EUROPEAN PATENT SPECIFICATION

<table>
<thead>
<tr>
<th>Date of publication and mention of the grant of the patent:</th>
<th>05.08.2009 Bulletin 2009/32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application number:</td>
<td>02755285.0</td>
</tr>
<tr>
<td>Date of filing:</td>
<td>30.08.2002</td>
</tr>
<tr>
<td>Int Cl.:</td>
<td>C07D 281/10 (2006.01)</td>
</tr>
<tr>
<td></td>
<td>C07D 417/12 (2006.01)</td>
</tr>
<tr>
<td></td>
<td>A61K 31/554 (2006.01)</td>
</tr>
<tr>
<td></td>
<td>A61P 3/06 (2006.01)</td>
</tr>
<tr>
<td>International application number:</td>
<td>PCT/GB2002/003983</td>
</tr>
<tr>
<td>BENZOTHIAZEPINE DERIVATIVES</td>
<td></td>
</tr>
<tr>
<td>BENZOTHIAZEPINDERIVATE</td>
<td></td>
</tr>
<tr>
<td>DERIVES DE BENZOTHIAZEPINE</td>
<td></td>
</tr>
<tr>
<td>Designated Contracting States:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR</td>
</tr>
<tr>
<td>Priority:</td>
<td>04.09.2001 GB 0121337</td>
</tr>
<tr>
<td>Date of publication of application:</td>
<td>23.06.2004 Bulletin 2004/26</td>
</tr>
<tr>
<td>Proprietor:</td>
<td>Albireo AB</td>
</tr>
<tr>
<td></td>
<td>431 46 Göteborg (SE)</td>
</tr>
<tr>
<td>Inventors:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• STARKE, Ingemar</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td></td>
<td>• DAHLSTROM, Mikael, Ulf, Johan</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td></td>
<td>• BLOMBERG, David</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td></td>
<td>• ALENFALK, Suzanne</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td></td>
<td>• NORDBERG, Peter</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td></td>
<td>• WALLBERG, Andreas, Christer</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td></td>
<td>• BOSTROM, Stig, Jonas</td>
</tr>
<tr>
<td></td>
<td>SE-431 83 (SE)</td>
</tr>
<tr>
<td>Representative:</td>
<td>Fagerlin, Hélène</td>
</tr>
<tr>
<td></td>
<td>Albhips AB</td>
</tr>
<tr>
<td></td>
<td>P.O. Box 5581</td>
</tr>
<tr>
<td></td>
<td>114 85 Stockholm (SE)</td>
</tr>
<tr>
<td>References cited:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EP-A- 0 864 582</td>
</tr>
<tr>
<td></td>
<td>WO-A-01/66533</td>
</tr>
<tr>
<td></td>
<td>WO-A-02/50051</td>
</tr>
<tr>
<td></td>
<td>WO-A-96/05188</td>
</tr>
<tr>
<td>Remarks:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The file contains technical information submitted after the application was filed and not included in this specification</td>
</tr>
</tbody>
</table>

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
This invention relates to benzothiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiazepines possess ileal bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiazepine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit IBAT in a warm-blooded animal, such as man.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. et al; Circulation 1999, 100, 1930-1938 and "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S, Benjamin I., Burke G., et al; Circulation, 1999, 100, 1134-46). 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 simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy ("Bile Acids and Lipoprotein Metabolism: a Renaissance for Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M; Current Opinion on Lipidology, 1999, 10, 269-74) involved the treatment with substances with an IBAT inhibitory effect.

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties", Biochemica et Biophysica Acta, 1210 (1994) 255-287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions.

Compounds possessing such IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/50051 and EP 0 864 582.

A further aspect of this invention relates to the use of the compounds of the invention in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hypercholesterolemia, hyperprebetalipoproteinemia, 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, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks.

The present invention is based on the discovery that certain benzothiazepine compounds surprisingly inhibit IBAT. Such properties are expected to be of value in the treatment of disease states associated with hyperlipidaemic conditions.

Accordingly, the present invention provides a compound of formula (I):
wherein:

- \( R^v \) and \( R^w \) are both hydrogen;
- One of \( R^1 \) and \( R^2 \) are selected from hydrogen or C\(_{1-6}\)alkyl and the other is selected from C\(_{1-6}\)alkyl;
- \( R^4 \) and \( R^5 \) are both hydrogen;
- \( R^2 \) is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carboxamoyl, mercapto, sulphamoyl, C\(_{1-6}\)alkyl, C\(_{2-6}\)alkenyl, C\(_{2-6}\)alkynyl, C\(_{1-6}\)alkoxy, \( N\)-(C\(_{1-6}\)alkyl)amino, \( N,N\)-(C\(_{1-6}\)alkyl)\(_2\)amino, \( N\)-(C\(_{1-6}\)alkyl)carboxamoyl, \( N\)-(C\(_{1-6}\)alkyl)\(_2\)carboxamoyl, \( C_1\)-(C\(_{1-6}\)alkyl)S(O)\(_a\) wherein \( a \) is 0 to 2, \( C_1\)-(C\(_{1-6}\)alkoxy)carboxamoyl, \( N\)-(C\(_{1-6}\)alkyl)sulphamoyl and \( N,N\)-(C\(_{1-6}\)alkyl)\(_2\)sulphamoyl;
- \( v \) is 0-5;
- one of \( R^4 \) and \( R^5 \) is a group of formula (IA):

\[ \text{(IA)} \]

\( R^3 \) and \( R^6 \) are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carboxamoyl, mercapto, sulphamoyl, C\(_{1-6}\)alkyl, C\(_{2-6}\)alkenyl, C\(_{2-6}\)alkynyl, C\(_{1-6}\)alkoxy, \( N\)-(C\(_{1-6}\)alkyl)amino, \( N,N\)-(C\(_{1-6}\)alkyl)\(_2\)amino, \( N\)-(C\(_{1-6}\)alkyl)carboxamoyl, \( N\)-(C\(_{1-6}\)alkyl)\(_2\)carboxamoyl, \( N\)-(C\(_{1-6}\)alkyl)S(O)\(_a\) wherein \( a \) is 0 to 2, \( N\)-(C\(_{1-6}\)alkoxy)carboxamoyl, \( N\)-(C\(_{1-6}\)alkyl)sulphamoyl and \( N,N\)-(C\(_{1-6}\)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 \( R^{17} \);
- \( X \) is -O-, -N(R\(_a\))- or -S(O)\(_b\)- or -CH(R\(_a\))- wherein \( R^4 \) is hydrogen or C\(_{1-6}\)alkyl and \( b \) is 0-2;
- Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from \( R^{18} \);
- \( R^7 \) is hydrogen, C\(_{1-6}\)alkyl, carboxycyclyl or heterocyclyl; wherein \( R^7 \) is optionally substituted on carbon by one or more substituents selected from \( R^{19} \); and wherein if said heterocyclyl contains an \(-\text{NH}-\) group, that nitrogen may be optionally substituted by a group selected from \( R^{20} \);
- \( R^8 \) is hydrogen or C\(_{1-6}\)alkyl;
- \( R^9 \) is hydrogen or C\(_{1-6}\)alkyl;
- \( R^{10} \) is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C\(_{1-10}\)alkyl, C\(_{2-10}\)alkenyl, C\(_{2-10}\)alkynyl, C\(_{1-10}\)alkoxy, \( N\)-(C\(_{1-10}\)alkyl)amino, \( N,N\)-(C\(_{1-10}\)alkyl)\(_2\)amino, \( N\)-(C\(_{1-10}\)alkyl)carboxamoyl, \( N,N\)-(C\(_{1-10}\)alkyl)\(_2\)carboxamoyl, \( N\)-(C\(_{1-10}\)alkyl)S(O)\(_a\) wherein \( a \) is 0 to 2, \( N\)-(C\(_{1-10}\)alkoxy)carboxamoyl, \( N,N\)-(C\(_{1-10}\)alkyl)\(_2\)sulphamoyl, \( N\)-(C\(_{1-10}\)alkyl)sulphamoylamino, \( N,N\)-(C\(_{1-10}\)alkyl)\(_2\)sulphamoylamino, \( C_1\)-(C\(_{1-10}\)alkyl)\(_2\)sulphamoylamino, carbocyclyl, carboxycyclylC\(_{1-10}\)alkyl, heterocyclyl, heterocyclylC\(_{1-10}\)alkyl, carboxycyclyl-(C\(_{1-10}\)alkylene)\(_p\)-R\(_{21}\) -(C\(_{1-10}\)alkylene)\(_q\)- or
heterocyclyl-(C\textsubscript{1-10}alkylene)\textsubscript{r} \cdot \textsubscript{s}; wherein R\textsubscript{10} is optionally substituted on carbon by one or more substituents selected from R\textsubscript{23}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\textsubscript{24}; or R\textsubscript{10} is a group of formula (IB):

\[
\text{(IB)}
\]

wherein:

- R\textsubscript{11} is hydrogen or C\textsubscript{1-6}alkyl;
- R\textsubscript{12} and R\textsubscript{13} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C\textsubscript{1-10}alkyl, C\textsubscript{2-10}alkenyl, C\textsubscript{2-10}alkynyl, C\textsubscript{1-10}alkoxy, C\textsubscript{1-10}alkanoyl, C\textsubscript{1-10}alkanoyloxy, N-(C\textsubscript{1-10}alkyl)aminono, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}amino, C\textsubscript{1-10}alkanoylamino, N-(C\textsubscript{1-10}alkyl)carbamoyl, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}carbamoyl, C\textsubscript{1-10}alkylS\textsubscript{O} a wherein a is 0 to 2, N-(C\textsubscript{1-10}alkyl)sulphamoylamino, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}sulphamoylamino, N,N-(C\textsubscript{1-10}alkyl)sulphamoylamino, carbocyclyl or heterocyclyl; wherein R\textsubscript{12} and R\textsubscript{13} may be independently optionally substituted on carbon by one or more substituents selected from R\textsubscript{25}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\textsubscript{26};
- R\textsubscript{14} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyminocarbonyl, C\textsubscript{1-10}alkyl, C\textsubscript{2-10}alkenyl, C\textsubscript{2-10}alkynyl, C\textsubscript{1-10}alkoxy, C\textsubscript{1-10}alkanoyl, C\textsubscript{1-10}alkanoyloxy, N-(C\textsubscript{1-10}alkyl)aminono, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}amino, N,N,N-(C\textsubscript{1-10}alkyl)\textsubscript{3}ammonio, C\textsubscript{1-10}alkanoylamino, N-(C\textsubscript{1-10}alkyl)carbamoyl, N,N-(C\textsubscript{1-10}alkyl)carbamoyl, C\textsubscript{1-10}alkylS\textsubscript{O} a wherein a is 0 to 2, N-(C\textsubscript{1-10}alkyl)sulphamoylamino, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}sulphamoylamino, N,N-(C\textsubscript{1-10}alkyl)sulphamoylamino, carbocyclyl, carbocyclylC\textsubscript{1-10}alkyl, heterocyclyl, heterocyclylC\textsubscript{1-10}alkyl, carbocyclyl-(C\textsubscript{1-10}alkylene)\textsubscript{r} \cdot \textsubscript{s}; wherein R\textsubscript{14} may be optionally substituted on carbon by one or more substituents selected from R\textsubscript{28}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\textsubscript{30}; or R\textsubscript{14} is a group of formula (IC):

\[
\text{(IC)}
\]

wherein:

- R\textsubscript{15} is hydrogen or C\textsubscript{1-6}alkyl;
- R\textsubscript{16} is hydrogen or C\textsubscript{1-6}alkyl; wherein R\textsubscript{16} may be optionally substituted on carbon by one or more groups selected from R\textsubscript{31};
- n is 1-3; wherein the values of R\textsubscript{7} may be the same or different;
- R\textsubscript{17}, R\textsubscript{18}, R\textsubscript{19}, R\textsubscript{23}, R\textsubscript{25}, R\textsubscript{29} or R\textsubscript{31} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyminocarbonyl, C\textsubscript{1-10}alkyl, C\textsubscript{2-10}alkenyl, C\textsubscript{2-10}alkynyl, C\textsubscript{1-10}alkoxy, C\textsubscript{1-10}alkanoyl, C\textsubscript{1-10}alkanoyloxy, N-(C\textsubscript{1-10}alkyl)aminono, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}amino, N,N,N-(C\textsubscript{1-10}alkyl)\textsubscript{3}ammonio, C\textsubscript{1-10}alkanoylamino, N-(C\textsubscript{1-10}alkyl)carbamoyl, N,N-(C\textsubscript{1-10}alkyl)carbamoyl, C\textsubscript{1-10}alkylS\textsubscript{O} a wherein a is 0 to 2, N-(C\textsubscript{1-10}alkyl)sulphamoylamino, N,N-(C\textsubscript{1-10}alkyl)\textsubscript{2}sulphamoylamino, N,N-(C\textsubscript{1-10}alkyl)sulphamoylamino, carbo-cyclyl, carbocyclylC\textsubscript{1-10}alkyl, heterocyclyl, heterocyclylC\textsubscript{1-10}alkyl, carbocyclyl-(C\textsubscript{1-10}alkylene)\textsubscript{r} \cdot \textsubscript{s}; wherein R\textsubscript{17}, R\textsubscript{18}, R\textsubscript{19}, R\textsubscript{23}, R\textsubscript{25}, R\textsubscript{29} or R\textsubscript{31} may be independently optionally substituted on carbon by one or more R\textsubscript{34}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\textsubscript{35};
- R\textsubscript{21}, R\textsubscript{22}, R\textsubscript{27}, R\textsubscript{28}, R\textsubscript{32} or R\textsubscript{33} are independently selected from -O-, -NR\textsubscript{36}-, -S(O)\textsubscript{x}-, -NR\textsubscript{36}C\textsubscript{1-10}alkyl, -NR\textsubscript{36}C\textsubscript{1-10}alkyl-C\textsubscript{1-10}alkyl, -OC(O)N=C-, -NR\textsubscript{36}C(O)- or -C(O)NR\textsubscript{36}-; wherein R\textsubscript{36} is selected from hydrogen or C\textsubscript{1-6}alkyl, and x is 0-2;
**EP 1 430 040 B1**

**[0008]** Accordingly, in another aspect of the present invention there is provided a compound of formula (I):

\[
\begin{align*}
\text{One of } R^1 \text{ and } R^2 & \text{ are selected from hydrogen or } C_1\text{-}C_6 \text{alkyl and the other is selected from } C_1\text{-}C_6 \text{alkyl;} \\
R^2 & \text{ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, } C_1\text{-}C_6 \text{alkyl, } C_2\text{-}C_6 \text{alkenyi, } C_1\text{-}C_6 \text{alkoxy, } C_1\text{-}C_6 \text{alkanoyl, } C_1\text{-}C_6 \text{alkanoyloxy, } N\text{-}(C_1\text{-}C_6 \text{alkyl})\text{amino, } N,N\text{-}(C_1\text{-}C_6 \text{alkyl})_2\text{amino, } C_1\text{-}C_6 \text{alkanoylamino, } N\text{-}(C_1\text{-}C_6 \text{alkyl})\text{carbamoyl, } N,N\text{-}(C_1\text{-}C_6 \text{alkyl})_2\text{carbamoyl, } C_1\text{-}C_6 \text{alkylS(O)}^a \text{ wherein } a \text{ is } 0 \text{ to } 2, \\
& C_1\text{-}C_6 \text{alkoxycarbonyl, } N\text{-}(C_1\text{-}C_6 \text{alkyl})\text{sulphamoyl and } N,N\text{-}(C_1\text{-}C_6 \text{alkyl})_2\text{sulphamoyl;} \\
v & \text{ is 0-5;} \\
\text{one of } R^4 \text{ and } R^5 & \text{ is a group of formula (IA):}
\end{align*}
\]

\[
\begin{align*}
\text{R}^3 & \text{ and } R^6 \text{ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, } C_1\text{-}C_6 \text{alkyl, } C_2\text{-}C_6 \text{alkenyi, } C_1\text{-}C_6 \text{alkoxy, } C_1\text{-}C_6 \text{alkanoyl, } C_1\text{-}C_6 \text{alkanoyloxy, } N\text{-}(C_1\text{-}C_6 \text{alkyl})\text{amino, } N,N\text{-}(C_1\text{-}C_6 \text{alkyl})_2\text{amino, } N\text{-}(C_1\text{-}C_6 \text{alkyl})\text{carbamoyl, } N,N\text{-}(C_1\text{-}C_6 \text{alkyl})_2\text{carbamoyl, } N\text{-}(C_1\text{-}C_6 \text{alkyl})\text{sulphamoyl and } N,N\text{-}(C_1\text{-}C_6 \text{alkyl})_2\text{sulphamoyl;} \\
& \text{ wherein } R^3 \text{ and } R^6 \text{ and the other of } R^4 \text{ and } R^5 \text{ may be optionally substituted on carbon by one or more } R^{17}; \\
X & \text{ is } -O^-, -N(R^a)^-, -S(O)^b_2^- \text{ or } -\text{CH}(R^a)^-; \text{ wherein } R^a \text{ is hydrogen or } C_1\text{-}C_6 \text{alkyl and } b \text{ is 0-2;}
\end{align*}
\]
**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R18;  

**R7** is hydrogen, C1-6 alkyl, carbocyclyl or heterocyclyl; wherein R7 is optionally substituted on carbon by one or more substituents selected from R19; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R20;  

**R8** is hydrogen or C1-6 alkyl;  

**R9** is hydrogen or C1-6 alkyl;  

**R10** is hydrogen, halo, nitro, cyano, amino, carbamoyl, mercapto, sulphamoyl, hydroxymino-carbonyl, C1-10 alkyll, C2-10 alkenyl, C2-10 alkynyl, C1-10 alkoxy, C1-10 alkanoyloxy, N-(C1-10 alkyl) amino, N,N-(C1-10 alkyl)2 amino, N,N,N-(C1-10 alkyl)3 ammonio, C1-10 alkanoylamino, N-(C1-10 alkyl) carbamoyl, N,N-(C1-10 alkyl)2 carbamoyl, C1-10 alkylS(O)a wherein a is 0 to 2, N-(C1-10 alkyl) sulphamoyl, N,N-(C1-10 alkyl)2 sulphamoyl, N-(C1-10 alkyl) sulphamoylamino, N,N-(C1-10 alkyl)2 sulphamoylamino, C1-10 alkoxy carbonylamino, carbocyclyl, carbocyclyl-C1-10 alkyl, heterocyclyl, heterocyclyl-C1-10 alkylene), R21-(C1-10 alkylene)m or heterocyclyl-(C1-10 alkylene), R22-(C1-10 alkylene)n; wherein R10 is optionally substituted on carbon by one or more substituents selected from R23; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R24; or R10 is a group of formula (IB):  

![IB](image)

wherein:  

**R11** is hydrogen or C1-6 alkyl;  

**R12 and R13** are independently selected from hydrogen, halo, nitro, cyano, amino, carbamoyl, mercapto, sulphamoyl, C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C1-10 alkoxy, C1-10 alkanoyloxy, N-(C1-10 alkyl) amino, N,N-(C1-10 alkyl)2 amino, C1-10 alkanoylamino, N-(C1-10 alkyl) carbamoyl, N,N-(C1-10 alkyl)2 carbamoyl, C1-10 alkylS(O)a wherein a is 0 to 2, N-(C1-10 alkyl) sulphamoyl, N,N-(C1-10 alkyl)2 sulphamoyl, N-(C1-10 alkyl) sulphamoylamino, N,N-(C1-10 alkyl)2 sulphamoylamino, carbocyclyl, carbocyclyl-C1-10 alkyl, heterocyclyl, heterocyclyl-C1-10 alkylene), R21-(C1-10 alkylene)m or heterocyclyl-(C1-10 alkylene), R22-(C1-10 alkylene)n; wherein R14 may be optionally substituted on carbon by one or more substituents selected from R25; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R26;  

**R14** is selected from hydrogen, halo, nitro, cyano, amino, carbamoyl, mercapto, sulphamoyl, hydroxymino-carbonyl, C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C1-10 alkoxy, C1-10 alkanoyloxy, N-(C1-10 alkyl) amino, N,N-(C1-10 alkyl)2 amino, N,N,N-(C1-10 alkyl)3 ammonio, C1-10 alkanoylamino, N-(C1-10 alkyl) carbamoyl, N,N-(C1-10 alkyl)2 carbamoyl, C1-10 alkylS(O)a wherein a is 0 to 2, N-(C1-10 alkyl) sulphamoyl, N,N-(C1-10 alkyl)2 sulphamoyl, N-(C1-10 alkyl) sulphamoylamino, N,N-(C1-10 alkyl)2 sulphamoylamino, carbocyclyl, carbocyclyl-C1-10 alkyl, heterocyclyl, heterocyclyl-C1-10 alkylene), R21-(C1-10 alkylene)m or heterocyclyl-(C1-10 alkylene), R22-(C1-10 alkylene)n; wherein R14 may be optionally substituted on carbon by one or more substituents selected from R23; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R24; or R14 is a group of formula (IC):  

![IC](image)

**R15** is hydrogen or C1-6 alkyl;
**EP 1 430 040 B1**

$R^{16}$ is hydrogen or C$_{1-6}$alkyl; wherein $R^{16}$ may be optionally substituted on carbon by one or more groups selected from R$_{31}$; $n$ is 1-3; wherein the values of $R^7$ may be the same or different; $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or $R^{31}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphanilamido, C$_{1-10}$alkyl, C$_{2-10}$alkenyl, C$_{2-10}$alkynyl, C$_{1-10}$alkoxy, C$_{1-10}$alkanoyloxy, N-(C$_{1-10}$alkyl)amino, N,N-(C$_{1-10}$alkyl)$_2$amino, N,N,N-(C$_{1-10}$alkyl)$_3$ammonio, C$_{1-10}$alkanoylamino, N-(C$_{1-10}$alkyl)carbamoyl, N,N-(C$_{1-10}$alkyl)$_2$carbamoyl, C$_{1-10}$alkylS(O)$_2$ wherein $a$ is 0 to 2, N-(C$_{1-10}$alkyl)sulphanilamido, N,N-(C$_{1-10}$alkyl)$_2$sulphanilamidomino, N,N-(C$_{1-10}$alkyl)$_3$sulphanilamidomino, C$_{1-10}$alkanoylcarbamidoxy, carboxycarbonyl, carboxycarbonyl(C$_{1-10}$alkyl), heterocyclyl, heterocyclyl(C$_{1-10}$alkyl), carbocyclyl(C$_{1-10}$alkyl)$_7$-$R^{32}$-(C$_{1-10}$alkyl))$_7$, or heterocyclyl-(C$_{1-10}$alkylene)$_7$-$R^{33}$-(C$_{1-10}$alkylene)$_7$ wherein $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or $R^{31}$ may be independently selected from carbon or more of the specified groups.

