A compound of formula (I) wherein the substituents have various meanings, optionally in salt and/or solvate form, and their use as pharmaceuticals.
The present invention relates to GPBAR1 modulators, e.g. compounds which mediate the activity of a specific G protein coupled receptor.

5 The G protein coupled receptor GPBAR1, e.g. disclosed in WO03051923 (nucleotide sequence SEQ ID NO:1, protein sequence SEQ ID:NO 2), is a member of the G protein-coupled receptor family of polypeptides. The biological properties of such immunomodulatory polypeptides include monocyte/macrophage migration/activation, regulation of dendritic cell differentiation, regulation of lymphocyte activation, proliferation and differentiation regulation of inflammation, regulation of cytokine production and/or release, regulation of pro-inflammatory mediator production and/or release, regulation of immune reaction, GLP (glucagon-like peptide)-1 secretion, insulin secretion, appetite, pancreatic regeneration, pancreatic β cell differentiation, pancreatic/? cell growth, insulin resistance, energy expenditure.

10 Thus, GPBAR1 is indicated to be of interest in relation to methods of treatment of disorders, wherein such biological properties play a causal or contributory role. Such disorders include but are not limited to (chronic) inflammatory diseases, autoimmune diseases, diseases or syndroms in which a significant pathological component is immune suppression, including viral diseases, transplant rejection crisis and other diseases following transplantation, cancer; neurological disorders, such as neurology CNS disorders, cardiovascular disorders, diabetes (type 2), obesity.

Compounds are herewith provided which surprisingly exert agonistic activity on GPBAR1, e.g. thus activating the GPBAR1 function.

In one aspect the present invention provides a compound of formula

![Chemical Structure](image)

wherein
Ri is (C₆₋₈)aryl or (C₆₋₈)aryl(C₁₋₄)alkyl, wherein aryl optionally is fused with aliphatic or aromatic heterocycyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N,O,S,
(C₃₋₁₂)cycloalkyl, wherein cycloalkyl optionally is fused with aliphatic or aromatic heterocycyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N,O,S,
(C₅₋₁₂)cycloalkenyl, wherein cycloalkenyl optionally is fused with aliphatic or aromatic heterocycyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N,O,S, or
heterocycyl, comprising 3 to 12 ring members and 1 to 4 heteroatoms selected from N,O,S;
wherein heterocycyl optionally is fused with (C₃₋₁₂)cycloalkyl, (C₅₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl, or optionally is fused with another heterocycyl comprising 3 to 12 ring members and 1 to 4 heteroatoms selected from N,O,S;
R₂ is alkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl cycloalkenyl, heterocyclyl, or (C₁₋₄)alkyl substituted by aryl, cycloalkyl, cycloalkenyl or heterocycyl, preferably aryl or
heterocycyl, wherein
- alkyl includes (C₁₋₁₂)alkyl,
- alkenyl includes (C₂₋₁₂)alkenyl,
- alkynyl includes (C₂₋₁₂)alkynyl,
- cycloalkyl includes (C₃₋₁₂)cycloalkyl,
- cycloalkenyl includes (C₅₋₆)cycloalkenyl,
- aryl includes (C₆₋₁₂)aryl and (C₆₋₁₂)aryl(C₁₋₄)aryl, wherein aryl optionally is fused with (C₃₋₁₂)cycloalkyl, (C₅₋₆)cycloalkenyl, aliphatic or aromatic heterocycyl comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N,O,S,
- heterocycyl includes aliphatic or aromatic heterocycyl comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N,O,S and wherein heterocycyl optionally is fused with (C₃₋₁₂)cycloalkyl, (C₅₋₆)cycloalkenyl, (C₆₋₁₂)aryl, or is fused with another heterocycyl, preferably fused with another heterocycyl, which other heterocycyl includes aliphatic or aromatic heterocycyl, preferably aromatic heterocycyl, comprising 3 to 12 ring members and 1 to 4 heteroatoms, selected from N,O,S;
R₃ is hydrogen or (C₁₋₄)alkyl; or
R₂ and R₃ together with the carbon atom to which they are attached form (C₃₋₁₂)cycloalkyl, (C₅₋₆)cycloalkenyl, phenyl, or heterocycyl;
which cycloalkyl cycloalkenyl, phenyl or heterocycyl optionally is fused with
(C<sub>3</sub>-i<sub>2</sub>)cycloalkyl, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenyl, (C<sub>6</sub>-i<sub>2</sub>)aryl, or is fused with another heterocyclyl comprising 5 to 6 ring members and 1 to 4 heteroatoms selected from N, O, S;

wherein aryl, cycloalkyl, cycloalkenyl and heterocyclyl in the meaning of R<sub>1</sub>, R<sub>2</sub> or R<sub>3</sub> and R<sub>4</sub>
together is unsubstituted or one or morefold substituted by (C<sub>1</sub>-i<sub>4</sub>)alkyl, e.g. (C<sub>1</sub>-i<sub>4</sub>)alkyl,
(C<sub>2</sub>-i<sub>6</sub>)alkenyl, (C<sub>2</sub>-i<sub>6</sub>)alkynyl, halo(C<sub>1</sub>-i<sub>4</sub>)alkyl, oxo, hydroxy, (C<sub>1</sub>-i<sub>4</sub>)alkoxy, halo<sup>^</sup>alkoxy, =S, SH, SO<sub>3</sub>H, SO<sub>2</sub>NH<sub>2</sub>, (d<sup>6</sup>alkylmercapto, hydroxycarbonyl, (C<sub>1</sub>-i<sub>4</sub>)alkylcarbonyl, (C<sub>6</sub>-i<sub>1</sub>)arylcarbonyl, (C<sub>3</sub>-i<sub>12</sub>)cycloalkylcarbonyl, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenylcarbonyl, heterocyclylcarbonyl, hydroxycarbo- noxy, (C<sub>1</sub>-i<sub>4</sub>)alkylcarbonyloxy, (C<sub>6</sub>-i<sub>2</sub>)arylcarbonyloxy, (C<sub>3</sub>-i<sub>12</sub>)cycloalkylcarbonyloxy, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenylcarbonyloxy, heterocyclylcarbonyloxy, (C<sub>6</sub>-i<sub>2</sub>)aryl, (C<sub>3</sub>-i<sub>12</sub>)cycloalkyl, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenyl, (C<sub>6</sub>-i<sub>2</sub>)aryl, (C<sub>3</sub>-i<sub>12</sub>)cycloalkoxy, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenylxy, cyano, nitro, amino, (C<sub>1</sub>-i<sub>4</sub>)alkylamino, (di(C<sup>6</sup>)*alkylamino, (C<sub>6</sub>-i<sub>2</sub>)arylalano, (C<sub>3</sub>-i<sub>12</sub>)cycloalkylalano, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenylalano, heterocyclylamino, (C<sub>1</sub>-i<sub>4</sub>)alkylcarbonylamino, (C<sub>6</sub>-i<sub>2</sub>)arylcarbonylamino, (C<sub>6</sub>-i<sub>2</sub>)arylcarbonylamino, (C<sub>3</sub>-i<sub>12</sub>)cycloalkylcarbonylamino, (C<sub>5</sub>-i<sub>6</sub>)cycloalkenylcarbonylamino, heterocyclylcarbonylamino, or halogen, and

wherein heterocyclyl comprises 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S, including aliphatic and aromatic heterocyclyl, e.g. heterocyclyl optionally fused with another ring system such as fused with (C<sub>3</sub>-i<sub>12</sub>)cycloalkyl, (C<sub>6</sub>-i<sub>12</sub>)aryl, or another heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S.

R<sub>4</sub> is a compound of formula

\[
\begin{array}{c}
\text{N} \\
\text{R}_6 \\
\end{array}
\]

(IA)

or of formula

\[
\begin{array}{c}
\text{N} \\
\text{X} \\
\text{Y} \\
\end{array}
\]

(IB)

wherein in a compound of formula (IA) R<sub>6</sub> is hydrogen or (C<sub>1</sub>-i<sub>4</sub>)alkyl, and

wherein in a compound of formula (IB)

X is O, S or NR<sub>6</sub>, wherein R<sub>6</sub> is hydrogen or (C<sup>6</sup>)*alkyl,

Y is O or S.

In another aspect the present invention provides a compound of formula (I) wherein

R<sub>1</sub> is (C<sub>6</sub>-i<sub>1</sub>)aryl or (C<sub>6</sub>-i<sub>2</sub>)aryl(C<sub>1</sub>-i<sub>4</sub>)alkyl, wherein aryl optionally is fused with aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N, O, S.
(C₃₋₁₂)cycloalkyl, wherein cycloalkyl optionally is fused with aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N, O, S, (C₅₋₁₂)cycloalkenyl, wherein cycloalkenyl optionally is fused with aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N, O, S, or

heterocyclyl, comprising 3 to 12 ring members and 1 to 4 heteroatoms selected from N, O, S; wherein heterocyclyl optionally is fused with (C₃₋₁₂)cycloalkyl, (C₅₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl, or optionally is fused with another heterocyclyl comprising 3 to 12 ring members and 1 to 4 heteroatoms selected from N, O, S,

R₂ is alkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl cycloalkenyl, heterocyclyl, or (C₁₋₄)alkyl substituted by aryl, cycloalkyl, cycloalkenyl or heterocyclyl, preferably aryl or heterocyclyl, wherein
- alkyl includes (C₁₋₁₂)alkyl,
- alkenyl includes (C₂₋₁₂)alkenyl,
- alkynyl includes (C₂₋₁₂)alkynyl,
- cycloalkyl includes (C₃₋₁₂)cycloalkyl,
- cycloalkenyl includes (C₅₋₆)cycloalkenyl,
- aryl includes (C₆₋₈)aryl and (C₆₋₈)aryl(C₁₋₄)alkyl, wherein aryl optionally is fused with (C₃₋₁₂)cycloalkyl, (C₅₋₆)cycloalkenyl, aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N, O, S,
- heterocyclyl includes aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N, O, S and wherein heterocyclyl optionally is fused with (C₃₋₁₂)cycloalkyl, (C₅₋₆)cycloalkenyl, (C₆₋₁₂)aryl, or is fused with another heterocyclyl, preferably fused with another heterocyclyl, which other heterocyclyl includes aliphatic or aromatic heterocyclyl, preferably aromatic heterocyclyl, comprising 3 to 12 ring members and 1 to 4 heteroatoms, selected from N, O, S,

R₃ is hydrogen or (C₁₋₄)alkyl,

R₄ is a compound of formula

\[
\text{[IA]}
\]

\[
\text{[IB]}
\]

wherein in a compound of formula [IA] R₅ is hydrogen or (C₁₋₄)alkyl, and
wherein in a compound of formula (IB)
X is O, S or NR₆, wherein R₆ is hydrogen or (C₁₋₄)alkyl,
Y is O or S selected from NO₅S, and
wherein aryl is unsubstituted or substituted by (Cₙ₋₄)alkyl, or (C₁₋₄)alkoxy,

5 In another aspect the present invention provides a compound of formula (I) wherein
R₁ is phenyl or phenyKC^alkyl, unsubstituted or substituted by one or more (C₁₋₄)alkyl,
(Ci₋₄)alkoxy, halo(C₁₋₄)alkyl, halo(Ci₋₄)alkoxy, halogen, cyano;
R₂ is phenyl, phenyl fused with another ring system, heterocyclyl comprising 5 or 6 ring
members, and 1 to 4 heteroatoms, including aromatic heterocyclyl and aliphatic
heterocyclyl, which heterocyclyl is optionally fused with another ring system, e.g. fused
with (C₃₋₁₂)cycloalkyl, (C₅₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl or another heterocyclyl comprising
5 to 6 ring members, and 1 to 4 heteroatoms, selected from N, O, S,
wherein cycloalkyl, cycloalkenyl, aryl, aryl fused with another ring system, heterocyclyl
or heterocyclyl fused with another ring system is unsubstituted or substituted by one or
more (C₁₋₄)alkyl, (C₁₋₄)alkoxy, cyano, halogen, phenyl,
R₃ is hydrogen or (Ci₋₄)alkyl,
R₄ is a compound of formula (IA), and
R₅ is hydrogen or (Ci₋₄)alkyl.

20 In another aspect the present invention provides a compound of formula (I) wherein
R₁ is unsubstituted phenyl or phenyl one or twofold substituted by methyl, halo, cyano,
or phenylmethyl,
R₂ is methoxyphenyl, halophenyl, dihalophenyl, (halo)(methoxy)phenyl, indolyl, triazolyl,
optionally substituted by phenyl, cyanophenyl, or imidazolyl fused with thiazolyl, and
R₃ is hydrogen or methyl,
R₄ is a compound of formula (IA),
R₅ is hydrogen or methyl.

In another aspect the present invention provides a compound of formula (I) wherein
R₁ is phenyl, wherein phenyl is one or morefold substituted by halogen, cyano or
(C₁₋₄)alkyl,
R₂ is phenyl, wherein phenyl optionally is fused with aliphatic or aromatic heterocyclyl
comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N, O, S, and
wherein aryl is unsubstituted or substituted by (Cₙ₋₄)alkyl, or (C₁₋₄)alkoxy,
$R_3$ is hydrogen or (C$_i$-4)alkyl,
$R_4$ is a compound of formula (IB), wherein X is O, NH or NCH$_3$ and Y is O,
$R_6$ is hydrogen or methyl.

In another aspect the present invention provides N-($C_6$-12)-aryl-6-oxo-6H-pyran-3-carboxylic acid amides wherein the nitrogen atom of the amide group is further substituted by ($C_6$-12)arylmethyl, which aryl optionally is fused with heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S, e.g. wherein the fused heterocyclyl forms aromatic heterocyclyl.

In another aspect the present invention provides 6-hydroxy-nicotinamides, wherein the nitrogen atom of the amide group is further substituted by ($C_6$-12)arylmethyl, which aryl optionally is fused with heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S, and wherein the nitrogen atom of the amide group is further substituted by ($C_6$-12)aryl.

In another aspect the present invention provides 1-((($C_1$)-alkyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid amides, wherein the nitrogen atom of the amide group is substituted by ($C_6$-12)arylmethyl, which aryl optionally is fused with heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S, and wherein the nitrogen atom of the amide group is further substituted by ($C_6$-12)aryl.

In a compound of formula I each single group or substituent defined may be a preferred group or substituent, e.g. independently of each other group, or substituent, respectively, defined; and each single compound defined above or below may be a preferred compound.

