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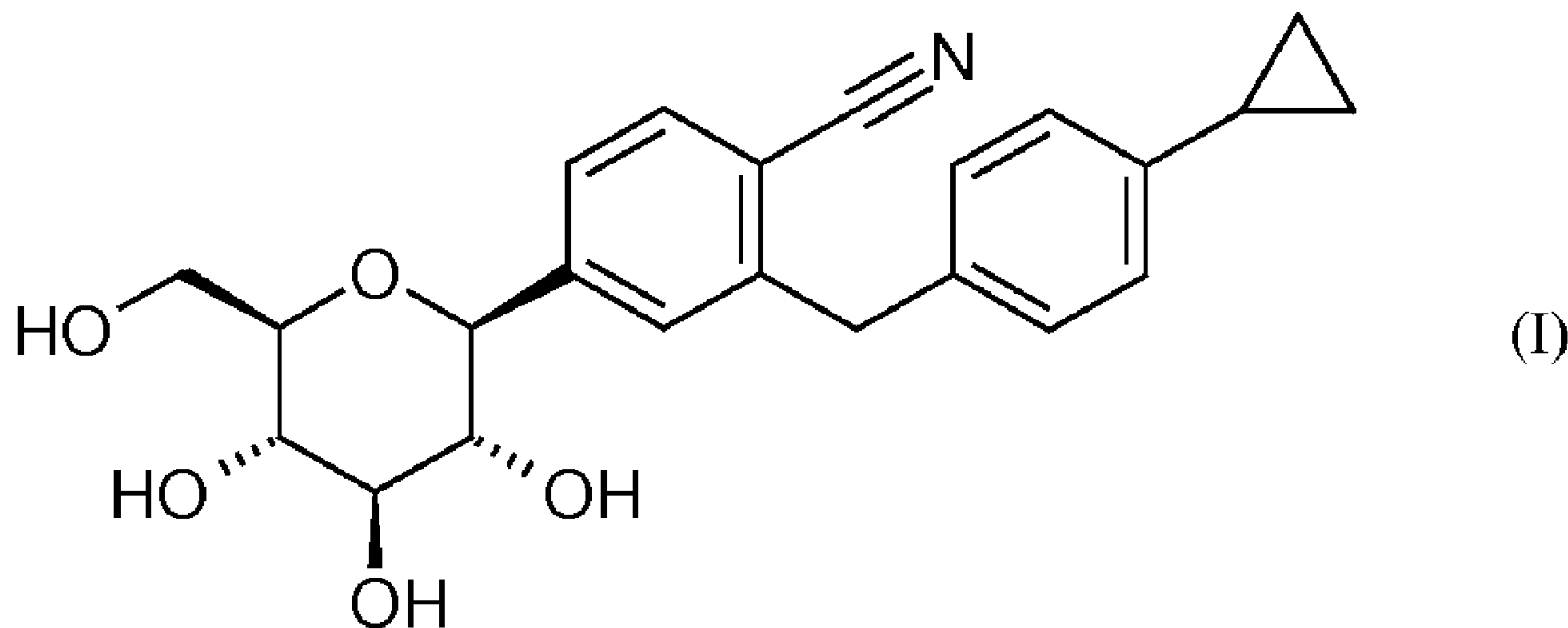
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(54) Titre : COMPOSITIONS PHARMACEUTIQUES LIQUIDES COMPRENANT DES INHIBITEURS DE SGLT-2

(54) Title: LIQUID PHARMACEUTICAL COMPOSITIONS COMPRISING SGLT-2 INHIBITORS



(57) Abrégé/Abstract:

The invention relates to novel liquid pharmaceutical compositions comprising at least one SGLT-2 inhibitor and one or more polar organic solvents, wherein the at least one SGLT-2 inhibitor comprises 1-cyano-2-(4-cyclopropylbenzyl)-4-(β-D-glucopyranos-1-yl)-benzene according to formula (I); as well as corresponding processes of manufacturing such liquid pharmaceutical compositions and their medical uses.

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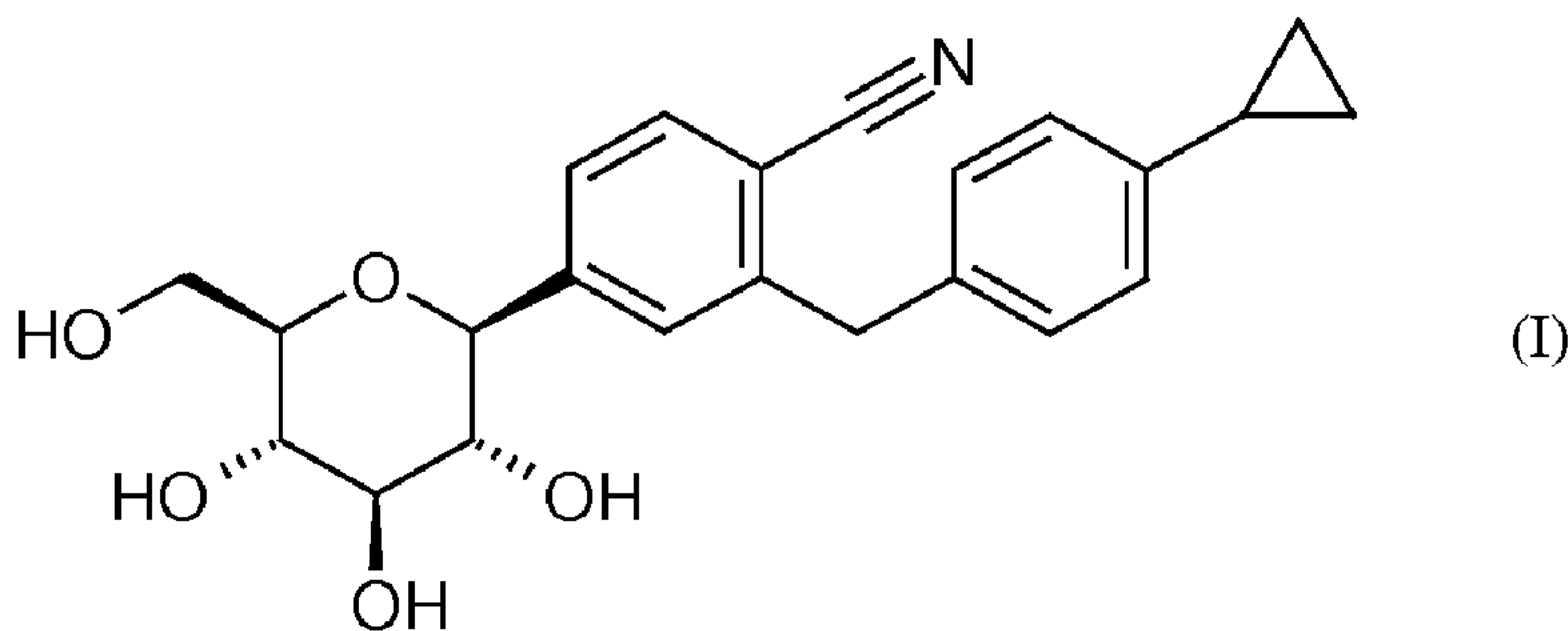
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(54) Title: LIQUID PHARMACEUTICAL COMPOSITIONS COMPRISING SGLT-2 INHIBITORS



(57) Abstract: The invention relates to novel liquid pharmaceutical compositions comprising at least one SGLT-2 inhibitor and one or more polar organic solvents, wherein the at least one SGLT-2 inhibitor comprises 1-cyano-2-(4-cyclopropylbenzyl)-4-(β-D-glucopyranos-1-yl)-benzene according to formula (I): as well as corresponding processes of manufacturing such liquid pharmaceutical compositions and their medical uses.



WO 2017/032799 A1

LIQUID PHARMACEUTICAL COMPOSITIONS COMPRISING SGLT-2 INHIBITORS

FIELD OF THE INVENTION

The invention relates to the field of medicine, particularly veterinary medicine. In particular, the invention
5 relates to novel pharmaceutical compositions comprising at least one SGLT-2 inhibitor.

BACKGROUND OF THE INVENTION

The treatment of diabetes and other metabolic disorders includes the inhibition of the renal sodium-dependent
glucose co-transporter SGLT-2. SGLT-2 in the kidney regulates glucose levels by mediating the reabsorption of
10 glucose back into the plasma following filtration of the blood. SGLT-2 inhibition thus induces glucosuria and
may reduce blood glucose levels.

A large variety of SGLT-2 inhibitors are known. A pharmaceutical formulation of SGLT-2 inhibitors is essential
in order to administer such compounds in an adequate way to the patient.

SGLT-2 inhibitors are for instance described in WO 2007/028814 which is directed to crystalline forms of 1-
15 chloro-4-([beta]-D-glucopyranos-1-yl)-2-(4-ethynyl-benzyl)-benzene, a method for the preparation thereof, as
well as the use thereof for preparing medicaments. It discloses solutions of 1-chloro-4-([beta]-D-glucopyranos-1-
yl)-2-(4-ethynyl-benzyl)-benzene in a solvent or a mixture of solvents and further specifies exemplarily suitable
organic solvents such as ethanol or ethanol/water mixtures.

