

BEFORE THE PATENT CONTROLLER AT DELHI

IN THE MATTER OF

Section 25(1) of

The Patents Act, 1970, as amended up to

the Patent(Amendment)

Act,2005

AND

IN THE MATTER OF

Rule 55 of the

Patents Rules, 2003, as

amended up to

the Patents (Amendment) Rules, 2016

AND

IN THE MATTER OF National Phase

Patent Application No.

6148/DELNP/2011 bearing title

“PHARMACEUTICAL COMPOSITION

COMPRISING LINAGLIPTIN AND

OPTIONALLY A SGLT2 INHIBITOR,

AND USES THEREOF” filed by

BOEHRINGER INGELHEIM

INTERNATIONAL

GMBH on 12/08/2011

and

claiming priority of 13/02/2009.

.....Applicant

AND

IN THE MATTER OF pre-grant representation

By way of opposition filed by

... VEE EXCEL DRUGS

& PHARMACEUTICAL (P) LTD.,

Indian , having residence at...

703,7TH FLOOR,DEVIKA TOWER,

CHANDER NAGAR,

GHAZIABZAD-201011.

.....Opponent

STATEMENT OF FACTS/EVIDENCE

- I.** We,... VEE EXCEL DRUGS& PHARMACEUTICAL (P) LTD ... having address at ...703,7TH FLOOR,DEVIKA TOWER, CHANDER NAGAR, GHAZIABZAD-201011 ... hereby file a pre grant opposition on the Patent No. **6148/DELNP/2011** filed in India by the Patentee **BOEHRINGER INGELHEIM INTERNATIONAL GMBH .**

The patent was filed on 12/08/2011 claiming a priority of 13/02/2009. The Opponent is a leading manufacturer of several active pharmaceutical ingredients and products including Type 2 diabetes drugs, hereby makes a representation by way of opposition against the grant of patent application, titled “PHARMACEUTICAL COMPOSITION COMPRISING LINAGLIPTIN AND OPTIONALLY A SGLT2 INHIBITOR, AND USES THEREOF” bearing Indian Patent Application No. **6148/DELNP/2011** (herein referred to as ”the present Application”) filed by **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** (herein referred to as “the patent Application”).

II. The Opponent submits as follows.

III. The representation by way of opposition is being filed on Form-7A under section 25(1) of the Patent Act, 1970 as amended by the Patents (Amendments) Act, 2005 (herein after referred to as "the Patent Act") and Rule 55 of the Patent Rules, 2003 as amended by the Patents (Amendment) Rules, 2016. Any submission made or evidence adduced with specific reference to any clause of section 25(1) may be treated as being made without prejudice to submissions made elsewhere in this representation by way of opposition or any other opposition proceeding before the Indian Patent Office

IV. The Opponent submits that he is opposing the grant of patent to the impugned present Application reciting Claims 1 to 20 by availing strong and valid grounds provided under section 25(1) of the Patent Act and is consequently filing the present representation by way of opposition to the impugned present Application.

V. LOCUS STANDI

That representation by way of opposition can be made by any person in writing under section 25(1) of the patent Act. Notwithstanding this, the opponent submits that he is a "person interested" under section 2(1)(t) in the field of the present invention and has *locus standi* to initiate the present representation by way of opposition. Being a leading manufacturer of several active pharmaceutical ingredients and products, the opponent has its own research and development team and constantly works towards the development of new products. The opponent is one of the key suppliers of linagliptin in India. Thus, the petitioner has real and substantial interest in matter at hand.

The opponent has learnt that the patentee has filed an Indian Patent No. 6148/DELNP/2011. The said application has been filed for "PHARMACEUTICAL COMPOSITION COMPRISING LINAGLIPTIN AND OPTIONALLY A SGLT2 INHIBITOR, AND USES THEREOF"

Accordingly, the opponent submits their opposition under Section 25(1) in respect of the said present application.

VI. JURISDICTION

The present Application has been filed the Patent Applicant at the Patent Office in Delhi. Therefore, the Patent Controller has the jurisdiction to hear this representation by way of opposition in Delhi.

VII. BACKGROUND

1. The present Application claims a core comprising of linagliptin or pharmaceutically acceptable salts. Linagliptin is admittedly known prior to the priority date of the present Application.
2. As of 2019, there is an estimate of 523 million people suffering with diabetes. The global prevalence of diabetes is 8.5 percent. The prevalence of diabetes in India is 7.8 per cent .
3. There are two types of diabetes—Type 1 and Type 2. Type 1 diabetes is believed to be an autoimmune condition. This means your immune system mistakenly attacks and destroys the beta cells in your pancreas that produce insulin. The damage is permanent. Whereas Type 2 diabetes starts as insulin resistance. This means your body can't use insulin efficiently that stimulates your pancreas to produce more insulin until it can no longer keep up with demand. Insulin production decreases, which leads to high blood sugar.
4. Patient with insulin resistance do not develop hyperglycaemia until their beta cells are unable to meet the demands for insulin. Thus, enhancement of insulin secretion from the islet beta cells is a practical target for treatment of patients with Type 2 diabetes. However, as noted by Lebovitz, insulin secretagogues, including sulfonylureas, meglitinides, and D-phenylalanine frequently exhibit a secondary failure and may cause hypoglycaemia in patients with Type 2 diabetes. [<https://www.researchgate.net/publication/279579350> Insulin secretagogues Old and new] .Therefore, there was an interest in identifying agents that enhanced insulin secretion in a sustained glucose-dependent manner in patients with Type 2 diabetes.
5. Glucose dependent insulin tropic polypeptide(GIP)and glucagon like peptide-I(GLP 1)are the two major incretin hormones released after meals by the

enteroendocrine cells in the intestine to enhance glucose-stimulated insulin secretion.

6. As noted by Holst and Gromada ,patients with Type 2 diabetes are characterized by two defects related to incretin effect: (i)while secretion of GLP-1 is decreased ,its insulinotropic effect is preserved and (ii) while secretion of GIP is near normal ,its insulinotropic effect is reduced [Holst and Gromada , " Role of incretin hormones in the regulation of insulin secretion in diabetic and non diabetic humans"(2004) *American Journal of Physiology Endocrinology and Metabolism* 287:E199-206].
7. GLP-1 was targeted as a mechanism for treating Type 2 diabetes .In addition, GLP-1 represented a more attractive treatment option for Type 2 diabetes because of its multiple effects ,including the stimulation of satiety in the central nervous system by crossing the blood-brain barrier. GLP-1 was known to stimulate glucose -dependent insulin secretion [Mojsov, *et al.*, "Insulinotropin :Glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas"(1987) *The Journal of Clinical Investigation* 79:616-19] and insulin gene expression [Drucker, *et al.* , "Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line " (1987) *Proceedings of the National Academy of Sciences of the United States of America* 84:3434--38] ,inhibit glucagon secretion [Matsuyama, *et al.* , " Glucagon like peptide-I (7-36 amide) : a potent glucagonostatic and insulinotropic hormone" (1988) *Diabetes Research and Clinical Practice* 5:28I-84 (abstract)] and delay gastric emptying[Wettergren ,*et al.* , " Truncated GLP-I (proglucagon 78-I07-amide) inhibits gastric and pancreatic functions in man" (1993) *Digestive Diseases and Sciences* 38:665-73 (abstract)] .*In vitro* and *in vivo* data showed that GLP-I increases beta cell mass by stimulating islet cell neogenesis and inhibiting apoptosis of islets [Li, *et al.* , "Glucagon- like peptide-I receptor signaling modulates beta cell apoptosis"(2003)*The Journal of Biological Chemistry* 278:47I-78].
8. Thus, DPP-IV inhibitors and their use for treatment of diabetes, both as a monotherapy and in combination with other anti-diabetic agents, were well-known prior to the priority date of the present Application.

9. Another mechanism of action that is targeted for the treatment of diabetes is sodium-glucose co-transporter-2. Sodium-glucose co-transporter-2 is present in the kidney and reabsorbs blood glucose filtered by the glomeruli of the kidneys, thus preventing glucose excretion through urine. Competitive inhibitors of sodium-glucose co-transporter-2 (herein referred to as “SGLT2 inhibitors”), which would provoke glucose excretion through urine, were identified as a treatment option for diabetes and several SGLT2 inhibitors were discovered [(i) Jabbour and Goldstein, "Sodium glucose co-transporter 2 inhibitors :blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes" (2008) *International Journal of Clinical Practice* 62(8):1279-84(abstract) and [(ii) Idris and Donnelly, "Sodium - glucose co-transporter-2 inhibitors :an emerging new class of oral anti-diabetic drug" (2009)*Diabetes, Obesity and Metabolism* 11(2):79-88 (issued online on 29 December 2008)] .

SGLT2 inhibitors were known to enhance renal glucose excretion and consequently lower plasma glucose levels.

10. Thus, SGLT2 inhibitors and their advantages were also known prior to the priority date of the present Application.
11. Patent documents such as WO 2008/055870 A1, titled "Glucopyranosyl-substituted benzyl-benzonitrile derivatives, medicaments containing such compounds, their use and process for their manufacture" and published on 2008-05-15, claiming a priority of 2006-11-06 disclosed a pharmaceutical composition comprising one of the Glucopyranosyl-substituted benzyl-benzonitrile derivatives.
12. In the light of this and as will be shown below, the composition of linagliptin claimed in the present invention is not new, is obvious to a person skilled in art, lacks inventive step and does not meet the standards of invention or patentability set out under the Indian patent law.

VIII. PATENT APPLICANT'S CONTENTION

13. The present Application, which was filed in India on 12 August 2011 and published in India on 3 February 2012, is the national phase application of WO2010/092124. The WO application was filed on 11 February 2010, claiming a priority of 13 February 2009. Thus, the priority date for the present Application is 13 February 2009. The complete specification of WO2010/092124 is enclosed here with as **Annexure 1**.
14. As originally filed, the present Application had 26 claims .On 26 October 2017, the claims were amended. As of today, the present Application has 15 claims. The bibliographic page along with amended claims of the impugned present Application, as retrieved from the website of the Indian Patent Office website, is enclosed herewith as **Annexure 2**.
15. The present Application claims a patent for a pharmaceutical dosage form comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4- (β -D-glucopyranos-1-yl)-2-[4-(S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 10 mg or 25 mg and one or more excipients.
16. *Linagliptin*, i.e.1-[(4-methyl-quinazolin-2-yl) methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine ,which was also identified as BI 1356, is a DPP-IV inhibitor . The Patent Applicant admits that *linagliptin*, its preferred crystalline forms and its pharmaceutical composition are known [see Complete Specification, internal pages 1, 2,18and34].
17. 1-Chloro-4-(B-D-glucopyranos-1-yl)-2-[4(S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, i.e. empagliflozin, is an SGLT2 inhibitor. The Patent Applicant also admits that empagliflozin and its preferred forms are known [see Complete Specification, internal pages 2 to3, 18and20].
18. The Patent Applicant describes the alleged problems of incompatibility and degradation of DPPIV inhibitors with a primary or secondary amino group, including *linagliptin*, with excipients due to the presence of amino groups. It characterizes this as an unforeseen difficulty for potent DPPIV inhibitors, such as *linagliptin* [see Complete Specification, internal pages 1 to 2] and

also sets out the preferred excipients [see Complete Specification ,internal pages 27 to 33] .Interestingly , the Patent Applicant admits that the degradation can be tested in standard tests [see Complete Specification, internal page 27].

19. Though the Patent Applicant discusses the combination of *linagliptin* with various SGLT2 inhibitors, it prefers and subsequently claims *empagliflozin* [see Complete Specification, internal pages 2 to 3, 5 to 6 and 18 to 20].
20. The Patent Applicant also discloses the preferred particle size and particle size distribution for the compounds [see Complete Specification ,internal pages 5 to 7 and 23 to 27]
21. The Patent Applicant sets out the various diseases and conditions that can be treated, including diabetes, and various treatment outcomes [see Complete Specification, internal pages 3 to 4, 7 to 11 and 48 to 54].

IX. SUMMARY OF CLAIMS

22. The claims as amended on 26 October 2017 may be summarized as follows:

- (i) A solid pharmaceutical dosage form comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4- (β -D-glucopyranos-1-yl)-2-[4(S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 10 mg or 25 mg and one or more excipients.

wherein the term "linagliptin" as employed herein refers to linagliptin and pharmaceutically acceptable salts thereof, including hydrates and solvates thereof, and crystalline forms thereof, and wherein the definition "1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene" also comprises its hydrates, solvates and polymorphic forms thereof.

- (ii) The solid pharmaceutical dosage form as claimed in claim 1 comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)- tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 10 mg.

- (iii) The solid pharmaceutical dosage form as claimed in claim 1 comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)- tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 25 mg.
- (iv) The solid pharmaceutical dosage form as claimed in any one of the claims 1 to 3 wherein the first active ingredient has a particle size distribution of $X_{90} < 200 \mu\text{m}$.
- (v) The solid pharmaceutical dosage form as claimed in one or more of the previous claims wherein the second active ingredient has a particle size distribution of $1 \mu\text{m} < X_{90} < 200 \mu\text{m}$.
- (vi) The solid pharmaceutical dosage form as claimed in claim one or more of the previous claims wherein the one or more excipients comprise one or more diluents and one or more binders.
- (vii) The solid pharmaceutical dosage form as claimed in claim one or more of the previous claims wherein the one or more excipients comprise one or more diluents, one or more binders and one or more disintegrants.
- (viii) The solid pharmaceutical dosage form as claimed in one or more of the previous claims comprising

0.5-25 %	of the active pharmaceutical ingredients,
40-88 %	of the one or more diluents,
0.5-20 %	of the one or more binders, and
0.5-20 %	of the one or more disintegrants,

wherein the percentages are by weight of the total composition.

- (ix) The solid pharmaceutical dosage form as claimed in one or more of the previous claims comprising

0.5-25 %	the active pharmaceutical ingredients,
----------	--

40-88 %	one or more diluents,
0.5-20 %	one or more binders,
0.5-20 %	one or more disintegrants,
0.1-15%	one or more lubricants

wherein the percentages are by weight of the total composition.

- (x) The solid pharmaceutical dosage form as claimed in one or more of the previous claims wherein the one or more diluents are selected from the group consisting of cellulose, dibasic calcium phosphate, erythritol, mannitol, starch, pregelatinized starch, and xylitol, including derivatives and hydrates of the before mentioned substances.
- (xi) The solid pharmaceutical dosage form as claimed in one or more of the previous claims wherein the one or more binders are the group consisting of copovidone, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), a polyvinylpyrrolidone, pregelatinized starch, low-substituted hydroxypropylcellulose (L-HPC), including derivatives and before mentioned substances.
- (xii) The solid pharmaceutical dosage form as claimed in one or more of the previous claims wherein the one or more disintegrants are selected from the group consisting of crospovidone, low-substituted hydroxyl propyl cellulose (L-HPC), and starches, such as native starches, in particular corn starch, and pregelatinized starch, including derivatives and hydrates of the before mentioned substances.
- (xiii) The solid pharmaceutical dosage form as claimed one or more of the previous claims wherein the one or more lubricants are selected from the group consisting of talc, polyethylene glycol, in particular polyethylene glycol with a molecular weight in a range from about 4400 to about 9000, hydrogenated castor oil, fatty acid and salts of fatty acids, in particular the calcium, magnesium, sodium or potassium salts thereof, for example calcium behenate, calcium stearate, sodium stearyl fumarate or magnesium stearate.

(xiv) The solid pharmaceutical dosage form as claimed one or more of the previous claims characterized in that it is a tablet or a film-coated tablet.

(xv) The pharmaceutical dosage form as claimed in one or more of the previous claims characterized in that it is a one-layer tablet in which the two active pharmaceutical ingredients are present in the one layer.

X. GROUNDS

25. The Opponent raises the following amongst other grounds, which are without prejudice to one another.

X.A. SECTION 25 (1) (c): ANTICIPATION BY PRIOR CLAIMING

Section 25 (1) (c) provides a ground of opposition on the ground that the claimed invention is claimed in a claim of complete specification filed in pursuance of an application for a patent in India and having a priority date earlier than that of the present application even though it may have been published on or after the priority date of the Applicant's claim.

26. Claims 1 to 9 and 14 to 15 are anticipated by the claims of the Indian patent having Application No. 1006/DELNP/2010 (**Exhibit A**) which have an earlier priority date. Therefore, Claims 1 to 9 and 14 to 15 are ought to be rejected under section 25(1)(c) of the Patents Act.

27. Indian Application No. 1006/DELNP/2010 (herein after referred to as "IN1006") titled "Pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative" was published on 27 August 2010 but claims a priority of 16 August 2007. As such, though published after the priority date of the Applicant's claim, it has an earlier priority date than that of the present Application. The bibliographic page and relevant extracts of the Complete Specification and claims of 'IN1006, as retrieved from the website of the Indian Patent Office, are hereto be annexed and marked as "**Exhibit A**". A tabular comparison of the claims of IN'1006 and the present Application is here to annexed and marked as "**Exhibit B**".

28. The claims of IN'1006 are directed to a pharmaceutical composition of linagliptin in combination with empagliflozin or its pharmaceutically acceptable salt and both generally and in an oral dosage form.

29. It is understood that a pharmaceutical composition would be a composition having ingredients of optimal particle size and particle size distribution.

Claims 1 and dependent 2 to 9 and 14 to 15

30. The complete specification of IN'1006 states that the claimed pharmaceutical composition and dosage forms preferably comprise "one or more pharmaceutically acceptable carriers which must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof [see 'IN1006, internal page 44] . The complete specification further states that "[tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents]" [see'IN1006,internal page 44] .It also states that"[examples of pharmaceutically acceptable carriers are known to one skilled in the art"[see'IN1006,internal page45].

31. Claim1of '1006 claims a pharmaceutical composition comprising empagliflozin in combination with the DPPIV inhibitor or a pharmaceutically acceptable salt thereof wherein the amount of empagliflozin is from 5mg to50mg and wherein the amount of the DPPIV inhibitor is from 0.5mg to10mg.

32. Therefore, Claim 1 of the present Application is anticipated by claim1 of IN'1006. Dependent Claims 2 to 3(preferred dosage strength) ,Claims 4 to 5(relating to partical size) , Claim 6 to 9(relating to a pharmaceutical composition comprising linagliptin, empagliflozin and excipients)and Claims 14 and 15 (preferred dosage form) of the present Application are also anticipated by claim 1 of IN'1006 read with its complete specification.

33. As set out Claims1to 9 and14 to 15 are anticipated by prior claiming by the claims of 1006/DELNP/2010 are ought to be rejected under section 25 (1) (c) of the Patents Act.

34. Therefore the claims of the Present Application are out to be rejected on the ground of 25(1) (c).

X.B. SECTION 25 (1) (e): LACK OF INVENTIVE STEP

35. Section 25(1)(e) provides a ground of opposition on the ground that the invention so far is claimed in a claim of complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published, *inter alia*, in India or elsewhere in any other document.
36. Section 2(1)(j) defines inventive step thus: "inventive step" means a feature of an invention that involves technical advancement as compared to existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art" (emphasis supplied).
37. Thus, to possess inventive step, the invention must have a feature that (i) involves technical advancement as compared to existing knowledge and (ii) is not obvious to a person skilled in the art. It is an established position of law that both these elements set out in the definition of "inventive step" have to be satisfied.
38. As shown below, the Claims of the present Application are obvious to a person skilled in the art. Further, they do not involve any technical advance.

Linagliptin and its pharmaceutical composition were known

39. It is an admitted position that linagliptin, methods of manufacture is known before the priority date of the Present application as shown in below mention journal by Silke Retlich, Barbara Withopf, Andreas Greishel, Alexander Staab, Ulrich Jaehde and Holger Fuchs, on [Binding to dipeptidyl peptidase-4 determine the disposition of linagliptin\(BI 1356\)- investigations in DPP-4 deficient and wildtype rats.](#)
40. Patent 9506/DELNP/2008 (herein referred to as IN'9506"), titled "DPP IV inhibitor formulations" and published on 23/03/2009, a copy of which is here to annexed and marked as "**Exhibit D**", the Patent Applicant sets out the alleged problem of incompatibilities and degradation faced by DPP-IV inhibitors with primary or secondary amino groups, including linagliptin [see claims of IN 9506]. IN'9506" discloses the choice of excipients-a first and second diluents, a binder, and a disintegrant. The Claim 1 of IN'9506" also set out the dosage of active ingredient 0.5 mg to 10 mg.
41. Thus, as of the priority date, linagliptin and its pharmaceutical composition comprising preferred excipients and their incompatibilities were known.

Empagliflozin was known

42. It is an admitted position that empagliflozin and its preferred crystalline forms were known [see Complete Specification, internal pages 2 and 18 to 20].
43. For instance, in patent number WO2007093610, herein referred to as WO'610 (**Exhibit C**), the Patent Applicant discloses a GLUCOPYRANOSYL-SUBSTITUTED BENZONITRILE DERIVATIVES , A PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS and THEIR USE AND PROCESS FOR THEIR MANUFACTURE. The main aim of the invention is to find new glucopyranosyl-substituted benzonitrile derivatives, particularly those which are active with regard to the sodium-dependent glucose cotransporter SGLT, particularly SGLT2. A further aim of the present invention is to discover glucopyranosyl-substituted benzene derivatives which have an enhanced inhibitory effect on the sodium-dependent glucose cotransporter SGLT2 in vitro and/or in vivo compared with known, structurally similar compounds and/or have better pharmacological or pharmacokinetic properties

Combination of linagliptin with other anti-diabetic drugs, including SGLT2 inhibitors, was known

44. As shown below, combinations of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, were known in the art as of the priority date.
45. Patent documents such as WO2005/085246 titled "8-[3-amino-piperidin-1-yl]-xanthine, the production thereof and the use in the form of a DPP inhibitor" (published on 15 September 2005) and US Publication No. 2006/0079541 titled "3-methyl-7-butinyl-xanthines ,the preparation thereof and their use a pharmaceutical compositions"(published on 13 April 2006) (equivalent of WO2006/029769 published on 23 March 2006) disclose DPP IV inhibit and their combination with SGLT2 inhibitors.
46. The rationale for combining different drugs was well-known. For example ,WO2007/033350 (herein after referred to as "WO'350") ,titled "Dipeptidyl peptidase inhibitors for treating diabetes" and published on 22 March 2007, is here to annexed and marked as "**Exhibit E**" discloses some such reasons. WO'350 disclosed pharmaceutical compositions comprising a DPPIV inhibitor (referred to as "Compound I") and other anti-diabetic compounds [see WO'350, internal pages

4 to 8].It stated that the combinations provide excellent effects such as (i) enhancement in therapeutic effects of either of Compound I and *I* or the anti-diabetic compounds,(ii) reduction in side-effects of Compound I and *I* or the anti-diabetic compounds and (iii) reduction in dose of Compound I and *I* or the anti-diabetic compounds [see WO'350, internal page 4]. These reflect the benefits that were expected to arise out of a combination of different active ingredients.

47. Thus, the combination of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, and the rationale for such combination was known in the art.
48. Thus, Claims 1 to 9 and 14 to 15 of the present Application lack inventive step because they are obvious to a person skilled in the art and do not involve a technical advance. They, therefore, ought to be rejected under section 2(1)(j) read with section 25(1)(e) of the Patents Act.

X.C. SECTION 25 (1) (f): FAILURE TO MEET SECTION 3(d)

49. Section 25(1)(f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.
50. Section 3(d) provides that new forms of known substances are not patentable unless they exhibit an enhanced efficacy. The explanation to section 3(d) provides that this includes combinations of known substances.
51. It is an established position of law that "efficacy" in section 3(d) means therapeutic efficacy [(i) Novartis AG v. Union of India and Others, (2007) 4 MLJ 1153, at para 13; (ii) Novartis AG v. Union of India and Others, IPAB order dated 26 June 2009, at pages 154- 58 and 187-88 and (iii) Novartis AG v. Union of India and Others, [2013] 13 SCR 148, at para 180].
52. It is also an established position of law that the burden of proof of showing enhanced efficacy, i.e. enhanced therapeutic efficacy, for the claimed compound is on the patent applicant and that the proof of enhanced efficacy is to be part of the complete specification [Novartis AG v. Union of India and Others, (2007) 4 MLJ 1153, at para 13].

53. Admittedly, as of the priority date, both active ingredients- linagliptin and empagliflozin as well as the excipients were known.
54. The efficacy of both linagliptin and empagliflozin were also known
55. The Patent Applicant has not shown significantly enhanced efficacy for linagliptin or empagliflozin or the claimed combination. Further, the Patent Applicant has not shown significantly enhanced efficacy for the combination over simultaneous or sequential administration of the known active ingredients. Therefore, the Patent Applicant has failed to discharge the burden of showing enhanced therapeutic efficacy for the claimed composition.
56. The Patent Applicant has also not shown any enhanced therapeutic efficacy for the any of the claim limitations claimed in Claims 2 to 9, 10 to 13 or 14 to 15.
57. Therefore, Claim 1 and all dependent claims, i.e. Claims 1 to 15, fail the test of section 3(d) and ought to be rejected under section 3(d) read with section 25(1)(f) of the Patents Act.

X.D. SECTION 25 (1) (f): FAILURE TO MEET SECTION 3(e)

58. Section 25 (1) (f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.
59. Section 3(e) provides that a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance are not inventions within the meaning of the Patents Act.
60. All the ingredients of the claimed pharmaceutical composition are admittedly known substances.
61. All the ingredients of the claimed pharmaceutical composition are admittedly known substances.
62. Indeed, the Patent Applicant itself admits that because of the independence of the SGLT2 inhibitor from the insulin levels or insulin resistance of patients , patients *can" still be treated with a pharmaceutical composition and a pharmaceutical dosage because of the combined or alternate administration of the SGLT2inhibitor"*[see Complete Specification, internal page 48].

63. Indeed, in various previous patent applications, the Patent Applicant itself has referred to the combined, simultaneous and sequential or staggered use of the combination of a DPP-IV inhibitor and an SGLT2 inhibitor.
64. For instance, in patent number WO2007093610, herein referred to as WO'610 (Exhibit C), the Patent Applicant discloses a GLUCOPYRANOSYL-SUBSTITUTED BENZONITRILE DERIVATIVES, A PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS and THEIR USE AND PROCESS FOR THEIR MANUFACTURE. The main aim of the invention is to find new glucopyranosyl-substituted benzonitrile derivatives, particularly those which are active with regard to the sodium-dependent glucose cotransporter SGLT, particularly SGLT2. A further aim of the present invention is to discover glucopyranosyl-substituted benzene derivatives which have an enhanced inhibitory effect on the sodium-dependent glucose cotransporter SGLT2 in vitro and/or in vivo compared with known, structurally similar compounds and/or have better pharmacological or pharmacokinetic properties.
65. In another admission, the Patent Applicant in IN'1006 (Exhibit A) states that the glucopyranosyl-substituted benzene derivative, i.e. *empagliflozin*, and the DPP IV inhibitor can be administered in combination, i.e. simultaneously, or in alternation [see IN'1006, internal pages 38, 42 and 43]. It further states that with regard to administration, both active ingredients may be present either in a single dosage form or a separate dosage form [see IN'1006, internal pages 42 to 43]. Pertinently, it also states that "[the effects mentioned above are observed both, when the glucopyranosyl-substituted benzene derivative and the DPPIV inhibitor are administered in combination, for example simultaneously, and when they are administered in alternation, for example successively in separate formulations]" [see IN'1006, internal page 38].
66. While IN'1006 was published after the priority date of the present Application, it is nonetheless indicative of the Patent Applicant's own admission with respect to the various ways in which the two drugs can be administered as a combination and as to the effect of the alternate and simultaneous administration of the two drugs.
67. The pharmaceutical composition claimed in the present Application is a single composition, more particularly an oral dosage form, combining both the active ingredients. In the complete Specification, there is no comparative data to show that

the claimed composition provides improved results than when the two active ingredients are administered simultaneously or sequentially.

68. Example I only provides data to show an alleged increasing glucose excursion for a combination against a control, *linagliptin* alone and *empagliflozin* alone. The comparison in the data is to the individual compounds administered alone. There is no comparison with the simultaneous or sequential administration of the two active ingredients.
69. A part from this data relating to glucose excursion, the Complete Specification does not provides any other data to claim any other effect.
70. With respect to the data relating to glucose excursion, there is only an additive effect for the claimed composition which is a mere admixture resulting only in the aggregation of the properties of the components thereof.
71. Therefore, the Patent Applicant has failed to show synergistic effect for the claimed composition. As Claim1 relates to a mere admixture of two or more substances that results only in the aggregation of the properties of the components thereof, it fails the test of section 3 (e).
72. Further, the Patent Applicant has not shown any synergistic effect for any of the claim limitations claimed in Claims 2 to 15.
73. Claim15 relates to a process for producing a pharmaceutical composition that is a mere admixture. Therefore, it too fails the test of section 3 (e).
74. Summarily, Claims 1 to 15 fail the test of section 3(e) and therefore ought to be rejected under section 3 (e) read with section 25 (1) (f) of the Patents Act.

X.E. SECTION 25 (1) (g): INSUFFICIENCY OF DESCRIPTION

75. Section 25(1)(g) provides a ground of opposition on the ground that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

76. Complete Specification of the Present Invention discloses a pharmaceutical composition used for manufacture of a medicament to treat various conditions that are listed therein and to achieve certain outcomes in a patient for treatment[see complete specification pages 4 to 5 and 8 to 9]
77. However, apart from Example I of the pharmacological examples, there is no test result or data that supports the claim to treat the diseases or conditions and the treatment outcomes listed in the complete specification of the Present Application.
78. Because the Complete Specification does not sufficiently and clearly describe the invention, Claims 1 to 15 ought to be rejected under section 25(1)(g) of the Patents Act.
79. Thus, for all the reasons stated above, the present Application ought to be rejected in its entirety.
80. As permitted under section 25(1) of the Patents Act read with Rule 55 of the Rules, the Opponent requests that the Patent Office immediately furnish the Opponent a copy of any reply and evidence, if any, filed by the Patent Applicant to this representation by way of opposition and amendment to the Complete Specification and / or claims, if any, and also permit it to file response / rejoinder to the same. The Opponent also craves leave to that it be permitted to amend the pleadings and / or grounds in its representation by way of opposition and submit further documents and evidence, as and when necessary and especially in reply to the Patent Applicant's reply and / or in response to any amendments that the Patent Applicant may make to the Complete Specification or claims
81. The Opponent also requests a hearing in the present matter.
82. The Opponent also craves leave to refer to and rely upon the full text of documents, both patent and non-patent literature, referred to in the representation by way of opposition
83. The Opponent reiterates that the fundamental right to health has paramount importance and states that a patent application that does not meet the patentability standards set out in the Indian patent law ought to be rejected.
84. The Opponent states that grant of patents to the Patent Applicant in other jurisdictions cannot be tantamount to a grant of a patent in India. The Indian patent

law is different from the patent laws of other jurisdictions. Indian Parliament has deliberately set higher standards to disallow patents for pharmaceutical products that are not new, are not genuinely inventive, that are obvious to a person skilled in the art or that do not involve a technical advance. The Indian patent law also specifically prohibits grant of patents for new forms of known substances and mere admixtures of known substances. These higher standards have been set to prevent abuse of the patenting mechanism and to prevent undeserving patents from being granted.

85. The Opponent submits that the present Application is directed at pharmaceutical composition, and more particularly , a pharmaceutical dosage form, of two known drugs and is clearly an attempt to evergreen by extending the period of monopoly already available to the Patent Applicant on account of other patents held by it over these drugs.

Having established non-patentability of the impugned invention and having adduced supporting evidence for each of the above grounds of Opposition, the Opponent prays for the following reliefs:-

- a) That Patent Application bearing No.6148/DELNP/2011 titled "Pharmaceutical composition comprising *linagliptin* and optionally a SGLT2 inhibitor, and uses thereof be rejected and the grant of patent to the said Application be refused;
- b) That copy of the reply of the Patent Applicant and evidence, if any, and /or amendment to the Complete Specification or claims, if any, be forwarded forthwith to the Opponent;
- c) That the Opponent be allowed to file response /rejoinder to the reply and evidence, if any, filed by the Patent Applicant;
- d) That the Opponent be allowed to amend the pleadings and /or grounds in its representation by way of opposition and submit further documents and evidence, as and when necessary and especially in reply to the Patent Applicant's reply and / or in response to any amendments that the Patent Applicant may make to the Complete Specification or claims;
- e) That the Opponent be granted a hearing under section 25(1) read with Rule 55;

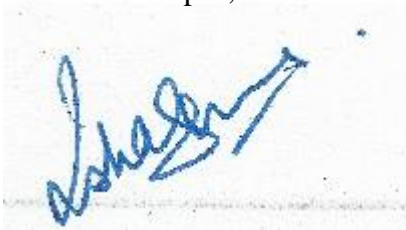
- f) That the Opponent be granted leave to refer to and rely upon the full text of documents ,both patent and non-patent literature, referred to in the representation by way of opposition;
- g) For costs;
- h) For such other and further reliefs that the Learned Controller may deem necessary in the facts and circumstances of this case.

All communications relating to these proceeding may be send to the following address in India.

Third Floor, B-43, Sector – 2

Noida-201301

Dated: 11th April, 2019



Isha Sharma

IN/PA 2386

(Agent of opponent)

To,

Controller of Patents

New Delhi



Description: WO2010092124 (A1) — 2010-08-19

PHARMACEUTICAL COMPOSITION COMPRISING LINAGLIPTIN AND OPTIONALLY A SGLT2 INHIBITOR, AND USES THEREOF

Description of WO2010092124 (A1)

A high quality text as facsimile in your desired language may be available amongst the following family members:

[AU2010212866 \(A1\)](#), [CA2752434 \(A1\)](#), [CN102316861 \(A\)](#), [DK2395984 \(T3\)](#), [EA201101190 \(A1\)](#),
[EP2395984 \(A1\)](#), [ES2606050 \(T3\)](#), [HUE031088 \(T2\)](#), [JP2012517458 \(A\)](#), [KR20110114658 \(A\)](#),
[MA33045 \(B1\)](#), [MX2011008171 \(A\)](#), [SG173036 \(A1\)](#), [TN2011000414 \(A1\)](#), [TW201040185 \(A\)](#),
[US2010209506 \(A1\)](#), [UY32427 \(A\)](#), [CN103751192 \(A\)](#), [more](#)

The EPO does not accept any responsibility for the accuracy of data and information originating from other authorities than the EPO; in particular, the EPO does not guarantee that they are complete, up-to-date or fit for specific purposes.

PHARMACEUTICAL COMPOSITION COMPRISING LINAGLIPTIN AND OPTIONALLY A SGLT2 INHIBITOR, AND USES THEREOF

Technical Field of the Invention

The present invention relates to pharmaceutical compositions comprising linagliptin as a first active pharmaceutical ingredients. Furthermore the present invention relates to a pharmaceutical dosage form comprising such a pharmaceutical composition. In addition the invention relates to a process for the preparation of such a pharmaceutical dosage form. In addition the invention relates to the use of the pharmaceutical composition and of the pharmaceutical dosage form in the treatment and/or prevention of selected diseases and medical conditions, in particular of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose and hyperglycemia inter alia. Furthermore the present invention relates to methods of treating and/or preventing of such diseases and medical conditions wherein a pharmaceutical composition or pharmaceutical dosage form according to the invention is administered to a patient in need thereof.

