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(54) **Title:**
A PHARMACEUTICAL COMBINATION COMPRISING AN IBAT INHIBITOR AND A BILE ACID BINDER

(57) **Abstract:**
The present invention relates to a combination comprising a substance with inhibiting effect on the ileal bile acid transport system (I BAT) and at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; wherein the IBAT inhibitor compound and the at least one other active substance are administered simultaneously, sequentially or separately.

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(54) **Title**: A PHARMACEUTICAL COMBINATION COMPRISING AN IBAT INHIBITOR AND A BILE ACID BINDER

(57) **Abstract**: The present invention relates to a combination comprising a substance with inhibiting effect on the ileal bile acid transport system (I BAT) and at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; wherein the IBAT inhibitor compound and the at least one other active substance are administered simultaneously, sequentially or separately.

A PHARMACEUTICAL COMBINATION COMPRISING AN IBAT INHIBITOR AND A BILE ACID BINDER

FIELD OF THE INVENTION

The present invention relates to a combination comprising a substance with inhibiting effect on the ileal bile acid transport system (IBAT) and at least one other active substance such as a bile acid binder.

BACKGROUND OF THE INVENTION

It is well known that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly artherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve for instance treatment with HMG-CoA reductase inhibitors, preferably statins such as simvastin and fluvastin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine, cholestipol and colesevelam. One recently proposed therapy involves the treatment with substances with inhibiting effect on the ileal bile acid transport system (IBAT).

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process, which mainly takes place in the ileum by an active transport mechanism called ileal bile acid transport (IBAT). Inhibitors of IBAT can be used in the treatment of hypercholesterolemia. See for instance “Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties”, Biochemica et Biophysica Acta, 1210 (1994) 255 - 287. Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidemic conditions.

Several chemical compounds possessing such IBAT activity have recently been described, see for instance hypolipidemic benzothiazepine compounds described in WO 93/16055 and WO 96/16051; condensed 1,4-thiazepines described in WO 94/18183;

different heterocyclic compounds described in WO 94/18184; and 1,4-benzothiazepine-1,1-dioxides described in WO 96/05188. Further; WO 96/08484; bile acid resorption inhibitors described in WO 97/33882, WO 98/07449, WO 98/03818, WO 98/40375, WO 99/35135, WO 9964409, , WO 99/64410, WO 00/01687, WO 00/47568, WO00/61568, DE 19825804, WO 00/38725, WO0038726, WO 00/38727, WO00/38728, WO00/38729, WO01/68096, WO 01/66533, WO 02/50051, WO 02/32428, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, WO 03/061663, WO 03/091232, WO 03/09106482, WO 04/006899, WO 04/076430, WO 07/009655,WO 07009656, WO 08/058630, EP 864582, EP 489423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 624 596, EP 0864582, EP 1173205.

In general, pharmaceutical drug substances will be absorbed in the upper small intestine, and therefore only a small amount will reach ileum when administered in a conventional oral dosage form. Irrespective of the construction of the pharmaceutical dosage form, it should provide contact for the active compound, e.g. inhibitor of IBAT, with the compound´s site of action in the body, for example in the ileum. The above prior art documents discuss in general terms suitable pharmaceutical dosage forms for the described IBAT inhibitor compounds. However, none of the documents describe a specific way to obtain a release of the active substance directly to or close to the site of action. Contact between the active drug and the site of action can be established in different ways.

The inhibition of the re-absorption of bile acids from the small intestine performed by an effective IBAT inhibitor may lead to increased levels of bile acids in the lower parts (colon) of the gastro-intestinal tract. Such an increase of bile acid concentrations in the distal regions could potentially generate diarrhoea and discomfort to the patient. The present invention provides a new approach to minimise the concentration of free bile acids in the colon and thereby reduce the potential risk of adverse events by co-administration of a bile acid binder together with the IBAT inhibitor. However, the combination of an IBAT inhibitor and a bile acid binder has previously been proposed in the above patent applications describing new IBAT inhibitor compounds. The purpose of such previously described combinations has been to enhance the cholesterol lowering efficacy of the therapy. EP1173205 describes that such a combination could be used to minimise a potential risk for diarrhoea connected with IBAT inhibitor therapy.

BRIEF DESCRIPTION OF THE INVENTION

The aim of the present invention is to provide a combination for simultaneous, separate or sequential administration which combination comprises an IBAT inhibitor and a bile acid binder. Such a combination will protect the patient from any possible side effect caused by excess of bile acids in the colon, such as diarrhoea. If the transport of bile acids is blocked by an IBAT inhibitor the bile acids might be deposited in the colon and induce a secretory diarrhoea as an undesired side effect caused by the treatment with an IBAT inhibitor.

In the provided combination therapy the bile acid binder, for instance a resin such as cholestyramine, cholestipol or colesevelam may be administered in a dosage form with colon release of the bile acid binder. A colon release formulation will provide protection of the bile acid binder to the luminal contents in the more proximal parts of the intestine, where the bile acid concentrations are high. Such a formulation will prevent binding of bile acids to the bile acid binder before the formulation reaches the colon. Thereby, maximal bile acid binding capacity will be obtained in the colon and any possible gastro-intestinal side effects, such as diarrhoea, may be avoided. Thus, any additional amount of bile acid presented in the colon due to the treatment with the IBAT inhibitor compound, would be bound to a bile acid binder, which the bile acid binder is preferably delivered in the colon, thereby any possible side effects such as diarrhoea is avoided and maximal excretion of bile acids will be obtained (IBAT blockade of IBAT will let more bile acids pass to colon where they will be bound to bile acid binders resulting in no passive absorption of bile acids from colon). The release of bile acid binders in colon will decrease the needed dose to archive pharmacological effects from the binder.

A further aspect of the invention is that an increased effect can be achieved by binding the unconjugated bile acids in colon and inhibit the uptake in colon. This leads to a further decrease in bile acid levels and an increase in use of cholesterol for bile acid synthesis, resulting in lower levels of cholesterol in plasma.

Further, the colon stimulating effect of bile acids is limited, which leads to decreases the occurrence of diarrhoea. Moreover, bile acid salts are eluated to a greater extent without affecting the absorption of lipid soluble vitamins A, D, E and K in the small bowel. According to one embodiment an increased efficacy is obtained by using an IBAT inhibitor according to formula (I) or formula (II) including compounds of examples 1-14.

DETAILED DESCRIPTION OF THE INVENTION

An aspect of the present invention is a combination designed to deliver the bile acid binder in the colon and the IBAT inhibitor in the small intestine, said combination being intended for the administration of the IBAT inhibitor and the bile acid binder simultaneously, separately or sequentially.

IBAT inhibitor compounds

Active ingredients suitable as IBAT inhibitor compounds in the present invention are those exhibiting activity when screening for IBAT inhibiting properties. 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.

Suitable examples of such compounds can be found in the references cited above under the heading “background of the invention and prior art.

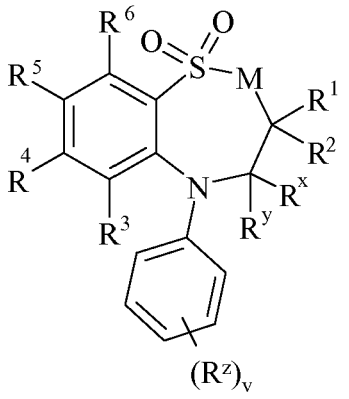
Active ingredients particularly suitable as IBAT inhibitor compounds in the present invention include benzothiazepines, and more particularly benzothiepines, 1,4-benzothiazepines, 1,5-benzothiazepines, 1,2,5-benzothiadiazepines exhibiting activity when screening for IBAT inhibiting properties.

In another aspect of the invention preferred IBAT inhibitors are those in WO 02/50051, WO 03/02286 and WO 03/106482.

Other useful bile IBAT inhibitors are described in WO9932478, WO0168637, WO03022804, WO0001687 and US 2010/0130472 A1 among those 1-[4-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]4-aza-1-azoniabicyclo[2.2.2]octane methane sulfonate.

