(51) International Patent Classification:

A61K 31/165 (2006.01)  A61K 31/21 (2006.01)
A61K 31/16 (2006.01)  A61K 31/22 (2006.01)
A61K 31/19 (2006.01)  A61P 9/10 (2006.01)

(57) Abstract: The present invention relates to the induction of hypothermia in humans, male and female, at any age, by use of a pharmaceutical composition to be administered parenterally by infusion or injection, comprising at least one compound selected among (1) vanilloid receptor agonists, capsaicinoids or capsaicinoid-like agonists reaching and binding to vanilloid receptors, and (2) cannabinoids or cannabimimetic agonists reaching and binding to cannabinoid receptors, and (3) adenosine receptor agonists, and (4) neurotensin receptor agonists, and (5) thyroxine derivatives, and (6) cytochrome c inhibitors, and (7) oxygen tension reducers, thereby inducing hypothermia, thus benefiting patients suffering from illnesses characterized by tissue anoxia.


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 February 2010 (11.02.2010)

(10) International Publication Number
WO 2010/015260 A2
Administration by infusion for the treatment of ischemic effects

This application is a non-provisional application of DK patent application DK 2008 01079 filed on August 7, 2008, which is hereby incorporated by reference in its entirety. All patent and non-patent references cited in the DK patent application, or in the present application, are also hereby incorporated by reference in their entirety.

Field of invention

The present invention relates to the use of compounds administered parenterally for the induction of hypothermia for the prophylaxis and treatment of ischemia. Ischemia is the lack of oxygenated blood flow to various body parts and may result from apoplexia, cardiac arrest and asphyxia. An aspect of the present invention regards administration of the compounds of the invention by infusion.

Background of invention

Ischemia is the lack of oxygenated blood flow to various body parts and organs. Cerebral ischemia is an ischemic condition where the brain or parts of the brain do not receive enough blood flow to maintain normal neurological function. Cerebral ischemia can be the result of various serious diseases such as stroke and cardiac arrest, or the result of arterial obstruction such as strangulation. Severe or prolonged cerebral ischemia will result in unconsciousness, brain damage or death.

The neuroprotective efficacy of induced hypothermia following or during ischemia of the brain is evident in experimental animal models of stroke [1-11]. In humans, two trials conducted in cardiac arrest patients have shown improved neurological outcome of inducing hypothermia [12;13]. The therapeutic hypothermia did not increase the complication rate in these two trials and the use of induced hypothermia in comatose survivors of cardiac arrest is now recommended internationally [14].

Hypothermia counteracts ischemic brain damage by several mechanisms:

1. Ischemia induces opening of the blood-brain barrier, a process that seems to be very sensitive to brain temperature [15]. This is evident from studies of
tracers and their migration across the blood-brain barrier, in which hypothermia attenuates extravasation several hours after ischemia [16] and prevents vasogenic oedema [17].

2. Reperfusion after brain ischemia results in the production of free radicals, which causes peroxidation and destruction of membrane lipids [18]. Hypothermia prevents the production of free radicals such as hydroxyl and nitric oxide during reperfusion after brain ischemia [19;20;24].

3. Amino acids, such as glutamate, aspartate, and glycine, act as excitotoxic neurotransmitters by over stimulation of neurons in the vicinity of ischemic damage, which causes further injury. Hypothermia lowers the release and may even cause a more rapid reuptake of these transmitters [21-23]. Release of excitotoxic neurotransmitters might also cause progressive neuronal death in the penumbra in stroke patients [22], and hypothermia after cerebral ischemia could attenuate this process.

4. During ischemia, cellular metabolism in the penumbra undergoes significant changes. As the neurons continue to fire, potassium ions flood into the extracellular space, calcium ions flow into the neurons leading to cytoskeletal degradation, and ATP concentrations fall as energy depletion continues [25]. Hypothermia reduces calcium influx and the subsequent breakdown of intracellular structures [26], improves potassium ion homoeostasis [27], and helps metabolic functions such as calcium or calmodulin-dependent protein kinase activity to recover [28;29].

5. By lowering of neutrophil and microglial activation after ischemia, hypothermia also has an anti-inflammatory effect [30;31].

6. Apoptosis and DNA changes are crucial stages in delayed neuronal death after transient cerebral ischemia [32]. Hypothermia directly inhibits apoptosis [33] and may also increase endogenous production of the anti-apoptotic protein Bcl-2 [34]. Hypothermia may even have effects at the DNA level: A slight lowering of brain temperature results in less DNA fragmentation [35] and less apoptosis [36].
Induction of hypothermia by lowering of the core temperature of the body has been attempted by mechanical cooling devices such as surface cooling and cooling using catheters placed in a large vessel. However, these mechanical inducers of hypothermia have been shown to have considerable unwanted side effects. These side effects include shivering, serious infections and lung puncture. Shivering causes an increased exertion of the heart of the patient, and this will in some cases result in ischemia of the heart and thereby increased morbidity and mortality.

The regulation of the core temperature of the body by a pharmaceutical composition comprising a one or more compounds capable of inducing hypothermia does not only solve the problem of reducing or preventing the effects of ischemia, such as tissue damaging effects, but is also relevant as a safer and less expensive alternative to the currently employed mechanical methods.

Summary of invention

The present invention relates to the induction of hypothermia in humans in a predictable and dose responsive fashion by use of a pharmaceutical composition comprising at least one compound capable of inducing hypothermia, thereby benefiting patients suffering from illnesses characterized by tissue anoxia. The inventors have found that such hypothermic effects can be obtained in humans as a result of several classes of compounds:

• Vanilloid receptor agonists, capsaicinoids or capsaicinoid-like agonists reaching and binding to vanilloid receptors, and

• Cannabinoids or cannabimimetic agonists reaching and binding to cannabinoid receptors.

• Adenosine receptor agonists, adenosine analogs or adenosine uptake inhibitors and agonist compounds reaching and binding to adenosine receptors.

• Neurotensin receptor agonists, neurotensin analogs and compounds reaching and binding neurotensin receptors.

• Thyroxine derivatives.

• Cytochrome c oxidase inhibitors.

• Oxygen tension reducers.
An aspect of the present invention regards the administration of the at least one compound of the invention. Parenteral administration e.g. by infusion and/or injection is a preferred administration form, and it follows that pharmaceutical formulations allowing this mode of administration are preferable as well.

It is an aspect of the present invention to provide a medicament for parenteral administration comprising at least one compound of the present invention, which is capable of inducing hypothermia in an individual.

The dosing of the medicaments of the present invention is also an aspect of the present invention.

A kit of parts comprising the medicament as herein disclosed is yet an aspect of the present invention.

**Brief description of figures**

- **Figure 1**: Plot of temperature curves
- **Figure 2**: Plot of diastolic blood pressure.
- **Figure 3**: Plot of temperature curves (Example 18; study 1) Dihydrocapsaicin.
- **Figure 4**: Plot of temperature curves (Example 18; study 2) Dihydrocapsaicin.
- **Figure 5**: Plot of temperature curves (Example 18; study 3) Dihydrocapsaicin.
- **Figure 6**: Plot of temperature curves (Example 18; study 4) Delta-8-THC phosphate
- **Figure 7**: Plot of temperature curves (Example 18; study 5) HU-210.
- **Figure 8**: Controlled normalization of temperature (Example 19) Dihydrocapsaicin.

**Detailed description of the invention**

In a main aspect, the present invention relates to at least one compound selected from the group consisting of a vanilloid receptor agonist, a cannabinoid or a cannabimimetic compound, an adenosine, or an adenosine analog, or an adenosine receptor agonist, or an adenosine uptake inhibitor, a neurotensin, or a neurotensin analog, or a neurotensin receptor agonist, or a neurotensin mimetic compound a thyroxine derivative, a cytochrome c oxidase inhibitor, or an oxygen tension reducer to be
administered parenterally such as by infusion or injection for use in the treatment of ischemia in an individual in need thereof by induction of hypothermia in said individual.

Definitions

Adenosine: Adenosine is a nucleoside composed of adenine attached to a ribose (ribofuranose) moiety via a β-N9-glycosidic bond as described by the formula below.

![Adenosine Structure]

Adenosine analog: An adenosine analog is any compound with a structure based on an adenosine and thus includes but is not limited to 5'-AMP, ADP, ATP and the like.

Agonist: A vanilloid receptor agonist is a vanilloid compound. A cannabinoid receptor agonist is a cannabinoid or a cannabimimetic compound. An adenosine receptor agonist is an adenosine, adenosine analog or adenosine-like compound. A neurotensin receptor agonist is a neurotensin or a neurotensin analog or a synthetic neurotensin or an artificial neurotensin or a neurotensin mimetic compound. A thyroxine receptor agonist is a thyroxine derivative or a thyronine.

Antagonist: A vanilloid receptor antagonist is a substance capable of inhibiting the effect of a vanilloid receptor agonist. A cannabinoid receptor antagonist is a substance capable of inhibiting the effect of a cannabinoid receptor agonist. An adenosine receptor antagonist is a substance capable of inhibiting the effect of an adenosine receptor agonist. A neurotensin receptor antagonist is a substance capable of inhibiting the effect of a neurotensin receptor agonist. A thyroxine receptor antagonist is a substance capable of inhibiting the effect of a thyroxine receptor agonist.

Alcohol: A class of organic compounds containing one or more hydroxyl groups (OH). In this context a saturated or unsaturated, branched or unbranched hydrocarbon group sitting as a substituent on a larger molecule.
Alicyclic group: means a cyclic hydrocarbon group having properties resembling those of aliphatic groups.

Aliphatic group: in the context of the present invention, the term "aliphatic group" means a saturated or unsaturated linear or branched hydrocarbon group. This term is used to encompass alkyl, alkenyl, and alkynyl groups, for example.

Alkoxy group: the term "alkoxy group" or "alkoxy" covers an alkyl linked to a larger moiety by oxygen.

Alkyl group: means a saturated linear or branched hydrocarbon group including, for example, methyl, ethyl, isopropyl, t-butyl, heptyl, dodecyl, octadecyl, amyl, 2-ethylhexyl, and the like.

Alkenyl group: means an unsaturated, linear or branched hydrocarbon group with one or more carbon-carbon double bonds, such as a vinyl group.

Alkynyl group: means an unsaturated, linear or branched hydrocarbon group with one or more carbon-carbon triple bonds.

Amphiphil: substance containing both polar, water-soluble and nonpolar, water-insoluble groups.

Aromatic group: the term "aromatic group" or "aryl group" means a mono- or polycyclic aromatic hydrocarbon group.

Apoptosis: Apoptosis is a process of suicide by a cell in a multi-cellular organism. It is one of the main types of programmed cell death (PCD), and involves an orchestrated series of biochemical events leading to a characteristic cell morphology and death.

Aromatic group: the term "aromatic group" or "aryl group" means a mono- or polycyclic aromatic hydrocarbon group.
Asystole: Cessation of electrical activity in the ventricles of the heart. Without electrical activity the heart ceases to contract and the result is cardiac arrest.

Bolus: the administration of a drug, medication or other substance in the form of a single, large dose. In medicine, a bolus is the administration of a medication, drug or other compound that is given to raise blood concentration to an effective level. The administration can be given intravenously, by intramuscular or subcutaneous injection.

Cerebral ischemia: Global cerebral ischemia is an ischemic condition where the brain does not receive enough blood flow to maintain normal neurological function. Cerebral ischemia can be the result of various diseases/conditions such as cardiac arrest, or the result of arterial obstruction such as strangulation.

Coma: A prolonged period of unconsciousness following brain injury or metabolic disorders. The person in coma may have a simple reflex in response to touch or pain, but essentially there is no meaningful response to external stimuli.

Cannabinoid: Compound capable of binding to a cannabinoid receptor and isolated from or identical to a compound isolated from an organism such a plant or animal. In the present context any compound capable of binding a cannabinoid receptor. Also, the term cannabinoid is used as a general term covering both cannabinoid and cannabimimetic compounds.

Cannabimimetic: Compound capable of binding to a cannabinoid receptor and produced or synthesized chemically by standard techniques known in the art. In the present context any compound capable of binding a cannabinoid receptor.

Capsaicinoid: Compound capable of binding to a capsaicinoid receptor / vanilloid receptor and isolated from or identical to a compound isolated from an organism such as a plant or animal. In the present context any compound capable of binding a capsaicinoid receptor / vanilloid receptor. A capsaicinoid may also be referred to as a vanilloid receptor agonist.

Capsaicinoid-like: Compound capable of binding to a capsaicinoid receptor / vanilloid receptor and produced or synthesized chemically by standard techniques known in the
In the present context any compound capable of binding a capsaicinoid receptor / vanilloid receptor. A capsaicinoid-like compound may also be referred to as a vanilloid receptor agonist.

Combination of compounds: Herein the term generally covers a combination of at least two compounds selected from the group consisting of vanilloid receptor agonist, capsaicinoid, capsaicinoid-like, cannabinoid and cannabimimetic compound, adenosine, adenosine analogs and derivatives, neurotensin, neurotensin analogs, thyroxine derivatives, thyronamine, cytochrome c oxidase inhibitors and oxygen tension reducers. The term may also include combinations of other compounds or drugs or the like.

Compound: A chemical substance formed from two or more elements, held together by chemical bonds, with a fixed ratio determining the composition. The elements lose their individual chemical properties and the compound has new properties. Herein a term covering all of the following: vanilloid receptor agonist, capsaicinoid, capsaicinoid-like, cannabinoid and cannabimimetic compound, adenosine, adenosine analogs and derivatives, neurotensin, neurotensin analogs and peptides having at least 50% sequence identity to human neurotensin (NT or NT1-13) of SEQ ID NO. 1, thyroxine derivative, thyronamine, cytochrome c oxidase inhibitor and oxygen tension reducer.

Cyclic group: the term "cyclic group" means a closed ring hydrocarbon group that is classified as an alicyclic group, aromatic group, or heterocyclic group.

Cycloalkenyl: means a monovalent unsaturated carbocyclic radical consisting of one, two or three rings, of three to eight carbons per ring, which can optionally be substituted with one or two substituents selected from the group consisting of hydroxy, cyano, lower alkenyl, lower alkoxy, lower haloalkoxy, alkenylthio, halo, haloalkenyl, hydroxyalkenyl, nitro, alkoxycarbonenyl, amino, alkenylamino, alkenylsulfonyl, arylsulfonyl, alkenylaminosulfonyle, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkenylaminocarbonyl, arylaminocarbonyl, alkenylcarbonylamino and arylcarbonylamino.

Cycloalkyl: means a monovalent saturated carbocyclic radical consisting of one, two or three rings, of three to eight carbons per ring, which can optionally be substituted with
one or two substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, haloalkyl, hydroxyalkyl, nitro, alkoxy carbonyl, amino, alkylamino, alky sulfanyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alky carbonylamino, alkylcarbonylamino and arylcarbonylamino.

**Cytochrome c oxidase inhibitor**: means a compound that binds to and interferes with the function of cytochrome c oxidase; a mitochondrial transmembrane complex involved in metabolism. These include but are not limited to \( \text{H}_2\text{S} \) (hydrogen sulfide); cyanide (CN) or its derivates such as hydrogen cyanide (HCN) or sodium nitroprusside (\( \text{Na}_2[\text{Fe(CN)}_5\text{NO}]-2\text{H}_2\text{O} \)); Azide and its derivates; Carbon monoxide (CO); and/or Sodium sulfide (\( \text{Na}_2\text{S} \)).

**Cationic group**: A chemical group capable of functioning as a proton donor when a compound comprising the chemical group is dissolved in a solvent, preferably when dissolved in water.

**Form a ring**: means that the atoms mentioned are connected through a bond when the ring structure is formed.

**Global ischemia**: Anoxia resultant from ceased blood supply to the entire body resulting in tissue damage through a variety of mechanisms including apoptosis.

**Global cerebral ischemia**: Anoxia resultant from ceased blood supply to the entire brain resulting in tissue damage through a variety of mechanisms including apoptosis.

**Group**: (Moiet y / substitution) as is well understood in this technical area, a large degree of substitution is not only tolerated, but is often advisable. Substitution is anticipated on the materials of the present invention. As a means of simplifying the discussion and recitation of certain terminology used throughout this application, the terms "group" and "moiety" are used to differentiate between chemical species that allow for substitution or that may be substituted and those that do not allow or may not be so substituted. Thus, when the term "group" is used to describe a chemical substituent, the described chemical material includes the unsubstituted group and that group with O, N, or S atoms, for example, in the chain as well as carbonyl groups or
other conventional substitution. Where the term "moiety" is used to describe a chemical compound or substituent, only an unsubstituted chemical material is intended to be included. For example, the phrase "alkyl group" is intended to include not only pure open chain saturated hydrocarbon alkyl substituents, such as methyl, ethyl, propyl, t-butyl, and the like, but also alkyl substituents bearing further substituents known in the art, such as hydroxy, alkoxy, alkylsulfonyl, halogen atoms, cyano, nitro, amino, carboxyl, etc. Thus, "alkyl group" includes ether groups, haloalkyls, nitroalkyls, carboxyalkyls, hydroxyalkyls, sulfoalkyls, etc. On the other hand, the phrase "alkyl moiety" is limited to the inclusion of only pure open chain saturated hydrocarbon alkyl substituents, such as methyl, ethyl, propyl, t-butyl, and the like. The same definitions apply to "alkenyl group" and "alkenyl moiety"; to "alkynyl group" and "alkynyl moiety"; to "cyclic group" and "cyclic moiety; to "alicyclic group" and "alicyclic moiety"; to "aromatic group" or "aryl group" and to "aromatic moiety" or "aryl moiety"; as well as to "heterocyclic group" and "heterocyclic moiety".

Heterocyclic group: the term "heterocyclic group" means a closed ring hydrocarbon in which one or more of the atoms in the ring is an element other than carbon (e.g., nitrogen, oxygen, sulphur, etc.).

Heterocyclic means a monovalent saturated cyclic radical, consisting of one to two rings, of three to eight atoms per ring, incorporating one or two ring heteroatoms (chosen from N, O or S(O)₂, and which can optionally be substituted with one or two substituents selected from the group consisting of hydroxyl, oxo, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, haloalkyl, hydroxyalkyl, nitro, alkoxy carbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, ary lacarbonylamino, or arylcarbonylamino.

Heteroaryl means a monovalent aromatic cyclic radical having one to three rings, of four to eight atoms per ring, incorporating one or two heteroatoms (chosen from nitrogen, oxygen, or sulphur) within the ring which can optionally be substituted with one or two substituents selected from the group consisting of hydroxy, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, haloalkyl, hydroxyalkyl, nitro, alkoxy carbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, ary-
aminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylamino-
carbonyl, alkylcarbonlamino and arylcarbonylamino.

**Hypothermia / hypothermic:** Generally the condition wherein the body temperature is below normal level. Herein the term is used for any lowering of body temperature disregarding the temperature of the individual at the onset of a treatment. For example hypothermia may be induced in an individual suffering from a fever, bringing the body temperature of the individual to normal level.

**Infusion:** the therapeutic introduction of a fluid other than blood, as saline solution, solution, into a vein.

**Injection:** to introduce (a drug or vaccine, for example) into a body part, especially by means of a syringe. Injection encompasses among others: intravenous (IV), intramuscular (IM), and subcutaneous (SC) injections.

**Ischemia:** Restriction in blood supply with resultant dysfunction or damage of tissue. Ischemia includes ischaemia and ischaemia.

**Ischemic tissue damage:** Tissue damage due to ischemia.

**Lactic acidosis:** Lactic acidosis is a condition caused by the buildup of lactic acid in the body. An important cause of lactic acidosis is inadequate oxygen supply to tissues. Lactic acidosis leads to acidification of the blood (acidosis), and is considered a distinct form of metabolic acidosis.

**Moieties** of a particular compound cover group(s) or part(s) of said particular compound.

**Neurotensin:** Neurotensin is the 13 amino acid peptide of SEQ ID NO. 1.

**Neurotensin analog:** A neurotensin analog is any sequence having at least 50% sequence identity to mature neurotensin of SEQ ID NO. 1.
Neurotensin receptor: The neurotensin receptors are transmembrane receptors which bind neurotensin. Two of the receptors encoded by the NTSR1 and NTSR2 genes contain 7 transmembrane helices and are G protein-coupled. The third receptor has a single transmembrane domain and is encoded by the SORT1 gene.

Neurotensin receptor agonist: is a compound capable of imposing an agonizing effect of a neurotensin receptor and include but is not limited to neurotensin, neuromedin, NT64D, NT64L, NT65L, NT66D, NT66L, NT67L, NT69L, NT71, NT72, NT73, NT74, NT75, NT76, NT77, Trp11NT, contulakin-G, EISAI-1, EISAI-2, JMV2004, JMV431, JMV449, JMV457, JMV458, large neuromedin, large neurotensin, $^{[125]}$I-neurotensin, Thr10contulakin-G, D-Trp11-neurotensin, levocabastine, SR48692, SR48692, xenin, PD-149163 and CGX-1 160.

Oxygen tension reducers: reduces the concentration of oxygen around or within the body. These include but are not limited to: Carbon monoxide (CO), Sodium sulfide (Na$_2$S) and hydrogen sulfide (H$_2$S).

Pharmaceutical composition: or drug, medicament or agent refers to any chemical or biological material, compound, composition or combinations of any of these especially combinations of compounds, capable of inducing a desired therapeutic effect when properly administered to a patient. Some drugs are sold in an inactive form that is converted in vivo into a metabolite with pharmaceutical activity. For purposes of the present invention, the terms "pharmaceutical composition" and "medicament" encompass both the inactive drug and the active metabolite.

Pulseless electrical activity: The electrical activity of the heart continues in a normal or abnormal pattern, but one that is consistent with contractions of the heart. Due to either damage of the heart muscle, blockage of the main arteries leading from the heart or lack of blood flowing to the heart there is no effective blood flow. The result is cardiac arrest.

Substituted lower alkyl means a lower alkyl having one to three substituents selected from the group consisting of hydroxyl, alkoxy, amino, amido, carboxyl, acyl, halogen, cyano, nitro and thiol.
Thyroxine derivatives: the term as used herein is meant to cover all forms and processed derivatives of the thyroid hormones, including thyroxine (T₄), triiodothyronine (T₃), thyronamine, 3-Iodothyronamine, 3,5-Diiodothyronamine, and 3,5,3'-triiodothyronamine.

Vanilloid receptor agonist: A capsaicinoid or capsaicinoid-like compound capable of binding a vanilloid receptor / capsaicinoid receptor.

Ventricular fibrillation: Very fast irregular electrical activity in the ventricles of the heart. Individual beats cannot be distinguished and the heart is in stand-still or vibrating slightly. The result is cardiac arrest.

Ventricular tachycardia: Very fast electrical activity in the ventricles of the heart. The electrical activity maintains a pattern where individual contractions can be distinguished. Ventricular tachycardia may be associated with normal cardiac function, reduced cardiac function or functional cardiac arrest. This depends on the rate of the tachycardia and the state of the heart muscle.

The principle of the present invention is the use of one or more vanilloid receptor agonists and/or cannabinoid receptor agonists and/or cannabinoids and/or cannabimimetic compounds and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for induction of hypothermia for alleviating the effects of ischemia, such as but not limited to, the tissue damaging effects of ischemia. Furthermore, one or more compounds of the present invention may be used for induction of hypothermia as herein defined for the reduction of temperature in an individual in need thereof.

Hypothermia

Hypothermia is generally the lowering of the core temperature of the body below normal level. Normal body temperature in an adult human measured rectally over 24 hours is 37 degree Celsius +/- 0.6 degree Celsius and is thus variable between individuals, and over time within the individual. Hypothermia as a medical condition is usually defined as the effects seen on the body once the core temperature drops below 35 degree Celsius. It may become critical, if the body temperature falls below 32 °C. In
the present application hypothermia is defined as the lowering of body temperature, preferably to below normal levels.

The term hypothermia is herein used to denote a lowering of temperature in an individual below the temperature measured in the individual prior to administration of the compounds and/or treatment herein disclosed. It is therefore an object of the present invention to lower the temperature in an individual in need thereof. Such individuals may be, but are not limited to, individuals suffering from ischemia, fever, hyperthermia, malign hyperthermia, and hyperpyrexia or in need of surgery such as neurosurgery, thorax surgery and cardiac surgery, where cooling of the body is beneficial to the outcome of the operation.

Body temperature may be measured by a variety of means such as by mercury, electronic or plastic strip thermometers on different areas of the body such as the forehead, mouth, armpit, ear or rectum. It is presently understood, that the temperature referred to in the present application is the core body temperature, and that some of the above methods of measurement will indicate a different temperature than the core temperature.

It is of importance, that induction of hypothermia in an individual can follow a predictable course and be responsive to the dose in which the at least one compound capable of inducing hypothermia is administered. The induction of the hypothermic condition may be rapid or slow depending on the situation of the individual in need of treatment. Also depending on the severity of the ischemic condition / hyperthermia, it is of interest to provide a medicament for retaining the individual in the hypothermic state for variable durations of time. At least one compound from the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives, and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers, may be used depending on dosage within a range of temperatures or for the induction of hypothermia to a specific temperature. At least one compound, from the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives, and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers, may furthermore be used for an initial rapid decrease in core body...
temperature, and the subsequent maintenance of the reached temperature over a prolonged period. It is furthermore beneficial if the hypothermic state can be reversed in a controlled fashion either slowly or rapidly depending on the status of the individual.

It is thus an object of the present invention to provide at least one compound for the production of a medicament to be administered parenterally for the induction of hypothermia in an individual in need thereof, wherein the compound or combination of compounds is capable of inducing hypothermia to any range of temperatures between 37 and 31 degree Celsius, such as between 36.5 and 31.5 degree Celsius, such as between 36 and 32 degree Celsius, such as between 35.5 and 32.5 degree Celsius, such as between 35 and 33 degree Celsius, such as between 34.5 and 33.5 degree Celsius. The ranges may furthermore be between 37 and 34 degree Celsius, such as between 36.5 and 34.5 degrees, such as 36 and 35 degrees, alternatively between 34 and 31 degree, such as between 33.5 and 31.5 degree, such as 33 and 32 degree Celsius, alternatively between 36 and 33 degree or 35 and 32 degree Celsius. Preferably, the combination of compounds of the present invention is capable of inducing hypothermia in the range of between 36 to 32 degree Celsius, more preferably between 35 and 33 degree Celsius, and most preferably between 34 and 32 degree Celsius.

It is also an object of the present invention to provide at least one compound capable of inducing hypothermia to a specific temperature such as 37 degree Celsius, 36.5 degree Celsius, 36 degree Celsius, 35.5 degree Celsius, 35 degree Celsius, 34.5 degree Celsius, 34 degree Celsius, 33.5 degree Celsius, 33 degree Celsius, 32.5 degree Celsius, 32 degree Celsius, 31.5 degree Celsius or 31 degree Celsius or most preferably, the compound or combination of compounds of the present invention is capable of inducing hypothermia to any of the above specific temperatures within a range of +/- 0.5 degree Celsius, the range thus being between +/- 0.4 degree Celsius, such as between +/- 0.3 degree Celsius, such as between +/- 0.2 degree Celsius, or such as between +/- 0.1 degree Celsius. The temperature range or specific temperature a given compound or combination of compounds is capable of inducing is herein also referred to as the target temperature of the compound or the combination of compounds and/or the medicament comprising the compound or the combination of compounds.
Preferably, the person in need of the hypothermic treatment e.g. the administration of at least one compound of the present invention suffers from ischemia, or is in need of surgery such as neurosurgery or cardiac surgery, e.g. the compound is administered pre-operatively.

Furthermore, it is an object of the present invention to induce hypothermia in individuals in whom the initial temperature prior to treatment is above the normal temperature for said individual. These individuals may be individuals suffering from fever, hyperthermia, malign hyperthermia, hyperpyrexia or other. It is common that individuals suffering from a heart attack or stroke e.g. suffering from ischemia develop a fever and it is an object of the present invention to reduce the fever and induce hypothermia in such individuals. Individuals otherwise suffering from fever, hyperthermia, malign hyperthermia, hyperpyrexia or other may benefit by administration of the compounds of the present invention to reduce the elevated temperature to normal that is to within 35 to 39 degrees Celsius, such as to within 35.5 to 38.5 degree Celsius, such as to within 36 to 38 degree Celsius, such as to within 37 degree Celsius +/- 0.6 degree Celsius, or to reduce their body temperature further to hypothermic levels as described above.

The individuals with elevated body temperatures may have any temperature considered to be above normal, which is any temperature above 36 degrees Celsius. The temperature of the individual in need of treatment according to the present invention may thus be a temperature of above 36 degree Celsius, such as above 36.5 degree Celsius, such as above 37 degree Celsius, such as above 37.5 degree Celsius, such as above 38 degree Celsius, such as above 38.5 degree Celsius, such as above 39 degree Celsius, such as above 39.5 degree Celsius, such as above 40 degree Celsius, such as above 40.5 degree Celsius, such as above 41 degree Celsius such as above 41.5 degree Celsius such as above 42 degree Celsius, such as above 42.5 degree Celsius, such as above 43 degree Celsius, such as above 43.5 degree Celsius and higher.

It is therefore also an object of the present invention to provide at least one compound capable of inducing hypothermia / reducing body temperature to a specific temperature such as 39 degree Celsius, 38.5 degree Celsius, 38 degree Celsius, 37.5 degree Celsius, 37 degree Celsius, 36.5 degree Celsius, 36 degree Celsius, 35.5 degree Celsius, 35 degree Celsius, or most preferably, the compound or combination of
compounds of the present invention is capable of inducing hypothermia to any of the above specific temperatures within a range of +/- 0.5 degree Celsius, the range thus being between +/- 0.4 degree Celsius, such as between +/-0.3 degree Celsius, such as between +/- 0.2 degree Celsius, or such as between +/- 0.1 degree Celsius. The temperature range or specific temperature a given compound or combination of compounds is capable of inducing is herein also referred to as the target temperature of the compound or the combination of compounds and/or the medicament comprising the compound or the combination of compounds.

An aspect of the present invention regards the treatment of an individual in need thereof by the use of a compound of the present invention for the induction of hypothermia. Preferably the use is the administration of the compound as a medicament by a parenteral route. Most preferably the parenteral administration route is intravenous or by injection. The individuals in need of the treatment are individuals suffering from conditions that are benefitted by the induction of hypothermia and/or reduction in body and/or brain temperature. Such individuals include but are not limited to: individuals suffering from or at risk of suffering from ischemia, elevated body temperatures due to fever, hyperthermia, hyperpyrexia, malign hyperpyrexia or are in need of treatment, such as but not limited to surgery, wherein the outcome of the procedure or the procedure itself is benefitted by a reduction in temperature of the individual undergoing the treatment and/or surgery.

**Ischemia**

Ischemia is the reduction or abolition of blood supply to a tissue. The associated deficiency of oxygen and nutrients may lead to cell death (necrosis) in areas of the affected tissue. The damage induced by the lack of oxygenated blood in the brain occurs in two stages. First cellular metabolism is arrested due to lack of oxygen and some cells and tissue will die within minutes as a consequence thereof. Secondly cascades of processes such as apoptosis are initiated and continue up to 12 hours after the event that initially induced the ischemic state has been abolished. The tissue damaged by the second cascade can be crucial and cause greater harm to the individual than the primary damage happening within the first minutes of ischemia.