WO 2007/080170 describes crystalline forms of 1'-(1-methylethyl)-4'-[(2-fluoro-4-methoxyphenyl) methyl]-5'-
20 methyl-1H-pyrazol-3'-O-[beta]-D-glucopyranoside, a method for the preparation thereof, as well as the use
thereof for preparing medicaments. It discloses solutions of 1'-(1-methylethyl)-4'-[(2-fluoro-4-methoxyphenyl)
methyl]-5'-methyl-1H-pyrazol-3'-O-[beta]-D-glucopyranoside in a solvent or a mixture of solvents and further
specifies exemplarily suitable organic solvents such as ethanol or ethanol/water mixtures.

In addition, WO 2007/093610 describes glucopyranosyl-substituted benzonitrile derivatives, pharmaceutical
25 compositions containing such compounds, their medical uses as well as processes for their manufacture. It
mentions that such glucopyranosyl-substituted benzonitrile derivatives can be formulated among other with one
or more inert carriers and/or diluents, such as water/ethanol, water/glycerol, propylene glycol and the like. It
further discloses among many other compounds also 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-
yl)-benzene.

30 Further SGLT-2 inhibitors are described in WO 2007/128749 which relates to glucopyranosyl-substituted
benzonitrile derivatives, pharmaceutical compositions containing such compounds, their medical uses as well as
processes for their manufacture. It mentions that such glucopyranosyl-substituted benzonitrile derivatives can be
formulated among other with one or more inert carriers and/or diluents, such as water/ethanol, water/glycerol,
propylene glycol and the like. It further discloses among many other compounds also 1-cyano-2-(4-cyclopropyl-
35 benzyl)-4-(β-D-glucopyranos-1-yl)-benzene.

WO 2008/144316 describes crystal structures of a specific glucopyranosyl-substituted benzene derivative being
an H-1 form, H-2 form or the (S)-propylene glycol form. It discloses solutions of such specific glucopyranosyl-
substituted benzene derivative in water-miscible organic solvents.

Another prior art document WO 2013/079501 is directed to crystalline dapagliflozin hydrate and a method for the preparation thereof. It discloses solutions of dapagliflozin in a solvent or a mixture of solvents and further specifies exemplarily suitable solvents such as water and C1-C4 alcohols or mixtures thereof.

WO 2014/016381 (US 2014/031540) describes crystalline complexes of 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene with natural amino acids, methods for the preparation thereof as well as the use thereof for preparing medicaments. It discloses solutions of 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene in a solvent or a mixture of solvents and further specifies exemplarily suitable organic solvents such as C1-C4 alkanols, ethanol and mixtures thereof, in particular with water.

Furthermore, WO 2014/195966 describes amorphous forms of canagliflozin and processes of manufacturing thereof as well as corresponding pharmaceutical compositions and their medicinal uses. It discloses solutions of canagliflozin in one or more organic solvents and further specifies exemplarily suitable organic solvents such as ethanol.

Further challenges known in the prior art are the limited solubility of SGLT-2 inhibitors in water due to their positive $\log_{10}P$ values, which typically influences the bioavailability in the body of a patient or makes it difficult to find adequate solvents to get the substance dissolved in an liquid formulation before administering it into the body of a patient.

Further prior art is as follows:

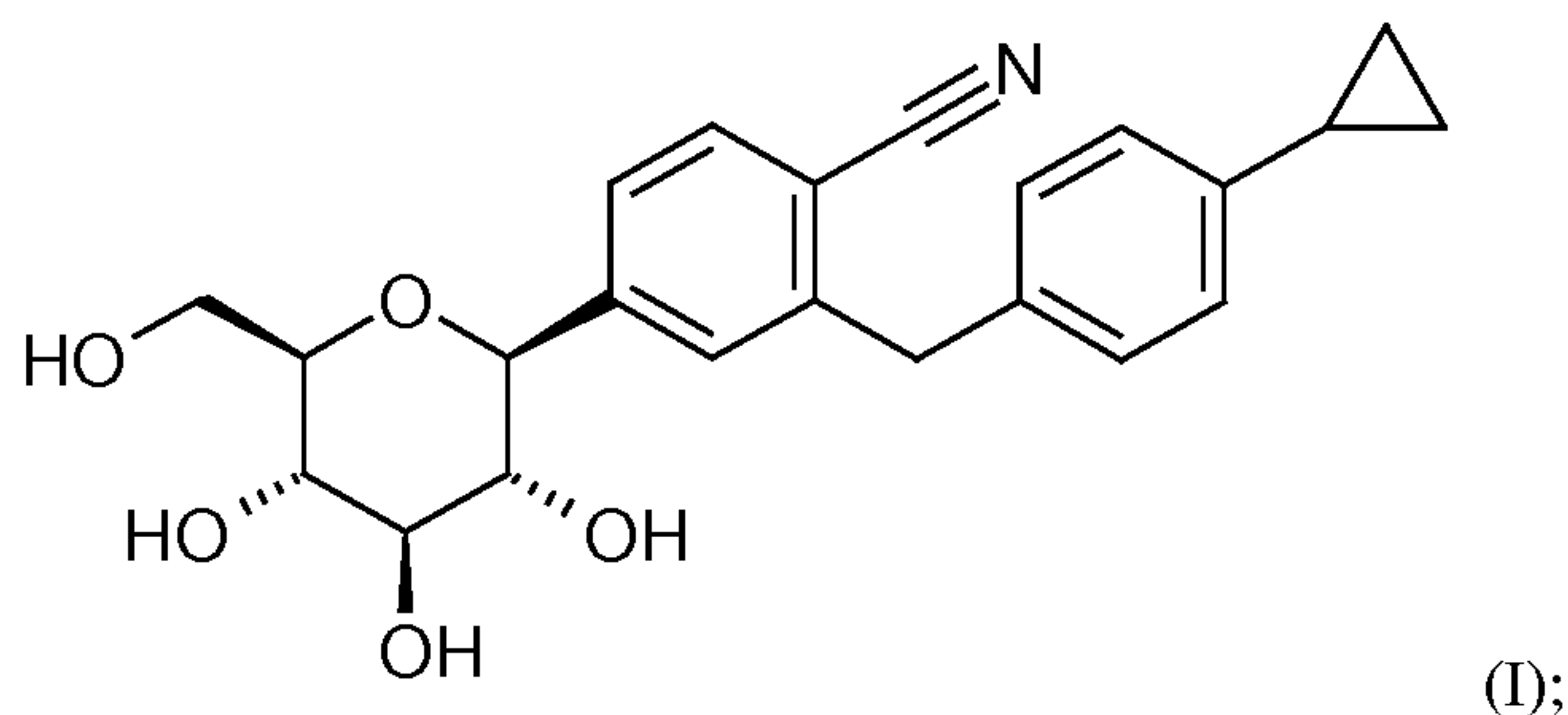
Xu G et al. (Journal of Medical Chemistry 2014, 57: 1236-1251) is directed to the design, synthesis and biological evaluation of deuterated C-aryl glycosides as potent and long-acting renal SGLT-2 inhibitors for the treatment of type 2 diabetes.

WO 2015/110402 relates to SGLT-2 inhibitors for use in the treatment and/or prevention of metabolic disorders in canine animals.

There is an urgent need for a directly administrable pharmaceutical composition comprising at least one SGLT-2 inhibitor which overcomes the problems of the prior art as described above.

SUMMARY OF THE INVENTION

The present invention concerns a liquid pharmaceutical composition comprising at least one SGLT-2 inhibitor and one or more polar organic solvents, wherein the at least one SGLT-2 inhibitor comprises, preferably is, 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene according to formula (I):



wherein more preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene is the only SGLT-2 inhibitor contained in such liquid pharmaceutical composition.

The present invention also concerns a liquid pharmaceutical composition as described and claimed herein for use in a method for treating and/or preventing one or more medicinal indications in a subject in need of such treatment and/or prevention, preferably an animal, more preferably a mammal, in particular a horse, cat or dog, selected from among the medicinal indications:

- (i) a metabolic disorder of an equine animal, wherein preferably the metabolic disorder is one or more disorders selected from insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity, wherein preferably the metabolic disorder is insulin resistance, hyperinsulinemia, and/or a clinical condition associated with insulin resistance and/or hyperinsulinaemia; wherein preferably said clinical condition is one or more conditions selected from impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity;
- (ii) a metabolic disorder of an equine animal, wherein the metabolic disorder is one or more disorders selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome, wherein preferably the metabolic disorder is a clinical condition/sign associated with insulin resistance and/or hyperinsulinaemia, wherein said clinical condition/sign preferably is one or more conditions selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome;
- (iii) a metabolic disorder of a feline animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, diabetes mellitus type 1 or type 2, insulin resistance, obesity, hyperglycemia, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, atherosclerosis, inflammation of the pancreas, neuropathy and/or Syndrome X (metabolic syndrome) and/or loss of pancreatic beta cell function and/or wherein the remission of the metabolic disorder, preferably diabetic remission, is achieved and/or maintained;
- (iv) a metabolic disorder of a canine animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, obesity, hyperglycemia, hyperglycemia induced cataract formation, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, inflammation of the pancreas, metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, and/or Syndrome X (metabolic syndrome), preferably pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, wherein preferably the development of hyperglycemia induced cataract formation is prevented or remission is achieved and/or wherein preferably the development of metabolic disorder consequences,

such as hypertension, renal dysfunction and/or musculooskeletal disorders, is prevented or progression is slowed or remission is achieved.

