A compound of general formula (I), wherein A together with the double bond of formula (I) forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine, pyrone, indole, pyrazole, imidazole, oxazole, isoxazole or thiiazole, R² is an optionally substituted C₁₋₆-alkyl, optionally substituted aralkyl, or COR³, R³ is an optionally substituted C₁₋₆-alkyl, optionally substituted aralkyl, or optionally substituted aryl, or optionally substituted heterocyclyl, R¹ is heterocarb, optionally substituted, or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer, a pharmaceutical composition containing them, and the use of such compounds for preparing medicaments for the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.
### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<table>
<thead>
<tr>
<th>AL</th>
<th>Albania</th>
<th>ES</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>Armenia</td>
<td>FI</td>
<td>Finland</td>
</tr>
<tr>
<td>AT</td>
<td>Austria</td>
<td>FR</td>
<td>France</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>GA</td>
<td>Gabon</td>
</tr>
<tr>
<td>AZ</td>
<td>Azerbaijan</td>
<td>GB</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>BA</td>
<td>Bosnia and Herzegovina</td>
<td>GE</td>
<td>Georgia</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>GH</td>
<td>Ghana</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>GN</td>
<td>Guinea</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>GR</td>
<td>Greece</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>HU</td>
<td>Hungary</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>IE</td>
<td>Ireland</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>IL</td>
<td>Israel</td>
</tr>
<tr>
<td>BY</td>
<td>Belarus</td>
<td>IS</td>
<td>Iceland</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>IT</td>
<td>Italy</td>
</tr>
<tr>
<td>CF</td>
<td>Central African Republic</td>
<td>JP</td>
<td>Japan</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>KE</td>
<td>Kenya</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>KG</td>
<td>Kyrgyzstan</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d’Ivoire</td>
<td>KP</td>
<td>Democratic People’s Republic of Korea</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>KR</td>
<td>Republic of Korea</td>
</tr>
<tr>
<td>CN</td>
<td>China</td>
<td>KZ</td>
<td>Kazakhstan</td>
</tr>
<tr>
<td>CU</td>
<td>Cuba</td>
<td>LC</td>
<td>Saint Lucia</td>
</tr>
<tr>
<td>CZ</td>
<td>Czech Republic</td>
<td>LI</td>
<td>Liechtenstein</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>LK</td>
<td>Sri Lanka</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
<td>LR</td>
<td>Liberia</td>
</tr>
<tr>
<td>EE</td>
<td>Estonia</td>
<td>LS</td>
<td>Lesotho</td>
</tr>
<tr>
<td>LT</td>
<td>Lithuania</td>
<td>LU</td>
<td>Luxembourg</td>
</tr>
<tr>
<td>LV</td>
<td>Latvia</td>
<td>MC</td>
<td>Monaco</td>
</tr>
<tr>
<td>MD</td>
<td>Republic of Moldova</td>
<td>MG</td>
<td>Madagascar</td>
</tr>
<tr>
<td>MK</td>
<td>The former Yugoslav Republic of Macedonia</td>
<td>ML</td>
<td>Mali</td>
</tr>
<tr>
<td>MN</td>
<td>Mongolia</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>MW</td>
<td>Malawi</td>
<td>MX</td>
<td>Mexico</td>
</tr>
<tr>
<td>NE</td>
<td>Niger</td>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>NO</td>
<td>Norway</td>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>PL</td>
<td>Poland</td>
<td>PT</td>
<td>Portugal</td>
</tr>
<tr>
<td>RO</td>
<td>Romania</td>
<td>RU</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>SD</td>
<td>Sudan</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>SG</td>
<td>Singapore</td>
<td>SI</td>
<td>Slovenia</td>
</tr>
<tr>
<td>SK</td>
<td>Slovakia</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>SZ</td>
<td>Swaziland</td>
<td>TD</td>
<td>Chad</td>
</tr>
<tr>
<td>TG</td>
<td>Togo</td>
<td>TJ</td>
<td>Tajikistan</td>
</tr>
<tr>
<td>TM</td>
<td>Turkmenistan</td>
<td>TR</td>
<td>Turkey</td>
</tr>
<tr>
<td>TT</td>
<td>Trinidad and Tobago</td>
<td>UA</td>
<td>Ukraine</td>
</tr>
<tr>
<td>UA</td>
<td>Uganda</td>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>UZ</td>
<td>Uzbekistan</td>
<td>VN</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>YU</td>
<td>Yugoslavia</td>
<td>ZW</td>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>
4,5,6,7-Tetrahydro-thieno[3,2-c]pyridine Derivatives.

Field of the invention
The present invention relates to 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivatives, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy, e.g. to their use for treatment of human and animal disorders. The invention relates to modulation of the activity of molecules with glucose-6-phosphate recognition units, including glucose-6-phosphatases (G-6-Pases) in in vitro systems, microorganisms, eukaryotic cells, whole animals and human beings, especially in the treatment of diseases related to glucose metabolic pathways.

Background of the invention
Glucose is the major energy substrate in mammals and regulation of blood glucose levels within a narrow range seems to be of crucial importance to avoid serious physiological complications as seen in diabetes (DeFronzo, Bonadonna, & Ferrannini. 1992). Blood glucose homeostasis is maintained by dietary intake of carbohydrates, the uptake of glucose by peripheral tissues and the brain, and storage or release of glucose from the liver. The liver therefore seems to play a major role in the homeostatic regulation of blood glucose levels. Gluconeogenesis and glycogenolysis are the two metabolic pathways from which glucose can be produced in the liver. These pathways are under tight hormonal control. Insulin resistance and insulin deficiency have a substantial impact on glucose production in the liver (Consoli. 1992; DeFronzo, Bonadonna, & Ferrannini. 1992; Clore, Stillman, Stevens, Blackard, Levy, & Richmond. 1996). Glucose-6-phosphatase (G-6-Pase) catalyses the terminal step in the above mentioned pathways by converting glucose-6-phosphate (G-6-P) to glucose, and is largely situated in the liver, with some expression in the kidney after prolonged fasting. The G-6-Pase is a multicomponent system comprising of the G-6-Pase catalytic enzyme with its active site located at the luminal site of the endoplasmic reticulum (microsomal fraction), a specific transporter T1 which mediates entry of G-6-P into the luminal compartment, and transporter T2 and T3 which mediates export to the cytosol of inorganic phosphate and glucose, respectively (Nordlie, Bode, & Foster. 1993; Sukalski & Nordlie. 1989). It has been shown that the rate of hydrolysis of G-6-P and the hepatic glucose output were increased under diabetic conditions (Lyall, Grant, Scott, & Burchell. 1992; DeFronzo, Bonadonna, & Ferrannini. 1992). The increased activity could mainly be accounted for by increased G-6-Pase catalytic enzyme protein (Argaud, Zhang, Pan, Maitra, Pilkis, &
Lange. 1996; Burchell & Cain. 1985). This makes G-6-Pase enzyme a potential target in control of excess glucose production seen in diabetes.

