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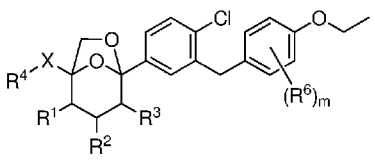
(54) Title: GLUCOPYRANOSYL DERIVATIVES AND THEIR USES IN MEDICINE



(I)

(57) Abstract: Provided herein are glucopyranosyl derivatives used as sodium dependent glucose cotransporters (SGLTs) inhibitors and pharmaceutical uses thereof, particularly 6,8-dioxabicyclo [3.2.1] octane derivatives represented by Formula (I), or pharmaceutically acceptable salts or all stereisomers thereof, pharmaceutical composition containing the derivatives and their uses for treatment of diabetic and diabetes-related diseases.

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GLUCOPYRANOSYL DERIVATIVES AND THEIR USES IN MEDICINE

PRIOR RELATED APPLICATION

[0001] This application claims priority to Chinese Patent Application Serial No. 201310441773.9, filed with the State Intellectual Property Office of China on September 25, 2013, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to glucopyranosyl derivatives as sodium dependent glucose cotransporters (SGLTs) inhibitors and pharmaceutical uses thereof, particularly pyranol derivatives represented by Formula (I), or pharmaceutically acceptable salts or all stereisomers thereof, pharmaceutical composition containing the derivatives and their uses for treating diabetes and diabetes-related diseases.

BACKGROUD OF THE INVENTION

[0003] Diabetes mellitus is a common chronic disease, characterized by hyperglycemia. The onset of diabetes associates with insulin resistance in peripheral tissue, reduction of insulin *in vivo* and increase of gluconeogenesis in liver. When the disease cannot be controlled effectively through diet and exercise, insulin or oral hypoglycemic drugs for treatment are needed. At present, hypoglycemic drugs comprise biguanides, sulfonylureas, insulin sensitizers, glinides, α-glucosidase inhibitors and DPP-IV inhibitors, *etc.* However, these current hypoglycemic drugs have shortcomings. Biguanides can cause lactic acidosis. Sulfonylureas can result in severe hypoglycemia. Insulin sensitizers can lead to edema, heart failure and weight gain. α-Glucosidase inhibitors can cause abdominal bloating and diarrhea. DPP-IV inhibitors need to combine with metformin to achieve the desired effect of hypoglycemia. Therefore, there is an urgent need to develop novel, safer, and more effective hypoglycemic agents.

[0004] It has been found by research that glucose transporter proteins are a class of carrier proteins embedded in the cell membrane for transporting glucose. Glucose must be in virtue of glucose transporter protein to cross lipid bilayer structure of cell membranes. Glucose transporter proteins are divided into two categories. The first category includes sodium-dependent glucose transporters (SGLTs), and the other category includes is glucose transporters (GLUTs). Two major family members of SGLTs are SGLT-1 and SGLT-2. SGLT-1 is mainly distributed in small intestine, kidney, heart and windpipe, predominantly expressed in the intestinal brush border and the distal S3 segment of the renal proximal tubule, and a few expressed in heart and windpipe, and transports glucose and galactose with a sodium to glucose ratio of 2:1. While SGLT-2 is mainly distributed in kidney, predominantly expressed in the distal S1 segment of the renal proximal tubule, and transports glucose with a sodium to glucose ratio of 1:1. In biological bodies, glucose is transported by SGLT through active transport against a concentration gradient with simultaneous energy consumption. While glucose

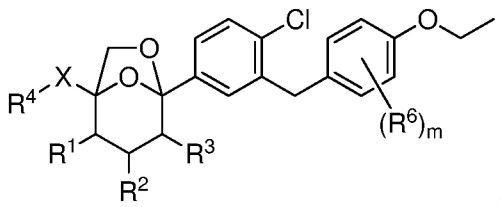
is transported by GLUTs through facilitated diffusion along a concentration gradient without energy consumption in the transport process. Research indicates that normally plasma glucose is filtered in the kidney glomeruli in which 90% of glucose in the early S1 segment of the renal tubule is actively transported to epithelial cells by SGLT-2 and 10% of glucose in the distal S3 segment of the renal tubule is actively transported to epithelial cells by SGLT-1, and then transported to peripheral capillary network by GLUT of epithelial basement membrane accomplishing reabsorption of glucose by renal tubules. Hence, SGLTs is the first stage in regulation of glucose metabolism in cells, and an ideal target for treating diabetes effectively. It has been found by research that the patients with SGLT-2 impairment would excrete large amounts of urine glucose. This provides the factual basis of treating diabetes by reducing glucose uptake through inhibiting SGLT-2 activity. Therefore, inhibiting activity of SGLTs transport protein could block reabsorption of glucose in renal tubules and increase excretion of glucose in urine to normalize the plasma glucose concentration and further control the diabetes and diabetic complications. Inhibiting SGLTs would not influence the normal anti-regulatory mechanism of glucose, which may cause the risk of hypoglycemia. Meanwhile, lowering blood glucose through an increase of renal glucose excretion could promote weight loss in obese patients. It has also been found by research that the mechanism of action of SGLT2 inhibitors is independent of pancreatic β cell dysfunction or the degree of insulin resistance. Therefore, the efficacy of SGLTs inhibitors will not decrease with the severe insulin resistance or β-cell failure. SGLTs inhibitors could be used alone or in combination with other hypoglycemic agents. Therefore, SGLTs inhibitors are ideal and novel hypoglycemic agents.

[0005] In addition, it has been also found by research that SGLTs inhibitors can be used for treating diabetes-related complications. Such as retinopathy, neuropathy, kidney disease, insulin resistance caused by glucose metabolic disorder, hyperinsulinemia, hyperlipidemia, obesity, and so on. Meanwhile, SGLTs inhibitors also be used in combination with current treatment regimens, such as sulphonamides, thiazolidinedione, metformin, and insulin, *etc*, which can reduce the dose without impacting on the effectiveness of the medicine, and thereby avoid or reduce side effects, and improve patient compliance.

[0006] In summary, SGLTs inhibitors, particularly the SGLT-2 protein inhibitors have a good prospect as novel antidiabetic drugs.

SUMMARY OF THE INVENTION

[0007] In one aspect, provided herein is a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



(I),

wherein each of R^1, R^2 and R^3 is independently hydroxy, $-OR^b$ or $-OC(=O)R^c$;

R^b is alkyl, alkoxyalkyl, silyl, silylalkoxyalkyl, alkenyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein optionally each of the alkyl, alkoxyalkyl, silyl, alkenyl, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino, mercapto and alkoxy;

R^c is alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein optionally each of the alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto;

R^4 is -H, hydroxy, alkyl, alkoxy, amino or alkylamino, wherein optionally each of the alkyl, alkoxy and alkylamino is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, -OC(=O)alkyl, hydroxy, carboxy, cyano, nitro and mercapto;

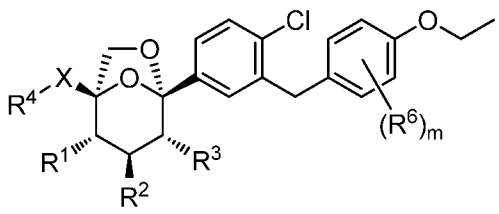
X is $-C(=O)-$, $-C(=NR^a)-$ or $-C\equiv C-$; or X is a bond when R^4 is cyano;

R^a is hydroxy, alkyl or alkoxy, wherein optionally each of the alkyl and alkoxy is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto;

m is 0, 1, 2, 3 or 4; and

each R^6 is independently -H, -F, -Cl or -Br.

[0008] In some embodiments, provided herein is a compound having Formula (II), or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



(II).

[0009] In some embodiments, provided herein is a compound having Formula (I) or (II), wherein R^4 is -H, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino or C_{1-6} alkylamino, wherein optionally each of the C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylamino is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, $-OC(=O)-C_{1-6}$ alkyl, hydroxy, carboxy, cyano, nitro and mercapto.

[0010] In some embodiments, provided herein is a compound having Formula (I) or (II), wherein R^4 is -H, hydroxy, methyl, ethyl, propyl, isopropyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, amino,

N-methylamino, *N*,*N*-dimethylamino, *N*-ethylamino, *N*,*N*-diethylamino or pivaloyloxymethoxy.

[0011] In some embodiments, provided herein is a compound having Formula (I) or (II), wherein R^a is hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy, wherein optionally each of the C_{1-6} alkyl and C_{1-6} alkoxy is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto.

[0012] In some embodiments, provided herein is a compound having Formula (I) or (II), wherein R^a is hydroxy, methoxy, ethoxy or 1-hydroxyethoxy.

[0013] In some embodiments, provided herein is a compound having Formula (I) or (II), wherein R^b is C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-18} silyl, C_{1-18} silyl-C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl or C_{1-9} heteroaryl-C_{1-6}-alkyl, wherein optionally each of the C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-18} silyl, C_{1-18} silyl-C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl and C_{1-9} heteroaryl-C_{1-6}-alkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino, mercapto and C_{1-6} alkoxy; and

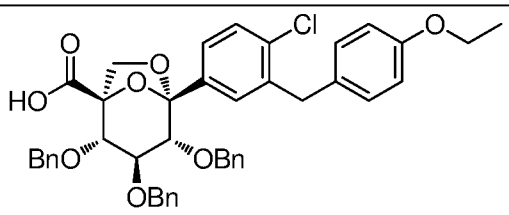
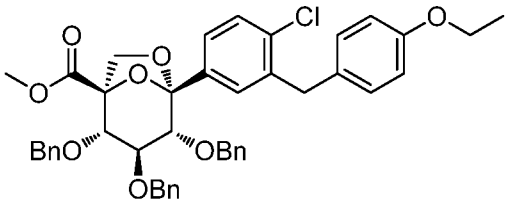
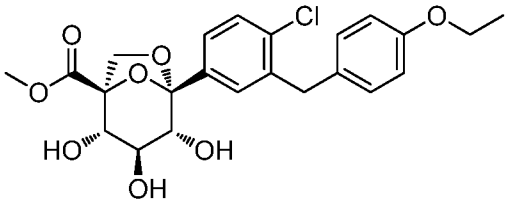
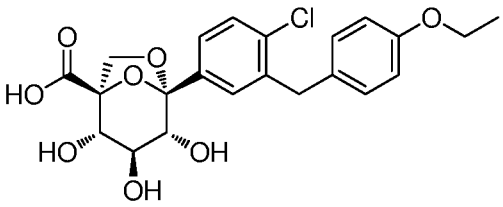
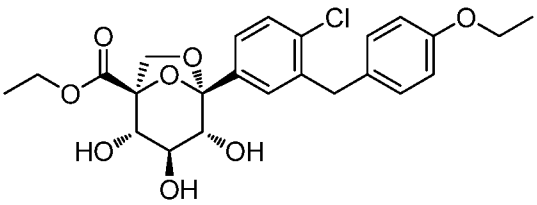
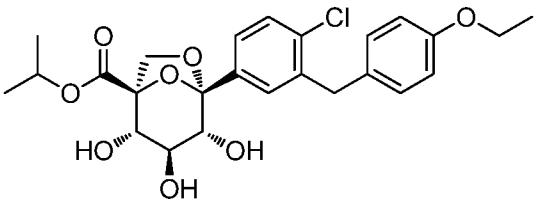
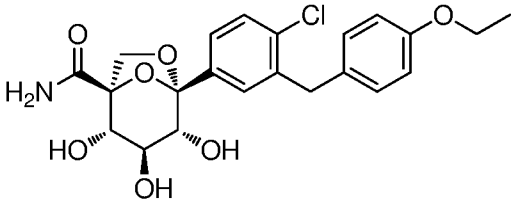
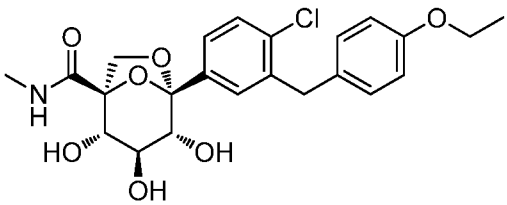
[0014] R^c is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl or C_{1-9} heteroaryl-C_{1-6}-alkyl, wherein optionally each of the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl and C_{1-9} heteroaryl-C_{1-6}-alkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto.

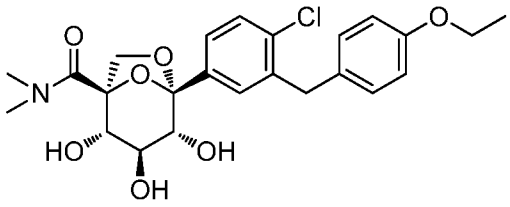
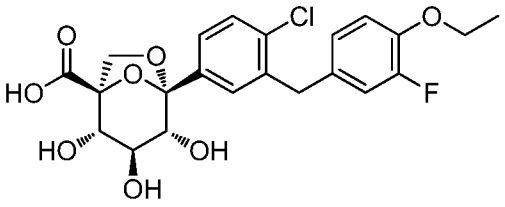
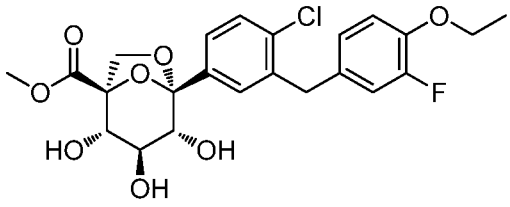
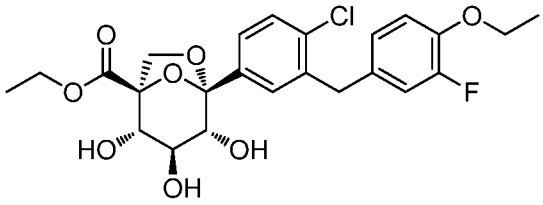
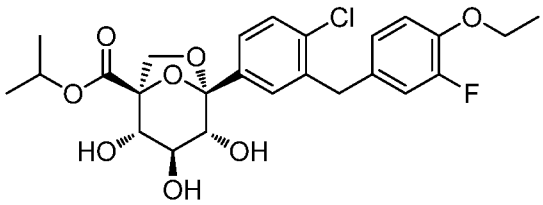
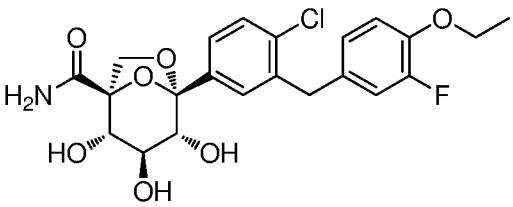
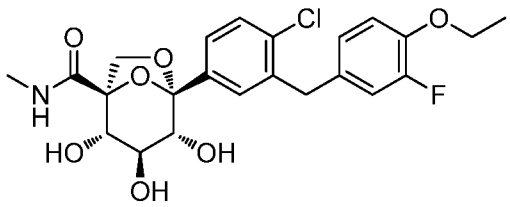
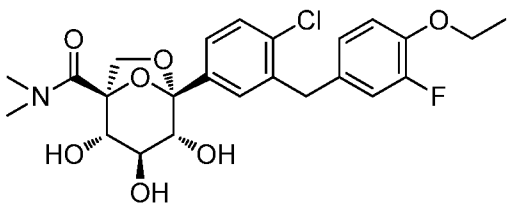
[0015] In some embodiments, provided herein is a compound having Formula (I) or (II), wherein R^b is methyl, ethyl, *tert*-butyl, methoxymethyl, allyl, trityl, benzyl, *p*-methoxybenzyl, acetyl, (*tert*-butyl)(dimethyl)silyl, trimethylsilyl, (*tert*-butyl)(diphenyl)silyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl or tetrahydropyranyl; and

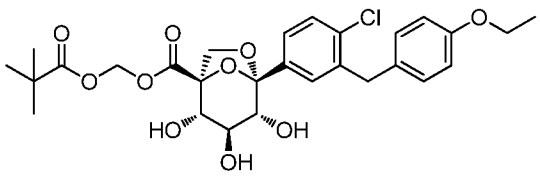
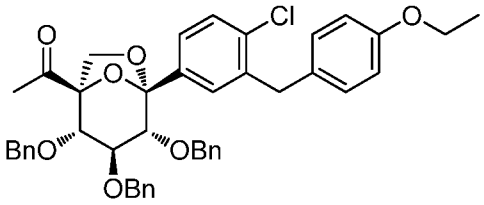
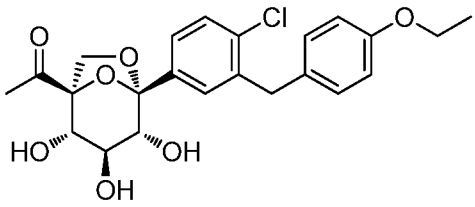
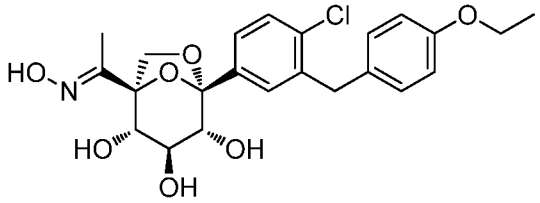
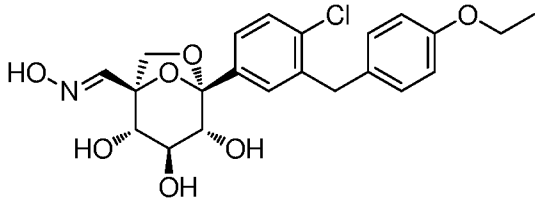
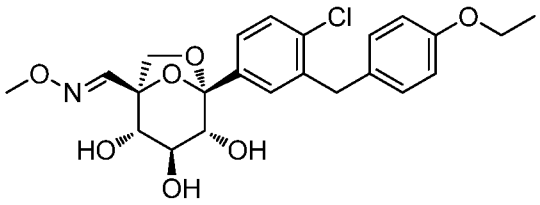
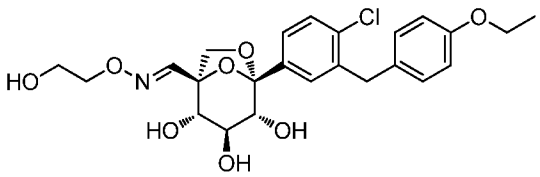
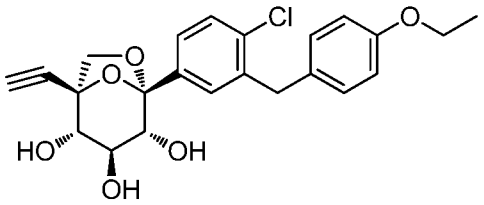
R^c is methyl, *tert*-butyl, methoxy, ethoxy, phenyl or benzyl.

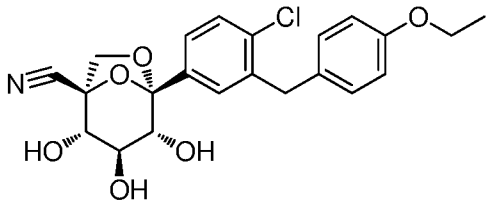
[0016] In some embodiments, provided herein is a compound having one of the following structures, or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, but not limited to these compounds:

Compound Number	Structure	Name

1.		(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tris(benzyloxy)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid
2.		methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tris(benzyloxy)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
3.		methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
4.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid
5.		ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
6.		isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
7.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide
8.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-*N*-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide

9.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-*N*,*N*-dimethyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide
10.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid
11.		methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
12.		ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
13.		isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
14.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide
15.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-*N*-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide
16.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-2,3,4-trihydroxy-*N*,*N*-dimethyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide

17.		2,2-dimethylpropanoyloxymethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate
18.		1-((1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tris(benzyloxy)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,8-dioxabicyclo[3.2.1]octan-1-yl)ethanone
19.		1-((1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octan-1-yl)ethanone
20.		(*E*)-1-((1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octan-1-yl)ethanone oxime
21.		(*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde oxime
22.		(*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde *O*-methyl oxime
23.		(*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde *O*-(2-hydroxyethyl) oxime
24.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-ethynyl-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol

25.		(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbonitrile

[0017] In other aspect, provided herein is a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0018] In some embodiments, provided herein is a pharmaceutical composition further comprising an additional therapeutic agent, wherein the additional therapeutic agent is an anti-diabetic agent other than an SGLT-2 inhibitor, an antihyperglycemic agent, an antiadipositas drug, an antihypertensive agent, an antiplatelet agent, an antiatherosclerotic drug, a lipid-lowering agent, an anti-inflammatory or a combination thereof.

[0019] In some embodiments, each of the anti-diabetic agent other than an SGLT-2 inhibitor and antihyperglycemic agent is independently a biguanide, a sulfonylurea, a glucosidase inhibitor, a PPAR agonist, an αP2 inhibitor, a PPARα/γ dual agonist, a dipeptidyl peptidase IV (DPP-IV) inhibitor, a meglitinide, insulin, a glucagon-like peptide-1(GLP-1) inhibitor, a PTP1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor or a combination thereof.

[0020] In some embodiments, the lipid-lowering agent is an MTP inhibitor, an HMGCoA reductase inhibitor, a squalene synthase inhibitor, a fibric acid derivative, an ACAT inhibitor, a lipoxygenase inhibitor, a cholesterol absorption inhibitor, an ileal Na(+)/bile acid cotransporter inhibitor, an upregulator of LDL receptor activity, niacin or a derivative thereof, a bile acid sequestrant or a combination thereof.

[0021] In some embodiments, the lipid-lowering agent is pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin, rosuvastatin or a combination thereof.

[0022] In other aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting the activity of SGLT-2 or increasing HDL level.

[0023] In other aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, wherein the disease is diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, a diabetic complication, atherosclerosis or hypertension.

[0024] In other aspect, provided herein is a method for inhibiting the activity of SGLT-2 or increasing HDL level, comprising administering to the patient in need thereof a therapeutically effective amount of the compound or the pharmaceutical composition disclosed herein.

[0025] In other aspect, provided herein is a method for preventing or treating a disease, lessening a disease

symptoms, delaying the progression or onset of a disease, comprising administering to the patient in need thereof a therapeutically effective amount of the compound or the pharmaceutical composition disclosed herein, wherein the disease is diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, a diabetic complication, atherosclerosis or hypertension.

[0026] In other aspect, provided herein is a compound or the pharmaceutical composition disclosed herein for use in inhibiting the activity of SGLT-2 or increasing HDL level.

[0027] In other aspect, provided herein is a compound or the pharmaceutical composition disclosed herein for use in preventing or treating a disease, lessening a disease symptom, delaying the progression or onset of a disease, wherein the disease is diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, a diabetic complication, atherosclerosis or hypertension.

[0028] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The present invention provides glucopyranosyl derivatives, preparation processes and pharmaceutical uses thereof. Skilled in the art can learn from this article to properly improve the process parameters. Of particular note is that all similar substitutions and modifications to the skilled person is obvious, and they are deemed to be included in the present invention.

[0030] The term "halogen" refers to fluoro (F), chloro (Cl), bromo (Br) or iodo (I).

[0031] The term "alkyl" or "alkyl group" refers to a saturated linear or branched-chain monovalent hydrocarbon radical of 1 to 20 carbon atoms. Unless otherwise specified, the alkyl group contains 1-20 carbon atoms. In some embodiments, the alkyl group contains 1-10 carbon atoms. In other embodiments, the alkyl group contains 1-8 carbon atoms. In other embodiments, the alkyl group contains 1-6 carbon atoms. In still other embodiments, the alkyl group contains 1-4 carbon atoms. Some non-limiting examples of the alkyl group include methyl, ethyl, propyl, isopropyl, *n*-butyl, *i*-butyl, *t*-butyl, *n*-pentyl, 1-methyl-butyl, 2-methyl-butyl, 3-methyl-l-butyl, neopentyl, 3,3-dimethyl-propyl, *n*-hexyl and 2-methyl-pentyl. The alkyl group containing 1 to 6 carbon atoms described herein is a lower alkyl group. The alkyl group is optionally substituted by one or more substituents independently selected from -F, -Cl, -Br, -I, hydroxy, cyano, amino, carboxy and carboxylic ester.

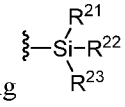
[0032] The term "haloalkyl" refers to an alkyl group substituted with one or more halogen atoms. Some non-limiting examples of the haloalkyl group include fluoromethyl, difluoromethyl, trifluoromethyl, perfluoroethyl, 1,1-dichloroethyl and 1,2-dichloropropyl.

[0033] The term "alkoxy" refers to an alkyl-O- group. Some non-limiting examples of the alkoxy group include methoxy, ethoxy, propoxy, isopropoxy, *tert*-butoxy and neopentyloxy.

[0034] The term "haloalkoxy" refers to an alkoxy group substituted with one or more halogen atoms, wherein the alkoxy group is as defined herein. Some non-limiting examples of the haloalkoxy group include difluoromethoxy, trifluoromethoxy, difluoroethoxy, trifluoroethoxy and perfluoroethoxy.

[0035] The term "alkylamino" refers to an amino group substituted with one or two alkyl groups. Some non-limiting examples of the alkylamino group include methylamino, ethylamino, propylamino, isopropylamino, *n*-butylamino, *n*-pentylamino, *N*,*N*-dimethylamino, *N*,*N*-diethylamino, *N*-ethyl-*N*-methylamino and *N*-methyl-*n*-propylamino.

[0036] The term "alkoxyalkyl" refers to an alkyl group substituted with one or more alkoxy groups. Some non-limiting examples of the alkoxyalkyl group include methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl.

