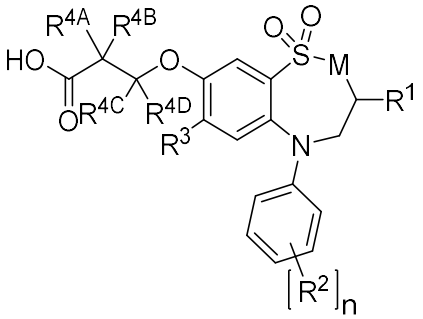
Despite the number of ASBT inhibitor compounds that have been previously reported, there is a need for additional bile acid modulating compounds that have an optimized profile with respect to potency, selectivity and bioavailability.

SUMMARY

In one aspect, the present disclosure relates to a compound of formula (I)



(I)

wherein

M is selected from $-CH_2-$ and $-NR^5-$;

R^1 is C_{1-4} alkyl;

R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, nitro, amino, *N*-(C_{1-4} alkyl)amino, *N,N*-di(C_{1-4} alkyl)amino, C_{1-6} alkylcarbonylamino, C_{3-6} cycloalkylcarbonylamino, *N*-(C_{1-4} alkyl)aminocarbonyl, *N,N*-di(C_{1-4} alkyl)aminocarbonyl, C_{1-4} alkyloxycarbonylamino, C_{3-6} cycloalkyloxycarbonylamino, C_{1-4} alkylsulfonamido and C_{3-6} cycloalkylsulfonamido;

n is an integer 1, 2 or 3;

R^3 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyloxy, C_{1-4} alkylthio, C_{3-6} cycloalkylthio, amino, *N*-(C_{1-4} alkyl)amino and *N,N*-di(C_{1-4} alkyl)amino;

R^{4A} and R^{4B} are each independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy; or R^{4A} and R^{4B}, together with the carbon atom to which they are attached, form a 3- to 5-membered saturated carbocyclic ring;

R^{4C} and R^{4D} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl; and

R^5 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof as disclosed herein, and one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure relates to a compound or a pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical composition as disclosed herein, for use as a medicament.

In another aspect, the present disclosure relates to use of a compound or a pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment or prevention of a cardiovascular disease or a disorder of fatty acid metabolism or a glucose utilization disorder, such as hypercholesterolemia; disorders of fatty acid metabolism; type 1 and type 2 diabetes mellitus; complications of diabetes, including cataracts, micro- and macrovascular diseases, retinopathy, neuropathy, nephropathy and delayed wound healing, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; diabetes-related diseases such as insulin resistance (impaired glucose homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, dyslipidemia, hyperlipidemia including hypertriglyceridemia, metabolic syndrome (syndrome X), atherosclerosis and hypertension; and for increasing high density lipoprotein levels.

In another aspect, the present disclosure relates to use of a compound or a pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment or prevention of a gastrointestinal disease or disorder, such as constipation (including chronic constipation, functional constipation, chronic idiopathic constipation (CIC), intermittent/sporadic constipation, constipation secondary to diabetes mellitus, constipation secondary to stroke, constipation secondary to chronic kidney disease, constipation secondary to multiple sclerosis, constipation secondary to Parkinson's disease, constipation secondary to systemic sclerosis, drug induced constipation, irritable bowel syndrome with constipation (IBS-C), irritable bowel syndrome mixed (IBS-M), pediatric functional constipation and opioid induced constipation); Crohn's disease; primary bile acid malabsorption; irritable bowel syndrome (IBS); inflammatory bowel disease (IBD); ileal inflammation; and reflux disease and complications thereof, such as Barrett's esophagus, bile reflux esophagitis and bile reflux gastritis.

