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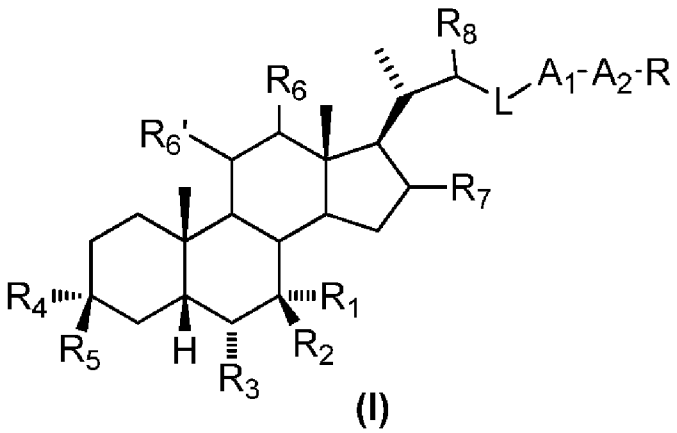
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(54) Title: SULFONYLAMINOCARBONYL DERIVATIVE, PHARMACEUTICAL COMPOSITION AND USES THEREOF



(I)

(57) Abstract: This disclosure is related to a sulfonylaminocarbonyl derivative of formula (I) and/or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the sulfonylaminocarbonyl derivatives of formula (I) and/or a pharmaceutically acceptable salt thereof, preparation methods thereof, and use thereof in treating FXR and/or TGR5 mediated diseases, including primary biliary cirrhosis, nonalcoholic fatty liver, portal hypertension, bile acid diarrhea and cholestasis, type II diabetes and obesity, etc.

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Sulfonylaminocarbonyl Derivative, Pharmaceutical Composition and Uses Thereof

FIELD OF THE INVENTION

The present invention relates to new sulfonylaminocarbonyl derivatives, isomers, prodrugs, pharmaceutical accept salts, stable isotope derivatives, pharmaceutical compositions containing the same, preparation method and uses thereof.

BACKGROUND OF THE INVENTION

Farnesoid X Receptor (FXR) belongs to a member of nuclear hormone receptor super family, which is one of the ligand-activated transcription factors. This super family includes steroid receptors, retinoid receptors and thyroid hormone receptors. FXR is widely present in the liver, intestine, kidney, adrenal gland and other bile acids presenting tissues. Bile acids, or their glycine and taurine conjugates, are known endogenous ligands for FXR. Bile acids, including chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), and lithocholic acid (LCA), bind to and activate FXR receptor at physiological concentrations. FXR plays an important role in regulating bile acid homeostasis, carbohydrate metabolism, and lipid metabolism.

Bile acids are metabolites of cholesterol, which are synthesized in the liver and secreted into the duodenum of the intestine. They play important roles in increasing solubility and absorption of dietary lipids and vitamins. Most of the bile acids in the ileum then returned to the liver by enterohepatic circulation. In the liver, conversion of cholesterol to bile acids is regulated by a feedback mechanism. Bile acids down-regulate cytochrome P450 CYP7A transcription, which encodes an enzyme that catalyzes the biosynthesis of bile acids in the rate-limiting step. In the ileum, bile acids increase the production of bile acid binding protein (IBABP). Through binding to bile acids with high affinity, cytoplasmic protein IBABP plays a role in bile acids cellular uptake and transport. In short, in bile acid and cholesterol homeostasis, FXR is involved in stimulating IBABP while suppressing CYP7A expression.

FXR is involved in many physiological processes playing a major role in controlling hepatic lipid, cholesterol and carbohydrates metabolism (Inflamm Res. 2015,64,9-20), including liver cholestasis, cholelithiasis, glucose metabolism, intestinal epithelial protection, liver cell regeneration, intestinal and liver tumor formation, kidney disease caused by diabetes, improve erectile dysfunction, vascular reactivity regulation, inhibition of pulmonary inflammation and infection and so on. Because of these different physiological functions, FXR is a valuable potential drug target. Many synthetic FXR agonists have been synthesized (Current Topics in Medicinal Chemistry, 2014, 14, 2188-2205). FXR agonists seem to have a specific liver protection effect, and can prevent fat accumulation in the liver and reduce liver fibrosis and inflammation. FXR agonists currently in clinical development are mainly for the treatment of severe liver disease, including primary biliary cirrhosis (PBC, one kind of

cholestasis caused by chronic inflammation of the liver), nonalcoholic fatty liver disease (NAFLD), non-alcoholic hepatitis (NASH), liver cell regeneration, and inflammatory bowel disease (IBD), and so on.

In addition to regulating the enterohepatic circulation, triglycerides, cholesterol and other liver-specific functions, bile acids also regulate energy and glucose homeostasis. FXR was found to control the expression of a key cytokine FGF-15/19 in the intestine (ileum) (Cell Metab. 2005, 2, 217). FGF-15/19 has the functions of sensitizing insulin, reducing weight and lowering lipid, thereby further extends the use of FXR agonists to all other FGF15 / 19 responding tissues.

Besides activating FXR, bile acids and secondary bile acids (such as LCA) can also activate the four other nuclear hormone receptors (PXR, CAR, VDR, and FXRS) and an important G protein-coupled receptor TGR5 (also known as GPBAR1 or M-BAR). Expression of TGR5 is organ specific. TGR5 is highly expressed in endocrine glands, on the plasma membrane of liver, adipose tissue, skeletal muscle cells, immune organs, spinal cord, intestines and nervous system. TGR5 promotes the secretion of glucagon-like peptide (GLP-1) and the production of cAMP , thereby achieving its role in a series of cellular and physiological activities by regulating metabolism of lipid and glucose, and energy homeostasis and so on (Br J Pharmacol, 2012,165:. 414-423). Activation of TGR5 can control blood sugar; regulate lipid homeostasis, increase energy expenditure, and play a role of anti-cancer and anti-inflammatory effects, and so on. Thus TGR5 is expected to become a drug target for the treatment of a range of metabolic diseases, autoimmune diseases, inflammatory diseases and cancer.

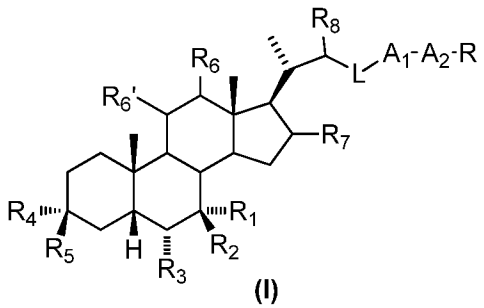
Role of TGR5 in bile acid metabolism has been confirmed on TGR5 knockout mice. Compared to wild-type mice, Bile acid level in TGR5 knockout mice was significantly reduced by 21% to 25%, indicating TGR5 promote bile acid homeostasis. Activation of TGR5 also increases expression of endothelial nitric oxide enzyme (Trends Pharmacol Sci, 2009, 30, 139-159), which may limit liver toxicity caused by bile acids and peroxidation of lipid. In addition, TGR5 is involved in sugar and energy metabolism. TGR5 agonists are expected to be used for the potential treatment of type-2 diabetes and obesity (Animal Cells and Systems, 2014, 18, 359-364). TGR5 also found to regulate inflammatory cytokines monocytes, suggesting that TGR5 is closely involved in the regulation of immune and inflammatory response of human diseases.

Recent studies show that FXR and TGR5 play an important role in regulating glucose and lipid metabolism, energy and bile homeostasis. Therefore, FXR and TGR5 are emerging as attractive targets for the treatment of the metabolic syndrome, diabetes, abnormal blood lipid disorders, atherosclerosis, cholestasis and other liver diseases. Although further studies of these two targets are being investigated, there is no marketed drug that targets these two targets; therefore there is still an unmet medical need to develop such drugs.

SUMMARY OF THE INVENTION

The present disclosure relates to new sulfonylaminocarbonyl derivatives, solvates, isomers, prodrugs, pharmaceutical accept salts, stable isotope derivatives, pharmaceutical compositions containing the same, preparation methods and uses thereof, particular for their pharmaceutical use for modulating the activity of farnesoid X receptor (FXR) and/or G protein-coupled bile acid receptor 1 (TGR5).

Provided is a compound of formula (I) and/or isomers, prodrugs, solvates, stable isotope derivatives thereof, and/or a pharmaceutically acceptable salt thereof;



(I)

Wherein, A_2 is $-C(O)N(R_{12})S(O)_2-$, or $-S(O)_2N(R_{12})C(O)-$;

A_1 is a bond, or $-(CH_2)_n-$; n is 1, 2, 3, or 4;

L is a bond, or $-CHR_9-$;

R is independently substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, or $-NR_{10}R_{10a}$, provided that when A_2 is $-S(O)_2N(R_{12})C(O)-$, R is not selected form $-NR_{10}R_{10a}$;

R_1 is independently hydrogen, hydroxyl, substituted or unsubstituted alkyl, or halogen;

R_2 is independently hydrogen, substituted or unsubstituted alkyl, or hydroxyl;

R_3 is independently hydrogen, substituted or unsubstituted alkyl, 2-propenyl or halogen;

R_4 and R_5 are independently hydrogen, hydroxyl, $-OC(O)CH_3$, $-OS(O)_3H$, $-OP(O)_3H$, $-P(O)_3H_2$, or $-OC_6H_8O_6H$; or R_4 and R_5 are taken together to form a carbonyl;

R_6 and $R_{6'}$ are independently hydrogen, or hydroxyl;

R_7 is independently hydrogen, hydroxyl, alkoxy, or halogen;

R_8 is independently hydrogen, or substituted or unsubstituted alkyl;

R_9 is independently hydrogen, substituted or unsubstituted alkyl, aryl, or heteroaryl; or R_8 and R_9 together with the carbon atom to which they are attached, form a 3- to 6-membered cycloalkyl ring.

In some embodiments, R is substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{3-10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl,

substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted 5- to 10-membered heteroaryl, substituted or unsubstituted C_{3-10}cycloalkyl C_{1-3}alkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkylC_{1-3}alkyl, substituted or unsubstituted phenylC_{1-3}alkyl; substituted or unsubstituted 5- to 10-membered heteroarylC_{1-3}alkyl.

When R is substituted, it is, for example, substituted by 1 to 3 R_{11} at any position.

Wherein, R_{11} is independently halogen, hydroxyl, amino, carboxyl, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkoxy, cycloalkylalkoxy, arylalkoxy, heteroarylalkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, aminoalkyl, hydroxyalkyl, sulfonyl, $-C(O)OR_{13}$, $-S(O)_{0-2}R_{13}$, $-S(O)_{0-2}NR_{13}R_{13a}$, $-OC(O)R_{13}$, $-OC(O)NR_{13}R_{13a}$, $-NR_{13}R_{13a}$, $-NHC(O)R_{13}$, $-NHC(O)NR_{13}R_{13a}$, $-NHS(O)_2R_{13}$, $-NHS(O)_2NR_{13}R_{13a}$, $-C(O)R_{13}$, $-C(O)NR_{13}R_{13a}$, or $-(CH_2)_nNR_{13}R_{13a}$; and wherein the substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl as R_{11} refer to cycloalkyl, heterocycloalkyl, aryl, or heteroaryl substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, amino, C_{1-3} alkyl, C_{1-3}alkoxy, halo- C_{1-3}alkyl, and halo- C_{1-3}alkoxy.

In some embodiments, R_{11} is independently halogen, hydroxyl, amino, carboxyl, $-NO_2$, -CN, C_{1-6}alkyl, halo- C_{1-6}alkyl, C_{1-6}alkoxy, halo- C_{1-6}alkoxy, substituted or unsubstituted C_{3-8}cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted 5- to 6-membered heteroaryl, C_{3-8}cycloalkyl C_{1-3}alkyl, 3- to 8-membered heterocycloalkylC_{1-3}alkyl, phenylC_{1-3}alkyl, 5- to 6-membered heteroarylC_{1-3}alkyl, 3- to 8-membered heterocycloalkylC_{1-3}alkoxy, C_{3-8}cycloalkylC_{1-3}alkoxy, phenylC_{1-3}alkoxy, 5- to 6-membered heteroarylC_{1-3}alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, amino-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, sulfonyl, $-C(O)OR_{13}$, $-S(O)_{0-2}R_{13}$, $-S(O)_{0-2}NR_{13}R_{13a}$, $-OC(O)R_{13}$, $-OC(O)NR_{13}R_{13a}$, $-NR_{13}R_{13a}$, $-NHC(O)R_{13}$, $-NHC(O)NR_{13}R_{13a}$, $-NHS(O)_2R_{13}$, $-NHS(O)_2NR_{13}R_{13a}$, $-C(O)R_{13}$, $-C(O)NR_{13}R_{13a}$, or $-(CH_2)_nNR_{13}R_{13a}$; and wherein the substituted C_{3-8}cycloalkyl, substituted 3- to 8-membered heterocycloalkyl, substituted phenyl, or substituted 5- to 6-membered heteroaryl as R_{11} refer to C_{3-8}cycloalkyl, 3- to 8-membered heterocycloalkyl, phenyl, or 5- to 6-membered heteroaryl substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, amino, C_{1-3} alkyl, C_{1-3}alkoxy, halo- C_{1-3}alkyl, and halo- C_{1-3}alkoxy.

R_{13} and R_{13a} are independently hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; or R_{13} and R_{13a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring.

In some embodiments, R_{13} and R_{13a} are independently hydrogen, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocycloalkyl, phenyl, or 5- to 6-membered heteroaryl; or R_{13} and R_{13a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring.

In some embodiments, when A_2 is -C(O)N(R_{12})S(O)$_2$-, R is –N$R_{10}R_{10a}$;

In some embodiments, R_{10} or R_{10a} in R is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, or heteroalkylalkyl; or R_{10} and R_{10a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring.

In some embodiments, R_{10} or R_{10a} in R is independently hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3- to 8-membered heterocycloalkyl, phenyl, 5- to 6-membered heteroaryl, C_{3-8}cycloalkylC_{1-3}alkyl, or 3- to 8-membered heteroalkylC_{1-3}alkyl; or R_{10} and R_{10a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring.

In some embodiments, R_{12} in A_2 is hydrogen or alkyl.

In some embodiments, R_{12} in A_2 is hydrogen or C_{1-6}alkyl.

In some embodiments, A_1 is a bond, -CH_2- or -CH_2CH_2-;

In some embodiments, L is a bond, -$CH(CH_3)$-,  , or  ;

In some embodiments, R_1 is hydrogen, hydroxyl, substituted or unsubstituted C_{1-3}alkyl, or halogen.

In some embodiments, R_2 is hydrogen, substituted or unsubstituted C_{1-3}alkyl, or hydroxyl.

In some embodiments, R_3 is hydrogen, substituted or unsubstituted C_{1-3}alkyl, 2-propenyl, or halogen.

In some embodiments, R_7 is hydrogen, hydroxyl, C_{1-3}alkoxy, or halogen.

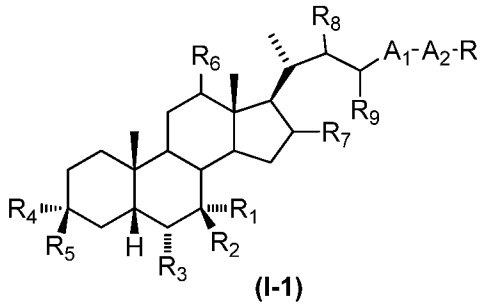
In some embodiments, R_8 is hydrogen, or substituted or unsubstituted C_{1-3}alkyl.

In some embodiments, R_9 is hydrogen, substituted or unsubstituted C_{1-3}alkyl, phenyl, or 5- to 6-membered heteroaryl; or R_8 and R_9 together with the carbon atom to which they are attached, form a 3- to 6-membered cycloalkyl ring.

In each embodiment, when R_1, R_2, R_3, R_8, or R_9 is the substituted alkyl, it is substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, alkyl and cycloalkyl.

In some embodiments, when R_1, R_2, R_3, R_8, or R_9 is the substituted C_{1-3}alkyl, it is substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, C_{1-3}alkyl and C_{3-8} cycloalkyl.

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is a compound of formula (I-1) and/or a pharmaceutically acceptable salt thereof,

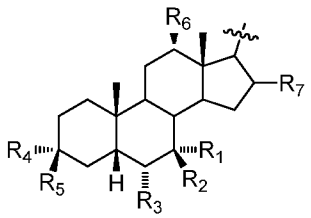


(I-1)

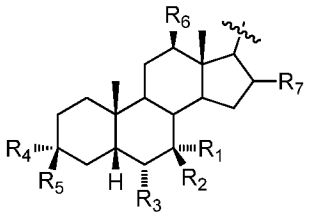
wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R, A_1 and A_2 are the same as described for formula (I), including each of the embodiments thereof.

In the present disclosure, the compound of formula (I-1), wherein when R_6 is hydroxyl, it can be α-OH or β-OH. In some embodiments, R_6 is hydrogen or α-OH.

When R_6 is hydroxyl, the stereo-configurations of R_6 are as bellow:

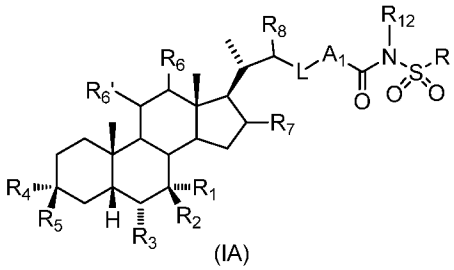


α -R_6 R_6 is hydroxyl

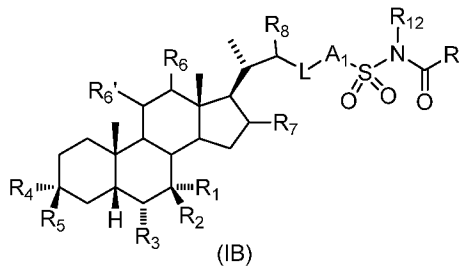


β -R_6 R_6 is hydroxyl .

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is 1) a compound of formula (IA) and/or a pharmaceutically acceptable salt thereof, or 2) a compound of formula (IB) and/or a pharmaceutically acceptable salt thereof,



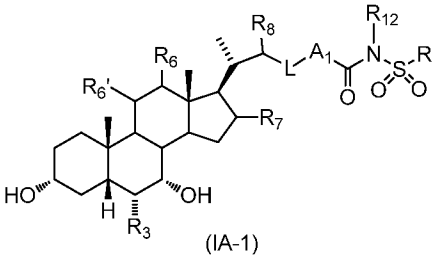
(IA)

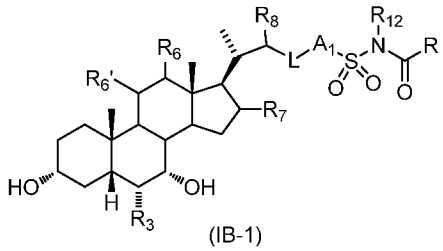


(IB)

wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_6', R_7, R_8, R_{12}, R, L and A_1 are the same as described for formula (I), including each of the embodiments thereof.

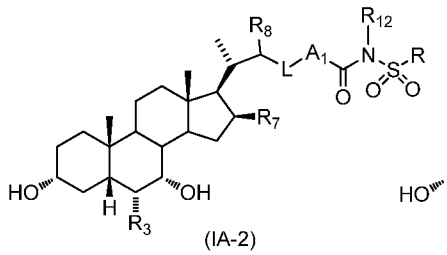
In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is 1) a compound of formula (IA-1) and/or a pharmaceutically acceptable salt thereof, or 2) a compound of formula (IB-1) and/or a pharmaceutically acceptable salt thereof,

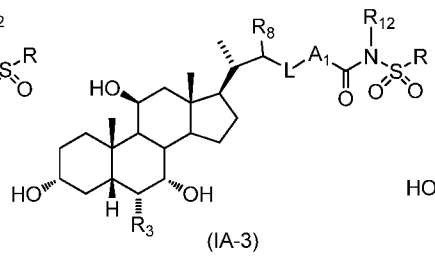

(IA-1)

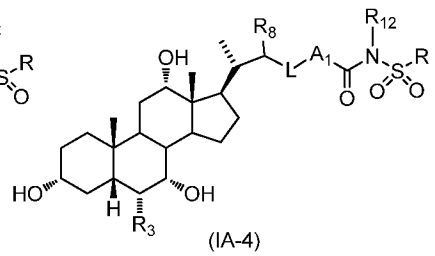

(IB-1)

wherein, R_3, R_6, $R_{6'}$, R_7, R_8, R_{12}, R, L and A_1 are the same as described for formula (I), including each of the embodiments thereof.

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is 1) a compound of formula (IA-2) and/or a pharmaceutically acceptable salt thereof, 2) a compound of formula (IA-3) and/or a pharmaceutically acceptable salt thereof, or 3) a compound of formula (IA-4) and/or a pharmaceutically acceptable salt thereof,

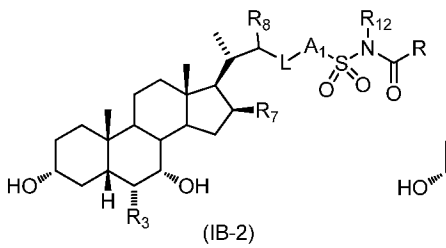

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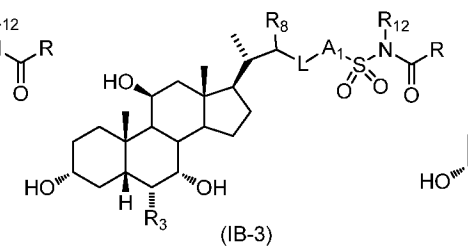

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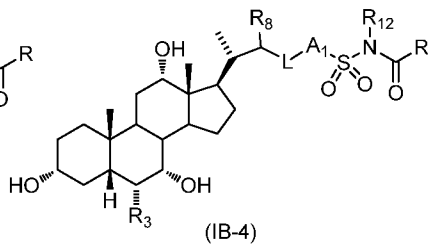

(IA-4)

wherein, R_3, R_7, R_8, R_{12}, R, L and A_1 are the same as described for formula (I), including each of the embodiments thereof.

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is 1) a compound of formula (IB-2) and/or a pharmaceutically acceptable salt thereof, 2) a compound of formula (IB-3) and/or a pharmaceutically acceptable salt thereof, or 3) a compound of formula (IB-4) and/or a pharmaceutically acceptable salt thereof,

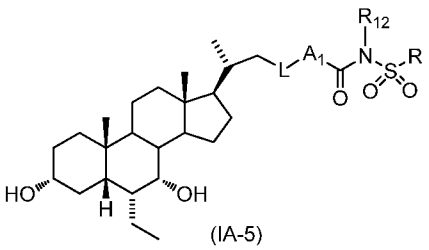

(IB-2)


(IB-3)

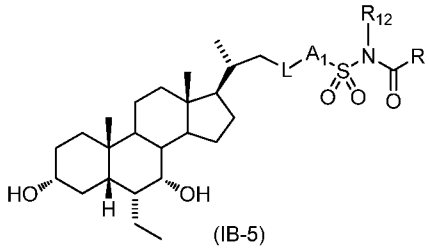

(IB-4)

wherein, R_3, R_7, R_8, R_{12}, R, L and A_1 are the same as described for formula (I), including each of the embodiments thereof.