Background of the Invention The compound linagliptin is a DPP-IV inhibitor. The enzyme DPP-IV (dipeptidyl peptidase IV) also known as CD26 is a serine protease known to lead to the cleavage of a dipeptide from the N-terminal end of a number of proteins having at their N-terminal end a prolin or alanin residue. Due to this property DPP-IV inhibitors interfere with the plasma level of bioactive peptides including the peptide GLP-1 and are considered to be promising drugs for the treatment of diabetes mellitus, in particular type 2 diabetes mellitus.

In attempts to prepare pharmaceutical compositions of selected DPP-IV inhibitors, such

as linagliptin, it has been observed, that the DPP-IV inhibitors with a primary or secondary amino group show incompatibilities, degradation problems, or extraction problems with a number of customary excipients such as microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, tartaric acid, citric acid, glucose, fructose, saccharose, lactose, maltodextrines. Though the compounds themselves are very stable, they react with many excipients used in solid dosage forms and with impurities of excipients, especially in tight contact provided in tablets and at high excipient/drug ratios. The amino group appears to react with reducing sugars and with other reactive carbonyl groups and with carboxylic acid functional groups formed for example at the surface of microcrystalline cellulose by oxidation. These unforeseen difficulties are primarily observed in low dosage ranges which are required due to the surprising potency of the selected inhibitors, such as linagliptin. Thus, pharmaceutical compositions are required so solve these technical problems associated with the unexpected potency of selected DPP-IV inhibitor compounds. Pharmaceutical compositions comprising linagliptin as the only active pharmaceutical ingredient are described in the WO 2007/128724.

Type 2 diabetes is an increasingly prevalent disease that due to a high frequency of complications leads to a significant reduction of life expectancy. Because of diabetes-associated microvascular complications, type 2 diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputations in the industrialized world. In addition, the presence of type 2 diabetes is associated with a two to five fold increase in cardiovascular disease risk.

After long duration of disease, most patients with type 2 diabetes will eventually fail on oral therapy and become insulin dependent with the necessity for daily injections and multiple daily glucose measurements.

Oral antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or (initial or add-on) combination therapy) include, without being restricted thereto, metformin, sulphonylureas, thiazolidinediones, glinides and α -glucosidase inhibitors.

The high incidence of therapeutic failure is a major contributor to the high rate of long-term hyperglycemia-associated complications or chronic damages (including micro- and macrovascular complications such as e.g. diabetic nephropathy, retinopathy or neuropathy, or cardiovascular complications) in patients with type 2 diabetes.

Therefore, there is an unmet medical need for methods, medicaments and pharmaceutical compositions with a good efficacy with regard to glycemic control, with regard to disease-modifying properties and with regard to reduction of cardiovascular morbidity and mortality while at the same time showing an improved safety profile.

SGLT2 inhibitors represent a novel class of agents that are being developed for the treatment or improvement in glycemic control in patients with type 2 diabetes. Glucopyranosyl-substituted benzene derivative are described in the prior art as SGLT2 inhibitors, for example in WO 01/27128, WO 03/099836, WO 2005/092877, WO 2006/034489, WO 2006/064033, WO 2006/117359, WO 2006/117360, WO 2007/025943, WO 2007/028814, WO 2007/031548, WO 2007/093610, WO 2007/128749, WO 2008/049923, WO 2008/055870, WO 2008/055940. The glucopyranosyl-substituted benzene derivatives are proposed as inducers of urinary sugar excretion and as medicaments in the treatment of diabetes.

Aim of the present invention

The aim of the present invention is to provide a pharmaceutical composition comprising linagliptin which shows no signs or only marginal signs of degradation of linagliptin and thus enables a good to very good shelf life.

Another aim of the invention is to provide a pharmaceutical composition comprising linagliptin which has high content uniformity and/or which allows an effective production with regard to time and costs of pharmaceutical dosage forms.

Another aim of the invention is to provide a pharmaceutical dosage form comprising linagliptin which has a good shelf life, which has a short disintegration time, which has good dissolution properties and/or which enables a high bioavailability of linagliptin in a patient.

A further aim of the present invention is to provide a pharmaceutical composition comprising a combination of a DPPIV inhibitor and an SGLT2 inhibitor.

Another aim of the present invention is to provide a pharmaceutical composition comprising linagliptin in combination with an SGLT2 inhibitor which shows no signs or only marginal signs of degradation of linagliptin and thus enables a good to very good shelf life.

Another aim of the invention is to provide a pharmaceutical composition comprising linagliptin in combination with a SGLT2 inhibitor which has high content uniformity and/or which allows an effective production with regard to time and costs of pharmaceutical dosage forms.

Another aim of the invention is to provide a pharmaceutical dosage form comprising linagliptin in combination with an SGLT2 inhibitor which has a good shelf life, which has a short disintegration time, which has good dissolution properties and/or which enables a high bioavailability of linagliptin in a patient. Another aim of the invention is to provide a pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, and a method for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular of type 2 diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, and a method for improving glycemic control in a patient in need thereof, in particular in patients with type 2 diabetes mellitus.

Another aim of the present invention is to provide a pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, and a method for improving glycemic control in a patient with insufficient glycemic control despite monotherapy with an antidiabetic drug, for example metformin or an SGLT2 inhibitor or a DPPIV inhibitor.

Another aim of the present invention is to provide a pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, and a method for preventing, slowing or delaying progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

Yet another aim of the present invention is to provide a pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, and a method for preventing, slowing progression of, delaying or treating of a condition or disorder from the group consisting of complications of diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, and a method for reducing the weight or preventing an increase of the weight

in a patient in need thereof.

Another aim of the present invention is to provide a new pharmaceutical composition and a pharmaceutical dosage form, each comprising linagliptin in combination with an SGLT2 inhibitor, with a high efficacy for the treatment of metabolic disorders, in particular of diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, which has good to very good pharmacological and/or pharmacokinetic and/or physicochemical properties.

Another aim of the present invention is to provide a process for the preparation of a pharmaceutical dosage form according to the invention which is highly effective in costs and/or time.

Further aims of the present invention become apparent to the one skilled in the art by the description hereinbefore and in the following and by the examples.

Summary of the Invention

In a first aspect the present invention provides a pharmaceutical composition comprising linagliptin as a first active pharmaceutical ingredient and one or more excipients, in particular one or more diluents, one or more binders and/or one or more disintegrants. The pharmaceutical composition according to the invention is preferably a solid pharmaceutical composition, for example a solid pharmaceutical composition for oral administration.

Within the scope of the present invention it has been found that a pharmaceutical composition comprising linagliptin as an active pharmaceutical ingredient with a particle size distribution of $X_{90} < 200 \mu\text{m}$ shows an advantageous dissolution profile and/or good bioavailability and allows a high content uniformity and an effective production with regard to time and costs of pharmaceutical dosage forms.

Therefore in another aspect the present invention provides a pharmaceutical composition comprising linagliptin as a first active pharmaceutical ingredient and one or more excipients, wherein the first active ingredient has a particle size distribution of $X_{90} < 200 \mu\text{m}$, preferably determined by volume by laser-diffraction method.

Furthermore within the scope of the present invention it has been found that linagliptin combined with certain excipients shows no signs or only marginal signs of degradation of linagliptin and thus enables a good to very good shelf life. In particular it has been found that the aims of the present invention can be achieved with a pharmaceutical composition as described above which comprises only one diluent.

Furthermore within the scope of the present invention it has been found that a pharmaceutical composition comprising linagliptin as a first active pharmaceutical ingredient in combination with a glucopyranosyl-substituted benzene derivative of the formula (I) as described hereinafter as an SGLT2 inhibitor shows no signs or only marginal signs of degradation of linagliptin and thus enables a good to very good shelf life. This result could not have been predicted in view of the chemical nature of linagliptin and the functional groups of the glucopyranosyl-substituted benzene derivative, in particular the glucopyranosyl-ring and the hydroxy-groups therein.

Therefore in another aspect the present invention provides a pharmaceutical composition comprising linagliptin as an active pharmaceutical ingredient, a glucopyranosyl-substituted benzene derivative of the formula (I)

Image available on "Original document"

wherein R<1> denotes chloro or methyl; and R<3> denotes ethyl, ethynyl, ethoxy, (R)-tetrahydrofuran-3-yloxy or (S)-tetrahydrofuran-3-yloxy, or a prodrug thereof, as an active pharmaceutical ingredient, one or more diluents, one or more binders and one or more disintegrants.

Within the scope of the present invention it has been found that a pharmaceutical composition comprising the glucopyranosyl-substituted benzene derivative as an active pharmaceutical ingredient with a particle size distribution of $1\ \mu\text{m} < X_{90} < 200\ \mu\text{m}$ shows an advantageous dissolution profile and/or good bioavailability and allows a high content uniformity and an effective production with regard to time and costs of pharmaceutical dosage forms.

Therefore in another aspect the present invention provides a pharmaceutical composition comprising linagliptin as a first active pharmaceutical ingredient and a glucopyranosyl-substituted benzene derivative of the formula (I) as described hereinafter as a second active pharmaceutical ingredient and one or more excipients, wherein the second active ingredient has a particle size distribution of $1\ \mu\text{m} < X_{90} < 200\ \mu\text{m}$, preferably determined by volume by laser-diffraction method. The pharmaceutical compositions according to the invention allow a high content uniformity and an effective production with regard to time and costs of pharmaceutical dosage forms, such as tablets and capsules. Furthermore these pharmaceutical dosage forms, in particular tablets, such as one-layer tablets or two-layer tablets, according to the invention show no signs or only marginal signs of degradation of linagliptin and thus enable a long shelf life.

Therefore in another aspect the present invention provides a pharmaceutical dosage form comprising a pharmaceutical composition according to the invention. The pharmaceutical dosage forms according to the invention are preferably solid pharmaceutical dosage forms, even more preferably solid pharmaceutical dosage forms for oral administration.

In another aspect the present invention provides a process for the preparation of a pharmaceutical dosage form according to the invention comprising one or more granulation processes wherein the one or two active pharmaceutical ingredients together with one or more excipients are granulated.

Furthermore it can be found that the pharmaceutical composition comprising linagliptin in combination with a glucopyranosyl-substituted benzene derivative of the formula (I) as described hereinafter can advantageously be used for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular for improving glycemic control in patients, for example in patients with inadequate glycemic control with existing therapy with oral antidiabetics. This opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighboring disease states.

According to another aspect of the invention, there is provided a method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient.

According to another aspect of the invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA_{1c} in a patient in need thereof characterized in that an a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient.

The pharmaceutical composition and pharmaceutical dosage form according to this invention may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome.

According to another aspect of the invention, there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient.

As by the use of a pharmaceutical composition and pharmaceutical dosage form according to this invention, an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or diseases related to or caused by an increased blood glucose level may be treated.

According to another aspect of the invention, there is provided a method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis, in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient. The term "tissue ischaemia" particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer. In particular one or more aspects of diabetic nephropathy such as hyperperfusion, proteinuria and albuminuria may be treated, their progression slowed or their onset delayed or prevented. The terms "micro- and macrovascular diseases" and "micro- and macrovascular complications" are used interchangeably in this application. By the administration of a pharmaceutical composition and pharmaceutical dosage form according to this invention and due to the activity of the SGLT2 inhibitor excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. Therefore, no gain in weight or even a reduction in body weight is the result.

According to another aspect of the invention, there is provided a method for reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient.

The pharmacological effect of the glucopyranosyl-substituted benzene derivative as an SGLT2 inhibitor in the pharmaceutical composition according to this invention is independent of insulin. Therefore, an improvement of the glycemic control is possible without an additional strain on the pancreatic beta cells. By an administration of a pharmaceutical composition or pharmaceutical dosage form according to this invention a beta-cell degeneration and a decline of beta-cell functionality such as for example apoptosis or necrosis of pancreatic beta cells can be delayed or prevented. Furthermore, the functionality of pancreatic cells can be improved or restored, and the number and size of pancreatic beta cells increased. It may be shown that the differentiation status and hyperplasia of pancreatic beta-cells disturbed by hyperglycemia can be normalized by treatment with a pharmaceutical composition or pharmaceutical dosage form according to this invention.

According to another aspect of the invention, there is provided a method for preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient.

By the administration of a pharmaceutical composition and pharmaceutical dosage form according to the present invention, an abnormal accumulation of fat in the liver may be reduced or inhibited. Therefore, according to another aspect of the present invention, there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient. Diseases or conditions which are attributed to an abnormal accumulation of liver fat are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver or toxic fatty liver.

As a result thereof, another aspect of the invention provides a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that a pharmaceutical composition or pharmaceutical dosage form as defined hereinbefore and hereinafter is administered to the patient.

According to another aspect of the invention there is provided the use of a pharmaceutical composition according to the invention for the manufacture of a medicament for - preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or

- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or

- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or

- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; or

- reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight; or

- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion; or - preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat; or

- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance; in a patient in need thereof.

According to another aspect of the invention, there is provided the use of a pharmaceutical composition or of a pharmaceutical dosage form according to the present invention for the manufacture of a medicament for a therapeutic and preventive method as described hereinbefore and hereinafter.

Definitions

The term "active ingredient" or "active pharmaceutical ingredient" of a pharmaceutical composition or pharmaceutical dosage form according to the present invention means linagliptin and optionally a glucopyranosyl-substituted benzene derivative of the formula (I) as according to the present invention, in particular the compound (1.3).

The term "body mass index" or "BMI" of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of kg/m^2 .

The term "overweight" is defined as the condition wherein the individual has a BMI greater than or 25 kg/m^2 and less than 30 kg/m^2 . The terms "overweight" and "pre-obese" are used interchangeably.

The term "obesity" is defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m^2 . According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 30 kg/m^2 but lower than 35 kg/m^2 ; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 kg/m^2 but lower than 40 kg/m^2 ; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m^2 .

The term "visceral obesity" is defined as the condition wherein a waist-to-hip ratio of greater than or equal to 1.0 in men and 0.8 in women is measured. It defines the risk for insulin resistance and the development of pre-diabetes. The term "abdominal obesity" is usually defined as the condition wherein the waist circumference is > 40 inches or 102 cm in men, and is > 35 inches or 94 cm in women. With regard to a Japanese ethnicity or Japanese patients abdominal obesity may be defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women (see e.g. investigating committee for the diagnosis of metabolic syndrome in Japan).

The term "euglycemia" is defined as the condition in which a subject has a fasting blood glucose concentration within the normal range, greater than 70 mg/dL (3.89 mmol/L) and less than 100 mg/dL (5.6 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term "hyperglycemia" is defined as the condition in which a subject has a fasting blood glucose concentration above the normal range, greater than 100 mg/dL (5.6 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term "hypoglycemia" is defined as the condition in which a subject has a blood glucose concentration below the normal range, in particular below 70 mg/dL (3.89 mmol/L).

The term "postprandial hyperglycemia" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 200 mg/dL (11.1 mmol/L).

The term "impaired fasting blood glucose" or "IFG" is defined as the condition in which

a subject has a fasting blood glucose concentration or fasting serum glucose concentration in a range from 100 to 125 mg/dl (i.e. from 5.6 to 6.9 mmol/l), in particular greater than 110 mg/dL and less than 126 mg/dl (7.00 mmol/L). A subject with "normal fasting glucose" has a fasting glucose concentration smaller than 100 mg/dl, i.e. smaller than 5.6 mmol/l.

The term "impaired glucose tolerance" or "IGT" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.78 mmol/L) and less than 200 mg/dL (11.1 mmol/L). The abnormal glucose tolerance, i.e. the 2 hour postprandial blood glucose or serum glucose concentration can be measured as the blood sugar level in mg of glucose per dL of plasma 2 hours after taking 75 g of glucose after a fast. A subject with "normal glucose tolerance" has a 2 hour postprandial blood glucose or serum glucose concentration smaller than 140 mg/dl (7.78 mmol/L). The term "hyperinsulinemia" is defined as the condition in which a subject with insulin resistance, with or without euglycemia, has fasting or postprandial serum or plasma insulin concentration elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ratio < 1.0 (for men) or < 0.8 (for women).

The terms "insulin-sensitizing", "insulin resistance-improving" or "insulin resistance-lowering" are synonymous and used interchangeably.

The term "insulin resistance" is defined as a state in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford ES, et al. JAMA. (2002) 287:356-9). A method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so called minimal models in which, during an intravenous glucose tolerance test, the insulin and glucose concentrations in the blood are measured at fixed time intervals and from these the insulin resistance is calculated. With this method, it is not possible to distinguish between hepatic and peripheral insulin resistance.

Furthermore, insulin resistance, the response of a patient with insulin resistance to therapy, insulin sensitivity and hyperinsulinemia may be quantified by assessing the "homeostasis model assessment to insulin resistance (HOMA-IR)" score, a reliable indicator of insulin resistance (Katsuki A, et al. Diabetes Care 2001 ; 24: 362-5). Further reference is made to methods for the determination of the HOMA-index for insulin sensitivity (Matthews et al., Diabetologia 1985, 28: 412-19), of the ratio of intact proinsulin to insulin (Forst et al., Diabetes 2003, 52(Suppl.1): A459) and to an euglycemic clamp study. In addition, plasma adiponectin levels can be monitored as a potential surrogate of insulin sensitivity. The estimate of insulin resistance by the homeostasis assessment model (HOMA)-IR score is calculated with the formula (Galvin P, et al. Diabet Med 1992;9:921-8):

$$\text{HOMA-IR} = [\text{fasting serum insulin } (\mu\text{U/mL})] \times [\text{fasting plasma glucose (mmol/L)/22.5}]$$
 As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

Patients with a predisposition for the development of IGT or IFG or type 2 diabetes are those having euglycemia with hyperinsulinemia and are by definition, insulin resistant. A typical patient with insulin resistance is usually overweight or obese. If insulin resistance can be detected, this is a particularly strong indication of the presence of pre-diabetes. Thus, it may be that in order to maintain glucose homeostasis a person

needs 2-3 times as much insulin as a healthy person, without this resulting in any clinical symptoms.

The methods to investigate the function of pancreatic beta-cells are similar to the above methods with regard to insulin sensitivity, hyperinsulinemia or insulin resistance: An improvement of beta-cell function can be measured for example by determining a HOMA- index for beta-cell function (Matthews et al., *Diabetologia* 1985, 28: 412-19), the ratio of intact proinsulin to insulin (Forst et al., *Diabetes* 2003, 52(Suppl.1): A459), the insulin/C- peptide secretion after an oral glucose tolerance test or a meal tolerance test, or by employing a hyperglycemic clamp study and/or minimal modeling after a frequently sampled intravenous glucose tolerance test (Stumvoll et al., *Eur J Clin Invest* 2001, 31: 380-81).

The term "pre-diabetes" is the condition wherein an individual is pre-disposed to the development of type 2 diabetes. Pre-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range ≥ 100 mg/dL (J. B. Meigs, et al. *Diabetes* 2003; 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration). The scientific and medical basis for identifying prediabetes as a serious health threat is laid out in a Position Statement entitled "The Prevention or Delay of Type 2 Diabetes" issued jointly by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases (*Diabetes Care* 2002; 25:742-749).

Individuals likely to have insulin resistance are those who have two or more of the following attributes: 1) overweight or obese, 2) high blood pressure, 3) hyperlipidemia, 4) one or more 1<st> degree relative with a diagnosis of IGT or IFG or type 2 diabetes. Insulin resistance can be confirmed in these individuals by calculating the HOMA-IR score. For the purpose of this invention, insulin resistance is defined as the clinical condition in which an individual has a HOMA-IR score > 4.0 or a HOMA-IR score above the upper limit of normal as defined for the laboratory performing the glucose and insulin assays.

The term "type 2 diabetes" is defined as the condition in which a subject has a fasting blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). The measurement of blood glucose values is a standard procedure in routine medical analysis. If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dl_ (1 1.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject, the blood sugar level before taking the glucose will be between 60 and 110 mg per dl_ of plasma, less than 200 mg per dl_ 1 hour after taking the glucose and less than 140 mg per dl_ after 2 hours. If after 2 hours the value is between 140 and 200 mg, this is regarded as abnormal glucose tolerance.

The term "late stage type 2 diabetes mellitus" includes patients with a secondary drug failure, indication for insulin therapy and progression to micro- and macrovascular complications e.g. diabetic nephropathy, or coronary heart disease (CHD).

The term "HbA1c" refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of diabetes mellitus the HbA1c value is of exceptional importance. As its production depends essentially on the blood sugar level and the life of the erythrocytes, the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar levels of the preceding 4-6 weeks. Diabetic patients whose HbA1c value is consistently well adjusted by intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin in the sample), are significantly better protected against diabetic microangiopathy. For example, metformin on its own achieves an average improvement in the HbA1c value

in the diabetic of the order of 1.0 - 1.5 %. This reduction of the HbA1 C value is not sufficient in all diabetics to achieve the desired target range of < 6.5 % and preferably < 6 % HbA1c.

The term "insufficient glycemic control" or "inadequate glycemic control" in the scope of the present invention means a condition wherein patients show HbA1c values above 6.5 %, in particular above 7.0 %, even more preferably above 7.5 %, especially above 8 %. The "metabolic syndrome", also called "syndrome X" (when used in the context of a metabolic disorder), also called the "dysmetabolic syndrome" is a syndrome complex with the cardinal feature being insulin resistance (Laaksonen DE, et al. Am J Epidemiol 2002;156:1070-7). According to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel

on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) JAMA: Journal of the American Medical Association (2001) 285:2486-2497), diagnosis of the metabolic syndrome is made when three or more of the following risk factors are present: 1. Abdominal obesity, defined as waist circumference > 40 inches or 102 cm in men, and > 35 inches or 94 cm in women; or with regard to a Japanese ethnicity or

Japanese patients defined as waist circumference \geq 85 cm in men and \geq 90 cm in women;

2. Triglycerides: \geq 150 mg/dL 3. HDL-cholesterol < 40 mg/dL in men

4. Blood pressure \geq 130/85 mm Hg (SBP \geq 130 or DBP \geq 85)

5. Fasting blood glucose \geq 100 mg/dL

The NCEP definitions have been validated (Laaksonen DE, et al. Am J Epidemiol. (2002) 156:1070-7). Triglycerides and HDL cholesterol in the blood can also be determined by standard methods in medical analysis and are described for example in Thomas L (Editor): "Labor und Diagnose", TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2000.

According to a commonly used definition, hypertension is diagnosed if the systolic blood pressure (SBP) exceeds a value of 140 mm Hg and diastolic blood pressure (DBP) exceeds a value of 90 mm Hg. If a patient is suffering from manifest diabetes it is currently recommended that the systolic blood pressure be reduced to a level below 130 mm Hg and the diastolic blood pressure be lowered to below 80 mm Hg.

The terms "treatment" and "treating" comprise therapeutic treatment of patients having already developed said condition, in particular in manifest form. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to stop or slow down progression of the disease. Thus the compositions and dosage forms and methods of the present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy. The terms "prophylactically treating", "preventively treating" and "preventing" are used interchangeably and comprise a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

The term "therapeutically effective amount" as used herein refers to an amount or dose of the active pharmaceutical ingredient that effects the desired therapeutic response, for example a reduction in blood glucose levels, a reduction of HbA1c or weight reduction, in a mammalian subject or patient, but preferably does not cause hypoglycemia in the subject or patient. In case the pharmaceutical composition or

pharmaceutical dosage form comprises two active pharmaceutical ingredients, the term "therapeutically effective amount" as used herein refers to an amount or dose of the respective active pharmaceutical ingredient that in combination with the other active pharmaceutical ingredient effects the desired therapeutic response, for example a reduction in blood glucose levels, a reduction of HbA1c or weight reduction, in a mammalian subject or patient, but preferably does not cause hypoglycemia in the subject or patient.

The term "tablet" comprises tablets without a coating and tablets with one or more coatings. Furthermore the "term" tablet comprises tablets having one, two, three or even more layers and press-coated tablets, wherein each of the beforementioned types of tablets may be without or with one or more coatings. The term "tablet" also comprises mini, melt, chewable, effervescent and orally disintegrating tablets.

The terms "pharmacopoe" and "pharmacopoeias" refer to standard pharmacopoeias such as the "USP 31-NF 26 through Second Supplement" (United States Pharmacopoeial

Convention) or the "European Pharmacopoeia 6.3" (European Directorate for the Quality of Medicines and Health Care, 2000-2009).

Brief Description of the Figures The Figure 1 shows an X-ray powder diffractogram of the crystalline form (1.3X) of the compound (1.3).

The Figure 2 shows the thermoanalysis and determination of the melting point via DSC of the crystalline form (1.3X) of the compound (1.3).

The Figure 3 shows the glucose excursion as quantified by the calculated reactive glucose AUC after a glucose challenge in four different groups of ZDF rats which received a control, linagliptin (Cpd. A), the compound (1.3) (Cpd. B) or a combination of linagliptin and the compound (1.3) (Combination A + B).

The Figure 4 shows dissolution profiles of tablets according to the Example 4 and the Example 6 wherein API 1 is the compound (1.3) and the API 2 is linagliptin. The Figure 5 shows dissolution profiles of tablets according to the Example 8 wherein API 1 is the compound (1.3) and the API 2 is linagliptin.

Detailed Description

The aspects according to the present invention, in particular the pharmaceutical compositions, pharmaceutical dosage forms, methods and uses, refer to linagliptin and glucopyranosyl-substituted benzene derivatives as defined hereinbefore and hereinafter.

The term "linagliptin" as employed herein refers to linagliptin and pharmaceutically acceptable salts thereof, including hydrates and solvates thereof, and crystalline forms thereof. Crystalline forms are described in WO 2007/128721. Preferred crystalline forms are the polymorphs A and B described therein. Methods for the manufacture of linagliptin are described in the patent applications WO 2004/018468 and WO 2006/048427 for example. Linagliptin is distinguished from structurally comparable DPP IV inhibitors, as it combines exceptional potency and a long-lasting effect with favourable pharmacological properties, receptor selectivity and a favourable side-effect profile or bring about unexpected therapeutic advantages or improvements when used in combination with a glucopyranosyl-substituted benzene derivative according to this invention.

The glucopyranosyl-substituted benzene derivative is defined by the formula (I)

Image available on "Original document"

wherein R<1> denotes chloro or methyl; and R<3> denotes ethyl, ethynyl, ethoxy, (R)-tetrahydrofuran-3-yloxy or (SJ-tetrahydrofuran-3-yloxy; or a prodrug thereof.

Compounds of the formula (I) and methods of their synthesis are described for example in the following patent applications: WO 2005/092877, WO 2006/117360, WO 2006/117359, WO 2006/120208, WO 2006/064033, WO 2007/028814, WO 2007/031548, WO 2008/049923.

In the above glucopyranosyl-substituted benzene derivatives of the formula (I) the following definitions of the substituents are preferred.

Preferably R<1> denotes chloro.

Preferably R<3> denotes ethynyl, (T[^]Metrahydrofuran-3-yloxy or (SJ-tetrahydrofuran-3-yloxy.

Most preferably R<3> denotes fR[^]-tetrahydrofuran-3-yloxy or (SJ-tetrahydrofuran-3-yloxy.

Preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the group of compounds (1.1) to (1.5):

Image available on "Original document"

Image available on "Original document"

Even more preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the compounds (1.2) and (1.3).

According to this invention, it is to be understood that the definitions of the above listed glucopyranosyl-substituted benzene derivatives of the formula (I) also comprise their hydrates, solvates and polymorphic forms thereof, and prodrugs thereof. With regard to the preferred compound (1.1) an advantageous crystalline form is described in the international patent application WO 2007/028814 which hereby is incorporated herein in its entirety. With regard to the preferred compound (1.2), an advantageous crystalline form is described in the international patent application WO 2006/1 17360 which hereby is incorporated herein in its entirety. With regard to the preferred compound (1.3) an advantageous crystalline form is described in the international patent application WO 2006/1 17359 which hereby is incorporated herein in its entirety. With regard to the preferred compound (1.5) an advantageous crystalline form is described in the international patent application WO 2008/049923 which hereby is incorporated herein in its entirety. These crystalline forms possess good solubility properties which enable a good bioavailability of the glucopyranosyl- substituted benzene derivative. Furthermore, the crystalline forms are physico-chemically stable and thus provide a good shelf-life stability of the pharmaceutical composition. A preferred crystalline form (1.3X) of the compound (1.3) can be characterized by an X-ray powder diffraction pattern that comprises peaks at 18.84, 20.36 and 25.21 degrees 2 Θ (± 0.1 degrees 2 Θ), wherein said X-ray powder diffraction pattern (XRPD) is made using CuK α radiation.

In particular said X-ray powder diffraction pattern comprises peaks at 14.69, 18.84, 19.16, 19.50, 20.36 and 25.21 degrees 2 Θ (± 0.1 degrees 2 Θ), wherein said X-ray powder diffraction pattern is made using CuK α radiation.

In particular said X-ray powder diffraction pattern comprises peaks at 14.69, 17.95, 18.43, 18.84, 19.16, 19.50, 20.36, 22.71 , 23.44, 24.81 , 25.21 and 25.65 degrees 2 Θ

(± 0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using CuK α radiation.

More specifically, the crystalline form (1.3X) is characterised by an X-ray powder diffraction pattern, made using CuK α radiation, which comprises peaks at degrees 2Θ (± 0.1 degrees

2Θ) as contained in Table 1.

Table 1 : X-ray powder diffraction pattern of the crystalline form (1.3X) (only peaks up to 30° in 2Θ are listed):

Image available on "Original document"

Image available on "Original document"

Even more specifically, the crystalline form (1.3X) is characterised by an X-ray powder diffraction pattern, made using CuK α radiation, which comprises peaks at degrees 2Θ (± 0.1 degrees 2Θ) as shown in Figure 1.

Furthermore the crystalline form (1.3X) is characterised by a melting point of about $149^\circ\text{C} \pm 3^\circ\text{C}$ (determined via DSC; evaluated as onset-temperature; heating rate 10 K/min). The obtained DSC curve is shown in Figure 2.

The X-ray powder diffraction patterns are recorded, within the scope of the present invention, using a STOE - STADI P-diffractometer in transmission mode fitted with a location-sensitive detector (OED) and a Cu-anode as X-ray source (CuK α radiation, $\lambda = 1.54056 \text{ \AA}$, 40kV, 40mA). In the Table 1 above the values " $2\Theta [^\circ]$ " denote the angle of diffraction in degrees and the values " $d [\text{\AA}]$ " denote the specified distances in \AA between the lattice planes. The intensity shown in the Figure 1 is given in units of cps (counts per second).

In order to allow for experimental error, the above described 2Θ values should be considered accurate to ± 0.1 degrees 2Θ , in particular ± 0.05 degrees 2Θ . That is to say, when assessing whether a given sample of crystals of the compound (1.3) is the crystalline form in accordance with the invention, a 2Θ value which is experimentally observed for the sample should be considered identical with a characteristic value described above if it falls within ± 0.1 degrees 2Θ of the characteristic value, in particular if it falls within ± 0.05 degrees 2Θ of the characteristic value.

The melting point is determined by DSC (Differential Scanning Calorimetry) using a DSC 821 (Mettler Toledo).

Regarding the active pharmaceutical ingredients it can be found that the dissolution properties of the pharmaceutical composition and dosage form and thus the bioavailability of the active ingredients is affected inter alia by the particle size and particle size distribution of the respective active pharmaceutical ingredient. In the pharmaceutical composition and pharmaceutical dosage form according to the invention the active pharmaceutical ingredients preferably have a particle size distribution such that at least 90 % of the respective active pharmaceutical ingredient particles, with regard to the distribution by volume, has a particle size smaller than $200 \mu\text{m}$, i.e. $X_{90} < 200 \mu\text{m}$. In particular in the pharmaceutical composition and pharmaceutical dosage form according to the invention linagliptin, for example a crystalline form thereof, preferably has a particle size distribution (by volume) such that at least 90 % of the respective active pharmaceutical ingredient has a particle size smaller than $200 \mu\text{m}$, i.e. $X_{90} < 200 \mu\text{m}$, more preferably $X_{90} < 150 \mu\text{m}$. More preferably the particle size distribution is such that $X_{90} < 100 \mu\text{m}$, even more preferably $X_{90} < 75 \mu\text{m}$. In addition the particle size distribution is preferably such that $X_{90} > 0.1 \mu\text{m}$, more preferably $X_{90} > 1 \mu\text{m}$, most preferably $X_{90} > 5 \mu\text{m}$. Therefore preferred particle size distributions are such that $0.1 \mu\text{m} < X_{90} < 200 \mu\text{m}$, particularly $0.1 \mu\text{m} <$

X90 < 150 μm , more preferably 1 μm < X90 < 150 μm , even more preferably 5 μm < X90 < 100 μm . A preferred example of a particle size distribution of linagliptin is such that X90 < 50 μm or 10 μm < X90 \leq 50 μm .

Furthermore in the pharmaceutical composition and pharmaceutical dosage form according to the invention linagliptin, for example a crystalline form thereof, preferably has a particle size distribution (by volume) such that X50 < 90 μm , more preferably X50 < 75 μm , even more preferably X50 < 50 μm , most preferably X50 < 40 μm . In addition the particle size distribution is preferably such that X50 > 0.1 μm , more preferably X50 > 0.5 μm , even more preferably X50 > 4 μm . Therefore preferred particle size distributions are such that 0.1 μm < X50 < 90 μm , particularly 0.5 μm < X50 < 75 μm , more preferably 4 μm < X50 < 75 μm , even more preferably 4 μm < X50 < 50 μm . A preferred example is 8 μm < X50 < 40 μm .

Furthermore in the pharmaceutical composition and pharmaceutical dosage form according to the invention linagliptin, for example a crystalline form thereof, preferably has a particle size distribution (by volume) such that X10 > 0.05 μm , more preferably X10 > 0.1 μm , even more preferably X10 > 0.5 μm .

In particular with regard to the glucopyranosyl-substituted benzene derivative of the formula (I), in particular the compound (1.3), it is surprisingly found that too small particle sizes influence the manufacturability, for example by sticking or filming. On the other hand too large particles negatively affect the dissolution properties of the pharmaceutical composition and dosage form and thus the bioavailability. In the following preferred ranges of the particle size distribution are described.

In the pharmaceutical composition and pharmaceutical dosage form according to the invention the glucopyranosyl-substituted benzene derivative of the formula (I), in particular the compound (1.3), for example its crystalline form (I3.X), preferably has a particle size distribution (by volume) such that at least 90 % of the respective active pharmaceutical ingredient has a particle size smaller than 200 μm , i.e. X90 < 200 μm , preferably X90 < 150 μm . More preferably the particle size distribution is such that X90 < 100 μm , even more preferably X90 < 90 μm . In addition the particle size distribution is preferably such that X90 > 1 μm , more preferably X90 > 5 μm , even more preferably X90 > 10 μm . Therefore preferred particle size distributions are such that 1 μm < X90 < 200 μm , particularly 1 μm < X90 < 150 μm , more preferably 5 μm < X90 < 150 μm , even more preferably 5 μm < X90 < 100 μm , even more preferably 10 μm < X90 < 100 μm . A preferred example X90 < 75 μm . Another preferred example is 20 μm < X90 < 50 μm .

Furthermore in the pharmaceutical composition and pharmaceutical dosage form according to the invention the glucopyranosyl-substituted benzene derivative of the formula (I), in particular the compound (1.3), for example its crystalline form (I3.X), preferably has a particle size distribution (by volume) such that X50 < 90 μm , more preferably X50 < 75 μm , even more preferably X50 < 50 μm , most preferably X50 < 40 μm . In addition the particle size distribution is preferably such that X50 > 1 μm , more preferably X50 > 5 μm , even more preferably X50 > 8 μm . Therefore preferred particle size distributions are such that 1 μm < X50 < 90 μm , particularly 1 μm < X50 < 75 μm , more preferably 5 μm < X50 < 75 μm , even more preferably 5 μm < X50 < 50 μm . A preferred example is 8 μm < X50 < 40 μm .