5 Bibliography


Description of the invention

The present invention relates to compounds of the general formula I:
wherein
A together with the double bond of formula I forms a cyclic system selected from the
group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine,
pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole or thiazole,

R¹ is furanyl; preferably 2-furanyl, 3-furanyl, 4-furanyl or 5-furanyl; thiényl, preferably 2-thiényl, 3-thiényl or 4-thiényl, 5-thiényl; pyrazolyl, preferably 4-pyrazolyl or 5-pyrazolyl;
tetrazolyl, preferably 5-tetrazolyl; isoxazolyl, preferably 3-isoxazolyl, 4-isoxazolyl or 5-isoxazolyl; isothiazolyl, preferably 3-isothiazolyl, 4-isothiazolyl or 5-isothiazolyl; 1,2,3-oxadiazolyl, preferably 1,2,3-oxadiazol-4-yl or 1,2,3-oxadiazol-5-yl; 1,2,3-thiadiazolyl,
preference 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-oxadiazolyl, preferably
1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl; 1,2,4-thiadiazolyl, preferably 1,2,4-
thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,3,4-oxadiazolyl, preferably 1,3,4-oxadiazol-2-yl,
or 1,3,4-oxadiazol-5-yl; 1,3,4-thiadiazolyl, preferably 1,3,4-thiadiazol-2-yl or 1,3,4-
thiadiazol-5-yl; 1,2,5-oxadiazolyl, preferably 1,2,5-oxadiazol-3-yl or 1,2,5-oxadiazol-5-
yl; 1,2,5-thiadiazolyl, preferably 1,2,5-thiadiazol-3-yl or 1,2,5-thiadiazol-5-yl;
benzo[d]isoxazolyl, preferably benzo[d]isoxazol-3-yl, benzo[d]isoxazol-4-yl,
benzo[d]isoxazol-5-yl, benzo[d]isoxazol-6-yl or benzo[d]isoxazol-7-yl;
benzo[d]isothiazolyl, preferably benzo[d]isothiazol-3-yl, benzo[d]isothiazol-4-yl,
benzo[d]isothiazol-5-yl, benzo[d]isothiazol-6-yl or benzo[d]isothiazol-7-yl, optionally sub-
tituted with one or more substituents,

R² is an optionally substituted C₁₋₄-alkyl, optionally substituted aralkyl, or COR³;
R³ is an optionally substituted C₁₋₄-alkyl, optionally substituted aralkyl, optionally sub-
tituted aryl,
or
W optionally substituted with one or more substituents.
W are independently selected from the list consisting of

\[
\text{\begin{align*}
\text{\includegraphics[width=0.5\textwidth]{diagram.png}}
\end{align*}}
\]

\]

X and Y are independently selected from the group consisting of NR\(^{10}\), O, S, >SO, >SO\(_2\), and R\(^{10}\) is selected from the list consisting of hydrogen,
a saturated straight or branched C\(_{1-8}\)-hydrocarbon chain optionally substituted with one
or more substituents,
an unsaturated straight or branched C\(_{2-8}\)-hydrocarbon chain optionally substituted op-
tionally substituted with one or more substituents,
a saturated C\(_{3-8}\)-alicyclic hydrocarbon group optionally substituted with one or more
substituents,
an unsaturated C\(_{5-8}\)-alicyclic hydrocarbon group optionally substituted with one or more
substituents,
C\(_{1-8}\)-acyl, C\(_{1-8}\)-alkoxycarbonyl, or mono- or dialkylcarbamoyl,

R\(^4\) and R\(^5\) independently are hydrogen, halogen, perhalomethyl, optionally substituted
C\(_{1-8}\)-alkyl, hydroxy, optionally substituted C\(_{1-8}\)-alkoxy, nitro, cyano, amino, optionally sub-
stituted mono- or optionally substituted di-C\(_{1-8}\)-alkylamino, acylamino, C\(_{1-8}\)-
alkoxycarbonyl, carboxy or carbamoyl,
or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, acetic, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethanesulfonic, picric and the like, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference; pharmaceutically acceptable metal salts, such as lithium, sodium, potassium, or magnesium salts and the like; or - optionally alkylated - ammonium salts; or amine salts of the compounds of this invention, such as the sodium, potassium, C_{1-6}-alkylamine, di (C_{1-6}-alkyl) amine, tri (C_{1-6}-alkyl) amine and the four (4) corresponding omega-hydroxy analogues (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, dipropylamine, trimethylamine, triethylamine, tripropylamine, di(hydroxyethyl)amine, and the like; Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

The term "C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated or unsaturated hydrocarbon chain. The C_{1-6}-alkyl residues include aliphatic hydrocarbon residues, unsaturated aliphatic hydrocarbon residues, alicyclic hydrocarbon residues. Examples of the aliphatic hydrocarbon residues include saturated aliphatic hydrocarbon residues having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, isopentyl, neopentyl, tert.pentyl, n-hexyl, iso-
hexyl. Example of the unsaturated aliphatic hydrocarbon residues includ those having 2 to 6
carbon atoms such as ethenyl, 1-propanyl, 2-propanyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-
methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-
hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, ethynyl, 1-propionyl, 2-propionyl, 1-butynyl, 2-
butynyl, 3-butylnyl, 1-pentynyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl. Examples of the alicyclic hydrocarbon residue include saturated alicyclic hydrocarbon residues having 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; and C5-6 unsaturated alicyclic hydrocarbon residues having 5 to 6 carbon
atoms such as 1-cyclopenteny1, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexeny1, 2-
cyclohexeny1, 3-cyclohexenyl.

The terms "lower alkyl" and "lower alkoxy" mean C1-6-alkyl and C1-6-alkoxy, respectively.

The term "aryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl, indene, fluorene, naphthyl (1-naphthyl, 2-naphthyl), anthracene (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), pyrrolyl (2-pyrrolyl), pyrazolyl (e.g. 3-pyrazolyl, 4-pyrazolyl and 5-pyrazolyl), imidazolyl (1-
imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-
yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl
(2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-
pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-
pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-
isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-
benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl),
2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-
dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-
benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-
benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-
benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl),
5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-
benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-
indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-
indazolyl, 7-indazolyl),
benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoazolyl (1-benzoazolyl, 2-benzoazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), furanyl (e.g. 2-furanyl, 3-furanyl, 4-furanyl and 5-furanyl), thiényl (e.g. 2-thienyl, 3-thienyl, 4-thienyl and 5-thienyl) optionally substituted with one or more substituents.

The term "optionally substituted" as used herein means an aryl residue as defined above or a C_{1-6} alkyl residue as defined above that may be unsubstituted or may have 1 or more preferably 1 to 5 substituents, which are the same as or different from one another. Examples of these substituents include, halogen (fluorine, chlorine, bromine, iodine), hydroxyl, cyano, nitro, trifluoromethyl, carbamoyl, C_{1-4}-acyl (e.g. acetyl, propionyl, isopropionyl), C_{1-6}-alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert.butoxy), C_{1-6}-alkyl as defined above, C_{1-6}-alkoxycarbonyl (e.g. ones having 2 to 6 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, and propoxycarbonyl), C_{1-6}-alkanoyloxy (e.g. ones having 2 to 6 carbon atoms such as acetyloxy, propionyloxy, isopropionyloxy), C_{1-4}-alkythio (e.g. ones having 1 to 4 carbon atoms such as methythio, ethylthio, propylthio, and isopropylthio), C_{1-4}-alkylsulphinyl (e.g. ones having 1-4 carbon atoms such as methylsulphinyl and ethylsulphinyl), C_{1-4}-alkylsulphonyl (e.g. ones having 1-4 carbon atoms such as methylsulphonyl and ethylsulphonyl), C_{1-4}-alkylamino (e.g. one having 1 to 4 carbon atoms such as methylamino, ethylamino, dimethylamino, and 1-pyrrolidinyl), aminoalkyl (e.g. one having an amino containing group connected to a C_{1-6}-alkyl group as defined above, such as 2-dimethylaminoethyl and 1-pyrrolidinylmethyl), aminoalkoxy (e.g. one having an amino containing group connected via a C_{1-6}-alkyl group as defined above to an oxygen atom, such as 2-dimethylaminoethoxy, 2-(4-morpholinyloxy and 1-pyrrolidinylmethoxy), aryl as defined above (e.g. phenyl and 4-pyridinyl), arloxy (e.g. phenoxy), and aralkyloxy (e.g. benzylxy).