An aspect of the present invention is a combination comprising

(i) A compound of Formula (I)



(I)

wherein:

M is CH_2, NH

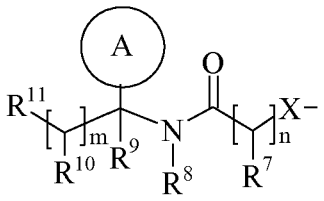
One of $\mathbf{R^1}$ and $\mathbf{R^2}$ are selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl;

$\mathbf{R^x}$ 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};

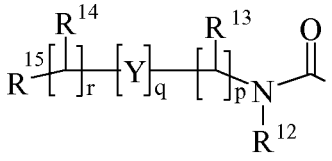
R^7 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18};

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

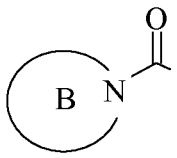
R^9 is hydrogen or C_{1-4}alkyl;

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; and

(ii) at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; or a pharmaceutically acceptable salt of any one of said active substances;

wherein the compound of formula (I) and the at least one other active substance is administered simultaneously, sequentially or separately.

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 selected from "one or more" groups it is to be understood that this definition includes all substituents being selected from one of the specified groups or the substituents being selected 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 selected 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 selected 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 selected 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 selected 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 selected 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 ethylamino-carbonyl. 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}alkoxy-carbonylamino" 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.

A prodrug of any compound mentioned herein as an IBAT inhibitor or a compound for use in combination therewith is a drug which is broken down in the human or animal body to give the compound.

The compounds of the 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-cyclohexyl-carbonyloxyethyl;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 $C_{1\text{-}6}$alkyl.

More preferably $\mathbf{R^x}$ and $\mathbf{R^Y}$ are both hydrogen.

Preferably $\mathbf{R^Z}$ is selected from halo, amino, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxycarbonylamino or *N'*-($C_{1\text{-}6}$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 $\mathbf{R^4}$ is a group of formula **(IA)** (as depicted above).

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

Preferably $\mathbf{R^3}$ and $\mathbf{R^6}$ are hydrogen.

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

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

Particularly the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ 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 $\mathbf{R^4}$ and $\mathbf{R^5}$ 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 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.
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 $\mathbf{R^{17}}$; wherein $\mathbf{R^{17}}$ is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein $\mathbf{R^{17}}$ may be optionally substituted on carbon by one or more $\mathbf{R^{21}}$; wherein $\mathbf{R^{21}}$ 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 $\mathbf{R^{13}}$ is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein $\mathbf{R^{13}}$ is optionally substituted by one or more substituents selected from $\mathbf{R^{20}}$; wherein $\mathbf{R^{20}}$ is hydroxy.
More preferably $\mathbf{R^{13}}$ is hydrogen, methyl or phenyl; wherein $\mathbf{R^{13}}$ is optionally substituted by one or more substituents selected from $\mathbf{R^{20}}$; wherein $\mathbf{R^{20}}$ is hydroxy.
Particularly $\mathbf{R^{13}}$ is hydrogen, hydroxymethyl or phenyl.
More particularly $\mathbf{R^{13}}$ is hydrogen or hydroxymethyl.

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

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

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

In a further aspect of the invention, preferably $\mathbf{R^{13}}$ is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein $\mathbf{R^{13}}$ is optionally substituted by one or more substituents selected from $\mathbf{R^{20}}$; wherein $\mathbf{R^{20}}$ is hydroxy, carboxy, carbocyclyl, heterocyclyl or amino; wherein $\mathbf{R^{20}}$ may be optionally substituted on carbon by one or more $\mathbf{R^{22}}$; $\mathbf{R^{22}}$ 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 $\mathbf{R^{15}}$ is carboxy.
In another aspect of the invention, more particularly $\mathbf{R^{15}}$ is sulpho.

Preferably $\mathbf{R^{15}}$ 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 $\mathbf{R^{15}}$ 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 $\mathbf{R^{15}}$ 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 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 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;

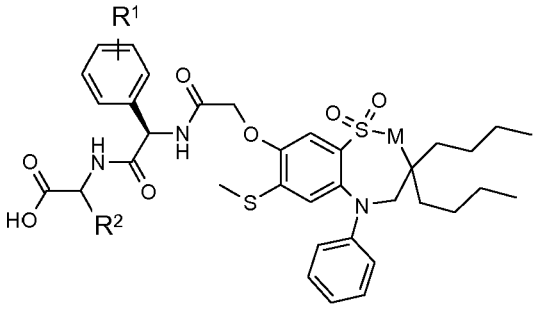
z is 0-1; wherein the values of R^{25} may be the same or different;

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.

An aspect of the present invention is a combination comprising

(i) a compound of formula II



II

wherein

M is $-CH_2$ or NH;

R^1 is H or OH; and

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 $-CH_2CH_2$-S-CH_3; or a

pharmaceutically acceptable salt thereof; and

(ii) at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; or a pharmaceutically acceptable salt of any one of said active substances;

wherein the compound of formula (II) and the at least one other active substance is administered simultaneously, sequentially or separately.

One aspect of the present invention is a combination comprising
a compound selected from
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;

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 of any such compound; and

(ii) at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; or a pharmaceutically acceptable salt of any one of said active substances;

wherein the compound of formula (I) and the at least one other active substance is administered simultaneously, sequentially or separately.

Compounds of the formula (I) 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 (1) 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 is 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.

Compounds for use in combination with an IBAT inhibitor compound of the invention.

Bile acid binders (bile acid sequestrants, resins)

The following bile acid binders may be used according to the invention
Cholestyramine, a hydrophilic polyacrylic quaternary ammonium anion exchange resin, which is 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. 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

Suitable bile acid binders for such a combination therapy 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 cholesterolemia 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, egg, 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.

<u>Other active compounds for use in combination with an IBAT inhibitor compound of the invention.</u>

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, wherein the formulation is designed to deliver the bile acid binder in the colon, with the simultaneous, sequential or separate

administration one or more of the following agents selected from:

Statins

In another aspect of the invention, an IBAT inhibitor compound e.g. a compound of formula (I) or (II) 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 statins are rosuvastatin calcium salt and pitavastatin, (HMG CoA reductase inhibitor).

In an additional aspect of the invention, the compound of formula (I), 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 the compound of formula (I), 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 the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering.

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

The other active compound may be a biguanide, which may lower blood and/or plasma glucose levels. Examples of biguanides include and are not limited to buformin, metformin, 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.

ACE inhibitors

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in

combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

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.

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.

Other useful active substances may be 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.

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 IBAT 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, Exenatide, Liraglutide, Taspoglutide, Tulaglutide, Pramlintide, Lixisenatide, Albiglutide, Pioglitazone, Sodelglitazar, Netoglitazone, Indeglitazar, Naveglitazar, Lobeglitazone, Aleglitazar, Bromocriptine, Tesofensine, 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 inhibitors of the present invention are combined with at least one other active substance selected from dipeptidyl peptidase-IV-inhibitors, statins, PPAR γ agonist, 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 statin e.g. Sitagliptin and Simvastatin and at least one DPPIV.

In certain instances, use of the compounds reduces or inhibits recycling of bile acid salts in the gastrointestinal tract. In some embodiments, the bile transport inhibitors are non-systemic compounds. In other embodiments, the bile acid transporter inhibitors are systemic compounds. In certain embodiments, the bile transport inhibitor s described herein enhance L-cell secretion of enteroendocrine peptides. In certain instances, increased L-cell secretion of enteroendocrine peptides is associated with induction of satiety and/or reduction of food intake (caloric intake) and subsequent weight loss. In some embodiments, increased L-cell secretion of enteroendocrine peptides is associated with a reduction in blood and/or plasma glucose levels in a hyperglycaemic individual. In some instances, increased L-cell secretion of enteroendocrine peptides is associated with increased insulin sensitivity.

Provided herein are methods for treating obesity or diabetes, comprising contacting the distal ileum of an individual in need thereof with an IBAT inhibitor of the invention.

