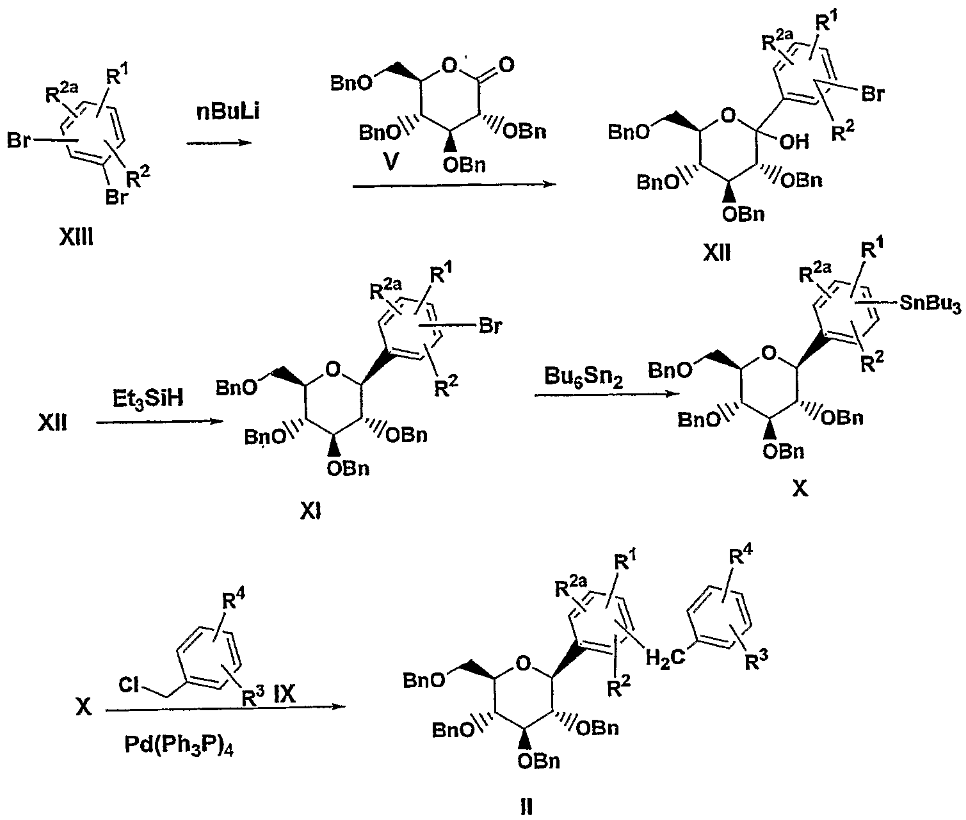
Compounds of formula XII (which are novel intermediates) can be prepared by coupling compound V with the organolithium obtained upon treatment of compounds of formula XIII

XIII



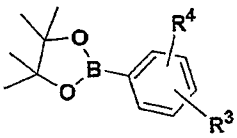
with *n*-BuLi or *t*-BuLi at −78° in THF.

Scheme 3



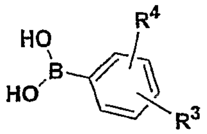
Compounds of formula II where A is a bond can be prepared as shown in Scheme 4 by coupling compounds of formula XI with compounds of formula XIV

XIV



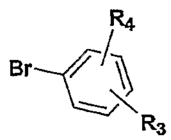
or the corresponding boronic acid XXIII.

XXIII



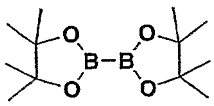
Coupling entails heating in the presence of a catalyst such as $Pd(PPh_3)_4$ employing a solvent such as 3:1 PhMe/EtOH containing Na_2CO_3. Compounds of formula XXIII are either commercially available or can be prepared upon treatment of compounds of formula XIV with BCl_3. Compounds of formula XIV can be prepared by heating compounds of formula XV

XV

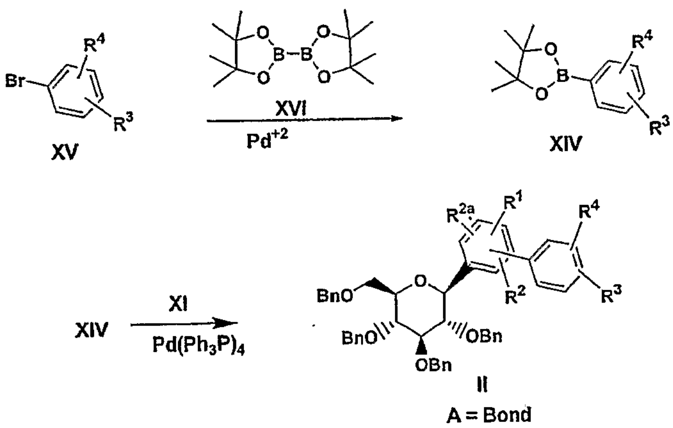


in a solvent such as DMSO containing a catalyst such as $PdCl_2$·dppf and a base such as KOAc with compound XVI.

XVI

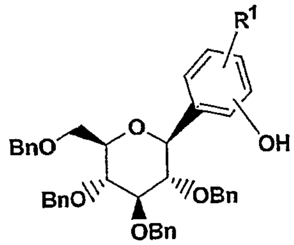


Scheme 4



Compounds of formula II, where A = CH_2 and R^2 = OH, can be prepared as shown in Scheme 5 upon sequential treatment of compounds of formula XVII

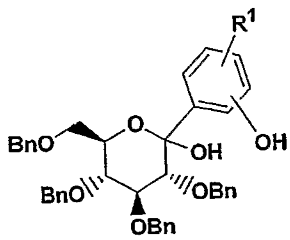
XVII



with a base such as NaH followed by heating with compounds of formula IX in a solvent such as PhMe.

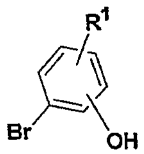
Compounds of formula XVII can be prepared from compounds of formula XVIII

XVIII



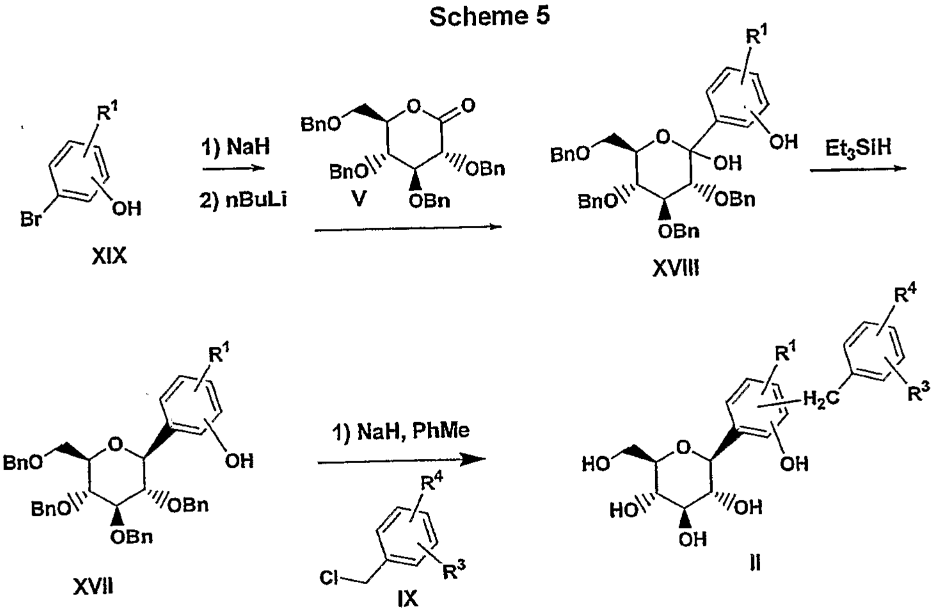
by treatment with silanes such as Et_3SiH in a solvent such as MeCN containing a Lewis acid such as $BF_3 \cdot Et_2O$ at -30°.

Compounds of compounds of formula XVIII can be prepared by coupling the compound of formula V with activated metalated derivatives of compounds of formula XIX



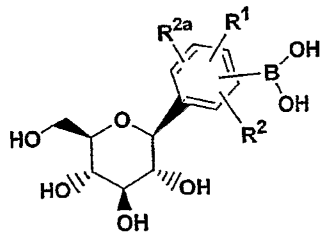
which are prepared by sequential treatment with a base such as NaH, KH, or KOtBu followed by an alkyllithium such as nBuLi or tBuLi in a solvent such as dry THF.

Scheme 5



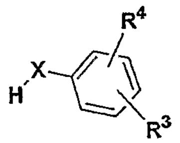
Compounds of formula I, where A = O or NH, can be prepared as shown in Scheme 6 by coupling compounds of formula XX

XX



with commercially available compounds of formula XXI where X = O or NH

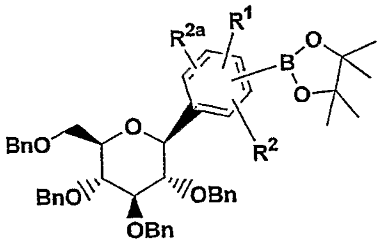
XXI



by heating in a solvent such as pyridine containing a base such as Et_3N, a catalyst such as $Cu(OAc)_2$ and molecular sieves.

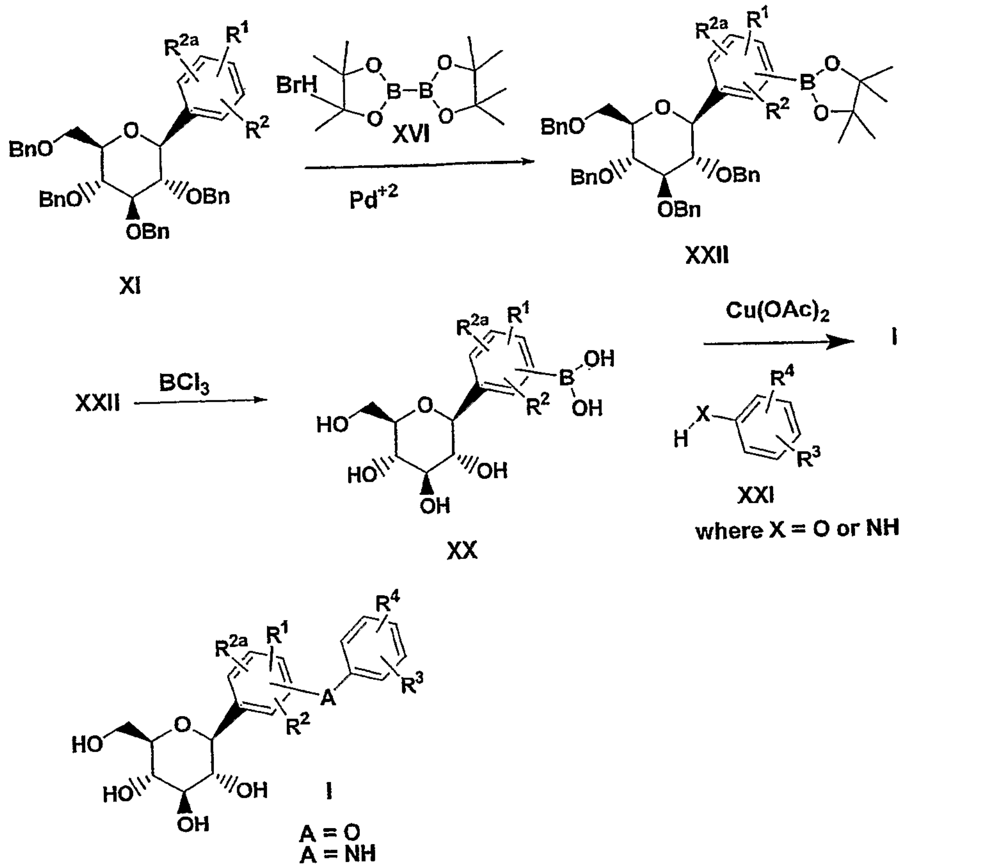
Compounds of formula XX (which are novel intermediates) can be prepared by treating compounds of formula XXII with BCl_3 in a solvent such as CH_2Cl_2 at -78°.