In another aspect, the present disclosure relates to use of a compound or a pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment or prevention of a liver disease or disorder, such as an inherited metabolic disorder of the liver; inborn errors of bile acid synthesis; congenital bile duct anomalies; biliary atresia; post-Kasai biliary atresia; post-liver transplantation biliary atresia; neonatal hepatitis; neonatal cholestasis; hereditary forms of cholestasis; cerebrotendinous xanthomatosis; a secondary defect of BA synthesis; Zellweger´s syndrome; cystic fibrosis-associated liver disease; alpha1-antitrypsin deficiency; Alagilles syndrome (ALGS); Byler syndrome; a primary defect of bile acid (BA) synthesis; progressive familial intrahepatic cholestasis (PFIC) including PFIC-1, PFIC-2, PFIC-3 and non-specified PFIC, post-biliary diversion PFIC and post-liver transplant PFIC; benign recurrent intrahepatic cholestasis (BRIC) including BRIC1, BRIC2 and non-specified BRIC, post-biliary diversion BRIC and post-liver transplant BRIC; autoimmune hepatitis; primary biliary cirrhosis (PBC); liver fibrosis; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); portal hypertension; cholestasis; Down syndrome cholestasis; drug-induced cholestasis; intrahepatic cholestasis of pregnancy (jaundice during pregnancy); intrahepatic cholestasis; extrahepatic cholestasis; parenteral nutrition associated cholestasis (PNAC); low phospholipid-associated cholestasis; lymphedema cholestasis syndrome 1 (LCS1); primary sclerosing cholangitis (PSC); immunoglobulin G4 associated cholangitis; primary biliary cholangitis; cholelithiasis (gallstones); biliary lithiasis; choledocholithiasis; gallstone pancreatitis; Caroli disease; malignancy of bile ducts; malignancy causing obstruction of the biliary tree; biliary strictures; AIDS cholangiopathy; ischemic cholangiopathy; pruritus due to cholestasis or jaundice; pancreatitis; chronic autoimmune liver disease leading to progressive cholestasis; hepatic steatosis; alcoholic hepatitis; acute fatty liver; fatty liver of pregnancy; drug-induced hepatitis; iron overload disorders; congenital bile acid synthesis defect type 1 (BAS defect type 1); drug-induced liver injury (DILI); hepatic fibrosis; congenital hepatic fibrosis; hepatic cirrhosis; Langerhans cell histiocytosis (LCH); neonatal ichthyosis sclerosing cholangitis (NISCH); erythropoietic protoporphyria (EPP); idiopathic adulthood ductopenia (IAD); idiopathic neonatal hepatitis (INH); non syndromic paucity of interlobular bile ducts (NS PILBD); North American Indian childhood cirrhosis (NAIC); hepatic sarcoidosis; amyloidosis; necrotizing enterocolitis; serum bile acid-caused toxicities, including cardiac rhythm disturbances (e.g., atrial fibrillation) in setting of abnormal serum bile acid profile, cardiomyopathy associated with liver cirrhosis (“cholecardia”), and skeletal muscle wasting associated with cholestatic liver disease; polycystic liver disease; viral hepatitis (including hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E); hepatocellular carcinoma (hepatoma); cholangiocarcinoma; bile acid-related

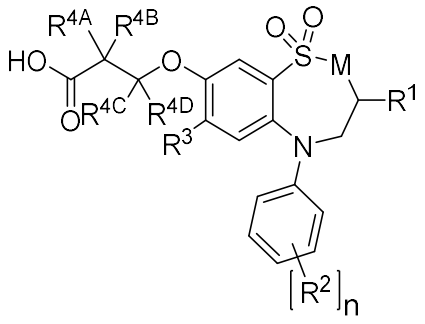
gastrointestinal cancers; and cholestasis caused by tumours and neoplasms of the liver, of the biliary tract and of the pancreas; or for the enhancement of corticosteroid therapy in liver disease.

In another aspect, the present disclosure relates to use of a compound or a pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment or prevention of hyperabsorption syndromes (including abetalipoproteinemia, familial hypobetalipoproteinemia (FHBL), chylomicron retention disease (CRD) and sitosterolemia); hypervitaminosis and osteopetrosis; hypertension; glomerular hyperfiltration; polycystic kidney disease (PKD), including autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD); and pruritus of renal failure; or for the protection against liver- or metabolic disease-associated kidney injury.