The present invention further concerns a process for producing the liquid pharmaceutical composition as described and claimed herein, comprising the steps:

- (i) mixing the one or more polar organic solvents;
- (ii) optionally, adding water to the mixture resulting from step (i);
- (iii) dissolving 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene in the mixture resulting from step (i) or optionally step (ii);
- (iv) optionally, dissolving further excipients, such as pH modifier(s), flavor(s), sweeteners, solubilizing agents, viscosity-enhancing agents and the like, in the mixture resulting from step (iii);
- (v) optionally, filtrating the mixture resulting from step (iii) or optionally step (iv);

whereby, optionally, independently from each other after any of the individual process steps – be they mandatory or optional – an additional mixing step is performed.

In the course of the present invention, such process steps (i) to (v) do not need to be carried out in the given order, but can also be performed in any other meaningful order, e.g. (ii)+(i)+(iv)+(iii)+(v). It is within the knowledge of the skilled person to vary the order of process steps in order to obtain the desired process result, i.e. the liquid pharmaceutical composition according to the present invention. For instance, if one or more viscosity-enhancing agents are added, it is preferred to heat the mixture up for complete dissolution of the one or more viscosity-enhancing agents. In turn such resulting mixture needs to be cooled down before the API 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene (in the form of its L-proline-water cocrystal) is added in order to avoid unnecessary and unwanted degradation of the substance through such heating steps.

The present invention further concerns a kit-of-parts comprising:

- (a) a liquid pharmaceutical composition as described and claimed herein; and
- (b) a package leaflet including the information that the liquid pharmaceutical composition is to be used for the prevention and/or treatment of one or more medicinal indications in a subject in need of such prevention and/or treatment, which are selected from among the medicinal indications:
 - (i) a metabolic disorder of an equine animal, wherein preferably the metabolic disorder is one or more disorders selected from insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity, wherein preferably the metabolic disorder is insulin resistance, hyperinsulinemia, and/or a clinical condition associated with insulin resistance and/or hyperinsulinaemia; wherein preferably said clinical condition is one or more conditions selected from impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity;
 - (ii) a metabolic disorder of an equine animal, wherein the metabolic disorder is one or more disorders selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis,

hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome, wherein preferably the metabolic disorder is a clinical condition/sign associated with insulin resistance and/or hyperinsulinaemia, wherein said clinical condition/sign preferably is one or more conditions selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome;

(iii) a metabolic disorder of a feline animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, diabetes mellitus type 1 or type 2, insulin resistance, obesity, hyperglycemia, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, atherosclerosis, inflammation of the pancreas, neuropathy and/or Syndrome X (metabolic syndrome) and/or loss of pancreatic beta cell function and/or wherein the remission of the metabolic disorder, preferably diabetic remission, is achieved and/or maintained;

(iv) a metabolic disorder of a canine animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, obesity, hyperglycemia, hyperglycemia induced cataract formation, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, inflammation of the pancreas, metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, and/or Syndrome X (metabolic syndrome), preferably pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, wherein preferably the development of hyperglycemia induced cataract formation is prevented or remission is achieved and/or wherein preferably the development of metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, is prevented or progression is slowed or remission is achieved.

The advantages of the liquid pharmaceutical compositions according to the present invention are as follows:

- They are suitable for direct administration to a subject without further mandatory processing and/or purification steps. Preferably they are therefore sterile and comply with GMP manufacturing conditions as well as GCP compliant clinical protocols.
- They are stable against undesired contamination by / growth of microorganisms.
- Ethanol is not necessarily needed as polar organic solvent or can be significantly reduced to a level which is expected to be accepted by animals.

DETAILED DESCRIPTION OF THE INVENTION

Before the embodiments of the present invention are described in further details it shall be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All given ranges and values may vary by 1 to 5 % unless indicated otherwise or known otherwise by the person skilled in the art, therefore, the term “about” was usually omitted from the description and claims. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the substances, excipients, carriers, and methodologies as reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

In the course of the present invention 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene is also referred to as “the substance” and is herewith understood to also comprise co-crystal 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene – L-proline as well as the co-crystal monohydrate 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene – L-proline – water (as disclosed in WO 2014/016381). Generally, in the case of disclosed and claimed mass concentrations (% w/w) and amounts (g, mg) the mass concentration or amount always refers to the “free base” 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene – L-proline, i.e. excluding L-proline and crystal water, unless otherwise explicitly stated –even though in practice (and in the example section) co-crystal 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene – L-proline – water is actually added/used.

In the course of the present invention the term “suitable for direct administration to a subject” in connection with “liquid pharmaceutical composition” means that such liquid pharmaceutical compositions can be directly administration to a subject without further mandatory processing and/or purification steps and explicitly excludes (mixtures of) organic solvents that are solely mentioned in the context of producing crystalline complexes of SGLT2 inhibitors. Preferably, such “liquid pharmaceutical composition” that are “suitable for direct administration to a subject” are therefore sterile and/or comply with GMP manufacturing conditions as well as GCP compliant clinical protocols.

In one aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein the liquid pharmaceutical composition is suitable for direct administration to a subject, preferably an animal, more preferably a mammal, in particular a horse, cat or dog; wherein preferably the liquid pharmaceutical composition is sterile.

In another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein the liquid pharmaceutical composition is a solution, an emulsion or a suspension, preferably a solution, an emulsion or a suspension with an NTU value of equal to or less than 10.0, more preferably equal to or less than 7.0, even more preferably equal to or less than 3.0, and most preferably a solution, in particular a solution with an NTU value of equal to or less than 3.0.

In the course of the present invention the term “NTU” refers to Nephelometric Turbidity Units and to an opalescent value as defined and described in European Pharmacopoeia 8th edition (Ph. Eur. 8, Chapter 2.2.1. “Clarity and degree of opalescence of liquids”).

- 5 In another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein the one or more polar organic solvents are independently from each other characterized by a negative $\log_{10}P$ value, preferably a negative decadic logarithmic partition coefficient (P) in an n-octanol/water system according to formula (II):

$$10 \quad \log_{10} P_{n\text{-octanol/water}} = \frac{\text{concentration of unionized compound in n-octanol}}{\text{concentration of unionized compound in water}} \quad (\text{II})$$

- In a further aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition as a whole is characterized by a negative LogP-Parameter, preferably a negative LogP-Parameter of equal to or less than -2.0 (i.e. $-2.0 \leq \text{LogP-Parameter} < 0$).
 15 For the avoidance of doubt, the LogP-Parameter is defined as in Eq. 4 of Example 1 and is not identical with and should not be mistaken for the (negative) $\log_{10}P$ value as given for the one or more polar organic solvent(s).

- In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and
 20 claimed herein, wherein the one or more polar organic solvents are selected from ethanol ($\log_{10}P$: -0.16), propane-1,2-diol (propylene glycol; $\log_{10}P$: -0.79), propane-1,2,3-triol (glycerol; $\log_{10}P$: -1.84). The $\log_{10}P$ values were taken from <http://www.chemicalize.org/>.

- In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and
 25 claimed herein, wherein such liquid pharmaceutical composition comprises at least two different polar organic solvents, preferably two or three different polar organic solvents, more preferably propane-1,2-diol (propylene glycol) and propane-1,2,3-triol (glycerol) or ethanol and propane-1,2-diol (propylene glycol) or ethanol and propane-1,2-diol (propylene glycol) and propane-1,2,3-triol (glycerol). Preferably, if ethanol is present in the liquid pharmaceutical composition as described and claimed herein, it is present at no more than 20 g/100 mL
 30 (20 % w/w), preferably it is present at no more than 15 g/100 mL (15 % w/w), more preferably it is present at no more than 10 g/100 mL (15 % w/w), most preferably it is present at 8 g/100 mL (8 % w/w).

- In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and
 claimed herein, wherein such liquid pharmaceutical composition does not comprise ethanol as the one or more
 35 polar organic solvents.

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition does not comprise only propane-1,2-diol (propylene glycol) as single polar organic solvent.

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition additionally comprises water, preferably aqueous buffer, such as citric acid buffer (preferably with pH 6.0) or phosphate buffer (preferably with pH 6.8).

5 In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition has a measured pH value of from 3 to 9, preferably from 4 to 9, more preferably from 5.0 to 8.5, even more preferably from 6.0 to 8.5 and most preferably from 6.0 to 7.5. For the avoidance of doubt, the term „measured pH value“ refers to the pH value actually measured for the whole liquid pharmaceutical composition according to the present invention, although
10 puristically only pH values of pure aqueous systems can be measured by means of standard pH determination methods.

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition additionally comprises one or more solubilizing
15 agents, preferably selected from the group consisting of: “surfactants, anionic surfactants, non-ionic surfactants, hydrogenated castor oils, polyoxyethylene-polyoxypropylene block copolymers, polyethylene glycols, propylenglycol derivatives”, more preferably selected from the group consisting of: “Sodium dodecyl sulphate (SDS), Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil, Macrogol glycerol hydroxystearate 40), polysorbate 20, Lutrol F 68 (Poloxamer 188), PEG 300, propylenglycol monolaurate” and/or additionally
20 comprises one or more viscosity-enhancing agents, preferably selected from the group consisting of: “inorganic gel forming agents, organic gel forming agents, cellulose derivatives”, more preferably selected from the group consisting of: “hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose, silicon dioxide” and/or additionally comprises one or more flavours and/or sweeteners, preferably selected from the group consisting of: “honey flavor, lime/salvia flavor, jasmine flavor, lavender flavor, peppermint flavor, raspberry flavor, lemon flavor,
25 herbs flavor, saccharine, aspartame”.

