Title: METHOD OF USING POTASSIUM CHANNEL INHIBITING COMPOUNDS

Abstract: The present invention relates to methods of treating various medical conditions by administering an effective amount of at least one potassium $K_{\text{a}}$ channel inhibitor or of an effective amount of at least compound having in addition to its potassium $K_{\text{a}}$ channel inhibiting properties also $C_{\text{b}}$ modulating properties and/or potassium $K_{\text{c}}$ channel opening properties to subjects in need thereof. The present invention further relates to the use of an effective amount of at least one potassium $K_{\text{a}}$ channel inhibitor or of an effective amount of at least one compound having in addition to its potassium $K_{\text{a}}$ channel inhibiting properties also $C_{\text{b}}$ modulating properties and/or potassium $K_{\text{c}}$ channel opening properties for the manufacture of a medicament for the prophylaxis, treatment, delayed progression, delayed onset and/or inhibition of various medical conditions in subjects in need thereof.

For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.

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Method of Using Potassium Channel Inhibiting Compounds

FIELD OF THE INVENTION

The present invention relates to methods of treating, preventing or inhibiting various medical conditions, such as type I and type II diabetes, by administering an effective amount of at least one potassium $K_{v1.3}$ channel inhibitor to subjects in need thereof. Optionally, the potassium $K_{v1.3}$ channel inhibitor can have in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $C_{Bx}$ modulating properties and/or potassium $K_{(lep)}$ channel opening properties.

BACKGROUND OF THE INVENTION

Insulin is a critical modulator of glucose and lipid homeostasis and cellular proliferation. It is secreted into the bloodstream by the pancreatic $\beta$-cells in response to a rise in serum glucose and amino acids, such as occurs following meal ingestion, but is also secreted as part of the pre-absorptive, cephalic phase of meal ingestion. This insulin binds to a specific insulin receptor (IR) at the plasma membrane of cells of insulin-responsive tissues, such as skeletal muscle, fat and liver. Brain cells expressing IR are believed to play a role in glucose homeostasis and appetite regulation. Binding of insulin to IR initiates a cascade of events that result in translocation of the glucose transporter GLUT4 to the plasma membrane e.g. of skeletal (and cardiac) muscle and adipocytes, or of GLUT2 to the plasma membrane of hepatocytes and this allows glucose uptake into the cell and its metabolism.

Type II diabetes (non-insulin-dependent diabetes mellitus or “NIDDM”) patients display a gradually increasing degree of insulin resistance. Early in the disease, insulin secretion is typically increased in an effort to maintain normal glucose metabolism but as the disease progresses, insulin secretion falls because of the chronic overstimulation of the pancreatic islets. At this late stage, NIDDM patients compare to type I diabetes (insulin-dependent diabetes mellitus or “IDDM”) patients, in that they do not produce enough insulin to maintain normal glucose metabolism. Present therapy for NIDDM, in addition to diet and exercise, comprises monotherapy or combination therapy with insulin-releasing agents (e.g. sulphonylureas) or injectable insulin, insulin-sensitizing agents (such as met-
formin, or the TDZ’s), alpha-glucosidase inhibitors (e.g., acarbose) or lipase inhibitors (e.g., Xenical®). Therapy of type I diabetes (IDDM) requires injectable insulin, diet and exercise.

The underlying causes of insulin resistance are the subject of intense research, but strongly implicated is an increase in plasma free fatty acid levels, which is believed to play a key role in development of insulin resistance, Ferrannini et al, "Effect of fatty acids on glucose production and utilization in man", J. Clin. Invest., 72: 1737-1747 (1983), probably by reducing glucose transport into the cells. Dresner et al, "Effects of free fatty acids on glucose transport and IRS-1 - associated phosphatidylinositol 3-kinase activity," J. Clin. Invest., 103: 253-259 (1999). In addition, e.g., in obesity, the release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (Il-6) from adipose tissue appear to be involved in development of insulin resistance, perhaps via activation of c-jun N-terminal kinase (JNK). Hirosumi et al, "A central role for JNK in obesity and insulin resistance," Nature, 420: 333-336 (2002).

The incidence of NIDDM continues to increase alarmingly and there is a clear need for new methods of treating obese- and non-obese type I and type II diabetes. It has now surprisingly been found that the administration of potassium K\textsubscript{v1.3} channel inhibitors significantly improve the medical condition of obese- and non-obese diabetes type I and type II patients.

The voltage gated potassium K\textsubscript{v1.3} channel, which belongs to the Shaker family of Kv channels that regulate cell membrane potential, is expressed in many tissues, including lymphocytes, kidney, adipocytes and skeletal muscle. It has six transmembrane domains, S1-S6, and a pore region. It contains consensus sequences for a protein kinase C (PKC) site between S4 and S5, which is believed to play an important role in channel function, a tyrosine kinase phosphorylation site at the amino terminus and an N-glycosylation site between S1 and S2.

PKC increases and tyrosine kinase (TK) inhibits potassium K\textsubscript{v1.3} channel activity. Chung & Schlichter, "Native K\textsubscript{v1.3} channels are up-regulated by protein kinase C," J. Membr. Biol., 156: 73-85 (1997); Fadool et al, "Brain insulin receptor causes activity-dependent current suppression in the olfactory bulb through multiple phosphorylation of K\textsubscript{v1.3}," J. Neurophysiol., 83: 2332-2348 (2000). Furthermore, channel activity is upregu-
lated by serum-glucocorticoid activated kinase, and at least in olfactory bulb neurons, the brain region with the highest insulin binding, its activity is downregulated by insulin via activation of receptor TK. Fadool et al, 2000.

It has been found that potassium $K_{v1.3}$ channel inhibitors increase metabolic rate. Xu et al, "The voltage-gated potassium channel $K_{v1.3}$ regulates energy homeostasis and body weight," Human Molecular Genetics, 12: 551-559 (2003). Furthermore, inhibition of potassium $K_{v1.3}$ increases peripheral insulin sensitivity. Xu et al, "The voltage-gated potassium channel $K_{v1.3}$ regulates peripheral insulin sensitivity," Proc. Nat. Acad. Sc.i 101: 3112-3117 (2004). This effect is primarily due to an increase in glucose uptake in fat and skeletal muscle, which in turn can be mainly attributed to an increase in translocation of the GLUT4 glucose transporter (the major transporter mediating glucose uptake in insulin-sensitive tissues) from intracellular stores to the plasma membrane of skeletal muscle and adipose cells. In addition, potassium $K_{v1.3}$ channel inhibition reduces production of IL-6 and TNF-α by adipocytes and decreases JNK activity, which further helps to improve insulin sensitivity. Xu et al, 2004. Therefore, potassium $K_{v1.3}$ channel inhibition is suited for both treatment and prophylaxis of NIDDM.

It is now further been found that development of IDDM appears to involve autoimmune destruction of pancreatic beta cells. Lemmark, "Type 1 Diabetes - does suppressing T cells increase insulin?" N. Engl. J. Med., 352 (25): 2642-2644 (2005). Potassium $K_{v1.3}$ channel blockade selectively suppresses the activation and proliferation of effector memory T-cells while sparing activation of naive or T central memory cells, Vennekamp et al, "$K_{v1.3}$-blocking 5-phenylalkoxypsoralens: A new class of immunomodulators." Mol. Pharmacol., 65: 1364-1374 (2004); Damjanovich Gaspar & Panyi, "An alternative to conventional immunosuppression: small-molecule inhibitors of $K_{v1.3}$ channels," Mol. Interv., 4 (5) 250-254 (2004), and thus offers great promise for therapy of IDDM patients with residual insulin secretion, by halting islet cell destruction and progression of the disease and reducing the need for insulin injection by prolonging the period of insulin secretion. Moreover, it may also cause further benefit in IDDM by allowing control of blood glucose with lower doses of insulin due to the improved insulin sensitivity. The selective immunosuppressive actions of potassium $K_{v1.3}$ blockade also offer promise for therapy of other auto-immune diseases such as multiple sclerosis, chronic graft rejection and graft-versus-host disease.
SUMMARY OF THE INVENTION

Accordingly, it is a first object of the present invention to provide methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of a at least one potassium $K_{v,1.3}$ channel inhibitor to subjects in need thereof.

In a second embodiment, the present invention provides methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one compound having in addition to its potassium $K_{v,1.3}$ channel inhibiting properties also $CB_x$ modulating properties and/or potassium $K_{(aip)}$ channel opening properties, to subjects in need thereof.

Furthermore, in a third embodiment, the present invention provides the use of an effective amount of at least one potassium $K_{v,1.3}$ channel inhibitor for the manufacture of a medicament for the prophylaxis, treatment, delayed progression, delayed onset and/or inhibition of obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence.
In another embodiment, the present invention relates to the use of an effective amount of at least one compound having in addition to its potassium $K_{v,1,3}$ channel inhibiting properties also CB$_x$ modulating properties and/or potassium $K_{(alp)}$ channel opening properties, for the manufacture of a medicament for the prophylaxis, treatment, delayed progression, delayed onset and/or inhibition of obesity, diabetes mellitus, metabolic syndrome X, insulinoma, familial hyperinsulenic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence.

Other objects, features and advantages will be set forth in the detailed description of the embodiments that follows, and in part will be apparent from the description or may be learned by practice of the claimed invention. These objects and advantages will be realized and attained by the processes and compositions particularly pointed out in the written description and claims hereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the stimulation protocol for investigation of the test compound. Figure 2 shows the test item application protocol Figure 3 shows the potassium $K_{v,1,3}$-mediated potassium current. Figure 4(A) shows 80 superimposed original potassium $K_{v,1,3}$-current traces recorded in absence and presence of 10 µM example compound 1. Figure 4(B) shows current amplitude plotted against time. Onset (indicated by the long dashed line) and offset (indicated by the short dashed line) of test compound application. Extrapolated time course of current amplitude under vehicle conditions was calculated by a biexponential fit of equation $Y = a \exp(-cx) + b \exp(-dx)$ and is depicted as the solid line.

Figure 5 shows the concentration-dependence effect of example compound 1 on the potassium $K_{v,1,3}$-mediated potassium current.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present
disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the invention in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Compounds having in addition to their potassium $K_{v,3}$ channel inhibiting properties also CB$_x$ modulating properties and/or potassium $K_{(atp)}$ channel opening properties, such CB$_x$ modulating properties are selected from the group consisting: of CB$_1$ antagonistic properties, CB$_1$ agonistic properties and/or CB$_2$ agonistic properties.

Compounds which inhibit the potassium $K_{v,3}$ channel by at least 40%, preferably by at least 60%, more preferably by at least 80%, even more preferably by at least 90% and most preferably by at least 95% or above, are suitable as effective potassium $K_{v,3}$ channel inhibiting compounds for the purpose of the present invention.

The present invention is directed to methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulenic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence.