Furthermore in the pharmaceutical composition and pharmaceutical dosage form according to the invention the glucopyranosyl-substituted benzene derivative of the formula (I), in particular the compound (1.3), for example its crystalline form (I3.X), preferably has a particle size distribution (by volume) such that X10 > 0.1 μm , more preferably X10 > 0.5 μm , even more preferably X10 > 1 μm .

Therefore a pharmaceutical composition or pharmaceutical dosage form according to

this invention may preferably be characterized by the above specified particle size distributions X90, X50 and/or X10 or one of the following embodiments:

Image available on "Original document"

Image available on "Original document"

The value X90 refers to the 90% value of the volume distribution measured using a laser diffractometer. In other words, for the purposes of the present invention, the X90 value denotes the particle size below which 90% of the quantity of particles is found based on the volume distribution. Analogously the value X50 refers to the 50% value (median) of the volume distribution measured using a laser diffractometer. In other words, for the purposes of the present invention, the X50 value denotes the particle size below which 50% of the quantity of particles is found based on the volume distribution. Analogously the value X10 refers to the 10% value of the volume distribution measured using a laser diffractometer. In other words, for the purposes of the present invention, the X10 value denotes the particle size below which 10% of the quantity of particles is found based on the volume distribution.

Preferably all X90, X50, X10 values hereinbefore and hereinafter are by volume and determined by laser-diffraction method, in particular low angle laser light scattering, i.e. Fraunhofer diffraction. A preferred test is described in the experimental section. The laser diffraction method is sensitive to the volume of a particle and provides a volume-average particle size, which is equivalent to the weight-average particle size if the density is constant. The skilled artisan knows that the results of the particle size distribution determination by one technique can be correlated with that from another technique, for example on an empirical basis by routine experimentation. Alternatively the particle size distribution in the pharmaceutical composition or dosage form can be determined by microscopy, in particular electron microscopy or scanning electron microscopy.

In order to provide suitable starting material consisting the active pharmaceutical ingredient, such as linagliptin or the glucopyranosyl-substituted benzene derivative, in particular the compound (1.3) and its crystalline form (1.3X), is milled, for example jet-milled or pin-milled.

In the following the preferred excipients and carriers in the pharmaceutical compositions according to the invention are described in further detail. Preferably the excipients are pharmaceutically acceptable.

Preferably the excipients are chosen such that they are compatible with linagliptin, i.e. such that there is no or only marginal degradation of linagliptin in the pharmaceutical composition. The degradation can be tested in standard tests, for example after a 6 months storage at 40°C and 75% relative humidity. In this context the term "marginal degradation" shall mean a chemical degradation of linagliptin of less than 5 %, preferably less than 3 %, even more preferably less than 2 % by weight of linagliptin. The content and thus the degradation can be determined by well-known analytical methods, for example using HPLC or UV methods.

In the pharmaceutical composition according to the invention the excipients preferably comprise one or more diluents.

Furthermore in the pharmaceutical composition according to the invention the excipients preferably comprise one or more diluents and one or more binders.

Furthermore in the pharmaceutical composition according to the invention the excipients preferably comprise one or more diluents and one or more binders and one or more disintegrants and optional further ingredients.

Furthermore in the pharmaceutical composition according to the invention the

excipients even more preferably comprise one or more diluents and one or more binders and one or more disintegrants and one or more lubricants and optional further ingredients.

Some of the excipients may have two or more functions at the same time, for example may act as a diluent and as a binder or as a binder and as disintegrant or as a diluent, as a binder and as disintegrant.

The one or more diluents, another term is filler, are added as the quantity of the active pharmaceutical ingredient(s) is small and thus to achieve a minimal tablet weight (for example 100 mg or more) and a satisfying content uniformity (for example $< 3\%$ standard deviation) according to the pharmacopeias. Common diluents as for example lactose, sucrose, and microcrystalline cellulose are observed as not being compatible with linagliptin.

Preferably the one or more diluents suitable for a pharmaceutical composition according to the invention are selected from the group consisting of cellulose, in particular cellulose powder, dibasic calciumphosphate, in particular anhydrous or dibasic calciumphosphate dihydrate, erythritol, mannitol, starch, pregelatinized starch, and xylitol, including derivatives and hydrates of the beforementioned substances. The diluents pre-gelatinized starch shows additional binder properties. Among the diluents listed above mannitol and pregelatinized starch are particularly preferred. In case the pharmaceutical composition according to the invention comprises one diluent, then the diluent is preferably mannitol or pregelatinized starch, most preferably mannitol.

In case the pharmaceutical composition according to the invention comprises two or more diluents, then the first diluent is preferably mannitol and the second diluent is selected from the group of diluents as described hereinbefore, even more preferably pregelatinized starch which shows additional binder properties.

Mannitol as mentioned hereinbefore and hereinafter is preferably a grade with small particle size suitable for granulation. An example is Pearlitol™ 50C (Roquette).

Pregelatinized starch as mentioned hereinbefore and hereinafter can be any of the commercially available grades. An example is Starch 1500™ (Colorcon).

The pharmaceutical composition according to the present invention preferably does not comprise a substance selected from the group glucose, fructose, sucrose, lactose and maltodextrines, in particular lactose. Preferably it does not comprise a substance of the beforementioned group, in particular lactose, above an amount of 2 % by weight of the total composition, even more preferably above an amount of 0.5 % by weight of the total composition.

The one or more binders in the pharmaceutical composition provide adhesiveness to the pharmaceutical composition, for example during the granulation, and to the compressed tablet. They add to the cohesive strength already available in the diluent. Common binders are for example sucrose and microcrystalline cellulose which were observed as not being compatible with linagliptin.

Preferably the one or more binders suitable for a pharmaceutical composition according to the invention are selected from the group consisting of copovidone, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) and a polyvinylpyrrolidone, pregelatinized starch, and low-substituted hydroxypropylcellulose (L-HPC), including derivatives and hydrates of the beforementioned substances. An even more preferred binder is copovidone and/or pregelatinized starch. Copovidone as mentioned hereinbefore and hereinafter is preferably a copolymerisate of vinylpyrrolidone with vinyl acetate, preferably with a molecular weight from about 45000 to about 70000. An example is Kollidon™ VA 64 (BASF).

Hydroxypropyl methylcellulose (also called HPMC or hypromellose) as mentioned hereinbefore and hereinafter is preferably hypromellose 2910. Hydroxypropyl methylcellulose has preferably a viscosity in the range from about 4 to about 6 cps. An example is Methocel™ E5 Prem LV (Dow Chemicals).

Hydroxypropyl cellulose (also called HPC) as mentioned hereinbefore and hereinafter has preferably a viscosity range in the range from about 300 to about 600 mPa·s. Hydroxypropyl cellulose has preferably a molecular weight from about 60000 to about 100000, for example around 80000. An example is Klucel™ EF (Aqualon).

Polyvinylpyrrolidone (also called PVP, polyvidone or povidone) as mentioned hereinbefore and hereinafter has preferably a molecular weight from about 28000 to about 54000. Polyvinylpyrrolidone has preferably a viscosity range from about 3.5 to about 8.5 mPa·s. An example is Kollidon™ 25 or Kollidon™ 30 (BASF).

Low-substituted hydroxypropylcellulose (also called L-HPC) as mentioned hereinbefore and hereinafter has preferably a hydroxypropoxy content in a range from about 5 to about 16 % by weight.

The above mentioned binders pregelatinized starch and L-HPC show additional diluent and disintegrant properties and can also be used as the second diluent or the disintegrant.

The one or more disintegrating agents serves to assist in the fragmentation of the pharmaceutical composition and dosage form after administration. A common disintegrant is for example microcrystalline cellulose which was observed as not being compatible with linagliptin.

Preferably the one or more disintegrants suitable for a pharmaceutical composition according to the present invention are selected from the group consisting of crospovidone, low- substituted hydroxypropylcellulose (L-HPC), and starches, such as native starches, in particular corn starch, and pregelatinized starch, including derivatives and hydrates of the beforementioned substances. Among the beforementioned disintegrants corn starch, pregelatinized starch and crospovidone are even more preferred.

Surprisingly it has been found that at least two disintegrants are preferred, if linagliptin and a glucopyranosyl-substituted benzene derivative of the formula (I) are combined in a pharmaceutical composition according to the invention, in particular in one dosage form, e.g. a tablet or a capsule. Preferred disintegrants are corn starch and crospovidone.

Even more preferred is a combination of at least three disintegrants, if linagliptin and a glucopyranosyl-substituted benzene derivative of the formula (I) inhibitor are combined in a pharmaceutical composition according to the invention, in particular in one dosage form, e.g. a tablet or a capsule. Preferred disintegrants are corn starch, pregelatinized starch and crospovidone.

Crospovidone as mentioned hereinbefore and hereinafter is preferably an insoluble polyvidone, i.e. a cross-linked form of PVP. An example is Kollidon™ CL or Kollidon™ CL-SF (BASF).

Corn starch as mentioned hereinbefore and hereinafter is preferably a native starch. An example is Maize starch (extra white) (Roquette).

The above mentioned disintegrants starch and pregelatinized starch show additional diluent properties, and thus can also be used as the second diluent for example.

The one or more lubricants in the pharmaceutical composition reduce friction in the preparation of the tablet, i.e. during the compression and ejection cycle. In addition, they aid in preventing adherence of tablet material to the dies and punches.

Preferably the pharmaceutical composition according to the present invention additionally comprises one or more lubricants. Preferably the one or more lubricants suitable for a pharmaceutical composition according to the invention are selected from the group consisting of talc (e.g. from Luzenac), polyethylene glycol, in particular polyethylene glycol with a molecular weight in a range from about 4400 to about 9000, hydrogenated castor oil, fatty acid and salts of fatty acids, in particular the calcium, magnesium, sodium or potassium salts thereof, for example calcium behenate, calcium stearate, sodium stearyl fumarate or magnesium stearate (for example (e.g. HyQual®, Mallinckrodt or Ligamed®, Peter Greven). More preferred lubricants are magnesium stearate and talc.

Surprisingly it has been found that at least two lubricants are preferred, if linagliptin and a glucopyranosyl-substituted benzene derivative of the formula (I) are combined in a pharmaceutical composition according to the invention, in particular in one dosage form, e.g. a tablet or a capsule. Preferred lubricants are talc and magnesium stearate. The combination of the two or more lubricants enables low ejection forces and avoids sticking of the final blend in the manufacture of tablets for example.

The one or more glidants are agents that improve powder fluidity in the pharmaceutical composition.

The pharmaceutical composition according to the present invention may additionally comprise one or more glidants. Preferably the one or more glidants suitable for a pharmaceutical composition according to the invention are selected from the group consisting of talc and colloidal silicon dioxide (e.g. Aerosil™ 200 Pharma (Evonik)).

It is preferred that the excipients, in particular the one or more diluents, such as mannitol, have a particle size in the range from 1 to 500 µm. A particle size from 25 to 160 µm is preferred in granulation processes. A particle size from 180 to 500 µm is preferred in direct tableting processes. The particle size is preferably analyzed via sieving. Preferably at least 80 %, more preferably at least 90 %, most preferably at least 95 % by weight of the particles is in the given range.

According to a first embodiment of the present invention the pharmaceutical composition comprises only one active pharmaceutical ingredient which is linagliptin.

A preferred composition according to the first embodiment of the present invention comprises a diluent, a binder and a disintegrant. Preferably said composition comprises only one diluent. Even more preferably said composition comprises only one diluent and only one binder. Even more preferably said composition comprises only one diluent, only one binder and only one disintegrant. The composition may additionally comprise at least one lubricant. Furthermore the composition may additionally comprise at least one glidant.

A pharmaceutical composition according to the first embodiment comprises preferably 0.5-20 % active pharmaceutical ingredient,

40-88 % one or more, preferably one diluent,

0.5-20 % one or more binders,

0.5-20 % one or more disintegrants, wherein the percentages are by weight of the total composition.

The following ranges are even more preferred: 0.5-10 % active pharmaceutical ingredient,

50-75 % one or more, preferably one diluent, 1-15 % one or more binders,

1-15 % one or more disintegrants, wherein the percentages are by weight of the total composition.

Another pharmaceutical composition according to the first embodiment comprises preferably 0.5-20 % active pharmaceutical ingredient,

40-88 % one or more, preferably one diluent,

0.5-20 % one or more binders,

0.5-20 % one or more disintegrants, and

0.1-4 % one or more lubricants, wherein the percentages are by weight of the total composition.

The following ranges are even more preferred: 0.5-10 % active pharmaceutical ingredient,

50-75 % one or more, preferably one diluent, 1-15 % one or more binders,

1-15 % one or more disintegrants, and

0.5-3 % one or more lubricant, wherein the percentages are by weight of the total composition.

In the above pharmaceutical compositions the preferred diluent is mannitol. The preferred binder is copovidone. The preferred disintegrant is corn starch. A preferred lubricant is magnesium stearate. In case the pharmaceutical composition comprises a second diluent, pregelatinized starch would be preferred. It has additional binder properties.

A pharmaceutical dosage form, for example a tablet or capsule, prepared with a pharmaceutical composition according to the first embodiment contains linagliptin as the active ingredient preferably in a therapeutically effective amount. A preferred dosage range is from 0.1 to 100 mg, more preferably from 0.5 to 20 mg, even more preferably from 1 to 10 mg. Preferred dosages are for example 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg.

According to a second embodiment of the present invention the pharmaceutical composition comprises two active pharmaceutical ingredients which are linagliptin and a glucopyranosyl- substituted benzene derivative of the formula (I) as defined hereinbefore and hereinafter, in particular linagliptin and the compound (1.3).

Surprisingly it could be observed that a glucopyranosyl-substituted benzene derivative of the formula (I), in particular the compound (1.3), although having a glucopyranosyl-moiety with free hydroxyl-groups, is compatible with linagliptin, i.e. linagliptin combined with the glucopyranosyl-substituted benzene derivative does not show or shows only marginal degradation.

A preferred pharmaceutical composition according to the second embodiment comprises linagliptin and the compound (1.3) as the two active pharmaceutical ingredients. Preferably the pharmaceutical composition or dosage form comprises

linagliptin and the compound (1.3) wherein at least 50 % by weight of the compound (1.3) is in the form of its crystalline form (1.3X) as defined hereinbefore. More preferably in said pharmaceutical composition or dosage form at least 80 % by weight, even more preferably at least 90 % by weight of the compound (1.3) is in the form of its crystalline form (1.3X) as defined hereinbefore. Preferably the pharmaceutical composition or dosage form comprises linagliptin in one or more of the crystalline forms, in particular the polymorphs A and B, as described WO 2007/128721 , which hereby is incorporated herein in its entirety.

A preferred pharmaceutical composition according to the second embodiment of the present invention comprises one or more diluents, one or more binders and one or more disintegrants. An even more preferred pharmaceutical composition according to the second embodiment of the present invention comprises one or more diluents, one or more binders, one or more disintegrants and one or more lubricants. Preferably said composition comprises one or two diluents. Even more preferably said composition does comprise one or two diluents and one binder. Even more preferably said composition does comprise one or two diluents, one binder and one disintegrant. Even more preferably said composition comprises one or two diluents, one binder and at least two disintegrants. Even more preferably said composition comprises one or two diluents, one or two binders and at least two disintegrants. Even more preferably said composition comprises one or two diluents, one or two binders, at least two disintegrants and one lubricant. Even more preferably said composition comprises one or two diluents, one or two binders, at least two disintegrants and one or two lubricants. Even more preferably said composition comprises one or two diluents, one or two binders, three disintegrants and two lubricants. Furthermore the composition may additionally comprise at least one glidant. Preferred diluents, binders, disintegrants, lubricants and glidants are described hereinbefore and hereinafter.

A pharmaceutical composition according to the second embodiment comprises preferably

0.5-25 % active pharmaceutical ingredient(s),

40-88 % one or more diluents,

0.5-20 % one or more binders,

0.5-20 % one or more disintegrants, wherein the percentages are by weight of the total composition.

The following ranges are even more preferred:

1-20 % active pharmaceutical ingredient(s),

50-75 % one or more diluents, 1-15 % one or more binders,

1 -15 % one or more disintegrants, wherein the percentages are by weight of the total composition.

Additionally said pharmaceutical composition may comprise one or more lubricants in a range from 0.1-15 % by weight of the total composition.

A pharmaceutical composition according to the second embodiment comprises preferably

0.5-25 % active pharmaceutical ingredient(s),

40-88 % one or more diluents,

0.5-20 % one or more binders, 0.5-20 % one or more disintegrants,

0.1-15% one or more lubricants wherein the percentages are by weight of the total composition.

In the above pharmaceutical compositions the preferred diluent is mannitol, the preferred binder is copovidone and the preferred disintegrants are selected from corn starch and crospovidone. Preferred lubricants are selected from magnesium stearate and talc. In case the pharmaceutical composition comprises a second diluent, pregelatinized starch is preferred. Pregelatinized starch has additional binder and disintegrant properties.

Therefore preferred pharmaceutical compositions according to the second embodiment are characterized by the following composition:

1-20 % active pharmaceutical ingredients,

50-75 % mannitol,

2-4 % copovidone,

8-12 % corn starch, wherein the percentages are by weight of the total composition.

Another preferred pharmaceutical compositions according to the second embodiment are characterized by the following composition:

1-20 % active pharmaceutical ingredients,

50-75 % mannitol,

0-15 % pregelatinized starch,

2-4 % copovidone,

8-12 % corn starch,

0-2 % crospovidone, wherein the percentages are by weight of the total composition.

Preferably the above described pharmaceutical compositions comprise additionally a lubricant. The lubricant is preferably magnesium stearate in an amount from 0.5-2 % by weight of the total composition.

Preferably the above described pharmaceutical compositions comprise additionally at least two lubricants. The first lubricant is preferably magnesium stearate in an amount from 0.5-2

% by weight of the total composition. The second lubricant is preferably talc in an amount from 0.5-10% by weight of the total composition.

Therefore preferred pharmaceutical compositions according to the second embodiment are characterized by the following composition:

1-20 % active pharmaceutical ingredients,

50-75 % mannitol, 0-15 % pregelatinized starch,

2-4 % copovidone, 8-12 % corn starch,

0-2 % crospovidone,

0.5-2% magnesium stearate, wherein the percentages are by weight of the total composition.

Another preferred pharmaceutical compositions according to the second embodiment are characterized by the following composition:

1-20 % active pharmaceutical ingredients,

50-75 % mannitol,

0-15 % pregelatinized starch,

2-4 % copovidone,

8-12 % corn starch,

0-2 % crospovidone,

0.5-2% magnesium stearate,

0.5-10% talc, wherein the percentages are by weight of the total composition.

The pharmaceutical composition according to the invention may additionally comprise one or more taste masking agents, for example sweeteners or flavours, and pigments.

The pharmaceutical composition according to the invention may additionally comprise one or more coatings. Preferred are non-functional coatings.

The pharmaceutical compositions according to the invention are preferably solid pharmaceutical compositions, in particular intended for oral administration. A pharmaceutical dosage form according to the present invention comprising a pharmaceutical composition according to the present invention is preferably a solid pharmaceutical dosage form, in particular for oral administration. Examples are a capsule, tablet, for example a film-coated tablet, or a granulate.

A pharmaceutical dosage form according to the first embodiment of the invention, for example a capsule or a tablet, comprises only one active pharmaceutical ingredient which is linagliptin.

A pharmaceutical dosage form according to the second embodiment of the invention, for example a capsule or a tablet, comprises two active pharmaceutical ingredients which are linagliptin and a glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinbefore and hereinafter, in particular linagliptin and the compound (1.3). The tablet may be a one-layer tablet in which the two active pharmaceutical ingredients are present in the one layer. Alternatively the tablet may be a two-layer tablet in which one of the two active pharmaceutical ingredients is present in a first layer and the other active pharmaceutical ingredient is present in a second layer. Alternatively the formulation may be a film-coated tablet in which one of the two active pharmaceutical ingredients is present in the core tablet and the other active pharmaceutical ingredient is present in the film-coating layer. Alternatively the tablet may be a three-layer tablet in which the two layers containing only one active pharmaceutical ingredient each are separated by a third layer which does not contain any active pharmaceutical ingredient. Alternatively the tablet may be a press-coated

tablet, i.e. a tablet in which the one active pharmaceutical ingredient is contained in small tablets, for example with a diameter of 2-6 mm, and the other active pharmaceutical ingredient is contained in a second granulation or blend and compressed together with one small tablet to one large press-coated tablet. All types of the hereinbeforementioned tablets may be without a coating or may have one or more coatings, in particular film-coatings. Preferred are non-functional coatings.

It will be appreciated that the amount of the one or more active pharmaceutical ingredients according to this invention to be administered to the patient and required for use in treatment or prophylaxis according to the present invention will vary with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician. In general, however, a preferred amount is such that by the administration of the pharmaceutical dosage form the glycemic control in the patient to be treated is improved.

In the following preferred ranges of the amount of linagliptin and the glucopyranosyl-substituted benzene derivative to be employed in the pharmaceutical dosage form according to this invention are described. These ranges refer to the amounts to be administered per day with respect to an adult patient, in particular to a human being, for example of approximately 70 kg body weight, and can be adapted accordingly with regard to an administration 2, 3, 4 or more times daily and with regard to other routes of administration and with regard to the age of the patient. The ranges of the dosage and amounts are calculated for the individual active moiety. A preferred pharmaceutical dosage form according to the second embodiment contains linagliptin in a therapeutically effective amount and the glucopyranosyl-substituted benzene derivative (in particular the compound (1.3)) in a therapeutically effective amount. A preferred amount of linagliptin is in a range from 0.1 to 30 mg, preferably from 0.5 to 20 mg, even more preferably from 1 to 10 mg, most preferably 2 to 5 mg. Preferred dosages are for example 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg. A preferred amount of the glucopyranosyl-substituted benzene derivative (in particular the compound (1.3)) is in a range from 0.5 to 100 mg, preferably from 0.5 to 50 mg, even more preferably from 1 to 25 mg, even more preferably 5 to 25 mg, most preferably 10 to 25 mg. Preferred dosages of the glucopyranosyl-substituted benzene derivative are for example 1 mg, 2 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg and 50 mg. A pharmaceutical dosage form according to the second embodiment contains for example a dosage combination selected from the embodiments as depicted in the following table:

Image available on "Original document"

Image available on "Original document"

A tablet according to the invention may be film-coated. Typically a film coat represents 2-5% by weight of the total composition and comprises preferably a film-forming agent, a plasticizer, a glidant and optionally one or more pigments. An exemplary coat composition may comprise hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), talc, titanium dioxide and optionally iron oxide, including iron oxide red and/or yellow. An exemplary coat composition may comprise hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), talc, titanium dioxide, mannitol and optionally iron oxide, including iron oxide red and/or yellow.

The pharmaceutical dosage form according to the invention preferably has dissolution properties such that after 45 minutes for each of the one or two pharmaceutical active ingredients at least 75 %, even more preferably at least 90 % by weight of the respective pharmaceutical active ingredients is dissolved. In a more preferred embodiment after 30 minutes for each of the one or two pharmaceutical active ingredients at least 75 %, even more preferably at least 90 % by weight of the

respective pharmaceutical active ingredients is dissolved. In a most preferred embodiment after 15 minutes for each of the one or two pharmaceutical active ingredients at least 75 %, even more preferably at least 90 % by weight of the respective pharmaceutical active ingredients is dissolved. The dissolution properties can be determined in a standard dissolution test, for example as described in pharmacopoeias, such as the USP31-NF26 S2, chapter 711 (dissolution). A preferred test is described in the experimental section.

The pharmaceutical dosage form according to the invention preferably has disintegration properties such that within 40 minutes, more preferably within 30 minutes, even more preferably within 20 minutes, most preferably within 15 minutes the pharmaceutical dosage form is disintegrated. The disintegration properties can be determined in a standard disintegration test, for example as described in pharmacopoeias, such as the USP31-NF26 S2, chapter 701 (disintegration). A preferred test is described in the experimental section.

The pharmaceutical dosage form according to the invention preferably has a high content uniformity, preferably within a range from 85 to 115 %, more preferably from 90 to 110 %, even more preferably from 95 to 105 % by weight with regard to the each of the one or two active pharmaceutical ingredients. The content uniformity can be determined in a standard test using for example randomly 30 selected pharmaceutical dosage forms, for example as described in pharmacopoeias such as the USP31-NF26 S2, chapter 905 (uniformity of dosage units).

A dosage form according to this invention, such as a tablet, capsule or film-coated tablet, may be prepared by methods well-known to the one skilled in the art.

Preferred methods of manufacturing a tablet are compression of the pharmaceutical composition in the form of a powder, i.e. direct compression, or compression of the pharmaceutical composition in the form of granules, and if needed with additional excipients.

Granules of the pharmaceutical composition according to the invention may be prepared by methods well-known to the one skilled in the art. Preferred methods for the granulation of the one or more active ingredients together with the excipients include wet granulation, for example high shear wet granulation or fluidized bed wet granulation, and dry granulation, also called roller compaction.

In a preferred wet granulation process the granulation liquid is just the solvent or mixture of solvents or a preparation of one or more binders in a solvent or mixture of solvents. Suitable binders are described hereinbefore. An example is copovidone. Suitable solvents are for example water, ethanol, methanol, isopropanol, acetone, preferably purified water, including mixtures thereof. The solvent is a volatile component, which does not remain in the final product. The one or more active ingredients and the other excipients, in particular the one or more diluents, optionally the one or more binders and optionally the one or more disintegrants, usually with exception of the lubricant, are premixed and granulated with the granulation liquid, for example using a high shear granulator. The wet granulation step is usually followed by one or more drying and sieving steps. Optionally a wet sieving step is inserted, followed by drying and dry sieving of the granules. For example a fluid bed dryer can then be used for drying.

The process for the preparation according to this invention is preferably characterized by a granulation process wherein the first and the second active pharmaceutical ingredient together with one or more diluents, one or more binders and one or more disintegrants are granulated.

The process for the preparation according to this invention is preferably characterized

by a at least two granulation processes wherein in one granulation process the first active pharmaceutical ingredient together with one or more diluents, one or more binders and one or more disintegrants is granulated and in another granulation process the second active pharmaceutical ingredient together with one or more diluents, one or more binders and one or more disintegrants is granulated.

Preferably in the above processes the granulate obtained by the one or more granulation processes is optionally blended with one or more additional disintegrant and is blended with one or more lubricants.

The dried granules are sieved through an appropriate sieve. After addition of the other excipients, in particular one or more disintegrants and the glidant and optionally the lubricant talc, with exception of the lubricant, in particular magnesium stearate, the mixture is blended in a suitable blender, for example a free fall blender, followed by addition of the one or more lubricants, for example magnesium stearate, and final blending in the blender.

Thus an exemplary wet granulation process for the preparation of granules comprising the pharmaceutical composition according to the present invention comprises a. optionally dissolving the one or more binders in a solvent or mixture of solvents such as purified water at ambient temperature to produce a granulation liquid; b. blending the one or more active pharmaceutical ingredients, the one or more diluents, optionally the one or more binders and optionally the one or more disintegrants in a suitable mixer, to produce a pre-mix; c. moistening the pre-mix with the granulation liquid and subsequently granulating the moistened pre-mix for example in a high shear mixer; d. optionally sieving the granulated pre-mix through a sieve with a mesh size of at least 1.0 mm and preferably 3 mm; e. drying the granulate at about 40-75°C and preferably 55-65°C inlet air temperature for example in a fluid bed dryer until the desired loss on drying value in the range of 1-5 % is obtained; f. delumping the dried granulate for example by sieving through a sieve with a mesh size of 0.6 mm-1.6 mm, preferably 1.0 mm; and g. adding preferably sieved lubricant(s) to the granulate for final blending for example in a cube mixer.

In an alternative process part of the excipients such as part of the one or more disintegrants, for example corn starch, or an additional disintegrant, for example croscopovidone, and/or the one or more diluents, for example pregelatinized starch, can be added extragranularly prior to final blending of step g.

In another alternative version of the process the granulate produced in steps a to e is produced in a one pot high shear granulation process and subsequent drying in a one pot granulator. Therefore one aspect of the present invention relates to granules comprising the pharmaceutical composition of this invention.

An exemplary dry granulation process for the preparation of granules comprising the pharmaceutical composition according to the present invention comprises

- (1) mixing the one or two active pharmaceutical ingredients with either all or a portion of the excipients in a mixer;
- (2) compaction of the mixture of step (1) on a suitable roller compactor;
- (3) reducing the ribbons obtained during step (2) to small granules by suitable milling or sieving steps;
- (4) optionally mixing the granules of step (3) with the remaining excipients in a mixer to obtain the final mixture;
- (5) tableting the granules of step (3) or the final mixture of step (4) by compressing it

on a suitable tablet press to produce the tablet cores; (6) optionally film-coating of the tablet cores of step (5) with a non-functional coat.

Granules according to the first embodiment of this invention comprise only one active pharmaceutical ingredient (drug) which is linagliptin.

Granules according to the second embodiment of this invention comprise two active pharmaceutical ingredients which are linagliptin and a glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinbefore and hereinafter, in particular linagliptin and the compound (1.3).

A preferred size of the granules is in the range from 25 to 800 μm , even more preferably from 40 μm to 500 μm . Preferably the size is measured via sieve analysis, for example with a sonic sifter. Preferably at least 80 %, more preferably at least 90 %, most preferably at least 95 % by weight of the granules is in the given range.

For the preparation of capsules the granules or the final blend for example as described above in steps (f.) and (g.) are further filled into capsules.

For the preparation of capsules according to the second embodiment of the invention granules according to the second embodiment of the invention, i.e. granules comprising the two active pharmaceutical ingredients, may be used. Alternatively granules according to the first embodiment of the invention, i.e. granules comprising linagliptin as the one active pharmaceutical ingredient, and granules comprising glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinbefore and hereinafter, in particular the compound (1.3), may be used.

For the preparation of tablets or tablet cores the granules or the final blend, for example of the above step (g.) is further compressed into tablets of the target tablet core weight with appropriate size and crushing strength, using an appropriate tablet press. The final blend comprises granules according to the invention and one or more lubricants and optionally one or more disintegrants and the optional one or more glidants. Such an additional disintegrant is crospovidone for example.

For the preparation of one-layer tablets according to the second embodiment of the invention granules according to the second embodiment of the invention, i.e. granules comprising the two active pharmaceutical ingredients, may be used. Alternatively granules according to the first embodiment of the invention, i.e. granules comprising linagliptin as the one active pharmaceutical ingredient, and granules comprising glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinbefore and hereinafter, in particular the compound (1.3), may be used.

For the preparation of two-layer tablets according to the second embodiment of the invention granules according to the first embodiment of the invention, i.e. granules comprising linagliptin as the one active pharmaceutical ingredient, may be used in a first layer and granules comprising glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinbefore and hereinafter, in particular the compound (1.3), may be used in the second layer.

A tablet, for example a one-layer tablet, according to the second embodiment of the invention comprises preferably

0.5-25 % active pharmaceutical ingredient(s),

40-88 % one or more diluents, 0.5-20 % one or more binders,

0.5-20 % one or more disintegrants,

0.1-15 % one or more lubricants, wherein the percentages are by weight of the total composition.

The following ranges are even more preferred:

0.5-20 % active pharmaceutical ingredient(s),

50-75 % one or more diluents,

1-15 % one or more binders,

1 -15 % one or more disintegrants, 0.5-10 % one or more lubricants, wherein the percentages are by weight of the total composition.

Furthermore the following excipients and ranges are preferred: 0.5-20 % active pharmaceutical ingredients, 50-75 % mannitol, (e.g. Pearlitol 50C, Roquette)

0-15 % pregelatinized starch (e.g. Maize starch 1500 INT (Colorcon)),

2-4 % copovidone (e.g. Polyvidone VA 64 INT (BASF)),

8-12 % corn starch (e.g. Maize starch undried (Roquette)),

0.5-2 % magnesium stearate (e.g. HyQual, (Mallinckrodt)), wherein the percentages are by weight of the total composition. An additional disintegrant, for example crospovidone, in an amount from 0 to 2 % by weight of the total composition, may be used, in particular in cases where a higher tablet weight is achieved, such as in one-layer tablets which are made of two kinds of granules (one for each of the active ingredients) or in two-layer tablets as described above.

Furthermore the following excipients and ranges are more preferred: 0.5-20 % active pharmaceutical ingredients,

50-75 % mannitol, (e.g. Pearlitol 50C, Roquette)

0-15 % pregelatinized starch (e.g. Maize starch 1500 INT (Colorcon)),

2-4 % copovidone (e.g. Polyvidone VA 64 INT (BASF)), 8-12 % corn starch (e.g. Maize starch undried (Roquette)),

0-2% crospovidone (Kollidon™ CL-SF, (BASF))

0.5-2 % magnesium stearate (e.g. HyQual, (Mallinckrodt)),

0-10% talc (Talc, (Luzenac)) wherein the percentages are by weight of the total composition.

To reduce the required amount of lubricant in the tablets it is an option to use an external lubrication system.

For the preparation of film-coated tablets a coating suspension is prepared and the compressed tablet cores are coated with the coating suspension to a weight gain of about 2-5 %, preferably about 3%, using a standard film coater. The film-coating solvent is a volatile component, which does not remain in the final product. In an alternative embodiment the film-coat may comprise one of the two active pharmaceutical ingredients.

Alternatively tablets according to the invention may be prepared by direct compression.

A suitable direct compression process comprises the following steps:

- (1) Premixing the one or two active ingredients and the main portion of the excipients in a mixer to obtain a pre-mixture;
- (2) optionally dry screening the pre-mixture through a screen in order to segregate cohesive particles and to improve content uniformity;
- (3) mixing the pre-mixture of step (1) or (2) in a mixer, optionally by adding remaining excipients to the mixture and continuing mixing;
- (4) tableting the final mixture of step (3) by compressing it on a suitable tablet press to produce the tablet cores; (5) optionally film-coating of the tablet cores of step (4) with a non-functional coat.

The pharmaceutical compositions and dosage forms, in particular tablets or capsules, according to this invention may be packaged using known packaging materials, such as PVC-blisters, PVDC-blisters, PVC/PVDC-blisters or a moisture-proof packaging material such as aluminium foil blister packs, alu/alu blister, transparent or opaque polymer blister with pouch, polypropylene tubes, glass bottles, PP bottles and HDPE bottles optionally containing a child-resistant feature (for example with a press-and-twist closure) or may be tamper evident. The primary packaging material may comprise a desiccant such as molecular sieve or silica gel to improve chemical stability of the active pharmaceutical ingredient(s). Opaque packaging such as colored blister materials, tubes, brown glass bottles or the like can be used to prolong shelflife of the active pharmaceutical ingredient(s) by reduction of photodegradation. An article for distribution may comprise the pharmaceutical composition or dosage form packaged in a packaging material as described hereinbefore and a label or package insert, which refer to instructions customarily included in commercial packages of therapeutic products, that may contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. In one embodiment, the label or package insert indicates that the composition can be used for any of the purposes described herein.