The term "halogen" as used herein means fluorine, chlorine, bromine or iodine.
The term "perhalomethyl" as used herein means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "perhalomethoxy" as used herein means trifluoromethoxy, trichloromethoxy, tribromomethoxy or triiodomethoxy.

The term "aralkyl" as used herein refers to an optionally substituted aryl residue as defined above, connected to an optionally substituted C₄₋₆-alkyl as defined above. Examples of the aralkyl residue include benzyl, 2-phenylethyl, 2-phenylethenyl, 3-(2-pyridyl)propyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

The term "C₄₋₆-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₄₋₆-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The term "carbamoyl" as used herein refers to a carbamoyl which can be optionally substituted by one or two residues selected from the list consisting of optionally substituted C₄₋₆-alkyl as defined above, optionally substituted aryl as defined above and optionally substituted aralkyl as defined above.

In a preferred embodiment the invention relates to compounds of general formula (I)

\[
\begin{align*}
A & \quad \text{(CH}_2\text{)}_n \quad N \quad R^2 \\
R^1 & \quad \text{(CH}_2\text{)}_n \\
R^4 & \\
R^5 &
\end{align*}
\]

wherein

A together with the double bond of formula I forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridaz-
ine, pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole or thiazole,

R¹ is furanyl; preferably 2-furanyl, 3-furanyl, 4-furanyl or 5-furanyl; thieryl, preferably 2-thieryl, 3-thieryl or 4-thieryl, 5-thieryl; pyrazolyl, preferably 4-pyrazolyl or 5-pyrazolyl; tetrazolyl, preferably 5-tetrazolyl; isoxazolyl, preferably 3-isoxazolyl, 4-isoxazolyl or 5-isoxazolyl; isothiazolyl, preferably 3-isothiazolyl, 4-isothiazolyl or 5-isothiazolyl; 1,2,3-oxadiazo[1,2-d]isoxazolyl, preferably 1,2,3-oxadiazo[1,2-d]azol-4-yl or 1,2,3-oxadiazo[1,2-d]azol-5-yl; 1,2,3-thiadiazolyl, preferably 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-oxadiazo[1,2,4]triazolyl, preferably 1,2,4-oxadiazo[1,2,4]triazol-3-yl or 1,2,4-oxadiazo[1,2,4]triazol-5-yl; 1,2,4-thiadiazolyl, preferably 1,2,4-thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,3,4-oxadiazo[1,3,4]triazolyl, preferably 1,3,4-oxadiazo[1,3,4]triazol-2-yl, or 1,3,4-oxadiazo[1,3,4]triazol-5-yl; 1,3,4-thiadiazolyl, preferably 1,3,4-thiadiazol-2-yl or 1,3,4-thiadiazol-5-yl; 1,2,5-oxadiazo[1,2,5]triazolyl, preferably 1,2,5-oxadiazo[1,2,5]triazol-3-yl or 1,2,5-oxadiazo[1,2,5]triazol-5-yl; 1,2,5-thiadiazolyl, preferably 1,2,5-thiadiazol-3-yl or 1,2,5-thiadiazol-5-yl; benzo[d]isoxazolyl, preferably benzo[d]isoxazol-3-yl, benzo[d]isoxazol-4-yl, benzo[d]isoxazol-5-yl, benzo[d]isoxazol-6-yl or benzo[d]isoxazol-7-yl; benzo[d]isothiazolyl, preferably benzo[d]isothiazol-3-yl, benzo[d]isothiazol-4-yl, benzo[d]isothiazol-5-yl, benzo[d]isothiazol-6-yl or benzo[d]isothiazol-7-yl, optionally substituted with one or more substituents,

R² is an optionally substituted C₇₋₁₅-alkyl, optionally substituted aralkyl, or COR³,

R³ is an optionally substituted C₇₋₁₅-alkyl, optionally substituted aralkyl, or optionally substituted aryl,

R⁴ and R⁵ independently are hydrogen, halogen, perhalomethyl, optionally substituted C₇₋₁₅-alkyl, hydroxy, optionally substituted C₇₋₁₅-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C₇₋₁₅-alkylamino, acylamino, C₁₋₅-alkoxy carbonyl, carboxy or carbamoyl,

n is 0, 1, or 2, and

m is 0, 1, or 2,

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.
In a preferred embodiment the invention relates to compounds of general formula (I) in which A is selected from benzene or thiophene, preferably thiophene.

In a preferred embodiment the invention relates to compounds of general formula (I) in which R¹ is furanyl, preferably 2-furanyl, 3-furanyl, 4-furanyl or 5-furanyl, or thienyl, preferably 2-thienyl, 3-thienyl or 4-thienyl, 5-thienyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein each one of R¹, R², and R³ is substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R¹ are selected from the group consisting of hydrogen, halogen, perhalomethyl, perhalomethoxy, or C₁₋₅-alkoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R¹ are selected from the group consisting of chloro, trifluoromethyl, methoxy, trifluoromethoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R² is COR³ or (CH₂)ᵦ-aryl, and q is 0, 1, 2, 3, 4, 5, or 6.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R² is COR³.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is optionally substituted alkyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is optionally substituted cyclohexyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is methoxycyclohexyl.
In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is optionally substituted aryl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is optionally substituted aralkyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is (3-furanyl)-ethen-2-yl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is selected from the group consisting of phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, dimethylamino-phenyl, 4-(2-carboxyethyl)phenyl, 4-(2-dimethylaminoethoxy)phenyl, 4-(2-morpholin-4-yloxy)phenyl, 1H-indol-5-yl, 3-chloro-4-methoxyphenyl, and 1H-benzimidazol-5-yl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R³ is W optionally substituted with one or more substituents wherein W is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein W is optionally substituted with one or more substituents and W is

\[ \text{X} \]

wherein X is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein X is NR⁺⁰, wherein R⁺⁰ is as defined above.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R⁺⁰ is a saturated straight or branched C₁₋₅-hydrocarbon chain optionally substituted with one or more substituents or R⁺⁰ is a C₁₋₅-acyl.
In another preferred embodiment the invention relates to compounds of general formula (I), wherein $R_1^0$ is methyl or methanoyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein $R^4$ and $R^5$ independently is hydrogen, chloro, or methoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein $n$ is 0 or 1 and $m$ is 0 or 1.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein $n$ is 0 and $m$ is 1.

