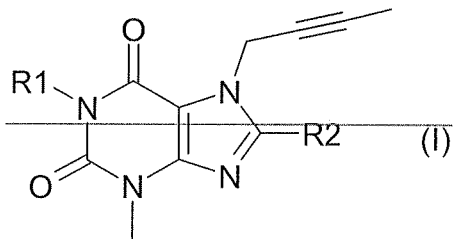
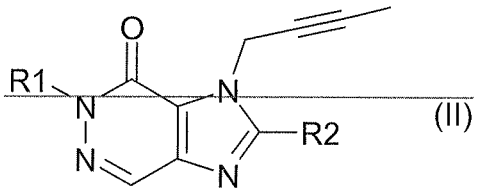
Claims

1. Use of a DPP-4 inhibitor, which is

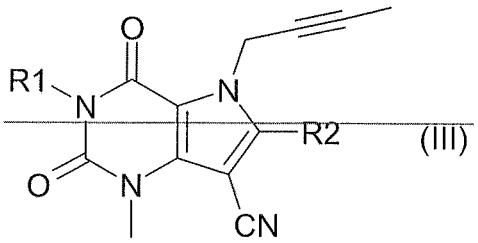
~~of formula (I)~~



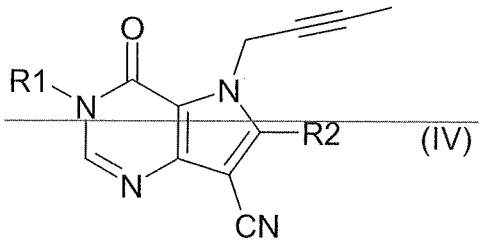
~~or of formula (II)~~



~~or of formula (III)~~

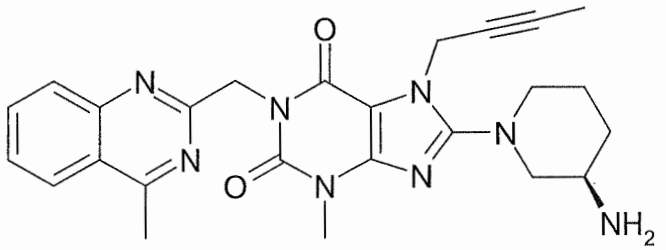


~~or of formula (IV)~~



~~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;

for the manufacture of a pharmaceutical composition for use in a method of treating and/or preventing of metabolic diseases in patients with insufficient glycemic control despite therapy with one or more conventional oral or non-oral antidiabetic drugs selected from metformin, sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 or GLP-1 analogues, and insulin or insulin analogues, wherein the DPP-4 inhibitor is administered in combination with said conventional antidiabetic dug(s),
wherein the DPP-4 inhibitor is administered in a daily oral amount of 5 mg.

2. Use ~~of the DPP-4 inhibitor~~ according to claim 1 ~~for the manufacture of a pharmaceutical composition~~ wherein the method is for treating and/or preventing of metabolic diseases in patients with insufficient glycemic control despite a therapy with one or more oral antidiabetic drugs selected from ~~metformin,~~ sulphonylureas, thiazolidinediones, glinides and α-glucosidase inhibitors.

3. Use ~~of the DPP-4 inhibitor~~ according to claim 1 or 2 ~~for the manufacture of a pharmaceutical composition~~wherein the method is for treating and/or preventing of metabolic diseases in patients with insufficient glycemic control despite a therapy with a sulphonylurea drug.

4. Use ~~of the DPP-4 inhibitor~~ according to claim 1 or 2 ~~for the manufacture of a pharmaceutical composition~~wherein the method is for treating and/or preventing ~~of metabolic diseases~~diabetes and/or diabetic complications in patients with insufficient glycemic control despite a therapy with a sulphonylurea drug alone.

5. Use ~~of the DPP-4 inhibitor~~ according to claim 1 or 2 ~~for the manufacture of a pharmaceutical composition~~wherein the method is for treating and/or preventing of ~~metabolic diseases~~diabetes and/or diabetic complications in patients with insufficient

glycemic control despite a combination therapy with a sulphonylurea drug and metformin.

6. Use ~~of the DPP-4 inhibitor~~ according to any one of claims 1 to 5 ~~for the manufacture of a pharmaceutical composition~~wherein the method is for achieving and/or maintaining glycemic control in type 2 diabetes patients with secondary sulphonylurea failure.

~~7. Use of the DPP-4 inhibitor according to any one of claims 1 to 6, wherein said DPP-4 inhibitor is used in combination with said conventional antidiabetic drug(s).~~

87. Use ~~of the DPP-4 inhibitor~~ according to any one of claims 1 to ~~76~~, wherein in said method said DPP-4 inhibitor is used in combination with said sulphonylurea, and, optionally, in combination with one or

more other therapeutic agents~~, such as e.g. metformin and/or a thiazolidinedione (e.g. pioglitazone)~~.

