IBAT INHIBITORS FOR THE TREATMENT OF LIVER DISEASES

BACKGROUND OF THE INVENTION

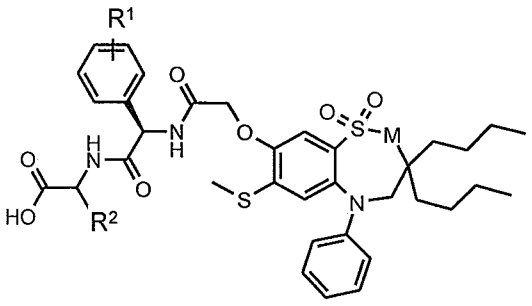
Ileal bile acid transporter (IBAT) is the main mechanism for re-absorption of bile acids from the GI tract. Partial or full blockade of that mechanism will result in lower concentration of bile acids in the small bowel wall, portal vein, liver parenchyma, intrahepatic biliary tree, extrahepatic biliary tree, including gall bladder.

Diseases which may benefit from partial or full blockade of the IBAT mechanism may be those either having as a primary pathophysiological defect, causing or having symptoms of too high concentration of bile acids in serum and in the above organs. WO 2008/058630 describes the effect of certain ileal bile acid transport (IBAT) in the treatment of liver disease related to fat disorders.

SUMMARY

The present disclosure regards specific IBAT inhibitors in the prophylaxis and/or treatment of a liver disease.

In one aspect, there is provided use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

R^1 is H or hydroxy;

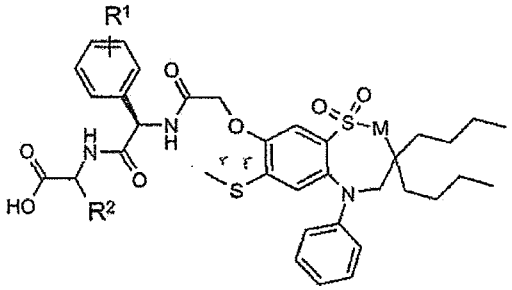
R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

$-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In one aspect, there is provided use of a pharmaceutical composition comprising a compound of Formula (II)



Formula II

wherein

M is CH_2 or NH;

R^1 is H or hydroxy;

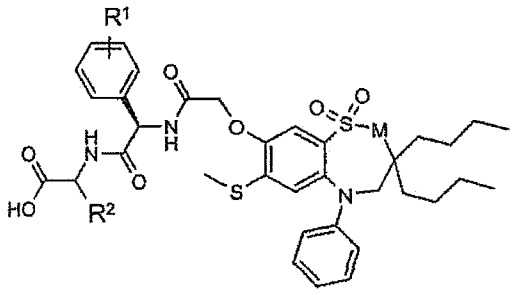
R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

$-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In one aspect, there is provided use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

$\mathbf{R^1}$ is H or hydroxy;

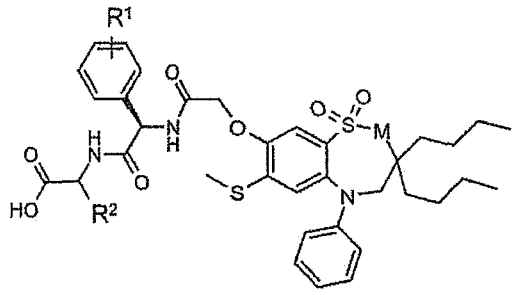
$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof;

and ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In one aspect, there is provided use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

R^1 is H or hydroxy;

R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

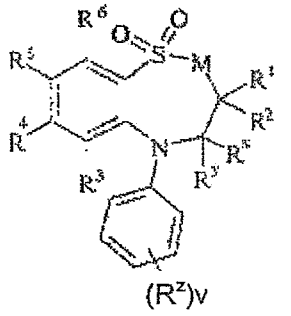
or a pharmaceutically acceptable salt thereof,

and nor-ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to IBAT inhibitor compounds of formula (I):



(I)

wherein:

M is CH_2, NH

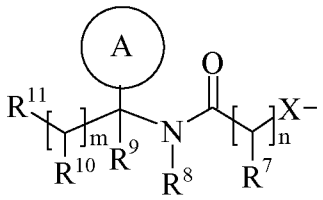
One of $\mathbf{R^1}$ and $\mathbf{R^2}$ are selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl;

$\mathbf{R^x}$ and $\mathbf{R^y}$ are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2

$\mathbf{R^z}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, , C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula **(IA)**:



(IA)

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16};

X is -O-, -N(R^a)-, -S(O)$_b$- or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6}alkyl and b is 0-2;

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17};

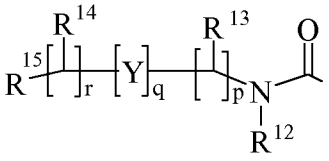
$\mathbf{R^7}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18};

$\mathbf{R^8}$ is hydrogen or C_{1-4}alkyl;

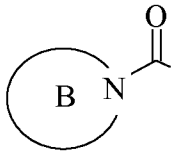
$\mathbf{R^9}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^{10}}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^{10} is optionally substituted by one or more substituents selected from R^{19};

R^{11} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl; or R^{11} is a group of formula **(IB)** or **(IC)**:



(IB)



(IC)

wherein:

Y is –N(R^n)-, -N(R^n)C(O)-, -N(R^n)C(O)(CR^sR^t)$_v$N(R^n)C(O)-, -O-, and -S(O)a-; wherein a is 0-2, v is 1-2, R^s and R^t are independently selected from hydrogen or C_{1-4}alkyl optionally substituted by R^{26} and R^n is hydrogen or C_{1-4}alkyl;

R^{12} is hydrogen or C_{1-4}alkyl;

R^{13} and **R^{14}** are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; and when q is 0, R^{14} may additionally be selected from hydroxy wherein R^{13} and R^{14} may be independently optionally substituted by one or more substituents selected from R^{20};

R^{15} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-6}alkyl;

p is 1-3; wherein the values of R^{13} may be the same or different;

q is 0-1;

r is 0-3; wherein the values of R^{14} may be the same or different;

m is 0-2; wherein the values of R^{10} may be the same or different;

n is 1-3; wherein the values of R^7 may be the same or different;

Ring B is a nitrogen linked heterocyclyl substituted on carbon by one group selected from R^{23}, and optionally additionally substituted on carbon by one or more R^{24}; and wherein if said nitrogen linked heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by a group selected from R^{25};

R^{16}, **R^{17}** and **R^{18}** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^{16}, R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21};

R^{19}, **R^{20}**, **R^{24}** and **R^{26}** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl,

C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C_{1-6}alkyl; wherein R^{19}, R^{20}, R^{24} and R^{26} may be independently optionally substituted on carbon by one or more R^{22};

R^{21} and **R^{22}** are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

R^{23} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^g)(OR^h), -P(O)(OH)(OR^g), -P(O)(OH)(R^g) or -P(O)(OR^g)(R^h) wherein R^g and R^h are independently selected from C_{1-6}alkyl;

R^{25} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof for use in the prophylaxis or treatment of a liver disease.

Compounds as used in accordance with the invention improve liver tests (serum amino transferases) and liver histology and significantly reduce hydroxyproline content and the number of infiltrating neutrophils and proliferating hepatocytes and cholangiocytes.

In the literature IBAT inhibitors are often referred to by different names. It is to be understood that where IBAT inhibitors are referred to herein, this term also encompasses compounds known in the literature as: i) ileal apical sodium co-dependent bile acid transporter (ASBT) inhibitors; ii) bile acid transporter (BAT) inhibitors; iii) ileal sodium/bile acid cotransporter system inhibitors; iv) apical sodium-bile acid cotransporter inhibitors; v) ileal sodium-dependent bile acid transport inhibitors; vi) bile acid reabsorption (BARI's) inhibitors; and vii) sodium bile acid transporter (SBAT) inhibitors; where they act by inhibition of IBAT.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, C_{1-3}alkyl, propyl, isopropyl and

t-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" would include phenylC_{1-4}alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3 - 12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. In another aspect of the invention, "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 8, 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl and quinolyl. Preferably the term "heteroaryl" refers to thienyl or indolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3 - 12 atoms. Preferably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3 - 12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl,

2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo [2.2.1] heptyl, 4-thiazolidonyl, morpholino, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, tetrahydropyranyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyranyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3 - 12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl.

An example of "C_{1-6}alkanoyloxy" and "C_{1-4}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" and "C_{1-4}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" and "C_{1-4}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" and "C_{1-4}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" and "C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" and "C_{1-4}alkanoyl" include C_{1-3}alkanoyl, propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" and "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" and "*N,N*-(C_{1-4}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" and "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" and "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" and "*N*-(C_{1-4}alkyl)sulphamoyl" are *N*-(C_{1-3}alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" and "*N*-4alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" and "*N*-(C_{1-4}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" and "*N,N*-(C_{1-4}alkyl)$_2$-carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" are ethoxycarbonylamino and *t*-butoxycarbonylamino. Examples of

"*N*'-(C_{1-6}alkyl)ureido" are *N*'-methylureido and *N*'-ethylureido. Examples of "*N*-(C_{1-6}alkyl)ureido are *N*-methylureido and *N*-ethylureido. Examples of "*N*',*N*'-(C_{1-6}alkyl)$_2$ureido are *N*',*N*'-dimethylureido and *N*'-methyl-*N*'-ethylureido. Examples of "*N*'-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido are *N*'-methyl-*N*-methylureido and *N*'-propyl-*N*-methylureido. Examples of "*N*',*N*'-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido are *N*',*N*'-dimethyl-*N*-methylureido and *N*'-methyl-*N*'-ethyl-*N*-propylureido.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid.

In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl) amine.

Compounds of formula **(I)** may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula **(I)**.
Examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula **(I)**.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl,C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters,C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl;1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxy-carbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and

2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3-or 4-position of the benzoyl ring.