In another aspect the present invention provides a compound of formula I, which is selected from the group consisting of
Pyridazine-4-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
Pyridazine-4-carboxylic acid [2-(4-cyano-phenyl)-2H-[1,2,3]triazol-4-ylmethyl]-(3,5-dichloro-phenyl)-amide,
Pyridazine-4-carboxylic acid (4-fluoro-2-methyl-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
Pyridazine-4-carboxylic acid (2-cyano-4-fluoro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
Pyridazine-4-carboxylic acid (3,5-dichloro-phenyl)-(1-(2-methoxy-phenyl)-ethyl)-amide,
Pyridazine-4-carboxylic acid [2-(4-cyano-phenyl)-2H-[1,2,3]triazol-4-ylmethyl]-(4-fluoro-2-methyl-phenyl)-amide,
Pyridazine-4-carboxylic acid (3-cyano-4-fluoro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
Pyridazine-4-carboxylic acid (2,4-difluoro-6-methoxy-benzyl)-(4-fluoro-2-methyl-phenyl)-amide,
Pyridazine-4-carboxylic acid (2,6-dimethylimidazo[2,1-b]thiazol-5-ylmethyl)-(4-fluoro-2-methyl-phenyl)-amide,
3-Methyl-pyridazine-4-carboxylic acid dibenzylamide,
S-Methyl-pyridazine-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
3-Methyl-pyridazine-4-carboxylic acid benzyl-phenyl-amide,
6-Oxo-6H-pyran-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
6-Oxo-6H-pyran-3-carboxylic acid (4-fluoro-2-methyl-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
N-(3,5-Dichloro-phenyl)-6-hydroxy-N-(2-methoxy-benzyl)-nicotinamide,
1-Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)O-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxyiic acid (3,5-dichloro-phenyl)-(1-(2-methoxy-phenyl)-ethyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxyiic acid (2,4-difluoro-5-methoxy-benzyl)-(4-fluoro-2-methyl-phenyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxyiic acid (2,6-dimethylimidazo[2,1-b]thiazol-5-ylmethyl)-(4-fluoro-2-methyl-phenyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxyiic acid (3,5-dichloro-phenyl)-[4-(2H-tetrazol-5-yl)-benzyl]-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-S-carboxylic acid (3,4-dichloro-phenyl)-(2-methyl-1H-indol-4-ylmethyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3,5-dichloro-phenyl)-(2,6-demethyl-imidazo[2,1-b]thiazol-5-ylmethyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-(3-phenyl-prop-2-ynyl)-amide,
1- Methyl-G-oxo-1,6-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-(6-methoxy-pyridin-3-ylmethyl)-amide,
5 N-(3,5-Dichloro-phenyl)-2-hydroxy-N-(2-methoxy-benzyl)-isonicotinamide (= 2-Oxo-1,2-dihydro-pyridine-4-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide),
e.g. which are compounds as indicated under "EX" 1 to 29 in TABLE 1 and TABLE 2 of the example part herein.

Any group indicated or defined herein may be unsubstituted or substituted, e.g. one or morefold., e.g. such as indicated herein. Substituents include groups which are conventional in organic chemistry, e.g. such as indicated herein.

Compounds provided by the present invention are hereinafter designated as "compound(s) of (according to) the present invention". A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

In another aspect the present invention provides a compound of the present invention in the form of a salt.

Such salts include preferably pharmaceutically acceptable salts, although pharmaceutically unacceptable salts are included, e.g. for preparation / isolation / purification purposes.

A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in non-solvated form; and vice versa.
A compound of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis/trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enantiomers or diastereoisomers and mixtures thereof, e.g. in the form of a racemat. A compound of the present invention may be present in the (R)-, (S)- or (R,S)-configuration preferably in the (R)- or (S)-configuration regarding specified positions in the compound. E.g. in a compound of formula 1, wherein \( R_2 \) is branched or substituted alkyl, or substituted cycloalkyl, e.g. or in a compound of formula 1, wherein \( R_3 \) is alkyl, asymmetric carbon atoms may exist, e.g. the carbon atom to which \( R_2 \) and \( R_3 \) are attached may be asymmetric, and compounds comprising an asymmetric carbon atom may be in the (R)-, (S)- or (R/S)-form regarding the position of such asymmetric carbon atom.

Isomeric mixtures may be separated as appropriate, e.g. according, e.g. analogously, to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

The present invention also includes tautomers of a compound of the present invention, where tautomers can exist.

In another aspect the present invention provides a process for the production of a compound of the present invention, e.g. of formula (IA), comprising reacting a compound of formula

\[
\text{IIA}
\]

wherein \( R_1, R_2 \) and \( R_3 \) are as defined above, with a compound of formula

\[
\text{IIIA}
\]

e.g. wherein a compound of formula IMA is in an activated form, e.g. reacted with 1-chloro-N,N,2-trimethyl-1-propenylamine, in the presence of an amine, e.g. triethylamine, and isolating a compound of formula IIA obtained from the reaction mixture.
A compound of formula \( HA \) wherein \( R_3 \) is hydrogen may be e.g. obtained by reacting a compound of formula

\[
\begin{align*}
R_2\text{CHO} & \quad \text{IVA} \\
\end{align*}
\]

wherein \( R_2 \) is as defined above, with a compound of formula

\[
\begin{align*}
R_1\text{-NH}_2 & \quad \text{VA} \\
\end{align*}
\]

wherein \( R_1 \) is as defined above, in the presence of a reducing agent, such as sodium triacetoxyborohydride, and isolating a compound of formula \( HA \) wherein \( R_1 \) and \( R_2 \) are as defined above and \( R_3 \) is hydrogen, obtained from the reaction mixture.

A compound of formula \( HA \) wherein \( R_3 \) is alkyl may be e.g. obtained by reacting a compound of formula \( VA \) with a compound of formula

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{R}_2 \\
\text{R}_3 \\
\end{array} & \quad \text{VIA} \\
\end{align*}
\]

wherein \( R_2 \) is as defined above and \( R_3 \) is alkyl, in the presence of an amine, e.g. triethylamine, followed by treating the reaction mixture obtained with titanium tetrachloride and sodium cyanoborohydride; and isolating a compound of formula \( HA \) wherein \( R_3 \) is alkyl, and \( R_1 \) and \( R_2 \) are as defined above, obtained from the reaction mixture.

In another aspect the present invention provides a process for the production of a compound of the present invention, e.g. of formula \( IB \), comprising reacting a compound of formula

\[
\begin{align*}
\begin{array}{c}
\text{R}_2 \\
\text{CH} \\
\text{R}_3 \\
\end{array} & \quad \text{IIB} \\
\end{align*}
\]

wherein \( R_1, R_2 \) and \( R_3 \) are as defined above, with a compound of formula

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{HO} \\
\end{array} & \quad \text{IIIIB} \\
\end{align*}
\]

wherein \( X \) and \( Y \) are as defined above, e.g. wherein a compound of formula \( IMB \) is in an activated form, e.g. reacted with 1-chloro-N,N,2-trimethyl-1-propenylamine, in the presence of an amine, e.g. triethylamine, and isolating a compound of formula \( IB \) obtained from the reaction mixture.
A compound of formula I wherein R₃ is hydrogen may be e.g. obtained by reacting a compound of formula

\[ R₂CHO \quad IVB \]

wherein R₂ is as defined above, with a compound of formula

\[ R₁-NH₂ \quad VB \]

wherein R₁ is as defined above, in the presence of a reducing agent, such as sodium triacetoxyborohydride, and isolating a compound of formula MB obtained from the reaction mixture.

A compound of formula MB wherein R₃ is alkyl may be e.g. obtained by reacting a compound of formula

\[ R₁-NH₂ \quad VB \]

wherein R₁ is as defined above, with a compound of formula

\[ \begin{array}{c}
O \\
\hline
R₂ \quad R₃ \\
\end{array} \quad VIB \]

wherein R₂ is as defined above and R₃ is alkyl, in the presence of an amine, e.g. triethylamine, followed by treating the reaction mixture obtained with titanium tetrachloride and sodium cyanoborohydride; and isolating a compound of formula MB wherein R₃ is alkyl, and R₁ and R₂ are as defined above, obtained from the reaction mixture.

In an intermediate of formula HA, MB, IMA, IMB, IVA, IVB, VA, VB, VIA or VIB (starting materials), functional groups, if present, optionally may be in protected form or in the form of a salt, if a salt-forming group is present. Protecting groups, optionally present, may be removed at an appropriate stage, e.g. according, e.g. analogously, to a method as conventional.

A compound thus obtained may be converted into another compound of formula I, e.g. or a compound of formula I obtained in free form may be converted into a salt of a compound of formula I and vice versa.

The above reaction between a compound of formula II and a compound of formula III is an acylation reaction and may be carried out as appropriate, e.g. according, e.g. analogously, to a method as conventional.
Intermediates (starting materials) of formula HA, MB, IMA, MIB, IVA, IVB, VA, VB, VIA or VIB are known or may be prepared according, e.g. analogously, to a method as conventional or as described herein.

Any compound described herein, e.g. a compound of the present invention and intermediates of formula NA, MB, IMA, NIB, IVA, IVB, VA, VB, VIA or VIB may be prepared as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. or as specified herein.

The compounds of the present invention, e.g. in free form or in the form of a salt, e.g. optionally in the form of a solvate, exhibit pharmacological activity and are therefore useful as pharmaceuticals.

The compounds of the present invention show agonistic activity on GPBAR1, and are prone for the treatment of disorders which are mediated by, e.g. dysfunctional, e.g. insufficient, GPBAR1 activity.

Pharmaceutical activity of the compounds of the present invention, e.g. may be shown in the cAMP Assay, e.g. GPBAR1 is a G\(_{\text{oS}}\)-coupled GPCR and ligands induce the formation of cAMP in cells expressing GPBAR1.

**cAMP Assay**

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine 3',5'-monophosphate</td>
</tr>
<tr>
<td>EC(_{50})</td>
<td>Agonist concentration that produces 50% of the maximal effect</td>
</tr>
<tr>
<td>GPCR</td>
<td>G protein-coupled receptor</td>
</tr>
<tr>
<td>G(_{\text{oS}})</td>
<td>Adenylate cyclase-stimulating G protein</td>
</tr>
<tr>
<td>GFP</td>
<td>Green fluorescent protein</td>
</tr>
<tr>
<td>HBSS</td>
<td>Hanks' Balanced Salt Solution</td>
</tr>
<tr>
<td>HTRF</td>
<td>Homogeneous Time-Resolved Fluorescence</td>
</tr>
<tr>
<td>FRET</td>
<td>Fluorescence Resonance Energy Transfer</td>
</tr>
<tr>
<td>IBMX</td>
<td>3-isobutyl-1-methylxanthine</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
</tbody>
</table>

The human lymphoblastoid cell line Jurkat is transduced with a murine leukaemia based replication-defective retroviral vector construct to mediate stable expression of the ORP9651 cDNA. Briefly, the cDNA of the human GPBAR1 gene is cloned into the retroviral expression vector pMXpie, which contains an IRES (internal ribosomal entry site)-GFP expression
cassette and a puromycin resistance gene. Phoenix™-Ampho packaging cells are transfected using LipofectAMINE (Invitrogen) as described by the manufacturer. At 24 h after transfection, supernatants containing retrovirus are harvested and filtered (0.2 µm). For retroviral infection of Jurkat cell lines, 2 x 10⁶ cells are incubated with virus-containing supernatants supplemented with 10 µg/ml of Polybrene (Sigma). After 48 h of culture, Jurkat cells expressing high levels of GFP are collected by fluorescence-activated cell sorting and subsequently cultured in AIM-V serum-free medium (GIBCO BRL) containing 1 µg/ml puromycin, 1 IE/ml penicillin and 1 µg/ml streptomycin. Expression of the GPBAR1 gene is verified by RT-PCR.

Experiments to determine changes in cAMP after compound addition to Jurkat cells expressing GPBAR1 are performed with the HTRF kit from CIS Bio International (Bagnols sur Ceze, France). The method is based on a competitive immunoassay between native cAMP produced by cells and added cAMP labeled with XL665 and is performed according to instructions by the manufacturer in 384 well black FIA plates (Greiner) and a final volume of 20 µl per well. Briefly, assay plates containing 5 µl of cell suspension, adjusted to 1x10⁶ cells per ml HBSS (GIBCO BRL) containing 1mM IBMX (Sigma), and 5 µl of compound dilution are incubated at RT for 30 minutes in a humidified box to stimulate cAMP production. The total cAMP concentration in cells is analyzed by adding 5 µl CAMP-XL655 and 5 µl of anti-cAMP-Cryptate antibody solution, both pre-diluted 1:20 in conjugation/lysis buffer, as supplied by the manufacturer. After another incubation for 1 hour in a humidified box FRET, measurements are performed with the PHERAstar (BMT Labtech) plate reader (excitation 337 nm, emission 620 and 665 nm). Data are calculated from intensities of emitted light filtered at two wavelengths L1 (665 nM) and L2 (620 nM) as the ratio L1/L2 and normalised by ΔF = [(sample ratio - negative ratio)/ negative ratio] x 100.

The selectivity of compounds for GPBAR1 is determined in cAMP assays using a Jurkat control cell line generated by transduction of empty pMXpie vector following exactly the same protocol as described above. All compounds are inactive up to a concentration of 20 µM in that cell line.

The specific GPBAR1 compounds of the present invention exhibit EC₅₀ values in the cAMP Assay as described above, from the low nanomolar range up to low micromolar range, e.g. 0.5 nM up to 25 µM. The compounds of the present are therefore prone to be useful for the treatment of disorders mediated by GPBAR1 activity, e.g. insufficient GPBAR1 activity.
Disorders as used herein include diseases. Disorders mediated by GPBAR1 activity which are prone to be successfully treated with GPBAR1 agonists, e.g. with a specific GPBAR1 activating compound of the present invention, include disorders, wherein the activity of GPBAR1 play a causal or contributory role, such as immune responses initiated by dendritic cells (DCs), monocytes or lymphocytes.