The current invention is aimed at correcting ischemia of the brain thereby minimizing the damage to the central nervous system. The invention does so by administering a
drug parenterally to induce hypothermia in patients. The hypothermic effect is presu
5 mmed to counteract ischemic damage by several mechanisms in the brain: Prevention of the blood-brain-barrier disruption that happens soon after ischemic onset that allows oedema formation from extravasation; Diminishing of the oxygen-based free-radical production; Reduction of the excitotoxic-neurotransmitter release that overstimulates neighboring neurons; Lowering of the metabolic rate and subsequent energy depletion; and anti-inflammatory action. Induction of hypothermia has a neuroprotective effect.

It is an object of the present invention to provide at least one compound capable of inducing hypothermia in an individual to be administered parenterally and further to provide the use of said compound for the production of a medicament for the treatment of ischemia in an individual, whereby said compound is administered parenterally.

Ischemia may occur under various circumstances; of special relevance to the present invention are the circumstances relating to cardiovascular diseases, asphyxia and traumatic brain injuries.

It is thus within the scope of the present invention to provide means for reducing the risk of ischemia as well as treating ischemia in an individual, under circumstances where ischemia is brought about by for example: cardiovascular diseases, asphyxia and traumatic brain injuries.

In a highly preferred embodiment, compounds of the present invention are administered parenterally to prevent or treat or treat and prevent tissue damaging effects subsequent to or in conjunction with ischemia.

Cardiovascular diseases
Cardiovascular disease is the most common cause of death and of physical as well as mental impairment in the developed world. A similar development is seen in the rest of the world as it emulates the lifestyle of the Western hemisphere with its fatty diets, lack of exercise and increasing average lifespan.

The main causes of death and disability among cardiovascular diseases are myocardial infarction, acute coronary syndrome, cardiac arrest and stroke, but many
other cardiovascular diseases may be equally detrimental to the individual affected. These other diseases include among others arterial aneurism, subarachnoid haemorrhage, arteriosclerosis (or atherosclerosis), angina pectoris, hypertension, hypercholesterolemia, cardiac arrhythmia, cardiomegaly, cardiomyopathy, heart valve regurgitation and heart valve stenosis.

Each of the abovementioned diseases follow a course of events leading to ischemia, and are thus all of interest in relation to the present invention. Myocardial infarction (heart attack) is a result of an atherosclerotic plaque slowly building up in the inner lining of a coronary artery which then suddenly ruptures, partially or totally occluding the artery and preventing blood flow. Cardiac arrest is the abrupt cessation of normal circulation of the blood due to failure of the heart to contract effectively. Brain damage is likely to occur after 3-4 minutes without medical intervention, except in cases of hypothermia. Stroke is an acute neurological injury, lasting more than 24 hours, in which the blood supply to a part of the brain is interrupted, either by a clot in the artery or if the artery bursts. Arterial aneurism is a localized ballooning of an artery by more than 50% of the diameter of the vessel. Aneurysms most commonly occur in the arteries at the base of the brain and in the aorta. This bulge in an artery carries the risk of bursting and leading to internal hemorrhage. The larger an aneurysm becomes, the more likely it is to burst. Subarachnoid haemorrhage (SAH) is bleeding into the subarachnoid space surrounding the brain, i.e., the area between the arachnoid and the pia mater. It may arise due to trauma or spontaneously, and is a medical emergency, which can lead to death or severe disability even if recognized and treated in an early stage. Arteriosclerosis is a disease in which arterial walls harden over years or decades as a result of the formation of collagen and calcium deposits. Atherosclerosis is the most common subgroup of arteriosclerosis, and is characterised by a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells ('foam cells') and promoted by low density lipoproteins (LDL; plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). Hypertension or high blood pressure is a medical condition wherein the blood pressure is chronically elevated. Hypercholesterolemia is the presence of high levels of cholesterol in the blood. It is a derangement that can contribute to many forms of disease, most notably cardiovascular disease. Arrhythmia is a group of conditions in which the muscle contraction of the heart is irregular or is
faster or slower than normal. Some arrhythmias are life threatening medical emergencies that can cause cardiac arrest and sudden death. Cardiomegaly is a medical condition wherein the heart is enlarged. It can often be associated with other serious medical conditions. Cardiomyopathy is the deterioration of the function of the myocardium (i.e., the actual heart muscle). People with cardiomyopathy are at risk of arrhythmia and/or sudden cardiac death. Heart valve regurgitation, also known as heart valve insufficiency, is the abnormal leaking of blood through heart valves. Heart valve stenosis is a heart condition caused by the incomplete opening of a heart valve, typically the aortic valve or the mitral valve, impairing blood flow through the heart.

Each of the cardiovascular diseases mentioned, as well as others not mentioned, may cause ischemia of organs. This ischemia, whether of the brain, heart or other organs, may lead to death or impairment if not treated rapidly.

It is an object of the present invention to provide at least one compound for the production of a medicament administered parenterally for the treatment or prophylaxis of an individual suffering from or at risk of suffering from of ischemia due cardiovascular diseases such as, but not limited to: myocardial infarction, acute coronary syndrome, cardiac arrest, stroke, arterial aneurism, subarachnoid haemorrhage, arteriosclerosis, angina pectoris, hypertension, hypercholesterolemia, cardiac arrhythmia, cardiomegaly, cardiomyopathy, heart valve regurgitation and heart valve stenosis.

Preferably, the medicament is for the treatment or prophylaxis of ischemia due to cardiac arrest, myocardial infarction, acute coronary syndrome, stroke, arterial aneurisms, sub-arachnoid haemorrhage or angina pectoris.

All of the above-mentioned cardiovascular diseases require specific diagnostic tests and treatments. These tests and treatments, as specified for sudden cardiac arrest, stroke and heart attack in the below, may be carried out in conjunction with the parenteral administration of medicaments defined in this patent.

Sudden cardiac arrest victims may be subjected to early CPR, early defibrillation and early advanced care. Further tests and treatments may include cardiac catheterization, electrophysiologic tests, coronary artery bypass surgery, balloon angioplasty or PTCA,
antiarrhythmic medicine, implantable cardioverter/defibrillator, implantable pacemaker and heart transplant.

Depending on whether patients suffer an ischemic or hemorrhagic stroke, acute treatment may include clot-busters (e.g. tPA) or surgical intervention (e.g. aneurysm clipping, and endovascular procedures such as insertion of "coils"). Preventive treatment includes the administration of anticoagulants/anti-platelet. It may furthermore include carotid endarterectomy and angioplasty and/or stents.

Patients suffering a heart attack (myocardial infarction) may have one or several treatments and procedures done to survive and diagnose the condition: These include resuscitation (early CPR, early defibrillation, early advanced care), thrombolysis, coronary angioplasty (also known as Percutaneous Transluminal Coronary Angioplasty [PTCA], Percutaneous Coronary Interventions [PCI], Balloon Angioplasty and Coronary Artery Balloon Dilation), and coronary artery bypass graft surgery (CABG).

Asphyxia

Asphyxia (suffocation) is a common cause of death and of physical as well as mental impairment in perinatals, neonatals or newborns, children and adults of all ages. According to WHO (World Health Organization), the perinatal period commences at 22 completed weeks (154 days) of gestation (the time when birth weight is normally 500 g), and ends seven completed days after birth or delivery. The neonatal period is most often and herein defined as four weeks after birth; regardless of whether or not birth occurs prematurely. A premature infant is born after a gestation period of less than the normal time (about 266 days in the human).

Asphyxia can be divided into perinatal asphyxia and non-perinatal asphyxia:Pre- or perinatal asphyxia is the medical condition resulting from deprivation of oxygen to an infant long enough to cause apparent harm; the infant may at the time of oxygen deprivation still reside in the mother's uterus and/or birth canal, it may occur during the process of delivery or may occur immediately after delivery. It results most commonly from a drop in maternal blood pressure or interference during delivery with blood flow to the infant's brain, but may also stem from umbilical cord entanglement. This can occur due to inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation. Extreme degrees of asphyxia can cause cardiac arrest and death. Hypoxic damage can occur to most of the infant's organs, but brain damage is of most concern
and perhaps the least likely to quickly and completely heal. In severe cases, an infant may survive, but with damage to the brain manifested as developmental delay and spasticity. In one embodiment of the present invention at least one compound hereof is administered to the infant while it resides within the uterus and/or birth canal, i.e. as soon as asphyxia is determined. Asphyxia may be determined for example by measuring the pH of the blood of the infant.

Non-perinatal asphyxia is a condition of severely deficient supply of oxygen to the body that arises from being unable to breathe normally. Common causes hereof include drowning, strangulation and exposure to toxic gasses. Asphyxia causes generalized hypoxia, which primarily affects the tissues and organs most sensitive to hypoxia first, such as the brain, hence resulting in cerebral hypoxia. The absence of effective remedial action will very rapidly lead to unconsciousness, brain damage and death.

Each kind of asphyxia mentioned, as well as others not mentioned, may cause ischemia of organs and is thus an object of the present invention.

It is an aspect of the present invention to provide at least one compound for the treatment of an individual suffering from ischemia due to asphyxia such as: pre-natal asphyxia, perinatal asphyxia and/or non-perinatal asphyxia.

Treatment by parenteral administration of the medicament defined in this patent may be carried out in conjunction with test and treatments of diseases and accidents including asphyxia (perinatal asphyxia, and non-perinatal asphyxia including, but not limited to, drowning, strangulation and exposure to toxic gasses). Such diseases and injuries may require early CPR, early defibrillation and both early and continued advanced care as well as other tests and treatments not specified.

Traumatic brain injury

Traumatic brain injury (TBI) is a common cause of death and of physical as well as mental impairment throughout the world. TBI may result from accidents, be due to violence or be self-inflicted.

Traumatic brain injury, also called intracranial injury, or simply head injury, occurs when a sudden trauma causes brain damage. TBI can result from a closed head injury or a
penetrating head injury. Parts of the brain that can be damaged include the cerebral hemispheres, cerebellum, and brain stem. Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain. Outcome can be anything from complete recovery to permanent disability or death. Ischemia is a significant factor contributing to the neurological damage frequently seen in patients suffering from TBI.

It is an aspect of the present invention to provide a compound or a combination of compounds administered parenterally for the treatment of an individual suffering from ischemia due to traumatic brain injury.

Treatment by parenteral administration of the medicament defined in this patent may also be carried out in conjunction with test and treatments in relation to traumatic head injury (closed head injury or penetrating head injury). Such injuries may require early CPR, early defibrillation and both early and continued advanced care as well as other tests and treatments not specified.

An embodiment of the present invention regards the use of at least one compound for the treatment of ischemia in an individual by induction of hypothermia in said individual, wherein said compound is administered parenterally.

**Other indications**

**Elevated body temperature**

Individuals suffering from elevated body temperatures due to an infection, ischemic damage, heat- or sunstroke or the like will also benefit from the administration of the compounds of the present invention.

Fever (also known as pyrexia, or a febrile response) is a frequent medical symptom that describes an increase in especially internal body temperature to levels above normal. Fever is most accurately characterized as a temporary elevation in the body's thermoregulatory set-point, meaning that the temperature is raised by the body in a controlled manner. Fever is a symptom of many different diseases such as infectious diseases, immunological diseases, cancers metabolic disorders and more.
Hyperpyrexia is an extreme degree of fever, where the set body temperature is elevated greater than or equal to 41 degree Celsius. Such a high temperature is considered a medical emergency and requires immediate medical attention.

Fever and hyperpyrexia differ from hyperthermia. Hyperthermia is an increase in body temperature over the body's thermoregulatory set-point, due to excessive heat production or insufficient thermoregulation, or both. Hyperthermia may be caused by heat- or sunstroke, exposure, dehydration and more. A special variant of hyperthermia is malignant hyperthermia which may arise due to administration of general anesthesia.

It is an object of the present invention to provide a compound or a combination of compounds for the induction of hypothermia and/or lowering of body temperature in an individual with an elevated body temperature, such as an individual suffering from fever, hyperpyrexia and/or hyperthermia. Preferably the one or more compounds are administered parenterally.

Pre-operative administration
The outcome of several types of surgery is improved if the individual undergoing the surgery is placed under hyperthermia prior to or during the surgery. Examples of such operations are neurosurgeries, thorax surgeries and especially cardiac surgeries. The lowering of the body temperature slows down the metabolic rate and thus reduces the need for e.g. oxygen during the surgery giving more time to the surgeon to perform complicated procedures.

It is an object of the present invention to provide one or more compounds for the induction of hypothermia in an individual prior to surgery. The compounds of the present invention are preferably administered pre-operatively by a parenteral route, such as by injection e.g. by intravenous administration or intramuscular injection. It is also an aspect of the invention to provide one or more compounds for the induction of hypothermia in an individual in need of surgery prior to and/or during transportation of said individual.

A specific procedure in which it is of interest to lower the body temperature is in the case of organ transplants, where it is beneficial that the organs to be transplanted are cooled prior to removal and especially prior to and during transport before
transplantation into the recipient. It is furthermore of interest for the preservation of organs, tissues, and cells that hypothermia may be induced in these by induction of hypothermia in the individual from which these are taken. Either prior to or after removal, stasis (very low or no detectable metabolic rate) may be induced by further administration of the compounds of the present invention. Therefore it is an object of the present invention to administer one or more compounds herein disclosed for the induction of hypothermia in an individual and in the organs, tissues and cells of said individual, prior to the excision of the organs, tissues and cells for the purpose of transplantation, implantation, cryopreservation or other.

Mode of Administration

Administration

When administering drugs or pharmaceutical compounds to an individual in need thereof, three major routes of delivery are frequently employed; namely topical (substance is applied directly where its action is desired), enteral (via the gastrointestinal or digestive tract) and parenteral (routes other than the gastrointestinal or digestive tract) delivery.

Topical administration includes epicutaneous (application onto the skin), inhalational, enema, eye drops (onto the conjunctiva), ear drops, intranasal route, and vaginal.

Enteral administration is any form of administration that involves any part of the gastrointestinal tract and includes oral administration (by mouth e.g. tablets, capsules or drops), intrarectal (e.g. suppository or enema) administration besides by gastric or duodenal feeding tube.

Parenteral delivery by injection or infusion are effective to deliver the drug to a target site or to introduce the drug into the bloodstream, and includes intravenous (into a vein), intra-arterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), subcutaneous (under the skin), intraosseous infusion (into the bone marrow), intradermal, (into the skin itself), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), transdermal (diffusion through the intact skin), transmucosal (diffusion through a mucous membrane, e.g. insufflation (snorting), sublingual, buccal and vaginal suppositories), inhalational, epidural (injection or infusion into the epidural space) and intravitreal (into the eye). Sublingual
administration (under the tongue) is also a form of parenteral administration, whereby
drugs diffuse into the bloodstream through the mucosal tissue under the tongue. The compounds and/or medicaments of the present invention may be administered by any parenteral route of delivery and preferably any of the above.

In a preferred embodiment, compounds or combinations of compounds of the invention are administered parenterally to induce hypothermia e.g. by intravenous, intra-arterial, intramuscular, intra-cardiac, intrathecal, epidural, intraspinal, sublingual or subcutaneous administration. Appropriate dosage forms for such administration may be prepared by conventional techniques. The compounds or combinations of compounds may also be administered by inhalation, such as by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

Another preferred embodiment of the present invention regards a medicament for administration by injection, infusion, sublingual spray or inhalation. Preferably the administration form is by injection, wherein the injection is intramuscular, intravenous, subcutaneous, intradermal, intraperitoneal, intrathecal, epidural, intraspinal, intracardiac, and intraosseous or intravitreal, a bolus or a continuous administration. Also preferably, the administration form is by infusion, wherein the infusion is intravenous, intra-arterial intra-cardiac, intrathecal, epidural or intraspinal, intermittent or continuous.

It is thus an aspect of the present invention to provide a medicament comprising one or more compounds to be administered by infusion for the induction of hypothermia. The compounds are to be administered together or separately, each at its most effective dosage relative to the effect wanted.

In one embodiment, a preferable mode of administration of a medicament comprising at least one compound of the present invention for the induction of hypothermia is by intravenous injection.
In another embodiment, a preferable mode of administration of a medicament comprising one or more compounds of the present invention for the induction of hypothermia is by intramuscular injection.

In one embodiment, the compounds or combination of compounds of the present invention is administered at intervals of 30 minutes to 48 hours. In another embodiment, the combination of compounds of the present invention is administered at intervals of 1 to 6 hours.

In a preferred embodiment, the intravenous injection is administered as a bolus i.e. the administration of a medicament comprising a compound of the present invention for the induction of hypothermia in the form of a single dose, which may or may not be a large dose. A bolus may equally refer to single or repeated single bolus injections.

In another preferred embodiment, the intravenous injection is administered as a continuous infusion i.e. the administration of a medicament comprising a compound of the present invention for the induction of hypothermia in the form of an intravenous drip.

It is also an aspect of the present invention to combine the modes of administration by injection. For example, bolus injection(s) may be employed initially or throughout the treatment period and/or said bolus injection(s) may be used in combination with continuous IV infusion. The bolus injection may be administered intravenously, intramuscularly or subcutaneously.

It is thus an aspect of the present invention to administer compounds parenterally for the induction of hypothermia, whereby intravenous, intramuscular and/or subcutaneous bolus injection(s) are to be combined, with or without also using continuous IV infusion for the administration.

The compounds and combinations of compounds according to the invention may be administered with at least one other compound. The compounds may be administered simultaneously, either as separate formulations or combined in a unit dosage form, or administered sequentially.
Injections
An injection introduces a drug or medicament into a body part, especially by means of a syringe. Injection encompasses intravenous (IV), intramuscular (IM), and subcutaneous (SC) injections.

Advantages of administration by injection include that it is fast: 15-30 seconds for IV, 3-5 minutes for IM and SC. Further, one injection can be formulated to last days or even months, and IV can deliver continuous medication. In acute situations, in emergency medicine and intensive care medicine, drugs are most often given intravenously. This is the most reliable route, as in acutely ill patients the absorption of substances from the tissues and from the digestive tract can often be unpredictable due to altered blood flow or bowel motility.

Intramuscular injection is the injection of a substance directly into a muscle. It is used for particular forms of medication that are administered in small amounts. Depending on the chemical properties of the drug, the medication may either be absorbed fairly quickly or more gradually. Intramuscular injections are often given in the deltoid, vastus lateralis, ventrogluteal and dorsogluteal muscles. When the gluteal muscles are used, injections should be made on the upper, outer quadrant of the buttock to avoid damaging the sciatic nerve. Injection fibrosis is a complication that may occur if the injections are delivered with great frequency or with improper technique.

Any type of injection is of relevance for the at least one compound and/or medicaments of the present invention.

Intravenous therapy
Intravenous therapy or IV therapy is the giving of liquid substances directly into a vein. It can be intermittent or continuous; continuous administration is called an intravenous drip. The intravenous route is the fastest way to deliver fluids and medications throughout the body.

The simplest form of intravenous access is a syringe with an attached hollow needle. The needle is inserted through the skin into a vein, and the contents of the syringe are injected through the needle into the bloodstream. This is most easily done with an arm vein, especially one of the metacarpal veins. Usually it is necessary to use a
constricting band first to make the vein bulge; once the needle is in place, it is common
to draw back slightly on the syringe to aspirate blood, thus verifying that the needle is
really in a vein; then the constricting band is removed before injecting.

This is a convenient way to deliver life-saving medications in an emergency. However,
in a controlled health-care setting, direct injection is rarely used since it only allows
delivery of a single dose of medication.

Peripheral IV lines are the most common intravenous access method in both hospitals
and pre-hospital services. A peripheral IV line consists of a short catheter (a few
centimeters long) inserted through the skin into a peripheral vein, any vein that is not in
the chest or abdomen. Arm and hand veins are typically used although leg and foot
veins are occasionally used. Veins in the arm are the common site in emergency
settings, commonly performed by paramedics and emergency physicians. On infants
the scalp veins are sometimes used. Part of the catheter remains outside the skin,
called the connecting hub, which can be connected to a syringe or an intravenous
infusion line, or capped with a bung between treatments. Ported cannulas have an
injection port on the top that is often used to administer medicine. The caliber of
cannulae is commonly indicated in gauge, with 14 being a very large cannula (used in
resuscitation settings) and 24-26 the smallest. The most common sizes are 16-gauge
(midsize line used for blood donation and transfusion), 18- and 20-gauge (all-purpose
line for infusions and blood draws), and 22-gauge (all-purpose pediatric line). 12- and
14-gauge peripheral lines actually deliver equivalent volumes of fluid faster than central
lines, accounting for their popularity in emergency medicine; these lines are frequently
called "large bores" or "trauma lines". All of the above modes of administration and
injection are aspects of the present invention.

Originally, a peripheral IV was simply a needle that was taped in place and connected
to tubing rather than to a syringe; this system is still used for blood donation sets, as
the IV access will only be needed for a few minutes and the donor may not move while
the needle is in place. Today, hospitals use a safer system in which the catheter is a
flexible plastic tube that originally contains a needle to allow it to pierce the skin; the
needle is then removed and discarded, while the soft catheter stays in the vein. This
method is a variation of the Seldinger technique. The external portion of the catheter,
which is usually taped in place or secured with a self-adhesive dressing, consists of an
inch or so of flexible tubing and a locking hub. For centrally placed IV lines, sets and flushes contain a small amount of the anticoagulant heparin to keep the line from clotting off, and frequently are called "heparin locks" or "hep-locks". However, heparin is no longer recommended as a locking solution for peripheral IVs; saline is now the solution of choice for a "vac lock".

A peripheral IV cannot be left in the vein indefinitely, because of the risk of insertion-site infection leading to phlebitis, cellulitis, sepsis and bacteremia. The CDC updated their guidelines and now advise the cannula need to be replaced every 96 hours (CDC Morbidity and Mortality Weekly Report Aug 2002. Guidelines for the Prevention of Intravascular Catheter-Related Infections. Retrieved on 2008-03-13). This was based on studies organized to identify causes of Methicilline Resistant Staphylococcus aureus (MRSA) infection in hospitals. In the United Kingdom, the UK Department of health published their finding about risk factors associated with increased MRSA infection; now include intravenous cannula, central venous catheters and urinary catheters as the main factors increasing the risk of spreading antibiotic resistant strain bacteria in hospitals. All of the herein disclosed methods and apparatuses regarding administration by peripheral IV are of relevance to the present invention.

Central IV lines, or central venous catheter, flow through a catheter with its tip within a large vein, usually the superior vena cava or inferior vena cava, or within the right atrium of the heart. This has several advantages over a peripheral IV: it can deliver fluids and medications that would be overly irritating to peripheral veins because of their concentration or chemical composition; medications reach the heart immediately, and are quickly distributed to the rest of the body; there is room for multiple parallel compartments (lumen) within the catheter, so that multiple medications can be delivered at once even if they would not be chemically compatible within a single tube; caregivers can measure central venous pressure and other physiological variables through the line. Disadvantages include the risks of bleeding, sepsis, and gas embolism.

There are several types of central IVs, depending on the route that the catheter takes from the outside of the body to the vein. Peripherally inserted central catheter (PICC) lines are used when intravenous access is required over a prolonged period of time. The PICC line is inserted into a peripheral vein using the Seldinger technique.
under ultrasound guidance, usually in the arm, and then carefully advanced upward until the catheter is in the superior vena cava or the right atrium. This is usually done by feel and estimation; an X-ray then verifies that the tip is in the right place.

A PICC may have two parallel compartments, each with its own external connector (double-lumen), or a single tube and connector (single-lumen). Triple connectors (triple-lumen) catheters and power-injectable PICCs are available as well. From the outside, a single-lumen PICC resembles a peripheral IV, except that the tubing is slightly wider.

The insertion site must be covered by a larger sterile dressing than would be required for a peripheral IV, due to the higher risk of infection if bacteria travel up the catheter. However, a PICC poses less of a systemic infection risk than other central IVs, because bacteria would have to travel up the entire length of the narrow catheter before spreading through the bloodstream. The chief advantage of a PICC over other types of central lines is that it is easy to insert, poses a relatively low risk of bleeding, is externally unobtrusive, and can be left in place for months to years for patients who require extended treatment. The chief disadvantage is that it must travel through a relatively small peripheral vein and is therefore limited in diameter, and also somewhat vulnerable to occlusion or damage from movement or squeezing of the arm.

The use of PICC lines is an aspect regarding the administration of the compounds and medicaments of the present invention.

There are several types of catheters that take a more direct route into central veins. These are collectively called central venous lines. In the simplest type of central venous access, a catheter is inserted into a subclavian, internal jugular, or (less commonly) a femoral vein and advanced toward the heart until it reaches the superior vena cava or right atrium. Because all of these veins are larger than peripheral veins, central lines can deliver a higher volume of fluid and can have multiple lumens.

Another type of central line, called a Hickman line or Broviac catheter, is inserted into the target vein and then “tunneled” under the skin to emerge a short distance away. This reduces the risk of infection, since bacteria from the skin surface are not able to
travel directly into the vein; these catheters are also made of materials that resist infection and clotting.

An implantable port (often referred to by brand names such as Port-a-Cath or MediPort) is a central venous line that does not have an external connector; instead, it has a small reservoir that is covered with silicone rubber and is implanted under the skin. Medication is administered intermittently by placing a small needle through the skin, piercing the silicone, into the reservoir. When the needle is withdrawn the reservoir cover reseals itself. The cover can accept hundreds of needle sticks during its lifetime. It is possible to leave the ports in the patient's body for years, if this is done however, the port must be accessed monthly and flushed with an anti-coagulant, or the patient risks it getting plugged up. If it is plugged it becomes a hazard as a thrombosis will eventually form with an accompanying risk of embolization. Removal of a port is usually a simple outpatient procedure, however installation is more complex and a good implant is fairly dependent on the skill of the Radiologist. Ports cause less inconvenience and have a lower risk of infection than PICCs, and are therefore commonly used for patients on long-term intermittent treatment.

Any type of central line or implantable port as disclosed in the above or indeed any type of IV therapy is a preferable administration form of the present invention.

Forms of intravenous therapy
An intravenous drip is the continuous infusion of fluids, with or without medications, through an IV access device. This may be to correct dehydration or an electrolyte imbalance, to deliver medications, or for blood transfusion.

There are two types of fluids that are used for intravenous drips; crystalloids and colloids. Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules. Colloids contain larger insoluble molecules, such as gelatin; blood itself is a colloid.

The most commonly used crystalloid fluid is normal saline, a solution of sodium chloride at 0.9% concentration, which is close to the concentration in the blood (isotonic). Ringer's lactate or Ringer's acetate (ASERING, patented brand name of Otsuka Indonesia) is another isotonic solution often used for large-volume fluid
replacement. A solution of 5% dextrose in water, sometimes called D5W, is often used instead if the patient is at risk for having low blood sugar or high sodium. The choice of fluids may also depend on the chemical properties of the medications being given.

Intravenous fluids must always be sterile.

Intermittent infusion is used when a patient requires medications only at certain times, and does not require additional fluid. It can use the same techniques as an intravenous drip (pump or gravity drip), but after the complete dose of medication has been given, the tubing is disconnected from the IV access device. Some medications are also given by IV push, meaning that a syringe is connected to the IV access device and the medication is injected directly (slowly, if it might irritate the vein or cause a too-rapid effect). Once a medicine has been injected into the fluid stream of the IV tubing there must be some means of ensuring that it gets from the tubing to the patient. Usually this is accomplished by allowing the fluid stream to flow normally and thereby carry the medicine into the bloodstream; however, a second fluid injection is sometimes used, a "flush", following the injection to push the medicine into the bloodstream more quickly.

In medicine, a bolus (from Latin bolus, ball) is the administration of a medication, drug or other compound that is given to raise blood concentration to an effective level. The administration can be given intravenously, by intramuscular or subcutaneous injection. The placement of the bolus depends on the systemic levels of the contents desired throughout the body. An intramuscular bolus is used in the administration of vaccines to allow a slow release of the antigen to stimulate the body's immune system and allow time to develop antibodies. A bolus delivered directly to the veins through an intravenous drip allows a much faster delivery which quickly raises the concentration of the substance in the blood to an effective level. This is typically done at the beginning of a treatment or after a removal of medicine from blood (e.g. through dialysis).

Infusion equipment
A standard IV infusion set consists of a pre-filled, sterile container (glass bottle, plastic bottle or plastic bag) of fluids; alternatively a two component kit consisting of: 1: a compound in dry form, and 2: a liquid (to be combined prior to administration); with an attached drip chamber which allows the fluid to flow one drop at a time, making it easy to see the flow rate (and also reducing air bubbles); a long sterile tube with a clamp to
regulate or stop the flow; a connector to attach to the access device; and connectors to allow "piggybacking" of another infusion set onto the same line, e.g., adding a dose of antibiotics to a continuous fluid drip.

An infusion pump infuses fluids, medication or nutrients into a patient's circulatory system. It allows precise control over the flow rate and total amount delivered, but in cases where a change in the flow rate would not have serious consequences, or if pumps are not available, the drip is often left to flow simply by placing the bag above the level of the patient and using the clamp to regulate the rate; this is a gravity drip.

A rapid infuser can be used if the patient requires a high flow rate and the IV access device is of a large enough diameter to accommodate it. This is either an inflatable cuff placed around the fluid bag to force the fluid into the patient or a similar electrical device that may also heat the fluid being infused.

Infusion pumps can administer fluids in ways that would be impractically expensive or unreliable if performed manually by nursing staff. For example, they can administer as little as 0.1 ml. per hour injections (too small for a drip), injections every minute, injections with repeated boluses or fluids whose volumes vary by the time of day.

There are two basic classes of pumps. Large volume pumps can pump nutrient solutions large enough to feed a patient. Small-volume pumps infuse hormones, such as insulin, or other medicines, such as opiates. Within these classes, some pumps are designed to be portable, others are designed to be used in a hospital, and there are special systems for charity and battlefield use.

Large-volume pumps usually use some form of peristaltic pump. Classically, they use computer-controlled rollers compressing a silicone-rubber tube through which the medicine flows. Another common form is a set of fingers that press on the tube in sequence. Small-volume pumps usually use a computer-controlled motor turning a screw that pushes the plunger on a syringe.

Infusion pumps for use according to the present invention may be selected from the group consisting of: small-volume pumps, large-volume pumps, volumetric infusion pumps, syringe infusion pumps, drop infusion pumps, pole-mounted infusion pumps,
constant infusion pumps, ambulatory infusion pumps, stationary infusion pumps, mechanical, electrical infusion pumps or others known to the person skilled in the art.

The Syringe Infusion Pumps are intended for precise dosage of drugs and uniform flow of fluid injected for medical treatment by means of disposable syringes, by precisely driving the plunger of a syringe down its barrel. They are especially effective for long-term injection of small volumes of solution where great accuracy is required. The Syringe Infusion Pumps administer critical drug infusions with accuracy and reliability, by simplifying clinical treatment and saving valuable patient care time.

The Volumetric Infusion Pumps are intended for use in IV therapy in both venous and arterial Infusion applications. They are designed to assure accurate, continuous, non-pulsatile delivery of fluid to the patient.

The constant infusion pump is an electrically driven device for delivery from a reservoir of a constant, often very small, volume of solution over a prolonged period of time.

An ambulatory infusion pump is an electrical or battery operated device, which is used to deliver solutions containing a parenteral drug under pressure at a regulated flow rate. It is small, portable, and designed to be carried by the patient.

A stationary infusion pump is an electrical device, which serves the same purpose as an ambulatory pump but is larger and typically mounted on a pole.