In one embodiment, the present invention describes methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulenic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one potassium $K_{v,3}$ channel inhibitor to subjects in need thereof. It has been found that patients, subject to treatment with an effective amount of at least one potassium $K_{v,3}$ channel inhibitors, show
an improved glycemic control and insulin management. In this embodiment, an effective amount of at least one potassium $K_{v,1,3}$ channel inhibitor is employed.

In another embodiment, the present invention provides methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardio- dioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one compound having in addition to its potassium $K_{v,1,3}$ channel inhibiting properties also $C_{bb}$ modulating properties and/or potassium $K_{(app)}$ channel opening properties, to subjects in need thereof. It has been found that patients, subject to treatment with an effective amount of at least one compound having in addition to its potassium $K_{v,1,3}$ channel inhibiting properties also $C_{bb}$ modulating properties and/or potassium $K_{(app)}$ channel opening properties, show an improved glycaemic control and insulin management. In this embodiment, an effective amount of at least one compound having in addition to its potassium $K_{v,1,3}$ channel inhibiting properties also $C_{bb}$ modulating properties and/or potassium $K_{(app)}$ channel opening properties is employed.

In another embodiment, the present invention provides methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardio- dioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one compound having in addition to its potassium $K_{v,1,3}$ channel inhibiting properties also $C_{bb}$ modulating properties, to subjects in need thereof. It has been found that patients, subject to treatment with an effective amount of at least one compound having in addition to its potassium $K_{v,1,3}$ channel inhibiting properties also $C_{bb}$ modulating properties, show an improved glycaemic control and insulin management. In this embodiment, an effective amount of at least one
compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $CB_x$ modulating properties is employed.

In another embodiment, the present invention provides methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also potassium $K_{(atp)}$ channel opening properties, to subjects in need thereof. It has been found that patients, subject to treatment with an effective amount of at least one compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also potassium $K_{(atp)}$ channel opening properties is employed.

In another embodiment, the present invention provides methods of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $CB_x$ modulating properties and potassium $K_{(atp)}$ channel opening properties, to subjects in need thereof. It has been found that patients, subject to treatment with an effective amount of at least one compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $CB_x$ modulating properties and potassium $K_{(atp)}$ channel opening properties, show an improved glycaemic control and insulin management. In this embodiment, an effective amount of at least one compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties
also CB\_x modulating properties and potassium K\_{(alp)} channel opening properties is employed.

In a specific embodiment of the present invention obese type I diabetes, obese type II diabetes, non-obese type I diabetes, non-obese type II diabetes and/or related conditions are treated, prevented or inhibited.

In an even more specific embodiment of the present invention, the related condition is selected from the group consisting of: glucose metabolism, insulin resistance, hyperglycaemia and/or glucose intolerance.

In the methods and uses described herein, any potassium K\_v1.3 channel inhibitor, or, any compound having in addition to its potassium K\_v1.3 channel inhibiting properties also CB\_x modulating properties and/or potassium K\_{(alp)} channel opening properties, can be utilized for the purposes described herein. However, the following compounds, being potassium K\_v1.3 channel inhibitors and/or compounds having in addition to its potassium K\_v1.3 channel inhibiting properties also CB\_x modulating properties and/or potassium K\_{(alp)} channel opening properties, are preferred:

a.)

\begin{align*}
\text{wherein:} \\
&\text{- } R \text{ and } R_i \text{ are independently selected from the group consisting of: naphthyl, phenyl, thienyl and pyridyl wherein phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents } Y; \\
&\text{- } R_2 \text{ is selected from the group consisting of: hydrogen, hydroxy, } d\_3\text{-alkoxy, acetyloxy and propionyloxy; } \\
&\text{- } R_3 \text{ is selected from the group consisting of: } C_{1-8}\text{-branched or unbranched alkyl, } C_{3-10}\text{-cycloalkyl, } C_{3-8}\text{-alkenyl, } C_{5-10}\text{-bicycloalkyl, } C_{6-10}\text{-tricycloalkyl, } C_{5-8}\text{-cycloalkenyl, } NR_{10}\text{-Rn, naphthyl, benzyl, phenyl, thienyl and pyridyl wherein benzyl, phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents } Y; \\
\end{align*}
Aa is selected from the group consisting of: substituents of formulae (i), (ii), (iii), (iv), (v) and (vi).

(i) 

(ii) 

(iii) 

(iv) 

(v) 

(vi) 

Bb is selected from the group consisting of: sulfonyl and carbonyl; each Y is independently selected from the group consisting of: d-3-alkyl, C1-3-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C2) amino, mono- or dialkyl (C2) amido, (C1-3)-alkyl sulfonyl, dimethylsulfamido, C1-3-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;

R4 is selected from the group consisting of: hydrogen, C1-8 branched or unbranched alkyl and C3-8 cycloalkyl; or R4 is selected from the group consisting of: acetamido, dimethylamino, 2,2,2-trifluoroethyl, phenyl and pyridyl with the proviso that R5 is hydrogen, wherein such C1-8 branched or unbranched alkyl and/or C3-8 cycloalkyl alkyl group may be substituted with a hydroxyl group;

R5 is selected from the group consisting of: hydrogen, C1-8 branched or unbranched alkyl, C3-8 cycloalkyl, C3-10 branched or unbranched heteroalkyl, C3-8 non-aromatic heterocycloalkyl, C4-10 non-aromatic heterocycloalkyl-alkyl, amino, hydroxy, phenoxy, benzyl, C1-8 alkenyl, C3-8 cycloalkenyl, C3-9 cycloalkenylalkyl, imidazolylalkyl, phenyl, benzyl, pyridyl, thiethyl, pyridinylmethyl and phenethyl; or R5 is NR6R9 with the proviso that R4 is H or methyl; or R4 and R5 together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, wherein such C1-8 branched or unbranched alkyl and/or C3-8 cycloalkyl group may be substituted with hydroxyl and/or fluoro, wherein such C2-10 branched or unbranched heteroalkyl, C3-8 non-aromatic heterocycloalkyl and/or C4-10 non-aromatic heterocycloalkyl-alkyl groups may contain one or more heteroatoms selected from the group consisting of: O, N and S,
wherein such C\textsubscript{2,10} branched or unbranched heteroalkyl, C\textsubscript{3,8} non-aromatic heterocycloalkyl and/or C\textsubscript{4,10} non-aromatic heterocycloalkyl-alkyl groups may contain a SO\textsuperscript{2} group,

wherein such C\textsubscript{2,10} branched or unbranched heteroalkyl group, C\textsubscript{3,8} non-aromatic heterocycloalkyl group and/or C\textsubscript{4,10} non-aromatic heterocycloalkyl-alkyl group may be substituted with keto, trifluoromethyl, C\textsubscript{1-3} alkyl, hydroxy, amino, monoalkylamino, dialkylamino or fluoro,

wherein such amino, hydroxy, phenoxy, benzylxoy, C\textsubscript{1-8} alkoxy, C\textsubscript{3-8} alkenyl, C\textsubscript{5-8} cycloalkenyl, C\textsubscript{6,9} cycloalkenylalkyl may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such amino, hydroxy, phenoxy, benzylxoy, C\textsubscript{1-8} alkoxy, C\textsubscript{3-8} alkenyl, C\textsubscript{5-8} cycloalkenyl, C\textsubscript{6,9} cycloalkenylalkyl may contain a keto Or-SO\textsuperscript{2} group,

wherein such C\textsubscript{1-8} alkoxy, C\textsubscript{3,8} alkenyl and C\textsubscript{5,8} cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom,

wherein such phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group may be substituted with 1, 2 or 3 of the substituents Y,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain a keto Or-SO\textsuperscript{2} group,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may be substituted with a C\textsubscript{1-4} alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group:

\begin{itemize}
  \item \(R_6\) is selected from the group consisting of: hydrogen and C\textsubscript{1-3} unbranched alkyl;
  \item \(R_7\) is C\textsubscript{1-3} unbranched alkyl;
  \item \(R_8\) and \(R_9\) are the same or different and are selected elected from the group consisting of: C\textsubscript{2,4} alkyl and C\textsubscript{2,3} trifluoroalkyl; or \(R_8\) is methyl with the proviso that \(R_9\) is C\textsubscript{2,4} alkyl; or \(R_8\) and \(R_9\) - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms,
  \item \(R_{1-8}\) and \(R_{9-10}\) are the same or different and are selected elected from the group consisting of: keto and -SO\textsuperscript{2} group,
\end{itemize}
wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may be substituted with C1-4 alkyl;

- R1 and Rn are independently selected from the group consisting of: hydrogen, branched or unbranched C1-6 alkyl, branched or unbranched C1-8 alkenyl, C3-8 cycloalkyl, C3-8 cycloalkenyl, naphtyl and phenyl; or R10 and R11 - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group,

wherein such branched or unbranched C1-8 alkyl and/or branched or unbranched C1-8 alkenyl groups may contain one or more heteroatoms selected from the group consisting of: O, N, and S,

wherein such branched or unbranched C1-8 alkyl and/or branched or unbranched C1-8 alkenyl groups may contain a group selected from the group consisting of: keto and -SO2-group and wherein such keto and -SO2-group may be substituted with a hydroxy or amino group,

wherein such C3-8 cycloalkyl and/or C3-8 cycloalkenyl group may contain one or more ring heteroatoms selected from the group consisting of: O, N, and S,

wherein such C3-8 cycloalkyl and/or C3-8 cycloalkenyl group may be substituted with hydroxy, C1-3 alkyl, -SO2-, keto, amino, C1-3 monoalkylamino and/or C1-3 dialkylamino,

wherein such phenyl group may be substituted with 1, 2 or 3 substituents Y with the proviso that R11 is selected from the group consisting of: hydrogen, branched or unbranched C1-5 alkyl group wherein such branched or unbranched C1-5 alkyl group may contain one or more heteroatoms selected from the group consisting of: O, N and S or wherein such branched or unbranched C1-5 alkyl group may contain SO2- and wherein such branched or unbranched C1-5 alkyl group may be substituted with a hydroxy, keto or amino group,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain ring heteroatoms selected from the group consisting of: O, N and S,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain a group selected from the group consisting of: keto and SO2-,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with hydroxy, C1-3 alkyl, SO2-, keto, amino, C1-3 monoalkylamino, C1-3 dialkylamino, pyrrolidinyl, or piperidinyl,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y; and

a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

b.)
wherein

- $R_{i_2}$ and $R_{i_3}$ are independently selected from the group consisting of: hydrogen, $C_i$-alkyl and $C_{3-6}$ cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;

- $R_{14}$ is phenyl which may be substituted with 1, 2 or 3 substituents $Z$ which can be the same or different and wherein $Z$ is selected from the group consisting of: $d$-$3$-alkyl, $d$-$3$-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_i$-)amino, mono- or dialkyl ($C_i$-)amido, ($C_i$-)alkyl sulfonyl, dimethylsulfamido, $C_i$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl; and a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

c.)

wherein

- $Q$ is phenyl which may be substituted with 1, 2 or 3 substituents $Z$ which can be the same or different and wherein $Z$ is selected from the group consisting of: $C_i$-alkyl, $C_{1-3}$-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$-)amino, mono- or dialkyl ($C_{1-2}$-)amido, ($C_i$-)alkyl sulfonyl, dimethylsulfamido, $C_{1-3}$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;

- $T$ is selected from the group consisting of: hydrogen, $C_i$-alkyl and $C_{3-6}$ cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;
- $R_{i5}$ is selected from the group consisting of: $C_{i-3}$ alkyl and $C_{3-6}$ cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S; and

a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

d.) Diazoxide, NN414, R(+)-WIN55212-2, HU-308, Rimonabant, SR-147778; and a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

e.) and mixtures thereof.