[0037] The term "silyl" refers to a group having  , wherein each of R^{21}, R^{22} and R^{23} is independently alkyl, haloalkyl or aryl. Some non-limiting examples of the silyl group include (*tert*-butyl)(dimethyl)silyl, trimethylsilyl, (*tert*-butyl)(diphenyl)silyl, triethylsilyl and triisopropylsilyl.

[0038] The term "silylalkoxyalkyl" refers to an alkoxyalkyl group substituted with one or more silyl groups, wherein the alkoxyalkyl group and the silyl group are as defined herein. Some non-limiting examples of the silylalkoxyalkyl group include 2-(trimethylsilyl)ethoxymethyl.

[0039] The term "alkenyl" refers to a linear or branched chain monovalent hydrocarbon radical of two to twelve carbon atoms, or two to eight carbon atoms, or two to six carbon atoms, or two to four carbon atoms, with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp^2 double bond, wherein the alkenyl radical is optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "*E*" and "*Z*" orientations. Some non-limiting examples of the alkenyl group include vinyl ($-CH=CH_2$) and allyl ($-CH_2CH=CH_2$).

[0040] The term "alkynyl" refers to a linear or branched chain monovalent hydrocarbon radical of two to twelve carbon atoms, or two to eight carbon atoms, or two to six carbon atoms, or two to four carbon atoms, with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp triple bond, wherein the alkynyl radical is optionally substituted independently with one or more substituents described herein. Some non-limiting examples of the alkynyl group include ethynyl ($-C\equiv CH$), prop-1-yn-1-yl (propargyl, $-CH_2C\equiv CH$), prop-2-yn-1-yl ($-CH_2C\equiv CH$), but-1-yn-1-yl, but-2-yn-1-yl, pent-1-yn-1-yl, pent-2-yn-1-yl, 3-methylbut-1-yn-1-yl, hex-1-yn-1-yl, hept-1-yn-1-yl and oct-1-yn-1-yl.

[0041] The term "cycloalkyl" refers to a saturated or partially saturated monocyclic or polycyclic (fused,

bridged and/or spiro ring), non-aromatic carbon ring containing 3 to n carbon atoms. In some embodiments, n is an integer from 3 to 30. In other embodiments, n is an integer from 3 to 15. In other embodiments, n is an integer from 3 to 10. Some non-limiting examples of the cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinanyl, adamantly, bicycle[3.2.1]octyl and spiro[4.5]decyl. The cycloalkyl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, carboxy, cyano, nitro, amino, acyl, alkenyl, alkynyl, carbonyl, mercapto, lower alkyl, cycloalkyl, lower alkylthio, lower alkoxy, lower hydroxyalkyl, lower alkylamino, lower alkylcarbonyl, lower alkyl-thio-lower alkyl, lower alkyl-sulfinyl, lower alkoxycarbonyl and lower alkylaminocarbonyl. In other embodiments, the cycloalkyl group relates to unsubstituted saturated monocyclic ring.

[0042] The term "heterocyclyl" refers to a saturated or partially unsaturated monocyclic or polycyclic (fused, bridged and/or spiro ring), non-aromatic carbon ring containing 3 to n carbon atoms having one or more heteroatoms independently selected from oxygen, sulfur, selenium, nitrogen, phosphorus or silicon. In some embodiments, n is an integer from 3 to 20. In other embodiments, n is an integer from 3 to 15. In other embodiments, n is an integer from 3 to 10. In other embodiments, n is an integer from 3 to 6. Some non-limiting examples of the heterocyclyl group include oxetanyl, tetrahydrofuranyl, pyranyl, pyrrolidinyl, imidazolidinyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, imidazolinyl, oxazolidinyl, pyrazolidinyl, pyrrolinyl, oxo-2(1H)-pyridyl and oxazolidin-2-one-5-yl. The heterocyclyl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, carboxy, cyano, nitro, amino, acyl, alkenyl, alkynyl, carbonyl, mercapto, lower alkyl, heteroalkyl, lower alkylthio, lower alkoxy, lower hydroxyalkyl, lower alkylamino, lower alkylcarbonyl, lower alkyl-thio-lower alkyl, lower alkyl-sulfinyl, lower alkoxycarbonyl and lower alkylaminocarbonyl. In other embodiments, the heterocyclyl group relates to unsubstituted saturated monocycle.

[0043] The term "aryl" refers to a cyclic hydrocarbon system of a monocyclic ring or multicyclic ring fused (each ring in the system shares an adjacent pair of atoms with another ring in the system) and/or connected (each ring in the system connected with another ring in the system by a single bond or a double bond) together, and also refers to a monocyclic aromatic hydrocarbon or multicyclic system having monocyclic aromatic ring or multicyclic hydrocarbon ring fused to one or more cycloalkyl and/or heterocyclyl. In some embodiments, the aryl group is a monocyclic aryl ring, 8 to 16 carbon atoms multicyclic ring, benzocycloalkyl, or benzoheterocyclicalkyl. Some non-limiting examples of the aryl group include phenyl, 1-naphthyl, 2-naphthyl, anthryl, *p*-aminophenyl, 2-aminophenyl, *p*-carboxyphenyl, 2-carboxyphenyl, *p*-trifluoromethylphenyl, *o*-nitrophenyl, *m*-nitrophenyl, *p*-nitrophenyl, *o*-cyanophenyl, *m*-cyanophenyl, *p*-cyanophenyl, 2,6-dinitrophenyl, benzodioxanyl, benzodioxolyl, chromanyl and benzodihydroindolyl. The aryl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, carboxy, cyano, nitro, amino, acyl, alkenyl, alkynyl, carbonyl, mercapto, lower alkyl, cycloalkyl, heterocyclicalkyl, lower alkylthio, lower alkoxy,

lower hydroxyalkyl, lower alkylamino, lower alkylcarbonyl, lower alkyl-thio-lower alkyl, lower alkyl-sulfinyl, lower alkoxycarbonyl, lower alkylaminocarbonyl, aryl, aryl-lower alkylcarbonyl, aryl-lower alkylthio, aryl-lower alkyl-sulfinyl, aryl-lower alkyl-sulfinyl-lower alky, aryl-lower alkoxycarbonyl, arylalkylaminocarbonyl and arylalkylaminocarbonyl lower alkyl. In other embodiments, the substituent is oprionally independently selected from one, or two of halogen, cyano, hydroxy, carboxy, amino, lower alkyl, cycloalkyl, heterocyclicalkyl and aryl.

[0044] The term "aralkyl" or "arylalkyl" refers to an alkyl group substituted by one or more aryl groups. In some embodiments, the aralkyl group refers to "lower aralkyl" group having one or more aryl groups attached to an alkyl group having one to six carbon atoms. In other embodiments, the aryl groups attached to an alkyl group having one to three carbon atoms. Some non-limiting examples of such group include benzyl, diphenylmethyl, phenylethyl, p-tolylmethyl and phenylpropyl. The aralkyl group can be further substituted by halo, alkyl, alkoxy, haloalkyl or haloalkoxy.

[0045] The term "heteroaryl" refers to an aryl group having one or more heteroatoms. The heteroatom is oxygen, sulfur, selenium, nitrogen, phosphorus or silicon. Some non-limiting examples of the heteroaryl group include furanyl, thiophenyl, pyrrolyl, pyridinyl, quinolinyl, thiazolyl, *N*-alkylpyrrolyl, pyrimidinyl, pyrazinyl, indolyl, imidazolyl, tetrazolyl, 2-formylfuranyl, 3-formylpyridinyl, 4-methylimidazolyl, 5-methylthiazolyl, 2,5-dimethylfuranyl, 3-acetoxyindolyl, benzopyranyl, and benzofuranyl. The heteroaryl group is optionally substituted by one or more substituents independently selected from halogen, hydroxy, carboxy, cyano, nitro, amino, acyl, alkenyl, alkynyl, carbonyl, mercapto, lower alkyl, cycloalkyl, heterocyclicalkyl, lower alkylthio, lower alkoxy, lower hydroxyalkyl, lower alkylamino, lower alkylcarbonyl, lower alkyl-thio-lower alkyl, lower alkyl-sulfinyl, lower alkoxycarbonyl, lower alkylaminocarbonyl, aryl, aryl-lower alkylcarbonyl, aryl-lower alkylthio, aryl-lower alkyl-sulfinyl, aryl-lower alkyl-sulfinyl-lower alky, aryl-lower alkoxycarbonyl, arylalkylaminocarbonyl, arylalkylaminocarbonyl lower alkyl, heteroaryl, heteroaryl-lower alkylcarbonyl, heteroaryl-lower alkylthio, heteroaryl-lower alkyl-sulfinyl, heteroaryl-lower alkyl-sulfinyl-lower alky, heteroaryl-lower alkoxycarbonyl, heteroarylalkylaminocarbonyl and heteroarylalkylaminocarbonyl lower alkyl. In other embodiments, the heteroaryl group is substituted by one, two or three substituents independently selected from halogen, cyano, hydroxy, carboxy, amino, lower alkyl, cycloalkyl, heterocyclicalkyl, aryl and heteroaryl.

[0046] The term "heteroarylalkyl" refers to an alkyl group substituted with one or more heteroaryl radicals, wherein the heteroaryl radical and the alkyl group are as defined herein. Some non-limiting examples of the heteroarylalkyl group include pyridin-2-ylmethyl, thiazol-2-ylethyl, midazol-2-ylethyl, pyrimidin-2-ylpropyl and pyrimidin-2-ylmethyl.

[0047] The term "nitro" refers to $-NO_2$.

[0048] The term "mercapto" refers to -SH.

[0049] The term "hydroxy" refers to -OH.

[0050] The term "amino" refers to $-NH_2$.

[0051] The term "cyano" refers to -CN.

[0052] The term "carboxy" refers to -C(=O)OH.

[0053] The term “pharmaceutical composition” refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts or prodrugs thereof, and other chemical components such as physiologically/pharmaceutically acceptable carriers excipients, diulentsdiluents, adjuvants, vihicles, and other additional therapeutic agents, such as anti-diabetic agents, antihyperglycemic agents, antiadipositas agents, antihypertensive agents, antiplatelet agents, antiatherosclerotic agents, lipid-lowering agents, anti-inflammatory agents, *etc*. The purpose of the pharmaceutical composition is to facilitate administration of a compound to an organism.

[0054] The term “optional” or “optionally” refers to that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance may or may not occur. For example, “heterocyclic group optionally substituted by an alkyl group” means that the alkyl may or may not be present, and the description includes situations where the heterocyclic group is substituted by the alkyl group and situations where the heterocyclic group is not substituted by the alkyl group.

[0055] The term “syndrome X”, also known as conditions, diseases of metabolic syndrome, the disorders are detailed in *Johannsson, J. Clin. Endocrinol. Metab.*, **1997**; *82*, 727-734, which is incorporated herein by reference.

[0056] The term "prodrug" refers to a compound that is transformed *in vivo* into a compound of Formula (I). Such a transformation can be affected, for example, by hydrolysis of the prodrug form in blood or enzymatic transformation to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C_{1-24}) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound disclosed herein that contains a hydroxy group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates such as those phosphate compounds derived from the phosphonation of a hydroxy group on the parent compound. A thorough discussion of prodrugs is provided in Higuchi *et al.*, *Pro-drugs as Novel Delivery Systems*, Vol. 14, A.C.S. Symposium Series; Roche, *et al.* ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, **1987**; Rautio *et al.*, Prodrugs: Design and Clinical Applications, *Nature Reviews Drug Discovery*, **2008**, *7*, 255-270, and Hecker *et al*, Prodrugs of Phosphates and Phosphonates, *J. Med. Chem.*, **2008**, *51*, 2328-2345, all of which are incorporated herein by reference in their entireties.

[0057] The term "metabolite" refers to a product produced through metabolism in the body of a specified

compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzyme cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds disclosed herein, including metabolites produced by contacting a compound disclosed herein with a mammal for a sufficient time period.

[0058] Stereochemical definitions and conventions used herein generally follow Parker *et al.*, *McGraw-Hill Dictionary of Chemical Terms* (**1984**) McGraw-Hill Book Company, New York and Eliel *et al.*, "*Stereochemistry of Organic Compounds*", John Wiley & Sons, Inc., New York, **1994**. The compounds disclosed herein may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds disclosed herein, including, but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical and chemical differences by methods well known to those skilled in the art, such as by chromatography, crystallization, distillation, or sublimation. Enantionmers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reacting with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (*e.g.*, hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. The intermediates and compounds of the invention may exist in tautomeric forms and all such tautomeric forms are within the scope of the invention. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The term "racemic mixture" or "racemate" refers to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0059] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. Some non-limiting examples of proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric,

diastereomeric, and geometric (or conformational)) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, or geometric (or conformational) mixtures of the present compounds are within the scope disclosed herein.

[0060] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms.

[0061] The term "pharmaceutically acceptable salts" refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, the pharmaceutically acceptable salts are described in detail in Berge *et al.*, *J. Pharmacol Sci*, **1977**, *66*: 1-19, which is incorporated herein by reference in its entirety. Some non-limiting examples of the pharmaceutically acceptable salt formed by non-toxic acid include salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid and malonic acid or salts obtained by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, laurylsulfate, malate, sodium malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oilsoluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

[0062] The term "solvate" refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Some non-limiting examples of solvents that form solvates include water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

THE PHARMACEUTICAL COMPOSITIONS OF THE COMPOUNDS IN THE INVENTION

[0063] The invention features pharmaceutical compositions that include a compound of Formula (I) or

Formula 1 to 25, a compound listed herein, or a compound named in Examples 1 to 25, or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof. The amount of the compound in the compositions disclosed herein is an effective and detectable amount for inhibiting sodium-dependent glucose transporters (SGLTs) activity in biological samples or patients.

[0064] It will also be appreciated that certain of the compounds disclosed herein can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. Some non-limiting examples of the pharmaceutically acceptable derivative include pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adducts or derivatives which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0065] As described above, the pharmaceutically acceptable compositions disclosed herein further comprise a pharmaceutically acceptable carrier, a diluent, an adjuvant, or a vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Troy *et al.*, *Remington: The Science and Practice of Pharmacy*, *21st ed.*, **2005**, Lippincott Williams & Wilkins, Philadelphia, and Swarbrick *et al.*, *Encyclopedia of Pharmaceutical Technology*, eds. **1988-1999**, Marcel Dekker, New York, both of which are herein incorporated by referencein their entireties, discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium incompatible with the compounds disclosed herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other components of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

[0066] Some non-limiting examples of materials which can serve as pharmaceutically acceptable carriers include ion exchangers; aluminium; aluminum stearate; lecithin; serum proteins such as human serum albumin; buffer substances such as phosphates; glycine; sorbic acid; potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids; water; salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride and zinc salts; colloidal silica; magnesium trisilicate; polyvinyl pyrrolidone; polyacrylates; waxes; polyethylene-polyoxypropylene-block polymers; wool fat; sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol and polyethylene

glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants.

[0067] Compounds disclosed herein can be administered as the sole pharmaceutical agent or in combination with one or more other additional therapeutic (pharmaceutical) agents where the combination causes no unacceptable adverse effects. This may be of particular relevance for the treatment of diabetes, diabetic complications and other related diseases. Some non-limiting examples of these diseases include diabetes mellitus type I, diabetes type II, diabeticretinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, diabetic complications, atherosclerosis and hypertension. As used herein, the additional therapeutic agents include an anti-diabetic agent other than an SGLT-2 inhibitor, an antihyperglycemic agent, an antiadipositas drug, an antihypertensive agent, an antiplatelet agent, an antiatherosclerotic drug, a lipid-lowering agent, an anti-inflammatory or a combination thereof.

[0068] Wherein, the anti-diabetic agents other than an SGLT-2 inhibitor include, but are not limited to a biguanide (*e.g.*, phenformin and metformin), a sulfonylurea (*e.g.*, acetohexamide, diabinese, glibenclamide, glipizide, gliclazide, glimepiride, glipentide, gliquidone, tolazamide and tolbutamide), a meglitinide, a glinide (*e.g.*, repaglinide and nateglinide), a glucosidase inhibitor (*e.g.*, acarbose, adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q and salbostatin), a PPAR agonist (*e.g.*, balaglitazone, ciglitazone, darglitazone, rosiglitazone, isaglitazone, pioglitazone, rosiglitazone and troglitazone), a PPARα/γ dual agonist (such as CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 and SB-219994), a DPP-IV inhibitor (*e.g.*, sitagliptin, vidagliptin, alogliptin and saxagliptin), a glucagon-like peptide-1(GLP-1) agonist (*e.g.*, exendin-3 and exendin-4), a protein tyrosine phosphatases-1B (PTP-1B) inhibitor (*e.g.*, trodusquemine, hyrtiosal extract and compounds are disclosed by Zhang, S. *et al.*, *Drug Discovery Today*, 12(9/10), 373-381, **2007**), insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, a glucokinase activator, a glycogen phosphorylase inhibitor or a glucose-6-phosphatase inhibitor, an αP2 inhibitor, an acetyl-CoA carboxylase-2 (ACC-2) inhibitor, a phosphodiesterase (PDE)-10 inhibitor, a diacylglycerol acyltransferase (DGAT) 1 or 2 inhibitor, a glucose transporter 4 (GLUT4) regulator and a glutamine - fructose-6 - phosphate amidotransferase (GFAT) inhibitor.

[0069] Wherein, the antihyperglycemic agents include, but are not limited to, a biguanide (*e.g.*, phenformin and metformin), a sulfonylurea (*e.g.*, acetohexamide, diabinese, glibenclamide, glipizide, gliclazide, glimepiride, glipentide, gliquidone, tolazamide and tolbutamide), a meglitinide, a glinide (*e.g.*, repaglinide and nateglinide), a glucosidase inhibitor (*e.g.*, acarbose, adiposine, camiglibose, emiglitate, miglitol, voglibose,

pradimicin-Q and salbostatin), a PPAR agonist (*e.g.*, balaglitazone, ciglitazone, darglitazone, rosiglitazone, isaglitazone, pioglitazone, rosiglitazone and troglitazone), a PPARα/γ dual agonist (such as CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 and SB-219994), a DPP-IV inhibitor (*e.g.*, sitagliptin, vidagliptin, alogliptin and saxagliptin), a glucagon-like peptide-1(GLP-1) agonist (*e.g.*, exendin-3 and exendin-4), a protein tyrosine phosphatases-1B (PTP-1B) inhibitor (*e.g.*, trodusquemine, hyrtiosal extract and compounds are disclosed by Zhang, S. *et al.*, *Drug Discovery Today*, 12(9/10), 373-381, **2007**), insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, a glucokinase activator, a glycogen phosphorylase inhibitor or a glucose-6-phosphatase inhibitor, an αP2 inhibitor, an acetyl-CoA carboxylase-2 (ACC-2) inhibitor, a phosphodiesterase (PDE)-10 inhibitor, a diacylglycerol acyltransferase (DGAT) 1 or 2 inhibitor, a glucose transporter 4 (GLUT4) regulator and a glutamine - fructose-6 - phosphate amidotransferase (GFAT) inhibitor.

[0070] Wherein, the lipid-lowering agents include, but are not limited to, an MTP inhibitor, an HMGCoA reductase inhibitor, a squalene synthase inhibitor, a fibric acid derivative, an ACAT inhibitor, a lipoxygenase inhibitor, a cholesterol absorption inhibitor, an ileal Na(+)/bile acid cotransporter inhibitor, an upregulators of LDL receptor activity, a bile acid sequestrant or niacin and a derivative thereof. In some embodiments, the lipid-lowering agent is selected from pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and rosuvastatin. Wherein, the anti-obesity agents include CB-1 antagonists (such as rimonabant, taranabant, surinabant, otenabant, SLV319 and AVE1625), gut-selective MTP inhibitors (such as dirlotapide, mitratapide and implitapide), CCKa agonists, 5-HT_{2c} agonists (such as lorcaserin), MCR4 agonists, lipase inhibitors (such as cetilistat), PYY_{3-36}, opioid antagonist (such as naltrexone), oleoyl-estrone, obinepitide, pramlintide, tesofensine, leptin, liraglutide, bromocriptine, orlistat, exenatide, AOD-9604 and sibutramide.

[0071] Wherein, the suitable anti-inflammatory agents include genital tract/urinary tract infection preventatives and treatments. Exemplary agents include cranberries (Vaccinium macrocarpon) and cranberry derivatives, such as cranberry juice, cranberry extracts or flavonols of cranberries. Moreover, other suitable anti-inflammatory agents include, but are not limited to, aspirin, non-steroidal anti-inflammatory drugs, glucocorticosteroid, sulfasalazine and selective cyclooxygenase-2 inhibitors.

[0072] The compositions disclosed herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intraocular, intrahepatic, intralesional and intracranial injection and infusion techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions disclosed herein include aqueous and oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic

parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that include water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, non-volatile can be conventionally employed as a solvent or suspending medium.

[0073] For this purpose, the non-volatile oil includes synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives, which are useful in the preparation of injectables, can be used as natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as *Tweens*, *Spans* and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

USE OF THE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS

[0074] The amount of the compound or the compound in the compositions disclosed herein is an effective and detectable amount for inhibiting sodium-dependent glucose transporters (SGLTs) activity, especially SGLT-2 activity. SGLT-2 is responsible for reabsorption of D-glucose from kidney spherule filtrate, which inhibits glucose reabsorption in blood vessel and this is beneficial to reduce glucose concentrations in blood. Hence, the compound of the invention would be used for preventing and treating the type II diabetes and related diseases or improving symptoms of these diseases.

[0075] Compounds disclosed herein would be useful for, but not limited to, preventing or treating diabetes or related diseases, or lessening diabetes or related diseases, delaying the progression or onset of diabetes or related diseases or increasing HDL level in a patient by administering to the patient a compound or a composition disclosed herein in an effective amount. Such diseases include, but not limited to, diabetes, especially type II diabetes, and diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, diabetic complications, atherosclerosis and hypertension.

[0076] Moreover, compounds or pharmaceutical compositions disclosed herein also suit for preventing or treating the damage of diabetes in later stages, such as kidney disease, retinopathy, neuropathy, myocardial infarction, peripheral arterial disease, thrombosis, arteriosclerosis, inflammation, immunological diseases, autoimmune diseases such as AIDS, asthma, osteoporosis, cancer, psoriasis, Alzheimer's disease, schizophrenia and infectious diseases.

[0077] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of animals such as companion animals, exotic animals and farm animals, including mammals, rodents, and the like. In other embodiments, the animals disclosed herein include horses, dogs, and cats. As used herein, the

compounds disclosed herein include the pharmaceutically acceptable derivatives thereof.

[0078] An "effective amount" or "effective dose" of the compound or pharmaceutically acceptable composition is an amount that is effective in treating or lessening the severity of one or more of the aforementioned disorders. The compound or the pharmaceutically acceptable composition disclosed herein is effective administered in a fairly wide dose range. For example, the daily dose is from about 0.1 mg to 1000 mg per person, the compounds or pharmaceutically acceptable compositions can be administered in a single dose or in several divided doses a day. The compounds and compositions, according to the method disclosed herein, may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder or disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. A compound or composition can also be administered with one or more other therapeutic agents as discussed above.

GENERAL SYNTHETIC PROCEDURES

[0079] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for Formula (I), above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention.

[0080] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[0081] The structures of the compounds were identified by nuclear magnetic resonance (*e.g.*, ^{1}H-NMR and ^{13}C-NMR). ^{1}H-NMR and ^{13}C-NMR chemical shifts were recorded as ppm (10^{-6}). ^{1}H-NMR and ^{13}C-NMR were performed on a Bruker Ultrashield-400 spectrometer. The appropriate solvent was deuterated-chloroform ($CDCl_3$), deuterated-methanol (CD_3OD) or deuterated-dimethyl sulfoxide (DMSO-d_6).

[0082] MS spectra were determined on Agilen-6120 Quadrupole LC/MS mass spectrometer.

[0083] The thin-layer silica gel used was Yantai Huanghai $HSGF_{254}$ silica gel plate.

[0084] The silica gel used in column chromatography generally was Qingdao Ocean Chemical Factory 300 to 400 mesh silica gel.

[0085] The staring materials of the present invention were purchased from Shanghai Accela Company,

Energy Company, J&K, Chengdu Aiertai Company, Alfa Company and the like, or they were prepared by conventional synthesis methods in the prior art.

[0086] Unless otherwise stated, the reactions disclosed herein were carried out in a nitrogen atmosphere.

[0087] The term "nitrogen atmosphere" refers to an atmosphere in a reaction flask equipped with a balloon or a stainless steel autoclave filled with about 1 L nitrogen.

[0088] The term "hydrogen atmosphere" refers to an atmosphere in a reaction flask equipped with a balloon or a stainless steel autoclave filled with about 1 L hydrogen.

[0089] Unless otherwise stated, the solution used in the examples disclosed herein was an aqueous solution.

[0090] Unless otherwise stated, the reaction temperature was room temperature.

[0091] Unless otherwise stated, the room temperature was from 20 °C to 30 °C.

[0092] The reaction process in the examples was monitored by thin layer chromatography (TLC). The solvent system for development of a TLC plate comprised dichloromethane and methanol, dichloromethane and ethyl acetate, or petroleum ether and ethyl acetate. The volume ratio of the solvents in the solvent system was adjusted according to the polarity of the compounds.