The pharmaceutical compositions and pharmaceutical dosage forms according to this invention show advantageous effects in the treatment and prevention of those diseases and conditions as described hereinbefore compared with antidiabetic monotherapies. Advantageous effects may be seen for example with respect to efficacy, dosage strength, dosage frequency, pharmacodynamic properties, pharmacokinetic properties, fewer adverse effects, convenience, compliance, etc..

A pharmaceutical composition and pharmaceutical dosage form according to this invention significantly improves the glycemic control, in particular in patients as described hereinafter, compared with a monotherapy using either a SGLT2 inhibitor or a DPP IV inhibitor alone or a monotherapy of metformin. The improved glycemic control is determined as an increased lowering of blood glucose and an increased reduction of HbA1 c. With monotherapy in a patient, in particular in patients as described hereinafter, the glycemic control can usually not be further improved significantly by an administration of the drug above a certain highest dose. In addition, a long term treatment using a highest dose may be unwanted in view of potential side effects. Therefore, a satisfying glycemic control cannot be achieved in all patients via a monotherapy using either the SLGT2 inhibitor or the DPP IV inhibitor alone or another antidiabetic drug, such as metformin. In such patients a progression of the diabetes mellitus may continue and complications associated with diabetes mellitus may occur, such as macrovascular complications. The pharmaceutical composition and pharmaceutical dosage form as well as the methods according to the present invention allow a reduction of the HbA1 c value to a desired target range, for example < 7 % and preferably < 6.5 %, for a higher number of patients and for a longer time of therapeutic

treatment compared with an antidiabetic monotherapy.

The pharmaceutical composition and the pharmaceutical dosage form according to the present invention allow a well tolerable therapy to the patient and an improvement of the patients compliance.

A monotherapy using a DPP IV inhibitor is not independent from the insulin secretory capacity or the insulin sensitivity of a patient. On the other hand, a treatment with the administration of a SGLT2 inhibitor does not depend on the insulin secretory capacity or the insulin sensitivity of the patient. Therefore, any patient independent of the prevailing insulin levels or insulin resistance and/or hyperinsulinemia may benefit from a therapy using a pharmaceutical composition and a pharmaceutical dosage combination according to this invention. Independent of their prevailing insulin levels or their insulin resistance or hyperinsulinemia these patients can still be treated with a pharmaceutical composition and a pharmaceutical dosage because of the combined or alternate administration of the SGLT2 inhibitor.

Linagliptin according to the present invention is able - via the increases in active GLP-1 levels - to reduce the glucagon secretion in a patient. This will therefore limit the hepatic glucose production. Furthermore, the elevated active GLP-1 levels produced by linagliptin will have beneficial effects on beta-cell regeneration and neogenesis. All these features render a pharmaceutical composition and a pharmaceutical dosage quite useful and therapeutically relevant.

When this invention refers to patients requiring treatment or prevention, it relates primarily to treatment and prevention in humans, but the pharmaceutical composition may also be used accordingly in veterinary medicine in mammals. In the scope of this invention adult patients are preferably humans of the age of 18 years or older. Also in the scope of this invention, patients are adolescent humans, i.e. humans of age 10 to 17 years, preferably of age 13 to 17 years. It is assumed that in a adolescent population the administration of the pharmaceutical composition according to the invention a very good HbA1c lowering and a very good lowering of the fasting plasma glucose can be seen. In addition it is assumed that in an adolescent population, in particular in overweight and/or obese patients, a pronounced weight loss can be observed. As described hereinbefore by the administration of a pharmaceutical composition and a pharmaceutical dosage and in particular in view of the high SGLT2 inhibitory activity of the glucopyranosyl-substituted benzene derivative therein, excessive blood glucose is excreted through the urine of the patient, so that no gain in weight or even a reduction in body weight may result. Therefore, a treatment or prophylaxis according to this invention is advantageously suitable in those patients in need of such treatment or prophylaxis who are diagnosed of one or more of the conditions selected from the group consisting of overweight and obesity, in particular class I obesity, class II obesity, class III obesity, visceral obesity and abdominal obesity. In addition a treatment or prophylaxis according to this invention is advantageously suitable in those patients in which a weight increase is contraindicated.

The pharmaceutical composition and pharmaceutical dosage form according to this invention exhibit a very good efficacy with regard to glycemic control, in particular in view of a reduction of fasting plasma glucose, postprandial plasma glucose and/or glycosylated hemoglobin (HbA1c). By administering a pharmaceutical composition or a pharmaceutical dosage form according to this invention, a reduction of HbA1c equal to or greater than preferably 1.0 %, more preferably equal to or greater than 2.0 %, even more preferably equal to or greater than 3.0 % can be achieved and the reduction is particularly in the range from 1.0 % to 3.0 %.

Furthermore, the method and/or use according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions: (a) a fasting blood glucose or serum glucose concentration greater than 100 mg/dL, in

particular greater than 125 mg/dL; (b) a postprandial plasma glucose equal to or greater than 140 mg/dL;

(c) an HbA1c value equal to or greater than 6.5 %, in particular equal to or greater than 7.0 %, especially equal to or greater than 7.5 %, even more particularly equal to or greater than 8.0 %.

The present invention also discloses the use of the pharmaceutical composition or the pharmaceutical dosage form for improving glycemic control in patients having type 2 diabetes or showing first signs of pre-diabetes. Thus, the invention also includes diabetes prevention. If therefore a pharmaceutical composition or pharmaceutical dosage form according to this invention is used to improve the glycemic control as soon as one of the above-mentioned signs of pre-diabetes is present, the onset of manifest type 2 diabetes mellitus can be delayed or prevented. Furthermore, the pharmaceutical composition and the pharmaceutical dosage form according to this invention is particularly suitable in the treatment of patients with insulin dependency, i.e. in patients who are treated or otherwise would be treated or need treatment with an insulin or a derivative of insulin or a substitute of insulin or a formulation comprising an insulin or a derivative or substitute thereof. These patients include patients with diabetes type 2 and patients with diabetes type 1.

Therefore, according to a preferred embodiment of the present invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof who is diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG) with insulin resistance, with metabolic syndrome and/or with type 2 or type 1 diabetes mellitus characterized in that a pharmaceutical composition or a pharmaceutical dosage form as defined hereinbefore and hereinafter are administered to the patient.

According to another preferred embodiment of the present invention, there is provided a method for improving glycemic control in patients, in particular in adult patients, with type 2 diabetes mellitus as an adjunct to diet and exercise.

It can be found that by using a pharmaceutical composition or a pharmaceutical dosage form according to this invention, an improvement of the glycemic control can be achieved even in those patients who have insufficient glycemic control in particular despite treatment with an antidiabetic drug, for example despite maximal recommended or tolerated dose of oral monotherapy with metformin, a SGLT2 inhibitor or a DPPIV inhibitor. A maximal recommended dose with regard to metformin is for example 2000 mg per day or 850 mg three times a day or any equivalent thereof. A maximal recommended dose with regard to a SGLT2 inhibitor according to this invention, in particular with regard to the compound (1.3), is for example 100 mg, preferably 50 mg or even 25 mg once per day or any equivalent thereof. A maximal recommended dose with regard to linagliptin is for example 10 mg, preferably 5 mg once daily or any equivalent thereof.

Therefore, the method and/or use according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions: (a) insufficient glycemic control with diet and exercise alone; (b) insufficient glycemic control despite oral monotherapy with metformin, in particular despite oral monotherapy at a maximal recommended or tolerated dose of metformin;

(c) insufficient glycemic control despite oral monotherapy with another antidiabetic agent, in particular despite oral monotherapy at a maximal recommended or tolerated dose of the other antidiabetic agent;

(d) insufficient glycemic control despite oral monotherapy with the SGLT2 inhibitor, in

particular despite oral monotherapy at a maximal recommended or tolerated dose of the SGLT2 inhibitor;

(e) insufficient glycemic control despite oral monotherapy with the DPPIV inhibitor, in particular despite oral monotherapy at a maximal recommended or tolerated dose of the DPPIV inhibitor.

The lowering of the blood glucose level by the administration of a glucopyranosyl-substituted benzene derivative according to this invention is insulin-independent. Therefore, a pharmaceutical composition according to this invention is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions insulin resistance, hyperinsulinemia, pre-diabetes, - type 2 diabetes mellitus, particular having a late stage type 2 diabetes mellitus, type 1 diabetes mellitus.

Furthermore, a pharmaceutical composition and a pharmaceutical dosage form according to this invention is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

(a) obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,

(b) triglyceride blood level ≥ 150 mg/dL,

(c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients, (d) a systolic blood pressure ≥ 130 mm Hg and a diastolic blood pressure ≥ 85 mm Hg, (e) a fasting blood glucose level ≥ 100 mg/dL.

It is assumed that patients diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), with insulin resistance and/or with metabolic syndrome suffer from an increased risk of developing a cardiovascular disease, such as for example myocardial infarction, coronary heart disease, heart insufficiency, thromboembolic events. A glycemic control according to this invention may result in a reduction of the cardiovascular risks.

A pharmaceutical composition and a pharmaceutical dosage form according to this invention exhibits a good safety profile. Therefore, a treatment or prophylaxis according to this invention is advantageously possible in those patients for which the monotherapy with another antidiabetic drug, such as for example metformin, is contraindicated and/or who have an intolerance against such drugs at therapeutic doses. In particular, a treatment or prophylaxis according to this invention may be advantageously possible in those patients showing or having an increased risk for one or more of the following disorders: renal insufficiency or diseases, cardiac diseases, cardiac failure, hepatic diseases, pulmonal diseases, catabolytic states and/or danger of lactate acidosis, or female patients being pregnant or during lactation.

Furthermore, it can be found that the administration of a pharmaceutical composition or a pharmaceutical dosage form according to this invention results in no risk or in a low risk of hypoglycemia. Therefore, a treatment or prophylaxis according to this invention is also advantageously possible in those patients showing or having an increased risk for hypoglycemia.

A pharmaceutical composition or a pharmaceutical dosage form according to this invention is particularly suitable in the long term treatment or prophylaxis of the diseases and/or conditions as described hereinbefore and hereinafter, in particular in the long term glycemic control in patients with type 2 diabetes mellitus.

The term "long term" as used hereinbefore and hereinafter indicates a treatment of or

administration in a patient within a period of time longer than 12 weeks, preferably longer than 25 weeks, even more preferably longer than 1 year.

Therefore, a particularly preferred embodiment of the present invention provides a method for therapy, preferably oral therapy, for improvement, especially long term improvement, of glycemic control in patients with type 2 diabetes mellitus, especially in patients with late stage type 2 diabetes mellitus, in particular in patients additionally diagnosed of overweight, obesity (including class I, class II and/or class III obesity), visceral obesity and/or abdominal obesity. In all hereinbefore and hereinafter described methods and uses, in particular the methods for treating, preventing, etc., the pharmaceutical composition or pharmaceutical dosage form according to this invention is administered to the patient preferably once daily.

Any of the above mentioned compositions and dosage forms within the scope of the invention may be tested by animal models known in the art as well as in clinical studies. In the following, in vivo experiments are described which are suitable to evaluate pharmacologically relevant properties of pharmaceutical compositions and dosage forms according to this invention:

Pharmaceutical compositions, dosage forms and methods according to this invention can be tested in genetically hyperinsulinemic or diabetic animals like db/db mice, ob/ob mice, Zucker Fatty (fa/fa) rats or Zucker Diabetic Fatty (ZDF) rats. In addition, they can be tested in animals with experimentally induced diabetes like HanWistar or Sprague Dawley rats pretreated with streptozotocin.

The effect on glycemic control of the pharmaceutical compositions and dosage forms according to this invention can be tested in an oral glucose tolerance test in the animal models described hereinbefore. The time course of blood glucose is followed after an oral glucose challenge in overnight fasted animals. The compositions and dosage forms according to the present invention significantly improve glucose excursion compared to each monotherapy as measured by reduction of peak glucose concentrations or reduction of glucose AUC. In addition, after multiple dosing of the active pharmaceutical ingredients alone and the pharmaceutical compositions or dosage forms in the animal models described hereinbefore, the effect on glycemic control can be determined by measuring the HbA1c value in blood. The compositions and dosage forms according to this invention significantly reduce HbA1c compared to each monotherapy.

The improved independence from insulin of the treatment according to this invention can be shown after single dosing in oral glucose tolerance tests in the animal models described hereinbefore. The time course of plasma insulin is followed after a glucose challenge in overnight fasted animals. The compositions and dosage forms according to the invention will exhibit lower insulin peak concentrations or insulin AUC at lower blood glucose excursion than linagliptin alone. The increase in active GLP-1 levels by treatment according to this invention after single or multiple dosing can be determined by measuring those levels in the plasma of animal models described hereinbefore in either the fasting or postprandial state. Likewise, a reduction in glucagon levels in plasma can be measured under the same conditions. The compositions and dosage forms according to the invention will exhibit higher active GLP-1 concentrations and lower glucagon concentrations than the glucopyranosyl-substituted benzene derivative alone.

A superior effect of the compositions and dosage forms according to the present invention on beta-cell regeneration and neogenesis can be determined after multiple dosing in the animal models described hereinbefore by measuring the increase in pancreatic insulin content, or by measuring increased beta-cell mass by morphometric analysis after immunohistochemical staining of pancreatic sections, or by measuring increased glucose-stimulated insulin secretion in isolated pancreatic islets.

Pharmacological Examples

The following examples show the beneficial effect on glycemic control of the combination according to the present invention.

Example I:

According to a first example an oral glucose tolerance test is performed in overnight fasted 9- weeks old male Zucker Diabetic Fatty (ZDF) rats (ZDF/Crl-Lepr^{fa}). A pre-dose blood sample is obtained by tail bleed. Blood glucose is measured with a glucometer, and the animals are randomized for blood glucose (n = 5 / group). Subsequently, the groups receive a single oral administration of either vehicle alone (0.5% aqueous hydroxyethylcellulose containing 3 mM HCl and 0.015% Polysorbat 80) or vehicle containing either the SGLT2 inhibitor or the DPPIV inhibitor or the combination of the SGLT2 inhibitor plus the DPP IV inhibitor plus. The animals receive an oral glucose load (2 g/kg) 30 min after compound administration. Blood glucose is measured in tail blood 30 min, 60 min, 90 min, 120 min, and 180 min after the glucose challenge. Glucose excursion is quantified by calculating the reactive glucose AUC. The data are presented as mean \pm SEM. The two-sided unpaired Student t-test is used for statistical comparison of the control group and the active groups.

The result is shown in Figure 3. "Cpd. A" is linagliptin at a dose of 1 mg/kg. Cpd. B is the compound (1.3), i.e. 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)- benzyl]-benzene, at a dose of 3 mg/kg. Combination A + B is the combination of linagliptin and the compound (1.3) at the same doses. P-values versus control are indicated by symbols above the bars. P-values of the combination versus the monotherapies are indicated below the figure (<*>, p < 0.05; <*>, p < 0.01 ; <*>, p < 0.001). Linagliptin reduces glucose excursion by 56%, the compound (1.3) reduces glucose excursion by 51 %. The combination decreased glucose excursion in the oral glucose tolerance test by 84%, and this reduction in glucose AUC is statistically significant versus each monotherapy.

Example II:

According to a second example an oral glucose tolerance test is performed in overnight fasted male Sprague Dawley rats (OkCD(SD)) with a body weight of about 200 g. A pre- dose blood sample is obtained by tail bleed. Blood glucose is measured with a glucometer, and the animals are randomized for blood glucose (n = 5 / group). Subsequently, the groups receive a single oral administration of either vehicle alone (0.5% aqueous hydroxyethylcellulose containing 0.015% Polysorbat 80) or vehicle containing either the SGLT2 inhibitor or the DPPIV inhibitor or the third antidiabetic agent or the combination of the SGLT2 inhibitor plus the DPP IV inhibitor plus the third antidiabetic agent. Alternatively the groups receive a single oral administration of either vehicle alone or vehicle containing either the SGLT2 inhibitor or the DPPIV inhibitor plus the third antidiabetic agent or the third antidiabetic agent or the combination of the SGLT2 inhibitor plus the DPP IV inhibitor plus the third antidiabetic agent. The animals receive an oral glucose load (2 g/kg) 30 min after compound administration. Blood glucose is measured in tail blood 30 min, 60 min, 90 min, and 120 min after the glucose challenge. Glucose excursion is quantified by calculating the reactive glucose AUC. The data are presented as mean \pm S. E. M. Statistical comparisons are conducted by Student's t test.

Example III: Treatment of pre-diabetes

The efficacy of a pharmaceutical composition or pharmaceutical dosage form according to the invention in the treatment of pre-diabetes characterised by pathological fasting glucose and/or impaired glucose tolerance can be tested using clinical studies. In

studies over a shorter period (e.g. 2-4 weeks) the success of the treatment is examined by determining the fasting glucose values and/or the glucose values after a meal or after a loading test (oral glucose tolerance test or food tolerance test after a defined meal) after the end of the period of therapy for the study and comparing them with the values before the start of the study and/or with those of a placebo group. In addition, the fructosamine value can be determined before and after therapy and compared with the initial value and/or the placebo value. A significant drop in the fasting or non-fasting glucose levels demonstrates the efficacy of the treatment. In studies over a longer period (12 weeks or more) the success of the treatment is tested by determining the HbA1c value, by comparison with the initial value and/or with the value of the placebo group. A significant change in the HbA1c value compared with the initial value and/or the placebo value demonstrates the efficacy of the composition or dosage form according to the invention for treating pre-diabetes.

Example IV: Preventing manifest type 2 diabetes

Treating patients with pathological fasting glucose and/or impaired glucose tolerance (prediabetes) is also in pursuit of the goal of preventing the transition to manifest type 2 diabetes. The efficacy of a treatment can be investigated in a comparative clinical study in which prediabetes patients are treated over a lengthy period (e.g. 1-5 years) with either a pharmaceutical composition according to this invention or with placebo or with a non-drug therapy or other medicaments. During and at the end of the therapy, by determining the fasting glucose and/or a loading test (e.g. oGTT), a check is made to determine how many patients exhibit manifest type 2 diabetes, for example a fasting glucose level of >125 mg/dl and/or a 2h value according to oGTT of >199 mg/dl. A significant reduction in the number of patients who exhibit manifest type 2 diabetes when treated with a pharmaceutical composition or dosage form according to this invention as compared to one of the other forms of treatment, demonstrates the efficacy in preventing a transition from pre-diabetes to manifest diabetes.

Example V: Treatment of type 2 diabetes

Treating patients with type 2 diabetes with the pharmaceutical composition or dosage form according to the invention, in addition to producing an acute improvement in the glucose metabolic situation, prevents a deterioration in the metabolic situation in the long term. This can be observed if patients are treated for a longer period, e.g. 3 months to 1 year or even 1 to 6 years, with the pharmaceutical composition or dosage form according to the invention and are compared with patients who have been treated with placebo or other antidiabetic medicaments. There is evidence of therapeutic success compared with patients treated with placebo or other antidiabetic medicaments if no or only a slight increase in the fasting glucose and/or HbA1c value is observed. Further evidence of therapeutic success is obtained if a significantly smaller percentage of the patients treated with a pharmaceutical composition or dosage form according to the invention, compared with patients who have been treated with other medicaments, undergo a deterioration in the glucose metabolic position (e.g. an increase in the HbA1c value to >6.5% or >7%) to the point where treatment with an additional oral antidiabetic medicament or with insulin or with an insulin analogue is indicated.

Example VI: Treatment of insulin resistance In clinical studies running for different lengths of time (e.g. 2 weeks to 12 months) the success of the treatment is checked using a hyperinsulinaemic euglycaemic glucose clamp study. A significant rise in the glucose infusion rate at the end of the study, compared with the initial value or compared with a placebo group, or a group given a different therapy, proves the efficacy of a pharmaceutical composition or dosage form according to the invention in the treatment of insulin resistance.

Example VII: Treatment of hyperglycaemia

In clinical studies running for different lengths of time (e.g. 1 day to 24 months) the success of the treatment in patients with hyperglycaemia is checked by determining the fasting glucose or non-fasting glucose (e.g. after a meal or a loading test with oGTT or a defined meal). A significant fall in these glucose values during or at the end of the study, compared with the initial value or compared with a placebo group, or a group given a different therapy, proves the efficacy of a pharmaceutical composition or dosage form according to the invention in the treatment of hyperglycaemia.

Example VIII: Prevention of micro- or macrovascular complications The treatment of type 2 diabetes or pre-diabetes patients with a pharmaceutical composition or dosage form according to the invention prevents or reduces or reduces the risk of developing microvascular complications (e.g. diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, diabetic foot, diabetic ulcer) or macrovascular complications (e.g. myocardial infarct, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders, vascular restenosis). Type 2 diabetes or patients with pre-diabetes are treated long-term, e.g. for 1-6 years, with a pharmaceutical composition or dosage form according to the invention or a combination of active ingredients according to the invention and compared with patients who have been treated with other antidiabetic medicaments or with placebo. Evidence of the therapeutic success compared with patients who have been treated with other antidiabetic medicaments or with placebo can be found in the smaller number of single or multiple complications. In the case of macrovascular events, diabetic foot and/or diabetic ulcer, the numbers are counted by anamnesis and various test methods. In the case of diabetic retinopathy the success of the treatment is determined by computer-controlled illumination and evaluation of the background to the eye or other ophthalmic methods. In the case of diabetic neuropathy, in addition to anamnesis and clinical examination, the nerve conduction rate can be measured using a calibrated tuning fork, for example. With regard to diabetic nephropathy the following parameters may be investigated before the start, during and at the end of the study: secretion of albumin, creatinin clearance, serum creatinin values, time taken for the serum creatinin values to double, time taken until dialysis becomes necessary.

Example IX: Treatment of Metabolic Syndrome The efficacy of a pharmaceutical composition or dosage form according to the invention can be tested in clinical studies with varying run times (e.g. 12 weeks to 6 years) by determining the fasting glucose or non-fasting glucose (e.g. after a meal or a loading test with oGTT or a defined meal) or the HbA1c value. A significant fall in these glucose values or HbA1c values during or at the end of the study, compared with the initial value or compared with a placebo group, or a group given a different therapy, proves the efficacy of a pharmaceutical composition or dosage form according to this invention in the treatment of Metabolic Syndrome. Examples of this are a reduction in systolic and/or diastolic blood pressure, a lowering of the plasma triglycerides, a reduction in total or LDL cholesterol, an increase in HDL cholesterol or a reduction in weight, either compared with the starting value at the beginning of the study or in comparison with a group of patients treated with placebo or a different therapy.

Examples of Pharmaceutical Compositions and Pharmaceutical Dosage Forms

In the following the term "API 1" denotes a glucopyranosyl-substituted benzene derivative of the formula (I), in particular the compound (1.3), preferably in its crystalline form (I3.X), and the term "API 2" denotes linagliptin.

The active pharmaceutical ingredients, i.e. linagliptin and the compound (1.3), preferably in the crystalline form (I3.X), are milled with a suitable mill like pin-mill or jet-mill in order to obtain the desired particle size distribution before manufacturing of the pharmaceutical composition or dosage form.

Examples of typical particle size distribution values X90, X50 and X10 for the preferred active pharmaceutical ingredients according to the invention are shown in the table below.

Image available on "Original document"

Example 1 : One granulation, mono-layer tablet

Copovidone is dissolved in purified water at ambient temperature (about 20°C) to produce a granulation liquid. The API 2 and API 1, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60°C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

Magnesium stearate is passed through a sieve for delumping and added to the granulate. Subsequently the final blend is produced by final blending in a suitable blender for three minutes and compressed into 8 mm round tablet cores with a compression force of 15 kM.

Hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide and iron oxide are suspended in purified water in a suitable mixer at ambient temperature to produce a coating suspension. The tablet cores are coated with the coating suspension to a weight gain of about 3 % to produce film-coated tablets. The following formulation variants can be obtained:

Image available on "Original document"

The resulting tablets have a tablet hardness around 85 N, the friability is below 0.5%. The content uniformity fulfills the requirement according to the USP. The disintegration time is around 7 minutes and the dissolution of both API 1 and API 2 is > 85% after 15 minutes, e.g. 97% of API 1 and 101% of API 2.

Example 2: One granulation, mono-layer tablet

Copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid. The API 1, API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60°C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

Magnesium stearate is passed through a sieve for delumping and added to the granulate. Subsequently the final blend is produced by final blending in a suitable blender for three minutes and compressed into 8 mm round tablet cores with a compression force of 17 kM.

Hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide and iron oxide are suspended in purified water in a suitable mixer at ambient temperature to produce a coating suspension. The tablet cores are coated with the coating suspension to a weight gain of about 3 % to produce film-coated tablets. The following formulation variants can be obtained:

Image available on "Original document"

The tablet hardness, the friability, the content uniformity, the disintegration time and the dissolution properties are determined as described hereinbefore.

Example 3: One granulation, mono-layer tablet

Copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid. API 1, API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm. Crospovidone is added to the dried granulate and mixed for 5 minutes to produce the main blend. Magnesium stearate is passed through a sieve for delumping and added to main blend. Subsequently the final blend is produced by final blending in a suitable blender for three minutes and compressed into 8 mm round tablet cores with a compression force of 16 kN.

Hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide and iron oxide are suspended in purified water in a suitable mixer at ambient temperature to produce a coating suspension. The tablet cores are coated with the coating suspension to a weight gain of about 3 % to produce film-coated tablets. The following formulation variants can be obtained:

Image available on "Original document"

The tablet hardness, the friability, the content uniformity, the disintegration time and the dissolution properties are determined as described hereinbefore.

Example 4: Two granulations, mono-layer tablet Two separate granulations containing only one active pharmaceutical ingredient each are prepared. For both granulations, copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid.

The API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

The API 1, mannitol, pregelatinized starch, corn starch and optionally pigments like iron oxides red are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

The two granulates are combined, crospovidone is added and all components are mixed for 5 minutes in a suitable mixer to produce the main blend. Magnesium stearate is passed through a sieve for delumping and added to main blend. Subsequently the final blend is produced by final blending in a suitable blender for three minutes and compressed into 15x6 mm oval-shaped tablet cores with a compression force of 17 kN. The following formulation variants can be obtained:

Image available on "Original document"

Image available on "Original document"

The resulting tablets have a tablet hardness around 105 N. The content uniformity fulfills the requirement according to the USP. The friability is below 0.5%. The

disintegration time is around 5 minutes and the dissolution of both APIs is > 85% after 15 minutes.

Example 5: Two granulations, mono-layer tablet

Two separate granulations containing only one active pharmaceutical ingredient each are prepared.

Copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid. The API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

The API 1, mannitol, microcrystalline cellulose, hydroxypropyl cellulose and optionally pigments like iron oxides red are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with purified water and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm. The two granulates are combined, croscopovidone is added and all components are mixed for 5 minutes in a suitable mixer to produce the main blend. Magnesium stearate is passed through a sieve for delumping and added to main blend. Subsequently the final blend is produced by final blending in a suitable blender for three minutes and compressed into 15x6 mm oval-shaped tablet cores with a compression force of 15 kN. The following formulation variants can be obtained:

Image available on "Original document"

The tablet hardness, the friability, the content uniformity, the disintegration time and the dissolution properties are determined as described hereinbefore.

Example 6: Two granulations, bi-layer tablet

Two separate granulations containing only one active pharmaceutical ingredient each are prepared. For both granulations, copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid. The API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

The API 1, mannitol, pregelatinized starch, corn starch and optionally pigments like iron oxides red are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm, croscopovidone is added and the components are mixed in a suitable mixer for 5 minutes.

Magnesium stearate is passed through a sieve for delumping and added to the two granulations separately. Subsequently two final blends are produced by final blending in a suitable blender for three minutes. The final blend containing API 1 is used for the first layer and the final blend containing API 2 is used for the second layer of the bi-

layer tablet. The bi- layer tablets are produced on a suitable tablet press with a first compression force of 2 kNm for the first layer and a main compression force of 12 kNm for producing 10 mm round tablet cores. The following formulation variants can be obtained:

Image available on "Original document"

Image available on "Original document"

The resulting tablets have a tablet hardness around 120 N, the friability is below 0.5%. The content uniformity fulfills the requirement according to the USP. The disintegration time is around 6 minutes and the dissolution of both APIs is > 85% after 15 minutes.

Example 7: Two granulations, bi-layer tablet

Two separate granulations containing only one active pharmaceutical ingredient each are prepared.

Copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid. The API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm.

The API 1, mannitol, microcrystalline cellulose, hydroxypropyl cellulose and optionally pigments like iron oxides red are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with purified water and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm, crospovidone is added and the components are mixed in a suitable mixer for 5 minutes.

Magnesium stearate is passed through a sieve for delumping and added to the two granulations separately. Subsequently two final blends are produced by final blending in a suitable blender for three minutes. The final blend containing API 1 is used for the first layer and the final blend containing API 2 is used for the second layer of the bi-layer tablet. The bi-layer tablets are produced on a suitable tablet press with a first compression force of 2 kNm for the first layer and a main compression force of 12 kNm for producing 10 mm round tablet cores. The following formulation variants can be obtained:

Image available on "Original document"

The tablet hardness, the friability, the content uniformity, the disintegration time and the dissolution properties are determined as described hereinbefore.

Example 8: One granulation, mono-layer tablet Copovidone is dissolved in purified water at ambient temperature (about 20 °C) to produce a granulation liquid. API 1, API 2, mannitol, pregelatinized starch and corn starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is sieved through a suitable sieve. The granulate is dried at about 60 °C inlet air temperature in a fluid bed dryer until a loss on drying value of 1-4 % is obtained. The dried granulate is sieved through a sieve with

a mesh size of 1.0 mm.

Crospovidone and talc are added to the dried granulate and mixed for 5 minutes to produce the main blend. Magnesium stearate is passed through a sieve for delumping and added to main blend. Subsequently the final blend is produced by final blending in a suitable blender for three minutes and compressed into 8 mm round tablet cores with a compression force of 16 kM. The combination of the two lubricants talc and magnesium stearate was discovered to be especially useful when API 1 and API 2 are combined in one granulation and subsequently in one tablet by enabling low ejection forces and by avoiding sticking of the final blend to the tablet punches.

Hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, mannitol and iron oxide are suspended in purified water in a suitable mixer at ambient temperature to produce a coating suspension. The tablet cores are coated with the coating suspension to a weight gain of about 3 % to produce film-coated tablets. The following formulation variants can be obtained:

Image available on "Original document"

Image available on "Original document"

The tablet hardness, the friability, the content uniformity, the disintegration time and the dissolution properties are determined as described hereinbefore.

Examples of Tests with regard to Properties of Pharmaceutical Compositions and Pharmaceutical Dosage Forms

1. Disintegration Test

Disintegration test was performed as described in USP31-NF26 S2, chapter 701 (disintegration).

2. Dissolution Test

The standard dissolution test is described in USP31-NF26 S2, chapter 71 1 (dissolution). The paddle method (Apparatus 2) with an agitation speed of 50 rpm was used. The dissolution media is 900 ml. 0.05 M Potassium phosphate buffer pH 6.8 at a temperature of 37°C. Samples are taken after 10, 15, 20, 30 and 45 minutes. The samples are analyzed via HPLC.

A dissolution profile of tablets according to the example 4 and the example 6 wherein API 1 is the compound (1.3) and the API 2 is linagliptin are depicted in the Figure 4.

A dissolution profile of tablets according to the example 8 wherein API 1 is the compound (1.3) and the API 2 is linagliptin are depicted in the Figure 5.

3. Particle Size Distribution Measurement by Laser Diffraction Particle size distribution measurement was performed for example via light scattering or laser diffraction technique. To determine the particle size the powder is fed into a laser diffraction spectrometer for example by means of a dispersing unit. The test method is described below in detail:

Equipment: Laser Diffraction Spectrometer Sympatec HELOS Particle

Sizer.

Lens: R31 (0.5/0.9µm - 175µm)

Sample Dispersing Unit: Dry disperser RODOS/M Vacuum: Nilfisk

Feeder: ASPIROS

Feed Velocity: 60.00 mm/s

Primary pressure: 2.00 bar Injector depression: maximize (mbar)²

Reference Measurement: 10 seconds

Cycle Time: 100 msec

Trigger Conditions: Start 0.0 seconds after optical concentration $\geq 1\%$ valid always
Stop after 5.0 seconds optical concentration $< 1\%$ or after 30 seconds real time Optical
Concentration: Approximately range 3 - 12 %

Evaluation: HRLD

Sample Size: Approximately 100 mg

Number of measurements: 2 (duplicate)

The instrument is set up according to the manufacturer's recommendation and using the manufacturer provided software. The sample container is thoroughly mixed and tumbled prior to removing a portion of the sample to ensure that a representative sample is tested. Duplicate samples are prepared by using a spatula to transfer approximately 100 mg of a sample into the ASPIROS glass vials and cap the vials. The capped vials are placed into the feeder.

4. Tablet hardness and friability

Tablet hardness and friability test was performed as described in USP31-NF26 S2, chapter 1217 (tablet breaking force).

We claim:

1. A solid pharmaceutical dosage form comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 10 mg or 25 mg and one or more excipients,

wherein the term "linagliptin" as employed herein refers to linagliptin and pharmaceutically acceptable salts thereof, including hydrates and solvates thereof, and crystalline forms thereof, and wherein the definition "1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene" also comprises its hydrates, solvates and polymorphic forms thereof.

2. The solid pharmaceutical dosage form according to claim 1 comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 10 mg

3. The solid pharmaceutical dosage form according to claim 1 comprising linagliptin as a first active pharmaceutical ingredient in an amount of 5 mg and 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene as a second pharmaceutical ingredient in an amount of 25 mg.

4. The solid pharmaceutical dosage form according to any one of the claims 1 to 3 wherein the first active ingredient has a particle size distribution of $X_{90} < 200 \mu\text{m}$.

5. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the second active ingredient has a particle size distribution of $1 \mu\text{m} < X_{90} < 200 \mu\text{m}$.

6. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the one or more excipients comprise one or more diluents and one or more binders.

7. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the one or more excipients comprise one or more diluents, one or more binders and one or more disintegrants.

8. The solid pharmaceutical dosage form according to one or more of the previous claims comprising

0.5-25 %	of the active pharmaceutical ingredients,
40-88 %	of the one or more diluents,
0.5-20 %	of the one or more binders, and
0.5-20 %	of the one or more disintegrants,

wherein the percentages are by weight of the total composition.

9. The solid pharmaceutical dosage form according to one or more of the previous claims comprising

0.5-25 %	the active pharmaceutical ingredients,
40-88 %	one or more diluents,
0.5-20 %	one or more binders,
0.5-20 %	one or more disintegrants,
0.1-15%	one or more lubricants,

wherein the percentages are by weight of the total composition.

10. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the one or more diluents are selected from the group consisting of cellulose, dibasic calcium phosphate, erythritol, mannitol, starch, pregelatinized starch, and xylitol, including derivatives and hydrates of the before mentioned substances.

11. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the one or more binders are selected from the group consisting of copovidone, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), a polyvinylpyrrolidone, pregelatinized starch, low-substituted hydroxypropylcellulose (L-HPC), including derivatives and hydrates of the before mentioned substances.

12. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the one or more disintegrants are selected from the group consisting of crospovidone, low-

substituted hydroxypropylcellulose (L-HPC), and starches, such as native starches, in particular corn starch, and pregelatinized starch, including derivatives and hydrates of the before mentioned substances.