In another preferred embodiment the invention relates to compounds of general formula (Ia):

\[
\text{[Diagram of chemical structure]}
\]

wherein $R^6$ and $R^8$ independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminooethoxy, 2-carboxyethenyl, 2-morpholin-4-yloethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

In another preferred embodiment the invention relates to compounds of general formula (Ia):

\[
\text{[Diagram of chemical structure]}
\]

wherein $R^6$ and $R^8$ independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminooethoxy, 2-carboxyethenyl, 2-morpholin-4-yloethoxy, perhalomethyl, pref-
erably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl wherein R11 is selected from the group consisting of is hydrogen, halogen, preferably chloro or C₁₋₆-alkoxy, preferably methoxy or perhalomethyl, preferably trifluoromethyl, or perhalomethoxy, preferably trifluoromethoxy.

In another preferred embodiment the invention relates to compounds of general formula (Ib):

\[
\text{X} \quad \text{R}^7
\]

(Ib)

wherein X is O or S and R⁷ is hydrogen, halogen, perhalomethyl, or perhalomethoxy.

In another preferred embodiment the invention relates to compounds of general formula (Ic):

\[
\text{X} \quad \text{R}^3 \quad \text{R}^9
\]

(Ic)

wherein R³ is as defined above and R⁹ is hydrogen, halogen, preferably chloro, methoxy or perhalomethyl, preferably trifluoromethyl, or perhalomethoxy, preferably trifluoromethoxy.

In another preferred embodiment the invention relates to compounds of general formula (Id):

\[
\text{X} \quad \text{R}^3 \quad \text{R}^9
\]

(Id)

wherein R³ and R⁹ are as defined above.

In another preferred embodiment the invention relates to compounds of general formula (Ie):
wherein $R'$ is hydrogen, halogen, perhalomethyl, or perhalomethoxy

The most preferred compounds of the invention are:

\[(5\text{-Chlorothiophen-2-yl})(4\text{-thiophen-2-yl}4,5,6,7\text{-tetrahydro-thieno[3,2-c]pyridin-5-yl})\text{-methanone,}\]

\[(4\text{-Hydroxymethylphenyl})(4\text{-thiophen-2-yl}4,5,6,7\text{-tetrahydro-thieno[3,2-c]pyridin-5-yl})\text{-methanone,}\]

\[(4\text{-Chlorophenyl})(4\text{-thiophen-2-yl}4,5,6,7\text{-tetrahydro-thieno[3,2-c]pyridin-5-yl})\text{-methanone,}\]

\[(4\text{-Methoxyphenyl})(4\text{-thiophen-2-yl}4,5,6,7\text{-tetrahydro-thieno[3,2-c]pyridin-5-yl})\text{-methanone,}\]

\[4\text{-}(5\text{-Chlorothiophen-2-yl})4,5,6,7\text{-tetrahydrothieno[3,2-c]pyridin-5-yl}-(4\text{-methoxyphenyl})\text{methanone,}\]

\[(4\text{-Chlorophenyl})\text{-}[4\text{-}(5\text{-Chlorothiophen-2-yl})4,5,6,7\text{-tetrahydrothieno[3,2-c]pyridin-5-yl}]\text{methanone,}\]

\[4\text{-}(5\text{-Chlorothiophen-2-yl})4,5,6,7\text{-tetrahydrothieno[3,2-c]pyridin-5-yl}-(4\text{-methoxycyclohexyl})\text{methanone,}\]

\[4\text{-}(5\text{-Chlorothiophen-2-yl})4,5,6,7\text{-tetrahydrothieno[3,2-c]pyridin-5-yl}-(1\text{-methylpiperidin-4-yl})\text{methanone and}\]

\[1\text{-}[4\text{-}(5\text{-Chlorothiophen-2-yl})4,5,6,7\text{-tetrahydrothieno[3,2-c]pyridin-5-yl}]\text{-3-furan-3-yl-propenone.}\]

or a salt thereof with a pharmaceutically acceptable acid or base.

The compounds of the present invention are normoglycaemic agents (i.e. compounds that are able to normalise blood glucose levels from hyper-/hypoglycemic conditions) that interact with the glucose-6-phosphatase catalytic enzyme activity, and hence make them useful in the treatment and prevention of various diseases of the endocrinological system, especially ailments related to carbohydrate metabolism and especially the glucose metabolism, e.g.
hyperglycaemia, diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM) including long-term complications, such as retinopathy, neuropathy, nephropathy, and micro- and macroangiopathy, and hypoglycaemia resulting from, e.g., glycogen storage disease (von Gierke’s Disease all types). Moreover, the present compounds are useful in the prophylactic treatment of hyperlipidaemia, hypertension, liver and bile diseases, and atherosclerosis associated with diabetes. The present compounds are especially useful in the treatment of diseases associated with an increased or reduced activity of the glucose-6-phosphatase complex, e.g. the G-6-Pase catalytic enzyme.

Accordingly, in another aspect the invention relates to a compound of the invention or a pharmaceutically acceptable acid addition salt or other salt as defined above thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of hyperglycaemia and treatment or prevention of diabetes.

Furthermore, the invention also relates to the use of the inventive compounds of the invention as medicaments useful for treating hyperglycaemia and treating or preventing diabetes.

In yet another aspect, the present invention relates to methods of preparing the above-mentioned compounds. Methods of preparing compounds of general formula I comprises:

**Method A:**

When R² is COR³:

Reacting a compound of formula X with a compound of formula Y to form compounds of general formula Ib:
wherein $R^1$, $R^3$, $R^4$, $R^5$, n, and m are as defined above and L is a leaving group and are selected from fluorine, chlorine, bromine, iodine, 1-imidazolyl, 1,2,4-triazolyl, 1-benzotriazolyl, 1-(4-aza benzotriazolyl)oxy, pentafluorophenoxy, N-succinylxy 3,4-dihydro-4-oxo-3-(1,2,3-benzotriazinyl)oxy, $R^3$COO where $R^3$ is as defined above, or any other leaving group known to act as a leaving group in acylation reactions. The base can be either absent (i.e. compound X acts as a base) or triethylamine, N-ethyl-N,N-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in acylation reactions.

**Method B:**

When $R^2$ is optionally substituted C$_{1-8}$ alkyl or aralkyl:

15 a) Reacting a compound of formula X with a compound of formula Z in an alkylation reaction to form compounds of general formula I:

\[
\begin{array}{c}
\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{N} \\
\text{(CH$_2$)$_n$} \\
\text{NH} \\
\text{(CH$_2$)$_m$} \\
\text{R}^5 \\
\end{array}
\rightarrow
\begin{array}{c}
\text{H} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{N} \\
\text{(CH$_2$)$_n$} \\
\text{R}^5 \\
\end{array}
\]

\[
\begin{array}{c}
\text{X} \\
\text{Z} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{I} \\
\end{array}
\]

wherein $R^1$, $R^2$, $R^3$, $R^4$, n, and m are as defined above, M is a leaving group and is selected from chlorine, bromine, iodine, methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy or any other group known to act as a leaving group in alkylation reactions. The base can be either absent (i.e. compound X acts as a base) or triethylamine, N-ethyl-N,N-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in alkylation reactions.

**Method C:**
Reacting a compound of formula X with an aldehyde of formula Zz in a reductive alkylation reaction to form compounds of general formula I:

\[ R^1(N(CH_3)_n)(CH_3)_m \quad \text{Reducing agent} \quad R^1(N(CH_3)_n)(CH_3)_m \]

\[ \text{X} \quad \text{Zz} \quad \text{I} \]

wherein R\(^1\), R\(^2\), R\(^4\), R\(^5\), n, and m are as defined above, R\(^{11}\) is as defined for R\(^2\) but one (1) carbon atom shorter. The reducing agent can be selected from the following list: NaCNBH\(_3\), NaBH(OAc)\(_3\), diborane, BH\(_3\)_ complexes (eg. with tetrahydrofuran or dimethylsulfide), metallic sodium, or H\(_2\)/catalyst or any reductant known to be effective in the reductive alkylation reaction.