~~9. Use of the DPP-4 inhibitor according to any one of claims 1 to 6, wherein said DPP-4 inhibitor is used as replacement of said sulphonylurea, and, optionally, in combination with one or more other therapeutic agents, such as e.g. metformin and/or a thiazolidinedione (e.g. pioglitazone).~~

~~10~~8. Use ~~of the DPP-4 inhibitor~~ according to any one of claims 1 to ~~9~~7, wherein said sulphonylurea is selected from glibenclamide, glipizide and glimepiride.

~~11~~9. Use of the DPP-4 inhibitor according to any of claims 1 to ~~8~~7, wherein in said method said DPP-4 inhibitor is used in add-on ~~or initial~~ combination therapy with said sulphonylurea selected from glibenclamide, glipizide and glimepiride, with or without metformin.

~~12~~10. Use ~~of the DPP-4 inhibitor~~ according to any one of claims 1 to ~~11~~9 wherein the method is for treating and/or preventing type 2 diabetes mellitus and/or diabetic complications selected from micro- and macrovascular diseases~~for the manufacture of a pharmaceutical composition for improving HbA1c, FPG and/or PPG, decreasing glucose excursion and/or improving insulin secretion in said patients~~.

~~13~~11. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~12~~10 wherein the method is for ~~the manufacture of a pharmaceutical composition for the treatment of~~treating diabetes~~, such as e.g. in lowering HbA1c and improving insulin secretion,~~ in patients with indication on first- or second-line sulphonylurea therapy.

~~14~~12. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~12~~10 wherein the method is for ~~the manufacture of a pharmaceutical composition for the treatment of~~treating diabetes in patients with indication on dual sulphonylurea combination therapy~~, such as e.g. sulphonylurea plus metformin or sulphonylurea plus thiazolidinedione or sulphonylurea plus insulin~~.

~~15~~13. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~12~~10 wherein the method is for ~~the manufacture of a pharmaceutical composition for the treatment of~~ treating diabetes in patients with indication on triple combination therapy of metformin, sulphonylurea and thiazolidinedione, or of metformin, sulphonylurea and insulin, or of sulphonylurea, thiazolidinedione and insulin.

~~16~~14. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~12~~ 10 wherein the method is for ~~the manufacture of a pharmaceutical composition for the treatment of~~ treating diabetes in patients with indication on insulin therapy.

~~17~~15. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~16~~14, wherein said patients ~~suffering from~~having inadequate HbA1c values from 7.5 to 11% or 7.0 to 10% or 7.5 to 10% despite therapy with a sulphonylurea drug.

~~18~~16. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~17~~15 wherein the method is~~for the manufacture of a pharmaceutical composition~~ for preventing or reducing the risk for adverse effects associated with sulphonylurea (SU) antidiabetic therapy, ~~such as e.g.~~ selected from hypoglycaemia and/or weight gain in said patients.

~~19~~17. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~18~~16 wherein the method is ~~for the manufacture of a pharmaceutical composition~~ for preventing or slowing progression of diabetes with secondary sulphonylurea (SU) failure in said patients.

~~20~~18. Use of the DPP-4 inhibitor according to any one of the claims 1 to ~~19~~17, wherein said patients are ineligible for metformin therapy or are in need of reduced-dose metformin therapy due to intolerability or contraindication against metformin, ~~such as e.g.~~including renally impaired and/or elderly patients.

~~21~~19. Use ~~of the DPP-4 inhibitor~~ according to any one of the claims 1 to ~~20~~18, wherein in said method said DPP-4 inhibitor is used further ~~for the manufacture of a pharmaceutical composition~~ in combination with pioglitazone or metformin.

~~22. Use of the DPP-4 inhibitor according to any one of claims 1 to 21, wherein said DPP-4 inhibitor is selected from the group consisting of~~

~~1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine,~~

~~1-[([1,5]naphthyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~1-[(quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~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,~~

~~1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(2-amino-2-methyl-propyl)-methylamino]-xanthine,~~

~~1-[(3-cyano-quinolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~1-(2-cyano-benzyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-(2-amino-propyl)-methylamino]-xanthine,~~

~~1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~1-[(4-methyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~1-[(4,6-dimethyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine and~~

~~1-[(quinoxalin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine,~~

~~or a pharmaceutically acceptable salt thereof.~~

~~23~~20. Use of the DPP-4 inhibitor according to any one of claims 1 to ~~22~~19, wherein said DPP-4 inhibitor is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine.