Any type of infusion pump may be attached to the top of a pole, and thus be denoted a Pole-mounted infusion pump.

Infusion pumps that may be used to administer the one or more compounds for inducing hypothermia according to the present invention may be commercially available from companies including, but not limited to: Abbott LifeCare, Abbott Laboratories, Abbott Plum, Aitecs, Alaris, Aria Medical Equipment, Baxter Healthcare, Baxter International, Becton Dickinson, Contec Medical Systems, Elitemedicalmall, Excelsior, Fresenius, Harvard Apparatus, Horizon, Hospira LifeCare, Instech Laboratories, M2, Medex Medfusion, MEQL, Micrel Medical Devices, Plenum Technologies, Sigma, and World Precision Instruments (WPI).
Dosage
The dosage requirements will vary with the particular drug composition employed, the route of administration and the particular subject being treated. Ideally, a patient to be treated by the present method will receive a pharmaceutically effective amount of the compound in the maximum tolerated dose, generally no higher than that required before drug resistance develops.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The dosage of the at least one compound according to the invention depends on the compound or combination of compounds in question; however, the amount to be used is also closely related to the pharmaceutical composition of the medicament, any third or more compound of the medicament or any second active ingredient of the medicament.

Any dosage may be administered over a varying amount of time; as one or more boluses that may be administered in an instant (usually less than 5 minutes such as less than 1 minute), or as a continuous administration over an extended period of time, such as by intravenous infusion (usually between 30 minutes to 48 hours).

For all methods of use disclosed herein for the compounds, the daily parenteral dosage regimen will be from about 0.001 to about 2,400 mg/kg of total body weight, such as from about 0.01 to about 80 mg/kg of total body weight.

Preferably, the dosage of the medicament according to the present invention is between 1 µg to 100 mg pr kg total body weight, such as between 10 µg to 50 mg pr kg
total body weight, for example between 20 µg to 20 mg pr kg total body weight, such as 
100 µg to 10 mg, for example 500 µg to 1 mg depending on the compound of choice. It 
follows, that the preferred dosage may be between 1 µg and 1 mg pr kg total body 
weight, such as between 10 µg and 100 µg pr kg total body weight, such as or about 
10 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg, 100 µg, 200 µg, 300 µg, 
400 µg, 500 µg, 600 µg, 700 µg, 800 µg, 900 µg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 
mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg or 100 mg pr kg total body weight, again 
depending on the compound chosen.

It has been found that vanilloids, cannabinoids, adenosines, neurotensins, thyroxine 
derivatives, cytochrome c oxidase inhibitors and oxygen tension reducers vary with 
respect to potency and affinity for the receptor as well as with respect to molecular 
weight. Also, the preferred dosage range may be between 100 µg and 100 mg pr kg 
total body weight, such as between 200 µg and 90 mg, between 300 µg and 80 mg, 
such as between 400 µg and 70 mg, such as between 500 µg and 60 mg, such as 
between 600 µg and 50 mg, such as between 700 µg and 40 mg, such as between 800 
µg and 30 mg, such as between 900 µg and 20 mg, such as between 1 mg and 10 mg 
pr kg total body weight. Alternatively, the dosage may be found in the range of from 
100 µg to 2000 µg, such as 200 µg to 1800 µg, or 300 µg to 1600 µg, 400 µg to 1400 
µg, 500 µg to 1200 µg, 600 µg to 1000 µg or 500 µg to 2000 µg.

When administering a compound according to the present invention by continuous 
infusion, the dosage may be expressed as mg/kg/h (milligrams per kilo total body 
weight per hour) or µg/kg/h, thereby introducing a time-factor for the delivery expressed 
per the hour. Preferably, the dosage to be administered by infusion is between 1 µg to 
100 mg/kg/h, such as between 10 µg to 50 mg/kg/h, for example between 20 µg to 20 
mg/kg/h, such as 100 µg to 10 mg/kg/h, for example 500 µg to 1 mg/kg/h, depending 
on the compound of choice. It follows, that the preferred dosage may be between 1 µg 
and 1 mg/kg/h, such as between 10 µg and 100 µg/kg/h, such as or about 10 µg, 20 
µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg, 100 µg, 200 µg, 300 µg, 400 µg, 
500 µg, 600 µg, 700 µg, 800 µg, 900 µg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 
20 mg, 30 mg, 40 mg, 50 mg or 100 mg/kg/h, again depending on the compound 
chosen. Also, the preferred dosage range may be between 100 µg and 100 mg/kg/h, 
such as between 200 µg and 90 mg/kg/h, between 300 µg and 80 mg/kg/h, such as 
between 400 µg and 70 mg/kg/h, such as between 500 µg and 60 mg/kg/h, such as
between 600 µg and 50 mg/kg/h, such as between 700 µg and 40 mg/kg/h, such as between 800 µg and 30 mg/kg/h, such as between 900 µg and 20 mg/kg/h, such as between 1 mg and 10 mg/kg/h. Alternatively, the dosage may be found in the range of from 100 µg to 2000 µg/kg/h, such as 200 µg to 1800 µg/kg/h, or 300 µg to 1600 µg/kg/h, 400 µg to 1400 µg/kg/h, 500 µg to 1200 µg/kg/h, 600 µg to 1000 µg/kg/h or 500 µg to 2000 µg/kg/h.

For any other receptor agonist compound according to the invention the exact dosage may be calculated based on the bovine study model described in Examples 16 and 17.

Based hereon, the preferred dosages of a cannabinoid compound such as, but not limited to HU-210 and KN38-7271 (BAY38-7271), is between 1 µg and 1 mg pr kg total body weight, such as between 10 µg and 100 µg pr kg total body weight, such as or about 10 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg or 100 µg pr kg total body weight. The dosage may depend on the administration form. For example, it is preferable to administer HU-210 in the range of from 10 µg and 100 µg pr kg total body weight intravenously.

For one of the compounds in this invention, HU-210, the dosage regime will be between 2 and 1000 microgram/kg of total body weight, such as between 4 and 900 microgram/kg of total body weight, such as between 6 and 800 microgram/kg of total body weight, such as between 8 and 700 microgram/kg of total body weight, such as between 10 and 600 microgram/kg of total body weight. Preferably, the dosage regime will be between 15 and 500 microgram/kg of total body weight, more preferably between 20 and 400 microgram/kg of total body weight. More preferably at least 40 microgram/kg of total body weight, such as at least 50 microgram/kg of total body weight, such as at least 60 microgram/kg of total body weight, such as at least 70 microgram/kg of total body weight, such as at least 80 microgram/kg of total body weight, such as at least 100 microgram/kg of total body weight. The dosages mentioned are the dosages for inducing hypothermia as defined herein. The dosage may be administered as one single bolus or divided into two or more dosages given over a period of time; alternatively it may be administered by continuous IV. Additionally the hypothermic effect may be maintained by administering one or more dosages some hours after the first dosage, such as at least 6 hours later, or such as at
least 12 hours later. Such additionally dosages may be of the same amount as the first dosage or an amount being at the most one-half or one-quarter of the first dosage.

For another compound in this invention, delta-8-THC phosphate, the dosage regime will be between 0.25 and 600 mg/kg of total body weight, such as between 0.5 and 500 mg/kg of total body weight, 1 and 400 mg/kg of total body weight, 2 and 300 mg/kg of total body weight, 3 and 200 mg/kg of total body weight. Preferably, the dosage regime will be between 4 and 150 mg/kg of total body weight, more preferably between 5 and 100 mg/kg of total body weight. More preferably at least 10 mg/kg of total body weight, such as at least 20 mg/kg of total body weight, such as at least 30 mg/kg of total body weight, such as at least 40 mg/kg of total body weight, such as at least 50 mg/kg of total body weight, such as at least 60 mg/kg of total body weight, such as at least 100 mg/kg of total body weight. The dosages mentioned are the dosages for inducing hypothermia as defined herein. The dosage may be administered as one single bolus or divided into two or more dosages given over a period of time; alternatively it may be administered by continuous IV. Additionally the hypothermic effect may be maintained by administering one or more dosages some hours after the first dosage, such as at least 6 hours later, or such as at least 12 hours later. Such additionally dosages may be of the same amount as the first dosage or an amount being at the most one-half or one-quarter of the first dosage.

Likewise, the preferred dosages of a vanilloid compound such as, but not limited to dihydrocapsaicin, is between 10 µg and 2000 µg pr kg total body weight, such as between 100 µg and 1000 µg such as or about 10 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg or 100 µg pr kg total body weight, or 150 µg, 200 µg, 250 µg, 300 µg, 350 µg, 400 µg, 450 µg, 500 µg, 600 µg, 700 µg, 800 µg, 900 µg, 1000, 1500 µg or 2000 µg pr kg total body weight when injected in the individual intravenously. Alternatively, dihydrocapsaicin and other vaniloids may be injected intramuscularly at dosages between 100 µg and 100 mg pr kg total body weight, such as between 200 µg and 90 mg, between 300 µg and 80 mg, such as between 400 µg and 70 mg, such as between 500 µg and 60 mg, such as between 600 µg and 50 mg, such as between 700 µg and 40 mg, such as between 800 µg and 30 mg, such as between 900 µg and 20 mg, such as between 1 mg and 10 mg pr kg total body weight. Alternatively, the dosage may be found in the range of from 100 µg to 2000 µg, such as 200 µg to 1800
µg, or 300 µg to 1600 µg, 400 µg to 1400 µg, 500 µg to 1200 µg, 600 µg to 1000 µg, or
500 µg to 2000 µg pr kg total body weight.

The optimal dosage of a drug in combination with at least one other drug according to
the present invention thus varies for a given class of drugs. It follows from the
administration of at least two drugs, such as two or more drugs, that the simultaneous
administration of at least two drugs may result in an advantageous reduction in the
dosage required for each drug to be effective. A reduction in dosage for each of the at
least two drugs when given simultaneously may occur without a reduction in the
desired effect of the drug. A reduction in dosage for each of the at least two drugs may
thus provide an effective means of reducing unwanted side-effects resulting from the
administration of otherwise optimal dosages of each of the at least two drugs.

A reduction in dosage for each of the at least two drugs when given simultaneously
may be in the order of 5 to 75% of the otherwise optimal dosages of each of the at
least two drugs, for example 5 to 10%, such as 10 to 15%, for example 15 to 20%,
such as 20 to 25%, for example 25 to 30%, such as 30 to 35%, for example 35 to 40%,
such as 40 to 45%, for example 45 to 50%, such as 50 to 55%, for example 55 to 60%,
such as 60 to 65%, for example 65 to 70%, such as 70 to 75% of the otherwise optimal
dosages of each of the at least two drugs.

The term "unit dosage form" as used herein refers to physically discrete units suitable
as unitary dosages for human and animal individuals, each unit containing a
predetermined quantity of a combination of compounds, alone or together with other
agents, calculated in an amount sufficient to produce the desired effect in association
with a pharmaceutically acceptable diluent, carrier, or vehicle. The specifications for the
unit dosage forms of the present invention depend on the particular combination
employed and the effect to be achieved, as well as the pharmacodynamics associated
with each of the compounds of the combination in the host. The dose administered
should be an "effective amount" or an amount necessary to achieve an "effective level"
in the individual patient.

Since the "effective level" is used as the preferred endpoint for dosing, the actual dose
and schedule can vary, depending on inter-individual differences in pharmacokinetics,
drug distribution, and metabolism. The "effective level" can be defined, for example, as
the blood or tissue level desired in the individual that corresponds to a concentration of one or more combinations according to the invention. The effective level can also be defined as the amount needed pr kg body weight, in other words the concentration, required to reach the peak effect for a specific combination of compounds. Also, the effective level depends on the severity of the ischemic condition, such as total amount of tissue experiencing hypoxia or anoxia, the duration of the ischemic condition, whether it is the first or a subsequent ischemic attack of the individual and so forth.

More preferably, the dosage of the medicament according to the present invention is between 10 µg to 80 mg pr kg total body weight, such as between 100 µg to 1 mg pr kg total body weight.

*Dosage regime and Duration of treatment*

The medicament may be administered in any suitable dosage regime, suitable as to the potency of the compound or combination of compounds, the target temperature to be reached, the speed of action of the compound or the combination of compounds, the metabolic stability of the compound or the combination of compounds, the duration of the treatment and how often the medicament optimally is to be administered.

It is within the scope of the invention to provide a medicament to be administered at intervals of 30 minutes to 48 hours, such as intervals of 1 to 47 hours, 2 to 45 hours, 3 to 43 hours, 4 to 41 hours, 5 to 39 hours, 6 to 37 hours, 7 to 35 hours, 8 to 33 hours, 9 to 31 hours, 10 to 29 hours, 11 to 27 hours, 12 to 25 hours, 13 to 23 hours, 14 to 21 hours, 15 to 19 hours or 16 to 18 hours. It is also within the scope of the present invention to provide a medicament to be administered at intervals of 30 minutes to 24 hours, such as 1 to 23 hours, 2 to 22 hours, 3 to 20 hours, 4 to 18 hours, 5 to 16 hours, 6 to 14 hours, 7 to 12 hours or 8 to 10 hours. Preferably, the administration occurs at intervals of 1 to 6 hours, such as 2 to 5 hours or 3 to 4 hours.

It is also within the scope of the invention to provide a medicament to be administered as a single intravenous continuous infusion over 30 minutes to 48 hours, such as 1 to 47 hours, 2 to 45 hours, 3 to 43 hours, 4 to 41 hours, 5 to 39 hours, 6 to 37 hours, 7 to 35 hours, 8 to 33 hours, 9 to 31 hours, 10 to 29 hours, 11 to 27 hours, 12 to 25 hours, 13 to 23 hours, 14 to 21 hours, 15 to 19 hours or 16 to 18 hours. It is also within the scope of the present invention to provide a medicament to be administered as a single
intravenous continuous infusion over 30 minutes to 24 hours, such as 1 to 23 hours, 2 to 22 hours, 3 to 20 hours, 4 to 18 hours, 5 to 16 hours, 6 to 14 hours, 7 to 12 hours or 8 to 10 hours. Preferably, the single intravenous infusion occurs continuously during a period of 1 to 48 hours, such as 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 25 hours, 26 hours, 27 hours, 28 hours, 29 hours, 30 hours, 31 hours, 32 hours, 33 hours, 34 hours, 35 hours, 36 hours, 37 hours, 38 hours, 39 hours, 40 hours, 41 hours, 42 hours, 43 hours, 44 hours, 45 hours, 46 hours, 47 hours or 48 hours.

It is also within the scope of the invention to provide a medicament to be administered as one or more bolus injection(s).

The optimal administration interval depends on the duration of the hypothermic treatment. The duration of the treatment depends among other things on the severity of the ischemic condition. It is within the scope of the present invention to provide medicaments for the induction of hypothermia wherein the duration of the treatment is from 6 to 72 hours, such as from 7 to 69 hours, such as from 8 to 66 hours, 9 to 63 hours, 10 to 60 hours, 11 to 57 hours, 12 to 54 hours, 13 to 51 hours, 14 to 48 hours, 15 to 45 hours, 16 to 42 hours, 17 to 39 hours, 18 to 36 hours, 1 to 35 hours, 20 to 32 hours, 21 to 29 hours, 22 to 26 hours 23 to 25 hours. Preferably, the duration of the treatment is between 6 and 48 hours, more preferably between 6 and 24 hours.

The medicament may thus comprise compounds of the present invention wherein at least one compound induces hypothermia rapidly or alternatively, wherein at least one compound induces hypothermia slowly. In the present context rapidly means within few hours, such as within 2 hours, such as within 1 hour, such as within 30 minutes, for example within 15 minutes; whereas slowly means after several hours, such as after 3 hours, for example 4 hours, such as after 5 hours, for example 6 hours, such as after 7 hours, for example 8 hours, such as after 9 hours, for example 10 hours, such as after 11 hours, for example 12 hours, such as after 13 hours, for example 14 hours, such as after 15 hours, for example 16 hours, such as after 17 hours, for example 18 hours, such as after 19 hours, for example 20 hours. A rapidly acting compound or combination of compounds may be administered prior to admission to the hospital such as at the scene of the complication or en route in an ambulance by medically trained
personnel. The individual suffering from the ischemic insult will thus already be experiencing a reduction in core body temperature upon arrival at a place of proper facilities enhancing the treatment and reducing the extent of the ischemic insult.

In one embodiment, the one or more compounds of the present invention to be used as a medicament are administered parenterally at a dosage of between 10 µg to 80 mg per kg body mass either sequentially or consecutively.

In one embodiment, the duration of the treatment with compounds of the present invention is from 6 to 72 hours.

To prevent a possible overshoot in the body's attempt to regain its normal temperature at the completion of the hypothermia-inducing treatment, the dosage of compounds according to the present invention may be reduced towards the end of the parenteral administration of said compound.

In one embodiment, the dosage may be reduced in a step-wise manner wherein the original dosage of compound(s) comprises 100% and will be reduced to at least 90%, such as 80%, for example 70%, such as 60%, for example 50%, such as 40%, such as 30%, for example 20%, such as 10% towards the end of the parenteral administration of said compound.

The end of the parenteral administration of said compound is meant to be at least 15 minutes before completion of administration, such as 30 minutes, for example 45 minutes, such as 1 hour, for example 2 hours, such as 3 hours, for example 4 hours, such as 5 hours, for example 6 hours, such as 7 hours, for example 8 hours, such as 9 hours, for example 10 hours, such as 11 hours, for example 12 hours, such as 13 hour, for example 14 hours, such as 15 hours, for example 16 hours, such as 17 hours, for example 18 hours, such as 19 hours, for example 20 hours before completion of administration.

**Compounds of the present invention**

**Cannabinoids**

Cannabinoids and cannabimimetic compounds are a group of chemicals which activate the body's cannabinoid receptors, CB1 and CB2. Before other types were discovered,
the term referred to a unique group of secondary metabolites found in the cannabis plant, which are responsible for the plant's peculiar pharmacological effects. Cannabinoids are generally grouped into five classes based mainly on chemical composition and in part on origin:

- The eicosanoids, also referred to as endocannabinoids are produced in the bodies of humans and other animals
- Classical cannabinoids, a group which includes natural cannabinoids found in larger or smaller amounts in the hemp plant *Cannabis sativa.*
- Non-classical cannabinoids
- Aminoalkylindoles
- Other compounds that are capable of binding cannabinoid receptors, but fall out of the four previous categories.

The current understanding recognizes the role that endocannabinoids play in almost every major life function in the human body. Cannabinoids act as a bioregulatory mechanism for most life processes, which reveals why medical cannabis has been cited as treatments for many diseases and ailments in anecdotal reports and scientific literature. Some of these ailments include: pain, arthritic conditions, migraine headaches, anxiety, epileptic seizures, insomnia, loss of appetite, GERD (chronic heartburn), nausea, glaucoma, AIDS wasting syndrome, depression, bipolar disorder (particularly depression-manic-normal), multiple sclerosis, menstrual cramps, Parkinson's, trigeminal neuralgia (tic douloureux), high blood pressure, irritable bowel syndrome, and bladder incontinence. Cannabinoids and cannabimimetic compounds (CB1/CB2 agonists) have furthermore received interest as putatively neuroprotective substances.

Several mechanisms have been proposed to account for the neuroprotective effects of various cannabinoids and cannabimimetic substances such as prevention of excitotoxicity by cannabinoid CB1-mediated inhibition of glutamatergic transmission, reduction of calcium influx, anti-oxidant activity, activation of the phosphatidylinositol 3-kinase/protein kinase B pathway, induction of phosphorylation of extracellular regulated kinases and the expression of transcription factors and neutrophins, lowering of the cerebrovasoconstriction and induction of hypothermia.
Any compound which can be defined as a cannabinoid or cannabimimetic compound falls within the scope of the present invention, i.e. any compound capable of binding to a cannabinoid receptor. The two terms cannabinoids and cannabimimetic are used interchangeably herein. Cannabinoids are generally termed such due to their ability to bind one or more of the cannabinoid receptors CB1 and CB2, but a cannabinoid / cannabimimetic compound is also a compound that in structure resembles a compound capable of binding a cannabinoid receptor without having the ability itself.

**Receptors**

There are currently two known types of cannabinoid receptors, CB1 and CB2, which are common in animals, and have been found in mammals, birds, fish, and reptiles.

CB1 receptors are found primarily in the brain, specifically in the basal ganglia and in the limbic system, including the hippocampus. They are also found in the cerebellum and in both male and female reproductive systems. CB1 receptors are essentially absent in the medulla oblongata, the part of the brain that is responsible for respiratory and cardiovascular functions. Thus, there is not a risk of respiratory or cardiovascular failure as there is with many other drugs. CB1 receptors appear to be responsible for the euphoric and anticonvulsive effects of cannabis.

CB2 receptors are almost exclusively found in the immune system, with the greatest density in the spleen. CB2 receptors appear to be responsible for the anti-inflammatory and possible other therapeutic effects of cannabis.

Researchers have noted that the behavioral effects, including hypothermia, seen when introducing animals to cannabinoids seems to be due to other factors besides CB1 receptor stimulation [46;49]. Inducing hypothermia by cannabinoids is therefore not solely equivalent to stimulating the CB1 receptor. Furthermore, there is evidence in the literature for other receptors than CB1 and CB2 as recipients of the cannabinoid ligands.

The receptors to which the cannabinoids and cannabimimetic compounds of the present invention may bind includes, apart from CB1 and CB2: a third CB receptor, herein termed CB3, GABA (gamma-aminobutyric acid) receptors, the NMDA (N-methyl-D-aspartate) receptor, the 5-HT(1A) receptor, also known as the serotonin
receptor, the Delta opioid receptor (DOR) and TRPV1 (transient receptor potential vanilloid 1). It is furthermore within the scope of the invention that at least one compound of the combination of compounds of the invention may bind CB1, CB2 or CB3 co-receptors. Compounds capable of binding any of the above-mentioned receptors thus fall within the scope of the present invention.

Structure

The cannabinoids of this application are, based on their structure, categorized as follows: classic cannabinoids, non-classic cannabinoids, aminoalkylindoles, eicosanoids (endogenous cannabinoids) and other compounds that fall out of the classification. Compounds belonging to any of these categories fall within the scope of the present invention.

It is within the scope of the invention that the compounds or the combination of compounds of the invention are capable of inducing hypothermia in an individual.

It is furthermore within the scope of the invention that at least one compound of the invention is capable of binding a cannabinoid receptor.

Accordingly, in the broadest aspect the present invention concerns the use of one or more compounds wherein at least one compound comprises a structure of one of the general formulas illustrated in the below for cannabinoid and cannabimimetic compounds. In these illustrations R is a chemical bond or a chemical moiety as defined in the above. R may be any moiety substituted any amount of times according to the following non-limiting list, whereby R is: C, H, S, N, O, optionally substituted one or more times with C, H, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, diphenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci\(_4\))-alkyl, heteroaryl-(Ci\(_4\))-alkyl, heterocyclyl-(Ci\(_4\))-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, S, N, O, P, OH, H, phenyl, amine (NH), halogen, substituted lower alkyl or alkyl such as (Ci-C\(_x\)) any of which may be further substituted one or more times with methyl, dimethyl, alkyl such as (Ci-C\(_x\)), phenyl, sulphate, phosphate, halogen or further substituted by fluoride, sulphate, phosphate, methyl, dimethyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci\(_4\))-alkyl, heteroaryl-(Ci\(_4\))-alkyl, heterocyclyl-(Ci\(_4\))-alkyl, cycloalkylalkyl, dicycloalkyl, tricycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen,
trifluoromethyl, cyano, amino, nitro, halogen or alcohol, and wherein \( x \) is an integer of from 1 to 30, and of which any of the mentioned substituents capable thereof may form a ring with another \( R \). \( R \) may furthermore be a chemical bond, or a pharmaceutically acceptable addition salt or hydrate thereof.

Phosphate residues have been implicated in the reduction of toxicity of certain cannabinoids without altering their hypothermic effect. It is therefore an object of the present invention that any of the cannabinoid and/or cannabimimetic compounds of the invention may carry one or more phosphate groups bound as phosphate esters.

For each general formula, a more specific choice of substituent for a given \( R \) is listed along with a preferred and a more preferred list of substituent groups.

The present invention concerns the use of at least one compound which is a cannabinoid or cannabimimetic compound such as a classic or non-classic cannabinoid comprising the general formula (I):

\[
\begin{array}{c}
R4 \\
R1 \\
R3 \\
R2
\end{array}
\]

- wherein \( R1 \) is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci-4)-alkyl, heteroaryl-(Ci-4)-alkyl, heterocyclyl-(Ci-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci-4)-alkyl, heteroaryl-(Ci-4)-alkyl, heterocyclyl-(Ci-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with methyl, alkyl or
phosphate and more preferably is C, optionally substituted with H, OH, OCH$_3$ or phosphate and

- wherein R$_2$ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, sulfonyl, any of which may or may not be branched or comprise substituents such as hydrogen, alkyl, alkenyl, alkynyl, fluoride, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl, phenyl and preferably is C substituted with C, O, P, H, OH, OSO$_2$, phosphate, alkyl, alkenyl, alkynyl, such as (Ci-C$_{2}$)$_x$ phenyl any of which may be substituted with methyl, dimethyl, sulfonyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, fluoride, phenyl, phosphate, and more preferably is C substituted with C, O, OSO$_2$, alkyl such as (C$_3$-C$_1$)$_x$ any of which may be further substituted with methyl, dimethyl, alkyl such as (Ci-C$_{2}$)$_x$, phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl and wherein X is an integer of from 1 to 20 and

- wherein R$_3$ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci$_4$)-alkyl, heteroaryl-(Ci$_4$)-alkyl, heterocyclyl-(Ci$_4$)-alkyl, cycloalkylalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, methyl, phenyl, diheterocycle, amine (NH), halogen, substituted lower alkyl, aryl, lower alcohol, heterocyclyl, heteroaryl, aryl-(Ci$_4$)-alkyl, heteroaryl-(Ci$_4$)-alkyl, heterocyclyl-(Ci$_4$)-alkyl, cycloalkylalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, preferably is C, O, N, S, optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted one or more times with methyl, diheterocycle, lower alcohol, alkyl or phosphate more preferably is C which may be substituted with C, O, N, OH, phosphate, any of which may be substituted one or more times with C, ethyl, methyl, phosphate, diheterocycle, lower alcohol, alkyl such as (CrC$_2$)$_x$ wherein C$_2$ binds to R$_4$ when R$_4$ is C, optionally further substituted by methyl, dimethyl or phosphate and
- wherein R4 is selected from the group of: C, H, S, N, O, optionally substituted with C, H, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, diphenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, ary-(C1-Cx)-alkyl, heteroaryl-(C1-Cx)-alkyl, heterocyclyl-(C1-Cx)-alkyl, cycloalkylalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, substituted lower alkyl, alkyl such as (C1-CX) any of which may be further substituted with methyl, dimethyl, alkyl such as (C1-CX), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl, aryl, heterocycl, heteroaryl, ary-(C1-Cx)-alkyl, heteroaryl-(C1-Cx)-alkyl, heterocyclyl-(C1-Cx)-alkyl, cycloalkylalkyl, dicycloalkyl, tricycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, (alcohol) and preferably is C, H, N, O optionally substituted with alkyl, alkenyl, alkynyl, alcohol, phenyl, diphenyl, dicycloalkyl, tricycloalkyl, cycloalkenyl any of which may bond with R1 or R3 forming a ring, optionally further substituted with one or more alkyl, alkenyl, alkynyl, OH, and more preferably is C, H, (C1-Cx), dicycloalkyl, or tricycloalkyl, cycloalkenyl any C of which may bond with R1 or R3 forming a ring, and optionally is substituted with methyl, dimethyl, phenyl, diphenyl, optionally further substituted with alkyl and/or OH and wherein x is an integer of from 1 to 15 and y is an integer of from 1 to 8.

Preferably, the present invention concerns the use of one or more compounds wherein at least one compound is a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (I) wherein R1 is C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with methyl, alkyl or phosphate, when R2 is C substituted with C, O, P, H, OH, OSO2, phosphate, alkyl, alkenyl, alkynyl such as (C1-CX), phenyl any of which may be substituted with methyl, dimethyl, sulfonfyl, heterocycloalkyl, fluoride, phenyl or phosphate, when R3 is C, O, N, S, optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted one or more times with methyl, diheterocycle, lower alcohol, alkyl or phosphate, when R4 is C, H, N, O optionally substituted with alkyl, alkenyl, alkynyl, alcohol, phenyl, diphenyl, dicycloalkyl, tricycloalkyl, cycloalkenyl any of which may bond with R1 or R3 forming a ring, optionally further substituted with one or more alkyl, alkenyl, alkynyl or OH.

Most preferably, the present invention concerns the use of one or more compounds wherein at least one compound is a cannabinoid or cannabimimetic compound such as
a compound comprising the general formula (I) wherein R\textsubscript{1} is C, optionally substituted with H, OH, OCH\textsubscript{3} or phosphate, when R\textsubscript{2} is C substituted with C, O, OSO\textsubscript{2}, alkyl such as (C\textsubscript{3}-C\textsubscript{15}) any of which may be further substituted with methyl, dimethyl, alkyl such as (CrCx), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl when R\textsubscript{3} is C which may be substituted with C, O, N, OH, phosphate, any of which may be substituted with C, ethyl, phosphate, alkyl such as (C\textsubscript{1}-C\textsubscript{2}) wherein C\textsubscript{2} binds to R\textsubscript{4} when R\textsubscript{4} is C, optionally further substituted by methyl, dimethyl or phosphate when R\textsubscript{4} is C, (C\textsubscript{1}-C\textsubscript{8}) any C of which may bond with R\textsubscript{3} and optionally is substituted with methyl, dimethyl, phenyl, diphenyl optionally further substituted with an alcohol and wherein x is an integer of from 1 to 15.