XXII



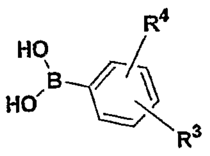
Compounds of formula XXII (which are novel intermediates) can be prepared by heating compounds of formula XI with compounds of formula XVI in a solvent such as DMSO containing a catalyst such as $PdCl_2$·dppf and a base such as KOAc.

Scheme 6



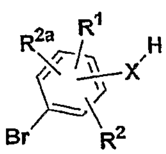
Compounds of formula IV where A is O or NH can be prepared as shown in Scheme 7 by coupling compounds of formula XXIII

XXIII



with compounds of formula XXIV where X = O or NH

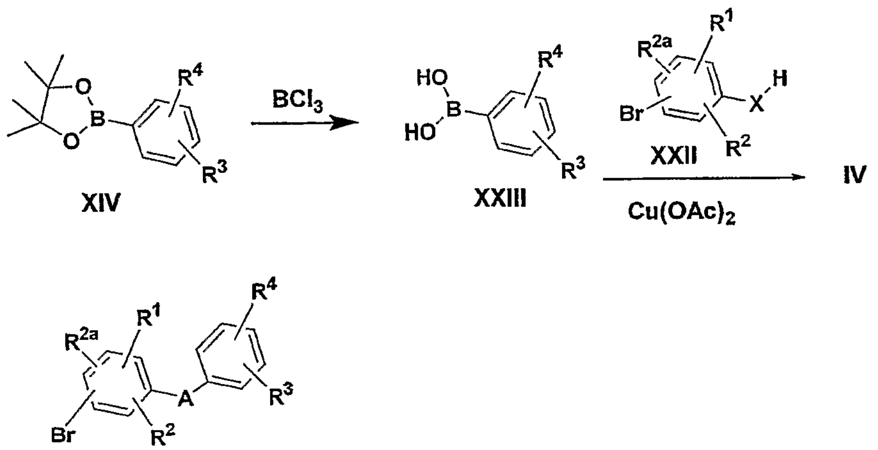
XXIV



by heating in a solvent such as pyridine containing a base such as Et_3N, a catalyst such as $Cu(OAc)_2$ and molecular sieves.

Compounds of formula XXIII can be prepared by treating compounds of formula XIV with BCl_3 in a solvent such as CH_2Cl_2.

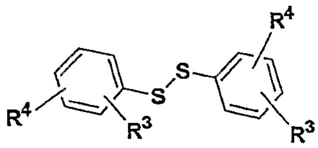
Scheme 7



IV A =O or NH

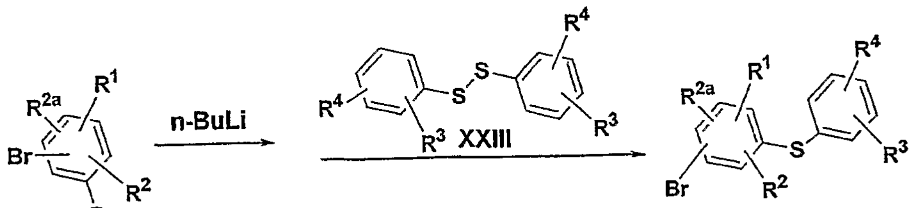
Compounds of formula IV where A is S can be prepared as shown in Scheme 8 by coupling aryl disulfides of formula XXV

XXV



with the organolithium obtained upon metalation of compounds of formula XIII with *n*-BuLi or *t*-BuLi at −78° in THF.

Scheme 8



XIII

IV A =S

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The following abbreviations are employed herein:

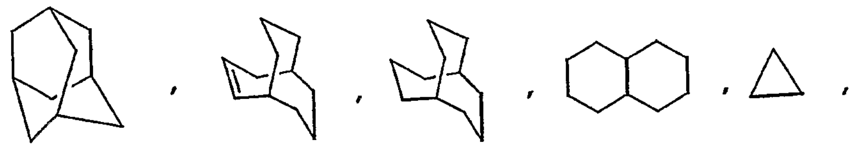
Ph = phenyl
Bn = benzyl
t-Bu = tertiary butyl
Me = methyl
Et = ethyl
TMS = trimethylsilyl
$TMSN_3$ = trimethylsilyl azide
TBS = tert-butyldimethylsilyl
THF = tetrahydrofuran
Et_2O = diethyl ether
EtOAc = ethyl acetate
DMF = dimethyl formamide
MeOH = methanol
EtOH = ethanol
i-PrOH = isopropanol
HOAc or AcOH = acetic acid
TFA = trifluoroacetic acid
$i\text{-}Pr_2NEt$ = diisopropylethylamine

Et_3N = triethylamine
DMAP = 4-dimethylaminopyridine
$NaBH_4$ = sodium borohydride
$LiAlH_4$ = lithium aluminum hydride
n-BuLi = n-butyllithium
Pd/C = palladium on carbon
KOH = potassium hydroxide
NaOH = sodium hydroxide
LiOH = lithium hydroxide
K_2CO_3 = potassium carbonate
$NaHCO_3$ = sodium bicarbonate
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)
HOBT or HOBT.H_2O = 1-hydroxybenzotriazole hydrate
HOAT = 1-Hydroxy-7-azabenzotriazole
Ph_3P = triphenylphosphine
$Pd(OAc)_2$ = Palladium acetate
$(Ph_3P)_4Pd^o$ = tetrakis triphenylphosphine palladium
Ar = argon
N_2 = nitrogen
min = minute(s)
h or hr = hour(s)
L = liter
mL = milliliter
μL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
meq = milliequivalent
RT = room temperature
sat or sat'd = saturated
aq. = aqueous

TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
NMR = nuclear magnetic resonance
mp = melting point
dppf = diphenylphosphinoferrocene

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkyloxy, optionally substituted amino, hydroxy, hydroxyalkyl, acyl, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the alkyl substituents.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

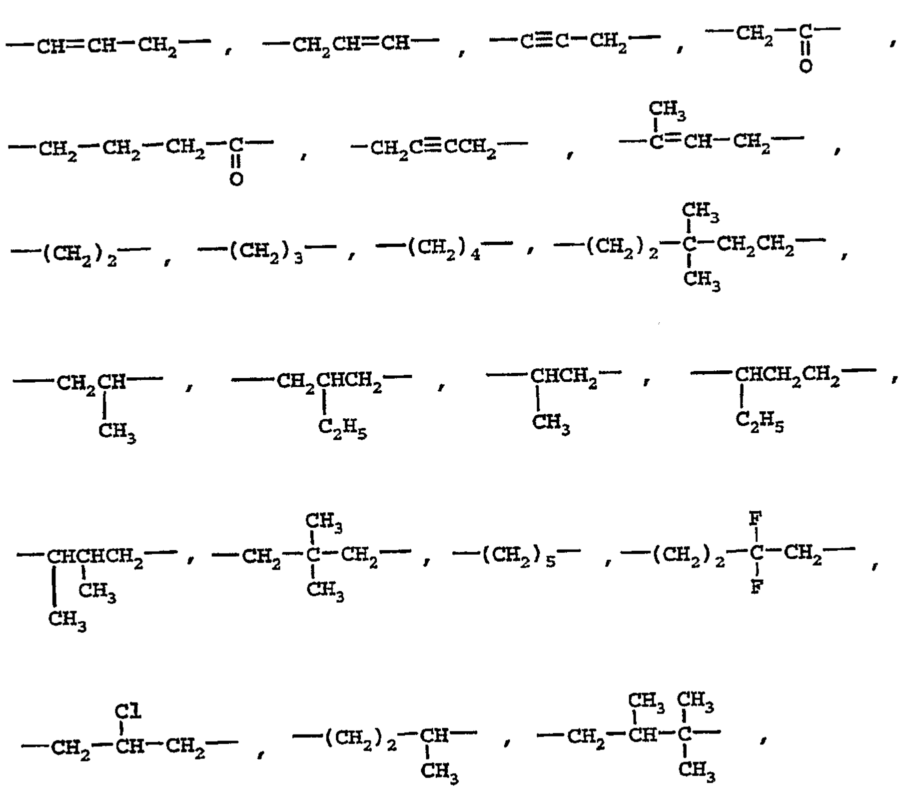
The terms "arylakyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent.

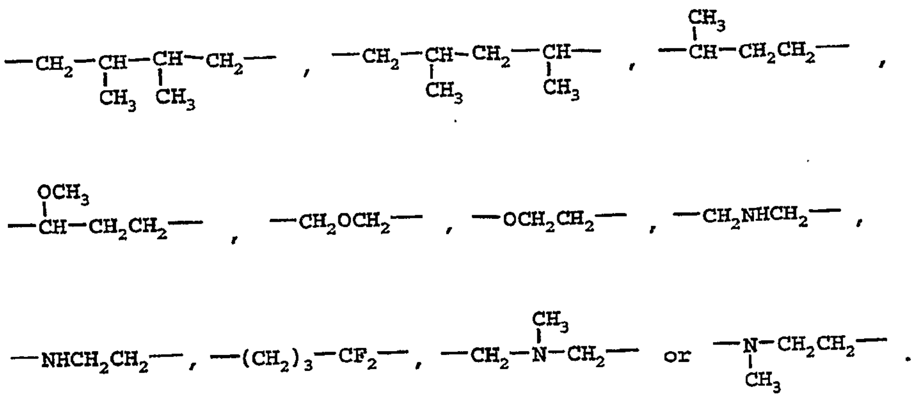
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

Suitable alkylene, alkenylene or alkynylene groups $(CH_2)_n$ or $(CH_2)_p$ (where p is 1 to 8, preferably 1 to 5, and n is 1 to 5, preferably 1 to 3, which includes alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 substituents which include alkyl, alkenyl, halogen, cyano, hydroxy, alkoxy, amino, thioalkyl, keto, C_3-C_6 cycloalkyl, alkylcarbonylamino or alkylcarbonyloxy.

Examples of $(CH_2)_n$ or $(CH_2)_p$, alkylene, alkenylene and alkynylene include $-CH_2-$, $-CH_2CH_2-$,

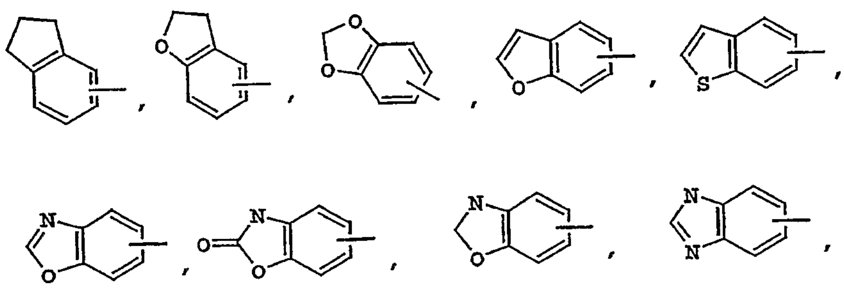


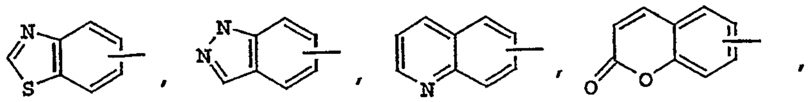


The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

Unless otherwise indicated, the term "aryl" or "Aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example





and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the other alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

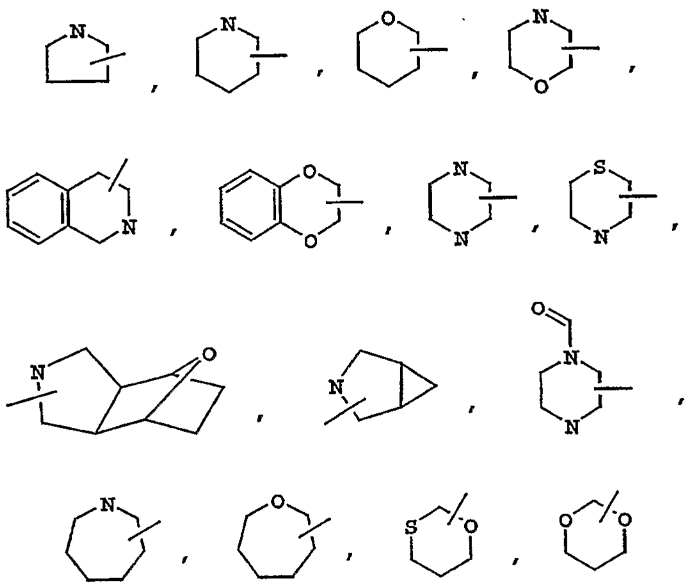
Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the alkyl substituents as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