Or the compounds of the invention may be prepared by art-recognized procedures from known compounds or readily prepared intermediates.


Pharmacological methods
The ability of compounds to inhibit glucose-6-phosphatase (G-6-Pase) catalytic enzyme activity from pig liver microsomes was tested in the following way:

Pig liver microsomes were prepared in a buffer containing 250 mM sucrose, 1 mM EDTA, 25 mM HEPES and 250 mg/l Bacitrazin (pH 7.5) essentially as described by Arion et al., 1980 (Arion, Lange, & Walls. 1980). Microsomes were kept at -80 °C until use.

Prior to measurement microsomes were treated with Triton X-100 (0.04%) ("disrupted microsomes"). G-6-Pase activity were assayed for 6 min at 30°C in a total volume of 325 μL containing 0.5 mM glucose-6-phosphate, 30 mM MES (pH 6.5), test compound and disrupted microsomes (0.05 mg). The reaction was terminated by addition of 100 μL Sigma phosphorus reagent (cat no 360-3C). This mixture was allowed to stand for 2 min, where the absorbance (A) was measured at 340 nm. All values were corrected for blank. The inhibitory effect was expressed as percent of control value, i.e. IC₅₀ is the concentration of a compound that produces 50% inhibition.

The compounds of the invention are preferably characterized by having a glucose-6-phosphatase inhibitory activity corresponding to an IC₅₀ value of less than 100 μM, more preferably less than 10 μM, even more preferably less than 1 μM, still more preferably less than 100 nM.

The compounds according to the invention are effective over a wide dosage range. In general satisfactory results are obtained with dosages from about 0.05 to about 1000 or 5000mg, preferably from about 0.1 to about 500 mg, per day. A most preferable dosage is about 5 mg to about 200 mg per day. The exact dosage will depend upon the mode of administration, form in which the compound is administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The dosage unit of the pharmaceutical compositions according to the invention typically contains from 0.05mg to 1000mg, preferably from 0.1mg to 500mg, or, preferably from 5mg to 200mg per day of the active ingredient, which is, preferably, a novel 4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivative as described herein or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of
optical isomers, including a racemic mixture, or any tautomeric form thereof; or the active ingredient is a previously described 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivative or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form thereof.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intrapulmonary, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more compounds exhibiting a different activity, e.g., a plasma lipid lowering compounds, sulphonylurea like compounds, or other oral agents useful in the treatment of diabetes, or other pharmacologically active material.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt or metal salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, sil-
ic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glycercy monoostearate or glycercy disteareate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated in any galenic dosage form so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For administration, preferably nasal administration, the preparation may contain a compound of formula I, Ia, Ib or Ic dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylycholine) or cyclodextrin, or preservatives such as parabenes. For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Core:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active compound (as free compound or salt thereof)</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Colloidal silicon dioxide (Aerosil)</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Cellulose, microcryst. (Avicel)</td>
<td>70 mg</td>
</tr>
<tr>
<td>Modified cellulose gum (Ac-Di-Sol)</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Ad.</td>
</tr>
</tbody>
</table>
Coating:

HPMC approx. 9 mg

*Mywacett 9-40 T approx. 0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

Due to their high degree of activity, the compounds of the invention may be administered to a mammal in need of such treatment, prevention, elimination, alleviation or amelioration of various diseases as mentioned above and especially of diseases of the endocrinological system such as hyperinsulinaemia and diabetes. Such mammals include both domestic animals, e.g. household pets, and non-domestic animals such as wildlife. Preferably the mammal is a human.

EXAMPLES

The process for preparing compounds of the invention and preparations containing them is further illustrated in the following examples which, however, are not to be construed as limiting.

Preparation of 4-((thiophen-2-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine:

![Chemical Structure]

2-(2-Thienyl)-ethyamine (2 g, 15.7 mmol), 2-thienylaldehyde (1.76 g, 15.7 mmol), triethylamine (1 ml) and ethanol (15 ml) were mixed, and the reaction mixture was stirred at room temperature for 96 hours. The mixture was evaporated in vacuo, and the residue was crystallised from hexane to give the imine (1.26 g). The imine was added trifluoroacetic acid (25 ml) and the reaction mixture was stirred at 60 °C for 12 hours. The reaction mixture was evaporated in vacuo. The residue was dissolved in dichloromethane (30 ml) and washed with 2 N sodium hydroxide (30 ml). The aqueous phase was extracted with dichloromethane
(3x25 mL). The combined organic phases were dried with MgSO₄, filtered and evaporated in vacuo. The residue (1.15 g) was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (19:1) to afford 0.18 g (5%) of the title compound.

M.p.: 96-97.3 °C.

**EXAMPLE 1:**

(5-Chlorothiophen-2-yl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

![Chemical structure image]

A solution of 4-(thiophen-2-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) was added to a solution of 5-chlorothiophene-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol). To this solution 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) was added. The mixture was shaken overnight at room temperature at 1000 rpm, added saturated NaCl (2 ml), and extracted with ethyl acetate (2 x 1 ml). The combined organic extracts were evaporated to afford the title compound.

HPLC-MS: Rₜ = 16.13 min. m/z: 366 (M+1)

**EXAMPLE 2:**

(4-Hydroxymethylphenyl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone
Similarly as described in example using a solution of 4-thiophen-2-yl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-hydroxymethylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: \( R_t = 11.88 \text{ min. } m/z: 356 (M+1) \)

**EXAMPLE 3:**
(4-Chlorophenyl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

Similarly as described in example using a solution of 4-thiophen-2-yl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: \( R_t = 15.62 \text{ min. } m/z: 360 (M+1) \)

**EXAMPLE 4:**
(4-Methoxyphenyl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone
Similarly as described in example using a solution of 4-thiophen-2-yl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'ethylenediamine dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: \( \text{Rt} = 14.58 \text{ min. m/z: 356 (M+1)} \)

**EXAMPLE 5:**

4-(5-Chloro-thiophen-2-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine

2-(2-Thienyl)-ethylamine (1g, 7.9 mmol) and 5-chloro-thiohene-2-carbaldehyde (1.15g, 7.9 mmol) were mixed, exothermic! The separated water was decanted and the remaining oil was heated until reflux. The mixture was allowed to cool to room temperature. Then TFA (10 mL) was added under stirring, then refluxed for 16 hours. The reaction mixture was evaporated in vacuo. Dissolved in dichloromethane (50 mL) washed with 1N NaOH (50 ml). The waterphase was back-extracted with dichloromethane (50 mL). The combined organic phase was dried with MgSO4, filtered, and evaporated in vacuo. The residue (1.2g) was purified on a silica gel column eluting with dichloromethane and then a mixture of dichloromethan:methanol (19:1) to afford the title compound 0.2 g as a yellow oil. The structure was confirmed by NMR-spectroscopy.
EXAMPLE 5:

5 [4-(5-Chlorothiophen-2-yl)4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)-(4-methoxyphenyl)methanone

4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (0.15 mmol), 4-
methoxybenzoic acid (0.15 mmol), HOBT, 1-hydroxybenzotriazole (0.15 mmol) and EDAC,
N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.225 mmol) were mixed in
N,N-dimethylamide (1 mL). The reaction mixture was shaken overnight at room temperature
at 1000 rpm, added saturated NaCl (2 mL) and extracted with ethyl acetate (1 mL). The organic
phase was evaporated to afford the title compound.

