The present invention relates to indanone compounds. The indanone compounds are GPR19 modulators and useful for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders. The invention furthermore relates to the use of indanone compounds as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.
Substituted Indanone Compounds as GPR1 19 Modulators for the Treatment of Diabetes, Obesity, Dyslipidemia and Related Disorders

The present invention relates to indanone compounds of the formula I

\[
\text{(I)}
\]

in which \(R_{1a}, R_{1b}, R_{1c}, R_{2a}, R_{2b}, R_{2c}, R_{3}, R_{4}, R_{11}, R_{12}, R_{30}, R_{31}, Y\) and \(Z\) are defined as indicated below. The indanone compounds \(I\) are GPR1 19 modulators and useful for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders. The invention furthermore relates to the use of indanone compounds of the formula \(I\) as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.

GPR1 19 is a G-protein coupled receptor which is expressed predominantly in the beta cells of the pancreas and in the K- and L-cells of the intestine. In vitro studies have shown, that agonists of GPR1 19, via activation of the cAMP pathway in gut and pancreas derived cell lines, mediate the secretion of GLP-1 and insulin respectively. This supports the hypothesis, that modulators of GPR1 19, agonists in particular, may have utility to treat diabetes and related disorders by augmenting the secretion of insulin and intestinal hormones like GIP, GLP-1 and PYY. As the secretion of insulin was found to be strictly glucose-dependent, induction of hypoglycemic episodes may largely be avoided. Furthermore beneficial effects like reduced food intake may be expected from the release of intestinal peptides. Stimulation of the beta cell by activation of GPR1 19 may also improve beta cell function and beta cell mass. Studies of GPR1 19 agonists in rodents showed the predicted glucose lowering effects. For some such animal studies decreased food intake and weight loss was reported. Recently clinical trials with
GPR1 19 agonists added evidence for a positive impact on lipid parameters i.e. elevation of HDL together with lowering of LDL and triglycerides in humans. WO2013/070463A2 discloses that GPR1 19 agonists may be used to treat abnormalities in blood lipids. In summary, modulators of GPR1 19, agonists in particular, may have therapeutic utility in the prevention and/or treatment of metabolic disorders in mammals and especially in humans. Examples of such disorders and diseases include type 2 diabetes mellitus, type 1 diabetes mellitus, impaired glucose tolerance, insulin resistance, loss of beta cell function, hyperglycemia, hypercholesterolemia, dyslipidemia, hypertriglyceridemia, syndrome X, metabolic syndrome, obesity, fatty liver, steatosis, steatohepatitis, cirrhosis, micro- and macrovascular disorders, high blood pressure, chronic low grade inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, coronary heart disease, endothelial dysfunction and bone-related diseases such as osteoporosis, rheumatoid arthritis or osteoarthritis.

Several modulators of GPR1 19 are known. For example WO2011146335 and WO2012037393 describe piperidinyl-substituted lactams as GPR1 19 modulators. WO2011048149 describes heterocyclic modulators of GPR1 19 for the treatment of disease and their preparation. WO2004110994 describes the preparation of piperazinyl-aryloxy and piperazinyl-heteroaryloxy-N-aryl lactams as 5-HT1B ligands.

It was an aim of the invention to provide novel compounds as active ingredients in pharmaceuticals.

It was another aim of the invention to provide novel compounds which will lower blood glucose in mammals and which are suitable for prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

A further aim was to provide novel GPR1 19 modulators, especially agonists, which can be used therapeutically for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

Accordingly a subject of the invention is a compound of the formula I
in which

R30 is (CR1' R1 2')\textsubscript{n}-R32, NR17R18 or OR17;

R31 is H or (CR1' R1 2')\textsubscript{m}-R32;

n is 0, 1 or 2;

m is 0, 1, 2 or 3;

R11, R12 are independently of each other H or (Ci-C-6)-alkyl;
or R11 and R12 form together the group =O;

R11', R12' are independently of each other H or (Ci-CeJ)-alkyl;

R32 is (Ci-C\textsubscript{6})-alkyl, COOR13, CONR14R15, SO\textsubscript{2}R16 or OH;

R13 is H or (Ci-C\textsubscript{6})-alkyl;

R14, R15 are independently of each other H, (Ci-C\textsubscript{6})-alkyl, (Ci-C\textsubscript{6})-alkyl substituted with OR17, or (C\textsubscript{3}-C\textsubscript{6})-cycloalkyl;
or R14 and R15 form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;

wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (Ci-C\textsubscript{4})-alkyl and OR19;
R\textsubscript{16} is \((\text{C}_3-\text{C}_6)\)-alkyl;

R\textsubscript{17} is H or \((\text{C}_3-\text{C}_6)\)-alkyl;

R\textsubscript{18} is H or \((\text{C}_3-\text{C}_6)\)-alkyl;

R\textsubscript{19} is H or \((\text{C}_3-\text{C}_6)\)-alkyl;

R\textsubscript{1a}, R\textsubscript{1b}, R\textsubscript{1c} are independently of each other H, F, Cl, Br, \((\text{C}_3-\text{C}_6)\)-alkyl or CN;

R\textsubscript{2a}, R\textsubscript{2b}, R\textsubscript{2c} are independently of each other H, F, Cl, Br, \((\text{C}_3-\text{C}_6)\)-alkyl or CN;

Y is N or CH;

Z is a bond, O, CR\textsubscript{5}R\textsubscript{5'}, NR\textsubscript{6}, C=O, S, SO or SO\textsubscript{2};

R\textsubscript{5}, R\textsubscript{5'}, R\textsubscript{6} are independently of each other H or \((\text{C}_3-\text{C}_4)\)-alkyl;

R\textsubscript{3} is a bond or \((\text{C}_3-\text{C}_7)\)\(_p\);

p is 0, 1, 2, 3 or 4;

R\textsubscript{7}, R\textsubscript{7'} are independently of each other H or \((\text{C}_3-\text{C}_6)\)-alkyl;

R\textsubscript{4} is \((\text{C}_3-\text{C}_6)\)-alkyl, OR\textsubscript{8}, \((\text{C}_3-\text{C}_8)\)-cycloalkyl, \((\text{C}_5-\text{C}_8)\)-bicycloalkyl, \((\text{C}_4-\text{C}_5)\)-alkenyl or \((\text{C}_4-\text{C}_5)\)-alkyne, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;

wherein the groups \((\text{C}_3-\text{C}_8)\)-cycloalkyl, \((\text{C}_3-\text{C}_8)\)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from \((\text{C}_3-\text{C}_4)\)-alkyl, \((\text{C}_1-\text{C}_4)\)-alkanoyl, hydroxy, hydroxy-\((\text{C}_3-\text{C}_4)\)-alkyl, \((\text{C}_1-\text{C}_3)\)-alkyloxy-\((\text{C}_3-\text{C}_4)\)-alkyl, oxo, \(\text{F}\) or \(\text{Cl}\);

R\textsubscript{8} is H, \((\text{C}_1-\text{C}_6)\)-alkyl, hydroxy-\((\text{C}_1-\text{C}_4)\)-alkyl or \((\text{C}_1-\text{C}_3)\)-alkyloxy-\((\text{C}_1-\text{C}_4)\)-alkyl;
wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments
the 3-position of the central pyrrolidinone ring has (R)-configuration.

In another group of embodiments
R30 is (CR1 1'R1 2')n-R32.

In another group of embodiments
R31 is H.

In another group of embodiments
R11, R12 are H.

In another group of embodiments
R11', R12' are H.

In another group of embodiments
R32 is COOR13, CONR14R15, SO2R16 or OH.

In another group of embodiments
R32 is COOR13, CONR14R15.

In another group of embodiments
R32 is CONR14R15.
R₁₄, R₁₅ are independently of each other H, (Ci-C₆)-alkyl or (Ci-C₆)-alkyl substituted with OR₁⁷.

In another group of embodiments

5  R₁₆ is CH₃.

In another group of embodiments

R₁₆ₐ, R₁₆ₜ are independently of each other H, F or CH₃.

In another group of embodiments

10 R₁₆ₚ is H.

In another group of embodiments

R₁₆ₐ is H or F.

In another group of embodiments

15 R₁₆ₜ and R₁₆ₚ are H.

In another group of embodiments

R₂₆ₐ is H, F or CH₃.

In another group of embodiments

R₂₆ₛ and R₂₆₅ are H.

20 Y is N.

In another group of embodiments

Z is O.

In another group of embodiments

R₇, R₇' are H.

In another group of embodiments

p is 0, 1 or 2.
In another group of embodiments
R4 is (C<sub>1</sub>-C<sub>6</sub>)-alkyl, OR<sub>8</sub>, (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl or phenyl;
wherein the groups (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl and phenyl may be
optionally substituted with 1 to 3 groups F;

In another group of embodiments
R4 is (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, which is unsubstituted or substituted by methyl.

In another group of embodiments
R3 is a bond.

In another group of embodiments
R3 is selected from the list CH<sub>2</sub> and CH<sub>2</sub>CH<sub>2</sub>.

In another group of embodiments
R3 is CH<sub>2</sub>.

In another group of embodiments the compound of the formula I is a compound of the
formula la

![Chemical structure](image)

in which

R<sub>30</sub> is (CR<sub>1</sub>′R<sub>1</sub>′′)<sub>n</sub>-R<sub>32</sub> or OR<sub>1</sub>7;

n is 0, 1 or 2;

R<sub>11′</sub>, R<sub>12′</sub> are independently of each other H or (C<sub>1</sub>-C<sub>6</sub>)-alkyl;
R32 is COOR13, CONR14R15, SO2R16 or OH;

R13 is H or (C6-alkyl);

R14, R15 are independently of each other H, (C6-alkyl), (C6-alkyl) substituted with OR17, or (C3-C6)-cycloalkyl;

or R14 and R15 form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;

wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C4-alkyl) and OR19;

R16 is (C6-alkyl);

R17 is H or (C6-alkyl);

R18 is H or (C6-alkyl);

R19 is H or (C6-alkyl);

R1a, R1c are independently of each other H, F, Cl, Br, (C6-alkyl) or CN;

R2a is H, F, Cl, Br, (C6-alkyl) or CN;

R3 is a bond or (CR7R7')p;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C6-alkyl);

R4 is (C6-alkyl), OR8, (C3-C6)-cycloalkyl, (C5-C8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups (C3-C8)-cycloalkyl, (Cs-CsJ-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from (Ci-C4)-alkyl, (Ci-C4)-alkanoyl, hydroxy, hydroxy-(Ci-C4)-alkyl, (Ci-C3)-alkyloxy-(Ci-C4)-alkyl, oxo, F or Cl;

R8 is H, (Ci-C6)-alkyl, hydroxy-(Ci-C4)-alkyl or (Ci-C3)-alkyloxy-(Ci-C4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

R30 is (CR11'R12')n-R32 or OR17;

n is 0, 1 or 2;

R11', R12' are independently of each other H or (Ci-C3)-alkyl;

R32 is COOR13, CONR14R15, SO2R16 or OH;

R13 is H or (Ci-C6)-alkyl;

R14, R15 are independently of each other H, (Ci-C3)-alkyl, (Ci-Ce)-alkyl substituted with OR17, or (C3-C6)-cycloalkyl;

or R14 and R15 form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list \((\text{C}_{3}-\text{C}_{4})\)-alkyl and OR19;

\[
\begin{align*}
\text{R16} & \text{ is } (\text{C}_{6})\text{-alkyl;} \\
\text{R17} & \text{ is H or } (\text{C}_{6})\text{-alkyl;} \\
\text{R18} & \text{ is H or } (\text{C}_{6})\text{-alkyl;} \\
\text{R19} & \text{ is H or } (\text{C}_{6})\text{-alkyl;} \\
\text{R1a, R1c} & \text{ are independently of each other H, F, Cl, Br, } (\text{C}_{6})\text{-alkyl or CN;} \\
\text{R2a} & \text{ is H, F, Cl, Br, } (\text{C}_{6})\text{-alkyl or CN;} \\
\text{R3} & \text{ is bond, } \text{C}_{2}H_{2} \text{ or } \text{C}_{2}H_{2}-\text{CH}_{2}; \\
\text{R4} & \text{ is } (\text{C}_{6})\text{-alkyl, OR8, (C}_{3}-\text{C}_{8})\text{-cycloalkyl, (C}_{5}-\text{C}_{8})\text{-bicyclocalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;} \\
& \text{wherein the groups } (\text{C}_{3}-\text{C}_{8})\text{-cycloalkyl, (C}_{5}-\text{C}_{8})\text{-bicyclocalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from } (\text{C}_{4})\text{-alkyl, (C}_{4})\text{-alkanoyl, hydroxy, hydroxy-(C}_{4})\text{-alkyl, (C}_{3})\text{-alkyloxy-(C}_{4})\text{-alkyl, oxo, F or Cl;} \\
\text{R8} & \text{ is H, (C}_{6})\text{-alkyl, hydroxy-(C}_{4})\text{-alkyl or (C}_{3})\text{-alkyloxy-(C}_{4})\text{-alkyl;} \\
& \text{wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;} \\
& \text{in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.}
\end{align*}
\]
In another group of embodiments the compound of the formula I is a compound of the formula la, in which

R30 is \((\text{CR}1 \, 1'\text{R}1 \, 2')_n \cdot \text{R}32\) or OR1 7;

\(n\) is 0, 1 or 2;

\(\text{R}11'\), \(\text{R}12'\) are independently of each other \(\text{H}\) or \((\text{Ci} - \text{C}_6)\)-alkyl;

R32 is COOR3, CONR14R15, SO2R16 or OH;

R13 is \(\text{H}\) or \((\text{Ci} - \text{C}_6)\)-alkyl;