13. The solid pharmaceutical dosage form according to one or more of the previous claims wherein the one or more lubricants are selected from the group consisting of talc, polyethylene glycol, in particular polyethylene glycol with a molecular weight in a range from about 4400 to about 9000, hydrogenated castor oil, fatty acid and salts of fatty acids, in particular the calcium, magnesium, sodium or potassium salts thereof, for example calcium behenate, calcium stearate, sodium stearyl fumarate or magnesium stearate.

14. The solid pharmaceutical dosage form according to one or more of the previous claims characterized in that it is a capsule, a tablet or a film-coated tablet.

15. The pharmaceutical dosage form according to one or more of the previous claims characterized in that it is a one-layer tablet in which the two active pharmaceutical ingredients are present in the one layer.

Dated this 12th day of August 2011

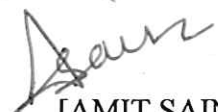


Archana Shanker
Of Anand And Anand Advocates
Attorney for the applicant

WE CLAIM

1. A pharmaceutical composition comprising the glucopyranosyl-substituted benzene derivative 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene in combination with the DPP IV inhibitor 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine or a pharmaceutically acceptable salt thereof wherein the amount of the glucopyranosyl-substituted benzene derivative is from 5 mg to 50 mg, and wherein the amount of the DPP IV inhibitor is from 0.5 mg to 10 mg.
2. The pharmaceutical composition as claimed in claim 1 wherein the glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor are present in a single dosage form.
3. The pharmaceutical composition as claimed in claim 1 or 2 comprising an amount of 5, 10, 15, 20, 25 or 50 mg of the glucopyranosyl-substituted benzene derivative.
4. The pharmaceutical composition as claimed in claim 3 comprising an amount of 10 mg of the glucopyranosyl-substituted benzene derivative.
5. The pharmaceutical composition as claimed in claim 3 comprising an amount of 25 mg of the glucopyranosyl-substituted benzene derivative.
6. The pharmaceutical composition as claimed in any one of the claims 1 to 5 comprising an amount of 1 mg to 5 mg of the DPP IV inhibitor.
7. The pharmaceutical composition as claimed in claim 6 comprising an amount of 5 mg of the DPP IV inhibitor.
8. The pharmaceutical composition as claimed in any one of the previous claims characterized in that the pharmaceutical composition is formulated for oral administration in solid form.

Dated February 15, 2010



[AMIT SAINI]

IN/PA 1642

OF REMFRY & SAGAR
ATTORNEYS FOR THE APPLICANT[S]

Pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative

Technical Field of the Invention

The invention relates to a pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative of the formula (I) as described hereinafter in combination with a DPP IV inhibitor as specified hereinafter which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose and hyperglycemia.

Furthermore the invention relates to methods

- for preventing, slowing progression of, delaying, or treating a metabolic disorder;
- for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
- for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, impaired fasting blood glucose, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;
- for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
- for reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight;
- for preventing or treating the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion;
- for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat;
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,

in patients in need thereof characterized in that a glucopyranosyl-substituted benzene derivative of formula (I) as defined hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinafter.

In addition the present invention relates to the use of a glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinafter for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

In addition, the present invention relates to the use of a DPP IV inhibitor as defined hereinafter for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

The invention also relates to a use of a pharmaceutical composition according to this invention for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

Background of the Invention

Glucopyranosyl-substituted benzene derivative are described in the prior art, for example in WO 01/27128, WO 03/099836, WO 2005/092877, WO 2006/034489, WO 2006/064033, WO 2006/117359, WO 2006/117360, WO 2007/025943, WO 2007/028814, WO 2007/031548, WO 2007/093610, WO 2007/128749, WO 2008/049923, WO 2008/055870, WO 2008/055940. The glucopyranosyl-substituted benzene derivatives are proposed as inducers of urinary sugar excretion and as medicaments in the treatment of diabetes.

Renal filtration and reuptake of glucose contributes, among other mechanisms, to the steady state plasma glucose concentration and can therefore serve as an antidiabetic target. Reuptake of filtered glucose across epithelial cells of the kidney proceeds via sodium-dependent glucose cotransporters (SGLTs) located in the brush-border membranes in the tubuli along the sodium gradient ⁽¹⁾. There are at least 3 SGLT isoforms that differ in their expression pattern as well as in their physico-chemical properties ⁽²⁾. SGLT2 is exclusively expressed in the kidney ⁽³⁾, whereas SGLT1 is expressed additionally in other tissues like intestine, colon, skeletal and cardiac muscle ^(4;5). SGLT3 has been found to be a glucose sensor in interstitial cells of the intestine without any transport function ⁽⁶⁾. Potentially, other related, but not yet characterized genes, may contribute further to renal glucose reuptake ^(7, 8, 9). Under normoglycemia, glucose is completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at glucose concentrations higher than 10mM, resulting in glucosuria ("diabetes mellitus"). This threshold concentration can be decreased by SGLT2-inhibition. It has been shown in experiments with the SGLT inhibitor phlorizin that SGLT-inhibition will partially inhibit the reuptake of glucose from the glomerular filtrate into the blood leading to a decrease in blood glucose concentrations and to glucosuria ^(10;11).

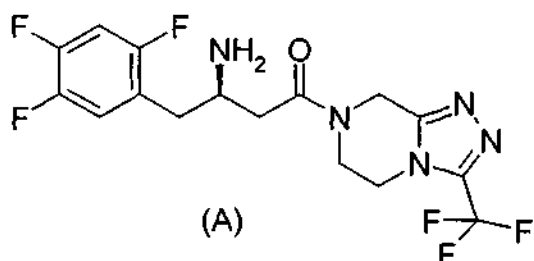
- (1) Wright, E.M. (2001) Am. J. Renal Physiol. 280, F10-F18;
- (2) Wright, E.M. et al. (2004) Pflugers Arch. 447(5):510-8;
- (3) You, G. et al. (1995) J. Biol. Chem. 270 (49) 29365-29371;
- (4) Pajor AM, Wright EM (1992) J Biol. Chem. 267(6):3557-3560;
- (5) Zhou, L. et al. (2003) J. Cell. Biochem. 90:339-346;
- (6) Diez-Sampedro, A. et al. (2003) Proc. Natl. Acad. Sci. USA 100(20), 11753-11758;
- (7) Tabatabai, N.M. (2003) Kidney Int. 64, 1320-1330;
- (8) Curtis, R.A.J. (2003) US Patent Appl. 2003/0054453;
- (9) Bruss, M. and Bonisch, H. (2001) Cloning and functional characterization of a new human sugar transporter in kidney (Genbank Acc. No. AJ305237);
- (10) Rossetti, L. Et al. (1987) J. Clin. Invest. 79, 1510-1515;
- (11) Gouvea, W.L. (1989) Kidney Int. 35(4):1041-1048.

DPP IV inhibitors represent a novel class of agents that are being developed for the treatment or improvement in glycemic control in patients with type 2 diabetes.

For example, DPP IV inhibitors and their uses are disclosed in WO 2002/068420, WO 2004/018467, WO 2004/018468, WO 2004/018469, WO 2004/041820, WO 2004/046148, WO 2005/051950, WO 2005/082906, WO 2005/063750, WO 2005/085246, WO 2006/027204, WO 2006/029769, WO2007/014886; WO 2004/050658, WO 2004/111051, WO 2005/058901, WO 2005/097798; WO 2006/068163, WO 2007/071738, WO 2008/017670; WO 2007/054201 or WO 2007/128761.

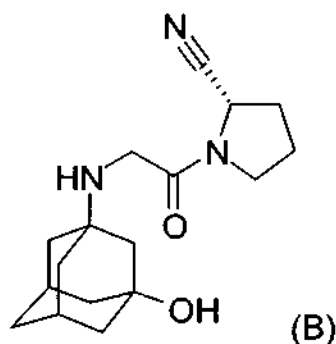
As further DPP IV inhibitors the following compounds can be mentioned:

- Sitagliptin (MK-0431) having the structural formula A below is (3*R*)-3-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, also named (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine,



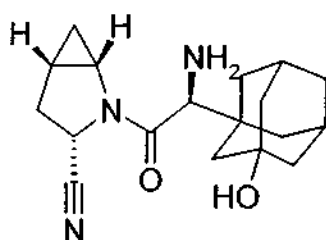
In one embodiment, sitagliptin is in the form of its dihydrogenphosphate salt, i.e. sitagliptin phosphate. In a further embodiment, sitagliptin phosphate is in the form of a crystalline anhydrate or monohydrate. A class of this embodiment refers to sitagliptin phosphate monohydrate. Sitagliptin free base and pharmaceutically acceptable salts thereof are disclosed in US Patent No. 6,699,871 and in Example 7 of WO 03/004498. Crystalline sitagliptin phosphate monohydrate is disclosed in WO 2005/003135 and in WO 2007/050485. For details, e.g. on a process to manufacture or to formulate this compound or a salt thereof, reference is thus made to these documents. A tablet formulation for sitagliptin is commercially available under the trade name Januvia®.

- Vildagliptin (LAF-237) having the structural formula B below is (2S)-{[(3-hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile, also named (S)-1-[(3-hydroxy-1-adamantyl)-amino]acetyl-2-cyano-pyrrolidine,



Vildagliptin is specifically disclosed in US Patent No. 6,166,063 and in Example 1 of WO 00/34241. Specific salts of vildagliptin are disclosed in WO 2007/019255. A crystalline form of vildagliptin as well as a vildagliptin tablet formulation are disclosed in WO 2006/078593. Vildagliptin can be formulated as described in WO 00/34241 or in WO 2005/067976. A modified release vildagliptin formulation is described in WO 2006/135723. For details, e.g. on a process to manufacture or to formulate this compound or a salt thereof, reference is thus made to these documents. A tablet formulation for vildagliptin is expected to be commercially available under the trade name Galvus®.

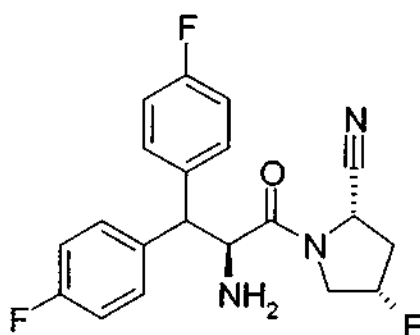
- Saxagliptin (BMS-477118) having the structural formula C below is (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, also named (S)-3-hydroxyadamantylglycine-L-cis-4,5-methanoprolinenitrile,



(C)

Saxagliptin is specifically disclosed in US Patent No. 6,395,767 and in Example 60 of WO 01/68603. In one embodiment, saxagliptin is in the form of its HCl salt or its mono-benzoate salt as disclosed in WO 2004/052850. In a further embodiment, saxagliptin is in the form of the free base. In a yet further embodiment, saxagliptin is in the form of the monohydrate of the free base as disclosed in WO 2004/052850. A process for preparing saxagliptin is also disclosed in WO 2005/106011 and WO 2005/115982. Saxagliptin can be formulated in a tablet as described in WO 2005/117841. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- Denagliptin (GSK-823093) having the structural formula D below is (2S,4S)-1-[(2S)-2-amino-3,3-bis(4-fluorophenyl)propionyl]-4-fluoropyrrolidine-2-carbonitrile, also named (2S,4S)-4-fluoro-1-[4-fluoro-beta-(4-fluorophenyl)-L-phenylalanyl]-2-pyrrolidinecarbonitrile

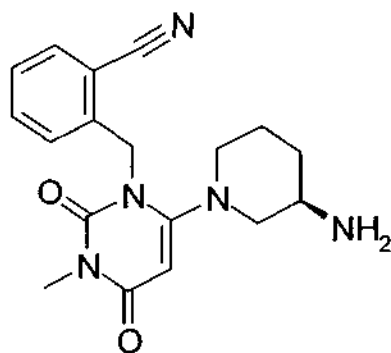


(D)

Denagliptin is specifically disclosed in US Patent No. 7,132,443 and in WO 03/002531. In one embodiment, denagliptin is in the form of its hydrochloride salt as disclosed in Example 2 of WO 03/002531 or its tosylate salt as disclosed in WO 2005/009956. A class of this embodiment refers to denagliptin tosylate. Crystalline anhydrous denagliptin tosylate is

disclosed in WO 2005/009956. For details on a process to manufacture this compound or a salt thereof, reference is thus made to these documents.

- Alogliptin (SYR-322) having the structural formula E below is 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)methyl}benzonitrile



(E)

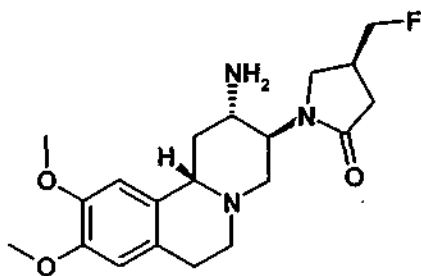
Alogliptin is specifically disclosed in US 2005/261271, EP 1586571 and in WO 2005/095381. In one embodiment, alogliptin is in the form of its benzoate salt, its hydrochloride salt or its tosylate salt each as disclosed in WO 2007/035629. A class of this embodiment refers to alogliptin benzoate. Polymorphs of alogliptin benzoate are disclosed in WO 2007/035372. A process for preparing alogliptin is disclosed in WO 2007/112368 and, specifically, in WO 2007/035629. Alogliptin (namely its benzoate salt) can be formulated in a tablet and administered as described in WO 2007/033266. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (2S)-1-([2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl)-pyrrolidine-2-carbonitrile or a pharmaceutically acceptable salt thereof, preferably the mesylate, or
(2S)-1-([1,1-Dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl)-pyrrolidine-2-carbonitrile or a pharmaceutically acceptable salt thereof.

These compounds and methods for their preparation are disclosed in WO 03/037327. The mesylate salt of the former compound as well as crystalline polymorphs thereof are disclosed in WO 2006/100181. The fumarate salt of the latter compound as well as crystalline polymorphs thereof are disclosed in WO 2007/071576. These compounds can be formulated

in a pharmaceutical composition as described in WO 2007/017423. For details, e.g. on a process to manufacture, to formulate or to use these compounds or a salt thereof, reference is thus made to these documents.

- (S)-1-((2S,3S,11bS)-2-Amino-9,10-dimethoxy-1,3,4,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-3-yl)-4-fluoromethyl-pyrrolidin-2-one or a pharmaceutically acceptable salt thereof.

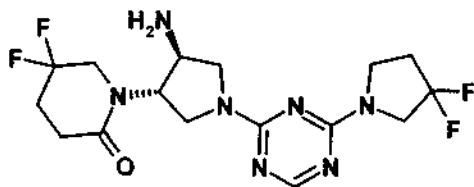


This compound and methods for its preparation are disclosed in WO 2005/000848. A process for preparing this compound (specifically its dihydrochloride salt) is also disclosed in WO 2008/031749, WO 2008/031750 and WO 2008/055814. This compound can be formulated in a pharmaceutical composition as described in WO 2007/017423. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (3,3-Difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone or a pharmaceutically acceptable salt thereof.

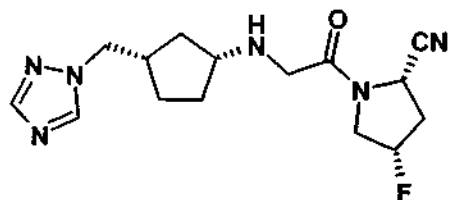
This compound and methods for its preparation are disclosed in WO 2005/116014 and US 7291618. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (1((3S,4S)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one or a pharmaceutically acceptable salt thereof.



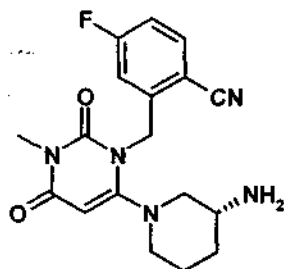
This compound and methods for its preparation are disclosed in WO 2007/148185 and US 20070299076. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (2S,4S)-1-{2-[(3S,1R)-3-(1H-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl}-4-fluoropyrrolidine-2-carbonitrile or a pharmaceutically acceptable salt thereof.



This compound and methods for its preparation are disclosed in WO 2006/040625 and WO 2008/001195. Specifically claimed salts include the methanesulfonate and p-toluenesulfonate. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluorobenzonitrile or a pharmaceutically acceptable salt thereof.



This compound and methods for its preparation and use are disclosed in WO 2005/095381, US 2007060530, WO 2007/035629, WO 2007/074884, WO 2007/112368 and WO 2008/033851. Specifically claimed salts include the succinate, benzoate, benzene-sulfonate, p-toluenesulfonate, (R)-mandelate and hydrochloride. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

For avoidance of any doubt, the disclosure of each of the foregoing documents cited above in connection with the specified DPP IV inhibitors is specifically incorporated herein by reference in its entirety.

Type 2 diabetes is an increasingly prevalent disease that due to a high frequency of complications leads to a significant reduction of life expectancy. Because of diabetes-associated microvascular complications, type 2 diabetes is currently the most frequent cause

of adult-onset loss of vision, renal failure, and amputations in the industrialized world. In addition, the presence of type 2 diabetes is associated with a two to five fold increase in cardiovascular disease risk.

After long duration of disease, most patients with type 2 diabetes will eventually fail on oral therapy and become insulin dependent with the necessity for daily injections and multiple daily glucose measurements.

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that intensive treatment with metformin, sulfonylureas or insulin resulted in only a limited improvement of glycemic control (difference in HbA1c ~0.9%). In addition, even in patients within the intensive treatment arm glycemic control deteriorated significantly over time and this was attributed to deterioration of β -cell function. Importantly, intensive treatment was not associated with a significant reduction in macrovascular complications, i.e. cardiovascular events.

Therefore, there is an unmet medical need for methods, medicaments and pharmaceutical compositions with a good efficacy with regard to glycemic control, with regard to disease-modifying properties and with regard to reduction of cardiovascular morbidity and mortality while at the same time showing an improved safety profile.

Aim of the present invention

The aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular of type 2 diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient in need thereof.

Another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing or delaying progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

Yet another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating of a condition or disorder from the group consisting of complications of diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for reducing the weight or preventing an increase of the weight in a patient in need thereof.

Another aim of the present invention is to provide a new pharmaceutical composition with a high efficacy for the treatment of metabolic disorders, in particular of diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, which has good to very good pharmacological and/or pharmacokinetic and/or physicochemical properties.

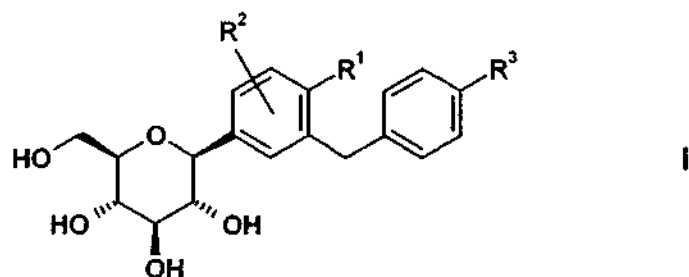
Further aims of the present invention become apparent to the one skilled in the art by description hereinbefore and in the following and by the examples.

Summary of the Invention

Within the scope of the present invention it has now surprisingly been found that a pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinafter can advantageously be used in combination with a DPP IV inhibitor as specified hereinafter for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular in improving glycemic control in patients. This

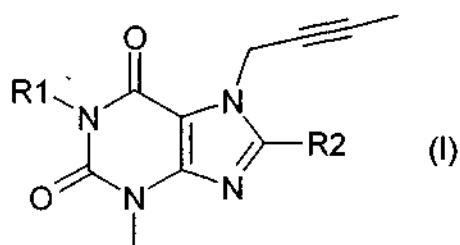
opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighboring disease states.

Therefore, in a first aspect the present invention provides a pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative of the formula (I)

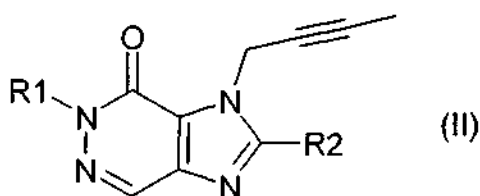


wherein R^1 denotes Cl, methyl or cyano; R^2 denotes H, methyl, methoxy or hydroxy and R^3 denotes ethyl, cyclopropyl, ethynyl, ethoxy, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy,

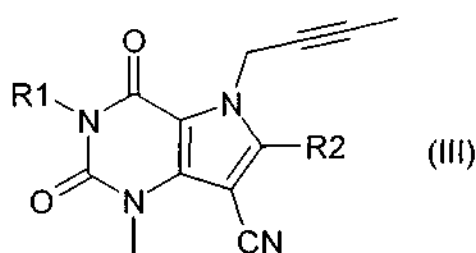
either, in a first embodiment (embodiment A), in combination with a DPP IV inhibitor of formula (I)



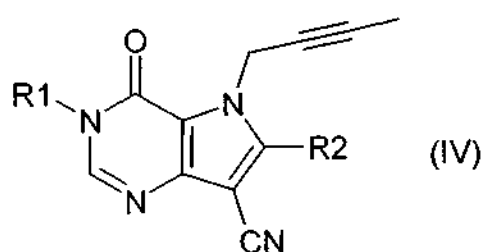
or formula (II)



or formula (III)



or formula (IV)



wherein R1 denotes ([1,5]naphthyridin-2-yl)methyl, (quinazolin-2-yl)methyl, (quinoxalin-6-yl)methyl, (4-methyl-quinazolin-2-yl)methyl, 2-cyano-benzyl, (3-cyano-quinolin-2-yl)methyl, (3-cyano-pyridin-2-yl)methyl, (4-methyl-pyrimidin-2-yl)methyl, or (4,6-dimethyl-pyrimidin-2-yl)methyl and R2 denotes 3-(*R*)-amino-piperidin-1-yl, (2-amino-2-methyl-propyl)-methylamino or (2-(*S*)-amino-propyl)-methylamino, or its pharmaceutically acceptable salt;

or, in a second embodiment (embodiment B), in combination with a DPP IV inhibitor selected from the group consisting of sitagliptin, vildagliptin, saxagliptin, alogliptin, denagliptin, (2*S*)-1-[[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile, (2*S*)-1-[[1,1,-Dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile, (*S*)-1-((2*S*,3*S*,11*bS*)-2-Amino-9,10-dimethoxy-1,3,4,7,11*b*-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-3-yl)-4-fluoromethyl-pyrrolidin-2-one, (3,3-Difluoropyrrolidin-1-yl)-((2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone, (1((3*S*,4*S*)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one, (2*S*,4*S*)-1-{2-[(3*S*,1*R*)-3-(1*H*-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl}-4-fluoropyrrolidine-2-carbonitrile, and

(R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile,
or its pharmaceutically acceptable salt thereof.

According to another aspect of the invention, there is provided a method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

According to another aspect of the invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

The pharmaceutical composition according to this invention may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome.

According to another aspect of the invention, there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

As by the use of a pharmaceutical composition according to this invention, an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or diseases related to or caused by an increased blood glucose level may be treated.

According to another aspect of the invention, there is provided a method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease, in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter. The term "tissue ischaemia" particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer.

By the administration of a pharmaceutical composition according to this invention and due to the SGLT2 inhibitory activity of the glucopyranosyl-substituted benzene derivative excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. Therefore, no gain in weight or even a reduction in body weight is the result.

According to another aspect of the invention, there is provided a method for reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

The pharmacological effect of the glucopyranosyl-substituted benzene derivative in the pharmaceutical composition according to this invention is independent of insulin. Therefore, an improvement of the glycemic control is possible without an additional strain on the pancreatic beta cells. By an administration of a pharmaceutical composition according to this invention a beta-cell degeneration and a decline of beta-cell functionality such as for example apoptosis or necrosis of pancreatic beta cells can be delayed or prevented. Furthermore, the functionality of pancreatic cells can be improved or restored, and the number and size of pancreatic beta cells increased. It may be shown that the differentiation status and hyperplasia of pancreatic beta-cells disturbed by hyperglycemia can be normalized by treatment with a pharmaceutical composition according to this invention.

According to another aspect of the invention, there is provided a method for preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of

the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

By the administration of a combination or pharmaceutical composition according to the present invention, an abnormal accumulation of fat in the liver may be reduced or inhibited. Therefore, according to another aspect of the present invention, there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter. Diseases or conditions which are attributed to an abnormal accumulation of liver fat are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver or toxic fatty liver.

As a result thereof, another aspect of the invention provides a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

According to another aspect of the invention there is provided the use of a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter for the manufacture of a medicament for

- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or

- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or
- reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight; or
- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion; or
- preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat; or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;

in a patient in need thereof characterized in that the glucopyranosyl-substituted benzene derivative is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

According to another aspect of the invention, there is provided the use of a DPP IV inhibitor as defined hereinbefore and hereinafter for the manufacture of a medicament for

- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or

- reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight; or
- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion; or
- preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal *accumulation of liver fat*; or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;

in a patient in need thereof characterized in that the DPP IV inhibitor is administered in combination or alternation with a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter.

According to another aspect of the invention, there is provided the use of a pharmaceutical composition according to the present invention for the manufacture of a medicament for a therapeutic and preventive method as described hereinbefore and hereinafter.

Definitions

The term **"active ingredient"** of a pharmaceutical composition according to the present invention means the glucopyranosyl-substituted benzene derivative and/or the DPP IV inhibitor according to the present invention.

The term **"body mass index"** or **"BMI"** of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of kg/m^2 .

The term **"overweight"** is defined as the condition wherein the individual has a BMI greater than or 25 kg/m^2 and less than 30 kg/m^2 . The terms "overweight" and "pre-obese" are used interchangeably.

The term **"obesity"** is defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m^2 . According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 30 kg/m^2 but lower than 35 kg/m^2 ; the term "class II obesity" is the condition wherein the

BMI is equal to or greater than 35 kg/m² but lower than 40 kg/m²; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m².

The term "**visceral obesity**" is defined as the condition wherein a waist-to-hip ratio of greater than or equal to 1.0 in men and 0.8 in women is measured. It defines the risk for insulin resistance and the development of pre-diabetes.

The term "**abdominal obesity**" is usually defined as the condition wherein the waist circumference is > 40 inches or 102 cm in men, and is > 35 inches or 94 cm in women. With regard to a Japanese ethnicity or Japanese patients abdominal obesity may be defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women (see e.g. investigating committee for the diagnosis of metabolic syndrome in Japan).

The term "**euglycemia**" is defined as the condition in which a subject has a fasting blood glucose concentration within the normal range, greater than 70 mg/dL (3.89 mmol/L) and less than 110 mg/dL (6.11 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term "**hyperglycemia**" is defined as the condition in which a subject has a fasting blood glucose concentration above the normal range, greater than 110 mg/dL (6.11 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term "**hypoglycemia**" is defined as the condition in which a subject has a blood glucose concentration below the normal range of 60 to 115 mg/dL (3.3 to 6.3 mmol/L).

The term "**postprandial hyperglycemia**" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 200 mg/dL (11.11 mmol/L).

The term "**impaired fasting blood glucose**" or "**IFG**" is defined as the condition in which a subject has a fasting blood glucose concentration or fasting serum glucose concentration in a range from 100 to 125 mg/dl (i.e. from 5.6 to 6.9 mmol/l); in particular greater than 110 mg/dL and less than 126 mg/dl (7.00 mmol/L). A subject with "normal fasting glucose" has a fasting glucose concentration smaller than 100 mg/dl, i.e. smaller than 5.6 mmol/l.

The term “**impaired glucose tolerance**” or “**IGT**” is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.78 mmol/L) and less than 200 mg/dL (11.11 mmol/L). The abnormal glucose tolerance, i.e. the 2 hour postprandial blood glucose or serum glucose concentration can be measured as the blood sugar level in mg of glucose per dL of plasma 2 hours after taking 75 g of glucose after a fast. A subject with “normal glucose tolerance” has a 2 hour postprandial blood glucose or serum glucose concentration smaller than 140 mg/dl (7.78 mmol/L).

The term “**hyperinsulinemia**” is defined as the condition in which a subject with insulin resistance, with or without euglycemia, has fasting or postprandial serum or plasma insulin concentration elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ratio < 1.0 (for men) or < 0.8 (for women).

The terms “insulin-sensitizing”, “insulin resistance-improving” or “insulin resistance-lowering” are synonymous and used interchangeably.

The term “**insulin resistance**” is defined as a state in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford ES, *et al. JAMA.* (2002) **287**:356-9). A method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so called minimal models in which, during an intravenous glucose tolerance test, the insulin and glucose concentrations in the blood are measured at fixed time intervals and from these the insulin resistance is calculated. With this method, it is not possible to distinguish between hepatic and peripheral insulin resistance.

Furthermore, insulin resistance, the response of a patient with insulin resistance to therapy, insulin sensitivity and hyperinsulinemia may be quantified by assessing the “homeostasis model assessment to insulin resistance (HOMA-IR)” score, a reliable indicator of insulin resistance (Katsuki A, *et al. Diabetes Care* 2001; **24**: 362-5). Further reference is made to methods for the determination of the HOMA-index for insulin sensitivity (Matthews *et al., Diabetologia* 1985, **28**: 412-19), of the ratio of intact proinsulin to insulin (Forst *et al., Diabetes* 2003, **52**(Suppl.1): A459) and to an euglycemic clamp study. In addition, plasma adiponectin levels can be monitored as a potential surrogate of insulin sensitivity. The

estimate of insulin resistance by the homeostasis assessment model (HOMA)-IR score is calculated with the formula (Galvin P, *et al.* Diabet Med 1992;9:921-8):

$$\text{HOMA-IR} = [\text{fasting serum insulin } (\mu\text{U/mL})] \times [\text{fasting plasma glucose}(\text{mmol/L})/22.5]$$

As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

Patients with a predisposition for the development of IGT or IFG or type 2 diabetes are those having euglycemia with hyperinsulinemia and are by definition, insulin resistant. A typical patient with insulin resistance is usually overweight or obese. If insulin resistance can be detected, this is a particularly strong indication of the presence of pre-diabetes. Thus, it may be that in order to maintain glucose homeostasis a person needs 2-3 times as much insulin as a healthy person, without this resulting in any clinical symptoms.

The methods to investigate the **function of pancreatic beta-cells** are similar to the above methods with regard to insulin sensitivity, hyperinsulinemia or insulin resistance: An improvement of beta-cell function can be measured for example by determining a HOMA-index for beta-cell function (*Matthews et al., Diabetologia* 1985, 28: 412-19), the ratio of intact proinsulin to insulin (*Forst et al., Diabetes* 2003, 52(Suppl.1): A459), the insulin/C-peptide secretion after an oral glucose tolerance test or a meal tolerance test, or by employing a hyperglycemic clamp study and/or minimal modeling after a frequently sampled intravenous glucose tolerance test (*Stumvoll et al., Eur J Clin Invest* 2001, 31: 380-81).

The term “**pre-diabetes**” is the condition wherein an individual is pre-disposed to the development of type 2 diabetes. Pre-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range ≥ 100 mg/dL (J. B. Meigs, *et al.* Diabetes 2003; 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration). The scientific and medical basis for identifying pre-diabetes as a serious health threat is laid out in a Position Statement entitled “The Prevention or Delay of Type 2 Diabetes” issued jointly by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases (Diabetes Care 2002; 25:742-749).

Individuals likely to have insulin resistance are those who have two or more of the following attributes: 1) overweight or obese, 2) high blood pressure, 3) hyperlipidemia, 4) one or more 1st degree relative with a diagnosis of IGT or IFG or type 2 diabetes. Insulin resistance can be confirmed in these individuals by calculating the HOMA-IR score. For the purpose of this invention, insulin resistance is defined as the clinical condition in which an individual has a HOMA-IR score > 4.0 or a HOMA-IR score above the upper limit of normal as defined for the laboratory performing the glucose and insulin assays.

The term "**type 2 diabetes**" is defined as the condition in which a subject has a fasting blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). The measurement of blood glucose values is a standard procedure in routine medical analysis. If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dL (11.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject, the blood sugar level before taking the glucose will be between 60 and 110 mg per dL of plasma, less than 200 mg per dL 1 hour after taking the glucose and less than 140 mg per dL after 2 hours. If after 2 hours the value is between 140 and 200 mg, this is regarded as abnormal glucose tolerance.

The term "**late stage type 2 diabetes mellitus**" includes patients with a secondary drug failure, indication for insulin therapy and progression to micro- and macrovascular complications e.g. diabetic nephropathy, or coronary heart disease (CHD).

The term "**HbA1c**" refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of diabetes mellitus the HbA1c value is of exceptional importance. As its production depends essentially on the blood sugar level and the life of the erythrocytes, the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar levels of the preceding 4-6 weeks. Diabetic patients whose HbA1c value is consistently well adjusted by intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin in the sample), are significantly better protected against diabetic microangiopathy. For example, metformin on its own achieves an average improvement in the HbA1c value in the diabetic of the order of 1.0 – 1.5 %. This reduction of the HbA1C value is not sufficient in all diabetics to achieve the desired target range of < 6.5 % and preferably < 6 % HbA1c.

The “**metabolic syndrome**”, also called “**syndrome X**” (when used in the context of a metabolic disorder), also called the “**dysmetabolic syndrome**” is a syndrome complex with the cardinal feature being insulin resistance (Laaksonen DE, *et al. Am J Epidemiol* 2002;156:1070-7). According to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) *JAMA: Journal of the American Medical Association* (2001) 285:2486-2497), diagnosis of the metabolic syndrome is made when three or more of the following risk factors are present:

1. Abdominal obesity, defined as waist circumference > 40 inches or 102 cm in men, and > 35 inches or 94 cm in women; or with regard to a Japanese ethnicity or Japanese patients defined as waist circumference \geq 85 cm in men and \geq 90 cm in women;
2. Triglycerides: \geq 150 mg/dL
3. HDL-cholesterol < 40 mg/dL in men
4. Blood pressure \geq 130/85 mm Hg-(SBP \geq 130 or DBP \geq 85)
5. Fasting blood glucose \geq 110 mg/dL

The NCEP definitions have been validated (Laaksonen DE, *et al. Am J Epidemiol.* (2002) 156:1070-7). Triglycerides and HDL cholesterol in the blood can also be determined by standard methods in medical analysis and are described for example in Thomas L (Editor): “Labor und Diagnose”, TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2000.

According to a commonly used definition, **hypertension** is diagnosed if the systolic blood pressure (SBP) exceeds a value of 140 mm Hg and diastolic blood pressure (DBP) exceeds a value of 90 mm Hg. If a patient is suffering from manifest diabetes it is currently recommended that the systolic blood pressure be reduced to a level below 130 mm Hg and the diastolic blood pressure be lowered to below 80 mm Hg.

The terms “treatment” and “treating” comprise therapeutic treatment of patients having already developed said condition, in particular in manifest form. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to stop or slow down progression of the disease. Thus the compositions and methods of the

present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy.

The terms "prophylactically treating", "preventively treating" and "preventing" are used interchangeably and comprise a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

Detailed Description

The aspects according to the present invention, in particular the pharmaceutical compositions, methods and uses, refer to glucopyranosyl-substituted benzene derivatives of the formula (I) as defined hereinbefore and hereinafter.

Preferably R^1 denotes chloro or cyano; in particular chloro.

Preferably R^2 denotes H.

Preferably R^3 denotes ethyl, cyclopropyl, ethynyl, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy. Even more preferably R^3 denotes cyclopropyl, ethynyl, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy.