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition does not comprise any apolar organic solvents, which are preferably and independently from each other characterized by a $\log_{10}P$ value of equal to or higher
30 than 0.

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, wherein such liquid pharmaceutical composition is for oral and/or parenteral administration, preferably oral administration.

35

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, comprising

- (i) 0.5 – 5.0 g/100 mL (% w/w), preferably 1.0 – 1.5 g/100 mL (% w/w) 1-cyano-2-(4-cyclopropylbenzyl)-4-(β -D-glucopyranos-1-yl)-benzene;

- (ii) 10 – 60 g/100 mL (% w/w), preferably 35 – 60 g/100 mL (% w/w), more preferably 50 – 60 g/100 mL (% w/w) propylene glycol;
- (iii) 0 – 60 g/100 mL (% w/w), preferably 0 – 52 g/100 mL (% w/w) glycerol;
- (iv) 0 – 20 g/100 mL (% w/w), preferably 0 – 15 g/100 mL (% w/w), more preferably 0 – 10 g/100 mL (% w/w), most preferably 0 – 8 g/100 mL (% w/w) ethanol;
- (v) 0 – 1 g/100 mL (% w/w), preferably 0 – 0.15 g/100 mL (% w/w) flavor and/or sweetener, more preferably selected from the group consisting of “honey flavor, lime/salvia flavor, jasmine flavor, lavender flavor, peppermint flavor, raspberry flavor, lemon flavor, herbs flavor, saccharine, and/or aspartame”;
- (vi) 0 – 52 g/100 mL (% w/w), preferably 0 – 40 g/100 mL (% w/w) aqueous buffer, preferably citric acid buffer pH 6.0 or phosphate buffer pH 6.8;
- (vii) 0 – 10 g/100 mL (% w/w), preferably 0 – 8 g/100 mL (% w/w) solubilizing agent, preferably selected from the group consisting of: “surfactants, anionic surfactants, non-ionic surfactants, hydrogenated castor oils, polyoxyethylene-polyoxypropylene block copolymers, polyethylene glycols, and/or propylenglycol derivatives”, more preferably selected from the group consisting of: “Sodium dodecyl sulphate (SDS), Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil, Macrogol glycerol hydroxystearate 40), polysorbate 20, Lutrol F 68 (Poloxamer 188), PEG 300, and/or propylenglycol monolaurate”;
- (viii) 0 – 5 g/100 mL (% w/w), preferably 0 – 0.5 g/100 mL (% w/w) viscosity-enhancing agent, preferably selected from the group consisting of “inorganic gel forming agents, organic gel forming agents, and/or cellulose derivatives”, more preferably selected from the group consisting of “hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose, and/or silicon dioxide”.

In yet another aspect, the present invention relates to a liquid pharmaceutical composition as described and claimed herein, selected from:

Ingredient	Compositi on 1 [% (w/w)]	Compositi on 2 [% (w/w)]	Compositi on 3 [% (w/w)]	Compositi on 4 [% (w/w)]	Compositi on 5 [% (w/w)]	Compositi on 6 [% (w/w)]	Compositi on 7 [% (w/w)]
1-cyano-2-(4-cyclopropylbenzyl)-4-(β-D-glucopyranos-1-yl)-benzene	1.5	1.5	1.5	1.5	1.5	1.5	1.0
Propylene glycol	60	60	60	60	60	60	52
Water	23.5	27.5	22.4	23.2	27.0	21.9	49.9
Glycerol 85%	17.6	0.0	11.8	17.6	0.0	11.8	-
Ethanol, abs.	-	8	5	-	8	5	-
NaOH, 1 N	4.71	5.51	4.49	4.63	5.41	4.39	-

Citric acid, monohydrate	0.36	0.42	0.34	0.35	0.41	0.33	-
Honey flavor	-	-	-	0.15	0.15	0.15	-
Disodium hydrogen phosphate dodecahydrate	-	-	-	-	-	-	0.890
Potassium hydrogen phosphate	-	-	-	-	-	-	0.350

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the correlation of Turbidity and the LogP-Parameter (according to Example 1, Eq. 4) of solvent mixtures as depicted in Table 2 used for preparing solutions of 1% (w/w) or 1.5% (w/w) 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene (the substance).

EXAMPLES

The following examples serve to further illustrate the present invention; but the same should not be construed as a limitation of the scope of the invention disclosed herein.

Example 1

The testing criteria applied are those for evaluation of the clarity of a liquid (formulation) comprising 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene according to Pharm. Eur. 8. Concerning the Ph. Eur. 8, Chapter 2.2.1. "Clarity and degree of opalescence of liquids", a liquid is considered clear if its opalescence is not more pronounced than that of reference suspension I having an opalescent value of 3 NTU (Table 1).

Table 1: Measurements of reference suspensions I-IV according Pharm. Eur. 8, Chapter 2.2.1

Formazin suspensions	Opalescent values (NTU)
Reference suspension I	3
Reference suspension II	6
Reference suspension III	18
Reference suspension IV	30
Standard of opalescence	60
Primary opalescent suspension	4000

In the following Table 2 exemplary pharmaceutical compositions of solvents which were mixed with 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene (the substance) according to the present invention are given in detail (Gly: glycerol; PG: propylene glycol, EtOH: ethanol). The turbidity was measured by using a Hach Lange 2100 N IS apparatus.

The following procedure was used to prepare the samples:

1. Weigh entire amount of solvents into vessel

2. Weigh entire amount of buffer into the vessel, close the vessel and mix it.
3. Weigh entire amount of 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene into the vessel, close the vessel and mix it over about 2 minutes.
4. Place the vessel into an ultrasonic bath until the solution is particle free and free of air bubbles.
5. Measure turbidity and pH value

Table 2:

V	Gly [%]	PG [%]	EtOH [%]	Buffer [%]	Buffer pH 6.8	Buffer pH 6.0	Addition of the substance [% (m/m)]	Turbidity [NTU]	pH	Instability at RT observed	log ₁₀ P - Parameter
1	10.0	49.9	0.0	40.0	X	-	1	2.2	7.6		-1.6
2	10.1	39.9	0.0	50.0	X	-	1	5.2	7.4	-	-1.9
3	30.0	40.0	0.0	30.0	X	-	1	1.2	7.5	-	-1.7
4	20.0	40.0	0.0	40.0	X	-	1	2.0	7.4	-	-1.8
5	10.1	44.9	0.0	45.0	X	-	1	3.1	7.5	-	-1.7
6	35.0	30.0	0.0	35.0	X	-	1	3.2	7.3	-	-2.0
7	30.0	35.0	0.0	35.0	X	-	1	2.4	7.3	-	-1.9
8	30.0	20.0	0.0	50.0	X	-	1	34.3	7.1	Yes	-2.7
9	20.0	30.0	0.0	50.0	X	-	1	10.1	7.2	Yes	-2.3
10	40.0	20.0	0.0	40.0	X	-	1	9.5	7.2	Yes	-2.4
11	30.0	10.0	0.0	60.0	X	-	1	3.4	7.0	Yes	-3.8
12	20.1	35.0	0.0	45.0	X	-	1	4.3	7.3	Yes	-2.1
13	25.0	35.0	0.0	40.0	X	-	1	4.0	7.5	-	-2.0
14	30.0	30.0	0.0	40.0	X	-	1	3.9	7.3	Yes	-2.1
15	25.7	36.2	0.0	38.0	X	-	1	3.5	7.4	-	-1.9
16	40.0	50.0	0.0	10.0	X	-	1	0.9	7.9	-	-1.3
17	20.0	50.0	0.0	30.0	X	-	1	2.7	7.6	-	-1.5
18	25.0	45.1	0.0	29.9	X	-	1	2.6	7.6	-	-1.6
19	30.1	49.9	0.0	20.0	X	-	1	1.3	7.7	-	-1.4
20	35.0	45.0	0.0	20.0	X	-	1	1.8	7.6	-	-1.5
21	40.1	40.0	0.0	20.0	X	-	1	1.8	8.0	-	-1.6
22	50.0	50.0	0.0	0.0	X	-	1	0.5	7.8	-	-1.3
23	49.9	40.1	0.0	10.0	X	-	1	0.6	-	-	-1.5
24	59.9	40.1	0.0	0.0	X	-	1	0.6	-	-	-1.4
25	10.0	60.0	0.0	30.0	X	-	1.5	3.0	7.8	-	-1.3
26	19.9	60.0	0.0	20.1	X	-	1.5	2.0	7.9	-	-1.3
27	0.0	60.0	5.0	35.0	X	-	1.5	2.9	7.9	-	-1.1
28	10.1	59.9	4.9	25.0	X	-	1.5	2.0	7.9	-	-1.1
29	20.0	59.9	5.0	15.0	X	-	1.5	1.5	8.1	-	-1.1
30	0.0	60.0	10.0	30.0	X	-	1.5	2.1	8.1	-	-0.9
31	10.0	60.0	10.0	20.0	X	-	1.5	1.6	8.2	-	-1.0
32	20.0	60.0	10.0	10.0	X	-	1.5	1.1	8.4	-	-1.0
33	15.0	59.9	0.0	25.0	X	-	1.5	1.7	7.9	-	-1.3
34	0.0	60.0	8.0	32.0	X	-	1.5	1.7	8.0	-	-1.0

35	15.0	60.0	2.5	22.6	X	-	1.5	1.2	8.0	-	-1.2
36	5.0	59.9	7.5	27.6	X	-	1.5	1.7	8.0	-	-1.0
37	14.2	56.8	0.0	28.9	-	X	1.5	2.9	7.2	-	-1.4
38	0.0	59.5	7.9	32.6	-	X	1.5	2.4	7.3	-	-1.0
39	9.7	58.1	4.8	27.4	-	X	1.5	2.2	7.3	-	-1.2

The mixtures of solvents applied for experiments V8 to V12 and V14 showed instability phenomena like visible sediments in the solution or on the bottom of the vessel within 3 weeks short term storage at room temperature.