R14, R15 are independently of each other \(\text{H}\), \((\text{Ci} - \text{C}_6)\)-alkyl, \((\text{Ci} - \text{Ce})\)-alkyl substituted with OR1 7, or \((\text{C}_3 - \text{C}_6)\)-cycloalkyl;

or R14 and R15 form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;

wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list \((\text{Ci} - \text{C}_4)\)-alkyl and OR1 9;

R16 is \((\text{Ci} - \text{C}_6)\)-alkyl;

R17 is \(\text{H}\) or \((\text{Ci} - \text{C}_6)\)-alkyl;

R18 is \(\text{H}\) or \((\text{Ci} - \text{C}_6)\)-alkyl;

R19 is \(\text{H}\) or \((\text{Ci} - \text{C}_6)\)-alkyl;

R1a, R1c are independently of each other \(\text{H}, \text{F}, \text{Cl}, \text{Br}, (\text{Ci} - \text{Ce})\)-alkyl or \(\text{CN}\);

R2a is \(\text{H}, \text{F}, \text{Cl}, \text{Br}, (\text{Ci} - \text{C}_6)\)-alkyl or \(\text{CN}\);
R3 is bond, CH₂ or CH₂CH₂;

R4 (C₃-C₆)-cycloalkyl;

5

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

10

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

R30 is R32;

15 R32 is CONR₁₄R₁₅, COOR₁₃;

R₁₃ is H or (Ci-C₆)-alkyl;

R₁₄, R₁₅ are independently of each other H, (Ci-C₆)-alkyl or (Ci-C₆)-alkyl substituted with OR₁₇;

or R₁₄ and R₁₅ form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the series O, S and NR₁₈;

20 R₁₇ is H or (Ci-C₆)-alkyl;

R₁₈ is H or (Ci-C₆)-alkyl;

R₁₉, R₁₅ are independently of each other H, F, Cl, Br, (Ci-C₆)-alkyl or CN;

30 R₂₉ is H, F, Cl, Br, (Ci-C₆)-alkyl or CN;

R₃ is CH₂;
R4 \((C_3-C_6)\)-cycloalkyl;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula la, in which

10 R30 is R32;

R32 is CONR14R15, COOR13;

R14, R15 are independently of each other H, \((C_i-C_6)\)-alkyl or \((C_i-C_6)\)-alkyl substituted with OR17;

R17 is H or \((C_i-C_6)\)-alkyl;

R1a is H or F;

20 R1c is H;

R2a is H;

R3 is CH2;

R4 \((C_3-C_6)\)-cycloalkyl;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another embodiment compounds of the formula I are encompassed selected from the list Examples 1-01 to 1-18, 2-01 to 2-05 and 3-01 to 3-11.
In another embodiment compounds of the formula I are encompassed selected from the following list:

(3R)-3-[[6-(4-Fluorophenoxy)-3-pyridyl]oxy]-1-[(2-hydroxyethyl)-3-oxo-indan-5-yl]pyrrolidin-2-one,

methyl 2-[6-[[3-(4-isopentyloxyphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-indan-2-yl]acetate,

methyl 2-[5-[[3(R)-3-[[4-(4-fluorophenoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]pyrrolidin-2-one,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

(6-[[R]-3-[[6-(cyclopropylmethoxy)-pyridin-3-yloxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-indan-2-yl]-acetic acid methyl ester,

(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-1-[7-fluoro-2-(2-hydroxyethyl)-3-oxo-indan-5-yl]pyrrolidin-2-one,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

methyl 6-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-indane-2-carboxylate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[3(R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[1 S]-5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

methyl 2-[5-[[1 R]-5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]acetate,

5-[[3(R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-N,N-dimethyl-3-oxo-indane-1-carboxamide,
(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-1-[7-fluoro-1-(hydroxymethyl)-3-oxo-indan-5-yl]pyrrolidin-2-one,
(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-1-[1-(hydroxynethyl)-3-oxo-indan-5-yl]pyrrolidin-2-one,
6-[{(R)-3-(6-cyclopropylmethoxy-pyridin-3-yloxy)-2-oxo-pyrrolidin-yl}-4-fluoro-1-oxo-indan-2-yl]-acetic acid,
{5-[(R)-3-(6-Cyclopropylmethoxy-pyridin-3-yloxy)-2-oxo-pyrrolidin-yl]-3-oxo-indan-yl]-acetic acid,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-7-fluoro-3-oxo-indan-1-yl]acetic acid,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-3-oxo-indan-1-yl]acetic acid,
2-[(1S)-5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-3-oxo-indan-1-yl] acetic acid,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-N,N-dimethyl-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-N-methyl-acetamide,
N-cyclopropyl-2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-3-oxo-indan-1-yl]acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-N,N-dimethyl-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-N-methyl-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-N-(2-hydroxy-ethyl)-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-yl]-N-methyl-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-pyridin-3-yloxy)-2-oxo-pyrrolidin-yl]-4-fluoro-1-oxo-indan-2-yl]-N,N-dimethyl-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-pyridin-3-yl]oxy]-2-oxo-pyrrolidin-yl]-N-(2-hydroxy-ethyl)-acetamide,
2-[(3R)-3-[[6-(cyclopropylmethoxy)-pyridin-3-yl]oxy]-2-oxo-pyrrolidin-yl]-7-fluoro-3-oxo-indan-1-yl]acetamide and
In another embodiment compounds of the formula I are encompassed selected from the following list:
5-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-N,N-dimethyl-3-oxo-indane-1-carboxamide,
2-[5-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-acetamide,
2-[5-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N-methyl-acetamide,
2-[6-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-acetamide,
2-[5-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[5-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[5-[3R]-3-[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide.

Structural elements such as groups, substituents, hetero ring members, numbers or other features, for example alkyl groups, groups like R5, R5', R7, R7' etc., which can occur several times in the compounds of the formula I, can all independently of one another have at each occurrence any of the indicated meanings and can in each case be identical to or different from one another. For example, the alkyl groups in a dialkylamino group can be identical or different.
Herein, the terms "including" and "comprising" are used in their open, non-limiting sense. As used herein, the terms "(C1-C6)" and so forth refer to moieties having 1 to 6 carbon atoms and so forth, respectively. Within composed terms like "hydroxy-(C8)-alkyl" the option "(C0)-alkyl" refers to a bond (i.e. in this case a directly bound hydroxy group), or in case of an unsubstituted "(C0)-alkyl" it refers to a hydrogen.

The term "alkyl", as used herein, refers to saturated, monovalent hydrocarbon radicals. The term "alkenyl", as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term "alkynyl", as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. The alkyl, alkenyl and alkynyl groups can be linear, i.e. straight-chain, or branched. This also applies when they are part of other groups, for example alkoxy groups (\(=\) alkoxy groups, O-alkyl groups), alkoxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. Depending on the respective definition, the number of carbon atoms in an alkyl group can be 1, 2, 3, 4, 5 or 6, or 1, 2, 3, or 4. Examples of alkyl are methyl, ethyl, propyl including n-propyl and isopropyl, butyl including n-butyl, sec-butyl, isobutyl and tert-butyl, pentyl including n-pentyl, 1-methylbutyl, isopentyl, neopentyl and tert-pentyl, hexyl including n-hexyl, 3,3-dimethylbutyl and iso-hexyl.

Double bonds and triple bonds in alkenyl groups and alkynyl groups respectively can be present in any positions. Examples of alkenyl and alkynyl are ethenyl, prop-1-enyl, prop-2-enyl (\(=\) allyl), but-2-enyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, hex-3-enyl, hex-4-enyl, prop-2-ynyl (\(=\) propargyl), but-2-ynyl, but-3-ynyl, hex-4-ynyl or hex-5-ynyl.

Substituted alkyl groups, alkenyl groups and alkynyl groups can be substituted in any positions, provided that the respective compound is sufficiently stable and is suitable for the desired purpose such as use as a drug substance. The prerequisite that a specific group and a compound of the formula I are sufficiently stable and suitable for the desired purpose such as use as a drug substance, applies in general with respect to the definitions of all groups in the compounds of the formula I.

Independently of one another and independently of any other substituents, alkyl groups, divalent alkyl groups, alkenyl groups, alkynyl groups, cycloalkyl groups and heterocycloalkyl groups are optionally substituted by one or more fluorine substituents which can be located in any positions, i.e., the said groups can be unsubstituted by
fluorine substituents or substituted by fluorine substituents, for example by 1, 2 or 3, by 1 or 2, or by 1 fluorine substituents. Examples of fluorine-substituted said groups are trifluoromethyl, difluoromethyl and fluoromethyl.

The term "alkanediyl" or "alkylene", as used herein, refers to saturated, divalent hydrocarbon radicals. The term "alkenediyl", as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term "alkynediyl", as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. As far as applicable, the preceding explanations regarding alkyl, alkenyl and alkynyl groups apply correspondingly to alkanediyl, alkenediyl and alkynediyl groups, which thus can likewise be linear and branched. Examples of divalent alkyl groups are \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\) and \(-\text{C(CH}_3\text{)}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\).

The term "cydoalkyi", as used herein, unless otherwise indicated, refers to a monovalent radical of a saturated hydrocarbon ring system, which is monocyclic. In a monocyclic cydoalkyi group the number of ring carbon atoms can be for example 3, 4, 5, 6, 7 or 8. In one embodiment of the invention, the number of ring carbon atoms in a cydoalkyi group, independently of the number of ring carbon atoms in any other cydoalkyi group is 3, 4, 5 or 6, in another embodiment 3 or 4, in another embodiment 3, in another embodiment 5 or 6, in another embodiment 5, in another embodiment 6.

Examples of cydoalkyi groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "heterocycle", as used herein, unless otherwise indicated, refers to a cydoalkyi as defined above, in which 1, 2, 3 or 4 carbon atoms are replaced by nitrogen or oxygen atoms, provided that the heterocycloalkyi system is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. Depending on the definition of the respective heterocyclic group, in one embodiment of the invention the number of ring heteroatoms which can be present in a heterocyclic group, independently of the number of ring heteroatoms in any other heterocyclic group, is 1 or 2, in another embodiment 2, in another embodiment 1, wherein the ring heteroatoms can be identical or different. The heterocycloalkyi group can be attached by any ring carbon atom or saturated ring nitrogen atom, with the exception of spiro- or bridgehead atoms.
Exemplary monocyclic heterocycloalkyl groups are derived from, but not limited to, the ring systems azetidine, oxetane, pyrrolidine, tetrahydrofuran, 1,3-dioxolane, piperidine, piperazine, morpholine, tetrahydropyran or 1,4-dioxane:

\[
\text{N} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{O}
\]

In one embodiment monocyclic heterocycloalkyl groups are derived from azetidine, pyrrolidine, piperidine, piperazine or morpholine:

\[
\text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN}
\]

The term "aryl", as used herein, refers to a radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl.

The term "heteroaryl" as used herein, refers to a radical derived from a fully unsaturated monocyclic ring system, in which 1, 2 or 3 carbon atoms are replaced by heteroatoms. The ring heteroatoms are generally chosen from N, O and S, wherein N includes ring nitrogen atoms which carry a hydrogen atom or a substituent as well as ring nitrogen atoms which do not carry a hydrogen atom or a substituent. Ring heteroatoms can be located in any position, provided that the heterocyclic system is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. Heteroaryl radicals are derived from 5-membered or 6-membered monocyclic rings.

Exemplary heteroaryl systems are derived from, but not limited to, the following ring systems: pyrrole, furan, thiophene, imidazole, pyrazole, oxazole (= [1,3]oxazole), isoxazole (= [1,2]oxazole), thiazole (= [1,3]thiazole), isothiazole (= [1,2]thiazole), [1,2,3]triazole, [1,2,4]triazole, [1,2,4]oxadiazole, [1,3,4]oxadiazole, [1,2,4]thiadiazole,
[1,3,4]thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, [1,2,3]triazine, [1,2,4]triazine or [1,3,5]triazine:

Groups like phenyl and residues of aromatic heterocycles which are optionally substituted by one or more substituents, can be unsubstituted or substituted, for example by 1, 2 or 3, or by 1 or 2, or by 1, identical or different substituents which can be located in any positions. Aromatic nitrogen heterocycles which in the parent ring system carry a hydrogen atom on a ring nitrogen atom in a 5-membered ring, such as a pyrrole or imidazole ring, for example, can be substituted on ring carbon atoms and/or on such ring nitrogen atoms. In one embodiment of the invention, substituents on such ring nitrogen atoms are chosen from (Ci-C₄)-alkyl groups, i.e. such ring nitrogen atoms in aromatic heterocycles carry a hydrogen atom or a (Ci-C₄)-alkyl substituent. When it is stated with respect to ring nitrogen atoms in aromatic heterocycles and any other heterocycles that they can carry a hydrogen atom or a substituent, such ring nitrogen atoms either carry a hydrogen atom or a substituent or they do not carry a hydrogen atom or substituent. Ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in a nitrogen-containing aromatic 5-membered ring as is present in pyrrole or imidazole for example, and in a non-aromatic ring including a saturated ring. Ring nitrogen atoms which do not carry a hydrogen atom or a substituent unless they are present in positively charged form, including any further ring nitrogen atoms in addition to ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in an aromatic ring as is present in thiazole, imidazole or pyridine, for example, and in a non-aromatic ring in which they are part of a double bond, and they occur as ring nitrogen atoms via which a ring is bonded. Suitable ring nitrogen atoms in aromatic heterocycles in the compounds of the formula I, such as the ring nitrogen atom in a pyridine ring, can in general also be present as N-oxide or as quaternary salt, for example as N-(Ci-C₄)-
alkyl salt such as N-methyl salt, wherein in one embodiment of the invention the counter anion in such quaternary salt is a physiologically acceptable anion which is derived from an acid that forms a physiologically acceptable salt.