Preferred glucopyranosyl-substituted benzene derivatives are selected from the group of compounds (1) to (10):

- (1) 6-(4-Ethylbenzyl)-4-(β -D-glucopyranos-1-yl)-2-methoxy-benzonitrile
- (2) 2-(4-Ethylbenzyl)-4-(β -D-glucopyranos-1-yl)-5-methoxy-benzonitrile
- (3) 1-Cyano-2-(4-ethylbenzyl)-4-(β -D-glucopyranos-1-yl)-5-methyl-benzene
- (4) 2-(4-Ethylbenzyl)-4-(β -D-glucopyranos-1-yl)-5-hydroxy-benzonitrile
- (5) 2-(4-Ethyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzonitrile
- (6) 2-(4-Cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzonitrile
- (7) 1-chloro-4-(β -D-glucopyranos-1-yl)-2-(4-ethynyl-benzyl)-benzene
- (8) 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((*R*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene
- (9) 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene
- (10) 1-Methyl-2-[4-((*R*)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β -D-glucopyranos-1-yl)-benzene

(11) 1-Methyl-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β -D-glucopyranos-1-yl)-benzene

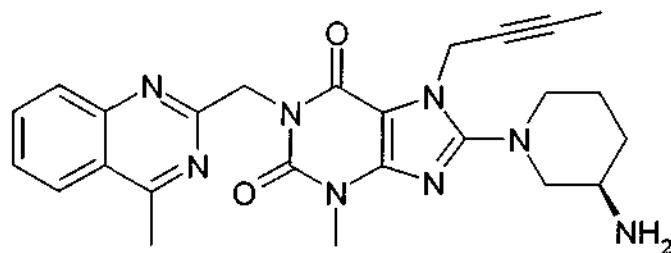
Even more preferred glucopyranosyl-substituted benzene derivative are selected from the compounds (6), (7), (8), (9) and (11).

According to this invention, it is to be understood that the definitions of the above listed glucopyranosyl-substituted benzene derivatives also comprise their hydrates, solvates and polymorphic forms thereof. With regard to the preferred compound (7) an advantageous crystalline form is described in the international patent application WO 2007/028814 which hereby is incorporated herein in its entirety. With regard to the preferred compound (8), an advantageous crystalline form is described in the international patent application WO 2006/117360 which hereby is incorporated herein in its entirety. With regard to the preferred compound (9) an advantageous crystalline form is described in the international patent application WO 2006/117359 which hereby is incorporated herein in its entirety. With regard to the preferred compound (11) an advantageous crystalline form is described in the international patent application WO 2008/049923 which hereby is incorporated herein in its entirety. These crystalline forms possess good solubility properties which enable a good bioavailability of the SGLT2 inhibitor. Furthermore, the crystalline forms are physico-chemically stable and thus provide a good shelf-life stability.

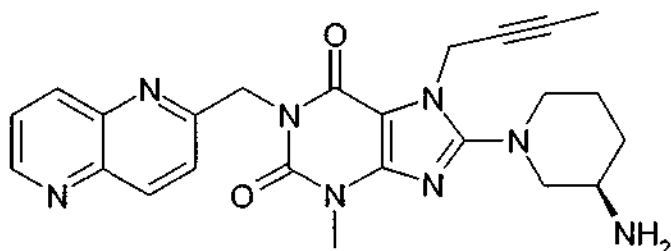
The aspects according to the present invention, in particular the pharmaceutical compositions, methods and uses, refer to a DPP IV inhibitor as defined hereinbefore and hereinafter, or prodrugs thereof, or pharmaceutically acceptable salts thereof.

Regarding the first embodiment (embodiment A), preferred DPP IV inhibitors are any or all of the following compounds and their pharmaceutically acceptable salts:

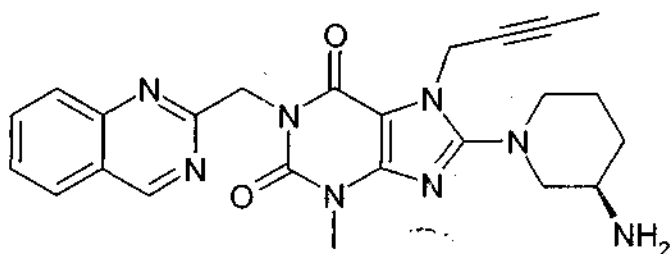
(A): 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (cf. WO 2004/018468, Example 2(142)):



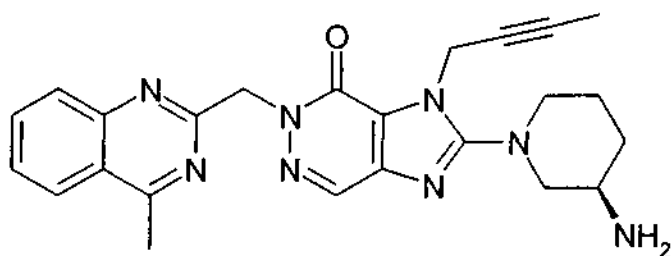
(B): 1-[(1,5)naphthyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2004/018468, Example 2(252)):



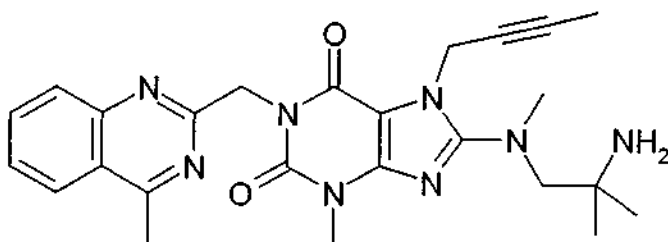
(C): 1-[(quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2004/018468, Example 2(80)):



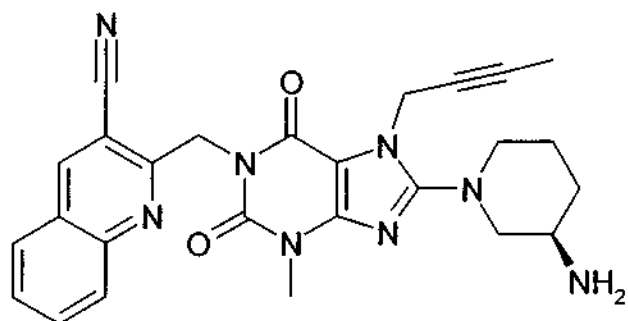
(D): 2-((*R*)-3-amino-piperidin-1-yl)-3-(but-2-ynyl)-5-(4-methyl-quinazolin-2-ylmethyl)-3,5-dihydro-imidazo[4,5-d]pyridazin-4-one (cf. WO 2004/050658, Example 136):



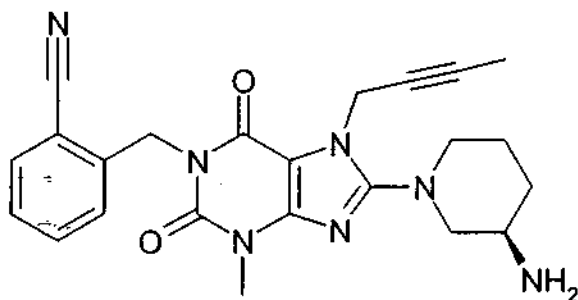
(E): 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(2-amino-2-methyl-propyl)-methylamino]-xanthine (cf. WO 2006/029769, Example 2(1)):



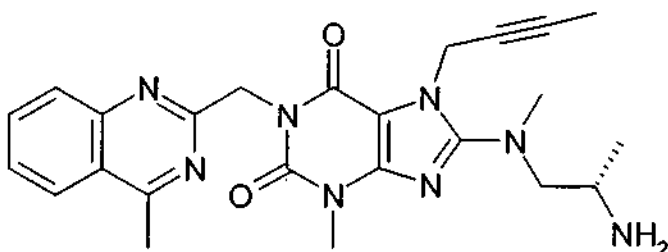
(F): 1-[(3-cyano-quinolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2005/085246, Example 1(30)):



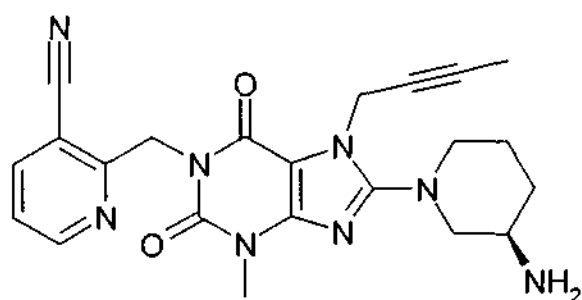
(G): 1-(2-cyano-benzyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2005/085246, Example 1(39)):



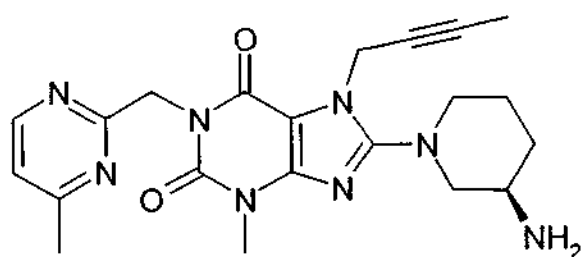
(H): 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-(2-amino-propyl)-methylamino]-xanthine (cf. WO 2006/029769, Example 2(4)):



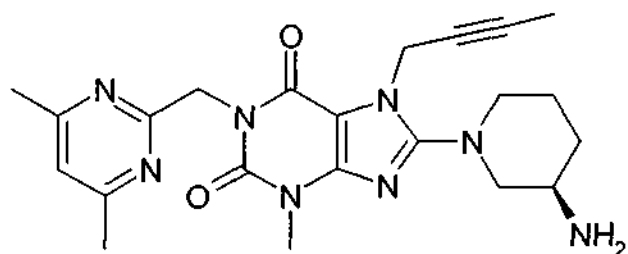
(I): 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2005/085246, Example 1(52)):



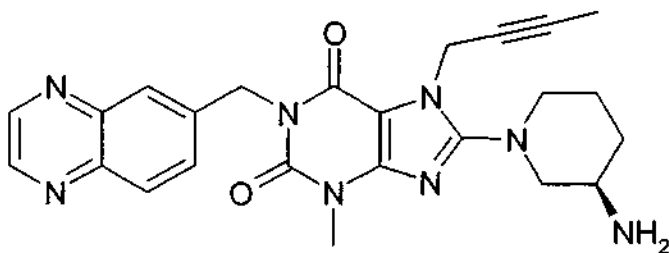
(J): 1-[(4-methyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2005/085246, Example 1(81)):



(K): 1-[(4,6-dimethyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2005/085246, Example 1(82)):



(L): 1-[(quinoxalin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (cf. WO 2005/085246, Example 1(83)):



These DPP IV inhibitors are distinguished from structurally comparable DPP IV inhibitors, as they combine exceptional potency and a long-lasting effect with favourable pharmacological

properties, receptor selectivity and a favourable side-effect profile or bring about unexpected therapeutic advantages or improvements when combined with other pharmaceutical active substances. Their preparation is disclosed in the publications mentioned.

Regarding the second embodiment (embodiment B), preferred DPP IV inhibitors are selected from the group consisting of sitagliptin, vildagliptin, saxagliptin and alogliptin.

According to this invention it is to be understood that the definitions of the above listed DPP IV inhibitors also comprise their pharmaceutically acceptable salts as well as hydrates, solvates and polymorphic forms thereof. With respect to salts, hydrates and polymorphic forms thereof, particular reference is made to those which are referred to hereinabove and hereinbelow.

The pharmaceutical compositions, methods and uses according to this invention most preferably relate to combinations which are selected from the Table 1.

Table 1

No.	Compound No. of the SGLT2 inhibitor	DPP IV Inhibitor
1	(1)	(A)
2	(1)	(B)
3	(1)	(C)
4	(1)	(D)
5	(1)	(E)
6	(1)	(F)
7	(1)	(G)
8	(1)	(H)
9	(1)	(I)
10	(1)	(J)
11	(1)	(K)
12	(1)	(L)
13	(2)	(A)
14	(2)	(B)
15	(2)	(C)
16	(2)	(D)

17	(2)	(E)
18	(2)	(F)
19	(2)	(G)
20	(2)	(H)
21	(2)	(I)
22	(2)	(J)
23	(2)	(K)
24	(2)	(L)
25	(3)	(A)
26	(3)	(B)
27	(3)	(C)
28	(3)	(D)
29	(3)	(E)
30	(3)	(F)
31	(3)	(G)
32	(3)	(H)
33	(3)	(I)
34	(3)	(J)
35	(3)	(K)
36	(3)	(L)
37	(4)	(A)
38	(4)	(B)
39	(4)	(C)
40	(4)	(D)
41	(4)	(E)
42	(4)	(F)
43	(4)	(G)
44	(4)	(H)
45	(4)	(I)
46	(4)	(J)
47	(4)	(K)
48	(4)	(L)
49	(5)	(A)
50	(5)	(B)
51	(5)	(C)

52	(5)	(D)
53	(5)	(E)
54	(5)	(F)
55	(5)	(G)
56	(5)	(H)
57	(5)	(I)
58	(5)	(J)
59	(5)	(K)
60	(5)	(L)
61	(6)	(A)
62	(6)	(B)
63	(6)	(C)
64	(6)	(D)
65	(6)	(E)
66	(6)	(F)
67	(6)	(G)
68	(6)	(H)
69	(6)	(I)
70	(6)	(J)
71	(6)	(K)
72	(6)	(L)
73	(7)	(A)
74	(7)	(B)
75	(7)	(C)
76	(7)	(D)
77	(7)	(E)
78	(7)	(F)
79	(7)	(G)
80	(7)	(H)
81	(7)	(I)
82	(7)	(J)
83	(7)	(K)
84	(7)	(L)
85	(8)	(A)
86	(8)	(B)

87	(8)	(C)
88	(8)	(D)
89	(8)	(E)
90	(8)	(F)
91	(8)	(G)
92	(8)	(H)
93	(8)	(I)
94	(8)	(J)
95	(8)	(K)
96	(8)	(L)
97	(9)	(A)
98	(9)	(B)
99	(9)	(C)
100	(9)	(D)
101	(9)	(E)
102	(9)	(F)
103	(9)	(G)
104	(9)	(H)
105	(9)	(I)
106	(9)	(J)
107	(9)	(K)
108	(9)	(L)
109	(10)	(A)
110	(10)	(B)
111	(10)	(C)
112	(10)	(D)
113	(10)	(E)
114	(10)	(F)
115	(10)	(G)
116	(10)	(H)
117	(10)	(I)
118	(10)	(J)
119	(10)	(K)
120	(10)	(L)
121	(11)	(A)

122	(11)	(B)
123	(11)	(C)
124	(11)	(D)
125	(11)	(E)
126	(11)	(F)
127	(11)	(G)
128	(11)	(H)
129	(11)	(I)
130	(11)	(J)
131	(11)	(K)
132	(11)	(L)
133	(1)	sitagliptin
134	(1)	vildagliptin
135	(1)	saxagliptin
136	(1)	alogliptin
137	(2)	sitagliptin
138	(2)	vildagliptin
139	(2)	saxagliptin
140	(3)	alogliptin
141	(3)	sitagliptin
142	(3)	vildagliptin
143	(3)	saxagliptin
144	(3)	alogliptin
145	(4)	sitagliptin
146	(4)	vildagliptin
147	(4)	saxagliptin
148	(4)	alogliptin
149	(5)	sitagliptin
150	(5)	vildagliptin
151	(5)	saxagliptin
152	(5)	alogliptin
153	(6)	sitagliptin
154	(6)	vildagliptin
155	(6)	saxagliptin
156	(6)	alogliptin

157	(7)	sitagliptin
158	(7)	vildagliptin
159	(7)	saxagliptin
160	(7)	alogliptin
161	(8)	sitagliptin
162	(8)	vildagliptin
163	(8)	saxagliptin
164	(8)	alogliptin
165	(9)	sitagliptin
166	(9)	vildagliptin
167	(9)	saxagliptin
168	(9)	alogliptin
169	(10)	sitagliptin
170	(10)	vildagliptin
171	(10)	saxagliptin
172	(10)	alogliptin
173	(11)	sitagliptin
174	(11)	vildagliptin
175	(11)	saxagliptin
176	(11)	alogliptin

Among the combinations No. 1-176 according to the present invention listed in Table 1, combinations No. 1, 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, and 133-176, in particular 61, 73, 85, 97, 121, 153 to 168 and 173 to 176, even more preferably 97, 165, 166, 167 and 168 are to be emphasized.

The combination of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor according to this invention significantly improves the glycemic control, in particular in patients as described hereinafter, compared with a monotherapy using either the glucopyranosyl-substituted benzene derivative or the DPP IV inhibitor. The improved glycemic control is determined as an increased lowering of blood glucose and an increased reduction of HbA1c. With monotherapy in a patient, in particular in patients as described hereinafter, the glycemic control can usually not be further improved significantly by an administration of the drug above a certain highest dose. In addition, a long term treatment using a highest dose may be unwanted in view of potential side effects. Therefore, a full glycemic control cannot be achieved in all patients via a monotherapy using either the glucopyranosyl-substituted

benzene derivative or the DPP IV inhibitor. In such patients a progression of the diabetes mellitus may continue and complications associated with diabetes mellitus may occur, such as macrovascular complications. The pharmaceutical composition as well as the methods according to the present invention allow a reduction of the HbA1c value to a desired target range, for example $< 7\%$ and preferably $< 6.5\%$, for a higher number of patients compared with a corresponding monotherapy.

In addition, the combination of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor according to this invention allows a reduction in the dose of either the glucopyranosyl-substituted benzene derivative or the DPP IV inhibitor or of both active ingredients. A dose reduction is beneficial for patients which otherwise would potentially suffer from side effects in a monotherapy using a higher dose of either the glucopyranosyl-substituted benzene derivative or the DPP IV inhibitor. Therefore, the pharmaceutical composition as well as the methods according to the present invention, show less side effects, thereby making the therapy more tolerable and improving the patients compliance with the treatment.

A monotherapy using a DPP IV inhibitor according to the present invention is not independent from the insulin secretory capacity or the insulin sensitivity of a patient. On the other hand, a treatment with the administration of a glucopyranosyl-substituted benzene derivative according the present invention does not depend on the insulin secretory capacity or the insulin sensitivity of the patient. Therefore, any patient independent of the prevailing insulin levels or insulin resistance and/or hyperinsulinemia may benefit from a therapy using a combination of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor according to this invention. Independent of their prevailing insulin levels or their insulin resistance or hyperinsulinemia these patients can still be treated with the DPP IV inhibitor because of the combined or alternate administration of the glucopyranosyl-substituted benzene derivative.

A DPP IV inhibitor according to the present invention is able – via the increases in active GLP-1 levels - to reduce the glucagon secretion in a patient. This will therefore limit the hepatic glucose production. Furthermore, the elevated active GLP-1 levels produced by the DPP IV inhibitor will have beneficial effects on beta-cell regeneration and neogenesis. All these features of DPP IV inhibitors render a combination with a glucopyranosyl-substituted benzene derivative quite useful and therapeutically relevant.

When this invention refers to patients requiring treatment or prevention, it relates primarily to treatment and prevention in humans, but the pharmaceutical composition may also be used accordingly in veterinary medicine on mammals.

As described hereinbefore by the administration of the pharmaceutical composition according to this invention and in particular in view of the high SGLT2 inhibitory activity of the glucopyranosyl-substituted benzene derivative therein, excessive blood glucose is excreted through the urine of the patient, so that no gain in weight or even a reduction in body weight may result. Therefore, a treatment or prophylaxis according to this invention is advantageously suitable in those patients in need of such treatment or prophylaxis who are diagnosed of one or more of the conditions selected from the group consisting of overweight, class I obesity, class II obesity, class III obesity, visceral obesity and abdominal obesity or for those individuals in which a weight increase is contraindicated.

The pharmaceutical composition according to this invention and in particular the glucopyranosyl-substituted benzene derivative therein exhibits a very good efficacy with regard to glycemic control, in particular in view of a reduction of fasting plasma glucose, postprandial plasma glucose and/or glycosylated hemoglobin (HbA1c). By administering a pharmaceutical composition according to this invention, a reduction of HbA1c equal to or greater than preferably 0.5 %, even more preferably equal to or greater than 1.0 % can be achieved and the reduction is particularly in the range from 1.0 % to 1.5 %.

Furthermore, the method and/or use according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions:

- (a) a fasting blood glucose or serum glucose concentration greater than 110 mg/dL, in particular greater than 125 mg/dL;
- (b) a postprandial plasma glucose equal to or greater than 140 mg/dL;
- (c) an HbA1c value equal to or greater than 6.5 %, in particular equal to or greater than 8.0 %.

The present invention also discloses the use of the pharmaceutical composition for improving glycemic control in patients having type 2 diabetes or showing first signs of pre-diabetes. Thus, the invention also includes diabetes prevention. If therefore a pharmaceutical composition according to this invention is used to improve the glycemic control as soon as one of the above-mentioned signs of pre-diabetes is present, the onset of manifest type 2 diabetes mellitus can be delayed or prevented.

Furthermore, the pharmaceutical composition according to this invention is particularly suitable in the treatment of patients with insulin dependency, i.e. in patients who are treated or otherwise would be treated or need treatment with an insulin or a derivative of insulin or a substitute of insulin or a formulation comprising an insulin or a derivative or substitute thereof. These patients include patients with diabetes type 2 and patients with diabetes type 1.

It can be found that by using a pharmaceutical composition according to this invention, an improvement of the glycemic control can be achieved even in those patients who have insufficient glycemic control in particular despite treatment with an antidiabetic drug, for example despite maximal tolerated dose of oral monotherapy with either metformin or a SGLT2 inhibitor, in particular a SGLT2 inhibitor according to this invention, or a DPP IV inhibitor, in particular a DPP IV inhibitor according to this invention. A maximal tolerated dose with regard to metformin is for example 850 mg three times a day or any equivalent thereof. A maximal tolerated dose with regard to a SGLT2 inhibitor according to this invention, in particular with regard to the compounds (6), (7), (8), (9) or (11), is for example 100 mg, preferably 50 mg or even 30 mg once per day or any equivalent thereof. A maximal tolerated dose with regard to a DPP IV inhibitor according to this invention, in particular with regard to the compound (A) (1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine), is for example 10 mg once daily or any equivalent thereof. A maximal tolerated dose with regard to a DPP IV inhibitor according to his invention is for example Sitagliptin 100 mg once daily or any equivalent thereof. In the scope of the present invention, the term "insufficient glycemic control" means a condition wherein patients show HbA1c values above 6.5 %, in particular above 8 %.

Therefore, according to a preferred embodiment of the present invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof who is diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG) with insulin resistance, with metabolic syndrome and/or with type 2 or type 1 diabetes mellitus characterized in that a glucopyranosyl-substituted benzene derivative as defined hereinbefore and hereinafter is administered in combination or alternation with a DPP IV inhibitor as defined hereinbefore and hereinafter.

The lowering of the blood glucose level by the administration of a glucopyranosyl-substituted benzene derivative according to this invention is insulin-independent. Therefore, a pharmaceutical composition according to this invention is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

- insulin resistance,
- hyperinsulinemia,
- pre-diabetes,
- type 2 diabetes mellitus, particular having a late stage type 2 diabetes mellitus,
- type 1 diabetes mellitus.

Furthermore, a pharmaceutical composition according to this invention is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

- (a) obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,
- (b) triglyceride blood level ≥ 150 mg/dL,
- (c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients,
- (d) a systolic blood pressure ≥ 130 mm Hg and a diastolic blood pressure ≥ 85 mm Hg,
- (e) a fasting blood glucose level ≥ 110 mg/dL.

It is assumed that patients diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), with insulin resistance and/or with metabolic syndrome suffer from an increased risk of developing a cardiovascular disease, such as for example myocardial infarction, coronary heart disease, heart insufficiency, thromboembolic events. A glycemic control according to this invention may result in a reduction of the cardiovascular risks.

A pharmaceutical composition according to this invention, in particular due to the glucopyranosyl-substituted benzene derivative therein, exhibits a good safety profile.

Therefore, a treatment or prophylaxis according to this invention is advantageously possible in those patients for which the mono-therapy with another antidiabetic drug, such as for example metformin, is contraindicated and/or who have an intolerance against such drugs at therapeutic doses. In particular, a treatment or prophylaxis according to this invention may be advantageously possible in those patients showing or having an increased risk for one or more of the following disorders: renal insufficiency or diseases, cardiac diseases, cardiac failure, hepatic diseases, pulmonal diseases, catabolytic states and/or danger of lactate acidosis, or female patients being pregnant or during lactation.

Furthermore, it can be found that the administration of a pharmaceutical composition according to this invention results in no risk or in a low risk of hypoglycemia. Therefore, a treatment or prophylaxis according to this invention is also advantageously possible in those patients showing or having an increased risk for hypoglycemia.

A pharmaceutical composition according to this invention is particularly suitable in the long term treatment or prophylaxis of the diseases and/or conditions as described hereinbefore and hereinafter, in particular in the long term glycemic control in patients with type 2 diabetes mellitus.

The term "long term" as used hereinbefore and hereinafter indicates a treatment of or administration in a patient within a period of time longer than 12 weeks, preferably longer than 25 weeks, even more preferably longer than 1 year.

Therefore, a particularly preferred embodiment of the present invention provides a method for therapy, preferably oral therapy, for improvement, especially long term improvement, of glycemic control in patients with type 2 diabetes mellitus, especially in patients with late stage type 2 diabetes mellitus, in particular in patients additionally diagnosed of overweight, obesity (including class I, class II and/or class III obesity), visceral obesity and/or abdominal obesity.

The effects mentioned above are observed both, when the glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor are administered in combination, for example simultaneously, and when they are administered in alternation, for example successively in separate formulations.

It will be appreciated that the amount of the pharmaceutical composition according to this invention to be administered to the patient and required for use in treatment or prophylaxis according to the present invention will vary with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician. In general, however, the glucopyranosyl-substituted benzene derivative according to this invention and the DPP IV inhibitor are included in the pharmaceutical composition or dosage form in an amount sufficient that by their administration in combination or alternation the glycemic control in the patient to be treated is improved.

In the following preferred ranges of the amount of glucopyranosyl-substituted benzene derivative and of the DPP IV inhibitor to be employed in the pharmaceutical composition and the methods and uses according to this invention are described. These ranges refer to the amounts to be administered per day with respect to an adult patient and can be adapted accordingly with regard to an administration 2, 3, 4 or more times daily and with regard to other routes of administration and with regard to the age of the patient.

Within the scope of the present invention, the pharmaceutical composition is preferably administered orally. Other forms of administration are possible and described hereinafter. Preferably the dosage form comprising the glucopyranosyl-substituted benzene derivative is administered orally. The route of administration of the DPP IV inhibitor is oral or usually well known.

In general, the amount of the glucopyranosyl-substituted benzene derivative in the pharmaceutical composition and methods according to this invention is preferably in the range from 1/5 to 1/1 of the amount usually recommended for a monotherapy using said glucopyranosyl-substituted benzene derivative. Advantageously, the combination therapy according to the present invention utilizes lower dosages of the individual glucopyranosyl-substituted benzene derivative or of the individual DPP IV inhibitor used in monotherapy or used in conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

The amount of the glucopyranosyl-substituted benzene derivative is preferably in the range from 0.5 mg to 200 mg, even more preferably from 1 to 100 mg, most preferably from 5 to 50 mg per day for a human being, for example for approximately 70 kg body weight. The oral administration is preferred. Therefore, a pharmaceutical composition may comprise the hereinbefore mentioned amounts for once daily administration and from 0.25 mg to 100 mg, even more preferably from 0.5 to 50 mg, most preferably from 2.5 to 25 mg for twice daily administration. Particular dosage strengths (e.g. per tablet or capsule) are for example 5, 10, 15, 20, 25 or 50 mg of the compound (6), (7), (8), (9) or (11), in particular of the compound (9).

In general, the amount of the DPP IV inhibitor in the pharmaceutical composition and methods according to this invention is preferably in the range from 1/5 to 1/1 of the amount usually recommended for a monotherapy using said DPP IV inhibitor.

With respect to the first embodiment (embodiment **A**), the dosage typically required of the DPP IV inhibitors mentioned herein in embodiment **A** when administered intravenously is 0.1 mg to 10 mg, preferably 0.25 mg to 5 mg, and when administered orally 0.5 mg to 100 mg, preferably 2.5 mg to 50 mg, or 0.5 mg to 10 mg, more preferably 2.5 mg to 10 mg or 1 mg to 5 mg, in each case 1 to 4 times a day. Thus, the dosage required of the compound (A) (1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine) when administered orally is 0.5 mg to 10 mg per patient per day, preferably 2.5 mg to 10 mg per patient per day (more preferably 5 mg to 10 mg per patient per day) or 1 mg to 5 mg per patient per day.

A dosage form prepared with a pharmaceutical composition comprising a DPP IV inhibitor mentioned herein in embodiment **A** contain the active ingredient in a dosage range of 0.1-100 mg, in particular 0.5 to 10 mg. Thus, particular dosage strengths of the compound (A) (1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine) are 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg, more particular dosage strengths thereof are 1 mg, 2.5 mg and 5 mg.

With respect to the second embodiment (embodiment **B**), the doses of DPP IV inhibitors mentioned herein in embodiment **B** to be administered to mammals, for example human beings, of, for example, approximately 70 kg body weight, may be generally from about 0.5 mg to about 350 mg, for example from about 10 mg to about 250 mg, preferably 20-200 mg, more preferably 20-100 mg, of the active moiety per person per day, or from about 0.5 mg to about 20 mg, preferably 2.5-10 mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Single dosage strengths comprise, for example, 10, 25, 40, 50, 75, 100, 150 and 200 mg of the DPP IV inhibitor active moiety.

A dosage strength of the DPP IV inhibitor sitagliptin is usually between 25 and 200 mg of the active moiety. A recommended dose of sitagliptin is 100 mg calculated for the active moiety (free base anhydrate) once daily. Unit dosage strengths of sitagliptin free base anhydrate (active moiety) are 25, 50, 75, 100, 150 and 200 mg. Particular unit dosage strengths of sitagliptin (e.g. per tablet) are 25, 50 and 100 mg. An equivalent amount of sitagliptin phosphate monohydrate to the sitagliptin free base anhydrate is used in the pharmaceutical compositions, namely, 32.13, 64.25, 96.38, 128.5, 192.75, and 257 mg, respectively. Adjusted dosages of 25 and 50 mg sitagliptin are used for patients with renal failure.

A dosage range of the DPP IV inhibitor vildagliptin is usually between 10 and 150 mg daily, in particular between 25 and 150 mg, 25 and 100 mg or 25 and 50 mg or 50 and 100 mg daily. Particular examples of daily oral dosage are 25, 30, 35, 45, 50, 55, 60, 80, 100 or 150 mg. In a more particular aspect, the daily administration of vildagliptin is between 25 and 150 mg or between 50 and 100 mg. In another more particular aspect, the daily administration of vildagliptin is 50 or 100 mg. The application of the active ingredient may occur up to three times a day, preferably one or two times a day. Particular dosage forms (e.g. tablets) comprise 50 mg or 100 mg vildagliptin.

Alogliptin may be administered to a patient at a daily dose of between 5 mg/day and 250 mg/day, optionally between 10 mg and 200 mg, optionally between 10 mg and 150 mg, and optionally between 10 mg and 100 mg of alogliptin (in each instance based on the molecular weight of the free base form of alogliptin). Thus, specific dosage amounts that may be used include, but are not limited to 10 mg, 12.5 mg, 20 mg, 25 mg, 50 mg, 75 mg and 100 mg of alogliptin per day. Alogliptin may be administered in its free base form or as a pharmaceutically acceptable salt.

Saxagliptin may be administered to a patient at a daily dose of between 2.5 mg/day and 100 mg/day, optionally between 2.5 mg and 50 mg. Specific dosage amounts that may be used include, but are not limited to 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg and 100 mg of saxagliptin per day.

The amount of the glucopyranosyl-substituted benzene derivative and of the DPP IV inhibitor in the pharmaceutical composition according to this invention correspond to the respective dosage ranges as provided hereinbefore. For example, a pharmaceutical composition comprises an amount of 5 to 50 mg of the compound (6), (7), (8), (9) or (11), in particular of the compound (9), and of the compound (A) (1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine) in an amount of 0.5 mg to 10 mg.

Another example of a pharmaceutical composition comprises an amount of 5 to 50 mg of the compound (6), (7), (8), (9) or (11), in particular of the compound (9), and of sitagliptin in an amount of 1 to 100 mg active moiety.

A further example of a pharmaceutical composition comprises an amount of 5 to 50 mg of the compound (6), (7), (8), (9) or (11), in particular of the compound (9), and of vildagliptin in an amount of 1 to 100 mg active moiety.

A further example of a pharmaceutical composition comprises an amount of 5 to 50 mg of the compound (6), (7), (8), (9) or (11) , in particular of the compound (9), and of alogliptin in an amount of 1 to 100 mg active moiety.

A further example of a pharmaceutical composition comprises an amount of 5 to 50 mg of the compound (6), (7), (8), (9) or (11) , in particular of the compound (9), and of saxagliptin in an amount of 1 to 100 mg active moiety.

In the methods and uses according to the present invention the glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor are administered in combination or alternation. The term "administration in combination" means that both active ingredients are administered at the same time, i.e. simultaneously, or essentially at the same time. The term "administration in alternation" means that at first a first active ingredient is administered and after a period of time the second active ingredient is administered, i.e. both active ingredients are administered sequentially. The period of time may be in the range from 30 min to 12 hours. The administration which is in combination or in alternation may be once, twice, three times or four times daily.

With regard to the administration of the glucopyranosyl-substituted benzene derivative in combination with the DPP IV inhibitor both active ingredients may be present in a single dosage form, for example in a tablet or capsule, or each active ingredient may be present in a separate dosage form, for example in two different or identical dosage forms.

With regard to their administration in alternation, each of the active ingredients is present in a separate dosage form, for example in two different or identical dosage forms.

Therefore, the pharmaceutical composition according to this invention may be present as single dosage forms which comprise both the glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor as well as separate dosage forms wherein one dosage form comprises the glucopyranosyl-substituted benzene derivative and the other dosage form comprises the DPP IV inhibitor.

The case may arise in which one active ingredient has to be administered more often, for example twice per day, than the other active ingredient, which for example needs administration once daily. Therefore the term "administration in combination or alternation"

also includes an administration scheme in which first both active ingredients are administered in combination or alternation and after a period of time only one active ingredient is administered again or *vice versa*.

Therefore, the present invention also includes pharmaceutical compositions which are present as separate dosage forms wherein one dosage form comprises the glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor and the other dosage form comprises either the glucopyranosyl-substituted benzene derivative or the DPP IV inhibitor.

A pharmaceutical composition which is present as a separate or multiple dosage form, preferably as a kit of parts, is useful in combination therapy to flexibly suit the individual therapeutic needs of the patient.

A preferred kit of parts comprises

- (a) a first containment containing a dosage form comprising the glucopyranosyl-substituted benzene derivative and at least one pharmaceutically acceptable carrier, and
- (b) a second containment containing a dosage form comprising the DPP IV inhibitor and at least one pharmaceutically acceptable carrier.

A further aspect of the present invention is a manufacture comprising the pharmaceutical composition being present as separate dosage forms according to the present invention and a label or package insert comprising instructions that the separate dosage forms are to be administered in combination or alternation.

A yet further aspect of the present invention is a manufacture comprising a medicament which comprises a glucopyranosyl-substituted benzene derivative according to the present invention and a label or package insert which comprises instructions that the medicament may or is to be administered in combination or alternation with a medicament comprising a DPP IV inhibitor according to the present invention.

Another further aspect of the present invention is a manufacture comprising a medicament which comprises a DPP IV inhibitor according to the present invention and a label or package insert which comprises instructions that the medicament may or is to be administered in combination or alternation with a medicament comprising a glucopyranosyl-substituted benzene derivative according to the present invention.