Unless otherwise indicated, the term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

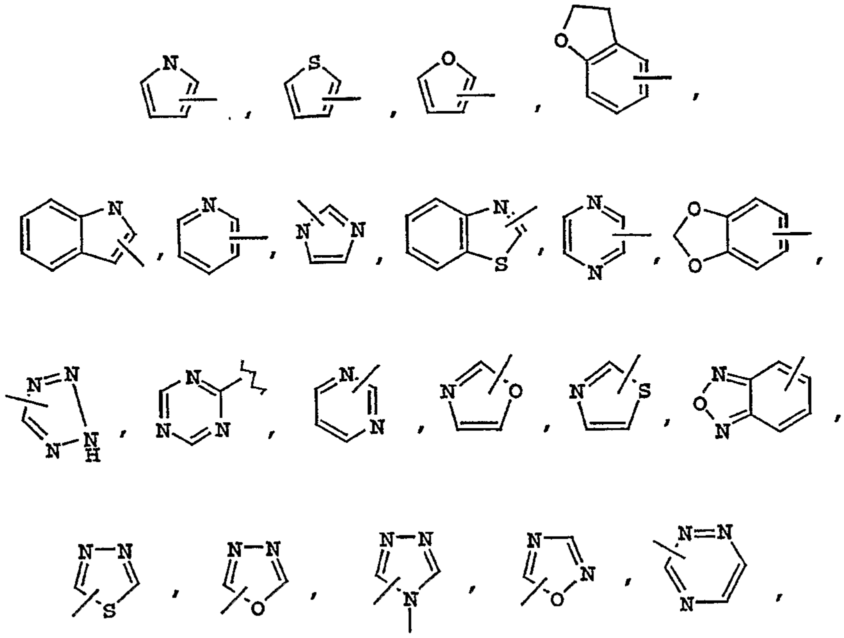
Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\overset{O}{\overset{\|}{C}}\right)$ group; examples of acyl groups include any of the alkyl substituents attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (where p is 1, 2 or 3), such as



and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the the alkyl substituents set out above. Examples of heteroaryl groups include the following:



and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

The term "five, six or seven membered carbocycle or heterocycle" as employed herein refers to cycloalkyl or cycloalkenyl groups as defined above or heteroaryl groups or cycloheteroaryl groups as defined above, such as thiadiazaole, tetrazole, imidazole, or oxazole.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

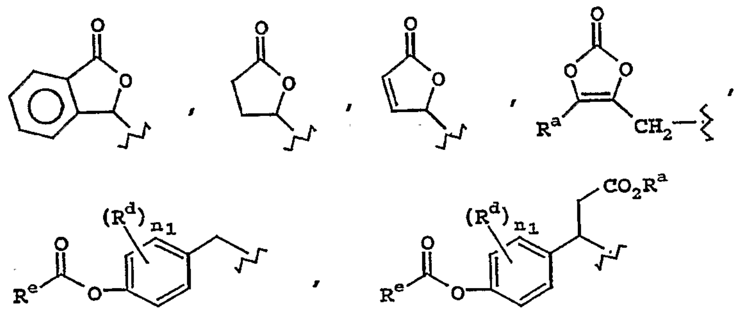
The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates and the like. In addition, prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl, ethyl, benzyl and the like.

Examples of such prodrug esters include

$CH_3CO_2CH_2—$, $CH_3CO_2CH_2(CH(CH_3)_2)—$, $t—C_4H_9CO_2CH_2—$, or

$C_2H_5OC(=O)OCH_2—$.

Other examples of suitable prodrug esters include



wherein R^a can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^d is H, alkyl, halogen or alkoxy, R^e is alkyl, aryl, arylalkyl or alkoxyl, and n_1 is 0, 1 or 2.

Where the compounds of structure I are in acid form they may form a pharmaceutically acceptable salt such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, lysine (D or L), ethylenediamine, t-butylamine, t-octylamine, tris-(hydroxymethyl)aminomethane (TRIS), N-methyl glucosamine (NMG), triethanolamine and dehydroabietylamine.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Where desired, the compounds of structure I may be used in combination with one or more other types of antidiabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The other type of antidiabetic agent which may be optionally employed in combination with the SGLT2 inhibitor of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from SGLT2 inhibition and may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, aP2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1).

It is believed that the use of the compounds of structure I in combination with 1, 2, 3 or more other antidiabetic agents produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive anti-hyperglycemic effects produced by these medicaments.

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the other antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylen) and LY-315902 (Lilly), which may be administered via injection, intranasal, or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. provisional application No. 60/155,400, filed September 22, 1999, (attorney file LA29) the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.

The other antidiabetic agent may be an aP2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. provisional application No. 60/127,745, filed April 5, 1999 (attorney file LA27*), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The other antidiabetic agent may be a DP4 inhibitor such as disclosed in WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) (preferred) as disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

The SGLT2 inhibitor of formula I will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, aP2 inhibitor or DP4 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

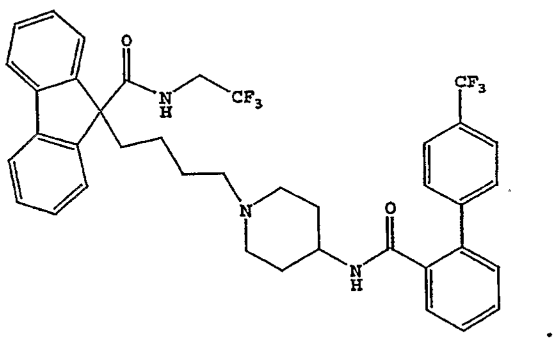
The hypolipidemic agent or lipid-lowering agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl] butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, atavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (ZD-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The other hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and ZD-4522.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The other hypolipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties, Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

The other type of therapeutic agent which may be optionally employed with the SGLT2 inhibitor of formula I may be 1, 2, 3 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug and/or an anorectic agent.

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

The serotonin (and dopoamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

The thyroid receptor beta compound which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio) and GB98/284425 (KaroBio), with compounds of the KaroBio applications being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

In carrying out the method of the invention, a pharmaceutical composition will be employed containing the compounds of structure I, with or without another antidiabetic agent and/or antihyperlipidemic agent, or other type therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations, or they can be administered intranasally or in transdermal patches. The dose for adults is preferably between 10 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

SGLT2 inhibitor activity of the compounds of the invention may be determined by use of an assay system as set out below.

Assay for SGLT2 Activity

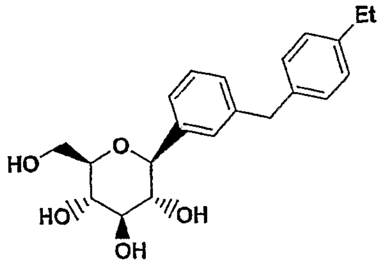
The mRNA sequence for human SGLT2 (GenBank #M95549) was cloned by reverse-transcription and amplification from human kidney mRNA, using standard molecular biology techniques. The cDNA sequence was stably transfected into CHO cells, and clones were assayed for SGLT2 activity essentially as described in Ryan et al. (1994). Evaluation of inhibition of SGLT2 activity in a clonally selected cell line was performed essentially as described in Ryan et al., with the following modifications. Cells were grown in 96-well plates for 2-4 days to 75,000 or 30,000 cells per well in F-12 nutrient mixture (Ham's F-

12), 10% fetal bovine serum, 300 ug/ml Geneticin and penicillin-streptomycin. At confluence, cells were washed twice with 10 mM Hepes/Tris, pH 7.4, 137 mM N-methyl-D-glucamine, 5.4 mM KCl, 2.8 mM $CaCl_2$, 1.2 mM $MgSO_4$. Cells then were incubated with 10 μM [^{14}C]AMG, and 10 μM inhibitor (final DMSO =0.5%) in 10 mM Hepes/Tris, pH 7.4, 137 mM NaCl, 5.4 mM KCl, 2.8 mM $CaCl_2$, 1.2 mM $MgSO_4$ at 37°C for 1.5 hr. Uptake assays were quenched with ice cold 1X PBS containing 0.5 mM phlorizin, and cells were then lysed with 0.1% NaOH. After addition of MicroScint scintillation fluid, the cells were allowed to shake for 1 hour, and then [^{14}C]AMG was quantitated on a TopCount scintillation counter. Controls were performed with and without NaCl. For determination of EC_{50} values, 10 inhibitor concentrations were used over 2 log intervals in the appropriate response range, and triplicate plates were averaged across plates.

Ryan MJ, Johnson G, Kirk J, Fuerstenberg SM, Zager RA and Torok-Storb B. **1994**. HK-2: an immortalized proximal tubule epithelial cell line from normal adult human kidney. Kidney International **45**: 48-57.

The following Working Examples represent preferred embodiments of the present invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated.

Example 1



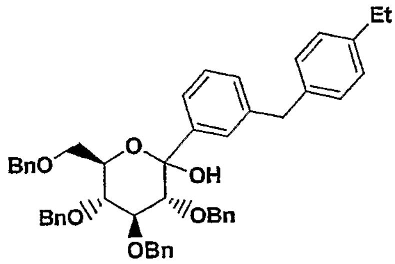
A. 3-Bromo-4′-ethylbenzylhydrol

Dry Mg turnings (4.4g, 0.178 mol) under Ar were stirred overnight whereupon 100 mL of dry Et_2O was added followed by addition over 1 hr of *p*-bromoethylbenzene (22g, 0.119 mol) in 20 mL of Et_2O. (In the event the reaction did not start, 0.5 ml of 1,2-dibromoethane was added). After stirring overnight, *m*-bromobenzaldehyde (11g, 0.06 mol) in 20 mL of Et_2O was slowly added. The resulting light solution was monitored by HPLC over 4-6 hr to determine when complete. The reaction, after quenching with saturated aq. NH_4Cl, was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated using a rotary evaporator. The resulting yellow oil was chromatographed on silica gel using 5% EtOAc/hexane to elute nonpolar impurities and 7-9% EtOAc/hexane to elute 12.4 g (71%) of 3-bromo-4′ethylbenzhydrol as a light yellow oil.

B. 3-Bromo-4′-ethyldiphenylmethane

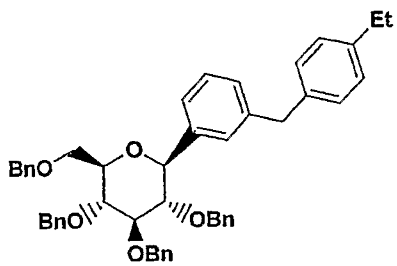
To a stirred -30° solution of Part A 3-bromo-4′-ethylbenzhydrol (12.4g, 0.0426 mol) in 120 mL of MeCN was added $BF_3 \cdot Et_2O$ (6.04g, 0.0426 mol) followed by Et_3SiH (9.9g, 0.852 mol). The dark reaction after stirring 1 hr at -30° was warmed slowly to -5°. When complete by tlc, the reaction was quenched by addition of saturated aq. K_2CO_3. After addition of 100 mL of H_2O, the mixture was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration using a rotary evaporator, 3-bromo-4′-ethyldiphenylmethane (11.17g, 95%) was obtained as a light yellow oil that was used without further purification.

C.