[0093] The elution system of column chromatography comprised: A: petroleum ether and ethyl acetate, B: dichloromethane and ethyl acetate, and C: dichloromethane and methanol. The volume ratio of the solvents in the elution system was adjusted according to the polarity of the compounds, and sometimes it was also adjusted by adding a basic agent such as aqueous ammonia or an acidic agent such as acetic acid.

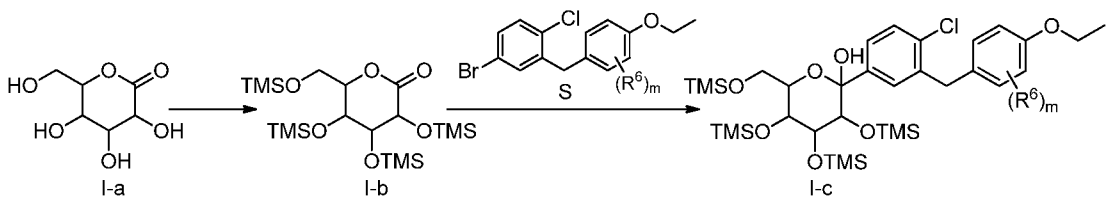
[0094] HPLC refers to High Performance Liquid Chromatography.

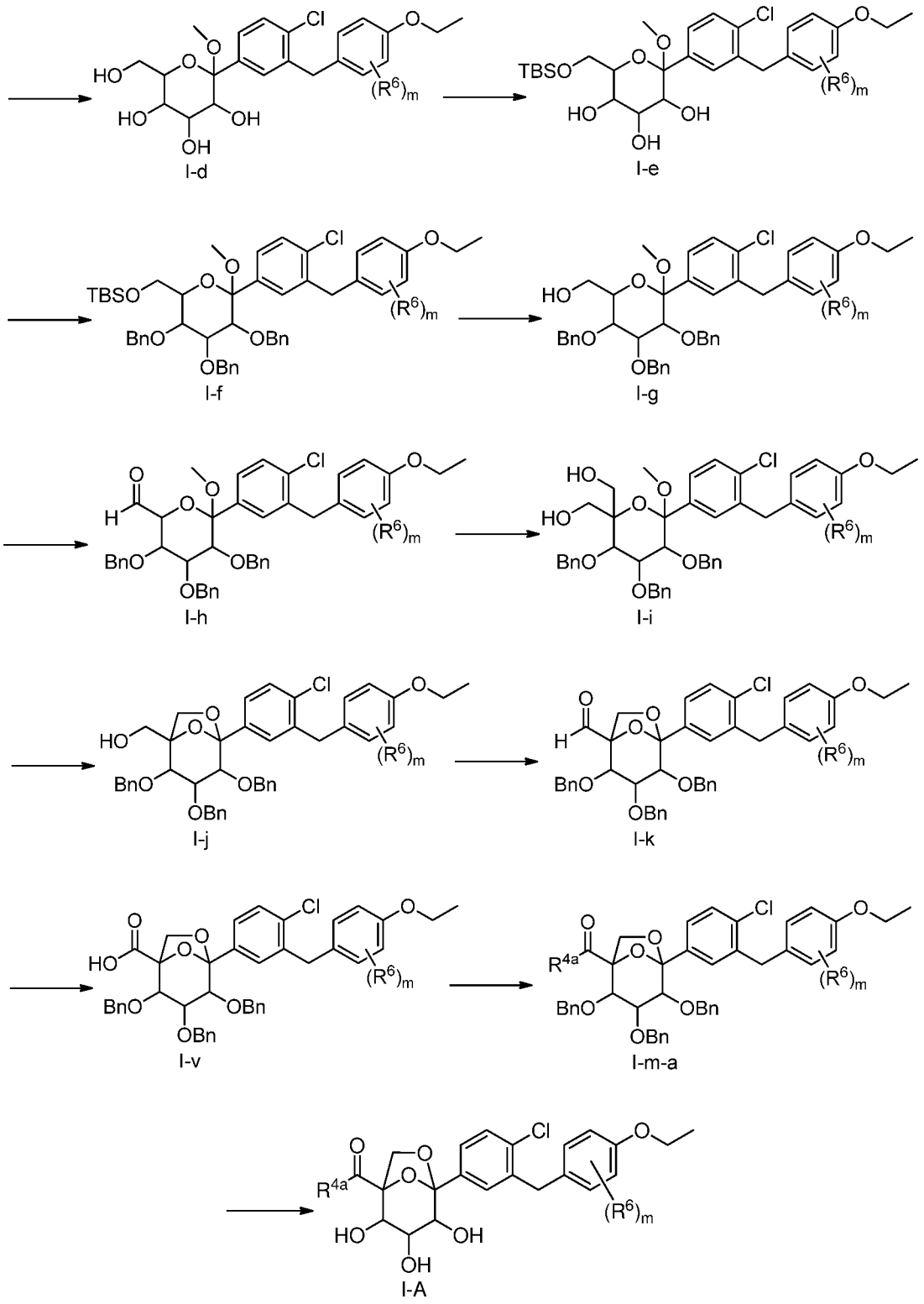
[0095] HPLC was determined on Agilent 1200DAD high pressure liquid chromatography spectrometer (Zorbax Eclipse Plus C18 150 × 4.6 mm chromatographic column).

[0096] The test condition of HPLC: the run time was 30 minutes; the column temperature was 35 °C; the detection was carried out at the wavelength of 210 nm and 254 nm using PDA detector; the mobile phase was H_2O (A) and acetonitrile (B); and the flow rate was 1.0 mL/min.

SCHEMES

Scheme 1



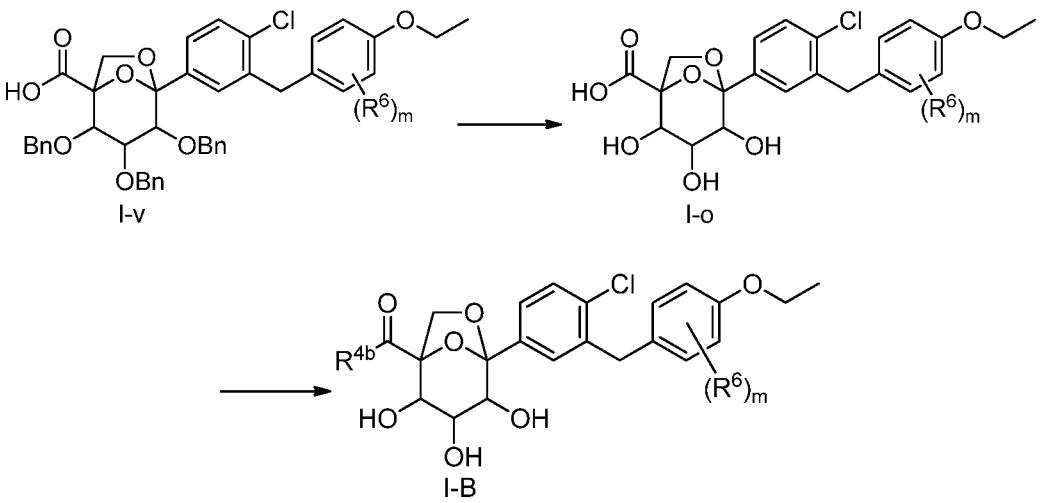


[0097] Compounds of formula (I-A) can be prepared by a general synthetic procedure illustrated in Scheme 1, wherein R^6 and m are as defined herein; R^{4a} is methoxy, ethoxy, isopropoxy, amino, *N*-methylamino, *N*,*N*-dimethylamino; Bn is benzyl.

[0098] Compound (I-a) can react with trimethylchlorosilane in the presence of *N*-methylmorpholine to afford compound (I-b). Coupling reaction of compound (I-b) with bromide fragment (S) in the presence of

n-butyllithium can give compound (I-c). Compound (I-c) can react with methanol in the presence of an acid to afford compound (I-d). Compound (I-d) can react with *tert*-butyldimethylsilyl chloride in the presence of a base to afford compound (I-e). Compound (I-e) can react with benzyl bromide in the presence of a base to afford compound (I-f). Compound (I-f) can react with tetrabutylammonium iodide in a polar solvent to afford compound (I-g). Compound (I-g) can be converted to compound (I-h) in the presence of an oxidizing agent; compound (I-h) can react with methanal in the presence of a base to afford compound (I-i). Cyclization of compound (I-i) in the presence of an acid can afford compound (I-j). Oxidizing reaction of compound (I-j) can afford compound (I-k). Compound (I-k) can be oxidized to afford compound (I-v). Compound (I-v) can react with a polar solvent (such as methanol, ethanol or isopropanol), ammonium hydroxide and methylamine hydrochloride (or dimethylamine hydrochloride) in the presence of an acid or a base to give compound (I-m-a). The protecting group of compound (I-m-a) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-A).

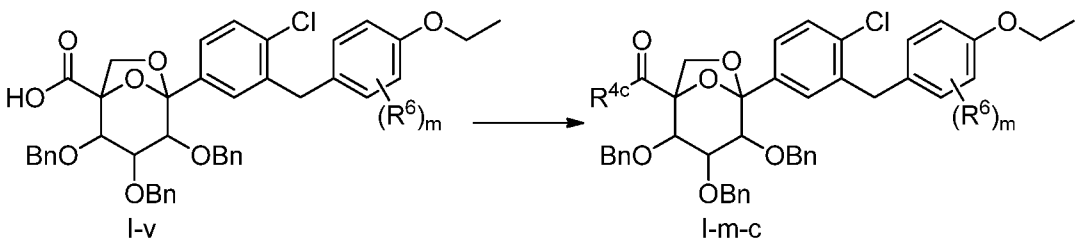
Scheme 2

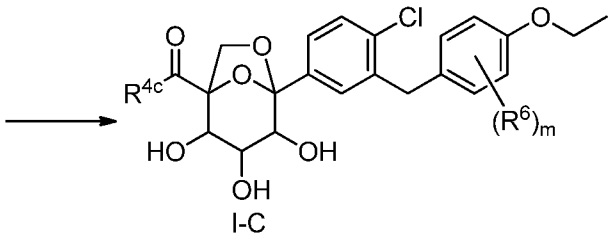


[0099] Compounds of formula (I-B) can be prepared by a general synthetic procedure illustrated in Scheme 2, wherein R^6 and m are as defined herein; R^{4b} is *N*,*N*-dimethylamino; Bn is benzyl.

[00100] The protecting group of compound (I-v) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-o). Compound (I-o) can react with dimethylamine hydrochloride in the presence of a base to give compound (I-B).

Scheme 3

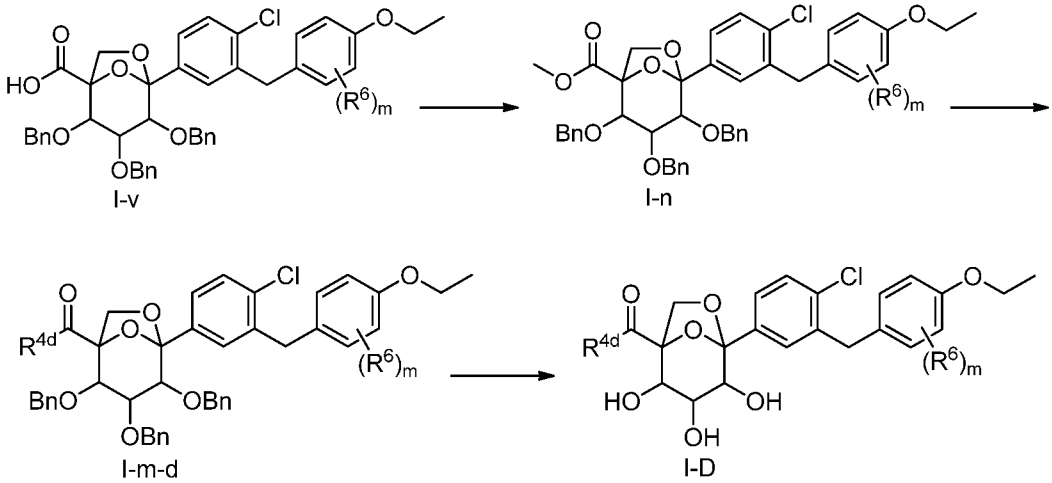




[00101] Compounds of formula (I-C) can be prepared by a general synthetic procedure illustrated in Scheme 3, wherein each of R^6 and m is as defined herein; R^{4c} is pivaloyloxymethoxy; Bn is benzyl.

[00102] Compound (I-v) can react with chloromethyl pivalate under alkaline conditions to give compound (I-m-c). The protecting group of compound (I-m-c) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-C).

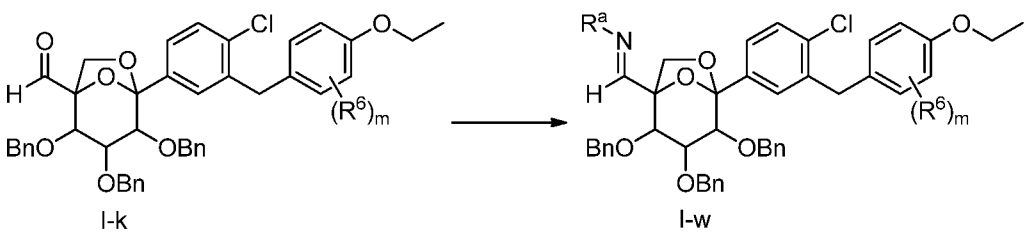
Scheme 4

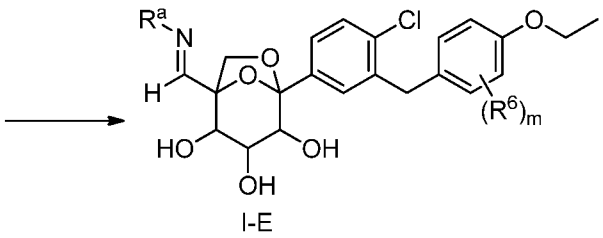


[00103] Compounds of formula (I-D) can be prepared by a general synthetic procedure illustrated in Scheme 4, wherein R^6 and m are as defined herein; R^{4c} is amino or *N*-methylamino; Bn is benzyl.

[00104] Compound (I-v) can react with (trimethylsilyl)diazomethane in a polar solvent to afford compound (I-n). Compound (I-n) can react with a halogenating agent under alkaline conditions to give compound (I-m-d). The protecting group of compound (I-m-d) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-D).

Scheme 5



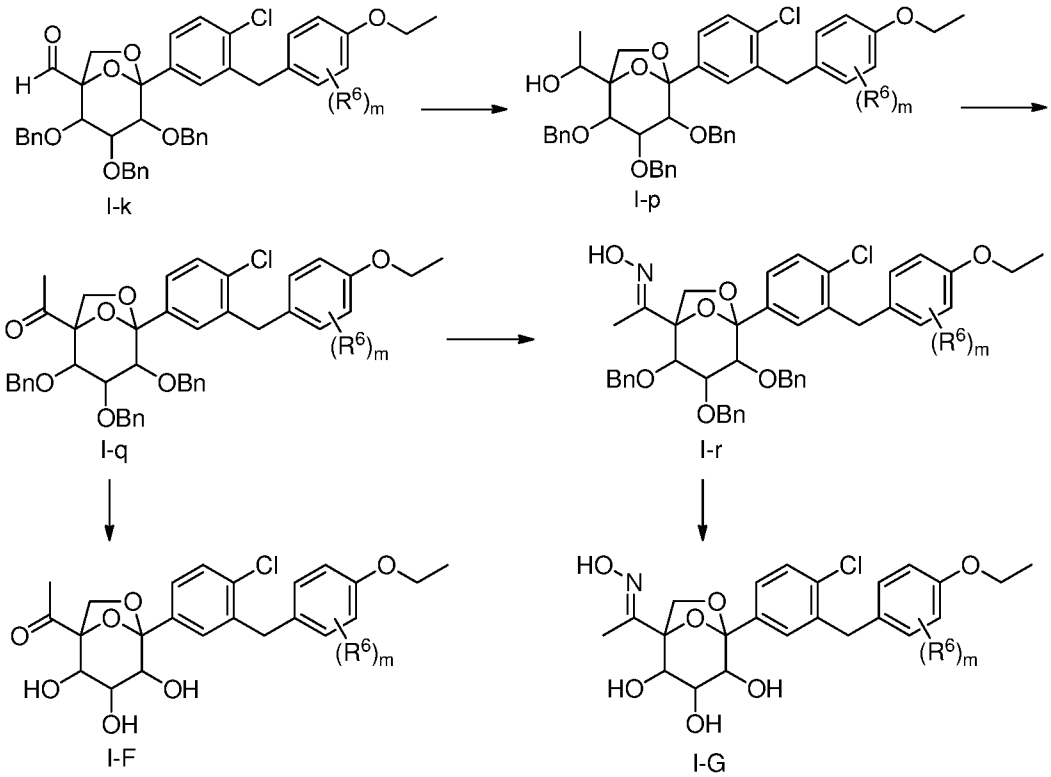


I-E

[00105] Compounds of formula (I-E) can be prepared by a general synthetic procedure illustrated in Scheme 5, wherein R^a, R^6 and m are as defined herein; Bn is benzyl.

[00106] Compound (I-k) can react with hydroxylamine hydrochloride or *N*-methylhydroxylamine hydrochloride in a polar solvent under alkaline conditions to afford compound (I-w). The protecting group of compound (I-w) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-E).

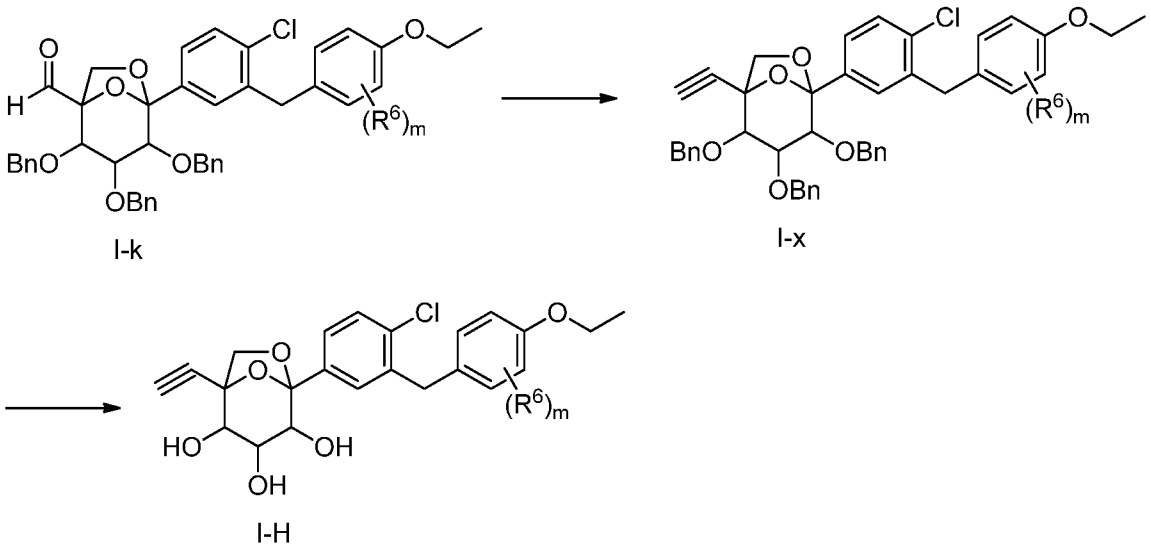
Scheme 6



[00107] Compounds of formula (I-F) or formula (I-G) can be prepared by a general synthetic procedure illustrated in Scheme 6, wherein R^6 and m are as defined herein; Bn is benzyl.

[00108] Grignard reaction of compound (I-k) to give compound (I-p); compound (I-p) can be oxidized to give compound (I-q). The protecting group of compound (I-q) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-F); or compound (I-q) can react with hydroxylamine hydrochloride under alkaline conditions to afford compound (I-r). The protecting group of compound (I-r) can be removed in the presence of an acid or by Pd/C catalysis under H_2 to afford compound (I-G).

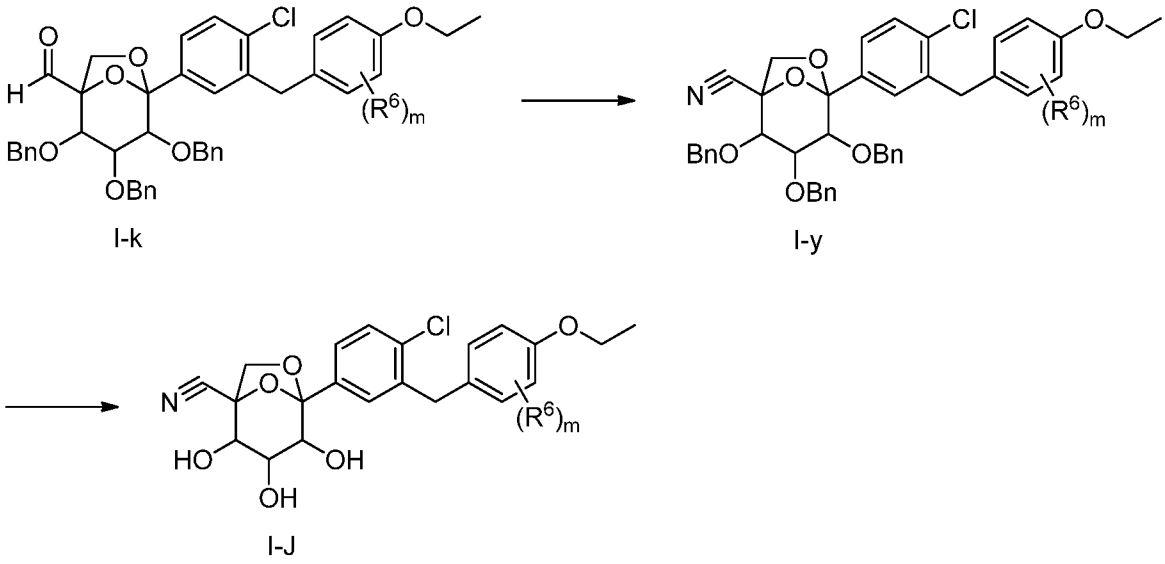
Scheme 7



[00109] Compounds of formula (I-H) can be prepared by a general synthetic procedure illustrated in Scheme 7, wherein R^6 and m are as defined herein; Bn is benzyl.

[00110] Seyferth-Gilbert homologation of compound (I-k) and (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester in the presence of potassium carbonate to give compound (I-x). The protecting group of compound (I-x) can be removed in the presence of boron trichloride at −78 °C to give compound (I-H).

Scheme 8



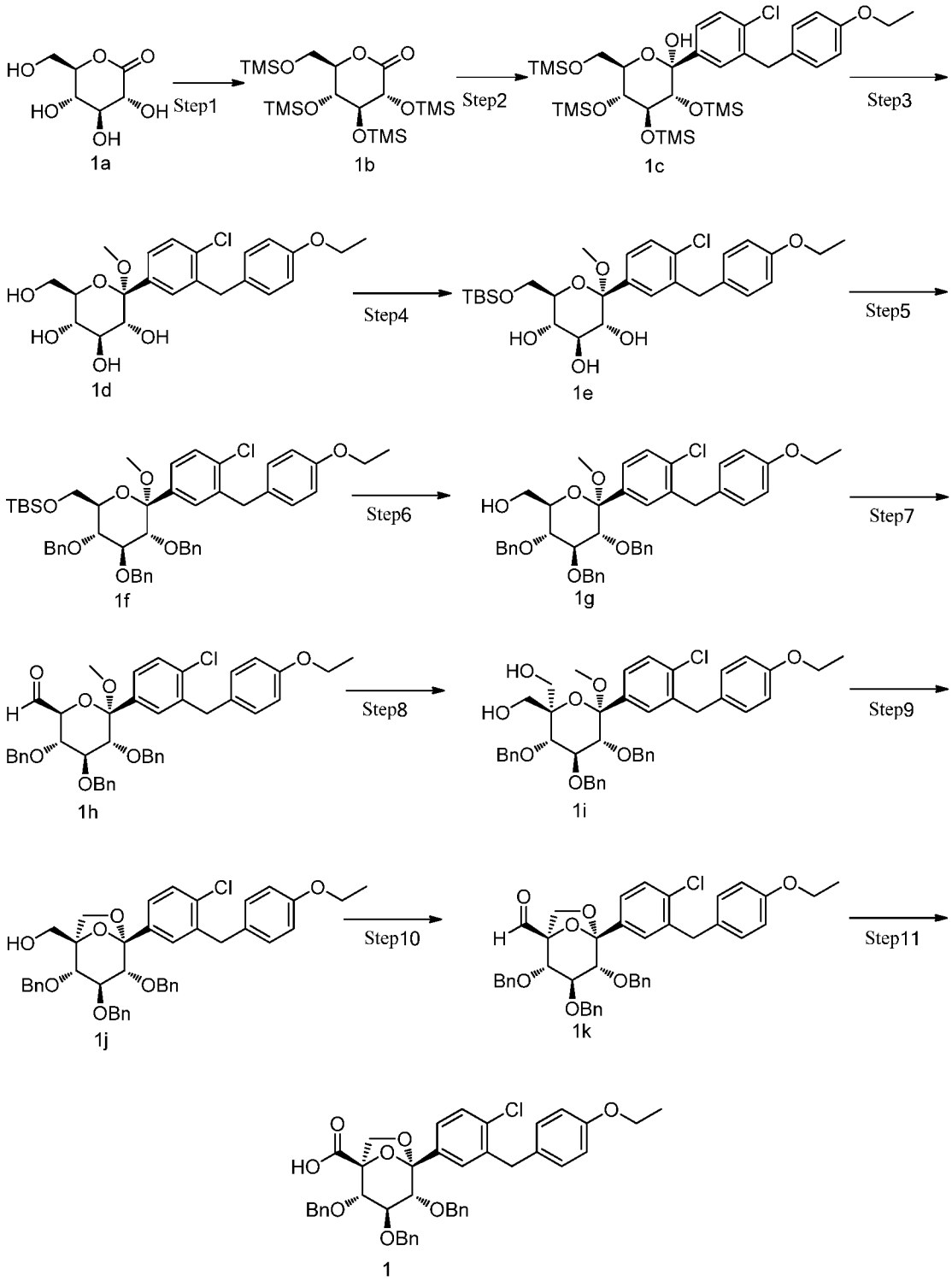
[00111] Compounds of formula (I-J) can be prepared by a general synthetic procedure illustrated in Scheme 8, wherein R^6 and m are as defined herein; Bn is benzyl.