In order to quantify the solvent characteristics of these mixtures regarding their suitability to form a physical stable solution with the substance, a LogP-Parameter was introduced (Eq. 4). The LogP-Parameter describes the hydrophilic/hydrophobic nature of solvent mixture containing organic and aqueous solvents and is calculated as follows:

$$Mo_i = \frac{mo_i}{\sum_{i=1}^n mo_i}$$
 (Eq. 1)

$$\text{LogPo} = \sum_{i=1}^n (Mo_i \cdot \text{LogP}_i)$$
 (Eq. 2)

$$X_o = 1 - \frac{a_w}{a_{sol}}$$
 (Eq. 3)

$$\text{LogP Parameter} = \frac{\text{LogPo}}{X_o}$$
 (Eq. 4)

- mo_i [mol/g]: molecular amount of an organic solvent in the organic phase of a solvent mixture
- Mo_i [-]: molecular fraction of organic solvent mo_i in the organic phase of a solvent mixture
- LogP_i [-]: $\log_{10} P_{\text{n-octanol/water}}$ = concentration of unionized compound in n-octanol / concentration of unionized compound in water of an organic solvent
- LogPo [-]: auxiliary parameter of the organic phase of a solvent mixture
- a_w [g]: mass of water or aqueous buffer in a solvent mixture
- a_{sol} [g]: mass of solvent mixture
- X_o [-]: mass fraction of organic phase in a solvent mixture

Exemplary calculation

For glycerol the $\log_{10}P$ value (= LogP_i) is given as -1.84 and the molecular weight as 92.09 g/mol. 1g of solvent mixture of V1 contains 10% glycerol which corresponds to 0.1g glycerol or 0.001086 mol (= mo_{glycerol}). The other organic solvent is propylene glycol (PG) having a $\log_{10}P$ value (= LogP_i) of -0.79 and a molecular weight of 76.09 g/mol. 1g of the solvent mixture of V1 contains 49.9% PG which corresponds to 0.499g PG or 0.006558 mol (= mo_{PG}). Concerning Eq. 1 Mo_{glycerol} is 0.142 and Mo_{PG} is 0.858. LogPo is calculated as -0.94 (Eq. 2). 1g of solvent mixture of V1 contains 40% aqueous buffer which results in a mass fraction of organic phase of $X_o = 0.6$ (Eq. 3). Following Eq. 4 a LogP Parameter of -1.6 is calculated for the solvent mixture of experiment V1. For mixtures containing ethanol, a $\log_{10}P$ value (= LogP_i) for ethanol of -0.16 and a molecular weight of 46.07 g/mol was used.

By correlating the measured Turbidity over the values for the LogP-Parameter between -3.0 and -0.5, an exponential function is observed (Figure 1). Furthermore it was found, that solvent mixtures prepared with the phosphate buffer pH 6.8 or the citric acid buffer pH 6.0 having a LogP-Parameter ≥ 2.1 are physically instable after preparing a solution with the substance.

5

Example 2

In the following Table 3 exemplary pharmaceutical compositions according to the present invention are given in detail (API: active pharmaceutical ingredient).

10 Table 3: Exemplary pharmaceutical compositions according to the present invention

Ingredient	Concentration [g/100 mL (% w/w)]	Function
1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene	0.5 – 5.0; preferably 1.0 – 1.5	API
Propylene glycol	10 – 60, preferably 35 – 60; more preferably 50 – 60	Solvent
Glycerol	0 – 60; preferably 0 – 52	Solvent
Ethanol, abs.	0 – 20; preferably 0 – 15; more preferably 0 – 10; most preferably 0 – 8	Solvent
Flavor	0 – 1; preferably 0 – 0.15	Flavor
Aqueous buffer (e.g. citric acid buffer pH 6.0 or phosphate buffer pH 6.8)	0 – 52; preferably 0 – 40	pH adjustment

The production procedure of an exemplary pharmaceutical composition according to the present invention for a single small scale batch (100 mL) in form of a general instruction is as follows:

Prepare buffer solution

15 Weigh aqueous buffer solution in a vessel.

Weigh propylene glycol and add to buffer solution under stirring.

Weigh glycerol and add to the solution under stirring.

Weigh ethanol and add to the solution under stirring.

Weigh flavor and add to the solution under stirring.

20 Weigh 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene and add in portions to the solution.

Stir until fully dissolved.

Filtration of the solution.

25 **Example 3**

Formulation samples were produced with compositions listed in the following Table 4.

Table 4:

Ingredient	Compositi on 1 [g/100 mL]	Compositi on 2 [g/100 mL]	Compositi on 3 [g/100 mL]	Compositi on 4 [g/100 mL]	Compositi on 5 [g/100 mL]	Compositi on 6 [g/100 mL]	Compositi on 7 [g/100 mL]
1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene	1.5	1.5	1.5	1.5	1.5	1.5	1.0
Propylene glycol	60	60	60	60	60	60	52
Water	23.5	27.5	22.4	23.2	27.0	21.9	49.9
Glycerol 85%	17.6	0.0	11.8	17.6	0.0	11.8	-
Ethanol. abs.	-	8	5	-	8	5	-
NaOH. 1 N	4.71	5.51	4.49	4.63	5.41	4.39	-
Citric acid. monohydrate	0.36	0.42	0.34	0.35	0.41	0.33	-
Honey flavor	-	-	-	0.15	0.15	0.15	-
Disodium hydrogen phosphate dodecahydrate	-	-	-	-	-	-	0.890
Potassium hydrogen phosphate	-	-	-	-	-	-	0.350

The following procedure was used to prepare the samples:

1. Weigh entire amount of water into vessel
- 5

2. Weigh entire amounts of NaOH 1N and citric acid monohydrate or disodium hydrogen phosphate dodecahydrate and potassium hydrogen phosphate into a beaker and add to stirred water. Stir until fully dissolved.
3. Weigh entire amount of propylene glycol into a beaker and add slowly to stirred solution.
4. Weigh entire amount of glycerol 85% into a beaker and add to stirred solution. Stir until fully mixed.
- 10

5. Weigh entire amount of ethanol, abs. into a beaker and add to stirred solution. Stir until fully mixed.
6. Weigh entire amount of flavor into a beaker and add to stirred solution. Stir until fully dissolved.
7. Weigh entire amount of 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene into a beaker and add in portions to stirred solution. Stir until fully dissolved.
8. Use a 8 μm Filter to filtrate the solution

15

The solutions were found to have the following densities and appearances (Table 5).

Table 5:

Formulation / Solution	Turbidity [NTU]	Density [g/mL]	Appearance
Composition 1	1.8	1.077	yellowish, clear solution, no particles
Composition 2	1.6	1.029	yellowish, clear solution, no particles
Composition 3	1.5	1.055	yellowish, clear solution, no particles
Composition 4	1.3	1.077	yellowish, clear solution, no particles
Composition 5	1.1	1.028	yellowish, clear solution, no particles
Composition 6	1.1	1.054	yellowish, clear solution, no particles
Composition 7	5.8	1.046	yellowish, clear solution, no particles

Example 4

The testing criteria applied are those for evaluation of antimicrobial activity for oral preparations according to Pharm. Eur. 7 (tests at 14 days and 28 days). The acceptance criteria of the Ph. Eur. 7, Method 5.1.3 "Efficacy of Antimicrobial Preservation", and USP 34, Method <51> "Antimicrobial Effectiveness Testing" are listed in the following Table 6.

Table 6: Criteria for evaluation of antimicrobial activity for oral preparations according to Pharm. Eur. 7 and USP 34

Type of micro-organism	Ph. Eur. 7 Method 5.1.3.		USP 34 Method <51>	
	Logarithmic reduction of microorganisms after			
	14 days	28 days	14 days	28 days
Bacteria	> 3	No increase from 14 days ¹⁾	> 1.0	No increase from 14 days ²⁾
Funghi	> 1	No increase from 14 days ¹⁾	No increase from initial calc. count ²⁾	No increase from initial calc. count ²⁾

¹⁾ for Ph. Eur: No increase = no increase in number
²⁾ for USP: No increase = not more than 0.5 log₁₀ units higher than reference value

The formulations tested in the trial are shown in the following Table 7.

Table 7

Ingredient	Trial 1 [g/100 mL]	Trial 2 [g/100 mL]	Trial 3 [g/100 mL]	Trial 4 [g/100 mL]	Trial 5 [g/100 mL]	Trial 6 [g/100 mL]
1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene	1.5	1.5	1.5	1.5	1.5	1.5
Propylene glycol	50.0	50.0	50.0	50.0	50.0	50.0
Glycerin	0.0	32.5	32.7	26.8	52.1	46.6
Ethanol abs.	-	-	-	5.00	-	5.00
Honey flavor	0.15	0.15	0.15	0.15	0.15	0.15

Propyl-hydroxy-benzoate	0.20	-	0.20	-	-	-
Phosphate buffer pH 6.8	52.2	20.0	20.0	20.0	-	-

After preparation of the samples, the solutions were filtrated via a 0.22 µm filter.