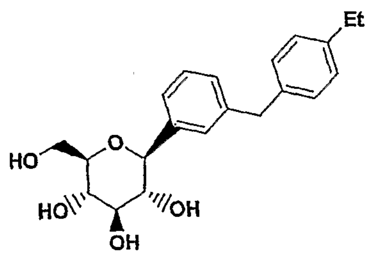
To a stirred -78° solution of Part B 3-bromo-4′-ethyldiphenylmethane (10.9g, 0.04 mol) in 100 mL of dry THF under Ar was added 25.7 mL of 1.7 M *t*-BuLi in hexane over 20 min. After 1hr 2,3,4,6-tetra-O-benzyl-β-D-glucolactone (23.5 g, 0.0437 mol) in 30 mL of THF was added over 15 min. The solution was stirred for 1 hr at -78° prior to quenching with saturated aq. NH_4Cl. After warming to 20°, the reaction was diluted 2 fold with EtOAc prior to washing with H_2O followed by brine. After drying over Na_2SO_4 and concentration using a rotary evaporator, 29.2 g of the desired title lactol was obtained as a colorless syrup that was carried forward without further purification.

D.



To a stirred -30° solution of Part C lactol (29.1g, 0.04 mol) in 100 mL of MeCN was added $BF_3 \cdot Et_2O$ (5.62g, 0.04 mol) followed by Et_3SiH (9.21g, 0.08 mol). After 2 hr, when tlc showed the reaction to be complete, saturated aq. K_2CO_3 was added and the suspension stirred 1 hr at 20° prior to diluting with H_2O and Et_2O. The combined organic layers from 3 Et_2O extractions were washed with brine, dried over Na_2SO_4, and concentrated using a rotary evaporator to yield 28.3 g of a light yellow syrup. Chromatography on silica gel with 5% EtOAc/hexane eluted nonpolar impurities followed slowly by the desired beta anomer and then the alpha anomer. Fractions enriched in the beta anomer could be further purified by either triterating with hexane or by recrystalization from EtOH to yield 6 g of the desired title beta tetra-O-benzyl C-glucoside. (Note when Et_3SiH is the reducing agent, a 5:1 beta/alpha anomer mixture is obtained whereas when *i*Pr_3SiH is substituted a 30:1 mixture is obtained.)

E.



A solution of Part D tetra-O-benzyl C-glucoside (2.4g, 3.35 mmol) in EtOAc (100 mL) containing 10% $Pd(OH)_2/C$ (0.35 g) was stirred overnight under 1 atmos. H_2. After HPLC showed the reaction to be complete, the catalyst was filtered and the solvent removed using a rotary evaporator to obtain 1.1 g of the desired beta C-glucoside (92%) as a white crystalline solid.

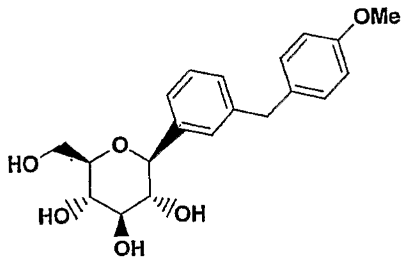
HPLC retention time: 7.04 min, 100% pure, YMC S5 C-18 4.6x50mm column, 2.5 mL/min, detection at 220nM; 8 min gradient 0-100% B hold 5 min at 100% B. Solvent A: 10% $MeOH/H_2O$ + 0.2 % H_3PO_4. Solvent B: 90% $MeOH/H_2O$ + 0.2 % H_3PO_4.

^{1}H NMR (500 MHz, CD_3OD) δ 7.27 (s, 1H), 7.23 (d, 2H, J=4.95 Hz), 7.1-7.0 (m, 5H), 4.08 (d, 1H, J=9.3Hz), 3.91 (s, 2H), 3.9 (dd, 1H, J=2.2, 11 Hz), 3.68 (dd, 1H, J=5.5, 11.5 Hz), 3.5-3.35 (m, 4H), 2.57 (q, 2H, J=7.2 Hz), 1.18 (t, 3H, J=7.2 Hz)

^{13}C NMR (125 MHz, CD_3OD) δ 143, 142.8, 141, 140, 129.9, 129.6, 129.5, 129.1, 128.8, 126.7, 83.8, 82.3, 79.9, 76.4, 72.0, 63.2, 42.5, 29.4, 16.2.

Anal Calcd for $C_{21}H_{26}O_5$ LC-MS [M+NH4] 376

<u>Example 2</u>



A. <u>3-Bromo-4'-methoxybenzhydrol</u>

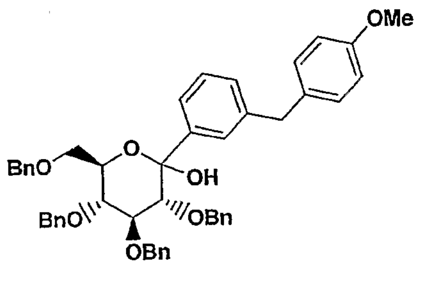
To a stirred -78° solution of *m*-dibromobenzene (70.9g, 0.3 mol) in 200 mL of dry THF under Ar was added 117 mL of 2.56 M *n*-BuLi (0.3 mol) in hexane over 10 min. After 30 min, *p*-methoxybenzaldehyde (27.2 g, 0.02 mol) in

50 mL of THF was added over 20 min. The solution was stirred for 1 hr at -78° (complete by tlc) prior to quenching with saturated aq. NH_4Cl. After warming to 20°, the reaction was diluted 2 fold with EtOAc prior to washing with H_2O followed by brine. After drying over Na_2SO_4 and concentration using a rotary evaporator, 103 g of 3-bromo-4'-methoxybenzhydrol was obtained as a yellow oil that was carried forward without further purification.

B. 3-Bromo-4'-methoxydiphenylmethane

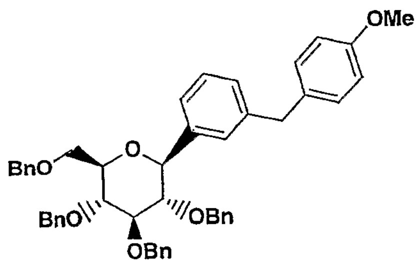
To a stirred -40° solution of crude Part A 3-bromo-4'-methoxybenzhydrol (103g, 0.2 mol) in 300 mL of MeCN was added Et_3SiH (64 mL, 0.4 mol) followed by $BF_3 \cdot Et_2O$ (27.7g, 0.2 mol). When complete by tlc, the reaction was quenched by addition of saturated aq. K_2CO_3 (25 mL). After addition of 100 mL of H_2O, the mixture was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration using a rotary evaporator, the crude title 3-bromo-4'-methoxydiphenylmethane (92g) was chromatographed on silica gel using 9% EtOAc/hexane to eluted 17 g of clean product followed by less pure fractions.

C.



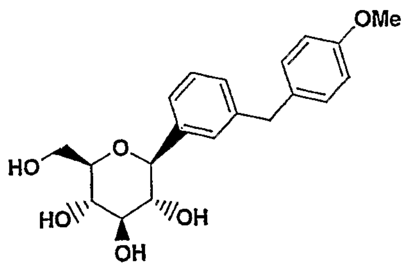
To a stirred -78° solution of Part B 3-bromo-4'-methoxydiphenylmethane (9.6g, 0.035 mol) in 50 mL of dry THF under Ar was added 14 mL of 2.5 M *n*-BuLi in hexane over 5 min. After stirring 30 min, 2,3,4,6-tetra-O-benzyl-β-D-glucolactone (12.5 g, 0.023 mol) in 20 mL of THF was added over 10 min. The solution was stirred for 1 hr at -78° whereupon tlc analysis indicated the reaction was complete. After quenching with saturated aq. NH_4Cl (25 mL) and warming to 20°, the reaction was diluted with EtOAc (200 mL). The organic layer was washed with H_2O followed by brine. After drying over Na_2SO_4 and concentration using a rotary evaporator, the desired title lactol was chromatographed on silica gel using 12.5% EtOAC/hexane to elute 8.1 g of >90% lactol followed by 9.7g of >80% purity.

D.



To a stirred -40° solution of Part C lactol (7.8g, 0.019 mol) in 100 mL of MeCN was added Et_3SiH (3.42 mL, 0.04 mol) followed by $BF_3 \cdot Et_2O$ (1.37 mL, 0.02 mol). After 1 hr, when tlc showed the reaction to be complete, saturated aq. K_2CO_3 (10mL) was added and the suspension stirred 1 hr at 20° prior to extracting 3x with EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and concentrated using a rotary evaporator to yield 8 g of crude product. Chromatography on silica gel with 5% EtOAc/hexane eluted nonpolar impurities followed by 0.92 g of pure title β-tetra-O-benzyl C-glucoside followed by a 6.5g containing both anomers.

E.



The above two fractions of Part D compound were hydrogenated separately over 10% $Pd(OH)_2$ (2% by weight) for overnight at 1 atomosphere H_2 in EtOAc (12.5 mL/g of Part D compound). After filtration and solvent removal, the hydrogenolysis product of the mixed fractions was purified by prep HPLC using a YMC S10 reverse phase column. The combined material yielded 1.85 g of pure β anomer as a white solid.

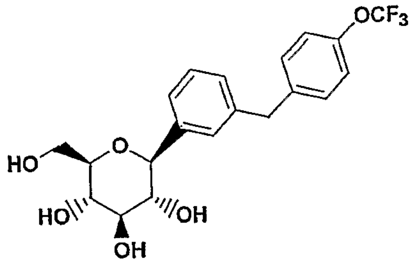
HPLC retention time: 6.04 min, Zorbax C-18 4.6x75mm column, 2.5 mL/min, detection at 220nM; 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% $MeOH/H_2O$ + 0.2 % H_3PO_4. Solvent B: 90% $MeOH/H_2O$ + 0.2 % H_3PO_4.

1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 7.24 (d , 2H, J=3Hz), 7.09 (m, 3H), 6.79 (d, 2H, J=7Hz), 4.08 (d, 1H, J= 8.8 Hz), 3.88 (s, 2H), 3.75 (d, 1H, J=12 Hz), 3.73 (s, 3H), 3.65 (dd, 1H, J=12, 3 Hz), 3.4 (m, 4H).

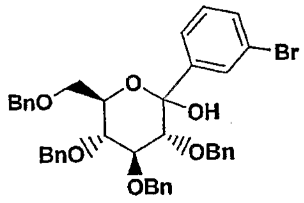
13C NMR (100MHz, CD_3OD) δ 158.6, 142.1, 140.2, 133.8, 130.0, 128.7, 128.6, 128.3, 125.8, 82.9, 81.3, 79.0, 75.5, 71.1, 62.5, 55.1, 41.1.

Anal Calcd for $C_{20}H_{24}O_6$ LC-MS (M-H) 359

Example 3

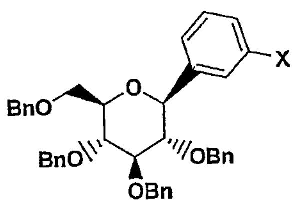


A.



To a stirred -78° solution of *m*-dibromobenzene (12.6g, 53 mmol) in 50 mL of dry THF under Ar was added 20 mL of 2.56 M *n*-BuLi (51 mmol) in hexane over 10 min. After 40 min, 2,3,4,6-tetra-O-benzyl-β-D-glucolactone (12 g, 22 mmol) in 30 mL of THF was added over 15 min. The solution was stirred for 1 hr at -78° (complete by tlc) prior to quenching with saturated aq. NH_4Cl (40 mL). After warming to 20°, the reaction was diluted 2 fold with EtOAc prior to washing with H_2O followed by brine. After drying over Na_2SO_4 and concentration using a rotary evaporator, 20 g of crude title lactol was obtained as an oil that was carried forward without further purification.

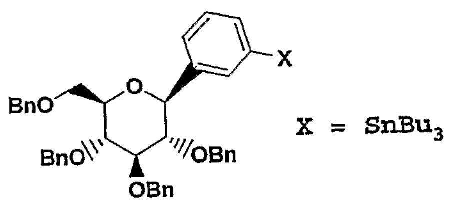
B.