The desired dose of the pharmaceutical composition according to this invention may conveniently be presented in a once daily or as divided dose administered at appropriate intervals, for example as two, three or more doses per day.

The pharmaceutical composition may be formulated for oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration in liquid or solid form or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredient with one or more pharmaceutically acceptable carriers, like liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

The pharmaceutical composition may be formulated in the form of tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, dry syrups, chewable tablets, troches, effervescent tablets, drops, suspension, fast dissolving tablets, oral fast-dispersing tablets, etc..

The pharmaceutical composition and the dosage forms preferably comprises one or more pharmaceutical acceptable carriers which must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredients may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives

such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention may also 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, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

The pharmaceutical compositions and methods according to this invention show advantageous effects in the treatment and prevention of those diseases and conditions as described hereinbefore compared with pharmaceutical compositions and methods which comprise only one of both active ingredients. Advantageous effects may be seen for example with respect to efficacy, dosage strength, dosage frequency, pharmacodynamic properties, pharmacokinetic properties, fewer adverse effects, etc..

Examples of pharmaceutically acceptable carriers are known to the one skilled in the art.

Methods for the manufacture of glucopyranosyl-substituted benzene derivatives according to this invention and of prodrugs thereof are known to the one skilled in the art.

Advantageously, the compounds according to this invention can be prepared using synthetic methods as described in the literature, in particular as described in the WO 01/27128, WO 03/099836, WO 2005/092877, WO 2006/034489, WO 2006/064033, WO 2007/025943 and WO 2007/031548. The compounds (1) to (6) may preferably be prepared following the synthetic methods described in WO 2007/093610 and WO 2008/055870. Advantageously, the compound (7) is prepared as described in the WO 2005/092877 (see example 12).

Advantageous methods of synthesis of the compounds (8) and (9) are described in the WO 2005/092877 (see examples 2 and 3), WO 2006/117360, WO 2006/117359 and WO 2006/120208. The compounds (10) and (11) are preferably obtained via the synthetic methods described in the WO 2006/064033.

With respect to embodiment A, the methods of synthesis for the DPP IV inhibitors according to embodiment A of this invention are known to the skilled person. Advantageously, the DPP IV inhibitors according to embodiment A of this invention can be prepared using synthetic methods as described in the literature. Thus, for example, purine derivatives of formula (I) can be obtained as described in WO 2002/068420, WO 2004/018468, WO 2005/085246, WO 2006/029769 or WO 2006/048427, the disclosures of which are incorporated herein. Purine derivatives of formula (II) can be obtained as described, for example, in WO 2004/050658 or WO 2005/110999, the disclosures of which are incorporated herein. Purine derivatives of formula (III) and (IV) can be obtained as described, for example, in WO 2006/068163, WO 2007/071738 or WO 2008/017670, the disclosures of which are incorporated herein. The preparation of those DPP IV inhibitors, which are specifically mentioned hereinabove, is disclosed in the publications mentioned in connection therewith. Polymorphous crystal modifications and formulations of particular DPP IV inhibitors are disclosed in WO 2007/054201 and WO 2007/128724, respectively, the disclosures of which are incorporated herein in their entireties.

With respect to embodiment B, the methods of synthesis for the DPP IV inhibitors of embodiment B are described in the scientific literature and/ or in published patent documents, particularly in those cited above in paragraph "background of the invention".

The DPP IV inhibitor may be present in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include, without being restricted thereto, such as salts of inorganic acid like hydrochloric acid, sulfuric acid and phosphoric acid; salts of organic carboxylic acid like oxalic acid, acetic acid, citric acid, malic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, succinic acid and glutamic acid and salts of organic sulfonic acid like methanesulfonic acid and p-toluenesulfonic acid. The salts can be formed by combining the compound and an acid in the appropriate amount and ratio in a solvent and decomposer. They can be also obtained by the cation or anion exchange from the form of other salts. The DPP IV inhibitor may be present in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include such as salts of inorganic acid like hydrochloric acid, sulfuric acid and phosphoric acid; salts of organic carboxylic acid like oxalic acid, acetic

acid, citric acid, malic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, succinic acid and glutamic acid and salts of organic sulfonic acid like methanesulfonic acid and p-toluenesulfonic acid. The salts can be formed by combining the compound and an acid in the appropriate amount and ratio in a solvent and decomposer. They can be also obtained by the cation or anion exchange from the form of other salts.

The glucopyranosyl-substituted benzene derivative and/or the DPP IV inhibitor or a pharmaceutically acceptable salt thereof may be present in the form of a solvate such as a hydrate or alcohol adduct.

Any of the above mentioned combinations and methods within the scope of the invention may be tested by animal models known in the art. In the following, *in vivo* experiments are described which are suitable to evaluate pharmacologically relevant properties of pharmaceutical compositions and methods according to this invention:

Pharmaceutical compositions and methods according to this invention can be tested in genetically hyperinsulinemic or diabetic animals like db/db mice, ob/ob mice, Zucker Fatty (fa/fa) rats or Zucker Diabetic Fatty (ZDF) rats. In addition, they can be tested in animals with experimentally induced diabetes like HanWistar or Sprague Dawley rats pretreated with streptozotocin.

The effect on glycemic control of the combinations according to this invention can be tested after single dosing of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor alone and in combination in an oral glucose tolerance test in the animal models described hereinbefore. The time course of blood glucose is followed after an oral glucose challenge in overnight fasted animals. The combinations according to the present invention significantly improve glucose excursion compared to each monotherapy as measured by reduction of peak glucose concentrations or reduction of glucose AUC. In addition, after multiple dosing of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor alone and in combination in the animal models described hereinbefore, the effect on glycemic control can be determined by measuring the HbA1c value in blood. The combinations according to this invention significantly reduce HbA1c compared to each monotherapy.

The possible dose reduction of either the glucopyranosyl-substituted benzene derivative or the DPP-IV inhibitor or of both active ingredients can be tested by the effect on glycemic control of lower doses of the combinations and monotherapies in the animal models

described hereinbefore. The combinations according to this invention at the lower doses significantly improve glycemic control compared to placebo treatment whereas the monotherapies at lower doses do not.

The improved independence from insulin of the treatment according to this invention can be shown after single dosing in oral glucose tolerance tests in the animal models described hereinbefore. The time course of plasma insulin is followed after a glucose challenge in overnight fasted animals. The glucopyranosyl-substituted benzene derivative in combination with the DPP IV inhibitor will exhibit lower insulin peak concentrations or insulin AUC at lower blood glucose excursion than the DPP IV inhibitor alone.

The increase in active GLP-1 levels by treatment according to this invention after single or multiple dosing can be determined by measuring those levels in the plasma of animal models described hereinbefore in either the fasting or postprandial state. Likewise, a reduction in glucagon levels in plasma can be measured under the same conditions. The glucopyranosyl-substituted benzene derivative in combination with the DPP IV inhibitor will exhibit higher active GLP-1 concentrations and lower glucagon concentrations than the glucopyranosyl-substituted benzene derivative alone.

A superior effect of the combination of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor according to the present invention than of the glucopyranosyl-substituted benzene derivative alone on beta-cell regeneration and neogenesis can be determined after multiple dosing in the animal models described hereinbefore by measuring the increase in pancreatic insulin content, or by measuring increased beta-cell mass by morphometric analysis after immunohistochemical staining of pancreatic sections, or by measuring increased glucose-stimulated insulin secretion in isolated pancreatic islets.

In the foregoing and following text, H atoms of hydroxyl groups are not explicitly shown in every case in structural formulae. The Examples that follow are intended to illustrate the present invention without restricting it. The terms "room temperature" and "ambient temperature" are used interchangeably and denote temperatures of about 20°C. The following abbreviations are used:

*t*Bu *tert.*butyl

dba dibenzylidenacetone

DMF dimethylformamide

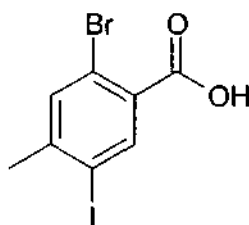
DMSO dimethyl sulfoxide

NMP *N*-methyl-2-pyrrolidone

THF tetrahydrofuran

Preparation of the starting compounds:

Example I



2-Bromo-5-iodo-4-methyl-benzoic acid

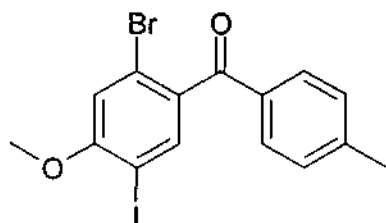
N-Iodosuccinimide (19.1 g) is added in portions to an ice-cold solution of 2-bromo-4-methylbenzoic acid (18.4 g) dissolved in sulphuric acid (20 mL). The resulting mixture is stirred at 5-10 °C for 3 h before warming to room temperature overnight. Then, the mixture is poured on crushed ice and the resultant solution is extracted with ethyl acetate. The combined extracts are washed in succession with aqueous 10% Na₂S₂O₃ solution (2x), water (3x), and brine (1x). After drying (MgSO₄), the organic solvent is evaporated under reduced. The remaining solid is taken up in water and the resulting slurry is stirred at 70 °C for 5 min. The non-dissolving part is separated by filtration and dried to give the desired product.

Yield: 27.2 g (96% of theory)

Mass spectrum (ESI⁺): m/z = 339/341 (Br) [M-H]⁺

The following compound may be obtained analogously to Example I:

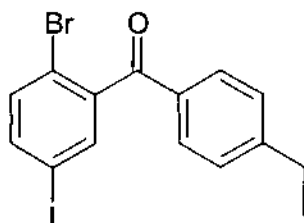
(1) (2-Bromo-5-iodo-4-methoxy-phenyl)-(4-ethyl-phenyl)-methanone



Mass spectrum (ESI⁺): m/z = 445/447 (Br) [M+H]⁺

The starting material, (2-bromo-4-methoxy-phenyl)-(4-ethyl-phenyl)-methanone, is prepared as described under Examples II and III.

Example II



(2-Bromo-5-iodo-phenyl)-(4-ethyl-phenyl)-methanone

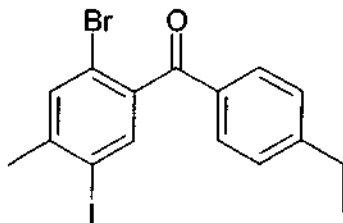
Oxalyl chloride (9.5 mL) is added to a solution of 2-bromo-5-iodo-benzoic acid (25.0 g) in dichloromethane (50 mL). A few drops of DMF are added and the mixture is stirred at room temperature overnight. Then, the reaction solution is concentrated under reduced pressure and the residue is taken up in dichloromethane (50 mL) and ethylbenzene (23 mL). The resulting solution is cooled in an ice-bath and aluminum trichloride (12.5 g) is added in portions. Then, the cooling bath is removed and the reaction mixture is stirred at room temperature for 4 h. After consumption of the intermediate substituted benzoyl chloride, the reaction mixture is poured onto crushed ice and the organic phase is separated off. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed in succession with 1 M hydrochloric acid, 1 M potassium hydroxide solution and brine. The organic phase is dried (sodium sulphate) and the solvent is removed under reduced pressure to give the product as an oil that crystallizes on standing.

Yield: 30.8 g (97% of theory)

Mass spectrum (ESI⁺): m/z = 415/417 (Br) [M+H]⁺

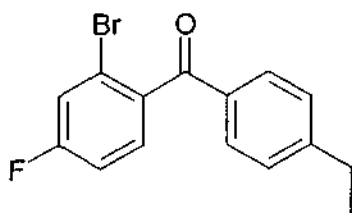
The following compounds may be obtained analogously to Example II:

(1) (2-Bromo-5-iodo-4-methyl-phenyl)-(4-ethyl-phenyl)-methanone



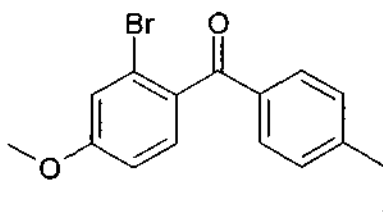
Mass spectrum (ESI⁺): m/z = 429/431 (Br) [M+H]⁺

(2) (2-Bromo-4-fluoro-phenyl)-(4-ethyl-phenyl)-methanone



Mass spectrum (ESI⁺): m/z = 307/309 (Br) [M+H]⁺

Example III



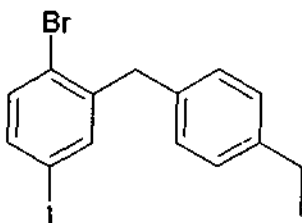
(2-Bromo-4-methoxy-phenyl)-(4-ethyl-phenyl)-methanone

Sodium methoxide (10.5 g) is added portionwise to (2-bromo-4-fluorophenyl)-(4-ethylphenyl)-methanone (43.0 g) dissolved in DMF (200 mL). The solution is stirred overnight, before another portion of sodium methoxide (5.5 g) is added. After another 3 h of stirring, water is added and the resulting mixture is extracted with ethyl acetate. The organic phase is dried (sodium sulphate), the solvent is removed and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 20:1→9:1).

Yield: 33.7 g (75% of theory)

Mass spectrum (ESI⁺): m/z = 319/321 (Br) [M+H]⁺

Example IV



4-Bromo-3-(4-ethyl-benzyl)-1-iodo-benzene

A solution of (2-bromo-5-iodophenyl)-(4-ethylphenyl)-methanone (32 g) and triethylsilane (50 mL) in dichloromethane (30 mL) and acetonitrile (100 mL) is cooled in an ice-bath. Then, boron trifluoride diethyletherate (20 mL) is added dropwise over 5 min. The cooling bath is removed and the solution is heated to 45-50 °C and stirred at this temperature for 4 h. After cooling to ambient temperature, 4 M aqueous KOH solution is added and the resulting mixture is extracted with ethyl acetate. The combined organic phases are washed with 2 M potassium hydroxide solution and brine and then dried (sodium sulphate). After the solvent is

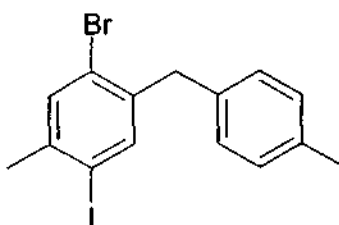
evaporated, the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 1:0->9:1).

Yield: 21 g (68% of theory)

Mass spectrum (ESI⁺): m/z = 418/420 (Br) [M+NH₄]⁺

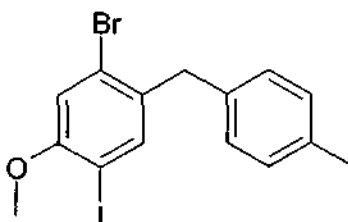
The following compounds may be obtained analogously to Example IV:

(1) 4-Bromo-5-(4-ethyl-benzyl)-1-iodo-2-methyl-benzene



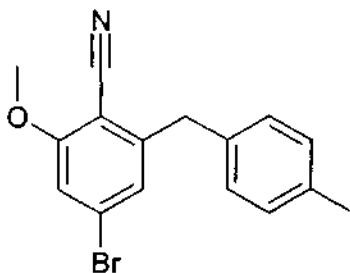
Mass spectrum (ESI⁺): m/z = 432/434 (Br) [M+NH₄]⁺

(2) 4-Bromo-5-(4-ethyl-benzyl)-1-iodo-2-methoxy-benzene



Mass spectrum (ESI⁺): m/z = 448/450 (Br) [M+NH₄]⁺

Example V



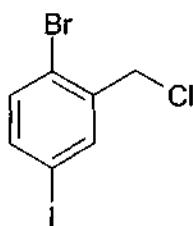
1-Bromo-4-cyano-3-methoxy-5-(4-ethyl-benzyl)-benzene

KOtBu (11.8 g) is added to a flask charged with a stir bar and dry NMP (40 mL) and chilled to -10 °C under argon atmosphere. A solution of ethyl (4-ethyl-phenyl)-acetate (10.1 g) and 1-bromo-4-cyano-3,5-difluoro-benzene (11.5 g) in NMP (40 mL) is added at such a rate that the reaction temperature maintains below 10°C. After stirring for 1 hour at room temperature, methanol (50 mL) and 1 M aqueous sodium hydroxide solution (39 mL) are added and the

resulting mixture is stirred overnight at 100 °C. Then, 4 M aqueous hydrochloric acid (100 mL) is added and the mixture is stirred for another h at 100 °C. The methanol fraction is evaporated, water (200 mL) is added to the residue and the resulting mixture is extracted with ethyl acetate. The combined organic extracts are washed twice with water, twice with brine and dried (MgSO₄). The solvent is evaporated and the residue is washed with methanol. The insoluble residue is separated by filtration and dried to give the white product. Yield: 10.0 g (58% of theory)

Mass spectrum (ESI⁺): m/z = 330/332 (Br) [M+H]⁺

Example VI

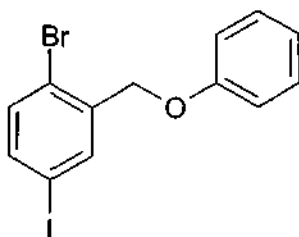


4-Bromo-3-chloromethyl-1-iodo-benzene

Thionyl chloride (13 mL) is added to a suspension of 4-bromo-3-hydroxymethyl-1-iodo-benzene (47.0 g) in dichloromethane (100 mL) containing DMF (0.1 mL). The mixture is stirred at ambient temperature for 3 h. Then, the solvent and the excess reagent is removed under reduced pressure. The residue is triturated with methanol and dried.

Yield: 41.0 g (82% of theory)

Example VII

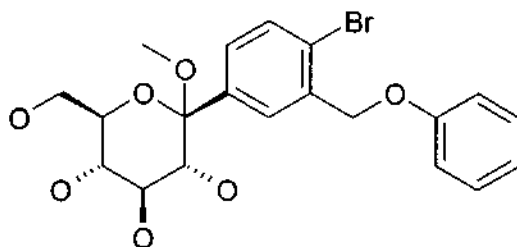


4-Bromo-1-iodo-3-phenoxymethyl-benzene

Phenol (13 g) dissolved in aqueous 4 M KOH solution (60 mL) is added to 4-bromo-3-chloromethyl-1-iodo-benzene (41.0 g) dissolved in acetone (50 mL). NaI (0.5 g) is added and the resulting mixture is stirred at 50 °C overnight. Then, water is added and the resulting mixture is extracted with ethyl acetate. The combined extracts are dried (Na₂SO₄) and the solvent is evaporated under reduced pressure. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 19:1).

Yield: 38.0 g (79% of theory)

Example VIII



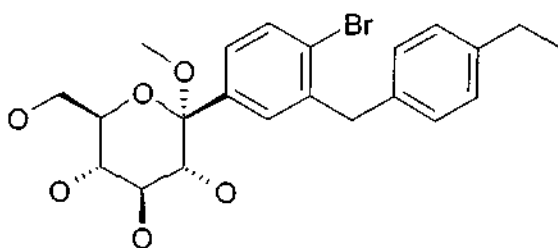
1-Bromo-4-(1-methoxy-D-glucopyranos-1-yl)-2-(phenoxy-methyl)-benzene

A 2 M solution of *i*PrMgCl in THF (11 mL) is added to dry LiCl (0.47 g) suspended in THF (11 mL). The mixture is stirred at room temperature until all the LiCl is dissolved. This solution is added dropwise to a solution of 4-bromo-1-iodo-3-phenoxy-methyl-benzene (8.0 g) in tetrahydrofuran (40 mL) cooled to -60 °C in argon atmosphere. The resulting solution is warmed to -40 °C and then 2,3,4,6-tetrakis-O-(trimethylsilyl)-D-glucopyranone (10.7 g, 90% pure) in tetrahydrofuran (5 mL) is added. The resulting solution is warmed to -5 °C in the cooling bath and stirred for another 30 min at this temperature. Aqueous NH₄Cl solution is added and the resultant mixture is extracted with ethyl acetate. The combined organic extracts are dried over sodium sulphate and the solvent is removed under reduced pressure. The residue is dissolved in methanol (80 mL) and treated with methanesulfonic acid (0.6 mL). After stirring the reaction solution at 35-40 °C overnight, the solution is neutralized with solid NaHCO₃ and the methanol is removed under reduced pressure. The remainder is diluted with aqueous NaHCO₃ solution and the resulting mixture is extracted with ethyl acetate. The combined extracts are dried over sodium sulphate and the solvent is evaporated to yield the crude product that is submitted to reduction without further purification.

Yield: 7.8 g (93% of theory)

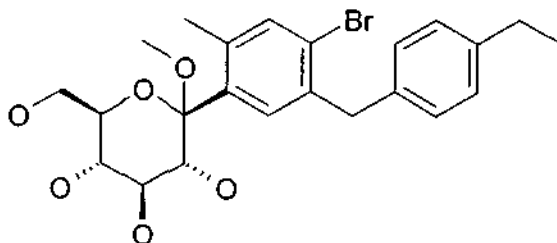
The following compounds may be obtained analogously to Example VIII:

(1) 1-Bromo-2-(4-ethylbenzyl)-4-(1-methoxy-D-glucopyranos-1-yl)-benzene



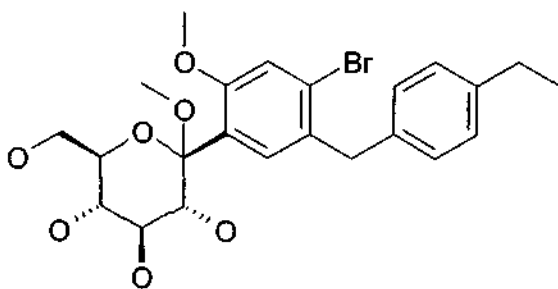
Mass spectrum (ESI⁺): $m/z = 511/513$ (Br) $[M+HCOO]^+$

(2) 1-Bromo-2-(4-ethylbenzyl)-4-(1-methoxy-D-glucopyranos-1-yl)-5-methyl-benzene

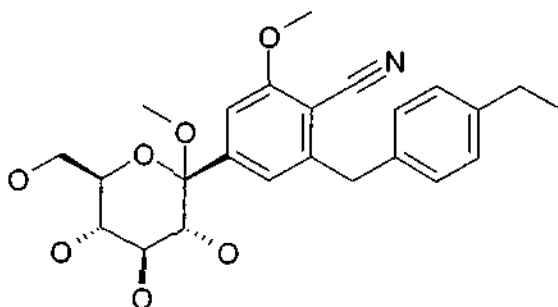


Alternatively, the reaction may be conducted with 2,3,4,6-tetra-O-benzyl-D-glucopyranone instead of 2,3,4,6-tetrakis-O-(trimethylsilyl)-D-glucopyranone to obtain the analogous tetra-O-benzyl protected addition product of this compound. The benzyl groups may be taken off after the reduction of the anomeric center by using BCl_3 in dichloromethane.

(3) 1-Bromo-2-(4-ethylbenzyl)-4-(1-methoxy-D-glucopyranos-1-yl)-5-methoxy-benzene



Example IX



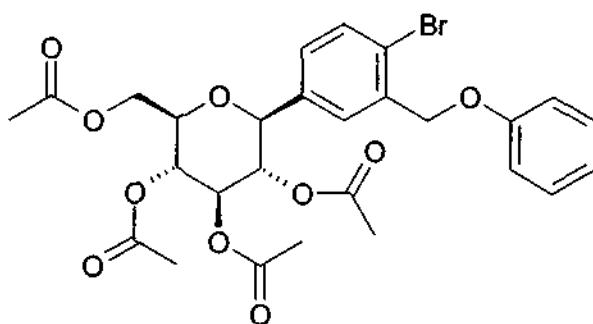
6-(4-Ethylbenzyl)-2-methoxy-4-(1-methoxy-D-glucopyranos-1-yl)-benzonitrile

A 1.7 M solution of *t*BuLi in pentane (18.3 mL) cooled to -78 °C is added dropwise to a solution of 1-bromo-4-cyano-5-(4-ethyl-benzyl)-3-methoxy-benzene (5.0 g) in hexane (40 mL) and THF (20 mL) chilled to -78 °C. *n*BuLi or *s*BuLi instead of *t*BuLi may be used as well. After complete addition and additional 15 min of stirring, a solution of 2,3,4,6-tetrakis-O-(trimethylsilyl)-D-glucopyranone (90%, 7.9 g) in hexane (30 mL) cooled to -78 °C is added via a transfer needle. The resulting solution is stirred at -70 °C for 2 h and then slowly warmed to -5 °C. The reaction is quenched with 1% acetic acid in water (100 mL) and the resulting mixture is extracted with ethyl acetate. The combined organic extracts are washed with brine and dried (sodium sulphate). After removal of the solvent, the residue is dissolved in methanol (50 mL) and treated with methanesulfonic acid (2.5 mL) to produce the desired more stable anomeric linkage. The solution is stirred at 50 °C overnight and then neutralized by the addition of solid NaHCO₃. The solvent is removed under reduced pressure and the residue is taken up in ethyl acetate. The organic solution is washed with water and brine and dried (sodium sulphate). After the removal of the solvent, the crude product is purified by chromatography on silica gel (dichloromethane/methanol 1:0->2:1).

Yield: 0.5 g (7% of theory)

Alternatively, the reaction may be conducted with 2,3,4,6-tetra-O-benzyl-D-glucopyranone instead of 2,3,4,6-tetrakis-O-(trimethylsilyl)-D-glucopyranone to obtain the analogous tetra-O-benzyl protected addition product of this compound. The benzyl groups may be taken off after the reduction of the anomeric center by using BCl₃ in dichloromethane.

Example X



1-Bromo-4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yl)-2-(phenoxy-methyl)-benzene

Boron trifluoride etherate (4.9 mL) is added to a solution of 1-bromo-4-(1-methoxy-D-glucopyranos-1-yl)-2-(phenoxy-methyl)-benzene (8.7 g) and triethylsilane (9.1 mL) in dichloromethane (35 mL) and acetonitrile (50 mL) cooled to -20 °C at such a rate that the temperature maintains below -10 °C. The resultant solution is warmed to 0 °C over a period of 1.5 h and then treated with aqueous sodium hydrogen carbonate solution. The resulting

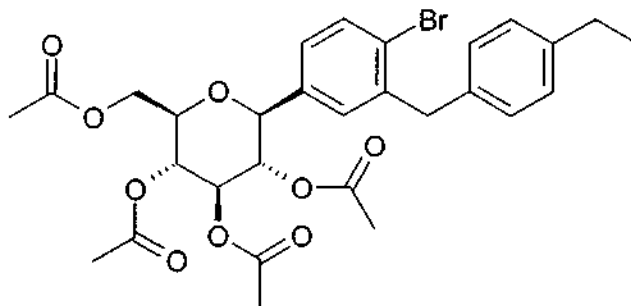
mixture is stirred for 0.5 h, the organic solvent is removed and the residue is extracted with ethyl acetate. The combined organic layers are dried over sodium sulphate and the solvent is removed. The residue is taken up in dichloromethane (50 mL) and pyridine (9.4 mL), acetic anhydride (9.3 mL) and 4-dimethylaminopyridine (0.5 g) are added in succession to the solution. The solution is stirred for 1.5 h at ambient temperature and then diluted with dichloromethane. This solution is washed twice with 1 M hydrochloric acid and dried over sodium sulfate. After the solvent is removed, the residue is recrystallized from ethanol to furnish the product as a colorless solid.

Yield: 6.78 g (60% of theory)

Mass spectrum (ESI⁺): $m/z = 610/612$ (Br) $[M+NH_4]^+$

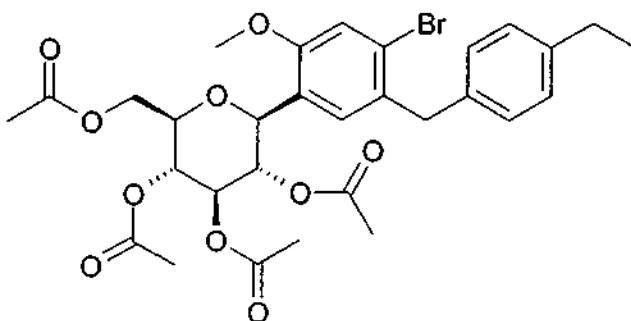
The following compounds may be obtained analogously to Example X:

(1) 1-Bromo-2-(4-ethylbenzyl)-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-benzene



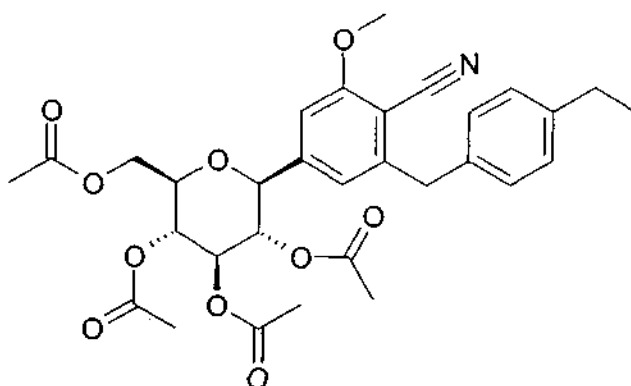
Mass spectrum (ESI⁺): $m/z = 622/624$ $[M+NH_4]^+$

(2) 1-Bromo-2-(4-ethylbenzyl)-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-5-methoxybenzene



Mass spectrum (ESI⁺): $m/z = 652/654$ (Br) $[M+NH_4]^+$

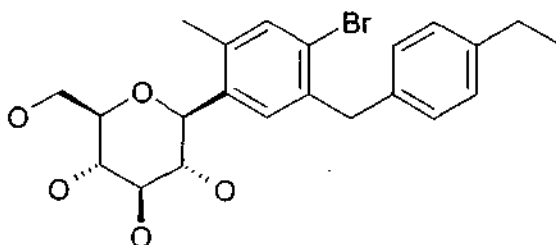
(3) 6-(4-Ethylbenzyl)-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-2-methoxy-benzonitrile



Mass spectrum (ESI⁺): $m/z = 599$ $[M+NH_4]^+$

The reduction is conducted on 6-(4-ethylbenzyl)-4-(1-methoxy-D-glucopyranos-1-yl)-2-methoxy-benzonitrile in analogy to the procedure described above.

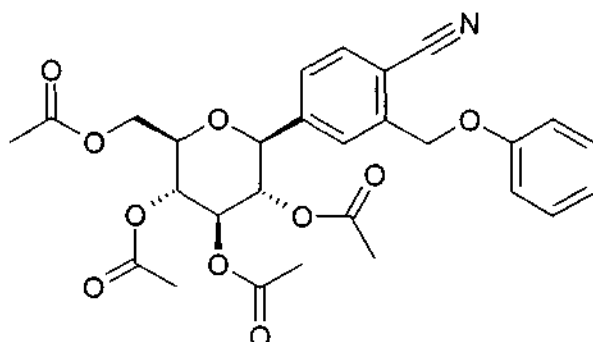
(4) 1-Bromo-2-(4-ethylbenzyl)-4-(β -D-glucopyranos-1-yl)-5-methyl-benzene



Mass spectrum (ESI⁺): $m/z = 468/470$ (Br) $[M+NH_4]^+$

This compound is isolated with the free hydroxyl groups after the reduction according to the procedure described above is finished.

Example XI



2-(Phenoxymethyl)-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-benzonitrile

A flask charged with a stir bar, 1-bromo-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-2-(phenoxymethyl)-benzene (5.4 g), zinc cyanide (1.0 g), zinc (30 mg), $Pd_2(dibenzylideneacetone)_3 \cdot CHCl_3$ (141 mg) and tri-*tert*-butylphosphonium tetrafluoroborate (111 mg) is flushed with argon. Then degassed NMP (12 mL) containing 0.1% water is

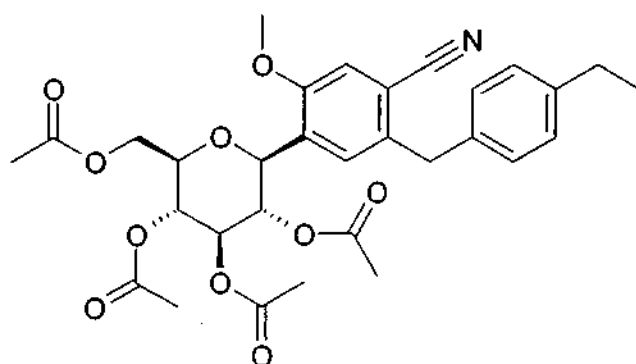
added (alternatively, the glucoside dissolved in NMP is added) and the resulting mixture is stirred at room temperature for 18 h. After dilution with ethyl acetate, the mixture is filtered and the filtrate is washed with aqueous sodium hydrogen carbonate solution. The organic phase is dried (sodium sulphate) and the solvent is removed. The residue is recrystallized from ethanol.

Yield: 4.10 g (84% of theory)

Mass spectrum (ESI⁺): $m/z = 557$ [M+NH₄]⁺

Alternatively, the compound may also be obtained employing the procedures described under Examples XII and 3

Example XII



2-(4-Ethylbenzyl)-5-methoxy-4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yl)-benzonitrile

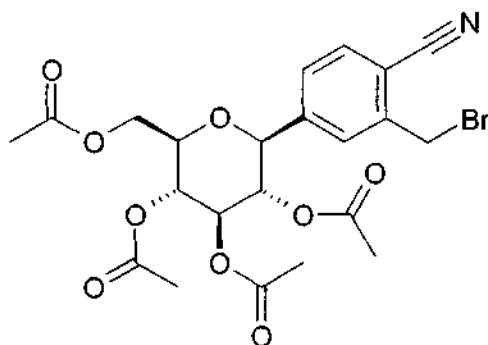
A flask charged with a stir bar, 1-bromo-2-(4-ethylbenzyl)-5-methoxy-4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yl)-benzene (1.6 g), copper(I) cyanide (0.56 g) and NMP (10 mL) is stirred at 215 °C for 3 h. Then, water is added and the precipitate is separated by filtration. The precipitate is dissolved in ethyl acetate (50 mL) and filtered over Celite. The filtrate is dried (Na₂SO₄) and concentrated. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 2:1->1:2).

Yield: 1.1 g (75% of theory)

Mass spectrum (ESI⁺): $m/z = 583$ [M+NH₄]⁺

This compound can also be prepared using the procedures described for Examples XI and 3.

Example XIII



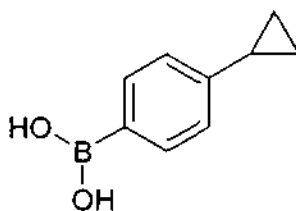
2-Bromomethyl-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-benzonitrile

A 33% solution of hydrobromic acid in acetic acid (15 mL) is added to a solution of 2-phenyloxymethyl-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-benzonitrile (0.71 g) and acetic anhydride (0.12 mL) in acetic acid (10 mL). The resulting solution is stirred at 55 °C for 6 h and then cooled in an ice-bath. The reaction mixture is neutralized with chilled aqueous potassium carbonate solution, and the resultant mixture is extracted with ethyl acetate. The combined organic extracts are dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is taken up in ethyl acetate/cyclohexane (1:5), and the precipitate is separated by filtration and dried at 50 °C to give the product.