The following microorganisms were tested: Pseudomonas aeruginosa, Straphylococcus aureus, Escherichia coli, Candida albicans, Aspergillus brasiliensis, Zygosaccharomyces rouxi.

5 In the performed tests the USP 34 Method <51> Criteria as listed in Table 6 were found to be fulfilled for all solutions for all microorganisms. It was also found, that an additional preservative like propyl-hydroxy-benzoate is not needed to get antimicrobial effectiveness.

Example 5

10 Formulation samples were produced as follows:

- 1) Preparation of a basic excipient solution consisting of an aqueous pH 6 phosphate buffer (21.05 mg/mL KH₂PO₄ and 8.82 mg/mL Na₂HPO₄*12H₂O) and 20% (m/v) propylene glycol
- 2) 1,34% (m/v) 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene *L-proline*H₂O (corresponds to 1.0% 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene) were
15 dissolved in the basic excipient solution (batch size: 2000 mL)
- 3) A solubilizing agent was weight into a 300 mL flask and filled up to the mark with the solution

The following solubilizing agents were used:

- Experiment 1: 0.1% (m/v) SDS
- 20 Experiment 2: 1% (m/v) Cremophor RH 40
- Experiment 3: 1% (m/v) Lutrol F 68
- Experiment 4 8% (m/v) PEG 300

For the experiments 1, 2, 3 and 4 no additional significant degradation are measured by HPLC analytics
25 (table 8).

Table 8

Experiment	Chemical byproduct / degradation measured by HPLC	
	3 months at 25°C/60% r.h.	3 months at 40°C/75% r.h.
1	no	no
2	no	no
3	no	no
4	no	no

Example 6

30 Formulation samples were produced as follows:

- 1) 1380 g propylene glycol and 619 g H₂O were mixed in a 3000 mL beaker.

- 2) 7.1 g hydroxyl ethyl cellulose, as a viscosity-enhancing agent, was slowly added during intensive mixing with a propeller mixer.
- 3) The mixture was kept for 30 minutes for swelling.
- 4) The mixture was heated up to 70°C during mixing and additionally mixed for further 10 minutes at 70°C.
- 5) The heater was switched off to cool down the mixture to room temperature during stirring.
- 6) 124.4 g NaOH 1N, 9.4 g citric acid monohydrate and 184 g ethanol absolute were added during stirring at room temperature until the solution is clear.
- 7) 46,1 g 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene*L-proline*H₂O is added and stirred until the solution was clear.
- 8) The mixture (called stock-solution) was filtered under pressure with an 8μm filter.

Trials with different flavors:

199.7 g stock-solution was filled in a separate beaker and 0.3 g of flavor was added (see table 9, experiments 2 to 7, experiment 1 is the stock solution).

Trials with different sweeteners:

199.98 g stock solution was filled in a separate beaker and 0.02 g of sweetener was added (see Table 9, experiments 8 and 9).

Table 9.

Experiment	Flavor / sweetener	pH-value	Turbidity [NTU]	Density [g/ml]
1	Stock solution	7.1	1.8	1.029
2	Honey flavor	7.1	2.0	1.031
3	Lime/Salvia flavor	7.2	1.9	1.031
4	Jasmine flavor	7.1	1.8	1,031
5	Lavender flavor	7.2	1.9	1.031
6	Peppermint flavor	7.1	1.9	1.030
7	Raspberry flavor	7.0	1.8	1.030
8	Saccharine	7.1	1.8	1.030
9	Aspartame	7.1	1.8	1.032

For all depicted experiments the solutions are considered as clear (opalescent value <3 NTU, see Table 1).

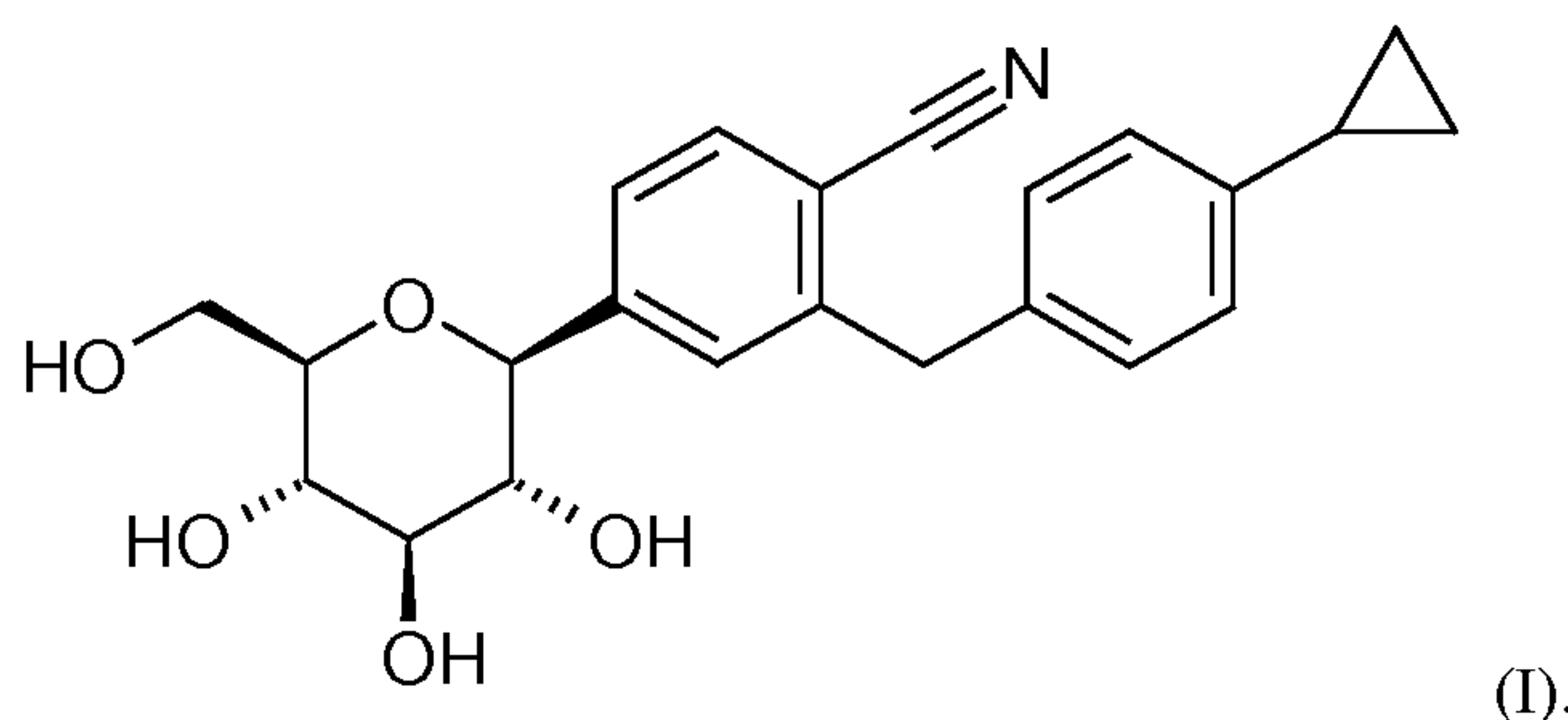
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CLAIMS

1. A liquid pharmaceutical composition comprising at least one SGLT-2 inhibitor and one or more polar organic solvents, wherein the at least one SGLT-2 inhibitor comprises, preferably is, 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene according to formula (I):



2. The liquid pharmaceutical composition according to claim 1, wherein 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene is the only SGLT-2 inhibitor contained in such liquid pharmaceutical composition.
3. The liquid pharmaceutical composition according to any one of claims 1 to 2, wherein the liquid pharmaceutical composition is suitable for direct administration to a subject, preferably an animal, more preferably a mammal, in particular a horse, cat or dog; wherein preferably the liquid pharmaceutical composition is sterile.
4. The liquid pharmaceutical composition according to any one of claims 1 to 3, wherein the liquid pharmaceutical composition is a solution, an emulsion or a suspension, preferably a solution, an emulsion or a suspension with an NTU value of equal to or less than 10.0, more preferably equal to or less than 7.0, even more preferably equal to or less than 3.0, and most preferably a solution, in particular a solution with an NTU value of equal to or less than 3.0.
5. The liquid pharmaceutical composition according to any one of claims 1 to 3, wherein the one or more polar organic solvents are independently from each other characterized by a negative $\log_{10}P$ value, preferably a negative decadic logarithmic partition coefficient (P) in an n-octanol/water system according to formula (II):

$$\log_{10} P_{n\text{-octanol/water}} = \frac{\text{concentration of unionized compound in } n\text{-octanol}}{\text{concentration of unionized compound in water}} \quad (\text{II});$$

wherein more preferably such liquid pharmaceutical composition as a whole is characterized by a negative LogP-Parameter, preferably a negative LogP-Parameter of equal to or less than -2.0 (i.e. $-2.0 \leq \text{LogP-Parameter} < 0$).