The present invention also concerns the use of at least one compound which is a cannabinoid or cannabimimetic compound such as a classic or non-classic cannabinoid comprising the general formula (II):

- wherein R\textsubscript{1} is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C\textsubscript{i}-C\textsubscript{j})-alkyl, heteroaryl-(C\textsubscript{i}-C\textsubscript{j})-alkyl, heterocyclyl-(C\textsubscript{i}-C\textsubscript{j})-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally bonding with the C in the ring next to R\textsubscript{5}, optionally further substituted one or more times with C, S, N, O, OH, phenyl, phosphate, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C\textsubscript{i}-C\textsubscript{j})-alkyl, heteroaryl-(C\textsubscript{i}-C\textsubscript{j})-alkyl, heterocyclyl-(C\textsubscript{i}-C\textsubscript{j})-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further
substituted with alkyl or phosphate and more preferably is C, optionally substituted one or more times with H, O, OH, OCH₃ or phosphate and

wherein R₂ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, heterocycloalkyl, cycloalkyl, cycloalkenyl, methyl, dimethyl, or may be further substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, sulfonyl, any of which may or may not be branched or comprise substituents such as hydrogen, alkyl, alkenyl, alkynyl, fluoride, phosphate, heterocycloalkyl, cycloalkyl, cycloalkenyl, dimethyl, phenyl and preferably is C substituted with C, O, P, H, OH, OSO₂, phosphate, alkyl, alkenyl, alkynyl such as (d-Cₓ), phenyl any of which may be substituted with methyl, dimethyl, sulfonyl, heterocycloalkyl, fluoride, phenyl, phosphate, and more preferably is C substituted with C, O, OSO₂, alkyl such as (C₃-C₁₅) any of which may be further substituted with methyl, dimethyl, alkyl such as (C₁-Cₓ), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl and wherein x is an integer of from 1 to 15, and

wherein R₃ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C₄₋)alkyl, heteroaryl-(C₄₋)alkyl, heterocyclyl-(C₄₋)alkyl, cycloalkylalkyl, cycloalkynyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C₄₋)alkyl, heteroaryl-(C₄₋)alkyl, heterocyclyl-(C₄₋)alkyl, cycloalkylalkyl, cycloalkynyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any of which may connect with R₄ and preferably is C, O, N, OH, phosphate optionally substituted one or more times with alkyl, OH, phosphate any of which may connect with R₄ and more preferably is O, OH, NH, optionally connecting with R₄ thus forming a ring and

wherein R₄ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C₄₋)alkyl, heteroaryl-(C₄₋)alkyl, heterocyclyl-(C₄₋)alkyl, cycloalkylalkyl, cycloalkynyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine
(NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C1-4)-alkyl, heteroaryl-(C1-4)-alkyl, heterocyclyl-(C1-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any of which may connect with R3 and preferably is C, N, O, P, OH, lower substituted alkyl, alkenyl, alkynyl, phenyl, optionally substituted with OH, methyl, dimethyl any of which may connect with R3 and more preferably is C, optionally connecting with R3 and optionally substituted with methyl, dimethyl or methyn and

- wherein R5 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C1-4)-alkyl, heteroaryl-(C1-4)-alkyl, heterocyclyl-(C1-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally bonding with R1, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C1-4)-alkyl, heteroaryl-(C1-4)-alkyl, heterocyclyl-(C1-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, phosphate or nitro, and preferably is C, N, O, optionally substituted with C, O, CH2OH, methyl, dimethyl, alkyl, alkenyl, alkynyl, phenyl, phosphate and more preferably is C, CO, optionally substituted with C, methyl, methyn (CH2), optionally substituted with CH2OH.

Preferably, the present invention concerns the use of a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (II) wherein R1 is C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with alkyl or phosphate, when R2 is C substituted with C, O, P, H, OH, OSO2, phosphate, alkyl, alkenyl, alkynyl such as (C1-CX), phenyl any of which may be substituted with methyl, dimethyl, sulfonyl, heterocycloalkyl, fluoride, phenyl or phosphate, when R3 is C, O, N, OH, phosphate optionally substituted one or more times with alkyl, OH, phosphate any of which may connect with R4 thus forming a ring, when R4 is C, N, O, P, OH, lower substituted alkyl, alkenyl, alkynyl, phenyl, optionally substituted one or more times with OH, methyl and/or dimethyl any of which may connect with R3, when R5 is C, N, O, optionally substituted with C, O, CH2OH, methyl, dimethyl, alkyl, alkenyl, alkynyl, phenyl or phosphate.
Most preferably, the present invention concerns the use of a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (II) wherein R1 is C, optionally substituted with H, OH, OCH₃ or phosphate when R2 is C substituted with C, O, OSO₂, alkyl such as (C3-C8) any of which may be further substituted with methyl, dimethyl, alkyl such as (Ci-Cₓ), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl when R3 is O, OH, NH, optionally connecting with R4, when R4 is C, optionally connecting with R3 and optionally substituted with methyl, dimethyl or methyn, when R5 is C, CO, optionally substituted with C, methyl, methyn (CH₂), optionally substituted with CH₂OH and wherein x is an integer of from 1 to 15.

In relation to the classic and non-classic cannabinoids and cannabimimetic compounds illustrated here by the general formulas (I) and (II), the presence of a phenolic hydroxyl group seems to play an essential role for ensuring high affinity binding of the compounds to the cannabinoid receptors.

An additional element of importance for especially CB1 receptor recognition is the side chain of R2. It is preferably a lipophilic carbon chain comprising from 1 to 15 carbon atoms, preferably from 3 to 11 carbon atoms. It may have any number and type of substituents, especially methyl and/or dimethyl groups. The methyl groups are preferably close to the phenol group, as this appears to induce the greatest effect of the drug. Interestingly, it appears that shorter side chains increase the intensity and decrease the duration of the activity of these compounds.

The present invention further concerns the use of at least one compound which is a cannabinoid or cannabimimetic compound such as an eicosanoids or other cannabinoid compound comprising the general formula (III):

\[
R1 \rightarrow R2
\]

- wherein R1 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci-₄)-alkyl, heteroaryl-(Ci-₄)-alkyl, heterocycyl-(Ci-₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine
(NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C1-C4)-alkyl, heteroaryl-(C1-C4)-alkyl, heterocyclyl-(C1-C4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is (C1-Cx) is saturated or unsaturated and optionally is substituted one or more times with lower alkyl, alkenyl, alkynyl, O, OH, N and where \( x \) is an integer of from 1 to 30, more preferably is (C1-CY), is saturated or unsaturated and optionally substituted with methyl, dimethyl, O, or N and wherein \( Y \) is an integer of from 15 to 21 and

- wherein \( R_2 \) is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C1-C4)-alkyl, heteroaryl-(C1-C4)-alkyl, heterocyclyl-(C1-C4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, OCH3, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C1-C4)-alkyl, heteroaryl-(C1-C4)-alkyl, heterocyclyl-(C1-C4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, N, O, NH2 optionally substituted one ore more times with lower alkyl, alkenyl, alkynyl, phenyl, OH, NH2 cycloalkane, methyl, OCH3, and more preferably is N, O, NH2 optionally substituted with C, CH2OH, CH(CH2)2, C2H4, C3H6, optionally further substituted one or more times with NH2, OH, CH2OH, CH2Cl, phenyl, CH3 and/or OCH3.

Preferably, the present invention concerns the use of a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (III) wherein \( R_1 \) is (C1-Cx) saturated or unsaturated, and optionally is substituted one or more times with lower alkyl, alkenyl, alkynyl, O, OH, N, when \( R_2 \) is C, N, O, NH2 optionally substituted one ore more times with lower alkyl, alkenyl, alkynyl, phenyl, OH, NH2 cycloalkane, methyl or OCH3 and wherein \( x \) is an integer of from 1 to 30.

Most preferably, the present invention concerns the use of a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (III) wherein \( R_1 \) is (C1-Cx), is saturated or unsaturated and optionally substituted with methyl, dimethyl, O, or N when \( R_2 \) is N, O, NH2 optionally substituted with C, CH2OH,
CH(CH2)2 (cyclopropane), optionally further substituted one or more times with CH2OH, CH2Cl and wherein \( x \) is an integer of from 1 to 21.

The present invention concerns the use of least one compound which is a cannabinoid or cannabimimetic compound such as an aminoalkylindole or other cannabinoid compound comprising the general formula (IV):

![Diagram of the general formula (IV)]

- wherein \( R_1 \) is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(\( \text{Ci}_{-4} \))-alkyl, heteroaryl-(\( \text{Ci}_{-4} \))-alkyl, heterocycl-(\( \text{Ci}_{-4} \))-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, O, N optionally substituted with O, phosphate, N, C, lower alkyl, OH, optionally further substituted with lower alkyl, OH, phosphate and more preferably is C, substituted with O, further substituted with methyl and

- wherein \( R_2 \) is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(\( \text{Ci}_{-4} \))-alkyl, heteroaryl-(\( \text{Ci}_{-4} \))-alkyl, heterocycl-(\( \text{Ci}_{-4} \))-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any of which may bond with R3, and preferably is C, N, O, optionally substituted with C, O, N,
phosphate, lower alkyl optionally further substituted with lower alkyl, OH, phosphate, any of which may bond with R 3 and more preferably is C, substituted with O, further substituted with C optionally bond forming with R 3 and

- wherein R 3 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Cl₄)-alkyl, heteroaryl-(Cl₄)-alkyl, heterocyclyl-(Cl₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Cl₄)-alkyl, heteroaryl-(Cl₄)-alkyl, heterocyclyl-(Cl₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any of which may bond R 2 and preferably is C, N, O, alkyl, alkenyl, alkynyl, optionally substituted with C, N, O, OH, phosphate, halogen any of which may bond R 2 and more preferably is (Cl-Cx) and wherein x is an integer of from 1 to 3, optionally substituted one or more times with O, dichloro-phenyl or morpholine and any of which may bond R 2 and

- wherein R 4 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Cl₄)-alkyl, heteroaryl-(Cl₄)-alkyl, heterocyclyl-(Cl₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Cl₄)-alkyl, heteroaryl-(Cl₄)-alkyl, heterocyclyl-(Cl₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, N, O optionally substituted with C, N, O, OH, lower alkyl, alkenyl, alkynyl, phosphate, optionally further substituted one or more times with O, OH, phenyl, diphenyl, morpholino, and halogen, and more preferably is C, optionally substituted with C, O and/or diphenyl, optionally further substituted with morpholine.

Preferably, the present invention concerns the use of a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (IV) wherein R 1 is C, O, N optionally substituted with O, phosphate, N, C, lower alkyl, OH, optionally further substituted with lower alkyl, OH or phosphate, when R 2 is C, N, O, optionally
substituted with C, O, N, phosphate, lower alkyl optionally further substituted with lower alkyl, OH, phosphate, any of which may bond with R3, when R3 is C, N, O, alkyl, alkenyl, alkynyl, optionally substituted with C, N, O, OH, phosphate, halogen any of which may bond R2, when R4 is C, N, O optionally substituted with C, N, O, OH, lower alkyl, alkenyl, alkynyl, phosphate, optionally further substituted one or more times with O, OH, phenyl, diphenyl, morpholino, and/or halogen.

Most preferably, the present invention concerns the use of a cannabinoid or cannabimimetic compound such as a compound comprising the general formula (IV) wherein, wherein R1 is C, substituted with O, further substituted with methyl when R2 is C, substituted with O, further substituted with C optionally bond forming with R3 when R3 is (Cl-Cx) and wherein x is an integer of from 1 to 3, optionally substituted one or more times with O, dichloro-phenyl or morpholine when R4 is C, optionally substituted with C, O and/or diphenyl, optionally further substituted with morpholine.

It is an aspect of the present invention to provide the use of at least one compound for induction of hypothermia in an individual, wherein said compound is administered parenterally; said parenteral administration may in one embodiment be injection or intravenous infusion. Preferably, the compounds / medicaments of the present invention are administered parenterally such as by injection or IV for the treatment of ischemia in an individual by induction of hypothermia.

In one embodiment, a cannabinoid or a cannabimimetic compound is administered by intravenous infusion for the induction of hypothermia.

In another embodiment, a cannabinoid or a cannabimimetic compound is administered by injection for the induction of hypothermia.

**Examples of cannabinoid or cannabimimetic compounds**

Examples of cannabinoid or cannabimimetic compounds specially relevant for the present invention include, but are not limited to classic cannabinoids such as (names in parenthesis are alternative names): delta-9-THC (Tetrahydrocannabinol), delta-8-THC, delta-8-THC phosphate, Cannabinol (CBN), Cannabidiol (CBD), Cannabidiol-type CBD, Cannabidivarin (CBDV), Cannabichromene-type CBG, Cannabigerol-type CBG, Tetrahydrocanna-bivarin (THCV, THV), Tetrahydrocanna-binol- and cannabinol-type
THC or CBN, Iso-Tetrahydro-cannabinol-type iso-THC, Cannabielsion-type CBE, Cannabicyclo l-type CBL, Cannabicitran-type CBT, HU-308, JWH-133, JWH-139, JWH-051, L-759633, L-759656, HU-210 ((−)-1-OH-delta-8-tetrahydrocannabinol-dimethylheptyl), HU-211 (Dexanabinol, 7-hydroxy-D6-tetrahydrocannabinol 1,1-dimethylheptyl), Desacetyl-L-nandrolol, Nabilone and Levonantradol, non-classic cannabinoids such as: CP-55940, CP55244 and CP47497, aminoalkylindoles such as: R(+)-WIN55212, S(-)-WIN-55213, JWH-015 and L-768242, eicosanoids / endogenous cannabinoids such as: Anandamide (arachidonyl ethanolamine), 2-Arachidonyl-glycerol (2-AG, Noladin ether), Palmitoylethanol-amine, Virodhamine (O-arachidonoyl-ethanolamine), Palmitoyl ethanolamide, Oleamide, other cannabinoid compounds such as: Arvanil, Metanandamide, ACEA, ACPA, KN38-7271 (BAY 38-7271) and 0-1812. Phosphate derivatives of these compounds are especially relevant for the present invention.

Examples of especially relevant cannabinoid or cannabimimetic compounds are anandamide, delta-9-THC, delta-8-THC, cannabidiol, HU-210, KN38-7271 (BAY 38-7271), WIN 55,212 and CP55940 and the phosphate derivatives of these.

Preferred cannabinoid and/or cannabimimetic compounds

The compounds of the present invention may apart from inducing hypothermia upon parenteral administration, induce secondary effects or have other characteristics. These may be related to the cannabinoid nature of the compounds and may thus be more or less desirable. It is preferable that the compounds of the invention do not induce any adverse psychotropic effects. The compound may furthermore have analgesic, anti-convulsive, anti-inflammatory, anti-anxiety, anti-nausea, pulse-lowering and blood-pressure modifying effects. Of these, it is preferable that the compound has analgesic effects. Furthermore, a compound of the present invention may be hydrophilic or hydrophobic. To facilitate the administration of a compound according to the present invention it is preferable for a compound to be hydrophilic. A preferred compound is moreover metabolically stable.

A preferred cannabinoid or cannabimimetic compound of the present invention is a compound capable of binding a cannabinoid receptor, such as CB1, thereby inducing hypothermia in an individual to a temperature in the range of 36 to 32 degree Celsius, and where said compound is hydrophilic.
It follows that it is an aspect of the present invention to induce hypothermia in / reduce the temperature of an individual in need thereof by the parenteral administration of at least one cannabinoid and/or cannabimimetic compound. The individual may be in need of hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or as part of a pre-operative preparation. Preferably, the compound administered parenterally is delta-9-THC, delta-8-THC, cannabidiol, HU-210, KN38-7271 (BAY 38-7271), WIN 55,212 and/or CP55940 and/or the phosphate derivatives of these.

Antagonists to cannabinoid and cannabimimetic compound function

It is an object of the present invention to provide compounds that are capable of obviating the effect of the compounds that induce hypothermia. These compounds are herein termed antagonists and exert their antagonistic effect by blocking the ability of any of the cannabinoids or cannabimimetic compounds herein described in binding to their receptors. The purpose of such an antagonist is to provide an additional safety mechanism whereby it is possible to stop the decline in core body temperature, stabilize the core body temperature and/or raise the core body temperature of an individual.

An embodiment of the present invention thus comprises the use of a compound according to any of the above for the preparation of a medicament for antagonizing the induction of hypothermia in an individual.

Examples of antagonists include but are not limited to: Rimonabant (SR141716, Acomplia, SR147778, SR141716A, SR144528, CP-272,871, NIDA-41020, LY320135, AM251, AM281, AM630, WIN56098 and WIN54461.

Novel use of cannabinoids and cannabimimetic compounds

Cannabinoids and cannabimimetic compounds have been used for a variety of purposes over time. It is an object of the present invention to provide a novel use of these compounds administered parenterally for the induction of hypothermia, especially for the preparation of a medicament comprising one or more compounds of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen...
tension reducers to be administered parenterally, for the induction of hypothermia in an individual suffering from ischemia or at risk of suffering from ischemia.

**Vanilloid receptor agonists**

Vanilloid receptor agonists are a group of chemicals which are capable of binding the Vaniloid Receptor 1 (VR1), also known as the Transient Receptor Potential Cation Channel, Subfamily V (TRPV1). The term vanilloid receptor agonist covers several groups of compounds including capsaicinoids and capsaicinoid-like compounds such as resiniferanoids and unsaturated dealdehydes. Before other types were discovered or synthesized, the term capsaicinoid referred to a group of secondary metabolites produced by plants belonging to the genus *Capsicum*, such as chili peppers. These compounds are the active components of chili peppers that produce the sensation of burning in the mouth, when ingested. Vanilloid receptor agonists may be divided into two classes based on origin and chemical composition:

- Classical vanilloid receptor agonists, a group which includes naturally occurring compounds of chili peppers and other vanillamide derivatives.
- Non-classical vanilloid receptor agonists, a group wherein the members generally do not comprise a vanillamide moiety.

Vanilloid receptor agonists are irritants for mammals, but have no effect on birds, indicating that the compounds may have evolved as a deterrent for herbivores. The various vanilloid receptor agonists have different pungencies as measured on the Scoville scale, with capsaicin and dihydrocapsaicin being the most potent of the classical vanilloid receptor agonists.

The use of capsaicin as a medicament is known both anecdotally and scientifically and is today widely used as a medicine to treat or relieve various ailments. The main clinical use of capsaicin is in the form of a topical ointment to successfully treat the pain of neuralgia such as caused by an infection with herpes zoster (shingles), diabetic neuropathy, rheumatism, fibromyalgia, various types of arthritis such as osteoarthritis or rheumatoid arthritis, and other forms of chronic pain. Capsaicin desensitizes nerves from pain by eliminating unneeded nerve cells through necrotic death and helps arthritis sufferers by lowering the levels of Decapeptide Substance P (DSP) in the synovial fluid of joints. Capsaicin breaks down DSP, which can destroy cartilage and
also magnify the sensing of pain. Recently studies demonstrate that capsaicin is a potent anticancer agent. Capsaicin induces apoptosis in pancreatic and prostate cancer cells with no significant damage to the surrounding healthy cells. Capsaicin is known to affect NF-kB, and it is believed that it is through this protein, that capsaicin activates apoptotic proteins, leading to cell death. In another cancer-related application, capsaicin-containing candy provides significant pain relief of ulcers in the mouth which often develop in chemotherapy patients. Capsaicin pastes and balms are used to treat muscle and joint pains and medications containing vanilloid receptor agonists are used as an anti-inflammatory agent as the chemicals causes blood vessels to dilate.

Capsaicin has furthermore been mentioned as a remedy to reduce serum cholesterol levels, relieve psoriasis and treat headaches, migraines and chronic sinus infections. Vanilloid receptor agonists have furthermore received interest as putatively neuroprotective substances. The neuroprotective effect is at least in part mediated by induction of hypothermia, as described in the below.

Any compound which can be defined as a vanilloid receptor agonist, capsaicinoid or capsaicinoid-like compound these being classical or non-classical vanilloid receptor agonist or compounds that otherwise bind vanilloid receptors falls within the scope of the present invention, along with compounds that in structure resembles a compound capable of binding a vanilloid receptor without having the ability itself. The terms vanilloid receptor agonist, capsaicinoid or capsaicinoid-like are used interchangeably herein.

**Receptors**

The sensation of burning pain elicited by vanilloid receptor agonists occurs by the selective activation of sensory neurons that convey information about noxious stimuli to the central nervous system. The selectivity is based primarily on the presence of the VR1 / TRPV1 receptor, a nonselective cation channel to which the vanilloid receptor agonists, capsaicinoids and capsaicinoid-like compounds bind as agonists. TRPV1 is also activated by extracellular protons, and temperatures in the noxious range, suggesting that it functions as a transducer of painful thermal stimuli in vivo. By binding to the TRPV1 receptor, the vanilloid receptor agonists produce the same effect that excessive heat or abrasive damage would cause, explaining why the spiciness of capsaicin, without causing an actual chemical burn, is described as eliciting a burning sensation.
A number of different mechanisms have been proposed to account for the various effects of vanilloid receptor agonists. The vanilloid receptors, that are likely to be multimeric, non-selective cation channels composed of 6 transmembrane domains, will upon activation induce Ca$^{2+}$ entry and subsequent release of sensory neuropeptides like calcitonin gene-related peptide (CGRP) and tachykinins (e.g. substance P) in addition to somatostatin. This in turn induces a range of actions that may vary depending on tissue types, and include vasodilatation, plasma protein extravasation and immune cell accumulation in the innervated area as well as systemic anti-inflammatory and analgesic actions. To date it is not known exactly which mechanisms are responsible for the hypothermic effect of vanilloid receptor agonists, but it is speculated that the abovementioned reactions may play a part in it.

The TRPV1 receptor was originally named the Vanilloid Receptor 1 (VR1), as a vanilloid moiety constitutes an essential component of classical vanilloid receptor agonists, but has since changed name to TRPV1 due to the receptors extended homology with other TRP family members. TRPV1 is a member of the subfamily of TRPV receptors, which includes TRPV1-6. Several of these receptors render the cells expressing them sensitive to heat at different intervals, mechanic pressure and various compounds such as vanilloid receptor agonists, camphor and others. Combinations of the subtypes and various oligomers of the vanilloid receptors may account for the variations in physiological outcome observed following activation of receptors by different vanilloid receptor agonists. The oligomeric structure of the receptors increase the likelihood of discovering active substances with specificity for certain of the many organs that harbor vanilloid receptor agonists, thereby activating only parts of the vanilloid receptor system.

Vanilloid receptors are abundant in many organs of the body including neuronal tissues of the preoptic area, locus ceruleus, medial hypothalamus, reticular formation, and ventral thalamus. Vanilloid receptors have furthermore been found in non-neuronal "port of entry" tissues (e.g., skin, gut, airways, conjunctiva), the various cell types lining such tissues (i.e., keratinocytes, epithelia, endothelia, etc.), and also in various peripheral non-neuronal tissues of rodents and humans (e.g., kidney, lung, testis, pancreas, spleen, liver, stomach, skin, vascular smooth muscle, placenta, cornea, uterus, and bladder). The hypothalamus, with its abundance of vanilloid receptors, is of
particular interest to this invention: It is a likely component in vanilloid receptor mediated hypothermia as it contains the temperature regulating centers of the CNS.

Receptors other than TRPV1 have been implicated in causing hypothermia upon binding of agonists hereto. Although some data suggests that capsaicin causes hypothermia by a cannabinoid receptor (CB1 and CB2) independent mechanism, there are hypothermia inducing vanilloid receptor agonists that are capable of interacting both with TRPV1 and especially CB2. Apart from TRPV3 mentioned above as a modulator of TRPV1 activity, the prokineticin receptors 1 and 2 (PKR1 and PKR2) have been shown to interact with TRPV1 and modulate its activity. Receptors to which the vanilloid receptor agonists, capsaicinoids and capsaicinoid-like compounds of the present invention may bind, includes, apart from TRPV1 and the other TRPV subfamily members, TRPV2, -3, -4, -5 and -6, CB1, CB2 and a third CB receptor, herein termed CB3, PKR1 and PKR2, GABA (gamma-aminobutyric acid) receptors, the NMDA (N-methyl-D-aspartate) receptor, the 5-HT(1A) receptor, also known as the serotonin receptor, the Delta opioid receptor (DOR). It is furthermore within the scope of the invention that at least one of compound of the combination of compounds of the invention may bind TRPV1 co-receptors. Compounds capable of binding any of the above-mentioned receptors thus fall within the scope of the present invention.

Preferably, at least one compound of the present invention binds TRPV1 and/or a TRPV1 associated receptor. The importance of the TRPV1 receptor for the induction of hypothermia in mammals is the dramatic hypothermic response that is elicited by systemic administration of capsaicin, a response which is absent in mice lacking the TRPV1 gene.

Structure
The vanilloid receptor agonists of this application are, largely based on their structure, categorized as follows: classic vanilloid receptor agonists and non-classic vanilloid receptor agonists. Compounds belonging to any of these categories fall within the scope of the present invention.

It is within the scope of the invention that the compounds or the combination of compounds of the invention are capable of inducing hypothermia in an individual.
It is furthermore within the scope of the invention that at least one compound of the invention is capable of binding the TRPV1 receptor and/or a receptor associated herewith.

Accordingly, in the broadest aspect the present invention concerns the use of one or more compounds, wherein at least one compound is a vanilloid receptor agonist comprising a structure of one of the general formulas of vanilloid receptor agonists illustrated in the below. In these illustrations R is a chemical bond or a chemical moiety as defined in the above. R may be any moiety substituted any amount of times according to the following non-limiting list, whereby R is: C, H, S, N, O, optionally substituted one or more times with C, H, S, N, O, B, P, OH, CHO, hydrogen, alkoxy, alkyl, alkenyl, alkynyl, phenyl, diphenyl, benzyl, amine (NH), halogen, substituted lower alkyl, alkenyl, aryl, heterocyclic group, heterocycloalkyl, heteroaryl, aryl-(Ci_4)-alkyl, heteroaryl-(Ci_4)-alkyl, heterocyclyl-(Ci_4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, S, N, O, P, OH, H, phenyl, amine (NH), halogen, alkoxy, substituted lower alkyl or alkenyl, alkenyl or alkynyl such as (d-C_4), acetyl, sulfonyl, phenyl, cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclic group any of which may or may not be branched or be further substituted one or more times with C, O, P, methyl, dimethyl, alkyl or alkenyl such as (d-C_4), alkoxy, phenyl, sulphate, phosphate, halogen or further substituted by fluoride, sulphate, phosphate, methyl, dimethyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci_4)-alkyl, heteroaryl-(Ci_4)-alkyl, heterocyclyl-(Ci_4)-alkyl, cycloalkylalkyl, dicycloalkyl, tricycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, nitro, halogen or alcohol, and further substituted at least once with O, OH, methyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl further substituted with alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocyclyl and wherein v is an integer of from 1 to 30, and of which any of the mentioned substituents capable thereof may form a ring with another R. R may furthermore be a chemical bond, or a pharmaceutically acceptable addition salt or hydrate of any of the above.

For each general formula, a more specific choice of substituent for a given R is listed along with along a preferred and a more preferred list of substituent groups.
The present invention concerns the use of at least one compound which is a vanilloid receptor agonist such as a classic or non-classic vanilloid receptor agonist comprising the general formula (I):

- wherein R₁ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, sulfonyle or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkylnyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkylnyl any of which may be (d-Cᵥ), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, any of which may be further substituted with methyl, ethyl or phenyl and more preferably is C substituted with alkyl, alkenyl, any of which may be (C₄₋C₆) any of which may be further substituted with O, OH, methoxy, ethoxy or methyl any of which may be further substituted with methyl, ethyl, or phenyl, wherein v is an integer of from 1 to 30 and w is an integer of from 5 to 18, and;

- wherein R₂ is selected from the group of: C, S, N, O, optionally substituted one or more times with C, S, N, O, P, OH, hydrogen, alkoxy, alkyl, alkenyl, alkynyl, phenyl, diphenyl, benzyl, amine (NH), halogen, substituted lower alkyl, alkenyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C₁₋₄)-alkyl, heteroaryl-(C₁₋₄)-alkyl, heterocyclyl-(C₁₋₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, S, N, O, P, OH, H, COOH, phenyl, amine (NH), halogen, alkoxy, substituted lower alkyl, alkyl or alkenyl such as (C₁₋₄), cycloalkenyl, sulphate, phosphate, aryl, heterocyclyl, heteroaryl, aryl-(C₁₋₄)-alkyl, heteroaryl-(C₁₋₄)-alkyl, heterocyclyl-(C₁₋₄)-alkyl, cycloalkylalkyl, dicycloalkyl, tricycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, cyano, amino, nitro, or alcohol, any of which may be further...
substituted one or more times with OH, methyl, dimethyl, alkyl or alkenyl such as (CrCv), alkoxy, phenyl, sulphate, phosphate, aryl, heteroaryl, carboxy, amino, nitro, alcohol or halogen and preferably is C, substituted one or more times with C, N, O, P, OH, hydrogen, alkoxy, alkyl, alkenyl, amine (NH), halogen, substituted lower alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, N, O, OH, COOH, hydrogen, amine (NH), halogen, alkoxy, substituted lower alkyl or alkenyl such as (CrCv), phosphate, cycloalkenyl, alkoxy, carboxy or halogen, any of which may be further substituted one or more times with OH, methyl, dimethyl, alkyl or alkenyl such as (Ci-Cw), alkoxy, phenyl, sulphate, phosphate, carboxy or halogen and more preferably is C substituted with either: cycloalkenyl further substituted at least twice with any of OH or methoxy, or: lower alkyl such as (C1-C2) at least once and further substituted one or more times with OH, COOH, Chloride, methyl or cycloalkenyl, optionally further substituted one or more times with OH or methoxy and wherein v is an integer of from 1 to 30 and x is an integer of from 1 to 5.

Preferably, the present invention concerns the use of one or more compounds wherein at least one compound is a vanilloid receptor agonist comprising the general formula (I) wherein R1 is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be (d-Cv), or phenyl, any of which may be further substituted one or more times with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, acetyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, any of which may be further substituted with methyl, ethyl or phenyl and R2 is C, substituted one or more times with C, N, O, P, OH, hydrogen, alkoxy, alkyl, alkenyl, amine (NH), halogen, substituted lower alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, N, O, OH, COOH, hydrogen, amine (NH), halogen, alkoxy, substituted lower alkyl or alkenyl such as (CrCv), phosphate, cycloalkenyl, alkoxy, carboxy or halogen, any of which may be further substituted one or more times with OH, methyl, dimethyl, alkyl or alkenyl such as (CrCv), alkxy, phenyl, sulphate, phosphate, carboxy or halogen and wherein v is an integer of from 1 to 30 wherein x is an integer of from 1 to 5.

Most preferably, the present invention concerns the use of one or more compounds wherein at least one compound is a vanilloid receptor agonist comprising the general formula (I) wherein R1 is C substituted with alkyl, alkenyl, any of which may be (C4-Cw)
any of which may be further substituted one or more times with O, OH, acetyl, methoxy, ethoxy or methyl any of which may be further substituted one or more times with methyl, ethyl, cycloalkenyl or phenyl and w is an integer of from 5 to 18, and R² is C substituted with either: cycloalkenyl further substituted at least twice with any of OH or methoxy, or: lower alkyl such as (CrC₂) at least once and further substituted one or more times with OH, COOH, Chloride, methyl or cycloalkenyl, optionally further substituted one or more times with OH or methoxy.