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is 1) a compound of formula (IA-5) and/or a pharmaceutically acceptable salt thereof, or 2) a compound of formula (IB-5) and/or a pharmaceutically acceptable salt thereof,



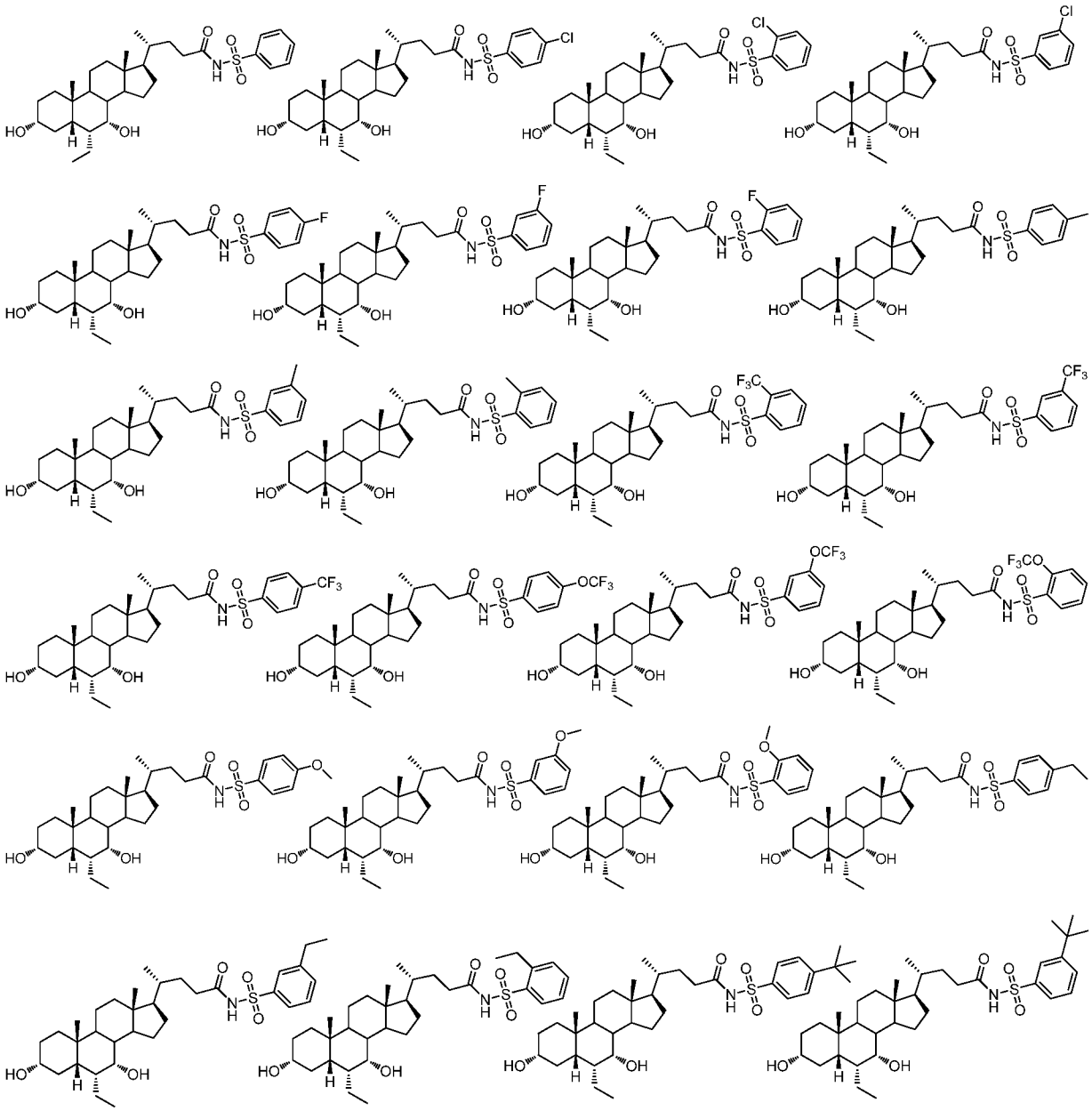
(IA-5)

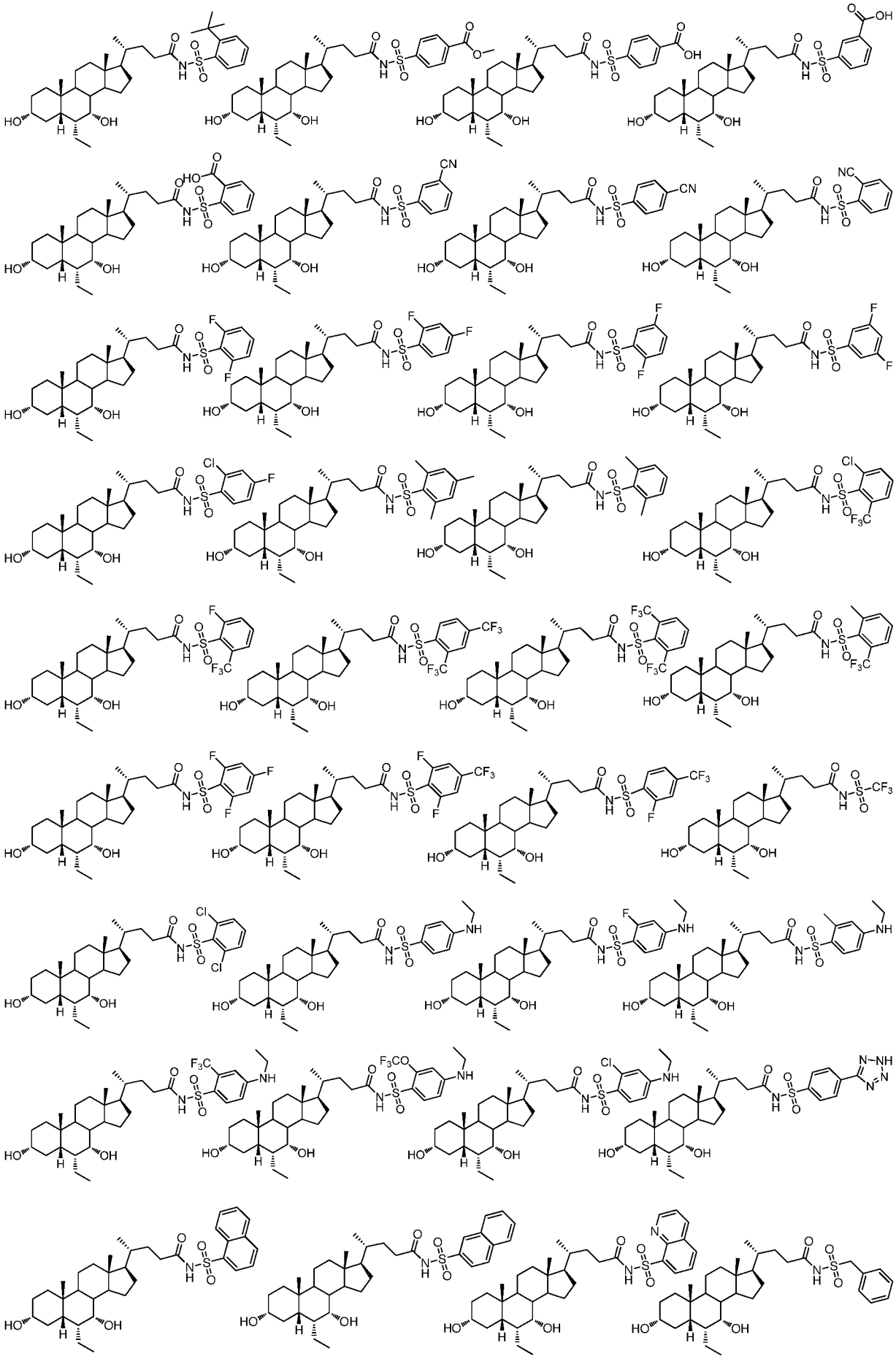


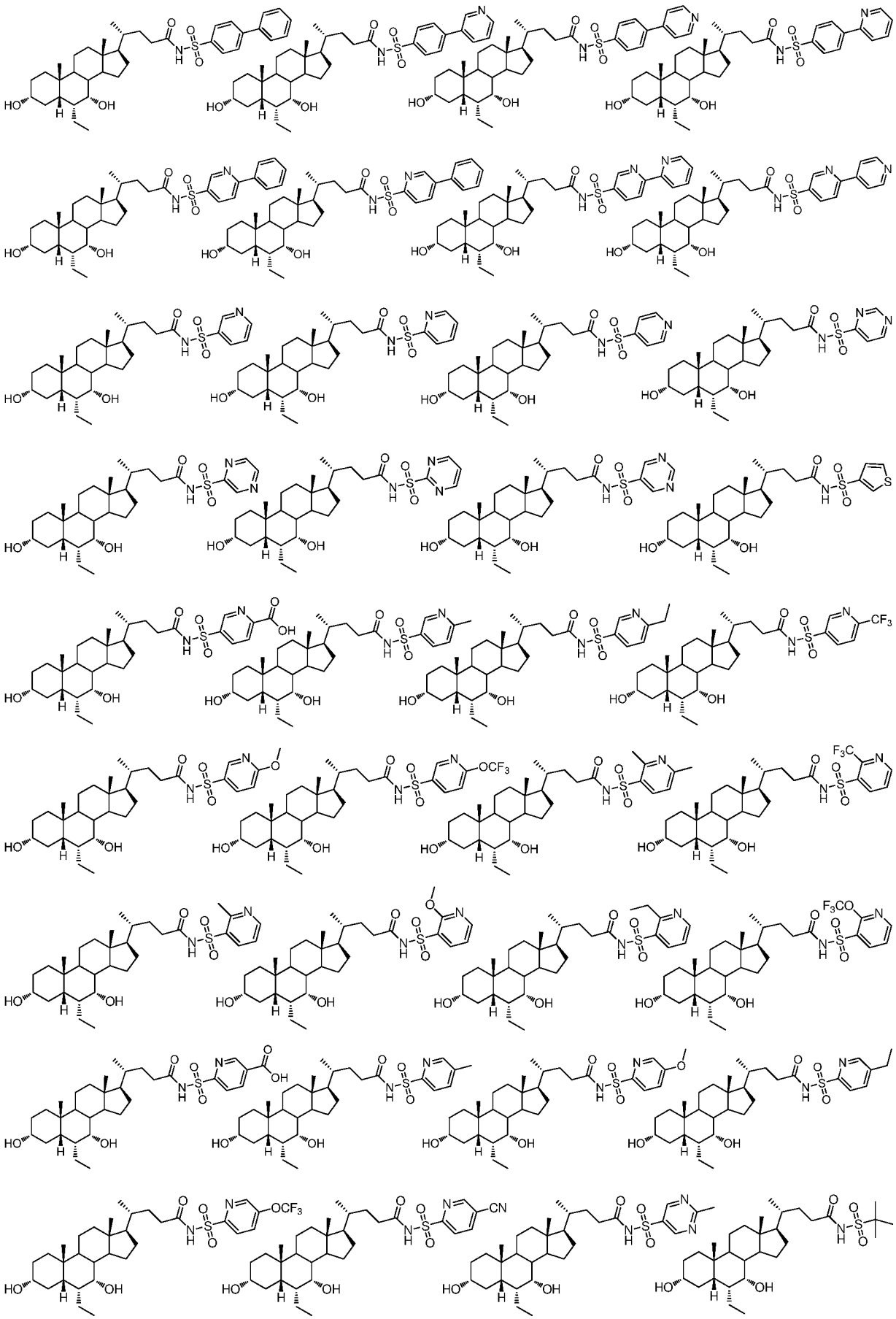
(IB-5)

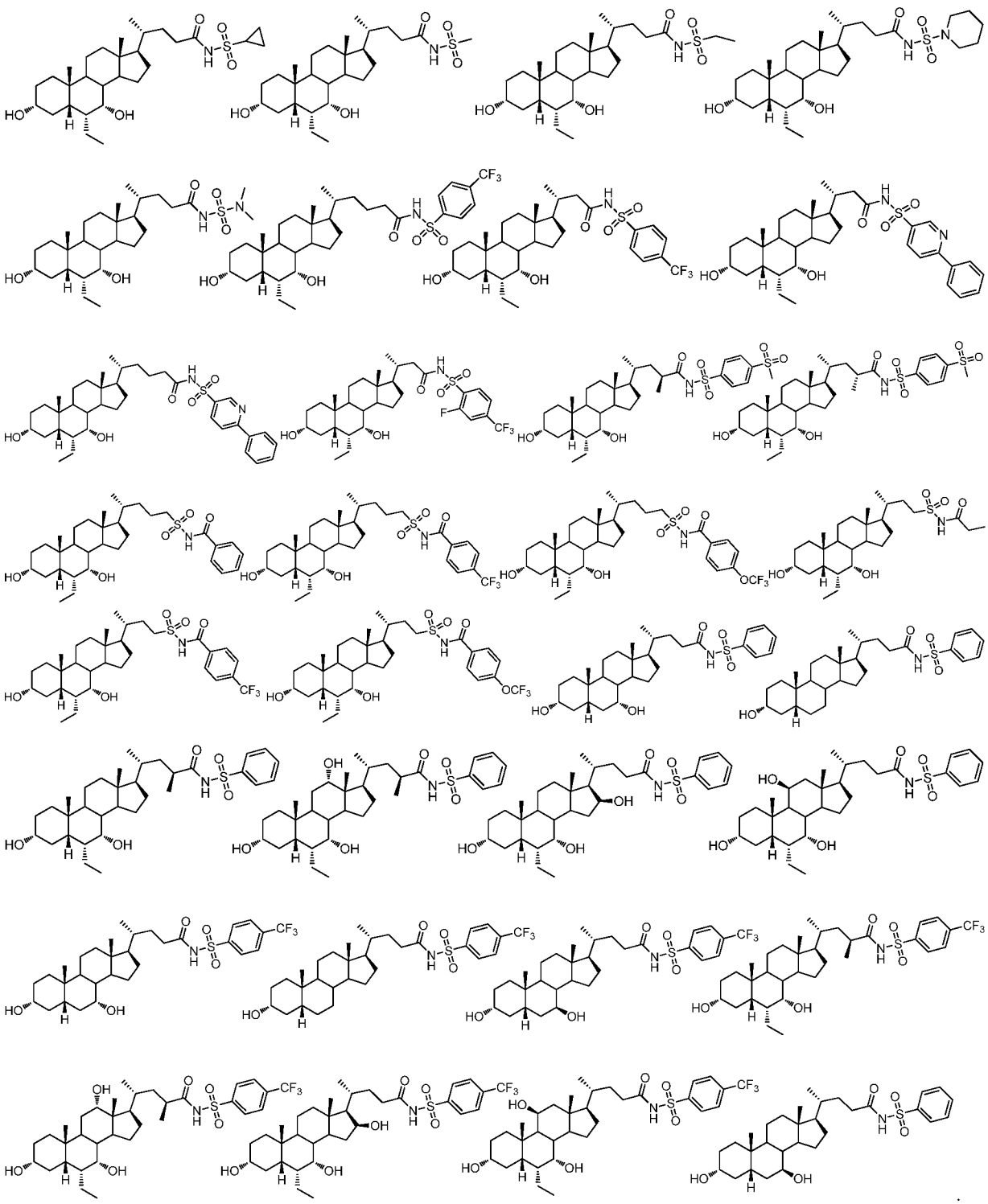
wherein, R_{12}, R, L and A_1 are the same as described for formula (I), including each of the embodiments thereof.

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is selected from the following compounds:









Also provided a pharmaceutical composition comprising 1) a compound of formula I, I-1, IA, IB, IA-1~IA-5, IB-1~IB-5, and/or stable isotope derivatives thereof, and/or a pharmaceutically acceptable salt thereof, and/or prodrugs thereof, and 2) a pharmaceutically acceptable excipient. The compound of formula I and/or a pharmaceutically acceptable salt can be any embodiment thereof disclosed herein.

A pharmaceutically acceptable excipient refers to an excipient that is useful in preparing a pharmaceutical composition that is compatible with active ingredients of the composition and

not deleterious to the subject to be treated. These excipients include, for example, binders, surfactants, diluents, buffering agents, antiadherents, glidants, hydrophilic or hydrophobic polymers, retardants, stabilizing agents or stabilizers, disintegrants or superdisintegrants, antioxidants, antifoaming agents, fillers, flavors, colors, lubricants, sorbents, preservatives, plasticizers, and sweeteners. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound disclosed herein. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

These pharmaceutical compositions can be prepared in various pharmaceutical formulations and dosage forms depending upon the therapeutic aims, for example, tablets, pills, powders, liquids, suspensions, emulsions, particles, capsules, suppositories and injections (solutions and suspensions), etc.

The compositions such as tablets can be prepared in a manner well known in the pharmaceutical art by using excipients to make the compositions to form into shapes. Said excipients include, for example, lactose, sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, and silicic acid, etc.; binders, for example, water, ethanol, propanol, common syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium carbonate, and polyvinyl pyrrolidone, etc.; disintegrating agents, for example, dry starch, sodium alginate, agar powder, kelp powder, calcium bicarbonate, calcium carbonate, polyoxyethylene sorbitan monooleate, lauryl sodium sulfate, glycerin monostearate, starch, and lactose, etc.; agents which inhibit disintegrating, for example, sugar, tristearin, coconut oil, and hardened vegetable oil, etc.; absorbent enhancers, for example, quaternary ammonium base, and lauryl sodium sulfate, etc.; wetting agents, for example, glycerin and starch, etc.; absorbent, for example, starch, lactose, bolus alba, bentonite, and silicious colloid, etc.; lubricants, for example, pure talcum, stearate, boric acid powder, and polyethylene glycol, etc. sugar coated tablets, gelatin film coated tablets, enteric coated tablets, film coated tablets, bilayer tablets, and multi-layer tablets can be made according to need by using common coating materials.

The compositions such as pills can be prepared in a manner well known in the pharmaceutical art by using excipients to make the compositions to form into shapes. Said excipients can be carriers, for example, lactose, starch, coconut oil, hardened vegetable oil, kaolin, and talcum powder, etc.; binders, for example, gum arabic powder, gum tragacanth powder, gelatin and ethanol, etc.; disintegrating agents, for example, agar powder, and kelp powder, etc.

The compositions such as suppositories can be prepared in a manner well known in the pharmaceutical art by using excipients to make the compositions to form into shapes, such as, polyethylene glycol, coconut oil, higher alcohols, higher esters, gelatin, and semi synthesis

glyceride, etc.

To prepare compositions such as injections, the solution or suspension is disinfected (it would be good to add suitable amount of sodium chloride, glucose, or glycerol), and then formulated as osmotic injections. The injections can be prepared in a manner well known in the pharmaceutical art by using excipients, such as, water, ethanol, propane diol, ethoxy stearic alcohol and polyvinylsorbitol ester and polyoxyethylene sorbitan monooleate, etc. In addition, the injections can contain commonly used solubilizers, buffering agents, and analgesic agents, etc.

The sulfonylaminocarbonyl derivatives of the formula I and/or a pharmaceutically acceptable salt thereof of any embodiment disclosed herein in the pharmaceutical composition can be effective over a wide range without a specific limitation, usually the amount of the active ingredient can be in a range of 10-90% w/w of the total mass of the composition, such as in a range of 30-80% w/w.

The compositions can be administered in a unit dosage form without specific limitation. The chosen dosage of administration is dependent upon the age, weight and sex of the individual patients, and other circumstances and the severity of the patient's symptoms. The dose forms can be tablets, pills, solutions, suspensions, emulsions, particles, or capsules; injections can be administered alone, or incorporated with injectable solutions (such as glucose or amino acid solutions) for intravenous injections; suppositories are administered into the rectum.

Also provided a pharmaceutical composition comprising 1) a compound of formula I, I-1, IA, IB, IA-1~IA-5, IB-1~IB-5, and/or stable isotope derivatives thereof, and/or a pharmaceutically acceptable salt thereof, and/or prodrugs thereof, and 2) a pharmaceutically acceptable excipient, further comprising one or more additional pharmaceutical agents for treating cholestasis, intrahepatic cholestasis, estrogen-induced intrahepatic cholestasis, drug-induced cholestasis, intrahepatic cholestasis of pregnancy (ICP), parenteral nutrition associated cholestasis (PNAC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chemotherapy related steatohepatitis (CASH), drug induced bile duck injury, liver cirrhosis, alcohol induced liver cirrhosis, cystic fibrosis, bile duct obstruction, cholelithiasis, hepatic fibrosis, dyslipidemia, atherosclerosis, obesity, diabetes, diabetic nephropathy, colitis, neonatal jaundice, the prevention of nuclear jaundice, venous obstruction, high blood pressure, portal hypertension, metabolic syndrome, high cholesterol blood disease, and inflammatory bowel disease. The additional pharmaceutical agents can be combined with the present compositions in a single dosage form, or can be administered simultaneously or sequentially as separate dosage forms.

Also provided use of a sulfonylaminocarbonyl derivative of the formula I and/or a

pharmaceutically acceptable salt thereof any embodiment disclosed herein or use of the pharmaceutical composition disclosed herein is not especially limited, provided is an use of a sulfonylaminocarbonyl derivative of the formula I and/or a pharmaceutically acceptable salt thereof of any embodiment disclosed herein or an use of the pharmaceutical composition disclosed herein in treating FXR and/or TGR5-associated diseases.

In some embodiments, the vitro assay showed that the aryl sulfonamido derivatives of the formula I and/or a pharmaceutically acceptable salt thereof of any embodiment disclosed herein with valuable pharmacological properties thus can be used as a drug. More specifically, a compound of formula I, and/or a pharmaceutical acceptable salt thereof for using as a farnesoid X receptor(FXR) and/or G protein-coupled bile acid receptor 1(TGR5) modulator, which can modulate the activities of FXR and/or TGR5, and can be used in the treatment of FXR and/or TGR5 mediated diseases, wherein the described FXR and/or TGR5 modulator including but are not limited to FXR and/or TGR5 agonist and FXR and/or TGR5 partial agonist, wherein the described diseases are metabolic disorder associated disease caused by carbohydrate metabolism, lipid metabolism, energy metabolism, or bile acid metabolism disorder or immune disease, inflammatory respond or cancer, etc., wherein said diseases include but are not limited to:

In some embodiments, the metabolism disorder associated diseases include but are not limited to: cholestasis, intrahepatic cholestasis, estrogen-induced intrahepatic cholestasis, drug-induced cholestasis, intrahepatic cholestasis of pregnancy (ICP), parenteral nutrition associated cholestasis (PNAC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chemotherapy related steatohepatitis (CASH), drug induced bile duck injury, liver cirrhosis, alcohol induced liver cirrhosis, cystic fibrosis, bile duct obstruction, cholelithiasis, hepatic fibrosis, dyslipidemia, atherosclerosis, obesity, diabetes, diabetic nephropathy, colitis, neonatal jaundice, the prevention of nuclear jaundice, venous obstruction, high blood pressure, portal hypertension, metabolic syndrome, high cholesterol blood disease, and inflammatory bowel disease.