HPLC-MS: Rt= 16.38 min, m/z: 381 (M+1)

EXAMPLE 6:

(4-Chlorophenyl)-[4-(5-chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-
yl)methanone
4-(5-Chloro-thiophen-2-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (0.15 mmol), 4-chlorobenzoic acid (0.15 mmol), HOBT, 1-hydroxybenzotriazole (0.15 mmol) and EDAC, N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (0.225 mmol) were mixed in N,N-dimethylamide (1 mL). The reaction mixture was shaken overnight at room temperature at 1000 rpm, added saturated NaCl (2 mL) and extracted with ethyl acetate (1 mL). The organic phase was evaporated to afford the title compound.

HPLC-MS: Rt= 17.32 min, m/z: 395 (M+1)

EXAMPLE 7:

[4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-(4-methoxycyclohexyl)methanone

4-(5-Chloro-thiophen-2-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (0.15 mmol), 4-methoxycyclohexylcarboxylic acid (0.15 mmol), HOBT, 1-hydroxybenzotriazole (0.15 mmol) and EDAC, N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (0.225 mmol) were mixed in N,N-dimethylamide (1 mL). The reaction mixture was shaken overnight at room temperature at 1000 rpm, added saturated NaCl (2 mL) and extracted with ethyl acetate (1 mL). The organic phase was evaporated to afford the title compound, as a cis/trans mixture.

HPLC-MS: Rt= 15.45 & 15.80 min ; m/z: 397 (M+1)

EXAMPLE 8:
5 4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (0.15 mmol), 1-methylpiperidin-4-yl-carboxylic acid (0.15 mmol), HOBT, 1-hydroxybenzotriazole (0.15 mmol) and EDAC, N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (0.225 mmol) were mixed in N,N-dimethylamide (1 mL). The reaction mixture was shaken overnight at room temperature at 1000 rpm, added saturated NaCl (2 mL) and extracted with ethyl acetate (1 mL). The organic phase was evaporated to afford the title compound.

HPLC-MS: Rt= 9.45 min; m/z: 382 (M+1)

EXAMPLE 9:

15 1-[4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-3-furan-3-yl-propenone

4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (0.15 mmol), 3-(3-furanyl)acrylic acid (0.15 mmol), HOBT, 1-hydroxybenzotriazole (0.15 mmol) and EDAC, N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (0.225 mmol) were mixed in N,N-dimethylamide (1 mL). The reaction mixture was shaken overnight at room temperature at 1000 rpm, added saturated NaCl (2 mL) and extracted with ethyl acetate (1 mL). The organic phase was evaporated to afford the title compound.
HPLC-MS: Rt = 15.97 min; m/z: 377 (M+1)

General:

The HPLC-MS analyses were performed on a PE Sciex API 100 LC/MS System using a WatersTM 3 mm x 150 mm 3.5 μ C-18 Symmetry column and positive ionspray with a flow rate at 20 μL/minute. The column was eluted with a linear gradient of 5-90% A, 85-0% B and 10% C in 15 minutes at a flow rate of 1 ml/min (solvent A = acetonitrile, solvent B = water and solvent C = 0.1% trifluoroacetic acid in water).
1. A compound of the general formula I

\[
\begin{array}{c}
\text{R}^4 \\
\text{A} \\
\text{R}^5 \\
\text{R}^1 \\
\text{N}--\text{R}^2 \\
\text{R}^3 (\text{CH}_2)_n \\
\end{array}
\]

wherein

A together with the double bond of formula I forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole or thiazole,

\(\text{R}^1\) is furanyl; preferably 2-furanyl, 3-furanyl, 4-furanyl or 5-furanyl; thienyl, preferably 2-thienyl, 3-thienyl or 4-thienyl, 5-thienyl; pyrazolyl, preferably 4-pyrazolyl or 5-pyrazolyl; tetrazolyl, preferably 5-tetrazolyl; isoxazolyl, preferably 3-isoxazolyl, 4-isoxazolyl or 5-isoxazolyl; isothiazolyl, preferably 3-isothiazolyl, 4-isothiazolyl or 5-isothiazolyl; 1,2,3-oxadiazolyl, preferably 1,2,3-oxadiazol-4-yl or 1,2,3-oxadiazol-5-yl; 1,2,3-thiadiazolyl, preferably 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-oxadiazolyl, preferably 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl; 1,2,4-thiadiazolyl, preferably 1,2,4-thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,3,4-oxadiazolyl, preferably 1,3,4-oxadiazol-2-yl, or 1,3,4-oxadiazol-5-yl; 1,3,4-thiadiazolyl, preferably 1,3,4-thiadiazol-2-yl or 1,3,4-thiadiazol-5-yl; 1,2,5-oxadiazolyl, preferably 1,2,5-oxadiazol-3-yl or 1,2,5-oxadiazol-5-yl; 1,2,5-thiadiazolyl, preferably 1,2,5-thiadiazol-3-yl or 1,2,5-thiadiazol-5-yl; benzo[d]isoxazolyl, preferably benzo[d]isoxazol-3-yl, benzo[d]isoxazol-4-yl, benzo[d]isoxazol-5-yl, benzo[d]isoxazol-6-yl or benzo[d]isoxazol-7-yl; benzo[d]isothiazolyl, preferably benzo[d]isothiazol-3-yl, benzo[d]isothiazol-4-yl, benzo[d]isothiazol-5-yl, benzo[d]isothiazol-6-yl or benzo[d]isothiazol-7-yl, optionally substituted with one or more substituents,

\(\text{R}^2\) is an optionally substituted \(\text{C}_{1-4}\)-alkyl, optionally substituted aralkyl, or COR\(^3\),
$R^3$ is an optionally substituted C$_{1,5}$-alkyl, optionally substituted aralkyl, optionally substituted aryl,
or
W optionally substituted with one or more substituents.

W are independently selected from the list consisting of

X and Y are independently selected from the group consisting of NR$^{10}$, O, S, >SO, >SO$_2$,

and R$^{10}$ is selected from the list consisting of hydrogen,
a saturated straight or branched C$_{1,5}$-hydrocarbon chain optionally substituted with one or more substituents,
an unsaturated straight or branched C$_{2,9}$-hydrocarbon chain optionally substituted optionally substituted with one or more substituents,
a saturated C$_{3,8}$-alicyclic hydrocarbon group optionally substituted with one or more substituents,
an unsaturated C$_{5,8}$-alicyclic hydrocarbon group optionally substituted with one or more substituents,
C$_{1,5}$-acyl, C$_{1,5}$-alkoxycarbonyl, or mono- or dialkylcarbamoyl,
R⁴ and R⁵ independently are hydrogen, halogen, perhalomethyl, optionally substituted C₁₋₄-alkyl, hydroxy, optionally substituted C₁₋₄-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C₁₋₄-alkylamino, acylamino, C₁₋₄-alkoxycarbonyl, carboxy or carbamoyl,

n is 0, 1, or 2, and
m is 0, 1, or 2,

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

2. A compound according to claim 1 wherein the general formula I is

\[
\begin{align*}
\text{A} & \quad \begin{array}{c}
\text{R}^4 \\
\text{R}^5
\end{array} \\
\text{N} & \quad \begin{array}{c}
\text{R}^2 \\
\text{R}^1 \\
\text{(CH}_2\text{)}_n
\end{array} \\
\text{(CH}_2\text{)}_m
\end{align*}
\]

wherein

A together with the double bond of formula I forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole or thiazole,