[00112] Compound (I-k) can react with hydroxylamine hydrochloride and dicyclohexylcarbodiimide under a base to give compound (I-y). The protecting group of compound (I-y) can be removed in the presence of boron trichloride at −78 °C to give compound (I-J).

EXAMPLES

Example 1

(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1] octane-1-carboxylic acid **1**



Step 1) (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(trimethylsilyloxy)-6-(trimethylsilyloxymethyl) tetrahydropyran-2-one **1b**

[00113] To a solution of *N*-methylmorpholine (246.8 mL, 2.24 mol) and (3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-one **1a** (50 g, 0.28 mol, purchased from Aladdin) in anhydrous tetrahydrofuran (500 mL) was added dropwise trimethylchlorosilane (213 mL, 1.68 mol) over a period of 2 hours. The mixture was stirred at room temperature for 8 hours and quenched with water (1 L). The organic layer was washed with saturated aqueous dipotassium hydrogen phosphate trihydrate (100 mL × 3) and saturated aqueous sodium chloride (100 mL × 3), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=40/1 to give the title compound **1b** as colorless oil (125.2 g, 100%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 4.17 (m, 1H), 3.99 (d, 1H), 3.89 (t, 1H), 3.81 (m, 3H), 0.18 (s, 9H), 0.17 (s, 9H), 0.15 (s, 9H), 0.11 (s, 9H).

Step 2) (2*S*,3*R*,4*S*,5*R*,6*R*)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-3,4,5-tris(trimethylsilyloxy)-6-(trimethylsilyloxymethyl)tetrahydropyran-2-ol **1c**

[00114] To a solution of 4-bromo-1-chloro-2-(4-ethoxyphenyl)methyl-benzene (30 g, 92.1 mmol, purchased from Shanghai Kinsey pharmaceutical company) in anhydrous tetrahydrofuran (250 mL) was added *n*-butyllithium (40.3 mL, 96.7 mmol, 2.4 M in hexane) dropwise at −78 °C. The mixture was stirred at −78 °C for 40 minutes, and then a solution of (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(trimethylsilyloxy)-6-(trimethylsilyloxymethyl) tetrahydropyran-2-one **1b** (47.3 g, 101.3 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise. After, the mixture was further stirred at −78 °C for 5 hours and quenched with 100 mL of saturated aqueous ammonium chloride. The mixture was allowed to warm up to room temperature and concentrated *in vacuo*. To the residue was added 150 mL of water. The resulting mixture was extracted with ethyl acetate (150 mL × 3). The combined organic layers were washed with saturated aqueous sodium chloride (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound **1c** as pale yellow oil (69.7 g, 100%). The crude product was used without further purification.

Step 3) (2*S*,3*R*,4*S*,5*S*,6*R*)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)-2-methoxy-tetrahydropyran-3,4,5-triol **1d**

[00115] To a solution of (2*S*,3*R*,4*S*,5*R*,6*R*)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-3,4,5-tris (trimethylsilyloxy)-6-(trimethylsilyloxymethyl)tetrahydropyran-2-ol **1c** (65.7 g, 92.13 mmol) in methanol (300 mL) was added *p*-toluenesulfonic acid monohydrate (8.76 g, 46.06 mmol). The mixture was stirred at room temperature for 12 hours, and neutralized with saturated aqueous sodium bicarbonate till pH becomes 7, and then concentrated *in vacuo*. To the residue was added water (100 mL). The resulting mixture was extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with saturated aqueous sodium chloride (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by re-crystallization from toluene/*n*-hexane(v/v) = 1/1 to give the title compound **1d** as a white solid (29.0 g, 71.6%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, DMSO-d_6)

δ(ppm): 7.52 (s, 1H), 7.39 (m, 2H), 7.08 (m, 2H), 6.83 (m, 2H), 4.96 (d, 1H), 4.73 (m, 2H), 4.52 (t, 1H), 4.09-3.94 (m, 4H), 3.76-3.72 (m, 1H), 3.61-3.51 (m, 2H), 3.38 (m, 1H), 3.23 (m, 1H), 2.92 (s, 3H), 2.89 (m, 1H), 1.29 (t, 3H).

Step 4) (2*S*,3*R*,4*S*,5*S*,6*R*)-6-[(*tert*-butyl(dimethyl)silyl)oxymethyl]-2-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-2-methoxy-tetrahydropyran-3,4,5-triol **1e**

[00116] To a solution of (2*S*,3*R*,4*S*,5*S*,6*R*)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl) -2-methoxy-tetrahydropyran-3,4,5-triol **1d** (82.2 g, 187.4 mmol) in dichloromethane (800 mL) was added imidazole (25.5 g, 374.7 mmol) at room temperature. The mixture was stirred at 0 °C and then *tert*-butyldimethylsilyl chloride (56.7 g, 374.7 mmol) was added. The resulting mixture was further stirred at 0 °C for 2 hours. The mixture was adjusted to pH 7 with saturated aqueous sodium bicarbonate at 0 °C,. The organic layer was washed with water (100 mL × 2) and saturated aqueous sodium chloride (100 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound **1e** as yellow oil (119 g, 100%). The crude product was used without further purification. The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 2H), 7.30 (m, 1H), 6.08 (m, 2H), 6.80 (m, 2H), 4.02 - 3.88 (m, 7H), 3.67 (m, 2H), 3.22 (m, 1H), 3.08 (s, 3H), 1.40 (t, 3H), 0.90(s, 9H), 0.12(s, 3H), 0.09(s, 3H).

Step 5) *tert*-butyl-dimethyl-[[(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-6-methoxy-tetrahydropyran-2-yl]methoxy]silane **1f**

[00117] To a suspension of sodium hydride (65.4 g, 1.627 mol, 60% dispersion in Mineral oil) in anhydrous tetrahydrofuran (100 mL) was added dropwise a solution of (2*S*,3*R*,4*S*,5*S*,6*R*)-6-[(*tert*-butyl (dimethyl)silyl)oxymethyl]-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2-methoxy-tetrahydropyran-3,4,5-t riol **1e** (150 g, 0.271 mol) in anhydrous tetrahydrofuran (800 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour and then allowed to warm up to room temperature. After benzyl bromide (113 mL, 951.84 mmol) and tetrabutylammonium iodide (3.91 g, 10.6 mmol) were added in turn, the mixture was stirred at 40 °C for 12 hours. The mixture was cooled to 0 °C and quenched with water (50 mL). Most of the solvent was removed *in vacuo*. To the residue was added water (200 mL). The resulting mixture was extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with saturated aqueous sodium chloride (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=20/1 to give the title compound **1f** as yellow oil (97 g, 43.5%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (m, 1H), 7.35 (m, 12H), 7.20 (m, 3H), 7.04 (m, 4H), 6.74 (m, 2H), 4.90(m, 3H), 4.72 (d, 1H), 4.50 (d, 1H), 4.15 (t, 1H), 4.05 (d, 1H), 3.97 (m, 3H), 3.80 (m, 3H), 3.75 (m, 1H), 3.65 (m, 1H), 3.29 (d, 1H), 3.05 (s, 3H), 1.38 (t, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H).

Step 6) [(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methoxy-

tetrahydropyran-2-yl]methanol **1g**

[00118] To a solution of *tert*-butyl-dimethyl-[[(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxy phenyl)methyl]phenyl]-6-methoxy-tetrahydropyran-2-yl]methoxy]silane **1f** (84.1 g, 102.1 mmol) in tetrahydrofuran (400 mL) was added tetrabutylammonium fluoride (53.4 g, 204.2 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours and quenched with saturated aqueous sodium bicarbonate (100 mL). The resulting mixture was washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with saturated aqueous sodium chloride (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **1g** as yellow oil (56.3 g, 77.8%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34(m, 13H), 7.25 (m, 3H), 7.04 (m, 2H), 6.99 (m, 2H), 6.77 (m, 2H), 4.90 (m, 3H), 4.69 (d, 1H), 4.49 (d, 1H), 4.16 (t, 1H), 4.10 (d, 1H), 4.00 (m, 2H), 3.98 (m, 2H), 3.81 (m, 1H), 3.70 (m, 1H), 3.68 (m, 1H), 3.66 (m, 1H), 3.29 (d, 1H), 3.06 (s, 3H), 1.75 (bs, 1H), 1.38 (t, 3H).

Step 7) (2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methoxy-tetrahydropyran-2-carbaldehyde **1h**

[00119] To a solution of [(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -6-methoxy-tetrahydropyran-2-yl]methanol **1g** (8.65 g, 12.19 mmol) in dichloromethane (300 mL) was added 2-iodoxybenzoic (6.83 g, 24.39 mmol) acid at room temperature. The mixture was refluxed at 45 °C for 36 hours and quenched with of water (150 mL). The organic layer was washed with saturated aqueous sodium chloride (150 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound **1h** as yellow oil (7.57 g, 87.8%). The crude product was used without further purification. The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.74 (d, 1H), 7.39 - 7.19 (m, 16H), 7.03 - 7.00 (m, 4H), 6.76 (m, 2H), 4.90 (m, 3H), 4.70 (d, 1H), 4.48 (d, 1H), 4.23 (t, 1H), 4.15 - 4.07 (m, 2H), 3.99 - 3.75 (m, 5H), 3.31 (d, 1H), 3.07 (s, 3H), 1.38(t, 3H).

Step 8) [(3*S*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2-(hydroxymethyl) -6-methoxy-tetrahydropyran-2-yl]methanol **1i**

[00120] To a solution of (2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -6-methoxy-tetrahydropyran-2-carbaldehyde **1h** (13.5 g, 19.1 mmol) in a isopropanol/dioxane mixture (95 mL, v/v=18/1) was added in portions sodium hydroxide (1.22 g, 30.56 mmol) at room temperature, and then formaldehyde (38.7 mL, 477.5 mmol, 37 wt% solution) was added. The mixture was stirred at room temperature for 48 hours and adjusted to pH 7 with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with water (25 mL × 2) and saturated aqueous sodium chloride (25 mL × 2), dried over anhydrous sodium sulfate and

concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=5/1 to give the title compound **1i** as yellow oil (4.63 g, 32.8%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 6H), 7.22 (m, 10H), 7.05 (m, 2H), 7.02 (m, 2H), 6.79 (m, 2H), 4.95 (m, 3H), 4.69 (d, 2H), 4.38 (m, 1H), 4.09 (m, 2H), 4.04 - 3.96 (m, 4H), 3.83 (m, 3H), 3.66 (m, 1H), 3.25 (m, 1H), 3.06 (s, 3H), 1.72 (t, 1H), 1.39 (t, 3H).

Step 9) [(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-6,8-dioxabicyclo [3.2.1]octan-1-yl]methanol **1j**

[00121] To a solution of [(3*S*,4*S*,5*R*,6*S*)-3,4,5-tribenzyloxy-6-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -2-(hydroxymethyl)-6-methoxy-tetrahydropyran-2-yl] methanol **1i** (2.49 g, 3.37 mmol) in dichloromethane (300 mL) was added *p*-toluenesulfonic acid monohydrate (0.32 g, 1.69 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour and quenched with saturated aqueous sodium bicarbonate (30 mL). The resulting mixture was extracted with dichloromethane (20 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=7/1 to give the title compound **1j** as pale yellow oil (1.06 g, 44.5%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (d, 1H), 7.40 (m, 12H), 7.30 (m, 3H), 7.09 (m, 2H), 6.91 (m, 2H), 6.78 (m, 2H), 4.88 (m, 3H), 4.78 (d, 1H), 4.29 (m, 2H), 4.11 - 3.96 (m, 6H), 3.88 (d, 1H), 3.80 (m, 2H), 3.71 (m, 2H), 1.85 (t, 1H), 1.41 (t, 3H).

Step 10) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k**

[00122] To a solution of [(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -6,8-dioxabicyclo[3.2.1]octan-1-yl]methanol **1j** (8.53 g, 12.08 mmol) in dichloromethane (350 mL) was added 2-iodoxybenzoic (6.77 g, 24.2 mmol) acid at room temperature. The mixture was refluxed at 45 °C for 36 hours and quenched with water (150 mL). The organic layer was washed with saturated aqueous sodium chloride (150 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **1k** as pale yellow oil (4.94 g, 60.0%).

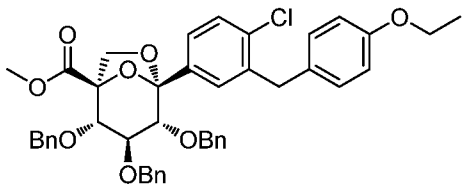
Step 11) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo [3.2.1]octane-1-carboxylic acid **1**

[00123] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (50 mg, 0.07 mmol) in *tert*-butanol (10 mL) were added monopotassium phosphate (70.24 mg, 0.52 mmol), sodium chlorite (60 mg, 0.66 mmol) and 2-methyl-2-butene (248.26 mg, 3.54 mmol) in turn at room temperature. The mixture was stirred at room temperature for 48 hours and adjusted to pH 7 with acetic acid. The resulting mixture was extracted with ethyl acetate (100 mL ×3). The

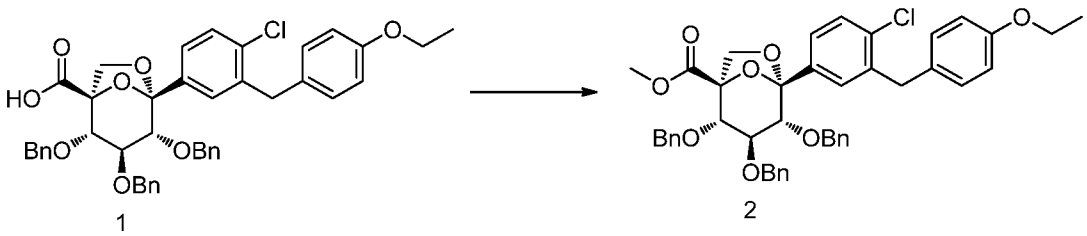
combined organic layers were washed with water (40 mL × 6) and saturated aqueous sodium chloride (50 mL × 3), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/2 to give the title compound **1** as colorless oil (7 mg, 15.0%). The compound was characterized by the following spectroscopic data: ^{1}H NMR(400MHz, $CDCl_3$) δ (ppm): 7.46 (d, 1H), 7.36 (m, 2H), 7.12 (m, 13H), 6.98 (m, 2H), 6.78 (m, 2H), 6.66 (m, 2H), 5.33 (m, 2H), 4.75 (s, 2H), 4.64 (m, 2H), 4.39 (d, 1H), 4.19 (m, 1H), 4.10 (d, 1H), 3.89 (m, 4H), 3.75 (d, 1H), 3.69 (d, 1H), 1.38 (t, 3H).

Example 2

Methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **2**



2

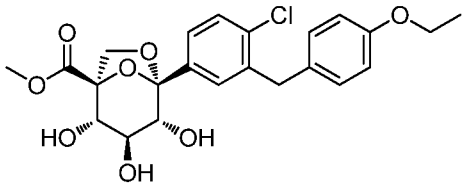


1 2

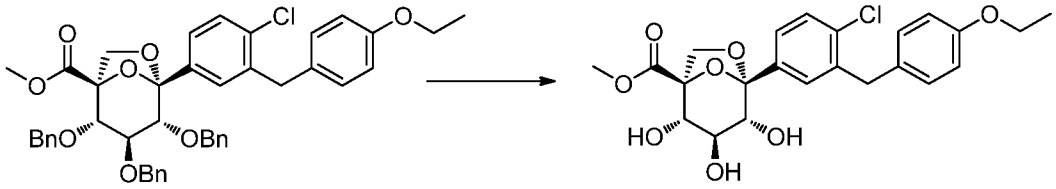
[00124] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **1** (0.41 g, 0.57 mmol, obtained from the synthetic method described in step 11 of example 1) in dichloromethane (50 mL) was added dropwise (trimethylsilyl)diazomethane (0.37 mL, 0.74 mmol, 2 M in hexane) at 0 °C. After the addition, the mixture was allowed to warm up to room temperature and stirred for 15 hours, and then quenched with water (40 mL). The resulting mixture was extracted with dichloromethane (40 mL × 3). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **2** as yellow oil (124 mg, 30.0%). The compound was characterized by the following spectroscopic data: ^{1}H NMR(400MHz, $CDCl_3$) δ (ppm): 7.46 (m, 1H), 7.37 (m, 2H), 7.30 (m, 7H), 7.24 (m, 3H), 7.16 (m, 3H), 7.06 (m, 2H), 6.86 (m, 2H), 6.76 (m, 2H), 4.83 (d, 2H), 4.76 (d, 1H), 4.62 (d, 1H), 4.52 (d, 1H), 4.25 (d, 1H), 4.19 (m, 2H), 4.09 (d, 1H), 3.97 (m, 4H), 3.86 (d, 1H),3.73(d, 1H), 3.69 (s, 3H),1.36(t, 3H).

Example 3

Methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **3**



3

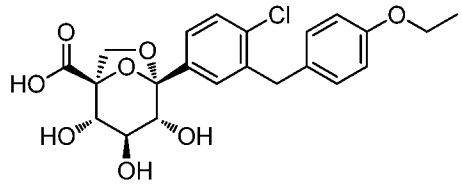


2 3

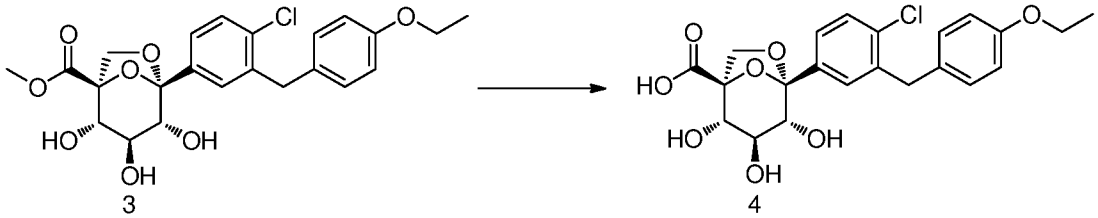
[00125] To a solution of *o*-dichlorobenzene (147 mg, 1.0 mmol) and methyl-(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **2** (150 mg, 0.2 mmol, obtained from the synthetic method described in example 2) in a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL) was added 10% Pd/C (30 mg, 0.02 mmol) at room temperature. The mixture was stirred under H_2 at room temperature for 4 hours and filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 3). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/5 to give the title compound **3** as colorless oil (95 mg, 75.0%, HPLC: 95.9%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 465.2[M+H]$^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 7.41 (m, 2H), 7.32 (m, 1H), 7.09(m, 2H), 6.84 (m, 2H), 5.71 (d, 1H), 5.22 (d, 1H), 5.10 (d, 1H), 4.28 (d, 1H), 4.01 (m, 5H), 3.75 (t, 1H), 3.69 (s, 3H), 3.47 (m, 2H), 1.31(t, 3H).

Example 4

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **4**



4



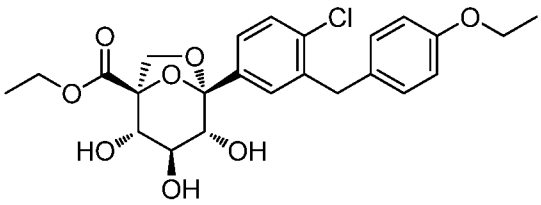
3 4

[00126] To a solution of methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-

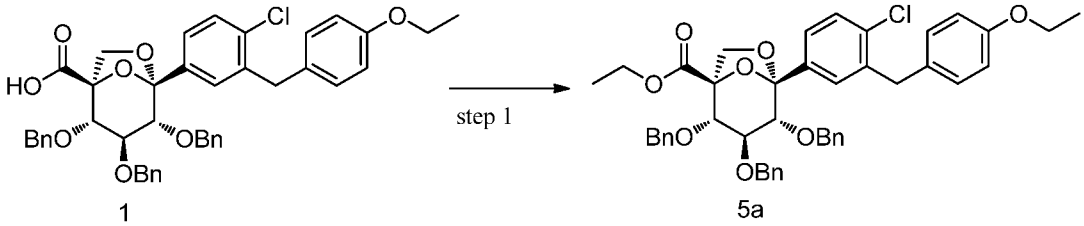
trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate (0.5 g, 1.09 mmol, obtained from the synthetic method described in example 3) in a methanol/tetrahydrofuran/water mixture (v/v/v=1/1/1, 15 mL) was added lithium hydroxide hydrate (120 mg, 3.2 mmol) at room temperature. The mixture was stirred at room temperature for 3 hours and quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (40 mL ×3). The combined organic layers were washed with water (20 mL × 2) and saturated aqueous sodium chloride (10 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative HPLC to give title compound **4** as a pale yellow solid (27 mg, 5.0%, HPLC: 70.0%). The compound was characterized by the following spectroscopic data: MS (ESI, neg. ion) *m/z*: 449.1[M-H]$^-$; ^{1}H NMR(400MHz, $CDCl_3$): δ 7.41 (m, 2H), 7.30 (m, 1H), 7.11 (m, 2H), 6.83 (m, 2H), 5.13 (d, 1H), 5.03 (d, 1H), 4.02 (d, 1H), 4.00 (m, 4H), 3.85 (d, 1H), 3.72 (d, 1H), 3.50 (m, 3H), 1.30 (t, 1H).

Example 5

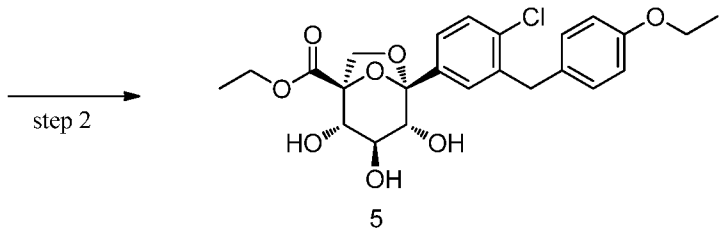
Ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **5**



5



1 5a



5

Step 1) ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **5a**

[00127] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **1** (0.1 g, 0.14 mmol, obtained from the synthetic method described in step 11 of example 1) in a tetrahydrofuran/ethanol mixture (v/v=1/3, 4 mL) was added dropwise

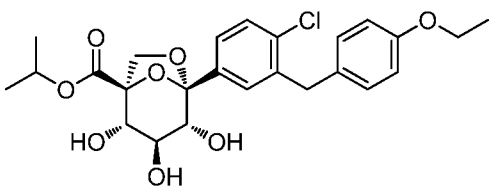
concentrated sulphuric acid (0.2 mL) at room temperature. The mixture was refluxed for 12 hours and quenched with saturated aqueous ammonium chloride (2 mL). The resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with water (5 mL × 2) and saturated aqueous sodium chloride (5 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=15/1 to give the title compound **5a** as colorless oil (55 mg, 52.9%). The compound was characterized by the following spectroscopic data: ^{1}H NMR(400MHz, $CDCl_3$) δ (ppm): 7.45 (s, 1H), 7.37 (m, 2H), 7.26(m, 10H), 7.15 (m, 3H), 7.05 (d, 2H), 6.85 (d, 2H), 6.73 (d, 2H), 4.80 (m, 3H), 4.62 (d, 1H), 4.49 (d, 1H), 4.23 (d, 1H), 4.18 (m, 3H), 4.13 (m, 1H), 4.06 (m, 1H), 3.98 (m, 2H), 3.95 (m, 2H), 3.84 (d, 1H), 3.71 (d, 1H), 1.38 (t, 3H), 1.22 (t, 3H).

