IBAT INHIBITORS FOR TREATMENT OF METABOLIC DISORDERS AND RELATED CONDITIONS

BACKGROUND OF THE INVENTION

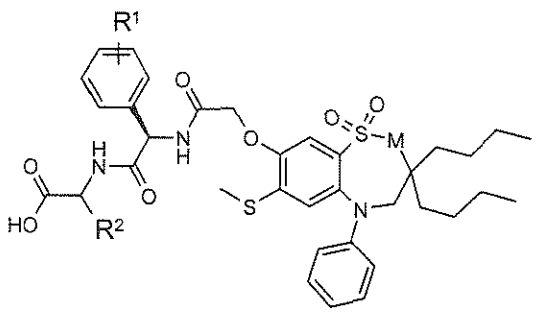
Obesity is a medical condition affecting numerous humans in a number of countries throughout the world, and is associated with or induces other diseases or conditions. In particular, obesity is a serious risk factor for diseases and conditions such as diabetes, hypertension, gallbladder disease, cancer, polycystic ovary disease and arteriosclerosis and can contribute to elevated levels of cholesterol in the blood. In addition, increased body weight due to obesity places a burden on joints causing arthritis, pain and stiffness. Overeating and obesity have become a problem in the general population. Consequently there is interest in reducing food intake, losing weight, reducing weight, and/or maintaining a healthy body weight and lifestyle.

WO10062861 and WO 2008/058630 describe the effect of ileal bile acid transport (IBAT) in the treatment of obesity and diabetes.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

The present ~~invention~~disclosure regards specific ileal bile acid transport (IBAT) inhibitors with effect in the prophylaxis and treatment of metabolic syndrome, obesity, disorders of fatty acid metabolism, glucose utilization disorders, disorders in which insulin resistance is involved, diabetes mellitus, type 1 and type 2 diabetes. It also relates to compositions comprising these IBAT inhibitors, a method for treatment of the disorders and a kit comprising the substances or the compositions. It has turned out that Interruption of bile acid circulation in mice improves triglyceride metabolism and normalizes elevated plasma glucose levels.

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



II

wherein

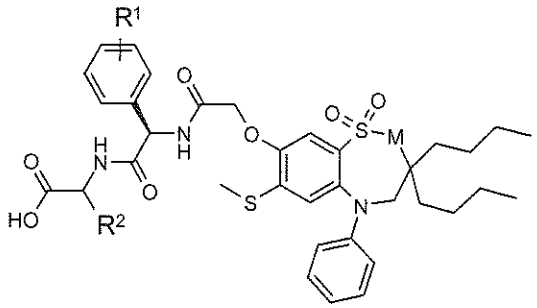
M is $-CH_2$ or NH;

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;

in the manufacture of a medicament for the prophylaxis or treatment of a glucose utilization disorder.

In a second aspect, there is provided the use of a pharmaceutical composition comprising a compound of formula II



II

wherein

M is $-CH_2$ or NH;

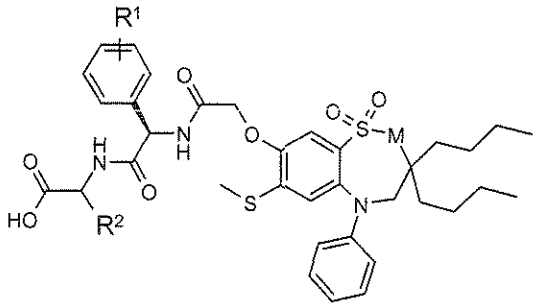
R^1 is H or OH; and

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;

in the manufacture of a medicament for the prophylaxis or treatment of a glucose utilization disorder.

In a third aspect, there is provided the use of 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; 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 the manufacture of a medicament for the prophylaxis or treatment of a glucose utilization disorder.

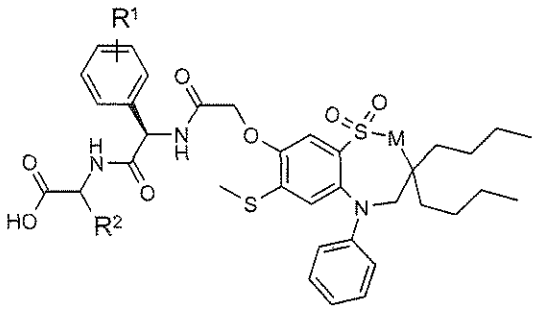
FIGURE LEGENDS

Fig. 1

(A) Schematic overview of vector and strategy used to target the *Slc10a2* wt allele in order to obtain a *Slc10a2* null mouse.

(B) A representative immunoblot employing a specific antibody directed against the Slc10a2 protein demonstrates absence of Slc10a2 protein expression in ileum of *Slc10a2-/-* mice.

1. Use of 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;

in the manufacture of a medicament for the prophylaxis or treatment of diabetes.

2. Use according to claim 1, wherein the diabetes is diabetes mellitus type 1.

3. Use according to claim 1, wherein the diabetes is diabetes mellitus type 2.

4. Use according to any one of claims 1-3, wherein the compound of formula II is selected from the group consisting of:

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

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

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

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((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;

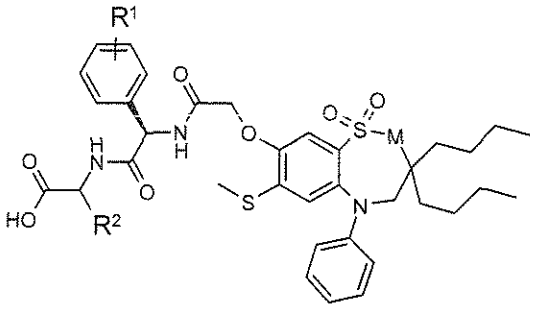
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

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.