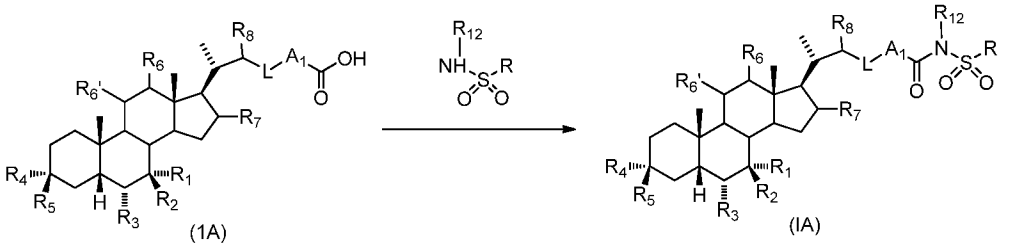
In some embodiments, immune disease and/or inflammatory respond include but are not limited to: allergies, arthritis, appendicitis, bronchial asthma, acute pancreatitis, allergic dermatitis, psoriasis, etc; inflammation bowel disease (Crohn's disease, ulcerative colitis), short bowel syndrome (radiation colitis), micro colitis, irritable bowel syndrome, bacteria overgrowth of digestive tract diseases; and rheumatoid arthritis, multiple sclerosis, type I diabetes, fibrosis, etc.

In some embodiments, cancer include but are not limited to: colorectal cancer, liver cancer, liver cancer, bile duct cancer, renal carcinoma, gastric cancer, pancreatic cancer, prostate cancer, brain cancer, etc.

All the diseases described above are modulated by FXR and/or TGR5. In some embodiments a compound of formula I is a FXR agonist. In some embodiments a compound of formula I is a TGR5 agonist. In some embodiments a compound of formula I is a FXR and TGR5 co-agonist. In some embodiments a compound of formula I is a FXR partial agonist or partial modulator.

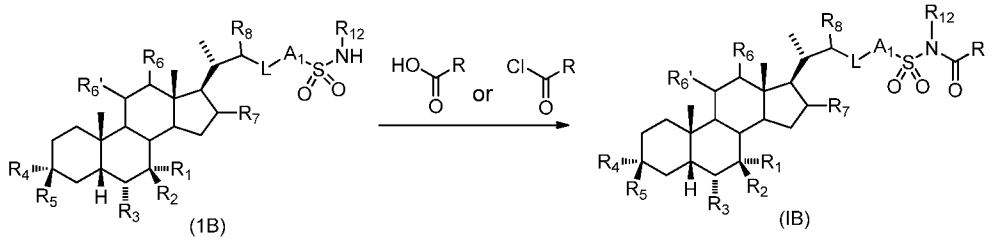
Further provided methods for synthesizing the sulfonylaminocarbonyl derivatives of formula (I), which can be any of the following:

Method 1: the synthetic methods for compounds IA include: compounds 1A are reacted with their corresponding sulfonamides under the condition of existence of base and condensation reagent in a proper solvent to give IA.



Herein, the reaction conditions and procedures are commonly used condensation reaction conditions and procedures well known in the art, solvents used in the described condensation reactions are preferred dichloromethane, condensation reagents are preferred EDCI, the bases are preferred DIPEA and TEA, the reaction temperature can be ranged from 0 to 30°C, the reaction time can be ranged from 0 to 24h, DMAP can be used in the described condensation reactions to catalyzed reaction. In method 1, compounds IA can be obtained though other procedures via compounds 1A are reacted with oxalyl chloride or thionyl chloride to afford acyl chlorides, which are further reacted with sulfonamides under the condition of existence of base (such as, DIPEA or TEA) in protic solvent (such as dichloromethane) to afford IA.

Method 2: the synthetic methods for compounds IB include: 1) compounds 1A are reacted with their corresponding sulfonamides under the condition of existence of base and condensation reagent in a proper solvent to give IB; 2) compounds 1B are reacted with their corresponding acyl chlorides under the condition of existence of base in a proper solvent to give IB.



Herein, the reaction conditions and procedures are commonly used reaction conditions and procedures well known in the art.

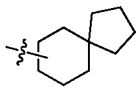
Wherein, in methods 1~2, if compounds 1A, 1B or R groups contain more amino,

hydroxyl or carboxylic acid groups, then the amino, hydroxyl or carboxylic acid groups should be protected to avoid any side reactions. If amino, hydroxyl or carboxylic acid protecting groups are present, they need to be deprotected to obtain the final compound (IA or IB). Any appropriate amino protecting group, such as t-butyloxycarbonyl group (Boc), can be used in the above reactions. If Boc is used as protecting group, the deprotection reaction can be done in the following commonly used conditions, for example, p-tuluenesulfonic acid/methanol, TFA/CH_2Cl_2, saturated HCl/ether, or trimethylsilyl trifluoromethanesulfonate / 2,6-lutidine /CH_2Cl_2; Any appropriate hydroxyl protecting group, such as benzyl, can be used in the above reactions. If benzyl is used as protecting group, the deprotection reaction can be done in the following commonly used conditions, for example, palladium-carbon catalyst and hydrogen system. Any appropriate carboxylic acid protecting group, such as forming carboxylic acid methyl ester or carboxylic acid ethyl ester, can be used in the above reactions. The deprotection reaction can be done in the following commonly used conditions, for example, a mixture of NaOH, KOH, or LiOH in a single or mixed solvent of methanol, ethanol, THF, or water.

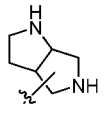
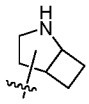
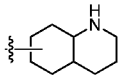
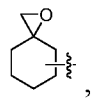
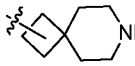
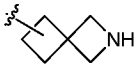
Unless otherwise stated, the following terms in the description and claims have the following definitions:

The term “alkyl” as used herein, refers to a saturated aliphatic hydrocarbon group including 1 to 20 carbon atoms straight chain and branched chain groups. Preferably an alkyl group is a moderate size alkyl having 1 to 10 carbon atoms, more preferably having 1 to 8 carbon atoms. Representative examples of alkyl include, but are not limited to: methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl , 4,4-dimethylpentyl, 2,2,4-trimethylpentyl, undecanyl, docecanyl, and their isomers. When an “alkyl” group is a linking group between two moieties, such as -$(CH_2)_m$-, then it may also be a straight or branched chain; examples include, but are not limited to -CH_2-、-CH_2CH_2-、-$CH_2CH(CH_3)$-.

The term “cycloalkyl” as used herein, refers to a saturated or partially unsaturated monocyclic or polycyclic cycloalkyl ring group containing 3 to 20 carbon atoms, and the C atoms can be oxidized in the cyclic ring system. “mono- cycloalkyl” are cyclic hydrocarbon groups containing 3 to 20 carbon atoms, more preferably having 3 to 10 carbon atoms, examples of monocyclic cycloalkyl include, but are not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecanyl, cyclodocecanyl, and cyclohexenyl. “polycyclic cycloalkyl” is preferred to “bi-cycloalkyl”, which includes “bridged bicycloalkyl”, “fused bicycloalkyl” and “spiro cycloalkyls”. “bridged cycloalkyl” contains a monocyclic cycloalkyl ring where two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of one to three additional carbon atoms (i.e. a bridging group of the form -$(CH_2)_q$-, where q is 1, 2, or 3). Representative examples of bridged cycloalkyl include, but are not limited to, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.1]heptyl,

bicyclo[2.2.2]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicycle[4.2.1]nonyl, etc. "fused cycloalkyl" contains a monocyclic cycloalkyl ring fused to either a phenyl, a cycloalkyl, or a heteroaryl. Representative fused bicycloalkyl include, but are not limited to, bicyclo[4.2.0]octa-1,3,5-triene, 2,3-dihydro-1H-indene, 6,7-dihydro-5H-cyclopenta [b]pyridine, 5,6-dihydro-4*H*-cyclopenta[b]thiophene, and decahydronaphthalene, etc. "Spiro cycloalkyl" contains two monocyclic ring systems which share a carbon atom forming a biclyclic ring system. Representative spiro cycloalkyls include, but are not limited to, , , etc. "polycyclic cycloalkyl" are more preferably having 7 to 12 carbon atoms, mono-cycloalkyl or polycyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the cycloalkyl ring. "3- to 10- membered cycloalkyl" refers to a 3- to 10-membered mono- cycloalkyl, bridged cycloalkyl, fused cycloalkyl or spiro cycloalkyl.

The term "heterocycloalkyl" refers to mono-heterocycloalkyl or a polycyclic heterocycloalkyl, which is a saturated or partially unsaturated (containing 1 or 2 double bonds) non-aromatic ring system consisting of carbon atoms and at least one heteroatom independently selected from O, N, and S. In the present disclosure, the heterocyclyl preferably contains 1, 2, 3, or 4 heteroatoms, and the N, C or S can independently be oxidized in the cyclic ring system. The N atom can further be substituted to form tertiary amine or ammonium salts. "heterocycloalkyl" is preferred to be 3- to 12-membered heterocycloalkyl, is more preferred to be 3- to 10-membered heterocycloalkyl. "mono- heterocycloalkyl" is preferred to be 3- to 10-membered monocyclic heterocycloalkyl, is more preferred to be 3- to 8-membered monocyclic heterocycloalkyl. Representative examples include: aziridinyl, tetrahydrofuran-2-yl, morpholin-4-yl, thiomorpholin-4-yl, thiomorpholin-4-yl-*S*-oxide, piperidin-1-yl, N-alkyl-piperidin-4-yl, pyrrolidin-1-yl, N-alkyl-pyrrolidin-2-yl, pyrazin-1-yl, and 4-alkyl-pyrazin-1-yl, etc. "polycyclic heterocycloalkyl" is preferred "bi-heterocycloalkyl", "polycyclic heterocycloalkyl" includes "bridged heterocycloalkyl", "fused heterocycloalkyl", and "spiro heterocycloalkyl"; Wherein the "bridged heterocycloalkyl" refers to a monocyclic heterocycloalkyl ring where two non-adjacent ring atoms are linked by a bridge linker, said bridge linker is selected from one to three additional carbon atoms or heteroatoms (the described linkers include, but are not limited to: $-CH_2-$, -O-, -NH-, -S-, $-CH_2CH_2-$, $-CH_2O-$, $-CH_2S-$, $-CH_2NH-$, $-CH_2CH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2O-$, $-CH_2CH_2NH-$, $-CH_2NHCH_2-$). said bridged heterocycloalkyl includes, but is not limited to: 2-oxabicyclo[2.2.1]heptyl, 2-azabicyclo[2.2.1]heptyl, 3-azabicyclo [3.2.1]octyl, 6-azabicyclo [3.2.1]octyl, 8-azabicyclo [3.2.1]octyl, 1-azabicyclo [2.2.2]octyl, 2-azabicyclo [2.2.2]octyl, 3-azabicyclo[3.3.1]heptyl, 3-oxabicyclo[3.2.1]heptyl, 8-azabicyclo[3.2.1]nonyl, etc. Wherein "fused heterocycloalkyl" contains a mono- heterocycloalkyl ring which is fused to a phenyl, a mono- cycloalkyl, a

mono- heterocycloalkyl, or a mono- heteroaryl. Representative examples of fused bi-heterocycloalkyl include, but are not limited to, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, indolinyl, 2,3-dihydrobenzo[b] thiophenyl, 4H-chromenyl, 1,2,3,4-tetrahydroquinolinyl, benzo[*d*][1,3]dioxolyl, , , or , etc. "Spiro heterocycloalkyl" contains two mono- heterocycloalkyl or one mono- cycloalkyl and one mono- heterocycloalkyl which share a carbon atom to form a biclyclic ring system. Representative spiro heterocycloalkyl includes, but is not limited to, , , , , or , etc. wherein, the polycyclic heterocycloalkyl prefers 7 to 12 membered polycyclic heterocycloalkyl. Mono- heterocycloalkyl or polycyclic heterocycloalkyl is appended to the parent molecular moiety through any ring atom contained within the ring system. Herein, the ring atoms are specifically referred to the carbon and/or nitrogen atoms which form the cyclic ring skeleton. "3- to 10-membered heterocycloalkyl" refers to a 3- to 10-membered mono-heterocycloalkyl, bridged heterocycloalkyl, fused heterocycloalkyl or spiro heterocycloalkyl.

The term "cycloalkylalkyl" refers to a cycloalkyl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Wherein, "cycloalkylalkyl" include the definitions of the above alkyl and cycloalkyl.

The term "heterocycloalkylalkyl" refers to a heterocyloalkyl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Wherein, "heterocycloalkylalkyl" include the definitions of the above alkyl and heterocycloalkyl.

The term "alkoxy" refers to an alkyl, cycloaklyl or heterocycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Alkoxy groups include alkyloxy, cycloalkyloxy, and heterocycloalkyloxy. Wherein, "alkoxy" includes the definitions of the above alkyl, heterocycloalkyl, and cycloalkyl.

The term "cycloalkylalkoxy" as used herein, refers to an alkyl hydrogen atom of the alkoxy group, as defined herein, is substituted by a cycloalkyl. Wherein, "cycloalkylalkoxy" includes the definitions of the above cycloalkyl and alkoxy.

The term "heterocycloalkylalkoxy" as used herein, refers to an alkyl hydrogen atom of the alkoxy group, as defined herein, is substituted by a heterocycloalkyl. Wherein, "heterocycloalkylalkoxy" includes the definitions of the above heterocycloalkyl and alkoxy.

The term "alkenyl" as used herein, refers to a straight, branched chain or cyclic non-aromatic hydrocarbon ring containing from 1 to 3 carbon-carbon double bonds, preferable one carbon-carbon double bond. Representative examples of alkenyl include, but are not

limited to, vinyl, 2-propenyl, 2-butenyl, 2-methylbutenyl and cyclohexenyl. The term "C_{2-4}alkenyl" means alkenyl containing 2 to 4 carbon atoms.

The term "alkynyl" as used herein, refers to a straight, branched chain or cyclic non-aromatic hydrocarbon ring containing from 1 to 3 carbon-carbon triple bonds, preferable one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, ethynyl, 2-propynyl, 2-butynyl, and 3-methylbutynyl. The term "C_{2-4} alkynyl" means alkynyl containing 2-4 carbon atoms.

The term "aryl" refers to any stable 6 to 10 membered mono or bicyclic aromatic group, for example, phenyl, naphthyl, tetrahydronaphthyl, 2,3-dihydro-1*H*-indenyl, or biphenyl, etc. The term "C_6 aryl" refers to phenyl.

The term "heteroaryl" refers to a 5- to 7-membered monocyclic heteroaryl or a 7- to 12-membered bicyclic ring group containing at least one heteroatom independently selected from O, N, and S. The monocyclic heteroaryl prefers a 5- to 6-membered ring. The bicyclic heteroaryl prefers a 7- to 12-membered heteroaryl. In the present disclosure, the number of heteroatoms prefers to be 1, 2 or 3. Representative heteroaryls include, but are not limited to, pyrrolyl, imidazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, pyridyl, pyrimidyl, indazolyl, isoindazolyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzo[d][1,3]dioxolyl, benzothiazolyl, quinolinyl, isoquinolinyl, and quinazolinyl, etc.

The term "arylalkyl", as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl. Wherein, "arylalkyl" includes the definitions of the above alkyl and aryl.

The term "heteroarylalkyl", as used hererin, refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an alkyl. Wherein, "heteroarylalkyl" includes the definitions of the above alkyl and heteroaryl.

The term "arylalkoxy" refers to an alkyl hydrogen atom of the alkoxy group, as defined herein, is substituted by an aryl. Wherein, "arylalkoxy" includes the definitions of the above aryl and alkoxy.

The term "heteroarylalkoxy" refers to an alkyl hydrogen atom of the alkoxy group, as defined herein, is substituted by a heteroaryl. Wherein, "heteroarylalkoxy" includes the definitions of the above heteroaryl and alkoxy.

The term "halo" or "halogen" refers to Cl, Br, I or F.

The term "haloalkyl" refers to an alkyl group as defined herein, is substituted by at least one halogen, as defined herein. Wherein, "haloalkyl" includes the definitions of the above halogen and alkyl.

The term "haloalkoxy" means an alkoxy group as defined herein, is substituted by at least one halogen, as defined herein. Wherein, "haloalkoxy" includes the definitions of the above halogen and alkoxy.

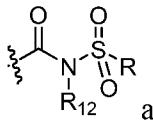
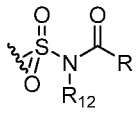
The term "amino" refers to $-NH_2$.

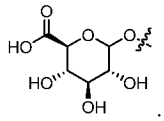
The term "aminoalkyl" refers to an alkyl group wherein any one of hydrogen atom is substituted with an amino group. Wherein, "aminoalkyl" includes the definitions of the above alkyl and amino.

The term "hydroxyl" refers to -OH.

The term "hydroxyalkyl" refers to an alkyl group wherein any one of hydrogen atom is substituted with a hydroxyl group. Wherein, "hydroxyalkyl" includes the definitions of the above alkyl and hydroxyl.

The term "sulfonyl" refers to $-S(O)_2-$, wherein said sulfonyl comprises alkyl sulfonyl, cycloalkyl sulfonyl, heterocycloalkyl, aryl sulfonyl, and heteroaryl sulfonyl, which refers to a alkyl, cycolalkyl, heterocycloalkyl, aryl or heteroaryl attached to the parent molecular moiety through $-S(O)_2-$, wherein said "alkyl sulfonyl, cycloalkyl sulfonyl, heterocycloalkyl, aryl sulfonyl, and heteroaryl sulfonyl" include the definitions of the above alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl and sulfonyl.

The term "sulfonylaminocarbonyl" refers to  and , wherein R and R_{12} are as described before. "sulfonylaminocarbonyl" can be appended to the parent molecular moiety through the carbon atom of the carbonyl group or through the sulfur atom of the sulfonyl group.

The term "$-OC_6H_8O_6H$" refers to a hexuronic acid which is appended to the parent molecular moiety through an O- glycosidic bond, such as, .

The term "=" as used herein, refers to a double bond.

The term "room temperature" as used herein, refers to 15-30 °C.

The compound of formula (I) as well as any embodiment thereof includes isotope-labelled derivatives thereof. The described isotope-labeled derivatives include: the hydrogen atom (1 to 5) of a compound of formula (I) is substituted by 1 to 5 deuterium atoms, respectively; the carbon atom (1 to 3) of a compound of formula (I) is substituted is substituted by 1 to 3 C_{14} atoms; or the oxygen atom of a compound of formula (I) is substituted by 1 to 3 O_{18} atoms.

The term "prodrug" as used herein, refers to compound which can be transformed to the original active compound after *in vivo* metabolism. In general, prodrug is not an active material, or is less active than the parent compound, but can provide convenient manipulation, administration, or improving metabolic properties. The term "compound" as used herein is intended to include prodrug thereof to the extent they can be made by one of ordinary skill in the art by routine experimentation.

The term "pharmaceutically acceptable salts" as used herein, has been discussed in Berge, et al., "Pharmaceutically acceptable salts", J. Pharm. Sci., 66, 1-19 (1977), and is apparent to all the medicinal chemists. The defined pharmaceutically acceptable salts are generally not toxic, and can provide needed pharmacokinetic properties, orally bioavailable, and ADME properties.

The pharmaceutically acceptable salts as used herein, is synthesized by conventional chemical methods.

Generally, the salt described above can be prepared by reacting the free acid or base forms of these compounds with stoichiometric amount of the base or acid in an appropriate solvent or a solvent mixture.

The term "solvates" refers to a corresponding solvate of the present disclosure compound or salts thereof, formed from the combination of stoichiometric amount or non-stoichiometric amount of solvent molecules with the present disclosure compound or a salt thereof (or ions of the solute). If the solvent is water, the solvate may be simply referred to as a hydrate, if the solvent is ethanol, the solvate may be referred to as an ethanol solvate, "hydrate" refers to one or more water molecules combined with the compound of the present disclosure, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

The compounds of the present disclosure may have asymmetric centers, creating "isomers." The term "isomers" as used herein, refers to the stereoisomers, which include, enantiomers and diastereomers, wherein cis/trans isomers belong to diastereomers. Therefore, in the present disclosure, the compounds of formula (I) can be enantiomers, diastereomers, and their mixtures, all of these stereoisomers are included in this disclosure. In the present disclosure, when compounds of formula (I) and their salts are stereoisomers (for example, they contain one or more chiral carbons), individual stereoisomers (enantiomers and diastereoisomers) and their mixtures (enantiomeric and diastereomeric mixtures) are included in the range of this disclosure. The present disclosure includes individual stereoisomers, and mixtures of these stereoisomers of compounds of formula (I) and there salts of any embodiment disclosed herein, in which the configurations of one or more chiral carbons are inverted. The disclosure includes all of the possibilities of the enantiomeric and diastereomeric mixtures, herein, the diastereomers include cis/trans isomers. The present disclosure includes all of the combinations of the stereoisomers of all of the above defined specific groups.

EXAMPLES

The following examples serve to illustrate the compounds in this disclosure and the preparation process, but the examples should not be considered as limiting the scope of the disclosure.

All the structures of the compounds in the present disclosure were confirmed by ^{1}H NMR and MS.

^{1}H NMR chemical shifts (δ) were recorded in ppm (10^{-6}). NMR Spectra: Bruker AVANCE-400 spectrometer in proper solvent: DMSO-d_6, $CDCl_3$, MeOD-d_4, δ in ppm rel. to Me_4Si as internal standard.

The analytical low-resolution mass spectra (MS) were recorded on Agilent 1200HPLC/6120 using a XBridge C18, 4.6×50 mm, 3.5 um using a gradient elution method. The gradient elution method 1 is: 80-5% (v/v%) solvent A_1 and 20-95% (v/v%) solvent B_1 (1.8min), then 95% (v/v%) solvent B_1 and 5% (v/v%) solvent A_1 (more than 3 mins). "v/v%" as used herein, means volume percentage. Solvent A_1: 0.01% TFA aqueous solution, B1: acetonitrile; The gradient elution method 2 is: 80-5% (v/v%) solvent A_2 and 20-95% (v/v%) solvent B_2 (1.5min), then 95% (v/v%) solvent B_2 and 5% (v/v%) solvent A_2 (more than 2min). "v/v%" as used herein, means volume percentage. Solvent A_2: 10 mM ammonium bicarbonate aqueous solution; Solvent B_2: acetonitrile.

All the compounds or intermediates in the present disclosure were purified by flash column chromatography, or column chromatography, the reaction process can be detected by thin layer chromatography (TLC). The commonly used elution systems were ethyl acetate/ petroleum ether and DCM/ methanol.

Flash chromatography was performed on Agela Technologies MP200 (flash system/Cheetah™), the corresponding column was Flash columm (Silica-CS80g), Cat No. CS140080-0.

Column chromatography generally used Yantai Huanghai 200-300 mesh silica gel as carrier.