X = Br

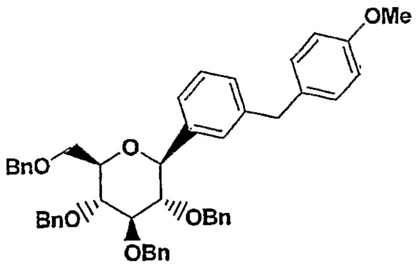
To a stirred -45° solution of crude Part A lactol (20g, 0.2 mol) in 60 mL of MeCN was added Et_3SiH (7.8 mL, 45 mmol) followed by slow addition over 20 min of $BF_3 \cdot Et_2O$ (4.2 mL, 22 mmol). When complete by tlc after an hour, the reaction was quenched by addition of saturated aq. K_2CO_3 (25 mL) and the mixture was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated using a rotary evaporator. The resulting oil was triterated with 50 mL hexane whereupon solid precipitated after standing for 1 hr. This material was collected by filtration, washed with cold hexane twice and air dried to yield 8.9 g of the desired title β-*m*-bromophenyl-C-glucoside.

C.



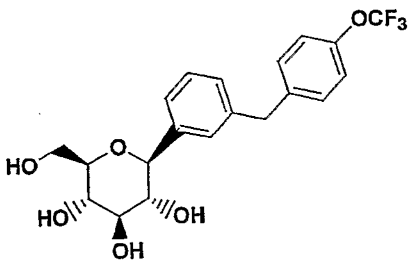
A solution of Part B β-*m*-bromophenyl C-glucoside (1.36 g, 2 mmol), $Pd(PPh_3)_4$ (70 mg, 0.06 mmol), and hexabutyldistanane (2.724 g, 6 mmol) in dry toluene (10 mL) was heated with stirring under Ar at 80° for 15 hr. After removal of toluene using a rotary evaporator, the residue was chromatographed on silica gel using 12:1 EtOAc/hexane to elute the desired title aryl stanane (761 mg), plus mixed fractions, which after a second column yielded an additional 92 mg of clean title stanane for a total yield of 48%, followed by 230 mg of recovered starting Part B β-*m*-bromophenyl-C-glucoside.

D.



A mixture of Part E stanane (2.66 g,3 mmol), *p*-trifluoromethoxybenzyl chloride (1.04 g, 6 mmol), and $Pd(PPh_3)_4$ (100 mg, 0.09 mmol) was refluxed under Ar in THF (1 ml) for 15 hr. After removal of THF with a rotary evaporator, the residue was chromatographed on silica gel using 10:1 hexane/EtOAc to elute 1.3 g of the desired title tetrabenzyl ether.

E.



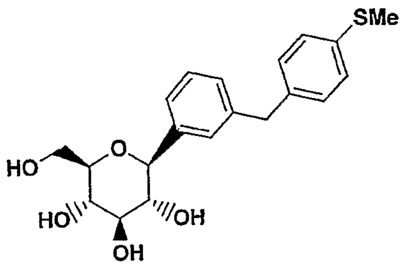
Conversion to the final free glucoside was achieved by stirring 295 mg of Part D tetrabenzyl ether with $Pd(OH)_2$ (15 mg) in EtOAc (3 mL) under 1 atmos of H_2 for 15 hr. The title product (104 mg) was isolated after filtration, Prep HPLC, and removal of solvent.

HPLC retention time: 7.21 min, Zorbax C-18 4.6x75mm column, 2.5 mL/min, detection at 220nM; 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H2O + 0.2 % H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2 % H_3PO_4.

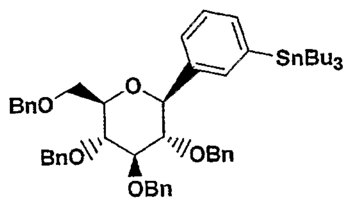
1H NMR (400 MHz, CD_3OD) δ 7.3 (m, 5H), 7.15 (m, 3H), 4.10 (d, 1H, J= 8.8 Hz), 3.99 (s, 2H), 3.9 (d, 1H, J=12 Hz), 3.7 (dd, 1H, J=12, 3 Hz), 3.4 (m, 4H).

Anal Calcd for $C_{20}H_{21}F_3O_6$ LC-MS (M-H) 413

Example 4

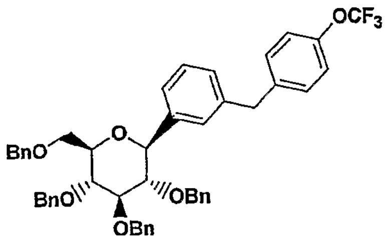


A.



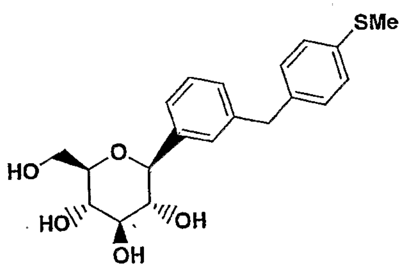
A mixture of Example 3 Part B β-*m*-bromophenyl-C-glucoside (3.0 g, 4.41 mmol) and $Pd(PPh_3)_4$ (153 mg, 0.13 mmol), and hexabutyldistanane (6.0 g, 13.2 mmol) in dry toluene (5 mL) was heated with stirring under Ar at 88° for 3 hr whereupon tlc analysis indicated the reaction was 90% complete. The reaction was terminated after a total of 5 hr. After removal of toluene using a rotary evaporator, the residue was chromatographed on silica gel using 1:8 EtOAc/hexane to elute the 2.95 g of desired aryl stanane.

B.



A mixture of Part A stanane (2.66 g, 3 mmol), p-methylthiobenzyl chloride (1.04 mg, 6.0 mmol), and tetrakis(triphenylphosphine)palladium (100 mg, 0.09 mmol) was refluxed under Ar in THF (5 mL) for 15 hr. After removal of THF with a rotary evaporator, the residue was chromatographed on silica gel using 6:1 hexane/EtOAc to elute 1.2 g of the desired title tetra-O-benzyl ether followed by 600 mg of title tetra-O-benzylether containing Ph_3P.

C.



1 M BCl_3/CH_2Cl_2 (6 mL, 8 mmol) was added over 5 minutes to a stirred -78° solution of Part B tetrabenzyl ether (295 mg, 0.4 mmol) under Ar in CH_2Cl_2 (0.25 ml). After 30 min, when tlc analysis indicated the reaction was complete, 30 mL of 2:1 CH_2Cl_2/PhMe followed by 2 mL of MeOH were added. The volume was reduced by half using a rotary evaporator and 10 mL of MeOH added. After repeating this process 3x, all the volatiles were removed under vacuum. The residue was chromatographed on silica gel using 5% $MeOH/CH_2Cl_2$ to eluted 143 mg of the desired

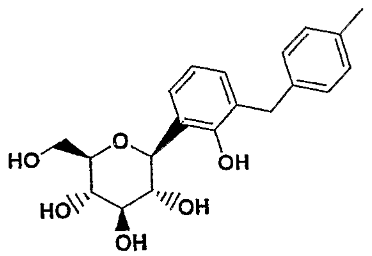
glucoside in 90% purity. This material was further purified by reverse phase preparative HPLC to yield 104 mg of the final desired glucoside.

HPLC retention time: 6.69 min, Zorbax C-18 4.6x75mm column, 2.5 mL/min, detection at 220nM; 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H_2O + 0.2 % H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2 % H_3PO_4.

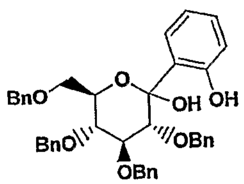
1H NMR (400 MHz, CD_3OD) δ 7.27 (s, 1H), 7.25 (d , 2H, J=2Hz), 7.15 (m, 5H), 4.09 (d, 1H, J= 8.8 Hz), 3.92 (s, 2H), 3.86 (d, 1H, J=12 Hz), 3.68 (dd, 1H, J=12, 3 Hz), 3.4 (m, 4H), 2.43 (s, 3H).

Anal Calcd for $C_{20}H_{24}O_6S$ LC-MS (M-H) 375

Example 5

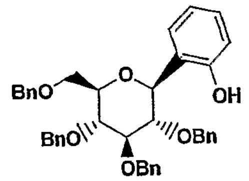


A.



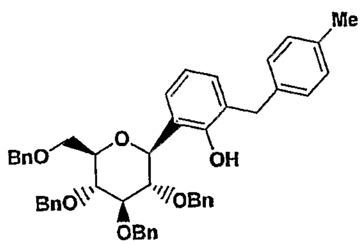
To a stirred suspension of 60% NaH (180 mg, 4.5 mmol) in THF (7 mL) under Ar was added 2-bromophenol (350 µL, 3 mmol). After stirring for 15 min, the reaction was cooled to -78° and 1.4 M *t*-BuLi/hexane (2.36 mL, 3.3 mmol) was added dropwise. After 10 min, the solution was transferred via cannula to a stirred -78° solution of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone (1.62 g, 3.0 mmol) in THF (5 mL). The reaction was quenched after 15 min by slow addition of sat. NH_4Cl/H_2O and then allowed to warm to 20° whereupon 200 mL of EtOAc was added. The organic layer was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated. Chromatography on silica gel with 3:1 hexane/EtOAc yielded 390 mg of the desired title lactol.

B.



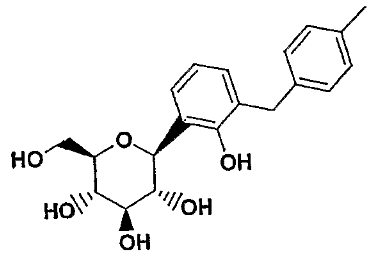
To a stirred 3:1 mixture of $MeCN/CH_2Cl_2$ (4 mL) containing Part A lactol (390 mg, 0.62 mmol) at -30° was added Et_3SiH (197 μL, 1.23 mmol) and $BF_3 \cdot Et_2O$ (78 μL, 0.62 mmol). After 1 hr the reaction was quenched by addition of 1 mL of sat. K_2CO_3, warmed to 20° and diluted with 100 mL EtOAc. The organic layer was washed successively with H_2O and brine, dried over MgSO4, and concentrated. Chromatography on silica gel with 3:1 hexane/EtOAc yielded 269 mg of desired title phenolic C-glucoside.

C.



To a PhMe solution (1.1 mL) of Part B phenol (139 mg, 0.22 mmol) under Ar was added 60% NaH (11 mg, 0.27 mmol). After 10 min, 4-methylbenzyl bromide (46 mg, 0.25 mmol) was added as a solid to the blue solution which was then heated at 80° for 3.5 hr until complete by tlc analysis. After cooling followed by addition of aqueous NH_4Cl, the reaction was diluted with EtOAc. The organic layer was washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated. Chromatography on silica gel with 5:1 hexane/EtOAc yielded 71 mg of the desired title tetra-O-benzylglucoside.

D.



Subsequent hydrogenolysis of Part C tetra-O-benzyl glucoside over Pd/C in MeOH under 1 atmos H_2 yielded the final title product which was purified by preparative HPLC using a C18 reverse phase column a 45-90% MeOH/H_2O gradient over 10 min to elute the desired β-C-glucoside (2 mg).

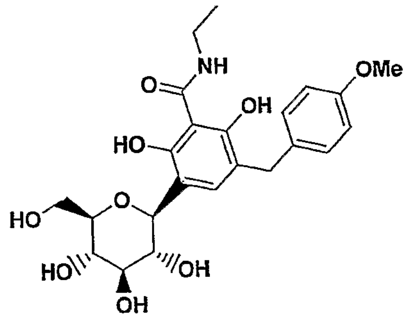
HPLC retention time: 6.754 min, 100% pure, YMC S3 ODS 4.6x50mm, 2.5 mL/min, detection at 220nM; 8 min gradient 0-100% B hold 5 min at 100% B. Solvent A: 10% MeOH/H_2O + 0.2 % H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2 % H_3PO_4.

^1H NMR (500 MHz, CD_3OD) δ 7.15 (dd, 1H, J = 1.1, 7.7 Hz), 7.07 (d, 2H, J= 8.3 Hz), 7.02 (d, 2H, J=8.3 Hz), 6.96 (dd, 1H, J=1.2, 7.7 Hz), 6.77 (t, 1H, J= 7.7 Hz), 4.44

(d, 1H, J= 8.8 Hz), 3.89 (s, 2H), 3.87 (d, 1H, J=2.2 Hz), 3.75 (dd, 1H, J=4.9, 12.1), 3.49-3.41 (m, 4H), 2.26 (s, 3H).

Anal Calcd for $C_{20}H_{24}O_6$ LC-MS [M+H] 361, [M+Na] 383.