More preferred are 4,5-dihydro-1H-pyrazole derivatives of the formula (I), prodrugs, tautomers or pharmaceutically acceptable salts thereof;

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{Aa} \\
\text{Bb} \\
\text{R_3} \\
\end{array}
\begin{array}{c}
\text{R_1} \\
\text{R_2} \\
\end{array}
\]

wherein the 4-position of the 4,5 dihydro pyrazole ring is in the S-configuration.

In another embodiment, compounds which inhibit the potassium $K_{V1.3}$ channel by at least 40%, preferably by at least 60%, more preferably by at least 80%, even more preferably by at least 90% and most preferably at least 95% or above, are preferred.

Compounds inhibiting the potassium $K_{V1.3}$ channel by at least 40% include the following:

\[
\begin{array}{c}
\text{Cl} \\
\text{SO} \\
\text{NH} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{CH}_2 \\
\end{array}
\text{Diazoxide ;}
\begin{array}{c}
\text{Cl} \\
\text{SO} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{\textbullet} \\
\end{array}
\text{NN414 ;}
\]
Compounds inhibiting the potassium $K_{v1.3}$ channel by at least 60% include the following:

Compounds inhibiting the potassium $K_{v1.3}$ channel by at least 80% include the following:
Compounds inhibiting the potassium \(K_{\text{v}1.3}\) channel by at least 90% include the following:

- Rimonabant

Compounds inhibiting the potassium \(K_{\text{v}1.3}\) channel by at least 95% include the following:

- Chiral
All the above compounds are effective $K_{v1.3}$ channel inhibitors or, are compounds having in addition to their potassium $K_{v1.3}$ channel inhibiting properties also $CB_x$ modulating properties and/or $K_{(all)}$ channel opening properties.

5 Combination with CB1 antagonist:

In another embodiment, the present invention is directed to methods of treating obese- and non-obese type I and type II diabetes and related conditions by administering an effective amount of at least one potassium $K_{v1.3}$ channel inhibitor in combination with an effective amount of at least one CB1 antagonist to subjects in need thereof. It has been found that obese diabetes type I and type II patients, subject to treatment with an effective amount of at least one potassium $K_{v1.3}$ channel inhibitor in combination with an effective amount of at least one CB1 antagonist, show a significantly improved glycaemic control and insulin management.

15 In still another embodiment, the present invention is directed to methods of treating obese- and non-obese type I and type II diabetes and related conditions by administering an effective amount of at least one dually acting compound having both, potassium $K_{v1.3}$ channel inhibiting properties and $CB_1$ antagonistic properties in combination with an effective amount of at least one CB1 antagonist to subjects in need thereof. It has been found that obese diabetes type I and type II patients, subject to treatment with an effective amount of at least one dually acting compound having both, potassium $K_{v1.3}$ channel inhibiting properties and $CB_1$ antagonistic properties, in combination with an effective amount of at least one CB1 antagonist, show a significantly improved glycaemic control and insulin management.

20 Obesity is a major cause of NIDDM and the combination of a CB1 antagonist, which causes weight loss principally by reduced food intake, with a potassium $K_{v1.3}$ channel inhibitor, which increases metabolic rate (Xu et al 2003) as well as directly improving insulin sensitivity is particularly suited for the prophylaxis and therapy of NIDDM.

30 Any CB1 antagonist known in the art, can be utilized for the purpose of the present invention. Suitable CB1 antagonists are, e.g., those which are useful to treat appetite disorders and/or obesity, e.g. SR 147778. A review is given in J.H.M. Lange and C. G. Kruse, Current Opinion in Drug Discovery & Development 7(4) (2004) 498-506. Further examples of such compounds are described in documents US 5,624,941; US 6,344,474;
Combination with potassium $K_{(atp)}$ channel opener:

In another embodiment, the present invention is directed to methods of treating obese- and non-obese type I and type II diabetes and related conditions by administering an effective amount of at least one potassium $K_{v1.3}$ channel inhibitor in combination with an effective amount of at least one potassium $K_{(atp)}$ channel opener to subjects in need thereof. It has been found that obese- and non-obese diabetes type I patients, subject to treatment with an effective amount of at least one potassium $K_{v1.3}$ channel inhibitors in combination with an effective amount of at least one potassium $K_{(atp)}$ channel opener, show a significantly improved glycaemic control and insulin management.

Still another embodiment of the present invention is directed to methods of treating obese- and non-obese type I and type II diabetes and related conditions by administering an effective amount of at least one dually acting compound having both, potassium $K_{v1.3}$ channel inhibiting properties and CB₁ antagonistic properties in combination with an effective amount of at least one potassium $K_{(atp)}$ channel opener to subjects in need thereof. It has been found that obese- and non-obese diabetes type I patients, subject to treatment with an effective amount of at least one dually acting compound having both, potassium $K_{v1.3}$ channel inhibiting properties and CB₁ antagonistic properties in combination with an effective amount of at least one potassium $K_{(atp)}$ channel opener, show a significantly improved glycaemic control and insulin management.

Reduction of insulin secretion by a SUR1 $K_{(atp)}$ channel opener, which may need to be combined at least initially with insulin therapy, protects against overstimulation of the pancreatic islets as in early stage NIDDM the β-cells attempt to overcome the developing insulin resistance by increased production of insulin. The reduced metabolic strain on the islet cells leads to improved function of the β-cell. Guldstrand et al, "Improved β-cell function after short term treatment with diazoxide in obese patients with Type 2 diabetes,"
Diabetes Metab., 28: 448-456 (2002). Chronic therapy with a SUR1 $K_{(\text{app})}$ channel opener also leads to improved insulin sensitivity, perhaps via reduction of hepatic gluconeogenesis. Pocal et al. "Hypothalamic $K_{(\text{app})}$ channels control hepatic glucose production," Nature, 434: 1026-1031 (2005). The combination of SUR1 $K_{(\text{app})}$ channel opener and potassium $K_{\text{i1}}} \text{ channel inhibitor will therefore be especially beneficial for treatment and prophylaxis of NIDDM. It may also benefit IDDM patients with residual insulin secretion.}

Potassium $K_{(\text{app})}$ channel openers and their potential use in the inhibition of insulin secretion and/or the treatment of metabolic disorders are known from various references, such as US 6,492,130; WO 02/00223; WO 02/00665 or from Carr et al., Diabetes, 52:2513-2518 (2003) or Hansen et al., Current Medicinal Chemistry, 11:1595-1615 (2004).

The beneficial role of the specific potassium $K_{(\text{app})}$ channel opener diazoxide in the treatment of metabolic syndrome is known from various references, such as US 5,284,845 or US 6,197,765 or from R. Alemzadeh et al., Endocrinology 133 (2) (1993) 705-712 or Alemzadeh et al., Journal of Clinical Endocrinology and Metabolism, 83(6): 1911-1915 (1998).

Any potassium $K_{(\text{app})}$ channel opener known to the one of skill in the art, can be utilized for the purpose of the present invention. Suitable potassium $K_{(\text{app})}$ channel openers are preferably compounds which have effects as openers at the Kir6.2/SUR1 $K_{(\text{app})}$ channel, at the Kir6.2/SUR2B $K_{(\text{app})}$ channel and/or the Kir6.1/ SUR2B $K_{(\text{app})}$ channel. Effective compounds are those which exhibit an IC$_{50}$ value [μmol] of less than 50 in a test for the affinity of the compounds in binding to the sulfonylurea (= SUR) and potassium channel opener site (= KCO) of rat and/or human isoforms of SUR1 and/or SUR2B - e.g. the test model provided below. Compounds with an effect as openers at the Kir6.2/SUR1 $K_{(\text{app})}$ channel, in particular as selective openers at the Kir6.2/SUR1 $K_{(\text{app})}$ channel are preferred. A compound with an effect as opener at the Kir6.2/SUR1 $K_{(\text{app})}$ channel is understood to be selective if its IC$_{50}$ value at the Kir6.2/SUR1 $K_{(\text{app})}$ channel, as measured in the aforementioned binding test, is at most half, more preferred only a quarter, of the IC$_{50}$ value of that same compound at the Kir6.2/SUR2B $K_{(\text{app})}$ channel and/or the Kir6.1/SUR2B $K_{(\text{app})}$ channel. Specific compounds which are suitable as potassium $K_{(\text{app})}$ channel openers according to the invention may be selected from the group consisting of pinacidil; cromakalim; diazoxide; BPDZ 44; BPDZ 49; BPDZ 62; BPDZ 73; BPDZ 79; BPDZ 83; BPDZ 109; BPDZ
BPDZ 216 (= NNC 55-9216); NN414 (all: see e.g. Hansen et al.); NNC 55-01 18 (see e.g. T.M. Tagmose et al., J. Med. Chem. 47 (2004) 3202-3211); NNC 55-0462 (see e.g. Hansen et al.), MCC-134 (see e.g. M. J. Coghan et al., J. Med. Chem. 44 (2001) 1627-1653); losimendan; SR 47063 and WAY 135201. Diazoxide; BPDZ 44; BPDZ 62; BPDZ 73; BPDZ 154; BPDZ 216 (= NNC 55-9216); NN414; NNC 55-0118; NNC 55-0462 and MCC-134 are preferred.

**Description of the pharmacological test methods**

1. Electrophysiological examination of test compounds on the potassium $K_{v,1,3}$-mediated potassium current

**METHODS**

**Molecular Biology**

cDNA coding for the human potassium $K_{v,1,3}$ was cloned into a standard vector. A C-terminal epitope-tag was introduced via PCR. The plasmid was sequenced and subsequently introduced into cells and a clonal cell line was established. Expression of protein was analysed by means of immunofluorescence using antibodies directed against the epitope-tag. The electrophysiological investigations have shown no difference of the biophysical properties of the tagged potassium $K_{v,1,3}$ channel versus the un-tagged form.

**Cell culture**

Experiments were performed in CHO cells stably expressing the potassium $K_{v,1,3}$ channel. Cells were grown at 37°C and 5% CO2 in 25 ml flasks in 6 ml MEM ALPHA Medium supplemented with 10% (v/v) heat inactivated fetal calf serum, 1% (v/v) P/S/G-solution and the appropriate selection marker.

