Claims

1. Use of ~~A~~ 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 or a pharmaceutically acceptable salt thereof, for preparing a medicament for oral administration for treating and/or preventing of metabolic diseases in patients for whom metformin therapy is inappropriate due to intolerability or contraindication against metformin and/or with renal disease, renal impairment or renal dysfunction, wherein said DPP-4 inhibitor in the medicament is administered in an oral dose of 5 mg per day to said patients.

2. The ~~DPP-4 inhibitor~~use according to claim 1, wherein the ~~for use in the treatment and/or prevention of metabolic diseases in~~ patients are ineligible for metformin therapy due to intolerability or contraindication against metformin.

3. The ~~DPP-4 inhibitor~~use according to claim 1, wherein the ~~for use in the treatment and/or prevention of metabolic diseases in~~ patients are in need of reduced dose metformin therapy due to reduced tolerability, intolerability or contraindication against metformin.

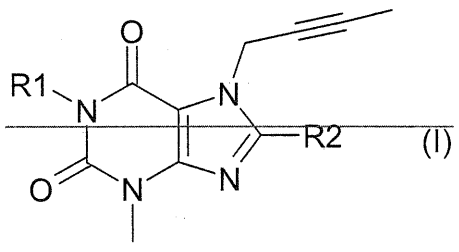
4. The ~~DPP-4 inhibitor~~use according to any one of the claims 1 to 3, wherein the medicament is for use in the treatment and/or prevention of type 2 diabetes mellitus in patients with at least one contraindication selected from:

renal disease, renal impairment or renal dysfunction,
dehydration,
unstable or acute congestive heart failure,
acute or chromic metabolic acidosis, and
hereditary galactose intolerance.

5. The ~~DPP-4 inhibitor~~use according to claim 4, wherein the medicament is for use in the treatment and/or prevention of type 2 diabetes mellitus in patients with renal disease, renal impairment or renal dysfunction.

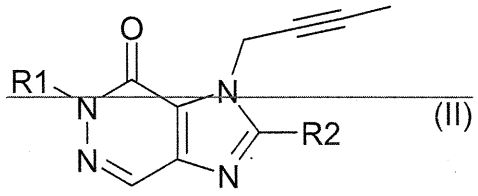
~~6. The DPP-4 inhibitor according to any one of the claims 1 to 5, which is either, in a first embodiment (embodiment A),~~

~~of formula (I)~~

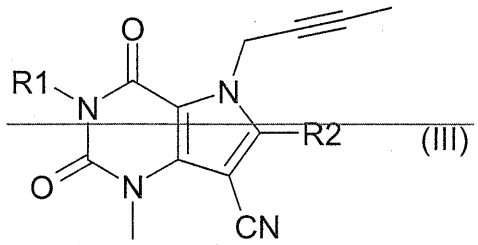


(I)

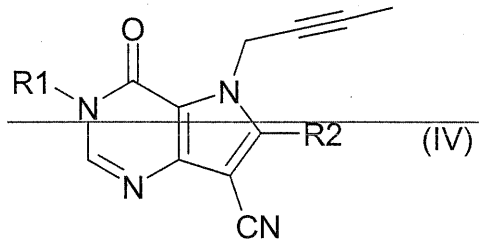
or of formula (II)



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;

or, in a second embodiment (embodiment **B**),

selected from the group consisting of

sitagliptin, vildagliptin, saxagliptin, alogliptin,

(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*,11b*S*)-2-Amino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-3-yl)-4-fluoromethyl-pyrrolidin-2-one,

(3,3-Difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone,

(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,

(2S,4S)-1-{2-[(3S,1R)-3-(1H-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl}-4-fluoropyrrolidine-2-carbonitrile,

(R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile,

5-{(S)-2-[2-((S)-2-Cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide,

3-{(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine,

[(2R)-1-{[(3R)-Pyrrolidin-3-ylamino]acetyl}pyrrolidin-2-yl]boronic acid,

(2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile,

2-({6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile, and

6-[(3R)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione,

or its pharmaceutically acceptable salt.