$R^{21}, R^{22}, R^{27}, R^{28}, R^{32}$ or $R^{33}$ are independently selected from -O-, -NR$_3$-, -S(O)$_2$-, -O-OC(O)-, -O-OC(O)(O)NR$_3$-, -NR$_3$C(O)O-, -OC(O)N=O-, -NR$_3$C(O)- or -C(O)NR$_3$- wherein the values of $R^7$ may be the same or different; $p, q, r$ and $s$ are independently selected from O-2.; $R^{34}$ is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphanilamido, trifluoroacetyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxyl, methylaminomino, dimethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N-methylsulphanilamido, N,N-dimethylsulphanilamido, N-methylsulphamidomino and N,N-dimethylsulphamidomino; $R^{20}, R^{24}, R^{26}, R^{30}$ or $R^{35}$ are independently selected from C$_{1-6}$alkyl, C$_{1-6}$alkanoyl, C$_{1-6}$alkylsulphonyl, C$_{1-6}$alkoxygeny, carboxamido, N-(C$_{1-6}$alkyl)carbamoyl, N,N-(C$_{1-6}$alkyl)$_2$carbamoyl, N,N,N-(C$_{1-6}$alkyl)$_3$carbamoyl, benzyl, benzoyloxycarbonyl, benzoyl and phenylsulphinyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

[0009] 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$_{1-6}$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$_{1-6}$alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

[0010] Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

[0011] "Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom, particularly 1-3 atoms, are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, 5,6-dihydropyridinyl, 1,1-dioxotetrahydrothiophenyl, 2,4-dioxoisothiazolyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodiazoxy, 1,2,4-oxadiazolyl, 2-azaindolyl[2.2.1]heptyl, 4-oxothiazolidonyl, morpholinono, 2-oxotetrahydrofuranyln, tetrahydrofuranyln, 2,3-dihydrobenzofuranyln, benzothienyl, tetrahydropranyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholinono, 1,1-dioxothiomorpholinono, tetrahydroprpyranyln, 1,3-dioxolanly, homopiper-
azinyl, thienyl, isoazolyl, 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. "Heterocyclyl" is not tetracycyl.

[0014] A "carbocyclcyloxy" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH2- group can optionally be replaced by a -C(O)-. Preferably "carbocyclcyloxy" is a monocylic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclcyloxy" include cyclopropyl, cycolbuty1, 1-oxacyclopentyl, cyclopropenyl, cyclopropenyl, cyclohexyl, cyclohexenyl, phenyl, napthyl, tetrayl, indanyl or 1-oxoindanyl. Particularly "carbocyclcyloxy" is cyclobutyl, 1-oxacyclopentyl, cyclopropenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl.

[0015] An example of "C1-10alkanoxyloxy" and "C1-6alkanoxyloxy" is acetoxy. Examples of "C1-10alkoxyacyloxy" and "C1-6alkoxyacyloxy" include methoxoyacetyl, ethoxycarbonyl, n- and t-butoxycarbonyl. Examples of "C1-10alkoxy" and "C1-6alkoxy" include methoxy, ethoxy and propoxy. Examples of C1,10alkanoylamino" and "C1,6alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C1,10alkyl(S)O(2)or wherein a is 0 to 2 and "C1,6alkyl(S)O(2)or wherein a is 0 to 2 include methylythio, ethylthio, methylsulphyny1, ethylsulphyny1, mesy1 and ethylsulphony1. Examples of "C1,10alkanoylamino" and "C1,6alkanoylamino" include C1,3alkanoylamino, propionyl and acetyl. Examples of "N,C1-10alkylamino" and "N,C1-6alkylamino" include methylylamino and ethylylamino. Examples of "N,N(C1-10alkyl)amino" and "N,N(C1-6alkyl)amino" include di-N-methylamino, di-N-ethylamino and N-ethyl,N-methylamino. Examples of "C2-10alkeny1" and "C2-6alkeny1" are vinyl, allyl and 1-propenyl. Examples of "C2-10alkeny1" and "C2-6alkeny1" are ethyl, 1-propynyl and 2-propynyl. Examples of "N(C1-10alkyl)sulphamoyl" and "N(C1,6alkyl)sulphamoyl" are N-C3alkyl sulphonamyl, N-(methyl)sulphamoyl and N-(ethyl)sulphamoyl. Examples of "N(C1-10alkyl)2sulphamoylamino" and "N(C1-6alkyl)2sulphamoylamino" are N,N-dimethylsulphamoylamino and N-(methyl)-N-(ethyl)sulphamoylamino. Examples of "N,C1-10alkylcarbamoyl" and "N,C1-6alkylcarbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "N,N(C1-10alkyl)carbamoylamino" and "N,N(C1-6alkyl)carbamoylamino" are dimethylaminocarbonylamino and methylythylaminocarbonyl. Examples of "N,N(C1-10alkyl)sulphamoylamino" and "N,N(C1,6alkyl)sulphamoylamino" are dimethylsulphamoylamino and N-ethylsulphamoylamino. Examples of "N,N,N(C1-10alkyl)ammonio" and "N,N,N(C1,6alkyl)ammonio" are trimethylamino and methylthlylamino. Examples of "C1,10alkoxyacylylaminoborony1" and "C1,6alkoxyacylylaminoborony1" are methoxyacylylamino and t-butoxyacylylamino. Examples of "N(C1,10alkyl)sulphamoylamino" and "N(C1,6alkyl)sulphamoylamino" are N-methylsulphamoylamino and N-ethylsulphamoylamino. Examples of "N,N(C1,10alkyl)sulphamoylamino" and "N,N(C1,6alkyl)sulphamoylamino" are N,N-dimethylsulphamoylamino and N-methyl-N-ethylsulphamoylamino. Examples of "C1,6alkylthio" and "C1,6alkylthio" are methylthio and ethylythio. Examples of "carbocyclcyloxy(C1,10alkyl) include benzyl and phenethyl. Examples of "heterocycly(C1-10alkyl) are morphinopropyl and pyridylmethyl. Examples of "(C1,10alkyl)2silyl" are trimethylsily1 and triethylsily1.

[0016] 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, acetic 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.

[0017] 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).

[0018] 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 the compound (I) include C1,6alkoxycarbonylmethyl esters for example methoxymethyl, C1,6alkoxycarbonyloxymethyl esters for example pivaloxymethyl, phthalidyl esters, C2,6cycloalkoxycarbonyloxycarbonyloxyl esters for example 1-cyclohexylcarboxyloxymethyl, 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C1,6alkoxycarbonyloxymethyl esters for example 1-methoxycarbonyloxymethyl and may be formed at any carboxy group in the compounds of this invention.

[0019] An in vivo hydrolysable ester of a compound of the formula (I) containing a hydroy group includes inorganic esters such as phosphates and α-acetoxyalkyl 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-acetoxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetate and substituted benzyloxyacetyl, alkoxyacetyl (to give alkyl carbonate esters), dialky carbamoyl and N-(dialkylaminomethyl)-N-alkyl carbamoyl (to give carbamates), dialkylaminocacetyl and carboxyacetyl. Examples of substituents on benzylo include morpholino and piperezino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzylo ring.

[0020] 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 \( N,N\text{-di-}C_{1-6} \)-alkyl amide such as \( N\text{-methyl, } N\text{-ethyl, } N\text{-propyl, } N,N\text{-dimethyl, } N\text{-ethyl-} N\text{-methyl or } N,N\text{-diethyl amide.} \)

[0021] Some 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.

[0022] The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess IBAT inhibitory activity.

[0023] 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.

[0024] Particular values are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

[0025] \( R^v \) and \( R^w \) are both hydrogen.

[0026] \( R^1 \) and \( R^2 \) are independently selected from \( C_{1-4} \)-alkyl.

[0027] One of \( R^1 \) and \( R^2 \) is ethyl or propyl and the other is butyl.

[0028] One of \( R^1 \) and \( R^2 \) is ethyl and the other is butyl.

[0029] \( R^1 \) and \( R^2 \) are both butyl.

[0030] One of \( R^1 \) and \( R^2 \) is ethyl and the other is butyl, or \( R^1 \) and \( R^2 \) are both butyl.

[0031] \( R^d \) and \( R^g \) are both hydrogen.

[0032] \( R^d \) is \( C_{1-4} \)-alkyl.

[0033] \( v \) is 0-2.

[0034] \( v \) is 0.

[0035] \( R^6 \) and \( R^8 \) and the other of \( R^4 \) and \( R^6 \) are independently selected from hydrogen and \( C_{1-6} \)-alkylthio.

[0036] \( R^6 \) and \( R^8 \) are hydrogen.

[0037] \( R^4 \) is halo.

[0038] \( R^4 \) is bromo or chloro.

[0039] \( R^4 \) is \( C_{1-6} \)-alkoxy.

[0040] \( R^4 \) is ethoxy or methoxy.

[0041] \( R^4 \) is methoxy.

[0042] \( R^d \) is ethylthio or methylthio.

[0043] \( R^4 \) is methylthio.

[0044] \( R^d \) is hydrogen.

[0045] \( R^d \) is hydrogen or methylthio.

[0046] \( R^5 \) is methylthio.

[0047] \( R^d \) is a group of formula (IA) as depicted above.

[0048] \( R^5 \) is a group of formula (IA) as depicted above.

[0049] \( R^4 \) is methylthio and \( R^5 \) is a group of formula (IA) as depicted above.

[0050] \( R^5 \) is methylthio and \( R^d \) is a group of formula (IA) as depicted above.

[0051] \( R^5 \) is a group of formula (IA) as depicted above wherein:

\[
\begin{align*}
X & = \text{-O-; } \\
R^7 & = \text{hydrogen; } \\
R^8 & = \text{hydrogen; } \\
R^9 & = \text{hydrogen; } \\
\text{Ring A is aryl; } \\
R^{10} & = \text{carbamoyl or } N-(C_{1-10}\text{-alkyl})\text{-carbamoyl or a group of formula (IB) (as depicted above) wherein } R^{10} \text{ is optionally substituted on carbon by one or more substituents selected from } R^{23} \text{ and wherein: } \\
R^{11} & = \text{hydrogen; } \\
R^{12} \text{ and } R^{13} & = \text{independently selected from hydrogen, carbamoyl or } C_{1-6}\text{-alkyl; wherein } R^{12} \text{ and } R^{13} \text{ may be independently optionally substituted on carbon by one or more substituents selected from } R^{25} \text{ and wherein: } \\
R^{14} & = \text{selected from carbamoyl, hydroxycarbamoyl, } C_{1-6}\text{-alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C_{1-6}\text{-alkylene})_p-R^{27}-(C_{1-6}\text{-alkylene})_p; wherein } R^{14} \text{ may be optionally substituted on carbon by one or more substituents selected from } R^{25} \text{; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from } R^{35} \text{; or } R^{14} \text{ is a group of formula (IC) (as depicted above) wherein: } \\
R^{15} & = \text{hydrogen; } \\
R^{16} & = C_{1-6}\text{-alkyl; wherein } R^{16} \text{ may be optionally substituted on carbon by one or more groups selected from } R^{31}; \text{ n is } 1; \\
R^{23} & = \text{hydroxy; }
\end{align*}
\]
EP 1 430 040 B1

R25, R29 or R31 are independently selected from halo, hydroxy, amino, sulphonylamino, C1-alkoxy, N,N,N-(C1-alkyl)3ammonio, N,N-(C1-alkyl)2-sulphamoylamino, C1-alkoxy-carbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C1-alkylene)p-R32-(C1-alkylene)q- or heterocyclyl-(C1-alkylene)R33-(C1-alkylene)q-; wherein R25, R29 or R31 may be independently optionally substituted on carbon by one or more R34; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R35; R27, R32 or R33 are independently selected from -O-, -NR36C(O)NR36-, -OC(O)N=Cor -NR36C(O)--; wherein R23 is hydrogen; p, q, r and s are independently selected from 0 or 1; R34 is selected from hydroxy, amino, carbamoyl, sulphonylamino or methoxy; R30 or R35 are independently selected from C1-alkyl or C1-alkoxy-carbonyl.

[0052] R5 is a group of formula (IA) as depicted above wherein:

X is -O-;
R7 is hydrogen;
R8 is hydrogen;
R9 is hydrogen;
Ring A is phenyl;
R10 is carbamoyl or a group of formula (IB) (as depicted above) wherein:
R11 is hydrogen;
R12 and R13 are independently selected from hydrogen, carbamoyl or C1-alkyl; wherein R12 and R13 may be independently optionally substituted on carbon by one or more substituents selected from R25;
R14 is selected from carbamoyl, hydroxyaminocarbonyl, C1-alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C1-alkylene)p-R27-(C1-alkylene)q-; wherein R14 may be optionally substituted on carbon by one or more substituents selected from R29; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R35; or R14 is a group of formula (IC) (as depicted above) wherein:
R15 is hydrogen;
R16 is C1-alkyl; wherein R16 may be optionally substituted on carbon by one or more groups selected from R31; n is 1; R25, R29 or R31 are independently selected from halo, hydroxy, amino, sulphonylamino, C1-alkoxy, N,N,N-(C1-alkyl)3ammonio, N,N-(C1-alkyl)2-sulphamoylamino, C1-alkoxy-carbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C1-alkylene)p-R32-(C1-alkylene)q- or heterocyclyl-(C1-alkylene)R33-(C1-alkylene)q-; wherein R25, R29 or R31 may be independently optionally substituted on carbon by one or more R34; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R35; R27, R32 or R33 are independently selected from -O-, -NR36C(O)NR36-, -OC(O)N=Cor -NR36C(O)--; wherein R23 is hydrogen; p, q, r and s are independently selected from 0 or 1; R34 is selected from hydroxy, amino, carbamoyl, sulphonylamino or methoxy; R30 or R35 are independently selected from C1-alkyl or C1-alkoxy-carbonyl.

[0053] R6 is a group of formula (IA) as depicted above wherein:

X is -O-;
R7 is hydrogen;
R8 is hydrogen;
R9 is hydrogen;
R10 is carbamoyl or a group of formula (IB) (as depicted above) wherein:
R11 is hydrogen;
R12 and R13 are independently selected from hydrogen, carbamoyl or methyl; wherein R12 and R13 may be independently optionally substituted on carbon by one or more substituents selected from R25;
R14 is selected from carbamoyl, hydroxyaminocarbonyl, methyl, ethyl, propyl, phenyl, 1,5-benzodioxepinyl, 2,3-dihydrobenzofuran-3-yl, pipedidinyl, anilinocarbonyl or anilinocarbonyl; wherein R14 may be optionally substituted on carbon by one or more substituents selected from R29; and wherein said piperidinyl may be optionally substituted on nitrogen by a group selected from R30; or R14 is a group of formula (IC) (as depicted above) wherein:
R15 is hydrogen;
R16 is methyl, ethyl or hexyl; wherein R16 may be optionally substituted on carbon by one or more groups selected from R31; n is 1; R25, R29 or R31 are independently selected from fluoro, hydroxy, amino, sulphonylamino, methoxy, N,N,N-trimethylamino,
Therefore in another aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein:

- R² is selected from:
  - N,N-dimethylsulphamoylamino, t-butoxycarbonylamino, phenyl, morpholino, imidazolyl, indolyl, 2,4-thiazolidinedi- onyl, piperezinyl, 2-imidazolidiononyl, phenoxy, benzoyloxycarboxylinominomethyloxy, N⁻-pyridinylureido or N⁻-pyrimidinylureido; wherein R²⁵, R²⁹ or R₃¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein said imidazolyl, indolyl, piperezinyl or 2-imidazolidiononyl may be optionally substituted on nitrogen by a group selected from R³⁵;
  - R²⁷, R³² or R³³ are independently selected from -O-, -NHC(O)NH-, -OC(O)N=O- or -NHC(O)-;
  - p, q, r and s are independently selected from 0 or 1;
  - R³⁴ is selected from hydroxy, amino, carboxamoyl, sulphamoyl or methoxy;
  - R³⁰ or R³⁵ are independently selected from methyl or C₁₋₆alkoxycarbonyl.

- [0054] R⁵ is selected from:
  - N\((\alpha\)-N'-(2-hydroxyethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(2-trimethylaminomethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(2-aminomethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(carboxamoylmethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(N-carbamoylbenzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(N,N,N,N-tetra-(2,2,2-trifluoroethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(N,N,N,N-tetra-(2-fluoroethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(N,N,N,N-tetra-(ethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(N,N,N,N-tetra-(2-hydroxyethyl)carbamoyl]benzyl]carbamoylmethoxy;
  - N\((\alpha\)-N'-(N,N,N,N-tetra-(2-oxoimidazolidin-1-yl)propyl]carbamoyl]benzyl]carbamoylmethoxy; and

- [0055] Ring A is aryl.
- [0056] Ring A is phenyl.
- [0057] X is -O-.
R¹ and R² are independently selected from C₁-₄alkyl;

v is 0;

R³ and R⁶ are hydrogen;

R⁴ is methylthio;

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is aryl;

R¹⁰ is carbamoyl or N-(C₁-₁₀alkyl)carbamoyl or a group of formula (IB) (as depicted above) wherein R¹⁰ is optionally substituted on carbon by one or more substituents selected from R²₃ and wherein:

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or C₁-₄alkyl; wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²₅;

R¹⁴ is selected from carbamoyl, hydroxaminocarbonyl, C₁-₄alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C₁-₆alkylene)ₚ-R₂₇-(C₁-₆alkylene)ₚ'- wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²₉; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R¹⁵ or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

R¹⁶ is C₁-₄alkyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹; n is 1;

R²₃ is hydroxy;

R²₅, R²₉ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, C₁-₄alkoxy, N,N, N-(C₁-₄alkyl)₃ammonio, N,N-(C₁-₄alkyl)₂sulphamoylamino, C₁-₄alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C₁-₆alkylene)ₚ-R₂₇-(C₁-₆alkylene)ₚ'- or heterocyclyl-(C₁-₄alkyl)ₚₗ-R₃₃-(C₁-₆alkylene)pₗ'- wherein R²₅, R²₉ or R³¹ may be independently optionally substituted on carbon by one or more R³₄; and wherein if said heterocycl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³₅;

R²₇, R³₂ or R₃₃ are independently selected from -O-, -NR₃₆C(O)NR₃₆-, -OC(O)N=Cor -NR₃₆C(O)_; wherein R²₃ is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R³₄ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³₀ or R³₅ are independently selected from C₁-₄alkyl or C₁-₄alkoxycarbonyl;

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

[0059] In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

[0060] In a further aspect of the invention, preferred compounds of the invention are Examples 3, 5, 8, 18, 19, 22, 27, 28, 34, 36, 37 or 41 or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

[0061] Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

[0062] Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1): oxidising a benzothiazepine of formula (II):
Process 2): for compounds of formula (I) wherein X is -O-, -NR^a or -S--; reacting a compound of formula (IIIa) or (IIIb):

with a compound of formula (IV):

wherein L is a displaceable group;

Process 3): reacting an acid of formula (Va) or (Vb):
or an activated derivative thereof; with an amine of formula (VI):

(VI)

Process 4): for compounds of formula (I) wherein R\textsuperscript{10} is a group of formula (IB); reacting a compound of formula (I) wherein R\textsuperscript{10} is carboxy with an amine of formula (VII):

(VII)

Process 5): for compounds of formula (I) wherein R\textsuperscript{10} is a group of formula (IB) and R\textsuperscript{14} is a group of formula (IC) reacting a compound of formula (I) wherein R\textsuperscript{14} is carboxy with an amine of formula (VIII):

\[ R^{15}R^{16}NH \] (VIII)

Process 6) for compounds of formula (I) wherein one of R\textsuperscript{4} and R\textsuperscript{5} are independently selected from C\textsubscript{1-6}alkylthio optionally substituted on carbon by one or more R\textsuperscript{17} ; reacting a compound of formula (IX\textsubscript{a}) or (IX\textsubscript{b}):
wherein L is a displaceable group; with a thiol of formula (X):

\[ \text{Ry-H} \quad (X) \]

wherein Ry is C\textsubscript{1-6}alkylthio optionally substituted on carbon by one or more R\textsubscript{16}; and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

[0063] L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

[0064] R\textsuperscript{x} is C\textsubscript{1-6}alkyl. Preferably R\textsuperscript{x} is methyl or ethyl. More preferably R\textsuperscript{x} is methyl.