**Experimental procedure**

Patch-clamp experiments were performed in the voltage-clamp mode (Hamill et al., 1981) and whole-cell currents were recorded. Patch pipettes were pulled from borosilicate glass tubes. Current signals were amplified and digitized by an EPC patch-clamp amplifier (HEKA-Electronics, Lambrecht, Germany), stored and analyzed on a personal computer using the Pulse/Pulsefit software (HEKA, Lambrecht, Germany). Experiments were conducted at room temperature.
Stimulation protocol for the potassium $K_{v1.3}$-mediated current.

For investigating effects and reversibility of a test compound on the potassium $K_{v1.3}$ channel, CHO cells were clamped at a holding potential (HP) of -80 mV. The following stimulation protocol (Figure 1) was applied successively and the induced currents have been recorded:

Duration of the +40 mV pulse is 1000 ms, and pulse cycling rate is 1/10 s (0.1 Hz) to investigate compound effect.

Compound application protocol

The application protocol of test compound is depicted in Figure 2. The first 14 stimuli are required to achieve steady state of the current amplitude. Nonspecific current reduction is calculated and serves for correction procedures during data analysis. After the 14th stimulus, the test compound was applied into the bath via Teflon and silicone tubings (indicated by an arrow) and is supposed to reach the cell after 6 additional stimuli. The perfusion is validated by using a defined drop rate of 10 drops per $10^{-12}$ s. Effect of the test compound is analyzed between stimulus nos. 20 and 50 (ca. 5 min.) and time of wash-out between stimulus nos. 51 and 80 (5 min.). Start of test compound application and of wash-out is indicated by arrows. Number of stimuli of each single episode is shown in the protocol of Figure 2.

Data compilation

The appropriate experiment was selected from the data tree in the Pulse software. The sampled pulses in this sequence were played back and displayed on the oscilloscope screen. The leak current amplitude during the prepulse to -90 mV and the peak current amplitude of the test-pulse to +40 mV were measured by placing the cursors on the oscilloscope screen (Figure 3). The values were automatically written and saved to a notebook in the Pulse software. The data from this notebook were imported into Excel for further analysis. The graphical presentation, the evaluation of run-down correction and compound effect of each experiment were performed in SigmaPlot, by copying the results from Excel.

Figure 3: $K_{v1.3}$-mediated potassium current. Example of a representative original current trace. The two cursors on the right indicate the range of the test pulse, where the...
peak current amplitude was evaluated (205-230 ms of the test pulse to +40 mV). The two cursors on the left indicate the area where the mean leak current was evaluated (100-140 ms of the test pulse to -90 mV).

Data analysis for potassium Kv3-mediated currents

The amplitude of the potassium Kv3-mediated current gradually decreases over time in some experiments, even in control conditions (called "run-down"). In order to accurately quantify the extent of block, the time course of the current amplitude during the initial period (first 20 stimuli) of the experiment was calculated by a biexponential fit of the equation:

\[ Y = a \cdot \exp(-cx) + b \cdot \exp(-dx) \]

where \( a, b, c, \) and \( d \) were calculated by the fitting routine in Excel or SigmaPlot.

The fit was extrapolated to the complete time of compound application and washout period. The value for the amplitude under control condition was given by the curve fit (curvexy value).

For the evaluation of compound effect, the curve value under control condition \( (I_{\text{curve}50}) \) and the current amplitude during test item application \( (I_{\text{drug}50}) \) were used.

The current reduction was calculated according to the following equation:

\[ (2) \text{relative remaining current} = (I_{\text{drug}50}/I_{\text{curve}50}) \]

The current recovery was calculated according to the following equation:

\[ (3) \text{relative current recovery} = (I_{\text{wash}80}/I_{\text{curve}50}) \]

Data are presented as mean±S.D. (standard deviation).

Concentration/response relations were calculated by non-linear least-squares fits of the equation.
(4) \( \frac{l}{l_{\text{max}}} = \frac{1}{1 + \left(\frac{C}{IC50}\right)^{nH}} \)

to the individual data points. The Hill coefficient \((nH)\) and the half-maximal inhibiting concentration \((IC50)\) were calculated by the fitting routine of the SigmaPlot software.

RESULTS

Effects on the potassium \(K_{v,1.3}\)-mediated current. The following chemical compound has been investigated:

![Chemical structure]

(referred hereinafter to as example compound 1)

In presence of example compound 1, the outward current amplitudes were reduced in a concentration-dependent manner, demonstrating an effect of example compound 1 on the \(K_{v,1.3}\)-mediated potassium current. For concentrations of 10 \(\mu\)M and 30 \(\mu\)M, the same effect for example compound 1 was measured in the presence of 0.1% Bovine Serum Albumine (BSA) to overcome the low solubility of example compound 1. In Figure 4B, a typical example for the time course upon application of 10 \(\mu\)M B example compound 1 is depicted, showing a significant current reduction of the initial amplitude.

Figure 5 shows the concentration-response relationship for the block of the potassium \(K_{v,1.3}\) channel by example compound 1. Equation (4) was fitted to the data points. The apparent IC50 in the presence of 0.1% BSA is 10.3 ± 3.7 \(\mu\)M, and \(nH\) is 0.72 ± 0.22. The extrapolated curve fit for concentrations higher than 10 \(\mu\)M is shown as dashed line: due to limited solubility, it could not be determined if a block of >50-60% may be achieved and therefore the IC50 value should be considered as an estimate.
Legend to table 1: Effects of example compound 1 on potassium $K_{v, i-3}$ in presence and absence of 1, 3, 10 and 30 µM in absence or presence of 0.1 % BSA. In the first column the corresponding experiments are listed. Current amplitudes in columns 2-5 represent the run-down and leak current corrected steady-state amplitudes measured at +40 mV.

<table>
<thead>
<tr>
<th>Current amplitude (pA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 µM&lt;sup&gt;a&lt;/sup&gt; example compound 1</td>
</tr>
<tr>
<td>0.72 ± 0.19</td>
</tr>
</tbody>
</table>

Table 1: potassium $K_{v, i-3}$-mediated current amplitude in absence and presence of example compound 1

- Relative remaining current amplitude calculated according to: $I_{\text{drug50}} / I_{\text{curve50}}$
- The relative remaining current amplitude reflects the reversibility of test item effect after wash-period. It was calculated according to: $I_{\text{wash}50} / I_{\text{curve50}}$.

2. Electrophysiological examination of test compounds on the $K_{v, i-3}$-mediated potassium current.

In another set of experiments, the inhibition of the potassium $K_{v, i-3}$ channel has been measured. For the purpose herein, it is hereby defined that an effective potassium $K_{v, i-3}$ channel inhibitor shall inhibit the potassium $K_{v, i-3}$ channel by at least 40%, preferably by at least 60%, more preferably by at least 80%, even more preferably by at least 90% and most preferably by at least 95% or above.

Cells stably transfected with cDNA for human potassium $K_{v, i-3}$ (in pcDNA3.1) were grown in Ex-cell 302 serum-free medium for CHO cells, supplemented with 10 µl/ml [100x] glutamine, 500 µg/ml G418, and 1 % HT supplement (5Ox, hypoxanthine and thymidine).
The cells were cultured in 350 ml spinner (Techne) spun at 80 rpm, at 37 °C in a water-saturated 5% CO₂ incubator. The day of the preparation an aliquot of cells was 5 times diluted in fresh media and counted with a glass counting chamber type Malassez. Then six tubes of 10 ml were prepared at 6x10⁶ c/ml. The tubes were then placed at 4 °C until their use.

The external bathing solution contained (in mM): 150 NaCl, 10 KCl, 1 MgCl₂, 3 CaCl₂ and 10 HEPES. The pH was adjusted to 7.4 with NaOH. Patch pipettes were filled with a pipette solution of composition (in mM): 100 K-Gluconate, 20 KCl, 1 MgCl₂, 1 CaCl₂, 10 HEPES, 11 EGTA, 5 ATP-Na₂ and 2 Glutathione. The pH was adjusted to 7.2 with KOH. Using fresh 100 ml bathing solution, 0.05% BSA re-suspension solution (0.05 g BSA/100ml bather) was prepared.

Compounds were dissolved in DMSO (100%) and made up in the external bather at concentrations of 1 µM and 10 µM. All experiments were conducted at room temperature.

Two tubes of cell suspension were centrifuged at 1000 rpm for 4 minutes at room temperature. 10 ml of supernatant was carefully aspirated and discarded from each tube, with care being taken not to aspirate the cell pellet sitting at the bottom of the tube. The cell pellet of each tube was broken-up by gentle manual agitation of the tube. 600 µl of re-suspension solution was added to the cell pellet, followed by a gentle trituration step to re-suspend the cells. Once re-suspended, 600 µl of solution per tube was removed from each tube, such that 1.2 ml of cell suspension was obtained in total and placed in a temperature-controlled cell hotel, set at either 4 °C or dew point. Cells were maintained in suspension in the hotel through gentle trituration every 30 s via an automatic cell suspension system.

Harvard borosilicate capillary glass (GC1507F-10, 1.5 mm ID x 1.17 mm OD, supplied in 100 mm lengths) was cut down to 24 mm lengths using a Dagen capillary cutter. Short (13 mm) patch pipettes were pulled using a 2-stage pull on a specially adapted DMZ pipette puller (Zeitz Instruments). Patch pipettes typically have resistances of 2.3-3.5 MΩ. As the patch pipettes were pulled in batches, pipette tip resistance were measured every tenth pipette using a Tenma meter in order to maintain consistency of tip resistance. Pulled pipettes were stored in Petri dish before filling.
Each pipette was fully back-filled (from the tip to the end) using the internal pipette solution and the pipette tip was dipped in Sigmacote (Sigma). The pipette was then precisely inserted, tip first, into a pipette holder using a custom-made, pneumatic insertion rig, with the blunt end of the patch pipette sitting proud of the bottom of the pipette holder.

Whole cell patch-clamp recordings (WCRs) were made using the AP2, which incorporated an EPC9 or EPC10 amplifier (HEKA, Germany) under control of Pulse software (v8.54 or v8.76, HEKA, Germany), the patch plate contact fixture, a Gilson autosampler for cell delivery (the cell sampler), a Gilson autosampler for drug preparation (the autosampler), the drug application system (DAS), a feedback-controlled suction device for enabling high resistance GΩ seals to be formed for the whole cell recording mode to be attained, a cell re-suspension system, a temperature-controlled cell hotel, a vacuum line and associated pumps for applying suction and for draining the patch plate wells of bather.

Under control of the AP2 software automated patch-clamping was initiated. A Gilson sampler needle visited the cell hotel and took up 15 µl of cell suspension. The sampler needle then visited the first designated patch pipette in the patch plate. The sampler needle slowly descended towards the patch pipette until the liquid interface was detected. The presence of a cell at the pipette tip was detected by the resistance of the tip exceeding 50 MΩ. Once a cell was detected, suction was applied to the pipette to obtain a GΩ seal. Once a GΩ seal was obtained and was stabilised for 60 s (at 0 mmHg suction), suction was again applied in ramps to enable membrane break-in and the gaining of the WCR configuration. During application of the suction ramp, the membrane holding voltage (V_m) was hyperpolarised in 10 mV steps until the experimental holding voltage (V_{10mV}) was obtained.