A suitable value for an *in vivo* hydrolysable amide of a compound of the formula **(I)** containing a carboxy group is, for example, a *N*-C_{1-6}alkyl or *N,N*-di-C_{1-6}alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.
It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess IBAT inhibitory activity.

Preferred values of $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$ and $\mathbf{R^6}$ are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Preferably $\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from C_{1-4}alkyl.
More preferably $\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from ethyl or butyl.
More preferably $\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from ethyl, propyl or butyl.
In one aspect of the invention particularly $\mathbf{R^1}$ and $\mathbf{R^2}$ are both butyl.
In a further aspect of the invention particularly $\mathbf{R^1}$ and $\mathbf{R^2}$ are both propyl.
In another aspect of the invention particularly one of $\mathbf{R^1}$ and $\mathbf{R^2}$ is ethyl and the other is butyl.

Preferably $\mathbf{R^x}$ and $\mathbf{R^Y}$ are independently selected from hydrogen or C_{1-6}alkyl.
More preferably $\mathbf{R^x}$ and $\mathbf{R^Y}$ are both hydrogen.
Preferably $\mathbf{R^Z}$ is selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkoxycarbonylamino or *N'*-(C_{1-6}alkyl)ureido.

More preferably $\mathbf{R^Z}$ is selected from chloro, amino, *t*-butyl, *t*-butoxycarbonylamino or *N'*-(*t*-butyl)ureido.

Preferably **v** is 0 or 1.
In one aspect of the invention, more preferably **v** is 0.
In one aspect of the invention, more preferably **v** is 1.

In one aspect of the invention preferably **R**^{4} is a group of formula **(IA)** (as depicted above). In another aspect of the invention preferably **R**^{5} is a group of formula **(IA)** (as depicted above).

Preferably **R**^{3} and **R**^{6} are hydrogen.
Preferably the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that **R**^{4} or **R**^{5} may be optionally substituted on carbon by one or more **R**^{16}; wherein **R**^{16} is independently selected from hydroxy and *N,N*-(C_{1-4}alkyl)$_2$amino.

More preferably the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from bromo, methoxy, isopropoxy, methylthio, ethylthio, isopropylthio or mesyl; wherein that **R**^{4} or **R**^{5} may be optionally substituted on carbon by one or more **R**^{16}; wherein **R**^{16} is independently selected from hydroxy and *N,N*-dimethylamino.

Particularly the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from bromo, methoxy, isopropoxy, methylthio, ethylthio, isopropylthio, 2-hydroxyethylthio, 2-(*N,N*-dimethylamino) ethylthio or mesyl.

More particularly the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is methylthio.
Preferably the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from hydrogen, halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that **R**^{4} or **R**^{5} may be optionally substituted on carbon by one or more **R**^{16}; wherein **R**^{16} is independently selected from hydroxy, carboxy and *N,N*-(C_{1-4}alkyl)$_2$amino.

More preferably the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from hydrogen, bromo, methoxy, isopropoxy, methylthio, ethylthio, isopropylthio or mesyl; wherein that **R**^{4} or **R**^{5} may be optionally substituted on carbon by one or more **R**^{16}; wherein **R**^{16} is independently selected from hydroxy, carboxy and *N,N*-dimethylamino.

Particularly the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from hydrogen, bromo, methoxy, isopropoxy, methylthio, carboxymethylthio, ethylthio, isopropylthio, 2-hydroxyethylthio, 2-(*N,N*-dimethylamino) ethylthio or mesyl.
In another aspect of the invention, more preferably the other of **R**^{4} and **R**^{5} that is not the group of formula **(IA)** is selected from hydrogen, chloro, bromo, methoxy, isopropoxy, methylthio, ethylthio or isopropylthio; wherein that **R**^{4} or **R**^{5} may be optionally substituted on

carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-dimethylamino.

In another aspect of the invention, particularly the other of R^4 and R^5 that is not the group of formula **(IA)** is selected from hydrogen, chloro, bromo, methoxy, isopropoxy, methylthio, carboxymethylthio, ethylthio, isopropylthio, 2-hydroxyethylthio or 2-(*N,N*-dimethylamino) ethylthio.

In another aspect of the invention, more particularly the other of R^4 and R^5 that is not the group of formula **(IA)** is bromo or chloro.
In another aspect of the invention, more particularly the other of R^4 and R^5 that is not the group of formula **(IA)** is methoxy.

In one aspect of the invention, preferably **Ring A** is aryl.
In another aspect of the invention, preferably **Ring A** is heteroaryl.
When **Ring A** is aryl, preferably **Ring A** is phenyl.
When **Ring A** is heteroaryl, preferably **Ring A** is thienyl or indolyl.
Preferably **Ring A** is aryl or heteroaryl; wherein **Ring A** is optionally substituted by one or more substituents selected from R^{17}; wherein R^{17} is selected from halo, hydroxy or Cl 4alkyl; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein R^{21} is selected from halo.
Preferably **X** is-O.

More preferably **Ring A** is phenyl, thienyl or indolyl; wherein **Ring A** is optionally substituted by one or more substituents selected from halo, hydroxy or trifluoromethyl.
Particularly **Ring A** is selected from phenyl, 4-hydroxyphenyl, thien-2-yl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 2-fluorophenyl, 2,3-dihydroxyphenyl or indol-3-yl.
More particularly **Ring A** is phenyl.

In another aspect of the invention, preferably **Ring A** is aryl or heteroaryl; wherein **Ring A** is optionally substituted by one or more substituents selected from R^{17}; wherein R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein R^{21} is selected from halo.

In another aspect of the invention, more preferably **Ring A** is phenyl, thienyl or indolyl; wherein **Ring A** is optionally substituted by one or more substituents selected from halo, hydroxy, methoxy or trifluoromethyl.

In another aspect of the invention, particularly **Ring A** is selected from phenyl, 4-hydroxyphenyl, 4-methoxyphenyl, thien-2-yl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 2-fluorophenyl, 2,3-dihydroxyphenyl or indol-3-yl.

In a further aspect of the invention, particularly **Ring A** is selected from phenyl, 4-hydroxyphenyl, 4-methoxyphenyl, thien-2-yl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 2,3-dihydroxyphenyl or indol-3-yl.

Preferably $\mathbf{R^7}$ is hydrogen, C_{1-4}alkyl or carbocyclyl.

More preferably $\mathbf{R^7}$ is hydrogen, methyl or phenyl.

Particularly $\mathbf{R^7}$ is hydrogen.

In one aspect of the invention, preferably $\mathbf{R^8}$ is hydrogen.

In another aspect of the invention, preferably $\mathbf{R^8}$ is C_{1-4}alkyl.

In another aspect of the invention, more preferably $\mathbf{R^8}$ is hydrogen or methyl.

In one aspect of the invention, preferably $\mathbf{R^9}$ is hydrogen.

In another aspect of the invention, preferably $\mathbf{R^9}$ is C_{1-4}alkyl.

In another aspect of the invention, more preferably $\mathbf{R^9}$ is hydrogen or methyl.

Preferably $\mathbf{R^{10}}$ is hydrogen.

In one aspect of the invention, preferably $\mathbf{R^{11}}$ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P (O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c) (R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl.

In another aspect of the invention, preferably $\mathbf{R^{11}}$ is a group of formula **(IB)** (as depicted above).

Preferably $\mathbf{R^{11}}$ is carboxy, -P(O)(OH)(OR^c) or a group of formula **(IB)** (as depicted above).

More preferably $\mathbf{R^{11}}$ is carboxy, -P(O)(OH)(OEt) or a group of formula **(IB)** (as depicted above).

In another aspect of the invention, preferably $\mathbf{R^{11}}$ is carboxy, sulpho, -P(O)(OH)(OR^c) wherein R^c is selected from C_{1-4}alkyl or a group of formula **(IB)** (as depicted above).

Preferably Y is -NH- or -NHC (O)-.

More preferably Y is -NHC (O)-.

In one aspect of the invention, preferably $\mathbf{R^{12}}$ is hydrogen.

In another aspect of the invention, preferably $\mathbf{R^{12}}$ is C_{1-4}alkyl.

In another aspect of the invention, more preferably $\mathbf{R^{12}}$ is hydrogen or methyl.

Preferably R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy.
More preferably R^{13} is hydrogen, methyl or phenyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy.
Particularly R^{13} is hydrogen, hydroxymethyl or phenyl.
More particularly R^{13} is hydrogen or hydroxymethyl.

In another aspect of the invention, preferably R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, carboxy, carbocyclyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22}; R^{22} is hydroxy.

In another aspect of the invention, more preferably R^{13} is hydrogen, methyl, ethyl, butyl or phenyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, carboxy, phenyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22}; R^{22} is hydroxy.

In another aspect of the invention, particularly R^{13} is hydrogen, hydroxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-hydroxybenzyl or phenyl.

In a further aspect of the invention, preferably R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, carboxy, carbocyclyl, heterocyclyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22}; R^{22} is hydroxy.

In a further aspect of the invention, more preferably R^{13} is hydrogen, methyl, ethyl, butyl or phenyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, carboxy, phenyl, imidazolyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22}; R^{22} is hydroxy.

In a further aspect of the invention, particularly R^{13} is hydrogen, hydroxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-hydroxybenzyl, imidazol-5-ylmethyl or phenyl.

In another further aspect of the invention, preferably R^{13} is hydrogen, C_{1-4}alkyl, carbocyclyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, C_{1-4}alkylS (O) a wherein a is 0, C_{1-4}alkoxy, amino, carbocyclyl,

heterocyclyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22}; R^{22} is selected from hydroxy; and R^{23} is carboxy.

In another further aspect of the invention, more preferably R^{13} is hydrogen, methyl, ethyl, butyl or phenyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, methylthio, methoxy, amino, imidazolyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22}; R^{22} is selected from hydroxy; and R^{23} is carboxy.

In another further aspect of the invention, particularly R^{13} is hydrogen, carboxy, hydroxymethyl, mercaptomethyl, methoxymethyl, methylthiomethyl, 2-methylthioethyl, 4-aminobutyl, 4-hydroxybenzyl, imidazol-5-ylmethyl or phenyl.