[0065] Specific reaction conditions for the above reactions are as follows.

**Process 1:** Benzothiazepines of formula (II) may be oxidised under standard sulphur oxidation conditions; for example using hydrogen peroxide and trifluoroacetic acid at a temperature in the range of 0°C to reflux, preferably at or near room temperature.

Compounds of formula (II) may be prepared according to Scheme I for compounds of formula (I) wherein R\textsuperscript{x} and Ry are hydrogen. The skilled person will appreciate that where R\textsuperscript{x} and Ry are not both hydrogen the following synthetic route needs to be manipulated using procedures known to the skilled person:
wherein L is a displaceable group as defined above, and Y is a displaceable group, for example halo.

Compounds of formula (IIa) and (IIc) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

**Process 2**: Compounds of formula (IIIa) or (IIIb) may be reacted with compounds of formula (IV) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (IIIa) or (IIIb) may be prepared in a similar manner to compounds of formula (II) (but wherein R₄ or R₅ is -OH, -NH(R₆) or -SH followed by the oxidation step of Process 1).

Compounds of formula (IV) are commercially available compounds, or they are known in the literature, or they are...
prepared by standard processes known in the art. 
*Process 3)* and *Process 4)* and *Process 5):* Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethyl-amine, pyridine, or 2,6-di-alkyl-pyridines such as 2,6-lutidine or 2,6-di-tert-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40˚C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40˚C.

Compounds of formula (Va) or (Vb) wherein X=-O-, -NR₃-, -S- may be prepared according to Scheme 2:

![Scheme 2](image)

wherein L is a displaceable group as defined above.

Compounds of formula (Va) and (Vb) where X is -SO- or -SO₂- may be prepared by oxidising the resulting compounds of formula (Va) and (Vb) from *Scheme 2* where X is -S-.

Compounds of formula (Va) or (Vb) wherein X is -CH₂- may be prepared according to *Scheme 3*. 
Compounds of formula (Vc), (VI), (VII) and (VIII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 6: Compounds of formula (IXa) and (IXb) may be reacted with thiols of formula (X) in the presence of base, for example an inorganic base such as sodium carbonate or an organic base such as Hunigs base, in the presence of a suitable solvent such as DMF or THF at a temperature in the range of 0˚C to reflux.

Compounds of formula (IXa) and (IXb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein one of R⁴ and R⁵ is L.

Compounds of formula (X) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment...
with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxyacarbonyl group, for example a methoxyacarbonyl, ethoxyacarbonyl or t-butoxyacarbonyl group, an aroyl group, for example benzoylcarbonyl, or an aryl group, for example benzoyl.

The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxyacarbonyl group or an aryl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a t-butoxyacarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an aroyl or aroxyacarbonyl group such as a benzoyloxyacarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron trifluoride.

A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aryl group, for example benzoyl, or an aroyl group, for example benzoyl.

The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aryl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-buty group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess IBAT inhibitory activity. These properties may be assessed, for example, using an in vitro test assay for studying the effect on bile acid uptake in IBAT-transfected cells (Smith. L., Price-Jones M. J., Hugnes K. T. and Jones N. R. A.; J Biomolecular Screening, 3, 227-230) or in vivo by studying the effect on radiolabelled bile acid absorption in mice (Kemp M. C., Breaedy L. E. and Root C. J. J Lip Res 1995, 36, 1998-1105).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravenous or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, preferably 0.02 -50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg, particularly 0.1-10 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, are effective IBAT inhibitors, and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions.
[0081] Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as defined hereinbefore for use as a medicament.

[0082] According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as defined hereinbefore in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

[0083] According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

[0084] According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

[0085] According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

[0086] Herein, where "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" is referred to particularly this refers to the treatment of hyperlipidaemic conditions. In another aspect, "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" refers to the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridaemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hyperalphalipoproteinemia (low HDL). In another aspect "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" refers to the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrythmia, 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, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks. In another aspect "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" refers to the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

[0087] According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal or an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

[0088] According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

[0089] The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 0.1-50 mg/kg preferably 0.1-10 mg/kg is envisaged.

[0090] The IBAT inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore and an additional IBAT inhibitory substance as defined hereinbefore and an additional hypolipidaemic agent for the conjoint treatment of hyperlipidaemia.

[0091] In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt 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 or solvates of such salts 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-enolic 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-enolic acid, or a pharmaceuti-
cally acceptable salt, solvate or solvate of such a salt thereof. A more particular statin is rosuvastatin calcium salt.

[0092] In an additional aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt 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 or solvate of such a salt thereof.

[0093] 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.

[0094] 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 cholesterolaemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

[0095] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

[0096] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

[0097] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

[0098] 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 an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

[0099] 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.

[0100] 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 an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof and a bile acid binder.

[0101] According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

[0102] According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in a prodrug thereof, in a first unit dosage form;

b) a bile acid binder; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

[0103] According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof; in a second unit dosage form;

c) a bile acid binder; in a third unit dosage form; and

d) container means for containing said first, second and third dosage forms.
According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and a bile acid binder, in the manufacture of a medicament 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 the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in the manufacture of a medicament 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 the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and a bile acid binder, in the manufacture of a medicament 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 the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates or solvate of such salts 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, altiopril, attiopril calcium, anconevin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, clazapril, clazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosfenoprilat, fosfenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, ychium A, lycium B, mixanapril, moxipril, moxiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pripipril, quinapril, quinapril hydrochloride, quin- aprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, tenodapril, tenodaprilat, utiapril, 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.
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.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt 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 or solvates of such salts thereof are all 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, NN622/Ragaglitazar, BMS 298555 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl] propanoic acid and pharmaceutically acceptable salts thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, or solvate of such a salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

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 or solvate of such a salt thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in the manufacture of a medicament 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 the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

Many of the intermediates described herein are novel and are thus provided as a further feature of the invention.

In the above other pharmaceutical composition, process, use and medicament manufacture features, the alternative and particular embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non-limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:
(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;
(iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 µm (Merck);
(iv) yields are given for illustration only and are not necessarily the maximum attainable;
(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated CD3OD (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-600 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; q', doublet; m, multiplet; br, broad; LCMS were recorded on a Waters ZMD, LC column xTerra MS C8(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH+);
(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Kromasil C8, 7µm, (Akzo Nobel); MeCN and de-ionised water 100 mM ammonium acetate as mobile phases, with suitable composition;
(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;
(viii) where solutions were dried sodium sulphate was the drying agent;
(ix) where an "ISOLUTE" column is referred to, this means a column containing 2 g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE"; “ISOLUTE” is a registered trade mark;
(x) the following abbreviations may be used hereinbefore or hereinafter: -

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM</td>
<td>dichloromethane;</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide;</td>
</tr>
<tr>
<td>TBTU</td>
<td>o-Benzotriazol-1-yl,N,N',N'-tetramethyluronium tetrafluoroborate;</td>
</tr>
<tr>
<td>EIOAc</td>
<td>ethyl acetate;</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile;</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid;</td>
</tr>
<tr>
<td>HATU</td>
<td>o-(7-azabenzo[1,5-]diazepin-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate; and</td>
</tr>
<tr>
<td>DIPEA</td>
<td>di-isopropylethylamine.</td>
</tr>
</tbody>
</table>

**Example 1**

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-((R)-α-[N-((2-hydroxyethyl) carbamoylbenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0125] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-((R)-α-carboxybenzyl) carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine Method 1; 50 mg, 0.082 mmol) and 2-aminoethanol (18 µl, 0.3 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. An additional amount of 2-aminoethanol (100 µl, 1.65 mmol), TBTU (90 mg, 0.28 mmol) and DMF (2 ml) were added. The reaction mixture was stirred at night at room temperature. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 7 mg (13%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.25 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.2 (s, 2H), 3.5-8.85 (m, 4H), 4.6-4.8 (m, 2H), 5.5 (s, 1H), 6.75 (s, 1H), 6.95-7.5 (m, 11H).

**Example 2**

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-[(R)-α-[N-((2-trimethylaminoethyl) carbamoyl)benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt

[0126] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-((R)-α-carboxybenzyl) carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), (2-aminoethyl)trimethylammonium chloride hydrochloride
Example 3

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-[\(N\)-\(\text{\'-(2-aminoethyl)carbamoyl] benzyncarbamoylmethoxy}\)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetic acid salt

[0127] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-carboxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol) and t-butyl N-(2-aminoethyl)carbamate (40 mg, 0.25 mmol) were added to DCM (5 ml). TBTU (42 mg, 0.13 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. TFA (1 ml) was added and the mixture was stirred for 1 hour at room temperature. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 8 mg (13%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.25 (m, 4H), 1.35-1.65 (m, 4H), 1.9 (s, 3H), 2.1 (s, 3H), 2.95-3.1 (m, 4H), 3.25 (s, 2H), 3.5-3.85 (m, 4H), 4.75 (s, 2H), 5.45 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H).

Example 4

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-[\(N\)-\(\text{\'-(carbamoylmethyl) carbamoyl] benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0128] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-carboxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), glycinamide hydrochloride (27 mg, 0.24 mmol) and N-methylmorpholine (44 ml, 0.4 mmol) were added to DCM (4 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred at room temperature for 2 hours. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (55:45) as eluent. The collected fractions were lyophilised to obtain 7 mg (13%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.35 (m, 4H), 1.4-1.65 (m, 4H), 3.25 (s, 2H), 3.7-4.0 (m, 3H), 4.7-4.8 (m, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H).

Example 5

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-[\(N\)-\(\text{\'-(S)-1-carbamoyl-2-hydroxyethyl)carbamoyl] benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0129] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-carboxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), L-serinamide hydrochloride (35 mg, 0.25 mmol) and N-methylmorpholine (44 ml, 0.4 mmol) were added to DCM (4 ml) and DMF (1 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred at room temperature for 2 hours. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 5 mg (9%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.35 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.25b (s, 2H), 3.6-3.9 (m, 4H), 4.35-4.5 (m, 1H), 4.7-4.8 (m, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H).

Example 6

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\(N\-{\text{(R)-\alpha}}\)-[\(N\)-\(\text{\'-(S)-1-carbamoyl-2-hydroxyethyl)carbamoyl] benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0130] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 17; 50 mg, 0.1 mmol), D-phenylglycinamide (18 mg, 0.12 mmol) and 2,6-lutidine (58 ml, 0.5 mmol) were added to DCM (3 ml). TBTU (42 mg, 0.13 mmol) was added and the reaction mixture was stirred for 3 hours at room temperature. The mixture was purified by column chromatography on silica gel using EtOAc as eluent. The residue was dissolved in toluene and was evaporated under reduced pressure. The residue was solved in MeCN/water (50/50) and the mixture
was lyophilised to obtain 27 mg (42%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.2 (s, 2H), 3.55-3.9 (m, 2H), 4.7 (ABq, 2H), 5.5 (s, 1H), 6.75 (s, 1H), 6.95-7.5 (m, 11H).

Example 7

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-(R)-\(\alpha\)-(N-(1,1-di-hydroxymethyl-2-hydroxyethyl)carbamoyl)benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0131] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(\(N\)-(R)-\(\alpha\)-carboxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), tris(hydroxymethyl)aminomethane (30 mg, 0.25 mmol) and 2,6-lutidine (58 \(\mu\)l, 0.5 mmol) were added to DCM (3 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred for 4 hours at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (55:45) as eluent. The collected fractions were lyophilised to obtain 5 mg (9%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.6-3.8 (m, 7H), 4.7-4.8 (m, 2H), 5.6 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H).

Example 8

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(\(N\)-(R)-\(\alpha\)-carboxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), glycine hydroxamic acid (22 mg, 0.24 mmol) and 2,6-lutidine (58 \(\mu\)l, 0.5 mmol) were added to DCM (3 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred for 3 hours at room temperature. The mixture was washed with water and the organic layer was dried and evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 7 mg (13%) of the title compound. NMR (500 MHz): 0.7-0.9 (m, 6H), 0.95-1.3 (m, 4H), 1.4-1.7 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7-3.95 (m, 4H), 4.6 (s, 2H), 5.6 (s, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H).

Example 9

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(\(N\)-(R)-\(\alpha\)-\(\alpha\)-[N-(2,2,2-trifluoroethyl)carbamoylmethyl]carbamoyl)benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0132] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(\(N\)-(R)-\(\alpha\)-carboxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 6; 50 mg, 0.072 mmol), trifluoroethylamine (8.5 mg, 0.086 mmol) and TBTU (27 mg, 0.084 mmol) were dissolved in DCM and 2,6-lutidine (0.020 ml, 0.18 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and was filtered through a short silica column. The product was further purified with preparative HPLC (MeCN/ammonium acetate buffer (50:50→100:0)) to give the title compound (45 mg, 81%). NMR (400 MHz, DMSO-\(d_6\)): 0.75 (m, 6 H), 0.95-1.46 (m, 12 H), 2.15 (s, 3 H), 3.28 (m, 2 H), 3.60-3.94 (m, 4 H), 4.73/4.84 (ABq, 2 H), 5.56 (d, 1 H), 6.67 (s, 1 H), 6.85 (t, 1 H), 6.99 (d, 2 H), 7.17-7.46 (8 H), 8.53 (t, 1 H), 8.61 (d, 1 H), 8.75 (t, 1 H).

Examples 10-17

[0134] The following examples were prepared by the procedure of Example 9 using 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(\(N\)-(R)-\(\alpha\)-[N-(carboxymethyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 6) and the appropriate amine.
<table>
<thead>
<tr>
<th>Ex</th>
<th>R</th>
<th>NMR 400 MHz, DMSO-d$_6$</th>
</tr>
</thead>
</table>
| 10$^1$ | \[
\begin{array}{c}
\text{HO} \\
\text{HO} \\
\end{array}
\] | 0.74 (m, 6H), 0.95-1.45 (m, 12H), 1.85 (s, 1H), 2.16 (s, 3H), 3.00 (m, 1H), 3.25-3.40 (br s, 5H), 3.45-3.85 (m, 4H), 4.72/4.84 (ABq, 2H), 5.60 (d, 1H), 5.75 (s, 1H), 6.65 (s, 1H), 6.86 (t, 1H), 6.98 (d, 2H), 7.17-7.46 (m, 8H), 7.76 (t, 1H), 8.58 (d, 1H), 8.66 (t, 1H) |
| 11 | \[
\begin{array}{c}
\text{H} \\
\end{array}
\] | 0.74 (m, 6H), 0.96-1.48 (m, 12H), 2.15 (s, 3H), 3.28 (m, 1H), 3.64 (dd, 1H), 3.90 (dd, 1H), 4.33 (t, 1H), 4.45 (t, 1H), 4.73/4.84 (ABq, 2H), 5.55 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.18-7.46 (m, 8H), 8.08 (t, 1H), 8.61 (d, 1H), 8.70 (t, 1H) |
| 12 | \[
\begin{array}{c}
\text{NH} \\
\end{array}
\] | 0.74 (m, 6H), 0.97 (t, 3H), 0.95-1.48 (m, 12H), 2.15 (s, 3H), 3.05 (m, 2H), 3.24 (m, 2H), 3.65 (dq, 2H), 4.74/4.84 (ABq, 2H), 5.53 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.17-7.46 (m, 8H), 7.73 (t, 1H), 8.62 (d, 1H), 8.68 (t, 1H) |
| 13 | \[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\end{array}
\] | 0.74 (m, 6H), 0.94-1.48 (m, 12H), 2.15 (s, 3H), 3.65-3.85 (m, 2H), 3.70 (s, 3H), 4.14 (t, 2H), 4.72/4.83 (ABq, 2H), 5.60 (d, 1H), 6.60-7.01 (m, 7H), 7.15-7.45 (m, 8H), 8.17 (t, 1H), 8.60 (d, 1H), 8.70 (t, 1H) |
| 14 | \[
\begin{array}{c}
\text{N} \\
\text{H} \\
\end{array}
\] | 0.75 (m, 6H), 0.95-1.46 (m, 12H), 2.15 (s, 3H), 3.20 (s, 3H), 3.30 (t, 2H), 3.60 (dd, 1H), 3.76 (dd, 1H), 4.74/4.86 (ABq, 2H), 5.54 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.17-7.45 (m, 8H), 7.85 (t, 1H), 8.61 (d, 1H), 8.69 (t, 1H) |
| 15$^1$ | \[
\begin{array}{c}
\text{O} \\
\end{array}
\] | 0.75 (m, 6H), 0.95-1.46 (m, 12H), 2.13 (s, 3H), 2.75 (t, 2H), 2.58 (dd, 1H), 3.74 (dd, 1H), 4.74/4.85 (ABq, 2H), 5.53 (d, 1H), 6.66 (s, 1H), 6.85 (t, 1H), 6.99 (d, 2H), 7.16-7.47 (m, 10H), 7.71 (m, 2H), 7.89 (t, 1H), 8.65 (d, 1H), 8.69 (t, 1H) |
| 16$^1$ | \[
\begin{array}{c}
\text{N} \\
\end{array}
\] | 0.75 (m, 6H), 0.95-1.46 (m, 12H), 2.15 (s, 3H), 2.62 (s, 6H), 2.91 (m, 2H), 3.13 (m, 2H), 3.61 (dd, 1H), 3.76 (dd, 1H), 4.74/4.84 (ABq, 2H), 5.56 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.14-7.48 (m, 8H), 7.91 (t, 1H), 8.60 (d, 1H), 8.68 (t, 1H) |
Example 18
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-(N-{(2)-(S)-(3)-(4)-(5)-(2,3,4,5-pentahydroxyhexyl) carbamoyl}benzyl)carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine)

[0135] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-carboxybenzyl) carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 8; 60 mg, 0.094 mmol) and 1-amino-1-deoxy-D-glucitol (20 mg, 0.11 mmol) were dissolved in DMF (2 ml) (40˚C for a few minutes was required). 2,6-Dimethylpyridine (22 ml, 0.19 mmol) and HATU (43 mg, 0.111 mmol) were added at room temperature to the solution and the mixture was stirred for 30 minutes. The solvent was evaporated under reduced pressure and the product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 52 mg (69%). NMR (400 MHz): 0.77-0.85 (brt, 6H), 1.0-1.35 (m, 8H), 1.35-1.6 (m, 4H), 2.15 (s, 3H), 3.16-3.27 (m, 3H), 3.51 (dd, 1H) 3.54-3.86 (m, 8H), 4.70 (ABq, 2H), 5.52 (s, 1H), 6.70 (s, 1H), 6.98 (t, 1H), 7.11 (brd, 2H), 7.24-7.41 (m, 6H), 7.44 (brd, 2H); m/z 802.5.

Example 19
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2)-(3)-(4)-(5)-(2,3,4,5-pentahydroxyhexyl)} carbamoyl}benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0136] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-(N-{(3-morpholinopropyl) carbamoyl}benzyl)carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 40 mg, 0.065 mmol), 1-amino-1-deoxy-D-glucitol (20 mg, 0.11 mmol) and DIPEA (55 µl, 0.32 mmol) were dissolved in DMF (2 ml) (40˚C for a few minutes was required). TBTU (25 mg, 0.079 mmol) was added at room temperature to the solution and the mixture was stirred over night. The solvent was evaporated under reduced pressure and the product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 31 mg (61%). NMR (400 MHz): 0.75-0.90 (m, 6H), 1.0-1.35 (m, 4H), 1.35-1.7 (m, 4H), 2.15 (s, 3H), 3.17-3.27 (m, 3H), 3.51 (dd, 1H) 3.54-3.86 (m, 8H), 4.70 (ABq, 2H), 5.52 (s, 1H), 6.70 (s, 1H), 6.98 (t, 1H), 7.11 (brd, 2H), 7.24-7.41 (m, 6H), 7.44 (brd, 2H); m/z 774.4.

Example 20
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(3-morpholinopropyl) carbamoyl}benzyl)carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0137] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-(N-{(3-morpholinopropyl) carbamoyl}benzyl)carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 40 mg, 0.065 mmol), 1-amino-1-deoxy-D-glucitol (20 mg, 0.11 mmol) and DIPEA (55 µl, 0.32 mmol) were dissolved in DMF (2 ml) (40˚C for a few minutes was required). TBTU (25 mg, 0.079 mmol) was added at room temperature to the solution and the mixture was stirred over night. The solvent was evaporated under reduced pressure and the product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 31 mg (61%). NMR (400 MHz): 0.75-0.90 (m, 6H), 1.0-1.35 (m, 4H), 1.35-1.7 (m, 4H), 2.15 (s, 3H), 3.17-3.27 (m, 3H), 3.51 (dd, 1H) 3.54-3.86 (m, 8H), 4.70 (ABq, 2H), 5.52 (s, 1H), 6.71 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.23-7.50 (m, 8H); m/z 774.4.
Examples 21-39

[0138] The following examples were prepared by the procedure of Example 20 using 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-((R)-α-carboxybenzyl) carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1) and the appropriate amine.