Such disorders e.g. include, but are not limited to

- **disorders associated with inflammation**
  e.g. including (chronic) inflammatory disorders, disorders related with the inflammation of the bronchi, e.g. including bronchitis, cervix, e.g. including cervicitis, conjunctiva, e.g. conjunctivitis, esophagus, e.g. esophagitis, heart muscle, e.g. myocarditis, rectum, e.g. proctitis, sclera, e.g. scleritis, gums, involving bone, pulmonary inflammation (alveolitis), airways, e.g. asthma, such as bronchial asthma, acute respiratory distress syndrome (ARDS), inflammatory skin disorders such as contact hypersensitivity, atopic dermatitis; fibrotic disease (e.g., pulmonary fibrosis), encephalitis, inflammatory osteolysis,
- **disorders associated with conditions of the immune system,**
  immune, such as autoimmune disorders e.g. including Graves’ disease, Hashimoto’s disease (chronic thyroiditis), multiple sclerosis, rheumatoid arthritis, arthritis, gout, osteoarthritis, scleroderma, lupus syndromes, systemic lupus erythematosus, Sjoegren’s syndrome, psoriasis, inflammatory bowel disease, including Crohn’s disease, colitis, e.g. ulcerative colitis; sepsis, septic shock, autoimmune hemolytic anemia (AHA), autoantibody triggered urticaria, pemphigus, nephritis, glomerulonephritis, Goodpastur syndrome, ankylosing spondylitis, Reiter’s syndrome, polymyositis, dermatomyositis, cytokine-mediated toxicity, interleukin-2 toxicity, alopecia areata, uveitis, lichen planus, bullous pemphigoid, myasthenia gravis, type I diabetes mellitus, immune-mediated infertility such as premature ovarian failure, polyglandular failure, hypothyroidism, pemphigus vulgaris, pemphigus l-oliaceus, paraneoplastic pemphigus, autoimmune hepatitis including that associated with hepatitis B virus (HBV) and hepatitis C virus (HCV), Addison’s disease, autoimmune skin diseases, such as psoriasis, dermatitis herpetiformis, epidermolysis bullosa, linear IgA bullous dermatosis, epidermolysis bullosa acquisita, chronic bullous disease of childhood, pernicious anemia, hemolytic anemia, vitiligo, type I, type II and type III autoimmune polyglandular syndromes, Autoimmune Hypoparathyroidism, Autoimmune Hypophysitis, Autoimmune Oophoritis, Autoimmune Orchitis, pemphigoid gestationis, cicatrical pemphigoid, mixed essential
cryoglobulinemia, immune thrombocytopenic purpura, Goodpasture's syndrome, autoimmune neutropenia, Eaton-Lambert myasthenic syndrome, stiff-man syndrome, encephalomyelitis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, cerebellar degeneration, retinopathy, primary biliary sclerosis, sclerosing cholangitis, autoimmune hepatitis, gluten-sensitive enteropathy, reactive arthritides, polymyositis/dermatomyositis, mixed connective tissue disease, Bechefs syndrome, polyarteritis nodosa allergic angitis and granulomatosis (Churg-Strauss disease), polyangiitis overlap syndrome (hypersensitivity) vasculitis, Wegener's granulomatosis, temporal arteritis Kawasaki's disease, sarcoidosis, cryopathies, Celiac disease,

- disorders associated with cytokine-mediated toxicity,
  e.g. including interleukin-2 toxicity,

- disorders associated with the bone,
  e.g. including osteoporosis, osteoarthritis,

- disorders associated with the brain and the nerves,
  - neurodegenerative disorders, e.g. including disorders of the central nervous system as well as disorders of the peripheral nervous system, e.g. CNS disorders including central nervous infections, brain injuries, cerebrovascular disorders and their consequences, Parkinson's disease, corticobasal degeneration, motor neuron disease, dementia including ALS, multiple sclerosis, traumatic disorders, including trauma and inflammatory consequences of trauma, traumatic brain injury, stroke, post-stroke, post-traumatic brain injury, small-vessel cerebrovascular disease, eating disorders; further dementias, e.g. including Alzheimer's disease, vascular dementia, dementia with Lewy-bodies, frontotemporal dementia and Parkinsonism linked to chromosome 17, frontotemporal dementias, including Pick's disease, progressive nuclear palsy, corticobasal degeneration, Huntington's disease, thalamic degeneration, Creutzfeld Jakob dementia, HIV dementia, schizophrenia with dementia, Korsakoff's psychosis, cognitive-related disorders, such as mild cognitive impairment, age-associated memory impairment, age-related cognitive decline, vascular cognitive impairment, attention deficit disorders, attention deficit hyperactivity disorders, and memory disturbances in children with learning disabilities; conditions associated with the hypothalamic-pituitary-adrenal axis, neuronal disorders, e.g. including neuronal migration disorders, hypotonia (reduced muscle tone), muscle weakness, seizures, developmental delay (physical or mental development...
difficulty), mental retardation, growth failure, feeding difficulties, lymphedema,
Difficulty), mental retardation, growth failure, feeding difficulties, lymphedema,
microcephaly, symptoms affecting the head and the brain, motor dysfunction;

- disorders associated with the eye,
e.g. including uveitis, vitreoretinopathy, corneal disease, iritis, iridocyclitis, cateracts,
uveitis, diabetic retinopathy, retinitis pigmentosa, conjunctivitis, keratitis,

- disorders associated with the gastrointestinal tract
e.g. including colitis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, peptic ulceration, gastritis, oesophagitis,

- disorders associated with the heart and vascular conditions
e.g. including cardiovascular disorders, e.g. including cardiac failure, cardiac infarction, cardiac hypertrophy, heart failure, e.g. including all forms of heart pumping failures such as high-output and low-output, acute and chronic, right sided or left-sided, systolic or diastolic, independent of the underlying cause; myocardial infarction (MI), MI prophylaxis (primary and secondary prevention), acute treatment of MI, prevention of complications; heart disorders, proliferative vascular disorders, vasculitides, polyarteritis nodosa, inflammatory consequences of ischemia, ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease, pulmonary hypertension, ischemic disorders, e.g. including myocardial ischemia, e.g. stable angina, unstable angina, angina pectoris, bronchitis; asymptomatic arrhythmias such as all forms of atrial and ventricular tachyarrhythmias, atrial tachycardia, atrial flutter, atrial fibrillation, atrio-ventricular reentrant tachycardia, preexitation syndrome, ventricular tachycardia, ventricular flutter, ventricular fibrillation, bradycardic forms of arrhythmias; arrhythmia, chronic obstructive pulmonary disease, hypertension, such as systolic or diastolic high blood pressure, e.g essential and secondary hypertension, e.g. including hypertensive vascular disorders, such as primary as well as all kinds of secondary arterial hypertension, renal, endocrine, neurogenic and others; peripheral vascular disorders in which arterial and/or venous flow is reduced resulting in an imbalance between blood supply and tissue oxygen demand, e.g. including atherosclerosis, chronic peripheral arterial occlusive disease (PAOD), acute arterial thrombosis and embolism, inflammatory vascular disorders, Raynaud’s phenomenon and venous disorders; atherosclerosis, a disease in which the vessel wall is remodeled, e.g. including accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in the intima of the vessel wall; hypotension,
- disorders associated with the liver and the kidneys,
e.g. including renal disorders, kidney disorders, e.g. acute kidney failure, acute renal
disease, liver disorders, e.g. cirrhosis, hepatitis, liver failure, cholestasis, acute/chronic
hepatitis, sclerosing cholangitis, primary biliary cirrhosis, acute/chronic
interstitial/glomerulonephritis, granulomatous diseases,

-disorders associated with stomach or pancreas conditions
 e.g. including stomach disorders, e.g. gastric ulcer, gastrointestinal ulcer, pancreatic
disorders, pancreatic fatigue,

-disorders associated with the respiratory tract and lung
 e.g. including pulmonary disorders, chronic pulmonary disease, acute (adult) respiratory
distress syndrome (ARDS), asthma, asthma bronchitis, bronchiectasis, diffuse interstitial
lung disorders, pneumoconioses, fibrosing aveolitis, lung fibrosis,

-disorders associated with skin and connective tissue conditions
 e.g. including eczema, atopic dermatitis, contact dermatitis, psoriasis, acne,
dermatomyositis, Sjögren's syndrome, Churg-Strauss syndrome, sunburn, skin cancer,
wound healing, urticaria, toxic epidermal necrolysis,

-disorders associated with allergic conditions,
 e.g. including delayed-type hypersensitivity, allergic conjunctivitis, drug allergies, rhinitis,
alergic rhinitis, vasculitis, contact dermatitis;

-disorders associated with angiogenesis,
 e.g. including insufficient ability to recruit blood supply, disorders characterized by odified
angiogenesis, tumor associated angiogenesis,

-disorders associated with cancer and cell overproliferation,
 e.g. including premalignant conditions, hyperproliferative disorders, all type of cancers,
cancers whether primary or metastatic, cervical and metastatic cancer, cancer originating
from uncontrolled cellular proliferation, solid tumors, unresponsiveness to normal death-
inducing signals (immortalization), increased cellular motility and invasiveness, increased
ability to recruit blood supply through induction of new blood vessel formation
(angiogenesis), genetic instability, dysregulated gene expression, solid tumors, such as
described in WO02066019, including non-small cell lung cancer, cervical cancer; tumor
growth, lymphoma, B-cell or T-cell lymphoma, benign tumors, benign dysproliferative
disorders, renal carcinoma, esophageal cancer, stomach cancer, renal carcinoma, bladder
cancer, breast cancer, colon cancer, lung cancer, melanoma, nasopharyngeal cancer,
osteocarcinoma, ovarian cancer, uterine cancer; prostate cancer, skin cancer, leukemia,
tumor neovascularization, angiomas, myelodysplastic disorders, unresponsiveness to normal death-inducing signals (immortalization), increased cellular motility and invasiveness, genetic instability, dysregulated gene expression, (neuro)endocrine cancer (carcinoids), blood cancer, lymphocytic leukemias, neuroblastoma; soft tissue cancer, cancer prevention, e.g. prevention of metastasis,

- disorders associated with infectious disorders, e.g. with chronic infectious conditions,
  e.g. including bacterial disorders, otitis media, Lyme disease, thyroditis, viral disorders, parasitic disorders, fungal disorders, malaria, e.g. malaria anemia, sepsis, severe sepsis, septic shock, e.g. endotoxin-induced septic shock, exotoxin-induced toxic shock, infective (true septic) shock, septic shock caused by Gram-negative bacteria, pelvic inflammatory disease, AIDS, enteritis, pneumonia; meningitis, encephalitis,

- disorders associated with myasthenia gravis,

- disorders associated with nephritis,
  e.g. including glomerulonephritis, interstitial nephritis, Wegener's granulomatosis, fibrosis,

- disorders associated with diabetic conditions,
  e.g. including diabetes (type I diabetes, type II diabetes, gestational diabetes), diabetic retinopathy, insulin-dependent diabetes, diabetes mellitus, gestational diabetes), insulin hyposcretion, obesity;

- disorders associated with endometriosis, testicular dysfunctions,

- disorders associated with pain,
  e.g. associated with CNS disorders, such as multiple sclerosis, spinal cord injury, sciatica, failed back surgery syndrome, traumatic brain injury, epilepsy, Parkinson's disease, post-stroke, and vascular lesions in the brain and spinal cord (e.g., infarct, hemorrhage, vascular malformation);
  non-central neuropathic pain, e.g. including that associated with post mastectomy pain, phantom feeling, reflex sympathetic dystrophy (RSD), trigeminal neuralgialradioculopathy, post-surgical pain, HIV/AIDS related pain, cancer pain, metabolic neuropathies (e.g., diabetic neuropathy, vasculitic neuropathy secondary to connective tissue disease),
  paraneoplastic polyneuropathy associated, for example, with carcinoma of lung, or leukemia, or lymphoma, or carcinoma of prostate, colon or stomach, trigeminal neuralgia, cranial neuralgias, and post-herpetic neuralgia;
pain associated with peripheral nerve damage, central pain (i.e. due to cerebral ischemia) and various chronic pain i.e. lumbago, back pain (low back pain), inflammatory and/or rheumatic pain; headache pain (for example, migraine with aura, migraine without aura, and other migraine disorders), episodic and chronic tension-type headache, tension-type like headache, cluster headache, and chronic paroxysmal hemicrania; visceral pain such as pancreatitis, intestinal cystitis, dysmenorrhea, irritable Bowel syndrome, Crohn's disease, biliary colic, ureteral colic, myocardial infarction and pain syndromes of the pelvic cavity, e.g., vulvodynia, orchialgia, urethral syndrome 15 and protatodynia; acute pain, for example postoperative pain, and pain after trauma;

- disorders associated with rheumatic disorders,
e.g. including arthritis, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, crystal arthropathies, gout, pseudogout, calcium pyrophosphate deposition disease, lupus syndromes, systemic lupus erythematousus, sclerosis, sclerodema, multiple sclerosis, artherosclerosis, arteriosclerosis, spondylarthropathies, systemic sclerosis, reactive arthritis, Reiter's syndrome, ankylosing spondylitis, polymyositis,

- disorders associated with sarcoidosis,

- disorders associated with transplantation,
e.g. including transplant rejection crisis and other disorders following transplantation, such as organ or tissue (xeno)transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, corneal transplants, graft versus host disease, such as following bone marrow transplantation, ischemic reperfusion injury,

Disorders mediated by, e.g. insufficient, GPBAR1 activity which are prone to be successfully treated with GPBAR1 agonists, such as a compound of the present invention, preferably include inflammatory, immune, e.g. autoimmune and allergic disorders, such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erytomatosus, multiple sclerosis, transplant rejection crisis, psoriasis, cancer, AIDS, diabetes (diabetes type II), obesity; more preferably rheumatoid arthritis, systemic lupus erytomatosus, multiple sclerosis, psoriasis, diabetes (diabetes type II), obesity; e.g. psoriasis.
In another aspect the present invention provides
- a compound of the present invention for use as a pharmaceutical,
- the use of a compound of the present invention as a pharmaceutical;
e.g. for the treatment of disorders mediated by, e.g. insufficient, GPBAR1 activity.

For pharmaceutical use one or more compounds of the present invention may be used, e.g. one, or a combination of two or more compounds of the present invention.
A compound of the present invention may be used as a pharmaceutical in the form of a pharmaceutical composition.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutically acceptable excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrators, flow conditioners, lubricants, sugars or sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers.

A pharmaceutical composition provided by the present invention is herein also designated as "pharmaceutical composition of (according to) the present invention".

In another aspect the present invention provides
- a pharmaceutical composition of the present invention for use of treating disorders which are mediated by, e.g. insufficient, GPBAR1 activity;
- the use of a pharmaceutical composition of the present invention for treating disorders which are mediated by, e.g. insufficient, GPBAR1 activity,

In a further aspect the present invention provides a method of treating disorders which are mediated by, e.g. insufficient, GPBAR1 activity, e.g. including disorders as specified above, which treatment comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of the present invention; e.g. in the form of a pharmaceutical composition.

In another aspect the present invention provides
- a compound of the present invention for the manufacture of a medicament,
- the use of a compound of the present invention for the manufacture of a medicament,
e.g. wherein the medicament comprises a pharmaceutical composition according to the
present invention,
for the treatment of disorders, which are mediated by, e.g. insufficient, GPBAR1 activity.

Treatment includes treatment and prophylaxis (prevention).
For such treatment, the appropriate dosage will, of course, vary depending upon, for
example, the chemical nature and the pharmacokinetic data of a compound of the present
invention used, the individual host, the mode of administration and the nature and severity of
the conditions being treated. However, in general, for satisfactory results in larger mammals,
for example humans, an indicated daily dosage includes a range
- from about 0.001 g to about 1.5 g, such as 0.001 g to 1.5 g;
- from about 0.01 mg/kg body weight to about 20 mg/kg body weight, such as 0.01 mg/kg
body weight to 20 mg/kg body weight,
for example administered in divided doses up to four times a day.

A compound of the present invention may be administered to larger mammals, for example
humans, by similar modes of administration, e.g. at similar dosages, than conventionally
used or indicated for other mediators, e.g. low molecular weight activators, of GPBAR1
activity.

A compound of the present invention may be administered by any conventional route, for
example enterally, e.g. including nasal, buccal, rectal, oral administration; parenterally, e.g.
including intravenous, intraarterial, intramuscular, intracardiac, subcutaneous, intraosseous
infusion, transdermal (diffusion through the intact skin), transmucosal (diffusion through a
mucous membrane), inhalational administration; topically; e.g. including epicutaneous,
intranasal, intratracheal administration; intraperitoneal (infusion or injection into the
peritoneal cavity); epidural (peridural) (infusion or injection into the epidural space);
intrathecal (infusion or injection into the cerebrospinal fluid); intravitreal (administration via
the eye); or via medical devices, e.g. for local delivery, e.g. stents,
e.g. in form of coated or uncoated tablets, capsules, (injectable) solutions, solid solutions,
suspensions, dispersions, solid dispersions; e.g. in the form of ampoules, vials, in the form
of creams, gels, pastes, inhaler powder, foams, tinctures, lip sticks, drops, sprays, or in the
form of suppositories.
A compound of the present invention may be administered in the form of a pharmaceutically acceptable salt, or in free form; optionally in the form of a solvate. A compound of the present invention in the form of a salt and/or in the form of a solvate exhibit the same order of activity as a compound of the present invention in free form.