Step 2) ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **5**

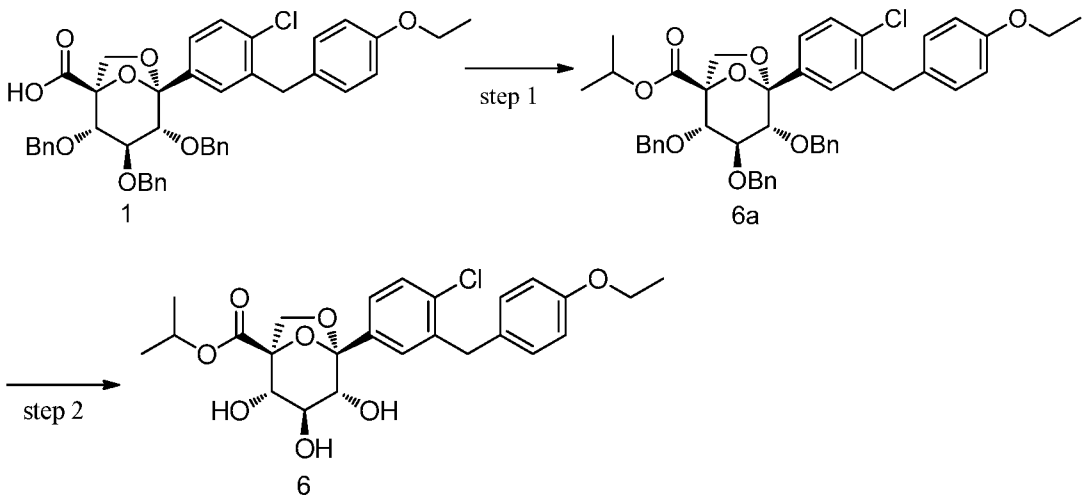
[00128] To a solution of *o*-dichlorobenzene (0.15 mL, 1.3 mmol) and ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **5a** (197 mg, 0.26 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL) was added 10% Pd/C (20 mg, 0.02 mmol) at room temperature. The mixture was stirred under H_2 at room temperature for 1 hour and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=5/1 to give the title compound **5** as a white solid (107 mg, 86.3%, HPLC: 96.6%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion)*m/z*: 480.0[M+H]$^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 7.41 (m, 2H), 7.30 (m, 1H), 7.08(d, 2H), 6.82 (d, 2H), 5.68 (d, 1H), 5.19 (d, 1H), 5.08 (d, 1H), 4.26 (d, 1H), 4.16 (m, 2H), 3.97 (m, 5H), 3.78 (t, 1H), 3.47 (m, 2H), 1.29 (t, 3H), 1.20 (t, 3H).

Example 6

Isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **6**



6



Step 1) isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **6a**

[00129] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **1** (0.3 g, 0.42 mmol, obtained from the synthetic method described in step 11 of example 1) in isopropanol (15 mL) was added dropwise concentrated sulphuric acid (0.1 mL) at room temperature. The mixture was stirred at 55 °C for 15 hours and quenched with saturated aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate (40 mL × 4). The combined organic layers were washed with water (20 mL × 2) and saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **6a** as pale yellow oil (0.2 g, 50%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.46 (d, 1H), 7.37 (m, 2H), 7.31 (m, 6H), 7.17 (m, 7H), 7.05 (m, 2H), 6.86 (m, 2H), 6.75 (m, 2H), 5.04 (m, 1H), 4.81 (m, 3H), 4.66 (d, 1H), 4.49 (d, 1H), 4.25 (m, 1H), 4.18 (m, 2H), 4.07 (d, 1H), 3.98 (m, 4H), 3.85 (d, 1H), 3.72 (d, 1H), 1.38 (t, 3H), 1.23 (d, 3H), 1.20 (d, 3H).

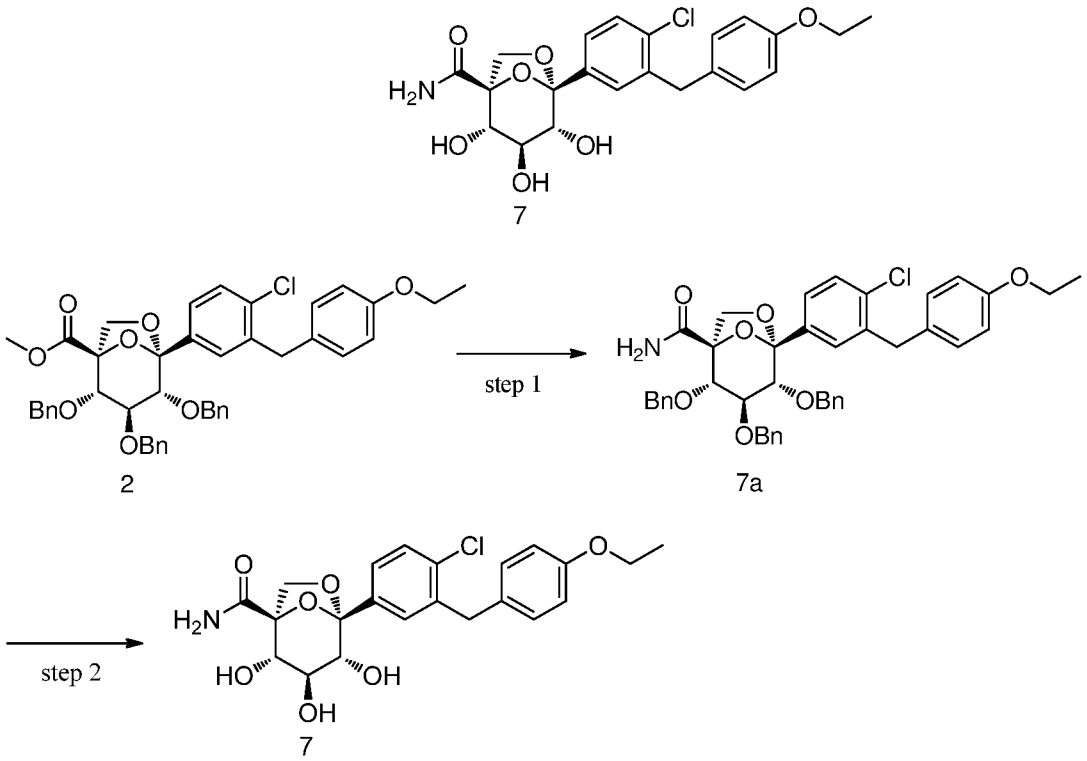
Step 2) isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **6**

[00130] To a solution of isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **6a** (0.2 g, 0.26 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 20 mL) were added *o*-dichlorobenzene (0.14 mL, 1.24 mmol) and 10% Pd/C (28 mg, 0.03 mmol) in turn. The mixture was stirred under H_2 at room temperature for 4 hours and filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/5 to give the title compound **6** as a white solid (98 mg, 75.4%, HPLC: 94.6%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion)*m/z*: 493.1[M+H]$^+$; ^{1}H

NMR (400MHz, DMSO-d_6) δ (ppm): 7.40 (m, 2H), 7.31 (m, 1H), 7.09(m, 2H), 6.81 (m, 2H), 5.66 (d, 1H), 5.17 (d, 1H), 5.07 (d, 1H), 4.95 (m, 1H), 4.25 (d, 1H), 3.99 (m, 4H), 3.89 (d, 1H), 3.75 (t, 1H), 3.48 (m, 2H), 1.28 (t, 3H), 1.20 (m, 6H).

Example 7

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **7**



Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8 -dioxabicyclo [3.2.1]octane-1-carboxamide **7a**

[00131] To a solution of methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4- ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **2** (0.3 g, 0.42 mmol, obtained from the synthetic method described in example 2) in anhydrous tetrahydrofuran (2 mL) was added ammonium hydroxide (4 mL). The mixture was stirred at 55 °C for 48 hours and extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with water (10 mL × 2) and saturated aqueous sodium chloride (10 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/1 to give the title compound **7a** as a white solid (51 mg, 18.2%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.36 (m, 5H), 7.29 (m, 6H), 7.23(m, 2H), 7.15 (m, 3H), 7.05 (m, 2H), 6.85 (m, 2H), 6.75 (m, 2H), 6.16 (s, 1H), 5.32 (s, 1H), 4.83 (m, 3H), 4.71 (d, 1H), 4.59 (d, 1H), 4.28 (d, 1H), 3.99 (m, 7H), 3.89 (d, 1H), 3.68 (m, 1H), 1.38 (t, 3H).

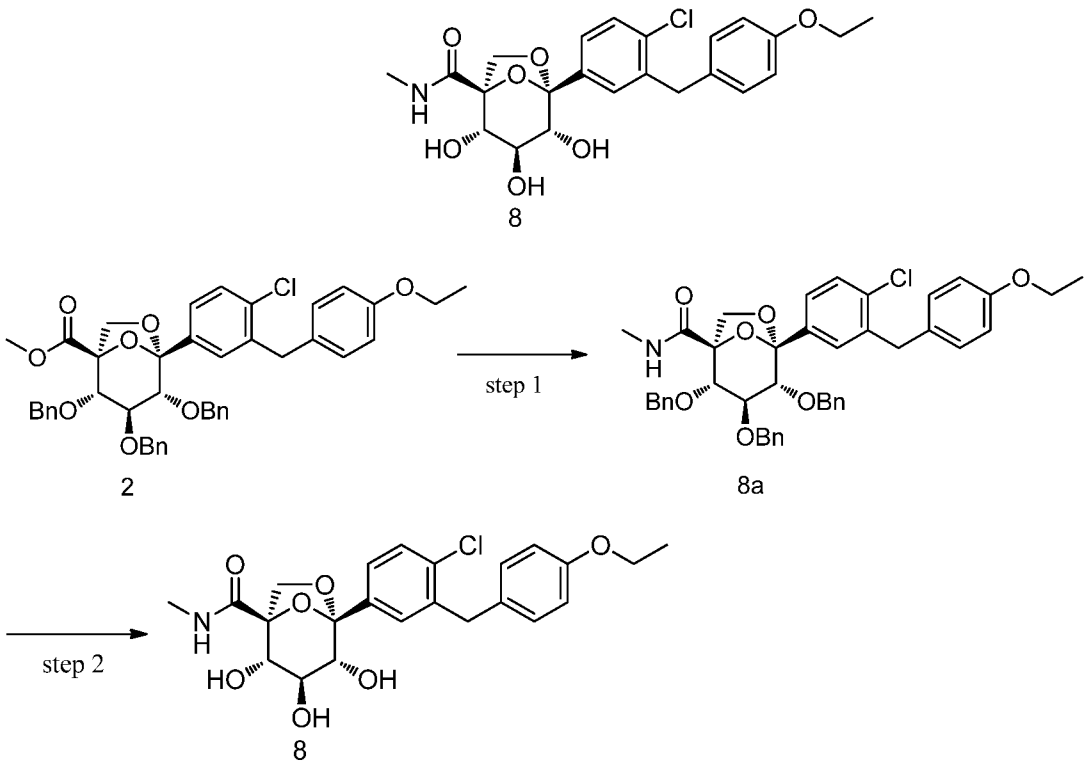
Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo

[3.2.1]octane-1-carboxamide **7**

[00132] To a solution of *o*-dichlorobenzene (0.04 mL, 0.35 mmol) and (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **7a** (49 mg, 0.11 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 5 mL) was added 10% Pd/C (8 mg, 0.008 mmol) at room temperature. The mixture was stirred under H_2 at room temperature for 4 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/5 to give the title compound **7** as colorless oil(19 mg, 60.0%, HPLC: 84.2%). The compound was characterized by the following spectroscopic data: MS (ESI, neg. ion)*m/z*: 448.2[M-H]$^-$; ^{1}H NMR(400MHz, DMSO-d_6) δ (ppm): 7.49 (m, 2H), 7.42 (m, 2H), 7.35(m, 1H), 7.09 (m, 2H), 6.83 (m, 2H), 5.24 (d, 1H), 5.19 (d, 1H), 5.03 (d, 1H), 4.22 (d, 1H), 3.97 (m, 4H), 3.75 (d, 1H), 3.69 (t, 1H), 3.43 (m, 2H), 1.29 (t, 3H).

Example 8

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*-methyl-6,8-dioxabicyclo [3.2.1]octane-1-carboxamide **8**



Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-*N*-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **8a**

[00133] To a solution of methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4- ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **2** (250 mg, 0.34 mmol, obtained from the synthetic

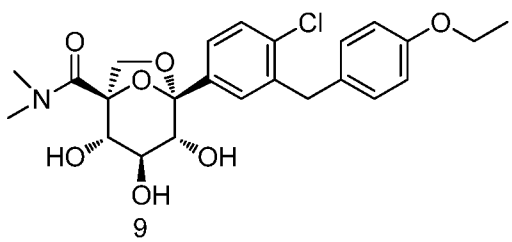
method described in example 2) in ethanol/tetrahydrofuran (v/v=2/1, 12 mL) was added dropwise methylamine (2.5 mL, 20.4 mmol). The mixture was stirred at 50 °C for 20 hours and quenched with water (15 mL). The resulting mixture was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with water (20 mL × 2) and saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **8a** as a white solid (173 mg, 69.2%). The compound was characterized by the following spectroscopic data: ^{1}H NMR(400MHz, $CDCl_3$) δ (ppm): 7.37 (t, 2H), 7.35 (s, 2H), 7.33(m, 1H), 7.31 (s, 2H), 7.28 (m, 4H), 7.24 (m, 2H), 7.15 (m, 3H), 7.05 (d, 2H), 6.82 (d, 2H), 6.75 (d, 2H), 6.20 (m, 1H), 4.80 (m, 3H), 4.62 (m, 2H), 4.26 (d, 1H), 4.02 (d, 2H), 3.97 (m, 4H), 3.87 (t, 2H), 3.66 (d, 1H), 2.79 (d, 3H), 1.38 (t, 3H).

Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **8**

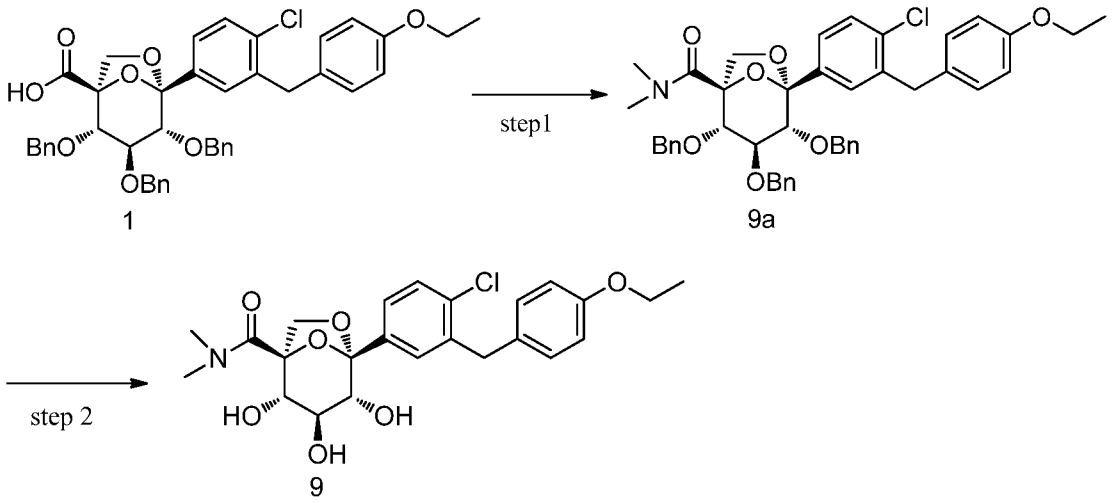
[00134] To a solution of *o*-dichlorobenzene (0.17 mL, 1.5 mmol) and (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-*N*-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **8a** (230 mg, 0.3 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL) was added 10% Pd/C (23 mg, 0.02 mmol) at room temperature. The mixture was stirred under H_2 at room temperature for 4 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/1 to give the title compound **8** as a white solid (103 mg, 73.6%, HPLC: 96.4%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion)*m/z*: 465.1[M+H]$^+$; ^{1}H NMR(400MHz, DMSO-d_6) δ (ppm): 7.95 (m, 1H), 7.45 (d, 1H), 7.41(d, 1H), 7.33(m, 1H), 7.08 (d, 2H), 6.82 (d, 2H), 5.37 (d, 1H), 5.21 (d, 1H), 4.85 (d, 1H), 4.24 (d, 1H), 3.98 (m, 4H), 3.76 (d, 1H), 3.67 (t, 1H), 3.46 (m, 2H), 2.60 (d, 3H), 1.30 (t, 3H).

Example 9

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*,*N*-dimethyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **9**



9



Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-*N*,*N*-dimethyl -6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **9a**

[00135] To a solution of methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **1** (0.19 g, 0.26 mmol, obtained from the synthetic method described in step 11 of example 1) in dichloromethane (10 mL) were added dimethylamine hydrochloride (32 mg, 0.39 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (101 mg, 0.53 mmol), 1-hydroxybenzotriazole (36 mg, 0.626 mmol) and 4-methylmorpholine (0.12 mL, 1.06 mmol) in turn. The mixture was stirred at room temperature for 16 hours, and then washed with water (5 mL × 2) and saturated aqueous sodium chloride (2 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=8/1 to give the title compound **9a** as a white solid (124 mg, 62.6%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.30 (m, 12H), 7.15 (m, 4H), 7.04 (d, 2H), 6.86(d, 2H), 6.74(d, 2H), 4.84(s, 2H), 4.63(m, 3H), 4.23(m, 2H), 4.00 (m, 6H), 3.87(d, 1H), 3.63(d, 1H), 3.03 (s, 3H), 3.84 (s, 3H), 1.39(t, 3H).

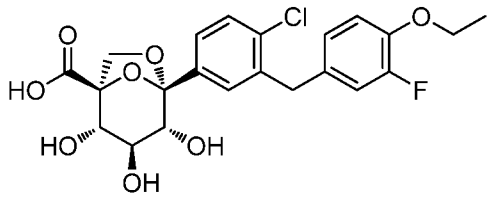
Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*,*N*-dimethyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **9**

[00136] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -*N*,*N*-dimethyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **9a** (142 mg, 0.19 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL) were added *o*-dichlorobenzene (0.11 mL, 0.95 mmol) and 10% Pd/C (15 mg, 0.01 mmol) at room temperature. The mixture was stirred under H_2 at room temperature for 3 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 5 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/4 to give the title compound **9** as a white solid (88 mg, 95.6%, HPLC: 96.5%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion)*m/z*: 478.1$[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 7.40 (d, 1H), 7.36 (d, 1H), 7.30(m, 1H), 7.09(d, 2H), 6.82 (d, 2H),

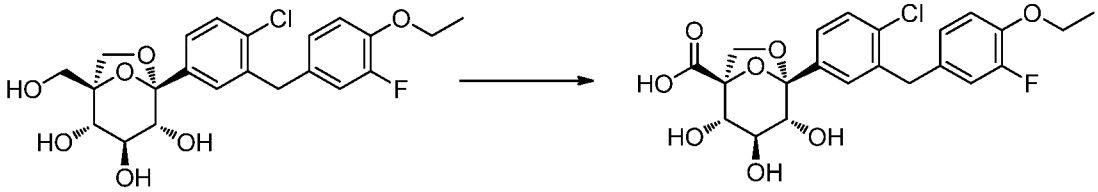
5.44 (d, 1H), 5.18 (d, 1H), 5.04 (d, 1H), 4.28 (d, 1H), 3.98 (m, 4H), 3.88 (d, 1H), 3.82 (t, 1H), 3.45 (m, 2H), 3.16 (s, 3H), 2.81(s, 3H), 1.29 (t, 3H).

Example 10

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **10**



10

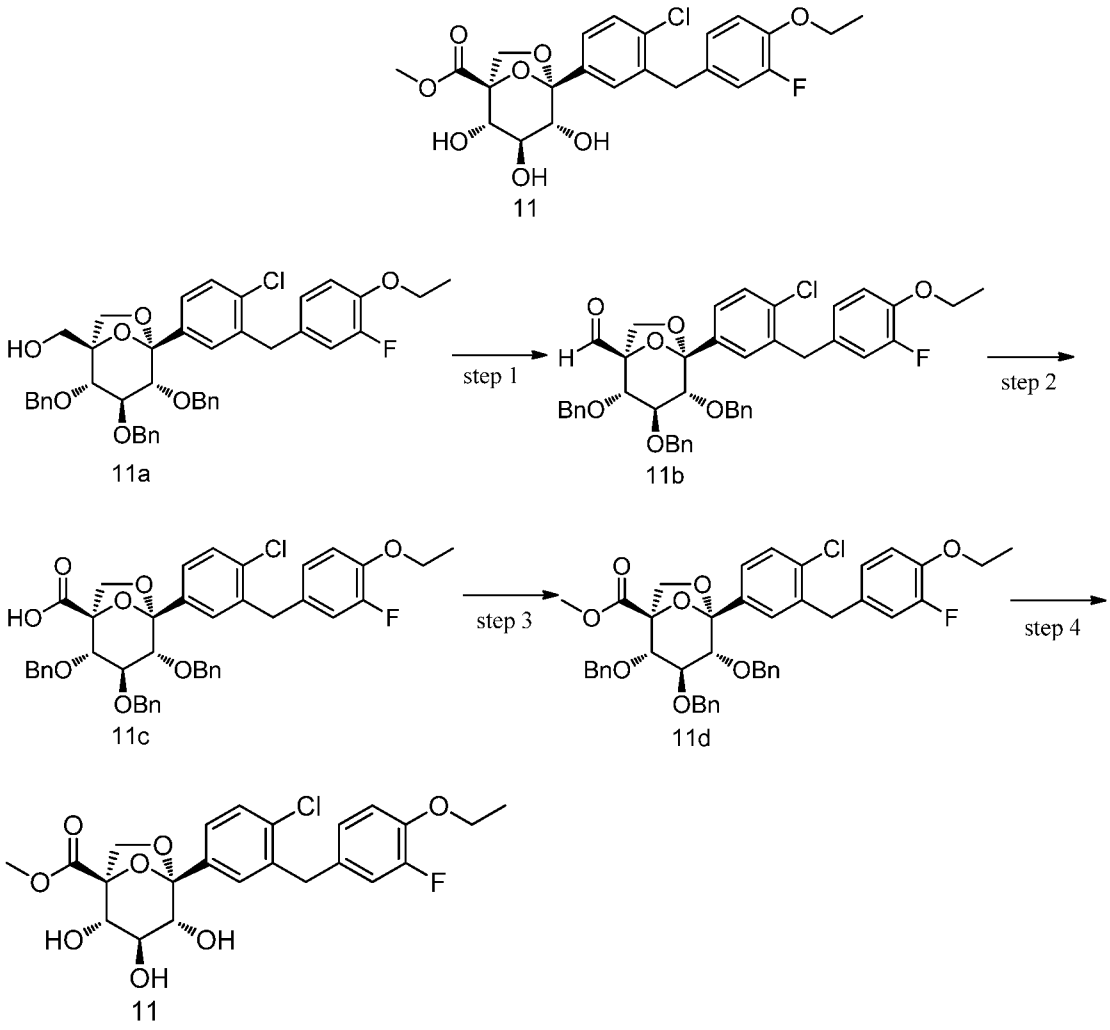


10a 10

[00137] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol **10a** (0.2 g, 0.44 mmol, bought from Carol cable Co., Ltd., Shanghai) in ethyl acetate (4 mL) were added sodium hypochlorite (0.45 mL, 0.66 mmol), 4-methoxy-2,2,6,6-tetramethylpiperidine 1-oxyl (19.7 mg, 0.11 mmol), saturated aqueous sodium bicarbonate (1 mL) and potassium bromide (5.23 mg, 0.04 mmol) in turn at room temperature. The mixture was stirred at room temperature for 28 hours and acidified with aqueous HCl. The resulting mixture was extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with water (20 mL × 2) and saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title compound **10** as a white solid (62 mg, 20.0%, HPLC: 98.3%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion)*m/z*: 469.0$[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ (ppm): 7.43 (m, 2H), 7.32 (m, 1H), 7.03(m, 2H), 6.91 (m, 1H), 5.60 (s, 1H), 5.10 (s, 3H), 4.23 (d, 1H), 4.06 (m, 2H), 4.01 (s, 2H), 3.88 (d, 1H), 3.78 (d, 1H), 3.48 (m, 2H), 1.32(t, 3H).

Example 11

Methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **11**



Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **11b**

[00138] To a solution of [(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy- 3-fluoro-phenyl) methyl] phenyl]- 6,8-dioxabicyclo[3.2.1]octan-1 -yl]methanol **11a** (1.9 g, 2.61 mmol, bought from Carol cable Co., Ltd., Shanghai) in dichloromethane (50 mL) was added 2-iodoxybenzoic acid (2.2 g, 7.86 mmol). The mixture was refluxed for 42 hours and then filtered. The filtrate was washed with water (20 mL × 2) and saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound **11b** as yellow oil (1.9 g, 100%). The crude product was used without further purification.

Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **11c**

[00139] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1- carbaldehyde **11b** (1.9 g, 2.62 mmol) in *tert*-butanol (50 mL) were added monopotassium phosphate (2.5 g, 18.3 mmol), sodium chlorite (2.13 g, 23.6 mmol) and 2-methyl-2-butene (13.3 mL, 125.6 mmol) in turn. The mixture was stirred at room temperature for 18 hours

and quenched with acetic acid (10 mL). The resulting mixture was extracted with ethyl acetate (40 mL ×3). The combined organic layers were washed with water (20 mL x 3) and saturated aqueous sodium chloride (20 mL × 3), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound **11c** as pale yellow oil (1.94g, 100%). The crude product was used without further purification.

