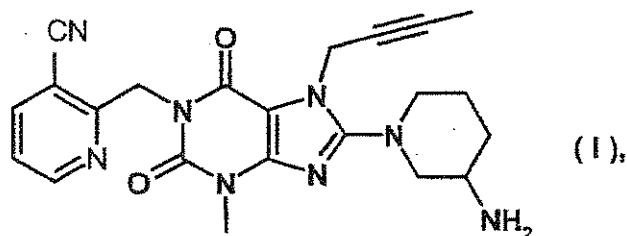


Hydrochlorides and hydrates of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)xanthine, their preparation and their use as medicaments

The present invention relates to new substituted xanthines of formula



the tautomers, the enantiomers, the mixtures thereof, the salts thereof and the hydrates thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids, such as hydrochlorides, for example, which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof for preventing or treating illnesses or conditions connected with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof and processes for the preparation thereof.

Xanthine derivatives with an inhibitory effect on DPP-IV are already known from WO 02/068420, WO 02/02560, WO 03/004496, WO 03/024965, WO 04/018468, WO 04/048379, JP 2003300977 and EP 1 338 595.

The aim of the invention is to provide new compounds of formula I, particularly salts with advantageous properties for pharmaceutical use.

In addition to its actual efficacy for the desired indication, an active substance must also meet other requirements in order to be capable of being used as a pharmaceutical composition. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restricted thereto, examples of these parameters are the stability of effect of the starting substance under different ambient conditions, stability in the course of the preparation of the pharmaceutical formulation and stability in the final compositions of the pharmaceutical preparation. The pharmaceutical active substance used to prepare the pharmaceutical compositions should therefore have high stability, which should also be guaranteed even under different environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the active substance itself, breakdown products thereof, for example. In such cases the content of active substance found in the pharmaceutical formulations might be less than specified.

The absorption of moisture reduces the content of pharmaceutically active substance as a result of the increased weight caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, e.g. by the addition of suitable drying agents or by storing the drug in an environment where it is protected from moisture. In addition, the uptake of moisture may reduce the content of pharmaceutically active substance during manufacture if the pharmaceutical substance is exposed to the environment without being protected from moisture in any way. Preferably, therefore, a pharmaceutically active substance should be only slightly hygroscopic.

As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance, care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances which are characterised by only slight polymorphism are preferred.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process for the formulation is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions), it is essential that the

active substance should be sufficiently soluble in physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible.

Surprisingly it has been found that the salts of the compound of formula I with hydrochloric acid, the enantiomers thereof, the mixtures and the hydrates thereof satisfy this requirement. Particularly suitable for the purposes of this disclosure are the mono- and dihydrochloride as well as the enantiomers thereof, the mixtures and the hydrates thereof.

The following terms are used synonymously:
salt with hydrochloric acid - hydrochloride

The disclosure therefore relates to the salts of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine with hydrochloric acid, as well as the enantiomers thereof, the mixtures and the hydrates thereof. These include for example the mono- and dihydrochloride of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine and 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*S*)-3-amino-piperidin-1-yl]-xanthine and the mixtures thereof, including the racemates. The disclosure further relates to pharmaceutical compositions containing at least one of the above-mentioned salts or hydrates thereof and processes for preparing pharmaceutical compositions.

In a first aspect, there is provided a hydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine.

In a second aspect, there is provided a monohydrochloride or dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine.

In a third aspect, there is provided a monohydrochloride or dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine in a crystalline non-hydrate form.

In a fourth aspect, there is provided 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine monohydrochloride.

In a fifth aspect, there is provided 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine dihydrochloride.

In a sixth aspect, there is provided 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine monohydrochloride having a melting point of $265 \pm 5^\circ\text{C}$.

In a seventh aspect, there is provided 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine dihydrochloride having a melting point of $205 \pm 5^\circ\text{C}$.

In an eighth aspect, there is provided the monohydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine, wherein an x-ray powder diagram of said monohydrochloride comprises characteristic d values at about 10.38 Å, 8.99 Å, 6.80 Å, 5.19 Å, 4.44 Å, 4.31 Å, 3.98 Å, 3.93 Å, 3.57 Å, 3.50 Å.

In a ninth aspect, there is provided the dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine, wherein an x-ray powder diagram of said dihydrochloride comprises characteristic d values at about 11.24 Å, 8.81 Å, 7.67 Å, 7.25 Å, 5.61 Å, 4.79 Å, 4.10 Å, 3.32 Å, 3.03 Å, 2.96 Å.

In a tenth aspect, there is provided the use of a compound as defined above for preparing a pharmaceutical composition which is suitable for the treatment of type I or type II diabetes mellitus, arthritis, obesity, allograft transplantation or osteoporosis caused by calcitonin.