R¹ is furanyl; preferably 2-furanyl, 3-furanyl, 4-furanyl or 5-furanyl; thiienyl, preferably 2-thiienyl, 3-thiienyl or 4-thiienyl, 5-thiienyl; pyrazolyl, preferably 4-pyrazolyl or 5-pyrazolyl; tetrazolyl, preferably 5-tetrazolyl; isoaxazolyl, preferably 3-isoaxazolyl, 4-isoaxazolyl or 5-isoaxazolyl; isothiazolyl, preferably 3-isothiazolyl, 4-isothiazolyl or 5-isothiazolyl; 1,2,3-oxadiazolyl, preferably 1,2,3-oxadiazol-4-yl or 1,2,3-oxadiazol-5-yl; 1,2,3-thiadiazolyl, preferably 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-oxadiazolyl, preferably 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl; 1,2,4-thiadiazolyl, preferably 1,2,4-thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,3,4-oxadiazolyl, preferably 1,3,4-oxadiazol-2-yl,
or 1,3,4-oxadiazol-5-yl; 1,3,4-thiadiazolyl, preferably 1,3,4-thiadiazol-2-yl or 1,3,4-thiadiazol-5-yl; 1,2,5-oxadiazolyl, preferably 1,2,5-oxadiazol-3-yl or 1,2,5-oxadiazol-5-yl; 1,2,5-thiadiazolyl, preferably 1,2,5-thiadiazol-3-yl or 1,2,5-thiadiazol-5-yl; benzo[d]isoxazolyl, preferably benzo[d]isoxazol-3-yl, benzo[d]isoxazol-4-yl, benzo[d]isoxazol-5-yl, benzo[d]isoxazol-6-yl or benzo[d]isoxazol-7-yl; benzo[d]isothiazolyl, preferably benzo[d]isothiazol-3-yl, benzo[d]isothiazol-4-yl, benzo[d]isothiazol-5-yl, benzo[d]isothiazol-6-yl or benzo[d]isothiazol-7-yl, optionally substituted with one or more substituents,

R² is an optionally substituted C₁₋₆-alkyl, optionally substituted aralkyl, or COR³; R³ is an optionally substituted C₁₋₆-alkyl, optionally substituted aralkyl, or optionally substituted aryl,

R⁴ and R⁵ independently are hydrogen, halogen, perhalomethyl, optionally substituted C₁₋₆-alkyl, hydroxy, optionally substituted C₁₋₆-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C₁₋₆-alkylamino, acylamino, C₁₋₆-alkoxycarbonyl, carboxy or carbamoyl,

n is 0, 1, or 2, and
m is 0, 1, or 2,
or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

3. A compound according to claim 1 or 2, wherein A is selected from benzene or thiophene, preferably thiophene.

4. A compound according to any one of the preceding claims, wherein R¹ is furanyl, preferably 2-furanyl, 3-furanyl, 4-furanyl or 5-furanyl, or thiienyl, preferably 2-thienyl, 3-thienyl or 4-thienyl, 5-thienyl.

5. A compound according to any one of the preceding claims, wherein each one of R¹, R², and R³ is substituted with one or more substituents.
6. A compound according to claim 5, wherein the substituents of R¹ is hydrogen, halogen, perhalomethyl, perhalomethoxy, or C₁₋₆-alkoxy.

7. A compound according to claim 5 or 6, wherein the substituents of R¹ are selected from the group consisting of hydrogen, halogen, perhalomethyl, perhalomethoxy, or C₁₋₆-alkoxy.

8. A compound according to claim 7, wherein the substituents of R¹ are selected from the group consisting of chloro, trifluoromethyl, methoxy, trifluoromethoxy.

9. A compound according to any one of the preceding claims wherein R² is COR³ or (CH₂)ₐ-aryl, and q is 0, 1, 2, 3, 4, 5, or 6.

10. A compound according to the preceding claim wherein R² is COR³.

11. A compound according to any one of the preceding claims, wherein R³ is optionally substituted alkyl.

12. A compound according to claim 11 wherein R³ is optionally substituted cyclohexyl.

13. A compound according to claim 12 wherein R³ is methoxy-cyclohexyl.

14. A compound according to any one of the preceding claims, wherein R³ is optionally substituted aryl.

15. A compound according to any one of the claims 1 to 10, wherein R³ is optionally substituted aralkyl.

16. A compound according to claim 15 wherein R³ is (3-furanyl)-ethen-2-yl.

17. A compound according to claim 14, wherein R³ is selected from the group consisting of phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, dimethylaminophenyl, 4-(2-carboxyethenyl)phenyl, 4-(2-
dimethylaminoethoxy)phenyl, 4-(2-morpholin-4-yloxy)phenyl, 1H-indol-5-yl, 3-chloro-4-methoxyphenyl, and 1H-benzimidazol-5-yl.

18. A compound according to any of the claims 1-10 wherein $R^3$ is $W$ optionally substituted with one or more substituents wherein $W$ is as defined above.

19. A compound according to claim 18 wherein $W$ is optionally substituted with one or more substituents and $W$ is

![Chemical structure image]

wherein $X$ is as defined above.

20. A compound according to claim 19 wherein $X$ is $\text{NR}^{10}$, wherein $R^{10}$ is as defined above.

21. A compound according to claim 20 wherein $R^{10}$ is a saturated straight or branched $\text{C}_{1-8}^-$ hydrocarbon chain optionally substituted with one or more substituents or $R^{10}$ is a $\text{C}_{1-8}^-$ acyl.

22. A compound according to claim 21 wherein $R^{10}$ is methyl or methanoyl.

23. A compound according to any one of the preceding claims, wherein $R^4$ and $R^5$ independently is hydrogen, chloro, or methoxy.

24. A compound according to any one of the preceding claims, wherein $n$ is 0 or 1 and $m$ is 0 or 1.

25. A compound according to any one of the preceding claims, wherein $n$ is 0 and $m$ is or 1.

26. A compound according to claim 1 and having the general formula Ia:
wherein $R^6$ and $R^8$ independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminoethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

27. A compound according to claim 1 and having the general formula (la):

wherein $R^6$ and $R^8$ independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminoethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl wherein R11 is selected from the group consisting of is hydrogen, halogen, preferably chloro or C$_{1-4}$-alkoxy, preferably methoxy or perhalomethyl, preferably trifluoromethyl or perhalomethoxy.

28. A compound according to claim 1 and having the general formula (lb):

wherein $X$ is O or S and $R^7$ is hydrogen, halogen, perhalomethyl, or perhalomethoxy.
29. A compound according to claim 1 and having the general formula (Ic):

\[
\begin{align*}
\text{(Ic)}
\end{align*}
\]

wherein \( R^3 \) is as defined above and \( R^9 \) is hydrogen, halogen, preferably chloro, methoxy or perhalomethyl, preferably trifluoromethyl, or perhalomethoxy, preferably trifluormethoxy.