Step 3) methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl)methyl]phenyl] -6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **11d**

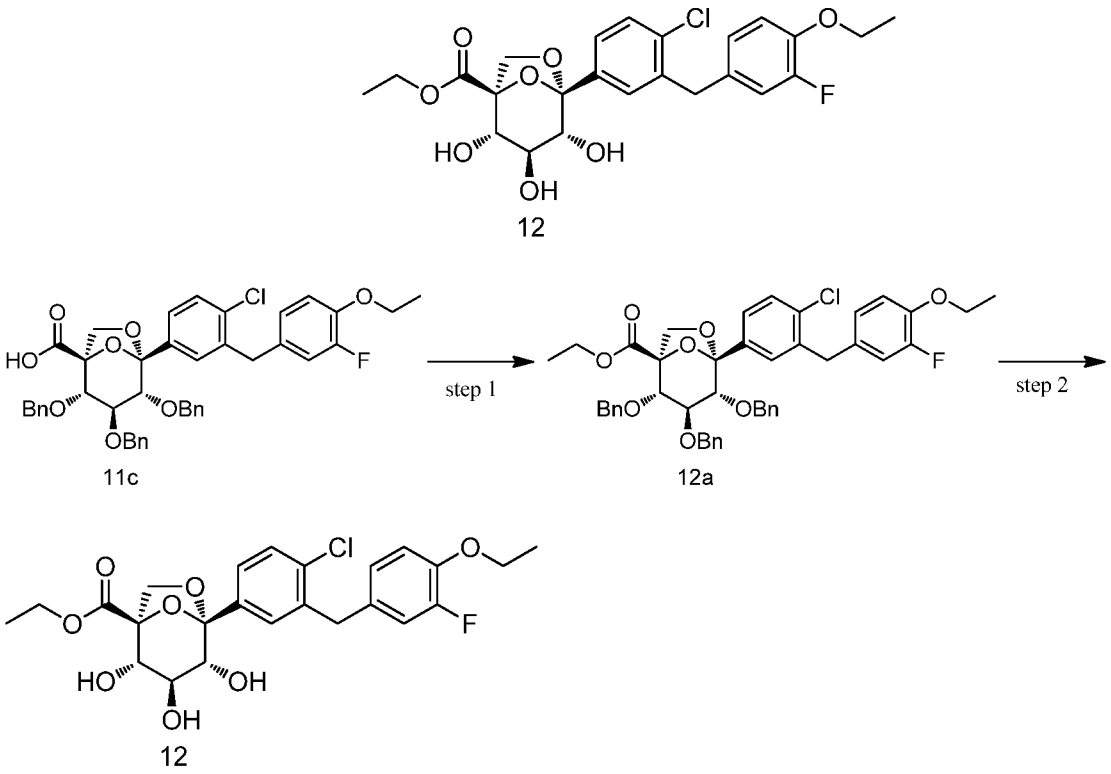
[00140] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **11c** (0.2 g, 0.27 mmol) in dichloromethane (20 mL) were added methanol (0.1 mL, 0.54 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (103.7 mg, 0.54 mmol), 1-hydroxybenzotriazole (36.6 mg, 0.27 mmol) and 4-methylmorpholine (0.12 mL, 1.08 mmol) in turn at room temperature. The mixture was stirred at room temperature for 48 hours, and then quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with water (20 mL × 2) saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=15/1 to give the title compound **11d** as yellow oil (88 mg, 43.3%).

Step 4) methyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **11**

[00141] To a solution of *o*-dichlorobenzene (0.08 mL, 0.73 mmol) and methyl(1*S*,2*S*,3*S*,4*R*,5*S*) -2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **11d** (110 mg, 0.15 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 5 mL) was added 10% Pd/C (6.5 mg, 0.006 mmol) at room temperature. The mixture was stirred under H_2 at room temperature for 3 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 5 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with DCM/MeOH(v/v)=25/1 to give the title compound **11** as a white solid (62 mg, 87.9%, HPLC: 94.0%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 483.2$[M+H]^+$; ^{1}H NMR(400MHz, DMSO-d_6) δ (ppm): 7.42 (m, 2H), 7.33 (m, 1H), 7.02 (m, 2H), 6.91 (m, 1H), 5.70 (d, 1H), 5.21 (d, 1H), 5.10 (d, 1H), 4.27 (d, 1H), 4.03 (m, 4H), 3.92 (d, 1H), 3.76 (t, 1H), 3.75 (t, 1H), 3.69 (s, 3H), 3.45 (m, 2H), 1.31 (t, 3H).

Example 12

Ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **12**



Step 1) ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **12a**

[00142] To a solution of ethanol (4 mL) and (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **11c** (0.35 g, 0.47 mmol, obtained from the synthetic method described in step 2 of example 11) in tetrahydrofuran (20 mL) was added sulphuric acid (0.1 mL, 0.05 mmol) at room temperature. The mixture was stirred at 55 °C for 14 hours and quenched with saturated aqueous ammonium chloride (5 mL). The resulting mixture was extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with water (10 mL × 2) and saturated aqueous sodium chloride (10 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **12a** as yellow oil (0.24 g, 69.6%). The compound was characterized by the following spectroscopic data: ^{1}H NMR(400MHz, $CDCl_3$) δ (ppm): 7.48 (d, 1H), 7.41 (m, 2H), 7.29 (m, 10H), 7.18 (m, 3H), 6.91 (m, 3H), 6.81 (m, 2H), 4.84 (m, 3H), 4.64 (d, 1H), 4.53 (d, 1H), 4.30 (d, 1H), 4.21 (m, 3H), 4.15 (m, 1H), 4.04 (m, 5H), 3.91 (d, 1H), 3.75 (d, 1H), 1.45 (t, 3H), 1.27 (t, 3H).

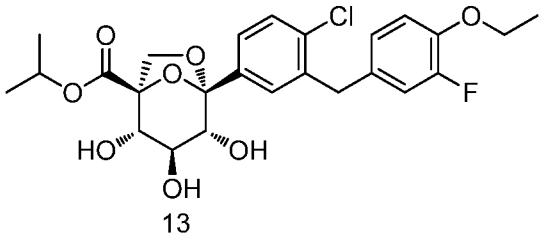
Step 2) ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **12**

[00143] To a solution of *o*-dichlorobenzene (0.18 mL, 1.56 mmol) and ethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **12a** (0.24 mg, 0.31 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 30 mL) was added 10% Pd/C

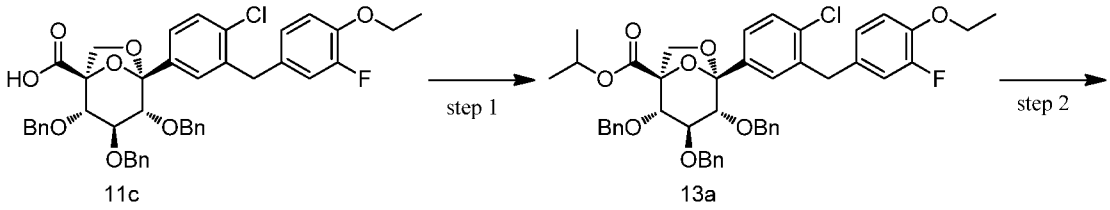
(40 mg, 0.03 mmol). The mixture was stirred at room temperature under H_2 for 4 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/5 to give the title compound **12** as colorless oil (0.11 g, 68.8%, HPLC: 93.2%). The compound was characterized by the following spectroscopic data: MS (ESI, neg. ion) *m/z*: 541.0[M+HCOO]$^-$; ^{1}H NMR(400MHz, DMSO-d_6) δ (ppm): 7.43 (m, 2H), 7.32 (m, 1H), 7.02 (m, 2H), 6.91 (m, 1H), 5.68 (d, 1H), 5.21 (d, 1H), 5.09 (d, 1H), 4.26 (d, 1H), 4.15 (m, 1H), 4.04 (m, 4H), 3.92 (d, 1H), 3.76 (t, 1H), 3.52 (d, 1H), 3.46 (m, 2H), 1.31 (t, 3H), 1.20 (t, 3H)

Example 13

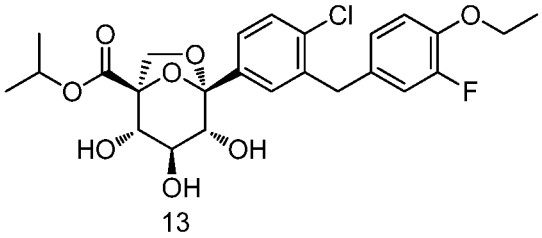
Isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **13**



13



11c 13a



13

Step 1) Isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **13a**

[00144] To a solution of isopropanol (20 mL) and (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **11c** (0.41 g, 0.55 mmol, obtained from the synthetic method described in step 2 of example 11) in tetrahydrofuran (50 mL) was added sulphuric acid (0.1 mL, 0.06 mmol) at room temperature. The mixture was stirred at 65 °C for 20 hours and then quenched with saturated aqueous ammonium chloride (10 mL). The resulting mixture was extracted with ethyl acetate (50 mL × 2). The combined organic layers were washed with water (30 mL × 2)

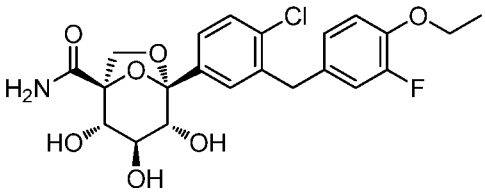
and saturated aqueous sodium chloride (30 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=10/1 to give the title compound **13a** as colorless oil (0.14 g, 33.3%). The compound was characterized by the following spectroscopic data: ^{1}H NMR(400MHz, $CDCl_3$) δ (ppm): 7.45 (d, 1H), 7.37 (m, 2H), 7.30 (m, 6H), 7.23 (m, 4H), 7.16 (m, 3H), 6.89 (m, 3H), 6.82 (m, 1H), 6.75 (m, 1H), 5.05 (m, 1H), 4.83 (m, 3H), 4.66 (d, 1H), 4.51 (d, 1H), 4.28 (d, 1H), 4.19 (d, 2H), 4.04 (m, 3H), 3.99 (s, 1H), 3.95 (d, 1H), 3.86 (d, 1H), 3.71 (d, 1H), 1.40 (t, 3H), 1.25 (d, 3H), 1.22 (d, 3H).

Step 2) isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **13**

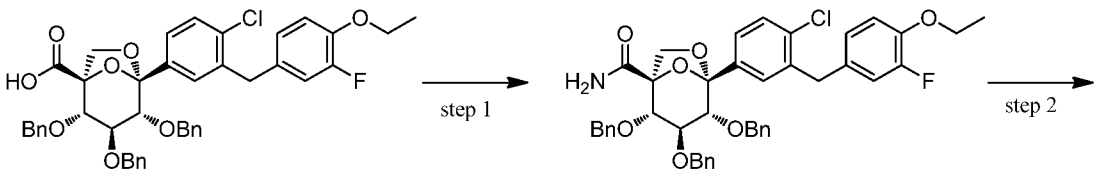
[00145] To a solution of *o*-dichlorobenzene (0.1 mL, 0.89 mmol) and isopropyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **13a** (0.14 mg, 0.18 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 20 mL) was added 10% Pd/C (22 mg, 0.02 mmol). The mixture was stirred at room temperature under H_2 for 4 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=1/4 to give the title compound **13** as colorless oil (50 mg, 55.0%, HPLC: 92.0%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 511.1[M+H]$^+$; ^{1}H NMR(400MHz, DMSO-d_6) δ (ppm): 7.43 (m, 2H), 7.32 (m, 1H), 7.07 (m, 1H), 7.01 (m, 1H), 6.92 (m, 1H), 5.68 (d, 1H), 5.19 (d, 1H), 5.07 (d, 1H), 4.95 (m, 1H), 4.25 (d, 1H), 4.03 (m, 4H), 3.90 (m, 1H), 3.76 (t, 1H), 3.51 (m, 1H), 3.46 (m, 1H), 1.31 (t, 3H), 1.21 (d, 3H), 1.18 (d, 3H).

Example 14

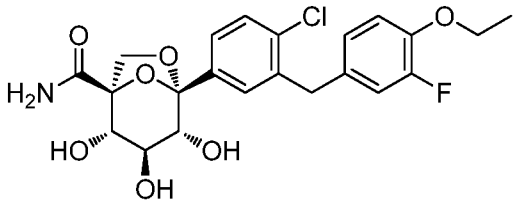
(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **14**



14



11c 14a



14

Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **14a**

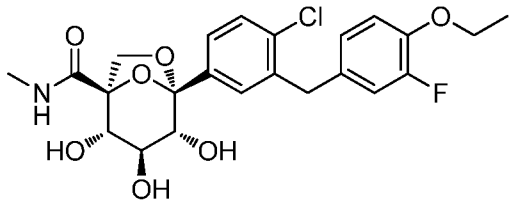
[00146] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **11c** (50 mg, 0.07 mmol, obtained from the synthetic method described in step 2 of example 11) in tetrahydrofuran (10 mL) were added ammonium hydroxide (4.7 mg, 0.14 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (26 mg, 0.14 mmol), 1-hydroxybenzotriazole (9.1 mg, 0.07 mmol) and 4-methylmorpholine *N*-oxide monohydrate (29 mg, 0.27 mmol) in turn at room temperature. The mixture was stirred at room temperature for 4 hours and then diluted with ethyl acetate 30 mL. The resulting mixture was washed with water (10 mL × 2) and saturated aqueous sodium chloride (10 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=4/1 to give the title compound **14a** as a white solid (38 mg, 76.0%).

Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **14**

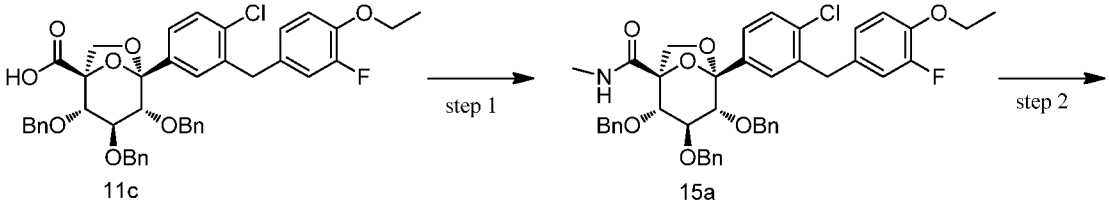
[00147] To a solution of *o*-dichlorobenzene (0.17 mL, 1.50 mmol) and (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbox amide **14a** (222 mg, 0.3 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL) was added 10% Pd/C (33 mg, 0.03 mmol). The mixture was stirred at room temperature under H_2 for 3 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with DCM/MeOH (v/v)=25/1 to give the title compound **14** as a white solid (62 mg, 44.2%, HPLC: 96.8%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 432.2[M-2H_2O+H]$^+$; ^{1}H NMR(400MHz, DMSO-d_6) δ (ppm): 7.47 (m, 2H), 7.40 (m, 3H), 7.05 (m, 2H), 6.92 (m, 1H), 5.39 (d, 1H), 5.20 (d, 1H), 5.04 (d, 1H), 4.22 (d, 1H), 4.03 (m, 4H), 3.76 (d, 1H), 3.73 (t, 1H), 3.43 (m, 2H), 1.31 (t, 3H).

Example 15

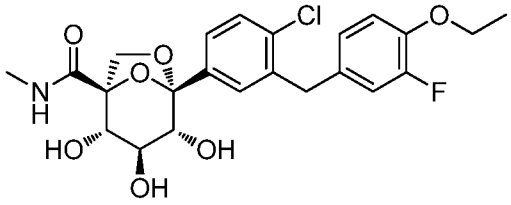
(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*-methyl-6,8-dio xabicyclo[3.2.1]octane-1-carboxamide **15**



15



11c 15a



15

Step 1)

(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-*N*-methyl -6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **15a**

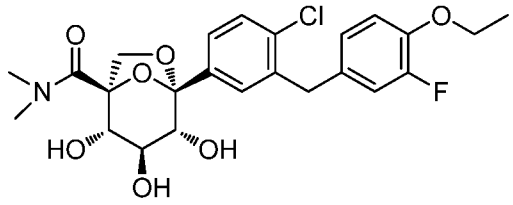
[00148] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluorophenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **11c** (0.25 g, 0.34 mmol, obtained from the synthetic method described in step 2 of example 11) in dichloromethane (50 mL) were added methylamine hydrochloride (45.7 mg, 0.68 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13g, 0.68 mmol), 1-hydroxybenzotriazole (45.7 mg, 0.34 mmol) and 4-methylmorpholine (0.15 mL, 1.35 mmol) in turn at room temperature. The mixture was stirred at room temperature for 18 hours and then quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with water (20 mL × 2) and saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=4/1 to give the title compound **15a** as a yellow solid (0.24 g, 71.0%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 11H), 7.26 (m, 2H), 7.18 (m, 3H), 6.86 (m, 5H), 6.23 (m, 1H), 4.83 (m, 3H), 4.65 (dd, 2H), 4.32 (d, 1H), 4.08 (m, 2H), 4.00 (m, 4H), 3.92 (m, 2H), 3.69 (d, 1H), 2.81 (d, 3H), 1.43 (t, 3H).

Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*-methyl -6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **15**

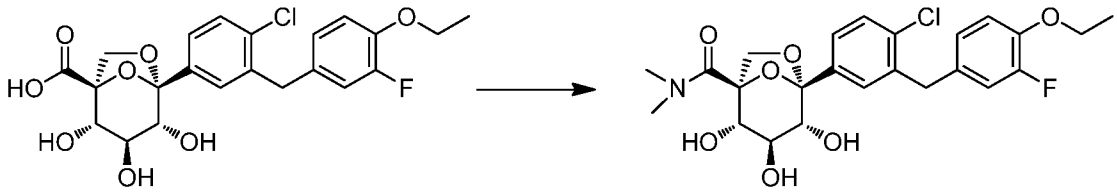
[00149] To a solution of *o*-dichlorobenzene (0.18 mL, 1.56 mmol) and (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-*N*-methyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **15a** (0.24 g, 0.32 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 30 mL) was added 10% Pd/C (36 mg, 0.03 mmol). The mixture was stirred at room temperature under H_2 for 4 hours and then filtered. The filter cake was washed with a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL × 2). The combined filtrates were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=1/5 to give the title compound **15** as colorless oil (0.12 g, 80.5%, HPLC: 95.1%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 482.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.95 (m, 1H), 7.49 (m, 1H), 7.43 (m, 1H), 7.35 (m, 1H), 7.04 (m, 2H), 6.91 (m, 1H), 5.36 (d, 1H), 5.21 (d, 1H), 5.06 (d, 1H), 4.24 (d, 1H), 5.05 (m, 4H), 3.77 (d, 1H), 3.67 (t, 1H), 3.45 (m, 2H), 2.60 (d, 3H), 1.32 (t, 3H).

Example 16

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxy-3-fluoro-phenyl)methyl]phenyl]-2,3,4-trihydroxy-*N*,*N*-dimethyl-6,8-dioxabicyclo[3.2.1]octane-1-carboxamide **16**



16



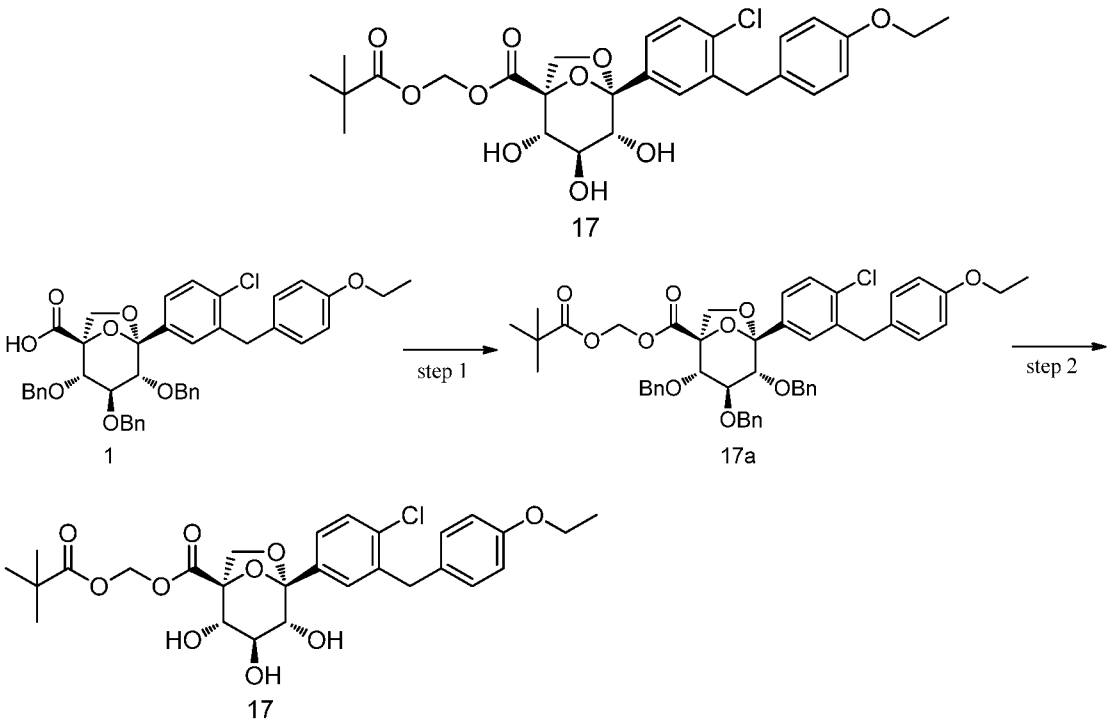
10 16

[00150] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxy-3-fluoro-phenyl) methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **10** (0.3 g, 0.64 mmol, obtained from the synthetic method described in example 10) in *N*,*N*-dimethylformamide (50 mL) were added dimethylamine hydrochloride (78.3 mg, 0.96 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.25 g, 1.28 mmol), 1-hydroxybenzotriazole (86.5 mg, 0.64 mmol) and 4-methylmorpholine (0.29 mL, 2.56 mmol) in turn. The mixture was stirred at room temperature for 12 hours, and then washed with water (20 mL × 3) and saturated aqueous sodium chloride (20 mL × 3), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified to give the title compound **16** as colorless oil (61.2 mg, 20.0%, HPLC: 94.5%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 496.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 (m, 2H), 7.32 (m, 1H), 7.05 (m, 2H), 6.94 (d, 1H), 5.46 (d, 1H),

5.19 (d, 1H), 5.07 (d, 1H), 4.29 (d, 1H), 4.05 (m, 4H), 3.89 (d, 1H), 3.83 (d, 1H), 3.44 (m, 1H), 3.29 (m, 1H), 3.17 (s, 3H), 2.81 (s, 3H), 1.32 (t, 3H)

Example 17

2,2-Dimethylpropanoyloxymethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **17**



Step 1) 2,2-dimethylpropanoyloxymethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1- carboxylate **17a**

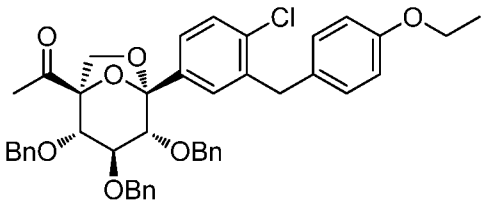
[00151] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3[(4- ethoxyphenyl)methyl]phenyl] -6,8-dioxabicyclo[3.2.1]octane-1-carboxylic acid **1** (0.5 g, 0.69 mmol, obtained from the synthetic method described in step 11 of example 1) and chloromethyl pivalate (0.15 mL, 1.04 mmol) in a *N*,*N*-dimethylformamide/dicholoromethane mixture (v/v=4/1, 16 mL) was added triethylamine (0.17 mL, 1.25 mmol). The mixture was stirred at room temperature for 3 hours and then quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (40 mL × 6). The combined organic layers were washed with water (50 mL × 2) and saturated aqueous sodium chloride (50 mL × 3), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=20/1 to give the title compound **17a** as a white solid (307 mg, 52.9%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (s, 1H), 7.38 (s, 2H), 7.35-7.27 (m, 6H), 7.25-7.18 (m, 7H), 7.17 (m, 2H), 7.07 (d, 2H), 6.87 (d, 2H), 5.74 (d, 2H), 4.82 (d, 1H), 4.79 (m, 2H), 4.69 (d, 1H), 4.53 (d, 1H), 4.26 (m, 1H), 4.06 (d, 1H), 4.02-3.96 (m, 4H), 3.86 (d, 1H), 3.72 (d, 1H), 1.40 (t, 3H), 1.14 (s, 9H).

Step 2) 2,2-dimethylpropanoyloxymethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1- carboxylate **17**

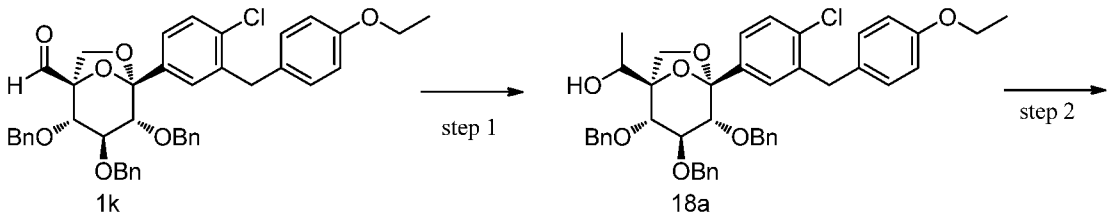
[00152] To a solution of 2,2-dimethylpropanoyloxymethyl(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3- [(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carboxylate **17a** (305 mg, 0.36 mmol) in a methanol/tetrahydrofuran mixture (v/v=4/1, 10 mL) were added *o*-dichlorobenzene (0.2 mL, 1.83 mmol) and 10% Pd/C (45.8 mg, 0.04 mmol) in turn at room temperature. The mixture was stirred at room temperature under H_2 for 4 hours and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=1/2 to give the title compound **17** as a white solid (108 mg, 54.0%, HPLC: 90.6%). The compound was characterized by the following spectroscopic data: MS(ESI, pos.ion) *m/z*:565.3[M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.42 (m, 2H), 7.31 (m, 1H), 7.08 (m, 2H), 6.83 (m, 2H), 5.78 (s, 2H), 5.63 (brs, 1H), 5.15 (brs, 2H), 4.31 (d, 1H), 4.02-3.95 (m, 4H), 3.88 (d, 1H), 3.75 (d, 1H), 3.48(m, 2H), 1.30 (t, 3H), 1.12 (s, 9H).