For topical use, e.g. including administration to the eye, satisfactory results may be obtained with local administration of a 0.5-10 %, such as 1-3% concentration of active substance several times daily, e.g. 2 to 5 times daily.

A compound of the present invention may be used for any method or use as described herein alone or in combination with one or more, at least one, other, second drug substance.

In another aspect the present invention provides
- A combination of a compound of the present invention with at least one second drug substance;
- A pharmaceutical combination comprising a compound of the present invention in combination with at least one second drug substance;
- A pharmaceutical composition comprising a compound of the present invention in combination with at least one second drug substance and one or more pharmaceutically acceptable excipient(s);
- A compound of the present invention in combination with at least one second drug substance, e.g. in the form of a pharmaceutical combination or composition, for use in any method as defined herein, e.g.

- A combination, a pharmaceutical combination or a pharmaceutical composition, comprising a compound of the present invention and at least one second drug substance for use as a pharmaceutical;
- The use as a pharmaceutical of a compound of the present invention in combination with at least one second drug substance, e.g. in the form of a pharmaceutical combination or composition;

- The use of a compound of the present invention for the manufacture of a medicament for use in combination with a second drug substance,
- A method for treating disorders mediated by, e.g. insufficient, GPBAR1 activity in a subject in need thereof, comprising co-administering, concomitantly or in sequence, a therapeutically effective amount of a compound of the present invention and at least one
second drug substance, e.g. in the form of a pharmaceutical combination or composition;
- A compound of the present invention in combination with at least one second drug
substance, e.g. in the form of a pharmaceutical combination or composition, for use in the
preparation of a medicament for use in disorders mediated by, e.g. insufficient, GPBAR1
activity.

Combinations include fixed combinations, in which a compound of the present invention and
at least one second drug substance are in the same formulation; kits, in which a compound
of the present invention and at least one second drug substance in separate formulations
are provided in the same package, e.g. with instruction for co-administration; and free
combinations in which a compound of the present invention and at least one second drug
substance are packaged separately, but instruction for concomitant or sequential
administration are given.

In another aspect the present invention provides
- A pharmaceutical package comprising a first drug substance which is a compound of the
present invention and at least one second drug substance, beside instructions for
combined administration;
- A pharmaceutical package comprising a compound of the present invention beside
instructions for combined administration with at least one second drug substance;
- A pharmaceutical package comprising at least one second drug substance beside
instructions for combined administration with a compound of the present invention.;

Treatment with combinations according to the present invention may provide improvements
compared with single treatment.

In another aspect the present invention provides
- A pharmaceutical combination comprising an amount of a compound of the present
invention and an amount of a second drug substance, wherein the amounts are appropriate
to produce a synergistic therapeutic effect;
- A method for improving the therapeutic utility of a compound of the present invention
comprising co-administering, e.g. concomitantly or in sequence, of a therapeutically
effective amount of a compound of the present invention and a second drug substance.
A method for improving the therapeutic utility of a second drug substance comprising co-administering, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the present invention and a second drug substance.

A combination of the present invention and a second drug substance as a combination partner may be administered by any conventional route, for example as set out above for a compound of the present invention. A second drug may be administered in dosages as appropriate, e.g. in dosage ranges which are similar to those used for single treatment, or, e.g. in case of synergy, even below conventional dosage ranges.

Pharmaceutical compositions according to the present invention may be manufactured according, e.g. analogously, to a method as conventional, e.g. by mixing, granulating, coating, dissolving or lyophilizing processes. Unit dosage forms may contain, for example, from about 0.1 mg to about 1500 mg, such as 1 mg to about 1000 mg.

Pharmaceutical compositions comprising a combination of the present invention and pharmaceutical compositions comprising a second drug as described herein, may be provided as appropriate, e.g. according, e.g. analogously, to a method as conventional, or as described herein for a pharmaceutical composition of the present invention.

By the term "second drug substance" is meant a chemotherapeutic drug, especially any chemotherapeutic agent other than a compound of the present invention.

For example, a second drug substance as used herein includes anti-inflammatory and/or immunomodulatory and/or anticancer drugs, e.g. including antiviral drugs, e.g. and/or anesthetics.

Anti-inflammatory and/or immunomodulatory drugs which are prone to be useful in combination with a compound of the present invention e.g include mediators, e.g. inhibitors, of mTOR activity, including rapamycin of formula
and rapamycin derivatives, e.g. including
40-O-alkyl-rapamycin derivatives, such as 40-O-hydroxyalkyl-rapamycin derivatives, such as 40-O-(2-hydroxy)-ethyl-rapamycin (everolimus),

32-deoxo-rapamycin derivatives and 32-hydroxy-rapamycin derivatives, such as 32-deoxorapamycin,

16-0-substituted rapamycin derivatives such as 16-pent-2-ynyloxy-32-deoxorapamycin,
16-pent-2-ynyloxy-32 (S or R) -dihydro-rapamycin, 16-pent-2-ynyloxy-32(S or R)-dihydro-40-O-(2-hydroxyethyl)-rapamycin,

rapamycin derivatives which are acylated at the oxygen group in position 40, e.g. 40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-rapamycin (also known as CCI779), rapamycin derivatives which are substituted in 40 position by heterocycl, e.g. 40-epi-(tetrazolyl)-rapamycin (also known as ABT578),
the so-called rapalogs, e.g. as disclosed in WO9802441, WO01 14387 and WO0364383, such as AP23573, and
compounds disclosed under the name TFAA-93, AP23464, AP23675, AP23841 and biolimus (e.g. biolimus A9).
- mediators, e.g. inhibitors, of calcineurin, e.g. cyclosporin A, FK 506, ISA-247 (voclosporin);
- ascomycins having immuno-suppressive properties, e.g. ABT-281, ASM981;
- corticosteroids; cyclophosphamide; cyclophosphamid IV (Revimmune®), azathioprene;
leflunomide; mizoribine;
- mycophenolic acid or salt; e.g. sodium, mycophenolate mofetil;
- 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof;
- mediators, e.g. inhibitors, of bcr-abl tyrosine kinase activity;
- mediators, e.g. inhibitors, of c-kit receptor tyrosine kinase activity;
- mediators, e.g. inhibitors, of PDGF receptor tyrosine kinase activity, e.g. Gleevec (imatinib);
- mediators, e.g. inhibitors, of p38 MAP kinase activity,
- mediators, e.g. inhibitors, of VEGF receptor tyrosine kinase activity,
- mediators, e.g. inhibitors, of PKC activity, e.g. as disclosed in WO0238561 or WO0382859, e.g. the compound of Example 56 or 70;
- mediators, e.g. inhibitors, of JAK3 kinase activity, e.g. N-benzyl-3,4-dihydroxy-benzylidenecyanoacetamide α-cyano-(3,4-dihydroxy)-]N-benzylcinnamamide (Tyrphostin AG 490), prodigiosin 25-C (PNU 156804), [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P131), -(S'-bromo^-'-hydroxylphenyO-amino-6J-dimethoxyquinazoline) WHI-P154, [4-(3',5'-dibromo^-'-hydroxylphenyO-amino-6J-dimethoxyquinazoline] WHI-P97, KRX-21 1, 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate (also called CP-690,550), or a compound as disclosed in WO2004052359 or WO2005066156;
- mediators, e.g. agonists or modulators of S1P receptor activity, e.g. FTY720 optionally phosphorylated or an analog thereof, e.g. 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol optionally phosphorylated or 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid or its pharmaceutically acceptable salts;
- immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g. Blys receptor, such as belimumab, lymphostat B, BAFF receptor, MHC, CD2, CD3, e.g. visilizumab, CD4, e.g. zanolimumab, CD7, CD8, CD1 1a, e.g. efalizumab (Raptiva®), CD20, e.g. rituximab (Rituxan®), ibritumomab tiuxetan conjugated to 111In or 90Y (Zevalin®), 131I tositumumab (Bexxa®), CD25, CD28, CD33, e.g. gemtuzumab (Mylotarg®), CD40, e.g. ant-CD40L or anti CD154 such as IDEC-131, CD45, CD52, CD54, e.g. Alemtuzumab (Campath-1®), CD58, CD80, CD86, IL-2 receptor, e.g. daclizumab (Zenapax®), IL6 receptor (e.g. tocilizumab, Actemra®), IL-12 receptor, IL-17 receptor, IL-23 receptor or their ligands; e.g. antibodies to IL-12, IL-23, such as CNTO 1275 (IL-12/IL23 imAb), IL-10, such as B-N10, e.g. antibodies to double-stranded DNA (dsDNA), such as abetimus sodium (Riquent®)),
- other compounds affecting the immune system, such as
- a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4lg (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; or an anti-CTLA4 agent, such as ipilimumab, ticitilimumab,
- glatirameracetat (copolymer-1, Copaxone®),
- MBP8298 (a synthetic peptide),
- laquinimod (ABR-215062),
- vaccines having immunomodulatory activity, e.g. Tovaxin®, NeuroVax®,
- pirfenidone,
- BG-12 (an oral fumarate),
- mediators, e.g. inhibitors of adhesion molecule activities, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists,
- mediators, e.g. antagonists of CCR9 activity,
- mediators, e.g. inhibitors, of MIF activity,
- 5-aminosalicylate (5-ASA) agents, such as sulfasalazine, Azulfidine®, Asacol®, Dipentum®, Pentasa®, Rowasa®, Canasa®, Colazal®, e.g. drugs containing mesalamine; e.g mesalamine in combination with heparin;
- mediators, e.g. inhibitors, of TNF-alpha activity, e.g. including antibodies which bind to TNF-alpha, e.g. infliximab (Remicade®), thalidomide, lenalidomide, golimumab, adalimumab (Humira®, fully human immunoglobulin G (IgGl) monoclonal antibody that is specific for human TNF alpha), etanercept (Enbrel®), alefacept (Amevive®), certolizumab pegol (Cimzia®, CDP 870), afelimomab, AME527 (Lilly),
- nitric oxide releasing non-steriodal anti-inflammatory drugs (NSAIDs), e.g. including COX-inhibiting NO-donating drugs (CINOD);
- phosphodiesterase, e.g. mediators, such as inhibitors of PDE4B activity,
- mediators, e.g. inhibitors, of caspase activity,
- mediators, e.g. agonists, of the G protein coupled receptor GPBAR1,
- mediators, e.g. inhibitors, of ceramide kinase activity,
- "multi-functional anti-inflammatory drugs (MFAIDs), e.g. cytosolic phospholipase A2 (cPLA2) inhibitors, such as membrane-anchored phospholipase A2 inhibitors linked to glycosaminoglycans;
- antibiotics and antifungals, such as penicillins, cephalosporins, erythromycins, tetracyclines, sulfonamides, such as sulfadiazine, sulfisoxazole; sulfones, such as dapsone;
pleuromutilins, fluoroquinolones, e.g. metronidazole, quinolones such as ciprofloxacin; levofloxacin; probiotics, commensal bacteria e.g. Lactobacillus, Lactobacillus reuteri; micafungin,

- antiviral drugs, such as ribivirin, vidarabine, acyclovir, ganciclovir, zanamivir, oseltamivir phosphate, famciclovir, atazanavir, amantadine, didanosine, efavirenz, foscamet, indinavir, lamivudine, nelfinavir, ritonavir, saquinavir, stavudine, valacyclovir, valganciclovir, cicaic, zidovudine, antibodies against RSV protein, e.g. RSV F protein, such as palivizumab (Synagis®), motavizumab,

- mediators, e.g. inhibitors of the blood protein "complement 5(a)", such as eculizumab, pelxelizumab,

- serum phosphorus controlling agents, e.g. sevelamer carbonate (Renagel®), phosphate binders that reduces high serum phosphate levels in renal disease patients, such as lanthanum carbonate (Fosrenol®).

- mediators, e.g. agonists, of GPBAR1 mediator activity, e.g. including antibodies and low molecular weight compounds which are different from a specific GBP1R1 activating compound of the present invention,

- mediators, e.g. inhibitors of ceramide kinase activity, e.g. including antibodies and low molecular weight compounds,

- alpha-4-integrin antibodies, e.g. natalizumab (Tysabri®),

- an erythropoiesis stimulating protein, such as epoietin (Procrit®), EPOETIN ALFA, (Epogen®), darbepoetin alfa (Aranesp®).

Anti-inflammatory drugs which are prone to be useful in combination with a compound of the present invention include e.g. non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (almiprofen, benoxaprofen, buclocix acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miopron, naproxen, oxapozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, aclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicsams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); cyclooxygenase-2 (COX-2)
inhibitors such as celecoxib; inhibitors of phosphodiesterase type IV (PDE-IV); e.g. MN-166, antagonists of the chemokine receptors, especially CCR1, e.g. ZK81 1752 (BX-471), CCR2, and CCR3; cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibrate acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), and probucol; anticholinergic agents such as muscarinic antagonists (ipratropium bromide); other compounds such as theophylline, sulfasalazine and aminosalicylates, e.g. 5-aminosalicylic acid and prodrugs thereof, antirheumatics, IgE antibodies, e.g. omalizumab (Xolair®).

Antiallergic drugs which are prone to be useful in combination with a compound of the present invention include e.g. antihistamines (H1-histamine antagonists), e.g. bromopheniramine, chlorpheniramine, dextchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelemnamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azadatine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and non-steroidal anti-asthmatics such as £2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, poblukast, SKB-1 06,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); bronchodilators, antiasthmatics (mast cell stabilizers).

Anesthetics which are prone to be useful as a combination partner with a compound of the present invention e.g. include ethanol, bupivacaine, chlorprocaine, levobupivacaine, lidocaine, mepivacaine, procaine, ropivacaine, tetracaine, desflurane, isoflurane, ketamine, propofol, sevoflurane, codeine, fentanyl, hydromorphone, marcaine, meperidine, methadone, morphine, oxycodone, remifentanil, sufentanil, butorphanol, nalbuphine, tramadol, benzocaine, dibucaine, ethyl chloride, xylocaine, and phenazopyridine.