Qualification stages prior to perfusion and drug application ensure that the observed potassium K_{v,3} current met the user-determined criteria for the experiment. Only those cells with an I_K > 400 pA were used. Cells were continuously perfused with external solution at a flow rate of 1.8-2 ml/minute. The perfusion chamber has a working volume 100 µl and allows for rapid exchange of drug solutions.

Once the qualification criteria have been met, test compound was applied to the cell via the DAS system. Compound at a stock concentration was held in a 96 well plate on
the autosampler. 80 µl of compound was drawn up by the autosampler and diluted with bather to the requisite concentration by the autosampler. The degree of dilution of each compound required was automatically determined by Autopatch.exe according to the final concentration required to be applied to the cell. Each compound was applied for 5 minutes, following which the compound was washed out by bather. Recovery, or otherwise, of the potassium \( K_{V_{1.3}} \) response was monitored by Autopatch.exe, such that a second compound was applied only when the potassium \( K_{V_{1.3}} \) current returned to the pre-drug application amplitude within a given time period. Should recovery not be sufficient during this period, Autopatch.exe terminates the experiment and moves on to the next recording site.

Online analysis of the potassium \( hK_{V_{1.3}} \) current during the application of compounds was performed by the Autopatch software.

Electrophysiology voltage-step protocols and analysis of data was performed as follows. Data was sampled at 5 kHz, and filtered with a -3 dB bandwidth of 2.5 kHz. Cells were held at a voltage of -80 mV. Currents were evoked by a voltage step to +30 mV for 500 ms in duration every 10 s. Total charge was measured during the whole of voltage step by AP2 and plotted by the APGraph.exe software.

During potassium \( K_{V_{1.3}} \) experiments charge was measured as the integral of the current with respect to time during 1-99 % (5-495 ms) of the 500 ms step to +30 mV in the absence (Q\text{control}) and presence (Q\text{drug}) of drug. Control potassium \( K_{V_{1.3}} \) charge measurements were taken as the average of the two sweeps immediately prior to drug addition. Percentage Charge inhibition was calculated as shown in Equation 1).

\[
\% \text{ Charge Inhibition} = \left(1 - \frac{Q_{\text{Drug}}}{Q_{\text{Control}}} \right) \times 100
\]  

Equation 1 - Percentage Charge Inhibition wherein \( Q_{\text{control}} \) and \( Q_{\text{drug}} \) are the charge measured prior to and following equilibration in drug, respectively.
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Relative Retention Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>88.7</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
<td>76.0</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure 3" /></td>
<td>88.1</td>
</tr>
<tr>
<td><img src="image4.png" alt="Chemical Structure 4" /></td>
<td>58.4</td>
</tr>
<tr>
<td><img src="image5.png" alt="Chemical Structure 5" /></td>
<td>96.2</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
</tr>
<tr>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td><img src="image1.png" alt="Structure 1" /></td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Structure 2" /></td>
</tr>
<tr>
<td></td>
<td><img src="image3.png" alt="Structure 3" /></td>
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<tr>
<td>HU-308</td>
<td><img src="image4.png" alt="Structure 4" /></td>
</tr>
<tr>
<td></td>
<td><img src="image5.png" alt="Structure 5" /></td>
</tr>
<tr>
<td>Diazoxide</td>
<td><img src="image6.png" alt="Structure 6" /></td>
</tr>
</tbody>
</table>
The potassium $K_{v,3}$ channel inhibitors of the present invention and/or the compounds having in addition to its potassium $K_{v,3}$ channel inhibiting properties also $C_{B_x}$ modulating properties and/or potassium $K_{(alp)}$ channel opening properties, either alone or in combination with an effective amount of at least one CBi antagonist and/or an effective amount of at least one potassium $K_{(alp)}$ channel opener, may be administered in conventional pharmaceutical preparations. The doses to be used may vary individually and will naturally vary according to the type of condition to be treated and the substance used. In general, however, medicinal forms with an active substance content of about 0.2 to about 500 mg, such as, e.g., about 0.2, about 0.4, about 0.6, about 0.8, about 1, about 2, about 3, about 4, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425,
about 450, about 475, or about 500 mg, in particular from about 1 to about 200 mg, such as, e.g., about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55, about 56, about 57, about 58, about 59, about 60, about 61, about 62, about 63, about 64, about 65, about 66, about 67, about 68, about 69, about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, about 80, about 81, about 82, about 83, about 84, about 85, about 86, about 87, about 88, about 89, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99, about 100, about 101, about 102, about 103, about 104, about 105, about 106, about 107, about 108, about 109, about 110, about 111, about 112, about 113, about 114, about 115, about 116, about 117, about 118, about 119, about 120, about 121, about 122, about 123, about 124, about 125, about 126, about 127, about 128, about 129, about 130, about 131, about 132, about 133, about 134, about 135, about 136, about 137, about 138, about 139, about 140, about 141, about 142, about 143, about 144, about 145, about 146, about 147, about 148, about 149, about 150, about 151, about 152, about 153, about 154, about 155, about 156, about 157, about 158, about 159, about 160, about 161, about 162, about 163, about 164, about 165, about 166, about 167, about 168, about 169, about 170, about 171, about 172, about 173, about 174, about 175, about 176, about 177, about 178, about 179, about 180, about 181, about 182, about 183, about 184, about 185, about 186, about 187, about 188, about 189, about 190, about 191, about 192, about 193, about 194, about 195, about 196, about 197, about 198, about 199, or about 200, active substance per individual dose are suitable for administration to humans and larger mammals. The potassium $K_{\text{v1.3}}$ channel inhibitors of the present invention and/or the compounds having in addition to their potassium $K_{\text{i.2}}$ channel inhibiting properties also $\text{CB}_x$ modulating properties and/or potassium $K_{\text{lab}}$ channel opening properties, either alone or in combination with an effective amount of at least one $\text{CB}_1$ antagonist and/or an effective amount of at least one potassium $K_{\text{lab}}$ channel opener, may be contained for the purposes described herein, together with conventional pharmaceutical auxiliaries and/or carriers, in solid or liquid pharmaceutical preparations. Examples of solid preparations are preparations which can be administered orally, such as tablets, coated tablets, capsules, powders or granules, or alternatively suppositories. These preparations may contain conventional pharmaceutical
inorganic and/or organic carriers, such as talcum, lactose or starch, in addition to conventional pharmaceutical auxiliaries, for example lubricants or tablet disintegrating agents. Liquid preparations such as suspensions or emulsions of the potassium $K_{v,1.3}$ channel inhibitors of the present invention and/or the compounds having in addition to their potassium $K_{v,1.3}$ channel inhibiting properties also CB$_x$ modulating properties and/or potassium $K_{(atP)}$ channel opening properties, either alone or in combination with an effective amount of at least one CB$_1$ antagonist and/or an effective amount of at least one potassium $K_{(atP)}$ channel opener contain the usual diluents such as water, oils and/or suspension agents such as polyethylene glycols and the like. Other auxiliaries may additionally be added, such as preservatives, taste masking agents and the like.

The potassium $K_{v,1.3}$ channel inhibitors of the present invention and/or the compounds having in addition to their potassium $K_{v,1.3}$ channel inhibiting properties also CB$_x$ modulating properties and/or potassium $K_{(atP)}$ channel opening properties, either alone or in combination with an effective amount of at least one CB$_1$ antagonist and/or an effective amount of at least one potassium $K_{(atP)}$ channel opener may be mixed and formulated with the pharmaceutical auxiliaries and/or carriers. For the production of solid medicament forms, the potassium $K_{v,1.3}$ channel inhibitors described herein and/or the compounds having in addition to their potassium $K_{v,1.3}$ channel inhibiting properties and also CB$_x$ modulating properties and/or potassium $K_{(atP)}$ channel opening properties, either alone or in combination with an effective amount of at least one CB$_1$ antagonist and/or an effective amount of at least one potassium $K_{(atP)}$ channel opener may for example be mixed with the auxiliaries and/or carriers in conventional manner and may be wet or dry granulated. The granules or powder can be poured directly into capsules or be pressed into tablet cores in conventional manner. These may be coated in known manner if desired.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference there individually and specifically indicated to be incorporated by reference were set forth in its entirety herein.

The use of the terms "a" and "an" and "the" and similar references in the context of this disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradiated by context. All methods described herein can be performed in any suitable order.
unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., such as, preferred, preferably) provided herein, is intended merely to further illustrate the content of the disclosure and does not pose a limitation on the scope of the claims. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Alternative embodiments of the claimed invention are described herein, including the best mode known to the inventors for carrying out the claimed invention. Of these, variations of the disclosed embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing disclosure. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein.

Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of individual numerical values are stated as approximations as though the values were preceded by the word "about" or "approximately" unless clearly indicated otherwise by context. Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the claimed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for dif-
different numerical values is not meant to limit how the use of the words "about" or "approximately" will serve to broaden a particular numerical value. Thus, as a general matter, "about" or "approximately" broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term "about" or "approximately". Thus, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.
Claims

1. Method of treating, preventing or inhibiting obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence by administering an effective amount of at least one potassium $K_{v1.3}$ channel inhibitor, to subjects in need thereof.

2. Method according to Claim 1 wherein the potassium $K_{v1.3}$ channel inhibitor has in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $C_{Bx}$ modulating properties and/or potassium $K_{(atP)}$ channel opening properties.

3. Method according to Claim 2 wherein the compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $C_{Bx}$ modulating properties and/or potassium $K_{(atP)}$ channel opening properties, such $C_{Bx}$ modulating properties are selected from the group consisting: of $C_{B1}$ antagonistic properties, $C_{B1}$ agonistic properties and/or $C_{B2}$ agonistic properties.

4. Method according to any of the preceding claims wherein obese type I diabetes, obese type II diabetes, non-obese type I diabetes, non-obese type II diabetes and/or related conditions are treated, prevented or inhibited.

5. Method according to Claim 4 wherein the related condition is selected from the group consisting of: glucose metabolism, insulin resistance, hyperglycaemia and/or glucose intolerance.