In monosubstituted phenyl groups, the substituent can be located in the 2-position, the 3-position or the 4-position. In disubstituted phenyl groups, the substituents can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl groups, the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position.

Ring heteroatoms can be located in any positions, provided that the heterocyclic system is known in the art and is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. In one embodiment of the invention, two ring oxygen atoms cannot be present in adjacent ring positions of any heterocycle, in another embodiment two ring heteroatoms chosen from oxygen and sulfur cannot be present in adjacent ring positions of any heterocycle. Substituents on heterocyclic groups can be located in any positions. For example, in a pyridin-2-yl group substituents can be located in the 3-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-3-yl group substituent can be located in the 2-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-4-yl group substituents can be located in the 2-position and/or 3-position and/or 5-position and/or 6-position.

When an oxo group is bonded to a carbon atom, it replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH₂ group in a chain or a ring is substituted by oxo, i.e. by a doubly bonded oxygen atom, it becomes a CO group. Evidently, an oxo group cannot occur as a substituent on a carbon atom in an aromatic ring such as in a phenyl group, for example.

The present invention includes all stereoisomeric forms of the compounds of the formula I and their salts and solvates. With respect to each chiral center, independently of any other chiral center, the compounds of the formula I can be present in S configuration or substantially S configuration, or in R configuration or substantially R configuration, or as a mixture of the S isomer and the R isomer in any ratio. The invention includes all possible enantiomers and diastereomers and mixtures of two or
more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in all ratios including racemates. In the case of a E/Z isomerism, or cis/trans isomerism, for example on double bonds or rings such as cycloalkyl rings, the invention includes both the E form and Z form, or the cis form and the trans form, as well as mixtures of these forms in all ratios. In one embodiment of the invention, a compound which can occur in two or more stereoisomeric forms is a pure, or substantially pure, individual stereoisomer. The preparation of individual stereoisomers can be carried out, for example, by separation of a mixture of isomers by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials in the synthesis, or by stereoselective synthesis. Optionally, a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compound of the formula I or at the stage of a starting material or an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of the formula I and their salts and solvates.

In case the compounds of the formula I contain one or more acidic and/or basic groups, i.e. salt-forming groups, the invention also includes their corresponding physiologically or toxicologically acceptable salts, i.e. non-toxic salts, in particular their pharmaceutically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols such as (C1-C4)-alkanols, active metabolites of the compounds of the formula I, and also prodrugs and derivatives of the compounds of the formula I which in vitro may not necessarily exhibit pharmacological activity but which in vivo are converted into pharmacologically active compounds, for example esters or amides of carboxylic acid groups.

The compounds of the present invention can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2014, e.g. all antidiabetics mentioned in the Rote Liste 2014, chapter 12, all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2014, chapter 06,
all lipid-lowering agents mentioned in the Rote Liste 2014, chapter 58, all antihypertensives mentioned in the Rote Liste 2014 chapter 17, all nephroprotectives mentioned in the Rote Liste, or all diuretics mentioned in the Rote Liste 2014, chapter 36.

The active ingredient combinations can be applied either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. When administered separately, administration may occur simultaneously or sequentially, in any order. The amount of the compound of the invention and the other pharmaceutically active ingredient(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration of the combination may be concomitantly in: (1) a unitary pharmaceutical composition including all pharmaceutically active ingredients; or (2) separate pharmaceutical compositions each including at least one of the pharmaceutically active ingredients. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2014.

Therapeutic agents which are suitable for combinations include, for example, antidiabetic agents such as:

Insulin and insulin derivatives, for example: insulin glargine (e.g. Lantus®), higher than 100U/mL concentrated insulin glargine, e.g. 270 - 330U/mL of insulin glargine or 300U/mL of insulin glargine (as disclosed in EP 2387989), insulin glulisine (e.g. Apidra®), insulin detemir (e.g. Levemir®), insulin lispro (e.g. Humalog®, Liprolog®), insulin degludec (e.g. DegludecPlus®, IdegLira (NN9068)), insulin aspart and aspart formulations (e.g. NovoLog®, basal insulin and analogues (e.g. LY2605541, LY2963016, NN1436), PEGylated insulin lispro (e.g. LY-275585), long-acting insulins (e.g. NN1436, Insumera (PE01 39), AB-1 01, AB-1 02, Sensulin LLC), intermediate-acting insulins (e.g. Humulin®N, Novolin®N), fast-acting and short-acting insulins (e.g. Humulin®R, Novolin®R, Linjeta® (VIAject®), PH20 insulin, NN1 218, HinsBet®), premixed
insulins, SuliXen®, NN1 045, insulin plus Symlin®, PE-01 39, ACP-002 hydrogel insulin, and oral, inhalable, transdermal and buccal or sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza®, insulin tregopil, TPM-02 insulin, Capsulin®, Oral-lyn®, Cobalamin® oral insulin, ORMD-0801, Oshadi oral insulin, NN1953, NN1 954, NN1 956, VIAtab®).

Also suitable are those insulin derivatives which are bonded to albumin or another protein by a bifunctional linker.

Glucagon-like-peptide 1 (GLP-1), GLP-1 analogues, and GLP-1 receptor agonists, for example: lixisenatide (e.g. Lyxumia®), exenatide (e.g. exendin-4, rExendin-4, Byetta®, Bydureon®, exenatide NexP), liraglutide (e.g. Victoza®), semaglutide, taspoglutide, albiglutide, dulaglutide, ACP-003, CJC-1 134-PC, GSK-2374697, PB-1 023, TTP-054, langlenatide (HM-1 1260C), CM-3, GLP-1 Eligen, AB-201, ORMD-0901, NN9924, NN9926, NN9927, Nodeexen, Viador-GLP-1, CVX-096, ZYOG-1, ZYD-1, ZP-3022, CAM-2036, DA-3091, DA-1 5864, ARI-2651, ARI-2255, exenatide-XTEN (VRS-859), exenatide-XTEN + Glucagon-XTEN (VRS-859 + AMX-808) and polymer-bound GLP-1 and GLP-1 analogues.

Dual GLP-1/GIP agonists (e.g. RG-7697 (MAR-701), MAR-709, BHM081, BHM089, BHM098).

Dual GLP-1/glucagon receptor agonists (e.g. BHM-034, OAP-1 89 (PF-0521 2389, TKS-1225), TT-401/402, ZP2929, LAPS-HM0XM25, MOD-6030).

Dual GLP-1/gastrin agonists (e.g. ZP-3022).

Other suitable combination partners are:

Further gastrointestinal peptides such as peptide YY 3-36 (PYY3-36) or analogues thereof and pancreatic polypeptide (PP) or analogues thereof.

Glucagon receptor agonists or antagonists, glucose-dependent insulinotropic polypeptide (GIP) receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof.

Dipeptidyl peptidase-IV (DPP-4) inhibitors, for example: alogliptin (e.g. Nesina®, Kazano®), linagliptin (e.g. Ondero®, Trajenta®, Tradjenta®, Trayenta®), saxagliptin (e.g.
Onglyza®, Komboglyze XR®, sitagliptin (e.g. Januvia®, Xelevia®, Tesavel®, Janumet®, Velmetia®, Juvisync®, Janumet XR®), anagliptin, teneligliptin (e.g. Tenelia®), trelagliptin, vildaglptin (e.g. Galvus®, Galvumet®), gemigliptin, omarigliptin, evogliptin, dutogliptin, DA-1229, MK-31 02, KM-223, KRP-1 04, PBL-1427, Pinoxacin hydrochloride, and Ari-
2243.

Sodium-dependent glucose transporter 2 (SGLT-2) inhibitors, for example: canagliflozin, dapagliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, ertugliflozin, EGT-0001442, LIK-066, SBM-TFC-039, and KGA-3235 (DSP-3235).

Dual inhibitors of SGLT-2 and SGLT-1 (e.g. LX-421 1, LIK066).

SGLT-1 inhibitors (e.g. LX-2761, KGA-3235) or SGLT-1 inhibitors in combination with anti-obesity drugs such as ileal bile acid transfer (IBAT) inhibitors (e.g. GSK-1 614235 + GSK-2330672).

Biguanides (e.g. metformin, buformin, phenformin).

Thiazolidinediones (e.g. pioglitazone, rosiglitazone), glitazone analogues (e.g. lobeglitazone).

Peroxisome proliferator-activated receptors (PPAR-) (alpha, gamma or alpha/gamma) agonists or modulators (e.g. saroglitazar (e.g. Lipaglyn®), GFT-505), or PPAR gamma partial agonists (e.g. Int-1 3 1).

Sulfonylureas (e.g. tolbutamide, glibenclamide, glimepiride, Amaryl®, glipizide) and meglitinides (e.g. nateglinide, repaglinide, mitiglinide).

Alpha-glucosidase inhibitors (e.g. acarbose, miglitol, voglibose).

Amylin and amylin analogues (e.g. pramlintide, Symlin®).

G-protein coupled receptor 119 (GPR1 19) agonists (e.g. GSK-1 292263, PSN-821, MBX-2982, APD-597, ARRY-981, ZYG-1 9, DS-8500, HM-47000, YH-Chem1).
GPR40 agonists (e.g. TUG-424, P-1 736, P-1 1187, JTT-851, GW9508, CNX-01 1-67, AM-1 638, AM-5262).

GPR120 agonists and GPR142 agonists.

Systemic or low-absorbable TGR5 (GPBAR1 = G-protein-coupled bile acid receptor 1) agonists (e.g. INT-777, XL-475, SB756050).

Other suitable combination partners are:

Diabetes immunotherapeutics, for example: oral C-C chemokine receptor type 2 (CCR-2) antagonists (e.g. CCX-140, JNJ-41443532), interleukin 1 beta (IL-1β) antagonists (e.g. AC-201), or oral monoclonal antibodies (MoA) (e.g. methalozamide, WP808, PAZ-320, P-1 736, PF-051751 57, PF-04937319).

Anti-inflammatory agents for the treatment of the metabolic syndrome and diabetes, for example: nuclear factor kappa B inhibitors (e.g. Triolex®).

Adenosine monophosphate-activated protein kinase (AMPK) stimulants, for example: Imeglimin (PXL-008), Debio-0930 (MT-63-78), R-1 18.

Inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11-beta-HSD-1) (e.g. LY25231 99, BMS770767, RG-4929, BMS81 6336, AZD-8329, HSD-016, BI-1 35585).

Activators of glucokinase (e.g. PF-04991 532, TTP-399 (GK1 -399), GKM-001 (ADV-1002401), ARRAY-403 (AMG-1 51), TAK-329, TMG-1 23, ZYGK1).

Inhibitors of diacylglycerol O-acyltransferase (DGAT) (e.g. pradigastat (LCQ-908)), inhibitors of protein tyrosine phosphatase 1 (e.g. trodusquemine), inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase.

Modulators of glucose transporter-4, somatostatin receptor 3 agonists (e.g. MK-4256).
One or more lipid lowering agents are also suitable as combination partners, for example: 3-hydroxy-3-methylglutaryl-coenzym-A-reductase (HMG-CoA-reductase) inhibitors such as simvastatin (e.g. Zocor®, Inegy®, Simcor®), atorvastatin (e.g. Sortis®, Caduet®), rosuavatatin (e.g. Crestor®), pravastatin (e.g. Lipostat®, Selipran®, fluvastatin (e.g. Lescol®), pitavastatin (e.g. Livazo®, Livalo®), lovastatin (e.g. Mevacor®, Advicor®), mevastatin (e.g. Compactin®), rivastatin, cerivastatin (Lipobay®), fibrates such as bezafibrate (e.g. Cedir® retard), ciprofibrate (e.g. Hypehipen®), fenofibrate (e.g. Antara®, Lipoven®, Lipanthyl®), gemfibrozil (e.g. Lopid®, Gevilon®), etofibrate, simfibrate, ronifibrate, clinofibrate, clofibrate, nicotinic acid and derivatives thereof (e.g. niacin, including slow release formulations of niacin), nicotinic acid receptor 1 agonists (e.g. GSK-256073), PPAR-delta agonists, acetyl-CoA-acetyltransferase (ACAT) inhibitors (e.g. avasimibe), cholesterol absorption inhibitors (e.g. ezetimibe, Ezetrol®, Zetia®, Liptruzet®, Vytorin®, S-556971, BMS-823778,®), bile acid-binding substances (e.g. cholestyramine, colestevelam, ileal bile acid transport (IBAT) inhibitors (e.g. GSK-2330672, LUM-002), microsomal triglyceride transfer protein (MTP) inhibitors (e.g. lomitapide (AEGRI-733), SLx-4090, granotapide), modulators of proprotein convertase subtilisin/kexin type 9 (PCSK9) (e.g. alirocumab (REGN727/SAR236553), AMG-145, LGT-209, PF-04950615, MPSK3169A, LY3015014, ALD-306, ALN-PCS, BMS-962476, SPC5001, ISIS-394814, 1B20, LGT-210, 1D05, BMS-PCS9Rx-2, SX-PCK9, RG7652), LDL receptor up-regulators, for example liver selective thyroid hormone receptor beta agonists (e.g. eprotirome (KB-21 15), MB0781 1, sobetirome (QRX-431), VIA-31 96, ZYT1), HDL-raising compounds such as: cholesteryl ester transfer protein (CETP) inhibitors (e.g. anacetrapib (MK0859), dalcetrapib, evacetrapib, JTT-302, DRL-1 7822, TA-8995, R-1658, LY-2484595, DS-1442), or dual CETP/PCSK9 inhibitors (e.g. K-31 2, ATP-binding cassette (ABC1) regulators, lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21 994, DRL-21 995), phospholipase A2 (PLA2) inhibitors (e.g. darapladib, Tyrisa®, varespladib, rilapladib), ApoA-I enhancers (e.g. RVX-208, CER-001, MDCO-21 6, CSL-1 12), cholesterol synthesis inhibitors (e.g. ETC-1 002), lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21 994, DRL-21 995) and omega-3 fatty acids and derivatives thereof (e.g. icosapent ethyl (AMR1 01), Epanova®, AKR-063, NKPL-66, PRC-401 6, CAT-2003).
Other suitable combination partners are one or more active substances for the treatment of obesity, such as for example:

Bromocriptine (e.g. Cycloset®, Parlodel®), phentermine and phentermine formulations or combinations (e.g. Adipex-P, lonamin, Qsymia®), benzphetamine (e.g. Didrex®), diethylpropion (e.g. Tenuate®), phendimetrazin (e.g. Adipost®, Bontril®), bupropion and combinations (e.g. Zyban®, Wellbutrin XL®, Contrave®, Empatic®), sibutramine (e.g. Reductil®, Meridia®), topiramat (e.g. Topamax®), zonisamid (e.g. Zonegran®), tesofensine, opioid antagonists such as naltrexone (e.g. Naltrexin®, naltrexone + bupropion), cannabinoid receptor 1 (CB1) antagonists (e.g. TM-38837), melanin-concentrating hormone (MCH-1) antagonists (e.g. BMS-830216, ALB-127158(a)), MC4 receptor agonists and partial agonists (e.g. AZD-2820, RM-493), neuropeptide Y5 (NPY5) or NPY2 antagonists (e.g. velneperit, S-234462), NPY4 agonists (e.g. PP-1420), beta-3-adrenergic receptor agonists, leptin or leptin mimetics, agonists of the 5-hydroxytryptamine 2c (5HT2c) receptor (e.g. lorcaserin, Belviq®).

pramlintide/metreleptin, lipase inhibitors such as cetilistat (e.g. Cametor®), orlistat (e.g. Xenical®, Calobalin®), angiogenesis inhibitors (e.g. ALS-L1023), betahistidin and histamine H3 antagonists (e.g. HPP-404), AgRP (agouti related protein) inhibitors (e.g. TTP-435), serotonin re-uptake inhibitors such as fluoxetine (e.g. Fluctine®), duloxetine (e.g. Cymbalta®), dual or triple monoamine uptake inhibitors (dopamine, norepinephrine and serotonin re-uptake) such as sertraline (e.g. Zoloft®), tesofensine, methionine aminopeptidase 2 (MetAP2) inhibitors (e.g. beloranib), and antisense oligonucleotides against production of fibroblast growth factor receptor 4 (FGFR4) (e.g. ISIS-FGFR4Rx) or prohibitin targeting peptide-1 (e.g. Adipotide®).

Moreover, combinations with drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, for example: nitric oxide donors, AT1 antagonists or angiotensin II (AT2) receptor antagonists such as telmisartan (e.g. Kinzal®, Micardis®), candesartan (e.g. Atacand®, Blopress®), valsartan (e.g. Diovan®, Co-Diovan®), losartan (e.g. Cosaar®), eprosartan (e.g. Teveten®), irbesartan (e.g. Aprovel®, CoAprovel®), olmesartan (e.g. Votum®, Olmetec®), tasosartan, azilsartan (e.g. Edarbi®), dual angiotensin receptor blockers (dual ARBs), angiotensin converting enzyme (ACE) inhibitors, ACE-2 activators, renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor (ET1/ETA) blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha-
blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists, calcium channel blockers (CCBs), nasal formulations of the calcium channel blocker diltiazem (e.g. CP-404), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vasopeptide inhibitors, dual vasopeptide inhibitors such as neprilysin-ACE inhibitors or neprilysin-ECE inhibitors, dual-acting AT receptor-neprilysin inhibitors, dual AT1/ETA antagonists, advanced glycation end-product (AGE) breakers, recombinant renalase, blood pressure vaccines such as anti-RAAS (renin-angiotensin-aldosteron-system) vaccines, AT1- or AT2-vaccines, drugs based on hypertension pharmacogenomics such as modulators of genetic polymorphisms with antihypertensive response, thrombocyte aggregation inhibitors, and others or combinations thereof are suitable.

In another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions which can be affected by binding to the GPR19 and modulating its activity. This is preferably a disease in the context of the metabolic syndrome, particularly one of the diseases or conditions listed above, most particularly diabetes or obesity or complications thereof.

The use of the compounds according to the invention, or a physiologically acceptable salt thereof, in combination with one or more active substances may take place simultaneously, separately or sequentially.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; if they are used at staggered times, the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.
Consequently, in another aspect, this invention relates to a medicament which comprises compounds according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

The compounds according to the invention, or physiologically acceptable salt or solvate thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as so-called kit-of-parts.

Compounds according to the invention can be administered to animals, in particular to mammals including humans, as pharmaceuticals by themselves, in mixtures with one another, or in the form of pharmaceutical compositions. The administration can be carried out orally, for example in the form of tablets, film-coated tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, solutions including aqueous, alcoholic and oily solutions, juices, drops, syrups, emulsions or suspensions, rectally, for example in the form of suppositories, or parenterally, for example in the form of solutions for subcutaneous, intramuscular or intravenous injection or infusion, in particular aqueous solutions.

Suitable pharmaceutical compositions for oral administration may be in the form of separate units, for example capsules, cachets, lozenges or tablets, each of which contains a defined amount of the compound of formula 1; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more)
surfactant(s)/dispersant(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and has been moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise lozenges which contain a compound of formula I with a flavoring, typically sucrose, and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Coated formulations and coated slow-release formulations, especially acid- and gastric juice-resistant formulations, also belong within the framework of the invention. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain 0.1 to 5% by weight of the active compound.

Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, creams, tinctures, sprays, powders or transdermal therapeutic systems, or inhalative administration, for example in the form of nasal sprays or aerosol mixtures, or forms such as microcapsules, implants or rods.
Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. The carriers used may be petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of 0.1 to 15% by weight of the composition, for example 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses may be in the form of single patches which are suitable for long-term close contact with the patient's epidermis. Such patches suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular option is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

Compounds according to the invention can additionally be used in systems for local drug delivery, for example in coated stents for preventing or reducing in-stent restenosis or by applying them locally by means of a catheter. The appropriate administration form depends, among others, on the disease to be treated and on its severity.

The dosing of compounds according to the invention to achieve the desirable therapeutic effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, 0.1 ng to 100 mg, typically 1 ng to 100 mg, per milliliter. Single doses may contain, for example, 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and orally administrable single-dose formulations, for example tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For prevention and/or treatment of the abovementioned conditions, the compounds of the formula I themselves may be used as the compound, but they are
preferably present with a compatible carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Another subject of the present invention are processes for the preparation of the compounds of the formula I and their salts and solvates, by which the compounds are obtainable and which are outlined in the following.

Abbreviations
Abbreviations within this document have their common meanings unless defined otherwise herein. An exemplary list of abbreviations used, can be found below.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>amu</td>
<td>atomic mass unit</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere (pressure unit, 101325 Pa)</td>
</tr>
<tr>
<td>BSA</td>
<td>bovine serum albumin</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst / catalyzed</td>
</tr>
<tr>
<td>CDI</td>
<td>carbonyl diimidazole</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropyl-ethyl-amine</td>
</tr>
<tr>
<td>DMEM</td>
<td>Dulbecco's modified eagle medium</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppf</td>
<td>diphenylphosphinoferrocene</td>
</tr>
<tr>
<td>EA</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EC50</td>
<td>concentration causing 50% of the maximal response</td>
</tr>
<tr>
<td>EDCI</td>
<td>ethyl dimethylaminopropyl carbodiimide</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>FA</td>
<td>formic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>FCS</td>
<td>fetal calf serum</td>
</tr>
<tr>
<td>GPR119</td>
<td>G-protein coupled receptor 119</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>Hal</td>
<td>halogen (atom)</td>
</tr>
<tr>
<td>HATU</td>
<td>O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate</td>
</tr>
<tr>
<td>HBSS</td>
<td>Hank's buffered salt solution</td>
</tr>
<tr>
<td>HEK 293</td>
<td>human embryonic kidney 293</td>
</tr>
<tr>
<td>HEPES</td>
<td>4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid</td>
</tr>
<tr>
<td>HOBt</td>
<td>1-hydroxy-benzotriazole</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HTRF</td>
<td>homogenous time-resolved fluorescence</td>
</tr>
<tr>
<td>IBMX</td>
<td>1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione</td>
</tr>
<tr>
<td>LCMS</td>
<td>liquid chromatography coupled mass spectroscopy</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>MeCN</td>
<td>methyl cyanide (acetonitrile)</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl tert.-butyl ether</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl pyrrolidin-2-one</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance (spectrum)</td>
</tr>
<tr>
<td>PBS</td>
<td>phosphate buffered saline</td>
</tr>
<tr>
<td>PE</td>
<td>petroleum ether</td>
</tr>
<tr>
<td>PMBCl</td>
<td>para-methoxybenzyl chloride</td>
</tr>
<tr>
<td>R₁</td>
<td>retention time</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SGC</td>
<td>silica gel chromatography</td>
</tr>
<tr>
<td>SiO₂</td>
<td>silica gel (for chromatography)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TM</td>
<td>transition metal</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>Ts</td>
<td>para-tolylsulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet (spectrum)</td>
</tr>
</tbody>
</table>

**Synthetic Methods**

Variables in the formulae of the schemes represent moieties as defined above unless other meanings are given. The variable R as used herein represents one or two substituents especially such as defined by CR₁R₂R₃₀ and R₃₁ of formula I.

Detailed descriptions of the Typical Procedures to which reference is made in this section can be found in the Examples section.
Compounds of the invention having the formula I may be prepared by combining known synthetic procedures. In a first method 3-hydroxy-pyrrolidin-2-one (A) (commercially available as racemic mixture and in both enantiomeric forms) is coupled with indanones B (typically Hal is Br or I) to provide intermediates C. An example for suitable coupling conditions (Cul, W,V-dimethyl-ethane-1,2-diamine, cesium carbonate) can be found in the Typical Procedure 1. Conversion of the hydroxy group in C to a suitable leaving group (LG is for example Br, I, OTs or OPPh₃⁺) can be accomplished with various well known reagents (e.g. PPh₃/I₂, PPh₃/CBr₄, PPh₃/DIAD or TsCl/NEt₃) providing the intermediates D, which may be isolated or may be reacted without isolation with hydroxy-aryl building blocks of type E using an appropriate base (e.g. Na₂CO₃, K₂CO₃, Cs₂CO₃ or NaH). For example the conditions in the Typical Procedure 3 may be applied to couple intermediates C and E to provide compounds I.

A second method of synthesizing compounds I starts with a pyrrolidin-2-one substituted with a leaving group (LG) in 3-position (structures F), which may be prepared by reacting A with the reagents mentioned above. Other procedures for making structures F are known (e.g. base-promoted cyclization of 2,4-dibromo-butyramide). Intermediates F may be isolated or generated in situ to react with hydroxy-aryls E (typically in the presence of a base as described above) to provide intermediates G. As a final step, copper-catalyzed coupling with aryl halides B provides the desired compounds I (Scheme 1).

Scheme 1.
Aryl halides B may be prepared by Friedel-Crafts-cyclization of carbonyl chlorides derived from 3-(4-halo-phenyl)-propionic acids (substituted by R), which may eventually be further substituted at the positions of R\textsuperscript{1a}, R\textsuperscript{1b} and R\textsuperscript{1c}. Other suitable methods to synthesize halides B include acid (e.g. sulfuric acid) catalyzed cyclizations of said substituted propionic acids.

Another method of synthesizing compounds I uses aryl bromides of structure H as starting points. Structures H may be obtained by the methods described above. For example an aryl halide B (R\textsuperscript{1a} = Br) may be coupled to a pyrrolidinone of type G. Further elaboration of structures H may be done by transition metal catalyzed reactions, which replace the bromo atom by other substituents like other halide, cyano or alkyl groups. Illustrative examples for such reactions can be found in Scheme 2.

Scheme 2.

Certain compounds I (Y = N; Z = O, S, NR\textsubscript{6}) may be prepared by coupling aryl halides B with hydroxy-pyridines E (Y = N; Z = O, S, NR\textsubscript{6}). Said hydroxy-pyridines E may be prepared by displacement of a halide (F, Cl, Br or I) in the 2-position of 5-bromo-2-halo-pyridines, which are substituted with R\textsuperscript{2a}, R\textsuperscript{2b} and R\textsuperscript{2c}, using nucleophiles of the type HZ-R\textsuperscript{3}-R\textsuperscript{4} (Z = O, S, NR\textsubscript{6}) followed by conversion of the 5-bromo-substituent to a hydroxy group (e.g. by oxidation of a boronate group introduced by palladium catalyzed
coupling with bis-pinacolato-diboron). See Typical Procedure 6 for exemplary conditions for the nucleophilic displacement reaction, Typical Procedures 5 and 5a for examples of boronate-oxidation conditions, Typical Procedure 4 for an example of conditions to install a boronate group and Scheme 3 for illustration of the overall method.

A benzyl group \((R^3 \cdot R^4 = \text{CH}_2 \cdot \text{Ph})\) in compounds \(I (Y = N; Z = O, S)\) may be cleaved for example by hydrogenolysis to provide intermediates \(J\), which may be alkylated by \(\text{LG} \cdot R^3 \cdot R^4\), \(R^3\) and \(R^4\) being defined like \(R^3\) and \(R^4\) respectively, to yield compounds \(I (Y = N; Z = O, S)\).