The present invention furthermore concerns the use of at least one compound which is a vanilloid receptor agonist such as a non-classic vanilloid receptor agonist comprising the general formula (II):

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R5
R4
R1
R3
R2
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- wherein R¹ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocyclic, heterocyclic group, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, sulfonyl or phenyl cycloalkyl, cycloalkenyl, heterocyclic, heterocyclic group any of which may or may not be branched or comprise substituents such as C, O, H, OH, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, further substituted at least once with O, OH, methyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl further substituted with alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl and preferably is C substituted with C, N, O, B, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocyclic, heterocyclic group, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocyclic group any of which may or may not be branched or comprise substituents such as C, O, H, OH, methyl, ethyl, alkyl, alkenyl, alkoxy, phosphate, further substituted at least once with O, OH, methyl, alkenyl, cycloalkyl, heterocycloalkyl,
cycloalkenyl, further substituted with alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocyclyl and more preferably is C substituted with alkyl or alkenyl which may be (C4-Cw), B, or heterocyclyl forming a ring with R6 thus comprising a pyrrolidine further substituted one or more times with O, methyl, alicyclic groups attached to one another, these being saturated or unsaturated or a heterocyclic group comprising said B, N and O, and being further substituted at least once with O, methyl or C further substituted at least once with cycloalkenyl, cycloalkyl, heterocyclyl further substituted at least once with O, OH, methyl, alkenyl, further substituted with lower alkyl and cycloalkenyl; wherein any of the above may form at least one bond with any of R2, R3, R4, R5 and/or R6, and w is an integer of from 5 to 18, and;

- wherein R2 is selected from the group of C, S, N, O, optionally substituted at least once with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be (d-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted at least once with OH or hydrogen, and wherein any of the above may form at least one bond with any of R1, and/or R3, and wherein v is an integer of from 1 to 30; and

- wherein R3 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, hydrogen, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl, alkenyl, any of which
may be (Ci-Cv), or phenyl, optionally substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted with OH, methoxy, lower alkyl (C1- Cv) and may at any point form a ring with R4, and wherein any of the above may form at least one bond with any of R2, and/or R4, and wherein ν is an integer of from 1 to 30, and γ is an integer of 2 or 3; and

- wherein R4 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, hydrogen, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl, alkenyl, any of which may be (Ci-Cv), or phenyl, optionally substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted with OH, methoxy, lower alkyl (C1- Cv) and may at any point form a ring with R4, and wherein any of the above may form at least one bond with any of R2, and/or R4, and wherein x is an integer of from 1 to 30; and γ is an integer of 2 or 3; and

- wherein R5 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, CHO, hydrogen, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, sulfonyl or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted at least once with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (d-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted one or more times with hydrogen, OH, CHO or methyl which may form a ring with R6 wherein ν is an integer of from 1 to 30, and;
- wherein R6 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, CHO, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkeny1, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (d-C\(_g\)). or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted one or more times with hydrogen, CHO, lower alkyl (C1-C\(_g\)) or methyl, which may form at least one bond with R5, or be at least one bond forming a ring with R1, wherein the at least one bond between any of R1, R2, R3, R4 and/or R5 may be single or double bonds and wherein \(g\) is an integer of from 1 to 30; and \(g\) is an integer of 2 or 3.

Preferably, the present invention concerns the use of one or more compounds wherein at least one compound is a vanilloid receptor agonist comprising the general formula (I) wherein R1 is C substituted with C, N, O, B, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycly1, heterocyclic group, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, cycloalkyl, cy-cloalkenyl, heterocyclyl, heterocyclic group any of which may or may not be branched or comprise substituents such as C, O, H, OH, methyl, ethyl, alkyl, alkenyl, alkoxy, phosphate, further substituted at least once with O, OH, methyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkeny1, further substituted with alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocyclyl any of the above of which may form bonds with R2, and/or R6, and R2 preferably is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be (d-C\(_v\)), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and R3 preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl, alkenyl, any of which may be (d-C\(_v\)), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and R4 preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl,
alkenyl, any of which may be (Ci-Cv), or phenyl, optionally substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and R5 preferably is C substituted at least once with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (Ci-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and R6 preferably is C substituted with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (d-C_v), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and wherein v is an integer of from 1 to 30.

Most preferably, the present invention concerns the use of one or more compounds wherein at least one compound is a vanilloid receptor agonist comprising the general formula (I) wherein R1 is C substituted with alkyl or alkenyl which may be (C4-C_2), Boron, or heterocyclic group forming a ring with R6 thus comprising a pyrroolidine further substituted one or more times with O, methyl, alicyclic groups attached to one another, these being saturated or unsaturated or a heterocyclic group comprising said Boron, N and O, and being further substituted at least once with O, methyl or C further substituted at least once with cycloalkenyl, cycloalkyl, heterocyclyl further substituted at least once with O, OH, methyl, alkenyl, further substituted with lower alkyl and cycloalkenyl; R2 is C substituted with OH or hydrogen; R3 is C substituted with OH, methoxy, lower alkyl (C1-C_2) and may at any point form a ring with R4; R4 is C substituted with OH, methoxy, lower alkyl (C1-C_2) and may at any point form a ring with R3; R5 is C substituted one or more times with hydrogen, OH, CHO or methyl which may form a ring with R6; and R6 is C substituted one or more times with hydrogen, CHO, lower alkyl (Cl-Cz) or methyl, which may form at least one bond with R5, or be forming a ring with R1, wherein at least one bond between any of R1, R2, R3, R4, R5 and/or R6 may be single or double bonds and v is an integer of either 2 or 3, and z is an integer of either 5 or 12.

Certain molecular modifications are preferable especially regarding the classical vanilloid receptor agonist compounds, as they seem to ensure a more favorable degree of vanilloid receptor activation. These modifications include an unbranched alkyl side chain of a certain minimum length, as shorter chain analogues decrease in potency and thus are not capable of inducing hypothermia to a satisfactory degree. It is therefore preferable that the compounds of the present invention have relatively long
alkyl or alkenyl chains (counted from R1 in the above formula) such as chains longer than 6 carbon atoms. Preferably the length of the alkyl / alkenyl chain is between 6 and 25 carbon atoms, most preferably between 7 and 18 carbon atoms, even more preferably between 8 and 9 carbon atoms.

In contrast hereto, substitution in the aromatic ring seems to abolish activity altogether and modification of many of the TRPV1 capsaicinoid and capsaicinoid-like agonists by halogenation of the aromatic ring tends to yield potent antagonists.

It is an aspect of the present invention to provide the se of at least one compound for the treatment of ischemia in an individual by induction of hypothermia in said individual, wherein said compound is administered parenterally; said parenteral administration may in one embodiment be injection or intravenous infusion.

In one embodiment, a vanilloid receptor agonist is administered by intravenous infusion for the induction of hypothermia.

In another embodiment, a vanilloid receptor agonist is administered by injection for the induction of hypothermia.

Examples of vanilloid receptor agonists
Examples of vanilloid receptor agonists specially relevant for the present invention include, but are not limited to classic vanilloid receptor agonists such as (names in parenthesis are alternative names): Capsaicin (C; 8-methyl-N-vallilyl-6-nonanamide), Dihydrocapsaicin (DHC), Nordihydro-capsaicin (NDHC), Homodihydro-capsaicin (HDHC), Homocapsaicin (HC), Olvanil (N-9-Z-octadecenoyl-vanillamide), Rinvanil (vanillamide of ricinoleic acid), Arvanil (N-vanillylarachidonamide), PhAR (phenylacetylrivanil), Nuvanil, Farvanil (vanillamide of farnesic acid), Ac-Rinvanil, Retvanil (vanillamide of retinoic acid), Nonivamide, and Ervanil (vanillamide of erucic acid).

Examples of non-classical vanilloid receptor agonist compounds specially relevant for the present invention include, but are not limited to compounds such as (names in parenthesis are alternative names): Resiniferatoxin (RTX), Anandamide (arachidonyl ethanolamine), N-arachidonoyldopamine (NADA), N-arachidonoyl-L-serine (ARA-S),

Preferred vanilloid receptor agonist compounds
The vanilloid receptor agonists of the present invention may apart from inducing hypothermia induce secondary effects or have other characteristics. These may be related to the capsaicinoid nature of the compounds and may thus be more or less desirable. It is preferable that the compounds of the invention do not induce any blood-pressure modifying effects or induce hyperalgesic, nocifensive, plasma extravasation, peripheral vasodilatation, bronchoconstriction, bradycardia, or apnea effects among others. A potential analgetic effect may not be considered an adverse effect and may even, depending on the application of this invention, be desirable. Furthermore, a compound of the present invention may be hydrophilic or hydrophobic. To facilitate the administration of a compound according to the present invention it is preferable for a compound to be hydrophilic. A preferred compound is moreover metabolically stable.

A preferred vanilloid receptor agonist of the present invention is a compound capable of binding the TRPV1 receptor, thereby inducing hypothermia in an individual to a temperature in the range of 36 to 32 degree Celsius, and where said compound is hydrophilic.

Examples of preferred or especially relevant vanilloid receptor agonists include:
Capsaicin and compounds closely related to capsaicin such as: Dihydrocapsaicin (DHC), Nordihydro-capsaicin (NDHC), Homodihydro-capsaicin (HDHC), and Homocapsaicin other especially relevant compounds include resiniferatoxin and compounds closely related hereto.

It follows that it is an aspect of the present invention to induce hypothermia in / reduce the temperature of an individual in need thereof by the parenteral administration of at least one vanilloid receptor agonist. The individual may be in need of hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or as part of a pre-operative preparation. Preferably, the compound administered parenterally is
Dihydrocapsaicin (DHC), Nordihydro-capsaicin (NDHC), Homodihydro-capsaicin (HDHC), and/or the phosphate derivatives of these.

**Antagonists of vanilloid receptor agonist function**

It is an object of the present invention to provide compounds that are capable of obviating the effect of the vanilloid receptor agonists that induce hypothermia. These compounds are herein termed antagonists and exert their antagonistic effect by blocking the ability of any of the vanilloid receptor agonists, capsaicinoids or capsaicinoid-like compounds herein described in binding to their receptors. The purpose of such an antagonist is to provide an additional safety mechanism whereby it is possible to stop the decline in core body temperature, stabilize the core body temperature and/or raise the core body temperature of an individual.

An embodiment of the present invention thus comprises the use of a compound according to any of the above for the preparation of a medicament for antagonizing the induction of hypothermia in an individual.

Examples of antagonists include but are not limited to: 5-iodoresiniferatoxin, Aminoquinazoline (Aminoquinazoline 70), 6-iodo-nordihydrocapsaicin, IBTU (N-(4-cholorobenzyl)-N'-(4-hydroxy-3-iodo-5-methoxybenzyl)thiourea), KJM429 and JYL1421, A-425619, AMG9810, SB 366791, Adenosine and Capsazepine.

**Novel use of compounds**

Vanilloid receptor agonists, capsaicinoids and capsaicinoid-like compounds have been used for a variety of purposes over time. It is an object of the present invention to provide a novel use of these compounds administered parenterally for the induction of hypothermia, especially for the preparation of a medicament comprising one or more compounds of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for the induction of hypothermia in an individual suffering from ischemia or at risk of suffering from ischemia, alternatively an individual who has an increased body temperature or faces surgery.
**Adenosine**

Adenosine is present in all body fluids and acts on four well-defined G protein-coupled receptors.

5 **Adenosine receptors**

These receptors are denoted adenosine receptors, but may also be called P1 receptors to distinguish them from the receptors for nucleotides, which belong either to the family of transmitter-gated ion channels (P2X receptors) or the family of G protein-coupled receptors (P2Y receptors). The adenosine receptors are a class of G-protein coupled receptors with adenosine as endogenous ligand. In humans, there are four adenosine receptors (A1, A2A, A2B, A3), each encoded by a separate gene (ADORAl, ADORAs, ADORA2B, and ADORA3).

The adenosine A1 receptor has been found to be ubiquitous throughout the entire body. This receptor has an inhibitory function on most of the tissues in which it rests. In the brain, it slows metabolic activity by a combination of actions. Presynaptically, it reduces vesicle release while postsynaptically it has been found to stabilize the magnesium on the NMDA receptor.

20 The A1 and A2A receptors of endogenous adenosine are both believed to play a role in regulating myocardial oxygen consumption and coronary blood flow. Stimulation of the A1 receptor has a myocardial depressant effect by decreasing the conduction of electrical impulses and suppressing pacemaker cell function, resulting in a decrease in heart rate. This makes adenosine a useful medication for treating and diagnosing tachyarrhythmias, or excessively fast heart rates. This effect on the A1 receptor also explains why there is a brief moment of cardiac standstill when adenosine is administered as a rapid IV push during cardiac resuscitation. The rapid infusion causes a momentary myocardial stunning effect.

30 In comparison, the A2A receptor is responsible for regulating myocardial blood flow by vasodilating the coronary arteries, which increases blood flow to the myocardium, but may lead to hypotension. In normal physiological states, both of these receptors serve as protective mechanisms. However, in altered cardiac function, such as hypoperfusion caused by hypotension, heart attack or cardiac arrest caused by nonperfusing bradycardias, adenosine has a negative effect on physiological functioning by
preventing necessary compensatory increases in heart rate and blood pressure that attempt to maintain cerebral perfusion.

Recent research on adenosine receptor function and adenosine receptor antagonists such as theophylline has led to several randomized controlled trials using these receptor antagonists to treat bradyasystolic arrest.

Specific antagonists include KW6002 and SCH-58261, while specific agonists include CGS21680 and ATL-146e.

The integral A2B receptor membrane protein stimulates adenylate cyclase activity in the presence of adenosine. This protein also interacts with netrin-1, which is involved in axon elongation.

The A3 adenosine receptor has been shown to inhibit some specific signal pathways of adenosine. It inhibits growth in human melanoma cells. Specific antagonists include MRS1 191, MRS1523 and MRE3008F20, while specific agonists include CI-IB-MECA and MRS3558.

**Examples of adenosine receptor agonists**

In addition to the vanilloid and cannabinoid compounds mentioned above, further compounds to be included according to the present invention are selected from adenosine or adenosine analogs, adenosine receptor agonists or an adenosine uptake inhibitors, i.e. in one embodiment, the invention relates to administration of at least one compound capable of increasing the amount of adenosine in the individual being treated.

Adenosine analogs include 5'-AMP, ATP, ADP, adenine nucleotides, as well as other substituted adenosine compounds, insofar the substituted adenosine compounds are capable of being an adenosine receptor agonist.

An adenosine receptor agonist is any compound capable of having an agonizing effect on the adenosine receptor. One example of an adenosine receptor agonist is 5'-(N-ethyl-carboxamido)-adenosine (NECA). Also included in the definition of adenosine
compounds are compounds that in structure resembles a compound capable of binding an adenosine receptor without having the ability itself.

Further compounds of the present invention include but is not limited to comprise one or more of the following compounds: 5'-AMP, (R)-PIA, (S)-PIA, AB-NECA, CCPA, CGS 21680, CGS 21680, CGS 24012, 2-chloroadenosine, 2-hexynyl-NECA, IB-MECA, N(6)-cyclopentyladenosine, (R,S)-PHPNECA, IAB-MECA, IB-MECA, CI-IB-MECA, cyclopentyladenosine, I-ABA, IAB-MECA, MCP-NECA, MPC-MECA, PENECA, AB-MECA, APNEA, CV-1674, CV-1808, cyclopentyladenosine, 2-hexynyl-NECA, metrifudil, N(6)-cyclohexyladenosine, LUF5831 and Tecadenoson (CV-510).

Thus, it is an embodiment of the present invention to administer 5'-AMP alone or in combination with other compounds of the present invention.

In another embodiment of the present invention the adenosine receptor agonist is selected from the group consisting of NECA, (R)-PIA, (S)-PIA, AB-NECA, CCPA, CGS 21680, CGS 21680, CGS 24012, 2-chloroadenosine, 2-hexynyl-NECA, IB-MECA, N(6)-cyclopentyladenosine, (R,S)-PHPNECA, IAB-MECA, IB-MECA, CI-IB-MECA, cyclopentyladenosine, I-ABA, IAB-MECA, MCP-NECA, MPC-MECA, PENECA, AB-MECA, APNEA, CV-1674, CV-1808, cyclopentyladenosine, 2-hexynyl-NECA, metrifudil, N(6)-cyclohexyladenosine, LUF5831 and Tecadenoson (CV-510).

In one embodiment the compounds of the present invention comprises the adenosine uptake inhibitor dipyridamole or theophyllin.

**Novel use of compounds**

Adenosine receptor agonists such as adenosine analogs 5'-AMP, ATP, ADP, adenine nucleotides, as well as other substituted adenosine compounds, have been used for a variety of purposes over time. It is an object of the present invention to provide a novel use of these compounds administered parenterally for the induction of hypothermia, especially for the preparation of a medicament comprising one or more compounds of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for the induction of
hypothermia in an individual suffering from ischemia or at risk of suffering from ischemia.

It follows that it is an aspect of the present invention to induce hypothermia in / reduce the temperature of an individual in need thereof by the parenteral administration of at least one adenosine receptor agonist or structurally similar compound. The individual may be in need of hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or as part of a pre-operative preparation. Preferably, the compound administered parenterally is NECA, (R)-PIA, (S)-PIA, AB-NECA, CCPA, CGS 21680, CGS 21680, CGS 24012, 2-chloroadenosine, 2-hexynyl-NECA, IB-MECA, N(6)-cyclopentyladenosine, (R,S)-PHPNECA, IAB-MECA, IB-MECA, CI-IB-MECA, cyclopentyladenosine, I-ABA, IAB-MECA, MCP-NECA, MPC-MECA, PENECA, AB-MECA, APNEA, CV-1674, CV-1808, cyclopentyladenosine, 2-hexynyl-NECA, metrifudil, N(6)-cyclohexyladenosine, LUF5831 and Tecadenoson (CV-510) and/or the phosphate derivatives of these.

**Neurotensin**

The tridecapeptide neurotensin (NT) mediates its central and peripheral effects through interaction with three identified receptor subtypes, referred to as NTS1, NTS2 and NTS3 (Sortilin 1). NTS1 and NTS2 belong to the 7 transmembrane domain/GPCR family, whereas Sortilin 1 is a single transmembrane domain receptor. The present invention relates to the effect of the NT ligand and analogues thereof through the two GPCRs NTS1 and NTS2.

Neurotensin, first isolated from bovine hypothalami by Carraway and Leeman in 1973, was also found in the intestine. Classically, NT was synthesized from a precursor that contains another peptide, Neuromedin N, closely related to NT in terms of sequence and activity. Cerebral administration of isolated NT modulates dopaminergic transmission and leads to hypothermic (WO 04/049901) and naloxone-independent analgesic responses. In the periphery, NT induces hypotension, decreases gastric acid secretion, and activates lipid digestion.

However, administration of the one or more compounds of the present invention, including NT, leads to a surprisingly improved effect of neuroprotection in connection with ischemia.
Neurotensin receptors
The existence of two distinct receptor sites for NT has been evidenced by ligand binding studies on rat brain synaptic membranes: a high affinity NT binding site later cloned as the NTS1 receptor, and a lower affinity NT binding site (sensitive to the H1 anti-histamine levocabastine); the NTS2 receptor.

Activation of NTS1 is probably responsible for the observed effects of NT on cancer cell proliferation and food intake. However, the most convincing implication of NTS1 is related to the NT-dopamine interactions in the brain. Indeed, NT modulates dopamine transmission in the nigro-striatal and mesocorticolimbic pathways through NTS1, indicating that NT analogues specifically targeting this receptor might represent a new class of antipsychotic drugs.

NTS2 has been described to be responsible for the analgesic response of centrally administered NT. This observation is enhanced by the cerebral localization of both its messenger RNA and its protein in structures implicated in the descending control of nociceptive inputs, especially in the periaqueductal gray and dorsal raphe. However, the expression of NTS2 immunoreactivity in areas devoid of neurotensinergic inputs indicates that NT might not be the exclusive endogenous ligand for NTS2.

Novel use of compounds
Neurotensin receptor agonists and analogues of neurotensin have been used for a variety of purposes over time. It is an object of the present invention to provide a novel use of these compounds administered parenterally for the induction of hypothermia, especially for the preparation of a medicament comprising one or more compounds of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally, for the induction of hypothermia in an individual suffering from ischemia or at risk of suffering from ischemia.

Neurotensin receptor agonists are generally termed such due to their ability to bind one or more of the neurotensin receptors; herein a neurotensin receptor agonist is also a
compound that in structure resembles a compound capable of binding a neurotensin receptor without having the ability itself.

Thus, in an aspect one of the compounds according to the present invention are selected from the group consisting of NT64D, NT64L, NT65L, NT66D, NT66L, NT67L, NT69L, NT71, NT72, NT73, NT74, NT75, NT76, NT77, Trp1 1NT, contulakin-G, EISAI-1, EISAI-2, JMV2004, JMV431, JMV449, JMV457, JMV458, large neuromedin, large neurotensin, neuromedin, neurotensin, neurotensin, \[^{125}\text{I}]\text{neurotensin}, \text{ThMOcontulakin-G}, \text{D-Trp1}\text{-1-neurotensin}, \text{levocabastine}, \text{SR48692}, \text{SR48692}, \text{xenin, PD-149163 and CGX-1 160}.

It follows that it is an aspect of the present invention to induce hypothermia in / reduce the temperature of an individual in need thereof by the parenteral administration of at least one cannabinoid and/or cannabimetic compound. The individual may be in need of hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or as part of a pre-operative preparation. Preferably, the compound administered parenteral\(^a\) is NT64D, NT64L, NT65L, NT66D, NT66L, NT67L, NT69L, NT71, NT72, NT73, NT74, NT75, NT76, NT77, Trp1 1NT, contulakin-G, EISAI-1, EISAI-2, JMV2004, JMV431, JMV449, JMV457, JMV458, large neuromedin, large neurotensin, neuromedin, neurotensin, \[^{125}\text{I}]\text{neurotensin}, \text{Thr10contulakin-G}, \text{D-Trp1}\text{-1-neurotensin}, \text{levocabastine}, \text{SR48692}, \text{SR48692}, \text{xenin, PD-149163 and CGX-1 160} and/or the phosphate derivatives of these.

**Thyroxine derivatives**

The thyroid hormones, thyroxine (\(T_4\)) and triiodothyronine (\(T_3\)) are tyrosine-based hormones produced by the thyroid gland. The major form of thyroid hormone in the blood is thyroxine (\(T_4\)). Thyroxine is converted to the active \(T_3\) (three to four times more potent than \(T_4\)) within cells by deiodinases (5'-iodinase). These are further processed by decarboxylation and deiodination to produce the thyronamines. Most of the thyroid hormone circulating in the blood is bound to transport proteins, such as thyroxine-binding globulin (TBG), transthyretin or "thyroxine-binding prealbumin" (TTR or TBPA), or albumin.

The thyroid hormones and their derivatives are involved in the regulation of several metabolic processes within the body. The thyroxine derivatives increase the basal
metabolic rate, affect protein synthesis and increase the body's sensitivity to catecholamines (such as adrenaline). These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. Thyroid hormone leads to heat generation in human. For example, the thyronamines function via an unknown mechanism to inhibit neuronal activity; this plays an important role in the hibernation cycles of mammals, and one effect of administering the thyronamines is a severe drop in body temperature.

Thyronamine refers both to a molecule, and to derivatives of that molecule: a family of decarboxylated and deiodinated metabolites of the thyroid hormones thyroxine (T4) and 3,5,3'-triiodothyronine (T3). The group includes apart from the above: Thyronamine (TOAM); 3-Iodothyronamine (T1AM), 3,5-Diiodothyronamine (T2AM); 3,5,3'-Triiodothyronamine (T3AM). Herein the term thyroxine derivatives includes both the thyroid hormones and their derivates; thyronamines and compounds that in structure resemble either the thyroid hormones, their derivatives or the thyronamines. Thus in an aspect of the present invention at least one of the two or more compounds of the present invention are selected from the group consisting of, but not limited to: thyroxine, 3,5,3'-triiodothyronine, thyronamine; 3-Iodothyronamine; 3,5-Diiodothyronamine; and 3,5,3'-Triiodothyronamine.

**Thyroxine derivative receptors**

T₃ and T₄ cross the cell membrane, probably via amino acid importins, and function via a well-studied set of nuclear receptors in the nucleus of the cell, the thyroid hormone receptors. T₁α and T₀α are positively charged and do not cross the membrane; they are believed to function via the trace amine-associated receptor TAAR1 (TAR1, TA1), a G-protein-coupled receptor located in the cell membrane.

The thyroid hormone receptor (TR) is a type of nuclear receptor that is activated by binding thyroid hormone. There are three forms of the thyroid hormone receptor designated alpha-1, beta-1 and beta-2 that are able to bind thyroid hormone. There are two TR-alpha receptor splice variants encoded by the THRA gene and two TR-beta isoform splice variants encoded by the THRβ gene: TR-α1 (widely expressed and especially high expression in cardiac and skeletal muscles); TR-α2 (homologous with viral oncogen c-erb-A, also widely expressed but unable to bind hormone); TR-β1
(predominately expressed in brain, liver and kidney); TR-β2 (expression primarily limited to the hypothalamus and pituitary).

According to the present invention, the term ‘thyroxine derivative receptor’ may refer to any receptor capable of binding of the thyroid hormones or their derivates such as thyronamines.

**Novel use of compounds**

Thyroxine derivatives have been used for a variety of purposes over time. It is an object of the present invention to provide a novel use of these compounds administered parenterally for the induction of hypothermia, especially for the preparation of a medicament comprising one or more compounds of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for the induction of hypothermia in an individual suffering from ischemia or at risk of suffering from ischemia.

It is thus an aspect of the present invention to induce hypothermia in / reduce the temperature of an individual in need thereof by the parenteral administration of at least one cannabinoid and/or cannabimetic compound. The individual may be in need of hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or as part of a pre-operative preparation. Preferably, the compound administered parenterally is thyroxine, 3,5,3'-triiodothyronine, thyronamine; 3-Iodothyronamine; 3,5-Diiodothyronamine; and 3,5,3'-triiodothyronamine and/or the phosphate derivatives of these.

**Cytochrome c oxidase inhibitors**

The enzyme cytochrome c oxidase or Complex IV is a large transmembrane protein complex found in bacteria and the mitochondrion. It is the last enzyme in the respiratory electron transport chain of mitochondria (or bacteria) located in the mitochondrial (or bacterial) membrane. It receives an electron from each of four cytochrome c molecules, and transfers them to one oxygen molecule, thereby converting molecular oxygen to two molecules of water. In the process, it binds four protons from the inner aqueous phase to make water, and in addition translocates four
protons across the membrane, helping to establish a transmembrane difference of  
proton electrochemical potential that the ATP synthase then uses to synthesize ATP.  

Several compounds have been found to bind to cytochrome c oxidase, which is very  
important for metabolism. By interfering with the function of cytochrome c oxidase the  
cellular and ultimately bodily metabolic rate is slowed causing among other things a  
reduction of body temperature / induction of hypothermia.  

Compounds that fall into this category are objects of the present invention and include,  
but are not limited to: H₂S (hydrogen sulfide); cyanide (CN) or its derivates such as  
hydrogen cyanide (HCN) or sodium nitroprusside (Na₂[Fe(CN)₅NO]-2H₂O); Azide and  
its derivates; Carbon monoxide (CO); and/or Sodium sulfide (Na₂S). Thus these  
compounds may be used alone or in combination with one or more of any of the other  
herein mentioned compounds.  

Novel use of compounds  
Cytochrome c oxidase inhibitors have been used for a variety of purposes over time. It  
is an object of the present invention to provide a novel use of these compounds  
administered parenterally for the induction of hypothermia, especially for the  
preparation of a medicament comprising one or more compounds of the group  
consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic  
compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists  
and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen  
tension reducers to be administered parenterally for the induction of hypothermia in an  
individual suffering from ischemia or at risk of suffering from ischemia.  

Therefore it is an aspect of the present invention to induce hypothermia in / reduce the  
temperature of an individual in need thereof by the parenteral administration of at least  
one cannabinoid and/or cannabimimetic compound. The individual may be in need of  
hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or  
as part of a pre-operative preparation. Preferably, the compound administered  
parenterally is H₂S (hydrogen sulfide); cyanide (CN) or its derivates such as hydrogen  
cyanide (HCN) or sodium nitroprusside (Na₂[Fe(CN)₅NO]-2H₂O); Azide and its  
derivates; Carbon monoxide (CO); and/or Sodium sulfide (Na₂S).  

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**Oxygen tension reducers**

Reducing the concentration of oxygen around or within the body has the effect on several organisms, that it sends them into a state of suspended animation / hibernation with reduced core body temperatures as one consequence thereof. Several compounds are capable of inhibiting the oxygen utilization of the body and thereby mimic lack of oxygen in the environment / body. These compounds are thus able to induce hypothermia and are objects of the present invention. These compounds, some of which also fall into the category of being cytochrome c oxides inhibitors, include, but are not limited to: Carbon monoxide (CO), Sodium sulfide (Na$_2$S) and hydrogen sulfide (H$_2$S). Any oxygen tension reducer may be used in combination with any of the herein mention compounds or in any combination of several of these.

Hemoglobin (Hb), an intracellular protein of erythrocytes, is the primary vehicle for transporting oxygen in the blood. Each Hb molecule has a limited capacity for holding oxygen molecules; how much of that capacity is filled by oxygen is called the oxygen saturation (SO$_2$).

The amount of oxygen bound to the hemoglobin at any time is related, in large part, to the partial pressure of oxygen to which the Hb is exposed (PO$_2$). In the lungs, at the alveolar-capillary interface, the partial pressure of oxygen is typically high, and therefore the oxygen binds readily to Hb. As the blood circulates to other body tissue in which the partial pressure of oxygen is less, the Hb releases the oxygen into the tissue.

The effectiveness of hemoglobin-oxygen binding can be affected by several factors; an increase in the affinity of Hb for oxygen (easier to bind but harder to release oxygen) is caused by decreased temperature, 2,3-DGP or PCO2 or an increase in pH.

Oxygen saturation may be measured directly via a blood sample (ex vivo) or via a non-invasive pulse oximeter, which is a medical device that indirectly measures the oxygen saturation of a patient's blood. A blood-oxygen monitor displays the percentage of arterial hemoglobin in the oxyhemoglobin configuration. Acceptable normal ranges are from 95 to 100 percent, although values down to 90% are common.

**Novel use of compounds**

Oxygen tension reducers have been used for a variety of purposes over time. It is an object of the present invention to provide a novel use of these compounds.
administered parenterally for the induction of hypothermia, especially for the preparation of a medicament comprising one or more compounds of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for the induction of hypothermia in an individual suffering from ischemia or at risk of suffering from ischemia.

It is an aspect of the present invention to induce hypothermia in / reduce the temperature of an individual in need thereof by the parenteral administration of at least one cannabinoid and/or cannabimimetic compound. The individual may be in need of hypothermic / temperature reducing treatment due to ischemia, fever, hyperthermia or as part of a pre-operative preparation. Preferably, the compound administered parenterally is Carbon monoxide (CO), Sodium sulfide (Na$_2$S) and hydrogen sulfide (H$_2$S).

**Medicament**

The induction of hypothermia by any compound or combination of the herein described compounds is performed by preparing, producing and thus providing a medicament or pharmaceutical composition comprising at least one compound of the group consisting of vanilloid receptor agonists and/or cannabinoids or cannabimimetic compounds and/or adenosine receptor agonists and/or neurotensin receptor agonists and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for the induction of hypothermia in an individual in need thereof for the treatment and/or prophylaxis of ischemia in said individual.

It is therefore an aspect of the present invention to provide a medicament for parenteral administration comprising at least one compound capable of inducing hypothermia in an individual in need thereof.

It is understood that parenteral administration according to the present invention may comprise intravenous, intramuscular or subcutaneous administration, including intravenous infusion, and may be administered continuously or by one or more boluses.
It is a further aspect of the present invention to provide a medicament for parenteral administration comprising at least one compound capable of inducing hypothermia in an individual in need thereof for prophylactic and/or therapeutic applications.

It is also an aspect of the present invention to provide a medicament for parenteral administration comprising at least one compound capable of inducing hypothermia in an individual in need thereof of between 32 and 36 degree Celsius.

It is also a further aspect of the present invention to provide a medicament for parenteral administration comprising at least one compound wherein at least one compound induces hypothermia rapidly.

In another aspect the present invention provides a medicament for parenteral administration comprising at least one compound wherein at least one compound induces hypothermia slowly.

In a further aspect the present invention provides a medicament for parenteral administration comprising at least one compound and a further active ingredient selected from the group of: analgesics, opioids, GABAs and adrenergic antagonists.

Combination treatment
The use of at least one compound comprises the use of one compound, such as two, for example three, such as four, for example five, such as six, for example seven compounds according to the present invention.