In an eleventh aspect, there is provided the use of a compound as defined above for preparing a pharmaceutical composition which is suitable for the treatment of type II diabetes mellitus or obesity.

In a twelfth aspect, there is provided a pharmaceutical composition, containing a salt as defined above optionally together with one or more inert carriers and/or diluents.

In a thirteenth aspect, there is provided a pharmaceutical composition, containing the monohydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine optionally together with one or more inert carriers and/or diluents.

In a fourteenth aspect, there is provided a pharmaceutical composition, containing the dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine optionally together with one or more inert carriers and/or diluents.

In a fifteenth aspect, there is provided a process for preparing a pharmaceutical composition as defined above comprising incorporating a salt as defined above in one or more inert carriers and/or diluents.

In a sixteenth aspect, there is provided a pharmaceutical composition, containing or made from a monohydrochloride salt as defined above and, optionally, one or more inert carriers and/or diluents.

In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for influencing any conditions or diseases which can be affected by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as type I and type II diabetes mellitus, prediabetes,

reduced glucose tolerance or changes in the fasting blood sugar, diabetic complications (e.g. retinopathy, nephropathy or neuropathies), metabolic acidosis or ketosis, reactive hypoglycaemia, insulin resistance, metabolic syndrome, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and osteoporosis caused by calcitonin. In addition, these substances are suitable for preventing B-cell degeneration such as e.g. Apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and additionally increasing the size and number of pancreatic B-cells. Additionally, on the basis of the role of the glucagon-like peptides such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is expected that the compounds according to the invention will be suitable for achieving, inter alia, a sedative or tranquillising effect, as well as having a favourable effect on catabolic states after operations or hormonal stress responses or possibly reducing mortality and morbidity after myocardial infarction. Moreover, they are suitable for treating any conditions connected with the effects mentioned above and mediated by GLP-1 or GLP-2. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute kidney failure. The compounds according to the invention may also be used to treat inflammatory complaints of the respiratory tract. They are also suitable for preventing and treating chronic inflammatory bowel diseases such as e.g. Irritable bowel syndrome (IBS), Crohn's disease or ulcerative colitis and also pancreatitis. It is also expected that they can be used for all kinds of injury or damage to the gastrointestinal tract such as may occur in colitis and enteritis, for example. Moreover, it is expected that DPP-IV inhibitors and hence the compounds according to the invention can be used to treat infertility or to improve fertility in humans or mammals, particularly if the infertility is connected with insulin resistance or with polycystic ovary syndrome. On the other hand these substances are suitable for influencing sperm motility and are thus suitable for use as male contraceptives. In addition, the substances are suitable for treating growth hormone deficiencies connected with restricted growth, and may reasonably be used for all indications for which growth hormone may be used. The compounds according to the invention are also suitable, on the basis of their inhibitory effect on DPP-IV, for treating various autoimmune diseases such as e.g. rheumatoid arthritis, multiple sclerosis, thyroiditis and Basedow's disease, etc.. They may also be used to treat viral diseases and

also, for example, in HIV infections, for stimulating blood production, in benign prostatic hyperplasia, gingivitis, as well as for the treatment of neuronal defects and neurodegenerative diseases such as Alzheimer's disease, for example. The compounds described may also be used for the treatment of tumours, particularly for modifying tumour invasion and also metastatisation; examples here are their use in treating T-cell lymphomas, acute lymphoblastic leukaemia, cell-based thyroid carcinomas, basal cell carcinomas or breast cancers. Other indications are stroke, ischaemia of various origins, Parkinson's disease and migraine. In addition, further indications include follicular and epidermal hyperkeratoses, increased keratinocyte proliferation, psoriasis, encephalomyelitis, glomerulonephritis, lipodystrophies, as well as psychosomatic, depressive and neuropsychiatric diseases of all kinds.

The compounds according to the invention may also be used in conjunction with other active substances. Suitable therapeutic agents for such combinations include for example antidiabetic agents such as metformin, sulphonylureas (e.g. glibenclamide, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), PPAR-gamma/alpha/delta modulators, AMPK activators, ACC1 and ACC2 inhibitors, DGAT-inhibitors, SMT3 receptor agonists, 11 β -HSD inhibitors, FGF19 agonists or mimetics, alpha-glucosidase inhibitors (e.g. Acarbose, voglibose), other DPPIV inhibitors, alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. Also, combinations with SGLT2 inhibitors such as T-1095 or KGT-1251 (869682), inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the liver, such as e.g. Inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. Avasimibe) or cholesterol absorption inhibitors such as for example ezetimibe, bile acid-binding substances such as for example cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or

LXRalpha antagonists, LXRbeta agonists or LXRalpha/beta regulators or active substances for the treatment of obesity, such as e.g. sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or β 3-agonists such as SB-418790 or AD-9677 as well as agonists of the 5HT2c receptor, are possible.