For example, the structure \(J\) may be a 2-hydroxy-pyridine \((Z = O)\), which may be alkylated under Mitsunobu-conditions \((\text{PPh}_3 / \text{DIAD}; \text{see for example Typical Procedure 3})\) starting with alcohols \(\text{HO} \cdot R^3 \cdot R^4\). Triphenylphosphine may be introduced into the reaction as polymer. \(\text{DIAD}\) may be replaced by other azodicarboxylates (e.g. \(\text{DEAD}\)).

Scheme 3.

Certain other compounds of the invention may be prepared by reaction of hydroxy-\(\text{pyrrolidinones C with 6-bromo-3-pyridinols under Mitsunobu-conditions and subsequent transition metal catalyzed replacement of the Br-atom by } Z \cdot R^3 \cdot R^4\).
Variation of the order of the steps in the synthetic sequence provides further methods to prepare compounds I. For example, intermediates F may be reacted with 6-bromo-pyridin-3-ols and subsequently the bromo-substituent may be exchanged for Z-R\textsuperscript{3},R\textsuperscript{4} to provide intermediates G (Y = N). In a last step, coupling with aryl halides B again provides compounds I (Y = N) as illustrated in Scheme 4.

Scheme 4.

In another method to prepare compounds I, the bicyclic alcohols K (obtained for example by reduction of ketones B) are used as substrates in the Cul-catalyzed coupling reaction with pyrrolidinones G. The resulting intermediates L are oxidized (e.g. by MnO\textsubscript{2} or Dess-Martin periodinane) to provide the desired compounds I as illustrated in Scheme 5.

Scheme 5.

Other compounds of formula I (R\textsubscript{30} = COOH) can be obtained by cleaving an ester functionality (R\textsubscript{30} = COO(Ci-C6)-alkyl) in the group R (see Typical Procedure 7 for exemplary conditions). Still other compounds I (R\textsubscript{30} = CONR\textsubscript{14}R\textsubscript{15}) are provided by
the reaction of said acids with amines of the structure HNR14R15 using for example EDCI as coupling reagent (see Typical Procedure 8 for exemplary conditions).

**Analytical Methods**

Examples were characterized by standard analytical methods. This includes at least two methods (e.g. selected from HPLC, MS, ^1^H-NMR). In particular, MS and HPLC data were obtained by combined analytical HPLC/MS (LCMS). For example the following LCMS methods were used.

**Method A**

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 μηη; mobile phase: (H₂O + 0.05% FA) : (MeCN + 0.035% FA) 98:2 (0 min) to 5:95 (2 min) to 5:95 (2.6 min) to 95:5 (2.7 min) to 95:5 (3 min); flow rate: 0.9 mL/min; temperature: 55°C; ionization method: ES⁺; UV wavelength: 220 nm.

**Method B**

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 μηη; mobile phase: (H₂O + 0.1% FA) : (MeCN + 0.08% FA) 95:5 (0 min) to 5:95 (1.1 min) to 5:95 (1.7 min) to 95:5 (1.8 min) to 95:5 (2 min); flow rate: 0.9 mL/min; temperature: 55°C; ionization method: ES⁺; UV wavelength: 220 nm.

**Method C**

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 μηη; mobile phase: (H₂O + 0.05% FA) : (MeCN + 0.035% FA) 95:5 (0 min) to 5:95 (1.1 min) to 5:95 (1.7 min) to 95:5 (1.9 min) to 95:5 (2 min); flow rate: 0.9 mL/min; temperature: 55°C; ionization method: ES⁺; UV wavelength: 220 nm.

**Method D**

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 μηη; mobile phase: (H₂O + 0.05% FA) : (MeCN + 0.035% FA) 95:5 (0 min) to 5:95 (1.2 min) to 5:95 (1.7 min) to 95:5 (1.8 min) to 95:5 (2 min); flow rate: 0.9 mL/min; temperature: 55°C; ionization method: ES⁺; UV wavelength: 220 nm.

**Method E**

Column: Phenomenex Luna C18(2) 100 A 2*10 mm, 3 μηη; mobile phase: (H₂O + 0.05% TFA) : MeCN 95:5 (0 min) to 5:95 (1.20 min) to 3:97 (1.40 min) to 96:4 (1.45 min); flow rate: 1.1 mL/min; temperature: 30°C; ionization method: ES⁺; UV wavelength: 220 nm.
In general, HPLC data is represented by the retention time ($R_t$; in min); MS data is given as the observed mass number (m/z) of the ion [M+H]$^+$ (if present) and $^1$H-NMR data is reported by lists of chemical shifts $\delta$ (in ppm vs. TMS) of the observed signals (the number of hydrogen atoms was determined using the area under the respective signal; signal multiplicity is characterized as follows: $s$ = singlet, $d$ = doublet, $dd$ = doublet of doublets, $t$ = triplet, $dt$ = doublet of triplets, $q$ = quartet, $m$ = multiplet, $br$ = broad; coupling constants $J$ are given in Hertz (Hz)). Deuterated solvents were used for NMR spectroscopy.

Examples

The following examples are particular embodiments of the invention. They partially illustrate the scope of the invention without limiting it.

Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated.

The examples were prepared, isolated and analyzed by the procedures and methods given. Alternatively they may be prepared by the general synthetic methods detailed above. Further variations of the synthetic procedures may be proposed by a person skilled in the art.

When example compounds containing a basic group were purified by preparative HPLC on reversed phase column material and, as customary, the eluent was a gradient mixture of water and acetonitrile containing trifluoroacetic acid (TFA), they were obtained in part in the form of their addition salt with TFA, depending on the details of the workup such as evaporation or lyophilization conditions. In the names of the example compounds and their structural formulae any such TFA present is not specified.

Preparation of Examples 1

Example 1-01 (Typical Procedure 1)

To a solution of 6-bromo-3-(2-hydroxyethyl)-2,3-dihydro-1 H-inden-1-one (62 mg) and (R)-3-((6-(4-fluorophenoxy)pyridin-3-yl)oxy)pyrrolidin-2-one (70 mg) in 1,4-dioxane (1 ml) was added N,N'-dimethyl-ethane-1,2-diamine (0.5 ml) and cesium carbonate (130 mg). The mixture was purged for 5 minutes with a flow of argon and Cul (30 mg) was added. The mixture was heated at 80°C for 30 minutes. After cooling to RT insoluble material was removed by filtration and the filtrate concentrated. The residue was purified by preparative HPLC to provide example 1-01.
Following essentially the Typical Procedure 1, the Examples 1 in Table 1 were prepared using the respective aryl bromides and 3-substituted pyrrolidinones.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>LCMS Method</th>
<th>$R_t$ [min]</th>
<th>ESI$^+$ m/z [amu]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-01</td>
<td><img src="image1" alt="Structure" /></td>
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Example 1-07 was obtained as product of partial hydrolysis from the reaction of (6-bromo-4-fluoro-2-methoxycarbonylmethyl-1-oxo-indan-2-yl)-acetic acid methyl ester and
(R)-3-[6-(2-cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one according to Typical Procedure 1.

Preparation of 3-Substituted Pyrrolidin-2-ones

3-[4-(3-Methyl-butoxy)-phenoxy]-pyrrolidin-2-one (Typical Procedure 2)

A mixture of NaH (1.07 g) and THF (30 mL) was added 2,4-dibromo-butyramide (3.0 g) at 0°C. After 3 hours, 4-(3-methyl-butoxy)-phenol (3.3 g) was added and the mixture was heated to 65°C for 4 hours. After standing at room temperature for 12 hours, water was added and the mixture was extracted with MTBE. The organic phase was washed twice (2 N NaOH), dried (Na₂SO₄) and concentrated to provide the title compound. MS ESI⁺: m/z = 264 [M+H]⁺.

4-(3-Methyl-butoxy)-phenol

A mixture of benzene-1,4-diol (20.0 g), DMF (100 mL), cesium carbonate (59.2 g) and 1-bromo-3-methyl-butane (13.7 g) was heated to 60°C for 12 hours. After the mixture reached room temperature, it was distributed between water and EA. The organic phase was washed twice (water), dried (Na₂SO₄) and concentrated. The residue was purified by chromatography (S102; EA/heptane 1:2) to provide the subtitle compound. MS ESI⁺: m/z = 181 [M+H]⁺.

(R)-3-[4-(4-Fluoro-phenoxy)-phenoxy]-pyrrolidin-2-one (Typical Procedure 3)

A mixture of THF (200 mL) and DCM (100 mL) under argon was added triphenylphosphine (polymer, 1.8 mmol/g, 20 g). Diisopropyl azodicarboxylate (8.87 g) was added. After 5 minutes (S)-3-hydroxy-pyrrolidin-2-one (3.1 g) and 6-(4-fluorophenoxo)-pyridin-3-ol (6.0 g) were added. After 30 minutes the mixture was filtered and the filtrate concentrated. The residue was purified by chromatography (S102; DCM/MeOH 15:1) to provide the title compound. MS ESI⁺: m/z = 289 [M+H]⁺.

6-(4-Fluoro-phenoxo)-pyridin-3-ol

A mixture of 6-bromo-pyridin-3-ol (8.0 g), 4-fluorophenol (15.5 g) and cesium carbonate (30 g) was heated to 170°C for 6 hours. After the mixture reached room temperature, it was distributed between water and MTBE. The organic phase was dried (Na₂SO₄) and concentrated. The residue was purified by chromatography (S102; EA/heptane 1:1.5) to provide the subtitle compound. MS ESI⁺: m/z = 206 [M+H]⁺.

(R)-3-[4-(4-Fluoro-phenoxo)-phenoxy]-pyrrolidin-2-one
Typical Procedure 3 was followed. Reaction of (S)-3-hydroxy-pyrrolidin-2-one with 4-(4-fluoro-phenoxy)-phenol provided the title compound. MS EST: m/z = 288 [M+H]⁺.

(R)-3-[6-(2-Cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

A mixture of (S)-3-hydroxy-pyrrolidin-2-one (3.00 g), 6-(2-cyclopropyl-methoxy)-pyridin-3-ol (4.90 g), triphenylphosphine (polymer, 8.56 g), DCM (30 mL) and THF (50 mL) was added DIAD (6.60 g) keeping the reaction temperature below 30°C. After 12 hours the mixture was filtered and the filtrate was evaporated. The residue was purified by SGC (eluent: EA/MeOH 9:1) to provide the title compound. MS ESI⁺: m/z = 249 [M+H]⁺.

6-Cyclopropylmethoxy-pyridin-3-ol ((Typical Procedure 4)

A mixture of 5-bromo-2-cyclopropylmethoxy-pyridine (8.00 g), bis(pinacolato)diboron (8.91 g) and 1,4-dioxane (53 mL) was purged with argon. Potassium acetate (3.44 g) and Pd(dppf)Cl₂ (2.57 g) were added and the mixture heated to 100°C for 1 hour by microwave irradiation. The mixture was filtered and the filtrate diluted with EA, washed with water, dried (Na₂SO₄) and concentrated. The residue was purified by SGC (eluent: EA/heptane 1:6) to provide the crude boronate. MS ESI⁺: m/z = 276 [M+H]⁺.

Typical Procedure 5

The boronate from above was dissolved in THF (60 mL). Aqueous NaOH (5 M) was added at 0°C. Hydrogen peroxide (30% in water, 30 mL) was added slowly. The mixture was allowed to warm to RT and stirred for 4 hours. The mixture was extracted with MTBE. The aqueous phase was adjusted to pH 3-4 by addition of diluted HCl and extracted with EA. The organic phase was dried (Na₂SO₄) and concentrated to provide the subtitle compound. MS ESI⁺: m/z = 166 [M+H]⁺.

5-Bromo-2-cyclopropylmethoxy-pyridine (Typical Procedure 6)

To a mixture of 2-cyclopropyl-methanol (6.15 g) and DMF (12 mL) was added NaH (60% in mineral oil, 1.5 g) at 0°C. After stirring for 4 hours at RT the mixture was diluted with DMF (5 mL) and 5-bromo-2-fluoro-pyridine (6.00 g) was slowly added keeping the reaction temperature below 30°C. After 30 minutes at RT the mixture was heated to 130°C for 1 hour by microwave irradiation. After cooling to RT the mixture was diluted with EA and washed with water (3 times). The organic phase was dried (Na₂SO₄) and concentrated. The residue was purified by SGC to provide the subtitle compound. MS ESI⁺: m/z = 228 [M+H]⁺.

(R)-3-[6-(2-Cyclopropoxy)-pyridin-3-yloxy]-pyrrolidin-2-one
Typical Procedure 3 was followed. Reaction of 6-cyclopropoxy-pyridin-3-ol and (S)-3-
hydroxy-pyrrolidin-2-one provided the title compound. MS EST: m/z = 235 [M+H]+.

6-Cyclopropoxy-pyridin-3-ol
A mixture of 5-bromo-2-cyclopropoxypyridine (Milestone Pharmtech, 500 mg) and THF
(10 mL) was cooled (-78°C) and n-BuLi (2.5 M in toluene, 1.49 mL) was added
dropwise within 10 minutes. After 20 minutes trimethyl borate (429 µL) was added. After
2 hours peracetic acid (32% in AcOH, 786 µL) was added dropwise. After 10 minutes
the reaction temperature was changed to 0°C. After 1 hour the mixture was poured into
aqueous NaHSO3-solution (5%, 5 mL). The mixture was extracted with EA. The organic
phase was dried (Na2SO4), filtered and concentrated. The residue was purified by
chromatography (silica gel, heptane to EA/heptane 2:3) to provide the subtitle
compound. MS ESI+: m/z = 152 [M+H]+.

Preparation of Aryl Bromides
6-Bromo-3-(2-hydroxyethyl)-2,3-dihydroinden-1 -one
To a solution of 6-bromo-3-(2-hydroxyethyl)-2,3-dihydro-1 H-inden-1 -ol (3.1 3 g) in DCM
(150 mL) was added MnO2 (5.3 g). The mixture was stirred at RT for 50 hours. The
solid was removed by filtration. The filtrate was evaporated and the residue was purified by
SGC (DCM/MeOH, 99:1) to provide the title compound. MS ESI+: m/z = 255 [M+H]+.