In some embodiments of the methods, contacting the distal ileum of an individual in need thereof with an IBAT inhibitor a. reduces food intake in the individual; b. induces satiety in the individual; c. reduces blood and/or plasma glucose levels in the individual; d. treats a metabolic disorder in the individual; e. reduces the weight of the individual; f. stimulates L-cells in the distal gastrointestinal tract of the individual; g. increases the concentration of bile acids and salts thereof in the vicinity of L-cells in the distal gastrointestinal tract of the individual; h. enhances enteroendocrine peptide secretion in the individual; or i. any combination thereof.

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

In some embodiments, the IBAT inhibitor is not systemically absorbed. In some other embodiments, the IBAT inhibitor is systemically absorbed.

In some embodiments, the methods described above further comprise administration of a second agent selected from a DPP-IV inhibitor, a biguanide, an incretin mimetic, a thiazolidinedione, GLP-1 or an analog thereof, and a TGR5 agonist. In some embodiments, the second agent is a DPP-IV inhibitor.

In some embodiments of the methods, the individual is an obese or morbidly overweight individual. In some embodiments of the methods, the individual is a diabetic individual. In some embodiments of the methods, the individual is a non-diabetic individual.

In some embodiments, provided herein are methods for the treatment of obesity and/or diabetes, comprising administration of a therapeutically effective amount of a combination of an IBAT inhibitor and a DPP-IV inhibitor to an individual in need thereof. In some embodiments, provided herein are methods for the treatment of obesity and/or diabetes, comprising administration of a therapeutically effective amount of a combination of an IBAT inhibitor and a TGR5 agonist to an individual in need thereof. In some embodiments, provided herein are methods for the treatment of obesity and/or diabetes, comprising administration of a therapeutically effective amount of a combination of an IBAT inhibitor and a thiazolidinedione to an individual in need thereof. In some embodiments, provided herein are methods for the treatment of obesity and/or diabetes comprising administration of a therapeutically effective amount of a combination of an IBAT inhibitor and an incretin mimic to an individual in need thereof. In some embodiments, provided herein are methods for the treatment of obesity and/or diabetes, comprising administration of a

therapeutically effective amount of a combination of an IBAT inhibitor and GLP-1 or an analogue thereof to an individual in need thereof. In some embodiments, provided herein are methods for the treatment of obesity and/or diabetes, comprising administration of a therapeutically effective amount of a combination of an IBAT INHIBITOR and a biguanide to an individual in need thereof.

In some embodiments, the methods described herein reduce food intake (caloric intake) in an individual in need thereof. In some embodiments, the methods described herein induce satiety in an individual in need thereof. In some embodiments, the methods described herein treat metabolic disorders in an individual in need thereof. In some embodiments, the methods described herein reduce the weight of an individual in need thereof. In some embodiments, the methods described herein stimulate L-cells in the distal gastrointestinal tract of an individual in need thereof. In some embodiments, the methods described herein increase the concentration of bile acid and salts thereof in the vicinity of L-cells in the distal gastrointestinal tract of an individual.

Provided herein are methods for reducing food intake in an individual in need thereof comprising administration of an IBAT inhibitor to an individual in need thereof wherein the IBAT inhibitor is delivered or released non-systemically in the distal ileum of the individual.

Provided herein are methods for reducing circulating blood or plasma glucose levels in an individual in need thereof comprising administration of an IBAT inhibitor to an individual in need thereof wherein the IBAT inhibitor is delivered or released non-systemically in the distal ileum of the individual.

Provided herein are methods for increasing insulin secretion in an individual in need thereof comprising administration of an IBAT inhibitor to an individual in need thereof wherein the IBAT inhibitor is delivered or released non-systemically in the distal ileum of the individual.

In some embodiments, the methods described herein enhance enteroendocrine peptide secretion in an individual in need thereof. In some of such embodiments, the enteroendocrine peptide is GLP-1, GLP-2, PYY, oxyntomodulin, or a combination thereof.

In some embodiments, contacting the distal ileum of an individual in need thereof with an IBAT inhibitor increases the level of GLP-1 in the blood and/or plasma of the individual by from about 2 times to about 6 times the level of GLP-1 in the blood and/or plasma of the individual prior to contacting the distal ileum of the individual with the IBAT inhibitor.

In some embodiments, contacting the distal ileum of an individual in need thereof with an IBAT inhibitor reduces the level of glucose in the blood and/or plasma of the individual by at least 30% compared to the level of glucose in the blood and/or plasma of the individual prior to contacting the distal ileum of the individual with the IBAT inhibitor.

In some embodiments, contacting the distal ileum of an individual in need thereof with an IBAT inhibitor maintains reduced blood and/or plasma glucose levels in the individual for at least 24 hours compared to blood and/or plasma glucose levels in the individual prior to contacting the distal ileum of the individual with the IBAT inhibitor.

In some embodiments, the IBAT inhibitor is administered orally. In some embodiments, the IBAT inhibitor is administered as an ileal-pH sensitive release formulation that delivers the IBAT inhibitor to the distal ileum and/or colon and/or rectum of an individual. In some embodiments, the IBAT inhibitor is administered as an enterically coated formulation.

In some embodiments of the methods described above, the IBAT inhibitor is a compound of Formula I as described herein. In some embodiments of the methods described above, the IBAT inhibitor is a compound of Formula II as described herein.

In some embodiments of the methods described above, the IBAT inhibitor is administered before ingestion of food. In some embodiments of the methods described above, the IBAT inhibitor is administered less than about 60 minutes before ingestion of food. In some embodiments of the methods described above, the IBAT inhibitor is administered less than about 30 minutes before ingestion of food. In some embodiments of the methods described above, the IBAT inhibitor is administered after ingestion of food.

Provided herein are methods for prevention and/or treatment of congestive heart failure, ventricular dysfunction, toxic hypervolemia, polycystic ovary syndrome, inflammatory bowel disease, impaired bowel integrity, short bowel syndrome, gastritis, peptic ulcer, or irritable bowel disease comprising contacting the distal ileum of an individual in need thereof with an IBAT inhibitor . In some embodiments, the methods further comprise administration of a DPP-IV inhibitor, a TGR5 agonist, a biguanide, an incretin mimetic, or GLP-1 or an analogue thereof. Provided herein are methods for prevention and/or treatment of radiation enteritis, comprising contacting the distal ileum of an individual in need thereof with an IBAT inhibitor. In some embodiments, the methods further comprise administration of a DPP-IV inhibitor, a TGR5 agonist, a biguanide, an incretin mimetic, or GLP-1 or an analogue thereof.

Provided herein are compositions for reducing caloric intake in an individual in need thereof comprising an IBAT inhibitor, and a pharmaceutically acceptable carrier, wherein the IBAT inhibitor is delivered or released non-systemically in the distal ileum of the individual. Provided herein are compositions for reducing circulating blood and/or plasma glucose levels in an individual in need thereof comprising an IBAT inhibitor, and a pharmaceutically acceptable carrier, wherein the IBAT inhibitor is delivered or released non-systemically in the distal ileum of the individual. Provided herein are compositions for increasing insulin secretion in an individual in need thereof comprising an IBAT inhibitor, and a pharmaceutically acceptable carrier, wherein the IBAT inhibitor is delivered or released non-systemically in the distal ileum of the individual. In any of the aforementioned embodiments, the compositions further comprise a DPP-IV inhibitor, a TGR5 agonist, a biguanide, an incretin mimetic, or GLP-1 or an analog thereof.

Provided herein, in some embodiments, are IBAT inhibitor s for reducing food intake (caloric intake) or for reducing circulating blood or plasma glucose levels wherein the IBAT inhibitor is not absorbed systemically following oral administration. In some of such embodiments, the IBAT inhibitor is a compound of Formula I, II, as described herein. In some of such embodiments, the IBAT inhibitor is prevented from being absorbed in the stomach by its presence in a formulation that releases it in the ileum. In some of such embodiments, the IBAT inhibitor is administered in combination with a second therapeutic agent selected from a DPP-IV inhibitor, a biguanide, a thiazolidinedione, an incretin mimetic, GLP-1 or an analogue thereof, or a TGR5 agonist.

All substances mentioned herein including both IBAT inhibitors and other active substances may also be used in the form of pharmaceutically acceptable salts and esters where applicable.

Incretines and hormones produced by the L cells

In one embodiment the other active substances may be Incretines and/or hormones produced by the L cells.