Anticancer drugs which are prone to be useful as a combination partner with which are prone to be useful in combination with a compound of the present invention, e.g. prone to be useful according to the present invention, e.g. include

i. a steroid; e.g. prednisone.
ii. an adenosine-kinase-inhibitor; which targets, decreases or inhibits nucleobase, nucleoside, nucleotide and nucleic acid metabolisms, such as 5-iodotubercidin, which is also known as 7H-pyrrolo[2,3-d]pyrimidin-4-amine, 5-iodo-7-β-D-ribofuranosyl.

iii. an adjuvant; which enhances the 5-FU-TS bond as well as a compound which targets, decreases or inhibits, alkaline phosphatase, such as leucovorin, levamisole; and other adjuvants used in cancer chemotherapy adjuvants, such as mesna (Uromitexan®, Mesnex®).

iv. an adrenal cortex antagonist; which targets, decreases or inhibits the activity of the adrenal cortex and changes the peripheral metabolism of corticosteroids, resulting in a decrease in 17-hydroxycorticosteroids, such as mitotane.

v. an AKT pathway inhibitor; such as a compound which targets, decreases or inhibits Akt, also known as protein kinase B (PKB), such as deguelin, which is also known as 3H-bis[1]benzopyrano[3,4-b:6',5'-e]pyran-7(7aH)-one, 13,13a-dihydro-9, 10-dimethoxy-3,3-dimethyl- (7aS, 13aS); and triciribine, which is also known as 1,4,5,6,8-pentaazaacenaphthylen-3-amine, 1,5-dihydro-5-methyl-1-E-D-ribofuranosyl; KP372-1 (QLT394).

vi. an alkylating agent; which causes alkylation of DNA and results in breaks in the DNA molecules as well as cross-linking of the twin strands, thus interfering with DNA replication and transcription of RNA, such as chlorambucil, chlorothemine, cyclophosphamide, ifosfamide, melphalan, estramustine; nitrosueras, such as carmustine, fotemustine, lomustine, streptozocin (streptozotocin, STZ), BCNU; Gliadel; dacarbazine, mechloethamine, e.g. in the form of a hydrochloride, procarbazine, e.g. in the form of a hydrochloride, thiopeta, temozolomide, nitrogen mustard, mitomycin, altretamine, busulfan, estramustine, uramustine. Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark CYCLOSTIN®, ifosfamide as HOLOXAN®, temozolomide as TEMODAR®, nitrogen mustard as MUSTARGEN®, estramustine as EMYCT®, streptozocin as ZANOSAR®.

vii. an angiogenesis inhibitor; which targets, decreases or inhibits the production of new blood vessels, e.g. which targets methionine aminopeptidase-2 (MetAP-2), macrophage inflammatory protein-1 (MIP-1 alpha), CCL5, TGF-beta, lipoxygenase, cyclooxygenase, and topoisomerase, or which indirectly targets p21, p53, CDK2 and collagen synthesis, e.g. including fumagillin, which is known as 2,4,6,8-decatetraenedioic acid, mono[3R,4S,5S,6R]-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranylo]-1-oxaspiro[2.5]oct-6-yl] ester, (2E,4E,6E,8E)- (9Cl);
shikonin, which is also known as 1,4-naphthalenedione, 5,8-dihydroxy-2-[(1 R)-1-hydroxy-4-methyl-3-pentenyl]- (9CI); tranilast, which is also known as benzoic acid, 2-[[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]amino]; ursolic acid; suramin; bengamide or a derivative thereof, thalidomide, TNP-470.

viii. an anti-androgen; which blocks the action of androgens of adrenal and testicular origin which stimulate the growth of normal and malignant prostatic tissue, such as nilutamide; bicalutamide (CASODEX®), which can be formulated, e.g., as disclosed in US4636505.

ix. an anti-estrogen; which antagonizes the effect of estrogens at the estrogen receptor level, e.g. including an aromatase inhibitor, which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively, e.g. including atamestane, exemestane, formestane, aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, letrozole, toremifene; bicalutamide; flutamide; tamoxifen, tamoxifen citrate; tamoxifen; fulvestrant; raloxifene, raloxifene hydrochloride. Tamoxifen may be e.g. administered in the form as it is marketed, e.g., NOLVADEX®; and raloxifene hydrochloride is marketed as EVISTA®. Fulvestrant may be formulated as disclosed in US4659516 and is marketed as FASLODEX®.

x. an anti-hypercalcemia agent; which is used to treat hypercalcemia, such as gallium (III) nitrate hydrate; and pamidronate disodium.

xi. an antimetabolite; which inhibits or disrupts the synthesis of DNA resulting in cell death, such as folic acids, e.g. methotrexate, pemetrexed, raltitrexed; purins, e.g. 6-mercaptopurine, cladribine, clofarabine; fludarabine, thioguanine (tioguanine), 6-thioguanine, nelarabine (compound 506), tiazofurin (inhibits inosine monophosphate dehydrogenase and guanosine triphosphate pools), pentostatin (deoxycoformycin); cytarabine; flexuridine; fluorouracil; 5-fluorouracil (5-FU), flouxuridine (5-FUdR), capecitabine; gemcitabine; gemcitabine hydrochloride; hydroxyurea (e.g. Hydrea®); DNA de-methylating agents, such as 5-azacytidine (Vidaza®) and decitabine; fluoromethylene deoxyctydite (FmdC), 5-aza-2'-deoxycytidine, troxactabine (L-isomer cytosine analogue), edatrexate. Capecitabine and gemcitabine can be administered e.g. in the marketed form, such as XELODA® and GEMZAR®.

xii. an apoptosis inducer; which induces the normal series of events in a cell that leads to its death, e.g. selectively inducing the X-linked mammalian inhibitor of apoptosis
protein XIAP, or e.g. downregulating BCL-xL; such as ethanol, 2-[[3-(2,3-dichlorophenoxy)propyl]amino]; gambogenic acid; embelin, which is also known as 2,5-cyclohexadiene-1,4-dione, 2,5-dihydroxy-3-undecyl- (9CI); arsenic trioxide arsenic trioxide (TRISENOX®).

xiii. an aurora kinase inhibitor; which targets, decreases or inhibits later stages of the cell cycle from the G2/M check point all the way through to the mitotic checkpoint and late mitosis; such as binucleine 2, which is also known as methanimidamide, N'-[1-(3-chloro^-fluorophenylH-cyano-I H-pyrazol-5-yll-N,N-dimethyl- (9CI).

xiv. a Bruton's Tyrosine Kinase (BTK) inhibitor; which targets, decreases or inhibits human and murine B cell development; such as terreic acid.

xv. a calcineurin inhibitor; which targets, decreases or inhibits the T cell activation pathway, such as cypermethrin, which is also known as cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-cyano(3-phenoxyphenyl)methyl ester; deltamethrin, which is also known as cyclopropanecarboxylic aci, 3-(2,2-dibromoethenyl)-2,2-dimethyl-(S)-cyano(3-phenoxyphenyl)methyl ester, (+R.3R); fenvalerate, which is also known as benzeneacetic acid, 4-chloro-α-(1-methylethyl)-,cyano(3-phenoxyphenyl)methyl ester; and Tyrphostin 8; but excluding cyclosporin or FK506.

xvi. a CaM kinase II inhibitor; which targets, decreases or inhibits CaM kinases; constituting a family of structurally related enzymes that include phosphorylase kinase, myosin light chain kinase, and CaM kinases I-IV; such as 5-isoquinolinesulfonic acid, 4-[(2S)-2-[(5-isoquinolinylsulfonyl)methylamino]-3-oxo-3-(4-phenyl-1-piperazinyl)propyl]phenyl ester (9CI); benzenesulfonamide, N-[2-[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl[phenyl]-N-(2-hydroxyethyl)-4-methoxy.

xvii. a CD45 tyrosine phosphatase inhibitor; which targets, decreases or inhibits dephosphorylating regulatory pTyr residues on Src-family protein-tyrosine kinases, which aids in the treatment of a variety of inflammatory and immune disorders; such as phosphonic acid, [[2-(4-bromophenoxy)-5-nitrophenyl]hydroxymethyl).

xviii. a CDC25 phosphatase inhibitor; which targets, decreases or inhibits overexpressed dephosphorylate cyclin-dependent kinases in tumors; such as 1,4-naphthalenedione, 2,3-bis[2-hydroxyethyl]thio).

xix. a CHK kinase inhibitor; which targets, decreases or inhibits overexpression of the antiapoptotic protein Bcl-2; such as debromohymenialdisine. Targets of a CHK kinase inhibitor are CHK1 and/or CHK2.
xx. a controlling agent for regulating genistein, olomucine and/or tyrphostins; such as daidzein, which is also known as 4H-1-benzopyran-4-one, 7-hydroxy-3-(4-hydroxyphenyl); Iso-Olomoucine, and Tyrphostin 1.

xxi. a cyclooxygenase inhibitor; e.g. including Cox-2 inhibitors; which targets, decreases or inhibits the enzyme Cox-2 (cyclooxygenase-2); such as 1H-indole-3-acetamide, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-N-(2-phenylethyl); 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, e.g. celecoxib (CELEBREX®), rofecoxib (VIOXX®), etoricoxib, valdecoxib; or a 5-alkyl-2-arylaminophenylacetic acid, e.g., 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib; and celecoxib.

xxii. a cRAF kinase inhibitor; which targets, decreases or inhibits the up-regulation of E-selectin and vascular adhesion molecule-1 induced by TNF; such as 3-(3,5-dibromo-4-hydroxybenzylidene)-5-iodo-1,3-dihydroindol-2-one; and benzamide, 3-(dimethylamino)-N-[3-[4-hydroxybenzoyl]amino]-4-methylphenyl. Raf kinases play an important role as extracellular signal-regulating kinases in cell differentiation, proliferation, and apoptosis. A target of a cRAF kinase inhibitor includes, but is not limited, to RAF1.

xxiii. a cyclin dependent kinase inhibitor; which targets, decreases or inhibits cyclin dependent kinase playing a role in the regulation of the mammalian cell cycle; such as N9-isopropyl-olomoucine; olomoucine; purvalanol B, which is also known as Benzoic acid, 2-chloro-4-[[2-[[1 R]-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]-9Cl); roascovitine; indirubin, which is also known as 2H-indol-2-one, 3-(1,3-dihydro-3-oxo-2H-indol-2-ylidene)-1,3-dihydro-9Cl); kenpaullone, which is also known as indolo[3,2-d][1]benzazepin-6(5H)-one, 9-bromo-7,12-dihydro-9Cl); purvalanol A, which is also known as 1-Butanol, 2-[[6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)-9Cl); indirubin-3'-monooxime. Cell cycle progression is regulated by a series of sequential events that include the activation and subsequent inactivation of cyclin dependent kinases (Cdks) and cyclins. Cdks are a group of serine/threonine kinases that form active heterodimeric complexes by binding to their regulatory subunits, cyclins. Examples of targets of a cyclin dependent kinase inhibitor include, but are not limited to, CDK, AHR, CDK1, CDK2, CDK5, CDK4/6, GSK3beta, and ERK.

xxiv. a cysteine protease inhibitor; which targets, decreases or inhibits cysteine protease which plays a vital role in mammalian cellular turnover and apoptosis; such as 4-
morpholinecarboxamide, N-[(1S)-3-fluoro-2-oxo-1-(2-phenylethyl)propyl]amino]-2-oxo-1-(phenyl methyl)ethyl.

xxv. a DNA intercalator; which binds to DNA and inhibits DNA, RNA, and protein synthesis; such as plicamycin, dactinomycin.

xxvi. a DNA strand breaker; which causes DNA strand scission and results in inhibition of DNA synthesis, inhibition of RNA and protein synthesis; such as bleomycin.

xxvii. an E3 Ligase inhibitor; which targets, decreases or inhibits the E3 ligase which inhibits the transfer of ubiquitin chains to proteins, marking them for degradation in the proteasome; such as N-((3,3,3-trifluoro-2-trifluoromethyl)propionyl)sulfanilamide.

xxviii. an endocrine hormone; which by acting mainly on the pituitary gland causes the suppression of hormones in males, the net effect being a reduction of testosterone to castration levels; in females, both ovarian estrogen and androgen synthesis being inhibited; such as leuprolide; megestrol, megestrol acetate,

xxix. compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, (HER-2), ErbB3, ErbB4 as homo- or heterodimers), such as compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB1, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF-related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 9702266, e.g. the compound of ex. 39, EP0564409, WO9903854, EP0520722, EP0566226, EP0787722, EP0837063, US5747498, WO9810767, WO9730034, WO9749688, WO9738983 and, especially, WO9630347, e.g. a compound known as CP 358774, WO9633980, e.g. a compound known as ZD 1839; and WO 9503283, e.g. a compound known as ZM105180, ZeNab®, e.g including the dual acting tyrosine kinase inhibitor (ErbB1 and ErbB2) lapatinib (GSK572016), e.g. lapatinib ditosylate; panitumab, trastuzumab (HERCEPTIN®), cetuximab (Erbitux®), iressa, OSI-774, CM 033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are e.g. disclosed in WO03013541, erlotinib, gefitinib. Erlotinib can be administered in the form as it is marketed, e.g. TARCEVA®, and gefitinib as IRESSA®, human monoclonal antibodies against the epidermal growth factor receptor including ABX-EGFR.

xxx. an EGFR, PDGFR tyrosine kinase inhibitor; such as EGFR kinase inhibitors, e.g. zalutumumab, tyrphostin 23, tyrphostin 25, tyrphostin 47, tyrphostin 51 and tyrphostin AG 825; 2-propenamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-phenyl-(2E); tyrphostin Ag
lavendustin A; 3-pyridineacetonitrile, \( \alpha \)-[(3,5-dichlorophenyl)methylene]-, (\( \alpha Z \)); an example of an EGFR, PDGFR tyrosine kinase inhibitor e.g. includes tyrphostin 46. PDGFR tyrosine kinase inhibitor including tyrphostin 46. Targets of an EGFR kinase inhibitor include guanylyl cyclase (GC-C) HER2, EGFR, PTK and tubulin.

a famesyltransferase inhibitor; which targets, decreases or inhibits the Ras protein; such as a-hydroxyfarnesylphosphonic acid; butanoic acid, 2-[[2(S)-2-[[2(S,3S)-2-[[2(R)-2-amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-,1-methylethyl ester, (2S); manumycin A; L-744,832 or DK8G557, tipifamib (R115777), SCH66336 (lonafarnib), BMS-214662.

a Flk-1 kinase inhibitor; which targets, decreases or inhibits Flk-1 tyrosine kinase activity; such as 2-propenamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-(2E). A target of a Flk-1 kinase inhibitor includes, but is not limited to, KDR.

glycogen synthase kinase-3 (GSK3) inhibitor; which targets, decreases or inhibits glycogen synthase kinase-3 (GSK3); such as indirubin-3'-monooxime. Glycogen Synthase Kinase-3 (GSK-3; tau protein kinase I), a highly conserved, ubiquitously expressed serine/threonine protein kinase, is involved in the signal transduction cascades of multiple cellular processes, which is a protein kinase that has been shown to be involved in the regulation of a diverse array of cellular functions, including protein synthesis, cell proliferation, cell differentiation, microtubule assembly/disassembly, and apoptosis.

a histone deacetylase (HDAC) inhibitor; which inhibits the histone deacetylase and which possess anti-proliferative activity; such as compounds disclosed in WO0222577, especially N-hydroxy-3-[4-[[2-hydroxyethyl][2-(1 H-indol-3-yl)]ethyl]-amino]methyl]phenyl]-2E-2-propenamide, and N-hydroxy-3-[4-[[2-(2-methyl-1 H-indol-3-yl)]ethyl]-amino]methyl]phenyl]-2E-2-propenamide and pharmaceutically acceptable salts thereof; suberoylanilide hydroxamic acid (SAHA); [4-(2-amino-phenylcarbamoyl)-benzyl]-carbamic acid pyridine-3-ylmethyl ester and derivatives thereof; butyric acid, pyroxamide, trichostatin A, oxamflatin, apicidin, depsipeptide; depudecin; trapoxin, HC toxin, which is also known as cyclo[L-alanyl-D-alanyl-(\( \pi S,2S \))-D-amino- \( \pi \)-oxooxiraneoctanoyl-D-prolyl] (9Cl); sodium phenylbutyrate, suberyl bis-hydroxamic acid; Trichostatin A, BMS-27275, pyroxamide, FR-901228, valproic acid, PXD101, Savicol®.
xxxv. a HSP90 inhibitor; which targets, decreases or inhibits the intrinsic ATPase activity of HSP90; degrades, targets, decreases or inhibits the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin-related compounds; radicicol and HDAC inhibitors. Other examples of an HSP90 inhibitor include geldanamycin, 17-demethoxy-17-(2-propenylamino). Potential indirect targets of an HSP90 inhibitor include FLT3, BCR-ABL, CHK1, CYP3A5∗3 and/or NFQ01∗2. Nilotinib is an example of an BCR-ABL tyrosine kinase inhibitor.