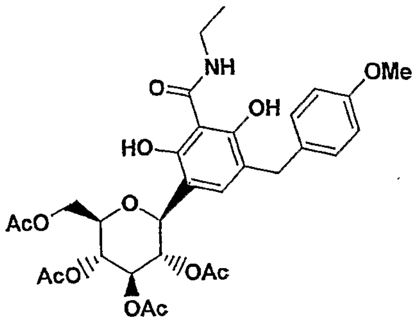
Example 6



A. N-Ethyl-N-4-methoxybenzyl-2,6-dihydroxybenzamide

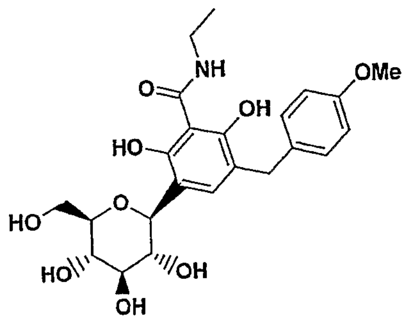
To a stirred solution of N-ethyl-4-methoxybenzyl amine (1.07 g, 6.49 mmol) in DMF (10 mL) was added 2,6-dihydroxybenzoic acid (1.0 g, 6.49 mmol) followed by HOAt (0.97 g, 7.14 mmol) and EDC (1.31 g, 6.81 mmol). After stirring overnight, the reaction was diluted with EtOAc prior to washing 3x with H_2O. The combined aqueous layers were extracted once with EtOAc. The organic fractions were combined, washed once with brine, and dried over Na_2SO_4 prior to concentrating using a rotary evaporator. The residue was chromatographed on silica gel using 75% EtOAc/hexane as the eluent. The resulting promising impure fractions were further purified by silica gel chromatography. A total of 631 mg of the desired N-ethyl-N-4-methoxybenzyl 2,6-dihydroxybenzamide was obtained.

B.



A stirred suspension of the Part A amide (630 mg, 2.09 mmol), $CdCO_3$ (939 mg, 5.44 mmol) in toluene (30 mL) was refluxed for 1.5 hr using a Dean Stark trap prior to the addition of 2,3,4,6-tetra-O-acetyl-α-D-glucosopyranosyl bromide (1.12 g, (2.72 mmol). After 15 hr of reflux, no starting amide remained by tlc analysis. The hot suspension was filtered through celite which was washed with hot PhMe and then 3x with hot $CHCl_3$. After removal of the volatiles using a rotary evaporator, the residue was chromatographed on silica gel. A mixture of O-glucosides was eluted with 1:1 EtOAc/hexane prior to the tetraacetate of the desired title C-glucoside; 172 mg of severely contaminated title C-glucoside was obtained.

C.



Impure Part B ester was stirred in 6:1 EtOH/H_2O (1.4 mL) containing KOH (140 mg, 2.5 mmol) for 16 hr. The resulting solution was cooled to 4°, acidified to pH 5, and then extracted 2x with EtOAc. The combined EtOAc layers were washed with brine, and dried over Na_2SO_4 prior to concentrating using a rotary evaporator. The residue was purified by prep HPLC with a C_{18} YMC reverse phase column using a 45-90% MeOH/H_2O gradient over 30 min to elute the desired title C-glucoside (7.8 mg).

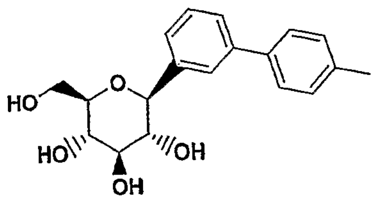
HPLC: 99.1%; Shimadzu LC-6A, YMC S3 ODS (6.0 X 150 mm); flow rate of 1.5 mL/min; detection at 220nM; gradient elution 0-100% B over 30 minutes (A = 90% H2O, 10% MeOH, 0.2% H3PO4,and B = 90% MeOH,10% H2O, 0.2% H3PO4); retention time = 23.4 minutes.

1H NMR (400 MHz, CD3OD): δ 1.22 (3H, t, J = 7.2 Hz), 3.4-3.5 (6H, m), 3.73 (3H, s), 3.74 (1H, m), 3.77 (1H, m), 3.8-3.9 (2H,m), 4.36 (1H, d, J = 9.3 Hz), 6.77 (2H, d, J = 8.6 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.18 (1H, s)

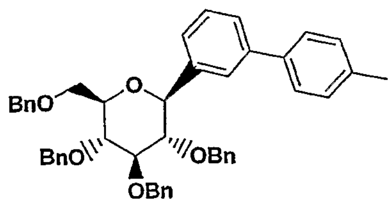
13C NMR (125 MHz, CD3OD): δ 14.9, 35.1, 35.1, 55.7, 62.5, 71.2, 75.8, 79.6, 80.3, 82.3, 104.8, 114.7, 117.1, 122.7, 130.7, 134.5, 134.6, 151, 159.3, 161, 171.9

MS (ESI +/-): (M + H)+ @ 464; (M - H)- @ 462

Example 7

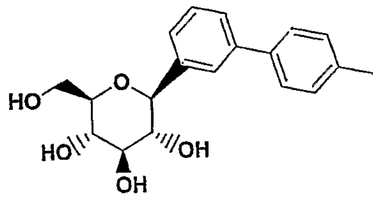


A.



A mixture of Example 3 Part B β-*m*-bromophenyl-C-glucoside (100 mg, 0.14 mmol), *p*-methylphenylboronic acid (59 mg, 0.43 mmol), Na_2CO_3 (46 mg, 0.43 mmol), and $Pd(PPh_3)_4$ (153 mg, 0.13 mmol) in 3:1 PhMe/EtOH were stirred under Ar at 80° for 15 hr. After removal of the volatiles using a rotary evaporator, the residue was chromatographed on silica gel. 10:1 hexane/EtOAc eluted the desired title biphenyl C-glucoside (90 mg) as a clear oil.

B.



To a -78° stirred CH_2Cl_2 solution (0.4 mL) of Part A tetra-O-benzyl ether (65 mg, 0.09 mmol) under Ar was added 0.37 mL of a 1M BCl_3 in CH_2Cl_2. After 1 hr, the reaction was quenched with 2 mL of MeOH and allowed to warm to 20°. After adjusting the pH to ~7 with aqueous $NaHCO_3$, the suspension was extracted 2x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting residue, after purification by preparative HPLC using a C18 reverse phase column, yielded 6.6 mg of final title product. (Note the product is partially destroyed by the strongly acidic medium generated after the MeOH quench of the BCl_3.)

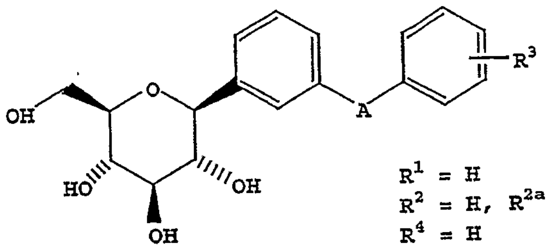
HPLC retention time: 6.353 min, 100% pure, Zorbax C-18 4.6x50mm, 2.5 mL/min, detection at 220nM; 8 min gradient 0-100% B hold 5 min at 100% B. Solvent A: 10% $MeOH/H_2O$ + 0.2 % H_3PO_4. Solvent B: 90% $MeOH/H_2O$ + 0.2 % H_3PO_4.

^1H NMR (400 MHz, CD_3OD) δ 7.65 (s, 1H), 7.53-7.50 (m, 3H), 7.39-3.37 (m, 2H), 7.23 (d, 2H, J= 7.9 Hz), 4.20 (d, 1H, J= 9.3 Hz), 3.89 (dd, 1H, J= 2.2, 11.9 Hz), 3.71 (dd, 1H, J= 5.7, 11.9 Hz), 3.50-3.40 (m, 4H), 2.36 (s, 3H)
Anal Calcd for $C_{19}H_{22}O_5$ Low Res MS [M-H] 329

Examples 8 to 53

The Examples 8 to 43 compounds set out in the following Table were prepared employing procedures of Examples 1 to 7 and reaction Schemes 1 to 8 above. The Examples 44 to 53 compounds may be prepared employing procedures of Examples 1 to 7 and reaction Schemes 1 to 8. It will be appreciated that compounds wherein A, which may linked at the ortho, meta, or para position of the aryl ring attached to the glucoside, may be any one of $(CH_2)_n$, O, NH or S, while R^1, R^2, R^{2a}, R^3 and R^4 may be any of the substituents as defined above may be prepared employing the procedures of Examples 1 to 7 and reaction Schemes 1 to 8.

Table 1



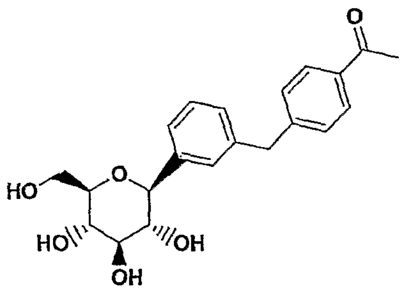
R^1 = H
R^2 = H, R^{2a} = H,
R^4 = H

Example	A	R^3	Method of Example #	LC/MS or MS $(M + H)^+$
8	CH_2	4-Me	1	345
9	CH_2	4-OH	1	347
10	CH_2	3-Me	2	345
11	CH_2	H	3	331
12	CH_2	3-OMe	3	361
13	CH_2	4-CO_2Me	3	389
14	CH_2	3,4-(OCH_2O)	3	375
15	CH_2	4-CF_3	3	399
16	CH_2	4-NHAc	3	388
17	CH_2	4-SO_2Me	3	409
18	CH_2	4-Ph	3	407
19	CH_2	4-$NHSO_2Ph$-4′-Me	3	500
20	CH_2	4-$NHSO_2Me$	3	424
21	CH_2	4-CO_2H	3	375
22	CH_2	4-Thiadiazole	3	415
23	CH_2	4-Tetrazole	3	399
24	CH_2	4-OCH_2Ph-4′-CN	1	462

25	CH_2	4-$OCHF_2$	1	397
26	CH_2	4-*i*Pr	3	373
27	CH_2	2-*i*Pr	3	373
28	CH_2	4-O*n*Pr	1	389
29	CH_2	4-Tetrazole-2'-Me	3	413
30	CH_2	4-Tetrazole-1'-Me	3	413
31	CH_2	4-OPh	1	423
32	CH_2	4-*n*Pr	1	373
33	CH_2	4-*n*Bu	1	387
34	CH_2	4-SO_2Et	1	423
35	CH_2	4-SO_2*n*Pr	1	437
36	CH_2	4-SO_2Ph	3	471
37	Bond	H	7	317
38	Bond	3-Me	7	331
39	Bond	4-MeO	7	347
40	$(CH_2)_2$	H	1	343 (M-H)
41	$(CH_2)_2$	4-Me	1	357 (M-H)
42	Bond (para link)	H	7	317
43	CH_2 (ortho link)	H	1	331
44	$(CH_2)_3$	H	1	
45	$(CH_2)_3$	4-Me	1	

46	O	H	Scheme 6	
47	O	4-Me	Scheme 6	
48	O	4-Et	Scheme 6	
49	O	4-MeS	Scheme 6	
50	NH	H	Scheme 7	
51	NH	4-Me	Scheme 7	
52	S	H	Scheme 8	
53	S	4-Me	Scheme 8	

Example 54

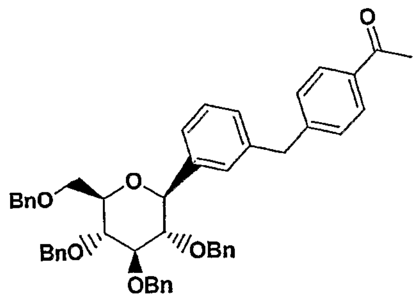


A. *p*-Chloromethylacetophenone

To a stirred solution of *p*-chloromethylbenzoyl chloride (390 mg, 2.06 mmol) in 8 mL THF at -20° under Ar was added tributylphosphine (406 mg, 2.29 mMol). After stirring the resulting yellow solution for 20 min at -20° - -15°, 0.7 mL of 3M methyl magnesium bromide in ether (2.1 mmol) was added in one portion to generate a red solution which subsequently became orange over a 10 min period. The reaction was quenched by addition of 1N aq. HCl. After dilution with H_2O, the mixture was extracted 3x with EtOAc, washed with H_2O prior to drying over Na_2SO_4. The residue obtained after removal of volatiles was chromatographed on silica gel using 5%

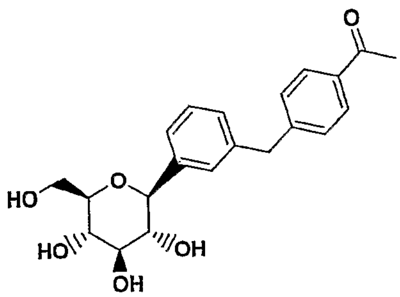
EtOAc/hexane to elute 171 mg (50%) of *p*-chloromethylacetophenone .