In another aspect more particularly R^{13} is methylthiomethyl, methylsulphinylmethyl or methylsulphonylmethyl.

Preferably R^{14} is hydrogen.

In another aspect of the invention, preferably R^{14} is selected from hydrogen, C_{1-4}alkyl or carbocyclyl; wherein said C_{1-4}alkyl or carbocyclyl may be optionally substituted by one or more substituents selected from R^{20}; and R^{20} is hydroxy.
In another aspect of the invention, more preferably R^{14} is selected from hydrogen, methyl or phenyl; wherein said methyl or phenyl may be optionally substituted by one or more substituents selected from R^{20}; and R^{20} is hydroxy.

In another aspect of the invention, particularly R^{14} is hydrogen, phenyl or hydroxymethyl.
Particularly R^{15} is carboxy or sulpho.

In one aspect of the invention, more particularly R^{15} is carboxy.
In another aspect of the invention, more particularly R^{15} is sulpho.

Preferably R^{15} is carboxy, sulpho,-P(O)(OR^e) (OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-4}alkyl.
More preferably R^{15} is carboxy, sulpho, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from methyl or ethyl.
Preferably R^{15} is carboxy, sulpho, -P(O)(OEt)(OEt), -P(O)(OH)(OEt), -P(O)(OH)(Me) or -P (O)(OEt)(Me).

Preferably $\mathbf{R^{15}}$ is carboxy, sulpho, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-4}alkyl or $\mathbf{R^{15}}$ is a group of formula **(IC)** (as depicted above).

More preferably $\mathbf{R^{15}}$ is carboxy, sulpho, phosphono,-P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from methyl or ethyl or $\mathbf{R^{15}}$ is a group of formula **(IC)** (as depicted above).

Preferably $\mathbf{R^{15}}$ is carboxy, sulpho, phosphono, -P(O)(OEt)(OEt), -P (O)(O*t*-Bu)(O*t*-Bu), -P(O)(OH)(OEt), -P (O)(OH)(Me) or -P(O)(OEt)(Me) or $\mathbf{R^{15}}$ is a group of formula **(IC)** (as depicted above).

In one aspect of the invention, preferably $\mathbf{R^{15}}$ is carboxy.
In another aspect of the invention, preferably $\mathbf{R^{15}}$ is sulpho.
In another aspect of the invention, preferably $\mathbf{R^{15}}$ is -P(O)(OH)(OEt).
In another aspect of the invention, preferably $\mathbf{R^{15}}$ is -P(O)(OH)(Me).
In another aspect of the invention, preferably $\mathbf{R^{15}}$ is -P(O)(OEt)(Me).
In one aspect of the invention, preferably $\mathbf{R^{24}}$ is hydrogen.
In another aspect of the invention, preferably $\mathbf{R^{24}}$ is C_{1-4}alkyl.

Preferably $\mathbf{R^{25}}$ is hydrogen.
Preferably $\mathbf{R^{26}}$ is carboxy.

Preferably **p** is 1 or 2; wherein the values of $\mathbf{R^{13}}$ may be the same or different.
In one aspect of the invention, more preferably **p** is 1.
In another aspect of the invention, more preferably **p** is 2; wherein the values of $\mathbf{R^{13}}$ may be the same or different.
In a further aspect of the invention, more preferably **p** is 3; wherein the values of $\mathbf{R^{13}}$ may be the same or different.
In one aspect of the invention, preferably **q** is 0.
In a further aspect of the invention, preferably **q** is 1.
In one aspect of the invention, preferably **r** is 0.
In one aspect of the invention, more preferably **r** is 1.
In another aspect of the invention, more preferably **r** is 2; wherein the values of $\mathbf{R^{14}}$ may be the same or different.

In a further aspect of the invention, more preferably **r** is 3; wherein the values of R^{14} may be the same or different.

Preferably **m** is 0.

In another aspect of the invention, preferably **m** is 0 or 1.

Preferably **n** is 1.

In another aspect of the invention, preferably **n** is 1 or 2.

Preferably **z** is 1.

The group of formula **(IA)** wherein R^7 is hydrogen, methyl or phenyl, **n** is 1, **Ring A** is phenyl, thienyl or indolyl; wherein **Ring A** is optionally substituted by one or more substituents selected from halo, hydroxy or trifluoromethyl, m is 0 and R^9 is carboxy, -P(O)(OH)(OR^c) or a group of formula **(IB)**.

The group of formula **(IA)** wherein: X is -0-.

Ring A is phenyl, thienyl or indolyl; wherein **Ring A** is optionally substituted by one or more substituents selected from halo, hydroxy, methoxy or trifluoromethyl;

R^7 is hydrogen, methyl or phenyl;

R^8 is hydrogen or methyl;

R^9 is hydrogen or methyl;

R^{10} is hydrogen;

m is 0-2 wherein the values of R^{10} may be the same or different; and R^{11} is carboxy, -P(O)(OH)(OEt) or a group of formula **(IB)** (as depicted in claim 1); The group of formula **(IB)** wherein R^{10} is hydrogen, hydroxymethyl or phenyl, **p** is 1 or 2; wherein the values of R^{10} may be the same or different and R^{11} is carboxy or sulpho.

The group of formula **(IB)** wherein:

R^{12} is hydrogen or methyl;

R^{13} is hydrogen, methyl, ethyl, butyl or phenyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; R^{20} is hydroxy, methylthio, methoxy, amino, imidazolyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more hydroxy; R^{23} is carboxy; **Y** is -NH- or -NHC (O)-; R^{14} is selected from hydrogen, methyl or phenyl; wherein said methyl or phenyl may be optionally substituted by one or more substituents selected from hydroxy; R^{15} is carboxy, sulpho, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from methyl or ethyl or R^{15} is a group of formula **(IC)** (as depicted in claim 1);

p is 1-3 wherein the values of R^{13} may be the same or different;

q is 0-1; and

r is 0-3 wherein the values of R^{14} may be the same or different;

The group of formula **(IC)** wherein

R^{24} is hydrogen;

R^{25} is hydrogen;

R^{26} is carboxy; and

z is 1;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in a further aspect of the invention, there is provided a compound of formula **(I)** as depicted above wherein:

R^1 and R^2 are independently selected from ethyl or butyl;

R^3 and R^6 are hydrogen;

R^4 is selected from halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy and *N,N*-(C_{1-4}alkyl)$_2$amino;

R^5 is a group of formula **(IA)**;

Ring A is aryl or heteroaryl; wherein **Ring A** is optionally substituted by one or more substituents selected from R^{17}; wherein

R^{17} is selected from halo, hydroxy or C_{1-4}alkyl; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein

R^{21} is selected from halo;

R^7 is hydrogen, C_{1-4}alkyl or carbocyclyl;

R^{11} is carboxy, -P(O)(OH)(OR^c) or a group of formula **(IB)** (as depicted above);

R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy;

R^{15} is carboxy or sulpho;

p is 1 or 2; wherein the values of R^{13} may be the same or different;

m is 0; and

n is 1;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional aspect of the invention, there is provided a compound of formula **(I)** as depicted above wherein:

R^1 and R^2 are both butyl or one of R^1 and R^2 is ethyl and the other is butyl;

R^4 is methylthio;

R^5 is a group of formula **(IA)** (as depicted above);

R^3 and R^6 are hydrogen;

Ring A is phenyl;

R^7 is hydrogen;

R^{11} is a group of formula **(IB)** (as depicted above);

R^{13} is hydrogen or hydroxymethyl;

R^{15} is carboxy or sulpho;

p is 1 or 2; wherein the values of R^{13} may be the same or different;

m is 0;

n is 1;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional further aspect of the invention, there is provided a compound of formula **(I)** as depicted above wherein:

R^1 and R^2 are independently selected from ethyl or butyl;

R^3 and R^6 are hydrogen;

R^4 is selected from halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy and *N,N*-(C_{1-4}alkyl)$_2$amino;

R^5 is a group of formula **(IA)**;

Ring A is aryl or heteroaryl; wherein **Ring A** is optionally substituted by one or more substituents selected from R^{17};

R^7 is hydrogen, C_{1-4}alkyl or carbocyclyl;

R^8 is hydrogen or methyl;

R^9 is hydrogen or methyl;

R^{11} is carboxy, -P(O)(OH)(OR^c) or a group of formula **(IB)** (as depicted above);

X is -NH- or -NHC(O)-;

R^{12} is hydrogen or methyl;

R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20};

R^{14} is hydrogen;

R^{15} is carboxy or sulpho;

R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21};

R^{20} is hydroxy, carboxy, carbocyclyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22};

R^{21} is selected from halo;

R^{22} is hydroxy;

p is 1-3; wherein the values of R^{13} may be the same or different.

q is 0-1;

r is 0-3; wherein the values of R^{14} may be the same or different; and wherein if q is 1, r is not 0;

m is 0-2; and

n is 1-3;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in another additional further aspect of the invention, there is provided a compound of formula **(I)** as depicted above wherein:

R^1 and R^2 are independently selected from C_{1-4}alkyl;

R^x and R^y are both hydrogen;

R^z is selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkoxycarbonylamino or *N'*-(C_{1-6}alkyl)ureido;

v is 0 or 1;

R^3 and R^6 are hydrogen;

one of R^4 and R^5 is a group of formula **(IA)** (as depicted above) and the other is selected from hydrogen, halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-(C_{1-4}alkyl)2amino;

X is -0-;

R^7 is hydrogen, methyl or phenyl;

R^8 is hydrogen or methyl;

Ring A is aryl or heteroaryl; wherein **Ring A** is optionally substituted by one or more substituents selected from R^{17}; wherein R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein R^{21} is selected from halo;

R^9 is hydrogen or methyl;

R^{10} is hydrogen;

R^{11} is carboxy, -P(O)(OH)(OR^c) wherein R^c is selected from C_{1-4}alkyl or a group of formula **(IB)** (as depicted above);

R^{12} is hydrogen or methyl;