In some embodiments, the additional therapeutic agent is an L-cell endocrine peptide enhancer. In some instances, the L-cell endocrine peptide enhancer is a GLP-1 enhancer. In some embodiments, the GLP-1 enhancer is GLP-1, a GLP-1 secretion enhancer, a GLP-1 degradation inhibitor, the like, or a combination thereof. In certain instances, enhanced GLP-1 concentration provides a reduction in food intake and/or a reduction in

gastric emptying in human subjects.

In some embodiments, the L-cell endocrine peptide enhancer is a GLP-2 enhancer. In certain instances, the GLP-2 enhancer is GLP-2, a GLP-2 secretion enhancer, a GLP-2 degradation inhibitor, the like, or a combination thereof. In certain instances, enhanced GLP-2 secretion inhibits gastric emptying and reduces intestinal permeability. In some instances, enhanced GLP-2 secretion inhibits gastric acid secretion. In some instances, enhanced GLP-2 secretion reduces or prevents inflammation in the gastrointestinal tract (gastrointestinal enteritis). In some instances, enhanced GLP-2 secretion regenerates and/or heals injury to gastrointestinal tissues (e.g., radiation enteritis).

In some instances, the L-cell endocrine peptide enhancer is a PYY enhancer. In some instances, enhanced secretion of PYY provides a reduction in sensation of hunger. In some instances, the L-cell endocrine peptide enhancer is an oxyntomodulin enhancer. In some instances, the enhanced secretion of oxyntomodulin inhibits meal-stimulated gastric secretion.

Incretin Mimetics

In some embodiments, the additional therapeutic agent is an incretin mimetic. In some embodiments, an incretic mimic augments pancreas response to ingestion of food. In some instances, administration of an incretin mimetic in combination with any of the compounds described herein lowers blood and/or plasma glucose levels. Examples of incretin mimetics include and are not limited to exenatide (Byetta.RTM.).

One currently used therapy for the treatment is a subcutaneous injection of exenatide (Byetta.RTM.). In some embodiments, an oral combination of an IBAT inhibitor and a DPP-IV inhibitor is equally or more effective than an injection of exenatide in reducing plasma glucose levels. In some embodiments, an oral combination of an IBAT inhibitor and a DPP-IV inhibitor reduces or eliminates discomfort associated with injections of glucose-lowering medications.

Enteroendocrine Peptides

In some embodiments, the additional therapeutic agent is an enteroendocrine peptide. In some embodiments, enteroendocrine peptides reverse insulin resistance and lower blood and/or plasma glucose levels. Examples of enteroendocrine peptides that are administered as additional therapeutic agents include and are not limited to GLP-1 or

GLP-1 analogs such as Taspoglutide.RTM. (Ipsen), or the like.

Combination Therapy with IBAT inhibitor and DPP-IV Inhibitor

In specific embodiments, the additional therapeutic agent inhibits degradation of L-cell enteroendocrine peptides. In certain embodiments, the additional therapeutic agent is a DPP-IV inhibitor. In certain instances, administration of an IBAT inhibitor to an individual in need thereof enhances the secretion of GLP-1; administration of a DPP-IV inhibitor in combination with the IBAT inhibitor reduces or inhibits degradation of GLP-1 thereby prolonging the therapeutic benefit of enhanced levels of GLP-1. In some embodiments, administration of an IBAT inhibitor reduces weight of an individual. In some embodiments, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor reduces weight of an individual.

Another therapy is a combination of metformin and sitagliptin (Janumet.RTM.). At doses of 0, 3, 30, 100, 300 mg/kg doses of metformin in combination with 30 mg/kg of sitagliption, reductions in plasma glucose concentrations are observed from 3 hours till about 6 hours post-dose. In some embodiments, a combination of an IBAT inhibitor and sitagliptin maintains reduced plasma glucose concentrations for a longer duration of time (e.g., at least 24 hours) compared to a combination of metformin and sitagliptin (about 6 hours). In some instances IBAT inhibitor therapy eliminates side effects associated with metformin therapy and/or DPP-IV inhibitor therapy.

DPP-IV inhibitors suitable for use with the methods described herein include and 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).

In some embodiments of any of the methods described herein, administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor increases the level of GLP-1 in the blood and/or plasma of an individual by from about 1.1 times to about 30 times compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT inhibitor in combination with the DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor increases the level of GLP-1 in

the blood and/or plasma of an individual by from about 1.1 times to about 20 times compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT inhibitor in combination with the DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor increases the level of GLP-1 in the blood and/or plasma of an individual by from about 1.5 times to about 10 times compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT inhibitor in combination with the DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor increases the level of GLP-1 in the blood and/or plasma of an individual by from about 2 times to about 8 times compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT inhibitor in combination with the DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor increases the level of GLP-1 in the blood and/or plasma of an individual by from about 2 times to about 6 times compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT INHIBITOR in combination with the DPP-IV inhibitor. In some instances, an increase in GLP-1 level of from about 2 times to about 3 times following the administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT INHIBITOR in combination with the DPP-IV inhibitor may be used. In some instances, an increase in GLP-1 level of from about 3 times to about 8 times following the administration of an ASBT inhibitor described herein in combination with a DPP-IV inhibitor compared to the level of GLP-1 in the blood and/or plasma of the individual prior to administration of the IBAT inhibitor in combination with a DPP-IV inhibitor may be used.

In certain embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor reduces blood and/or plasma sugar levels by at least 20%, at least 30%, at least 40%, at least 50% at least 60%, at least 70% or at least 80% compared to blood and/or plasma sugar levels prior to administration of the IBAT inhibitor in combination with a DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor reduces blood and/or plasma sugar levels by at least 20% compared to blood and/or plasma sugar levels prior to administration of the IBAT inhibitor in combination with a DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor reduces blood and/or plasma sugar levels by at least 30% compared to blood and/or plasma sugar levels

prior to administration of the IBAT inhibitor in combination with a DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor reduces blood and/or plasma sugar levels by at least 40% compared to blood and/or plasma sugar levels prior to administration of the IBAT INHIBITOR in combination with a DPP-IV inhibitor.

In some embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor reduces blood and/or plasma sugar levels for a longer period of time (e.g., at least 24 hours) compared to reduction in blood and/or plasma sugar levels upon administration of metformin in combination with a DPP-IV inhibitor. In some embodiments of any of the methods described herein, administration of a single dose of an IBAT inhibitor in combination with a DPP-IV inhibitor sustains reduced blood and/or plasma sugar levels for at least 6 hours, at least 12 hours, at least 14 hours, at least 16 hours, at least 18 hours, at least 20 hours, at least 24 hours, at least 30 hours, at least 36 hours or at least 48 hours compared to reduction in blood and/or plasma sugar levels upon administration of a single dose of metformin in combination with a DPP-IV inhibitor.

In some embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor results in higher levels of GLP-1 in blood and/or plasma of an individual compared to levels of GLP-1 in blood and/or plasma of a normal individual. In some embodiments of any of the methods described herein, administration of an IBAT inhibitor in combination with a DPP-IV inhibitor results in higher levels of GLP-1 in blood and/or plasma of an individual compared to levels of GLP-1 in blood and/or plasma of an individual undergoing therapy with metformin and/or a DPP-IV inhibitor.

TGR5 Receptor Modulators

In some instances, the additional therapeutic agent modulates bile acid receptors in the gastrointestinal lumen. In some embodiments, the additional therapeutic agent agonizes or partially agonizes bile acid receptors (e.g., TGR5 receptors or Farnesoid-X receptors) in the gastrointestinal tract. In some embodiments, the additional therapeutic agent is a bile acid analogue. In certain instances the additional therapeutic agent is a TGR5 agonist. In certain instances, administration of a TGR5 agonist in combination with any of the compounds described herein enhances the secretion of enteroendocrine peptides from L-cells. TGR5 modulators (e.g., agonists) include, and are not limited to, the compounds described in, WO 2008/091540, WO 2008/067219 and U.S. Appl. No.

2008/0221161.