The following abbreviations have been used:

DMSO-d_6: deuterated-dimethyl sulfoxide

$CDCl_3$: deuterated-chloroform

CD_3OD: deuterated-methanol

CDCA: chenodeoxycholic acid

TBAB: tetrabutyl ammonium bromide

TBAF: tetrabutyl ammonium fluoride

TMSCN: trimethylsilane cyanide

DMAP: 4-dimethylaminopyridine

TFA: trifluoroacetic acid

TFAA: trifluoroacetic anhydride

DIPEA: *N,N*-diisopropylethylamine

LDA: lithium diisopropylamide

EDCI: *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

TEA: trimethylamine

p-TsOH: *p*-toluenesulfonic acid

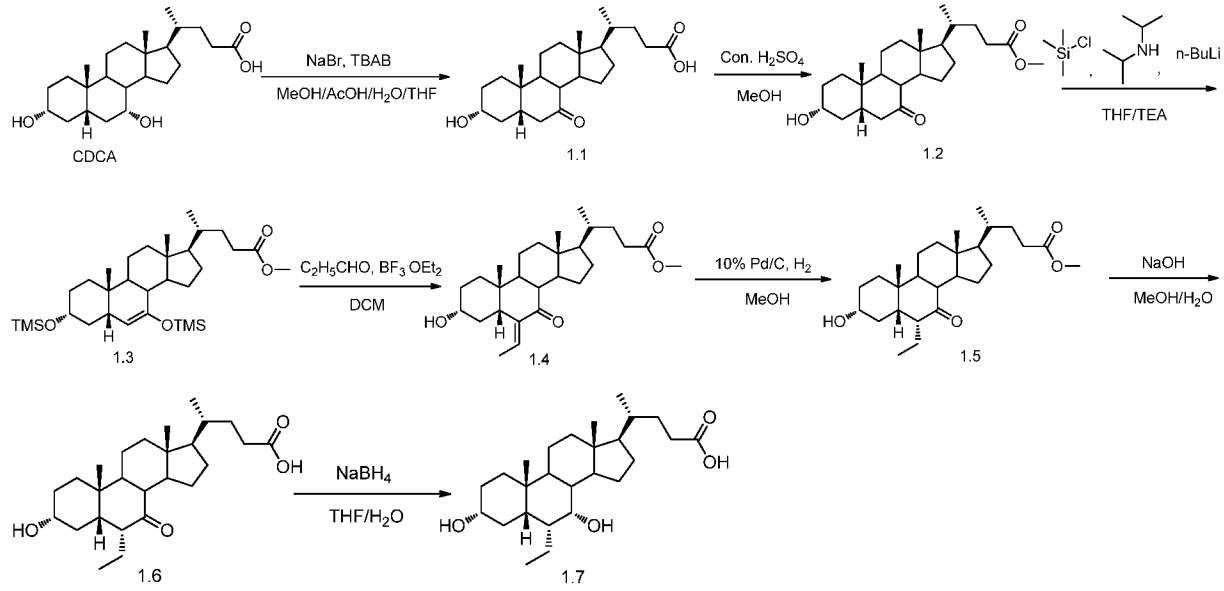
DCM: dichloromethane

DMF: *N,N*-dimethylformamide

THF: tetrahydrofuran

MeOH: methanol

Example 1: synthesis of compound 1.7



Step 1: synthesis of compound 1.1

A mixture of CDCA (190 g, 0.474 mol), NaBr (2.5 g, 24 mmol), TBAB (0.5 g, 1.55 mmol), methanol (616 mL), acetic acid (200 mL), H_2O (49 mL) and THF (1330 mL) in round-bottom flask (5.0 L) was stirred at room temperature for 15min until the solution was clear, and then the solution was cooled down to 0°C, $NaClO_2$ (~5%, 756 g, 531 mmol) was added to above clear solution and kept inner temperature at 1~2 °C (exothermic). The resulted mixture was stirred at 0°C for 30min, then warmed to 5 °C slowly and stirred for 3h, until the starting material was disappeared under the monitor of TLC. The reaction was quenched by addition of a saturated solution of aqueous $NaHSO_3$ (3.3 %, 83 g, 13.5 mmol) until the detection of peroxide is free with KI-starch test paper, water (2 L) was then added, the mixture was stirred for 10min, and then cooled down to 10 °C, allowed to separate to layers. The organic layer was separated and filtered, the filter cake was washed with cold water (200 mL) and dried under vacuum to afford compound 1.1 (149 g, yield: 79%) as a white powder.

m/z: $[M-H]^-$ 389

Step 2: synthesis of compound 1.2

To a solution of compound 1.1 (20 g, 51.2 mmol) in methanol (100 mL) was added concentrated H_2SO_4 (1 g). The resulted mixture was stirred at reflux for overnight until the starting material was disappeared under the monitor of TLC. The solvent was evaporated under vacuum, the residue was partitioned between water (100 mL) and ethyl acetate (100 mL), and

the organic layer was separated and washed with a saturated solution of aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (DCM/ MeOH = 95: 5) to afford compound 1.2 (16 g, yield: 77%) as a light yellow oil.

m/z: $[M+H]^+$405

Step 3: synthesis of compound 1.3

To a dry ice- acetone bath cooling three-necked, round-bottomed flask (100 mL) was added dry THF (10 mL) and diisopropylamine (1.5 g, 14.9 mmol) under nitrogen, then n-BuLi (6.0 mL, 15 mmol, 2.5 M solution in n-hexane) was added slowly, the mixture was stirred at -78°C for 0.5h, and then chlorotrimethylsilane (2.15 g, 19.9 mmol) was added, and the mixture was stirred for 10min. A solution of compound 1.2 (1 g, 2.5 mmol) was added, and the resulted mixture was stirred at -78°C for 0.5h, and then TEA (3.75 g, 37 mmol) was added, and the resulted mixture was stirred at -78°C for 1h. The inner temperature was warmed up to -28°C, the reaction was quenched by addition of a saturated solution of aqueous $NaHCO_3$ (10 mL). The mixture was warmed up to room temperature and allowed to separate to layers. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×20 mL), the combined organic layer was successively washed with saturated a solution of aqueous $NaHCO_3$, water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude compound 1.3, which can be used directly for next step by stored in a refrigerator.

^1H NMR (400 MHz, $CDCl_3$): δ 4.75 (dd, J = 1.8, 6.0 Hz, 1 H), 3.69 (s, 3 H), 3.53 (m, 1 H), 2.33 - 2.41 (m, 1 H), 2.15 - 2.28 (m, 1 H), 1.02 - 2.02 (m, 22 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.84 (s, 3 H), 0.70 (s, 3 H), 0.13 - 0.18 (m, 18 H).

Step 4: synthesis of compound 1.4

A solution of compound 1.3 (5.5 g, 10 mmol), dry DCM (30 mL), and acetaldehyde (1.1 mL, 25 mmol) in a three-necked, round-bottomed flask (250 mL) under nitrogen was cooled by a dry- ice acetone bath to -60°C, and then a solution of boron trifluoride etherate (5.22 g, 37 mmol) in DCM (15 mL) was slowly added under nitrogen. The resulted mixture was stirred at -60°C for 2h, and then the mixture was warmed up to room temperature, the reaction was quenched by addition of a saturated solution of aqueous $NaHCO_3$ (40 mL). The mixture was extracted with DCM (3×40 mL), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7: 3) to afford compound 1.4 (3.0 g, yield: 69%) as an off- white solid.

^1H NMR (400 MHz, $CDCl_3$): δ 6.14 - 6.18 (m, 1 H), 3.56 - 3.69 (m, 4 H), 2.55 - 2.58 (m, 1 H), 2.20 - 2.44 (m, 4 H), 1.62 - 2.06 (m, 9 H), 1.68 (d, J = 7.2 Hz, 3 H), 1.07 - 1.51 (m, 10 H), 1.00 (s, 3 H), 0.92 (d, J = 6.2 Hz, 3 H), 0.63 (s, 3 H).

m/z: $[M+H]^+$431

Step 5: synthesis of compound 1.5

To a solution of compound 1.4 (1.3 g, 3.02 mmol) in methanol (50 mL) was added Pd/C (130 mg, 10%). The resulted mixture was stirred under hydrogen (1 atm) at room temperature for 48h until the starting materials was disappeared. Then the mixture was filtered through a celite pad, and the filtrate was concentrated to afford compound 1.5 (1.1 g, yield: 95%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3 H), 3.57 (m, 1 H), 2.57 (t, *J* = 11.6 Hz, 1 H), 2.37 (m, 1 H), 2.24 (dd, *J* = 6.6, 9.6 Hz, 1 H), 2.20 (m, 1 H), 1.22 (s, 3 H), 1.01 - 1.98(m, 23 H), 0.93 (d, *J* = 6.2 Hz, 3 H), 0.85 (t, *J* = 7.4 Hz, 3 H), 0.67 (s, 3 H).

m/z: $[M+H]^+$433

Step 6: synthesis of compound 1.6

To a solution of compound 1.5 (1.23 g, 2.84 mmol) in a mixed solvent of methanol (10 mL) and water (1 mL) was added sodium hydroxide (284 mg, 7.1 mmol), and the resulted mixture was stirred at reflux for overnight. Then the solvent was evaporated under vacuum, the residue was diluted with water and acidified with hydrochloric acid (6.0 M), and the mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford compound 1.6 (1.1 g, yield: 92%) as an off-white solid.

^{1}HNMR (400 MHz, $CDCl_3$): δ 3.46 (m, 1 H), 2.83 (dd, *J* = 13.0, 5.5 Hz, 1 H), 2.50 (t, *J* = 11.2 Hz, 1 H), 2.34 (m, 1 H), 2.20 (m, 1 H), 1.22 (s, 3 H), 0.99 - 1.88 (m, 23 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.81 (t, *J* = 7.3 Hz, 3 H), 0.71 (s, 3 H).

m/z: $[M-H]^-$417

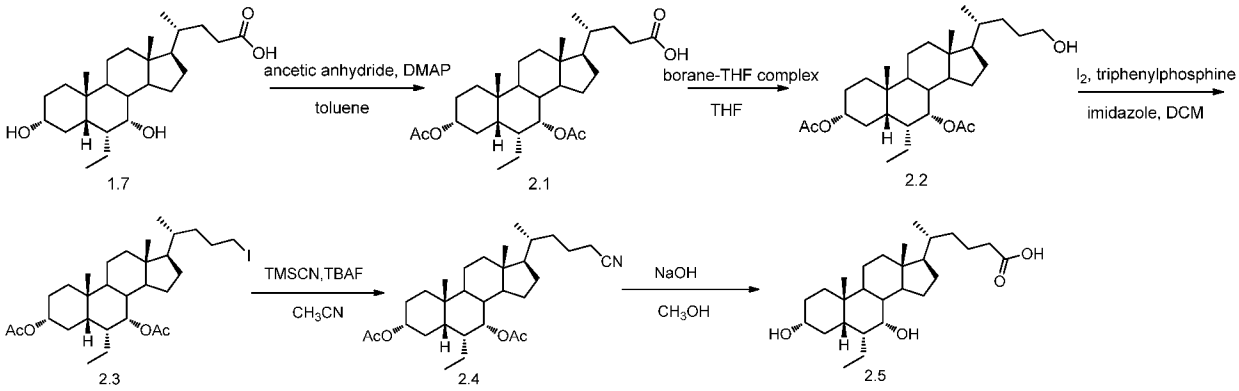
Step 7: synthesis of compound 1.7

To an ice- cooling solution of compound 1.6 (1.1 g, 2.63 mmol) in a mixed solvent of THF (10 mL) and water (2 mL) was added $NaBH_4$ (495 mg, 13.1 mmol). The resulted mixture was stirred at room temperature for 1h, and then the reaction was quenched by addition of methanol (10 mL). The solvent was evaporated under vacuum. The residue was dissolved in water, acidified with hydrochloric acid (1.0 M), and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (DCM/ MeOH = 9: 1) to afford compound 1.7 (600 mg, yield: 54%) as a white powder.

^{1}H NMR (400 MHz, CD_3OD): δ 3.60 (br, s, 1 H), 3.32 (m, 1 H), 2.33 (m, 1 H), 2.20 (m, 1 H), 1.01 - 2.04 (m, 25 H), 0.97 (d, *J* = 6.2 Hz, 3 H), 0.91 (s, 3 H), 0.90 (t, *J* = 7.0 Hz, 3 H), 0.69 (s, 3 H).

m/z: $[M-H]^-$419

Example 2: synthesis of compound 2.5



Step 1: synthesis of compound 2.1

A solution of compound 1.7 (10 g, 24 mmol), DMAP (300 mg, 2.4 mmol) in a mixed solvent of acetic anhydride (50 mL) and toluene (100 mL) was stirred at 110°C for 2d, and then the resulted mixture was cooled down to room temperature and the solvent was evaporated under vacuum, the residue was dissolved in ethyl acetate (200 mL), the organic layer was washed with cooled water (3×50 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~50%) to afford compound 2.1 (10.4 g, yield: 86%) as a white solid.

m/z: $[M-H]^-$ 503

Step 2: synthesis of compound 2.2

To an ice- cooling solution of compound 2.1 (1.0 g, 2.0 mmol) in dry THF (30 mL) was added borane-THF complex (5.0 mL, 1.0 M in THF) dropwise. The resulted mixture was stirred at 10°C for 4h, and then the reaction was quenched by addition of cold hydrochloric acid (1.0 M, 5.0 mL). The mixture was stirred for 30min and extracted with ethyl acetate, the organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~40%) to afford compound 2.2 (780 mg, yield: 80%) as a white powder.

Step 3: synthesis of compound 2.3

A solution of compound 2.2 (1.3 g, 2.65 mmol), iodine (1.35 g, 5.30 mmol), imidazole (270 mg, 3.98 mmol) and triphenylphosphine (1.04 g, 3.98 mmol) in DCM (60 mL) was stirred at room temperature for 5h, and then the reaction was quenched by addition of a saturated solution of aqueous $Na_2S_2O_3$ (50 mL). The mixture was extracted with ethyl acetate (2×50 mL), the combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~10%) to afford compound 2.3 (1.3 g, yield: 82%) as a white powder.

^1H NMR (400 MHz, $CDCl_3$): δ 5.12 (s, 1 H), 4.54 - 4.63 (m, 1 H), 3.11 - 3.25 (m, 2 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.05 - 2.02 (m, 27 H), 0.88 - 0.96 (m, 9 H), 0.66 (s, 3 H).

Step 4: synthesis of compound 2.4

A solution of compound 2.3 (1.0 g, 1.66 mmol), TMSCN (1.65 g, 16.7 mmol), TBAF

(2.63 g, 8.33 mmol) in acetonitrile (60 mL) was stirred at room temperature for overnight, and then the solvent was evaporated under vacuum. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~10%) to afford compound 2.4 (800 mg, yield: 96%) as a white powder.

^{1}H NMR (400MHz, $CDCl_3$-*d*): δ 5.12 (s, 1 H), 4.56 - 4.59 (m, 1 H), 2.31 - 2.34 (m, 2 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.12 - 2.10 (m, 27 H), 0.82 - 0.96 (m, 9 H), 0.64 (s, 3 H).

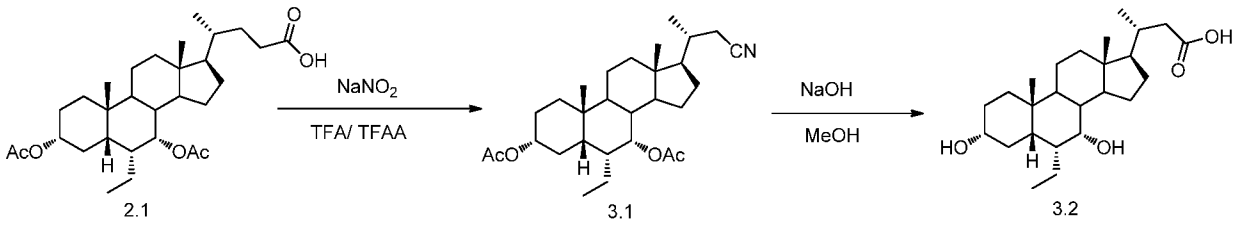
Step 5: synthesis of compound 2.5

A solution of compound 2.4 (300 mg, 0.60 mmol) in sodium hydroxide methanol solution (15 mL, 10%, w/w) was stirred at 70°C for overnight, and then the mixture was cooled down to room temperature and adjusted pH to 5~6 with hydrochloric acid (2.0 M). The mixture was stirred for 30min, and then extracted with DCM (3×30 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~80%) to afford compound 2.5 (260 mg, yield: 98%) as a white powder.

^{1}H NMR (400MHz, $CDCl_3$): δ 3.73 (s, 1 H), 3.42 - 3.44 (m, 1 H), 2.31 - 2.35 (m, 2 H), 0.98 - 1.98 (m, 27 H), 0.90 - 0.95 (m, 9 H), 0.68 (s, 3 H).

m/z: $[M-H]^-$433

Example 3: synthesis of compound 3.2



Step 1: synthesis of compound 3.1

An ice- cooling mixture of compound 2.1 (3.65 g, 7.24 mmol), TFA (6.6 mL) and TFAA (11.4 g, 54.3 mmol) was stirred until the solution became clear, and then $NaNO_2$ (1.5 g, 21.7 mmol) was added in small portions. The resulted mixture was stirred at 0°C for 1h, and then the mixture was warmed up to 40°C and stirred for 2h. After cooling down to room temperature, the mixture was neutralized with a saturated solution of aqueous $NaHCO_3$, and then extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~20%) to afford compound 3.1 (2.4 g, yield: 70%) as a light yellow oil.

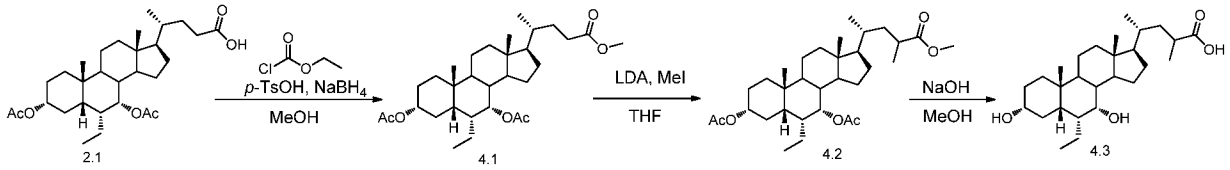
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (s, 1 H), 4.54 - 4.62 (m, 1 H), 2.22 - 2.38 (m, 2 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.16 - 1.98 (m, 26 H), 0.95 (s, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.68 (s, 3 H).

Step 2: synthesis of compound 3.2

A solution of compound 3.1 (317 mg, 0.67 mmol) in sodium hydroxide methanol solution (15 mL, 10%, w/w) was stirred at 100°C for overnight, and then the mixture was cooled down to room temperature and adjusted pH to 6~7 with hydrochloric acid (3.0 M). The mixture was stirred for 30min, and then extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (MeOH/ DCM = 0~3%) to afford compound 3.2 (175 mg, yield: 64%) as a white solid.

m/z: $[M-H]^-$ 405

Example 4: synthesis of compound 4.3



Step 1: synthesis of compound 4.1

To a solution of compound 2.1 (1.0 g, 1.90 mmol) and *p*-TsOH (20 mg, 0.12 mmol) in methanol was added ethyl carbonochloridate (7.2 mL, 6.32 mmol). The resulted mixture was stirred at room temperature for 2h, and then a solution of aqueous $NaBH_4$ (96 mL, 0.1 g/mL) was added dropwise, the resulted mixture was stirred at room temperature for 3h. The reaction was quenched by addition of water (300 mL), and adjusted pH to neutral with hydrochloric acid (1.0 M). The mixture was extracted with ethyl acetate (3×100 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate = 5: 1) to afford compound 4.1 (700 mg, yield: 68%) as an off- white solid.

Step 2: synthesis of compound 4.2

A dry ice- acetone bath cooling solution of compound 4.1 (500 mg, 0.96 mmol) in dry THF (20 mL) was kept for 15min. After this, a solution of LDA in THF (1.44 mL, 1.0 M) was added dropwise. The resulted mixture was stirred at -78°C for 1h, and then iodomethane (203 mg, 1.44 mmol) was added, the mixture was stirred at -78°C for 2h, and then the reaction was quenched by addition of a saturated solution of aqueous NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~10%) to afford compound 4.2 (350 mg, yield: 68%) as a white solid.

m/z: $[M-H]^-$ 531

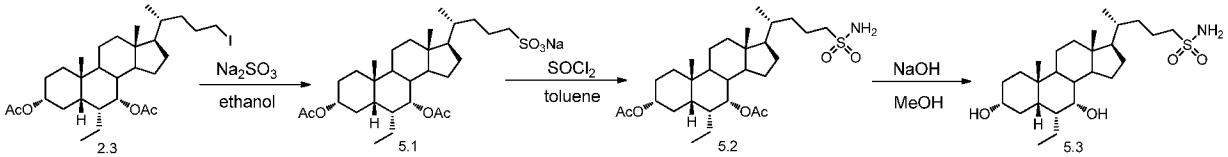
Step 3: synthesis of compound 4.3

To an ice- cooling solution of compound 4.2 (320 mg, 0.60 mmol) in methanol (10 mL) was added sodium hydroxide methanol solution (15 mL, 10%, w/w), and then the resulted

mixture was stirred at reflux for overnight. After this, the mixture was cooled down to room temperature and adjusted pH to 5~6 with hydrochloric acid (2.0 M). The mixture was stirred for 30min, and then extracted with DCM (3×20 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (MeOH/ DCM = 1~ 10%) to afford compound 4.3 (200 mg, yield: 76%) as an off- white solid.

m/z: $[M-H]^-$ 433

Example 5: synthesis of compound 5.3



Step 1: synthesis of compound 5.1

To a solution of compound 2.3 (1.0 g, 1.66 mmol) in ethanol (10 mL) was added a solution of aqueous Na_2SO_3 (150 mL, 5%, w/w). The resulted mixture was stirred at 100°C for 24h, and then cooled down to room temperature. The mixture was concentrated under vacuum to remove most of ethanol. The resulting solution was applied to a column MCI-Gel HP-20 (polymer of styrene and divnylbenezene). After washing with water (400 mL) to remove inorganic ions, the column was eluted with a solution of aqueous methanol (70%, w/w). The elution was evaporated to afford compound 5.1 (1.0 g, yield: 100%) as an off- white solid.

m/z: $[M-Na]^-$ 553

Step 2: synthesis of compound 5.2

A solution of compound 5.1 (1.0 g, 1.73 mmol) in thionyl chloride (5 mL) and toluene (20 mL) was stirred at reflux for 5h, and then the resulted mixture was cooled down to room temperature, the solvent was evaporated under vacuum. The residue was dissolved in THF (5 mL), a solution of aqueous NH_4OH was added. The resulted mixture was stirred at room temperature for overnight, and then the solvent was evaporated under vacuum. The residue was purified by Flash chromatography (MeOH/ DCM = 0~5%) to afford compound 5.2 (550 mg, yield: 39%) as a white solid.

m/z: $[M-H]^-$ 552

Step 3: synthesis of compound 5.3

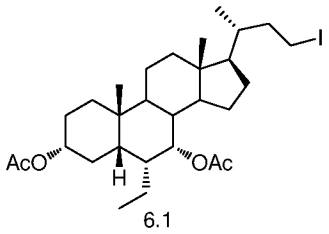
A solution of compound 5.2 (400 mg, 0.72 mmol) in sodium hydroxide methanol solution (15 mL, 10%, w/w) was stirred at 70°C for overnight, and then the mixture was cooled down to room temperature, the solvent was evaporated under vacuum, the residue was dissolved in cooled water (20 mL) and adjusted pH to 5~6 with hydrochloric acid (3.0 M). The mixture was stirred for 30min, and then extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated.