<table>
<thead>
<tr>
<th>Ex</th>
<th>R</th>
<th>I NMR 400 MHz</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td></td>
<td>0.75-0.87 (m, 6H), 1.01-1.35 (m, 4H), 1.35-1.67 (m, 4H), 2.15 (s, 3H), 2.81 (t, 2H), 3.23 (s, 3H), 3.40-3.53 (m, 2H), 3.60-3.86 (m, 2H), 4.70 (ABq, 2H), 5.38 (s, 1H), 6.71 (s, 1H), 6.85 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.27 (t, 2H), 7.31-7.43 (m, 6H), 8.21 (s, 1H)</td>
<td>704.5</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>0.74-0.87 (m, 6H), 1.0-1.3 (m, 4H), 1.37-1.66 (m, 4H), 2.16 (s, 3H), 2.69 (s, 6H), 3.05-3.15 (m, 4H), 3.23 (s, 2H), 3.55-3.9 (m, 2H), 4.70 (ABq, 2H), 5.47 (s, 1H), 6.71 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.23-7.48 (m, 8H)</td>
<td>760.4</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>0.73-0.86 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.65 (m, 4H), 2.15 (s, 3H), 3.21 (s, 2H), 3.54-3.9 (m, 4H), 3.94-4.06 (m, 2H), 4.69 (ABq, 2H), 5.51 (s, 1H), 6.68-6.85 (m, 5H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.22-7.34 (m, 5H), 7.37-7.46 (m, 3H)</td>
<td>746.4</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>0.75-0.85 (m, 6H), 1.0-1.27 (m, 4H), 1.36-1.66 (m, 4H), 2.15 (s, 3H), 3.23 (s, 2H), 3.45 (ABq, 2H), 3.6-4.05 (m, 6H), 4.70 (ABq, 2H), 5.54 (s, 1H), 6.71 (s, 1H), 6.86 (s, 4H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.23-7.37 (m, 5H), 7.40 (s, 1H), 7.45 (brd, 2H)</td>
<td>788.4</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>0.76-0.84 (m, 6H), 1.0-1.3 (m, 4H), 1.3-1.67 (m, 13H), 2.16 (s, 3H), 3.20 (s, 2H), 3.58-3.9 (m, 2H), 4.34 (s, 2H), 4.72 (ABq, 2H), 5.53 (s, 1H), 6.71 (s, 1H), 6.78 (d, 1H), 6.96 (t, 1H), 7.06-7.16 (m, 3H), 7.22-7.47 (m, 10H)</td>
<td>815.5</td>
</tr>
<tr>
<td>Ex</td>
<td>R</td>
<td>I NMR 400 MHz</td>
<td>m/z</td>
</tr>
<tr>
<td>----</td>
<td>---</td>
<td>---------------</td>
<td>-----</td>
</tr>
<tr>
<td>26</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>0.72-0.9 (m, 6H), 0.95-1.35 (m, 4H), 1.35-1.67 (m, 4H), 2.13 (s, 3H), 3.21 (brs, 2H), 3.57-3.9 (m, 2H), 4.46 (brs, 2H), 4.70 (ABq, 2H), 5.27 (brs, 2H), 5.51 (s, 1H), 6.68-6.73 (m, 1H), 6.96 (t, 1H), 7.05-7.15 (m, 2H), 7.20-7.54 (m, 15H), 7.68-7.79 (m, 2H)</td>
<td>876.4</td>
</tr>
<tr>
<td>27</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(600 MHz, 1:1 diastereomeric mixture) 0.74-0.82 (m, 6H), 1.0-1.3 (m, 4H), 1.3-1.65 (m, 4H), 2.15 (s, 3H), 3.04 (s, 1.5H), 3.12 (s, 1.5MHz), 3.18-3.3 (m, 3H), 3.35-3.44 (m, 1H), 3.55-3.9 (m, 2H), 3.98 (dd, 0.5H), 4.04 (dd, 0.5H), 4.63-4.74 (m, 2H), 5.48 (s, 0.5H), 5.50 (s, 0.5H), 6.42 (dd, 0.5H), 6.55 (dd, 0.5H), 6.62 (d, 0.5H), 6.66-6.72 (m, 2.5H), 6.95 (t, 1H), 7.08 (brd, 2H), 7.23-7.40 (m, 8H)</td>
<td>774.5</td>
</tr>
<tr>
<td>28</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(600 MHz) 0.75-0.83 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.63 (m, 4H), 2.15 (s, 3H), 3.14-3.44 (m, 6H), 3.59-3.88 (m, 3H), 4.69 (ABq, 2H), 5.50 (s, 1H), 6.70 (s, 1H), 6.95 (t, 1H), 7.08 (d, 2H), 7.24-7.32 (m, 3H), 7.34 (t, 2H), 7.39 (s, 1H), 7.43 (brd, 2H)</td>
<td>684.4</td>
</tr>
<tr>
<td>29</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>(600 MHz) 0.77 (brt, 6H), 0.95-1.28 (m, 4H), 1.33-1.60 (m, 4H), 2.14 (s, 3H), 2.77-2.89 (m, 2H), 3.18 (brs, 2H), 3.39-3.50 (m, 2H), 3.50-3.85 (m, 5H), 4.66 (ABq, 2H), 5.43 (s, 1H), 6.68-6.72 (m, 2H), 6.77 (s, 1H), 6.94 (t, 1H), 6.99 (d, 1H), 7.06 (brd, 2H), 7.16 (d, 1H), 7.2-7.36 (m, 7H), 7.38 (s, 1H)</td>
<td>783.4</td>
</tr>
<tr>
<td>30</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>(600 MHz) 0.75-0.85 (m, 6H), 1.0-1.27 (m, 4H), 1.38-1.63 (m, 4H), 2.17 (s, 3H), 3.22 (brs, 2H), 3.33-3.39 (m, 1H), 3.47-3.53 (m, 1H), 3.57-3.96 (m, 6H), 4.69 (ABq, 2H), 5.38 (s, 1H), 6.71 (s, 1H), 6.95 (t, 1H), 7.08 (brd, 2H), 7.23-7.40 (m, 8H)</td>
<td>753.5</td>
</tr>
<tr>
<td>31</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>(600 MHz) 0.74-0.83 (m, 6H), 1.0-1.28 (m, 4H), 1.38-1.62 (m, 4H), 1.7 (m, 2H), 2.14 (s, 3H), 2.44-2.56 (m, 2H), 2.56-2.86 (m, 5H), 2.86-3.10 (m, 4H), 3.22 (brs, 2H), 3.25 (t, 2H), 3.57-3.87 (m, 4H), 4.69 (ABq, 2H), 5.38 (s, 1H), 6.70 (s, 1H), 6.96 (t, 1H), 7.08 (brd, 2H), 7.26 (t, 2H), 7.30-7.40 (m, 4H), 7.43 (d, 2H)</td>
<td>750.6</td>
</tr>
<tr>
<td>32</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>(600 MHz) 0.74-0.85 (m, 6H), 1.0-1.3 (m, 4H), 1.37-1.65 (m, 4H), 2.17 (s, 3H), 2.81 (t, 2H), 3.22 (brs, 2H), 3.32-3.41 (m, 1H), 3.50-3.59 (m, 1H), 3.6-3.85 (m, 2H), 4.68 (ABq, 2H), 5.40 (s, 1H), 6.72 (s, 1H), 6.97 (t, 1H), 7.09 (d, 2H), 7.17 (d, 2H), 7.27 (t, 2H), 7.31-7.37 (m, 5H), 7.39 (s, 1H), 7.69 (d, 2H)</td>
<td>793.5</td>
</tr>
<tr>
<td>33</td>
<td><img src="image8.png" alt="Structure" /></td>
<td>(600 MHz, 1:1 diastereomeric mixture) 0.72-0.84 (m, 6H), 0.98-1.28 (m, 4H), 1.36-1.61 (m, 4H), 2.13-2.16 (m, 3H), 2.68 (dd, 0.5H), 2.82 (dd, 0.5H), 3.02-3.14 (m, 1H), 3.14-3.23 (m, 2H), 3.38-3.45 (m, 1H), 3.46-3.53 (m, 1H), 3.55-3.9 (m, 8H), 4.61-4.66 (m, 3H), 5.48 (s, 0.5H), 5.49 (s, 0.5H), 6.36 (s, 0.5H), 6.37 (s, 0.5H), 6.65 (s, 0.5H), 6.69-6.71 (m, 1H), 6.75 (s, 0.5H), 6.95 (t, 1H), 7.07 (brd, 2H), 7.18-7.40 (m, 8H)</td>
<td>802.5</td>
</tr>
</tbody>
</table>
Example 40

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[(N-(R)-α-[N-(3-aminobenzyl) carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0139] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-1,5-α-[N-3-(t-butoxycarbonylamino)benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 25; 10 mg, 0.012 mmol) was dissolved in EtOAc (15 ml) saturated with HCl (gas). The reaction mixture was left for 1 hour. The solvent was evaporated under reduced pressure and the residue was freeze-dried to give the title compound in quantitative yield. NMR (600 MHz) 0.74-0.85 (m, 6H), 1.0-1.1 (m, 4H), 1.3-1.66 (m, 4H), 2.16 (s, 3H), 3.13-3.45 (m, 8H), 3.6-4.0 (m, 4H), 4.70 (Abq, 2H), 5.45 (s, 1H), 6.72 (s, 1H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.22-7.45 (m, 8H); m/z 722.5.
Example 41

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-[((R)-α-[N-(piperidin-4-ylmethyl) carbamoyl]benzyl)carbamoyl]methoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt (Compound 2)

[0140] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-(N-(t-butoxycarbonyl)piperidin-4-ylmethyl)carbamoyl]benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 34; 7.3 mg, 0.00904 mmol) was dissolved in ethyl acetate saturated with hydrogen chloride gas (15 ml). After 1.5 hours the reaction mixture was evaporated under reduced pressure. The product was lyophilised giving 4.6 mg (68%) of the title compound. NMR (400 MHz): 0.74-0.87 (m, 6H), 0.9-1.7 (m, 10H), 1.73-1.9 (m, 3H), 2.15 (s, 3H), 2.83-2.98 (m, 2H), 3.04-3.40 (m, 6H), 3.6-3.9 (m, 2H), 4.71 (ABq, 2H), 5.42 (s, 1H), 6.72 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.22-7.49 (m, 8H); 707.6.

Example 42

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-(R)-α-[N-(4-amidinobenzyl)carbamoyl]benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt (Compound 1)

Example 43

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-[N-((R)-α-[N-(4-amidinobenzyl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt (Compound 2)

[0141] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-(N-R)-α-[N'-4-(N'-benzylxocarbonylamidino)benzyl]carbamoyl]benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 26; 18 mg, 0.020 mmol) was dissolved in ethanol (10 ml), palladium on activated carbon (5%, 10 mg) was added and a few drops of acetic acid. The mixture was treated under a hydrogen atmosphere for a couple of hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated under reduced pressure. The reaction was not complete. The above had to be repeated two times. The mixture was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give 59 mg (58%) of the title compound. NMR (600 MHz): 0.79 (t, 6H), 1.0-1.25 (m, 8H), 1.36-1.54 (m, 4H), 2.13 (s, 3H), 3.19 (dd, 1H), 3.23 (bs, 2H), 3.49 (dd, 2H), 3.55-3.85 (m, 8H), 4.68 (ABq, 2H), 5.13 (dd, 1H), 7.04 (d, 2H), 7.13 (d, 1H), 7.23 (d, 1H), 7.3-7.46 (m, 6H), 7.53 (d, 1H), 7.69 (d, 2H).

Example 44

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N-(2-ylmethyl)carbamoyl]-4-hydroxybenzyl]carbamoylmethoxy)-2,3,4,5,6-pentahydroxyhexyl]carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0142] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[carboxyl]-4-hydroxybenzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 2 of WO 02/50051; 81 mg, 0.124 mmol), (2R,3R,4R,5S)-6-aminoheptane-1,2,3,4,5-pentol (28.9 mg, 0.15 mmol) and 2,6-dimethylpyridine (28.8 mg, 0.25 mmol) was dissolved in DMF (3 ml). TBTU (48 mg, 0.15 mmol) was added. The reaction mixture was stirred for 3-4 hours. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give 59 mg (58%) of the title compound. NMR (600 MHz): 0.79 (t, 6H), 1.0-1.25 (m, 8H), 1.36-1.54 (m, 4H), 2.13 (s, 3H), 3.19 (dd, 1H), 3.23 (bs, 2H), 3.49 (dd, 2H), 3.55-3.85 (m, 8H), 4.68 (ABq, 2H), 5.38 (s, 1H), 6.68 (s, 1H), 6.74 (d, 2H), 6.96 (d, 1H), 7.10 (brd, 2H), 7.21-7.29 (m, 4H), 7.37 (s, 1H).

Example 45


[0143] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-1-phenyl-1-carboxyethyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 1 of WO 02/50051; 40 mg, 0.063 mmol), (2R,3R,4R,5S)-6-(methylamino)hexane-1,2,3,4,5-pentol (16 mg, 0.082 mmol) and N-Methylmorpholine (30 mg, 0.30 mmol) was dissolved in DMF (1ml). TBTU (25 mg, 0.078 mmol) was added. The mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/ammonium acetate buffer to give, after lyophilisation, 6 mg (12%) of the title compound. M/z 817.2.
Preparation of Starting Materials

[0144] The starting materials for the Examples above are either commercially available or are readily prepared by standard Methods from known materials. For Example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-\([N-(\text{R})-\alpha\text{-carboxybenzyl})\text{ carbamoylmethoxyl}\]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0145] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-\([N-(\text{R})-\alpha\text{-carboxybenzyl})\text{ carbamoylmethoxyl}\]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 2; 50 mg, 0.078 mmol) was dissolved in DMF (1.5 ml). Sodium methanethiolate (20 mg, 0.29 mmol) was added and the mixture was stirred for 1.5 hours at 50°C. Acetic acid (40 mg) was added and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (45:55) as eluent to give the title compound 29 mg (61%). NMR (400 MHz, DMSO-d6): 0.7-0.8 (m, 6H), 0.9-1.6 (m, 8H), 2.2 (s, 3H), 3.1-3.7 (m, 4H), 4.6-4.8 (m, 3H), 6.7 (s, 1H), 6.8-7.4 (m, 11H), 8.3 (d, 1H).

Method 2

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-\([N-(\text{R})-\alpha\text{-carboxybenzyl})\text{ carbamoylmethoxyl}\]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0146] The title compound was synthesised from 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-\([N-(\text{R})-\alpha\text{-methoxycarbonylbenzyl})\text{ carbamoylmethoxyl}\]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 3) by the procedure of Example 9, except that the water layer was extracted with EtOAc. The product was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. NMR (400 MHz): 0.75-0.83 (m, 6H), 1.0-1.25 (m, 4H), 1.32-1.52 (m, 3H), 1.55-1.70 (m, 1H), 3.20 (ABq, 2H), 3.65-3.83 (m, 2H), 4.62 (ABq, 2H), 5.68 (d, 1H), 7.04-7.15 (m, 4H), 7.3-7.5 (m, 8H), 7.87 (brd, 1H); m/z 643.1.

Method 3

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-\([N-(\text{R})-\alpha\text{-methoxycarbonylbenzyl})\text{ carbamoylmethoxyl}\]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0147] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 4; 50 mg, 0.098 mmol) was dissolved in DCM (2 ml). Methyl (2R)-amino(phenyl)acetate hydrochloride (23.7 mg, 0.12 mmol) and DIPEA (0.068 ml, 0.39 mmol) was added and the reaction was stirred for 2 minutes. TBTU (38 mg, 0.12 mmol) was added and the mixture was stirred for 1.5 hours at room temperature. The mixture was directly put on an ISOLUTE-column (Silica, 2 g) and eluted stepwise with 10 ml DCM/EtOAc 100:1; then 8:2. 58 mg (90%) of the title compound was obtained. M/z 657.5

Method 4

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0148] 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 5; 0.34 g) and sodium hydroxide (0.3 g) were dissolved in ethanol and the mixture was heated to reflux for 1 hour. Acetic acid (1 ml) was added and the solvent was removed at reduced pressure. The residue was partitioned between DCM/H₂O and the organic layer was separated and dried. Trituration of the residue with n-hexane gave the title compound 0.29 g (90%) as a solid. NMR (500 MHz, CDCl₃): 0.7-0.8 (m, 6H), 1.0-1.7 (m, 8H), 3.1-3.3 (m, 2H), 4.62 (ABq, 2H), 5.68 (d, 1H), 7.2 (m, 2H), 7.5 (s, 1H).

Method 5

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine
(WO 96/16051; 0.3 g), ethyl bromoacetate (0.14 g), sodium carbonate (0.3 g), tetrabutylammonium bromide (0.02 g) in MeCN (10 ml) were refluxed for 4 hours. The solvent was removed under reduced pressure. The residue was partitioned between DCM/H2O and the organic layer was separated. The solvent was evaporated and the residue was purified by chromatography (DCM/EtOAc, 90:10) to give the title compound 0.34 g (95%). NMR (500 MHz; CDCl3): 0.7-0.9 (m, 6H), 1.0-1.8 (m, 11H), 3.2 (m, 2H), 3.6-3.8 (br s, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.1 (m, 3 H), 7.15 (s, 1H), 7.3 (m, 2H), 7.4 (s, 1H).

Method 6
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-N-((R)-α-[N-(carboxymethyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0150] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-N-((R)-α-[N-(t-butoxycarbonylmethyl)carbamoyl][benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 7; 120 mg, 0.17 mmol) was dissolved in DCM (2 ml). TFA (0.7 ml) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent to give the title compound 95 mg (85%). NMR (300 MHz, DMSO-d6): 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 2.2 (s, 3H) 3.2-3.3 (m, 2H), 3.5-3.8 (m, 4H), 4.8 (ABq, 2H), 5.6 (d;1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 8.5-8.7 (m, 2H).

Method 7
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-α-[N-(t-butoxycarbonylmethyl)carbamoyl]benzyl -5-carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0151] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-N-((R)-α-[N-(t-butoxycarbonylmethyl)carbamoylmethyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 8; 110 mg, 0.17 mmol), glycine tert-butyl ester (30 mg, 0.23 mmol) and DIPEA (120 mg, 0.93 mmol) were dissolved in DCM (2 ml). The mixture was stirred for 5 mins at room temperature. TBTU (72 mg, 0.22 mmol) was added and the mixture was stirred for 1 h at room temperature. The solvent was evaporated at reduced pressure and the residue was placed on a silica column and the product was eluted with DCM/EtOAc (90:10) to give the title compound 122 mg (94%). NMR (300 MHz): 0.7-0.8 (m, 6H), 1.0-1.6 (m, 21H), 2.2 (s, 3H) 3.2 (s, 2H), 3.7-4.0 (m, 4H), 4.6 (ABq, 2H), 5.6 (d;1H), 6.4 (t, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 8.1 (d, 1H).

Method 8
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-α-[N-(t-butoxycarbonylmethyl)carbamoylmethyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0152] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-N-((R)-α-[N-(methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 9; 300 mg, 0.46 mmol) was dissolved in methanol (5 ml). NaOH (100 mg in 0.2 ml water) was added to the solution and the mixture was stirred at room temperature for 1 hour. Acetic acid (0.3 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The DCM layer was separated, dried and evaporated under reduced pressure to give the title compound 270 mg (92%). NMR, 500 MHz): 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 2H), 4.6 (s, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.8 (d, 1H).

Method 9
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N-(methoxycarbonylbenzyl)]carbamoyl)methoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0153] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N-(methoxycarbonylbenzyl)]carbamoyl)methoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 10; 250 mg, 0.49 mmol), (R)-2-phenylglycine methyl ester hydrochloride (120 mg, 0.60 mmol) and DIPEA (300 mg, 2.3 mmol) were dissolved in DCM (10 ml) and the mixture was stirred for 5 min in room temperature. TBTU (210 mg, 0.65 mmol) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was placed on a silica column and the product was eluted with DCM/EtOAc (90:10) to give the title compound 306 mg (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.9 (d, 1H).
Method 10

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0154] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 11; 500 mg, 0.93 mmol) was dissolved in DMF (10 ml). Sodium methanethiolate (200 mg, 2.85 mmol) was added and the mixture was stirred for 2 hours at 50°C. Acetic acid (0.4 ml) was added and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc/water. The EtOAc layer was separated, dried and evaporated under reduced pressure to give the title compound 450 mg (96%). NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 2H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.8 (s, 2H), 6.6 (s, 1 H), 6.9-7.1 (m, 3H), 7.2-7.4 (m, 3H).