Thiazolidinediones

In some embodiments, the additional therapeutic agent is a thiazolidinedione. In some instances thiazolidinediones reverse insulin resistance and lower blood and/or plasma glucose levels. Examples of thiazolidinediones include and are not limited to Rosiglitazone (Avandia), Pioglitazone (Actos), Troglitazone (Rezulin), MCC-555, rivoglitazone, ciglitazone or the like.

Combination Therapy with IBAT I inhibitor, Biliary Shunt and DPP-IV Inhibitor

In some embodiments, an IBAT INHIBITOR is administered in combination with a DPP-IV inhibitor and/or a biliary shunt. Examples of biliary shunts include and are not limited to the shunts described in WO 2007/0050628, the disclosure of biliary shunts described therein is incorporated herein by reference. In some of such embodiments, a biliary shunt moves bile acid to the distal ileum and/or the rectum and/or the colon thereby increasing the concentration of bile acids in the vicinity of L-cells present in the distal portion of the gastrointestinal tract. In some instances such an increase in the concentration of bile acids in the vicinity of L-cells increases the secretion of GLP-1 from L-cells thereby inducing satiety and/or reduction in hunger and/or weight loss and/or reduction in plasma glucose levels or any combination thereof.

An IBAT inhibitor and a second active ingredient are used such that the combination is present in a therapeutically effective amount. That therapeutically effective amount arises from the use of a combination of an IBAT inhibitor and the other active ingredient (e.g., a DPP-IV inhibitor) wherein each is used in a therapeutically effective amount, or by virtue of additive or synergistic effects arising from the combined use, each can also be used in a subclinical therapeutically effective amount, i.e., an amount that, if used alone, provides for reduced effectiveness for the therapeutic purposes noted herein, provided that the combined use is therapeutically effective. In some embodiments, the use of a combination of an IBAT inhibitor and any other active ingredient as described herein encompasses combinations where the IBAT inhibitor or the other active ingredient is present in a therapeutically effective amount, and the other is present in a subclinical therapeutically effective amount, provided that the combined use is therapeutically effective owing to their additive or synergistic effects. 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 ASBIT 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 is 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.

Diseases

One or more of the IBAT inhibitor compounds of the invention possibly together with one or more of any of the mentioned active compounds for use in combination with an IBAT inhibitor compound of the invention may be used in prophylactic of therapeutic treatment of dyslipidemic conditions and disorders such as hyperlipidemia, hypertrigliceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In addition, these compounds are expected to be useful for the prevention and treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocyte, monocytes and/or macrophage infiltrate, intimital thickening, medial thinning, infectious

and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks; gallstones, diarrhoea.

Disorders of fatty acid metabolism and glucose utilization disorders, disorders in which insulin resistance is involved. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith. Particular aspects in this connection are hyperglycaemia, improvement in insulin resistance, improvement in glucose tolerance, protection of the pancreatic beta cells, prevention of macro- and microvascular disorders. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors: high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations, low HDL cholesterol concentration low apoA lipoprotein concentrations high LDL cholesterol concentrations small dense LDL cholesterol particles, high apoB lipoprotein concentrations, desaturation index (e.g. ratio 18:1/18:0n-9, 16:1/16:0 n-7 or 18:1n-9+16:1n-7/16:0 fatty acids). Various other conditions which may be associated with the metabolic syndrome or syndrome X, such as: increased abdominal girth dyslipidemia (e.g. hypertriglyceridemia and/or low HDL) insulin resistance, hypercoagulability, hyperuricemia, microalbuminemia, thromboses, hypercoagulable and prothrombotic states (arterial and venous), high blood pressure, heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy. Hepatic disorders and conditions related thereto, fatty liver, hepatic steatosis, non-alcoholic hepatitis, 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. Skin disorders and conditions and those associated with polyunsaturated fatty acids eczema acne, psoriasis, keloid scar formation or prevention other diseases related to mucous membrane fatty acid composition. Primary hypertriglyceridemia or secondary, hyperlipoproteinemias, apolipoprotein deficiency (e.g. apoCII or apoE deficiency). Diseases or conditions related to neoplastic cellular proliferation, benign or malignant tumours cancer, neoplasia, metastases, carcinogenesis. Diseases or conditions related to neurological, psychiatric or immune disorders or conditions. Other diseases or conditions in which inflammatory reactions or cell differentiation may for example be involved are: atherosclerosis such as, for example (but not restricted thereto), coronary sclerosis including angina pectoris or myocardial infarction, stroke, ischemic stroke and transient ischemic attack (TIA) peripheral occlusive disease, vascular restenosis or reocclusion, chronic inflammatory bowel diseases such as, for example, Crohn's disease and ulcerative colitis, pancreatitis sinusitis, other inflammatory conditions, retinopathy, ischemic retinopathy, adipose cell tumours,

lipomatous carcinomas such as, for example, liposarcomas, solid tumours and neoplasms such as, for example (but not restricted thereto), carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumours, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas etc acute and chronic myeloproliferative disorders and lymphomas, angiogenesis, neurodegenerative disorders, Alzheimer's disease, multiple sclerosis, Parkinson's disease, erythemato-squamous dermatoses such as, for example, psoriasis, acne vulgaris, other skin disorders and dermatological conditions which are modulated by PPAR, eczemas and neurodermatitis, dermatitis such as, for example, seborrheic dermatitis or photodermatitis, keratitis and keratoses such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis, keloids and keloid prophylaxis, warts, including condylomata or condylomata acuminate, human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum, leukoplakia, papular dermatoses such as, for example, lichen planus, skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas, localized benign epidermal tumours such as, for example, keratoderma, epidermal naevi, chilblains, high blood pressure, syndrome X, polycystic ovary syndrome (PCOS), asthma, cystic fibrosis, osteoarthritis, lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis, vasculitis, wasting (cachexia), gout ischemia/reperfusion syndrome, acute respiratory distress syndrome (ARDS), viral diseases and infections, lypodystrophy and lipodystrophic conditions, also for treating adverse drug effects (e.g. after taking medicaments for treating HIV or tumours), myopathies and lipid myopathies (such as carnitine palmitoyltransferase I or II deficiency).

An aspect of the present invention is a combination as herein described, for use in the prophylactic or therapeutic treatment of a liver disease. Examples of liver diseases where a combination as herein described may be useful include 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; 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 and of the biliary tract.

Medicinal and pharmaceutical use of the invention.

According to another feature of the invention there is provided an oral pharmaceutical formulation comprising an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder, wherein the formulation is designed to deliver the bile acid binder in the colon for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided an oral pharmaceutical formulation comprising an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder, and at least one of the above mentioned other active compounds and a bile acid binder of the invention wherein the formulation is designed to deliver the bile acid binder in the colon for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided an oral pharmaceutical formulation comprising an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder, wherein the formulation is designed to deliver the bile acid binder in the colon for use in prophylaxis or treatment of any of the herein mentioned medical indications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided an oral pharmaceutical formulation comprising an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder, and at least one of the above mentioned other active compounds and a bile acid binder of the invention wherein the formulation is designed to deliver the bile acid binder in the colon for use in prophylaxis or treatment of any of the herein mentioned medical indications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided an oral pharmaceutical formulation comprising an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder, wherein the formulation is designed to deliver the bile acid binder in the colon for use in the preparation of a pharmaceutical for use in prophylaxis or treatment of any of the herein mentioned medical indications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided an oral pharmaceutical formulation comprising an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder, and at least one of the above mentioned other active compounds and a bile acid binder of the invention wherein the formulation is designed to deliver the bile acid binder in the colon for use in the preparation of a pharmaceutical for use in prophylaxis or treatment of any of the herein mentioned medical indications in a warm-blooded animal, such as man.

In an additional feature of the invention, there is provided a method of treating any of the herein mentioned medical conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof f in simultaneous, sequential or separate administration with an effective amount of a bile acid binder.

In an additional feature of the invention, there is provided a method of treating any of the herein mentioned medical conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an IBAT inhibitor compound or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and at least one of the above mentioned other active compounds in simultaneous, sequential or separate administration with an effective amount of a bile acid binder.