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that certain 1,5-benzothiazepine and 1,2,5-benzothiadiazepine derivates are potent inhibitors of apical sodium-dependent bile acid transporter (ASBT) and/or liver bile acid transporter (LBAT), and may be useful for treating diseases wherein inhibition of bile acid circulation is desirable.

In a first aspect, the invention relates to a compound of formula (I)



(I)

wherein

M is selected from $-CH_2-$ and $-NR^5-$;

R^1 is C_{1-4} alkyl;

R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, nitro, amino, *N*-(C_{1-4} alkyl)amino,

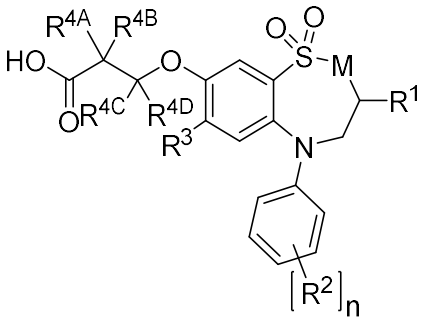
N,N-di(C_{1-4} alkyl)amino, C_{1-6} alkylcarbonylamino, C_{3-6} cycloalkylcarbonylamino, *N*-(C_{1-4} alkyl)amino-carbonyl, *N,N*-di(C_{1-4} alkyl)aminocarbonyl, C_{1-4} alkyloxycarbonylamino, C_{3-6} cycloalkyloxycarbonyl-amino, C_{1-4} alkylsulfonamido and C_{3-6} cycloalkylsulfonamido;

n is an integer 1, 2 or 3;

R^3 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyloxy, C_{1-4} alkylthio, C_{3-6} cycloalkylthio, amino, *N*-(C_{1-4} alkyl)amino and *N,N*-di(C_{1-4} alkyl)amino;

CLAIMS

1. A compound of formula (I)



(I)

wherein

M is selected from -CH_2- and -NR^5-;

R^1 is C_{1-4} alkyl;

R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, cyano, nitro, amino, *N*-(C_{1-4} alkyl)amino, *N,N*-di(C_{1-4} alkyl)amino, C_{1-6} alkylcarbonylamino, C_{3-6} cycloalkylcarbonylamino, *N*-(C_{1-4} alkyl)-aminocarbonyl, *N,N*-di(C_{1-4} alkyl)aminocarbonyl, C_{1-4} alkyloxycarbonylamino, C_{3-6} cycloalkyl-oxycarbonylamino, C_{1-4} alkylsulfonamido and C_{3-6} cycloalkylsulfonamido;

n is an integer 1, 2 or 3;

R^3 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyloxy, C_{1-4} alkylthio, C_{3-6} cycloalkylthio, amino, *N*-(C_{1-4} alkyl)amino and *N,N*-di(C_{1-4} alkyl)amino;

R^{4A} and R^{4B} are each independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy; or R^{4A} and R^{4B}, together with the carbon atom to which they are attached, form a 3- to 5-membered saturated carbocyclic ring;

R^{4C} and R^{4D} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl; and

R^5 is selected from the group consisting of hydrogen and C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is C_{2-4} alkyl.

3. A compound according to claim 1 or 2, wherein R^1 is *n*-propyl or *n*-butyl.

4. A compound according to any one of claims 1 to 3, wherein R^2 is independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methoxy, amino, methylamino and dimethylamino.

5. A compound according to any one of claims 1 to 4, wherein R^3 is selected from the group consisting of fluoro, chloro, bromo, methyl, cyclopropyl, methoxy, ethoxy, methylthio, ethylthio, amino, methylamino and dimethylamino.

6. A compound according to any one of claims 1 to 5, wherein R^{4A} and R^{4B} are each independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy, or R^{4A} and R^{4B}, together with the carbon atom to which they are attached, form a cyclopropyl ring.

7. A compound according to any one of claims 1 to 6, wherein R^{4C} and R^{4D} are each independently hydrogen or methyl.