Thus, in one embodiment the at least one compound is one compound, and in another embodiment the at least one compound is a combination of two or more compounds.

It is therefore an embodiment of the present invention to provide a medicament comprising one or more of a vanilloid receptor agonists and/or CB1 and CB2 receptor agonists and/or cannabinoids and/or cannabinoid mimetics compounds and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to be administered parenterally for the induction of hypothermia. The
compounds are to be administered together or separately, each at its most effective dosage.

In one embodiment, a vanilloid receptor agonist is administered parenterally together with one or more of the following compounds: cannabinoids and/or cannabimimetic compounds and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to induce hypothermia.

In another embodiment, a cannabinoid and/or cannabimimetic compound is administered parenterally together with one or more of the following compounds: vanilloid receptor agonists and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to induce hypothermia.

It follows that in one embodiment, the cannabinoid or cannabimimetic compounds used in combination therapy may be selected from anandamide, delta-9-THC, delta-8-THC, cannabidiol, HU-210, KN38-7271 (BAY 38-7271), WIN 55,212 and CP55940 and the phosphate derivatives of these; while the vanilloid receptor agonists used in combination therapy may be selected from Capsaicin and compounds closely related to capsaicin such as: Dihydrocapsaicin (DHC), Nordihydro-capsaicin (NDHC), Homodihydro-capsaicin (HDHC), Homocapsaicin, resiniferatoxin and compounds closely related hereto.

It is also an embodiment of the present invention to provide a medicament comprising a combination of a vanilloid and a cannabinoid compound to be administered parenterally for the induction of hypothermia. The compounds are to be administered together or separately, each at its most effective dosage. The combination of compounds according to the present invention to be administered parenterally for induction of hypothermia may therefore comprise dihydrocapsaicin and delta-8-THC and delta-8-THC-phosphate or dihydrocapsaicin and HU-210.

In another embodiment the use is with the proviso that if the combination comprises two compounds, said two compounds are not vanilloid receptor agonists and cannabinoids or vanilloid receptor agonists and cannabimimetic compounds.
Feedback treatment regime

Induction of hypothermia and/or reduction of body temperature are procedures that should be approached with care as the thermo-tolerance of especially warm-blooded individuals such as mammals is restricted.

It is therefore an aspect of the present invention to provide a feedback system which in effect has three purposes:

1. It will enable the maintenance of the target temperature within a narrow interval.
2. It will increase the efficacy of the medicaments / compounds.
3. It will reduce the risk of unwanted side-effects.

A feedback system may be based on the administration of a medicament / compound according to a measured temperature of the individual receiving the treatment, or according to metabolic rate of the individual receiving the treatment i.e. oxygen consumption or other. For example, an individual undergoing treatment as herein disclosed may be constantly or intermittently monitored in regards to body temperature and or metabolic rate and the dosage of the medicament administered may be varied in accordance herewith. This feedback system may be automated or conducted manually.

Pharmaceutical composition

Whilst it is possible for the compounds or salts of the present invention to be administered as the raw chemical, it is preferred to present them in the form of a pharmaceutical formulation. Accordingly, the present invention further provides a pharmaceutical formulation, for medicinal application, which comprises one or a combination of compounds of the present invention or pharmaceutically acceptable salts thereof, as herein defined, and a pharmaceutically acceptable carrier therefore.

Pharmaceutical compositions containing one or more compounds of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pa.
The one or more compounds of the present invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or non-aqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive or coconut oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents, colorants, buffers, thickeners, solubilizing agents and the like. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

A stated above, there are two different kinds of IV fluids: crystalloids and colloids. Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules. Colloids contain larger insoluble molecules, such as gelatin. Examples of crystalloid IV fluids that may be used in combination with the compounds of the present invention include, but are not limited to: Saline (0.9%) (Normal saline); Half normal saline, Dextrose 4% / Saline 0.18%, Dextrose 5% (D5W), 3.3% Dextrose / 0.3% Saline (2/3D & 1/3S), Hartmann's, Bicarbonate 8.4%; and Ringer's lactate. Examples of colloid IV fluids that may be used in combination with the compounds of the present invention include, but are not limited to: Haemaccel; Gelofusine; Pentastarch; Hetastarches and Albumin 4.5%; Tween 80 or any Tween solution. Furthermore, the compounds of the present invention may be added to blood products such as whole blood, plasma, fresh frozen plasma, plasma protein fractions and various concentrates such as concentrates prepared for factor VIII deficiency (hemophilia) or other.

Oils useful in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils useful in such formulations include coconut, peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Oils of any kind that may be used for parenteral administration, and preferably for IV, IM, SC,
IP or other forms of injectable administration forms are aspects of the present invention.

Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides; (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulphates, and sulfosuccinates, (c) non-ionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

The parenteral formulations typically will contain from about 0.5 to about 25% by weight of the active ingredient in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more non-ionic surfactants having a hydrophilic - lipophilic balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

Thus, in one embodiment the medicament of the present invention comprises a pharmaceutically acceptable carrier.

**Pharmaceutically acceptable salts**
Pharmaceutically acceptable salts of the instant compounds, where they can be prepared, are also intended to be covered by this invention. These salts will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant
that the salt will retain the biological activity of the parent compound and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

Pharmaceutically acceptable salts are prepared in a standard manner. If the parent compound is a base it is treated with an excess of an organic or inorganic acid in a suitable solvent. If the parent compound is an acid, it is treated with an inorganic or organic base in a suitable solvent.

The combination of compounds of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by topical, enteral or parenteral route, in an effective amount.

A pharmaceutically acceptable salt means any salt of the compounds mentioned. In particular, it means a pharmaceutically acceptable acid addition salt. Pharmaceutically acceptable acid addition salts of the compounds include salts derived from non-toxic inorganic acids such as hydrochloric, nitric, phosphoric, sulphuric, hydrobromic, hydriodic, hydrofluoric, phosphorous and the like, as well as the salts derived from non-toxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanediioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulphate, pyrosulphate, bisulphate, sulphite, bisulphite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like.

Further active ingredient
An embodiment of the present invention is a pharmaceutical composition comprising a compound or a combination of compounds as herein described to induce hypothermia and furthermore comprising a further active ingredient. The further active ingredient may be administered simultaneously or sequentially with the compounds according to
the present invention. The further active ingredient may increase the hypothermic effect of the combination of compounds of the invention, or may have an alternative medical effect such as inducing pain relief or vasodilation.

5 The further active ingredient may thus be selected from the non-limiting group of: analgesics, opioids, antipyretics, GABAs and adrenergic antagonists.

The further active ingredient may thus be an antipyretic. Antipyretics are drugs that reduce body temperature in situations such as fever; however, they will not affect the normal body temperature if one does not have fever. Antipyretics cause the hypothalamus to override an interleukin-induced increase in temperature. The body will then work to lower the temperature and the result is a reduction in fever. It is an object of the present invention to induce hypothermia in an individual. To prevent a possible overshoot in the body's attempt to regain its normal temperature at the completion of the hypothermia-inducing treatment, an antipyretic may be provided in combination with the compounds of the present invention.

There are at least 3 classes of antipyretic medications all of which are of relevance to the present invention, that include, but are not limited to: (1) Salicylates - aspirin (acetylsalicylic acid), choline salicylate (Arthropan), magnesium salicylate (Arthriten), and sodium salicylate (Scot-Tussin Original); (2) Acetaminophen / Paracetamol (Panodil / Tylenol); and (3) Nonsteroidal anti-inflammatory drugs (NSAIDs) - ibuprofen (Advil), naproxen (Naprosyn, Aleve), and ketoprofen.

It is an aspect of the present invention to provide a medicament for parenteral administration comprising one or more vanilloid receptor agonists and/or cannabinoids and/or cannabimimetic compounds and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers which may be formulated and/or administered together with an antipyretic drug simultaneously or sequentially.

The further active ingredient may also be an analgesic (or painkiller). Some drugs that are antipyretics will also have an analgesic effect, and thus there will be an overlap between these two groups. Analgesics are a diverse group of drugs that relieve pain.
Analgesic drugs act in various ways on the peripheral and central nervous systems and include paracetamol (acetaminophen); the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates - aspirin, ibuprofen, naproxen; opioids such as morphine, codeine, oxycodone, hydrocodone, diamorphine, pethidine; synthetic drugs with opioid properties such as tramadol and buprenorphine; and various others. Desflurane and desflurane both of which are analgesics may also be administered especially for the purpose of reducing shivering as the individual to whom the compounds of the present invention are administered is brought down in temperature. It is especially relevant to use analgesics when inducing actual hypothermia e.g. temperatures below normal.

pH
An aspect of the present invention regards the pH of the medicament. The pH of the medicament depends on the administration form, as the pH of the medicament preferably is suitable for the route of administration chosen. An embodiment of the present invention comprises a medicament wherein the pH of the composition is between pH 5 and pH 9, such as between pH 5.5 and 8.5 such as between pH 6 and 8, such as between pH 6.5 and 7.5. Most preferably the pH of the medicament is in accordance with the route of administration and the tissue to which the medicament is administered.

Thus, in an embodiment the present invention provides a composition comprising a compound or a combination of compounds for parenteral administration to induce hypothermia, wherein the pH of the composition is between pH 5 and pH 9.

Indications
The invention provides for one or more compounds for the production of a medicament for the treatment of ischemia in an individual by parenteral administration. Ischemia may arise due to various circumstances and thus it is an object of the present invention to treat ischemia arising from a plurality of medical indications.

These indications include, but are not limited to, cardiovascular diseases such as myocardial infarction, cardiac arrest, stroke, arterial aneurism, subarachnoid hemorrhage, arteriosclerosis, angina pectoris, hypertension, hypercholesterolemia, cardiac arrhythmia, cardiomegaly, cardiomyopathy, heart valve regurgitation and heart
valve stenosis, perinatal asphyxia and non-perinatal asphyxia as well as traumatic brain injury.

Thus, it is an aspect of the present invention to provide one or more compounds for parenteral administration for the induction of hypothermia in an individual suffering from or at risk of suffering from ischemia.

Individuals at risk of suffering from ischemia are often individuals who have previously suffered from an event that was capable of or did induce ischemia such as a heart attack, stroke or other. These individuals may benefit from having rapid access to pills, capsules, ampoules, pre-loaded syringes, suppositories or other administration forms of the medicaments of the present invention for self-administration. It is envisioned that these individuals at the onslaught of a new ischemic attack self-administer a dose of the compounds of the present invention prior to receiving medical aid by medical professionals. This is of relevance, as the faster the temperature drops, the better the chances of reducing the detrimental effects of the ischemic attack.

It is also an aspect of the present invention to provide one or more compounds for parenteral administration for the prophylaxis and/or treatment of ischemia in connection with cardiovascular diseases, asphyxia and/or traumatic brain injuries.

In a preferred embodiment one or more compounds of the present invention are used alone or in combination to treat adverse effects of ischemia in the kidney.

It is also an aspect of the present invention to provide prophylaxis and/or treatment of ischemia or tissue damaging effects occurring during or after ischemia in the kidney or nephroischemia.

In one embodiment, the present invention provides one or more compounds for parenteral administration to induce hypothermia for treating the effects of ischemia, wherein the ischemia is due to cardiovascular diseases such as myocardial infarction, cardiac arrest, stroke, arterial aneurism, subarachnoid hemorrhage, arteriosclerosis, angina pectoris, hypertension, hypercholesterolemia, cardiac arrhythmia, cardiomegaly, cardiomyopathy, heart valve regurgitation and heart valve stenosis.
Another group of indications are the situations where an individual has an increased body temperature such as fever, hyperpyrexia, hyperthermia or other. It is an aspect of the present invention to provide one or more compounds and or medicaments for the purpose of inducing hypothermia and/or lowering the body temperature of these individuals.

It is furthermore an aspect of the present invention to provide means for selectively inducing hypothermia in either the brain or the body or both simultaneously. This is of relevance, as a severe stroke is known to cause an increase in brain temperature, often subsequently followed by an increase in body temperature. Thus it is an aspect of the present invention to induce hypothermia in the brain, by parenteral administration of the compounds of the invention, just as it is an aspect of the present invention to induce hypothermia in the body without, as far as it is physically possible, inducing hypothermia in the brain. Likewise it is as often stated herein an aspect of the present invention to induce hypothermia and/or lower the body temperature of an individual in need thereof.

In a further embodiment, the present invention provides a combination of compounds for treating effects of ischemia, wherein the ischemia is due to asphyxia such as: perinatal asphyxia, perinatal asphyxia and/or non-perinatal asphyxia.

**Target temperature and peak effect**

The target temperature of the medicament is the core body temperature that can be reached upon administering the medicament according to the present invention as prescribed according to potency, dosage and so on. Various ranges and specific hypothermic / reduced core body temperatures that fall within the scope of the present invention are equal to the temperatures that the combinations of compounds themselves may induce as listed in the section on hypothermia.

An embodiment of the present invention is thus a medicament administered parenterally capable of inducing hypothermia below 36 °C, such as below 35.5 °C, such as below 35 °C, such as below 34.5 °C, such as below 34.0 °C in the range of between 36 to 32 degree Celsius, and more preferably between 35 and 33 degree Celsius.
Another embodiment is the reduction of body temperature from an elevated temperature to a specific temperature such as 39 degree Celsius, 38.5 degree Celsius, 38 degree Celsius, 37.5 degree Celsius, 37 degree Celsius, 36.5 degree Celsius, 36 degree Celsius, 35.5 degree Celsius, 35 degree Celsius, or most preferably, the compound or combination of compounds of the present invention is capable of inducing hypothermia to any of the above specific temperatures within a range of +/- 0.5 degree Celsius, the range thus being between +/- 0.4 degree Celsius, such as between +/- 0.3 degree Celsius, such as between +/- 0.2 degree Celsius, or such as between +/- 0.1 degree Celsius. The temperature range or specific temperature a given compound or combination of compounds is capable of inducing is herein also referred to as the target temperature of the compound or the combination of compounds and/or the medicament comprising the compound or the combination of compounds.

The use of one or more compounds of this invention will often show a peak in hypothermia-inducing effect 30 minutes to 120 minutes after administration, but may potentially peak sooner or later than described by this interval. The hypothermia inducing effect will frequently last from 1 hour to 12 hours, but may potentially last shorter or longer than described by this interval.

It is an object of the present invention to provide medicaments suitable for a quick induction of hypothermia which may be of long or short duration and medicaments suitable for a slow reduction in core body temperature which may be of long or short duration.

It is an aspect of the present invention that the compounds / medicaments / treatments herein may be given while the individual receiving the treatment is surrounded by any given temperature. In other words, the temperature of the surroundings, especially the room in which the individual resides, is not of relevance to the treatment. The treatment will reduce the temperature of the individual and/or induce hypothermia whether the room temperature is ambient, high or low such as at any temperature between 5 and 45 degree Celsius.

Individual

The individual that may benefit from the parenteral administration of a medicament as described herein to induce hypothermia may be an individual in need thereof. This
individual may be in need of said treatment as the individual is suffering from ischemia or at risk of suffering from ischemia. Also, the individual may have an elevated body temperature and may be in need of a reduction hereof; alternatively the medicaments of the present invention may be given pre-operatively to lower the body temperature of the individual prior to and/or during surgery. Being in need of treatment thus indicates that the health of the individual is benefitted by the administration of the at least one compound of the present invention.

The individual may be any human being, male or female, infant or old. The ischemic condition and/or elevated temperature to be treated or prevented and/or the need for surgery in the individual may relate to the age of the individual, the general health of the individual and whether or not the individual has a prior history of suffering from diseases or disorders that may have or have induced ischemic conditions and/or elevated temperatures in the individual.

Kit of parts
Another embodiment of the present invention comprises a kit of parts, wherein the kit includes at least one pharmaceutical composition according to any of the above, a means for administering said composition and the instruction(s) on how to do so. It is within the scope of the present invention to include multiple dosages of the same composition or several different compositions. In a preferred embodiment the kit of parts further comprises a further active ingredient.

One kit may be specifically targeted to persons at risk of suffering from ischemic attacks, such that the kit, apart from instructions, comprises pharmaceutical forms of the medicaments that allow self administration of the medicaments and devices with which to administer the medicaments.

An alternative embodiment is an ambulance kit that facilitates the administration of the medicaments of the present invention in a manner most efficient for the rescue personnel. Such a kit may comprise medicaments for bolus injections / and IV bags comprising the medicament in an IV fluid for subsequent follow-up treatment / induction of hypothermia / reduction of temperature.
**Detailed description of figures**

**Figure 1:** Plot of temperature curves from Day 2 of Example 14.

**Figure 2:** Plot of diastolic blood pressure against time relative to injection for from Day 2 of Example 14.

**Figure 3:** Plot of temperature curves of Example 18; study 1. Dihydrocapsaicin is administered into calves by intravenous infusion at a dosage of 1 mg/kg/h for 12 hours. The resulting temperature difference from baseline is measured at t = -1 until t = 24h.

**Figure 4:** Plot of temperature curves of Example 18; study 2. Dihydrocapsaicin is administered into calves by intravenous infusion at a dosage of 0.6 mg/kg/h for 4 hours. The resulting temperature difference from baseline is measured at t = -1 until t = 24h.

**Figure 5:** Plot of temperature curves of Example 18; study 3. Dihydrocapsaicin is administered into calves by single intramuscular bolus injection at doses of 0.5, 1.0 or 2.0 mg/kg. The resulting temperature difference from baseline is measured at t = -1 until t = 24h.

**Figure 6:** Plot of temperature curves of Example 18; study 4. Delta-8-THC phosphate is administered into calves by single intravenous bolus injection at a dosage of 20 mg/kg. The resulting temperature difference from baseline is measured at t = -1 until t = 24h.

**Figure 7:** Plot of temperature curves of Example 18; study 5. HU-210 is administered into calves by single intravenous bolus injection at doses of 20, 30 or 40 µg/kg. The resulting temperature difference from baseline is measured at t = -1 until t = 24h.

**Figure 8:** Controlled normalization of temperature in Example 19. A total of 4 calves receives ongoing IV infusions of Dihydrocapsaicin (0.6 mg/kg body weight) for 5 hours and experience a reduction in body temperature of between approx. 3.5 to 4.5 degrees Celsius. At the end of the hypothermia period, the infusion is brought to a sudden stop in 2 of the calves (Temp 2198' and Temp 1718'), or the infusion is gradually slowed down in 2 of the calves (Temp 2254' and Temp 2389'). The first group (sudden infusion stop) reaches normothermia in about 60 minutes after infusion stop, whereas the second group (gradual slowing down of infusion) reaches normothermia in about 210 minutes.
Examples

Example 1 - Cardiac arrest

A 57-year-old woman is taken care of by the ambulance staff that finds her in ventricular fibrillation approximately 5 minutes after having collapsed without warning. The patient is immediately defibrillated and spontaneous circulation and ventilations occurred. On arrival to the hospital, 21 minutes after having collapsed, the patient has a palpable pulse. Staff at the emergency room has been alerted in advance. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist, administered via a peripheral IV line connected to an infusion pump.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

Example 2 - Cardiac arrest

A 22-year-old male athlete collapses when doing sports. Medical staff finds ventricular fibrillation/ventricular tachycardia approximately 6 minutes after collapse. He is successfully defibrillated and the patient is rushed to the hospital. In the ambulance, the physician present in the ambulance team decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.
Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous infusion or injection of a vanilloid agonist as described in this invention. The dose will likely be in the interval 0.01 mg/kg/h to 80 mg/kg/h.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

**Example 3 - Cardiac arrest**

A 66-year-old man is undergoing elective heart surgery. He suffers from irregular cardiac rhythm during the procedure and goes into cardiac arrest with much impaired circulation for 6 minutes after which the surgical team manages to restore circulation. Subsequent to restoration of circulation, the surgeon in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

Hypothermia therapy is initiated as described in this invention. Two compounds are administered simultaneously or in succession at intervals of 1-6 hours:

1. An intravenous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist, administered continuously via a central venous catheter connected to an infusion pump, and

2. An intramuscular injection of a vanilloid agonist as described in this invention. The dose will likely be in the interval 0.01 mg/kg to 80 mg/kg.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).
At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

Example 4 - Cardiac arrest
An electrician accidentally receives a high-voltage jolt and immediately slips into a coma. The company physician manages to resuscitate the cardiac arrest patient after just 7 minutes. The patient is rushed to hospital where the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight) or delta-8-THC phosphate (e.g. 40 mg/kg body weight) or a third cannabinoid agonist, administered via a peripheral IV line connected to an infusion pump

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

Example 5 - Perinatal asphyxia
A newborn baby suffers cerebral ischemia during delivery as the umbilical cord gets wrapped around his neck. The APGAR score 10 minutes after delivery is 6. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

Hypothermia therapy is initiated as described in this invention. One compound is administered:
An intravenous intermittent infusion of a vanilloid agonist as described in this invention. The dose will likely be in the interval 0.01 mg/kg/h to 80 mg/kg/h, administered via a peripheral IV line.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

Example 6 - Asphyxia
A 9-year-old boy is in a coma when he is rescued out of a burning house. CPR is commenced on the spot but he is not awake when the ambulance arrives at hospital after a 15 minutes drive. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain and other tissues.

Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist, administered via a peripheral IV line connected to an infusion pump

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.
Example 7 - Stroke
A 72-year-old is brought to hospital 1 hour and 30 minutes after waking up with the entire right side of his body feeling numb and weak. The patient is evaluated in the neurology department and the physician in charge decides, suspecting a stroke, that the patient shall receive hypothermia therapy immediately to lessen damage to the brain. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight) or delta-8-THC phosphate (e.g. 40 mg/kg body weight) is administered via a peripheral IV line connected to an infusion pump.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12 to 24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such treatments and examinations proceed uninterrupted.

Example 8 - Stroke
A 78-year-old woman is admitted to hospital 50 minutes after experiencing sudden onset lack of mobility of the left arm and leg and as well and difficulties speaking. The patient is diagnosed with a stroke. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

Hypothermia therapy is initiated as described in this invention. Two compounds are administered simultaneously or in succession:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist, and

2. An intravenous continuous infusion of a vanilloid agonist as described in this invention. The dose will likely be in the interval 0.01 mg/kg to 80 mg/kg/h.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).
At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

**Example 9 - Stroke**
A 29-year-old man suffers continuous pains in the back of his head for two weeks after which he suddenly collapses and slips into a coma. The patient is diagnosed with a stroke. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist, administered via a peripheral IV line connected to an infusion pump.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

**Example 10 - Myocardial infarction**
A 48-year-old man is brought to hospital 35 minutes after experiencing sudden severe chest pain, shortness of breath, and very unpleasant palpitations. Staff at the emergency room is alerted in advance. The patient is evaluated and the cardiologist in charge decides that the patient shall receive hypothermia therapy immediately to lessen damage to the heart and other tissues. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight) or delta-8-THC phosphate (e.g. 40 mg/kg body weight) is administered.
The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12 to 24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such treatments and examinations proceed uninterrupted.

**Example 11 - Myocardial infarction**

A 55-year-old man is admitted to hospital 18 minutes after experiencing nausea, shortness of breath, and severe chest pains. The patient who is suffering myocardial infarction is evaluated by the physician in charge who decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the heart and other tissues.

Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of a vanilloid agonist as described in this invention. The dose will likely be in the interval 0.01 mg/kg/h to 80 mg/kg/h.

The purpose of hypothermia therapy is to lower the patient's core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

**Example 12 - Traumatic brain injury**

A 41-year-old man receives a severe blow to the head from a falling brick on a construction site. The patient is still unconscious when he 24 minutes after the trauma is brought to the Emergency Room. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.
Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist administered via a peripheral IV line.

The purpose of hypothermia therapy is to lower the patient’s core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

**Example 13 - Pulmonary embolism**

A 60-year-old woman is feeling rather well two days after major surgery when she suddenly slips into a coma. Following acute surgery, brought on by a pulmonary embolism, she is stabilized. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain and other tissues.

Hypothermia therapy is initiated as described in this invention. One compound is administered:

1. An intravenous continuous infusion of HU-210 (e.g. 100 microgram/kg body weight/hour) or delta-8-THC phosphate (e.g. 40 mg/kg body weight/hour) or a third cannabinoid agonist, administered continuously via a central venous catheter.

The purpose of hypothermia therapy is to lower the patient’s core body temperature to 32-34 degrees Celsius for 12-24 hours (current American Heart Association recommendation).
At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.

**Example 14 - Modified pyrogenicity test on rabbits**

Each compound or combination of compounds in a low, medium and high dose(s) will be screened initially on 3 rabbits. Temperature, blood pressure, pulse will be measured for 72 hours following administration of active substances. These parameters will be recorded as follows:

- Continuous recording (time=0-3h),
- every 30 minutes (time=3-6h),
- every 1 hour (time=6-12h),
- every 2 hours (time=12-24h),
- every 6 hours (time=24-48h),
- every 12 hours (time=48-72h)

These are the specifics of the initial screening:

Type of rabbits: New Zealand White, Charles River

Weight: >1.5 kg

Gender: Female

Room temperature: 21°C (+/- 1°C)

Relative humidity: 55% (+/- 5%)

Type of temperature probe: PC Based pyrogen testing system, Ellab APT 91

Cage type: Pro Plast Noryl, 2475 cm²

Number of rabbits in a cage: 1

Water and food access: Ad lib in cage.

12-hour light period: Yes

**Example 15 - Receptor studies**

Modulation of CB and TRPV1 activities will be assessed *in vitro* by measuring cannabinoid and/or cannabimimetic compound and vanilloid receptor agonist induced Ca²⁺ flux, respectively. This will be done using FLIPR and HEK293 cells stably expressing recombinant human (h) and rat (r) TRPV1 (hTRPV1-HEK293 and rTRPV1-HEK293, respectively) and recombinant human (h) and rat (r) CB receptors (hCB1-HEK293, hCB2-H293, rCB1-HEK293 and rCB2-H293) and especially in cells co-expressing human or rat TRPV1 and CB receptors (hTRPV1-hCB1-HEK293 and hTRPV1-hCB2-HEK293). Intracellular Ca²⁺ levels will be measured in CB, TRPV1 and
coCB/TRPVI-expressing cells during exposure to compounds and combinations of compounds. A concentration dependent increase in Ca2+ influx will be observed. The efficacy of vanilloid agonists will be estimated by comparing these to the maximum response induced by capsaicin, likewise the efficacy of cannabinoids will be estimated by comparing these to the maximum response induced by cannabidiol. A combination of capsaicin and cannabidiol will be used as reference for measuring combinations of drugs.

Example 16 - Bovine study model

In order to evaluate an effective hypothermic dose of a receptor agonist compound according to the invention, the compound(s) are tested in the bovine study model. The bovine model is used because the body weight of the calves is comparable to the body weight of humans. The efficacy of a compound tested in the bovine study model may be correlated with the efficacy of the cannabinoid and/or vanilloid compound tested in the same bovine study model. Calves in the weight target range from 65 to 95 kilo are of primary interest. Calves of higher weight are not be comparable to overweight/obese humans since their weight gain does not arise from increased amount of fatty tissue, but on the contrary from a larger muscle percentage.

Study subjects

Fifteen male Danish Holstein calves were moved to an intensive research barn. The calves were kept separated from other cattle throughout the trial. The insulated barn had 4 separate rooms (sections) each with 4 pens and no windows. A 16 hour light and 8 hour dark program was imposed. Each pen was equipped with a rubber mattress and further bedded with sawdust. Pens were cleaned daily and new sawdust added. Calves were loose housed, but each day around milk-feeding calves were tied for 1 hour to get accustomed to the experimental sampling situation, where calves had to be tied due to the fitted cords from the probes and catheters (see below). Rooms were automatically heated and ventilated and temperatures were set at 20°C. Real time recordings of room temperature and humidity were performed. The calves were kept in the intensive barn for 29 days before the experimental sampling periods were initiated. At an age of app. 50 days (body weight 75 to 85 kg) calves are assigned to the sections of four and injected with test compound. Body temperature, arterial blood pressure, and heart rate are monitored 60 min prior to injection and during 24 h following injection.
During the pre-trial period all calves received surgery. Calves were surgically implanted with permanent indwelling catheters in the right jugular vein and right carotid artery under total anesthesia prior to the experimental sampling periods.

Four of the calves were used to test the sampling procedure, blood pressure probes, equipment and the recording of data without receiving test compound or vehicle.

Table 1. Birth weight and age and weights of calves when entering and finishing the pre-trial period.

<table>
<thead>
<tr>
<th>Calf</th>
<th>Weight at birth (kg)</th>
<th>Age when entering pre-trial period (days)</th>
<th>Weight when entering pre-trial period (kg)</th>
<th>Age when finishing pre-trial period (days)</th>
<th>Weight when finishing pre-trial period (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6086</td>
<td>41</td>
<td>45</td>
<td>81.8</td>
<td>74</td>
<td>109.5</td>
</tr>
<tr>
<td>6089</td>
<td>31</td>
<td>40</td>
<td>73.5</td>
<td>69</td>
<td>99.0</td>
</tr>
<tr>
<td>6090</td>
<td>41</td>
<td>35</td>
<td>75.0</td>
<td>64</td>
<td>96.8</td>
</tr>
<tr>
<td>6092</td>
<td>42</td>
<td>33</td>
<td>74.5</td>
<td>62</td>
<td>104.0</td>
</tr>
<tr>
<td>6093</td>
<td>40</td>
<td>33</td>
<td>67.5</td>
<td>62</td>
<td>86.0</td>
</tr>
<tr>
<td>6094</td>
<td>45</td>
<td>32</td>
<td>77.3</td>
<td>61</td>
<td>104.5</td>
</tr>
<tr>
<td>6096</td>
<td>41</td>
<td>27</td>
<td>73.8</td>
<td>56</td>
<td>91.5</td>
</tr>
<tr>
<td>6097</td>
<td>48</td>
<td>27</td>
<td>72.0</td>
<td>56</td>
<td>95.0</td>
</tr>
<tr>
<td>6101</td>
<td>42</td>
<td>23</td>
<td>61.5</td>
<td>52</td>
<td>83.8</td>
</tr>
<tr>
<td>6102</td>
<td>40</td>
<td>19</td>
<td>59.3</td>
<td>48</td>
<td>70.3</td>
</tr>
<tr>
<td>6104</td>
<td>46</td>
<td>18</td>
<td>61.5</td>
<td>47</td>
<td>71.8</td>
</tr>
<tr>
<td>6105</td>
<td>36</td>
<td>18</td>
<td>53.0</td>
<td>47</td>
<td>66.5</td>
</tr>
<tr>
<td>6106</td>
<td>41</td>
<td>17</td>
<td>56.8</td>
<td>46</td>
<td>71.3</td>
</tr>
<tr>
<td>6108</td>
<td>47</td>
<td>15</td>
<td>64.5</td>
<td>44</td>
<td>78.8</td>
</tr>
<tr>
<td>6110</td>
<td>41</td>
<td>13</td>
<td>51.3</td>
<td>42</td>
<td>64.3</td>
</tr>
</tbody>
</table>

All calves stayed healthy during the trial and none of the calves received veterinary treatments during the trial except for the preplanned treatments with antibiotics and analgesics connected with surgical procedures.

The calves were fed milk-replacer restrictively (4 kg of milk-replacer with 123 g DM/kg supplied once daily) and had ad libitum access to artificially-dried hay and starter concentrate during the trial. During the 29-day pre-trial period, the daily gain was on average 666 gram/day. Calves growing at this level of daily gain will usually be considered as well performing calves.