Y is -NH- or -NHC(O)-;

R^{13} is hydrogen, C_{1-4}alkyl, carbocyclyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, C_{1-4}alkylS(O)$_a$ wherein a is 0, C_{1-4}alkoxy, amino, carbocyclyl, heterocyclyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22}; R^{22} is selected from hydroxy; and R^{23} is carboxy;

R^{14} is selected from hydrogen, C_{1-4}alkyl or carbocyclyl; wherein said C_{1-4}alkyl or carbocyclyl may be optionally substituted by one or more substituents selected from **R^{20}**; and **R^{20}** is hydroxy;

R^{15} is carboxy, sulpho, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-4}alkyl or **R^{15}** is a group of formula **(IC)** (as depicted above);

R^{24} is hydrogen;

R^{25} is hydrogen;

R^{26} is carboxy;

p is 1-3; wherein the values of **R^{13}** may be the same or different;

q is 0-1;

r is 0-3; wherein the values of **R^{14}** may be the same or different;

m is 0-2; wherein the values of **R^{10}** may be the same or different;

n is 1-2; wherein the values of **R^7** may be the same or different;

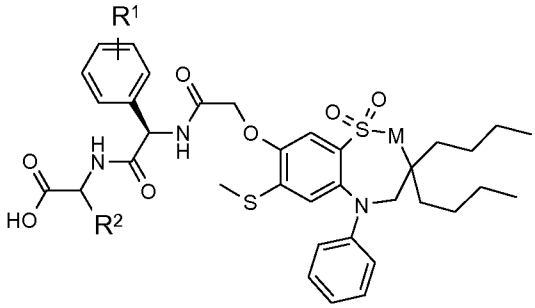
z is 0-1; wherein the values of **R^{25}** may be the same or different;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An aspect of the invention is a compound of formula II



Formula II

wherein

M is CH_2 or NH;

$\mathbf{R^1}$ is H or hydroxy;

$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

for use in the prophylaxis or treatment of a liver disease.

Examples of useful substances in accordance with the invention are:
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl] benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl] benzyl} carbamoylmethoxy)-2,3,4, 5-tetrahydro-1, 5-benzothiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,

1,1-Dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy) -2,3,4,5-tetrahydro-1, 5-benzothiazepine, 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{ (R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine.

Compounds of formula (I) or formula (II) may have chiral centres and/or geometric isomeric centres (E-and Z-isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess IBAT inhibitory activity. The invention relates to any and all tautomeric forms of the compounds of the formula (I) or formula (II) that possess IBAT inhibitory activity.

The invention also relates all possible isomers of the compounds of the invention such as, optical and/or geometrical, pure or as a mixture, in all proportions, of the said compounds of formulas I and II and those specifically mentioned and the possible tautomeric forms

In certain embodiments, compounds described herein have one or more chiral centres. As such, all stereoisomers are envisioned herein. In various embodiments, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds of the present invention encompasses racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein. Preparation of optically active forms is achieve in any suitable manner, including by way of non-limiting example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase. In some embodiments, mixtures of one or more isomer are utilized as the therapeutic compound described herein. In certain embodiments, compounds described herein, contains one or more chiral centres. These compounds are prepared by any means, including enantioselective synthesis and/or separation of a mixture of enantiomers and/or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, chromatography, and the like.

The compounds may exist in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In certain embodiments, a compound described herein exists in an unsolvated or solvated form, wherein solvated forms comprise any pharmaceutically acceptable solvent, e.g., water, ethanol, and the like.

The invention further regards a composition comprising at least one IBAT inhibitor of Formula (I) or Formula (II), for use in the prophylaxis and/or treatment of a liver disease.

An aspect of the invention is the use of a compound of Formula (I) or Formula (II), for the preparation of a medicine for the treatment of a liver disease.

An IBAT inhibitor of Formula I or Formula II) may be used together with at least one other therapeutically active compound as described herein, in the preparation of a medicament for the prophylactic and/or therapeutic treatment of a liver disease.

Liver diseases

Liver disease is herein defined as any Bile Acid (BA) dependent disease in the liver and in organs connected therewith, such as the pancreas portal vein, the liver parenchyma, the intrahepatic biliary tree, the extrahepatic biliary tree, and the gall bladder.
Ileal bile acid transporter (IBAT) is the main mechanism for re-absorption of bile acids from the GI tract. Partial or full blockade of that mechanism will result in lower concentration of bile acids in the small bowel wall, the portal vein, the liver parenchyma, the intrahepatic biliary tree, the extrahepatic biliary tree, and in the gall bladder. Diseases which may benefit from partial or full blockade of the IBAT mechanism may be those having a primary pathophysiological defect, causing or having symptoms of too high concentration of bile acids in serum and in the above organs.

An aspect of the invention is a compound of Formula (I) or Formula (II) as defined above, for use in the prophylaxis or treatment of liver parenchyma; an Inherited metabolic disorder of the liver; Byler syndrome; a primary defect of bile acid (BA) synthesis such as cerebrotendinous, or xanthomatosis; a secondary defect such as Zellweger´s syndrome, neonatal hepatitis, cystic fibrosis, manifestations in the liver, ALGS (Alagilles syndrome), PFIC (progressive familial intrahepatic cholestasis, autoimmune hepatitis, primary biliary cirrhosis (PBC), liver fibrosis, non alcoholic fatty liver disease, NAFLD/NASH, portal hypertension, general cholestasis such as in jaundice due to drugs or during pregnancy, intra

and extrahepatic cholestasis such as hereditary forms of cholestasis such as PFIC1, Primary sclerosing cholangitis, gall stones and choledocholithiasis, malignancy causing obstruction of the biliary tree, symptoms (scratching, pruritus) due to cholestasis/jaundice, pancreatitis, chronic autoimmune liver disease leading to progressive cholestasis, or pruritus of cholestatic liver disease.

An aspect of the invention is a compound of Formula (I) or Formula (II) as defined above, for use in the prophylaxis or treatment of a hepatic disorder or a hepatic related condition, fatty liver, hepatic steatosis, non-alcoholic steatohepatitis (NASH), alcoholic hepatitis, acute fatty liver, fatty liver of pregnancy, drug-induced hepatitis, iron overload disorders, hepatic fibrosis, hepatic cirrhosis, hepatoma, viral hepatitis and problems in relation to tumours and neoplasmas of the liver, of the biliary tract and of the pancreas.

Combination with other active substances

An aspect of the invention is an IBAT inhibitor according to formula (I) or Formula (II) as defined above, in combination with at least one other therapeutically active substance. The at least one other therapeutically active substance may be an IBAT inhibitor compound.

Incretines and hormones produced by the L cells

The at least one other therapeutically active substance may be an Incretine or a hormone produced by the L cells.

In an aspect of the invention, the at least one other therapeutically active substance is a L-cell endocrine peptide enhancer such as a GLP-1 enhancer. Examples of a GLP-1 enhancer useful in accordance with the invention are GLP-1, a GLP-1 secretion enhancer, a GLP-1 degradation inhibitor, or a combination thereof.

In an aspect of the invention, the L-cell endocrine peptide enhancer is a GLP-2 enhancer such as GLP-2, a GLP-2 secretion enhancer, a GLP-2 degradation inhibitor, or a combination thereof.
In an aspect of the invention the L-cell endocrine peptide enhancer is a PYY enhancer such as an oxyntomodulin enhancer.

Incretin Mimetics

In an aspect of the invention, the at least one other therapeutically active substance is an incretin mimetic such as exenatide (Byetta®).

One aspect of the invention is an oral combination of an IBAT inhibitor of Formula (I) or Formula (II) as disclosed herein and a DPP-IV inhibitor.

Enteroendocrine Peptides

In an aspect of the invention, the at least one other therapeutically active substanceis an enteroendocrine peptide such as GLP-1 or GLP-1 analogs, for example Taspoglutide® (Ipsen), or the like.

Combination Therapy with an IBAT inhibitor and a DPP-IV Inhibitor

In an aspect of the invention, the at least one other therapeutically active substance is a DPP-IV inhibitor.

One aspect of the invention is a combination of an IBAT-inhibitor and metformin and/or sitagliptin (Janumet®) and/or DPP-IV inhibitors suitable for use with the methods described herein include but are not limited to (2S)-1-{2-[(3-hydroxy-1-adamantyl)amino]-acetyl}pyrrolidine-2-carbonitrile (vildagliptin), (3R)-3-amino-1-[9-(trifluoromethyl)-1,4,7,8-tetrazabicyclo[4.3.0]nona-6,8- -dien-4-yl]-4-(2,4,5-trifluorophenyl)butan-1-one (sitagliptin), (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[- 3.1.0]hexane-3-carbonitrile (saxagliptin), and 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidi- n-1(2H)-yl}methyl)benzonitrile (alogliptin).

TGR5 Receptor Modulators

In one aspect of the invention, the at least one other therapeutically active substance is a TGR5 agonist. TGR5 modulators (e.g. agonists) include, but are not limited to, the compounds described in WO 2008/091540, WO 2008/067219 and U.S. Appl. No. 2008/0221161.

Thiazolidinediones

In one embodiment of the invention, the at least one other therapeutically active substance is a thiazolidinedione such as Rosiglitazone (Avandia), Pioglitazone (Actos), Troglitazone (Rezulin), MCC-555, rivoglitazone, ciglitazone or the like.

Combination Therapy with an IBAT INHIBITOR, a Biliary Shunt and a DPP-IV Inhibitor

In one embodiment of the invention, an IBAT INHIBITOR of Formula (I) or Formula (II) as described herein, is administered in combination with a DPP-IV inhibitor and/or a biliary shunt. Examples of biliary shunts include but are not limited to shunts described in WO 2007/0050628, which disclosure is incorporated herein by reference.

As used herein, the term "additive effect" describes the combined effect of two (or more) pharmaceutically active agents that is equal to the sum of the effect of each agent given alone. A synergistic effect is one in which the combined effect of two (or more) pharmaceutically active agents is greater than the sum of the effect of each agent given alone. Any suitable combination of an ASBTI with one or more of the aforementioned other active ingredients and optionally with one or more other pharmacologically active substances is contemplated as being within the scope of the methods described herein.