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

6. Use according to any one of claims 1-4, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl] methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine.

7. Use of pharmaceutical composition comprising a compound of formula II



II

wherein

M is $-CH_2$ or NH;

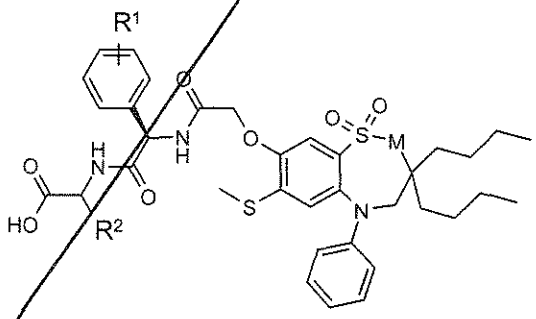
$\mathbf{R^1}$ is H or OH; and

$\mathbf{R^2}$ 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;

in the manufacture of a medicament for the prophylaxis or treatment of diabetes.

8. Use of 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; 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 the manufacture of a medicament for the prophylaxis or treatment of diabetes.

9. Use according to claim 8, wherein the diabetes is diabetes mellitus type 1.

10. Use according to claim 8, wherein the diabetes is diabetes mellitus type 2.

11. Use according to any one of claims 8-10, wherein the compound of formula (II) is selected from the group consisting of:
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((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.

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

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

14. Use according to any one of claims 8-13, wherein the at least one other active substance is a bile acid binder.

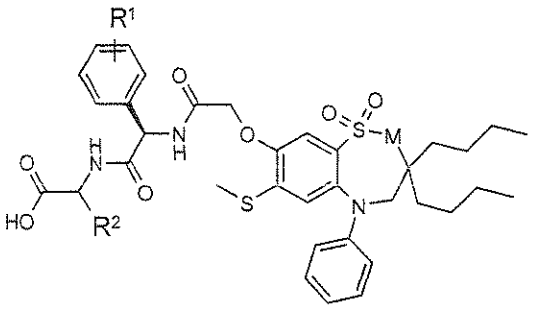
15. Use according to claim 14, wherein the bile acid binder is cholestyramine, cholestipol or colesevelam.

16. Use according to any one of claims 8-13, wherein the at least one other active substance is a HMG Co-A reductase inhibitor.

17. Use according to claim 16, wherein the HMG Co-A reductase inhibitor is a statin.

CLAIMS

1. Use of 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;

in the manufacture of a medicament for the prophylaxis or treatment of a glucose utilization disorder.

2. Use according to claim 1, wherein the glucose utilization disorder is a disorder in which insulin resistance is involved.

3. Use according to claim 2, wherein the disorder is diabetes mellitus type 1.

4. Use according to claim 2, wherein the disorder is diabetes mellitus type 2.

5. Use according to any one of claims 1 to 4, wherein the compound of formula II is selected from the group consisting of:

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

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

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

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((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;

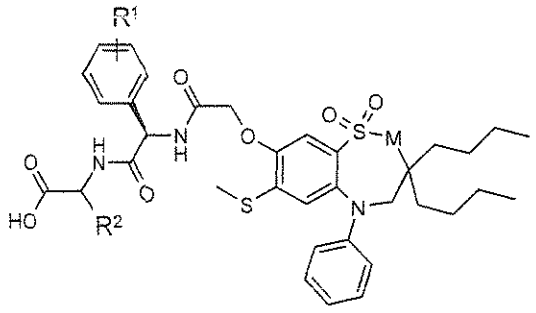
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

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.

6. Use according to any one of claims 1 to 4, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine.

7. Use according to any one of claims 1 to 4, wherein the compound of formula II is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine.

8. Use of a pharmaceutical composition comprising a compound of formula II



II

wherein

M is $-CH_2$ or NH;

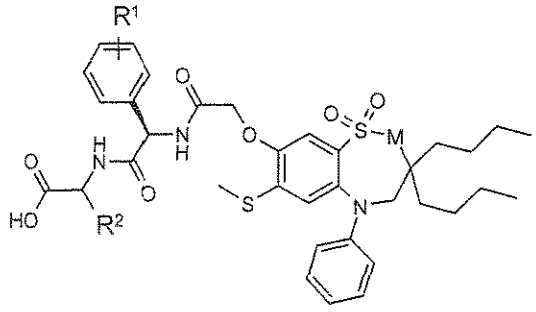
$\mathbf{R^1}$ is H or OH; and

$\mathbf{R^2}$ 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;

in the manufacture of a medicament for the prophylaxis or treatment of a glucose utilization disorder.

9. Use of 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; 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 the manufacture of a medicament for the prophylaxis or treatment of a glucose utilization disorder.

10. Use according to claim 9, wherein the compound of formula (II) is selected from the group consisting of:
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-Dioxo-3, 3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-((S)-1-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((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.

11. Use according to claim 9, wherein the compound of formula (II) is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine.

12. Use according to claim 9, wherein the compound of formula (II) is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-phenyl-1'-[N'-(carboxymethyl)carbamoyl] methyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine.

13. Use according to any one of claims 9 to 12, wherein the at least one other active substance is a bile acid binder.

14. Use according to claim 13, wherein the bile acid binder is cholestyramine, cholestipol or colesevelam.

15. Use according to any one of claims 9 to 12, wherein the at least one other active substance is a HMG Co-A reductase inhibitor.

16. Use according to claim 15, wherein the HMG Co-A reductase inhibitor is a statin.