On the sampling days, 8 calves were fitted with a temperature probe (MLT 1401; ADInstruments) inserted into the jugular vein via the permanent catheter. The arterial
catheter was connected to a pressure transducer and filled with saline containing 100 IU sodium heparin. Data were recorded using Powerlab (Chart 5 version 5.5.4, ADInstruments) at 100 Hz. All pressure probes were individually tested and calibrated against a 2-m water column.

The test compound was injected into the left-side jugular vein via a temporary catheter implanted at least one day before injection.

**Data analyzed within sampling period**

All calves completed the planned injections and recordings with no loss of data apart from shorter periods of time (minutes) where temperature probes accidentally were disconnected or repositioned. Pressure transducers were flushed when needed and pressure data are only missing or invalid for shorter periods before these flushings and during the flushing procedure.

The recorded data were averaged in 15-min intervals prior to data analysis. Data were sampled from exactly 60 min before injection of test compound and until 23 hours after injection. Data recorded during the 60 min prior to injection were defined as baseline.

Variables describing temperature, blood pressure and heart rate were considered as repeated measures and analyzed by using the autoregressive order 1 structure in the mixed model procedure of SAS (SAS Institute, 2001). The model included the effects of block (calves housed in the same room), treatment and time as well as the interaction between treatment and time. Orthogonal polynomial contrasts were used to estimate the linear, quadratic, and cubic effects of treatment.

Variables describing number of hours where the body temperature deviated from baseline were constructed within calf and period. Variables were constructed for +0.5, +1.0, +2.0, +2.5, -0.5, -1.0, -2.0, and -2.5°C.

A variable describing time when body temperature returns to or exceed baseline after injection was calculated as the minimum value for time fulfilling the conditions: time > 0.25 h post injection & (15 min average temperature - baseline temperature) > 0.
Variables with only one observation within period and calf were analyzed using a model including the effects of block and treatment. Orthogonal polynomial contrasts were used to estimate the linear, quadratic, and cubic effects of treatment.

Means are given as least squares means ± residual standard error of the mean.

Allocation of animals

Three test days (October 4, 8 and 12) were planned involving testing on 16 calves. Eight calves were tested each day. The calves used at the first two days had not been used previously in the study, while all the calves used at day 3 had been used either 4 or 8 days earlier. At Day 3, seven out of eight calves had received the test compound and one out of eight had gotten placebo at either Day 1 or 2.

Test days:

Day 1 was designed at dose finding.

Day 2 was designed at dose finding.

Day 3 was designed to test the effect of repetitive doses.

Drug formulation:

HU-210 is a lipophilic compound and thus may be formulated in several ways, three of which are: Fractionated coconut oil, Tween 80 or in a cyclodextrin complex solution. During the testing phase, our compound precipitated in a cyclodextrin complex solution from the very beginning which ruled that option out. HU-210 was, however, easily dissolved in both coconut oil and Tween 80, and a coconut oil solution was chosen.

Day 1: Five calves received 2.0, 4.0, 4.0, 6.0 and 6.0 µg HU-210 respectively. As seen in table 5 there was a dose response relationship both in terms of body temperature reduction and the duration of hypothermia. 2.0, 4.0 and 6.0 µg resulted in an average reduction of body temperature of approx 1.0, 2.0 and 2.5 °C respectively. In 3 out of 4 calves a reduction of body temperature of 2.0 °C was achieved within 2-3 hours. One of the 4.0 µg and one of the 6.0 µg calves were above and at the upper edge of the target weight range respectively. Both responded less to HU-210 than their lighter counterparts.

Day 2: The eight calves received the same doses as tested at Day 1. The results reminded of the results of Day 1. The 6.0 µg calves both had less pronounced
reduction of body temperature (1.8-1.9 °C) while the 4.0 µg calf with a proper weight responded as the 4.0 µg calves of Day 1. The 4.0 µg calf with a weight above the target range (6086 - weight: 115 kilo) responded less to the test compound. See figures 1 and 2.

Day 3: All calves had been used at either Day 1 or Day 2. Seven out of eight had received the active compound while one had received placebo. The doses (5.0+2.5 µg), 10 and 15 µg resulted in less behavioral alterations than seen in the 4.0 and 6.0 µg calves at Day 1 and 2, both in regards to psychotropic behavior as well as the induction of somnolence. At Day 3 there was also a tendency to a more pronounced temperature reduction in the calves weighing within the predefined range (65-95 kilo) compared to heavier calves.

Conclusion
The studies clearly demonstrated that HU-210 causes hypothermia in calves. The doses tested induced at temporary drop in core body temperature of up to 2.6 °C in a dose dependent manner.

The following effects of HU-210 were observed in calves:
1. Decreased body temperature for 6 to 15 h after injection
2. Overshoot in body temperature starting 6 to 15 h after injection
3. Decreasing heart rate following injection
4. No clear effects on systolic and diastolic blood pressure

Example 17 - Extended Bovine study #1
Study subjects
The evaluation is carried out on 80 Holstein bull calves purchased for the study that is conducted over 8 study days. At an age of app. 50 days (body weight 75 to 85 kg) calves are assigned to the sections and injected with test compound. Body temperature, arterial blood pressure, and heart rate are monitored 60 min prior to injection and during 24 h following injection. Each calf is receiving experimental injection one time. See the above for further specifications.

Each study week consisted of two study days. For each study week 20 calves are purchased. These calves will be at the test facilities for approximately 2 weeks before
the operation period. Two calves served as a buffer in case of sickness or unexpected high or low weight gain in the first two weeks after the animals arrive at test facilities. The remaining 18 calves are operated and 16 are ultimately included in the study. The surplus of two operated calves is an extra measure in order to deal with sickness and unexpected high or low weight gain in the two-week period from operation to the study day.

Calf study outline
The study days are allocated to the examination of the following compounds and purposes:

<table>
<thead>
<tr>
<th>Day</th>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dihydrocapsaicin</td>
<td>4</td>
<td>0, 0.5, 1.0, 1.0 mg/kg im</td>
<td>Dose titration</td>
</tr>
<tr>
<td></td>
<td>HU-210</td>
<td>4</td>
<td>0, 20, 30, 40 μg/kg iv</td>
<td>Maximum effect evaluation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day</th>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Dihydrocapsaicin</td>
<td>4</td>
<td>0, 0.5, 2.0, 2.0 mg/kg im</td>
<td>Dose titration</td>
</tr>
<tr>
<td></td>
<td>HU-210</td>
<td>4</td>
<td>0, 20, 30, 40 μg/kg iv</td>
<td>Maximum effect evaluation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day</th>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Dihydrocapsaicin</td>
<td>4</td>
<td>0, 0.25 - 1 mg/kg/h iv</td>
<td>Continuous doses – see below</td>
</tr>
<tr>
<td></td>
<td>HU-210</td>
<td>4</td>
<td>0, 20, 30, 40 μg/kg iv</td>
<td>Maximum effect evaluation in a Tween 80 solution</td>
</tr>
</tbody>
</table>

The dihydrocapsaicin at day 3 was used to investigate continuous doses. The calves were given the indicated doses until a stable temperature was reached; the reached temperature was then kept stable by administering 0.5 mg to 1.0 mg/kg/h. The calves remained stable at the reached temperature for the duration of the experiment. For three calves, a reduction in core body temperature of 3.5 degree Celsius was reached for the last calf a reduction of 2.5 degree Celsius was reached.

<table>
<thead>
<tr>
<th>Day</th>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Disodium Δ8THC phosphate</td>
<td>4</td>
<td>0, 1, 3, 9 mg/kg iv</td>
<td>Dose titration</td>
</tr>
<tr>
<td></td>
<td>Disodium Δ8THC phosphate</td>
<td>4</td>
<td>0, 1, 3, 9 mg/kg iv</td>
<td>Dose titration</td>
</tr>
</tbody>
</table>
### Day 5

<table>
<thead>
<tr>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disodium Δ8THC phosphate</td>
<td>8</td>
<td>Depending on the results from the previous study days</td>
<td>Maximum effect evaluation</td>
</tr>
</tbody>
</table>

### Day 6

<table>
<thead>
<tr>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Full dose + full dose after X hours (X is determined on the basis of the temperature curve obtained at the previous 5 study days)</td>
<td>Effect duration</td>
</tr>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Full dose + half dose after X hours</td>
<td>Effect duration</td>
</tr>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Full dose + full dose after X hours</td>
<td>Effect duration</td>
</tr>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Placebo + placebo after X hours</td>
<td>Effect duration</td>
</tr>
</tbody>
</table>

### Day 7

<table>
<thead>
<tr>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Full dose + full dose when the temperature is moving back towards normothermia (rise by 0.4°C for 15 minutes or more)</td>
<td>Effect duration</td>
</tr>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Full dose + half dose when the temperature is moving back towards normo-thermia (rise by 0.4°C for 15 minutes or more)</td>
<td>Effect duration</td>
</tr>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Full dose + infusion (if possible)</td>
<td>Effect duration</td>
</tr>
<tr>
<td>Front-runner</td>
<td>2</td>
<td>Placebo + placebo after 4 hours</td>
<td>Effect duration</td>
</tr>
</tbody>
</table>

### HU-210

<table>
<thead>
<tr>
<th>Compound</th>
<th>Doses</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ8-THC-phosphate</td>
<td></td>
<td>Best option: Fractionated coconut oil (C8.0/C10.0-triglyceride): 10.9 mg/ml</td>
</tr>
<tr>
<td>Dihydrocapsaicin</td>
<td></td>
<td>Best option: Water.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Best option: 20% (w/v)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tween 80: 16 mg/ml, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fractionated coconut oil</td>
</tr>
</tbody>
</table>
Day 1-5: Each calf received a single intravenous bolus injection of 2 ml administered over 7-8 minutes followed by saline flush of 5 ml. Day 6-7: Each calf will receive an initial intravenous bolus injection of 2 ml administered over 7-8 minutes, followed by one or several similar intravenous injections for up to 12 hours after the initial injection.

Pharmacokinetics / Pharmacodynamics (PK/PD)
Blood samples will be taken before and after injection of compounds in order to examine PK/PD. The specifics depend on a meeting with Xendo (www.xendo.dk) where the topic will be a tailor-made pharmacokinetic/pharmacodynamic model for the calf study.

Drug administration
The compound investigated are administered i.v. as bolus injections and may consist of 1 solitary injection, alternatively 2-4 repeated injections within a timeframe of 24 hours from the initial injection, alternatively as a continuous administration.

Generally 4 different doses plus vehicle are tested producing varying degrees of hypothermic responses.

Hypothermic effect
The primary effect evaluated is hypothermia. Temperature is measured using a temperature probe that is surgically positioned in a femoral artery two weeks prior to commencement of the study. The probe is connected to telemetry equipment (e.g. implanted telemetry from Data Sciences International) ensuring the required read-outs.

Temperature is measured every 15 minutes from 1 hour prior to drug administration to 12 hours after drug administration, and every 30 minutes subsequently until 24 hours after drug administration. Temperature measurement will be conducted via a permanent femoral artery temperature probe (telemetry).

The minimum temperature as well as a graph of the temperature at each point of measurement is recorded for each dose of compound or compound mixture.
Other effects
Blood pressure, heart rate and ECG will be registered every 15 minutes from 1 hour prior to drug administration to 12 hours after drug administration, and every 30 minutes subsequently until 24 hours after drug administration.

Example 18 - Extended Bovine study #2
Study subjects
The evaluation is carried out on Holstein bull calves purchased for the study. At an age of app. 50 days (body weight 75 to 85 kg) calves are assigned to the test compound and administration mode under examination. Body temperature, arterial blood pressure, and heart rate are monitored 60 min prior to administration and during 24 h following injection. See Example 16 above for further specifications.

Calf study outline
The studies are allocated to the examination of the following compounds and administrations:

<table>
<thead>
<tr>
<th>Study</th>
<th>Compound</th>
<th>Calves</th>
<th>Doses</th>
<th>Duration</th>
<th>Administration mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dihydrocapsaicin</td>
<td>8 (+2 placebo)</td>
<td>1 mg/kg/h</td>
<td>12 hours</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>2</td>
<td>Dihydrocapsaicin</td>
<td>8 (+2 placebo)</td>
<td>0.6 mg/kg/h</td>
<td>4 hours</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>3</td>
<td>Dihydrocapsaicin</td>
<td>1+2+2 per dose (+2 placebo)</td>
<td>0.5 mg/kg; 1.0 mg/kg; 2.0 mg/kg</td>
<td>NA</td>
<td>Single intramuscular injection</td>
</tr>
<tr>
<td>4</td>
<td>Disodium Δ8THC phosphate</td>
<td>6 (+2 placebo)</td>
<td>20 mg/kg</td>
<td>NA</td>
<td>Single intravenous bolus injection</td>
</tr>
<tr>
<td>5</td>
<td>HU-210</td>
<td>1 pr dose</td>
<td>20 μg/kg; 30 μg/kg; 40 μg/kg;</td>
<td>NA</td>
<td>Single intravenous bolus injection</td>
</tr>
</tbody>
</table>

Administration
Study 1-2:
Study 4-5: Each calf received a single intravenous bolus injection of 2 ml administered over 7-8 minutes followed by saline flush of 5 ml.
Pharmacokinetics / Pharmacodynamics (PK/PD)

Blood samples will be taken before and after administration of compounds in order to examine PK/PD. The specifics depend on a meeting with Xendo (www.xendo.dk) where the topic will be a tailor-made pharmacokinetic/pharmacodynamic model for the calf study.

Drug administration

The compounds investigated are administered i.v. as bolus injections and may consist of 1 solitary injection, alternatively 2-4 repeated injections within a timeframe of 24 hours from the initial injection, alternatively as a continuous administration.

Hypothermic effect

The primary effect evaluated is hypothermia. Temperature is measured using a temperature probe that is surgically positioned in a femoral artery two weeks prior to commencement of the study. The probe is connected to telemetry equipment (e.g. implanted telemetry from Data Sciences International) ensuring the required read-outs.

Temperature is measured every 15 minutes from 1 hour prior to drug administration to 12 hours after drug administration, and every 30 minutes subsequently until 24 hours after drug administration. Temperature measurement will be conducted via a permanent femoral artery temperature probe (telemetry).

The minimum temperature as well as a graph of the temperature at each point of measurement is recorded for each dose and administration form of compound.

Other effects

Blood pressure, heart rate and ECG will be registered every 15 minutes from 1 hour prior to drug administration to 12 hours after drug administration, and every 30 minutes subsequently until 24 hours after drug administration.

Example 19 - gradual reduction of Dihydrocapsaicin by infusion

A total of 4 calves receives ongoing IV infusions of Dihydrocapsaicin (0.6 mg/kg body weight) for 5 hours and experience a reduction in body temperature of between approx. 3.5 to 4.5 degrees Celsius. At the end of the hypothermia period two scenarios is tested (as shown in figure 8):


• the infusion is brought to a sudden stop in 2 of the calves (Temp 2198' and Temp 1718'), or
• the infusion is gradually slowed down in 2 of the calves (Temp 2254' and Temp 2389')

The difference in temperature outcome is dramatically different between the two groups. The first group (sudden infusion stop) reaches normothermia in about 60 minutes after infusion stop, whereas the second group (gradual slowing down of infusion) reaches normothermia more slowly; in about 210 minutes. This is shown in figure 8.

The principle of slowing down the infusion rate to reach exactly the optimal temperature gradient in order to avoid/minimize post-hypothermia therapy overshooting applies to Dihydrocapsaicin as well as all other compounds of this invention.

Example 20 - gradual reduction of hypothermia-inducing compound
A patient is admitted in a hospital and diagnosed with a stroke. The patient is evaluated and the physician in charge decides that the patient shall receive hypothermia therapy immediately to minimize the risk of damage to the brain.

In another example, the patient may be diagnosed with for example cardiac arrest, perinatal asphyxia, myocardial infarction, traumatic brain injury or pulmonary embolism.

Hypothermia therapy is conducted as described in this invention. One or more compounds are administered that induces hypothermia. These are known to cause hyperthermia (over-shooting) frequently associated with hypothermia therapy as the patient approaches post-therapeutic normothermia. Hypothermia inducing compounds of this invention include:

a. Cannabinoid receptor agonists. Including, but not limited to HU-210 (intravenous bolus injection of e.g. 100 microgram/kg body weight) and/or delta-8-THC phosphate (intravenous bolus injection of e.g. 40 mg/kg body weight)

b. Vanilloid receptor agonists. Including, but not limited to dihydrocapsaicin (subcutaneous or intravenous bolus injection of 0.01 mg/kg to 80 mg/kg)

c. Adenosine receptor agonists (including, but not limited to 5'-AMP)
d. Neurotensin receptor agonists

e. Thyroxine derivatives

f. Cytochrome C oxidase inhibitor

g. Oxygen tension reducers

In order to prevent over-shooting, the dosis of the hypothermia-inducing compound(s) given is reduced towards the end of treatment. If for example dihydrocapcaisin is administered to the patient by an intravenous infusion of 0.6 microgram/kg body weight per hour, said infusion may be administered by a gradual decrease in dosage of dihydrocapcaisin, such that the majority of the dosage is given within the first hour, and lower amounts of the dosage is given in the subsequent hours.

At the hospital, concurrent treatments and examinations are not influenced by the administration of the hypothermia-inducing drug. Such other treatments and examinations proceed uninterrupted.
References


Claims

1. Use of at least one compound for induction of hypothermia in an individual in need thereof, wherein said compound is administered parenterally.

2. The use of a compound according to claim 1, wherein said parenteral administration is by infusion.

3. The use of a compound according to claim 1, wherein said parenteral administration is an injection.

4. The use of a compound according to claim 1, wherein the at least one compound is selected from the group consisting of:
   a. a vanilloid receptor agonist,
   b. a cannabinoid or a cannabimimetic compound,
   c. an adenosine, or an adenosine analog, or an adenosine receptor agonist, or an adenosine uptake inhibitor
   d. a neurotensin, or a neurotensin analog, or a neurotensin receptor agonist, or a neurotensin mimetic compound
   e. a thyroxine derivative
   f. a cytochrome c oxidase inhibitor
   g. an oxygen tension reducer

5. The use according to claim 2, wherein said infusion is intravenous, intra-arterial intra-cardiac, intrathecal, epidural or intraspinal.

6. The use according to claim 2 or 5, wherein said infusion occurs through a peripheral or central IV line.

7. The use according to claim 2 or 5 to 6, wherein said infusion is continuous or intermittent, an IV push or a bolus.

8. The use according to claim 2 or 5 to 7, wherein said infusion comprises an IV infusion set including a pre-filled, sterile container of a fluid comprising the compounds; alternatively a two component kit consisting of: 1: a compound in dry
form, and 2: a liquid (to be combined prior to administration); an attached drip chamber; a sterile tube with a clamp to regulate or stop the flow; a connector to attach to the access device; optionally connectors to allow "piggybacking" of another infusion set onto the same line; and optionally an infusion pump.

9. The use according to claim 2, wherein a cannabinoid or a cannabimimetic compound is administered by intravenous infusion for the induction of hypothermia.

10. The use according to claim 2, wherein a vanilloid receptor agonist is administered by intravenous infusion for the induction of hypothermia.

11. The use according to claim 3, wherein said injection is intramuscular, intravenous, subcutaneous, intradermal, intraperitoneal, intrathecal, epidural, intraspinal, intracardiac, intraosseous or intravitreal.

12. The use according to claim 3 or 11, wherein said injection is one or more bolus injections.

13. The use according to claim 3 or 11 to 12, wherein a cannabinoid or a cannabimimetic compound is administered by injection for the induction of hypothermia.

14. The use according to claim 3 or 11 to 12, wherein a vanilloid receptor agonist is administered by injection for the induction of hypothermia.

15. The use according to any of the preceding claims, wherein the duration of the treatment is from 6 to 72 hours.

16. The use according to any of the preceding claims, wherein parenteral administration occurs at intervals of 30 minutes to 48 hours.

17. The use according to any of the preceding claims, wherein parenteral administration occurs at intervals of 1 to 6 hours.
18. The use according to any of the preceding claims, wherein the dosage of the medicament is between 10 µg to 80 mg per kg body mass.

19. The use of a compound according to claim 4, wherein the at least one compound is capable of binding a vanilloid receptor and/or a cannabinoid receptor and/or an adenosine receptor and/or a neurotensin receptor and/or a thyroxine derivative receptor and/or cytochrome c oxidase and/or capable of reducing oxygen tension.

20. The use of a compound according to claim 4, wherein the vanilloid receptor agonist is selected from the group of classical vanilloid receptor agonists, non-classical vanilloid receptor agonists and other vanilloid receptor binding compounds; and the cannabinoid is selected from the group of classical cannabinoids, non-classical cannabinoids, eicosanoids, aminoalkylindoles and other cannabinoid receptor binding compounds; and the adenosine receptor agonist is selected from the group of adenine nucleotides; and the neurotensin receptor agonist is selected from the group of natural and artificial neurotensins; and the thyroxine derivative is selected from the group of natural and artificial thyroid hormones and its thyronamine derivates; and the cytochrome c inhibitor is selected from the group of natural and artificial cytochrome c inhibitors; and the oxygen tension reducer is selected from the group of natural and artificial oxygen tension reducers.

21. The use of at least one compound according to claim 4, wherein the individual in need of said treatment suffers from or is at risk of suffering from one or more of the following: ischemia, fever, hyperpyrexia, malign hyperpyrexia, hypothermia and/or requires surgery; wherein the outcome of said surgery is benefitted by reducing the temperature of the individual undergoing the surgery prior to and/or during the surgery.

22. The use of at least one compound according to claim 4, comprising a classic or non-classic vanilloid receptor agonist of the general formula (I):

\[
\begin{align*}
&H \\
&\text{R}_1 \text{N} \text{R}_2 \text{O}
\end{align*}
\]
wherein R1 and R2 are chemical moieties or chemical bonds.

23. The use of a vanilloid receptor agonist as defined in claim 22, wherein R1 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkenyl, alkynyl, sulfonyl or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkenyl, alkenyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be (d-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, any of which may be further substituted with methyl, ethyl or phenyl and more preferably is C substituted with alkyl, alkenyl, any of which may be (C4-Cw) any of which may be further substituted with O, OH, methoxy, ethoxy or methyl any of which may be further substituted with methyl, ethyl, or phenyl, wherein v is an integer of from 1 to 30 and w is an integer of from 5 to 18.

24. The use of a vanilloid receptor agonist as defined in claim 22, wherein R2 is selected from the group of: C, S, N, O, optionally substituted one or more times with C, S, N, O, P, OH, hydrogen, alkoxy, alkyl, alkenyl, alkynyl, phenyl, diphenyl, benzyl, amine (NH), halogen, substituted lower alkyl, alkenyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci4)-alkyl, heteroaryl-(Ci4)-alkyl, heterocyclyl-(Ci4)-alkyl, cycloalkylalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, S, N, O, P, OH, H, COOH, phenyl, amine (NH), halogen, alkoxy, substituted lower alkyl, alkyl or alkenyl such as (C1-Cv), cycloalkenyl, sulphate, phosphate, aryl, heterocyclyl, heteroaryl, aryl-(Ci4)-alkyl, heteroaryl-(Ci4)-alkyl, heterocyclyl-(Ci4)-alkyl, heterocyclyl-(Ci4)-alkyl, cycloalkylalkyl, dicycloalkyl, tricycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, cyano, amino, nitro, or alcohol, any of which may be further substituted one or more times with OH, methyl, dimethyl, alkyl or alkenyl such as (Ci-Cv), alkoxy, phenyl, sulphate, phosphate, aryl, heteroaryl, carboxy, amino, nitro, alcohol or halogen and preferably is C, substituted one or more times with C, N, O, P, OH, hydrogen, alkoxy, alkyl, alkenyl, amine (NH),
halogen, substituted lower alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, N, O, OH, COOH, hydrogen, amine (NH), halogen, alkoxy, substituted lower alkyl or alkenyl such as (CrCx), phosphate, cycloalkenyl, alkoxy, carboxy or halogen, any of which may be further substituted one or more times with OH, methyl, dimethyl, alkyl or alkenyl such as (CrCx), alkoxy, phenyl, sulphate, phosphate, carboxy or halogen and more preferably is C substituted with either: cycloalkenyl further substituted at least twice with any of OH or methoxy, or: lower alkyl such as (C₁-C₂) at least once and further substituted one or more times with OH, COOH, Chloride, methyl or cycloalkenyl, optionally further substituted one or more times with OH or methoxy and wherein ν is an integer of from 1 to 30 and x is an integer of from 1 to 5.

25. The use of a vanilloid receptor agonist as defined in claim 22, wherein R₁ is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be (Cr Cv), or phenyl, any of which may be further substituted one or more times with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, acetyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, any of which may be further substituted with methyl, ethyl or phenyl and R₂ is C, substituted one or more times with C, N, O, P, OH, hydrogen, alkoxy, alkyl, alkenyl, amine (NH), halogen, substituted lower alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl or phosphate, optionally further substituted one or more times with C, N, O, OH, COOH, hydrogen, amine (NH), halogen, alkoxy, substituted lower alkyl or alkenyl such as (CrCx), phosphate, cycloalkenyl, alkoxy, carboxy or halogen, any of which may be further substituted one or more times with OH, methyl, dimethyl, alkyl or alkenyl such as (C₁-C₂), alkoxy, phenyl, sulphate, phosphate, carboxy or halogen and wherein ν is an integer of from 1 to 30 wherein x is an integer of from 1 to 5.

26. The use of a vanilloid receptor agonist as defined in claim 22, wherein R₁ is C substituted with alkyl, alkenyl, any of which may be (C₄-C₂w) any of which may be further substituted one or more times with O, OH, acetyl, methoxy, ethoxy or methyl any of which may be further substituted one or more times with methyl, ethyl, cycloalkenyl or phenyl and w is an integer of from 5 to 18, and R₂ is C substituted with either: cycloalkenyl further substituted at least twice with any of OH or methoxy, or: lower alkyl such as (CrC₂) at least once and further substituted one or
more times with OH, COOH, Chloride, methyl or cycloalkenyl, optionally further
substituted one or more times with OH or methoxy.

27. The use of at least one compound according claim 4, comprising a non-classic
vanilloid receptor agonist of the general formula (II):

wherein R1, R2, R3, R4, R5 and R6 are chemical moieties or chemical bonds.

28. The use of a vanilloid receptor agonist as defined in claim 27, wherein R1 is
selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, B, P,
OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or
comprise substituents such as phosphate, cycloalkyl, heterocyclyl, heterocyclic
group, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or
more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl,
alkynyl, sulfonyl or phenyl cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclic group
any of which may or may not be branched or comprise substituents such as C, O,
H, OH, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, further substituted
at least once with O, OH, methyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl,
dimethyl or phenyl further substituted with alkyl, alkenyl, cycloalkyl, cycloalkenyl,
heterocyclyl and preferably is C substituted with C, N, O, B, P, OH, hydrogen, alkyl,
alkenyl, alkynyl, any of which may or may not be branched or comprise substituents
such as phosphate, cycloalkyl, heterocyclyl, heterocyclic group, cycloalkenyl,
methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N,
O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, cycloalkyl, cycloalkenyl,
heterocyclyl, heterocyclic group any of which may or may not be branched or
comprise substituents such as C, O, H, OH, methyl, ethyl, alkyl, alkenyl, alkoxy,
phosphate, further substituted at least once with O, OH, methyl, alkenyl, cycloalkyl,
heterocycloalkyl, cycloalkenyl, further substituted with alkyl, alkenyl, cycloalkyl,
cycloalkenyl, heterocyclyl and more preferably is C substituted with alkyl or alkenyl
which may be (C4-Cw), B, or heterocyclyl forming a ring with R6 thus comprising a
pyrrolidine further substituted one or more times with O, methyl, alicyclic groups attached to one another, these being saturated or unsaturated or a heterocyclic group comprising said B, N and O, and being further substituted at least once with O, methyl or C further substituted at least once with cycloalkenyl, cycloalkyl, heterocycl further substituted at least once with O, OH, methyl, alkenyl, further substituted with lower alkyl and cycloalkenyl; wherein any of the above may form at least one bond with any of R2, R3, R4, R5 and/or R6, and \( w \) is an integer of from 5 to 18.

29. The use of a vanilloid receptor agonist according to claim 27, wherein R2 is selected from the group of C, S, N, O, optionally substituted at least once with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be \( (\text{d-C}_w) \), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted at least once with OH or hydrogen, and wherein any of the above may form at least one bond with any of R1, and/or R3, and wherein \( \gamma \) is an integer of from 1 to 30.

30. The use of a vanilloid receptor agonist according to claim 27, wherein R3 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, hydrogen, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl,
alkenyl, any of which may be (Ci-Cv), or phenyl, optionally substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted with OH, methoxy, lower alkyl (C1-Cv) and may at any point form a ring with R4, and wherein any of the above may form at least one bond with any of R2, and/or R4, and wherein \( \gamma \) is an integer of from 1 to 30, and \( \gamma \) is an integer of 2 or 3.

31. The use of a vanilloid receptor agonist according to claim 27, wherein R4 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, hydrogen, methoxy, ethoxy, acetyl, alkoxy, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl, alkenyl, any of which may be (C1-Cv), or phenyl, optionally substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted with OH, methoxy, lower alkyl (C1-Cv) and may at any point form a ring with R4, and wherein any of the above may form at least one bond with any of R2, and/or R4, and wherein \( x \) is an integer of from 1 to 30; and \( \gamma \) is an integer of 2 or 3.

32. The use of a vanilloid receptor agonist according to claim 27, wherein R5 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, CHO, hydrogen, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, sulfonyl or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl or phenyl and preferably is C substituted at least once with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (d-Cv), or phenyl, any of which may be
substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted one or more times with hydrogen, OH, CHO or methyl which may form a ring with R6 wherein \( \nu \) is an integer of from 1 to 30.

33. The use of a vanilloid receptor agonist according to claim 27, wherein R6 is selected from the group of C, S, N, O, optionally substituted with C, S, N, O, B, P, OH, CHO, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, alkynyl, or phenyl any of which may or may not be branched or comprise substituents such as hydrogen, methyl, ethyl, alkyl, alkenyl, alkynyl, alkoxy, phosphate, dimethyl or phenyl and preferably is C substituted with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (d-C\( \nu \)), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and more preferably is C substituted one or more times with hydrogen, CHO, lower alkyl (C1-C\( \gamma \)) or methyl, which may form at least one bond with R5, or be at least one bond forming a ring with R1, wherein the at least one bond between any of R1, R2, R3, R4 and/or R5 may be single or double bonds and wherein \( \nu \) is an integer of from 1 to 30; and \( \gamma \) is an integer of 2 or 3.