Method 11

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0155] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 12; 2.2 g, 3.88 mmol) was dissolved in ethanol (15 ml). NaOH (0.8 g in 1.5 ml water) was added to the solution and the mixture was stirred for 30 min at room temperature. Acetic acid (2 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc/water. The EtOAc layer was separated, dried and evaporated under reduced pressure to give the title compound 2.0 g (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.5 (m, 12H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

Method 12

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0156] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the procedure of WO9616051 for the corresponding 3-butyl-3-ethyl analogue; 2.0 g, 4.16 mmol), ethyl bromoacetate (0.84 g, 5.03 mmol), sodium carbonate (2.0 g, 18.9 mmol) and tetrabutylammonium bromide (80 mg, 0.25 mmol) were added to MeCN (20 ml). The mixture was refluxed for 2 hours and then evaporated under reduced pressure. The residue was extracted with DCM/water. The DCM layer was separated and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The product was eluted with DCM / EtOAc (90:10) to give the title compound 2.2 g (93%). NMR (400 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 15H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.5 (s, 1H).

Method 13

5,6-Dimethoxy-2,3-dihydrobenzofuran-2-ylmethylamine

[0157] 5,6-Dimethoxy-2,3-dihydrobenzofuran-2-carbonitrile (Method 16; 2.63 g, 12.94 mmol) was dissolved in ethanol (700 ml) and hydrochloric acid (conc, 2.3 ml) and Pd on charcoal (10%, 1 g) were added. The mixture was hydrogenated under 3.5 atmosphere of hydrogen at 72°C for 3 days. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in water and washed once with diethyl ether. The pH of the aqueous phase was adjusted to 10-11 with NaOH(aq) and the resulting solution was extracted several times with diethyl ether, then with DCM. The organic layers were dried, filtered and evaporated under reduced pressure. The diethyl ether extraction gave 0.6 g (22%) of pure product and the DCM extraction gave 2.0 g (74%) of pure product. NMR (400 MHz) 2.80-2.87 (m, 3H), 3.21 (dd, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 4.72-4.82 (m, 1H), 6.47 (s, 1H), 6.82 (s, 1H).

Method 14

N-(2-Aminoethyl)-N-pyrimidin-2-ylurea

[0158] Phenyl pyrimidin-2-ylcarbamate (121.3 g, 0.57 mol) and ethane-1,2-diamine (380 ml, 5.7 mol) were mixed and cooled with an ice-bath. Sodium (0.5 g, 0.0217 mol) was added in small pieces. The reaction was exothermic and the temperature went up to 38°C and then the temperature was kept at approximately 8°C for 5 days. The remaining ethane-1,2-diamine was evaporated under reduced pressure and co-evaporated with toluene three times. The residue was dissolved in ethanol (99%, 11) and filtered. Hydrochloric acid (conc, 78 ml) was added. The mixture was kept at 8°C overnight. The crystals formed were collected and washed with ethanol (99%) to yield the product as a HCl-salt in 97%
5 N-(2-Aminoethyl)-N'-pyridin-2-ylurea

[0159] Phenyl pyridin-2-ylcarbamate (163.5 g, 0.929 mol) and ethane-1,2-diamine (620 ml, 9.29 mol) was mixed and cooled with an ice-bath. Sodium (0.5 g, 0.0217 mol) was added in small pieces. The reaction was exothermic and the temperature went up to 42˚C and then the temperature was kept at 8˚C for 5 days. The remaining ethane-1,2-diamine was evaporated under reduced pressure and co-evaporated with toluene three times. The residue was dissolved in MeCN and the crystals formed were filtered off. Hydrochloric acid (conc, 110 ml) was added to the solution. The crystals formed were collected and washed with MeCN:MeOH 1:1 to yield the product as a HCl-salt in 72% (145.1 g) yield. NMR (400 MHz) 3.16 (t, 2H), 3.28 (brs, NH), 3.60 (t, 2H), 7.40-7.47 (m, 2H), 8.27-8.36 (m, 2H).

Method 16

5,6-Dimethoxy-2,3-dihydrobenzofuran-2-carbonitrile

[0160] 2-Hydroxy-4,5-dimethoxybenzaldehyde (25.5 g, 0.14 mol), chloroacetonitrile (12.4 g, 0.168 mol) and potassium carbonate (116 g, 0.84 mol) was dissolved in DMF (150 ml). The mixture was stirred for 10 minutes at 165˚C. The solvent was concentrated under reduced pressure. The residue was separated in two parts, water was added and the first part was extracted with diethyl ether and the second part extracted with DCM. The second part was evaporated under reduced pressure and dissolved in ether and washed once with water. The organic layers was combined and evaporated under reduced pressure. The crystalline residue was washed with warm methanol (700 ml) and filtered. The residue was dissolved in 225 ml DCM and diethyl ether (450 ml) was added. The crystals formed was collected giving 14.6 g (51% yield) of product. Mp. 162˚C.

Method 17

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0161] To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 18; 478 mg, 0.95 mmol) was added THF (15 ml), water (3 ml) and LiOH (34 mg, 1.4 mmol). The reaction was then stirred for 1 hour. Then acetic acid (0.2 ml) was added along with water (10 ml) and DCM (10 ml) The aqueous layer was then extracted three times with DCM. The combined organic phases were then dried and concentrated to give the title compound 450 mg (99%). NMR (400 MHz) 0.7-0.9 (m, 6H), 1.0-1.8 (m, 11H), 2.2 (s, 3H), 3.2 (q, 2H) 3.75 (brd, 2H), 4.3 (q, 2H), 4.75 (s, 1H), 6.7 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.35 (s, 1H).

Method 18

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0162] To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 19; 500 mg, 1.2 mmol) was added MeCN (30 ml), tetrabutylammonium bromide (30 mg, 0.08 mmol), anhydrous sodium carbonate (116 g, 0.84 mol), ethyl bromoacetate (0.14 ml, 1.26 mmol) and caesium carbonate (20 mg, 0.06 mmol). This reaction mixture was then stirred over night at 80˚C. Then the solvent was removed under reduced pressure, water and DCM were added and the aqueous phase was extracted three times with DCM. The combined organic phases were then dried and purified by flash chromatography [DCM : EtOAc, 1:0, 9:1] to give the title compound 600 mg (99%). NMR (300 MHz) 0.8-1.0 (m, 6H), 1.0-1.8 (m, 11H), 2.2 (s, 3H), 3.2 (q, 2H) 3.75 (br, 2H), 4.3 (q, 2H), 4.75 (s, 1H), 6.7 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.3 (s, 1H).

Method 19

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

[0163] To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO9616051; 600 mg, 1.29 mmol) were added DMF (5 ml) and sodium methanethiolate (450 mg, 6.42 mmol). The reaction was then heated to 60˚C for 1 hour. The oil bath was then heated to 120˚C for 4 hours. To quench the reaction,
the temperature was lowered to room temperature and excess acetic acid was added quickly. The reaction was kept under a flow of nitrogen through sodium hypochlorite for 2 hours. Water and EtOAc were added and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with water, dried and concentrated under reduced pressure. The residue was then purified by flash chromatography [DCM : EtOAc, 9:1] to give the title compound 0.5 g (92%). NMR (400 MHz) 0.65-0.8 (m, 6H), 0.95-1.6 (m, 8H), 3.1 (q, 2H), 3.6 (brq, 2H), 6.75 (s, 1H), 6.8 (t, 1H), 6.9 (d, 2H), 7.15 (t, 2H), 7.55 (s, 1H).

Claims

1. A compound of formula (I):

![Chemical Structure](image)

wherein:

- \( R^v \) and \( R^w \) are both hydrogen;
- One of \( R^1 \) and \( R^2 \) is selected from hydrogen or \( C_1-6 \text{alkyl} \) and the other is selected from \( C_1-6 \text{alkyl} \);
- \( R^3 \) and \( R^4 \) are both hydrogen;
- \( R^2 \) is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \( C_1-6 \text{alkyl} \), \( C_2-6 \text{alkenyl} \), \( C_2-6 \text{alkynyl} \), \( C_1-6 \text{alkoxy} \), \( C_1-6 \text{alkanoyloxyl} \), \( N-(C_1-6 \text{alkyl}) \text{amino} \), \( N,N-(C_1-6 \text{alkyl})_2 \text{amino} \), \( C_1-6 \text{alkanoylamino} \), \( N-(C_1-6 \text{alkyl}) \text{carbamoyl} \), \( N,N-(C_1-6 \text{alkyl})_2 \text{carbamoyl} \), \( C_1-6 \text{alkylS}(O)_a \) wherein \( a \) is 0 to 2, \( C_1-6 \text{alkoxycarbonyl} \), \( N-(C_1-6 \text{alkyl}) \text{sulphamoyl} \) and \( N,N-(C_1-6 \text{alkyl})_2 \text{sulphamoyl} \);
- \( v \) is 0-5;
- one of \( R^4 \) and \( R^5 \) is a group of formula (IA):

![Chemical Structure](image)

(RA)

- \( R^3 \) and \( R^6 \) and the other of \( R^4 \) and \( R^5 \) are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \( C_1-6 \text{alkyl} \), \( C_2-6 \text{alkenyl} \), \( C_2-6 \text{alkynyl} \), \( C_1-6 \text{alkoxy} \), \( C_1-6 \text{alkanoyloxyl} \), \( N-(C_1-6 \text{alkyl}) \text{amino} \), \( N,N-(C_1-6 \text{alkyl})_2 \text{amino} \), \( C_1-6 \text{alkanoylamino} \), \( N-(C_1-6 \text{alkyl}) \text{carbamoyl} \), \( N,N-(C_1-6 \text{alkyl})_2 \text{carbamoyl} \), \( C_1-6 \text{alkylS}(O)_a \) wherein \( a \) is 0 to 2, \( C_1-6 \text{alkoxycarbonyl} \), \( N-(C_1-6 \text{alkyl}) \text{sulphamoyl} \) and \( N,N-(C_1-6 \text{alkyl})_2 \text{sulphamoyl} \); 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 \( R^{17} \);
- \( X \) is \(-O-, -N(R^a), -S(O)_b, \) or \(-CH(R^a)\); wherein \( R^a \) is hydrogen or \( C_1-6 \text{alkyl} \) and \( b \) is 0-2;
- Ring \( A \) is aryl or heteroaryl; wherein Ring \( A \) is optionally substituted on carbon by one or more substituents...
EP 1 430 040 B1

selected from R18.

R7 is hydrogen, C1-6alkyl, carbocyclyl or heterocyclyl; wherein R7 is optionally substituted on carbon by one or more substituents selected from R19, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R20.

R8 is hydrogen or C1-6alkyl;

R9 is hydrogen or C1-6alkyl;

R10 is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C1-10alkyl, C2-10alkenyl, C2-10alkynyl, C1-10alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, N-(C1-10alkyl)amino, N, N-(C1-10alkyl)2-amino, N,N,N-(C1-10alkyl)ammonio, C1-10alkanoylamino, N-(C1-10alkyl)carbamoyl, N, N-(C1-10alkyl)2-carbamoyl, C1-10alkylS(O)a wherein a is 0 to 2, N-(C1-10alkyl)sulphamoyl, N,N-(C1-10alkyl)2-sulphamoylamino, N,N,N-(C1-10alkyl)3-sulphamoylamino, carboxycyclyl, carbocyclylC1-10alkyl, heterocyclyl, heterocyclylC1-10alkyl, carbocyclyl-(C1-10alkylene)p-R21-(C1-10alkylene)q or heterocyclyl-(C1-10alkylene)r-R22-(C1-10alkylene)s-; wherein R10 is optionally substituted on carbon by one or more substituents selected from R23; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R24; or R10 is a group of formula (IB):

wherein:

R11 is hydrogen or C1-6alkyl;

R12 and R13 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C1-10alkyl, C2-10alkenyl, C2-10alkynyl, C1-10alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, N-(C1-10alkyl)amino, N,N-(C1-10alkyl)2-amino, C1-10alkanoylamino, N-(C1-10alkyl)carbamoyl, N, N-(C1-10alkyl)2-carbamoyl, C1-10alkylS(O)a wherein a is 0 to 2, N-(C1-10alkyl)sulphamoyl, N,N-(C1-10alkyl)2-sulphamoylamino, N,N,N-(C1-10alkyl)3-sulphamoylamino, carboxycycl or heterocyclyl; wherein R12 and R13 may be independently optionally substituted on carbon by one or more substituents selected from R25; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R26;

R14 is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C1-10alkyl, C2-10alkenyl, C2-10alkynyl, C1-10alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, N-(C1-10alkyl)amino, N,N-(C1-10alkyl)2-amino, N,N,N-(C1-10alkyl)ammonio, C1-10alkanoylamino, N-(C1-10alkyl)carbamoyl, N, N-(C1-10alkyl)2-carbamoyl, C1-10alkylS(O)a wherein a is 0 to 2, N-(C1-10alkyl)sulphamoyl, N,N-(C1-10alkyl)2-sulphamoylamino, N,N,N-(C1-10alkyl)3-sulphamoylamino, carboxycyclyl, carbocyclylC1-10alkyl, heterocyclyl, heterocyclylC1-10alkyl, carbocyclyl-(C1-10alkylene)p-R27-(C1-10alkylene)q- or heterocyclyl-(C1-10alkylene)r-R28-(C1-10alkylene)s-; wherein R14 may be optionally substituted on carbon by one or more substituents selected from R29; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R30; or R14 is a group of formula (IC):

wherein:

R15 is hydrogen or C1-6alkyl;

R16 is hydrogen or C1-6alkyl; wherein R16 may be optionally substituted on carbon by one or more
groups selected from $R^{31}$;

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

$R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$ or $R^{31}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxymonomocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoxy, $N-(C_{1-10}$alkyl)$amino$, $N,N-(C_{1-10}$alkyl)2-amino, $N,N,N-(C_{1-10}$alkyl)3-ammonio, $C_{1-10}$alkanoylamino, $N-(C_{1-10}$alkyl)carbamoyl, $N,N-(C_{1-10}$alkyl)2-carbamoyl, $C_{1-10}$alkylS(O)$a$ wherein $a$ is 0 to 2, $N-(C_{1-10}$alkyl)sulphamoyl, $N,N-(C_{1-10}$alkyl)2 sulpha-moylamino, $N,N-(C_{1-10}$alkyl)$3$-sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocycl, carbocycl$C_{1-10}$alkyl, heterocycl, heterocycl$C_{1-10}$alkyl, carbocycl$-(C_{1-10}$alkylene)$p$-$R^{32}$-$(C_{1-10}$alkylene)$q$- or heterocycl$-(C_{1-10}$alkylene)$r$-$R^{33}$-$(C_{1-10}$alkylene)$s$-; wherein $R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ or $R^{31}$ may be independently optionally substituted on carbon by one or more $R^{34}$; and wherein if said heterocycl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{35}$;

$p$, $q$, $r$ and $s$ are independently selected from 0-2; $R^{34}$ is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethyny, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, $N$-methylcarbamoyl, $N,N$-dimethylcarbamoyl, methylthio, methylsulphanyl, mesyl, $N$-methylsulphamoyl, $N,N$-dimethylsulphamoyl and $N,N$-dimethylsulphamoylamino; $R^{20}$, $R^{24}$, $R^{26}$, $R^{30}$ or $R^{35}$ are independently 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, benzoxycarbonyl, benzoyl and phenylsulphonyl;

wherein aryl is totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; heteroaryl is totally unsaturated, mono or bicyclic carbon ring containing 3-12 atoms of which at least one atom are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked; wherein heteroaryl is not tetrazoyl;

wherein carbocycl 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)-; and wherein heterocycl is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring containing 3-12 atoms of which at least one atom, particularly 1-3 atoms, are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH$_2$- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

2. A compound of formula (I) as claimed in claim 1 wherein one of $R^1$ and $R^2$ is ethyl and the other is butyl, or $R^1$ and $R^2$ are both butyl, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

3. A compound of formula (I) as claimed in any one of claims 1-2 wherein $v$ is 0, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

4. A compound of formula (I) as claimed in any one of claims 1-3 wherein $R^3$ and $R^6$ are both hydrogen, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

5. A compound of formula (I) as claimed in any one of claims 1-4 wherein $R^4$ is hydrogen or methylthio, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

6. A compound of formula (I) as claimed in any one of claims 1-5 wherein $R^5$ is a group of formula (IA) as depicted above, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

7. A compound of formula (I) as claimed in any one of claims 1-6 wherein $R^5$ is a group of formula (IA) as depicted above wherein:

\[
X = -O-; \\
R^7 = \text{hydrogen};
\]
R\(^8\) is hydrogen;
R\(^9\) is hydrogen;
Ring A is aryl;
R\(^{10}\) is carbamoyl or \(N-(C_{1-10} \text{alkyl})\text{carbamoyl or a group of formula (IB)}\) (as depicted above) wherein R\(^{10}\) is optionally substituted on carbon by one or more substituents selected from R\(^{23}\) and wherein:
R\(^{11}\) is hydrogen;
R\(^{12}\) and R\(^{13}\) are independently selected from hydrogen, carbamoyl or C\(_{1-6}\)alkyl;
wherein R\(^{12}\) and R\(^{13}\) may be independently optionally substituted on carbon by one or more substituents selected from R\(^{25}\);
R\(^{14}\) is selected from carbamoyl, hydroxyaminocarbonyl, C\(_{1-6}\)alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C\(_{1-6}\)alkylene)\(_p\)-R\(^{27}\)-(C\(_{1-6}\)alkylene)\(_q\)\(^\text{a}\); wherein R\(^{14}\) may be optionally substituted on carbon by one or more substituents selected from R\(^{29}\); and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\(^{30}\); or R\(^{14}\) is a group of formula (IC) (as depicted above) wherein:
R\(^{15}\) is hydrogen;
R\(^{16}\) is C\(_{1-6}\)alkyl; wherein R\(^{16}\) may be optionally substituted on carbon by one or more groups selected from R\(^{31}\); n is 1;
R\(^{23}\), R\(^{29}\) or R\(^{31}\) are independently selected from halo, hydroxy, amino, sulphamoyl, C\(_{1-6}\)alkoxy, N,N\(^3\)ammonio, N,N\(^2\)N-(C\(_{1-6}\)alkyl)sulphamoylamino, C\(_{1-6}\)alkoxy carbamoyl amino, carbocyclyl, heterocyclyl, carbocyclyl-(C\(_{1-6}\)alkylene)\(_p\)-R\(^{32}\)-(C\(_{1-6}\)alkylene)\(_q\)^\(\text{a}\) or heterocyclyl-(C\(_{1-6}\)alkylene)\(_p\)-R\(^{33}\)-(C\(_{1-6}\)alkylene)\(_q\)^\(\text{a}\); wherein R\(^{29}\), R\(^{29}\) or R\(^{31}\) may be independently optionally substituted on carbon by one or more R\(^{34}\); and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\(^{35}\);
R\(^{32}\), R\(^{33}\) are independently selected from -O-, -NR\(^{36}\)C(O)NR\(^{36}\)-, -OC(O)N=Cor -NR\(^{36}\)C(O)-; wherein R\(^{23}\) is hydrogen; p, q, r and s are independently selected from 0 or 1;
R\(^{34}\) is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;
R\(^{30}\) or R\(^{35}\) are independently selected from C\(_{1-6}\)alkyl or C\(_{1-6}\)alkoxycarbonyl.

8. A compound of formula (I) as defined in claim 1 wherein:

R\(^v\) and R\(^w\) are both hydrogen;
R\(^x\) and R\(^y\) are both hydrogen;
R\(^1\) and R\(^2\) are independently selected from C\(_{1-4}\)alkyl; v is 0;
R\(^3\) and R\(^6\) are hydrogen;
R\(^4\) is methythio;
R\(^f\) is a group of formula (IA) as depicted above wherein:
X is -O-;
R\(^7\) is hydrogen;
R\(^8\) is hydrogen;
R\(^9\) is hydrogen;
Ring A is aryl;
R\(^{10}\) is carbamoyl or \(N-(C_{1-10} \text{alkyl})\text{carbamoyl or a group of formula (IB)}\) (as depicted above) wherein R\(^{10}\) is optionally substituted on carbon by one or more substituents selected from R\(^{23}\) and wherein:
R\(^{11}\) is hydrogen;
R\(^{12}\) and R\(^{13}\) are independently selected from hydrogen, carbamoyl or C\(_{1-6}\)alkyl; wherein R\(^{12}\) and R\(^{13}\) may be independently optionally substituted on carbon by one or more substituents selected from R\(^{25}\);
R\(^{14}\) is selected from carbamoyl, hydroxyaminocarbonyl, C\(_{1-6}\)alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C\(_{1-6}\)alkylene)\(_p\)-R\(^{27}\)-(C\(_{1-6}\)alkylene)\(_q\)^\(\text{a}\); wherein R\(^{14}\) may be optionally substituted on carbon by one or more substituents selected from R\(^{29}\); and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R\(^{30}\); or R\(^{14}\) is a group of formula (IC) (as depicted above) wherein:
R\(^{15}\) is hydrogen;
R\(^{16}\) is C\(_{1-6}\)alkyl; wherein R\(^{16}\) may be optionally substituted on carbon by one or more groups selected from R\(^{31}\); n is 1;
R\(^{23}\) is hydroxy;
R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphonamoyl, N,N,N-(C₁₋₆alkyl)₃ammonio, N,N(N₁₋₆alkyl)sulphamoylamino, C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C₁₋₆alkylene)α⁻ or heterocyclyl-(C₁₋₆alkylene)α⁺; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=Cor -NR³⁶C(O)-; wherein R²₃ is hydrogen;
p, q, r and s are independently selected from 0 or 1;
R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;
R³⁰ or R³⁵ are independently selected from C₁₋₆alkyl or C₁₋₆alkoxycarbonyl;
or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

9. A compound of formula (I) according to claim 1 selected from:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N'-{(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy})-2,3,4,5-tetrahydro-1,5-benzothiazepine;
or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.