~~24~~21. Use of a DPP-4 inhibitor, which is ~~preferably~~ 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a pharmaceutical composition for use in a method of treating and/or preventing a metabolic disease in patients with insufficient glycemic control despite a therapy with a sulphonylurea drug, wherein in said method said DPP-4 inhibitor is used in combination with a sulphonylurea drug, and wherein the DPP-4 inhibitor is administered in a daily oral amount of 5 mg.

~~25~~22. Use of a DPP-4 inhibitor, which is ~~preferably~~ 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a pharmaceutical composition for use in a method of treating ~~and/or preventing a metabolic disease~~ type 2 diabetes in a patients with insufficient glycemic control despite a therapy with a sulphonylurea drug alone, wherein in said method said DPP-4 inhibitor is used in combination with the sulphonylurea drug, and wherein the DPP-4 inhibitor is administered in a daily oral amount of 5 mg.

~~26~~23. Use of a DPP-4 inhibitor, which is ~~preferably~~ 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a pharmaceutical composition for use in a method ~~for~~of treating ~~and/or preventing a metabolic disease~~type 2 diabetes in a patients with insufficient glycemic control despite a combination therapy with a sulphonylurea drug and metformin, wherein in said method said DPP-4 inhibitor is used in combination with

the sulphonylurea drug and metformin, and wherein the DPP-4 inhibitor is administered in a daily oral amount of 5 mg.

~~27. Use of a DPP-4 inhibitor, which is preferably 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a pharmaceutical composition for treating and/or preventing a metabolic disease in patients with insufficient glycemic control despite a therapy with a sulphonylurea drug, wherein said patients are ineligible for metformin therapy due to intolerability or contraindication against metformin, such as e.g. renally impaired and/or elderly patients.~~

~~28. Use of a DPP-4 inhibitor, which is preferably 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a pharmaceutical composition for treating and/or preventing a metabolic disease in patients with insufficient glycemic control despite a therapy with a sulphonylurea drug, wherein said DPP-4 inhibitor is used in combination with the sulphonylurea drug, thereby preventing or reducing the risk for adverse effects associated with sulphonylurea antidiabetic therapy, such as e.g. hypoglycaemia and/or weight gain in said patients.~~

~~29. Use of a DPP-4 inhibitor, which is preferably 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a pharmaceutical composition in combination with a sulphonylurea drug in treating type 2 diabetes in patients with insufficient glycemic control despite a therapy with the sulphonylurea drug.~~

~~30. Use of a DPP-4 inhibitor, which is preferably 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a medicament in combination with a sulphonylurea in the treatment of type 2 diabetes patients with insufficient glycemic control despite mono-therapy with a maximal tolerated dose of a sulphonylurea.~~

~~31. Use of a DPP-4 inhibitor, which is preferably 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for the manufacture of a medicament in combination with a sulphonylurea and metformin in the treatment of type 2 diabetes patients with insufficient glycemic control despite dual combination therapy with a sulphonylurea and metformin.~~

~~32. Use of a DPP-4 inhibitor according to any of the preceding claims for the manufacture of a pharmaceutical composition for oral therapeutic use in diabetic patients wherein < 10%, preferably ≤ 7%, of the administered oral dose of the DPP-4 inhibitor is excreted via the kidneys.~~

~~33. Use of the DPP-4 inhibitor according to claim 32 wherein it is primarily excreted unchanged via the bile.~~

~~34. Use of the DPP-4 inhibitor according to any one of claims 32 or 33 wherein > 80%, preferably ≥ 90%, of the administered oral dose of the DPP-4 inhibitor is excreted unchanged as parent drug.~~

~~35. Use of the DPP-4 inhibitor according to any one of claims 32 to 34 wherein its main metabolite is pharmacologically inactive.~~

24. Use according to claim 1, wherein said patients are patients with insufficient glycemic control despite mono-therapy with metformin, a sulphonylurea, pioglitazone or (basal) insulin, or despite dual combination therapy with a metformin/pioglitazone, metformin/sulphonylurea, metformin/(basal) insulin, sulphonylurea/pioglitazone, sulphonylurea/(basal) insulin or pioglitazone/(basal) insulin combination.

25. Use of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine for the manufacture of a pharmaceutical composition for use in a method of treating type 2 diabetes in a patient with insufficient glycemic control despite therapy with one antihyperglycemic agent selected from metformin, sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 and GLP-1 analogues, and insulin and insulin analogues, wherein said method is characterized in that a daily oral amount of 5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine in combination with said one antihyperglycemic agent is administered to the patient.

26. Use of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine for the manufacture of a pharmaceutical composition for use in a method of treating type 2 diabetes in a patient with insufficient glycemic control despite therapy with two antihyperglycemic agents selected from metformin, sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 and GLP-1 analogues, and insulin and insulin analogues, wherein said method is characterized in that a daily oral amount of 5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine in combination with said two antihyperglycemic agents is adminstered to the patient.