34. The use of a vanilloid receptor agonist according to claim 27, wherein R1 is C substituted with C, N, O, B, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocyclyl, heterocyclic group, cycloalkenyl, methyl, ethyl, dimethyl, or may be further substituted one or more times with C, N, O, P, OH, methoxy, ethoxy, acetyl, alkoxy, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclic group any of which may or may not be branched or comprise substituents such as C, O, H, OH, methyl, ethyl, alkyl, alkenyl, alkoxy, phosphate, further substituted at least once with O, OH, methyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, further substituted with alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocyclyl any of the above of which may form bonds with R2, and/or R6, and R2 preferably is C substituted with C, O, P, H, OH, phosphate, alkyl, alkenyl, alkynyl any of which may be (d-C\( v \)), or phenyl, any of which may be substituted with O, OH, methyl,
dimethyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and R3 preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkoxy, alkyl, alkenyl, any of which may be (Ci-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and R4 preferably is C substituted with C, O, P, H, OH, phosphate, acetyl, alkyl, alkenyl, any of which may be (d-Cv), or phenyl, optionally substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, phenyl, methoxy, ethoxy, alkoxy or phosphate, and R5 preferably is C substituted at least once with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (d-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and R6 preferably is C substituted with C, O, P, H, OH, CHO, phosphate, alkyl, alkenyl, any of which may be (Ci-Cv), or phenyl, any of which may be substituted with O, OH, methyl, dimethyl, alkyl, alkenyl, methoxy, ethoxy, alkoxy or phosphate, and wherein v is an integer of from 1 to 30.

35. The use of a vanilloid receptor agonist according to claim 27, wherein R1 is C substituted with alkyl or alkenyl which may be (C4-C2) Boron, or heterocyclic group forming a ring with R6 thus comprising a pyrroline further substituted one or more times with O, methyl, alicyclic groups attached to one another, these being saturated or unsaturated or a heterocyclic group comprising said Boron, N and O, and being further substituted at least once with O, methyl or C further substituted at least once with cycloalkenyl, cycloalkyl, heterocyclyl further substituted at least once with O, OH, methyl, alkenyl, further substituted with lower alkyl and cycloalkenyl; R2 is C substituted with OH or hydrogen; R3 is C substituted with OH, methoxy, lower alkyl (C1- C2) and may at any point form a ring with R4; R4 is C substituted with OH, methoxy, lower alkyl (Cl-C2) and may at any point form a ring with R3; R5 is C substituted one or more times with hydrogen, OH, CHO or methyl which may form a ring with R6; and R6 is C substituted one or more times with hydrogen, CHO, lower alkyl (C1-C2) or methyl, which may form at least one bond with R5, or be forming a ring with R1, wherein the at least one bond between any of R1, R2, R3, R4, R5 and/or R6 may be single or double bonds and v is an integer of either 2 or 3, and z is an integer of either 5 or 12.
36. The use of at least one compound according to claim 4, wherein the vanilloid receptor agonist is selected from the group consisting of Capsaicin and compounds closely related to capsaicin such as: Dihydrocapsaicin (DHC), Nordihydro-capsaicin (NDHC), Homodihydro-capsaicin (HDHC), and Homocapsaicin; resi"feratoxin and compounds closely related hereto.

37. The use of at least one compound according to claim 4, comprising a classic or non-classic cannabinoid of the general formula:

\[
R4 \quad R1 \quad R3 \quad R2
\]

wherein R1, R2, R3 and R4 individually is a chemical moiety or a chemical bond.

38. The use of a cannabinoid as defined in claim 37, wherein R1 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci-4)-alkyl, heteroaryl-(Ci-4)-alkyl, heterocyclyl-(Ci-4)-alkyl, cycloalkylalkyl, cycloalkyl or phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci-4)-alkyl, heteroaryl-(Ci-4)-alkyl, heterocyclyl-(Ci-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with methyl, alkyl or phosphate and more preferably is C, optionally substituted with H, OH, OCH3 or phosphate.

39. The use of a cannabinoid as defined in claim 37, wherein R2 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, any of which may or may not be branched or comprise substituents such as phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, methyl, dimethyl, or may be further substituted one or more times with C, S, N, O, P, OH, hydrogen,
alkyl, alkenyl, alkynyl, sulfonyl, any of which may or may not be branched or comprise substituents such as hydrogen, alkyl, alkenyl, alkynyl, fluoride, phosphate, cycloalkyl, heterocycloalkyl, cycloalkenyl, dimethyl, phenyl and preferably is C substituted with C, O, P, H, OH, OSO₂, phosphate, alkyl, alkenyl, alkynyl such as (Ci-Cₓ), phenyl any of which may be substituted with methyl, dimethyl, sulfonyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, fluoride, phenyl, phosphate, and more preferably is C substituted with C, O, OSO₂, alkyl such as (C₃-Cₙ) any of which may be further substituted with methyl, dimethyl, alkyl such as (Ci-Cₓ), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl and wherein x is an integer of from 1 to 20.

40. The use of a cannabinoid as defined in claim 37, wherein R₃ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ciₓ)-alkyl, heteroaryl-(Ciₓ)-alkyl, heterocyclyl-(Ciₓ)-alkyl, cycloalkylalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, methyl, phenyl, diheterocycle, amine (NH), halogen, substituted lower alkyl, aryl, lower alcohol, heterocyclyl, heteroaryl, aryl-(Ciₓ)-alkyl, heteroaryl-(Ciₓ)-alkyl, heterocyclyl-(Ciₓ)-alkyl, cycloalkylalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, preferably is C, O, N, S, optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted one or more times with methyl, diheterocycle, lower alcohol, alkyl or phosphate more preferably is C which may be substituted with C, O, N, OH, phosphate, any of which may be substituted one or more times with C, ethyl, methyl, phosphate, diheterocycle, lower alcohol, alkyl such as (CrCₓ) wherein Cₓ binds to R₄ when R₄ is C, optionally further substituted by methyl, dimethyl or phosphate.

41. The use of a cannabinoid as defined in claim 37, wherein R₄ is selected from the group of: C, H, S, N, O, optionally substituted with C, H, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, diphenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ciₓ)-alkyl, heteroaryl-(Ciₓ)-alkyl, heterocyclyl-(Ciₓ)-alkyl, cycloalkylalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, substituted lower alkyl, alkyl such as (Ci-Cₓ) any of which may be
further substituted with methyl, dimethyl, alkyl such as (Ci-CX), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci-CX)-alkyl, heteroaryl-(Ci-CX)-alkyl, heterocyclyl-(Ci-CX)-alkyl, cycloalkylalkyl, dicycloalkyl, tricyclocalklyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, (alcohol) and preferably is C, H, N, O optionally substituted with alkyl, alkenyl, alkynyl, alcohol, phenyl, diphenyl, dicycloalkyl, tricyclocalklyl, cycloalkenyl any of which may bond with R1 or R3 forming a ring, optionally further substituted with one or more alkyl, alkenyl, alkynyl, OH, and more preferably is C, H, (C1-CX), dicycloalkyl, or tricyclocalkyl, cycloalkenyl any C of which may bond with R1 or R3 forming a ring, and optionally is substituted with methyl, dimethyl, phenyl, diphenyl, optionally further substituted with alkyl and/or OH and wherein χ is an integer of from 1 to 15 and γ is an integer of from 1 to 8.

42. The use of a cannabinoid as defined in claim 37, wherein R1 is selected from the group of: C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with methyl, alkyl or phosphate, when R2 as defined in claim 39 is C substituted with C, O, P, H, OH, OSO2, phosphate, alkyl, alkenyl, alkynyl such as (C1-CX), phenyl any of which may be substituted with methyl, dimethyl, sulfonyl, heterocycloalkyl, fluoride, phenyl or phosphate, when R3 as defined in claim 40 is C, O, N, S, optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted one or more times with methyl, diheterocycle, lower alcohol, alkyl or phosphate, when R4 as defined in claim 41 is C, H, N, O optionally substituted with alkyl, alkenyl, alkynyl, alcohol, phenyl, diphenyl, dicycloalkyl, tricyclocalkyl, cycloalkenyl any of which may bond with R1 or R3 forming a ring, optionally further substituted with one or more alkyl, alkenyl, alkynyl or OH.

43. The use of a cannabinoid as defined in claim 37, wherein R1 is selected from the group of: C, optionally substituted with H, OH, OCH3 or phosphate, when R2 as defined in claim 39 is C substituted with C, O, OSO2, alkyl such as (C3-C11) any of which may be further substituted with methyl, dimethyl, alkyl such as (Ci-CX), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl when R3 as defined in claim 40 is C which may be substituted with C, O, N, OH, phosphate, any of which may be substituted with C, ethyl, phosphate, alkyl such as
(C₁⁻C₂) wherein C₂ binds to R₄ when R₄ is C, optionally further substituted by methyl, dimethyl or phosphate when R₄ as defined in claim 41 is C, (C₁⁻C₈) any C of which may bond with R₃ and optionally is substituted with methyl, dimethyl, phenyl, diphenyl optionally further substituted with an alcohol and wherein x is an integer of from 1 to 15.

44. The use of at least one compound according to claim 4, wherein the compound comprise a cannabinoid which is a classical cannabinoid of the general formula:

```
    R₅
     |
     |
R₄----R₁----R₂
     |
     |
R₃
```

wherein R₁, R₂, R₃, R₄ and R₅ individually is a chemical moiety or a chemical bond.

45. The use of a cannabinoid as defined in claim 44, wherein R₁ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, arylo-(C₁⁻C₄)-alkyl, heteroaryl-(C₁⁻C₄)-alkyl, heterocyclyl-(C₁⁻C₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally bonding with the C in the ring next to R₅, optionally further substituted one or more times with C, S, N, O, OH, phenyl, phosphate, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, arylo-(C₁⁻C₄)-alkyl, heteroaryl-(C₁⁻C₄)-alkyl, heterocyclyl-(C₁⁻C₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with alkyl or phosphate and more preferably is C, optionally substituted one or more times with H, O, OH, OCH₃ or phosphate.
46. The use of a cannabinoid as defined in claim 44, wherein R2 is selected from the
group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl,
alkenyl, alkynyl, any of which may or may not be branched or comprise substituents
such as phosphate, heterocycloalkyl, cycloalkyl, cycloalkenyl, methyl, dimethyl, or
may be further substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl,
sulfonyle, any of which may or may not be branched or comprise substituents such
as hydrogen, alkyl, alkenyl, alkynyl, fluoride, phosphate, heterocycloalkyl,
cycloalkyl, cycloalkenyl, dimethyl, phenyl and preferably is C substituted with C, O,
P, H, OH, OSO₂, phosphate, alkyl, alkenyl, alkynyl such as (C₁-C₄), phenyl any of
which may be substituted with methyl, dimethyl, sulfate, heterocycloalkyl, fluoride,
phenyl, phosphate, and more preferably is C substituted with C, O, OSO₂, alkyl
such as (C₃-C₁₅), any of which may be further substituted with methyl, dimethyl, alkyl
such as (C₁-C₄), phenyl, phosphate or further substituted by fluoride, phosphate,
methyl, dimethyl and wherein x is an integer of from 1 to 15.

47. The use of a cannabinoid as defined in claim 44, wherein R3 is selected from the
group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl,
alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl,
heterocycloalkyl, heteroaryl, aryl-(C₁-C₄)-alkyl, heteroaryl-(C₁-C₄)-alkyl, heterocyclyl-(C₁-
₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further
substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen,
methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C₁-C₄)-alkyl,
heteroaryl-(C₁-C₄)-alkyl, heterocyclyl-(C₁-C₄)-alkyl, cycloalkylalkyl, cycloalkyl,
cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any
of which may connect with R4 and preferably is C, O, N, OH, phosphate optionally
substituted one or more times with alkyl, OH, phosphate any of which may connect
with R4 and more preferably is O, OH, NH, optionally connecting with R4 thus
forming a ring.

48. The use of a cannabinoid as defined in claim 44, wherein R4 is selected from the
group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl,
alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl,
heterocycloalkyl, heteroaryl, aryl-(C₁-C₄)-alkyl, heteroaryl-(C₁-C₄)-alkyl, heterocyclyl-(C₁-
₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further
substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen,
methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C1-4)-alkyl, heteroaryl-(C1-4)-alkyl, heterocyclyl-(C1-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any of which may connect with R3 and preferably is C, N, O, P, OH, lower substituted alkyl, alkenyl, alkynyl, phenyl, optionally substituted with OH, methyl, dimethyl any of which may connect with R3 and more preferably is C, optionally connecting with R3 and optionally substituted with methyl, dimethyl or methyn.

49. The use of a cannabinoid as defined in claim 44, wherein R5 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C1-4)-alkyl, heteroaryl-(C1-4)-alkyl, heterocyclyl-(C1-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally bonding with R1, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C1-4)-alkyl, heteroaryl-(C1-4)-alkyl, heterocyclyl-(C1-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, phosphate or nitro, and preferably is C, N, O, optionally substituted with C, O, CH2OH, methyl, dimethyl, alkyl, alkenyl, alkynyl, phenyl, phosphate and more preferably is C, CO, optionally substituted with C, methyl, methn (CH2), optionally substituted with CH2OH.

50. The use of a cannabinoid as defined in claim 44, wherein R1 is selected from: C, O, N optionally substituted with O, OH, alkyl, alkenyl, alkynyl, or phosphate, optionally further substituted with alkyl or phosphate, when R2 as defined in claim 46 is C substituted with C, O, P, H, OH, 0S02, phosphate, alkyl, alkenyl, alkynyl such as (C1-CX), phenyl any of which may be substituted with methyl, dimethyl, sulfonyl, heterocycloalkyl, fluoride, phenyl or phosphate, when R3 as defined in claim 47 is C, O, N, OH, phosphate optionally substituted one or more times with alkyl, OH, phosphate any of which may connect with R4 thus forming a ring, when R4 as defined in claim 48 is C, N, O, P, OH, lower substituted alkyl, alkenyl, alkynyl, phenyl, optionally substituted one or more times with OH, methyl and/or dimethyl any of which may connect with R3, when R5 as defined in claim 49 is C, N, O, optionally substituted with C, O, CH2OH, methyl, dimethyl, alkyl, alkenyl, alkynyl, phenyl or phosphate.
51. The use of a cannabinoid according to claim 44, wherein R₁ as defined in claim 45 preferably is C, optionally substituted with H, OH, OCH₃ or phosphate when R₂ as defined in claim 46 preferably is C substituted with C, O, OSO₂, alkyl such as (C₃-C₉)ₙ any of which may be further substituted with methyl, dimethyl, alkyl such as (d-Cₓ), phenyl, phosphate or further substituted by fluoride, phosphate, methyl, dimethyl when R₃ as defined in claim 47 preferably is O, OH, NH, optionally connecting with R₄, when R₄ as defined in claim 48 preferably is C, optionally connecting with R₃ and optionally substituted with methyl, dimethyl or methyn, when R₅ preferably is C, CO, optionally substituted with C, methyl, methyn (CH₂), optionally substituted with CH₂OH and wherein x is an integer of from 1 to 15.

52. The use of at least one compound according to claim 4, wherein the cannabinoid or cannabimimetic compound is an eicosanoid or other of the general formula:

```
R₁ —— R₂
```

wherein R₁ and R₂ individually is a chemical moiety or a chemical bond.

53. The use of a cannabinoid or cannabimimetic compound of claim 52, wherein R₁ is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci₋₄)-alkyl, heteroaryl-(Ci₋₄)-alkyl, heterocyclyl-(Ci₋₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci₋₄)-alkyl, heteroaryl-(Ci₋₄)-alkyl, heterocyclyl-(Ci₋₄)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is (Ci-Cₓ) is saturated or unsaturated and optionally is substituted one or more times with lower alkyl, alkenyl, alkynyl, O, OH, N and wherein x is an integer of from 1 to 30, more preferably is (C₁-Cₓ) is saturated or unsaturated and optionally substituted with methyl, dimethyl, O, or N and wherein Y is an integer of from 15 to 21.
54. The use of a cannabinoid or cannabimimetic compound of claim 52, wherein R2 is
selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH,
hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted
lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(C_i-4)-alkyl, heteroaryl-(C_i-4)-alkyl,
heterocyclyl-(C_i-4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate,
optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine
(NH), halogen, methyl, OCH3, substituted lower alkyl, aryl, heterocyclyl, heteroaryl,
aryl-(C_i-4)-alkyl, heteroaryl-(C_i-4)-alkyl, heterocyclyl-(C_i-4)-alkyl, cycloalkylalkyl,
cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or
nitro, and preferably is C, N, O, NH2 optionally substituted one or more times with
lower alkyl, alkenyl, alkynyl, phenyl, OH, NH2 cycloalkane, methyl, OCH3, and
more preferably is N, O, NH2 optionally substituted with C, CH2OH, OH(CH2)2,
C2H4, C3H6, optionally further substituted one or more times with NH2, OH,
CH2OH, CH2Cl, phenyl, CH3 and/or OCH3.

55. The use of a cannabinoid or cannabimimetic compound as defined in claim 52,
wherein R1 as defined in claim 53 is (Cl-C_i-x) saturated or unsaturated, and
optionally is substituted one or more times with lower alkyl, alkenyl, alkynyl, O, OH,
N, when R2 as defined in claim 54 is C, N, O, NH2 optionally substituted one or
more times with lower alkyl, alkenyl, alkynyl, phenyl, OH, NH2 cycloalkane, methyl
or OCH3 and wherein x is an integer of from 1 to 30.

56. The use of a cannabinoid or cannabimimetic compound as defined in claim 52,
wherein R1 as defined in claim 53 preferably is (Cl-C_i-x), is saturated or unsaturated
and optionally substituted with methyl, dimethyl, O, or N when R2 as defined in
claim 54 preferably is N, O, NH2 optionally substituted with C, CH2OH, CH(CH2)2
(cyclopropane), optionally further substituted one or more times with CH2OH,
CH2Cl and wherein x is an integer of from 1 to 21.

57. The use of at least one compound according to claim 4, wherein the cannabinoid is
an aminoalkylindole of the general formula:
58. The use of a cannabinoid as defined in claim 57, wherein R1 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci_4)-alkyl, heteroaryl-(Ci_4)-alkyl, heterocycl-(Ci_4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci_4)-alkyl, heteroaryl-(Ci_4)-alkyl, heterocyclyl-(Ci_4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and preferably is C, O, N optionally substituted with O, phosphate, N, C, lower alkyl, OH, optionally further substituted with lower alkyl, OH, phosphate and more preferably is C, substituted with O, further substituted with methyl.

59. The use of a cannabinoid as defined in claim 57, wherein R2 is selected from the group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl, alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl, heterocycloalkyl, heteroaryl, aryl-(Ci_4)-alkyl, heteroaryl-(Ci_4)-alkyl, heterocycl-(Ci_4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen, methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(Ci_4)-alkyl, heteroaryl-(Ci_4)-alkyl, heterocycly-l-(Ci_4)-alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any of which may bond with R3, and preferably is C, N, O, optionally substituted with C, O, N, phosphate, lower alkyl optionally further substituted with lower alkyl, OH,
phosphate, any of which may bond with R3 and more preferably is C, substituted
with O, further substituted with C optionally bond forming with R3.

60. The use of a cannabinoid as defined in claim 57, wherein R3 is selected from the
group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl,
alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl,
heterocycloalkyl, heteroaryl, aryl-(C)-alkyl, heteroaryl-(C)-alkyl, heterocyclyl-(C)
alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further
substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen,
methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C)-alkyl,
heteroaryl-(C)-alkyl, heterocyclyl-(C)-alkyl, cycloalkylalkyl, cycloalkyl,
cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, any
of which may bond R2 and preferably is C, N, O, alkyl, alkenyl, alkynyl, optionally
substituted with C, N, O, OH, phosphate, halogen any of which may bond R2 and
more preferably is (C-Cx) and wherein x is an integer of from 1 to 3, optionally
substituted one or more times with O, dichloro-phenyl or morpholine and any of
which may bond R2.

61. The use of a cannabinoid as defined in claim 57, wherein R4 is selected from the
group of: C, S, N, O, optionally substituted with C, S, N, O, P, OH, hydrogen, alkyl,
alkenyl, alkynyl, phenyl, benzyl, amine (NH), halogen, substituted lower alkyl, aryl,
heterocycloalkyl, heteroaryl, aryl-(C)-alkyl, heteroaryl-(C)-alkyl, heterocyclyl-(C)
alkyl, cycloalkylalkyl, cycloalkyl, cycloalkenyl, phosphate, optionally further
substituted one or more times with C, S, N, O, OH, phenyl, amine (NH), halogen,
methyl, substituted lower alkyl, aryl, heterocyclyl, heteroaryl, aryl-(C)-alkyl,
heteroaryl-(C)-alkyl, heterocyclyl-(C)-alkyl, cycloalkylalkyl, cycloalkyl,
cycloalkenyl, alkoxy, carboxy, halogen, trifluoromethyl, cyano, amino, or nitro, and
preferably is C, N, O optionally substituted with C, N, O, OH, lower alkyl, alkenyl,
alynyl, phosphate, optionally further substituted one or more times with O, OH,
phenyl, diphenyl, morpholino, and halogen, and more preferably is C, optionally
substituted with C, O and/or diphenyl, optionally further substituted with morpholine.

62. The use of a cannabinoid as defined in claim 57, wherein R1 as defined in claim 58
is C, O, N optionally substituted with O, phosphate, N, C, lower alkyl, OH,
optionally further substituted with lower alkyl, OH or phosphate, when R2 as defined
in claim 59 is C, N, O, optionally substituted with C, O, N, phosphate, lower alkyl optionally further substituted with lower alkyl, OH, phosphate, any of which may bond with R3, when R3 as defined in claim 60 is C, N, O, alkyl, alkenyl, alkylnyl, optionally substituted with C, N, O, OH, phosphate, halogen any of which may bond R2, when R4 as defined in claim 61 is C, N, O optionally substituted with C, N, O, OH, lower alkyl, alkenyl, alkylnyl, phosphate, optionally further substituted one or more times with O, OH, phenyl, diphenyl, morpholino, and/or halogen.

63. The use of a cannabinoid as defined in claim 57, wherein R1 as defined in claim 58 preferably is C, substituted with O, further substituted with methyl when R2 as defined in claim 59 preferably is C, substituted with O, further substituted with C optionally bond forming with R3 when R3 as defined in claim 60 preferably is (C1-Cx) and wherein x is an integer of from 1 to 3, optionally substituted one or more times with O, dichloro-phenyl or morpholine when R4 as defined in claim 61 preferably is C, optionally substituted with C, O and/or diphenyl, optionally further substituted with morpholine.

64. The use of at least one compound according to claim 4, wherein the cannabinoid or cannabimimetic compound is selected from the group consisting of anandamide, delta-9-THC, delta-8-THC, cannabidiol, HU-210, KN38-7271 (BAY 38-7271), WIN 55,212 and CP55940 and the phosphate derivatives of these.

65. The use of at least one compound according to claim 4, wherein the adenosine analog is 5'-AMP.

66. The use of at least one compound according to claim 4, wherein the adenosine receptor agonist is selected from the group consisting of NECA, (R)-PIA, (S)-PIA, AB-NECA, CCPA, CGS 21680, CGS 21680, CGS 24012, 2-chloroadenosine, 2-hexynyl-NECA, IB-MECA, N(6)-cyclopentyladenosine, (R,S)-PHPNECA, IAB-MECA, IB-MECA, CI-IB-MECA, cyclopentyladenosine, I-ABA, IAB-MECA, MCP-NECA, MPC-MECA, PENECA, AB-MECA, APNEA, CV-1674, CV-1808, cyclopentyladenosine, 2-hexynyl-NECA, metrifudil, N(6)-cyclohexyladenosine, LUF5831 and Tecadenoson (CV-510).
67. The use of at least one compound according to claim 4, wherein the adenosine uptake inhibitor is dipyridamole or theophyllin.

68. The use of at least one compound according to claim 4, wherein the neurotensin analog is selected from the group consisting of NT64D, NT64L, NT65L, NT66D, NT66L, NT67L, NT69L, NT71, NT72, NT73, NT74, NT75, NT76, NT77, Trp11NT, contulakin-G, EISAI-1, EISAI-2, JMV2004, JMV431, JMV449, JMV457, JMV458, large neuromedin, large neurotensin, neuromedin, neurotensin, [125I]neurotensin, Thr10contulakin-G, D-Trp11-neurotensin, levocabastine, SR48692, SR48692, xenin, PD-149163 and CGX-1160.

69. The use of at least one compound according to claim 4, wherein the thyroxine derivative is selected from the group consisting of Thyroxine (T4), 3,5,3'-triiodothyronine (T3), Thyronamine (TOAM); 3-lodothyronamine (T1AM), 3,5-Diiodothyronamine (T2AM) and 3,5,3'-Triiodothyronamine (T3AM).

70. The use of at least one compound according to claim 4, wherein the cytochrome c oxidase inhibitor is selected from the group consisting of hydrogen sulfide (H₂S), cyanide (CN) or its derivates such as hydrogen cyanide (HCN) or sodium nitroprusside (Na₂[Fe(CN)₅NO]-2H₂O), Azide and its derivates, Carbon monoxide (CO) and Sodium sulfide (Na₂S).

71. The use of at least one compound according to claim 4, wherein the oxygen tension reducer is selected from the group consisting of Carbon monoxide (CO), Sodium sulfide (Na₂S) and hydrogen sulfide (H₂S).

72. The use according to claim 1, wherein the at least one compound is selected among the vanilloid receptor agonist of any of claims 22 to 36 and the cannabinoid or cannabimimetic compound is the cannabinoid of any of claims 37 to 64 and the adenosine compound of any of claims 65 to 67 and the neurotensin or neurotensin analog of claim 68 and the thyroxine derivative of claim 69 and the cytochrome c oxidase inhibitor of claim 70 and the oxygen tension reducer of claim 71.

73. The use of at least one compound according to claim 1, wherein the at least one compound is one compound.
74. The use of at least one compound according to claim 1, wherein the at least one compound is a combination of two, such as three, for example four, such as five for example six, such as seven compounds.

75. The use of at least one compound according to claim 1, wherein the at least one compound is a combination of a vanilloid receptor agonist administered parenterally together with one or more of the following compounds: cannabinoids and/or cannabimimetic compounds and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to induce hypothermia.

76. The use of at least one compound according to claim 1, wherein the at least one compound is a combination of a cannabinoid and/or cannabimimetic compound administered parenterally together with one or more of the following compounds: vanilloid receptor agonists and/or adenosine and/or adenosine analogs and/or neurotensin and/or neurotensin analogs and/or thyroxine derivatives and/or cytochrome c oxidase inhibitors and/or oxygen tension reducers to induce hypothermia.

77. The use according to claims 74 to 76 wherein the combination comprises at least one compound selected from: dihydrocapsaicin, delta-8-THC, delta-8-THC-phosphate, and HU-210.

78. The use according to claims 74 to 76 wherein the combination comprises one of the following combinations: dihydrocapsaicin and delta-8-THC or dihydrocapsaicin and delta-8-THC-phosphate or dihydrocapsaicin and HU-210.

79. The use according to claim 1 for the manufacture of a medicament according to claims 22 to 71 for the induction of hypothermia in an individual suffering from or at risk of suffering from ischemia.
80. The use according to claim 1 for the manufacture of a medicament according to any of claims 22 to 71 for prophylaxis and/or treatment of ischemia in connection with cardiovascular diseases, asphyxia and/or traumatic brain injuries.

81. The use according to claim 1 and/or 80, wherein the ischemia is due to cardiovascular diseases such as: myocardial infarction, cardiac arrest, stroke, arterial aneurism, subarachnoid hemorrhage, arteriosclerosis, angina pectoris, hypertension, hypercholesterolemia, cardiac arrhythmia, cardiomegaly, cardiomyopathy, heart valve regurgitation and heart valve stenosis.

82. The use according to claims 1 and/or 80, wherein the ischemia is due to asphyxia such as: perinatal asphyxia and/or non-perinatal asphyxia.

83. A medicament comprising at least one compound according to any of claims 22 to 71 capable of inducing hypothermia in an individual as defined in any of claims 1 and 79 to 82.

84. The medicament according to claim 83, for prophylactic and/or therapeutic applications.

85. The medicament according to any of claims 83 and 84, for therapeutic applications.

86. The medicament according to any of claims 83 to 85, wherein the medicament induces hypothermia of between 32 and 36 degree Celsius.

87. The medicament according to any of claims 83 to 86, comprising at least one compound selected from the vanilloid receptor agonist of any of claims 22 to 36 and the cannabinoid or cannabimimetic compound of any of claims 37 to 64 and the adenosine compound of any of claims 65 to 67 and the neurotransin or neurotensin analog of claim 68 and the thyroxine derivative of claim 69 and the cytochrome c oxidase inhibitor of claim 70 and the oxygen tension reducer of claim 71.

88. The medicament according to any of claims 83 to 87, wherein at least one compound induces hypothermia rapidly.
89. The medicament according to any of claims 83 to 88, wherein at least one compound induces hypothermia slowly.

90. The medicament according to any of claims 83 to 89, comprising a further active ingredient.

91. The medicament according to claim 90, wherein the further active ingredient is selected from the group of: neurotensins, analgesics, opioids, GABAs and adrenergic antagonists.

92. The medicament according to any of claims 83 to 91, comprising a pharmaceutically acceptable carrier.

93. The medicament according to any of claims 83 to 92, wherein the pH of the composition is between pH 5 and pH 9.

94. A kit of parts comprising the medicament as defined in any of claims 83 to 93.

95. Use of a combination of compounds according to any of claims 22 to 71 for the preparation of a medicament for obviating the effect of the compounds according to claim 1.

96. A method for treating ischemia in an individual in need thereof comprising administering to said individual an effective amount of at least one compound capable of inducing hypothermia, said compounds being as defined in any of claims 1 to 95.

97. The use of at least one compound for induction of hypothermia in a human being for treatment of ischemic damages, wherein the compound is as defined in any of claims 1 to 95.

98. The use of at least one compound for induction of hypothermia in a human being suffering from or at risk of suffering from ischemia, wherein the compound is as defined in any of claims 1 to 95.
99. The use of at least one compound according to claim 97 or 98, for prophylaxis and/or treatment of ischemic damages in connection with cardiovascular diseases, asphyxia, traumatic brain injuries and/or organ transplantation.

100. The use of at least one compound according to claim 99, wherein the ischemia is due to cardiovascular diseases such as: myocardial infarction, acute coronary syndrome, cardiac arrest, stroke, arterial aneurism, subarachnoid haemorrhage, arteriosclerosis, angina pectoris, hypertension, hypercholesterolemia, cardiac arrhythmia, cardiomegaly, cardiomyopathy, cardiac surgery, heart valve regurgitation and heart valve stenosis.

101. The use of at least one compound according to claim 98, wherein the ischemia is due to asphyxia such as: pre-natal, perinatal asphyxia and/or non-perinatal asphyxia.

102. The use of at least one compound for induction of hypothermia and/or reduction in body temperature in a human being for treatment of fever, hyperpyrexia, hyperthermia, and/or malignant hyperpyrexia, wherein the compound is as defined in any of claims 1 to 71.

103. The use of at least one compound for induction of hypothermia and/or reduction in body temperature in a human being before and/or during a surgical procedure to improve the outcome of said surgical procedure, wherein the compound is as defined in any of claims 1 to 71.
Fig. 2.
Fig. 4

Dihydrocapsaicin (Temperature difference) Intravenous infusion: start dose 0.6 mg/kg/hr, 4-hour treatment; n=8

Hours from infusion start

Treatment group

Temp diff from baseline (°C)
Fig. 5

Dihydrocapsaicin (Temperature difference) Single intramuscular bolus injection

Temporal Diff from baseline (°C)
Fig. 8

IV infusion of Dihydropasacain in calves, start dose 0.6 mg/kg/h, 4 hours in temperature target, n=4
(225 and 2198: sudden stop of infusion; 2389 and 1718: infusion slowly stopped over three hours)

Temperature difference from baseline (°C)