6-Bromo-3-(2-hydroxyethyl)-2,3-dihydro-1 H-inden-1 -ol
To a solution of methyl 2-(5-bromo-3-oxo-2,3-dihydro-1 H-inden-1 -yl)acetate (4.5 g) in
THF (250 mL) was added LiAlH4 (725 mg) at 0°C and the mixture was allowed to warm
to RT with stirring for 2 hours. The mixture was quenched by addition of water (20 mL)
at 0°C, and then NaOH (15%, 9 mL) was added, followed by water (20 mL). The mixture
was extracted with EA (50 mL x 3). The organic phase was washed with brine (10 mL)
and then dried over Na2SO4. After filtration and evaporation of the solvent, the residue
was purified by SGC (DCM/MeOH, 99:1) to provide the subtitle compound. MS ESI+: m/z = 257 [M+H]+.

Methyl 2-(5-bromo-3-oxo-2,3-dihydro-1 H-inden-1 -yl)acetate
A solution of 3-(4-bromophenyl)pentanedioic acid (10.0 g) in cone. H2SO4 (60 mL) was
heated at 100°C with stirring for 3 hours. The mixture was cooled to 0°C and then
MeOH (120 mL) was added. The mixture was heated at 50°C with stirring for 1 hour and
then cooled to room temperature. The reaction mixture was poured into ice water and
then extracted with ethyl acetate (200 mL x 3). The organic phase was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (7:1) to provide the title compound. MS EST: m/z = 283 [M+H]$^+$. Separation of enantiomers was accomplished by chiral HPLC (column: AY-H 250°4.6 mm, 5 µm; column temperature: 39.1 °C; eluent: CO$_2$, co-solvent: EtOH/MeCN = 1:1 (0.1 % DEA); co-solvent: 20%) to provide ((S')-5-bromo-3-oxo-indan-1-yl)-acetic acid methyl ester (faster eluting isomer; preliminary assigned to S-configuration) and ((R')-5-bromo-3-oxo-indan-1-yl)-acetic acid methyl ester (slower eluting isomer; preliminary assigned to R-configuration).

3-(4-Bromophenyl)pentanedioic acid

To a solution of 4-bromobenzaldehyde (25.0 g) in ethyl 3-oxobutanoate (35.1 g) was added piperidine (2.3 g). The mixture was stirred at room temperature for 16 hours and the precipitate was washed with ethanol (50 mL) to give 38.2 g of a solid. The solid (30.2 g) was added in portions into NaOH (50%, 500 g) with stirring. The resulting yellow slurry was heated to reflux with stirring for 3 hours. After cooling to RT, the mixture was acidified with cone. HCl to give a white precipitate. The solid was collected by filtration, washed with water, and dried under vacuum to provide the subtitle compound as a white solid. MS ESI$^+$: m/z = 309 [M+Na]$^+$.

Methyl 2-(6-bromo-1-oxo-2,3-dihydro-1 H-inden-2-yl)acetate

To a solution of 6-bromo-2,3-dihydroinden-1-one (3.0 g) in THF (80 mL) was added LDA (8.5 mL, 2 M solution) dropwise at -78°C and the mixture was allowed to warm to 0°C with stirring for 20 minutes. The mixture was cooled to -78°C and methyl 2-bromoacetate (4.35 g) was added. The mixture was allowed to warm to RT with stirring for 3 hours. The mixture was poured into water and then extracted with EA (100 mL x 3). The organic phase was washed with brine and then dried over Na$_2$SO$_4$. The solvent was removed by evaporation under reduced pressure and the residue was purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 283 [M+H]$^+$.

Methyl 2-(6-bromo-4-fluoro-1-oxo-2,3-dihydro-1 H-inden-2-yl)acetate

To a mixture of diisopropylamine (1.4 mL) and THF (25 mL) was added n-BuLi (3.4 mL, 2.6 M in toluene) at -78°C. After 30 minutes a solution of 6-bromo-4-fluoro-2,3-dihydro-1H-inden-1-one (2.0 g) in THF (10 mL) was added dropwise. After 30 minutes methyl 2-bromoacetate (1.34 g) was added dropwise. The mixture was allowed to warm to RT
with stirring for 2 hours. The mixture was poured into an ammonium chloride solution (10\%, aqueous) and then extracted with EA (100 ml x 3). The organic phase was washed with brine and then dried over Na2SO4. The solvent was removed by evaporation under reduced pressure and the residue was purified by SGC (heptane to EA/heptane = 4:1) to provide the title compound. MS ESI+: m/z = 301 [M+H]+. As a second product (6-bromo-4-fluoro-2-methoxycarbonylmethyl-1-oxo-indan-2-yl)-acetic acid methyl ester was isolated. MS ESI+: m/z = 373 [M+H]+.

6-Bromo-4-fluoro-2-(2-hydroxyethyl)-2,3-dihydro-1H-inden-1-one

To a solution of 6-bromo-4-fluoro-2-(2-hydroxy-ethy)-indan-1-ol (100 mg) in 1,4-dioxane (5 ml) was added activated MnO2 (250 mg). The mixture was stirred at 90°C for 5 hours. The solid was removed by filtration and the filtrate was concentrated. The residue was purified by preparative HPLC to provide the title compound. MS EST: m/z = 273 [M+H]+.

6-Bromo-4-fluoro-2-(2-hydroxy-ethyl)-indan-1-one

To a mixture of methyl 2-(6-bromo-4-fluoro-2-methoxycarbonylmethyl-1H-inden-2-yl)acetate (0.30 g) and THF (5 ml) at -20°C was added LiAlH4 (1 ml, 1 M in THF). The mixture was allowed to warm to RT with stirring for 1 hour. The volatiles were removed and the residue was partitioned between EA and water. The organic phase was washed with brine and dried over Na2SO4. The solvent was removed by evaporation under reduced pressure to provide the title compound. MS EST: m/z = 275 [M+H]+.

Methyl 2-(5-bromo-7-fluoro-3-oxo-2,3-dihydro-1H-inden-1-yl)acetate

To methanol (45 ml) was added SOCl2 (2.49 g) at 0°C, followed by the addition of a solution of 2-(5-bromo-7-fluoro-3-oxo-2,3-dihydro-1H-inden-1-yl)acetic acid (1.5 g) in MeOH (5 ml). The mixture was allowed to warm to RT with stirring for 4 hours. The solvent was removed by evaporation under reduced pressure. The residue was purified by SGC (PE/EA = 20:1) to provide the title compound. MS ESI+: m/z = 303 [M+H]+.

2-(5-bromo-7-fluoro-3-oxo-2,3-dihydro-1H-inden-1-yl)acetic acid

To a solution of 3-(4-bromo-2-fluorophenyl)pentanedioic acid (5.0 g) in DCM (100 ml) was added SOCl2 (7.8 g) slowly at RT. The mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was dried under high vacuum. To the residue, AlCl3 (8.7 g) was added, and then heated to 130°C for 12 hours. The reaction was cooled to RT and the solid was dissolved in EA. The organic
phase was washed with water and brine and then dried over Na₂SO₄. After filtration and evaporation of the solvent, the residue was purified by SGC (DCM/MeOH = 99:1) to provide the subtitle compound. MS ESI⁺: m/z = 287 [M+H]⁺.

3-(4-Bromo-2-fluorophenyl)pentanedioic acid

To a solution of 4-bromo-2-fluorobenzaldehyde (35 g) in ethyl 3-oxobutanoate (44.8 g) was added piperidine (2.93 g) at RT and the mixture was stirred for 15 hours. The crude was purified by SGC (PE/EA = 6:1) to give 39 g of a colorless oil. The oil (12 g) was added to NaOH (20 mL, 50%). The resulting slurry was heated to reflux with stirring for 16 hours. After cooling in an ice bath the mixture was acidified by the addition of cone. HCl to give a white precipitate. The solid was collected by filtration and dried to provide the subtitle compound. MS ESI⁺: m/z = 305 [M+H]⁺.

5-Bromo-7-fluoro-N,N-dimethyl-3-oxo-2,3-dihydro-1 H-indene-1-carboxamide

To a solution of 5-bromo-7-fluoro-3-oxo-2,3-dihydro-1 H-indene-1-carboxylic acid (850 mg) in DMF (20 mL) was added DIPEA (1.6 g), EDCI (1.2 g) and HOBt (840 mg). The mixture was stirred for 30 minutes. A solution of dimethyl amine (3.1 mL, 2 M in THF) was added. The mixture was stirred for 20 hours. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (50 mL x 3). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by SGC (PE/EA = 2:1) to provide the title compound. MS ESI⁺: m/z = 300 [M+H]⁺.

5-Bromo-7-fluoro-3-oxo-2,3-dihydro-1 H-indene-1-carboxylic acid

To a solution of 5-bromo-7-fluoro-3-oxo-2,3-dihydro-1 H-indene-1-carbonitrile (470 mg) in MeOH (3 mL) was added cone. HCl (12 mL). The mixture was heated to reflux with stirring for 6 hours. The organic solvent was removed under reduced pressure and the aqueous phase was extracted with EA (20 mL x 3). The organic phase was washed with brine and dried over Na₂SO₄. Filtration and evaporation of the solvent provided the subtitle compound. MS ESI⁺: m/z = 273 [M+H]⁺.

5-Bromo-7-fluoro-3-oxo-2,3-dihydro-1 H-indene-1-carbonitrile

To a solution of 3-(4-bromo-2-fluorophenyl)-3-cyanopropanoic acid (1.0 g) in DCM (20 mL) was added SOCl₂ (1.75 g) at RT and the mixture was stirred for 6 hours. The volatiles were removed under reduced pressure. To the residue, AlCl₃ (2.0 g) was added and then heated to 130°C for 2.5 hours. The mixture was cooled to RT and dissolved in EA (100 mL). The organic phase was washed with water and brine, and then dried over Na₂SO₄. After filtration and evaporation of the solvent, the crude was
purified by SGC (PE/EA = 10:1) to provide the subtitle compound. MS ESI⁺: m/z = 254 [M+H]⁺.

3-(4-Bromo-2-fluorophenyl)-3-cyanopropanoic acid

To a stirred suspension of K₂CO₃ (17.3 g) in DMF (100 mL), 2-chloroacetic acid (10 g) was added. From the resulting suspension, DMF (approx. 10 mL) was distilled off under reduced pressure at approx. 54°C. The suspension was cooled to RT and a solution of 2-(4-bromo-2-fluorophenyl)acetonitrile (20.6 g) was added. Powdered KOH (10.8 g) was added in portions at 20-25°C. The reaction mixture was stirred further for 3 hours at RT. The mixture was poured into ice water (800 mL) and then washed with EA (100 mL). The aqueous layer was acidified with HCl (2 N) and then extracted with EA (200 mL x 3). The organic phase was dried over Na₂SO₄ and then purified by SGC (DCM/MeOH = 99:1) to provide the subtitle compound. MS ESI⁻: m/z = 270 [M-H]⁻.

6-Bromo-4-fluoro-3-(hydroxymethyl)-2,3-dihydroinden-1-one

To a solution of 6-bromo-4-fluoro-3-(hydroxymethyl)-2,3-dihydro-1-H-inden-1-ol (150 mg) in DCM (5 mL) was added activated MnO₂ (250 mg). The mixture was stirred at 25°C for 20 hours. The solid was removed by filtration and the filtrate was concentrated. The residue was purified by SGC (DCM/MeOH = 200:1) to provide the title compound. MS ESI⁺: m/z = 259 [M+H]⁺.

6-Bromo-4-fluoro-3-(hydroxymethyl)-2,3-dihydro-1-H-indene-1-carboxylic acid

To a solution of 5-bromo-7-fluoro-3-oxo-2,3-dihydro-1-H-indene-1-carboxylic acid (680 mg) in THF (15 mL) was added borane (7.5 mL, 1 M in THF) at RT. The mixture was heated to reflux for 30 minutes. After cooling, the mixture was quenched with water and the solvent was removed under reduced pressure. The aqueous phase was extracted with EA (10 mL x 3). The combined organic phases were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by SGC (DCM/MeOH = 99:1) to provide the subtitle compound. MS ESI⁺: m/z = 283 [M+Na]⁺.

6-Bromo-3-(hydroxymethyl)-2,3-dihydroinden-1-one

To a solution of 6-bromo-3-(hydroxymethyl)-2,3-dihydro-1-H-inden-1-ol (1.3 g) in DCM (20 mL) was added activated MnO₂ (2.3 g). The mixture was stirred at 25°C for 15 hours. Additional activated MnO₂ (930 mg) was added, and the suspension was stirred at 25°C for 20 hours. The solid was removed by filtration and the filtrate was...
concentrated. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 99:1 to provide the title compound. MS ESI+: m/z = 241 [M+H]+.

6-Bromo-3-(hydroxymethyl)-2,3-dihydro-1 H-inden-1 -ol

To a solution of methyl 5-bromo-3-oxo-2,3-dihydro-1-H-indene-1-carboxylate (1.5 g) in THF (40 mL) was added LiAlH₄ (4 mL, 1 M in THF) at 0°C. The mixture was stirred at 0°C for 30 minutes and then quenched by the addition of brine (20 mL). The mixture was extracted with EA (30 mL x 3). The organic phase was washed with brine (10 mL) and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure to provide the subtitle compound. MS EST: m/z = 265 [M+Na]+.