B.



A mixture of the stanane described in Example 3 Part C (300 mg, 0.33 mmol), *p*- chloromethylacetophenone (114 mg, 0.66 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.09 mmol), triphenylphosphine oxide (180 mg, 0.65 mmol), K_2CO_3 (75 mg, 0.55 mmol) was heated at 70° under Ar in THF (0.3 ml) for 16 hr. After removal of THF with a rotary evaporator, the residue was chromatographed on silica gel using 20:1 to 10:1 hexane/EtOAc to elute the desired tetrabenzyl ether (170 mg, 70%).

C.

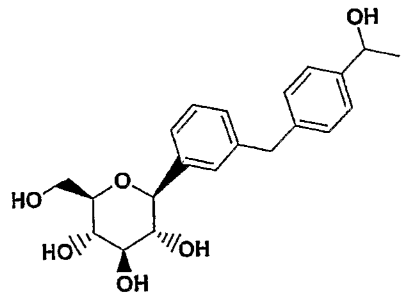


A solution of Part B tetrabenzyl ether (60 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) under Ar was cooled to −78° prior to the addition of 0.8 mL of 1 M BCl_3 in CH_2Cl_2. After stirring for 1 hr at −78°, a second 0.8 mL portion of

1 M BCl_3 was added to the stirred reaction. After a second hour, 0.5 mL of PhMe was added followed by dropwise addition of 0.5 mL of MeOH. The volatiles were removed using a rotary evaporator; the process repeated after addition of 3 mL of a 2:1 mixture of CH_2Cl_2/MeOH. Chromatography of the resulting residue on silica gel eluting with 5% MeOH/EtOAc yielded 20 mg of tetraol final product in 67% yield.

^{1}H-NMR (500 MHz, CD3-OD): δ 7.88 (d, 2H), 7.27-7.34 (m, 5H), 7.13 (d, 1H), 4.09 (d, 1H), 4.03 (s, 2H), 3.85 (d, 1H), 3.68 (dd, 1H), 3.35-3.48 (m, 4H), 2.55 (s, 3H)
^{13}C-NMR (500 MHz, CD3-OD): δ 200.3, 148.8, 141.4, 141.2, 136.3, 130.2, 129.7, 129.6, 129.3, 127.0, 83.6, 82.2, 79.8, 76.4, 71.9, 63.1, 42.7, 26.6
LRMS Calculated for C21H24O6 (M+NH4+): 390.2, Found: 390.2
LCMS YMC S5 ODS 4.6 X 50 mm Ballistic, 4 minute gradient, 4 ml/min, 1 minute hold, retention time = 2.35 min, MS found 372 (M+).

Example 55



A stirred solution of the final product of Example 1 (15 mg, 0.04 mmol) in 5 mL of EtOH was cooled to −20° whereupon $NaBH_4$ (5 mg, 0.13 mmol) was added. After 20 min being complete by tlc analysis, the reaction was quenched with a few drops of saturated aq. NH_4Cl. After removal of the volatiles, the residue was chromatographed on silica gel. Elution with 5% MeOH/EtOAc yielded 10 mg (67%) of the desired product.

^{1}H-NMR (500 MHz, CD3-OD): δ 7.21-7.32 (m, 5H), 7.16 (d, 2H), 7.10-7.11 (m, 1H), 4.77 (q, 1H), 4.08 (d, 1H), 3.94 (s, 2H), 3.86 (dd, 1H), 3.68 (dd, 1H), 3.34-3.48 (m, 4H), 1.40 (d, 3H)

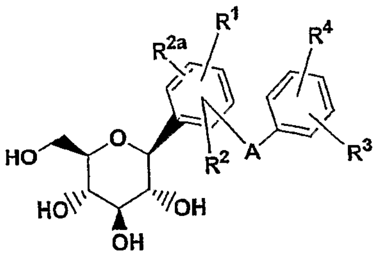
^{13}C-NMR (500 MHz, CD3-OD): δ 145.2, 142.5, 141.5, 140.9, 129.8, 129.6, 129.5, 129.2, 126.7, 126.6, 83.7, 82.2, 79.8, 76.4, 72.0, 63.2, 42.5, 25.5

LRMS Calculated for C21H26O6 (M+NH4+): 392.2, Found: 392.1

HPLC YMC S5 ODS 4.6 X 50 mm Ballistic, 8 minute gradient, 2.5 ml/min, 3 minute hold, retention time = 5.20 min.

What is Claimed:

1. A compound having the structure



wherein

R^1, R^2 and R^{2a} are independently hydrogen, OH, OR^5, lower alkyl, CF_3, OCF_3, or halogen, or two of R^1, R^2 and R^{2a} together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^3 and R^4 are independently hydrogen, OH, OR^{5a}, OAryl, OCH_2Aryl, lower alkyl, cycloalkyl, CF_3, $-OCHF_2$, $-OCF_3$, halogen, -CN, $-CO_2R^{5b}$, $-CO_2H$, COR^{6b}, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $-CONR^6R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2$Aryl, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2$Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2, or R^3 and R^4 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

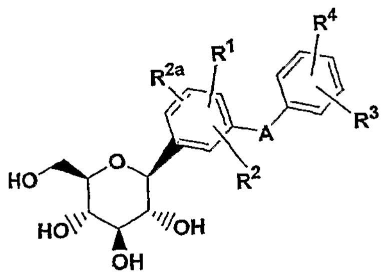
R^5, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} and R^{5h} are independently lower alkyl;

R^6, R^{6a}, R^{6b}, R^{6c}, and R^{6d} are independently hydrogen, alkyl,aryl, alkylaryl or cycloalkyl, or R^6 and R^{6a} together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

A is O, S, NH, or $(CH_2)_n$ where n is 0 - 3, or a pharmaceutically acceptable salt thereof, all stereoisomers thereof, and a prodrug ester thereof; with the proviso that where A is $(CH_2)_n$ where n is 0,1,2, or 3 or A is O, and at least one of R^1, R^2, and R^{2a} is OH or OR^5, then at least one of R^1, R^2, and R^{2a} is CF_3, OCF_3, or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3, $-OCHF_2$, $-OCF_3$, -CN, $-CO_2R^{5b}$, $CH(OR^{5h})R^{6d}$, $CH(OH)R^{6c}$, COR^{6b}, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$.

2. The compound as defined in Claim 1 with the proviso that where A is $(CH_2)_n$ where n is 0,1,2, or 3 or A is O, and at least one of R^1, R^2, R^{2a}, R^3 and R^4 is OH or OR^5, then at least one of R^1, R^2, and R^{2a} is CF_3, OCF_3, or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3, $-OCHF_2$, $-OCF_3$, -CN, $-CO_2R^{5b}$, $CH(OR^{5h})R^{6d}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$.

3. The compound as defined in Claim 1 having the structure



4. The compound as defined in Claim 1 wherein A is $(CH_2)_n$.

5. The compound as defined in Claim 3 wherein A is CH_2 or O or S.

6. The compound as defined in Claim 1 wherein A is CH_2 or O or S;

R^1, R^2 and R^{2a} are independently selected from H, alkyl or $OCHF_2$, or two of R^1, R^2 and R^{2a} are H and the other is $OCHF_2$;

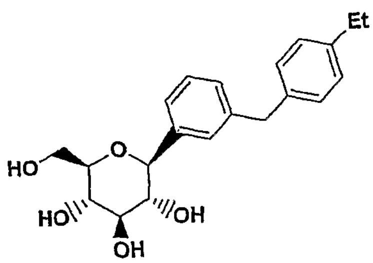
R^3 and R^4 are independently selected from alkyl, alkoxy, CHF_2O, $R^{5e}S$, OH, $R^{5a}O$, CO_2R^{5b}, -3,4-(O-CH_2-O)-, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, CF_3, $R^{5c}-C(=O)-NH-$, $R^{5f}SO_2$, Aryl, ArylSO_2NH-, $R^{5d}SO_2NH$-, CO_2H, thiadizole, tetrazole, Aryl-CH_2O-, CF_3O, Aryloxy, or H.

7. The compound as defined in Claim 6 wherein A is CH_2, R^1 is hydrogen or alkyl, R^2 and R^{2a} are each H, R^3 is H, R^4 is alkyl, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $R^{5a}O$, CHF_2O, CF_3O or $R^{5e}S$.

8. The compound as defined in Claim 3 where A is CH_2, R^1, R^2 and R^{2a} are each H, and one of R^3 and R^4 is alkyl, and the other is H.

9. The compound as defined in Claim 3 wherein A is CH_2, R^1, R^2 and R^{2a} are each H, R^3 is H, and R^4 is 4-C_2H_5.

10. The compound as defined in Claim 3 having the structure



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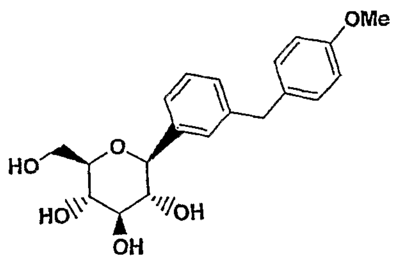

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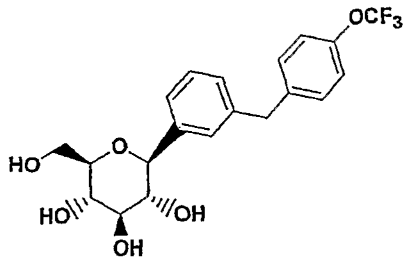

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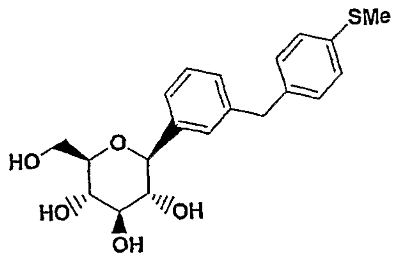

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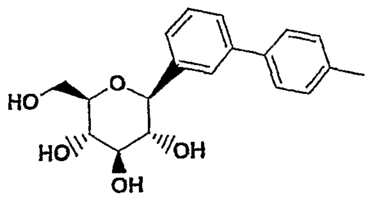

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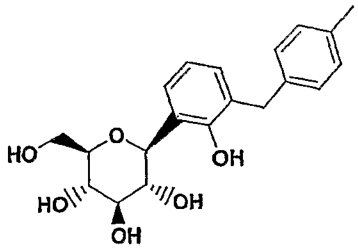

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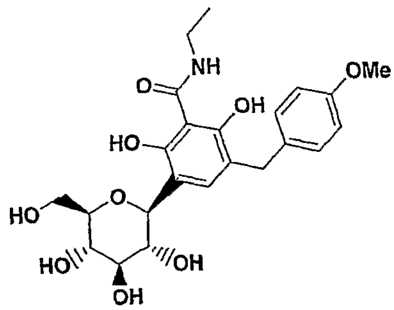

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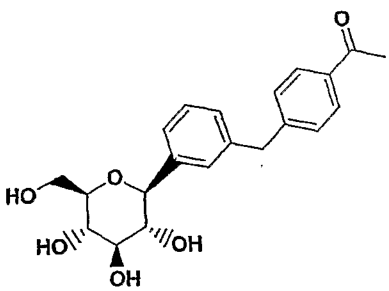