30. A compound according to claim 1 and having the general formula (Id):

\[
\begin{align*}
\text{(Id)}
\end{align*}
\]

wherein \( R^3 \) and \( R^9 \) are as defined above.

31. A compound according to claim 1 and having the general formula (Ie):

\[
\begin{align*}
\text{(Ie)}
\end{align*}
\]

wherein \( R^7 \) is hydrogen, halogen, perhalomethyl, or perhalomethoxy.

32. A compound according to claim 1, selected from the group consisting of

(5-Chlorothiophen-2-yl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone,

(4-Hydroxymethylphenyl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone,

(4-Chlorophenyl)-(4-thiophen-2-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone, and
(4-Methoxyphenyl)-(4-thiophen-2-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone,
[4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-4-methoxyphenyl)methanone
5
(4-Chlorophenyl)-[4-(5-chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]methanone
[4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-4-methoxycyclohexyl)methanone
[4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-(1-methylpiperidin-4-yl)methanone
10
1-[4-(5-Chlorothiophen-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-3-furan-3-yl-propanone
or a salt thereof with a pharmaceutically acceptable acid or base.

33. A salt of a compound according to the preceding claim with a pharmaceutically acceptable base.

34. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of claims 1 - 32, or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

35. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as hyperglycaemia and diabetes comprising, as an active ingredient, a compound according to any of the claims 1 - 32 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

36. The pharmaceutical composition according to claim 34 or 35 in the form of an oral dosage unit or a parenteral dosage unit.
37. A pharmaceutical composition according to claim 35 or 36 wherein said ingredient is present in a unit dose in a range from about 0.05 to 1000, preferably from about 0.1 to 500 and especially in the range from 5 to 200 mg.

38. A compound according to any of the claims 1 - 32 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

39. A compound according to any of the claims 1 - 32 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

40. A compound according to any of the claims 1 - 32 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form, characterized by having a glucose-6-phosphatase inhibitory activity corresponding to an IC$_{50}$ value of less than 100 μM, preferably less than 10 μM, more preferably less than 1 μM, still more preferably less than 100 nM.

41. The use of a compound according to any of the claims 1 - 32 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

42. The use of a compound according to any of the claims 1 - 32 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of glycogen storage disease or hypoglycaemia.
43. A method of treating or preventing diseases of the endocrinological system, preferably hyperglycaemia or diabetes in a subject in need thereof comprising administering an effective amount of a compound according to any one of claims 1 - 32 to said subject.

44. A method of treating or preventing hyperglycaemia or hypoglycaemia in a subject in need thereof comprising administering an effective normoglycaemic amount of a compound according to any one of claims 1 - 32 to said subject.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC6:** C07D 495/04, A61K 31/435  
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)

**IPC6:** C07D, A61K

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

SE, DK, FI, NO classes as above

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

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P,X</td>
<td>WO 9840385 A1 (NOVO NORDISK), 17 Sept 1998 (17.09.98)</td>
<td>1-44</td>
</tr>
<tr>
<td>X</td>
<td>NL 7807819 A (SMITHKLINE CORPORATION TE PHILADELPHIA), 23 January 1980 (23.01.80), see the examples</td>
<td>1-7,9,23-24, 34-40</td>
</tr>
<tr>
<td>X</td>
<td>US 5440033 A (JOEL G. BERGER ET AL), 8 August 1995 (08.08.95), see examples 2-3</td>
<td>1-3,5-7, 34-40</td>
</tr>
<tr>
<td>X</td>
<td>US 4174448 A (ANDRE BOUSQUET ET AL), 13 November 1979 (13.11.79), see example 3</td>
<td>1-7,9,23-24, 40</td>
</tr>
</tbody>
</table>

* Further documents are listed in the continuation of Box C.  
* See patent family annex.

* "A" document defining the general state of the art which is not considered to be of particular relevance  
"E" other document not published on or after the international filing date  
"I" 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 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 to involve 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  
"&" document member of the same patent family

Date of the actual completion of the international search: 28 May 1999  
Date of mailing of the international search report: 30 June 1999

Name and mailing address of the ISA:  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No.: + 46 8 666 02 86

Authorized officer:  
Anna Sjölund  
Telephone No.: + 46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 9634870 A1 (SYNTHELABO), 7 November 1996 (07.11.96)</td>
<td>1-44</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Box I</th>
<th>Observations where certain claims were found unsearable (Continuation of item 1 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:</td>
</tr>
</tbody>
</table>

1. ☒ Claims Nos.: 43–44  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   see next sheet

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:

<table>
<thead>
<tr>
<th>Box II</th>
<th>Observations where unity of invention is lacking (Continuation of item 2 of first sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This International Searching Authority found multiple inventions in this international application, as follows:</td>
</tr>
</tbody>
</table>

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 fee, this Authority did not invite payment of any additional fee.

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.
☐ No protest accompanied the payment of additional search fees.
Claims 43-44 relate to a methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/rule. 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL 7807819 A</td>
<td>23/01/80</td>
<td>AU 515236 B</td>
<td>26/03/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 3747178 A</td>
<td>03/01/80</td>
</tr>
<tr>
<td>US 5440033 A</td>
<td>08/08/95</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>US 4174448 A</td>
<td>13/11/79</td>
<td>AR 224501 A</td>
<td>15/12/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 366691 B</td>
<td>26/04/82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 468978 A</td>
<td>15/09/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 516506 B</td>
<td>04/06/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 3794078 A</td>
<td>17/01/80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BE 868866 A</td>
<td>10/01/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 1113469 A</td>
<td>01/12/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH 633013 A</td>
<td>15/11/82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DD 136838 A</td>
<td>01/08/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 311078 A</td>
<td>13/01/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0000453 A,B</td>
<td>24/01/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE 0000453 T3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI 67852 B,C</td>
<td>28/02/85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI 782044 A</td>
<td>13/01/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2397417 A,B</td>
<td>09/02/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 1599728 A</td>
<td>07/10/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GR 64796 A</td>
<td>02/06/80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 941023 A,B</td>
<td>29/02/96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IE 46929 B</td>
<td>02/11/83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 1490170 C</td>
<td>07/04/89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 54019994 A</td>
<td>15/02/79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LU 79823 A</td>
<td>07/12/78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PH 14288 A</td>
<td>04/05/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 68251 A</td>
<td>01/08/78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SI 7811482 A</td>
<td>31/08/97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SU 900813 A</td>
<td>23/01/82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 7803296 A</td>
<td>25/07/79</td>
</tr>
<tr>
<td>WO 9634870 A1</td>
<td>07/11/96</td>
<td>AU 699120 B</td>
<td>19/11/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 5652096 A</td>
<td>21/11/96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BG 102015 A</td>
<td>31/08/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9608309 A</td>
<td>26/01/99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2220015 A</td>
<td>07/11/96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 9703466 A</td>
<td>18/02/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0823912 A</td>
<td>18/02/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2733750 A,B</td>
<td>08/11/96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 118119 D</td>
<td>00/00/00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 975020 A</td>
<td>05/01/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 307230 A</td>
<td>25/11/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 323177 A</td>
<td>16/03/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SK 147897 A</td>
<td>06/05/98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5869518 A</td>
<td>09/02/99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 9603485 A</td>
<td>25/11/96</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (July 1992)