In some embodiments, the particular choice of compounds depends upon the diagnosis of the attending physicians and their judgment of the condition of the individual and the appropriate treatment protocol. The compounds are optionally administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, disorder, or condition, the condition of the individual, and the actual choice of compounds used. In certain instances, the determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is based on an evaluation of the disease being treated and the condition of the individual.

In some embodiments, therapeutically-effective dosages vary when the drugs are used in treatment combinations. Methods for experimentally determining therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens are described in the literature.

In some embodiments of the combination therapies described herein, dosages of the co-

administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the compound provided herein is optionally administered either simultaneously with the biologically active agent(s), or sequentially. In certain instances, if administered sequentially, the attending physician will decide on the appropriate sequence of therapeutic compound described herein in combination with the additional therapeutic agent.

The multiple therapeutic agents (at least one of which is a therapeutic compound described herein) are optionally administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents are optionally provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). In certain instances, one of the therapeutic agents is optionally given in multiple doses. In other instances, both are optionally given as multiple doses. If not simultaneous, the timing between the multiple doses is any suitable timing, e.g., from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations are also envisioned (including two or more compounds described herein).

In certain embodiments, a dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors. These factors include the disorder from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, in various embodiments, the dosage regimen actually employed varies and deviates from the dosage regimens set forth herein.

In some embodiments, the pharmaceutical agents which make up the combination therapy described herein are provided in a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. In certain embodiments, the pharmaceutical agents that make up the combination therapy are administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. In some embodiments, two-step administration regimen calls for sequential administration of the active agents or spaced-apart administration of the separate active agents. In certain embodiments, the time period between the multiple administration steps varies, by way of non-limiting example, from a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent.

The invention also regards IBAT inhibitor compounds described herein in combination with at least one bile acid binder e.g. a resin such as cholestyramine, cholestipol and colesevelam.

Bile acid binders (bile acid sequestrants, resins)

In one embodiment of the invention, an IBAT inhibitor of formula (I) or Formula (II) as defined above, may be administered as a pharmaceutical formulation also comprising at least one bile acid binder, said formulation being designed to deliver the bile acid binder in the colon and the IBAT inhibitor in the small intestine.

Examples of useful bile acid binders according to the invention are Cholestyramine, which is a hydrophilic polyacrylic quaternary ammonium anion exchange resin, known to be effective in reducing blood cholesterol levels. Cholestyramine, and various compositions including cholestyramine, are described, for example, in British Pat Nos. 929,391 and 1,286, 949; and U. S. Patent Nos. 3,383, 281; 3,308, 020; 3,769, 399; 3,846, 541; 3,974, 272; 4,172, 120; 4,252, 790; 4,340, 585; 4,814, 354; 4,874, 744; 4,895, 723; 5,695, 749; and 6,066, 336. Cholestyramine is commercially available from Novopharm, USA Inc (Questrans Light), Upsher-Smith (PREVALITE (D), and Apothecon. As used herein, "cholestyramine" includes any such composition comprising cholestyramine, or pharmaceutically acceptable salts thereof. These are also called Questrans ™
Questran Light Questrans Light (cholestyramine) is a non-absorbable anion binding resin FDA approved for the treatment of hypercholesterolemia.

An amine polymer having a first substituent, bound to a first amine of the amine polymer, that includes a hydrophobic aliphatic moiety, and a second substituent, bound to a second amine of the amine polymer, that includes an aliphatic quaternary amine-containing moiety as described in USP 5,693,675 and 5,607,669.

The salt of an alkylated and cross linked polymer comprising the reaction product of: (a) one or more cross linked polymers, or salts and copolymers thereof having a repeat unit selected from the group consisting of: (NR-CH_2CH_2)n (2) and (NR-CH_2CH_2-NR-CH_2CH_2-NR-CH_2CHOH-CH_2)n (3) where n is a positive integer and each R, independently, is H or a C1-C8 alkyl group; (b) at least one aliphatic alkylating agent, said reaction product characterized in that: (i) at least some of the nitrogen atoms in said repeat units unreacted with said alkylating agent; (ii) less than 10 mol percent of the nitrogen atoms in said repeat units reacting with said alkylating agent forming quaternary ammonium units; and (iii) a fixed

positive charge and one or more counter ions, such as Colesevelam and colesevelam hydrochloride.

Useful bile acid binders in accordance with the invention are resins, such as cholestyramine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

Another useful bile acid binder is a water insoluble non-toxic polymeric amine having a molecular weight in excess of 3,000, having the property of binding at least 30% of the available glycocholic acid within 5 minutes when exposed to an aqueous solution of an equal weight of said acid, having a polymer skeleton inert to digestive enzymes, and having a water content greater than 65% after equilibration with air at 100% relative humidity, e.g., cholestipol described in USP 3,383,281,

In a further aspect of the invention a suitable bile acid binder is one of cholestyramine, cholestipol or colesevelam.

A preferred aspect of the present invention is the use of colesevelam as the bile acid binder.

The compositions of the invention may further comprise statins e.g an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

One embodiment of the invention relates to a combined oral pharmaceutical formulation comprising an IBAT inhibitor compound of formula (I) or Formula (II) as defined above or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, said formulation being designed to deliver the bile acid binder in the colon and the IBAT inhibitor in the small intestine.

One embodiment of the present invention is a pharmaceutical formulation comprising a core of a bile acid binder formulated for release in the colon, surrounded by an outer layer comprising an IBAT inhibitor of formula (I) or Formula (II) as defined above, and formulated for immediate release or for delayed release in the distal jejunum or the proximal ileum.

Statins

In another aspect of the invention, an IBAT inhibitor compound e.g. a compound of formula (I) or formula (II) as defined above or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and (E)-7- [4- (4- fluorophenyl)-6-isopropyl-2- [methyl (methylsulphonyl) amino] pyrimidin-5-yl] (3R, 5S)-3,5- dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is (E)-7- [4- (4- fluorophenyl)-6-isopropyl-2- [methyl (methylsulphonyl) amino] pyrimidin-5-yl] (3R, 5S)-3,5- dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. Other particular statin are rosuvastatin calcium salt and pitavastatin (HMG Co A reductase).

In an additional aspect of the invention, the compound of formula (I) or formula (II) as defined above, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be administered in association with an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and/or a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising a compound of formula (I) or formula (II) as defined above, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An HMG CoA-reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with a compound of formula (I) or formula (II) as defined above, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering.

The composition may further comprise a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof.

A CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22-page 10, line 17 which are incorporated herein by reference.

A cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

MTP (microsomal transfer protein) inhibitor for example those described in Science, 282,751-54, 1998 which are incorporated herein by reference;

A fibric acid derivative; for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;

A nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and niceritrol ;

A phytosterol compound for example stanols ;

Probucol ;

An anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

An antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;

Insulin;

Sulphonylureas including glibenclamide and/or tolbutamide.

Biguanides

In some embodiments, the additional therapeutic agent is a biguanide. In some instances, biguanides reduce blood and/or plasma glucose levels. Examples of biguanides include and are not limited to metformin, buformin, phenformin, proguanil or the like.

Acarbose;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Angiotensin II antagonists

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan,

valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

PPAR alpha and/or gamma and/or delta agonists or a pharmaceutical acceptable salt thereof.

In another aspect of the invention, the IBAT inhibitor compound, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996,39,665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000,43,527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433.

Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3- [4- (2- {4-methanesulphonyloxyphenyl} ethoxy) phenyl] propanoic acid and pharmaceutically acceptable salts thereof.

According to one embodiment the substances of the invention are used together with one or more antidiabetics hypoglycaemic active ingredients, cholesterol absorption inhibitors, PPAR delta agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, polymeric bile acid adsorbents, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP-citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, HM74A receptor agonists, lipase inhibitors, insulins, sulfonylureas, biguanides, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, active ingredients which act on the ATP-dependent potassium channel of the beta cells, glycogen phosphorylase inhibitors, glucagon receptor antagonists, activators of glucokinase, inhibitors of gluconeogenesis, inhibitors of fructose-1,6-bisphosphatase, modulators of glucose transporter 4, inhibitors of glutamine-fructose-6-phosphate amidotransferase, inhibitors of dipeptidylpeptidase IV, inhibitors of 11-beta-hydroxysteroid dehydrogenase 1, inhibitors of protein tyrosine

phosphatase 1B, modulators of the sodium-dependent glucose transporter 1 or 2, modulators of GPR40, inhibitors of hormone-sensitive lipase, inhibitors of acetyl-CoA carboxylase, inhibitors of phosphoenolpyruvate carboxykinase, inhibitors of glycogen synthase kinase-3 beta, inhibitors of protein kinase C beta, endothelin-A receptor antagonists, inhibitors of I kappaB kinase, modulators of the glucocorticoid receptor, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, beta 3 agonists, CB1 receptor antagonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotoninergic and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-beta agonists or amphetamines.

One aspect of the invention is a method for the treatment of a liver disease, whereby an IBAT inhibitor of Formula (I) or Formula (II) as defined above is brought into contact with the distal ileum of an individual in need of such treatment.

In one embodiment of the invention, an IBAT inhibitor of Formula (I) or Formula (II) as defined above, is administered in combination with a second therapeutic agent selected from a DPP-IV inhibitor, a thiazolidinedione, or an analogue thereof, or a TGR5 agonist.

In certain embodiments, IBAT inhibitor compounds described herein are combined with or utilized in combination with one or more of the following therapeutic agents in any combination: insulin, insulin-mimetics, DPP-IV inhibitors, or TGR5 modulators.