Methyl 5-bromo-3-oxo-2,3-dihydro-1 H-indene-1 -carboxylate

Thionylchloride (15.6 g) was added to MeOH (100 mL) at 0°C, followed by the addition of a solution of 5-bromo-3-oxo-2,3-dihydro-1-H-indene-1-carbonitrile (2.06 g) in MeOH (50 mL). The mixture was allowed to warm to RT and then heated to reflux with stirring for 4 hours. After cooling, the solvent was removed in vacuo. The residue was purified by SGC (PE/EA = 8:1) to provide the subtitle compound. MS ESI+: m/z = 269 [M+H]+.

5-Bromo-3-oxo-2,3-dihydro-1 H-indene-1 -carbonitrile

To a solution of 3-(4-bromophenyl)-3-cyanopropanoic acid (1 g) in DCM (15 mL) was added SOCl₂ (2.3 g) at RT and stirred for 6 hours. The solvent was removed under reduced pressure. To the residue, AlCl₃ (2.6 g) was added and the mixture was heated to 130°C for 1.5 hours. After cooling, the solid was dissolved in EA (100 mL). The organic phase was washed with water (100 mL) and brine (20 mL) and then dried over Na₂SO₄. After filtration and evaporation of the solvent, the residue was purified by SGC (PE/EA = 7:1) to provide the subtitle compound. MS ESI+: m/z = 236 [M+H]+.

3-(4-Bromophenyl)-3-cyanopropanoic acid

To a stirred suspension of K₂CO₃ (5.03 g) in DMF (20 mL), 2-chloroacetic acid (2.93 g) was added. From the resulting suspension, DMF (approx. 5 mL) was distilled off under reduced pressure at approx. 54°C (for 30 min). The suspension was cooled to RT. A solution of 2-(4-bromophenyl)acetonitrile (5.5 g) in DMF (20 mL) was added. Powdered KOH (3.14 g) was added in portions at 20-25°C. The suspension was stirred for 2 hours. The reaction mixture was poured into water (300 mL) and then washed with EA (50 mL x 2). The aqueous phase was adjusted to pH 2 with 2 N HCl and extracted with EA (100 mL x 3). The combined organic phases were washed with brine (30 mL) and dried over Na₂SO₄. After filtration and evaporation of the solvent, the residue was purified by SGC (DCM/MeOH = 99:1) to provide the subtitle compound. MS ESI+: m/z = 252 [M-H]-.
6-Bromo-1-oxo-indan-2-carboxylic acid methyl ester
To a mixture of 6-bromo-indan-1-one (10.0 g) and dimethylcarbonate (107 g) was added NaH (4.17 g, 60% in mineral oil). After heating at 80°C for 2 hours the mixture was allowed to cool to rt, quenched by addition of ammonium chloride solution and extracted with EA. The organic phase was washed with brine, dried over Na2SO4 and concentrated to provide the title compound. MS ESI⁺: m/z = 269 [M+H]⁺.

Preparation of Examples 2
Example 2-01 (Typical Procedure 7)
A mixture of methyl 2-(6-((R)-3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxo-2,3-dihydro-1H-inden-2-yl)acetate (11 mg) and THF (0.2 ml) was added LiOH (13 µL, 2 M in water) and stirred for 12 hours. The mixture was acidified (0.1 M HCl) and extracted with EA. The organic phase was dried (Na2SO4) and concentrated. The residue was purified by preparative HPLC to provide Example 2-01.
Following essentially this procedure, the Examples 2 in Table 2 were obtained by saponification of the respective methyl esters.

Table 2.

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Preparation of Examples 3
Example 3-01 (Typical Procedure 8)
To a mixture of 2-(((R)-5-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-3-oxo-2,3-dihydro-1H-inden-1-yl)acetic acid (100 mg), DIPEA (148 mg) and DMF (2 mL) was added EDCI (54 mg) and HOBt (31 mg). After 30 minutes dimethyl amine (340 µL, 1 M in THF) was added and the mixture stirred for 12 hours. Evaporation of the reaction mixture gave a residue which was purified by preparative HPLC to provide Example 3-01.

Following essentially this procedure the Examples 3 in Table 3 were obtained by coupling the appropriate acid (selected from Examples 2) with the respective amine.

Table 3.
Pharmacological Utility
The biological activity of the compounds of the invention may be demonstrated by known in vitro assays. Examples include in vitro cellular assays for recombinant and non-recombinant GPR19 as described in the following.

Functional Cellular Assays Measuring GPR19-mediated cAMP Release
Compounds of the invention, which are agonists of GPR119, were characterized by functional assays measuring the cAMP response of HEK-293 cell lines stably expressing recombinant GPR119 from man, mouse or rat, or by using a hamster cell line HIT-T15 expressing GPR119 endogenously. The cAMP content was determined using a kit based on homogenous time-resolved fluorescence (HTRF) from Cisbio Corp. (cat. no. 62AM4PEC). For preparation, cells were split into T175 culture flasks and grown to near confluency in medium (DMEM / 10% FCS for HEK-293 cells, and F-12K medium / 10% horse serum / 2.5% FCS for HIT-T15 cells, respectively). Medium was then removed and cells washed with PBS lacking calcium and magnesium ions, followed by proteinase treatment with accutase (Sigma-Aldrich, cat. no. A6964). Detached cells were washed and resuspended in assay buffer (1 x HBSS; 20 mM HEPES, 0.1% BSA, 2 mM IBMX) and cellular density determined. They were then diluted to 400000 cells/mL and 25 µL-aliquots dispensed to the wells of 96-well plates. For measurement, 25 µL of test compound in assay buffer was added and incubated for 30 minutes at room temperature. After addition of HTRF reagents diluted in lysis buffer, the plates were incubated for 1 hour, followed by measuring the fluorescence ratio at 665 vs. 620 nm. Potency of the agonists was quantified by determining the concentrations that caused 50% of the maximal response/activation (EC50). See Table 4 for exemplary data obtained using the cell line expressing human GPR119.

Compounds of the invention show EC50 values typically in the range of about 0.001 to 100 µM, preferably from about 0.001 to 10 µM, more preferably from about 0.001 to 1 µM and most preferably from about 0.001 to 0.3 µM.

Table 4.

<table>
<thead>
<tr>
<th>Example</th>
<th>EC50 [µM]</th>
<th>Example</th>
<th>EC50 [µM]</th>
<th>Example</th>
<th>EC50 [µM]</th>
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<td>1-01</td>
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<td>3-02</td>
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</table>

Based on the demonstrated ability of the compounds of the invention to activate GPR1 19 it is predicted that said compounds are useful for treatment of diseases and/or prevention of conditions which are modulated by GPR1 19.

Especially, the compounds of the invention may be useful to treat GPR1 19-related diseases and/or prevent GPR1 19-mediated conditions in humans.

The compounds of the invention are especially suitable for the treatment and/or prevention of:

1a) Disorders of fatty acid metabolism and glucose utilization disorders  
1b) Disorders in which insulin resistance is involved  
2) Diabetes mellitus, especially type 2 diabetes mellitus, including the prevention of the sequelae associated therewith. Particular aspects in this context are:

   a) Improvement of hyperglycemia  
   b) Improvement of insulin resistance  
   c) Improvement of glucose tolerance  
   d) Protection of pancreatic beta cells  
   e) Improvement of beta cell function  
   f) Prevention of micro- and macrovascular disorders, such as  
      a. Retinopathy  
      b. Atherosclerosis  
      c. Nephropathy and microalbuminuria  
      d. Neuropathy  
   g) Chronic low grade inflammation
3) Various other conditions which may be associated with the metabolic syndrome or the syndrome X, such as
   a) Increased abdominal girth
   b) Obesity
   c) Liver disorders
      a. Fatty liver
      b. Steatosis
      c. Steatohepatitis
      d. Cirrhosis
   d) Dyslipidemia (e.g. hypertriglyceridemia, hypercholesterolemia, hyperlipoproteinemia and/or low HDL)
   e) Insulin resistance
   f) Hypercoagulability
   g) Hyperuricemia
   h) Thromboses, hypercoagulable and prothrombotic states (arterial and venous)
      i) High blood pressure
      j) Endothelial dysfunction
      k) Heart failure, for example (but not limited to) following myocardial infarction, hypertensive heart disease or cardiomyopathy
4) Cardiovascular diseases, for example (but not limited to) myocardial infarction and stroke
5) Bone-related diseases and disorders characterized by reduced bone mass, such as:
   a) Osteoporosis
   b) Rheumatoid arthritis
   c) Osteoarthritis.
Claims:

1. A compound of the formula I in which

\[ \text{R}^{30} = (\text{CR}_{1} \text{R}_{12})^{n} - \text{R}^{32}, \text{NR}_{17}\text{R}_{18} or \text{OR}_{17} \]

\[ \text{R}^{31} = \text{H or (CR}_{1} \text{R}_{12})^{m} - \text{R}^{32}; \]

\[ n = 0, 1 or 2; \]

\[ m = 0, 1, 2 or 3; \]

\[ \text{R}_{11}, \text{R}_{12} \ are \ independently \ of \ each \ other \ H or (\text{C}-\text{C}_{6})-\text{alkyl}; \]

\[ \text{or R}_{11} \ and \ \text{R}_{12} \ form \ together \ the \ group =O; \]

\[ \text{R}_{11}', \text{R}_{12}' \ are \ independently \ of \ each \ other \ H or (\text{C}-\text{C}_{6})-\text{alkyl}; \]

\[ \text{R}^{32} = (\text{C}-\text{C}_{6})-\text{alkyl, COOR}_{13}, \text{CONR}_{14}\text{R}_{15}, \text{SO}_{2}\text{R}_{16} or \text{OH}; \]

\[ \text{R}_{13} = \text{H or (C}_{4}-\text{C}_{6})-\text{alkyl}; \]

\[ \text{R}_{14}, \text{R}_{15} \ are \ independently \ of \ each \ other \ H, (\text{C}-\text{C}_{6})-\text{alkyl, (C}-\text{C}_{6})-\text{alkyl substituted with OR}_{17}, \text{or (C}_{3}-\text{C}_{6})-\text{cycloalkyl}; \]
or R14 and R15 form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;

wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (Ci-C4)-alkyl and OR19;

R16 is (Ci-C6)-alkyl;

R17 is H or (Ci-C6)-alkyl;

R18 is H or (Ci-C6)-alkyl;

R19 is H or (Ci-C6)-alkyl;

R1a, R1b, R1c are independently of each other H, F, Cl, Br, (Ci-Ce)-alkyl or CN;

R2a, R2b, R2c are independently of each other H, F, Cl, Br, (Ci-C6)-alkyl or CN;

Y is N or CH;

Z is a bond, O, CR5R5', NR6, C=O, S, SO or SO2;

R5, R5', R6 are independently of each other H or (Ci-C4)-alkyl;

R3 is a bond or (CR7R7')p;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (Ci-Ce)-alkyl;

R4 is (Ci-C6)-alkyl, OR8, (C3-C8)-cycloalkyl, (C5-C8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups (C3-C8)-cycloalkyl, (Cs-CsJ-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from (Ci-C$_4$)-alkyl, (Ci-C$_4$)-alkanoyl, hydroxy, hydroxy-(Ci-C$_4$)-alkyl, (Ci-C3)-alkyloxy-(Ci-C$_4$)-alkyl, oxo, F or Cl;

R8 is H, (Ci-C$_6$)-alkyl, hydroxy-(Ci-C$_4$)-alkyl or (Ci-C$_3$)-alkyloxy-(Ci-C$_4$)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

2. A compound of the formula I as claimed in claim 1, wherein the 3-position of the pyrrolidinone ring has (R)-configuration.

3. A compound of the formula I as claimed in claim 1 or 2, wherein Y is N.

4. A compound of the formula I as claimed in any of claims 1 to 3, wherein Z is O.

5. A compound of the formula I as claimed in any of claims 1 to 4, wherein R3 is CH$_2$.

6. A compound of the formula I as claimed in any of claims 1 to 5, wherein
R4 is (C₃-C₈)-cycloalkyl.

7. A compound of the formula I as claimed in any of claims 1 to 4, which is a compound of the formula Ia

![Chemical Structure](image)

in which

R₃₀ is (CR₁₁'R₁₂')ₙ-R₃₂ or OR₁₇;

n is 0, 1 or 2;

R₁₁', R₁₂' are independently of each other H or (C₁-C₆)-alkyl;

R₃₂ is COOR₁₃, CONR₁₄R₁₅, SO₂R₁₆ or OH;

R₁₃ is H or (C₁-C₆)-alkyl;

R₁₄, R₁₅ are independently of each other H, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted with OR₁₇, or (C₃-C₆)-cycloalkyl;

or R₁₄ and R₁₅ form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR₁₈;

wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C₁-C₄)-alkyl and OR₁₉;
R16 is (C₆₋₆)-alkyl;

R17 is H or (C₆₋₆)-alkyl;

R18 is H or (C₆₋₆)-alkyl;

R19 is H or (C₆₋₆)-alkyl;

R1a, R1c are independently of each other H, F, Cl, Br, (C₆₋₆)-alkyl or CN;

R2a is H, F, Cl, Br, (C₆₋₆)-alkyl or CN;

R3 is a bond or (CR₇R’₇)ₚ;

p is 0, 1, 2, 3 or 4;

R7, R₇’ are independently of each other H or (C₆₋₆)-alkyl;

R4 is (C₆₋₆)-alkyl, OR₈, (C₃₋₆)-cycloalkyl, (C₅₋₆)-bicycalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;

wherein the groups (C₃₋₆)-cycloalkyl, (Cs-CsJ-bicycalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from (C₆₋₆)-alkyl, (C₆₋₆)-alkanoyl, hydroxy, hydroxy-(C₆₋₆)-alkyl, (C₄₋₆)-alkyloxy-(C₆₋₆)-alkyl, oxo, F or Cl;