8. A compound according to any one of claims 1 to 7, wherein R^5 is hydrogen or methyl.

9. A compound according to claim 1, selected from the group consisting of:

3-((3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

(S)-3-((3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

(R)-3-((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

1-(((3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(S)-1-(((3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(R)-1-(((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

3-((3-Butyl-7-(ethylthio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

(S)-3-((3-Butyl-7-(ethylthio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

(R)-3-((3-butyl-7-(ethylthio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

1-(((3-Butyl-7-(ethylthio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(S)-1-(((3-butyl-7-(ethylthio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(R)-1-(((3-butyl-7-(ethylthio)-2-methyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

3-((3-butyl-5-(4-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

1-(((3-butyl-5-(4-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

1-(((3-butyl-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(S)-1-(((3-butyl-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(R)-1-(((3-butyl-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

3-((3-butyl-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

(S)-3-((3-butyl-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

(R)-3-((3-butyl-5-(4-fluorophenyl)-2-methyl-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-dimethylpropanoic acid;

1-(((3-butyl-7-(ethylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

1-(((3-butyl-5-(4-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(S)-1-(((3-butyl-5-(4-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(R)-1-(((3-butyl-5-(4-fluorophenyl)-7-(methylthio)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

1-(((3-butyl-7-(ethylthio)-5-(4-fluorophenyl)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(S)-1-(((3-butyl-7-(ethylthio)-5-(4-fluorophenyl)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

(R)-1-(((3-butyl-7-(ethylthio)-5-(4-fluorophenyl)-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)methyl)cyclopropane-1-carboxylic acid;

3-((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-difluoropropanoic acid;

(S)-3-((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-difluoropropanoic acid;

(R)-3-((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2,2-difluoropropanoic acid;

3-((3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxy-2-methylpropanoic acid;

(S)-3-(((R)-3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxy-2-methylpropanoic acid;

(S)-3-(((S)-3-Butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxy-2-methylpropanoic acid;

(R)-3-(((R)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxy-2-methylpropanoic acid;

(R)-3-(((S)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxy-2-methylpropanoic acid;

3-((3-butyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)propanoic acid;

(S)-3-((3-butyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)propanoic acid;

(R)-3-((3-butyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)propanoic acid;

3-((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-ethoxypropanoic acid;

3-((3-butyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)-2-hydroxypropanoic acid;

3-((3-ethyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yl)oxy)propanoic acid;

3-((3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid;

3-(((S)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid;

3-(((R)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid;

(S)-3-(((R)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid;

(R)-3-(((R)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid;

(S)-3-(((S)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid;

(R)-3-(((S)-3-butyl-2-methyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-methoxypropanoic acid; and

3-((3-butyl-7-(ethylthio)-5-(4-fluorophenyl)-2-methyl-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-8-yl)oxy)-2-hydroxypropanoic acid;

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, and one or more pharmaceutically acceptable excipients.

11. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10, for use as a medicament.

12. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10, in the manufacture of a medicament for the treatment or prevention of a cardiovascular disease or a disorder of fatty acid metabolism or a glucose utilization disorder, such as hypercholesterolemia; disorders of fatty acid metabolism; type 1 and type 2 diabetes mellitus; complications of diabetes, including cataracts, micro- and macrovascular diseases, retinopathy, neuropathy, nephropathy and delayed wound healing, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; diabetes-related diseases such as insulin resistance (impaired glucose

homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, dyslipidemia, hyperlipidemia including hypertriglyceridemia, metabolic syndrome (syndrome X), atherosclerosis and hypertension; and for increasing high density lipoprotein levels.

13. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10, in the manufacture of a medicament for the treatment or prevention of a gastrointestinal disease or disorder, such as constipation (including chronic constipation, functional constipation, chronic idiopathic constipation (CIC), intermittent/sporadic constipation, constipation secondary to diabetes mellitus, constipation secondary to stroke, constipation secondary to chronic kidney disease, constipation secondary to multiple sclerosis, constipation secondary to Parkinson's disease, constipation secondary to systemic sclerosis, drug induced constipation, irritable bowel syndrome with constipation (IBS-C), irritable bowel syndrome mixed (IBS-M), pediatric functional constipation and opioid induced constipation); Crohn's disease; primary bile acid malabsorption; irritable bowel syndrome (IBS); inflammatory bowel disease (IBD); ileal inflammation; and reflux disease and complications thereof, such as Barrett's esophagus, bile reflux esophagitis and bile reflux gastritis.

14. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10, in the manufacture of a medicament for the treatment or prevention of a liver disease or disorder, such as an inherited metabolic disorder of the liver; inborn errors of bile acid synthesis; congenital bile duct anomalies; biliary atresia; post-Kasai biliary atresia; post-liver transplantation biliary atresia; neonatal hepatitis; neonatal cholestasis; hereditary forms of cholestasis; cerebrotendinous xanthomatosis; a secondary defect of BA synthesis; Zellweger´s syndrome; cystic fibrosis-associated liver disease; alpha1-antitrypsin deficiency; Alagilles syndrome (ALGS); Byler syndrome; a primary defect of bile acid (BA) synthesis; progressive familial intrahepatic cholestasis (PFIC) including PFIC-1, PFIC-2, PFIC-3 and non-specified PFIC, post-biliary diversion PFIC and post-liver transplant PFIC; benign recurrent intrahepatic cholestasis (BRIC) including BRIC1, BRIC2 and non-specified BRIC, post-biliary diversion BRIC and post-liver transplant BRIC; autoimmune hepatitis; primary biliary cirrhosis (PBC); liver fibrosis; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); portal hypertension; cholestasis; Down syndrome cholestasis; drug-induced cholestasis; intrahepatic cholestasis of pregnancy (jaundice during pregnancy); intrahepatic cholestasis; extrahepatic cholestasis; parenteral

nutrition associated cholestasis (PNAC); low phospholipid-associated cholestasis; lymphedema cholestasis syndrome 1 (LCS1); primary sclerosing cholangitis (PSC); immunoglobulin G4 associated cholangitis; primary biliary cholangitis; cholelithiasis (gallstones); biliary lithiasis; choledocholithiasis; gallstone pancreatitis; Caroli disease; malignancy of bile ducts; malignancy causing obstruction of the biliary tree; biliary strictures; AIDS cholangiopathy; ischemic cholangiopathy; pruritus due to cholestasis or jaundice; pancreatitis; chronic autoimmune liver disease leading to progressive cholestasis; hepatic steatosis; alcoholic hepatitis; acute fatty liver; fatty liver of pregnancy; drug-induced hepatitis; iron overload disorders; congenital bile acid synthesis defect type 1 (BAS defect type 1); drug-induced liver injury (DILI); hepatic fibrosis; congenital hepatic fibrosis; hepatic cirrhosis; Langerhans cell histiocytosis (LCH); neonatal ichthyosis sclerosing cholangitis (NISCH); erythropoietic protoporphyria (EPP); idiopathic adulthood ductopenia (IAD); idiopathic neonatal hepatitis (INH); non syndromic paucity of interlobular bile ducts (NS PILBD); North American Indian childhood cirrhosis (NAIC); hepatic sarcoidosis; amyloidosis; necrotizing enterocolitis; serum bile acid-caused toxicities, including cardiac rhythm disturbances (e.g., atrial fibrillation) in setting of abnormal serum bile acid profile, cardiomyopathy associated with liver cirrhosis (“cholecardia”), and skeletal muscle wasting associated with cholestatic liver disease; polycystic liver disease; viral hepatitis (including hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E); hepatocellular carcinoma (hepatoma); cholangiocarcinoma; bile acid-related gastrointestinal cancers; and cholestasis caused by tumours and neoplasms of the liver, of the biliary tract and of the pancreas; or for the enhancement of corticosteroid therapy in liver disease.

15. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10, in the manufacture of a medicament for the treatment or prevention of hyperabsorption syndromes (including abetalipoproteinemia, familial hypobetalipoproteinemia (FHBL), chylomicron retention disease (CRD) and sitosterolemia); hypervitaminosis and osteopetrosis; hypertension; glomerular hyperfiltration; polycystic kidney disease (PKD), including autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD); and pruritus of renal failure; or for the protection against liver- or metabolic disease-associated kidney injury.