10. A process for preparing a compound of formula (I), as claimed in any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process comprises of:

Process 1): oxidising a benzothiazepine of formula (II):
Process 2): for compounds of formula (I) wherein X is -O-, -NRa or -S-; reacting a compound of formula (IIIa) or (IIIb):

with a compound of formula (IV):

wherein L is a displaceable group;

Process 3): reacting an acid of formula (Va) or (Vb):
or an activated derivative thereof; with an amine of formula (VI):

Process 4): for compounds of formula (I) wherein \( R^{10} \) is a group of formula (IB); reacting a compound of formula (I) wherein \( R^{10} \) is carboxy with an amine of formula (VII):

Process 5): for compounds of formula (I) wherein \( R^{10} \) is a group of formula (IB) and \( R^{14} \) is a group of formula (IC) reacting a compound of formula (I) wherein \( R^{14} \) is carboxy with an amine of formula (VIII):

Process 6) for compounds of formula (I) wherein one of \( R^4 \) and \( R^5 \) are independently selected from C1-6alkythio optionally substituted on carbon by one or more \( R^{17} \); reacting a compound of formula (IXa) or (IXb):
wherein L is a displaceable group; with a thiol of formula (X):

\[ R^y - H \]

wherein \( R^y \) is \( \text{C}_{1-6}\text{alkylthio} \) optionally substituted on carbon by one or more \( R^{16} \); and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate or solvate of such a salt.

11. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9 for use as a medicament.

12. A compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9 for use in prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

13. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

14. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9, in association with a pharmaceutically acceptable diluent or carrier.

15. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

17. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

18. A composition according to claim 15 or claim 17 wherein the HMG Co-A reductase inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof.
19. A composition according to claim 15 or claim 17 wherein the HMG Co-A reductase inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate or solvate of such a salt thereof, as claimed in any one of claims 1 to 9 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

21. A composition according to claim 20 wherein the PPAR alpha and/or gamma agonist is (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid or a pharmaceutically acceptable salt thereof.

**Patentansprüche**

1. Verbindung der Formel (I):

   ![Chemical Structure](image)

   worin:

   - \(R^r\) und \(R^w\) beide Wasserstoff sind;
   - eines von \(R^1\) und \(R^2\) aus Wasserstoff oder \(C_{1-6}\)-Alkyl ausgewählt ist und das andere aus \(C_{1-6}\)-Alkyl ausgewählt ist;
   - \(R^4\) und \(R^5\) beide Wasserstoff sind;
   - \(R^2\) ausgewählt ist aus Halogen, Nitro, Cyano, Hydroxy, Amino, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, \(C_{1-6}\)-Alkyl, \(C_{2-6}\)-Alkenyl, \(C_{2-6}\)-Alkinyl, \(C_{1-6}\)-Alkoxy, \(C_{1-6}\)-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, \(C_{1-6}\)-Alkyl-\(S(O)\)_a, worin a 0 bis 2 ist, \(C_{1-6}\)-Alkoxy, \(N-(C_{1-6}\)-Alkyl)sulfamoyl und \(N,N-(C_{1-6}\)-Alkyl)2-sulfamoyl;
   - \(v\) 0 bis 5 ist;
   - eines von \(R^4\) und \(R^5\) eine Gruppe der Formel (IA) ist:

   ![Chemical Structure](image)

   worin:

   - \(R^3\) und \(R^6\) und das andere von \(R^4\) und \(R^5\) unabhängig ausgewählt sind aus Wasserstoff, Halogen, Nitro, Cyano, Hydroxy, Amino, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, \(C_{1-6}\)-Alkyl, \(C_{2-6}\)-Alkenyl, \(C_{2-6}\)-Alkinyl, \(C_{1-6}\)-Alkoxy, \(C_{1-6}\)-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)
kyl)carbamoyl, N,N-(C_{1-6}Alkyl)_{2-carbamoyl}, C_{1-6}Alkyl-S(O)_{a,worina0bis2ist,C_{1-6}Alkyl}sulfamoyl und N,N-(C_{1-6}Alkyl)_{2-sulfamoyl}; worin R^2 und R^6 und das andere von R^4 und R^5 optional durch ein oder mehrere R^{17} an Kohlenstoff substituiert sein können; X′-O-, -N(R^6)-, S(O)_b- oder -CH(R^9)- ist; worin R^8 Wasserstoff oder C_{1-6}Alkyl ist und b 0 bis 2 ist; Ring A Aryl oder Heteroaryl ist; worin der Ring A optional mit einem oder mehreren Substituieren, ausgewählt aus R^{18}, an Kohlenstoff substituiert sein kann; R^7 Wasserstoff, C_{1-4}Alkyl, Carbocycl oder Heterocycl ist; worin R^7 optional mit einem oder mehreren Substituieren, ausgewählt aus R^{19}, an Kohlenstoff substituiert ist; und falls das Heterocycl eine -NH-Gruppe enthält, der Stickstoff optional mit einer aus R^{20} ausgewählten Gruppe substituiert sein kann; R^8 Wasserstoff oder C_{1-6}Alkyl ist; R^9 Wasserstoff oder C_{1-6}Alkyl ist; R^{10} Wasserstoff, Halogen, Nitro, Cyano, Hydroxy, Amino, Carbamoyl, Mercapto, Sulfamoyl, Hydroxyaminocarbonyl, C_{1-10}Alkyl, C_{2-10}Alkenyl, C_{2-10}Alkinyl, C_{1-10}Alkoxy, C_{1-10}Alkanoyl, C_{1-10}Alkanoyloxy, N-(C_{1-10}Alkyl)amino, N,N-(C_{1-10}Alkyl)_{2-amino}, N,N,N-(C_{1-10}Alkyl)_{3-ammonio}, C_{1-10}Alkanoylamino, N-(C_{1-10}Alkyl)carbamoyl, N,N-(C_{1-10}Alkyl)_{2-carbamoyl}, C_{1-10}AlkylS(O)_{a}, worin a 0 bis 2 ist, N-(C_{1-10}Alkyl)sulfamoyl, N, N-(C_{1-10}Alkyl)_{2-sulfamoyl}, N-(C_{1-10}Alkyl)sulfamoylamino, N,N-(C_{1-10}Alkyl)_{2-sulfamoylamino}, Carbocycl, Carbocycl-C_{1-10}alkyl, Heterocycl, Heterocycl-C_{1-10}alkyl, Carbocycl-(C_{1-10}alkylen)p-R^{21}-(C_{1-10}alkylen)q oder Heterocycl-(C_{1-10}alkylen)p-R^{22}-(C_{1-10}alkylen)q ist; worin R^{10} optional mit einem oder mehreren Substituenten, ausgewählt aus R^{23}, an Kohlenstoff substituiert ist; und falls das Heterocycl eine -NH-Gruppe enthält, der Stickstoff optional mit einer aus R^{24} ausgewählten Gruppe substituiert sein kann; oder R^{10} eine Gruppe der Formel (IB) ist:

worin:

R^{11} Wasserstoff oder C_{1-4}Alkyl ist; R^{12} und R^{13} unabhängig ausgewählt sind aus Wasserstoff, Halogen, Nitro, Cyano, Hydroxy, Amino, Carbamoyl, Mercapto, Sulfamoyl, Hydroxyaminocarbonyl, C_{1-10}Alkyl, C_{2-10}Alkenyl, C_{2-10}Alkinyl, C_{1-10}Alkoxy, C_{1-10}Alkanoyl, C_{1-10}Alkanoyloxy, N-(C_{1-10}Alkyl)amino, N,N-(C_{1-10}Alkyl)_{2-amino}, N,N,N-(C_{1-10}Alkyl)_{3-ammonio}, C_{1-10}Alkanoylamino, N-(C_{1-10}Alkyl)carbamoyl, N,N-(C_{1-10}Alkyl)_{2-carbamoyl}, C_{1-10}AlkylS(O)_{a}, worin a 0 bis 2 ist, N-(C_{1-10}Alkyl)sulfamoyl, N,N-(C_{1-10}Alkyl)_{2-sulfamoyl}, N-(C_{1-10}Alkyl)sulfamoylamino, N,N-(C_{1-10}Alkyl)_{2-sulfamoylamino}, Carbocycl oder Heterocycl, worin R^12 und R^13 unabhängig optional mit einem oder mehreren Substituenten, ausgewählt aus R^{23}, an Kohlenstoff substituiert sein können; und falls das Heterocycl eine -NH-Gruppe enthält, der Stickstoff optional mit einer aus R^{24} ausgewählten Gruppe substituiert sein kann; R^{14} ausgewählt ist aus Wasserstoff, Halogen, Nitro, Cyano, Hydroxy, Amino, Carbamoyl, Mercapto, Sulfamoyl, Hydroxyaminocarbonyl, C_{1-10}Alkyl, C_{2-10}Alkenyl, C_{2-10}Alkinyl, C_{1-10}Alkoxy, C_{1-10}Alkanoyl, C_{1-10}Alkanoyloxy, N-(C_{1-10}Alkyl)amino, N,N-(C_{1-10}Alkyl)_{2-amino}, N,N,N-(C_{1-10}Alkyl)_{3-ammonio}, C_{1-10}Alkanoylamino, N-(C_{1-10}Alkyl)carbamoyl, N,N-(C_{1-10}Alkyl)_{2-carbamoyl}, C_{1-10}AlkylS(O)_{a}, worin a 0 bis 2 ist, N-(C_{1-10}Alkyl)sulfamoyl, N,N-(C_{1-10}Alkyl)_{2-sulfamoyl}, N-(C_{1-10}Alkyl)sulfamoylamino, N,N-(C_{1-10}Alkyl)_{2-sulfamoylamino}, Carbocycl, Carbocycl-C_{1-10}alkyl, Heterocycl, Heterocycl-C_{1-10}alkyl, Carbocycl-(C_{1-10}alkylen)p-R^{21}-(C_{1-10}alkylen)q oder Heterocycl-(C_{1-10}alkylen)p-R^{22}-(C_{1-10}alkylen)q ist; worin R^14 optional mit einem oder mehreren Substituenten, ausgewählt aus R^{23}, an Kohlenstoff substituiert sein kann; und falls das Heterocycl eine -NH-Gruppe enthält, der Stickstoff optional mit einer Gruppe, ausgewählt aus R^{25}, substituiert sein kann; oder R^{14} eine Gruppe der Formel (IC) ist:
worin:

$R^{15}$ Wasserstoff oder C$_{1-6}$-Alkyl ist;
$R^{16}$ Wasserstoff oder C$_{1-6}$-Alkyl ist; worin $R^{16}$ optional mit einer oder mehreren Gruppen, ausgewählt aus $R^{31}$, an Kohlenstoff substituiert sein kann;

n 1 bis 3 ist; worin die Werte von $R^7$ gleich oder verschieden sein können;
$R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ oder $R^{31}$ unabhängig ausgewählt sind aus Halogen, Nitro, Cyano, Hydroxy, Amino, Carbamoyl, Mercapto, Sulfamoyl, Hydroxyaminocarbonyl, C$_{1-10}$-Alkyl, C$_{2-10}$-Alkenyl, C$_{2-10}$-Alkinyl, C$_{1-10}$-Alkoxy, C$_{1-10}$-Alkanoylamino, N-(C$_{1-10}$-Alkyl)amino, N,N-(C$_{1-10}$-Alkyl)$_2$-amino, N,N,N-(C$_{1-10}$-Alkyl)$_3$-ammonio, C$_{1-10}$-Alkanoylamino, N-(C$_{1-10}$-Alkyl)carbamoyl, N,N-(C$_{1-10}$-Alkyl)$_2$-carbamoyl, C$_{1-10}$-Alkyl-S(O)$_a$, worin $a$ 0 bis 2 ist, N-(C$_{1-10}$-Alkyl)sulfamoyl, N,N-(C$_{1-10}$-Alkyl)$_2$-sulfamoyl, N-(C$_{1-10}$-Alkyl)sulfamoylamino, N,N-(C$_{1-10}$-Alkyl)$_2$-sulfamoylamino, N-(C$_{1-10}$-Alkyl)$_2$-sulfamoylamino, Carbocyclyl, Carbocyclyl-C$_{1-10}$-alkyl, Heterocyclyl, Heterocyclyl-C$_{1-10}$-alkyl, Carbocyclyl-(C$_{1-10}$-alkylene)$_p$-R$_{32}$-(C$_{1-10}$-alkylene)$_q$- oder Heterocyclyl-(C$_{1-10}$-alkylene)$_r$-R$_{33}$-(C$_{1-10}$-alkylene)$_s$-; worin $R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ oder $R^{31}$ unabhängig optional mit einem oder mehreren $R^{34}$ an Kohlenstoff substituiert sein können; und falls das Heterocyclyl eine -NH-Gruppe enthält, kann der Stickstoff optional mit einer aus $R^{35}$ ausgewählten Gruppe substituiert sein;
$R^{21}$, $R^{22}$, $R^{27}$, $R^{28}$, $R^{32}$ oder $R^{33}$ unabhängig ausgewählt sind aus -O-, -NR$_{36}$-, -S(O)$_x$-, -NR$_{36}$C(O)NR$_{36}$-, -NR$_{36}$C(S)NR$_{36}$-, -OC(O)N=C-, -NR$_{36}$C(O)- oder -C(O)NR$_{36}$-; worin $R^{36}$ aus Wasserstoff oder C$_{1-6}$-Alkyl ausgewählt ist und x 0 bis 2 ist;

$R^{34}$ ausgewählt ist aus Halogen, Hydroxy, Cyano, Carbamoyl, Ureido, Amino, Nitro, Carbamoyl, Mercapto, Sulfamoyl, Trifluormethyl, Trifluormethoxy, Methyl, Ethyl, Methoxy, Ethoxy, Vinyl, Allyl, Ethinyl, Formyl, Acetyl, Formamido, Acetylamino, Acetoxy, Methyliamino, Dimethylamino, N-Methylcarbamoyl, N,N-Dimethylcarbamoyl, Methylthio, Methylysulfinyl, Mesyl, N-Methylsulfamoylamino, N,N-Dimethylsulfamoylamino, N,N-Dimethylsulfamoylamino und N,N-Dimethylsulfamoylamino;
$R^{20}$, $R^{24}$, $R^{26}$, $R^{30}$ oder $R^{35}$ unabhängig ausgewählt sind aus C$_{1-6}$-Alkyl, C$_{1-6}$-Alkanoyl, C$_{1-6}$-alkylsulfonyl, C$_{1-6}$-Alkoxy carbonyl, Carbamoyl, N-(C$_{1-6}$-Alkyl)carbamoyl, N,N-(C$_{1-6}$-Alkyl) carbamoyl, Benzyl, Benzylxoycarbonyl, Benzyl und Phenylsulfonyl; worin Aryl ein vollständig ungesättigter, monocyclischer oder bicyclischer Kohlenstoffring ist, der 3 bis 12 Atome umfasst; Heteroaryl ein vollständig ungesättigter, monocyclischer oder bicyclischer Ring ist, der 3 bis 12 Atome umfasst, von denen zumindest ein Atom aus Stickstoff, Schwefel oder Sauerstoff ausgewählt ist, die Kohlenstoff- oder Stickstoff- verknüpft sein können, ausser es ist anders angegeben; worin Heteroaryl nicht Tetrazolyl ist,

worin Carbocyclyl ein gesättigter, teilweise gesättigter oder ungesättigter, monocyclischer oder bicyclischer Kohlenstoffring ist, der 3 bis 12 Atome umfasst; worin eine -CH$_2$-Gruppe optional durch -C(O)- ersetzt sein kann; und worin Heterocyclyl ein gesättigter, teilweise gesättigter oder ungesättigter, monocyclischer oder bicyclischer Ring ist, der 3 bis 12 Atome umfasst, von denen zumindest ein Atom, insbesondere 1 bis 3 Atome, aus Stickstoff, Schwefel oder Sauerstoff ausgewählt ist; worin eine -CH$_2$-Gruppe optional durch -C(O)- ersetzt sein kann; oder ein Ring-Schwefelatom optional oxidiert sein kann, um die S-Oxide zu bilden; oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

2. Verbindung der Formel (I) gemäss Anspruch 1, worin eines von $R^1$ und $R^2$ Ethyl ist und das andere Butyl ist, oder $R^1$ und $R^2$ beide Butyl sind, oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

3. Verbindung der Formel (I) gemäss irgendeinem der Ansprüche 1 bis 2, worin v 0 ist, oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

4. Verbindung der Formel (I) gemäss irgendeinem der Ansprüche 1 bis 3, worin $R^3$ und $R^6$ beide Wasserstoff sind,
oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

5. Verbindung der Formel (I) gemäss irgendeinem der Ansprüche 1 bis 4, worin R⁴ Wasserstoff oder Methylthio ist, oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

6. Verbindung der Formel (I) gemäss irgendeinem der Ansprüche 1 bis 5, worin R⁵ eine Verbindung der Formel (IA), wie vorstehend gezeigt, ist, oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

7. Verbindung der Formel (I) gemäss irgendeinem der Ansprüche 1 bis 6, worin R⁵ eine Gruppe der Formel (IA), wie vorstehend gezeigt, ist, worin:

X -0- ist;
R⁷ Wasserstoff ist;
R⁸ Wasserstoff ist;
Ring A Aryl ist;
R₁₀ Carbamoyl oder N-(C₁₋₁₀-Alkyl)carbamoyl oder eine Gruppe der Formel (IB) (wie vorstehend gezeigt) ist, worin R₁₀ optional mit einem oder mehreren Substituenten, ausgewählt aus R²₃, an Kohlenstoff substituiert ist und worin:
R¹¹ Wasserstoff ist;
R¹² und R¹³ unabhängig aus Wasserstoff, Carbamoyl oder C₁₋₆-Alkyl ausgewählt sind; worin R¹² und R¹³ unabhängig voneinander optional mit einem oder mehreren Substituenten, ausgewählt aus R²₉, an Kohlenstoff substituiert sein können;
R¹⁴ ausgewählt ist aus Carbamoyl, Hydroxyaminocarbonyl, C₁₋₆-Alkyl, Carbocycl, Heterocycl oder Carbocycl-(C₁₋₆-alkyl)ₚ-(C₁₋₆-alkylen)ₜ-q; worin R¹⁴ optional mit einem oder mehreren Substituenten, ausgewählt aus R²₉, an Kohlenstoff substituiert sein kann; und falls das Heterocycl eine -NH-Gruppe enthält, der Stickstoff optional mit einer Gruppe, ausgewählt aus R³₁, substituiert sein kann; oder R¹⁴ eine Gruppe der Formel (IC) (wie vorstehend gezeigt) ist, worin:
R¹⁵ Wasserstoff ist;
R¹⁶ C₁₋₆-Alkyl ist; worin R¹⁶ optional mit einer oder mehreren Gruppe(n), ausgewählt aus R²₃, an Kohlenstoff substituiert sein kann;
n 1 ist;
R²₃ Hydroxy ist;
R²₅, R²₇ oder R²₉ unabhängig ausgewählt sind aus Halogen, Hydroxy, Amino, Sulfamoyl, C₁₋₆-Alkoxy, N,N,N-(C₁₋₆-alkyl)₃-ammonio, N,N-(C₁₋₆-Alkyl)₂-sulfamoylamino, C₁₋₆-Alkoxy carbonylamino, Carbocycl, Heterocycl, Carbocycl-(C₁₋₆-alkyl)ₚ-(C₁₋₆-alkylen)ₜ-q oder Heterocycl-(C₁₋₆-alkyl)ₚ-(C₁₋₆-alkylen)ₜ-q; worin R²₅, R²₇ oder R²₉ unabhängig voneinander optional mit einem oder mehreren R³₄ an Kohlenstoff substituiert sein kann; und falls das Heterocycl eine -NH-Gruppe enthält, der Stickstoff optional mit einer aus R³₅ ausgewählten Gruppe substituiert sein kann;
R²₇, R²₉ oder R³₃ unabhängig ausgewählt sind aus -O-, -NR₃₆C(O)NR₃₆-, -OC(O)N=C- oder -NR₃₆C(O)-; worin R²₃ Wasserstoff ist;
p, q, r und s unabhängig ausgewählt sind aus 0 oder 1;
R³₄ ausgewählt ist aus Hydroxy, Amino, Carbamoyl, Sulfamoyl oder Methoxy;
R³₀ oder R³₅ unabhängig ausgewählt sind aus C₁₋₆-Alkyl oder C₁₋₆-Alkoxy carbonyl.