Pharmaceutical formulations

Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including, e.g., excipients and auxiliaries which facilitate processing of the active compounds into preparations which are suitable for pharmaceutical use. In certain embodiments, proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, 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 pharmaceutical composition, as used herein, refers to a mixture of a compound described herein, such as, for example, 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 other excipients. In certain instances, the pharmaceutical composition facilitates administration of the compound to an individual or cell. In certain embodiments of practicing the methods of treatment or use provided herein, 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. As discussed herein, the compounds described herein are either utilized singly 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 or buccal administration routes.

In certain embodiments, a pharmaceutical compositions described herein includes one or more compound described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In some embodiments, the compounds described herein are utilized as an N-oxide. In some situations, a compound described herein exists as tautomers. All tautomers are included within the scope of the compounds presented herein. 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 solvated forms of the compounds presented herein are also considered to be described herein.

According to the invention, the IBAT inhibitor and the bile acid binder may be administered simultaneously, separately or sequentially. According to the invention, the IBAT inhibitor and the bile acid binder may be formulated in separate formulations with the IBAT inhibitor

formulation releasing the drug immediately or delayed in the distal jejunum or the proximal ileum and the bile acid binder formulation releasing the drug in the colon.

According to the invention, the IBAT inhibitor and the bile acid binder may be combined in one formulation with the bile acid binder in the core and formulated for release in the colon and the IBAT inhibitor in a outer layer formulated for immediate release or for delayed release in the distal jejunum or the proximal ileum.

According to one embodiment there is provided a novel dosage regime by administrating an IBAT inhibitor of the invention once a day and a bile acid binder once, twice or three times a day.

According to one embodiment the IBAT inhibitor and the bile acid binder are administrated together once, twice or three times a day.

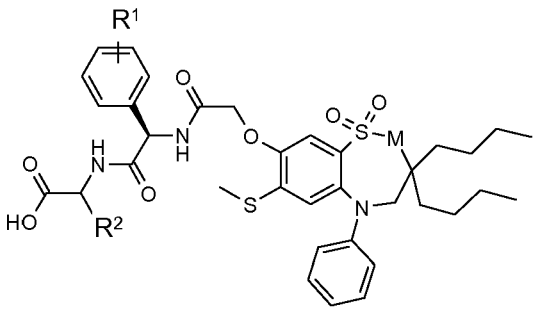
According to one embodiment the IBAT inhibitor is administrated in a formulation releasing it in the small intestine.

According to one embodiment the bile acid binder is administrated in a formulation releasing it in the colon.

An aspect of the present invention is a pharmaceutical combination formulation, comprising

(i) an inner core comprising a bile acid binder;
(ii) a colon release layer onto the core;
(iii) an IBAT inhibitor layer onto said colon release layer; and
(iv) an outer protective coating

In yet an aspect of the invention, the IBAT inhibitor layer comprises a compound of formula II



II

wherein

M is $-CH_2$ or NH;

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

$\mathbf{R^2}$ 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 $-CH_2CH_2$-S-CH_3; or a pharmaceutically acceptable salt thereof.

In the dosage regime or the formulations mentioned above, the acid binder may be colesvelam and the IBAT inhibitor a compound with formula I, II or the 14 Examples below.

Dosage forms with different release regimens can be constructed in different ways for instance as described in the following.

Release in distal jejunum or ileum and/or colon

In certain embodiments, a dosage form comprises a matrix (e.g., a matrix comprising hypermellose) 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.R$^{TM.}$ polymers) 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 inhibitor to the distal ileum. In some embodiments, a dosage form comprising an IBAT inhibitor 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 amylose, 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.

A controlled lag time can be triggered by pH changes, redox potential differences or luminal metabolic changes in the gastro-intestinal tract as described in Aliment Pharmacol Ther 1997, 11 (suppl 3): 109-115. Such a controlled lag time could be obtained for instance by a programmed disintegration of the formulation due to erosion, dissolution or in general by components present in the formulation interacting with the environment in the gastro-intestinal tract. Preferably, the drug release from the dosage form could be triggered by the pH variation between jejunum and ileum.

Alternatively, the drug release from the dosage form can be chronographic controlled to obtain the above specified time limits, such as for instance described in the European Patent Application, Publication No. EP-A-0384642.

According to another aspect of the invention, a sustained release formulation can be constructed by any known principle, such as eroding or non-eroding matrices, membrane-coating layers or by diffusion or osmotically driven drug release. Suitable techniques for the construction of such formulations are for instance described in M. E. Aulton, Pharmaceutics, The science of dosage form design. (1988).

In the present invention an IBAT inhibitor compound is combined with 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 IBAT inhibitor compounds.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyrmine, cholestipol or colesevelam. One advantage is that the dose of bile acid binder might be kept lower than the therapeutical dose for treatment of cholesterolemia 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.

The bile acid binder is administered in a dosage form with colon release, i.e. delivery of the active dose of bile acid binder in the colon. A possible risk of receiving an excess of bile acid in the colon by treatment with an IBAT inhibitor could be avoided by co-

administration of a bile acid binder with colon release. Thus, any excess of bile acid in the colon, with a possible risk to cause diarrhoea, will be bound into a resin. The dose of the bile acid binder could be kept low due to an effective use of the dose by such a colon release. The colon delivery of the bile acid binder can be obtained by a formulation comprising a core containing the bile acid binder and optionally pharmaceutically acceptable excipients, and a coating of said core with a release membrane adapted for colonic delivery. Technologies to obtain such a delivery of drugs to the colon are for example described in Drug development and Industrial Pharmacy 1997, 23: 893-913.

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.

Preparation of core material

The core material for the units, i.e. the tablets or the individual pellets can be constituted

according to different principles. The core material may be homogenous or heterogeneous. The core containing the active principle may be differently formulated such as monolithic tablets, capsules, granules, pellets, other particles or crystals.

With a homogenous core material is meant, that it has a homogenous distribution of active substance throughout the core material.

Depending on if the IBAT inhibitor and the bile acid binder are formulated separately or combined, the active substances are optionally mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Such components can be binders, surfactants, lubricants, glidants, fillers, additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

Said core material may be produced either by direct compression of the mixed ingredients, or by granulation of the ingredients followed by compression of the granulated material.

In direct compression, the ingredients are mixed and compressed by using ordinary tabletting equipment.

For the granulation there are numerous alternatives of granulating procedures mentioned in the literature, dry methods like roller compaction (Chilsonator) and wet methods utilizing granulating solutions with and without the addition of binders. A variant of the wet methods is to make a spray-granulation in a fluid bed.

For the wet granulating methods, either organic solvents, aqueous solutions or pure water may be utilized to prepare the granulating solutions. Due to environmental considerations pure water is preferred, if it is possible due to the composition of the mixture.

Homogenous core particles can also be prepared by techniques such as dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, controlled crystallisation, supercritical crystallisation, emulsion solvent evaporation and emulsion solvent extraction.

The core material may also be produced by extrusion/spheronization, balling or compression, utilizing different process equipments.

The size of the formulated core materials is approximately between 2 and 20 mm, preferably between 3 and 15 mm for a tablet preparation, and between 0.001 and 4 mm, preferably between 0.001 and 2 mm for a pellet preparation.

The manufactured core material may be further layered with additional ingredients comprising the active substance and/or be used for further processing.

Alternatively, the core material may be heterogeneous with an inner zone, for instance a seed or sphere, not containing the active substance. A layer comprising the active substance, and optionally pharmaceutically acceptable excipients, surrounds this seed or sphere.

The seed or sphere may be soluble or insoluble. Optionally, the seed or sphere (inner zone) may be coated with an inert layer to prepare a smooth surface before the layer containing active substance is applied onto the seed/sphere.

Insoluble seeds/spheres may comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures. Water-soluble seeds/spheres may comprise different inorganic salts, sugars and other materials, alone or in mixtures. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with the matrix containing the active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Processes for application of release modifying membranes

A release modifying membrane can be applied to the core material, being a monolithic tablet, multiple units or a hard or soft gelatine capsule, by coating or layering procedures in suitable equipment such as coating pans, coating granulators or in a fluidized bed apparatus using water and/or organic solvents for the coating process. Also powder-coating principles may be applied. Another possibility is to apply the coating by microencapsulation techniques such as coacervation, emulisification with subsequent removal of the solvent by extraction or evaporation, ionotropic gelation or congealing.