The residue was purified by Flash chromatography (methanol: DCM = 0~5%) to afford compound 5.3 (260 mg, yield: 77%) as a white solid.

m/z: $[M-H]^-$ 468

Example 6: synthesis of compound 6.1

Compound 6.1 was prepared according to Example 2 compound 2.3, by using compound 3.2 as a starting material.

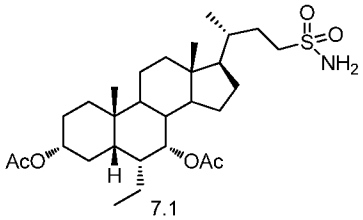


6.1

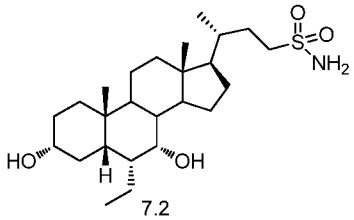
m/z: $[M-H]^-$ 585

Example 7: synthesis of compounds 7.1 and 7.2

Compounds 7.1 and 7.2 were prepared according to Example 5 compounds 5.2 and 5.3, by using compound 6.1 as a starting material.



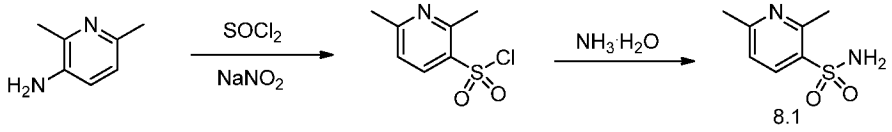
7.1



7.2

Compound 7.2: m/z: $[M-H]^-$ 454

Example 8: synthesis of compounds 8.1~8.13



8.1

Step 1: synthesis of 2, 6-dimethylpyridine-3-sulfonyl chloride

Thionyl chloride (2 mL) was added to water (5 mL) dropwise. The resulted mixture was stirred at room temperature for overnight, and then CuCl (1.1 g, 8.2 mmol) was added to above mixture under ice- bath to form a CuCl solution. To an ice- cooling solution of 2,6-dimethylpyridin-3-amine (1.0 g, 8.2 mmol) in a mixed solvent of hydrochloric acid (1 mL, 37%, v/v) and water (10 mL) was added a solution of aqueous $NaNO_2$ (5 mL, 0.82 mol), the resulted mixture was stirred for 0.5h, and then the CuCl solution prepared before was added. The resulted mixture was stirred for 1h, and extracted with DCM (3×20 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to afford 2,6-dimethylpyridine-3- sulfonyl chloride (500 mg, yield: 30%) as a yellow oil.

m/z: $[M+H]^+$ 187

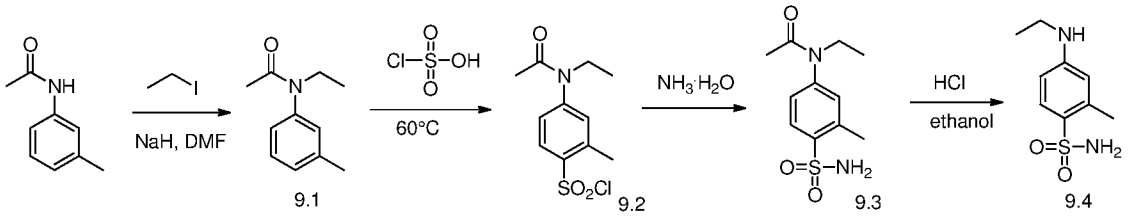
Step 2: synthesis of compound 8.1

To a solution of 2,6-dimethylpyridine-3-sulfonyl chloride (500 mg, 2.4 mmol) in 1,4-dioxane (5 mL) was added ammonia water (2 mL), the resulted mixture was stirred at room temperature for overnight, and then the solvent was evaporated under vacuum, the residue was purified by column chromatography on silica gel (DCM/methanol = 30:1) to afford 2,6-dimethylpyridine-3- sulfonamide (8.1) (100 mg, yield: 26%) as a white solid.

m/z: $[M+H]^+$ 187

pyridine-3-sulfonamide (8.2), thiophene-3-sulfonamide (8.3), methyl 5-sulfamoyl picolinate (8.4), 6-(trifluoromethyl)pyridine-3-sulfonamide (8.5), 6-methoxypyridine-3-sulfonamide (8.6), 6-phenylpyridine-3-sulfonamide (8.7), 2-isopropylbenzenesulfonamide (8.8), 2-(*tert*-butyl)benzenesulfonamide (8.9), 2,4-bis(trifluoromethyl)benzenesulfonamide (8.10), 2-fluoro-6-(trifluoromethyl) benzenesulfonamide (8.11), 2-methyl-6-(trifluoromethyl) benzenesulfonamide (8.12), and methyl 4-sulfamoylbenzoate (8.13) were prepared according to compound 8.1, by using corresponding amino or sulfonyl chloride as starting materials.

Example 9: synthesis of compound 9.4



Step 1: synthesis of compound 9.1

To an ice- cooling solution of *N*-(m-tolyl)acetamide (3.0 g, 20.1 mmol) in DMF (30 mL) was added NaH (0.97 g, 24.1 mmol, 60%) in small portions under nitrogen. The resulted mixture was stirred at 0°C for 20min, and then iodoethane (3.45 g, 22.1 mmol) was added. The mixture was warmed up to room temperature and stirred for 1h, the reaction was quenched by addition of cold water (100 mL). The mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (ethyl acetate/ petroleum ether = 0~100%) to afford compound 9.1 (2.86 g, yield: 80%) as a light yellow oil.

m/z: $[M+H]^+$178

Step 2: synthesis of compound 9.2

A solution of compound 9.1 (2.86 g, 16.1 mmol) in chlorosulfonic acid (10 mL) was stirred at 60°C for 2h, and then the mixture was poured into cold water (200 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to afford compound 9.2 (3.77 g, yield: 85%) as a yellow oil.

Step 3: synthesis of compound 9.3

A solution of compound 9.2 (3.77 g, 13.7 mmol) in ammonia water (40 mL) was stirred at 20°C for overnight, and then the mixture was filtered, the filter cake was washed with *tert*-Butyl methyl ether (3×10 mL) and dried under vacuum to afford compound 9.3 (2.46 g, yield: 70%) as a light yellow solid.

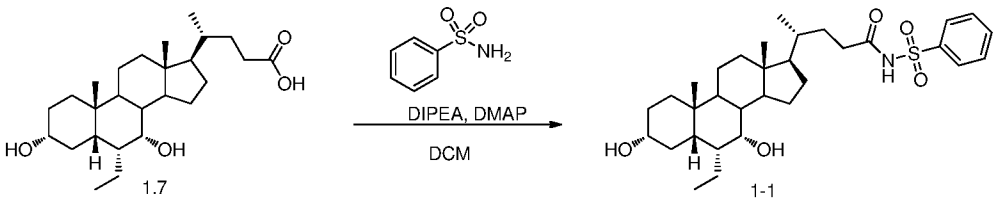
m/z: $[M-H]^-$ 255

Step 4: synthesis of compound 9.4

To a suspension of compound 9.3 (1.0 g, 3.90 mmol) in ethanol (10 mL) was added hydrochloric acid (6.0 M, 10 mL). The resulted mixture was stirred at reflux for 3h, and then cooled down to room temperature. The mixture was concentrated under vacuum to remove most of ethanol. The resulting solution was filtered, the filter cake was successively washed with *tert*-Butyl methyl ether (10 mL) and a mixed solution of petroleum ether/ ethyl acetate (10/1, 2×20 mL), the filter cake was dried under vacuum to afford compound 9.4 (307 mg, yield: 37%) as a white solid.

m/z: $[M+H]^+$ 215

Example 10: synthesis of compound 1-1



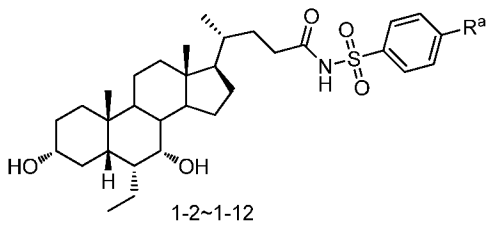
To an ice- cooling round-bottom flask was added compound 1.7 (117 mg, 0.28 mol), DCM (10 mL) and benzenesulfonamide (65 mg, 0.42 mmol), and then DMAP (4 mg), DIPEA (144 mg) and EDCI (134 mg) were successively added. The resulted mixture was stirred at room temperature for overnight and then washed with hydrochloric acid (1.0 M) and brine, the organic layer was separated and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate = 1: 3) to afford compound 1-1 (62 mg, yield: 40%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 7.91 (d, J = 7.2 Hz, 2 H), 7.70 - 7.74 (m, 1 H), 7.63 (d, J = 7.8 Hz, 2 H), 4.31 (d, J = 4.4 Hz, 1 H), 4.05 (d, J = 4.8 Hz, 1 H), 3.49 (s, 1 H), 3.10 - 3.17 (m, 1 H), 2.19 - 2.26 (m, 1 H), 2.09 - 2.17 (m, 1 H), 1.65 - 1.87 (m, 6 H), 0.89 - 1.50 (m, 19 H), 0.79 - 0.85 (m, 9 H), 0.52 (s, 3 H).

m/z: $[M-H]^-$ 558

Example 11: synthesis of compounds 1-2~1-53

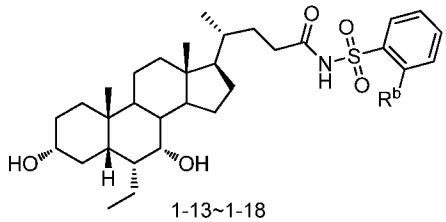
Compounds 1-2~1-53 were prepared according to Example 10 compound 1-1, by replacing benzenesulfonamide to corresponding sulfonamide as a starting material.



1-2~1-12

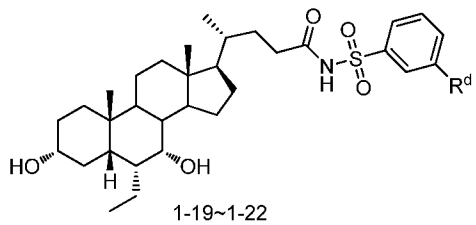
No.	R^a	^1H NMR and / or MS
1-2	methyl	^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 3.71 (br, s, 1 H), 3.42 - 3.49 (m, 1 H), 2.46 (s, 3 H), 2.13 - 2.34 (m, 2 H), 1.02 - 1.99 (m, 25 H), 0.86 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M+H]^+$574
1-3	ethyl	^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (br, s, 1 H), 7.98 (d, *J* = 8.4 Hz, 2 H) , 7.35 (d, *J* = 8.8 Hz, 2 H), 3.71 (br, s, 1 H), 3.42 - 3.49 (m, 1 H), 2.75 (q, *J* = 8.0 Hz, 2 H), 2.12 - 2.35 (m, 2 H), 1.02 - 1.99 (m, 25 H), 1.28 (t, *J* = 7.6 Hz, 3 H), 0.86 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M+H]^+$588
1-4	*tert*-butyl	^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 3.71 (s, 1 H), 3.42 - 3.49 (m, 1 H), 2.28 - 2.35 (m, 1 H), 2.14 - 2.22 (m, 1 H), 1.70 - 1.94 (m, 8 H), 0.98 - 1.54 (m, 28 H), 0.86 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$614
1-5	Cl	^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 3.71 (br, s, 1 H), 3.42 - 3.50 (m, 1 H), 2.13 - 2.35 (m, 2 H), 1.02 - 1.99 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M+H]^+$594
1-6	F	^1H NMR (400 MHz, $CDCl_3$): δ 8.10 - 8.14 (m, 2 H), 7.22 - 7.28 (m, 2 H), 3.71 (br, s, 1 H), 3.42 - 3.50 (m, 1 H), 2.13 - 2.35 (m, 2 H), 1.02 - 1.99 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M+H]^+$578
1-7	$-CF_3$	^1HNMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.4 Hz, 2 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 3.71 (br, s, 1 H), 3.44 - 3.53 (m, 1 H), 2.14 - 2.36 (m, 2 H), 0.99 - 1.95 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.61 (s, 3 H); m/z: $[M+H]^+$628
1-8	$-OCF_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1 H), 8.14 - 8.17 (m, 2 H), 7.38 (d , *J* = 8.4 Hz, 2 H), 3.71 (s, 1 H), 3.44 - 3.51 (m, 1 H), 2.25 - 2.36 (m, 1 H), 2.14 - 2.22 (m, 1 H), 1.71 - 1.95 (m, 8 H), 1.02 - 1.53 (m, 17 H), 0.88 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$642
1-9	$-OCH_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1 H), 8.00 - 8.04 (m, 2 H), 7.00 - 7.04 (m, 2 H), 3.90 (s, 3 H), 3.71 (s, 1 H), 3.40 - 3.47 (m, 1 H), 2.26 - 2.33 (m, 1 H), 2.12 - 2.20 (m, 1 H), 1.68 - 1.95 (m, 8 H), 1.06 -

		1.50 (m, 19 H), 0.87 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$588
1-10	$-NHC_2H_5$	m/z: $[M-H]^-$601
1-11	-CN	^1H NMR (400 MHz, CDCl3): δ 8.17 (d, *J* = 8.4 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 3.68 - 3.72 (m, 2 H), 3.38 - 3.48 (m, 2 H), 2.96 - 3.06 (m, 1 H), 2.27 - 2.36 (m, 2 H), 1.02 - 2.22 (m, 24 H), 0.89 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$583
1-12	$-C(O)OCH_3$	m/z: $[M-H]^-$616



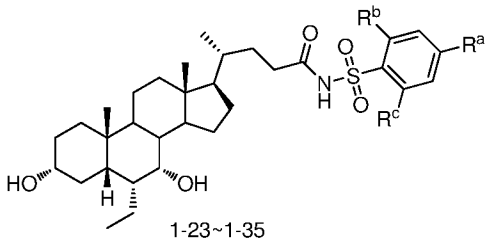
1-13~1-18

No.	R^b	^1H NMR and / or MS
1-13	*tert*-butyl	^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.14 (br, s, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.54 - 7.58 (m, 1 H), 7.38 - 7.42 (m, 1 H), 3.71 (br, s, 1 H), 3.40 - 3.49 (m, 1 H), 2.31 - 2.39 (m, 1 H), 2.18 - 2.25 (m, 1 H), 1.72 - 1.95 (m, 7 H), 1.62 (s, 9 H), 1.02 - 1.55 (m, 18 H), 0.87 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$614
1-14	isopropyl	m/z: $[M-H]^-$600
1-15	F	^1H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1 H), 8.09 - 8.14 (m, 1 H), 7.64 - 7.70 (m, 1 H), 7.34 - 7.39 (m, 1 H), 7.21 - 7.26 (m, 1 H), 3.71 (s, 1 H), 3.43 - 3.51 (m, 1 H), 2.32 - 2.39 (m, 1 H), 2.19 - 2.28 (m, 1 H), 1.71 - 1.96 (m, 8 H), 0.99 - 1.54 (m, 17 H), 0.88 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$576
1-16	Cl	^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.48 - 7.62 (m, 3 H), 3.71 (br, s, 1 H), 3.42 - 3.50 (m, 1 H), 2.19 - 2.39 (m, 2 H), 0.98 - 1.95 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M+H]^+$594
1-17	$-CF_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.53 - 8.56 (m, 1 H), 7.90 - 7.92(m, 1 H), 7.80 - 7.82 (m, 2 H), 3.71 (s, 1 H), 3.41 - 3.49 (m, 1 H), 2.28 - 2.36 (m, 1 H), 2.15 - 2.23 (m, 1 H), 1.80 - 1.95 (m, 8 H), 1.02 - 1.53 (m, 19 H), 0.87 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$626
1-18	$-OCH_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.07 - 8.10 (m, 1 H), 7.61 - 7.66 (m, 1 H), 7.13 - 7.17 (m, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 4.02 (s, 3 H), 3.71 (s, 1 H), 3.39 - 3.47 (m, 1 H), 2.20 - 2.39 (m, 2 H), 1.68 - 1.94 (m, 8 H), 0.98 - 1.52 (m, 19 H), 0.85 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$588



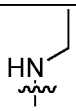
1-19~1-22

No.	R^d	^1H NMR and / or MS
1-19	$-CF_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.32 - 8.35 (m, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 3.71 (br s, 1 H), 3.45 - 3.52 (m, 1 H), 2.14 - 2.36 (m, 2 H), 1.02 - 1.99 (m, 25 H), 0.87 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M+H]^+$628
1-20	$-OCF_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, *J*= 1.2, 8.4 Hz, 1 H), 7.70 - 7.74 (m, 1 H), 7.43 - 7.52(m, 2.0 H), 3.71 (br, s, 1 H), 3.45 - 3.50 (m, 1 H), 2.16 - 2.38 (m, 2 H), 0.99 - 1.96 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M+H]^+$644
1-21	F	^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 1 H), 7.78 - 7.81(m, 1 H), 7.53 - 7.59 (m, 1 H), 7.34 - 7.39 (m, 1 H), 3.71 (br, s, 1 H), 3.45 - 3.52 (m, 1 H), 2.14 - 2.36 (m, 2 H), 0.99 - 1.95 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M+H]^+$578
1-22	-CN	^1H NMR (400 MHz, $CDCl_3$): δ 8.35 - 8.37 (m, 2 H), 7.92 - 7.95 (m, 1 H), 7.70 - 7.74 (m, 1 H), 3.72 (s, br, 1 H), 3.47 - 3.54 (m, 1 H), 2.15 - 2.37 (m, 2 H), 1.02 - 1.99 (m, 25 H), 0.89 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M+H]^+$585

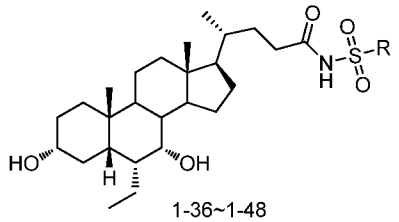


1-23~1-35

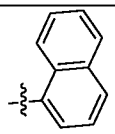
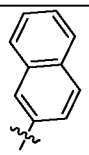
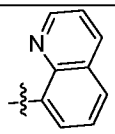
No.	R^a	R^b	R^c	^1H NMR and / or MS
1-23	H	Cl	Cl	^1H NMR (400 MHz, $CDCl_3$): δ 9.24 (br, s, 1 H), 7.41 - 7.53 (m, 3 H), 3.68 - 3.74 (m, 2 H), 3.40 - 3.48 (m, 1 H), 3.11 - 3.15 (m, 1 H), 2..25 - 2.45 (m, 2 H), 1.01 - 1.96 (m , 24 H), 0.89 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$626
1-24	H	F	F	^1H NMR (400 MHz, $CDCl_3$): δ 7.57 - 7.64 (m, 1 H), 7.06 - 7.10 (m, 2 H), 3.71 (br, s, 1 H) , 3.43 - 3.51 (m, 1 H), 2.21 - 2.41 (m, 2 H), 0.99 - 1.96 (m, 25 H), 0.90 - 0.94 (m, 9 H), 0.64 (s, 3 H); m/z: $[M+H]^+$596

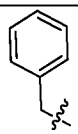
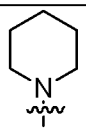
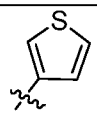
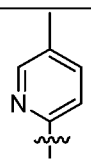
1-25	H	$-CH_3$	$-CF_3$	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.2 Hz, 1 H), 7.37 - 7.47 (m, 2 H), 3.70 (s, 1 H), 3.37 - 3.46 (m, 1 H), 2.87 (s, 3 H), 2.71 - 2.78 (m, 1 H), 2.25 - 2.34 (m, 1H), 2.10 - 2.18 (m, 1 H), 1.00 - 1.96 (m, 24 H), 0.87 - 0.93 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$ 640
1-26	H	Cl	$-CF_3$	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 1 H), 7.65 - 7.68 (m, 1 H), 7.42 (t, *J* = 7.6Hz, 1 H), 3.71 (s, 1 H), 3.38 - 3.46 (m, 1 H), 2.26 - 2.36 (m, 1 H), 2.13 - 2.21 (m, 1 H), 1.01 - 1.97 (m, 25 H), 0.87 - 0.93 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$ 660
1-27	H	F	$-CF_3$	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (br, s, 1 H), 7.73 - 7.80 (m, 2 H), 7.47 - 7.52 (m, 1 H), 3.71 (br, s, 1 H), 3.42 - 3.50 (m, 1 H), 2.36 - 2.44 (m, 1 H), 2.23 - 2.31 (m, 1 H), 0.99 - 1.96 (m, 25 H), 0.89 - 0.94 (m, 9 H), 0.64 (s, 3 H); m/z: $[M-H]^-$ 644
1-28	F	F	H	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 - 8.18 (m, 1 H), 7.06 - 7.10 (m, 1 H), 6.95 - 7.00 (m, 1 H), 3.71 (br, s, 1 H), 3.41 – 3.48 (m, 1 H), 2.74 - 2.82 (m, 1 H), 2.18 - 2.39 (m, 2 H), 1.02 - 1.96 (m, 24 H), 0.89 - 0.94 (m, 9 H), 0.64 (s, 3 H); m/z: $[M-H]^-$ 594
1-29		$-CH_3$	H	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br, s, 1 H), 7.94 (d, *J* = 8.8 Hz, 1 H), 6.47 (dd, *J* =2.4, 8.8 Hz, 1 H), 6.40 (d, *J* = 2.4 Hz, 1 H), 3.71 (s, 1 H), 3.43 - 3.49 (m, 1 H), 3.23 (dd, *J* = 7.2, 14.8 Hz, 2 H), 2.56 (s, 3 H), 2.15 - 2.34 (m, 2 H), 1.32 - 1.93 (m, 19 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 0.98 - 1.25 (m, 6 H), 0.87 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$ 615
1-30	F	Cl	H	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 - 8.93 (br, s, 1 H), 8.33 (dd, *J* =6.0, 9.2 Hz, 1 H), 7.28 - 7.31 (m, 1 H), 7.18 - 7.23 (m, 1 H), 3.71 (s, 1 H), 3.43 - 3.50 (m, 1 H), 2.31 - 2.39 (m, 1 H), 2.18 - 2.26 (m, 1 H), 0.99 - 1.96 (m, 25 H), 0.89 - 0.94 (m, 9 H), 0.64 (s, 3 H); m/z: $[M-H]^-$ 610
1-31	$-CF_3$	$-CF_3$	H	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (br, s, 1H), 8.70 (d, *J* = 8.0 Hz, 1 H), 8.12 (s, 1 H), 8.06 (d, *J* = 7.2 Hz, 1 H), 3.71 (br, s, 1 H), 3.42 - 3.50 (m, 1 H) 2.30 - 2.38 (m, 1 H), 2.16 - 2.24 (m, 1 H), 1.02 - 1.95 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$ 694
1-32	$-CF_3$	F	H	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (t, *J* = 7.6 Hz, 1 H), 7.63