7. The DPP-4 inhibitor according to any one of claims 1 to 6, 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.~~

~~8~~6. The ~~DPP-4 inhibitor~~use according to any one of claims 1 to ~~7~~5, wherein ~~said~~ the 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.

~~9. The DPP-4 inhibitor according to any one of claims 1 to 6, wherein said DPP-4 inhibitor is selected from the group consisting of~~

~~saxagliptin, alogliptin,~~

~~(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*,11b*S*)-2-Amino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-3-yl)-4-fluoromethyl-pyrrolidin-2-one,~~

~~(3,3-Difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone,~~

~~(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,~~

~~(2S,4S)-1-{2-[(3S,1R)-3-(1H-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl}-4-fluoropyrrolidine-2-carbonitrile,~~

~~(R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile,~~

~~5-{(S)-2-[2-((S)-2-Cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide,~~
~~3-{(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine,~~
~~[(2R)-1-{[(3R)-pyrrolidin-3-ylamino]acetyl}pyrrolidin-2-yl]boronic acid,~~
~~(2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile,~~
~~2-({6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile, and~~
~~6-[(3R)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione,~~
~~or a pharmaceutically acceptable salt thereof.~~

~~107~~. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~96~~, wherein the medicament is for use in the treatment and/or prevention of type 2 diabetes mellitus in patients with renal disease, renal impairment or renal dysfunction, wherein said DPP-4 inhibitor in the medicament is used for said patients in the same dose as for patients with normal renal function.

~~118~~. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~107~~, ~~characterized in that~~wherein said DPP-4 inhibitor and its major active metabolite(s) have a relatively wide therapeutic window and/or are primarily eliminated via hepatic metabolism or biliary excretion.

~~129~~. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~118~~, wherein said DPP-4 inhibitor is excreted mainly via the liver.

~~1310~~. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~129~~, wherein for ~~which~~ said DPP-4 inhibitor excretion via the kidney represents a minor elimination pathway.

~~1411~~. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~1310~~, wherein said DPP-4 inhibitor is excreted mainly unchanged.

~~1512~~. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~1411~~, wherein for said DPP-4 inhibitor~~which~~ elimination via metabolism represents a minor elimination pathway.

~~16~~13. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~15~~12, wherein said DPP-4 inhibitor has placebo-like safety / tolerability and/or is eliminated primarily as the parent drug via the liver.

~~17~~14. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~16~~13, wherein the main metabolite of said DPP-4 inhibitor is pharmacologically inactive or has a relatively wide therapeutic window.

~~18~~15. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~17~~14, wherein the medicament is for use in patients with mild, moderate or severe renal impairment or end-stage renal disease.

~~19~~16. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~18~~15, wherein the medicament is for use in combination with one or more further active substances selected from antidiabetics, active substances that lower the blood sugar level, active substances that lower the lipid level in the blood, active substances that raise the HDL level in the blood, active substances that lower the blood pressure, active substances that are indicated in the treatment of atherosclerosis, and active substances that are indicated in the treatment of obesity.

~~20~~17. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~19~~16, wherein the medicament is for use in combination with one or more further active substances selected from sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 and GLP-1 analogues, and insulin and insulin analogues.

~~21~~18. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~20~~17, wherein the medicament is for use in combination with one or more further active substances selected from repaglinide, pioglitazone, and insulin and insulin analogues.

~~22~~19. The ~~DPP-4 inhibitor~~use according to any one of claims 1-~~21~~18, wherein the medicament is for use in combination with pioglitazone.