Further active substances to be combined with one or more IBAT inhibitors of the invention may be chosen from one or more of the following substances:
Ursodeoxycholic acid; nor-ursodeoxycholic acid; Rifampicin and related rifamycin derivatives as described in US 3,342,810; opiat antagonists such as Naloxone and Naltrexone; serotonin antagonists such as 5-HT3 receptor antagonists and 5 HT2 antagonists, e.g. Trazodone, Nefazodone , Amoxapine, Clozapine; antihistamines such as Brompheniramine, Chlorpheniramine Dimenhydrinate, Diphenhydramine, Doxylamine Loratadine Cetirizine; serotonin reuptake inhibitors such as Citalopram, Dapoxetine, Escitalopram, Fluoxetine, Fluvoxamine, lindalpine, Pparoxetine , Sertraline, Zimelidine; corticosteroids such as glucocorticoids and mineralocorticoids e.g. chosen from Hydrocortisone (Cortisol), Cortisone and acetate, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone,

Betamethasone, Triamcinolone, Beclometasone, Fludrocortisone and acetate, Deoxycorticosterone and acetate (DOCA) Aldosterone.

Examples of PPAR delta agonists are GW-501516 (501516, GSK-516, GW-516, GW-1516;a peroxisome proliferator-activated receptor (PPAR)-delta agonist, and several other compounds developed from GW-501516, including GI-262570, GW-0072, GW-7845 and GW-7647.

According to one embodiment the BAT inhibitor may be combined with one or more of Atreleuton, Eprotirome, Losmapimod, Ezetimibe(SCH58235) Bezafibrate, Fenofibrate, Varespladib, Darapladib, Lomitapide, Implitapide , Rosiglitazone, Dalcetrapib, Anacetrapib, Lorcaserin, Dapagliflozin, Canagliflozin, Sergliflozin ASP-1941 Orlistat, Pioglitazone, Sodelglitazar, Netoglitazone, Indeglitazar, Naveglitazar, Lobeglitazone, Aleglitazar, Bromocriptine, Tesofensine, Monoamine, Alogliptin , Vildagliptin , Saxagliptin , Sitagliptin , Denagliptin , Gemigliptin, Linagliptin , Dutogliptin ,Teneligliptin, LC-150444, Laropiprant extended release niacin, Simvastatin ezetimibe, Rosuvastatin fenofibrate, Rosuvastatin ezetimibe and Atorvastatin ezetimibe.

Combinations with Tredaptive, Vytorin and Certriad may be used.

According to one embodiment the IBAT inhibitor may be combined with one or more of any of the above mentioned other compounds.

According to one embodiment the IBAT inhibitors of the present invention are combined with at least one other active substance selected from dipeptidyl peptidase-IV-inhibitors, PPAR γ agonists, statins and bile acid binders in any combination.

According to one embodiment the IBAT inhibitors of the present invention are combined with at least one DPPIV, at least one PPAR γ agonist, such as Sitagliptin and Pioglitazon.

According to one other embodiment the IBAT inhibitors of the present invention are combined with at least one DPPIV and at least one statin e.g. Sitagliptin and Simvastatin.

Another active substance which may be combined with the IBAT inhibitors of the invention is ursodeoxycholic acid.

According to one embodiment the invention relates to a composition comprising one or more IBAT inhibitors of the invention and cholestyramin and/or colesevelam and/or cholestipol.

According to one embodiment the invention relates to a composition comprising one or more of the compounds of Example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 and cholestyramin and/or colesevelam and/or cholestipol.

According another embodiment the invention relates to a composition comprising one or more of the compounds of 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)-carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 5) and cholestyramin and/or colesevelam and/or cholestipol.

According another embodiment the invention relates to a composition comprising one or more of the compounds of 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 13), and cholestyramin and/or colesevelam and/or cholestipol.

According another embodiment the invention relates to a composition comprising one or more of the compounds of 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 14) and cholestyramin and/or colesevelam and/or cholestipol.

Carriers and excipients

The compositions of the invention may further comprise a pharmaceutically acceptable diluent or carrier.

Pharmaceutical compositions may be formulated as known in the art using one or more physiologically acceptable carriers including, e.g., excipients and depending on the route of administration chosen.

A carrier includes, in some embodiments, a pharmaceutically acceptable excipient and is selected on the basis of compatibility with compounds described herein, such as, compounds of any of Formula I and II, and the release profile properties of the desired dosage form.

Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents.

Pharmaceutical compositions and carriers are described, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. 1975; Liberman, H. A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

A mixture of a compound of Formula I and II and possibly also other active compounds mentioned herein, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients may be formulated into a composition. In certain embodiments, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to an individual having a disease, disorder, or condition to be treated. In specific embodiments, the individual is a human. The compounds described herein are either utilized separately or in combination with one or more additional therapeutic agents.

In certain embodiments, the pharmaceutical formulations described herein are administered to an individual in any manner, including one or more of multiple administration routes, such as, by way of non-limiting example, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes.

The pharmaceutical compositions described herein are formulated as a dosage form. As such, in some embodiments, provided herein does a dosage form comprise a compound described herein, suitable for administration to an individual. In certain embodiments, suitable dosage forms include, by way of non-limiting example, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

The pharmaceutical solid dosage forms described herein optionally include an additional therapeutic compound described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavouring

agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In some aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the formulation of the compound of Formula I-II. In one embodiment, a compound described herein is in the form of a particle and some or all of the particles of the compound are coated. In certain embodiments, some or all of the particles of a compound described herein are microencapsulated. In some embodiments, the particles of the compound described herein are not microencapsulated and are uncoated.

Method of treatment

The invention also regards a method for treatment and/or prophylaxis of a liver disease, in a warm-blooded animal, such as man, in need of such treatment and/or prophylaxis comprising administering an effective amount of a compound or a composition according to the invention to the individual.

A method for treating any of the diseases or conditions described herein in an individual in need of such treatment, may involve administration of pharmaceutical compositions containing at least one IBAT inhibitor described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said individual.

Dosage forms

The pharmaceutical solid dosage forms may optionally include additional therapeutic compounds and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavouring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In some aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the formulation of the compound of Formula I-II. In one embodiment, a compound described herein is in the form of a particle and some or all of the particles of the compound are coated. In certain embodiments, some or all of the particles of a compound described herein are

microencapsulated. In some embodiments, the particles of the compound described herein are not microencapsulated and are uncoated.

An IBAT inhibitor of Formula I and II may be used in the preparation of medicaments for the prophylactic and/or therapeutic treatment of obesity and/or diabetes. A method for treating any of the diseases or conditions described herein in an individual in need of such treatment, involves administration of pharmaceutical compositions containing at least one IBAT inhibitor described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said individual.

A dosage form comprises a matrix that allows for controlled release of an active agent in the distal jejunum, proximal ileum, distal ileum and/or the colon. In some embodiments, a dosage form comprises a polymer that is pH sensitive (e.g., a MMX.TM. matrix from Cosmo Pharmaceuticals) and allows for controlled release of an active agent in the ileum and/or the colon. Examples of such pH sensitive polymers suitable for controlled release include and are not limited to polyacrylic polymers (e.g., anionic polymers of methacrylic acid and/or methacrylic acid esters, e.g., Carbopol.RTM. polymers, (CAS number 9063-87-0;) that comprise acidic groups (e.g., -COOH, $-SO_3H$) and swell in basic pH of the intestine (e.g., pH of about 7 to about 8). In some embodiments, a dosage form suitable for controlled release in the distal ileum comprises microparticulate active agent (e.g., micronized active agent). In some embodiments, a non-enzymatically degrading poly(dl-lactide-co-glycolide) (PLGA) core is suitable for delivery of an IBAT to the distal ileum. In some embodiments, a dosage form comprising an IBAT is coated with an enteric polymer (e.g., Eudragit.RTM. S-100, cas number 25086-15-1), cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, anionic polymers of methacrylic acid, methacrylic acid esters or the like) for site specific delivery to the ileum and/or the colon. In some embodiments, bacterially activated systems are suitable for targeted delivery to the ileum. Examples of micro-flora activated systems include dosage forms comprising pectin, galactomannan, and/or Azo hydrogels and/or glycoside conjugates (e.g., conjugates of D-galactoside, beta -D-xylopyranoside or the like) of the active agent. Examples of gastrointestinal micro-flora enzymes include bacterial glycosidases such as, for example, D-galactosidase, beta-D-glucosidase, alpha-L-arabinofuranosidase, beta-D-xylopyranosidase or the like.

Coated units may be filled into hard gelatine capsules or mixed with tablet excipients, such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives, and be compressed into tablets. The compressed tablet is optionally covered with film-forming agents to obtain a smooth surface of the tablet and further enhance the mechanical stability of the tablet during packaging and transport. Such a tablet coat, which may be applied on a multiple unit tablet or a conventional tablet, may further comprise additives like anti-tacking agents, colorants and pigments or other additives to improve the tablet appearance.

Suitable drugs for the new formulations are IBAT inhibitor compounds such as described in the above-discussed documents, hereby incorporated by references.

The IBAT inhibitor compound could alternatively be a low permeability drug as defined in the Biopharmaceutical Classification System proposed by FDA.

A combination therapy according to the invention should preferably comprise simultaneously, separately or sequentially administration of an IBAT inhibitor compound and a bile acid binder. The IBAT inhibitor could preferably be formulated for ileum delivery and the bile acid binder could preferably be formulation for colon release.

Dosage

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg or 0.01-50 mg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg is employed. In another aspect a daily dose in the rage of 0.02-20 mg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated.
Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100, preferably 1-50 is

envisaged. The daily dose can be administered as a single dose or divided into one, two, three or more unit doses.

A pharmaceutical formulation according to the present invention with a targeted delivery in the gastro intestinal tract provides a reduced systemic exposure, as can be measured by the area under the drug plasma concentration versus time curve (AUC) or 7α-hydroxy-4-cholesten-3-one (C4), while maintaining or even increasing the therapeutic effect, as e.g. measured by serum cholesterol reduction.

A combination therapy comprising an IBAT inhibitor and a bile acid binder comprises preferably a low daily dose of the bile acid binder, such as less than 5 g of a resin, and more preferably less than 2 g. A dosage form with colon release of the bile acid binder could be constructed by any of the above described principles for delayed release formulations.