R8 is H, (C₆₋₆)-alkyl, hydroxy-(C₆₋₆)-alkyl or (C₆₋₆)-alkyloxy-(C₆₋₆)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.
8. A compound of the formula as claimed in claim 7, wherein

\[ R_{30} = (C'R_1'R_2')_n R_{32} \text{ or } OR_{17} \]

\( n \) is 0, 1 or 2;

\( R_1', R_2' \) are independently of each other \( H \) or \((C_1-C_6)-\text{alkyl}\)

\[ R_{32} = (C_1-C_6)-\text{alkyl}, \text{COOR}_{13}, \text{CONR}_{14}R_{15}, \text{SO}_2R_{16} \text{ or } OH; \]

\[ R_{13} = H \text{ or } (C_1-C_6)-\text{alkyl}; \]

\[ R_{14}, R_{15} \] are independently of each other \( H, (C_1-C_6)-\text{alkyl}, (C_1-C_6)-\text{alkyl} \) substituted with \( OR_{17} \), or \((C_3-C_6)-\text{cycloalkyl} \);

\[ \text{or } R_{14} \text{ and } R_{15} \text{ form together with the } N\text{-atom on which they are attached, } \]

\[ \text{a } 4-, 5-, \text{ or } 6\text{-membered heterocycle, optionally containing an additional } \]

\[ \text{heteroatom selected from the list } O, S \text{ and } NR_{18}; \]

\[ \text{wherein the } 4-, 5-, \text{ or } 6\text{-membered heterocycle may be optionally } \]

\[ \text{substituted with } 1 \text{ to } 3 \text{ groups selected from the list } (C_1-C_4)-\text{alkyl} \]

\[ \text{and } OR_{19}; \]

\[ R_{16} = (C_1-C_6)-\text{alkyl}; \]

\[ R_{17} = H \text{ or } (C_1-C_6)-\text{alkyl}; \]

\[ R_{18} = H \text{ or } (C_1-C_6)-\text{alkyl}; \]

\[ R_{19} = H \text{ or } (C_1-C_6)-\text{alkyl}; \]

\[ R_{1a}, R_{1c} \] are independently of each other \( H, F, Cl, Br, (C_1-C_6)-\text{alkyl} \) or CN;

\[ R_{2a} = H, F, Cl, Br, (C_1-C_6)-\text{alkyl} \text{ or } CN; \]

\[ R_3 = \text{bond, } CH_2 \text{ or } CH_2-CH_2; \]
R4 is (C\textsubscript{i} - C\textsubscript{6})-alkyl, OR\textsubscript{8}, (C\textsubscript{3} - C\textsubscript{8})-cycloalkyl, (C\textsubscript{5} - C\textsubscript{8})-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring; wherein the groups (C\textsubscript{3} - C\textsubscript{8})-cycloalkyl, (C\textsubscript{3} - C\textsubscript{6})-alkyl, hydroxy (C\textsubscript{3} - C\textsubscript{6})-alkyl, hydroxy-(C\textsubscript{1} - C\textsubscript{4})-alkyl, (C\textsubscript{1} - C\textsubscript{3})-alkyloxy-(C\textsubscript{1} - C\textsubscript{4})-alkyl, oxo, F or Cl;

R8 is H, (C\textsubscript{i} - C\textsubscript{6})-alkyl, hydroxy-(C\textsubscript{1} - C\textsubscript{4})-alkyl or (C\textsubscript{i} - C\textsubscript{3})-alkyloxy-(C\textsubscript{i} - C\textsubscript{4})-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms; in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

9. A compound of the formula Ia as claimed in claim 7 or 8, wherein

R30 is (CR\textsubscript{1} 1'R\textsubscript{1} 2')\textsubscript{n}=R32 or OR\textsubscript{1 7};

n is 0, 1 or 2;

R\textsubscript{11'}, R\textsubscript{12'} are independently of each other H or (C\textsubscript{i} - C\textsubscript{6})-alkyl;

R32 is COOR\textsubscript{13}, CONR\textsubscript{14}R\textsubscript{1 5}, SO\textsubscript{2}R\textsubscript{1 6} or OH;

R\textsubscript{13} is H or (C\textsubscript{i} - C\textsubscript{6})-alkyl;

R\textsubscript{14}, R\textsubscript{15} are independently of each other H, (C\textsubscript{i} - C\textsubscript{6})-alkyl, (C\textsubscript{i} - C\textsubscript{5})-alkyl substituted with OR\textsubscript{1 7}, or (C\textsubscript{3} - C\textsubscript{6})-cycloalkyl;
or R\textsubscript{14} and R\textsubscript{15} form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR\textsubscript{18};
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C1-C4)-alkyl and OR17;

R16 is (C1-C6)-alkyl;

R17 is H or (C1-C6)-alkyl;

R18 is H or (C1-C6)-alkyl;

R19 is H or (C1-C6)-alkyl;

R1a, R1c are independently of each other H, F, Cl, Br, (C1-C6)-alkyl or CN;

R2a is H, F, Cl, Br, (C1-C6)-alkyl or CN;

R3 is bond, CH2 or CH2-CH2;

R4 (C3-C8)-cycloalkyl;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

10. A compound of the formula la as claimed in claim 7 to 9, wherein

R30 is R32;

R32 is CONR14R15, COOR13;

R13 is H or (C1-C6)-alkyl;

R14, R15 are independently of each other H, (C1-C6)-alkyl or (C1-C6)-alkyl substituted with OR17;
or R14 and R15 form together with the N-atom on which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the series O, S and NR18;

5 \( R17 \) is H or \((\text{Cl}-\text{C}_6)\)-alkyl;

\( R18 \) is H or \((\text{Cl}-\text{C}_6)\)-alkyl;

\( R1a, R1c \) are independently of each other H, F, Cl, Br, \((\text{Cl}-\text{C}_6)\)-alkyl or CN;

10 \( R2a \) is H, F, Cl, Br, \((\text{Cl}-\text{C}_6)\)-alkyl or CN;

\( R3 \) is \( \text{CH}_2 \);

15 \( R4 \) \((\text{C}_3-\text{C}_6)\)-cycloalkyl;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

20

11. A compound of the formula la as claimed in claim 7 to 10, wherein

\( R30 \) is \( R32 \);

25 \( R32 \) is \( \text{CONR14R15}, \text{COOR13} \);

\( R14, R15 \) are independently of each other H, \((\text{Cl}-\text{C}_6)\)-alkyl or \((\text{Cl}-\text{C}_6)\)-alkyl substituted with OR17;

30 \( R17 \) is H or \((\text{Cl}-\text{C}_6)\)-alkyl;

\( R1a \) is H or F;

\( R1c \) is H;
R2a is H;

R3 is CH₂;

R4 (C₃-C₆)-cycloalkyl;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

12. A compound selected from the list

5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-N,N-dimethyl-3-oxo-indane-1-carboxamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]-N-methyl-acetamide,
2-[[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-indan-2-yl]-N,N-dimethyl-acetamide,
2-[[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]acetamide and
2-[[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide

or a pharmaceutically acceptable salt thereof.

13. The compound

2-[[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide
or a pharmaceutically acceptable salt thereof.

14. The compound

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-7-fluoro-3-oxo-indan-1-yl]-N,N-dimethyl-acetamide

or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising at least one compound as claimed in any of claims 1 to 14 or a physiologically acceptable salt of any of them, for use as a pharmaceutical.

16. A pharmaceutical composition as claimed in claim 15, comprising additionally one or more active ingredients selected from the list:
Insulin and insulin derivatives, GLP-1, GLP-1 analogues and GLP-1 receptor agonists, polymer bound GLP-1 and GLP-1 analogues, dual GLP-1/GIP agonists, dual GLP-1/glucagon receptor agonists, PYY3-36 or analogues thereof, pancreatic polypeptide or analogues thereof, glucagon receptor agonists or antagonists, GIP receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof, DDP-IV inhibitors, SGLT-2 inhibitors, dual SGLT-2/SGLT-1 inhibitors, biguanides, thiazolidinediones, PPAR agonists, PPAR modulators, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, amylin and amylin analogues, GPR1 19 agonists, GPR40 agonists, GPR1 20 agonists, GPR142 agonists, TGR5 agonists, AMPK stimulants, AMPK activators, inhibitors of 11-beta-HSD, activators of glucokinase, inhibitors of DGAT, inhibitors of protein tyrosine phosphatase 1, inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase, CCR-2 antagonists, modulators of glucose transporter-4, somatostatin receptor 3 agonists, HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and derivatives thereof, nicotinic acid receptor 1 agonists, ACAT
inhibitors, cholesterol absorption inhibitors, bile acid-binding substances, IBAT inhibitors, MTP inhibitors, modulators of PCSK9, LDL receptor up-regulators (liver selective thyroid hormone receptor beta agonists), HDL-raising compounds, lipid metabolism modulators, PLA2 inhibitors, ApoA-I enhancers, cholesterol synthesis inhibitors, omega-3 fatty acids and derivatives thereof, active substances for the treatment of obesity, CB1 receptor antagonists, MCH-1 antagonists, MC4 receptor agonists and partial agonists, NPY5 or NPY2 antagonists, NPY4 agonists, beta-3 adrenergic receptor agonists, leptin or leptin mimetics, 5HT2c receptor agonists, lipase inhibitors, angiogenesis inhibitors, H3 antagonists, AgRP inhibitors, triple monoamine uptake inhibitors, MetAP2 inhibitors, antisense oligonucleotides against production of fibroblast growth factor receptor 4 or prohibitin targeting peptide-1, drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, angiotensin II receptor antagonists, dual angiotensin receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitors, angiotensin converting enzyme 2 (ACE-2) activators, renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha-blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists/calcium channel blockers (CBBs), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vasopeptide inhibitors, dual vasopeptide inhibitors, neprilysin-ACE inhibitors, neprilysin-ECE inhibitors, dual-acting Angiotensin (AT) receptor-neprilysin inhibitors, dual AT1/endothelin-1 (ETA) antagonists, advanced glycation end-product breakers, recombinant renalase, blood pressure vaccines, anti-RAAS vaccines, AT1- or AT2-vaccines, modulators of genetic polymorphisms with antihypertensive response and thrombocyte aggregation inhibitors.

17. A pharmaceutical composition as claimed in claim 15, comprising additionally metformin.

18. A pharmaceutical composition as claimed in claim 15, comprising additionally at least one DPP-IV inhibitor.
19. A pharmaceutical composition as claimed in claim 18, wherein the DPP-IV inhibitor is selected from the list alogliptin, linagliptin, saxagliptin, sitagliptin, anaglaptin, teneligliptin, trelagliptin, vildagliptin, gemigliptin, omarigliptin, evogliptin and dutogliptin.

20. A pharmaceutical composition as claimed in claim 15, comprising additionally at least one SGLT-2 inhibitor.

21. A pharmaceutical composition as claimed in claim 20, wherein the SGLT-2 inhibitor is selected from the list canagliflozin, dapagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin and ertugliflozin.

22. A pharmaceutical composition as claimed in claim 15, comprising additionally at least one GPR40 agonist.

23. A pharmaceutical composition as claimed in claim 22, wherein the GPR40 agonist is selected from the list TUG-424, P-1 736, P-1 1187, JTT-851, GW9508, CNX-011-67, AM-1 638 and AM-5262.


25. A pharmaceutical composition as claimed in claim 15, comprising additionally at least one HMG-CoA reductase inhibitor.
26. A pharmaceutical composition as claimed in claim 25, wherein the HMG-CoA reductase inhibitor is selected from the list simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin, lovastatin, mevastatin, rivastatin and cerivastatin.

27. A pharmaceutical composition as claimed in claim 15, comprising additionally at least one PPAR agonist or PPAR modulator.

28. A pharmaceutical composition as claimed in claim 27, wherein the PPAR agonist or PPAR modulator is saroglitazar.

29. A pharmaceutical composition as claimed in claim 27, wherein the PPAR agonist or PPAR modulator is selected from the list pioglitazone, rosiglitazone and lobeglitazone.

30. A pharmaceutical composition as claimed in claim 15, comprising additionally acarbose.

31. A compound of the formula I as claimed in any of claims 1 to 14 for use as a pharmaceutical.

32. A compound of the formula I as claimed in any of claims 1 to 14 for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

33. A compound of the formula I as claimed in any of claims 1 to 14 for the prevention and/or treatment of diabetes.
34. A compound of the formula I as claimed in any of claims 1 to 14 for the prevention and/or treatment of obesity.

35. A compound of the formula I as claimed in any of claims 1 to 14 for the prevention and/or treatment of dyslipidemia.

36. A compound of the formula I as claimed in any of claims 1 to 14 for prevention and/or treatment of a disease associated with the GPR19.

37. A method for treating diabetes, obesity or dyslipidemia in a patient, the method comprising administering to the patient an effective amount of at least one compound of formula I as claimed in any of claims 1 to 14.

38. A method for treating diabetes, obesity, dyslipidemia or high blood pressure in a patient, the method comprising administering to the patient an effective amount of at least one compound of formula I as claimed in any of claims 1 to 14 and an effective amount of at least one other compound useful for treating diabetes, obesity, dyslipidemia or high blood pressure.

39. The method as claimed in claim 38 wherein the effective amount of at least one compound of formula I as claimed in any of claims 1 to 14 and the additional active ingredient are administered to the patient simultaneously.

40. The method as claimed in claim 38 wherein the effective amount of at least one compound of formula I as claimed in any of claims 1 to 14 and the additional active ingredient are administered to the patient sequentially.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/EP2015/057413

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D401/12  C07D207/26  A61K31/402  A61K31/4439

ADD. A61P3/00

According to International Patent Classification (IPC) of both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PAJ, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

**Date of the actual completion of the international search**

28 May 2015

**Date of mailing of the international search report**

05/06/2015

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2

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Rudolf, Manfred
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