6. Method according to any of the preceding claims wherein the potassium $K_{v1.3}$ channel inhibitor and/or the compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $C_{Bx}$ modulating properties and/or potassium $K_{(atP)}$ channel opening properties, is selected from the group consisting of:

   a.)
wherein:
- \( R \) and \( R_i \) are independently selected from the group consisting of: napthyl, phenyl, thienyl and pyridyl wherein phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents \( Y \);
- \( R_2 \) is selected from the group consisting of: hydrogen, hydroxy, \( C_{1-3} \)-alkoxy, acetyloxy and propionyloxy;
- \( R_3 \) is selected from the group consisting of: \( C_{3-10} \) branched or unbranched alkyl, \( C_{3-10} \) cycloalkyl, \( C_{3-8} \) alkenyl, \( C_{5-10} \) tricyclic alkyl, \( C_{3-8} \) cycloalkenyl, \( NR_1R_2 \), napthyl, benzyl, phenyl, thienyl and pyridyl wherein benzyl, phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents \( Y \);
- \( Aa \) is selected from the group consisting of: substituents of formulae (i), (ii), (iii), (iv), (v) and (vi);
- \( Bb \) is selected from the group consisting of: sulfonfyl and carbonyl;
- each \( Y \) is independently selected from the group consisting of: \( C_{1-3} \)-alkyl, \( C_{1-3} \)-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (d-2)-amino, mono- or dialkyl (d-2)-amido, \( (C_{1-3}) \)-alkyl sulfonyl, dimethylsulfamido, \( C_{1-3} \)-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;
- \( R_4 \) is selected from the group consisting of: hydrogen, \( C_{1-3} \) branched or unbranched alkyl and \( C_{3-8} \) cycloalkyl; or \( R_4 \) is selected from the group consisting of: acetamido, dimethylamino, 2,2,2-trifluoroethyl, phenyl and pyridyl with the proviso that \( R_5 \) is hydrogen,
wherein such C_{1-8} branched or unbranched alkyl and/or C_{3-8} cycloalkyl alkyl group may be substituted with a hydroxyl group;

- R_5 is selected from the group consisting of: hydrogen, C_{1-8} branched or unbranched alkyl, C_{3-8} cycloalkyl, C_{2-10} branched or unbranched heteroalkyl, C_{3-8} non-aromatic heterocycloalkyl, C_{4-10} non-aromatic heterocycloalkyl-alkyl, amino, hydroxy, phenoxy, benzyloxy, C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl, C_{6-9} cycloalkenylalkyl, imidazolylalkyl, phenyl, benzyl, pyridyl, thienyl, pyridylmethyl and phenethyl; or R_5 is NR_{3}R_{9} with the proviso that R_{4} is H or methyl; or R_{4} and R_{5} together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms,

wherein such C_{1-8} branched or unbranched alkyl and/or C_{3-8} cycloalkyl group may be substituted with hydroxyl and/or fluoro,

wherein such C_{2-10} branched or unbranched heteroalkyl, C_{3-8} non-aromatic heterocycloalkyl and/or C_{4-10} non-aromatic heterocycloalkyl-alkyl groups may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such C_{2-10} branched or unbranched heteroalkyl, C_{3-8} non-aromatic heterocycloalkyl and/or C_{4-10} non-aromatic heterocycloalkyl-alkyl groups may contain a SO_{2}^- group,

wherein such C_{2-10} branched or unbranched heteroalkyl group, C_{3-8} non-aromatic heterocycloalkyl group and/or C_{4-10} non-aromatic heterocycloalkyl-alkyl group may be substituted with keto, trifluoromethyl, C_{1-3} alky, hydroxy, amino, monoalkylamino, dialkylamino or fluoro,

wherein such amino, hydroxy, phenoxy, benzyloxy, C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl, C_{6-9} cycloalkenylalkyl may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such amino, hydroxy, phenoxy, benzyloxy, C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl, C_{6-9} cycloalkenylalkyl may contain a keto or -SO_{2}^- group,

wherein such C_{1-8} alkoxy, C_{3-8} alkenyl and C_{5-8} cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom,

wherein such phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group may be substituted with 1, 2 or 3 of the substituents Y,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain a keto or -SO_{2}^- group,
wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring
atoms may be substituted with a C1-4 alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1 H-azepinyl group;

- R6 is selected from the group consisting of: hydrogen and C1-3 unbranched alkyl;
- R7 is C1-3 unbranched alkyl;
- R8 and R9 are the same or different and are selected from the group consisting of: C2-4 alkyl and C2-4 trifluoroalkyl; or R8 is methyl with the proviso that R9 is C2-4 alkyl; or R8 and R9 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms,

wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may contain an additional heteroatom selected from the group consisting of: N, O and S or may contain a group selected from the group consisting of: a keto or -SO2 group,

wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may be substituted with C1-4 alkyl;

- R10 and R11 are independently selected from the group consisting of: hydrogen, branched or unbranched C1-5 alkyl, branched or unbranched C1-5 alkenyl, C3-8 cycloalkyl, C3-8 cycloalkenyl, naphthyl and phenyl; or R10 and R11 - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkynyl group,

wherein such branched or unbranched C1-5 alkyl and/or branched or unbranched C1-8 alkenyl groups may contain one or more heteroatoms selected from the group consisting of: O, N, and S,

wherein such branched or unbranched C1-8 alkyl and/or branched or unbranched C1-8 alkenyl groups may contain a group selected from the group consisting of: keto and -SO2 group and wherein such keto and -SO2 group may be substituted with a hydroxy or amino group,

wherein such C3-8 cycloalkyl and/or C3-8 cycloalkenyl group may contain one or more ring heteroatoms selected from the group consisting of: O, N and S,

wherein such C3-8 cycloalkyl and/or C3-8 cycloalkenyl group may be substituted with hydroxy, C1-3 alkyl, -SO2-, keto, amino, C1-3 monoalkylamino and/or C1-3 dialkylamino,

wherein such phenyl group may be substituted with 1, 2 or 3 substituents Y with the proviso that R11 is selected from the group consisting of: hydrogen, branched or unbranched C1-5 alkyl group wherein such branched or unbranched C1-5 alkyl group may contain one or more heteroatoms selected
from the group consisting of: O, N and S or wherein such branched or unbranched \( \text{C}_{1-5} \) alkyl group may contain \( \text{SO}_2^- \) and wherein such branched or unbranched \( \text{C}_{1-5} \) alkyl group may be substituted with a hydroxy, keto or amino group,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain ring heteroatoms selected from the group consisting of: O, N and S,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain a group selected from the group consisting of: keto and \( \text{SO}_2^- \),

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with hydroxy, \( \text{C}_{1-3} \) alkyl, \( \text{SO}_2^- \), keto, amino, d-3 monoalkylamino, \( \text{C}_{3-3} \) dialkylamino, pyrrolidinyl, or piperidinyl,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an aneled phenyl group which aneled phenyl group may be substituted with 1 or 2 substituents \( Y \); and

a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

b.)

![Diagram](II)

wherein

- \( R_{i2} \) and \( R_{i3} \) are independently selected from the group consisting of: hydrogen, \( \text{C}_{1-3} \) alkyl and \( \text{C}_{3-6} \) cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;

- \( R_{i4} \) is phenyl which may be substituted with 1, 2 or 3 substituents \( Z \) which can be the same or different and wherein \( Z \) is selected from the group consisting of: d-3 alkyl, \( \text{C}_{1-3} \) alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (\( \text{C}_{1-2} \)) amino, mono- or dialkyl (\( \text{C}_{1-2} \)) amido, \( \text{C}_{1-3} \) alkoxy carbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl; and

a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;
c.)

\[
\begin{align*}
\text{III} & \\
Q & \text{phenyl which may be substituted with 1, 2 or 3 substituents } Z \text{ which can be the same or different and wherein } Z \text{ is selected from the group consisting of: } \\
& \text{Ci-3-alkyl, Ci-3-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (Ci-2)-amino, mono- or dialkyl (Ci-2)-amido, (d-3)-alkyl sulfonyl, dimethylsulfamido, Ci-3-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;} \\
\end{align*}
\]

wherein

- Q is phenyl which may be substituted with 1, 2 or 3 substituents Z which can be the same or different and wherein Z is selected from the group consisting of: Ci-3-alkyl, Ci-3-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (Ci-2)-amino, mono- or dialkyl (Ci-2)-amido, (d-3)-alkyl sulfonyl, dimethylsulfamido, Ci-3-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;
- T is selected from the group consisting of: hydrogen, Ci-3 alkyl and C_{36} cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;
- R_{15} is selected from the group consisting of: Ci-3 alkyl and C_{36} cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S; and
- a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

\[
\begin{align*}
\text{C.)} & \\
\end{align*}
\]

d.) Diazoxide, NN414, R(+)-WIN55212-2, HU-308, Rimonabant, SR-147778; and a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

e.) and mixtures thereof.

7. Method according to Claim 6 wherein R_{2} is hydrogen and wherein the 4-position of the 4,5 dihydro pyrazole ring is in the S-configuration.

8. Method according to any of the preceding claims wherein the potassium K_{13} channel inhibitor and/or the compound having in addition to its potassium K_{13} channel inhibiting properties also CB_{x} modulating properties and/or potassium K_{(atp)} channel opening properties, is selected from the group consisting of:
and mixtures thereof.

9. Use of an effective amount of at least one potassium $K_{v13}$ channel inhibitor for the manufacture of a medicament for the prophylaxis, treatment, delayed progression, delayed onset and/or inhibition of obesity, diabetes mellitus, metabolic syndrome, syndrome X, insulinoma, familial hyperinsulemic hypoglycemia, male pattern baldness, detrusor hyperreactivity, asthma, glucose metabolism - in particular, insulin resistance, hyperglycaemia and/or glucose intolerance - neuroprotection, epilepsy, analgesia, cardioprotection, angina, cardioplegia, arrhythmia, coronary spasm, peripheral vascular disease, cerebral vasospasm, appetite regulation, neurodegeneration, pain - including neuropathic pain and chronic pain - and impotence.

10. Use according to Claim 9 wherein the potassium $K_{v13}$ channel inhibitor has in addition to its potassium $K_{v13}$ channel inhibiting properties also $CB_x$ modulating properties and/or potassium $K_{(ATP)}$ channel opening properties.

11. Use according to Claim 10 wherein the compound having in addition to its potassium $K_{v13}$ channel inhibiting properties also $CB_x$ modulating and/or potassium $K_{(ATP)}$ channel opening properties, such $CB_x$ modulating properties are selected from the group consisting: of $CB_1$ antagonistic properties, $CB_1$ agonistic properties and/or $CB_2$ agonistic properties.

12. Use according to any of Claims 9 to 11 wherein obese type I diabetes, obese type II diabetes, non-obese type I diabetes, non-obese type II diabetes and/or related conditions are treated, prevented or inhibited.

13. Use according to Claim 12 wherein the related condition is selected from the group consisting of: glucose metabolism, insulin resistance, hyperglycaemia and/or glucose intolerance.