xxxvi.a I-kappa B-alpha kinase inhibitor (IKK); which targets, decreases or inhibits NF-kappaB, such as 2-propenenitrile, 3-[(4-methylphenyl)sulfonyl]-(2E).

xxxvii. an insulin receptor tyrosine kinase inhibitor; which modulates the activities of phosphatidylinositol 3-kinase, microtubule-associated protein, and S6 kinases; such as hydroxyl-2-naphthalenylmethylphosphonic acid, LY294002.

xxxviii.a c-Jun N-terminal kinase (JNK) kinase inhibitor; which targets, decreases or inhibits Jun N-terminal kinase; such as pyrazoleanthrone and/or epigallocatechin gallate. Jun N-terminal kinase (JNK), a serine-directed protein kinase, is involved in the phosphorylation and activation of c-Jun and ATF2 and plays a significant role in metabolism, growth, cell differentiation, and apoptosis. A target for a JNK kinase inhibitor includes, but is not limited to, DNMT.

xxxix a microtubule binding agent; which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular function; such as vinca alkaloids, e.g. vinblastine, vinblastine sulfate; vincristine, vincristine sulfate; vindesine; vinorelbine; taxanes, such as taxanes, e.g. docetaxel; paclitaxel; discodermolides; colchicine, epothilones and derivatives thereof, e.g. epothilone B or a derivative thereof. Paclitaxel is marketed as TAXOL®; docetaxel as TAXOTERE®; vinblastine sulfate as VINBLASTIN R.P®; and vincristine sulfate as FARMISTIN®. Also included are the generic forms of paclitaxel as well as various dosage forms of paclitaxel. Generic forms of paclitaxel include, but are not limited to, betaxolol hydrochloride. Various dosage forms of paclitaxel include, but are not limited to albumin nanoparticle paclitaxel marketed as ABRAXANE®; ONXOL®, CYTOTAX®. Discodermolide can be obtained, e.g., as disclosed in US5010099. Also included are Epotholine derivatives
which are disclosed in US6194181, WO98/0121, WO9825929, WO9808849, WO9943653, WO9822461 and WO0031247. Especially preferred are Epotholine A and/or B.

xl. a mitogen-activated protein (MAP) kinase-inhibitor; which targets, decreases or inhibits

Mitogen-activated protein, such as benzenesulfonamide, N-[2-[[3-(4-chlorophenyl)-2-propenyl]methyl]amino[methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy. The mitogen-activated protein (MAP) kinases are a group of protein serine/threonine kinases that are activated in response to a variety of extracellular stimuli and mediate signal transduction from the cell surface to the nucleus. They regulate several physiological and pathological cellular phenomena, including inflammation, apoptotic cell death, oncogenic transformation, tumor cell invasion, and metastasis.

xli. a MDM2 inhibitor; which targets, decreases or inhibits the interaction of MDM2 and the p53 tumor suppressor; such as trans-4-iodo, 4'-boranyl-chalcone.

xlii. a MEK inhibitor; which targets, decreases or inhibits the kinase activity of MAP kinase MEK; such as sorafenib, e.g. Nexavar® (sorafenib tosilate), butanedinitrile, bis[amino[2-aminophenyl]thio]methylene]. A target of a MEK inhibitor includes, but is not limited to ERK. An indirect target of a MEK inhibitor includes, but is not limited to, cyclin D1.

xliii. a matrix metalloproteinase inhibitor (MMP) inhibitor; which targets, decreases or inhibits a class of protease enzyme that selectively catalyze the hydrolysis of polypeptide bonds including the enzymes MMP-2 and MMP-9 that are involved in promoting the loss of tissue structure around tumors and facilitating tumor growth, angiogenesis, and metastasis such as actinonin, which is also known as butanediamide, N-4-hydroxy-N1-[[1(S)-1-[[2S]-2-(hydroxymethyl)-1-pyrrolidinyl]carbonyl]-2-methyl[propyl]-2-pentyl-, (2R)-(9CI); epigallocatechin gallate; collagen peptidomimetic and non-peptidomimetic inhibitors; tetracycline derivatives, e.g., hydroxamate peptidomimetic inhibitor batimastat; and its orally-bioavailable analogue marimastat, prinomastat, metastat, neovastat, tanomastat, TAA21 1, BMS-279251, BAY 12-9566, MII270B or AAJ996. A target of a MMP inhibitor includes, but is not limited to, polypeptide deformylase.

xliv. a NGFR tyrosine-kinase-inhibitor; which targets, decreases or inhibits nerve growth factor dependent p140tyro tyrosine phosphorylation; such as tyrphostin AG 879. Targets of a NGFR tyrosine-kinase-inhibitor include, but are not limited to, HER2, FLK1, FAK, TrkA, and/or TrkC. An indirect target inhibits expression of RAF1.
xlvi. a p38 MAP kinase inhibitor, including a SAPK2/p38 kinase inhibitor; which targets, decreases or inhibits p38-MAPK, which is a MAPK family member, such as phenol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]. An example of a a SAPK2/p38 kinase inhibitor includes, but is not limited to, benzamide, 3-(dimethylamino)-N-[3-{(4-hydroxybenzoyl)amino]-4-methylphenyl]. A MAPK family member is a serine/threonine kinase activated by phosphorylation of tyrosine and threonine residues. This kinase is phosphorylated and activated by many cellular stresses and inflammatory stimuli, thought to be involved in the regulation of important cellular responses such as apoptosis and inflammatory reactions.

xlvii. a p56 tyrosine kinase inhibitor; which targets, decreases or inhibits p56 tyrosine kinase, which is an enzyme that is a lymphoid-specific src family tyrosine kinase critical for T-cell development and activation; such as dammancal, which is also known as 2-anthracene-carboxaldehyde,9,10-dihydro-3-hydroxy-1methoxy-9,10-dioxo, Tyrphostin 46. A target of a p56 tyrosine kinase inhibitor includes, but is not limited to, Lck. Lck is associated with the cytoplasmic domains of CD4, CD8 and the beta-chain of the IL-2 receptor, and is thought to be involved in the earliest steps of TCR-mediated T-cell activation.

xlviii. a PDGFR tyrosine kinase inhibitor; targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases (part of the PDGFR family), such as targeting, decreasing or inhibiting the activity of the c-Kit receptor tyrosine kinase family, especially inhibiting the c-Kit receptor. Examples of targets of a PDGFR tyrosine kinase inhibitor includes, but are not limited to PDGFR, FLT3 and/or c-KIT; such as tyrphostin AG 1296; tyrphostin 9; 1,3-butadiene-1,1,3-tricarbonitrile,2-amino-4-(1H-indol-5-yl); N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, IRESSA®. PDGF plays a central role in regulating cell proliferation, chemotaxis, and survival in normal cells as well as in various disease states such as cancer, atherosclerosis, and fibrotic disease. The PDGF family is composed of dimeric isoforms (PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, and PDGF-DD), which exert their cellular effects by differentially binding to two receptor tyrosine kinases. PDGFR-w and PDGFR-β have molecular masses of -170 and 180 kDa, respectively.

xl. a phosphatidylinositol 3-kinase inhibitor; which targets, decreases or inhibits PI 3-kinase; such as wortmannin, which is also known as 3H-Furo[4,3,2-de]indenono[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11 1,11b-octahydro-1-(methoxymethyl)-9a,1 1b-dimethyl-, (1S,6bR,9aS,1 R,11bR)-(9Cl); 8-phenyl-2-
(morpholin-4-yl)-chromen-4-one; quercetin, quercetin dihydrate. PI 3-kinase activity has been shown to increase in response to a number of hormonal and growth factor stimuli, including insulin, platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, colony-stimulating factor, and hepatocyte growth factor, and has been implicated in processes related to cellular growth and transformation. An example of a target of a phosphatidylinositol 3-kinase inhibitor includes, but is not limited to, PI3K.

a phosphatase inhibitor; which targets, decreases or inhibits phosphatase; such as cantharidic acid; cantharidin; and L-leucinamide, N-[4- (2-carboxyethenyl)benzoyl]glucylyl-L-γ-glutamyKε). Phosphatases remove the phosphoryl group and restore the protein to its original dephosphorylated state. Hence, the phosphorylation- dephosphorylation cycle can be regarded as a molecular "on-off" switch.

a platinum agent; which contains platinum and inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules; such as carboplatin; cisplatin; oxaliplatin; cisplatinum; satraplatin and platinum agents such as ZD0473, BBR3464. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. CARBOPLAT®; and oxaliplatin as ELOXATIN®.

a protein phosphatase inhibitor, including a PP1 and PP2 inhibitor and a tyrosine phosphatase inhibitor; which targets, decreases or inhibits protein phosphatase. Examples of a PP1 and PP2A inhibitor include cantharidic acid and/or cantharidin. Examples of a tyrosine phosphatase inhibitor include, but are not limited to, L-P-bromotetramisole oxalate; 2(5H)-furanone,4-hydroxy-5-(hydroxymethyl)-3-(1-oxohexadecyl)-, (5R); and benzylphosphonic acid.

The term "a PP1 or PP2 inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Ser/Thr protein phosphatases. Type I phosphatases, which include PP1, can be inhibited by two heat-stable proteins known as Inhibitor-1 (I-1) and Inhibitor-2 (I-2). They preferentially dephosphorylate a subunit of phosphorylase kinase. Type II phosphatases are subdivided into spontaneously active (PP2A), Ca2+- dependent (PP2B), and Mg2+-dependent (PP2C) classes of phosphatases.

The term "tyrosine phosphatase inhibitor", as used here, relates to a compounds which targets, decreases or inhibits tyrosine phosphatase. Protein tyrosine phosphatases (PTPs) are relatively recent additions to the phosphatase family. They remove phosphate groups from phosphorylated tyrosine residues of proteins. PTPs display
diverse structural features and play important roles in the regulation of cell proliferation, differentiation, cell adhesion and motility, and cytoskeletal function.

Examples of targets of a tyrosine phosphatase inhibitor include, but are not limited to, alkaline phosphatase (ALP), heparanase, PTPase, and/or prostatic acid phosphatase. A PKC inhibitor and a PKC delta kinase inhibitor: The term "a PKC inhibitor", as used herein, relates to a compound which targets, decreases or inhibits protein kinase C as well as its isozymes. Protein kinase C (PKC), a ubiquitous, phospholipid-dependent enzyme, is involved in signal transduction associated with cell proliferation, differentiation, and apoptosis. Examples of a target of a PKC inhibitor include, but are not limited to, MAPK and/or NF-kappaB. Examples of a PKC inhibitor include, but are not limited to, 1-H-pyrrolo-2,5-dione, 3-[1-3-(dimethylamino)propyl]-1H-indol-3-yl]-4-(1H-indol-3-yl); bisindolylmaleimide IX; sphingosine, which is known as 4-octadecene-1,3-diol, 2-amino-, (2S,3R,4E)-(9Cl); staurosporine, which is known as 9,13-Epoxy-1H.9H-diindololll^-S-g13S^'a'.r-lmpyrrol0S,4^-ttlbenzodiazonin-i-one, staurosporine derivatives such as disclosed in EP0296110, e.g. midostaurin; 2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-(methylamino)-, (9S,10R,11R,13R)-(9Cl); tyrphostin 51; and hypericin, which is also known as phenanthro[1,10,9,8-opqra]perylene-7, 14-dione, 1,3,4,6,8,13-hexahydroxy-1,0,11-dimethyl-, stereoisomer (6Cl,7Cl,8Cl,9Cl), UCN-01, saflingol, BAY 43-9006, bryostatin 1, perifosine;limofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196. The term "a PKC delta kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the delta isozymes of PKC. The delta isozyme is a conventional PKC isozymes and is Ca^{2+}-dependent. An example of a PKC delta kinase inhibitor includes, but is not limited to, Rottlerin, which is also known as 2-Propen-1-one, 1-[6-[(3-acetyl-2,4,6-trihydroxy-5-methylphenyl)methyl]-5,7-dihydroxy-2,2-dimethyl-2H-1-benzopyran-8-yl]-3-phenyl-, (2E)-(9Cl).

lii. a polyamine synthesis inhibitor; which targets, decreases or inhibits polyamines spermidine; such as DMFO, which is also known as (-)-2-difluoromethylomithin; \( N_1 \), \( N_{12} \)-diethylsperrmine 4HCl. The polyamines spermidine and spermine are of vital importance for cell proliferation, although their precise mechanism of action is unclear.

Tumor cells have an altered polyamine homeostasis reflected by increased activity of biosynthetic enzymes and elevated polyamine pools.

liv. a proteosome inhibitor; which targets, decreases or inhibits proteasome, such as aclacinomycin A; gliotoxin; PS-341; MLN 341; bortezomib; velcade. Examples of
targets of a proteosome inhibitor include, but are not limited to, O(2)(-)-generating NADPH oxidase, NF-kappaB, and/or farnesyltransferase, geranyltransferase, a PTP1B inhibitor; which targets, decreases or inhibits PTP1B, a protein tyrosine kinase inhibitor; such as L-leucinamide, N-[4-(2-carboxyethenyl)benzoyl]glycyl-L- glutamyl(E).

iv. a protein tyrosine kinase inhibitor including a SRC family tyrosine kinase inhibitor; a Syk tyrosine kinase inhibitor; and a JAK-2 and/or JAK-3 tyrosine kinase inhibitor; The term "a protein tyrosine kinase inhibitor", as used herein, relates to a compound which which targets, decreases or inhibits protein tyrosine kinases. Protein tyrosine kinases (PTKs) play a key role in the regulation of cell proliferation, differentiation, metabolism, migration, and survival. They are classified as receptor PTKs and non-receptor PTKs. Receptor PTKs contain a single polypeptide chain with a transmembrane segment. The extracellular end of this segment contains a high affinity ligand-binding domain, while the cytoplasmic end comprises the catalytic core and the regulatory sequences. Examples of targets of a tyrosine kinase inhibitor include, but are not limited to, ERK1, ERK2, Bruton's tyrosine kinase (Btk), JAK2, ERK V2, PDGFR, and/or FLT3. Examples of indirect targets include, but are not limited to, TNFalpha, NO, PGE2, IRAK, iNOS, ICAM-1, and/or E-selectin. Examples of a tyrosine kinase inhibitor include, but are not limited to, tyrphostin AG 126; tyrphostin Ag 1288; tyrphostin Ag 1295; geldanamycin; and genistein.

Non-receptor tyrosine kinases include members of the Src, Tec, JAK, Fes, Abl, FAK, Csk, and Syk families. They are located in the cytoplasm as well as in the nucleus. They exhibit distinct kinase regulation, substrate phosphorylation, and function. Deregulation of these kinases has also been linked to several human diseases.