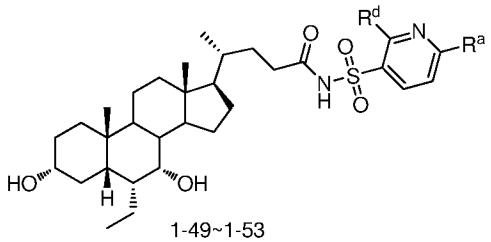
				(d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 9.6 Hz, 1 H), 3.71 (br, s, 1 H), 3.47 - 3.54 (m, 1 H) 2.32 - 2.40 (m, 1 H), 2.19 - 2.27 (m, 1 H), 1.03 - 1.96 (m, 25 H), 0.89 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$644
1-33	$-CF_3$	F	F	^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.4 Hz, 2 H), 3.72 (br, s, 1 H), 3.42 - 3.53 (m, 1 H), 2.34 - 2.42 (m, 1 H), 2.22 - 2.30 (m, 1 H), 1.04 - 1.97 (m, 25 H), 0.91 - 0.94 (m, 9 H), 0.64 (s, 3 H); m/z: $[M-H]^-$662
1-34	F	F	F	^1H NMR (400 MHz, $CDCl_3$): δ 6.82 (t, *J* = 8.6 Hz, 2 H), 3.71 (br, s, 1 H), 3.45 - 3.53 (m, 1 H), 2.33 - 2.41 (m, 1 H), 2.21 - 2.29 (m, 1 H), 1.02 - 1.96 (m, 25 H), 0.89 - 0.94 (m, 9 H), 0.57 (s, 3 H); m/z: $[M-H]^-$612
1-35	$-CH_3$	$-CH_3$	$-CH_3$	^1H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 2 H), 3.70 (s, 1 H), 3.40 - 3.48 (m, 1 H), 2.71 (s, 6 H), 2.33 - 2.37 (m, 1 H), 2.32 (s, 3 H), 2.27 - 2.31 (m, 1 H), 2.13 - 2.21 (m, 1 H), 1.02 - 1.95 (m , 24 H), 0.87 - 0.92 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$600



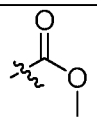
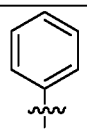
1-36~1-48

No.	R	^1H NMR and / or MS
1-36		^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.8 Hz, 1 H), 8.54 (d, *J* = 7.6 Hz, 1 H) , 8.16 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.62 - 7.72 (m, 3 H), 3.69 (br, s, 1 H), 3.43 - 3.51 (m, 1 H), 2.10 - 2.30 (m, 2 H), 0.97 - 1.87 (m, 25 H), 0.90 - 0.94 (m, 6 H), 0.77 (d, *J* = 6.4 Hz, 3 H), 0.53 (s, 3 H); m/z: $[M+H]^+$610
1-37		^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.93-8.05 (m, 4H), 7.64-7.70 (m, 2H) , 3.69 (s, br, 1H), 3.40-3.49 (m, 1H), 2.07-2.36 (m, 2H), 0.97-1.91 (m , 25H) , 0.84-0.93 (m, 9H), 0.57 (s, 3H); m/z: $[M+H]^+$610
1-38		^1H NMR (400 MHz, $CDCl_3$): δ 8.97 - 9.03 (m, 1 H), 8.53 - 8.63 (m, 1 H), 8.21 - 8.29 (m, 1 H), 7.98 - 8.06 (m, 1 H), 7.48 - 7.69 (m, 2 H), 3.68 - 3.74 (m, 1 H), 3.36 - 3.50 (m, 2 H), 2.39 - 2.54 (m, 2 H), 0.98 - 2.15 (m, 24 H), 0.87 - 0.94 (m, 9 H), 0.62 - 0.69 (m, 3 H); m/z: $[M-H]^-$609

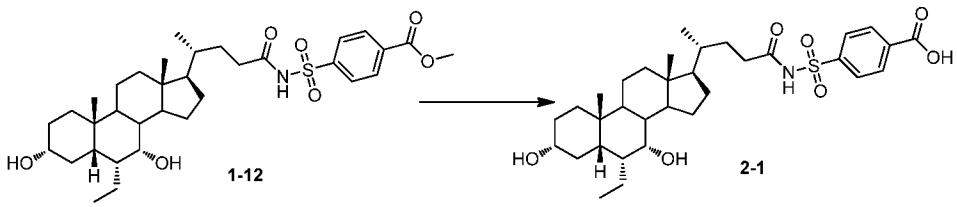
1-39		^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 - 7.44 (m, 5 H), 4.67 (s, 2 H), 3.72 (br, s, 1 H), 3.37 - 3.46 (m, 1 H), 2.10 - 2.32 (m, 2 H), 1.01 - 1.91 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.68 (s, 3 H); m/z: $[M+H]^+$574
1-40	-CH_3	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.65 (s, 1 H), 4.31 (d, *J* = 4.8 Hz, 1 H), 4.07 (d, *J* = 5.2 Hz, 1 H), 3.50 (s, 1 H), 3.22 (s, 3 H), 3.09 - 3.17 (m, 1 H), 2.26 - 2.34 (m, 1 H), 2.14 - 2.22 (m, 1 H), 1.67 - 1.93 (m, 7 H), 1.06 - 1.54 (m, 18 H), 0.81 - 0.89 (m, 9 H), 0.61 (s, 3 H); m/z: $[M-H]^-$496
1-41	ethyl	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1 H), 4.31 (d, *J* = 4.0 Hz, 1 H), 4.06 (d ，*J* = 4.8 Hz, 1 H), 3.50 (s, 1 H) ，3.30 - 3.36 (m, 2 H), 3.07 - 3.18 (m, 1 H), 2.27 - 2.34 (m, 1 H), 2.16 - 2.23 (m, 1 H), 1.70 - 2.01 (m, 7 H), 0.97 - 1.54 (m, 21 H), 0.81 - 0.90 (m, 9 H), 0.61 (s, 3 H); m/z: $[M-H]^-$510
1-42	*tert*-butyl	^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 1 H), 3.37 - 3.44 (m, 1 H), 2.45 - 2.52 (m, 1 H), 2.31 - 2.39 (m, 1 H), 1.79 - 1.99 (m, 6 H), 1.16 - 1.70 (m, 30 H), 0.97 - 1.05 (m ，9 H), 0.68 (s, 3 H); m/z: $[M-H]^-$538
1-43		^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (br, s, 1H), 3.41 - 3.48 (m, 1 H), 2.94 - 3.01 (m, 1 H), 2.22 - 2.44 (m, 2 H), 1.02 - 1.99 (m, 29 H), 0.93 - 0.97 (m, 9 H), 0.68 (s, 3 H); m/z: $[M+H]^+$524
1-44	-CF_3	m/z: $[M-H]^-$550
1-45		^{1}H NMR (400 MHz, DMSO-d_6): δ 11.34 (s, 1 H), 4.33 (d, *J* = 4.8 Hz, 1 H), 4.07 (d, *J* = 5.2 Hz, 1 H), 3.50 (s, 1 H), 3.09 - 3.17 (m, 1 H), 2.79 (m, 6 H), 2.23 - 2.31 (m, 1 H), 2.13 - 2.21 (m, 1 H), 1.68 - 1.93 (m, 7 H), 1.06 - 1.50 (m, 18 H), 0.83 - 0.90 (s, 9 H), 0.61 (s, 3 H); m/z: $[M-H]^-$525
1-46		^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (br, s, 1 H), 3.42 - 3.47 (m, 1 H), 3.36 - 3.38 (m, 3 H), 2.16 - 2.41 (m, 2 H), 0.98 - 1.95 (m, 32 H), 0.91 - 0.97 (m, 9 H), 0.68 (s, 3 H); m/z: $[M+H]^+$567
1-47		^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1 H), 8.28 - 8.29 (m, 1 H), 7.54 - 7.56 (m, 1 H), 7.43 - 7.45 (m, 1 H), 3.71 (s, 1 H), 3.42 - 3.49 (m, 1 H), 2.30 - 2.37 (m, 1 H), 2.16 - 2.24 (m, 1 H), 1.75 - 1.96 (m, 7 H), 0.98 - 1.52 (m, 20 H), 0.89 - 0.98 (m, 9 H), 0.64 (s, 3 H); m/z: $[M-H]^-$564
1-48		^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 - 8.50 (m, 1 H), 7.93 - 8.00 (m, 1 H), 7.64 - 7.73 (m, 1 H), 3.68 - 3.74 (m, 1 H), 3.32 - 3.46 (m, 2 H), 2.45 - 2.51 (m, 2 H), 2.42 (s, 3 H), 1.08 - 1.99 (m, 24 H), 0.89 - 0.93 (m, 9 H), 0.66 - 0.68 (m, 3 H); m/z: $[M-H]^-$573



1-49~1-53

No.	R^a	R^d	^1H NMR and / or MS
1-49	H	H	^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (d, *J* = 2.0 Hz, 1 H), 8.89 (dd, *J* = 1.6, 4.8 Hz, 1 H), 8.45 - 8.89 (m, 1 H), 7.52 - 7.56 (m, 1 H), 3.72 (br, s, 1 H), 3.42 - 3.51 (m, 1 H), 2.14 - 2.38 (m, 2 H), 0.98 - 1.95 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M+H]^+$561
1-50		H	^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 2.4 Hz, 1 H), 8.68 (br, s, 1 H), 8.22 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 4.04 (s, 3 H), 3.71 (br, s, 1 H), 3.42 - 3.50 (m, 1 H), 2.26 - 2.35 (m, 1 H), 2.13 - 2.21 (m, 1 H), 1.02 - 1.95 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.63 (s, 3 H); m/z: $[M-H]^-$617
1-51	$-CF_3$	H	m/z: $[M-H]^-$627
1-52		H	^1H NMR (400 MHz, $CDCl_3$): δ 9.90 (br, s, 1 H), 9.27 (s, 1 H), 8.50 (dd, *J* = 2.0, 8.4 Hz, 2 H), 8.05 - 8.08 (m, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.52 - 7.53 (m, 3 H), 3.66 (br, s, 1 H), 3.41 - 3.51 (m, 1 H), 0.98 - 2.36 (m, 27 H), 0.86 - 0.92 (m, 9 H), 0.57 (s, 3 H); m/z: $[M-H]^-$635
1-53	$-CH_3$	$-CH_3$	^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 3.71 (s, 1 H), 3.38 - 3.46 (m, 1 H), 2.90 (s, 3 H), 2.56 (s, 3 H), 2.11 - 2.33 (m, 2 H), 1.01 - 1.96 (m, 25 H), 0.88 - 0.94 (m, 9 H), 0.62 (s, 3 H); m/z: $[M-H]^-$587

Example 12: synthesis of compound 2-1



1-12 2-1

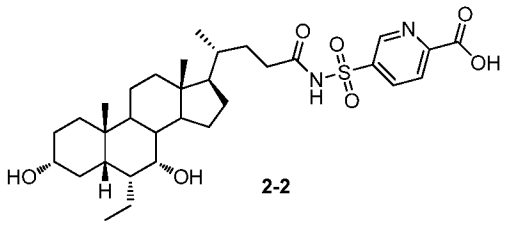
A mixture of compound 1-12 (80 mg, 0.13 mmol) in a solution of aqueous NaOH (2.0 M, 10 mL) and methanol (5 mL) was stirred at room temperature for overnight. The resulted mixture was adjusted pH=3 with hydrochloric acid (1.0 M). The mixture was extracted with ethyl acetate (60 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate = 1: 2) to afford compound 2-1 (65 mg, yield: 83%) as

a white solid.

^{1}HNMR (400 MHz, DMSO-d_6): δ 12.86 (s, 2 H), 8.10 (d, J = 8.4 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 2 H), 4.31 (s, 1 H), 4.05 (d, J = 4.8 Hz, 1 H), 3.48 (s, 1 H), 3.09 - 3.17 (m, 1 H), 2.04 - 2.22 (m, 2 H), 1.68 - 1.86 (m, 6 H), 0.92 - 1.58 (m, 19 H), 0.78 - 0.82 (m, 9 H), 0.50 (s, 3 H).

m/z: [M-H]$^-$602

Example 13: synthesis of compound 2-2



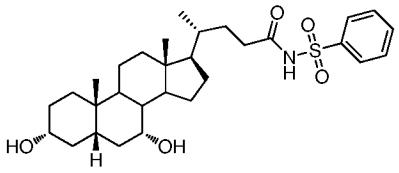
2-2

Compound 2-2 was prepared according to Example 12 compound 2-1, by using compound 1-50 as a starting material.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 - 9.18 (m, 1 H), 8.23 - 8.51 (m, 1 H), 8.23 - 8.24 (m, 1 H), 3.71 (br, s, 1 H), 3.32 - 3.48 (m, 1 H), 2.06 - 2.28 (m, 2 H), 0.99 - 1.96 (m, 25 H), 0.89 - 0.94 (m, 9 H), 0.64 (s, 3 H).

m/z: [M-H]$^-$603

Example 14: synthesis of compound 3-1



3-1

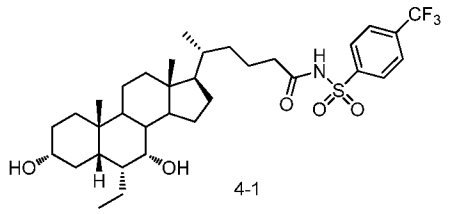
Compound 3-1 was prepared according to Example 10 compound 1-1, by using compound 1.7 and corresponding sulfonamide as starting materials.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1 H), 7.91 (d, J = 7.6 Hz, 2 H), 7.69 - 7.73 (m, 1 H), 7.60 - 7.64 (m, 2 H), 4.34 (d, J = 4.4 Hz, 1 H), 4.12 (d, J = 3.6 Hz, 1 H), 3.61 (s, 1 H), 3.15 - 3.22 (m, 1 H), 2.09 - 2.26 (m, 3 H), 1.55 - 1.87 (m, 7 H), 1.32 - 1.48 (m, 6 H), 0.90 - 1.26 (m, 10 H), 0.78 - 0.83 (m, 6 H), 0.52 (s, 3 H).

m/z: [M-H]$^-$530

Example 15: synthesis of compounds 4-1 and 4-2

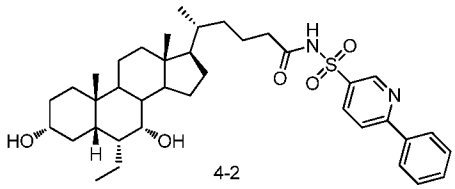
Compounds 4-1 and 4-2 were prepared according to Example 10 compound 1-1, by using compound 2.5 and corresponding sulfonamide as starting materials.



4-1

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 3.72 (s, 1 H), 3.44 - 3.46 (m, 1 H), 2.22 - 2.24 (m, 2 H), 0.96 - 1.83 (m, 27 H), 0.89 - 0.94 (m, 9 H), 0.64 (s, 3 H).

m/z: $[M-H]^-$ 640



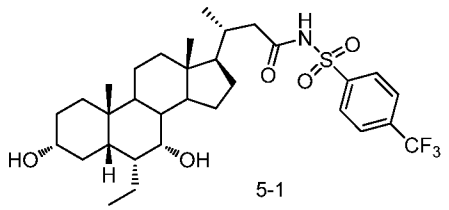
4-2

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (d, *J* = 1.6 Hz, 1H), 8.67 - 9.09 (m, 1 H), 8.50 (dd, *J* = 2.4, 8.8 Hz, 1 H), 8.08 - 8.11 (m, 2 H), 7.93 (d, *J* = 8.8 Hz, 1 H), 7.53 - 7.57 (m, 3 H), 3.66 (s, 1 H), 3.42 - 3.50 (m, 1 H), 2.21 - 2.30 (m, 2 H), 0.98 - 1.94 (m, 27 H), 0.87 - 0.94 (m, 9 H), 0.61 (s, 3 H).

m/z: $[M-H]^-$ 649

Example 16: synthesis of compounds 5-1~ 5-3

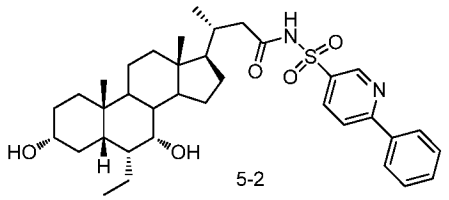
Compounds 5-1~ 5-3 were prepared according to Example 10 compound 1-1, by using compound 3.2 and corresponding sulfonamide as starting materials.



5-1

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 3.71 (s, 1 H), 3.48 (s, 1 H), 2.37 - 2.40 (m, 1 H), 0.99 - 1.96 (m, 24 H), 0.92 - 0.99 (m, 9 H), 0.66 (s, 3 H).

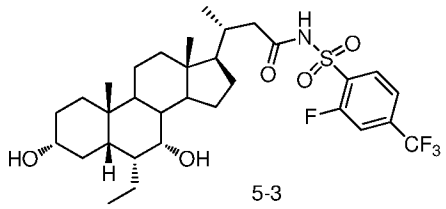
m/z: $[M-H]^-$ 612



5-2

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1 H), 9.08 (s, 1 H), 8.49 (dd, *J* = 2.4, 8.4 Hz, 1 H), 8.08 - 8.10 (m, 2 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.53 - 7.56 (m, 3 H), 3.68 (s, 1 H), 3.45 (s, 1 H), 2.35 - 2.47 (m, 1 H), 0.96 - 1.98 (m, 24 H), 0.87 - 0.94 (m, 9 H), 0.65 (s, 3 H).

m/z: $[M-H]^-$ 621

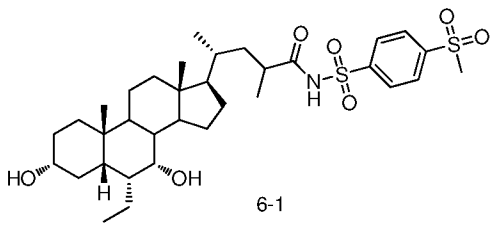


5-3

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1 H), 8.27 (t, *J* = 7.6 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.51 (d, *J* = 10.0 Hz, 1 H), 3.72 (s, 1 H), 3.47 - 3.52 (m, 1 H), 2.44 (d, *J* = 11.6 Hz, 1 H), 1.00 - 1.97 (m, 24 H), 0.91 - 0.95 (m, 9 H), 0.66 (s, 3 H).

m/z: $[M-H]^-$ 630

Example 17: synthesis of compounds 6-1~ 6-3



6-1

Compound 6-1 was prepared according to Example 10 compound 1-1, by using compound 4.3 and corresponding sulfonamide as starting materials.

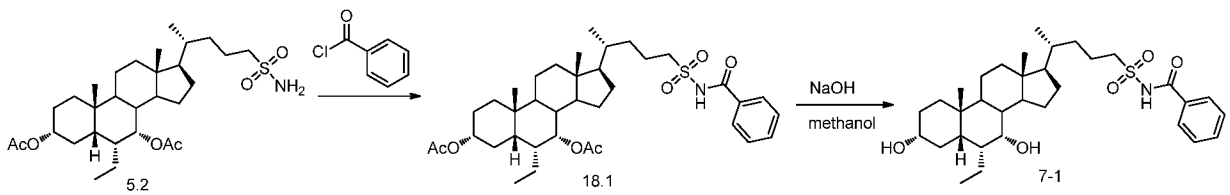
Compound 6-1 was separated by Flash chromatography to afford two stereoisomers, the less polar isomer 6-2 was first collected, and then the more polar isomer 6-3 was collected.

6-2: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (br, s, 1 H), 8.31 (d, *J* = 8.4 Hz, 2 H), 8.14 (d, *J* = 8.4 Hz, 2 H), 3.71 (br, s, 1 H), 3.43 - 3.53(m, 1 H), 3.12 (s, 3 H), 2.43 - 2.49 (m, 1 H), 1.26 - 1.92(m, 22 H), 1.12 (d, *J* = 7.2, 3 H), 0.99 - 1.07 (m, 3 H), 0.85 - 0.95 (m, 9 H), 0.51 (s, 3 H).

6-3: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (br, s, 1 H), 8.34 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, *J* = 8.4 Hz, 2 H), 3.71 (br, s, 1H), 3.44 - 3.52(m, 1 H), 3.14 (s, 3 H), 2.37 - 2.45 (m, 1 H), 1.27 - 1.95 (m, 22 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.02 - 1.18 (m, 3 H), 0.86 - 0.94 (m, 9 H), 0.64 (s, 3 H).

m/z: $[M-H]^-$ 650

Example 18: synthesis of compounds 7-1



5.2 18.1 7-1

Step 1: synthesis of compound 18.1

To an ice- cooling solution of compound 5.2 (100 mg, 0.18 mmol), DIPEA (94 mg, 0.72 mmol) and DMAP (2.2 mg, 0.02 mmol) in DCM (5 mL) was added benzoyl chloride (26 mg, 0.18 mmol). The resulted mixture was stirred at room temperature for 3h, and then the solvent

was evaporated under vacuum. The residue was purified by column chromatography on silica gel (MeOH/ DCM = 0~5%) to afford compound 18.1 (80 mg, yield: 67%) as a white solid.

m/z: $[M-H]^-$ 656

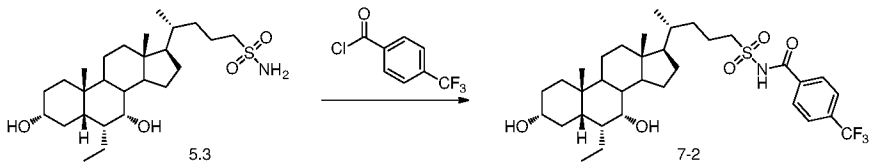
Step 2: synthesis of compound 7-1

A solution of compound 18.1 (80 mg, 0.12 mmol) in sodium hydroxide methanol solution (5 mL, 10%, w/w) was stirred at 70°C for overnight, and then the mixture was cooled down to room temperature, the solvent was evaporated under vacuum, the residue was dissolved in cooled water (20 mL) and adjusted pH to 5~6 with hydrochloric acid (3.0 M). The mixture was stirred for 30min, and then extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by Flash chromatography (MeOH/ DCM = 0~5%) to afford compound 7-1 (20 mg, yield: 29%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 - 8.84 (m, 1 H), 7.89 (d, *J* = 7.6 Hz, 2 H), 7.64 - 7.68 (m, 1 H), 7.52 - 7.56 (m, 2 H), 3.71 (s, 1 H), 3.59 - 3.66 (m, 1 H), 3.49 - 3.57 (m, 1 H), 3.39 - 3.47 (m, 1 H), 1.13 - 1.98 (m, 27 H), 0.89 - 0.96 (m, 9 H), 0.66 (s, 3 H).

m/z: $[M-H]^-$ 572

Example 19: synthesis of compounds 7-2

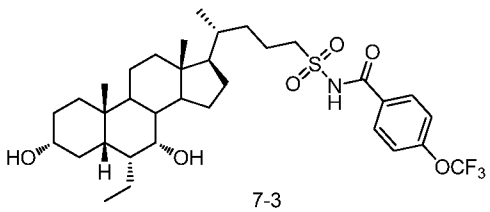


To an ice- cooling solution of compound 5.3 (50 mg, 0.11 mmol), TEA (32 mg, 0.32 mmol) in DCM (5 mL) was added 4-(trifluoromethyl)benzoyl chloride (21 mg, 0.10 mmol) dropwise. The resulted mixture was stirred at room temperature for 3h, and then the solvent was evaporated, the residue was purified by Flash chromatography (methanol/ DCM = 0~5%) to afford compound 7-2 (15 mg, yield: 22%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 8.10 - 8.17 (m, 2 H), 7.66 - 7.70 (m, 2 H), 3.68 (s, 1 H), 3.22 - 3.41 (m, 3 H), 1.10 - 1.96 (m, 27 H), 0.88 - 0.99 (m, 9 H), 0.64 (s, 3 H).

m/z: $[M-H]^-$ 640

Example 20: synthesis of compound 7-3



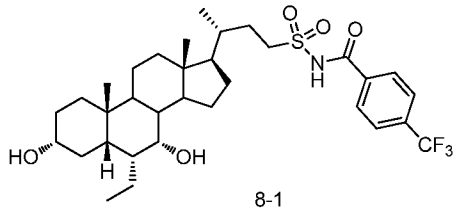
Compound 7-3 was prepared according to Example 19 compound 7-2, by using compound 5.3 and corresponding acyl chloride as starting materials.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 2 H), 7.30 (d, *J* = 10.4 Hz, 2 H), 3.69 (s, 1 H), 3.52 - 3.63 (m, 1 H), 3.40 - 3.47 (m, 2 H), 1.12 - 1.96(m, 27 H), 0.86 - 1.02 (m, 9 H), 0.64 (s, 3 H).

m/z: $[M-H]^-$ 656

Example 21: synthesis of compounds 8-1~8-2

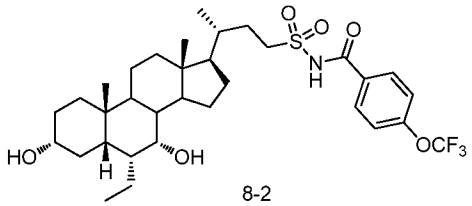
Compounds 8-1~8-2 were prepared according to Example 19 compound 7-2, by using compound 7.2 and corresponding acyl chloride as starting materials.