14. Use according to any of Claims 9 to 13 wherein the potassium $K_{v13}$ channel inhibitor and/or the compound having in addition to its potassium $K_{v13}$ channel inhibiting properties also $CB_x$ modulating properties and/or potassium $K_{(ATP)}$ channel opening properties, is selected from the group consisting of:

a.)
wherein:

- $R$ and $R_i$ are independently selected from the group consisting of: napthyl, phenyl, thienyl and pyridyl wherein phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents $Y$;
- $R_2$ is selected from the group consisting of: hydrogen, hydroxy, $C_{1-3}$-alkoxy, acetyloxy and propionyloxy;
- $R_3$ is selected from the group consisting of: $C_{1-8}$ branched or unbranched alkyl, $C_3$-$10$ cycloalkyl, $C_{3-8}$ alkenyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl, $C_{5-8}$ cycloalkenyl, $NR_{10}R_n$, naphtyl, benzyl, phenyl, thienyl and pyridyl wherein benzyl, phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents $Y$;
- $Aa$ is selected from the group consisting of: substituents of formulae (i), (ii), (iii), (iv), (v) and (vi)
- $Bb$ is selected from the group consisting of: sulfonyl and carbonyl;
- each $Y$ is independently selected from the group consisting of: $C_{1-3}$-alkyl, $C_{1-3}$-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (d-$2$)-amino, mono- or dialkyl (d-$2$)-amido, $(C_1-3)$-alkyl sulfonyl, dimethylsulfamido, $C^-$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;
- $R_4$ is selected from the group consisting of: hydrogen, $C_{1-8}$ branched or unbranched alkyl and $C_{3-8}$ cycloalkyl; or $R_4$ is selected from the group consisting of: acetamido, dimethylamino, 2,2,2-trifluoroethyl, phenyl and pyridyl with the proviso that $R_6$ is hydrogen, wherein such $C_{1-8}$ branched or unbranched alkyl and/or $C_{3-8}$ cycloalkyl alkyl group may be substituted with a hydroxyl group;
- $R_5$ is selected from the group consisting of: hydrogen, $C_{1-8}$ branched or unbranched alkyl, $C_{3-8}$ cycloalkyl, $C_{2-10}$ branched or unbranched heteroalkyl, $C_{3-8}$ non-aromatic heterocycloalkyl, $C_{4-10}$ non-aromatic heterocycloalkyl-alkyl, amino, hydroxy, phenoxy, benzlyoxy, $C_{1-8}$ alkoxy, $C_{3-8}$ alkenyl, $C_{5-8}$ cycloalkenyl, $C_{6-9}$ cycloalkenylalkyl, imidazolylalkyl, phenyl, benzyl, pyridyl, thienyl, pyridylmethyl and phenethyl; or $R_5$ is $NR_8R_9$ with the proviso that $R_4$ is H or methyl; or $R_4$ and $R_5$ together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms,

wherein such $C_{1-8}$ branched or unbranched alkyl and/or $C_{3-8}$ cycloalkyl group may be substituted with hydroxyl and/or fluoro,

wherein such $C_{2-10}$ branched or unbranched heteroalkyl, $C_{3-8}$ non-aromatic heterocycloalkyl and/or $C_{4-10}$ non-aromatic heterocycloalkyl-alkyl groups may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such $C_{2-10}$ branched or unbranched heteroalkyl, $C_{3-8}$ non-aromatic heterocycloalkyl and/or $C_{4-10}$ non-aromatic heterocycloalkyl-alkyl group may be substituted with keto, trifluoromethyl, $C_{1-3}$ alkyl, hydroxy, amino, monoalkylamino, dialkylamino or fluoro,

wherein such amino, hydroxy, phenoxy, benzlyoxy, $C_{1-8}$ alkoxy, $C_{3-8}$ alkenyl, $C_{5-8}$ cycloalkenyl, $C_{6-9}$ cycloalkenylalkyl may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such amino, hydroxy, phenoxy, benzlyoxy, $C_{1-8}$ alkoxy, $C_{3-8}$ alkenyl, $C_{5-8}$ cycloalkenyl, $C_{6-9}$ cycloalkenylalkyl may contain a keto or $-SO_2^-$ group,

wherein such $C_{1-8}$ alkoxy, $C_{3-8}$ alkenyl and $C_{5-8}$ cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom,

wherein such phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group may be substituted with 1, 2 or 3 of the substituents Y,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain a keto or $-SO_2^-$ group,

wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may be substituted with a $C_{1-4}$ alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino,
dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1 H-azepinyl group;
- \( R_6 \) is selected from the group consisting of: hydrogen and \( \text{Ci}_3 \) unbranched alkyl;
- \( R_7 \) is \( \text{Ci}-3 \) unbranched alkyl;
- \( R_8 \) and \( R_9 \) are the same or different and are selected from the group consisting of: \( \text{C}_2 \text{A} \) alkyl and \( \text{C}_2 \text{A} \text{trifluoroalkyl} \); or \( R_8 \) is methyl with the proviso that \( R_9 \) is \( \text{C}_2 \text{A} \) alkyl; or \( R_8 \) and \( R_9 \) - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms, wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may contain an additional heteroatom selected from the group consisting of: \( \text{N} \), \( \text{O} \) and \( \text{S} \) or may contain a group selected from the group consisting of: keto or \(-\text{SO}_2\) group, wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may be substituted with \( \text{Ci}_4 \) alkyl;
- \( \text{R}_{10} \) and \( \text{R}_n \) are independently selected from the group consisting of: hydrogen, branched or unbranched \( \text{Ci}_8 \) alkyl, branched or unbranched \( \text{Ci}_8 \) alkenyl, \( \text{C}_3 \text{B} \) cycloalkyl, \( \text{C}_3 \text{B} \text{cycloalkenyl} \), naphtyl and phenyl; or \( \text{R}_{10} \) and \( \text{R}_n \) - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group, wherein such branched or unbranched \( \text{Ci}_8 \) alkyl and/or branched or unbranched \( \text{Ci}_8 \) alkenyl groups may contain one or more heteroatoms selected from the group consisting of: \( \text{O} \), \( \text{N} \) and \( \text{S} \), wherein such branched or unbranched \( \text{Ci}_8 \) alkyl and/or branched or unbranched \( \text{Ci}_8 \) alkenyl groups may contain a group selected from the group consisting of: keto and \(-\text{SO}_2\) group and wherein such keto and \(-\text{SO}_2\) group may be substituted with a hydroxy or amino group, wherein such \( \text{C}_3 \text{B} \) cycloalkyl and/or \( \text{C}_3 \text{B} \text{cycloalkenyl} \) group may contain one or more ring heteroatoms selected from the group consisting of: \( \text{O} \), \( \text{N} \) and \( \text{S} \), wherein such \( \text{C}_3 \text{B} \) cycloalkyl and/or \( \text{C}_3 \text{B} \text{cycloalkenyl} \) group may be substituted with hydroxy, \( \text{C}_1 \text{B} \) alkyl, \(-\text{SO}_2\) , keto, amino, \( \text{C}_1 \text{B} \) monoalkylamino and/or \( \text{d}_3 \) dialkylamino, wherein such phenyl group may be substituted with 1, 2 or 3 substituents \( Y \) with the proviso that \( \text{R}_n \) is selected from the group consisting of: hydrogen, branched or unbranched \( \text{Ci}_5 \) alkyl group wherein such branched or unbranched \( \text{Ci}_5 \) alkyl group may contain one or more heteroatoms selected from the group consisting of: \( \text{O} \), \( \text{N} \) and \( \text{S} \) or wherein such branched or unbranched \( \text{Ci}_5 \) alkyl group may contain \( \text{SO}_2\) - and wherein such branched or
unbranched C\textsubscript{\textit{i}-5} alkyl group may be substituted with a hydroxy, keto or amino group,
wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain ring heteroatoms selected from the group consisting of: O, N and S,
wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain a group selected from the group consisting of: keto and SO\textsubscript{2},
wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with hydroxy, C\textsubscript{1-3} alkyl, SO\textsubscript{2}-, keto, amino, C\textsubscript{3} monoalkylamino, C\textsubscript{3-}i\textsubscript{3} dialkylamino, pyrrolidinyl, or piperidinyl,
wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents \textit{Y}; and
a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;
b.)
\[
\begin{align*}
\text{\textit{R}_{14}} & \quad \text{\textit{R}_{13}} \\
\text{\textit{R}_{12}} & \quad \text{(II)} \end{align*}
\]
wherein
- \textit{R}_{12} and \textit{R}_{13} are independently selected from the group consisting of: hydrogen, C\textsubscript{3} alkyl and C\textsubscript{3-6} cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;
- \textit{R}_{14} is phenyl which may be substituted with 1, 2 or 3 substituents \textit{Z} which can be the same or different and wherein \textit{Z} is selected from the group consisting of: d \textsubscript{3}-alkyl, Cl\textsubscript{3}-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C\textsubscript{2})-amino, mono- or dialkyl (C\textsubscript{2})-amido, (Cl\textsubscript{3})-alkyl sulfonyl, dimethylsulfamido, Cl\textsubscript{3}-alkoxycarbonyl, carbobxy, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl; and
a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;
c.)
\[
\begin{align*}
\text{\textit{T}} & \quad \text{\textit{R}_{15}} \\
\text{(III)} \end{align*}
\]
wherein

- \( Q \) is phenyl which may be substituted with 1, 2 or 3 substituents \( Z \) which can be the same or different and wherein \( Z \) is selected from the group consisting of: \( \text{Cl-3-alkyl, Cl-3-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (Cl-2)-amino, mono- or dialkyl (C^\-amido), (C^\-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;}
- \( T \) is selected from the group consisting of: hydrogen, \( C_{1-3} \) alkyl and \( C_{3-6} \) cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;
- \( R_i5 \) is selected from the group consisting of: \( C_{1-3} \) alkyl and \( C_{3-6} \) cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S; and
- a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;
- d.) Diazoxide, NN414, R(+)-WIN55212-2, HU-308, Rimonabant, SR-147778; and a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;
- e.) and mixtures thereof.

15. Use according to Claim 14 wherein \( R_2 \) is hydrogen and wherein the 4-position of the 4,5 dihydro pyrazole ring is in the S-configuration.

16. Use according to any of Claims 9 to 15 wherein the potassium \( K_{v,1,3} \) channel inhibitor and/or the compound having in addition to its potassium \( K_{v,1,3} \) channel inhibiting properties also \( C_{Bx} \) modulating properties and/or potassium \( K_{(ATP)} \) channel opening properties, is selected from the group consisting of:
and mixtures thereof.