20. The use of a DPP-4 inhibitor, which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for preparing a pharmaceutical composition for oral administration for treating and/or preventing of metabolic diseases in patients for whom metformin therapy is inappropriate due to intolerability or contraindication against metformin and/or with renal disease, renal impairment or renal dysfunction, said composition being for use in combination with one or more further active substances selected from sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-

1 and GLP-1 analogues, and insulin and insulin analogues, wherein said DPP-4 inhibitor in the composition is administered in an oral dose of 5 mg per day to said patients.

21. The use of a DPP-4 inhibitor, which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for preparing a pharmaceutical composition for oral administration for use in the treatment and/or prevention of type 2 diabetes mellitus in patients with renal disease, renal impairment or renal dysfunction, said composition being for use in combination with one or more further active substances selected from repaglinide, pioglitazone, and insulin and insulin analogues, wherein said DPP-4 inhibitor in the composition is administered in an oral dose of 5 mg per day to said patients.

~~23~~22. The ~~DPP-4 inhibitor~~use according to any one of the claims 1-3, wherein the medicament is for use in the treatment and/or prevention of type 2 diabetes mellitus in patients suffering from gastrointestinal side effects associated with metformin, such as e.g. at least one gastrointestinal side effect selected from:

nausea,

vomiting,
diarrhoea,
intestinal gas, and
severe abdominal discomfort.

~~24~~23. Use of ~~A~~ 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 preparing a pharmaceutical composition for oral therapeutic use in diabetic patients ~~characterized in that~~wherein < 10%, preferably ≤ 7%, of the administered oral dose of the DPP-4 inhibitor is excreted via the kidneys, wherein said DPP-4 inhibitor in the composition is administered in an oral dose of 5 mg per day to said patients.

~~25~~24. Use of the ~~The~~ DPP-4 inhibitor according to claim ~~24~~ 23 ~~characterized in that~~wherein it is primarily excreted unchanged via the bile.

~~26~~25. Use of the ~~The~~ DPP-4 inhibitor according to claim ~~24~~ 23 or ~~25~~ 24 ~~characterized in that~~wherein > 80%, preferably ≥ 90%, of the administered oral dose of the DPP-4 inhibitor is excreted unchanged as parent drug.

~~27~~26. Use of the~~The~~ DPP-4 inhibitor according to any one of claims ~~24~~ 23 to ~~26~~ 25 ~~characterized in that~~wherein its main metabolite is pharmacologically inactive.

27. Use of a DPP-4 inhibitor, which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for preparing a medicament for oral administration for use in the treatment and/or prevention of type 2 diabetes mellitus in patients with renal disease, renal impairment or renal dysfunction, wherein said DPP-4 inhibitor in the medicament is administered in an oral dose of 5 mg per day to said patients.

28. Use of a DPP-4 inhibitor, which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for preparing a medicament for oral administration for use in the treatment of type 2 diabetes mellitus in patients with renal disease, renal impairment or renal dysfunction, wherein said DPP-4 inhibitor is used for said patients in the same dose as for patients with normal renal function, wherein said DPP-4 inhibitor in the medicament is administered in an oral dose of 5 mg per day to said patients.

29. The use according to claim 27 or 28, wherein the patient has moderate or severe renal impairment or end-stage renal disease.

30. The use according to claim 27 or 28, wherein the patient has severe renal impairment.

31. Use of a DPP-4 inhibitor, which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, for preparing a medicament for oral administration for use in the treatment and/or prevention of metabolic diseases, particularly diabetes (especially type 2 diabetes mellitus), in patients having chronic renal insufficiency or impairment of moderate, severe or terminal stage, wherein said DPP-4 inhibitor in the medicament is administered in an oral dose of 5 mg per day to said patients.

32. Use of a DPP-4 inhibitor, which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, for preparing a medicament for oral administration for use in the treatment and/or prevention of metabolic diseases, particularly diabetes (especially type 2 diabetes mellitus), in elderly patients;
wherein said DPP-4 inhibitor in the medicament is administered in an oral dose of 5 mg per day to said patients.

33. Use according to any of the preceding claims, wherein 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine is used in a dosage of 5 mg for oral once daily administration.