8-1

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1 H), 8.02 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 3.65 - 3.71 (m, 2 H), 3.41 - 3.56 (m, 2 H), 1.05 - 2.04 (m, 25 H), 0.90 - 1.03 (m, 9 H), 0.67 (s, 3 H).

m/z: $[M-H]^-$ 626

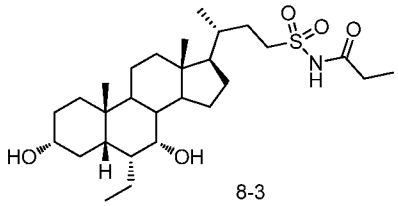


8-2

^{1}H NMR (400 MHz, CD_3OD): δ 8.15 (d, *J* = 9.2 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 3.66 (s, 1 H), 3.14 - 3.40 (m, 3 H), 1.08 - 2.23 (m, 25 H), 0.92 - 1.02(m, 9 H), 0.68 (s, 3 H).

m/z: $[M-H]^-$ 642

Example 22: synthesis of compound 8-3



8-3

Compound 8-3 was prepared according to Example 18 compound 7-1, by using compound 7.1 and corresponding acyl chloride as starting materials.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J* = 14.8 Hz, 1 H), 3.72 (s, 1 H), 3.33 - 3.56 (m, 3 H), 2.36 - 2.42 (m, 2 H), 1.18 - 1.98 (m, 28 H), 0.90 - 1.07 (m, 9 H), 0.68 (s, 3 H).

m/z: $[M-H]^-$ 510

BIOLOGY ASSAYS

Exampel 1: FXR TR-FRET Assay

FXR agonist screening used TR-FRET (Time-resolved fluorescence resonance energy transfer) method bioassay. The method measures ability of compounds to regulate the interaction between FXR ligand binding domain protein (LBD) and its biotin-labeled coenzyme polypeptide (SRC-1). Binding of a ligand to the FXR ligand binding domain changes the conformational in this area, resulting in binding to its coenzyme SRC-1 in high affinity. When the two are in very close proximity, the photon energy excited from one fluorophore can transferred to another fluorophore, which induces the latter to generate fluorescence that can be detected. Compounds with higher affinity for FXR, the stronger the signal induced fluorescence.

Testing was performed in 384-well plates, Mix the N-terminus GST-tagged FXR protein binding domains FXR-LBD (3nM, Life Technology) and europium labeled anti-GST antibody (50nl, Cisbio) in the Tris-HCl buffer at pH 7.5; the biotinylated peptide SRC-1 (500nM, GL) and APC-labeled streptavidin (50nl, Cisbio) were mixed in the buffer. After mixing the above two buffer solutions in the ratio of 1: 1, 20ul solution was added to each well of the 384-well plate, followed by adding 100% DMSO solution of the compounds so that the concentration was 1% in the final 20 uL mixture. The plate was incubated at room temperature for 3 hours. Signal detection in relative fluorescence units (RFU) was measured by EnVision Muti-Label Reader (Perkin Elmer Corporation) at wavelength of 615nm and 665nm. Signal RFU665nm / RFU615nm were calculated. The activity of a compound is expressed as % activation = (compound signal – base signal) / [maximum signal – base signal base] × 100%. If the compound can promote the binding of FXR and its ligand binding domain protein to form a complex, it will induce fluorescence signal in a concentration dependent manner. Dose response data points were curve fitted using the standard logistic regression model and the EC_{50} values were calculated using GraphPad Prism 5.

Example 2: FXR Reporter Assay

The compounds were tested in GAL4 luciferase reporter gene assay in HepG2 liver cells. The HepG2 liver cells were inoculated at 60,000 per well in 96-well plates, and pBIND-FXR_LBD (50 ng) and pGL5Luc (50 ng) were co-transfected into HepG2 cells by transfection reagent FuGENE (Promega). After the plates were incubated at 37°C under 5% CO2 in an incubator for 24 hours, the compounds in DMSO solution were added to the cells so that final concentration of DMSO was 0.6%. The plates were incubated at 37 °C under 5% CO2 in an incubator for another 18 hours. The luciferase activity was measured using a dual luciferase reporter gene assay kit (Promega) according to the vendor's protocol of the assay kit. Relative Light Units (RLU) were measured by the EnVision Muti-Label reader (Perkin Elmer Corporation). The activity of a compound is expressed as % activation = (RLU- base RLU) / (maximum RLU- base RLU) × 100%. If the compound is able to activate FXR activity, it will induce luminescence signal in a concentration dependent manner. Dose response data points

were curve fitted using the standard logistic regression model and the EC_{50} values were calculated using GraphPad Prism 5.

Example 3: TGR5-cAMP Reporter Assay

HEK293 cells overexpressing human TGR5 were resuspended in Stimulation Buffer (HBSS 1X (Invitrogen) containing 5mM HEPES (Invitrogen), 0.1% BSA (PerkinElmer) and 0.5mM IBMX (Sigma)) at a concentration of 10,000 cells / 6 μL / well. Add the Alexa Fluor 647-labeled cAMP Antibody from the LANCE cAMP 384 Kit (PerkinElmer) to the cell suspension by 1/100. Dilute the compounds serially in DMSO for 10-pts, 3-fold using Bravo (Agilent). Then transfer 120nl of compounds to the 384-well OptiPlate (PerkinElmer) using POD (Labcyte). Add 6μL of Stimulation buffer to the OptiPlate using Multi-drop (Thermo). Then add 6 μL of the cell suspension (containing the Alexa-labeled antibodies) using Multi-drop (Thermo). After 1h incubation at RT, add 12μL of Detection Mix from the LANCE cAMP 384 Kit (PerkinElmer). Plate was then incubated 1 h at RT and emissions at 620 nM and 665 nM were read on the Envision (PerkinElmer). Data were expressed as a ratio of emission at 665/620 and the percent efficacy was determined based on the High control (DMSO alone) and Low control (Lithocholic acid) (%Activity = 100 x (HC - Sample) / (HC - LC)). Dose response data points were curve fitted using the standard logistic regression model and the EC_{50} values were calculated using GraphPad Prism 5.

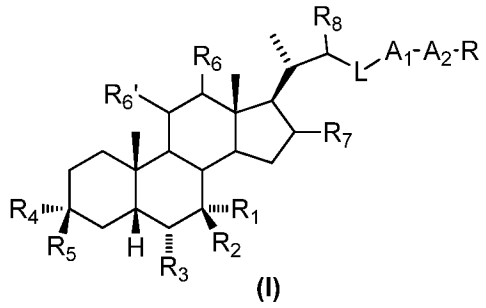
The assay results of the test compounds in this disclosure are given in the table bellow, the EC_{50} range is as follow: + represents 1-100 μM, ++ represents 0.5-1 μM, +++ represents 0.1-0.5 μM, ++++ represents 0.05-0.1 μM, +++++ represents ≤0.05 μM.

No.	FXR TR-FRET EC_{50}	FXR Reporter EC_{50}	TGR5 Reporter EC50
1-1	+++++	+++	+
1-2	+++++	/	+
1-3	+++++	/	+
1-4	+++++	+++++	+
1-5	+++++	++++	+
1-6	+++++	/	+
1-7	+++++	+++++	+
1-8	+++++	/	+
1-9	+++++	/	+
1-10	+++++	/	+
1-11	+++++	++	+
1-13	+++++	/	+
1-14	+++++	/	+
1-15	+++++	/	+
1-16	+++++	/	+
1-17	+++++	++	+
1-18	+++++	/	+
1-19	+++++	/	+
1-20	+++++	/	+
1-21	+++++	/	+

1-22	+++++	+++	+
1-23	+++++	++	+
1-24	+++++	+++	+
1-25	+++++	++	+
1-26	+++++	/	+
1-27	+++++	/	+
1-28	+++++	/	+
1-29	+++++	+++	+
1-30	+++++	/	+
1-31	+++++	/	+
1-32	+++++	+++++	+
1-33	+++++	+++	+
1-34	+++++	/	+
1-35	+++++	++	+
1-36	+++++	+++	+
1-37	+++++	/	+
1-39	+++++	/	+
1-40	+++++	++	++
1-41	+++++	+++	++
1-42	+++++	/	+
1-43	+++++	/	+++
1-44	+++++	+	+
1-45	+++++	+++	++
1-46	+++++	/	+
1-47	+++++	/	+
1-49	+++++	+++++	+
1-50	+++++	/	+
1-51	+++++	+++	+
1-52	+++++	++++	/
1-53	+++++	/	+
2-1	+++++	+	+
2-2	+++++	+	+
3-1	++	/	/
4-1	+++++	/	+
4-2	+++++	+++	+
5-1	+++++	/	+
5-2	+++++	++	+
5-3	+++++	/	++
6-2	++++	/	+
6-3	+++++	/	+
7-1	+++++	/	+++
7-2	+++++	/	+
7-3	+++++	/	+
8-1	+++++	/	+
8-2	++++	/	+
8-3	++++	/	+++
1.7	++++	++	+
GW4064	++++	+++	+

Claims

1. A compound of formula (I) and/or isomers, prodrugs, solvates, stable isotope derivatives thereof, and/or a pharmaceutically acceptable salt thereof;



(I)

wherein,

A_2 is $-C(O)N(R_{12})S(O)_2-$, or $-S(O)_2N(R_{12})C(O)-$;

A_1 is a bond, or $-(CH_2)_n-$;

L is a bond, or $-CHR_9-$;

R is independently substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl or $-NR_{10}R_{10a}$, provided that when A_2 is $-S(O)_2N(R_{12})C(O)-$, R is not selected form $-NR_{10}R_{10a}$; wherein the substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted cycloalkylalkyl, substituted heterocycloalkylalkyl, substituted arylalkyl, or substituted heteroarylalkyl is substituted by 1 to 3 R_{11} at any position;

R_1 is independently hydrogen, hydroxyl, substituted or unsubstituted alkyl, or halogen;

R_2 is independently hydrogen, substituted or unsubstituted alkyl, or hydroxyl;

R_3 is independently hydrogen, substituted or unsubstituted alkyl, 2-propenyl or halogen;

R_4 and R_5 are independently hydrogen, hydroxyl, $-OC(O)CH_3$, $-OS(O)_3H$, $-OP(O)_3H$, $-P(O)_3H_2$, or $-OC_6H_8O_6H$; or R_4 and R_5 are taken together to form a carbonyl;

R_6 and $R_{6'}$ are independently hydrogen, or hydroxyl;

R_7 is independently hydrogen, hydroxyl, alkoxy, or halogen;

R_8 is independently hydrogen, or substituted or unsubstituted alkyl;

R_9 is independently hydrogen, substituted or unsubstituted alkyl, aryl, or heteroaryl; or R_8 and R_9 together with the carbon atom to which they are attached, form a 3- to 6-membered cycloalkyl ring;

when R_1, R_2, R_3, R_8, or R_9 is the substituted alkyl, it is substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, alkyl and cycloalkyl;

R_{10} and R_{10a} are independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl,

heteroaryl, cycloalkylalkyl, or heteroalkylalkyl; or R_{10} and R_{10a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring;

R_{11} is independently halogen, hydroxyl, amino, carboxyl, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkoxy, cycloalkylalkoxy, arylalkoxy, heteroarylalkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, aminoalkyl, hydroxyalkyl, sulfonyl, $-C(O)OR_{13}$, $-S(O)_{0-2}R_{13}$, $-S(O)_{0-2}NR_{13}R_{13a}$, $-OC(O)R_{13}$, $-OC(O)NR_{13}R_{13a}$, $-NR_{13}R_{13a}$, $-NHC(O)R_{13}$, $-NHC(O)NR_{13}R_{13a}$, $-NHS(O)_2R_{13}$, $-NHS(O)_2NR_{13}R_{13a}$, $-C(O)R_{13}$, $-C(O)NR_{13}R_{13a}$, or $-(CH_2)_nNR_{13}R_{13a}$; and wherein the substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl as R_{11} refer to cycloalkyl, heterocycloalkyl, aryl, or heteroaryl substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, amino, C_{1-3}alkyl, C_{1-3}alkoxy, halo-C_{1-3}alkyl, and halo-C_{1-3}alkoxy;

R_{12} is hydrogen or alkyl;

R_{13} and R_{13a} are independently hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; or R_{13} and R_{13a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring;

n is 1, 2, 3, or 4.

2. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein R is substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{3-10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted 5- to 10-membered heteroaryl, substituted or unsubstituted C_{3-10}cycloalkylC_{1-3}alkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkylC_{1-3}alkyl, substituted or unsubstituted phenylC_{1-3}alkyl, or substituted or unsubstituted 5- to 10-membered heteroarylC_{1-3}alkyl; wherein the substituted C_{1-6}alkyl, substituted C_{3-10}cycloalkyl, substituted 3- to 10-membered heterocycloalkyl, substituted phenyl, substituted naphthyl, substituted 5- to 10-membered heteroaryl, substituted C_{3-10}cycloalkylC_{1-3}alkyl, substituted 3- to 10-membered heterocycloalkylC_{1-3}alkyl, substituted phenylC_{1-3}alkyl, or substituted 5- to 10-membered heteroarylC_{1-3}alkyl is substituted by 1 to 3 R_{11} at any position.

3. The compound of claim 2 and/or a pharmaceutically acceptable salt thereof, wherein R_{11} is independently halogen, hydroxyl, amino, carboxyl, $-NO_2$, -CN, C_{1-6}alkyl, halo- C_{1-6}alkyl, C_{1-6}alkoxy, halo- C_{1-6}alkoxy, substituted or unsubstituted C_{3-8}cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted 5- to 6-membered heteroaryl, C_{3-8}cycloalkylC_{1-3}alkyl, 3- to

8-membered heterocycloalkylC_{1-3}alkyl, phenylC_{1-3}alkyl, 5- to 6-membered heteroarylC_{1-3}alkyl, 3- to 8-membered heterocycloalkylC_{1-3}alkoxy, C_{3-8}cycloalkylC_{1-3}alkoxy, phenylC_{1-3}alkoxy, 5- to 6-membered heteroarylC_{1-3}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, aminoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, $-C(O)OR_{13}$, $-S(O)_{0-2}R_{13}$, $-S(O)_{0-2}NR_{13}R_{13a}$, $-OC(O)R_{13}$, $-OC(O)NR_{13}R_{13a}$, $-NR_{13}R_{13a}$, $-NHC(O)R_{13}$, $-NHC(O)NR_{13}R_{13a}$, $-NHS(O)_2R_{13}$, $-NHS(O)_2NR_{13}R_{13a}$, $-C(O)R_{13}$, $-C(O)NR_{13}R_{13a}$, or $-(CH_2)_nNR_{13}R_{13a}$; and wherein the substituted C_{3-8}cycloalkyl, substituted 3- to 8-membered heterocycloalkyl, substituted phenyl, or substituted 5- to 6-membered heteroaryl as R_{11} refer to C_{3-8}cycloalkyl, 3- to 8-membered heterocycloalkyl, phenyl, or 5- to 6-membered heteroaryl substituted by 1 to 3 substituent(s) at any position independently selected from halogen, hydroxyl, amino, C_{1-3}alkyl, C_{1-3}alkoxy, halo-C_{1-3}alkyl, and halo-C_{1-3}alkoxy;

and n is 1, 2, 3, or 4.

4. The compound of claim 3 and/or a pharmaceutically acceptable salt thereof, wherein R_{13} and R_{13a} are independently hydrogen, C_{1-3}alkyl, halo-C_{1-3}alkyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocycloalkyl, phenyl, or 5- to 6-membered heteroaryl; or R_{13} and R_{13a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring.

5. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein A_2 is $-C(O)N(R_{12})S(O)_2-$; R is $-NR_{10}R_{10a}$; R_{10} and R_{10a} are independently hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3- to 8-membered heterocycloalkyl, phenyl, 5- to 6-membered heteroaryl, C_{3-8}cycloalkylC_{1-3}alkyl, or 3- to 8-membered heteroalkylC_{1-3}alkyl; or R_{10} and R_{10a} together with the nitrogen atom to which they are attached, form a 4- to 8-membered mono-heterocycloalkyl ring; and R_{12} is the same as described in claim 1.

6. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein R_{12} is hydrogen or C_{1-6}alkyl;

and/or, A_1 is a bond, $-CH_2-$, or $-CH_2CH_2-$;

and/or, L is a bond, $-CH(CH_3)-$,  , or  ;

and/or, R_1 is hydrogen, hydroxyl, substituted or unsubstituted C_{1-3}alkyl, or halogen;

and/or, R_2 is hydrogen, substituted or unsubstituted C_{1-3}alkyl, or hydroxyl;

and/or, R_3 is hydrogen, substituted or unsubstituted C_{1-3}alkyl, 2-propenyl, or halogen;

and/or, R_7 is hydrogen, hydroxyl, C_{1-3}alkoxy, or halogen;

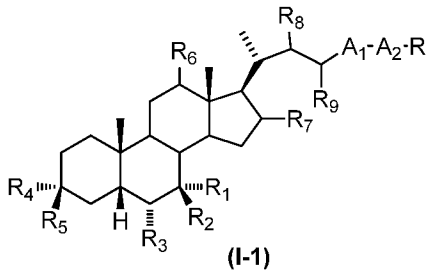
and/or, R_8 is hydrogen, or substituted or unsubstituted C_{1-3}alkyl;

and/or, R_9 is hydrogen, substituted or unsubstituted C_{1-3}alkyl, phenyl, or 5- to 6-membered heteroaryl; or R_8 and R_9 together with the carbon atom to which they are attached, form a 3- to 6-membered cycloalkyl ring;

when R_1, R_2, R_3, R_8, or R_9 is substituted C_{1-3}alkyl, it is substituted by 1 to 3 substituent(s)

at any position independently selected from halogen, hydroxyl, C_{1-3}alkyl and C_{3-8} cycloalkyl.

7. The compound of any one of claims 1 to 6 and/or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is a compound of formula (I-1) and/or a pharmaceutically acceptable salt thereof,



(I-1)

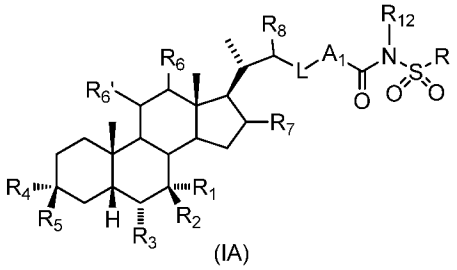
Wherein,

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R, A_1 and A_2 are the same as described in any one of claims 1 to 6.

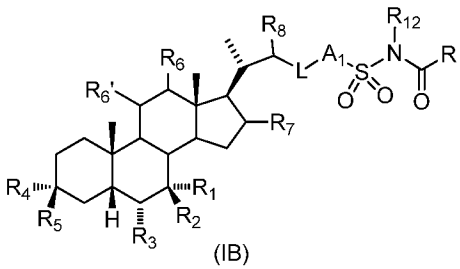
8. The compound of any one of claims 1 to 6 and/or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is

1) a compound of formula (IA) and/or a pharmaceutically acceptable salt thereof, or

2) a compound of formula (IB) and/or a pharmaceutically acceptable salt thereof,



(IA)



(IB)

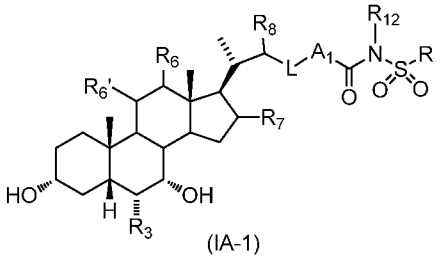
wherein,

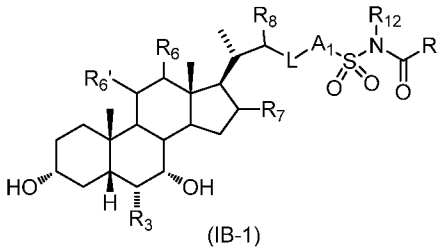
R_1, R_2, R_3, R_4, R_5, R_6, $R_{6'}$, R_7, R_8, R_{12}, R, L and A_1 are the same as described in any one of claims 1 to 6.

9. The compound of any one of claims 1 to 6 and/or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is

1) a compound of formula (IA-1) and/or a pharmaceutically acceptable salt thereof, or

2) a compound of formula (IB-1) and/or a pharmaceutically acceptable salt thereof,


(IA-1)


(IB-1)

Wherein,

R_3, R_6, $R_{6'}$, R_7, R_8, R_{12}, R, L, and A_1 are the same as described in any one of claims 1 to 6.