17. Pharmaceutical composition comprising a potassium K_v1.3 channel inhibitor and/or a compound having in addition to its potassium K_v1.3 channel inhibiting properties also
CB<sub>x</sub> modulating properties and/or potassium K<sub>(ATP)</sub> channel opening properties, selected from the group consisting of:

a.)

wherein:
- R and R<sub>1</sub> are independently selected from the group consisting of: naphthyl, phenyl, thienyl and pyridyl wherein phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents Y;
- R<sub>2</sub> is selected from the group consisting of: hydrogen, hydroxy, C<sub>1-3</sub>-alkoxy, acetyloxy and propionyloxy;
- R<sub>3</sub> is selected from the group consisting of: C<sub>1-8</sub> branched or unbranched alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-8</sub> alkenyl, C<sub>5-10</sub>bicycloalkyl, C<sub>6-10</sub> tricycloalkyl, C<sub>5-8</sub> cycloalkenyl, NR<sub>10</sub> R<sub>n</sub>, naphtyl, benzyl, phenyl, thienyl and pyridyl wherein benzyl, phenyl, thienyl and pyridyl may be substituted with 1, 2 or 3 substituents Y;
- Aa is selected from the group consisting of: substituents of formulae (i), (ii), (iii), (iv), (v) and (vi)

- Bb is selected from the group consisting of: sulfonyl and carbonyl;
- each Y is independently selected from the group consisting of: C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C<sub>1-3</sub>)-amino, mono- or dialkyl (C<sub>1-3</sub>)-amido, (C<sub>1-3</sub>)-alkyl sulfonyl, dimethylsulfamido, C<sub>1-3</sub>-alkoxycarbonyl, carboxyl, trifluoromethylsulfonfyl, cyano, carbamoyl, sulfamoyl and acetyl;
- \( R_4 \) is selected from the group consisting of: hydrogen, \( \text{C}_1^8 \) branched or unbranched alkyl and \( C_{3-8} \) cycloalkyl; or \( R_4 \) is selected from the group consisting of: acetamido, dimethylamino, 2,2,2-trifluoroethyl, phenyl and pyridyl with the proviso that \( R_5 \) is hydrogen,

wherein such \( \text{C}_1^8 \) branched or unbranched alkyl and/or \( C_{3-8} \) cycloalkyl alkyl group may be substituted with a hydroxyl group;

- \( R_5 \) is selected from the group consisting of: hydrogen, \( \text{C}_1^8 \) branched or unbranched alkyl, \( C_{3-8} \) cycloalkyl, \( C_{2-10} \) branched or unbranched heteroalkyl, \( C_{3-8} \) non-aromatic heterocycloalkyl, \( C_{4-10} \) non-aromatic heterocycloalkyl-alkyl, amino, hydroxy, phenoxy, benzylxoy, \( \text{C}_1^8 \) alkoxy, \( C_{3-8} \) alkenyl, \( C_{5-8} \) cycloalkenyl, \( C_{6-9} \) cycloalkenylalkyl, imidazolylalkyl, phenyl, benzyl, pyridyl, thiienyl, pyridylmethyl and phenethyl; or \( R_5 \) is \( \text{NR}_8 \text{R}_9 \) with the proviso that \( R_4 \) is hydrogen, or \( R_4 \) and \( R_5 \) together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms,

wherein such \( \text{C}_1^8 \) branched or unbranched alkyl and/or \( C_{3-8} \) cycloalkyl group may be substituted with hydroxyl and/or fluoro,

wherein such \( C_{2-10} \) branched or unbranched heteroalkyl, \( C_{3-8} \) non-aromatic heterocycloalkyl and/or \( C_{4-10} \) non-aromatic heterocycloalkyl-alkyl groups may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such \( C_{2-10} \) branched or unbranched heteroalkyl, \( C_{3-8} \) non-aromatic heterocycloalkyl and/or \( C_{4-10} \) non-aromatic heterocycloalkyl-alkyl groups may contain a \( \text{SO}_2^- \) group,

wherein such \( C_{2-10} \) branched or unbranched heteroalkyl group, \( C_{3-8} \) non-aromatic heterocycloalkyl group and/or \( C_{4-10} \) non-aromatic heterocycloalkyl-alkyl group may be substituted with keto, trifluoromethyl, \( \text{C}_1^3 \) alkyl, hydroxy, amino, monoalkylamino, dialkylamino or fluoro,

wherein such amino, hydroxy, phenoxy, benzylxoy, \( \text{C}_1^8 \) alkoxy, \( C_{3-8} \) alkenyl, \( C_{5-8} \) cycloalkenyl, \( C_{6-9} \) cycloalkenylalkyl may contain one or more heteroatoms selected from the group consisting of: O, N and S,

wherein such amino, hydroxy, phenoxy, benzylxoy, \( \text{C}_1^8 \) alkoxy, \( C_{3-8} \) alkenyl, \( C_{5-8} \) cycloalkenyl, \( C_{6-9} \) cycloalkenylalkyl may contain a keto or -\( \text{SO}_2^- \) group,

wherein such \( \text{C}_1^8 \) alkoxy, \( C_{3-8} \) alkenyl and \( C_{5-8} \) cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom,

wherein such phenyl, benzyl, pyridyl, thiienyl, pyridylmethyl or phenethyl group may be substituted with 1, 2 or 3 of the substituents \( Y \),
wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain one or more heteroatoms selected from the group consisting of: O, N and S,
wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may contain a keto or -SO₂⁻ group,
wherein such monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms may be substituted with a C₁₄ alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1 H-azepinyl group;
- R₆ is selected from the group consisting of: hydrogen and C₃₋₈ unbranched alkyl;
- R₇ is C₃₋₈ unbranched alkyl;
- R₈ and R₉ are the same or different and are selected elected from the group consisting of: C₂₋₄ alkyl and C₂₋₄ trifluoroalkyl; or R₈ is methyl with the proviso that R₉ is C₂₋₄ alkyl; or R₈ and R₉ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms,
wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may contain an additional heteroatom selected from the group consisting of: N, O and S or may contain a group selected from the group consisting of: a keto or -SO₂⁻ group,
wherein such saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms may be substituted with C₁₋₄ alkyl;
- R₁₀ and Rₙ are independently selected from the group consisting of: hydrogen, branched or unbranched C₁₋₄ alkyl, branched or unbranched C₁₋₄ alkenyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, naphtyl and phenyl; or R₁₀ and Rₙ - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group,
wherein such branched or unbranched C₁₋₄ alkyl and/or branched or unbranched C₁₋₄ alkenyl groups may contain one or more heteroatoms selected from the group consisting of: O, N and S,
wherein such branched or unbranched C₁₋₄ alkyl and/or branched or unbranched C₁₋₄ alkenyl groups may contain a group selected from the group consisting of: keto and -SO₂⁻ group and wherein such keto and -SO₂⁻ group may be substituted with a hydroxy or amino group,
wherein such C₃₋₈ cycloalkyl and/or C₃₋₈ cycloalkenyl group may contain one or more ring heteroatoms selected from the group consisting of: O, N and S,
wherein such C₃₋₈ cycloalkyl and/or C₃₋₈ cycloalkenyl group may be substituted with hydroxy, C₁₋₃ alkyl, -SO₂⁻, keto, amino, C₁₋₃ monoalkylamino and/or C₁₋₃ dialkylamino,

wherein such phenyl group may be substituted with 1, 2 or 3 substituents Y with the proviso that Rn is selected from the group consisting of: hydrogen, branched or unbranched C₁₋₅ alkyl group wherein such branched or unbranched C₁₋₅ alkyl group may contain one or more heteroatoms selected from the group consisting of: O, N and S or wherein such branched or unbranched C₁₋₅ alkyl group may contain SO₂⁻ and wherein such branched or unbranched C₁₋₅ alkyl group may be substituted with a hydroxy, keto or amino group,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain ring heteroatoms selected from the group consisting of: O, N and S,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain a group selected from the group consisting of: keto and SO₂⁻.

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with hydroxy, C₁₋₃ alkyl, SO₂⁻, keto, amino, C₁₋₃ monoalkylamino, C₁₋₃ dialkylamino, pyrrolidinyl, or piperidinyl,

wherein such monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y and a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

b.)

\[
\text{(II)}
\]

wherein

- R₁₁₂ and R₁₃ are independently selected from the group consisting of: hydrogen, C₁₋₃ alkyl and C₃₋₈ cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;
- Ru is phenyl which may be substituted with 1, 2 or 3 substituents Z which can be the same or different and wherein Z is selected from the group consisting of: C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₃)-amino, mono- or dialkyl (C₁₋₃)-amido, (d-₃)-alkyl sulfonyl, dimethylsulfamido, C₁₋₃-alkoxy carbonyl, carboxyl, trifluoromethylsulfonyl, cyan, carbamoyl, sulfamoyl and acetyl; and
a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

c.)

![Chemical Structure](image)

(III)

wherein

- $Q$ is phenyl which may be substituted with 1, 2 or 3 substituents $Z$ which can be the same or different and wherein $Z$ is selected from the group consisting of: d) $\alpha$-alkyl, C$^\alpha$-alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C$_3$H$_7$)-amino, mono- or dialkyl (C$_3$H$_7$)-amido, (C$_3$H$_7$)-alkyl sulfonyl, dimethylsulfamido, C$_3$H$_7$-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl;

- $T$ is selected from the group consisting of: hydrogen, C$_3$H$_7$ alkyl and C$_3$-6 cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;

- $R_{i5}$ is selected from the group consisting of: C$_i$-3 alkyl and C$_3$-6 cycloalkyl which may contain from 1 to 3 heteroatoms selected from the group consisting of: N, O and S;

a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

d.) Diazoxide, NN414, R(+)-WIN55212-2, HU-308, Rimonabant, SFM 47778; and a prodrug thereof, a tautomer thereof or a pharmaceutically acceptable salt thereof;

e.) and mixtures thereof.

wherein the potassium $K_{V,3}$ channel inhibitor and/or the compound having in addition to its potassium $K_{V,3}$ channel inhibiting properties also CB$_x$ modulating properties and/or potassium $K_{(atp)}$ channel opening properties, inhibits the potassium $K_{V,3}$ channel by at least 40%.

18. Pharmaceutical composition according to Claim 17 wherein $R_2$ is hydrogen and wherein the 4-position of the 4,5 dihydro pyrazole ring is in the S-configuration.
19. Pharmaceutical composition according to Claims 17 and 18 wherein the potassium $K_{v1.3}$ channel inhibitor and/or the compound having in addition to its potassium $K_{v1.3}$ channel inhibiting properties also $CB_x$ modulating properties and/or potassium $K_{(a,t)}$ channel opening properties, is selected from the group consisting of:
Chiral and mixtures thereof.
Figure 1: Stimulation protocol for the investigation of compound effects

Figure 2: Scheme of test item application protocol

Figure 3: $K_{v,1.3}$-mediated potassium current. Example of a representative original current trace. The two cursors on the right indicate the range of the test pulse, where the peak current amplitude was evaluated (205-230 ms of the test pulse to +40 mV). The two cursors on the left indicate the area where the mean leak current was evaluated (100-140 ms of the test pulse to −90 mV).
Figure 4A: Effect of 10 μM example compound 1 on $K_{v1.3}$-mediated current. 80 superimposed original $K_{v1.3}$-current traces recorded in absence and presence of 10 μM of example compound 1.

Figure 4B: Effect of 10 μM example compound 1 on $K_{v1.3}$-mediated current. Current amplitude is plotted against time. Onset (indicated by the long dashed line) and offset (indicated by the short dashed line) of test compound application. Extrapolated time course of current amplitude under vehicle conditions was calculated by a biexponential fit of equation $Y = a\exp(-cx) + b\exp(-dx)$ and is depicted as the solid line.
Figure 5: Concentration-dependence of the effect of example compound 1 on the $\text{K}_{\text{v}1.3}$-mediated potassium current, in the presence of 0.1% BSA. Current amplitudes were measured at the peak of the test pulse to +40 mV. Data points are given as mean ± SEM from 3 experiments each.