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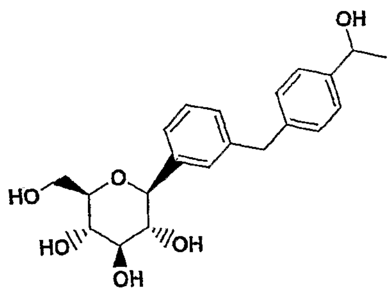

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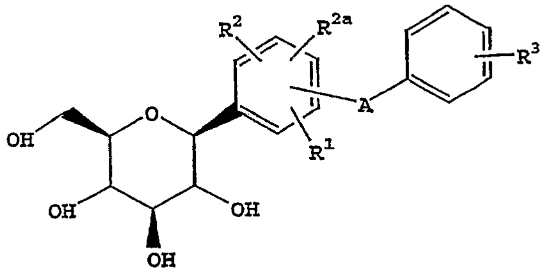
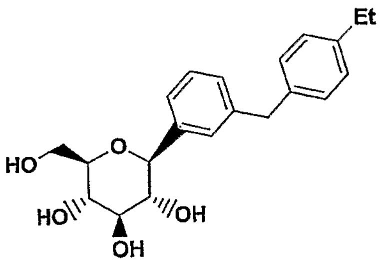
11. The compound as defined in Claim 1 having the structure set out as follows:



where A is CH_2 and meta to the glucoside, R^1, R^2 and R^{2a} are each H, unless indicated otherwise, R^3 is as follows: 4-Me, 4-OH, 3-Me, H, 3-OMe, 4-CO_2Me, 3,4-(OCH_2O), 4-CF_3, 4-NHAc, 4-SO_2Me, 4-Ph, 4-$NHSO_2$Ph-4′-Me, 4-$NHSO_2$Me, 4-CO_2H, 4-Thiadiazole, 4-Tetrazole, 4-OCH_2Ph-4′-CN, 4-OCF_3, 4-^{i}Pr, 2-^{i}Pr, 4-O^{n}Pr, 4-Tetrazole-2′-Me, 4-Tetrazole-1′-Me, 4-OPh, 4-^{n}Pr, 4-^{n}Bu, 4-SO_2Et, 4-SO_2^{n}Pr, 4-SO_2Ph, H (A is a bond), 3-Me (A is a bond), 4-MeO (A is a bond), H (A is $(CH_2)_2$), 4-Me (A is $(CH_2)_2$), H (A is *ortho* CH_2), H (A is *para* bond).

12. The compound as defined in Claim 1 having the structure



13. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

14. A pharmaceutical combination comprising an SGLT2 inhibitor compound as defined in Claim 1 and an antidiabetic agent other than an SGLT2 inhibitor, an anti-obesity agent, and/or a lipid-lowering agent.

15. The pharmaceutical combination as defined in Claim 18 comprising said SGLT2 inhibitor compound and an antidiabetic agent.

16. The combination as defined in Claim 15 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an aP2 inhibitor, a DP4 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide.

17. The combination as defined in Claim 16 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, and/or NVP-DPP-728A.

18. The combination as defined in Claim 15 wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 300:1.

19. The combination as defined in Claim 14 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta compound, and/or an anorectic agent.

20. The combination as defined in Claim 19 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677,

L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol.

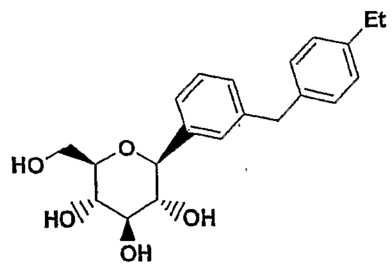
21. The combination as defined in Claim 14 wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor.

22. The combination as defined in Claim 21 wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, and/or LY295427.

23. The combination as defined in Claim 21 wherein the SGLT2 inhibitor is present in a weight ratio to the lipid-lowering agent within the range from about 0.01 to about 300:1.

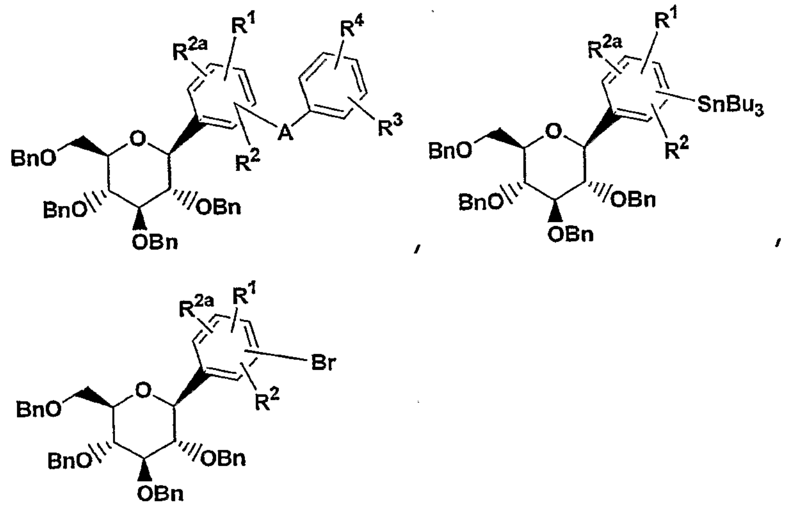
24. A method for treating diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, hypertension, or for increasing high density lipoprotein levels, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

25. The method as defined in Claim 19 where the compound as defined in Claim 1 has the structure



26. A method for treating type II diabetes which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1 alone or in combination with another antidiabetic agent and/or a hypolipidemic agent.

27. A compound having the structure



wherein

R^1, R^2 and R^{2a} are independently hydrogen, OH, OR^5, lower alkyl, CF_3, OCF_3, or halogen, or two of R^1, R^2 and R^{2a} together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^3 and R^4 are independently hydrogen, OH, OR^{5a}, OAryl, OCH_2Aryl, lower alkyl, cycloalkyl, CF_3, $-OCHF_2$,

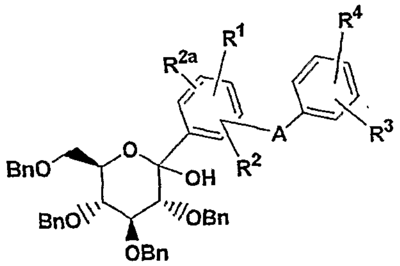
$-OCF_3$, halogen, $-CN$, $-CO_2R^{5b}$, $-CO_2H$, $-CONR^6R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2, or R^3 and R^4 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^5, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} are independently lower alkyl;

R^6 and R^{6a} are independently hydrogen, alkyl, aryl, alkylaryl, cycloalkyl, or R^6 and R^{6a} together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

A is O, S, NH, or $(CH_2)_n$ where n is 0 - 3, or a pharmaceutically acceptable salt thereof, all steroisomers thereof, and a prodrug ester thereof with the proviso that where A is $(CH_2)_n$ where n is 0,1,2, or 3 or A is O, and at least one of R^1, R^2, R^{2a}, R^3 and R^4 is OH or OR^5, then at least one of R^1, R^2, and R^{2a} is CF_3, OCF_3, or $OCHF_2$ and/or at least one of R^3 and R^4 is CF_3, $-OCHF_2$, $-OCF_3$, $-CN$, $-CO_2R^{5b}$, $CH(OR^{5h})R^{6d}$, $CH(OH)R^{6c}$, COR^{6b}, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2Aryl$, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2Aryl$;

or a compound of the structure



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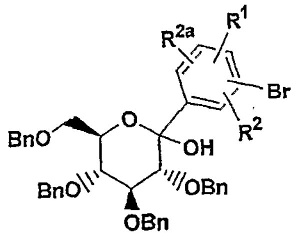

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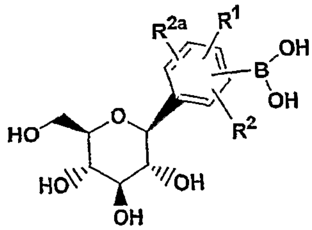

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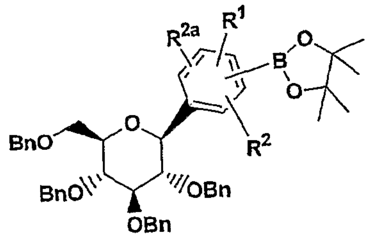


wherein

R^1, R^2 and R^{2a} are independently hydrogen, OH, OR^5, lower alkyl, CF_3, OCF_3, or halogen, or two of R^1, R^2 and R^{2a} together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^3 and R^4 are independently hydrogen, OH, OR^{5a}, OAryl, OCH_2Aryl, lower alkyl, cycloalkyl, CF_3, $-OCHF_2$, $-OCF_3$, halogen, -CN, $-CO_2R^{5b}$, $-CO_2H$, $-CONR^6R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2$Aryl, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2$Aryl, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2, or R^3 and R^4 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^5, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} are independently lower alkyl;

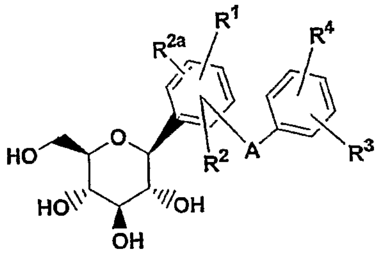
R^6 and R^{6a} are independently hydrogen, alkyl, aryl, alkylaryl, cycloalkyl, or R^6 and R^{6a} together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

A is O, S, NH, or $(CH_2)_n$ where n is 0 - 3, or a pharmaceutically acceptable salt thereof, all steroisomers thereof, and a prodrug ester thereof.

C-ARYL GLUCOSIDE SGLT2 INHIBITORS AND METHOD

Abstract of the Disclosure

SGLT2 inhibiting compounds are provided having the formula



where

R^1, R^2, and R^{2a} are independently hydrogen, OH, OR^5, lower alkyl, CF_3, OCF_3, halogen, or two of R^1, R^2 and R^{2a} together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle;

R^3 and R^4 are independently hydrogen, OH, OR^{5a}, OAryl, OCH_2Aryl, lower alkyl, cycloalkyl, CF_3, $-OCHF_2$, $-OCF_3$, halogen, -CN, $-CO_2R^{5b}$, $-CO_2H$, $-COR^{6b}$, $-CH(OH)R^{6c}$, $-CH(OR^{5h})R^{6d}$, $-CONR^6R^{6a}$, $-NHCOR^{5c}$, $-NHSO_2R^{5d}$, $-NHSO_2$Aryl, Aryl, $-SR^{5e}$, $-SOR^{5f}$, $-SO_2R^{5g}$, $-SO_2$Aryl, or a five, six or seven membered heterocycle, or R^3 and R^4 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle;

R^5, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} and R^{5h} are independently lower alkyl;

R^6, R^{6a}, R^{6b}, R^{6c} and R^{6d} are independently hydrogen, alkyl, aryl, alkylaryl or cycloalkyl, or R^6 and R^{6a} together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle;

A is O, S, NH, or $(CH_2)_n$ where n is 0 - 3.

A method is also provided for treating diabetes and related diseases employing an SGLT2 inhibiting amount of the above compound alone or in combination with another antidiabetic agent or a hypolipidemic agent.

POWER OF ATTORNEY
FOR PROVISIONAL APPLICATION

Attorney's Docket Number LA0049(PSP-2)
Bruce Ellsworth; William N. Washburn, Philip M. Sher, Gang Wu and Wei Meng, named inventor(s) of the provisional application for United States Patent for C-ARYL GLUCOSIDE SGLT2 INHIBITORS AND METHOD

[x] a copy of which is attached hereto

[ ] having Application No. ________ filed ________________, 2000

do(es) hereby appoint Burton Rodney, Reg. No. 22,076, Stephen B. Davis, Reg. No. 26,693, Suzanne E. Babajko, Reg. No. 32,880, Joan E. Switzer, Reg. No. 34,740, John M. Kilcoyne, Reg. No. 33,100, Ronald S. Hermenau, Reg. No. 34,620, and Timothy J. Babcock, Reg. No. 39,097, Post Office Box 4000, Princeton, New Jersey, 08543-4000; all of Bristol-Myers Squibb Company, my agents and/or attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith.

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