Example 18

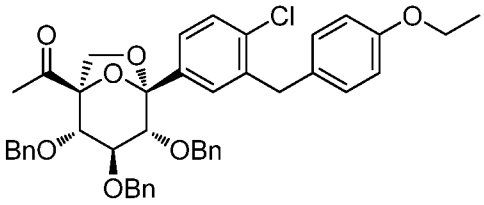
1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanoe **18**



18



1k 18a



18

Step 1) 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanol **18a**

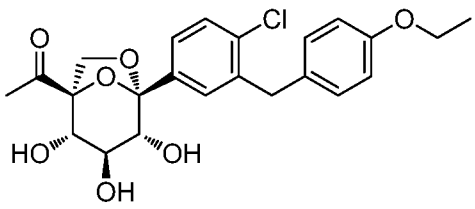
[00153] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] -6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (3.02 g, 4.26 mmol, obtained from the synthetic method described in step 10 of example 1) in tetrahydrofuran (40 mL) was added dropwise methylmagnesium bromide (2.13 mL, 6.39 mmol, 3 M in ethyl ether) over a period of 5 min at −10 °C. The mixture was stirred at room temperature for 16 hours and then quenched with 5 mL of water. The aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified to give the title compound **18a** as pale yellow oil (2.0 g, 65.0%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.48 (m, 2H), 7.45 (m, 1H), 7.30 (m, 10H), 7.19 (m, 3H), 7.05 (m, 2H), 6.85 (m, 2H), 6.75 (m, 2H), 5.04 (m, 1H), 4.80 (m, 3H), 4.30 (d, 1H), 4.11 (m, 1H), 4.01 (m, 3H), 3.98 (m, 5H), 3.79 (m, 2H), 1.28 (t, 3H), 1.13 (d, 3H).

Step 2) 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanoe **18**

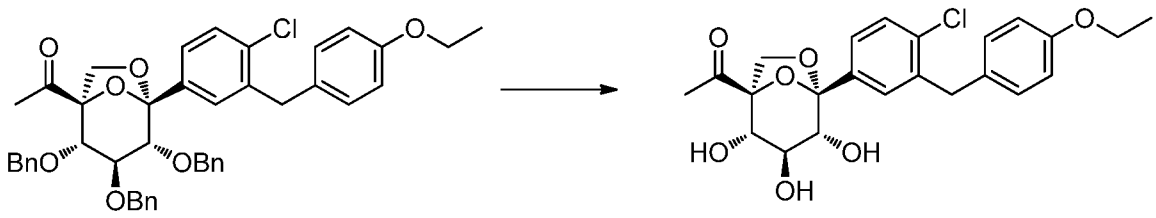
[00154] To a solution of 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanol **18a** (0.5 g, 0.69 mmol) in dichloromethane (10 mL) were added saturated aqueous sodium bicarbonate (7.4 mL, 6.9 mmol), potassium bromide (50 mg, 0.42 mmol) and 2,2,6,6-tetramethylpiperidinooxy (10 mg, 64 mmol) in turn at 0 °C, and then sodium hypochlorite (1.5 mL, 1.8 mmol, 3.28% available chlorine) was added dropwise. The mixture was stirred at 0 °C for 0.5 hour and then extracted with dichloromethane (10 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc(v/v)=4/1 to give the title compound **18** as a white solid (0.25 g, 50%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 12H), 7.20 (m, 4H), 7.08 (d, 2H), 6.90 (d, 2H), 6.77 (d, 2H), 4.86 (dd, 2H), 4.73 (d, 1H), 4.62 (d, 1H), 4.51 (d, 1H), 4.27 (d, 1H), 4.00 (m, 7H), 3.88 (d, 1H), 3.73 (d, 1H), 2.14 (s, 3H), 1.41 (t, 3H).

Example 19

1-[(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanone **19**



19

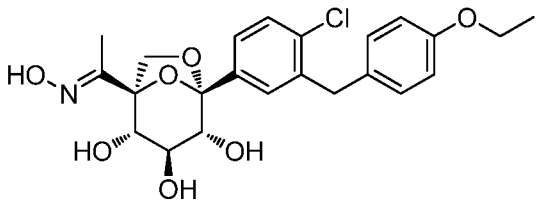


18 19

[00155] To a solution of 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanoe **18** (0.25 g, 0.35 mmol, obtained from the synthetic method described in step 2 of example 18) in a methanol/tetrahydrofuran mixture (v/v=10/1, 16.5 mL) were added *o*-dichlorobenzene (0.09 mL, 0.74 mmol) and 10% Pd/C (37 mg, 0.03 mmol) in turn at room temperature. The mixture was stirred at room temperature under H_2 for 2 hours and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=2/1 to give the title compound **19** as a pale yellow solid (0.14 g, 89.0%, HPLC: 98.0%). The compound was characterized by the following spectroscopic data: MS (ESI, neg. ion) *m/z*: 493.10 $[M+HCOO]^-$; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.42 (d, 2H), 7.33 (d, 1H), 7.10 (d, 2H), 6.84 (d, 2H), 5.59 (d, 1H), 5.26 (d, 1H), 5.11 (d, 1H), 4.22 (d, 1H), 3.97 (m, 4H), 3.75 (m, 2H), 3.49 (m, 2H), 2.23 (s, 3H), 1.30 (t, 3H).

Example 20

(*E*)-1-[(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3. 2.1]octan-1-yl]ethanone oxime **20**



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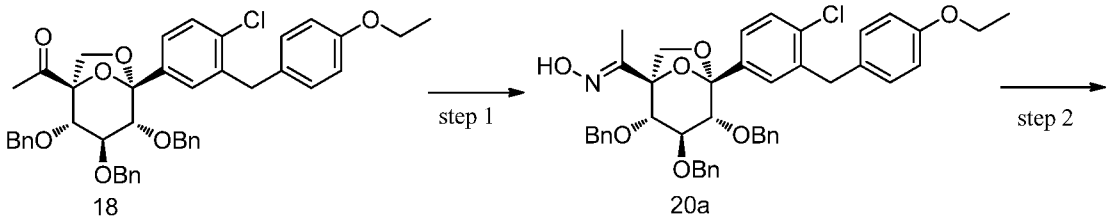
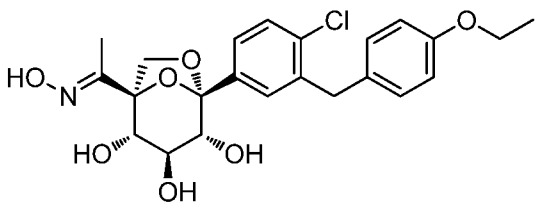


18 20a



20

Step 1) 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanoe oxime **20a**

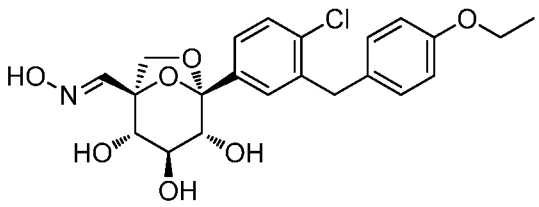
[00156] To a solution of 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanoe **18** (0.25 g, 0.35 mmol, obtained from the synthetic method described in step 2 of example 18) in a ethanol/tetrahydrofuran mixture (v/v =10/1, 33 mL) were added hydroxylamine hydrochloride (70 mg, 1.0 mmol) and pyridine (0.03 mL, 0.35 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=9/1 to give the title compound **20a** as a white solid (0.15 g, 59.0%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.32 (s, 1H), 7.48 (m, 2H), 7.42 (d, 1H), 7.24 (m, 13H), 7.05 (d, 2H), 6.83 (d, 2H), 6.75 (d, 2H), 4.77 (dd, 2H), 4.63 (d, 1H), 4.48 (d, 1H), 4.31 (m, 2H), 3.89 (m, 9H), 1.94 (s, 3H), 1.28 (t, 3H).

Step 2) 1-[(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanone oxime **20**

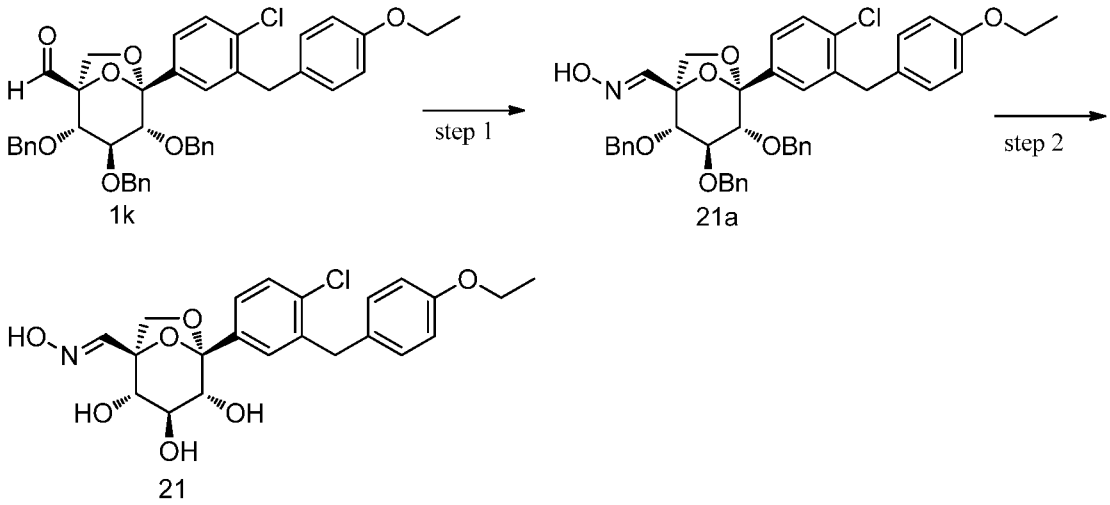
[00157] To a solution of 1-[(1*R*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]ethanoe oxime **19a** (0.15 g, 0.02 mmol) in a methanol/tetrahydrofuran mixture (v/v=1/4, 20 mL) were added *o*-dichlorobenzene (0.14 mL, 1.0 mmol) and 10% Pd/C (21 mg, 0.02 mmol) at room temperature. The mixture was stirred at room temperature under H_2 for 1.5 hours and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=2/1 to give the title compound **20** as a white solid (60 mg, 65.0%, HPLC: 98.3%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 464.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.99 (s, 1H), 7.40 (d, 2H), 7.30 (d, 1H), 7.09 (d, 2H), 6.83 (d, 2H), 5.30 (d, 1H), 5.13 (d, 1H), 5.01 (d, 1H), 4.15 (d, 1H), 3.97 (m, 5H), 3.63 (m, 1H), 3.46 (m, 2H), 1.84 (s, 3H), 1.30 (t, 3H).

Example 21

(1*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde oxime **21**



21



Step 1) (1*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde oxime **21a**

[00158] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (3.5 g, 4.9 mmol, obtained from the synthetic method described in step 10 of example 1) in ethanol (20 mL) were added hydroxylamine hydrochloride (1.02 g, 14.7 mmol) and pyridine (3 mL) at room temperature. The mixture was stirred at room temperature for 1 hour and concentrated *in vacuo* to afford white sticky oil. To the white sticky oil was added 10 mL of deionized water. The mixture was stirred, and white solid was precipitate out. The mixture was filtered. The filtrate was extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=5/1 to give the title compound **21a** as a white solid (2.85 g, 79.8%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.73 (m, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.38 (d, 2H),7.33 (m, 6H), 7.29 (s, 2H), 7.28 (s, 2H), 7.19 (m, 3H), 7.07 (d, 2H), 6.88 (d, 2H), 6.76 (d, 2H), 4.86 (dd, 2H), 4.79 (d, 1H), 4.70 (d, 1H), 4.49 (d, 1H), 4.26 (d, 1H), 4.02 (m, 6H), 3.89 (m, 2H), 3.71 (d,1H), 1.40 (t, 3H).

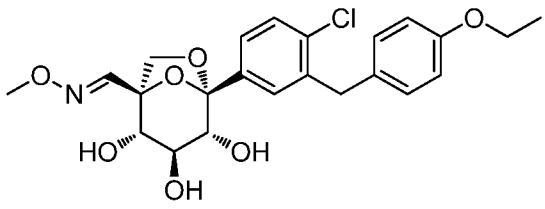
Step 2) (1*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde oxime **21**

[00159] To a solution of (1*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4- ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde oxime **21a** (0.3 g, 0.42 mmol) in a methanol/tetrahydrofuran mixture (v/v=10/1, 5.5 mL) were added *o*-dichlorobenzene (0.3 mL, 2.7 mmol) and 10% Pd/C (45 mg, 0.04 mmol) at room temperature. The mixture was stirred at room temperature under H_2 for 2 hours and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=1/1 to give the title compound **21** as a pale yellow solid (0.15 g, 79.4%, HPLC: 90.9%). The compound was characterized by the following spectroscopic data: MS (ESI, pos.

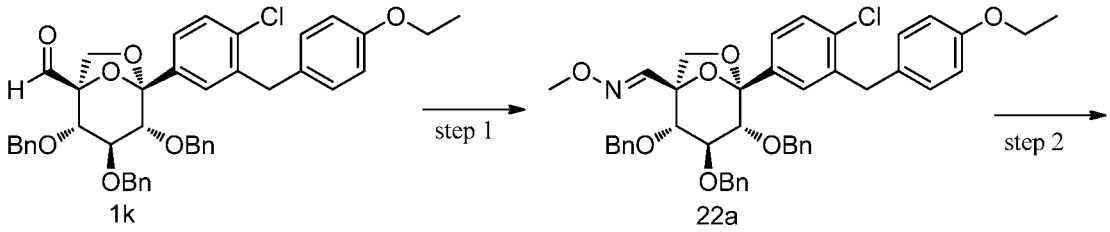
ion) *m/z*: 450.1[M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.26(m, 1H), 7.42(m, 3H), 7.30 (dd, 2H), 7.09 (d, 2H), 6.83 (d, 1H), 4.17 (d, 1H), 4.01 (m, 5H), 3.89 (d, 1H), 3.59 (dd, 1H), 3.45 (d, 4H), 1.30 (t, 3H).

Example 22

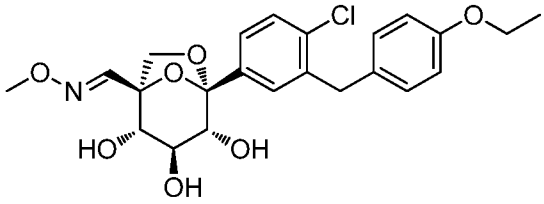
(*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde *O*-methyl oxime **22**



22



1k 22a



22

[00160] Step 1) *N*-methoxy-1-[(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3- [(4-ethoxyphenyl)methyl] phenyl] -6,8-dioxabicyclo[3.2.1]octan-1-yl]methanimine **22a**

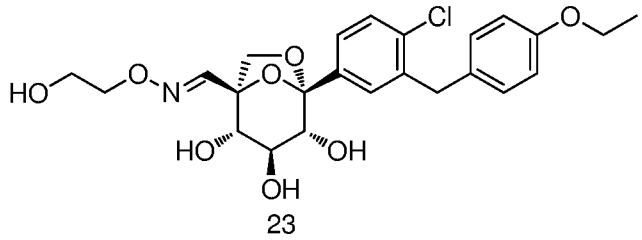
[00161] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (0.7 g, 0.99 mmol, obtained from the synthetic method described in step 10 of example 1) in dichloromethane (5 mL) were added methoxyammonium chloride (0.25 g, 2.98 mmol), ethanol (3 mL) and pyridine (0.1 mL) in turn at room temperature. The mixture was stirred at room temperature under N_2 for 0.5 hour and then quenched with water (10 mL). The resulting mixture was extracted with dichloromethane (20 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=5/1 to give the title compound **22a** as a pale yellow soild (0.45 g, 61.8%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.76 (s, 1H), 7.48 (dd, 2H), 7.41 (dd, 1H), 7.29 (m, 10H), 7.18 (m, 3H), 7.05 (d, 2H), 6.83 (d, 2H), 6.75 (d, 2H), 4.75 (dd, 3H), 4.66 (d, 1H), 4.30 (dd, 2H), 3.99 (m, 4H), 3.92 (q, 2H), 3.86 (dd, 1H), 3.82 (d, 1H), 3.79 (d, 3H), 3.75 (d, 1H), 1.28 (t, 3H).

Step 2) (*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1] octane-1-carbaldehyde *O*-methyl oxime **22**

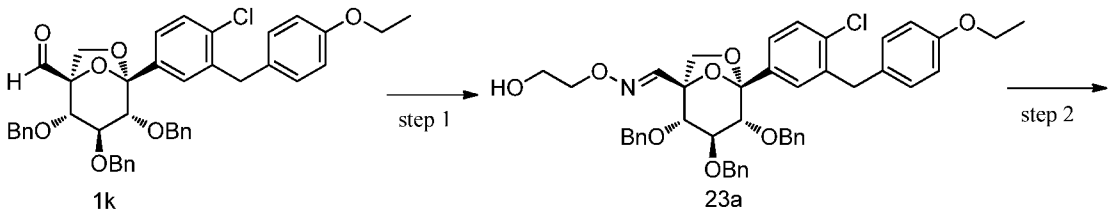
[00162] To a solution of *N*-methoxy-1-[(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]methanimine **22a** (0.4 g, 0.54 mmol) in a methanol/tetrahydrofuran mixture (v/v=10/1, 7.7 mL) were added *o*-dichlorobenzene (0.4 mL) and 10% Pd/C (57 mg, 0.05 mmol) at room temperature. The mixture was stirred at room temperature under H_2 for 1.5 hours and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=1/1 to give the title compound **22** as a pale yellow solid (0.187 g, 74.1%, HPLC: 96.2%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*:464.1[M+H]$^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.55 (s, 1H), 7.40 (m, 2H), 7.30 (m, 1H), 7.09 (d, 2H), 6.83 (d, 2H), 5.52 (s, 1H), 5.07 (s, 2H), 4.17 (d, 1H), 3.99 (m, 5H), 3.86 (d, 1H), 3.77 (s, 3H), 3.61 (d, 1H), 1.98 (d, 1H), 1.30 (t, 3H).

Example 23

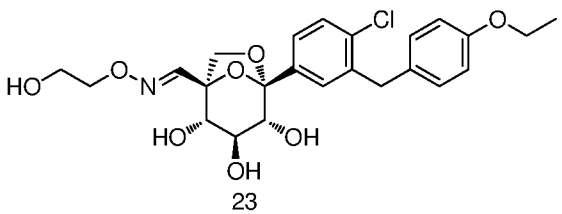
(*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1 -carbaldehyde *O*-(2-hydroxyethyl) oxime **23**



23



1k 23a



23

Step 1) 2-[(*E*)-[(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]methyleneamino]oxyethanol **23a**

[00163] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (1.0 g, 1.4 mmol, obtained from the synthetic

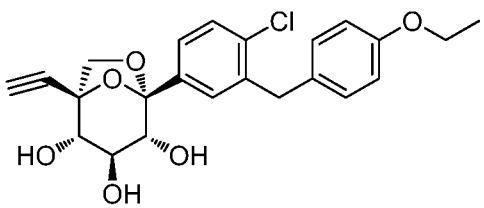
method described in step 10 of example 1) in dichloromethane (5 mL) were added 2-(aminooxy)ethanol (324 mg, 4.2 mmol), ethanol (4 mL) and pyridine (0.1 mL) in turn at room temperature. The mixture was stirred at room temperature for 12 hours and then quenched with water (10 mL). The resulting mixture was extracted with dichloromethane (20 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=5/1 to give the title compound **23a** as a pale yellow soild (0.71 g, 65.4%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 1H), 7.48 (d, 2H), 7.41 (d, 1H), 7.31 (dt, 10H), 7.17 (m, 3H), 7.05 (d, 2H), 6.83 (d, 2H), 6.75 (d, 2H), 4.71 (m, 4H), 4.30 (t, 2H), 4.03 (dd, 5H), 3.93 (dd, 3H), 3.86 (d, 1H), 3.79 (dd, 2H), 3.56 (s, 2H), 3.44 (s, 1H), 1.28 (t, 3H).

Step 2) (*E*)-(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1] octane-1-carbaldehyde *O*-(2-hydroxyethyl) oxime **23**

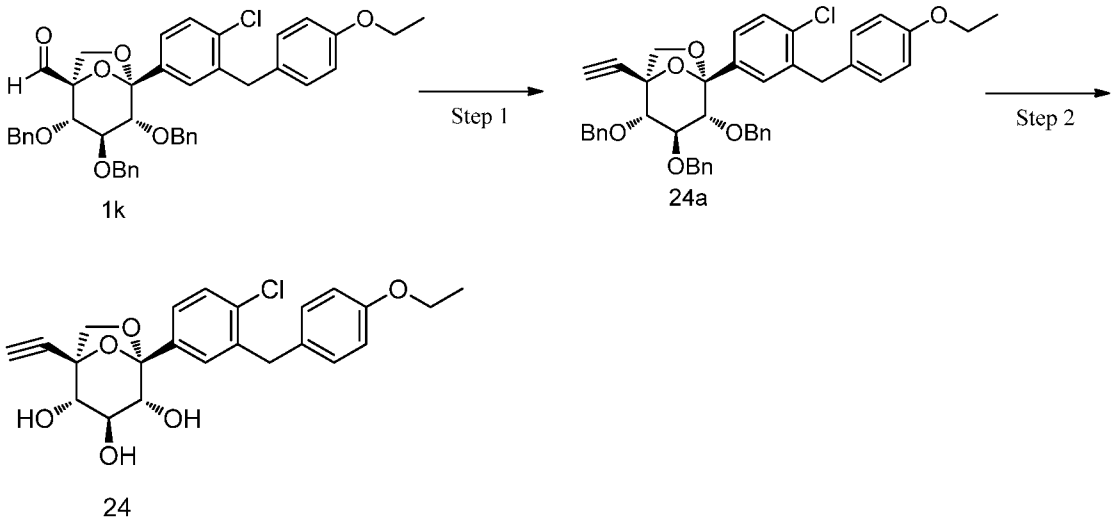
[00164] To a solution of 2-[(*E*)-[(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3- [(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octan-1-yl]methyleneamino]oxyethanol **23a** (0.7 g, 0.92 mmol) in a methanol/tetrahydrofuran mixture (v/v=10/1, 16.5 mL) were added *o*-dichlorobenzene (0.8 mL, 7.07 mmol) and 10% Pd/C (98 mg, 0.09 mmol) at room temperature. The mixture was stirred at room temperature under H_2 for 2 hours and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=1/1 to give the title compound **23** as a pale yellow solid (378 mg, 83.6%, HPLC: 94.9%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 494.2[M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.57 (s, 1H), 7.41 (d, 2H), 7.30 (d, 1H), 7.10 (d, 2H), 6.84 (d, 2H), 5.48 (d, 1H), 5.18 (d, 1H), 5.05 (d, 1H), 4.67 (t, 1H), 4.18 (d, 1H), 4.00 (dq, 6H), 3.87 (d, 1H), 3.62 (t, 1H), 3.56 (dd, 2H), 3.46(m, 2H), 1.30 (t, 3H).

Example 24

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-1-ethynyl-6,8-dioxabicyclo[3.2.1]octane-2,3 ,4-triol **24**



24



Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-1-ethynyl-6,8-dioxabicyclo[3.2.1]octane **24a**

[00165] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4- ethoxyphenyl)methyl]phenyl] -6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (0.8 g, 1.14 mmol) in a methanol/acetonitrile mixture (v/v = 5/1, 24 mL) were added potassium carbonate (0.24 g, 1.7 mmol) and (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester (0.25 g, 1.36 mmol) at room temperature in turn. The mixture was stirred at room temperature for 6 hours under N_2. Most of the solvent was removed *in vacuo*. The residue was diluted with ethyl acetate (20 mL). The resulting mixture was washed with water (10 mL × 2) and saturated aqueous sodium chloride (10 mL × 2), and then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=8/1 to give the title compound **24a** as a white soild (0.74 g, 93.5%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (s, 1H), 7.39(m, 6H), 7.30 (m, 6H), 7.19(m, 3H), 7.09 (d, 2H), 6.86 (m, 2H), 6.78 (m, 2H), 5.08 (d, 1H), 4.88 (d, 1H), 4.82 (dd, 2H), 4.53 (d, 1H), 4.27 (d, 1H), 3.96 (m, 8H), 3.68 (d, 1H), 2.67 (s, 1H), 1.41 (t, 3H).