A combination therapy comprising an IBAT inhibitor and a bile acid binder may comprise a low daily dose of the bile acid binder, such as less than 5 g of a resin, and more preferably less than 4, 3, 2 or less than 1 g. Suitable ranges may be 0,1-5 g, 0.5- 4 g, 1-3 g, 2-4 g, 2-3 g per day. A dosage form with colon release of the bile acid binder could be constructed by any of the above described principles for delayed release formulations.

A tablet may consist of an inner core of 1-1000 mg, e.g. 200-800 mg, 10-400mg, 10-200mg or 20-80 mg acid binder in a colonic delivery formulation and an outer lamina with 1-100 mg, 5-50 mg e.g. 1-20 mg of an IBAT inhibitor.

The daily dose of IBAT inhibitor and /or bile acid binder can be administered as a single dose or divided into one, two, three or more unit doses.

Dosing three times a day with 400 mg of colesevelam in a colonic release formulation will give an adequate binding of bile acids in the colon as the total luminal volume is expected to be about 100 ml, which is in accordance to an accepted pharmacokinetic calculation volume of 250 to 300 ml for the small gut. The daily recommended total dose of colesevelam to block bile acid absorption in total gut of humans is 3750 mg/day.

Kit

Further, the invention relates to a kit comprising compound or a composition according to the invention and possibly also an instruction for use.

According to a further aspect of the present invention there is provided a kit comprising an IBAT inhibitor according to the invention or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an instruction for use.

According to a further aspect of the present invention there is provided a kit comprising an IBAT inhibitor according to the invention or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and any of the above mentioned substances for use in combination, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising: a) an IBAT inhibitor according to the invention or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form ; b) any of the above mentioned substances for use in combination or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and c) container means for containing said first and second dosage forms.

The following contemplated Examples are intended to illustrate, but in no way limit the scope of the invention. All references cited herein are hereby incorporated by reference in their entirety.

The expression "comprising" as used herein should be understood to include, but not be limited to, the stated items.

Example 1

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl] benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 696,89.
This compound is prepared as described in Example 2 of WO3022286.

Example 2

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl] benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, Mw. 709,92.
This compound is prepared as described in Example 2 of WO03106482.

Example 3

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 724,94.

This compound is prepared as described in Example 6 of WO3022286.

Example 4

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 757,01.

This compound is prepared as described in Example 7 of WO3022286.

Example 5

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 740,94.

This compound is prepared as described in Example 29 of WO3022286.

Example 6

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 773,00.

This compound is prepared as described in Example 30 of WO3022286.

Example 7

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 738,97.

This compound is prepared as described in Example 15 of WO3022286.

Example 8

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 756,94.
This compound is prepared as described in Example 26 of WO3022286.

Example 9

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 754,97.
This compound is prepared as described in Example 28 of WO3022286.

Example 10

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 710,91.
This compound is prepared as described in Example 5 of WO3022286.

Example 11

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy) -2,3,4,5-tetrahydro-1,5-benzothiazepine, Mw. 739,95.
This compound is prepared as described in Example 1 of WO3022286.

Example 12

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 726,91.
This compound is prepared as described in Example 11 of WO3022286.

Example 13

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, Mw. 754,97.
This compound is prepared as described in Example 27 of WO3022286.

Example 14

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{ (R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, Mw. 695,90.
This compound is prepared as described in Example 43 of WO0250051.

Example 15

Pharmaceutical effect Mean Inhibitory effect (%)

ISBT Hu HEK Uptake SPA 13203 IBAT HUM Ileal Bile Acid Transporter Human HEK Glycocholic acid Uptake Radiometric - SPA Inhibitor IC50 Mean IC50 (nM) was determined for the compounds of examples 1-14

Test system
Animals
Species Mouse; Strain ApoE knock out; Sub strain C57BL/6; Sex Female; Total No. of animals 70; Body weight range 20 g to 22 g; Supplier Möllegaard's Breeding (Skensved, Denmark); Identification method ID cards (bar code).

Acclimatisation At least one week at the Section of Laboratory; Animal Resource at AstraZeneca; Housing conditions Kept five by five in cages (Makrolon III, 7 dm2) in a room with regulated temperature (22°C), relative humidity (40% to 60%) and a 12/12 hours light/dark cycle. Diet Free access to R3 pellets (Lactamin, Vadstena, Sweden) during the housing and experimental period. Water, free access to tap water during the housing and experimental period.

Bedding Sprinkle bedding of aspen wood (Tapvei, Finland).

Experimental procedures

The animals were orally administered vehicle (n=3) or the compound of Example 14 (0.156 (n=3) , 0.625 (n=3) or 2.5 µmol/kg (n=3)) at 13:00 o'clock on the experimental day. Thirty minutes later, a trace amount of ^{75}SeHCAT (^{75}Se-homo-tauro-cholic acid) (0.1 mCi per 0.1 mL per mouse) was orally given to each mouse. Twenty-four hours after ^{75}SeHCAT administration, the animals were killed by CO2 inhalation. At sacrifice, the gall bladder and the whole intestine were removed, and the faeces during the 24-hour period after ^{75}SeHCAT administration was collected for each mouse. The gamma radioactivities of ^{75}SeHCAT in the faeces and in the gall bladder-intestine were separately counted by 1282 CompuGamma CS Gamma counter (Wallac oy, Turku, Finland). The stability as well as the quantity of the ^{75}SeHCAT administered to each mouse, were controlled with an additional ^{75}SeHCAT aliquot following the same experimental process as other tested samples in the study.

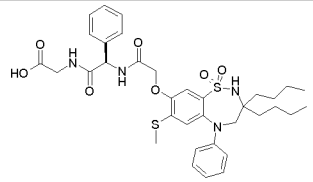
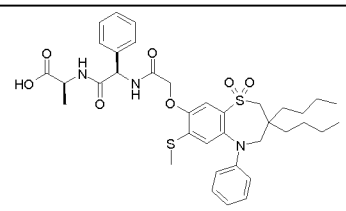
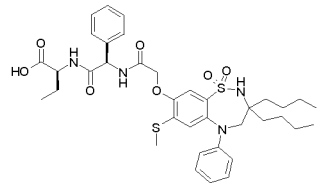
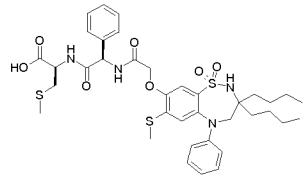
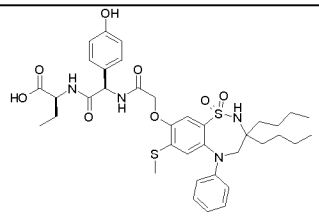
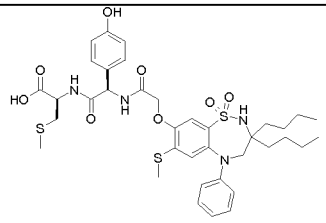
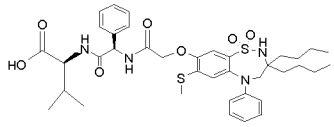
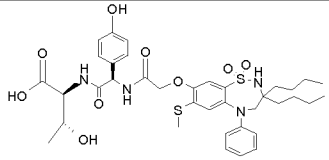
Data analysis

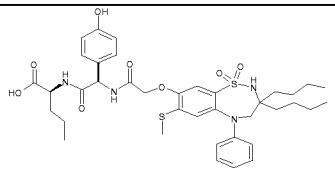
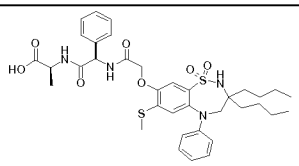
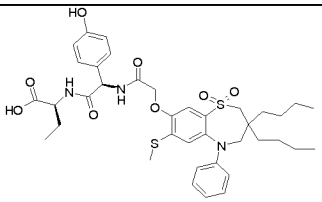
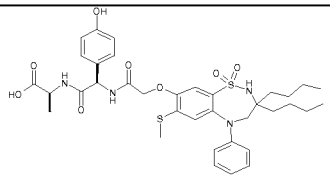
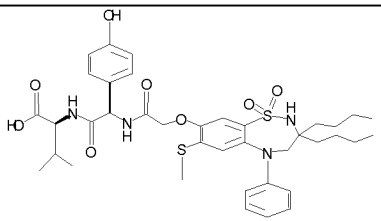
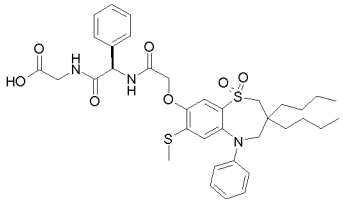
The sum of the gamma counts from both the faeces and the gall bladder-intestine was considered as the total recovered ^{75}SeHCAT, which was averaged around 85% of the total ^{75}SeHCAT administered to each mouse. Of the recovered radioactivity of ^{75}SeHCAT, the percentage of the ^{75}SeHCAT detected in the faeces was considered as the faecal excretion while that in the gall bladder-intestine as body retention. Inhibitory effect of the compound of Example 14 on ^{75}SeHCAT intestinal absorption was calculated following the ^{75}SeHCAT body retention and the faecal excretion, and the ED50 of the compound was estimated following the dose-effect curve.

Results

The mean IBAT inhibitory effect (%) at a dose (µmol/kg): 0.156 was determined for the compounds of examples 1-14 and is reported in Table 1.