10. The compound of any one of claims 1 to 6 and/or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is

1) a compound of formula (IA-2) and/or a pharmaceutically acceptable salt thereof,

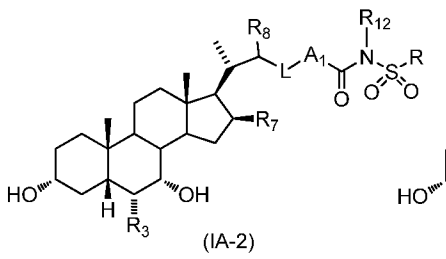
2) a compound of formula (IA-3) and/or a pharmaceutically acceptable salt thereof,

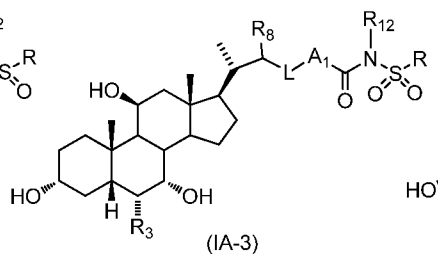
3) a compound of formula (IA-4) and/or a pharmaceutically acceptable salt thereof,

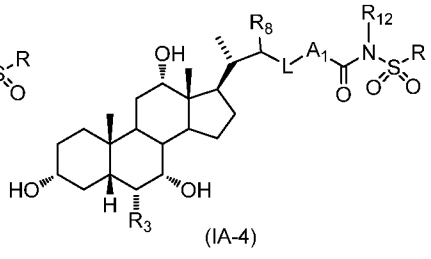
4) a compound of formula (IB-2) and/or a pharmaceutically acceptable salt thereof,

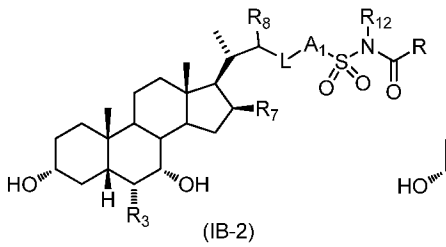
5) a compound of formula (IB-3) and/or a pharmaceutically acceptable salt thereof, or

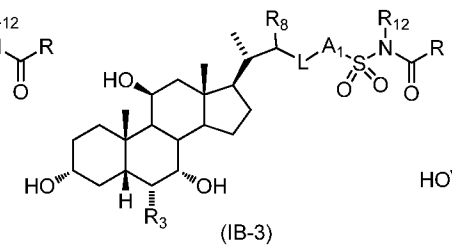
6) a compound of formula (IB-4) and/or a pharmaceutically acceptable salt thereof,

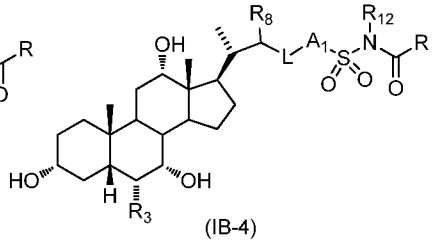

(IA-2)


(IA-3)


(IA-4)


(IB-2)


(IB-3)


(IB-4)

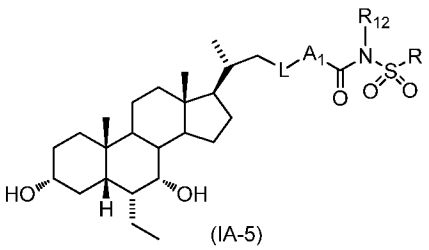
Wherein,

R_3, R_7, R_8, R_{12}, R, L, and A_1 are the same as described in any one of claims 1 to 6.

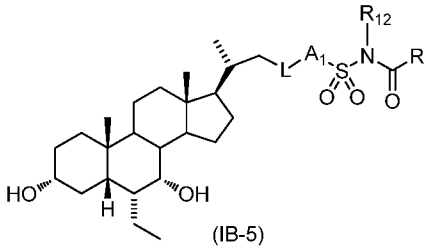
11. The compound of claim 10 and/or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) and/or a pharmaceutically acceptable salt thereof is

1) a compound of formula (IA-5) and/or a pharmaceutically acceptable salt thereof, or

2) a compound of formula (IB-5) and/or a pharmaceutically acceptable salt thereof,



(IA-5)

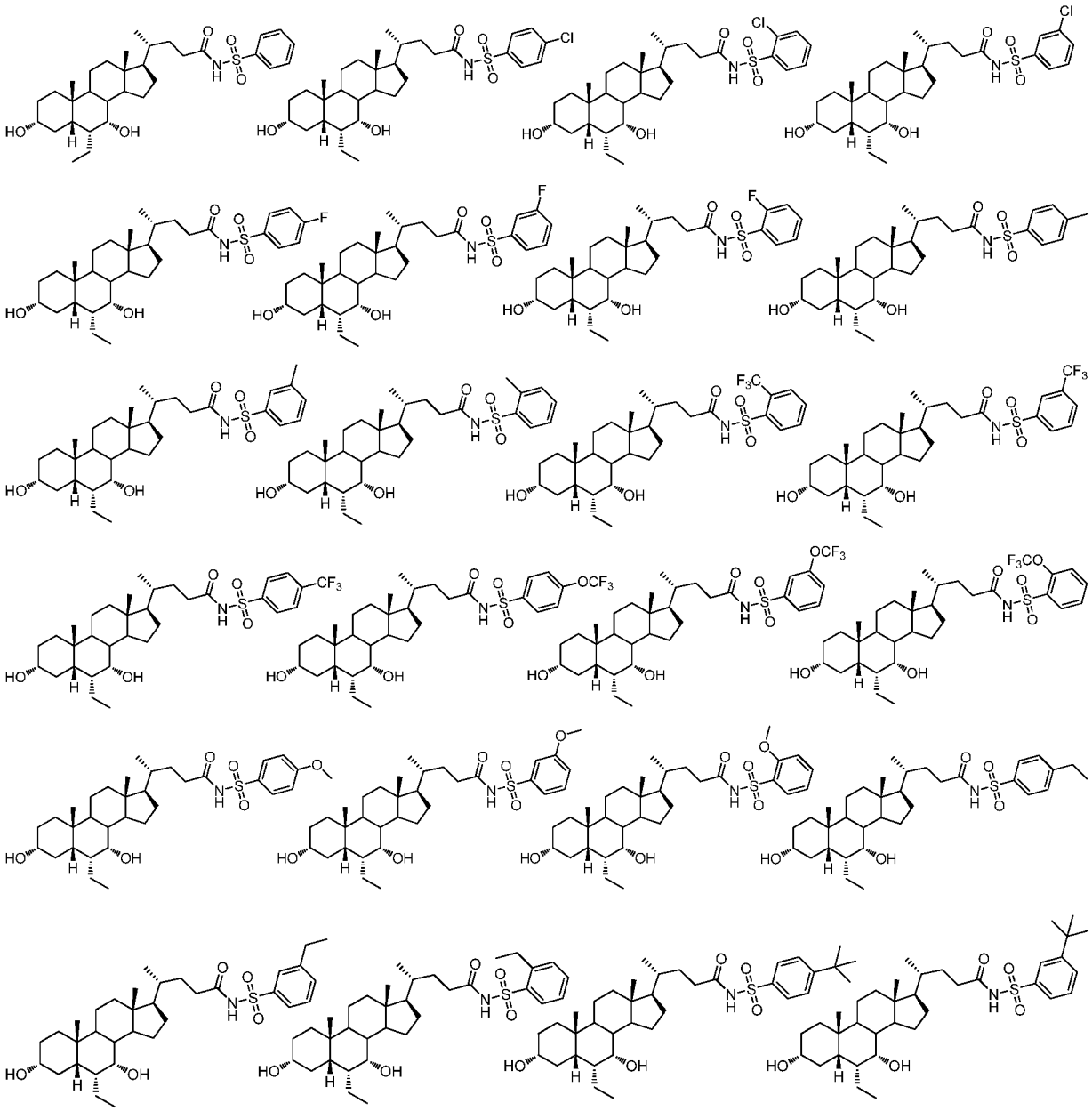


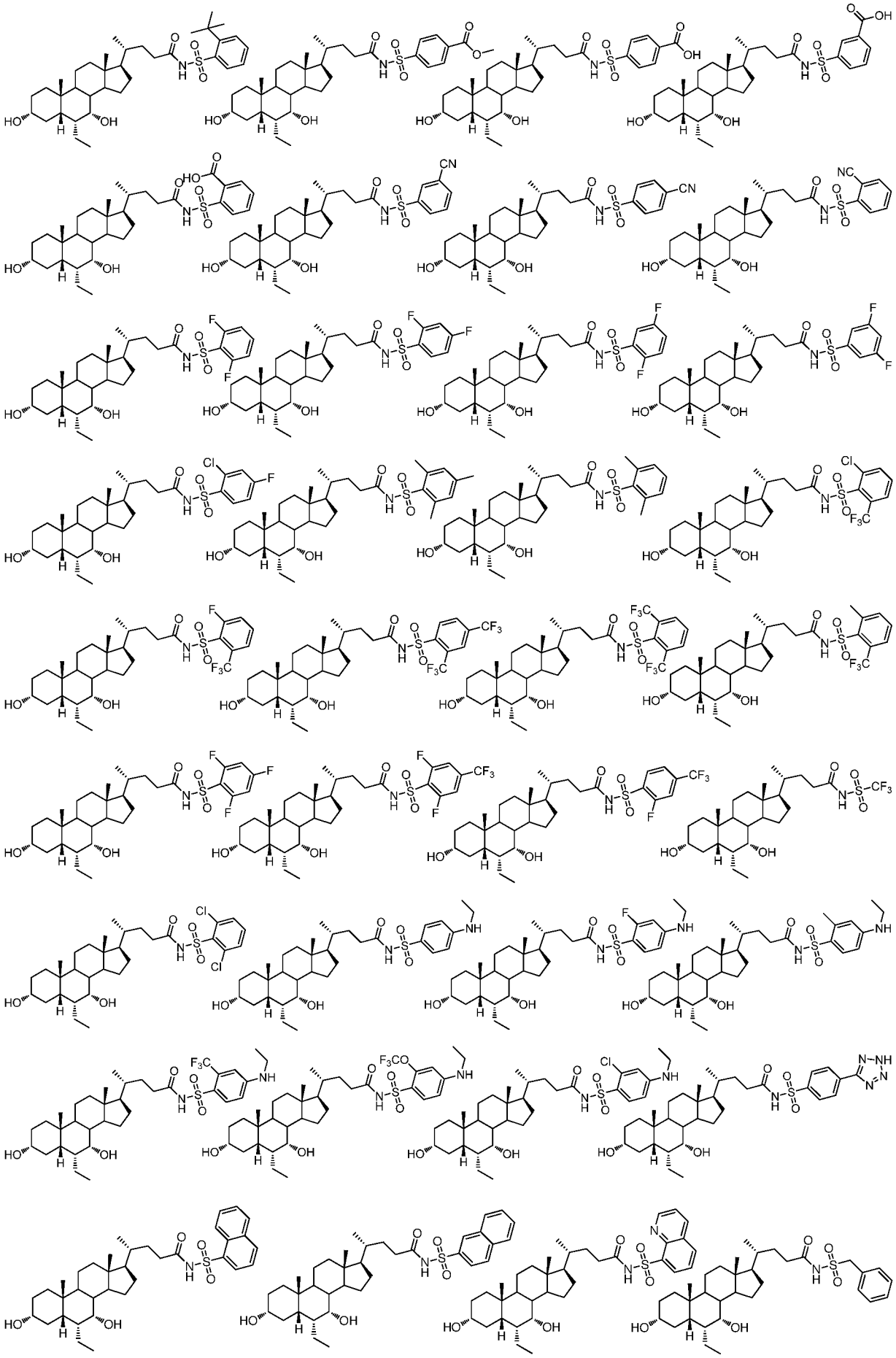
(IB-5)

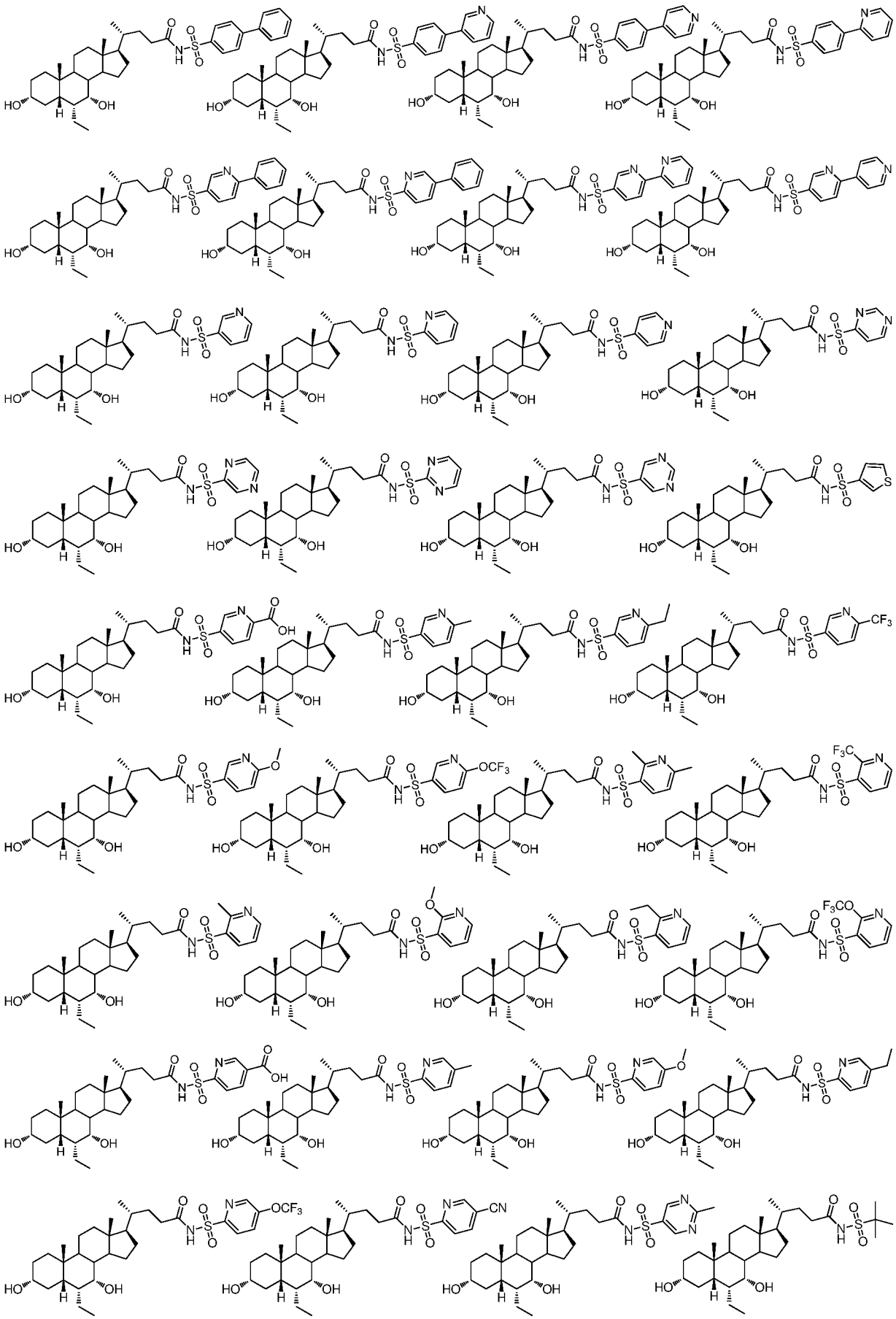
Wherein,

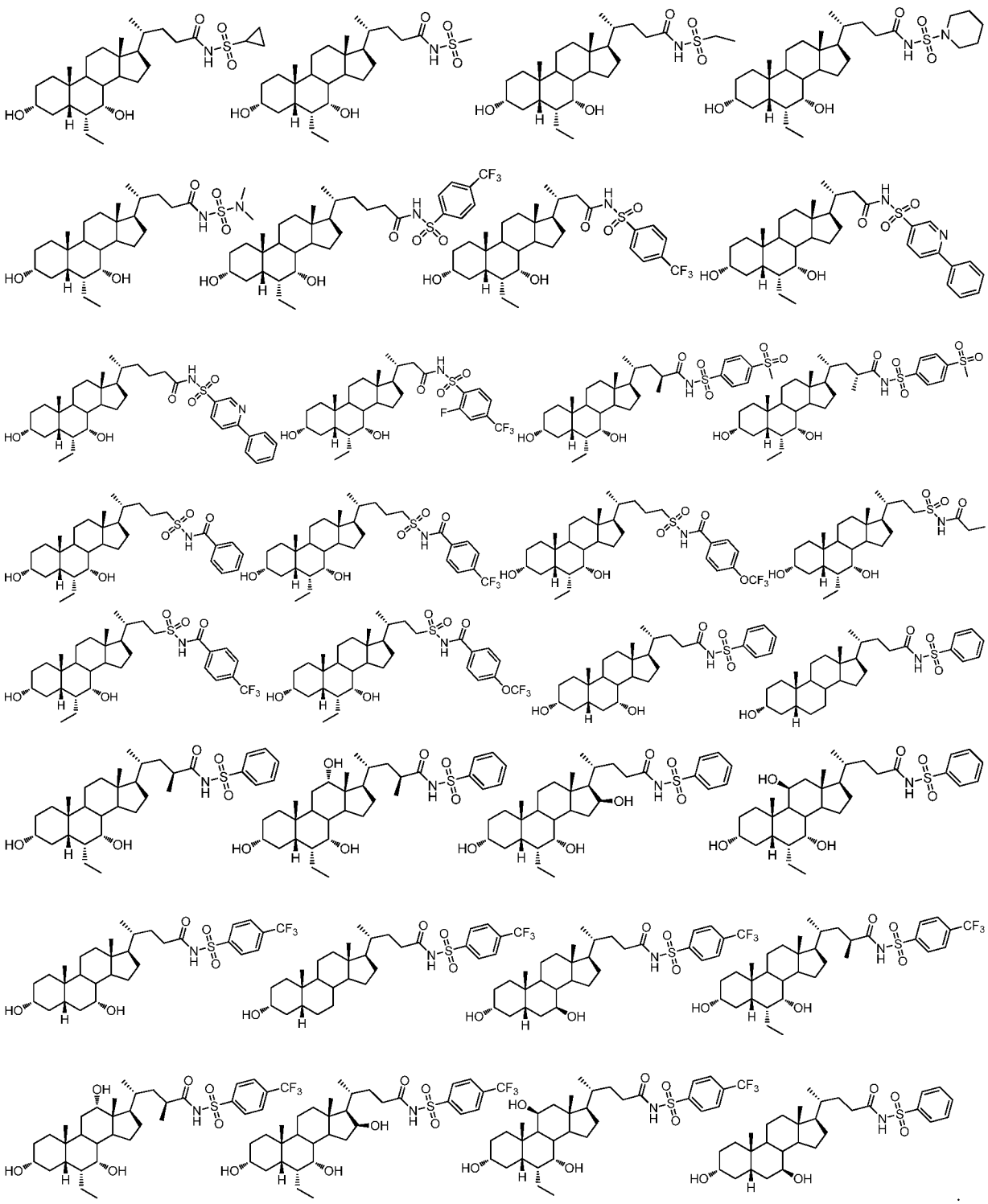
R, R_{12}, L, and A_1 are the same as described in claim 10.

12. The compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein the compound is









13. A pharmaceutical composition comprising 1) a compound of any one of claims 1 to 12 and/or a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable excipient.

14. A pharmaceutical composition of claim 13, wherein the composition further comprising one or more additional pharmaceutical agents for treating cholestasis, intrahepatic cholestasis, estrogen-induced intrahepatic cholestasis, drug-induced cholestasis, intrahepatic cholestasis of pregnancy (ICP), parenteral nutrition associated cholestasis (PNAC), primary

biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chemotherapy related steatohepatitis (CASH), drug induced bile duck injury, liver cirrhosis, alcohol induced liver cirrhosis, cystic fibrosis, bile duct obstruction, cholelithiasis, hepatic fibrosis, dyslipidemia, atherosclerosis, obesity, diabetes, diabetic nephropathy, colitis, neonatal jaundice, the prevention of nuclear jaundice, venous obstruction, high blood pressure, portal hypertension, metabolic syndrome, high cholesterol blood disease, and inflammatory bowel disease.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of the claims 1 to 12 or a pharmaceutical composition thereof as defined in claims 13 to 14 for preparation of a medicament as FXR and /or TGR5 modulator.

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of the claims 1 to 12 or a pharmaceutical composition thereof as defined in claims 13 to 14 for preparation of a medicament for treating FXR and /or TGR5-mediated diseases.

17. The use of claim 16 for preparation of a medicament for treating FXR and /or TGR5-mediated diseases, wherein the disease is selected from: cholestasis, intrahepatic cholestasis, estrogen-induced intrahepatic cholestasis, drug-induced cholestasis, intrahepatic cholestasis of pregnancy (ICP), parenteral nutrition associated cholestasis (PNAC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chemotherapy related steatohepatitis (CASH), drug induced bile duck injury, liver cirrhosis, alcohol induced liver cirrhosis, cystic fibrosis, bile duct obstruction, cholelithiasis, hepatic fibrosis, dyslipidemia, atherosclerosis, obesity, diabetes, diabetic nephropathy, colitis, neonatal jaundice, the prevention of nuclear jaundice, venous obstruction, high blood pressure, portal hypertension, metabolic syndrome, high cholesterol blood disease, and/or inflammatory bowel disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/080331

A. CLASSIFICATION OF SUBJECT MATTER

C07J 41/00(2006.01)i; C07J 43/00(2006.01)i; A61K 31/575(2006.01)i; A61K 31/58(2006.01)i; A61P 1/16(2006.01)i; A61P 3/06(2006.01)i; A61P 9/10(2006.01)i; A61P 3/04(2006.01)i; A61P 3/10(2006.01)i; A61P 13/12(2006.01)i; A61P 1/00(2006.01)i; A61P 9/00(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)

C07J 41/-, C07J 43/-

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)

CNKI, CNABS, DWPI, REGISTRY, CAPLUS substructure search according to formula (I), TGR5,FXR, farnesoid X receptors, bile acid, chenodeoxycholic acid, CDCA, deoxycholic acid, DCA,lithocholic acid, LCA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008091540 A2 (INTERCEPT PHARMACEUTICALS INC) 31 July 2008 (2008-07-31) claims	1-17
A	WO 2007095174 A2 (INTERCEPT PHARMACEUTICALS INC) 23 August 2007 (2007-08-23) claims	1-17
A	WO 2008002573 A2 (INTERCEPT PHARMACEUTICALS INC) 03 January 2008 (2008-01-03) claims	1-17

☐ 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
15 July 2016	**28 July 2016**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **ZHAO,Zhenzhen** Telephone No. **(86-10)62086358**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/080331

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		AU 2008209566 C1	14 February 2013
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		KR 101555716 B1	25 September 2015
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		EP 2112995 B1	31 July 2013
		HK 1142611 A1	13 February 2015
		US 2016096862 A1	07 April 2016
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		US 8410083 B2	02 April 2013
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		ES 2438271 T3	16 January 2014
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		EP 2040713 A4	29 August 2012

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/080331

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		PT	2040713	E	13 October 2014
		CA	2656320	A1	03 January 2008
		US	2015359805	A1	17 December 2015
		EP	2040713	A2	01 April 2009
		IL	196169	D0	22 September 2009
		US	8546365	B2	01 October 2013
		JP	5222846	B2	26 June 2013
		HK	1130187	A1	15 May 2015
		CN	101522703	A	02 September 2009
		WO	2008002573	A3	28 February 2008
		ES	2523591	T3	27 November 2014
		AU	2007265457	B2	14 June 2012
		CN	101522703	B	17 April 2013
		US	2014057886	A1	27 February 2014