The term "a SRC family tyrosine kinase inhibitor", as used herein, relates to a compound which which targets, decreases or inhibits SRC. Examples of a SRC family tyrosine kinase inhibitor include, but are not limited to, PP1, which is also known as 1H-pyrazolo[3,4-d]pyrimidin-4-amine, 1-(1,1-dimethylethyl)-3-(1-naphthalenyl)- (9CI); and PP2, which is also known as 1H-Pyrazolo[3,4-d]pyrimidin-4-amine, 3-(4-chlorophenyl)-1-(1,1-dimethylethyl)- (9CI).

The term "a Syk tyrosine kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Syk. Examples of targets for a Syk tyrosine kinase inhibitor include, but are not limited to, Syk, STAT3, and/or STAT5. An example of a
Syk tyrosine kinase inhibitor includes, but is not limited to, piceatannol, which is also known as 1,2-benzenediol, 4-[(1E)-2-(3,5-dihydroxyphenyl)ethenyl]J-(9CI).

The term "a Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits janus tyrosine kinase.

Janus tyrosine kinase inhibitor are shown anti-leukemic agents with antithrombotic, anti-allergic and immunosuppressive properties. Targets of a JAK-2 and/or JAK-3 tyrosine kinase inhibitor include, but are not limited to, JAK2, JAK3, STAT3. An indirect target of an JAK-2 and/or JAK-3 tyrosine kinase inhibitor includes, but is not limited to CDK2. Examples of a JAK-2 and/or JAK-3 tyrosine kinase inhibitor include, but are not limited to, Tyrphostin AG 490; and 2-naphtyl vinyl ketone.

Compounds which target, decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. include PD180970; AG957; or NSC 680410.

a retinoid; which target, decrease or inhibit retinoid dependent receptors; such as isotretinoin, tretinoin, alitretinoin, bexarotene, e.g. including an agent which interact with retinoic acid responsive elements on DNA, such as isotretinoin (13-c/s-retinoic acid).

a RNA polymerase II elongation inhibitor; which targets, decreases or inhibits insulin-stimulated nuclear and cytosolic p70S6 kinase in CHO cells; targets, decreases or inhibits RNA polymerase II transcription, which may be dependent on casein kinase II; and targets, decreases or inhibits germinal vesicle breakdown in bovine oocytes; such as 5,6-dichloro-1 -beta-D-ribofuranosylbenzimidazole.

a serine/threonine kinase inhibitor; which inhibits serine/threonine kinases; such as 2-amino purine. An example of a target of a serine/threonine kinase inhibitor includes, but is not limited to, dsRNA-dependent protein kinase (PKR). Examples of indirect targets of a serine/threonine kinase inhibitor include, but are not limited to, MCP-1, NF-kappaB, eIF2alpha, COX2, RANTES, IL8, CYP2A5, IGF-1, CYP2B1, CYP2B2, CYP2H1, ALAS-1, HIF-1, erythropoietin, and/or CYP1A1.

a sterol biosynthesis inhibitor; which inhibits the biosynthesis of sterols such as cholesterol; such as terbinadine. Examples of targets for a sterol biosynthesis inhibitor include, but are not limited to, squalene epoxidase, and CYP2D6.

a topoisomerase inhibitor; including a topoisomerase I inhibitor and a topoisomerase II inhibitor. Examples of a topoisomerase I inhibitor include, but are not limited to, topotecan, gimatecan, irinotecan, camptothecan and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148
(compound A 1 in WO9917804); 10-hydroxycamptothecin e.g. the acetate salt; idarubicin, e.g. the hydrochloride; irinotecan, e.g. the hydrochloride; etoposide; teniposide; topotecan, topotecan hydrochloride; doxorubicin; epirubicin, epirubicin hydrochloride; 4'-epidoxorubicin, mitoxantrone, mitoxantrone, e.g. the hydrochloride; daunorubicin, daunorubicin hydrochloride, valrubicin, dasatinib (BMS-354825).

Irinotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark CAMPTOSAR®. Topotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark HYCAMTIN®. The term "topoisomerase II inhibitor", as used herein, includes, but is not limited to, the anthracyclines, such as doxorubicin, including liposomal formulation, e.g., CAELYX®, daunorubicin, including liposomal formulation, e.g., DAUNOSOME®, epirubicin, idarubicin and nemorubicin; the anthraquinones mitoxantrone and losoxantrone; and the podophillotoxines etoposide and teniposide. Etoposide is marketed as ETOPOPHOS®; teniposide as VM 26-BRISTOL®; doxorubicin as ADRIABLASTIN® or ADRIAMYCIN®; epirubicin as FARMORUBICIN® idarubicin as ZAVEDOS®; and mitoxantrone as NOVANTRON®.

VEGFR tyrosine kinase inhibitor; which targets, decreases and/or inhibits the known angiogenic growth factors and cytokines implicated in the modulation of normal and pathological angiogenesis. The VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D) and their corresponding receptor tyrosine kinases [VEGFR-1 (Flt-1), VEGFR-2 (Flk-1, KDR), and VEGFR-3 (Flt-4)] play a paramount and indispensable role in regulating the multiple facets of the angiogenic and lymphangiogenic processes. An example of a VEGFR tyrosine kinase inhibitor includes 3-(4-dimethylaminobenzylidenyl)-2-indolinone. Compounds which target, decrease or inhibit the activity of VEGFR are especially compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO9835958, e.g. 1- (4- chloroanilino)-4- (4-pyridyl)methyl) phthalazine or a pharmaceutical acceptable salt thereof, e.g. the succinate, or in WO0009495, WO0027820, WO0059509, WO981 1223, WO0027819 and EP0769947; e.g. those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, Dec. 1996, by Z. Zhu et al in Cancer Res. 58,1998,3209-3214, and by J. Mordenti et al in Toxicologic Pathology, Vol. 27, no. 1, pp 14-21,1999; in WO0037502 and WO9410202; Angiostatin, described by M. S. O'Reilly et al, Cell 79,1994,315-328; Endostatin described by M. S. O'Reilly et
al, Cell 88,1997,277-285; anthranilic acid amides; ZD4190; ZD6474 (vandetanib); SU5416; SU6668, AZD2171 (Recentin®); or anti-VEGF antibodies, such as anti-VEGF-alpha antibody tanibizumab (Lucentis®), or anti-VEGF receptor antibodies, e.g. RhuMab (bevacizumab, Avastin®). By antibody is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity. an example of an VEGF-R2 inhibitor e.g. includes axitinib,

Ixxiii. a gonadorelin agonist, such as abarelix, goserelin, goserelin acetate,

Ixiv. a compound which induce cell differentiation processes, such as retinoic acid, alpha-, gamma- or 8- tocopherol or alpha-, gamma- or 8-tocotrienol.

Ixv. a bisphosphonate, e.g. including etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid.

Ixvi. a heparanase inhibitor which prevents heparan sulphate degradation, e.g. PI-88,

Ixvii. a biological response modifier, preferably alymphokine or interferons, e.g. interferon alpha,

Ixviii. a telomerase inhibitor, e.g. telomestatin,

Ixix. mediators, such as inhibitors of catechol-O-methyltransferase, e.g. entacapone,

Ixx: ispinesib, permetrexed (Alimta®), sunitinib (SU11248), diethylstilbestrol (DES), BMS224818 (LEA29Y), vatanalib,

Ixxi somatostatin or a somatostatin analogue, such as octreotide (Sandostatin® or Sandostatin LAR®).

Ixxii. Growth Hormone-Receptor Antagonists, such as pegvisomant, filgrastim or pegfilgrastim, or interferon alpha:

Ixxiii. monoclonal antibodies, e.g. useful for leukemia (AML) treatment, such as alemtuzumab (Campath®, rituximab /Rituxan®), gemtuzumab, (ozogamicin, Mylotarg®),epratuzumab.

Ixxiv. altretamine, amsacrine, asparaginase (Elspar®), denileukin diftitox, masoprocol, pegaspargase, gemtuzumab (MYLOTARG®),

Ixxv. a phosphodiesterase inhibitor, e.g. anagrelide (Agrylin®, Xagrid®).

Ixxvi. a cancer vaccine, such as MDX-1379.

Ixxvii. an immunosuppressive monoclonal antibody, e.g., monoclonal antibodies to leukocyte receptors,
e.g. CD20, such as rituximab (Rituxan®, ibritumomab tiuxetan conjugated to $^{111}$In or $^{90}$Y (Zevalin®), $^{131}$I tositumumab (Bexxar®), ofatumumab, ocrelizumab, hA20 (Immunomedics), CD22, such as epratuzumab, inotizumab ozogamicin (CMC544), CAT-3888, CD33, such as gemtuzumab (Mylotarg®), CD52, e.g. alemtuzumab (Campath-I®),
or their ligands,
LD1 1a, e.g. efalizumab (Raptiva®),
LD3, e.g. visilzumab,
Ixxxii. antibodies against carcinoembryonic antigen (CEA), e.g. lapetuzumab, e.g.
lapetuzumab-yttrium90, KSB-303, MFECP1, MFE-23

Cancer treatment optionally in combination with an anticancer drug may be associated with radiotherapy, e.g. including DOTATATE therapy, such as $^{90}$Y-DOTATATE therapy.

Cancer treatment may also be associated with vitamin or vitamin derivative (e.g. Leucovorin®) treatment.
Anti-cancer drugs, e.g. for the treatment of breast cancer, e.g. may be used in combination with abraxane® which may improve the release of drugs, and even may enhance the drug benefit, e.g. such as in case of administration of paclitaxel in combination with abraxane®.
(wherein abraxane® combines the drug paclitaxel with the protein albumin, which turns into a nanoparticle when injected into the bloodstream allowing a greater concentration of the drug in the tumor and starving the malignant cells of the nutrients they need to grow).

If a compound of the present invention is administered in combination with other drugs, dosages of the co-administered second drug will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated, as in case of a compound of the present invention. In general dosages similar than those as provided by the second drug supplier may be appropriate

The chemical names of the compounds of the present invention as indicated herein are copied from ISIS, version 2.5 (AutoNom 2000 Name). Chemical names of second drug substances and other substances may be derived from the Internet, e.g. via a search program such as the SCI FINDER.
In the following examples all temperatures indicated are in degree Celsius (°).

The following abbreviations are used:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>CH2Cl2</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethylacetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
</tbody>
</table>
Example 1

Pyridazine-4-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide

840 g of 2-methoxybenzaldehyde and 93.8 mg of dibutyltindichloride are added to a solution of 1.0 g of 3,5 dichloroaniline in 10 ml of THF. The mixture obtained is stirred for 5 minutes, 2.67 g of phenylsilane are added and the mixture obtained is stirred overnight at RT. The reaction is quenched with a drop of H2O, diluted with EtOAc, washed with a sat. solution of NaHCO3, dried over Na2SO4 and solvent is evaporated.

(3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amine is obtained.

68.3 mg of (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amine are dissolved in 2 ml of 1,5 dichloroethane. To the mixture obtained 30 mg of pyridazine-4-carboxylic acid, 95 mg of pyridine and 61 mg of POCl3 are added. The mixture obtained is microwaved at 80° for 10 minutes. The organic layer obtained is washed with 2 ml of a sat. aq. solution of NaHCO3 and solvent is evaporated.

Pyridazine-4-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide is obtained.

Analogously to a method as described in Example 1 but using appropriate starting materials (intermediates) compounds of formula

\[
\text{R}_1\text{CH}_2\text{R}_2\text{NCH}_2\text{N} = \text{R}_3 \quad \text{(IA)}
\]

wherein R1, R2 and R3 are as defined in TABLE 1 below and R5 is H, except for examples 10 to 12 where R5 is CH3, are obtained.

<table>
<thead>
<tr>
<th>EX</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="Cl" alt="Cl" /></td>
<td><img src="OCH3" alt="OCH3" /></td>
<td>H</td>
<td>411.99 [M Na]+</td>
</tr>
<tr>
<td>EX</td>
<td>R₁</td>
<td>R₂</td>
<td>R₃</td>
<td>Data</td>
</tr>
<tr>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>--------</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>H</td>
<td>471.99 [M Na]⁺</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>H</td>
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<tr>
<td>4</td>
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<td><img src="image6.png" alt="Image" /></td>
<td>H</td>
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<tr>
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<td>CH₃</td>
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<td>EX</td>
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<tr>
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<td>H</td>
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</table>
Under DATA in TABLE 1 characterization data for the corresponding compound is set out.

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<tr>
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<th>R₃</th>
<th>Data</th>
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<td>![C₆H₄]</td>
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</tbody>
</table>

Example 13

β-Oxo-6H-pyran-S-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide

840 g of 2-methoxybenzaldehyde and 93.8 mg of dibutyltindichloride are added to a solution of 1.0 g of 3,5 dichloroaniline in 10 ml of THF. The mixture obtained is stirred for 5 minutes, 2.67 g of phenylsilane are added and the mixture obtained is stirred overnight at RT. The reaction is quenched with a drop of H₂O, diluted with EtOAc, washed with a sat. solution of NaHCO₃, dried over Na₂SO₄ and solvent is evaporated. (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amine is obtained.

40 mg of (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amine are dissolved in 2 ml of 1,2-dichloroethane, 56 mg of pyridine and 35 mg of POCl₃ are added and the mixture obtained is microwaved at 80°C for 20 minutes. The organic layer obtained is washed with 2 ml of a sat. aq. solution of NaHCO₃ and solvent is evaporated.

6-Oxo-6H-pyran-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide is obtained.

Example 14

1-Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide

35 mg of 6-Oxo-1,6-dihydro-pyridine-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide obtained analogously to Example 1, but using appropriate starting materials, are dissolved in 2 ml of DMF. 12.3 mg of potassium t-butyllate are added and the mixture obtained is stirred for 5 minutes. 19.9 mg of MeJ are added and the mixture obtained is
stirred at RT for further 2 hours. The reaction is quenched with 5 ml of H₂O and 15 ml of a 10% solution of NH₃ in H₂O are added along with 2 ml of brine. The mixture obtained is extracted with 10 ml of CH₂Cl₂. The aq. layer is diluted with further 10 ml of brine and extracted twice with 10 ml of CH₂Cl₂. The combined organic layers obtained are dried over Na₂SO₄ and solvent is evaporated.

1-Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide is obtained.

Analogously to a method as described in Example 13 and 14, but using appropriate starting materials (intermediates) compounds of formula

```
R₂
\( \text{\( \text{OHC} \)} \)R₃
\( \text{\( \text{X} \)} \) \( \text{\( \text{Y} \)} \)
```

wherein X, Y, R₁, R₂ and R₃ are as defined in TABLE 2 below are obtained.

<table>
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<th>R₃</th>
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<th>Y</th>
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<td>( \text{( \text{H} )} )</td>
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<td>R₂</td>
<td>R₃</td>
<td>X</td>
<td>Y</td>
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INTERMEDIATES: Synthesis of S-Methyl-pyridazine^-carboxylic acid

A solution of 1.0 g of 2-acetyl-pent-4-enoic acid ethyl ester and 0.5 mg of Sudan III in 30 ml of $\text{CH}_2\text{Cl}_2$ and 3 ml of MeOH at -78° is subjected to a stream of $\text{O}_3$ in $\text{O}_2$ until decolorisation of the solution. 4.2 g of PL-TPP (polymer bound triphenylphosphine, loading 1.42 mMol/g, 2.96 mMol) are added and the reaction mixture obtained is allowed to warm up to RT. After slow stirring for 1 hour, the reaction mixture obtained is filtered and solvent is evaporated. 3-oxo-2-(2-oxo-ethyl)-butyric acid ethyl ester is obtained.