Such modifying release membranes may be applied on core material comprising the IBAT inhibitor for delivery to the distal small intestine and optionally also be applied to the bile acid binder for delivery to the colon.

Pharmaceutical additives

Modifying release coatings may be obtained by one or more, separately or in compatible combinations of pharmaceutically acceptable ingredients, in amounts carefully titrated to reach the intended release properties. As delayed release coating layer, the following pH sensitive polymers can be applied; e.g. methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s). The coating layer may also be composed of film-forming polymers being sensitive to other luminal components than pH, such as bacterial degradation or a component that has such a sensitivity when it is mixed with another film-forming polymer. Examples of such components providing delayed release to the intended regions are; polymers comprising azo bond(s), polysaccharides such as pectin and its salts, galactomannans, amylose and chondroitin, disulphide polymers and glycosides.

The delayed release coating or an additional coating of the formulation may contain other film-forming polymers being non-sensitive to the luminal conditions for technical reasons or chronographic control of the drug release. Materials to be used for such purpose includes, but are not limited to; sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the coating layer. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the core material.

The coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimized for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

In preparation of tablets, either as monolithic drug containing cores for subsequent coating with a modified release membrane or as a matrix for coated multiple units, additional

ingredients may be needed to obtain suitable technical properties such as binders, disintegrants, bulk agents, glidants, lubricants, and coatings agents without effects on the drug release such as water soluble polymers, anti-tacking agents, colourants, pigments and waxes. Ingredients well known for such usage are for example described in "Handbook of pharmaceutical excipients", 2nd edition, 1994, Pharmaceutical Press, London.

Preparation of final dosage forms

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, colourants 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

A suitable unit dose will vary with respect to the patient's body weight, condition and disease severity. The dose will also depend on if it is to be used for prophylaxis or in the treatment of severe conditions, as well as the route of administration. The daily dose can be administered as a single dose or divided into two or more unit doses. An orally administered daily dose of an IBAT inhibitor is preferably within 0.1 - 5,000 mg, e.g. 0.01-1000 mg, such as 0.1-800 mg more preferable 1 - 500 mg e.g. 100 - 400 mg.

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), 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 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, 50-400 mg, 10-200 mg 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.

The predicted dose to treat constipation with Example 14 is 10 mg/day, as full efficacy in lowering of bile acids in the human body is targeted a total dose of 20 mg/day is predicted to be adequate, which will induce colonic side effects in accordance with table 2. The tablet will consist of an inner core of 400 mg colesevelam in a colonic delivery formulation and an outer lamina with 7 mg of Example 14 or 0.7 mg of Examples 5, 8 or 13 in an immediate release form.

The invention also regards a method of treatment and/or prophylaxis of hypercholesterolaemia, in a warm-blooded animal, such as man, in need of such treatment and/or prophylaxis which comprises administering an effective amount of a composition according to any of claims 1-14.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder.

The invention also regards a kit comprising a an IBAT inhibitor compound, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in the same or separate pharmaceutical formulation and possibly also an instruction for use.

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.

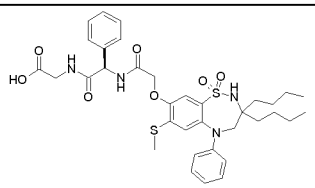
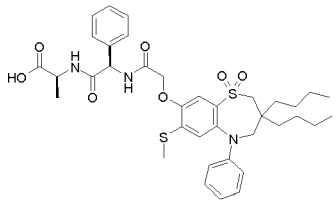
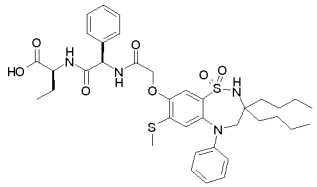
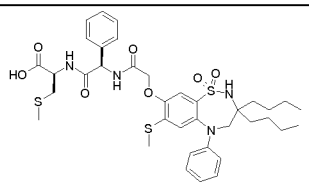
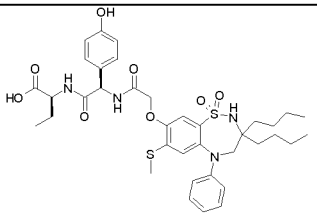
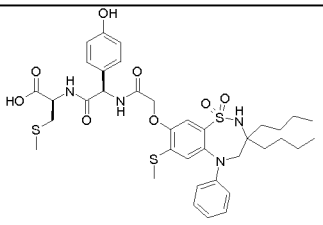
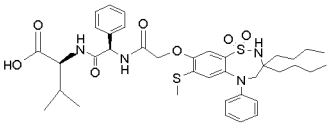
Data analysis

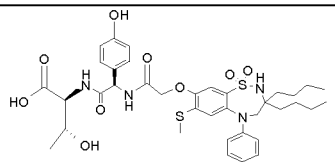
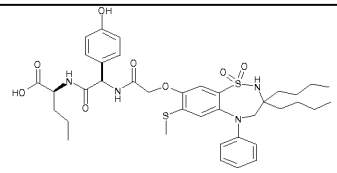
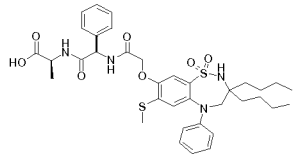
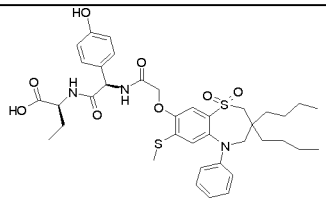
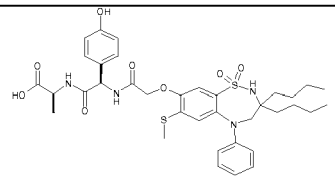
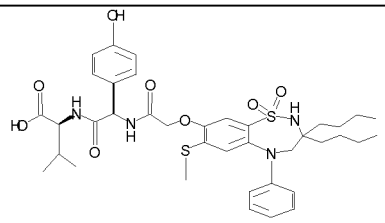
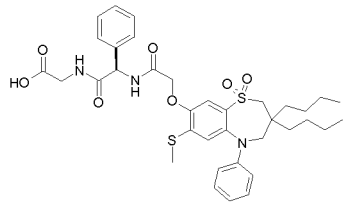
The sum of the gamma counts from both the faeces and the gall bladder-intestine was considered as the total recovered ^{75}SeHCAT, which was averaged around 85% of the total ^{75}SeHCAT administered to each mouse. Of the recovered radioactivity of ^{75}SeHCAT, the percentage of the ^{75}SeHCAT detected 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

A Phase IIb, Double-blind, Randomized, Placebo-controlled, Multi-centre, Dose-finding, Efficacy and Safety Study of a Range of Doses of the compound of Example 14 in about 200 patients with Chronic Idiopathic Constipation, where patients were treated for 56 days, was performed. The patients were males or non-pregnant females ≥20 years of age and ≤80 years of age, having a body mass index (BMI) ≥18.5 but <35.

All patients with adverse events of diarrhea and abdominal pain type related to treatment with the compound of Example 14 are presented in table 2.

Table 2 Number patients with diarrhea and abdominal pain in a treatment study of Chronic idiopathic Constipation

Dose		**Placebo**	**5 mg**	**10 mg**	**15 mg**
Diarrhoea	Number of Patients,(% of Population)	2 (4.3)	4 (8.3)	5 (10.6)	8 (16.7)
Abdominal Pain	Number of Patients,(% of Population)	0 (0.0)	5 (10.4)	5 (10.6)	13 (27.1)

Contradictory patients receiving also colonic delivery of 400mg 3 times a day of "colesevelam" showed little increase in the two bile acid dependent side effects generated from colon.

Thus, the compound of Example 14 in combination with the bile acid binder "colesevelam" turned out to effectively block bile acid side effects generated from the colon.

Example 17

A formulation for delayed release of the IBAT inhibitor having the following composition is 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 active drug 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 into 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 active drug is 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 onto the beads from an ethanolic solution in a fluidized bed apparatus. A final coat of Eudragit FS30D dispersion is thereafter applied 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

A combination tablet comprising an IBAT inhibitor of Formula (I) or Formula (II) as described above, and colesevelam, having an immediate release of the IBAT inhibitor and

colon release of the bile acid binder, 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 of 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 into 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 is 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	
Amylose30	
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.