8. Verbindung der Formel (I) gemäss Anspruch 1, worin:

R⁺ und R⁻⁺ beide Wasserstoff sind;
R⁺ und R⁻⁺ beide Wasserstoff sind;
R¹ und R² unabhängig ausgewählt sind aus C₁₋₄-Alkyl; v 0 ist;
R³ und R⁶ Wasserstoff sind;
R⁴ Methylthio ist;
R⁵ eine Gruppe der Formel (IA), wie vorstehend gezeigt, ist, worin:
X -0- ist;
R⁷ Wasserstoff ist;
R⁸ Wasserstoff ist;
R⁹ Wasserstoff ist;
der Ring A Aryl ist;
R^{10} Carbamoyl oder N-(C_{1-10}-Alkyl)carbamoyl oder eine Gruppe der Formel (IB) (wie vorstehend gezeigt) ist, worin R^{10} optional mit einem oder mehreren Substituenten, ausgewählt aus R^{23}, an Kohlenstoff substituiert ist und worin:
R^{11} Wasserstoff ist;
R^{12} und R^{13} unabhängig aus Wasserstoff, Carbamoyl oder C_{1-6}-Alkyl ausgewählt sind; worin R^{12} und R^{13} unabhängig voneinander optional mit einem oder mehreren Substituenten, ausgewählt aus R^{25}, an Kohlenstoff substituiert sein können;
R^{14} ausgewählt ist aus Carbamoyl, Hydroxaminocarbonyl, C_{1-6}-Alkyl, Carbocyclyl, Heterocyclyl oder Carbocyclyl-(C_{1-6}-alkylen)p-R^{27},(C_{1-6}-alkylen)q; worin R^{14} optional mit einem oder mehreren Substituenten, ausgewählt aus R^{29}, an Kohlenstoff substituiert sein kann; und falls das Heterocyclyl eine -NH-Gruppe enthält, der Stickstoff optional mit einer Gruppe, ausgewählt aus R^{30}, substituiert sein kann; oder R^{14} eine Gruppe der Formel (IC) (wie vorstehend gezeigt) ist, worin:
R^{15} Wasserstoff ist;
R^{16} C_{1-6}-Alkyl ist; worin R^{16} optional mit einer oder mehreren Gruppe(n), ausgewählt aus R^{31}, an Kohlenstoff substituiert sein kann; n 1 ist;
R^{23} Hydroxy ist;
R^{25}, R^{29} oder R^{31} unabhängig ausgewählt sind aus Halogen, Hydroxy, Amino, Sulfamoyl, C_{1-6}-Alkoxy, N,N,N-(C_{1-6}-alkyl)ammonio, N,N-(C_{1-6}-alkyl)sulfamoylamino, C_{1-6}-Alkoxy carbonylamino, Carbocyclyl, Heterocyclyl, Carbocyclyl-(C_{1-6}-alkylen)p-R^{32},(C_{1-6}-alkylen)q oder Heterocyclyl-(C_{1-6}-alkylen)p-R^{33},(C_{1-6}-alkylen)q; worin R^{25}, R^{29} oder R^{31} unabhängig voneinander optional mit einem oder mehreren R^{34} an Kohlenstoff substituiert sein können; und falls das Heterocyclyl eine -NH-Gruppe enthält, der Stickstoff optional mit einer aus R^{35} ausgewählten Gruppe substituiert sein kann;
R^{27}, R^{32} oder R^{33} unabhängig ausgewählt sind aus -O-, -NR^{36}C(O)NR^{36}, -OC(O)N=C- oder -NR^{36}C(O)-; worin R^{25}, R^{29} oder R^{31} unabhängig voneinander optional mit einem oder mehreren R^{34} an Kohlenstoff substituiert sein können; und falls das Heterocyclyl eine -NH-Gruppe enthält, der Stickstoff optional mit einer aus R^{35} ausgewählten Gruppe substituiert sein kann;
R^{23}, Wasserstoff ist;
p, q, r und s unabhängig ausgewählt sind aus 0 oder 1;
R^{34} ausgewählt ist aus Hydroxy, Amino, Carbamoyl, Sulfamoyl oder Methoxy;
R^{30} oder R^{35} unabhängig ausgewählt sind aus C_{1-6}-Alkyl oder C_{1-6}-Alkoxy carbonyl; oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon. 9. Verbindung der Formel (I) gemäß Anspruch 1, ausgewählt aus:
1.1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[(N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl][benzyl]carbamoylmethoxy})-2,3,4,5,6-pentahydroxyhexyl]carbamoylmethoxy})-2,3,4,5,6-pentahydroxyhexyl]carbamoylmethoxy})-2,3,4,5,6-pentahydro-1,5-benzothiazepin;
1.1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[(N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl][benzyl]carbamoylmethoxy})-2,3,4,5,6-pentahydroxyhexyl]carbamoylmethoxy})-2,3,4,5,6-pentahydro-1,5-benzothiazepin;
1.1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[(N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl][benzyl]carbamoylmethoxy})-2,3,4,5,6-pentahydroxyhexyl]carbamoylmethoxy})-2,3,4,5,6-pentahydro-1,5-benzothiazepin;
1.1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[(N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl][benzyl]carbamoylmethoxy})-2,3,4,5,6-pentahydroxyhexyl]carbamoylmethoxy})-2,3,4,5,6-pentahydro-1,5-benzothiazepin;
oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon.

10. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäss irgendeinem der Ansprüche 1 bis 9 oder eines pharmazeutisch akzeptablen Salzes, Solvats, Solvats eines solchen Salzes oder eines Wirkstoffvorläufers (prodrug) hiervon, wobei das Verfahren die Schritte umfasst:

Verfahren (1): Oxidieren eines Benzothiazepins der Formel (II):

Verfahren (2): für Verbindungen der Formel (I), worin X \(-\text{O}, -\text{NR}^a\) oder \(-\text{S}\) ist, Umsetzen einer Verbindung der Formel (IIIa) oder (IIIb):

mit einer Verbindung der Formel (IV):
worin L eine entfernbare Gruppe ist;
Verfahren (3): Umsetzen einer Säure der Formel (Va) oder (Vb):

\begin{align*}
\text{(Va)} \\
\text{(Vb)}
\end{align*}

oder eines aktivierten Derivats hiervon, mit einem Amin der Formel (VI):

\begin{align*}
\text{(VI)}
\end{align*}

Verfahren (4): für Verbindungen der Formel (I), worin R\textsuperscript{10} eine Gruppe der Formel (IB) ist; Umsetzen einer Verbindung der Formel (I), worin R\textsuperscript{10} Carboxy ist, mit einem Amin der Formel (VII):

\begin{align*}
\text{(VII)}
\end{align*}
Verfahren (5): für Verbindungen der Formel (I), worin $R^{10}$ eine Gruppe der Formel (IB) ist und $R^{14}$ eine Gruppe der Formel (IC) ist: Umsetzen einer Verbindung der Formel (I), worin $R^{14}$ Carboxy ist, mit einem Amin der Formel (VIII):

$$R^{15}R^{16}NH \quad \text{(VIII)}$$

Verfahren (6): für Verbindungen der Formel (I), worin eines von $R^4$ und $R^5$ unabhängig ausgewählt ist aus $C_{1-6}$-Alkylthio, optional mit einem oder mehreren $R^{17}$ an Kohlenstoff substituiert: Umsetzen einer Verbindung der Formel (IXa) oder (IXb):

$$R^yH \quad \text{(X)}$$

worin $R^y$ $C_{1-6}$-Alkylthio ist, optional mit einem oder mehreren $R^{16}$ an Kohlenstoff substituiert; und danach, falls notwendig oder wünschenswert:

(i) Umwandeln einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I);
(ii) Entfernen von Schutzgruppen;
(iii) Bilden eines pharmazeutisch akzeptablen Salzes, Solvats oder Solvats eines solchen Salzes.

11. Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon gemäss irgendeinem der Ansprüche 1 bis 9 zur Verwendung als Medikament.

12. Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon gemäss irgendeinem der Ansprüche 1 bis 9 zur Verwendung bei der prophylaktischen oder therapeutischen Behandlung eines warmblütigen Lebewesens, wie z.B. Menschen.

13. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch akzeptablen Salzes, Solvats oder Solvats eines solchen Salzes, wie in irgendeinem der Ansprüche 1 bis 9 beansprucht, bei der Herstellung eines Medikaments zur Verwendung in der Herbeiführung einer IBAT-inhibierenden Wirkung in einem warmblütigen Lebewesen, wie z.B. Menschen.

14. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon, wie in irgendeinem der Ansprüche 1 bis 9 beansprucht, zusammen mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger umfasst.

15. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon, wie in irgendeinem der Ansprüche 1 bis 9 beansprucht, und
einen HMG-Co-A-Reduktaseinhibitor oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon zusammen mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger umfasst.

16. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon, wie in irgendeinem der Ansprüche 1 bis 9 beansprucht, und ein Gallensaure-Bindemittel zusammen mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger umfasst.

17. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon, wie in irgendeinem der Ansprüche 1 bis 9 beansprucht, und einen HMG-Co-A-Reduktaseinhibitor oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon und ein Gallensaure-Bindemittel zusammen mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger umfasst.


20. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz, Solvat oder Solvat eines solchen Salzes hiervon, wie in irgendeinem der Ansprüche 1 bis 9 beansprucht, und einen PPAR-\(\alpha\)- und/oder -\(\gamma\)-Agonisten oder ein pharmazeutisch akzeptables Salz hiervon zusammen mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger umfasst.

21. Zusammensetzung gemäss Anspruch 20, worin der PPAR-\(\alpha\)-und/oder -\(\gamma\)-Agonist (S)-2-Ethoxy-3-[4-(2-{4-methansulfonyloxyphenyl}ethoxy)phenyl]propansäure oder ein pharmazeutisch akzeptables Salz hiervon ist.

Revendications

1. Composé de formule (I) :

\[ \text{dans laquelle} \]

\[ R^1 \text{ et } R^m \text{ représentent chacun un atome d'hydrogène ;} \]

\[ \text{l'un de } R^1 \text{ et } R^2 \text{ est choisi parmi un atome d'hydrogène ou un groupe alkyle en } C_{1\text{ à }6} \text{ et l'autre est choisi parmi un groupe alkyle en } C_{1\text{ à }6} ; \]

\[ R^x \text{ et } R^y \text{ représentent chacun un atome d'hydrogène ;} \]

\[ R^2 \text{ est choisi parmi les groupes halogéno, nitro, cyano, hydroxy, amino, carboxy, carbamoyle, mercapto, sul-} \]
famoyle, alkyle en C\textsubscript{1} à C\textsubscript{6}, alcényle en C\textsubscript{2} à C\textsubscript{6}, alcoxy en C\textsubscript{1} à C\textsubscript{6}, alcanoyloxy en C\textsubscript{1} à C\textsubscript{6}, N-(alkyl en C\textsubscript{1} à C\textsubscript{6})amino, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{6})\textsubscript{2}amino, alcanoylamino en C\textsubscript{1} à C\textsubscript{6}, N-(alkyl en C\textsubscript{1} à C\textsubscript{6})carbamoyle, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{6})\textsubscript{2}carbamoyle, alkyl en C\textsubscript{1} à C\textsubscript{6}S(O)\textsubscript{a} où a vaut 0 à 2, alcoxycarbonyle en C\textsubscript{1} à C\textsubscript{6}, N-(alkyl en C\textsubscript{1} à C\textsubscript{6})sulfamoyle et N,N-(alkyl en C\textsubscript{1} à C\textsubscript{6})\textsubscript{2}sulfamoyle ;
v vaut de 0 à 5.
l'un de R\textsuperscript{4} et R\textsuperscript{5} est un groupe de formule (IA) :

![Diagramme (IA)](image)

R\textsuperscript{3} et R\textsuperscript{6} et l'autre groupe parmi R\textsuperscript{4} et R\textsuperscript{5} sont choisis indépendamment parmi un atome d'hydrogène, un groupe halogéno, nitro, cyano, hydroxy, amino, carboxy, carbamoyle, mercapto, sulfamoyle, alkylier en C\textsubscript{1} à C\textsubscript{6}, alcényle en C\textsubscript{2} à C\textsubscript{6}, alcoxy en C\textsubscript{1} à C\textsubscript{6}, alcanoyloxy en C\textsubscript{1} à C\textsubscript{6}, N-(alkyl en C\textsubscript{1} à C\textsubscript{6})amino, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{6})\textsubscript{2}amino, alcanoylamino en C\textsubscript{1} à C\textsubscript{6}, N-(alkyl en C\textsubscript{1} à C\textsubscript{6})carbamoyle, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{6})\textsubscript{2}carbamoyle, alkyl en C\textsubscript{1} à C\textsubscript{6}S(O)\textsubscript{a} où a vaut 0 à 2, alcoxycarbonyle en C\textsubscript{1} à C\textsubscript{6}, N-(alkyl en C\textsubscript{1} à C\textsubscript{6})sulfamoyle et N,N-(alkyl en C\textsubscript{1} à C\textsubscript{6})\textsubscript{2}sulfamoyle ;

le cycle A est un groupe aryle ou hétéroaryle ; le cycle A étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsuperscript{18} ;

R\textsuperscript{7} est un atome d'hydrogène, un groupe alkylier en C\textsubscript{1} à C\textsubscript{6}, carbocycle ou hétérocycle ; R\textsuperscript{7} étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsuperscript{19} ; et où si ledit hétérocycle contient un groupe -NH-, cet azote peut être facultativement substitué par un groupe choisi parmi R\textsuperscript{20} ;

R\textsuperscript{8} est un atome d'hydrogène ou un groupe alkylier en C\textsubscript{1} à C\textsubscript{6} et b vaut 0 à 2 ;

X est -O-, -N(R\textsuperscript{a}) -, -S(O)\textsubscript{b}- ou -CH(R\textsuperscript{a})- ; où R\textsuperscript{a} est un atome d'hydrogène ou un groupe alkylier en C\textsubscript{1} à C\textsubscript{6} et b vaut 0 à 2 ;

le cycle A est un groupe aryle ou hétéroaryle ; le cycle A étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsuperscript{18} ;

R\textsuperscript{10} est un atome d'hydrogène, un groupe alkylier en C\textsubscript{1} à C\textsubscript{6}, carbocycle ou hétérocycle ; R\textsuperscript{10} étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsuperscript{19} ;

R\textsuperscript{9} est un atome d'hydrogène ou un groupe alkylier en C\textsubscript{1} à C\textsubscript{6} ;

R\textsuperscript{9} est un atome d'hydrogène ou un groupe alkylier en C\textsubscript{1} à C\textsubscript{6} ;

R\textsuperscript{10} est un atome d'hydrogène, un groupe halogéno, nitro, cyano, hydroxy, amino, carboxy, mercapto, sulfamoyle, hydroxyaminocarbonyle, alkylier en C\textsubscript{1} à C\textsubscript{10}, alcényle en C\textsubscript{2} à C\textsubscript{10}, alcoxy en C\textsubscript{1} à C\textsubscript{10}, alcanoyloxy en C\textsubscript{1} à C\textsubscript{10}, N-(alkyl en C\textsubscript{1} à C\textsubscript{10})amino, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{10})\textsubscript{2}amino, alcanoylamino en C\textsubscript{1} à C\textsubscript{10}, N-(alkyl en C\textsubscript{1} à C\textsubscript{10})carbamoyle, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{10})\textsubscript{2}carbamoyle, alkyl en C\textsubscript{1} à C\textsubscript{10}S(O)\textsubscript{a} où a vaut 0 à 2, alcoxycarbonyle en C\textsubscript{1} à C\textsubscript{10}, N-(alkyl en C\textsubscript{1} à C\textsubscript{10})sulfamoyle,

R\textsuperscript{9} et R\textsuperscript{10} sont choisis indépendamment parmi un atome d'hydrogène, un groupe halogéno, nitro, cyano, hydroxy, amino, carboxy, mercapto, sulfamoyle, hydroxyaminocarbonyle, alkylier en C\textsubscript{1} à C\textsubscript{10}, alcényle en C\textsubscript{2} à C\textsubscript{10}, alcoxy en C\textsubscript{1} à C\textsubscript{10}, alcanoyloxy en C\textsubscript{1} à C\textsubscript{10}, N-(alkyl en C\textsubscript{1} à C\textsubscript{10})amino, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{10})\textsubscript{2}amino, alcanoylamino en C\textsubscript{1} à C\textsubscript{10}, N-(alkyl en C\textsubscript{1} à C\textsubscript{10})carbamoyle, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{10})\textsubscript{2}carbamoyle, alkyl en C\textsubscript{1} à C\textsubscript{10}S(O)\textsubscript{a} où a vaut 0 à 2, alcoxycarbonyle en C\textsubscript{1} à C\textsubscript{10}, N-(alkyl en C\textsubscript{1} à C\textsubscript{10})sulfamoyle, N,N-(alkyl en C\textsubscript{1} à C\textsubscript{10})\textsubscript{2}sulfamoyle, alcoxycarbonyle, alcoxycarbonylalkyle en C\textsubscript{1} à C\textsubscript{10}, hétérocyclique, hétérocyclalkyle en C\textsubscript{1} à C\textsubscript{10}, carbocyclé-(alkylène en C\textsubscript{1} à C\textsubscript{10}), R\textsuperscript{21}-(alkylène en C\textsubscript{1} à C\textsubscript{10}) ou hétérocyclé-(alkylène en C\textsubscript{1} à C\textsubscript{10}), R\textsuperscript{22}-(alkylène en C\textsubscript{1} à C\textsubscript{10}) d' où R\textsuperscript{10} étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsuperscript{23} ; et où si ledit hétérocycle contient un groupe -NH-, cet azote peut être facultativement substitué par un groupe choisi parmi R\textsuperscript{24} ; ou R\textsuperscript{10} est un groupe de formule (IB) :

![Diagramme (IB)](image)

dans laquelle :
R11 est un atome d'hydrogène ou un groupe alkyle en C\textsubscript{1 à 6} ; 
R12 et R13 sont choisis indépendamment parmi un atome d'hydrogène, un groupe halogéno, nitro, cyano, hydroxy, amino, mercapto, sulfamoyle, alkyne en C\textsubscript{2 à 10}, alcynyle en C\textsubscript{2 à 10}, alcoxy en C\textsubscript{2 à 10}, alcaneoxy en C\textsubscript{2 à 10}, N-(alkyl en C\textsubscript{1 à 10})amino, N,N-(alkyl en C\textsubscript{1 à 10})2amino, N,N,N-(alkyl en C\textsubscript{1 à 10})3amino, N,N,N,N-(alkyl en C\textsubscript{1 à 10})4amino, N,N,N,N,N-(alkyl en C\textsubscript{1 à 10})5amino, N-(alkyl en C\textsubscript{1 à 10})carbamoyle, N,N-(alkyl en C\textsubscript{1 à 10})2carbamoyle, alkyne en C\textsubscript{1 à 10}, alcaneoxy en C\textsubscript{1 à 10}, N-(alkyl en C\textsubscript{1 à 10})amino, N,N-(alkyl en C\textsubscript{1 à 10})2amino, N,N,N-(alkyl en C\textsubscript{1 à 10})3amino, N,N,N,N-(alkyl en C\textsubscript{1 à 10})4amino, N,N,N,N,N-(alkyl en C\textsubscript{1 à 10})5amino, alcone en C\textsubscript{1 à 10}, alcaneoxy en C\textsubscript{1 à 10}, N-(alkyl en C\textsubscript{1 à 10})amino, N,N-(alkyl en C\textsubscript{1 à 10})2amino, N,N,N-(alkyl en C\textsubscript{1 à 10})3amino, N,N,N,N-(alkyl en C\textsubscript{1 à 10})4amino, N,N,N,N,N-(alkyl en C\textsubscript{1 à 10})5amino, carbocycle ou hétérocycle ; R12 et R13 pouvant être facultativement et indépendamment substitués sur un carbone par un ou plusieurs substituants choisis parmi R25 ; et où si ledit hétérocycle contient un groupe -NH-, cet azote peut être facultativement substitué par un groupe choisi parmi R26 ; 
R14 est choisi parmi un atome d'hydrogène, un groupe halogéno, nitro, cyano, hydroxy, amino, mercapto, sulfamoyle, hydroxyaminocarboyne, alkyne en C\textsubscript{1 à 10}, alcynyle en C\textsubscript{1 à 10}, alcoxy en C\textsubscript{1 à 10}, alcaneoxy en C\textsubscript{1 à 10}, N-(alkyl en C\textsubscript{1 à 10})amino, N,N-(alkyl en C\textsubscript{1 à 10})2amino, N,N,N-(alkyl en C\textsubscript{1 à 10})3amino, N,N,N,N-(alkyl en C\textsubscript{1 à 10})4amino, N,N,N,N,N-(alkyl en C\textsubscript{1 à 10})5amino, N-(alkyl en C\textsubscript{1 à 10})carbamoyle, N,N-(alkyl en C\textsubscript{1 à 10})2carbamoyle, alkyne en C\textsubscript{1 à 10}, alcaneoxy en C\textsubscript{1 à 10}, N-(alkyl en C\textsubscript{1 à 10})amino, N,N-(alkyl en C\textsubscript{1 à 10})2amino, N,N,N-(alkyl en C\textsubscript{1 à 10})3amino, N,N,N,N-(alkyl en C\textsubscript{1 à 10})4amino, N,N,N,N,N-(alkyl en C\textsubscript{1 à 10})5amino, carbocycle, carbocyclylalkyle en C\textsubscript{1 à 10}, hétérocycle, hétérocyclylalkyle en C\textsubscript{1 à 10} ; R14 pouvant être facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R29 ; et où si ledit hétérocycle contient un groupe -NH-, cet azote peut être facultativement substitué par un groupe choisi parmi R30; ou R14 est un groupe de formule (IC) : 