A solution of 3.64 g of 3-oxo-2-(2-oxo-ethyl)-butyric acid ethyl ester in 35 ml of EtOH at 0° is slowly treated with a solution of 724 µl of hydrazine hydrate in 10 ml of EtOH. The reaction mixture obtained is allowed to come to RT and stirred for 2.5 hours. A solution of 2.21 g of sodium nitrite in 1 ml of $\text{H}_2\text{O}$ is added, followed by the addition of 7.0 ml of AcOH. After 1 hour, a sat. aq. solution of NaHCO$_3$ is added until gas formation is stopped. The reaction mixture obtained is extracted with EtOAc. The combined organic layers obtained are dried over Na$_2$SO$_4$ and solvent is evaporated. 3-methyl-pyridazine-4-carboxylic acid ethyl ester is obtained.

A solution of 704 mg of 3-methyl-pyridazine-4-carboxylic acid ethyl ester in 2 ml of THF is treated with an aq. solution of 2.2 ml of LiOH and stirred for 1.5 hours at RT. Solvent is evaporated.

The lithium salt of 3-methyl-pyridazine-4-carboxylic acid is obtained.
Patent Claims

1. A compound of formula

\[
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{R}_4 \\
\text{R}_3 \\
\text{R}_2
\end{array}
\]

wherein

- \( R_1 \) is \((C_6-i8)\)aryl or \((C_6-i8)\)aryl\((C_{1-4})\)alkyl, wherein aryl optionally is fused with aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N, O, S,
- \((C_{3-12})\)cycloalkyl, wherein cycloalkyl optionally is fused with aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N, O, S,
- \((C_{5-12})\)cycloalkenyl, wherein cycloalkenyl optionally is fused with aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, e.g. 6, and 1 to 4 heteroatoms selected from N, O, S, or
- heterocyclyl, comprising 3 to 12 ring members and 1 to 4 heteroatoms selected from N, O, S;
- wherein heterocyclyl optionally is fused with \((C_{3-12})\)cycloalkyl, \((C_{5-12})\)cycloalkenyl, \((C_{6-12})\)aryl, or optionally is fused with another heterocyclyl comprising 3 to 12 ring members and 1 to 4 heteroatoms selected from N, O, S,
- \( R_2 \) is alkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl cycloalkenyl, heterocyclyl, or \((C_{1-4})\)alkyl substituted by aryl, cycloalkyl, cycloalkenyl or heterocyclyl, preferably aryl or
- heterocyclyl, wherein
  - alkyl includes \((C_{1-12})\)alkyl,
  - alkenyl includes \((C_{2-12})\)alkenyl,
  - alkynyl includes \((C_{2-12})\)alkynyl,
  - cycloalkyl includes \((C_{3-12})\)cycloalkyl,
  - cycloalkenyl includes \((C_{5-6})\)cycloalkenyl,
  - aryl includes \((C_{6-12})\)aryl and \((C_{6-12})\)aryl\((C_{1-4})\)alkyl, wherein aryl optionally is fused with \((C_{3-12})\)cycloalkyl, \((C_{5-6})\)cycloalkenyl, aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N, O, S,
  - heterocyclyl includes aliphatic or aromatic heterocyclyl comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N, O, S and wherein heterocyclyl optionally is fused with \((C_{3-12})\)cycloalkyl, \((C_{5-6})\)cycloalkenyl, \((C_{6-12})\)aryl, or is fused with another heterocyclyl,
preferably fused with another heterocyclyl, which other heterocyclyl includes aliphatic or aromatic heterocyclyl, preferably aromatic heterocyclyl, comprising 3 to 12 ring members and 1 to 4 heteroatoms, selected from N, O, S.

R₅ is hydrogen or (C intellectuals) alkyl; or

R₂ and R₃ together with the carbon atom to which they are attached form (C₃ intellectuals) cycloalkyl, (C intellectuals) cycloalkenyl, phenyl, or heterocyclyl;

which cycloalkyl cycloalkenyl, phenyl or heterocyclyl optionally is fused with (C intellectuals) cycloalkyl, (C intellectuals) cycloalkenyl, (C intellectuals) aryl, or is fused with another heterocyclyl comprising 5 to 6 ring members and 1 to 4 heteroatoms selected from N, O, S;

therein aryl, cycloalkyl, cycloalkenyl and heterocyclyl in the meaning of R₁, R₂ or R₂ and R₃ together is unsubstituted or one or morefold substituted by (C intellectuals) alkyl, e.g. (C intellectuals) alkyl, (C intellectuals) alkynyl, halo(C intellectuals) alkyl, hydroxy, (C intellectuals) alkoxy, halo(C intellectuals) alkoxy, =S, SH, SO₃H, SO₂NH₂, (C intellectuals) alkylmercapto, hydroxycarbonyl, (C intellectuals) alkylcarbonyl, (C intellectuals) arylcarbonyl, (C intellectuals) cycloalkylcarbonyl, (C intellectuals) cycloalkenylcarbonyl, heterocyclylcarbonyl,

hydroxycarbonyloxy, (C intellectuals) alkylcarbonyloxy, (C intellectuals) arylcarbonyloxy, (C intellectuals) cycloalkylcarbonyloxy, (C intellectuals) cycloalkenylcarbonyloxy, heterocyclylcarbonyloxy, (C intellectuals) aryl, (C intellectuals) cycloalkyl, (C intellectuals) cycloalkenyl, (C intellectuals) arylcarbonyloxy, (C intellectuals) cycloalkylcarbonyloxy, cyano, nitro, amino, (C intellectuals) alkylamino, (di(C intellectuals) alkylamino, (C intellectuals) arylamino, (C intellectuals) cycloalkylamino, (C intellectuals) cycloalkenylamino, heterocyclylamino, (C intellectuals) alkylcarbonylamino, (C intellectuals) arylcarbonylamino, (C intellectuals) cycloalkylcarbonylamino, (C intellectuals) cycloalkenylcarbonylamino, heterocyclylcarbonylamino, or halogen, and

therein heterocyclyl comprises 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S, including aliphatic and aromatic heterocyclyl, e.g. heterocyclyl optionally fused with another ring system such as fused with (C intellectuals) cycloalkyl, (C intellectuals) aryl, or another heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N, O, S.

R₄ is a compound of formula

or of formula

wherein in a compound of formula (IA) R₅ is hydrogen or (C intellectuals) alkyl, and

wherein in a compound of formula (IB)
X is O, S or NR₆, wherein R₆ is hydrogen or (C₁₋₄)alkyl,
Y is O or S.

2. A compound according to claim 1, wherein
   Ri is phenyl or phenyl(C₁₋₄)alkyl, unsubstituted or substituted by one or more (C₁₋₄)alkyl,
   (C₁₋₄)alkoxy, halo(Cr₋₄)alkyl, halo(C₁₋₄)alkoxy, halogen, cyano;
   R₂ is phenyl, phenyl fused with another ring system, heterocyclyl comprising 5 or 6 ring
   members, and 1 to 4 heteroatoms, including aromatic heterocyclyl and aliphatic
   heterocyclyl, which heterocyclyl is optionally fused with another ring system, e.g. fused
   with (C₃₋₁₂)cycloalkyl, (C₅₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl or another heterocyclyl comprising
   5 to 6 ring members, and 1 to 4 heteroatoms, selected from N,O,S,
   wherein cycloalkyl, cycloalkenyl, aryl, aryl fused with another ring system, heterocyclyl
   or heterocyclyl fused with another ring system is unsubstituted or substituted by one or
   more (C₁₋₄)alkyl, (C₁₋₄)alkoxy, cyano, halogen, phenyl,
   R₃ is hydrogen or (C₁₋₄)alkyl,
   R₄ is a compound of formula (IA), and
   R₅ is hydrogen or (C₁₋₄)alkyl.

3. A compound according to any one of claims 1 or 2, wherein
   R₁ is unsubstituted phenyl or phenyl one or twofold substituted by methyl, halo, cyano,
   or phenylmethyl,
   R₂ is methoxyphenyl, halophenyl, dihalophenyl, (halo)(methoxy)phenyl, indolyl, triazolyl,
   optionally substituted by phenyl, cyanophenyl, or imidazolyl fused with thiazolyl, and
   R₃ is hydrogen or methyl,
   R₄ is a compound of formula (IA),
   R₅ is hydrogen or methyl.

4. A compound according to claim 1, wherein
   R₁ is phenyl, wherein phenyl is one ore morefold substituted by halogen, cyano or
   (C₁₋₄)alkyl,
   R₂ is phenyl, wherein phenyl optionally is fused with aliphatic or aromatic heterocyclyl
   comprising 3 to 12 ring members, and 1 to 4 heteroatoms selected from N,O,S, and
   wherein aryl is unsubstituted or substituted by (C₁₋₄)alkyl, or (C₁₋₄)alkoxy,
   R₃ is hydrogen or (C₁₋₄)alkyl,
R₄ is a compound of formula (IB), wherein X is O, NH or NCH₃ and Y is O,
R₆ is hydrogen or methyl.

5. N-(C₆,i₂)-aryl-6-oxo-6H-pyran-3-carboxylic acid amides wherein the nitrogen atom of the amide group is further substituted by (C₆,i₂)arylmethyl, which aryl optionally is fused with heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N,O,S, e.g. N, e.g. wherein the fused heterocyclyl forms aromatic heterocyclyl.

6. 6-hydroxy-nicotinamides, wherein the nitrogen atom of the amide group is substituted by (C₆,i₂)arylmethyl, which aryl optionally is fused with heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N,O,S, and wherein the nitrogen atom of the amide group is further substituted by (C₆,i₂)aryl.

7. 1-((C₁-₄)alkyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid amides, wherein the nitrogen atom of the amide group is substituted by (C₆,i₂)arylmethyl, which aryl optionally is fused with heterocyclyl comprising 5 or 6 ring members and 1 to 4 heteroatoms selected from N,O,S, and wherein the nitrogen atom of the amide group is further substituted by (C₆,i₂)aryl.

8. A compound of any preceding claim which is selected from the group consisting of
   Pyridazine-4-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
   Pyridazine-4-carboxylic acid [2-(4-cyano-phenyl)-2H-[1,2,3]triazol-4-ylmethyl]-(3,5-dichloro-phenyl)-amide,
   Pyridazine-4-carboxylic acid (4-fluoro-2-methyl-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
   Pyridazine-4-carboxylic acid (2-cyano-4-fluoro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
   Pyridazine-4-carboxylic acid (3,5-dichloro-phenyl)-[1 -(2-methoxy-phenyl)-ethyl]-amide,
   Pyridazine-4-carboxylic acid [2-(4-cyano-phenyl)-2H-[1,2,3]triazol-4-ylmethyl]-(4-fluoro-2-methyl-phenyl)-amide,
   Pyridazine-4-carboxylic acid (3-cyano-4-fluoro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
   Pyridazine-4-carboxylic acid (2,4-difluoro-6-methoxy-benzyl)-(4-fluoro-2-methyl-phenyl)-amide,
Pyridazine-4-carboxylic acid (2,6-dimethyl-imidazo[2, 1-b]thiazol-5-ylmethyl)-(4-fluoro-2-methyl-phenyl)-amide,
S-Methyl-pyridazine^-carboxylic acid dibenzylamide,
S-Methyl-pyridazine^-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
S-Methyl-pyridazine^-carboxylic acid benzyl-phenyl-amide,
6-Oxo-6H-pyran-3-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
6-Oxo-6H-pyran-3-carboxylic acid (4-fluoro-2-methyl-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
N-(3,5-Dichloro-phenyl)-6-hydroxy-N-(2-methoxy-benzyl)-nicotinamide,
1-Methyl-6-oxo-1,e-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide,
1- Methyl-6-oxo-1 ,β-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-[1-(2-methoxy-phenyl)-ethyl]-amide,
1- Methyl-6-oxo-1 ,β-dihydro-pyridine-S-carboxylic acid (3-cyano-4-fluoro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
1- Methyl-6-oxo-1 ,6-dihydro-pyridine-S-carboxylic acid (2,4-difluoro-5-methoxy-benzyl)-(4-fluoro-2-methyl-phenyl)-amide,
1- Methyl-6-oxo-1 ,6-dihydro-pyridine-S-carboxylic acid (2,6-dimethyl-imidazo[2,1-b]thiazol-5-ylmethyl)-(4-fluoro-2-methyl-phenyl)-amide,
1- Methyl-6-oxo-1,e-dihydro-pyridine-S-carboxylic acid (2-cyano-4-fluoro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (4-fluoro-2-methyl-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-S-carboxylic acid (4-fluoro-2-methyl-phenyl)naphthalen-1-ylmethyl-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-(4-(2H-tetrazol-5-yl)-benzyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-S-carboxylic acid (3,4-dichloro-phenyl)-(2-methyl-1 H-indol-4-ylmethyl)-amide,
1- Methyl-6-oxo-1,6-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-(2,6-demethyl-imidazo[1-b]thiazol-S-ylmethylO-amide,
1- Methyl-\(\delta\)-oxo-i \(\theta\)-dihydro-pyridine-S-carboxylic acid (3,5-dichloro-phenyl)-(6-methoxy-pyridin-3-ylmethyl)-amide, and

N-(3,5-Dichloro-phenyl)-2-hydroxy-N-(2-methoxy-benzyl)-isonicotinamide \(=\) \(2\)-Oxo-1,2-dihydro-pyridine-4-carboxylic acid (3,5-dichloro-phenyl)-(2-methoxy-benzyl)-amide

9. A compound according to any preceding claim in the form of a salt.

10. A compound according to any one of claims 1 to 9 for use as a pharmaceutical.

11. A compound according to any one of claims 1 to 9 for the manufacture of a medicament for the treatment of disorders mediated by GPBAR1 activity.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 in association with at least one pharmaceutical excipient.

13. A method of treating disorders mediated by GPBAR1 activity, which treatment comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of claims 1 to 9.

14. A combination of a compound of any one of claims 1 to 9 with at least one second drug substance.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K  A61P

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 03/051923 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; CHIRN GUNG-WEI [US]; DENG) 26 June 2003 (2003-06-26) cited in the application the whole document</td>
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* Special categories of cited documents:

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered as novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered as involving an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- 'A' document member of the same patent family

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

3 June 2008

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

11/06/2008

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl Fax: (+31-70) 340-3016

Fritz, Martin

Form PCT/ISA/210 (second sheet) (April 2005)
**INTERNATIONAL SEARCH REPORT**

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**INTERNATIONAL SEARCH REPORT**

**Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. 
   
   **Claims Nos.:**
   
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   *Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.*

2. 
   
   **Claims Nos.:**
   
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. 
   
   **Claims Nos.:**
   
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. 
   
   **As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.**

2. 
   
   **As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.**

3. 
   
   **As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:**

4. 
   
   **No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos:**

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
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