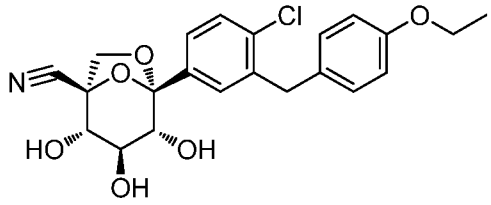
Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo [3.2.1]octane-1-carbonitrile **24**

[00166] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-1-ethynyl -6,8-dioxabicyclo[3.2.1]octane **24a** (0.64 mg, 0.92 mmol) in dichloromethane (10 mL) was added dropwise a solution of boron trichloride in dichloromethane (5 mL, 5.52 mmol, 1 M) at −78 °C. The mixture was stirred at −78 °C for 5 hours and then quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=2/1 to give the title compound **24** as a pale yellow soild (250 mg, 63.3%, HPLC: 96.7%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) *m/z*: 431.2[M+H]$^+$; and

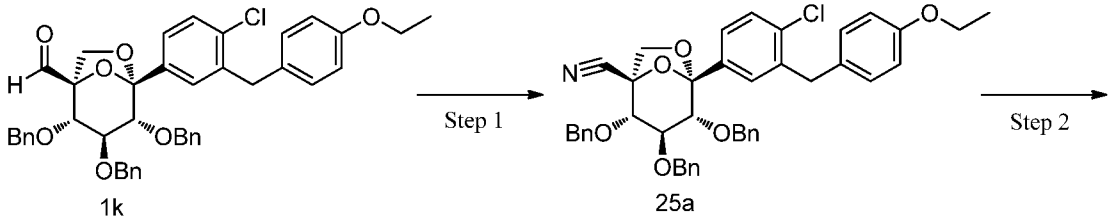
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41(m, 2H), 7.30 (m, 1H), 7.10 (d, 2H), 6.84(m, 2H), 5.78 (d, 1H), 5.18 (d, 1H), 5.05 (d, 1H), 4.25 (d, 1H),3.97 (m, 4H), 3.68 (s, 1H), 3.66 (d, 1H), 3.53 (m, 1H), 3.39(m, 2H), 1.30 (t, 3H).

Example 25

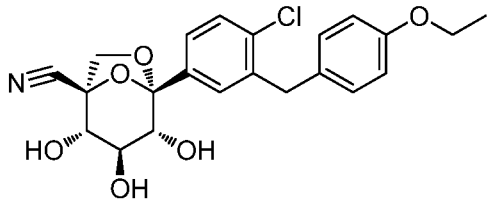
(1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-Chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo[3.2.1]octane-1-carbonitrile **25**



25



1k 25a



25

Step 1) (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbonitrile **25a**

[00167] To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-6,8-dioxabicyclo[3.2.1]octane-1-carbaldehyde **1k** (0.4 g, 0.57 mmol) in pyridine (5 mL) was added a solution of hydroxylamine hydrochloride (43.8 mg, 0.63 mmol) in water (2 mL) at room temperature. The mixture was stirred at room temperature for 1 hour. To the mixture were added copper sulfate monohydrate (0.2 mg, 1.14 mmol), triethylamine (0.14 mL, 1.14 mmol) and a solution of dicyclohexylcarbodiimide (0.1 mL, 0.68 mmol) in dichloromethane (15 mL). The mixture was stirred at room temperature for 12 hours and quenched with saturated aqueous sodium chloride (10 mL). The resulting mixture was filtered. The aqueous layer of the filtrate was extracted with dichloromethane (10 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=5/1 to give the title

compound **25a** as pale yellow oil (0.27 g, 67.6%). The compound was characterized by the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (m, 11H), 7.21 (m, 3H), 7.15 (m, 2H), 7.05 (m, 2H), 6.83 (m, 2H), 6.76 (m, 2H), 4.98 (d, 1H), 4.86 (d, 1H), 4.80 (s, 2H), 4.55 (d, 1H), 4.21 (d, 1H), 4.06 (m, 3H), 4.01 (m, 3H), 3.85 (dd, 2H), 3.63 (d, 1H), 1.39 (t, 3H).

Step 2) (1*S*,2*S*,3*S*,4*R*,5*S*)-5-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-2,3,4-trihydroxy-6,8-dioxabicyclo [3.2.1]octane-1-carbonitrile **25**

To a solution of (1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tribenzyloxy-5-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl] -6,8-dioxabicyclo[3.2.1]octane-1-carbonitrile **25a** (138 mg, 0.2 mmol) in dichloromethane (5 mL) was added dropwise a solution of boron trichloride in dichloromethane (0.6 mL, 0.59 mmol, 1 M) at −78 °C. The mixture was stirred at −78 °C for 3 hours and then quenched with saturated aqueous sodium chloride (5 mL). The aqueous layer was extracted with dichloromethane (10 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluted with PE/EtOAc (v/v)=1/2 to give the title compound **25** as a light orange soild (35 mg, 41.2%, HPLC: 77.3%). The compound was characterized by the following spectroscopic data: MS (ESI, pos. ion) m/z: 432.0$[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.44 (m, 2H), 7.33 (m, 1H), 7.10 (d, 2H), 6.82 (m, 2H), 6.43 (d, 1H), 5.46 (d, 1H), 5.28 (d, 1H), 4.39 (d, 1H), 4.00 (m, 5H), 3.73 (m, 1H), 3.49 (m, 1H), 3.40 (m, 1H), 1.29 (t, 3H).

BIOLOGICAL ACTIVITY

SGLT-1 and SGLT-2 Activity Measurement

Experimental purposes

[00168] The following methods can be used to determine the inhibitory activity of the compounds described in the invention against SGLT-1 and SGLT-2.

Experimental materials

[00169] ^{14}C-AMG solution was purchased from PerkinElmer, Cat. No. NEZ080001MC.

[00170] α-Methylglucoside was purchased from Sigma, Cat. No.M9376-100G.

[00171] *N*-methyl-*D*-glucosamine was purchased from Sigma, Cat. No.M2004-100G.

[00172] Phloridzin was purchased from Sigma, Cat. No. P3449-1G.

[00173] 96-Well plate was purchased from Corning, Cat. No.3903.

Experimental methods

[00174] Mock-transfected FIP-in CHO cells (3 x 10^4 cells) and expressing human SGLT1/SGLT2 CHO cells were seeded into 96-well plates respectively. The cells were incubated for 12 hours. Each well of the 96-well

plates was washed with 150 μL of sodium-free buffer once. To each well was added 50 μL of sodium-containing buffer containing test compounds having different concentrations and 0.5 μM [^{14}C]-AMG. The incubation mixture was incubated at 37 °C for 1 hour. To each well was added 150 μL of precooled sodium-free buffer to terminate the reaction. The cell pellet was washed with sodium–free buffer three times and the residual liquid in well was removed. To each well was added 20 μL of precooled 100 mM NaOH. The 96-well plates were vibrated at 900 rpm for 5 minutes. Scintillation fluid (80 μL) was added to each well which was then vibrated at 600 rpm for 5 minutes. The amount of ^{14}C was quantitatively detected using liquid scintillation. The results are shown in table 1:

Table 1:

Example Number	IC_{50}(SGLT-1)/ nM	IC_{50}(SGLT-2)/ nM
3	2090	4.8
5	-	14.6
6	-	117.9
7	75900	10.6
8	-	12.7
9	-	335
10	-	354.3
11	-	26.22
12	-	35.74
13	-	243
14	-	40.94
15	-	38.84
16	-	370.4
19	400	1.65
20	-	19.21
21	3070	5.66
22	-	12.26
23	-	50.6

Example Number	IC_{50}(SGLT-1)/ nM	IC_{50}(SGLT-2)/ nM
24	7270	0.81
25	8380	3.04

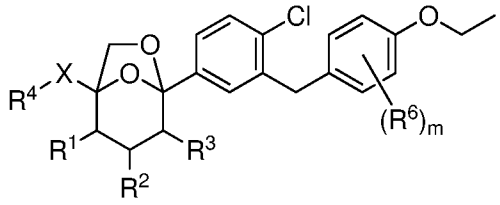
[00175] Conclusions: The compounds described in the present invention have significant inhibitory effect on SGLT-2.

[00176] Reference throughout this specification to "an embodiment", "some embodiments", "one embodiment", "another example", "an example", "a specific example", or "some examples", means that a particular feature, structure, material, or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as "in some embodiments", "in one embodiment", "in an embodiment", "in another example", "in an example", "in a specific example", or "in some examples", in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments or examples.

[00177] Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments cannot be construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the embodiments without departing from spirit, principles and scope of the present disclosure.

What is claimed is:

1. A compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



(I),

wherein each of R^1, R^2 and R^3 is independently hydroxy, $-OR^b$ or $-OC(=O)R^c$;

R^b is alkyl, alkoxyalkyl, silyl, silylalkoxyalkyl, alkenyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein optionally each of the alkyl, alkoxyalkyl, silyl, alkenyl, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino, mercapto and alkoxy;

R^c is alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, wherein optionally each of the alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto;

R^4 is -H, hydroxy, alkyl, alkoxy, amino or alkylamino, wherein optionally each of the alkyl, alkoxy and alkylamino is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, -OC(=O)alkyl, hydroxy, carboxy, cyano, nitro and mercapto;

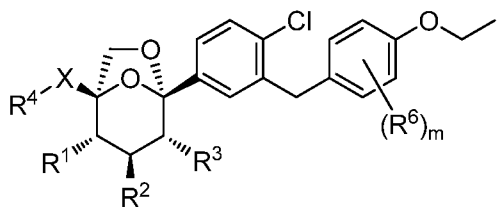
X is -C(=O)-, $-C(=NR^a)-$ or -C≡C-; or X is a bond when R^4 is cyano;

R^a is hydroxy, alkyl or alkoxy, wherein optionally each of the alkyl and alkoxy is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto;

m is 0, 1, 2, 3 or 4; and

each R^6 is independently -H, -F, -Cl or -Br.

2. The compound of claim 1 having Formula (II) or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug,



(II).

3. The compound of claim 1 or 2, wherein R^4 is -H, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino or C_{1-6} alkylamino, wherein optionally each of the C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkylamino is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, -OC(=O)-C_{1-6} alkyl, hydroxy, carboxy, cyano, nitro and mercapto.

4. The compound of claim 1 or 2, wherein R^4 is -H, hydroxy, methyl, ethyl, propyl, isopropyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, amino, *N*-methylamino, *N*,*N*-dimethylamino, *N*-ethylamino, *N*,*N*-diethylamino or pivaloyloxymethoxy.

5. The compound of claim 1 or 2, wherein R^a is hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy, wherein optionally each of the C_{1-6} alkyl and C_{1-6} alkoxy is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto.

6. The compound of claim 1 or 2, wherein R^a is hydroxy, methoxy, ethoxy or 1-hydroxyethoxy.

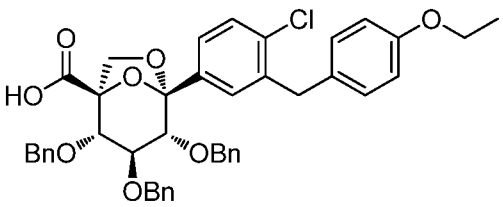
7. The compound of claim 1 or 2, wherein R^b is C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-18} silyl, C_{1-18} silyl-C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl or C_{1-9} heteroaryl-C_{1-6}-alkyl, wherein optionally each of the C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-18} silyl, C_{1-18} silyl-C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl and C_{1-9} heteroaryl-C_{1-6}-alkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino, mercapto and C_{1-6} alkoxy; and

R^c is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl or C_{1-9} heteroaryl-C_{1-6}-alkyl, wherein optionally each of the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl and C_{1-9} heteroaryl-C_{1-6}-alkyl is independently substituted by one or more substituents independently selected from -H, -F, -Cl, -Br, -I, hydroxy, carboxy, cyano, nitro, amino and mercapto.

8. The compound of claim 1 or 2, wherein R^b is methyl, ethyl, *tert*-butyl, methoxymethyl, allyl, trityl, benzyl, *p*-methoxybenzyl, acetyl, (*tert*-butyl)(dimethyl)silyl, trimethylsilyl, (*tert*-butyl)(diphenyl)silyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl or tetrahydropyranyl; and

R^c is methyl, *tert*-butyl, methoxy, ethoxy, phenyl or benzyl.

9. The compound of claim 1 or 2 having one of the following structures or a stereoisomer, a geometric isomer, a tautomer, a racemate, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug,



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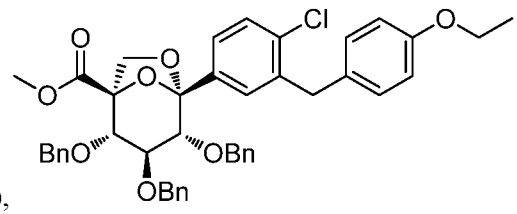

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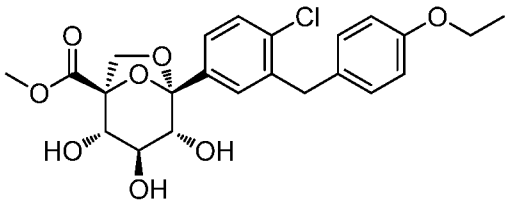

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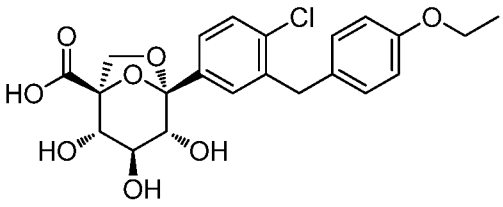

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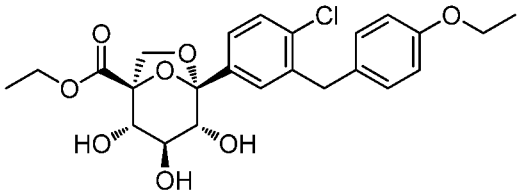

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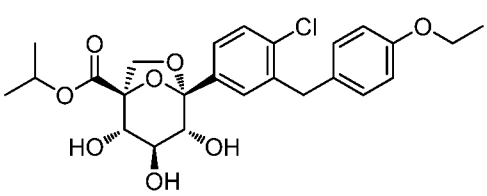

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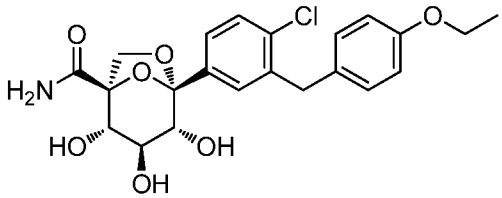

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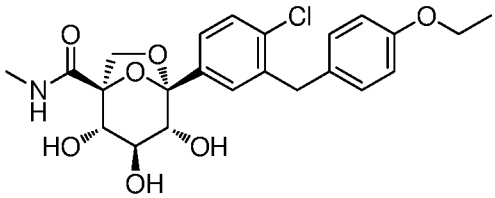

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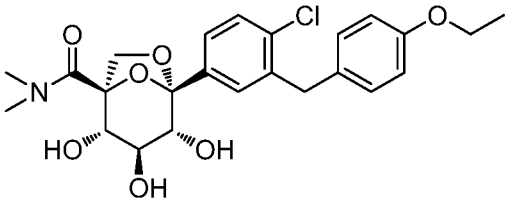

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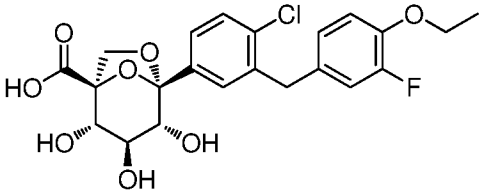

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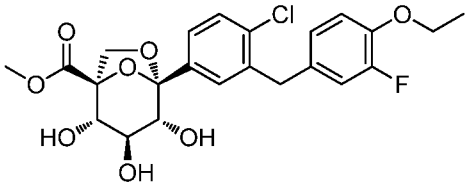

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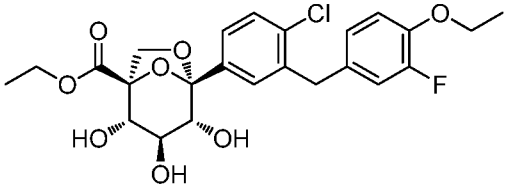

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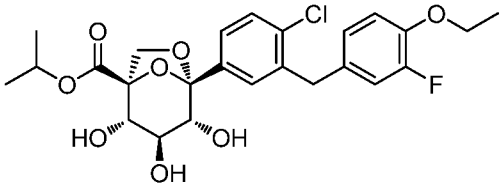

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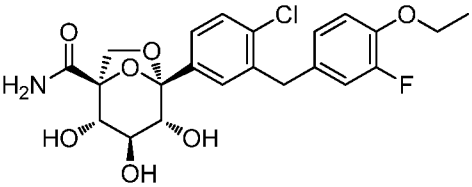

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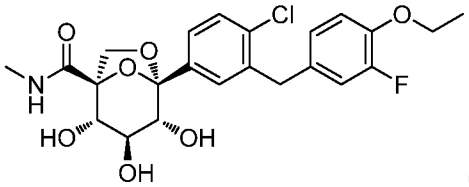

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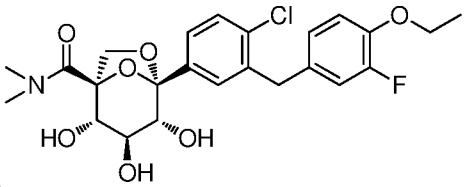

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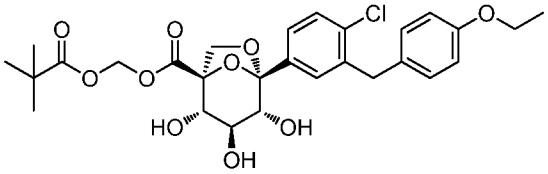

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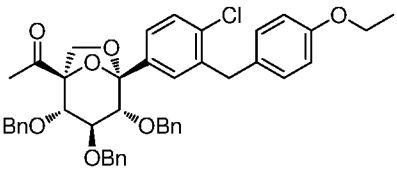

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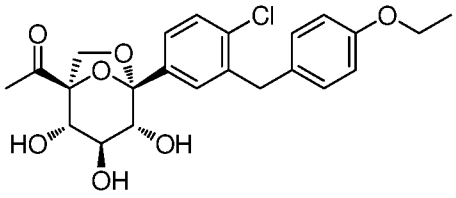
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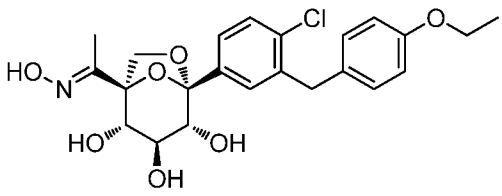
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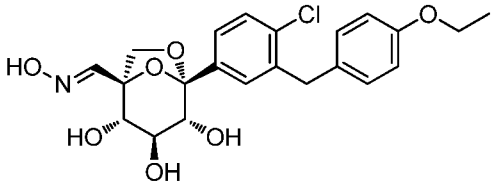
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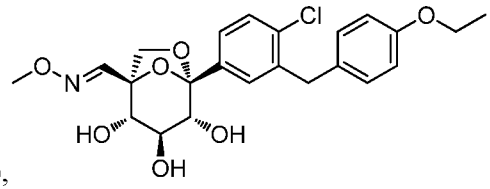
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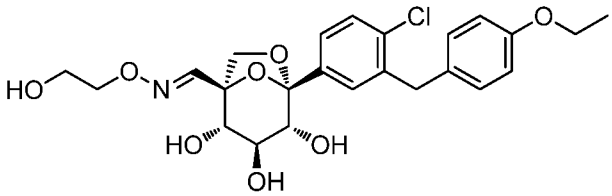
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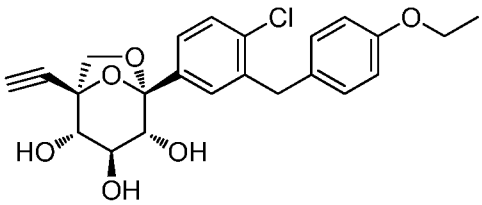
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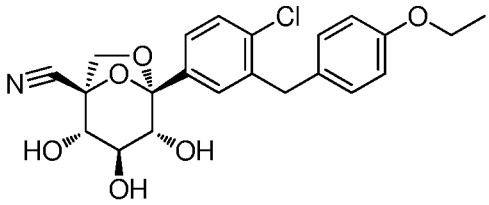
(25).

10. A pharmaceutical composition comprising the compound of any one of claims 1 to 9, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

11. The pharmaceutical composition of claim 10 further comprising an additional therapeutic agent, wherein the additional therapeutic agent is an anti-diabetic agent other than an SGLT-2 inhibitor, an antihyperglycemic agent, an antiadipositas drug, an antihypertensive agent, an antiplatelet agent, an antiatherosclerotic drug, a lipid-lowering agent, an anti-inflammatory or a combination thereof.

12. The pharmaceutical composition of claim 11, wherein each of the anti-diabetic agent other than an SGLT-2 inhibitor and antihyperglycemic agent is independently a biguanide, a sulfonylurea, a glucosidase inhibitor, a PPAR agonist, an αP2 inhibitor, a PPARα/γ dual agonist, a dipeptidyl peptidase IV (DPP-IV) inhibitor, a glinides, insulin, a glucagon-like peptide-1(GLP-1) inhibitor, a PTP1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor or a combination thereof.

13. The pharmaceutical composition of claim 11, wherein the lipid-lowering agent is an MTP inhibitor, an HMGCoA reductase inhibitor, a squalene synthase inhibitor, a fibric acid derivative, an ACAT inhibitor, a lipoxygenase inhibitor, a cholesterol absorption inhibitor, an ileal Na(+)/bile acid cotransporter inhibitor, an upregulator of LDL receptor activity, niacin or a derivative thereof, a bile acid sequestrant or a combination thereof.

14. The pharmaceutical composition of claim 13, wherein the lipid-lowering agent is pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin, rosuvastatin or a combination thereof.

15. Use of the compound of any one of claims 1 to 9 or the pharmaceutical composition of any one of claims 10 to 14 in the manufacture of a medicament for inhibiting the activity of SGLT-2 or increasing HDL level.

16. Use of the compound of any one of claims 1 to 9 or the pharmaceutical composition of any one of claims 10 to 14 in the manufacture of a medicament for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, wherein the disease is diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, a diabetic complication, atherosclerosis or hypertension.

17. A method for inhibiting the activity of SGLT-2 or increasing HDL level, comprising administering to the patient in need thereof a therapeutically effective amount of the compound of any one of claims 1 to 9 or the pharmaceutical composition of any one of claims 10 to 14.

18. A method for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, comprising administering to the patient in need thereof a therapeutically effective amount of the compound of any one of claims 1 to 9 or the pharmaceutical composition of any one of claims 10 to 14, wherein the disease is diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, a diabetic complication, atherosclerosis or hypertension.

19. The compound of any one of claims 1 to 9 or the pharmaceutical composition of any one of claims 10 to 14 for use in inhibiting the activity of SGLT-2 or increasing HDL level.

20. The compound of any one of claims 1 to 9 or the pharmaceutical composition of any one of claims 10 to 14 for use in preventing or treating a disease, lessening a disease symptom, delaying the progression or onset of a disease, wherein the disease is diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, a diabetic complication, atherosclerosis or hypertension.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/087320

A. CLASSIFICATION OF SUBJECT MATTER

C07H 9/04(2006.01)i; A61K 31/7048(2006.01)i; A61P 3/10(2006.01)i; A61P 27/02(2006.01)i; A61P 25/00(2006.01)i; A61P 13/12(2006.01)i; A61P 5/50(2006.01)i; A61P 9/10(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H 9/04, A61K 31/7048

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, CNKI, WPI, EPODOC, REG, CAPLUS: glucopyranosyl, dioxabicyclo, octane, diabetic, diabetes, SGLT, substructure search according to formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013038429 A2 (PANACEA BIOTEC LTD) 21 March 2013 (2013-03-21) claims and examples	1-16, 19, 20
A	WO 2012019496 A1 (SHANGHAI HENGRUI PHARM CO LTD) 16 February 2012 (2012-02-16) claims and examples	1-16, 19, 20
E	WO 2014187365 a1 (SICHUAN HAISCO PHARMACEUTICAL CO LTD) 27 November 2014 (2014-11-27) example 15, compound 15c	1-9

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2014	**06 January 2015**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN) **6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088 China**	**YANG,Yi**
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/087320

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **17-18**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] The subject matter of claims 17-18 is directed to a method of treatment of the human/animal body (Rule 39.1(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2014/087320

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2013038429	A2	21 March 2013	EP	2755722	A2	23 July 2014
				WO	2013038429	A3	28 November 2013
				JP	2014530186	A	17 November 2014
WO	2012019496	A1	16 February 2012	EP	2604612	A1	19 June 2013
				US	2013130997	A1	23 May 2013
				HK	1167395	A1	29 August 2014
				RU	2013107748	A	20 September 2014
				KR	20130095741	A	28 August 2013
				US	8609622	B2	17 December 2013
				CA	2807034	A1	16 February 2012
				MX	2013001098	A	05 June 2013
				CN	102372722	A	14 March 2012
				EP	2604612	A4	24 July 2013
				CN	102482290	A	30 May 2012
				JP	2013533291	A	22 August 2013
				CN	102482290	B	15 January 2014
WO	2014187365	a1	27 November 2014		Non	e	