Yield: 0.52 g (75% of theory)

Mass spectrum (ESI⁺): m/z = 543/545 (Br) $[M+NH_4]^+$

Example XIV



4-Cyclopropyl-phenylboronic acid

2.5 M *n*Butyllithium in hexane (14.5 mL) is added dropwise to a solution of 1-bromo-4-cyclopropyl-benzene (5.92 g) in THF (14 mL) and toluene (50 mL) chilled to -70 °C. The resultant solution is stirred at -70 °C for 30 min before triisopropyl borate (8.5 mL) is added. The solution is warmed to -20 °C and then treated with 4 M aqueous hydrochloric acid (15.5 mL). The reaction mixture is further warmed to room temperature and then the organic phase is separated. The aqueous phase is extracted with ethyl acetate and the combined organic

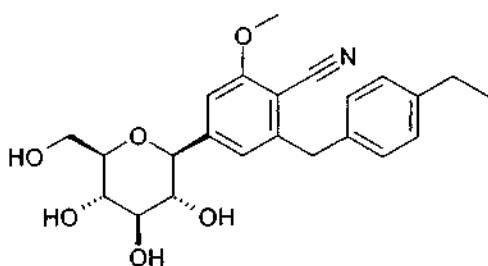
phases are dried (sodium sulphate). The solvent is evaporated and the residue is triturated with a mixture of ether and cyclohexane to give the product as a colorless solid.

Yield: 2.92 g (60% of theory)

Mass spectrum (ESI⁻): $m/z = 207$ (Cl) [M+HCOO]⁻

Preparation of the end compounds:

Example (1): 6-(4-Ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-2-methoxy-benzonitrile



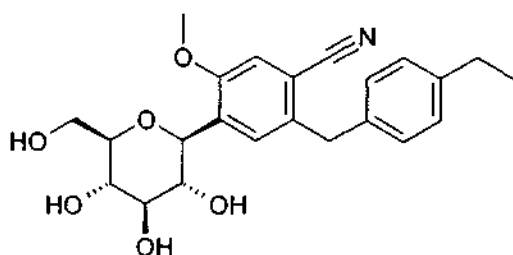
Aqueous sodium hydroxide solution (1.4 mL, 1 mol/L) is added to 6-(4-ethylbenzyl)-4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yl)-2-methoxy-benzonitrile (0.16 g) dissolved in methanol (1 mL) and THF (1 mL). The solution is stirred at room temperature for 1 h and then neutralized with hydrochloric acid (1 mol/L). After removal of the organic solvents, the residue is diluted with aqueous sodium bicarbonate solution and the resulting mixture is extracted with ethyl acetate. The combined organic extracts are dried (sodium sulphate) and the solvent is evaporated. The remainder is purified by chromatography on silica gel (dichloromethane/methanol 1:0→8:1).

Yield: 65 mg (57% of theory)

Mass spectrum (ESI⁺): $m/z = 431$ [M+NH₄]⁺

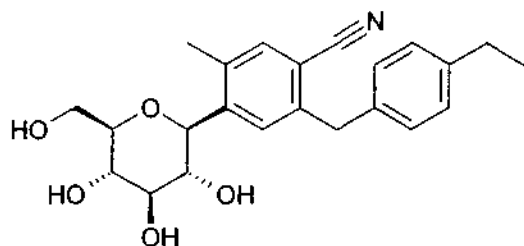
The following compound is obtained analogously to Example 1:

Example (2): 2-(4-Ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methoxy-benzonitrile



Mass spectrum (ESI⁺): $m/z = 431$ [M+NH₄]⁺

Example (3): 1-Cyano-2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methyl-benzene

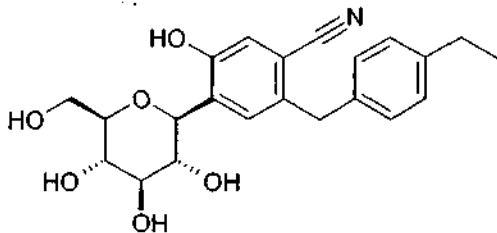


A microwave oven-suited vessel charged with a stir bar, 1-bromo-2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methyl-benzene (0.40 g), Ni(CN)₂ (0.10 g) and NMP (4 mL) and flushed with argon is heated in a microwave oven at 220 °C for 1 h. Then, water is added and the resulting mixture is extracted with ethyl acetate. The combined organic extracts are dried (sodium sulphate) and the solvent is evaporated. The remainder is purified by HPLC on reversed phase (YMC C18, acetonitrile/water).

Yield: 0.30 g (85% of theory)

Mass spectrum (ESI⁺): m/z = 415 [M+NH₄]⁺

Example (4): 2-(4-Ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-hydroxy-benzonitrile

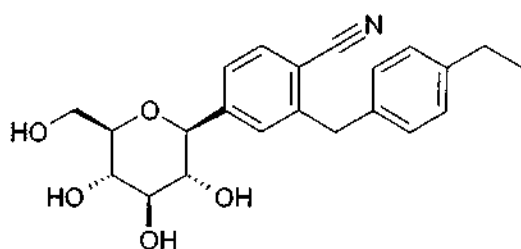


A mixture of 2-(4-ethylbenzyl)-5-methoxy-4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yl)-benzonitrile (0.80 g) and pyridinium hydrochloride (9.0 g) is heated at 215 °C for 1 h. After cooling to ambient temperature, water is added and the resulting solution is extracted with ethyl acetate. The combined organic extracts are dried (MgSO₄) and the solvent is removed under reduced pressure. The residue is dissolved in methanol (10 mL) and treated with 4 M aqueous NaOH solution (2.2 mL). The solution is stirred at room temperature for 1 h and then acidified using hydrochloric acid (4 mol/L). After removal of the organic solvents, the residue is extracted with ethyl acetate, the combined organic extracts are dried (sodium sulphate) and the solvent is evaporated. The remainder is purified by HPLC on reversed phase (YMC C18, acetonitrile/water).

Yield: 0.25 g (46 % of theory)

Mass spectrum (ESI⁻): m/z = 398 [M-H]⁻

Example (5): 2-(4-Ethyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzonitrile

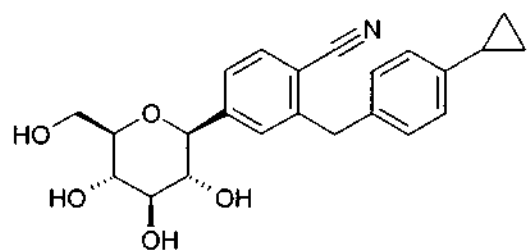


A flask is charged with a stir bar, zinc (10 mg), zinc cyanide (0.12 g), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (42 mg) and tri-*tert*-butylphosphonium tetrafluoroborate (26 mg) and put under Ar atmosphere. Then, 1-bromo-2-(4-ethylbenzyl)-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-benzene (1.0 g) dissolved in degassed NMP containing 0.1% water (2 mL) is added and the mixture is stirred at room temperature for 18 h. Then, ethyl acetate is added, the resulting mixture is filtered and the filtrate is washed with aqueous NaHCO_3 solution. After drying (sodium sulphate) of the organic solution, the solvent is removed under reduced pressure and the residue is dissolved in methanol (10 mL). 4 M aqueous potassium hydroxide solution (2 mL) is added and the solution is stirred at ambient temperature for 1 h. The solution is neutralized with 1 M hydrochloric acid and the methanol is evaporated. The residue is extracted with ethyl acetate, the combined extracts are dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by chromatography on silica gel (dichloromethane/methanol 1:0 \rightarrow 4:1).

Yield: 0.51 g (81% of theory)

Mass spectrum (ESI⁺): $m/z = 401$ $[\text{M} + \text{NH}_4]^+$

Example (6): 2-(4-Cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzonitrile



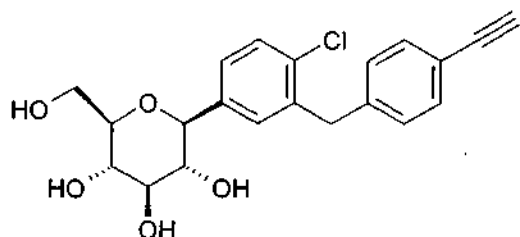
An Ar filled flask is charged with a stir bar, 2-bromomethyl-4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-yl)-benzonitrile (1.78 g), 4-cyclopropyl-phenylboronic acid (1.00 g), potassium carbonate (1.85 g) and a 3:1 mixture of degassed acetone and water (22 mL). The mixture is stirred at room temperature for 5 min, before it is cooled in an ice-bath. Then palladium dichloride (30 mg) is added and the reaction mixture is stirred for 16 h at ambient temperature. The mixture is then diluted with brine and extracted with ethyl acetate. The combined extracts are dried over sodium sulfate and the solvent is removed under reduced

pressure. The residue is dissolved in methanol (20 mL) and treated with 4 M aqueous potassium hydroxide solution (3.8 mL). The resulting solution is stirred at ambient temperature for 1 h and then neutralized with 1 M hydrochloric acid. The methanol is evaporated, and the residue is diluted with brine and extracted with ethyl acetate. The organic extracts collected are dried over sodium sulfate, and the solvent is removed. The residue is chromatographed on silica gel (dichloromethane/methanol 1:0 → 8:1).

Yield: 0.91 g (76% of theory)

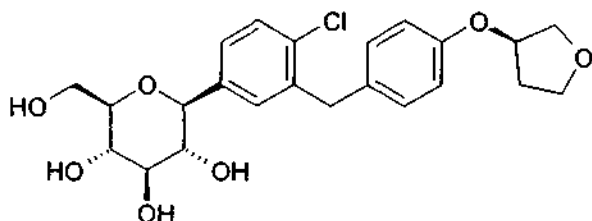
Mass spectrum (ESI⁺): $m/z = 413$ [M+NH₄]⁺

Example (7): 1-chloro-4-(β-D-glucopyranos-1-yl)-2-(4-ethynyl-benzyl)-benzene



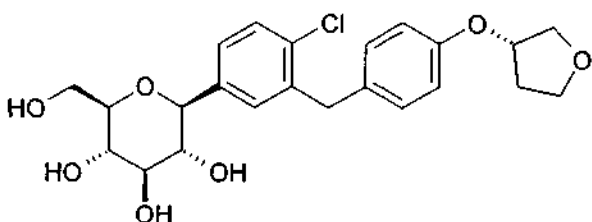
The compound (7) can advantageously be prepared according to the example 12 described in the WO 2005/092877.

Example (8): 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((R)-tetrahydrofuran-3-yloxy)-benzyl]-benzene



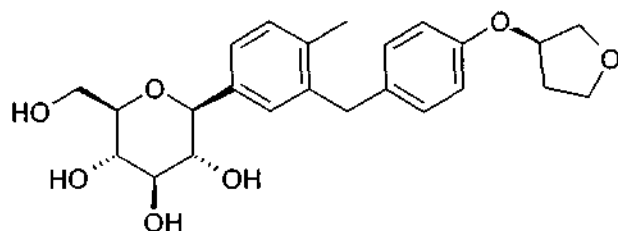
The compound (8) can advantageously be prepared according to the example 2 described in the WO 2005/092877.

Example (9): 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene



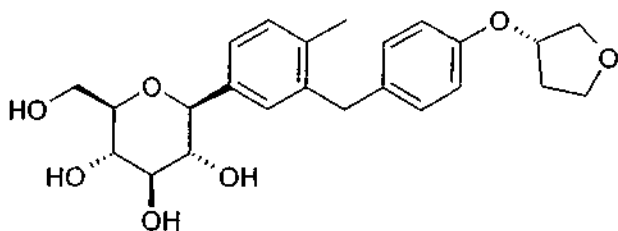
The compound (9) can advantageously be prepared according to the example 3 described in the WO 2005/092877.

Example (10): 1-methyl-2-[4-((*R*)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β -D-glucopyranos-1-yl)-benzene



The compound (10) can advantageously be prepared according to the example 2 described in the WO 2006/064033.

Example (11): 1-methyl-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β -D-glucopyranos-1-yl)-benzene



The compound (10) can advantageously be prepared according to the example 3 described in the WO 2006/064033.

Pharmacological Examples

The following examples show the beneficial effect on glycemic control of the combination of a glucopyranosyl-substituted benzene derivative and a DPP IV inhibitor according to the present invention as compared to the respective monotherapies. All experimental protocols concerning the use of laboratory animals are reviewed by a federal Ethics Committee and approved by governmental authorities.

1st Example:

According to a first example an oral glucose tolerance test is performed in overnight fasted 9-weeks old male Zucker Diabetic Fatty (ZDF) rats (ZDF/Cri-Lepr^{fa}). A pre-dose blood sample is obtained by tail bleed. Blood glucose is measured with a glucometer, and the animals are randomized for blood glucose (n = 5 / group). Subsequently, the groups receive a single oral administration of either vehicle alone (0.5% aqueous hydroxyethylcellulose containing 3 mM HCl and 0.015% Polysorbat 80) or vehicle containing either the glucopyranosyl-substituted benzene derivative or the DPP IV inhibitor or the combination of the glucopyranosyl-substituted benzene derivative with the DPP IV inhibitor. The animals receive an oral glucose load (2 g/kg) 30 min after compound administration. Blood glucose is measured in tail blood 30 min, 60 min, 90 min, 120 min, and 180 min after the glucose challenge. Glucose excursion is quantified by calculating the reactive glucose AUC. The data are presented as mean \pm SEM. The two-sided unpaired Student t-test is used for statistical comparison of the control group and the active groups.

The result is shown in Figure 1. "Cpd. A" is the DPP IV inhibitor 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine at a dose of 1 mg/kg. Cpd. B is the glucopyranosyl-substituted benzene derivative (9), i.e. 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, at a dose of 3 mg/kg. Combination A + B is the combination of said DPP IV inhibitor and said glucopyranosyl-substituted benzene derivative at the same doses. P-values versus control are indicated by symbols above the bars. P-values of the combination versus the monotherapies are indicated below the figure (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$). The DPP IV inhibitor reduces glucose excursion by 56%, the glucopyranosyl-substituted benzene derivative reduces glucose excursion by 51%. The combination decreased glucose excursion in the oral glucose tolerance test by 84%, and this reduction in glucose AUC is statistically significant versus each monotherapy.

2nd Example:

According to a second example an oral glucose tolerance test is performed in overnight fasted male Sprague Dawley rats (CrI:CD(SD)) with a body weight of about 200 g. A pre-dose blood sample is obtained by tail bleed. Blood glucose is measured with a glucometer, and the animals are randomized for blood glucose ($n = 5$ / group). Subsequently, the groups receive a single oral administration of either vehicle alone (0.5% aqueous hydroxyethylcellulose containing 0.015% Polysorbat 80) or vehicle containing either the glucopyranosyl-substituted benzene derivative or the DPPIV inhibitor or the combination of the glucopyranosyl-substituted benzene derivative with the DPPIV inhibitor. The animals receive an oral glucose load (2 g/kg) 30 min after compound administration. Blood glucose is measured in tail blood 30 min, 60 min, 90 min, and 120 min after the glucose challenge. Glucose excursion is quantified by calculating the reactive glucose AUC. The data are presented as mean \pm S.E.M. Statistical comparisons are conducted by Student's *t* test.

The result is shown in Figure 2. "Cpd. A" is the glucopyranosyl-substituted benzene derivative (9), i.e. 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, administered at a dose of 3 mg/kg. The DPPIV inhibitor saxagliptin is administered at a dose of 0.3 mg/kg. In the combination, the glucopyranosyl-substituted benzene derivative and saxagliptin are administered together at the same doses as in the respective monotherapies. *P* values versus control are indicated by symbols above the bars. (*, $p < 0.05$). The glucopyranosyl-substituted benzene derivative and saxagliptin reduces glucose excursion by 21% and 12%, respectively, albeit the reduction is not statistically significant in these non-diabetic animals. The combination decreases glucose excursion in the oral glucose tolerance test by 50%, and this reduction in glucose AUC is statistically significant.

3rd Example:

In a third example the same experimental setting is employed as in the second example as described herein before. The glucopyranosyl-substituted benzene derivative (9), i.e. 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, is administered at a dose of 3 mg/kg. The DPPIV inhibitor sitagliptin is administered at a dose of 10 mg/kg. In the combination, the glucopyranosyl-substituted benzene derivative and sitagliptin are administered together at the same doses as in the respective monotherapies. The result is shown in the Figure 3 wherein "Cpd. A" is said glucopyranosyl-substituted benzene derivative (9). *P* values versus control are indicated by symbols above the bars. (*, $p < 0.05$). The glucopyranosyl-substituted benzene derivative and sitagliptin reduces glucose

excursion by 21% and 16%, respectively, albeit the reduction is not statistically significant in these non-diabetic animals. The combination decreases glucose excursion in the oral glucose tolerance test by 51%, and this reduction in glucose AUC is statistically significant.

Examples of Formulations

The following examples of formulations, which may be obtained analogously to methods known in the art, serve to illustrate the present invention more fully without restricting it to the contents of these examples. The term "active substance" denotes one or more compounds according to the invention, i.e. denotes a glucopyranosyl-substituted benzene derivative according to this invention or a DPP IV inhibitor according to this invention or a combination of said glucopyranosyl-substituted benzene derivative with said DPP IV inhibitor, for example selected from the combinations 1 to 176 as listed in Table 1. Additional suitable formulations for the DPP IV inhibitors of embodiment **A** may be those formulations disclosed in the application WO 2007/128724, the disclosure of which is incorporated herein in its entirety. Additional suitable formulations for the DPP IV inhibitors of embodiment **B** may be those formulations which are available on the market, or formulations described in the patent applications cited above in paragraph "background of the invention", or those described in the literature, for example as disclosed in current issues of "Rote Liste[®]" (Editio Cantor Verlag Aulendorf, Germany) or of "Physician's Desk Reference".

Example 1: Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 2: Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 3: Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	<u>2.0 mg</u>
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 9 mm.

Example 4: Tablet containing 350 mg of active substance

Preparation:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	<u>4.0 mg</u>
	600.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 12 mm.

Example 5: Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	<u>2.0 mg</u>
	160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing. This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

Example 6: Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	<u>4.0 mg</u>
	430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing. This powder mixture is packed into size 0 hard gelatin capsules in a capsule filling machine.

Exhibit B**Claim Mapping****1**

Title - PHARMACEUTICAL COMPOSITION COMPRISING A GLUCOPYRANOSYL-SUBSTITUTED BENZENE DERIVATIVE

Application number/Patent Number – 1006/DELNP/2010

Applicant Name –BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Priority date –16/08/2007

Status- Application in Amended stage

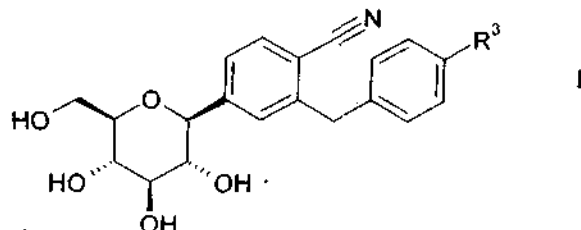
Filing Country : India

Invention disclosure	Relevant text	Image/Illustration
Key feature 1- LINAGLIPTIN	Claim 1: A Pharmaceutical composition comprising the glucopyranosyl substituted benzene derivative 1-chloro-4(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]benzene in combination with the DPP Iv inhibitor 1-[(4-methyl-quinazolin-2-yl)methyl]3-methyl-7-(2-butyne-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine or a pharmaceutically acceptable salt thereof wherein the amount of the glucopyranosyl-substituted benzene derivative is from 5mg to 50 mg , and wherein the amount of DppIV inhibitor is from	No figure

	<p>0.5 mg to 10mg.</p> <p>The common name of 1-[(4-methyl-quinazolin-2-yl)methyl]3-methyl-7-(2-butyln-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine is linagliptin.</p> <p>Composition of linagliptin:</p> <p>Claim 1: the amount of DppIV inhibitor is from 0.5 mg to 10mg.</p>	
--	--	--

Claims

1. Glucopyranosyl-substituted benzonitrile derivative of formula I



wherein

R³ denotes hydrogen, fluorine, chlorine, bromine, iodine, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, 3-methyl-but-1-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 2-hydroxyl-ethyl, hydroxymethyl, 3-hydroxy-propyl, 2-hydroxy-2-methyl-prop-1-yl, 3-hydroxy-3-methyl-but-1-yl, 1-hydroxy-1-methyl-ethyl, 2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl, 2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl, 2-methoxy-ethyl, 2-ethoxy-ethyl, hydroxy, methyloxy, ethyloxy, isopropoxy, difluoromethyloxy, trifluoromethyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, (S)-tetrahydrofuran-3-yloxy, (R)-tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 1-acetyl-piperidin-4-yloxy, 2-methyloxy-ethyloxy, methylsulfanyl, methylsulfinyl, methylsulfonyl, ethylsulfinyl, ethylsulfonyl, trimethylsilyl and cyano,

or a derivative thereof wherein one or more hydroxyl groups of the β -D-glucopyranosyl group are acylated with groups selected from (C₁₋₁₈-alkyl)carbonyl, (C₁₋₁₈-alkyl)oxycarbonyl, phenylcarbonyl and phenyl-(C₁₋₃-alkyl)-carbonyl;

including tautomers, stereoisomers thereof or mixtures thereof; and physiologically acceptable salts thereof.

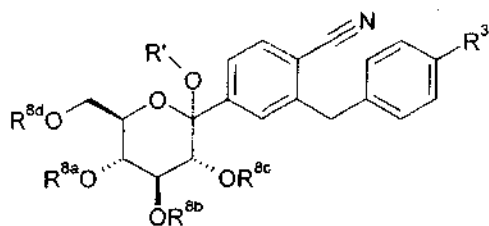
2. Glucopyranosyl-substituted benzonitrile derivative according to claim 1 characterized in that the hydrogen atom of the hydroxyl group O-6 of the β -D-glucopyranosyl-group is replaced by a group selected from among (C₁₋₈-alkyl)carbonyl, (C₁₋₈-alkyl)oxycarbonyl and phenylcarbonyl, or a physiologically

acceptable salt thereof.

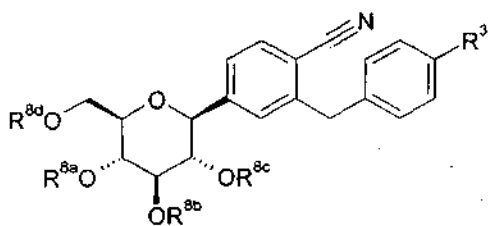
3. Physiologically acceptable salts of the compounds according to claim 1 or 2 with inorganic or organic acids.
4. Pharmaceutical composition, comprising a compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3, optionally together with one or more inert carriers and/or diluents.
5. Use of at least one compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3 for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions which can be influenced by inhibiting the sodium-dependent glucose cotransporter SGLT.
6. Use of at least one compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3 for preparing a pharmaceutical composition which is suitable for the treatment or prevention of one or more metabolic disorders.
7. Use according to claim 6, characterised in that the metabolic disorder is selected from the group consisting of type 1 and type 2 diabetes mellitus, complications of diabetes, metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia.
8. Use of at least one compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3 for preparing a pharmaceutical composition for inhibiting the sodium-dependent glucose cotransporter SGLT2.
9. Use of at least one compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3 for preparing a pharmaceutical composition for preventing the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells.
10. Use of at least one compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3 for preparing a pharmaceutical composition for

preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat in a patient in need thereof.

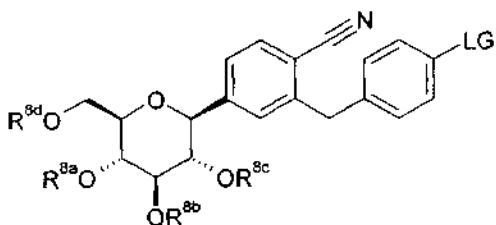
11. Use of at least one compound according to claim 1 or 2 or a physiologically acceptable salt according to claim 3 for preparing diuretics and/or antihypertensives.
12. Glucopyranosyl-substituted benzonitrile derivative of formula II, III, i.1, i.2, i.3, i.4, i.5 or i.6



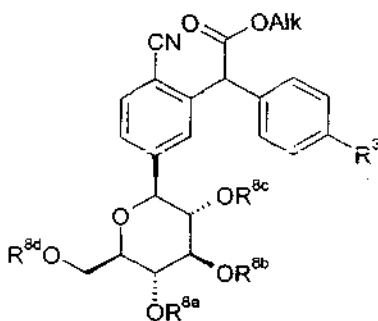
II



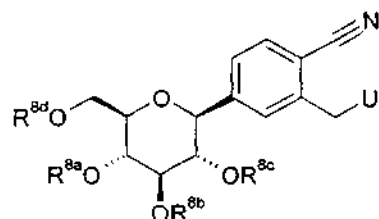
III



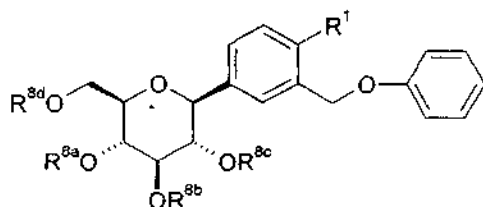
i.1



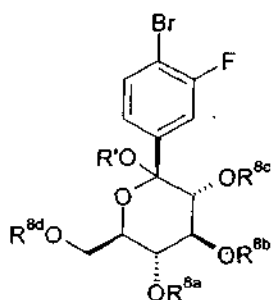
i.2



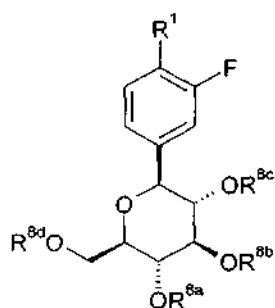
i.3



i.4



i.5



i.6

wherein

R^3 is defined as in claim 1 and

R' denotes H, C_{1-4} -alkyl, $(C_{1-18}$ -alkyl)carbonyl, $(C_{1-18}$ -alkyl)oxycarbonyl, arylcarbonyl or aryl- $(C_{1-3}$ -alkyl)-carbonyl, wherein the alkyl or aryl groups may be mono- or polysubstituted by halogen;

R^{8a} , R^{8b} , R^{8c} , R^{8d} independently of one another denote hydrogen or an allyl group, a benzyl group, a $(C_{1-4}$ -alkyl)carbonyl, $(C_{1-4}$ -alkyl)oxycarbonyl, arylcarbonyl, aryl- $(C_{1-3}$ -alkyl)-carbonyl and aryl- $(C_{1-3}$ -alkyl)-oxycarbonyl or a $R^aR^bR^cSi$ group or a ketal or

acetal group, particularly an alkylidene or arylalkylidene ketal or acetal group, while in each case two adjacent groups R^{8a} , R^{8b} , R^{8c} , R^{8d} may form a cyclic ketal or acetal group or a 1,2-di(C_{1-3} -alkoxy)-1,2-di(C_{1-3} -alkyl)-ethylene bridge, while the above-mentioned ethylene bridge forms, together with two oxygen atoms and the two associated carbon atoms of the pyranose ring, a substituted dioxane ring, particularly a 2,3-dimethyl-2,3-di(C_{1-3} -alkoxy)-1,4-dioxane ring, and while alkyl, allyl, aryl and/or benzyl groups may be mono- or polysubstituted by halogen or C_{1-3} -alkoxy, and while benzyl groups may also be substituted by a di-(C_{1-3} -alkyl)amino group; and

R^a , R^b , R^c independently of one another denote C_{1-4} -alkyl, aryl or aryl- C_{1-3} -alkyl, wherein the aryl or alkyl groups may be mono- or polysubstituted by halogen;

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, preferably phenyl groups; and

Alk denotes C_{1-4} -alkyl; and


R^1 denotes chlorine, bromine, cyano, carboxy, carboxylic ester, carboxamide or a derivative thereof, a boron or silyl group, a protected or masked aldehyde group, or a protected or masked amino group, preferably R^1 denotes Br or CN; and

LG denotes a leaving group such as Br, I or $-O-(SO_2)-CF_3$; and

U denotes Cl, Br, I, $-O-CO-C_{1-4}$ -alkyl, $-O-C(=O)-O-C_{1-4}$ -alkyl or $-OPO(O-C_{1-4}-alkyl)_2$;

including tautomers, stereoisomers thereof or mixtures thereof; and physiologically acceptable salts thereof.

Dated this 14/7/2008


 [HRISHIKESH RAY CHAUDHURY]
 OF REMFRY & SAGAR
 ATTORNEY FOR THE APPLICANTS

WE CLAIM

1. A pharmaceutical composition, preferably for oral use, comprising as an active ingredient a DPP IV inhibitor compound with an amino group which is
 - 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine,

or a salt thereof,

a first diluent which is mannitol, a second diluent which is pregelatinized starch, a binder which is copovidone, a disintegrant which is corn starch, and a lubricant which is magnesium stearate,

wherein the DPP IV inhibitor is present in an amount of 0.5 mg to 10 mg.
2. ~~The pharmaceutical composition of claim 1 comprising an additional disintegrant.~~
3. ~~The pharmaceutical composition of claims 1 or 2 comprising an additional glidant.~~
4. ~~The pharmaceutical composition of claim 1, wherein the diluent is cellulose powder, dibasic calciumphosphate anhydrous, dibasic calciumphosphate dihydrate, erythritol, low substituted hydroxypropyl cellulose, mannitol, pregelatinized starch or xylitol,~~
5. ~~The pharmaceutical composition of claim 1, wherein the lubricant is tale, polyethyleneglycol, calcium behenate, calcium stearate, hydrogenated castor oil or Magnesium stearate.~~
6. ~~The pharmaceutical composition of claim 2, wherein the binder is copovidone (copolymerisates of vinylpyrrolidon with other vinylderivates), hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) or polyvinylpyrrolidon (Povidone).~~
7. ~~The pharmaceutical composition of claim 1, wherein the disintegrant is corn starch.~~

Formatted: Bullets and Numbering

Formatted: Indent: First line: 0 cm

8. ~~The pharmaceutical composition of claim 2, wherein the additional disintegrant is croscopolvidone.~~
9. ~~The pharmaceutical composition of claim 1, wherein the optional glidant is colloidal silicon dioxide.~~
10. ~~The pharmaceutical composition of claim 1 wherein the first diluent is mannitol, the second diluent is pregelatinized starch, the binder is copovidone, the disintegrant is corn starch, and the lubricant is magnesium stearate.~~

2. The pharmaceutical composition as claimed in claim 1, wherein the DPP IV inhibitor compound is present in an amount 0.5-7% based on the total weight of DPP IV inhibitor compound, first diluent, second diluent, binder, disintegrant and lubricant.

113. The pharmaceutical composition as claimed in ~~of~~ claim 1 or 2 comprising
- | | |
|----------|--------------------|
| 0.5-20 % | active ingredient, |
| 40-88 % | diluent 1, |
| 3-40 % | diluent 2, |
| 1-5 % | binder, |
| 5-15 % | disintegrant, and |
| 0.1-4 % | lubricant |

Formatted: Indent: Left: 0 cm, First line: 0 cm

124. The pharmaceutical composition as claimed in ~~of~~ claim 1 or 2 comprising
- | | |
|---------|--------------------|
| 0.5-7 % | active ingredient, |
| 50-75 % | diluent 1, |
| 5-15 % | diluent 2, |
| 2-4 % | binder, |
| 8-12 % | disintegrant, and |
| 0.5-2 % | lubricant |

135. A pharmaceutical composition as claimed in ~~according to~~ claim 1 or 2 in the dosage form of a capsule, a tablet or a film-coated tablet.

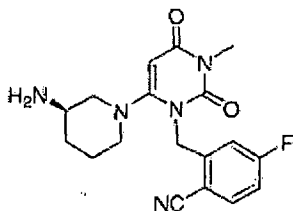
146. The pharmaceutical composition as claimed in ~~of claim 13-5~~ comprising 2-4 % film coat.
157. The pharmaceutical composition as claimed in ~~of claim 16~~ wherein the film coat comprises a film-forming agent, a plasticizer, a glidant and optionally one or more pigments.
168. The pharmaceutical composition as claimed in ~~of claim 15-7~~ wherein the film coat comprises hydroxypropylmethylcellulose (HPMC), -polyethylene glycol (PEG), talc, titanium dioxide and iron oxide.
179. A process for the preparation of a pharmaceutical composition as claimed in ~~according to claim 1 or 2~~ comprising
- dissolving thea binder in a solvent to produce a granulation liquid;
 - blending thea DPP-IV inhibitor, ~~a~~ the diluents, and ~~a~~ the disintegrant to produce a pre-mix;
 - moistening the pre-mix with the granulation liquid and subsequently granulating the moistened pre-mix;
 - optionally sieving the granulated pre-mix through a sieve with a mesh size of at least 1.0 mm;
 - drying the granulate at about 40-75°C until the desired loss on drying value in the range of 1-5 % is obtained;
 - sieving ~~the~~ dried granulate through a sieve with a mesh size of at least 0.6 mm;
 - adding the lubricant to the granulate for final blending.
1810. The process as claimed in ~~according to claim 17-9~~ further comprising
- compressing the final blend into tablet cores;
 - preparing a coating suspension;
 - coating the tablet cores with the coating suspension to a weight gain of about 2-4 % to produce film-coated tablets.
1911. The process as claimed in ~~according to claim 179~~, wherein part of the excipients are added extragranular prior to the final blending of step g.

2012. The process as claimed in ~~according to claim 179~~, wherein the granulate produced in steps a-e is produced in a one pot high shear granulation process and subsequent drying in a one pot granulator.
13. The pharmaceutical composition as claimed in any one of claims 1 to 8, wherein 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine is present in an amount of 0.5 mg, 1 mg, 2.5 mg, 5 mg or 10 mg.
14. The process as claimed in any one of claims 9 to 12, wherein 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine is present in an amount of 0.5 mg, 1 mg, 2.5 mg, 5 mg or 10 mg.
15. A pharmaceutical oral dosage form comprising
1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine in an amount 5 mg,
a first diluent which is mannitol, a second diluent which is pregelatinized starch, a binder which is copovidone, a disintegrant which is corn starch, and a lubricant which is magnesium stearate.
16. The pharmaceutical oral dosage form as claimed in claim 15, which is a tablet.
17. The pharmaceutical oral dosage form as claimed in claim 15, which is a film-coated tablet.
18. The pharmaceutical oral dosage form as claimed in claim 17 comprising 2-4 % film coat, wherein the film coat comprises a film-forming agent, a plasticizer, a glidant and optionally one or more pigments.
19. The pharmaceutical oral dosage form as claimed in claim 18 wherein the film coat comprises hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), talc, titanium dioxide and iron oxide.

Formatted: Indent: Left: 0 cm,
Hanging: 1.25 cm

WE CLAIM :

1. A pharmaceutical composition formulated in a single dose form wherein such single dose form comprises between 1 mg and 250 mg of Compound I, as a free base thereof or a pharmaceutically acceptable salt thereof, wherein Compound I has the formula



2. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises between 5 mg and 200 mg of Compound I.

3. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises between 5 mg and 150 mg of Compound I.

4. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises between 15 mg and 100 mg of Compound I.

5. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 5mg of Compound I.

6. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 6.25mg of Compound I.

7. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 10mg of Compound I.
8. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 20mg of Compound I.
9. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 25 mg of Compound I.
10. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 50 mg of Compound I.
11. A pharmaceutical composition as claimed in claim 1, wherein such single dose form comprises 100 mg of Compound I.
12. A pharmaceutical composition as claimed in any one of claims 1-11, wherein Compound I is present in the pharmaceutical composition as a free base.
13. A pharmaceutical composition as claimed in any one of claims 1-11, wherein Compound I is present in a pharmaceutical acceptable salt.
14. A pharmaceutical composition as claimed in any one of claims 1-11, wherein Compound I is present in the pharmaceutical composition in a succinate salt.

DATED THIS 3rd DAY OF APRIL, 2008


I. BANERJEE
OF L.S. DAVAR & CO.
APPLICANTS' AGENT