6. The liquid pharmaceutical composition according to any one of claims 1 to 5, wherein the one or more polar organic solvents are selected from ethanol, propane-1,2-diol (propylene glycol), propane-1,2,3-triol (glycerol), and/or preferably wherein such liquid pharmaceutical composition comprises at least two different polar organic solvents, preferably two or three different polar organic solvents, more preferably propane-1,2-diol (propylene glycol) and propane-1,2,3-triol (glycerol) or ethanol and propane-1,2-diol (propylene glycol) or ethanol and propane-1,2-diol (propylene glycol) and propane-1,2,3-triol (glycerol).
7. The liquid pharmaceutical composition according to any one of claims 1 to 6, wherein such liquid pharmaceutical composition does not comprise ethanol as the one or more polar organic solvents and/or wherein such liquid pharmaceutical composition does not comprise only propane-1,2-diol (propylene glycol) as single polar organic solvent.
8. The liquid pharmaceutical composition according to any one of claims 1 to 7, wherein such liquid pharmaceutical composition additionally comprises water, preferably aqueous buffer, such as citric acid buffer or phosphate buffer.
9. The liquid pharmaceutical composition according to claim 8, wherein such liquid pharmaceutical composition has a measured pH value of from 3 to 9, preferably from 4 to 9, more preferably from 5.0 to 8.5, even more preferably from 6.0 to 8.5 and most preferably from 6.0 to 7.5.
10. The liquid pharmaceutical composition according to any one of claims 1 to 9, wherein such liquid pharmaceutical composition additionally comprises one or more solubilizing agents, preferably selected from the group consisting of: "surfactants, anionic surfactants, non-ionic surfactants, hydrogenated castor oils, polyoxyethylene-polyoxypropylene block copolymers, polyethylene glycols, propylenglycol derivatives", more preferably selected from the group consisting of: "Sodium dodecyl sulphate (SDS), Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil, Macrogol glycerol hydroxystearate 40), polysorbate 20, Lutrol F 68 (Poloxamer 188), PEG 300, propylenglycol monolaurate" and/or additionally comprises one or more viscosity-enhancing agents, preferably selected from the group consisting of: "inorganic gel forming agents, organic gel forming agents, cellulose derivatives", more preferably selected from the group consisting of: "hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose, silicon dioxide" and/or additionally comprises one or more flavours and/or sweeteners, preferably selected from the group consisting of: "honey flavor, lime/salvia flavor, jasmine flavor, lavender flavor, peppermint flavor, raspberry flavor, lemon flavor, herbs flavor, saccharine, aspartame".
11. The liquid pharmaceutical composition according to any one of claims 1 to 10, wherein such liquid pharmaceutical composition does not comprise any apolar organic solvents, which are preferably and independently from each other characterized by a $\log_{10}P$ value of equal to or higher than 0.
12. The liquid pharmaceutical composition according to any one of claims 1 to 11, wherein such liquid pharmaceutical composition is for oral and/or parenteral administration, preferably oral administration.

13. The liquid pharmaceutical composition according to any one of claims 1 to 12, comprising

- (i) 0.5 – 5.0 g/100 mL (% w/w), preferably 1.0 – 1.5 g/100 mL (% w/w) 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene;
- 5 (ii) 10 – 60 g/100 mL (% w/w), preferably 35 – 60 g/100 mL (% w/w), more preferably 50 – 60 g/100 mL (% w/w) propylene glycol;
- (iii) 0 – 60 g/100 mL (% w/w), preferably 0 – 52 g/100 mL (% w/w) glycerol;
- (iv) 0 – 20 g/100 mL (% w/w), preferably 0 – 15 g/100 mL (% w/w), more preferably 0 – 10 g/100 mL (% w/w), most preferably 0 – 8 g/100 mL (% w/w) ethanol;
- 10 (v) 0 – 1 g/100 mL (% w/w), preferably 0 – 0.15 g/100 mL (% w/w) flavor and/or sweetener, more preferably selected from the group consisting of “honey flavor, lime/salvia flavor, jasmine flavor, lavender flavor, peppermint flavor, raspberry flavor, lemon flavor, herbs flavor, saccharine, and/or aspartame”;
- (vi) 0 – 52 g/100 mL (% w/w), preferably 0 – 40 g/100 mL (% w/w) aqueous buffer, preferably citric acid
15 buffer pH 6.0 or phosphate buffer pH 6.8;
- (vii) 0 – 10 g/100 mL (% w/w), preferably 0 – 8 g/100 mL (% w/w) solubilizing agent, preferably selected from the group consisting of: “surfactants, anionic surfactants, non-ionic surfactants, hydrogenated
20 castor oils, polyoxyethylene-polyoxypropylene block copolymers, polyethylene glycols, and/or propylenglycol derivatives”, more preferably selected from the group consisting of: “Sodium dodecyl sulphate (SDS), Cremophor RH 40 (PEG-40 Hydrogenated Castor Oil, Macrogol glycerol hydroxystearate 40), polysorbate 20, Lutrol F 68 (Poloxamer 188), PEG 300, and/or propylenglycol monolaurate”;
- (viii) 0 – 5 g/100 mL (% w/w), preferably 0 – 0.5 g/100 mL (% w/w) viscosity-enhancing agent, preferably
25 selected from the group consisting of “inorganic gel forming agents, organic gel forming agents, and/or cellulose derivatives”, more preferably selected from the group consisting of “hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose, and/or silicon dioxide”.

14. The liquid pharmaceutical composition according to claim 13 selected from the group consisting of the following compositions 1 to 7:

Ingredient	Compositi on 1 [% (w/w)]	Compositi on 2 [% (w/w)]	Compositi on 3 [% (w/w)]	Compositi on 4 [% (w/w)]	Compositi on 5 [% (w/w)]	Compositi on 6 [% (w/w)]	Compositi on 7 [% (w/w)]
1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene	1.5	1.5	1.5	1.5	1.5	1.5	1.0
Propylene glycol	60	60	60	60	60	60	52
Water	23.5	27.5	22.4	23.2	27.0	21.9	49.9

Glycerol 85%	17.6	0.0	11.8	17.6	0.0	11.8	-
Ethanol, abs.	-	8	5	-	8	5	-
NaOH, 1 N	4.71	5.51	4.49	4.63	5.41	4.39	-
Citric acid, monohydrate	0.36	0.42	0.34	0.35	0.41	0.33	-
Honey flavor	-	-	-	0.15	0.15	0.15	-
Disodium hydrogen phosphate dodecahydrate	-	-	-	-	-	-	0.890
Potassium hydrogen phosphate	-	-	-	-	-	-	0.350

15. The liquid pharmaceutical composition according to any of claims 1 to 14 for use in a method for treating and/or preventing one or more medicinal indications in a subject in need of such treatment and/or prevention, preferably an animal, more preferably a mammal, in particular a horse, cat or dog, selected from among the medicinal indications:

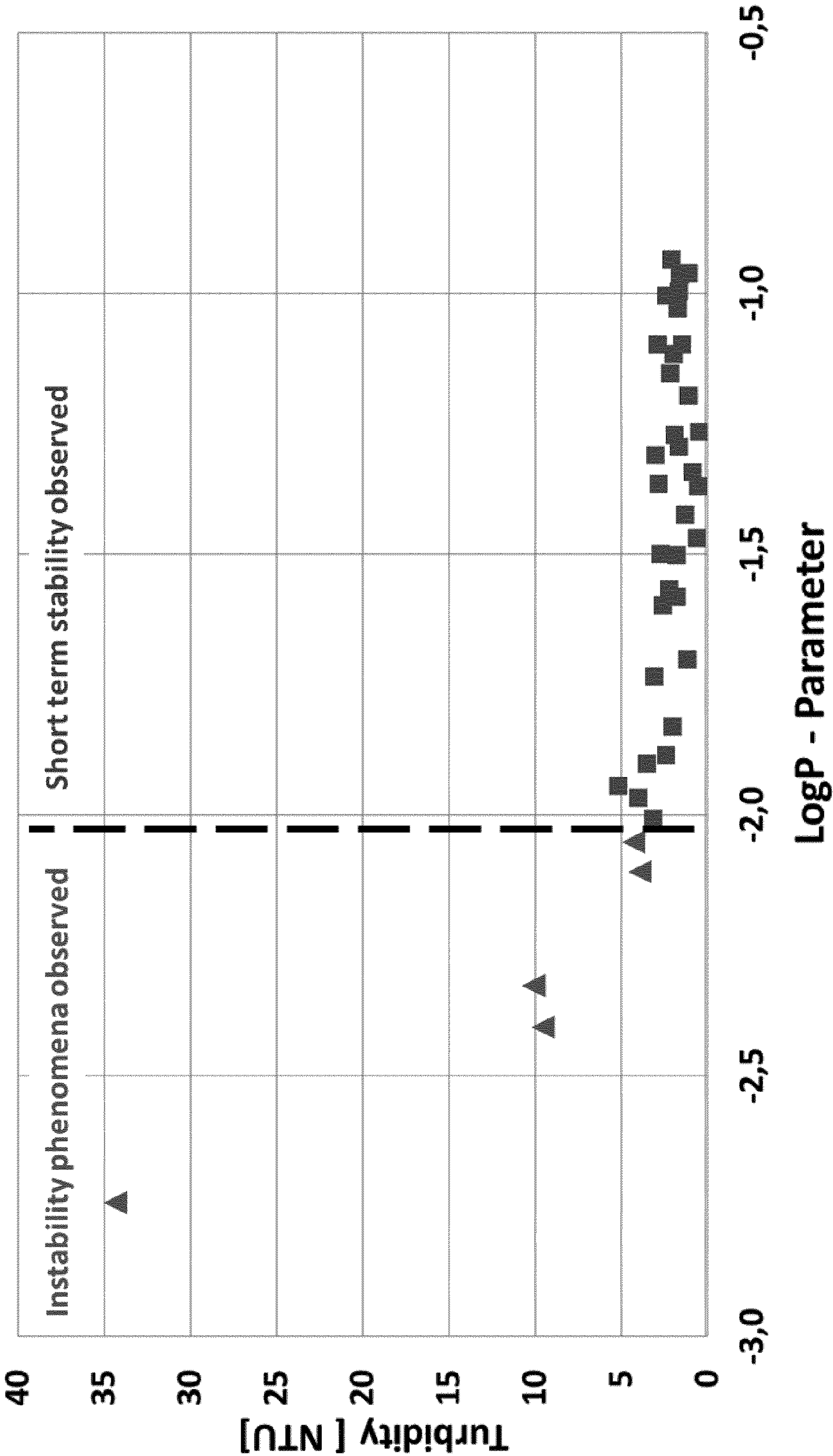
- (i) a metabolic disorder of an equine animal, wherein preferably the metabolic disorder is one or more disorders selected from insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity, wherein preferably the metabolic disorder is insulin resistance, hyperinsulinemia, and/or a clinical condition associated with insulin resistance and/or hyperinsulinaemia; wherein preferably said clinical condition is one or more conditions selected from impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity;
- (ii) a metabolic disorder of an equine animal, wherein the metabolic disorder is one or more disorders selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome, wherein preferably the metabolic disorder is a clinical condition/sign associated with insulin resistance and/or hyperinsulinaemia, wherein said clinical condition/sign preferably is one or more conditions selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome;
- (iii) a metabolic disorder of a feline animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, diabetes mellitus type 1 or type 2, insulin resistance, obesity, hyperglycemia, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, atherosclerosis, inflammation of the pancreas, neuropathy and/or Syndrome X (metabolic syndrome) and/or loss of pancreatic beta cell function and/or wherein the remission of the metabolic disorder, preferably diabetic remission, is achieved and/or maintained;