\[
\begin{align*}
R_{15} & \text{ est un atome d'hydrogène ou un groupe alkyle en C_{1 à 6} ;} \\
R_{16} & \text{ est un atome d'hydrogène ou un groupe alkyle en C_{1 à 6} ; où R_{16} peut être facultativement substitué sur un carbone par un ou plusieurs groupes choisis parmi R_{31} ; n vaut 1 à 3 ; où les valeurs de R_{7} peuvent être identiques ou différentes ;} \\
R_{17}, R_{18}, R_{19}, R_{23}, R_{25}, R_{29} et R_{31} & \text{ sont choisis indépendamment parmi un groupe halogéno, nitro, cyan, hydroxy, amino, mercapto, sulfamoyle, hydroxyaminocarbonyle, alkyne en C_{1 à 10}, alcynyle en C_{2 à 10}, alcoxy en C_{2 à 10}, alcaneoxy en C_{2 à 10}, N-(alkyl en C_{1 à 10})amino, N,N-(alkyl en C_{1 à 10})2amino, N,N,N-(alkyl en C_{1 à 10})3amino, N,N,N,N-(alkyl en C_{1 à 10})4amino, N,N,N,N,N-(alkyl en C_{1 à 10})5amino, alcone en C_{2 à 10}, alcaneoxy en C_{2 à 10}, N-(alkyl en C_{1 à 10})amino, N,N-(alkyl en C_{1 à 10})2amino, N,N,N-(alkyl en C_{1 à 10})3amino, N,N,N,N-(alkyl en C_{1 à 10})4amino, N,N,N,N,N-(alkyl en C_{1 à 10})5amino, carbocycle en C_{1 à 10}, hétérocycle, hétérocyclylalkyle en C_{1 à 10}, carbocyclylalkyle en C_{1 à 10} ; R_{17}, R_{18}, R_{19}, R_{23}, R_{25}, R_{29} et R_{31} pouvant être facultativement et indépendamment substitués sur un carbone par un ou plusieurs R_{34} ; et où si ledit hétérocycle contient un groupe -NH-, cet azote peut être facultativement substitué par un groupe choisi parmi R_{35} ; R_{21}, R_{22}, R_{27}, R_{28} et R_{33} & \text{ sont choisis indépendamment parmi -O-, -NR_{36}-, -S(O)_{x}-, -NR_{36}C(O)- ou -C(O)NR_{36}- ; où R_{36} est choisi parmi un atome d'hydrogène ou un groupe alkyle en C_{1 à 6}, et x vaut 0 à 2 ; p, q, r et s sont choisis indépendamment parmi 0 à 2 ; R_{34} & \text{ est choisi parmi les groupes halogéno, hydroxy, cyan, carbamyl, uréido, amino, nitro, carbamoyl, mercapto, sulfamoyle, trifluorométhyle, trifluorométhoxy, méthyle, éthyle, méthoxy, éthoxy, vinyle, allyle, éthylénylformyle, formamido, acétylényle, acétylényle, méthylénéthynyle, mésyle, N-méthylsulfamoyle, N,N-méthélysulsamoylamine et N,N-diméthylsulsamoylamine ; R_{20}, R_{24}, R_{26}, R_{30} et R_{35} & \text{ sont choisis indépendamment parmi un groupe alkyle en C_{1 à 6}, alcaneoxy en C_{1 à 6},}
\end{align*}
\]
alkylsulfonyle en C\textsubscript{1} à \textsubscript{6}, alcoxycarbonyle en C\textsubscript{1} à \textsubscript{6}, carbamoyle, N-(alkyl en C\textsubscript{1} à \textsubscript{10})carbamoyle, N,N-(alkyl en C\textsubscript{1} à \textsubscript{6})carbamoyle, benzyle, benzoxycarbonyle, benzoyle et phénylsulfonyle ; où le groupe aryle est un cycle carboné mono- ou bicyclic totalement insaturé qui contient 3 à 12 atomes ; le groupe hétéroaryle est un cycle mono- ou bicyclic totalement insaturé contenant 3 à 12 atomes dont au moins un atome est choisi parmi l’azote, le soufre ou l’oxygène qui peut, sauf spécification contraire, être lié par carbone ou azote ; où le groupe hétéroaryle n’est pas le tétrazolyle ; où le groupe carbocyclyle est un cycle carboné mono- ou bicyclic saturé, partiellement saturé ou insaturé qui contient 3 à 12 atomes ; où un groupe -CH\textsubscript{2}- peut être facultativement remplacé par un -C(O)- ; et

où le groupe hétérocyclyle est un cycle mono- ou bicyclic saturé, partiellement saturé ou insaturé contenant 3 à 12 atomes dont au moins un atome, en particulier 1 à 3 atomes, est choisi parmi l’azote, le soufre ou l’oxygène, qui peut, sauf spécification contraire, être lié par carbone ou azote, où un groupe -CH\textsubscript{2}- peut être facultativement remplacé par un -C(O)- ou un atome de soufre de cycle peut être facultativement oxydé pour former les S-oxydes ; ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

2. Composé de formule (I) selon la revendication 1, dans lequel l’un de R\textsubscript{1} et R\textsubscript{2} est un groupe éthyle et l’autre est un groupe butyle, ou bien R\textsubscript{1} et R\textsubscript{2} sont tous deux un groupe butyle, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

3. Composé de formule (I) selon l’une quelconque des revendications 1 et 2, dans lequel v vaut 0, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

4. Composé de formule (I) selon l’une quelconque des revendications 1 à 3, dans lequel R\textsubscript{3} et R\textsubscript{6} sont tous deux un atome d’hydrogène, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

5. Composé de formule (I) selon l’une quelconque des revendications 1 à 4, dans lequel R\textsubscript{4} est un atome d’hydrogène ou un groupe méthylthio, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

6. Composé de formule (I) selon l’une quelconque des revendications 1 à 5, dans lequel R\textsubscript{5} est un groupe de formule (IA) tel que représenté ci-dessus, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

7. Composé de formule (I) selon l’une quelconque des revendications 1 à 6, dans lequel R\textsubscript{5} est un groupe de formule (IA) tel que représenté ci-dessus dans laquelle :

\begin{itemize}
  \item X est -O- ;
  \item R\textsubscript{7} est un atome d’hydrogène ;
  \item R\textsubscript{8} est un atome d’hydrogène ;
  \item R\textsubscript{9} est un atome d’hydrogène ;
  \item le cycle A est un groupe aryle ;
  \item R\textsubscript{10} est un groupe carbamoyle ou N-(alkyl en C\textsubscript{1} à \textsubscript{10})carbamoyle ou un groupe de formule (IB) (tel que représenté ci-dessus), R\textsubscript{10} étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsubscript{23} et où :
    \begin{itemize}
      \item R\textsubscript{11} est un atome d’hydrogène ;
      \item R\textsubscript{12} et R\textsubscript{13} sont indépendamment choisis parmi un atome d’hydrogène, un groupe carbamoyle ou alkyle en C\textsubscript{1} à \textsubscript{6}, et R\textsubscript{12} et R\textsubscript{13} pouvant être facultativement et indépendamment substitués sur un carbone par un ou plusieurs substituants choisis parmi R\textsubscript{25} ;
      \item R\textsubscript{14} est choisi parmi un groupe carbamoyle, hydroxyaminocarbonyle, alkyle en C\textsubscript{1} à \textsubscript{6}, carbocyclyle, hétérocyclyle ou carbocyclyle(alkylène en C\textsubscript{1} à \textsubscript{6})p-R\textsubscript{27}-(alkylène en C\textsubscript{1} à \textsubscript{6})q ; R\textsubscript{14} pouvant être facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R\textsubscript{29} ; et où si ledit hétérocyclyle contient un groupe \(-\text{NH}-\), cet azote peut être facultativement substitué par un groupe choisi parmi R\textsubscript{30} ; ou R\textsubscript{14} est un groupe de formule (IC) (tel que représenté ci-dessus) dans laquelle :
        \begin{itemize}
          \item R\textsubscript{15} est un atome d’hydrogène ;
          \item R\textsubscript{16} est un groupe alkyle en C\textsubscript{1} à \textsubscript{6} ; R\textsubscript{16} pouvant être facultativement substitué sur un carbone par un ou plusieurs groupes choisis parmi R\textsubscript{31} ;
          \item n vaut 1 ;
          \item R\textsubscript{23} est un groupe hydroxy ;
          \item R\textsubscript{25} et R\textsubscript{29} sont indépendamment choisis parmi les groupes halogéné, hydroxy, amino, sulfamoyle, alcoxy en C\textsubscript{1} à \textsubscript{6}, N,N,N-(alkyl en C\textsubscript{1} à \textsubscript{6})3ammonio, N,N-(alkyl en C\textsubscript{1} à \textsubscript{6})3sulfamoylamino, alcoxy carbonylamino en
    \end{itemize}
\end{itemize}
C₁₆, carboxyle, hétérocyclyle, carboxycarbonyl-(alkylène en C₁₆)ₚ-R⁳²-(alkylène en C₁₆)ₚ ou hétérocyclyl-(alkylène en C₁₆, R³₃₃-(alkylène en C₁₆)ₚ-R⁳₃₃-(alkylène en C₁₆)ₚ pouvant être facultativement et indépendamment substitués sur un carbone par un ou plusieurs R³₄ ; et où si ledit hétérocyclyle contient un groupe -NH₂, cet azote peut être facultativement substitué par un groupe choisi parmi R³₅ ; R³₇, R³² et R³₃ sont indépendamment choisis parmi -O-, -NR³₆C(O)NR³₆_, -OC(O)N=C- ou -NR³₆C(O)-; où R³₆ est un atome d’hydrogène ; p, q, r et s sont indépendamment choisis parmi 0 ou 1 ; R³⁴ est choisi parmi les groupes hydroxy, amino, carboxamoyl, sulfamoyle ou méthoxy ; R³₀ et R³₅ sont indépendamment choisis parmi un groupe alkyle en C₁₆ ou alcoxycarbonyl en C₁₆.

8. Composé de formule (I) selon la revendication 1, dans lequel :

- R⁷ et R⁸ sont tous deux un atome d’hydrogène ;
- R⁴ et R⁵ sont tous deux un atome d’hydrogène ;
- R¹ et R² sont indépendamment choisis parmi un groupe alkyle en C₁₄ ;
- v vaut 0 ;
- R³ et R⁶ sont un atome d’hydrogène ;
- R⁴ est un groupe méthylthio ;
- R⁶ est un groupe de formule (IA) tel que représenté ci-dessus, dans lequel ;
- X est -O- ;
- R⁷ est un atome d’hydrogène ;
- R⁸ est un atome d’hydrogène ;
- R⁹ est un atome d’hydrogène ;
- le cycle A est un groupe arylique ;
- R⁴₀ est un groupe carbamoyl ou N-(alkyl en C₁₀-carbamoyl ou un groupe de formule (IB) (tel que représenté ci-dessus), R⁴₀ étant facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R²₃ et où :
- R¹₁ est un atome d’hydrogène ;
- R¹₂ et R¹₃ sont indépendamment choisis parmi un atome d’hydrogène, un groupe carbamoyl ou alkyle en C₁₆ ; R¹₂ et R¹³ pouvant être facultativement et indépendamment substitués sur un carbone par un ou plusieurs substituants choisis parmi R⁵₂ ;
- R¹₄ est choisi parmi un groupe carbamoyl, hydroxyaminocarbonyl, alkyle en C₁₆, carboxycarbonyl, hétérocyclyl ou carboxycarbonyl-(alkylène en C₁₆)ₚ-R⁷₇-(alkylène en C₁₆)ₚ-R¹₄ ; R¹₄ pouvant être facultativement substitué sur un carbone par un ou plusieurs substituants choisis parmi R²₉ ; et où si ledit hétérocyclyle contient un groupe -NH₂, cet azote peut être facultativement substitué par un groupe choisi parmi R³₀ ; ou R¹₄ est un groupe de formule (IC) (tel que représenté ci-dessus) où :
- R¹₅ est un atome d’hydrogène ;
- R¹₆ est un groupe alkyle en C₁₆ ; où R¹₆ peut être facultativement substitué sur un carbone par un ou plusieurs groupes choisis parmi R²₁ ;
- n égal à 1 ;
- R²₃ est un groupe hydroxy ;
- R²₅, R²₉ et R³₁ sont indépendamment choisis parmi les groupes halogéno, hydroxy, amino, sulfamoyle, alcoxycarbonyl ammnonio, N,N-(alkyl en C₁₆)ₚ-sulfamoyle, alcoxycarbonyl amino en C₁₆, carboxy, hétérocyclyl, carboxycarbonyl-(alkylène en C₁₆)ₚ-R³₂-(alkylène en C₁₆)ₚ ou hétérocyclyl-(alkylène en C₁₆)ₚ-R³₃_(alkylène en C₁₆)ₚ-R³₅ ; R²₅, R²₉ et R³₁ pouvant être facultativement et indépendamment substitués sur un carbone par un ou plusieurs R³₄ ; et où si ledit hétérocyclyle contient un groupe -NH₂, cet azote peut être facultativement substitué par un groupe choisi parmi R³₅ ; R²₇, R³₂ et R³₃ sont indépendamment choisis parmi -O-, -NR³₆C(O)NR³₆_, -OC(O)N=C- ou -NR³₆C(O)- ; où R³₆ est un atome d’hydrogène ;
- p, q, r et s sont indépendamment choisis parmi 0 ou 1 ;
- R³⁴ est choisi parmi les groupes hydroxy, amino, carbamoyl, sulfamoyle ou méthoxy ;
- R³₀ et R³₅ sont indépendamment choisis parmi un groupe alkyle en C₁₆ ou alcoxycarbonyl en C₁₆ ;

ou sel, solvate ou solvate d’un tel sel pharmaceutiquement acceptable de celui-ci.

9. Composé de formule (I) selon la revendication 1, qui est choisi parmi les composés suivants :

1.1- dioxo-3,3- dibutyl-5- phényl-7- méthylthio-8-(N-(R)-(R)-(N)-(N'-2-2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6- pentahy-
droxyhexyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-[(R)-α-([N-(2-S)-(3-(R)-4-(R)-5-(R)-2,3,4,5,6-penta-
hydroxyhexyl)carbamoyl]benzyl)carbamoylméthoxy]-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N-(N'-hydroxy-2-méthoxyéthyl)carba-
moyl]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-1-carbamoyl-2-hydroxyéthyl)carba-
moyl]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-[2-(N'-pyrimidin-2-yluréido)éthyl]carba-
moyl]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-[2-(N'-pyridin-2-yluréido)éthyl]carba-
moyl]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-[1-t-butoxycarbonylpipéridin-4-ylméthyl]car-
bamoyl]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-2,3-dihydroxypropyl]carbamoyl]benzyl)car-
bamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-[(1-t-butoxycarbonylpipéridin-4-ylméthyl]car-
bamoyl]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-[2-aminoéthyl]carbamoyl]méthoxy]-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
1,1-dioxo-3-butyl-3-éthyl-5-phényl-7-méthylthio-8-(N-((R)-α-([N'-[2-t,N,N-diméthylaminosulfamoyléthyl]carba-
moval]benzyl)carbamoylméthoxy)-2,3,4,5-tétrahydro-1,5-benzothiazépine ;
or un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

10. Procédé de préparation d’un composé de formule (I), tel que revendiqué dans l’une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel ou promédicament, ledit procédé comprend :

   Traitement 1) : oxydation d’une benzothiazépine de formule (II) :

   Traitement 2) : pour des composés de formule (I) où X est -O-, -NR° ou -S- ; réaction d’un composé de formule (IIIa) ou(IIIb) :
avec un composé de formule (IV) :

où L est un groupe déplaçable ;

_Traitement 3) : réaction d’un acide de formule (Va) ou (Vb) :

ou d’un dérivé activé de celui-ci ; avec une amine de formule (VI) :
Traitement 4) : pour des composés de formule (I) où R^{10} est un groupe de formule (IB) ; réaction d'un composé de formule (I) où R^{10} est un groupe carboxyl avec une amine de formule (VII) :

![Image of compound VI]

Traitement 5) : pour des composés de formule (I) où R^{10} est un groupe de formule (IB) et R^{14} est un groupe de formule (IC), réaction d'un composé de formule (I) où R^{14} est un groupe carboxyl avec une amine de formule (VIII) :

\[ R^{15}R^{16}NH \]  
(VIII)

Traitement 6) : pour des composés de formule (I) où l'un de R^{4} et R^{5} est indépendamment choisi parmi les groupes alkylthio en C_{1-6} facultativement substitués sur un carbone par un ou plusieurs R^{17} ; réaction d'un composé de formule (IXa) ou (IXb) :

![Image of compounds IXa and IXb]

où L est un groupe déplaçable ; avec un thiol de formule (X) :

\[ R^{y}-H \]  
(X)

où R^{y} est un groupe alkylthio en C_{1-6} facultativement substitué sur un carbone par un ou plusieurs R^{16} ; et ensuite si nécessaire ou souhaitable :

i) conversion d'un composé de formule (I) en un autre composé de formule (I) ;
ii) élimination de tout groupe protecteur ;
iii) formation d’un sel pharmaceutiquement acceptable, solvate ou solvate d’un tel sel.

11. Composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, pour une utilisation à titre de médicament.

12. Composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, à utiliser dans le traitement prophylactique ou thérapeutique d’un animal à sang chaud, tel que l’homme.

13. Utilisation d’un composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, pour la fabrication d’un médicament destiné à être utilisé dans la production d’un effet inhibiteur d’IBAT chez un animal à sang chaud, tel que l’homme.

14. Composition pharmaceutique qui comprend un composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, en association avec un diluant ou support pharmaceutiquement acceptable.

15. Composition pharmaceutique qui comprend un composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, et un inhibiteur de HMG Co-A réductase, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, en association avec un diluant ou support pharmaceutiquement acceptable.

16. Composition pharmaceutique qui comprend un composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, et un liant d’acide biliaire, en association avec un diluant ou support pharmaceutiquement acceptable.

17. Composition pharmaceutique qui comprend un composé de formule (I), ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, et un inhibiteur de HMG Co-A réductase, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, et un liant d’acide biliaire en association avec un diluant ou support pharmaceutiquement acceptable.

18. Composition selon la revendication 15 ou la revendication 17, dans laquelle l’inhibiteur de HMG Co-A réductase est l’atorvastatine, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

19. Composition selon la revendication 15 ou la revendication 17, dans laquelle l’inhibiteur de HMG Co-A réductase est la rosuvastatine, ou un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel.

20. Composition pharmaceutique qui comprend un composé de formule (I), un de ses sels pharmaceutiquement acceptable, solvate, ou solvate d’un tel sel, tel que revendiqué dans l’une quelconque des revendications 1 à 9, et un agoniste alpha et/ou gamma de PPAR, ou un sel pharmaceutiquement acceptable de celui-ci, en association avec un diluant ou support pharmaceutiquement acceptable.

21. Composition selon la revendication 20, dans laquelle l’agoniste alpha et/ou gamma de PPAR est l’acide (S)-2-éthoxy-3-[4-(2-(4-méthanesulfonyloxyphényl)éthoxy)phényl]propanoïque ou un sel pharmaceutiquement acceptable de celui-ci.
REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader’s convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 9316055 A [0004]
- WO 9418183 A [0004]
- WO 9418184 A [0004]
- WO 9605188 A [0004]
- WO 9616051 A [0004] [0149] [0156] [0163]
- WO 9733882 A [0004]
- WO 9838182 A [0004]
- WO 9935135 A [0004]
- WO 9840375 A [0004]
- WO 9935153 A [0004]
- WO 9964409 A [0004]
- WO 9964410 A [0004]
- WO 0001687 A [0004]
- WO 0047568 A [0004]
- WO 0061568 A [0004]
- WO 0168906 A [0004] [0004]
- DE 19825804
- WO 0038725 A [0004]
- WO 0038726 A [0004]
- WO 0038727 A [0004]
- WO 0038728 A [0004]
- WO 0038729 A [0004]
- WO 0166533 A [0004]
- WO 0250051 A [0004] [0142] [0143]
- EP 0864582 A [0004]
- WO 0112187 A [0115]
- WO 0112612 A [0115]
- WO 9962870 A [0115]
- WO 9962872 A [0115]
- WO 9962871 A [0115]
- WO 9857941 A [0115]
- WO 0140170 A [0115]
- Expert Opinion on Therapeutic Patents, vol. 10 (5), 623-634 [0115]