Example 21

This study is performed in 4 male beagle dogs (weight approximately10 kg). A commercially available diet, Teklad 2021 from Harlan Teklad-Europe, Blackthorn, England, is offered in portions of 175 g per animal twice daily with an equal amount of water added.

The animals are trained in the procedures using a commercially available diet, GLP-Diet from Dechra Veterinary Products, Denmark, as a reward. The amount used per animal is minimal and is not recorded.

On dosing days (Days 1 and 4) the animals are offered 50 g GLP diet during the rectal dosing procedure and the remaining meal (125 g) was given 1 hour after the rectal dosing procedure.

Example 5 substance (30 mg /kg, 5 mL/kg suspension in 20% v/v propylene glycol in purified water) is administered by oral dosing according to the most recent body weight data. All groups receive Example 5 substance orally in combination with rectal administration of cholestyramine or placebo.

Rectal administration of cholestyramin (total 1.2-2.2 g, 12 mL suspension in water) and a placebo formulation (exploration gel) are used in order to comply with the intended human

route of administration. Cholestyramin and placebo is given by rectal catheterisation using a 40 cm flexible plastic tube (unomedical "feeding tube") in order to apply the test substances into the proximal part of colon. Treatment is performed on Day 1 and Day 4

Following each dosing occasion, all animals are continuously monitored for a period of 6 hours. The number of defaecations is counted. Faeces consistency is evaluated using the Bristol Stool form Scale (seven grades scale; lowest 1, separate hard lumps, like nuts (hard to pass); highest 7, watery, no solid pieces, entirety liquid). The amount of passed faeces for each defecation event is scored according to the following grading system: 1-minimal, 2-slight, 3-moderate, 4-marked.

Score data is analysed with the t-test. Significant inter-group differences are detected, the subsequent identification of the groups is carried out with one-sided t-test.-For all tests, the level of significance is defined as $p<0.05$.

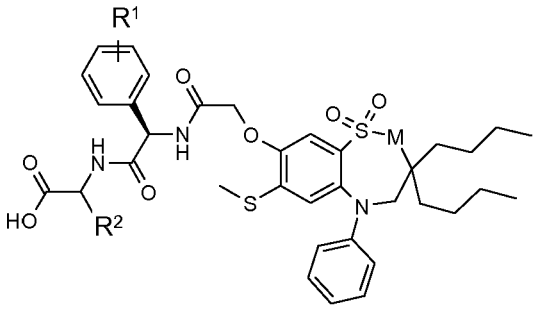
The placebo and cholestyramin groups provide a Bristol Stool form Scale (BSS) mean value of 6.7+-0.3, 5.3+-0.6, (mean+-SEM), respectively. This difference is statistical significant on the significance level $p\leq0.05$. The placebo group has watery faeces, as expected the cholestyramin group has a more solid faeces.

The placebo and cholestyramin group pass the following amount of faeces according to the scale above for each defaecation event and provide a mean value of 3.5+-0.6, 2.3+-0.8, (mean+-SEM), respectively. This difference is not statistical significant on the significance level $p\leq0.05$. The placebo treated group pass more amount of faeces compared with the cholestyramin group, even if not significant. Both parameters BSS and "pass amount of faeces" indicates that the colestyramin group has lower free bile acid concentrations within in colon compared with the placebo group. As bile acids in the colon have a laxative effect this experiment confirms that a colon release of bile acid binders works according to the invention.

CLAIMS

1. A combination comprising

(i) a compound of formula II



II

wherein

M is $-CH_2$ or NH;

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

$\mathbf{R^2}$ 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 $-CH_2CH_2$-S-CH_3; or a pharmaceutically acceptable salt thereof; and

(ii) at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; or a pharmaceutically acceptable salt of any one of said active substances;

wherein the compound of formula (II) and the at least one other active substance is administered simultaneously, sequentially or separately.

2. A combination according to claim 1, wherein the compound of formula (II) and the at least one other active substance are administered simultaneously.

3. A combination according to claim 2, wherein the compound of formula (II) and the at least one other active substance are administered as a fix dosage combination.

4. A combination according to claim 1, wherein the compound of formula (II) and the at least one other active substance are administered sequentially.

5. A combination according to claim 1, wherein the compound of formula (II) and the at least one other active substance are administered separately.

6. A combination according to any one of claims 1-5, wherein the compound of formula (II) is selected from

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.

7. A combination according to any one of claims 1-6, wherein the at least one other active substance is a bile acid binder.

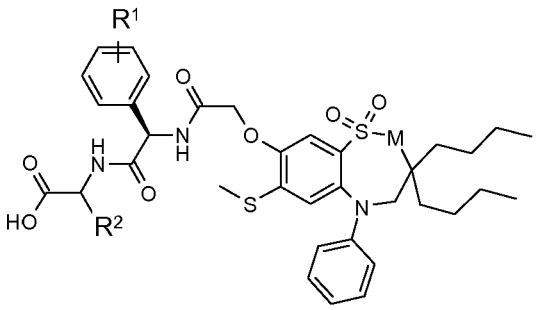
8. A combination according to claim 7, wherein the bile acid binder is cholestyramine, cholestipol or colesevelam.

9. A combination according to any one of claims 1-6, wherein the at least one other active substance is a HMG Co-A reductase inhibitor.

10. A combination according to claim 9, wherein the HMG Co-A reductase inhibitor is a statin.

11. A pharmaceutical combination formulation comprising

(i) a compound of formula II



II

wherein

M is -CH_2 or NH;

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

$\mathbf{R^2}$ 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_2-S-CH_3; or a pharmaceutically acceptable salt thereof; and

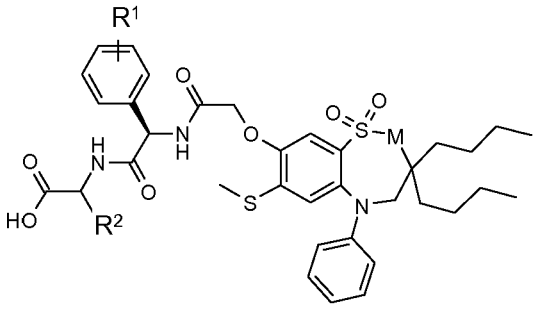
(ii) at least one other active substance selected from an IBAT inhibitor; an enteroendocrine peptide or enhancer thereof; a dipeptidyl peptidase-IV inhibitor; a biguanidine; an incretin mimetic; a thiazolidinone; a PPAR agonist; a HMG Co-A reductase inhibitor; a bile acid binder; and a TGR5 receptor modulator; or a pharmaceutically acceptable salt of any one of said active substances;

in admixture with a pharmaceutically and pharmacologically acceptable excipient.

12. A pharmaceutical combination formulation according to claim 11, comprising

(v) an inner core comprising a bile acid binder;
(vi) a colon release layer onto the core;
(vii) an IBAT inhibitor layer onto said colon release layer; and
(viii) an outer protective coating.

13. A pharmaceutical combination formulation according to claim 12, wherein the IBAT inhibitor layer comprises a compound of formula II



II

wherein

M is -CH_2 or NH;

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

$\mathbf{R^2}$ 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_2-S-CH_3; or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical combination formulation according to claim 13, wherein the IBAT inhibitor layer comprises a compound selected from

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.

15. A combination according to any one of claims 1-14, for use in the prophylactic or therapeutic treatment of hypercholesterolaemia, a metabolic syndrome, diabetes, obesity, a liver disease, ordyslipidemia.

16. A combination according to claim 15, for use in the treatment of a liver disease.

17. A combination according to claim 15, for use in the treatment of a metabolic syndrome.

18. A combination according to claim 15, for use in the treatment of a glucose utilization disorder.

19. A combination according to any one of claims 1-14, for use in the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhoea during therapy comprising an IBAT inhibitor compound.

20. A method for the treatment and/or prophylaxis of hypercholesterolaemia, a metabolic syndrome, diabetes, obesity, a liver disease, or dyslipidemia, whereby a combination according to any one of claims 1-14 is administered to a subject in need of such treatment.