Table 1

Example	Structure	% inhibition 0.156 µmol/kg	Mean IC50 nM
1.		43	0,45
2.		55	0,39
3.		63	0,18
4.		63	0,35
5.		74	0,16
6.		59	-
7.		66	0,36
8.		46	0,11

9.		67	-
10.		68	0,2
11.		63	0,15
12.		63	0,3
13.		68	0,13
14.		28	1,2

Example 16

In Vivo Animal Model of Primary sclerosing cholangitis (PSC)

A genetic mice with targeted disruption of the Multidrug resistant *Mdr2 (Abcb4)* gene encoding a canalicular phospholipid flippase (*Mdr2 –/–* mice) spontaneously develop sclerosing cholangitis with macroscopic and microscopic features of human Primary sclerosing cholangitis. Bile duct injury in these mice is linked to defective biliary phospholipid secretion resulting in an increased concentration of free non-micellar bile acids which

subsequently cause bile duct epithelial cell (cholangiocyte) injury, pericholangitis, periductal fibrosis with ductular proliferation and finally sclerosing cholangitis. Gene expression profiling has revealed remarkable similarities between *Mdr2 –/–* and human PSC. In analogy to the *Mdr2– /–* mouse model of sclerosing cholangitis, Multidrug resistant protein *MDR3/ABCB4* (the human orthologue of rodent *Mdr2/Abcb4)* defects play a role in the pathogenesis of various cholangiopathies in humans. *MDR3* variants play a role as a modifier gene in the pathogenesis of various cholangiopathies such as PSC, Primary Biliary cirrhosis (PBC) and adulthood idiopathic ductopenia/ biliary fibrosis.

Mdr2 –/– mice were given daily oral doses of the compound of Example 14 by gavage for 2-4 weeks and controls were dosed the vehicle in the same way. Serum liver tests, liver histology and fibrosis were investigated. The compound of Example 14 improves liver tests, liver histology and fibrosis.

Example 17

A formulation for delayed release of the IBAT inhibitor having the following composition is be prepared:

Substance	amount/capsule (mg)
IBAT inhibitor compound Example 14	10
Non pareil spheres	500
Ethyl cellulose	2
Hydroxypropylmethyl cellulose	10
Eudragit L100-55 , CAS No: 25212 – 88 – 8	25
Triethylcitrate	2.4

The IBAT inhibitor compound of Example 14 is dissolved together with ethyl cellulose and hydroxypropyl cellulose in ethanol 99 %. The mixture is then sprayed onto the non-pareil spheres in a fluidized bed apparatus. Thereafter, the pellets are dried and aerated to remove residual ethanol. The Eudragit L100-55 dispersion with addition of triethyl citrate is then

sprayed onto the drug beads in a fluidized bed apparatus. Subsequently, the coated beads are filled in hard gelatine capsules after drying and sieving.

Example 18

A formulation for delayed release of the IBAT inhibitor having the following composition is prepared:

Ingredient	amount/tablet (mg)
IBAT inhibitor compound Example 14	10
Silicon dioxide	200
Povidone K-25	20
Eudragit FS30D, CAS no: 26936 – 24 – 3	30
Microcrystalline cellulose	250
Sodium stearyl fumarate	5

The IBAT inhibitor compound of Example 14is suspended in water and sprayed onto silicon dioxide cores of a predefined size in a fluidized bed apparatus. The drug pellets are dried in an oven at 40°C for 24 h. Thereafter, a layer of Povidone K-25 is applied on the beads from an ethanolic solution in a fluidized bed apparatus. A final coat of Eudragit FS30D dispersion is applied thereafter in a fluidized bed. The coated beads are mixed with microcrystalline cellulose and sodium stearyl fumarate in a mixer and subsequently compressed to tablets.

Example 19

An IBAT inhibitor – colesevelam combination tablet with immediate release of the IBAT inhibitor and colon release of the bile acid binder having the following composition is prepared:

Ingredient	amount/tablet (mg)
Core	
Colesevelam hydrochloride	400
Microcrystalline cellulose	150
Hydroxypropyl methyl cellulose	50

Colloidal silicon dioxide	10
Magnesium stearate	5
Colon release layer	
Eudragit FS30D	60
PlasACRYL T20, CAS no 123-94-4	6
IBAT inhibitor layer	
IBAT inhibitor Example 14	7
Hydroxypropylmethyl cellulose	12
Croscarmellose sodium	6
Protective coating	
Hydroxypropylmethyl cellulose	12
Polyethylene glycol	2

Colesevelam hydrochloride, microcrystalline cellulose and colloidal silicon dioxide are mixed and granulated with hydroxypropyl methyl cellulose dissolved in water. The granules are dried and mixed with magnesium stearate and compressed to tablets. The EUDRAGIT FS30D dispersion and water are stirred into the PlasACRYL T20 and sprayed onto the core tablets using a suitable coating machine. The IBAT inhibitor coating suspension is prepared by mixing the IBAT inhibitor, hydroxypropyl methyl cellulose and croscarmellose sodium in water and sprayed onto the tablet cores with the colon release layer using a suitable coating machine. Finally the protective coating solution of hydroxypropylmethyl cellulose and polyethylene glycol are sprayed onto the tablets using a suitable coating machine.

Example 20

A Colesevelam colon release tablet having the following composition is prepared:

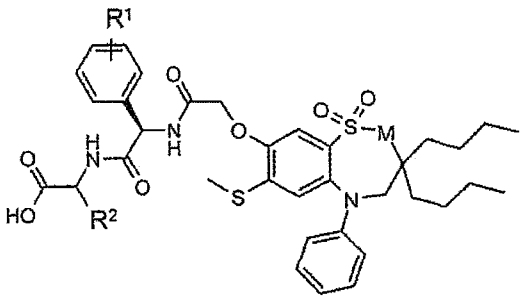
Ingredient	amount /tablet (mg)
Core	
Colesevelam hydrochloride	400
Microcrystalline cellulose	150
Hydroxypropyl methyl cellulose	50
Colloidal silicon dioxide	10
Magnesium stearate	5
Colon release layer	
Amylose	30
Eudragit S100	60

Triethylcitrate	6
Glycerolmonostearate	3

Colesevelam hydrochloride, microcrystalline cellulose and colloidal silicon dioxide are mixed and granulated with hydroxypropyl methyl cellulose dissolved in water. The granules are dried and mixed with magnesium stearate and compressed to tablets. Amylose, Eudragit 100, triethylcitrate and glycerolmonosterate are dissolved in suitable solvents and sprayed onto the tablet cores using a suitable coating machine.

CLAIMS

1. Use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;
R^1 is H or hydroxy;
R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;
or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

2. Use according to claim 1, wherein the compound of formula II is selected from the group consisting of:

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxyethyl) carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- (N-{(R)-α-[N'-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1, 5-benzothiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{ (R)-1'-phenyl-1'-[N'-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

or a pharmaceutically acceptable salt thereof.

3. Use according to claim 1 or 2, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, or a pharmaceutically acceptable salt thereof.

4. Use according to claim 1 or 2, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl]methyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, or a pharmaceutically acceptable salt thereof.

5. Use according to any one of claims 1 to 4, wherein the liver disease is Alagille syndrome (ALGS).

6. Use according to any one of claims 1 to 4, wherein the liver disease is progressive familial intrahepatic cholestasis (PFIC).

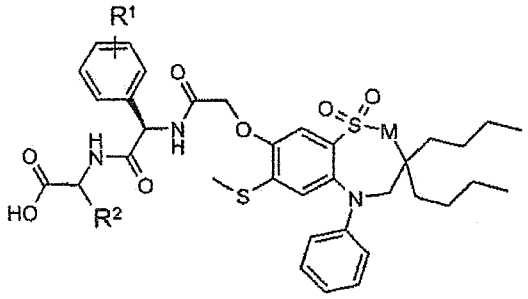
7. Use according to any one of claims 1 to 4, wherein the liver disease is primary biliary cirrhosis (PBC).

8. Use according to any one of claims 1 to 4, wherein the liver disease is primary sclerosing cholangitis (PSC).

9. Use according to any one of claims 1 to 4, wherein the liver disease is non-alcoholic steatohepatitis (NASH).

10. Use according to any one of claims 1 to 4, wherein the liver disease is pruritus of cholestatic liver disease.

11. Use of a pharmaceutical composition comprising a compound of Formula (II)



Formula II

wherein

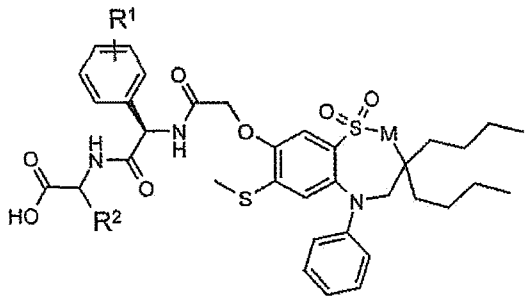
M is CH_2 or NH;
$\mathbf{R^1}$ is H or hydroxy;
$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;
or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

12. Use according to claim 11, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, or a pharmaceutically acceptable salt thereof.

13. Use according to claim 11, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl]methyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, or a pharmaceutically acceptable salt thereof.

14. Use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;

$\mathbf{R^1}$ is H or hydroxy;

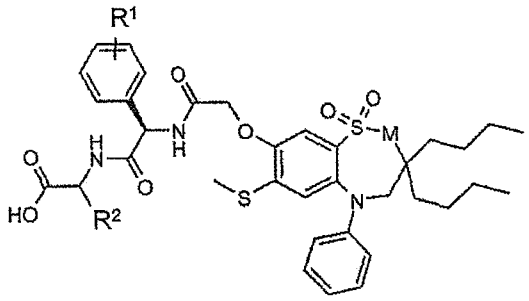
$\mathbf{R^2}$ is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;

or a pharmaceutically acceptable salt thereof;

and ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

15. Use of a compound of formula II



Formula II

wherein

M is CH_2 or NH;
R^1 is H or hydroxy;
R^2 is H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2SCH_3$;
or a pharmaceutically acceptable salt thereof,

and nor-ursodeoxycholic acid,

in the manufacture of a combination for simultaneous or sequential administration in the prophylaxis and/or treatment of a liver disease selected from the group consisting of Alagilles syndrome (ALGS), progressive familial intrahepatic cholestasis, (PFIC), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

16. Use according to claim 14 or 15, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, or a *pharmaceutically acceptable salt thereof.*

17. Use according to claim 14 or 15, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl]methyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, or a pharmaceutically acceptable salt thereof.