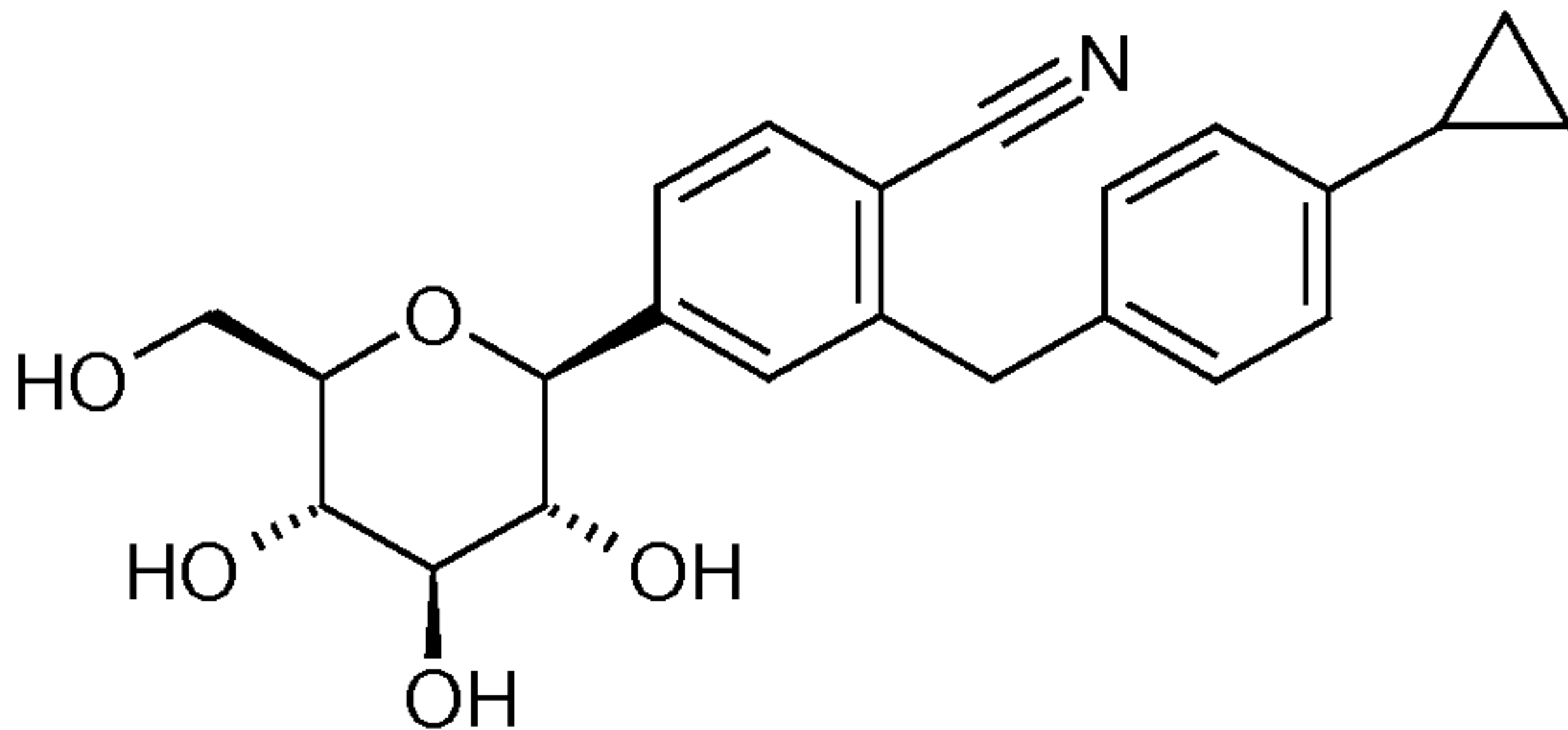
- (iv) a metabolic disorder of a canine animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, obesity, hyperglycemia, hyperglycemia induced cataract formation, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, inflammation of the pancreas, metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, and/or Syndrome X (metabolic syndrome), preferably pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, wherein preferably the development of hyperglycemia induced cataract formation is prevented or remission is achieved and/or wherein preferably the development of metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, is prevented or progression is slowed or remission is achieved.
16. A process for producing the liquid pharmaceutical composition according to any of the claims 1 to 14, comprising the steps (in any meaningful order)
- (i) mixing the one or more polar organic solvents;
 - (ii) optionally, adding water to the mixture resulting from step (i);
 - (iii) dissolving 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzene in the mixture resulting from step (i) or optionally step (ii);
 - (iv) optionally, dissolving further excipients, such as pH modifier(s), flavor(s), sweeteners, solubility enhancing agents, viscosity enhancing agents and the like, in the mixture resulting from step (iii);
 - (v) optionally, filtrating the mixture resulting from step (iii) or optionally step (iv);
- whereby, optionally, independently from each other after any of the individual process steps – be they mandatory or optional – an additional mixing step is performed.
17. A kit-of-parts comprising:
- (a) a liquid pharmaceutical composition according to any of claims 1 to 14; and
 - (b) a package leaflet including the information that the liquid pharmaceutical composition is to be used for the prevention and/or treatment of one or more medicinal indications in a subject in need of such prevention and/or treatment, which are selected from among the medicinal indications:
 - (i) a metabolic disorder of an equine animal, wherein preferably the metabolic disorder is one or more disorders selected from insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity, wherein preferably the metabolic disorder is insulin resistance, hyperinsulinemia, and/or a clinical condition associated with insulin resistance and/or hyperinsulinaemia; wherein preferably said clinical condition is one or more conditions selected from impaired glucose tolerance, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, obesity, and/or regional adiposity;

- (ii) a metabolic disorder of an equine animal, wherein the metabolic disorder is one or more disorders selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome, wherein preferably the metabolic disorder is a clinical condition/sign associated with insulin resistance and/or hyperinsulinaemia, wherein said clinical condition/sign preferably is one or more conditions selected from laminitis, vascular dysfunction, hypertension, hepatic lipidosis, atherosclerosis, hyperadrenocorticism, Pituitary Pars Intermedia Dysfunction and/or Equine Metabolic Syndrome;
- (iii) a metabolic disorder of a feline animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, diabetes mellitus type 1 or type 2, insulin resistance, obesity, hyperglycemia, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, atherosclerosis, inflammation of the pancreas, neuropathy and/or Syndrome X (metabolic syndrome) and/or loss of pancreatic beta cell function and/or wherein the remission of the metabolic disorder, preferably diabetic remission, is achieved and/or maintained;
- (iv) a metabolic disorder of a canine animal, wherein preferably the metabolic disorder is one or more selected from the group consisting of: ketoacidosis, pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, obesity, hyperglycemia, hyperglycemia induced cataract formation, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, dysadipokinemia, subclinical inflammation, systemic inflammation, low grade systemic inflammation, hepatic lipidosis, inflammation of the pancreas, metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, and/or Syndrome X (metabolic syndrome), preferably pre-diabetes, insulin dependent diabetes mellitus, insulin resistance diabetes, insulin resistance, wherein preferably the development of hyperglycemia induced cataract formation is prevented or remission is achieved and/or wherein preferably the development of metabolic disorder consequences, such as hypertension, renal dysfunction and/or musculoskeletal disorders, is prevented or progression is slowed or remission is achieved.

1 / 1

Figure 1





(I)