It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. All antagonists or ACE inhibitors, diuretics, β -blockers, Ca-antagonists, etc., or combinations thereof.

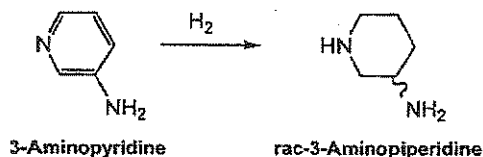
The dosage required to expediently achieve such an effect is, by intravenous route, 1 to 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

Figures 1, 3, 5 and 8 show the X-ray powder diagrams of Examples 2 (anhydrous form as well as the monohydrate), 3 and 4; Figures 2, 6 and 9 show the thermoanalyses of Examples 2, 3 and 4 and Figures 4, 7 and 10 show the absorption characteristics of the free base as well as of the mono- and dihydrochlorides of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (Example 2, 3 and 4).

The Examples that follow are intended to illustrate the invention.

D-tartaric acid salt of the R-enantiomer of 3-(phthalimido)piperidine

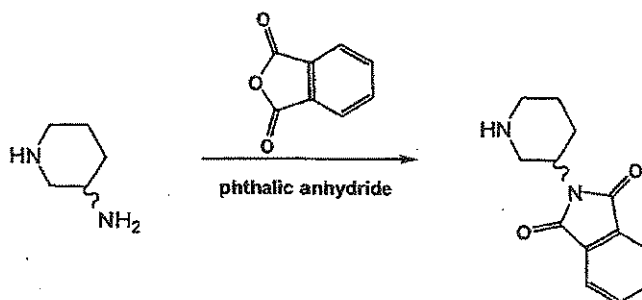
a. Hydrogenation:



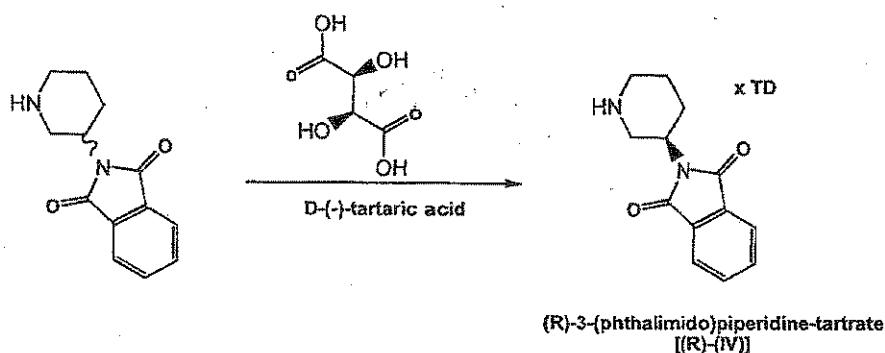
10.00 kg (106.25 mol) of 3-aminopyridine, 500 g of industrial grade activated charcoal and 65 litres of acetic acid are placed in the hydrogenation reactor. 50 g of Nishimura catalyst (a commercially obtainable mixed rhodium/platinum catalyst) are added, suspended in 2.5 litres of acetic acid, and the mixture is rinsed with 2.5 litres of acetic acid. It is hydrogenated at 50°C and 100 bar excess hydrogen pressure until the hydrogen uptake has stopped and then hydrogenated for a further 30 minutes at 50°C. The catalyst and the activated charcoal are filtered off and washed with 10 litres of acetic acid.

The reaction will also succeed under less drastic pressures.

b. Acylation:



15.74 kg (106.25 mol) phthalic anhydride are placed in the reactor and combined with the filtrate from the hydrogenation. The mixture is rinsed with 7.5 litres of acetic acid, and then the reaction mixture is refluxed, while about 30% of the acetic acid used are distilled off within one hour. The reaction solution is cooled to 90°C.

c. Racemate cleavage:

A solution of 11.16 kg D-(-)-tartaric acid (74.38 mol) in 50 litres of absolute ethanol heated to 50°C is metered at 90°C into the acylation reaction solution. This is rinsed with 10 litres of absolute ethanol and stirred for 30 minutes at 90°C, during which time the product crystallises out. After cooling to 5°C the product is centrifuged off and washed with absolute ethanol.

d. Recrystallisation:

The moist crude product is refluxed in a mixture of 50 litres of acetone and 90 litres of water until a solution has formed. Then the mixture is cooled to 5°C, during which time the product crystallises out. The suspension is stirred for 30 minutes at 5°C, the product is centrifuged and finally washed with a mixture of 20 litres of acetone and 10 litres of water. It is dried in the drying cupboard while being rendered inert at 45°C.

Yields: 11.7-12.5 kg

Example 2

Preparation of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine base

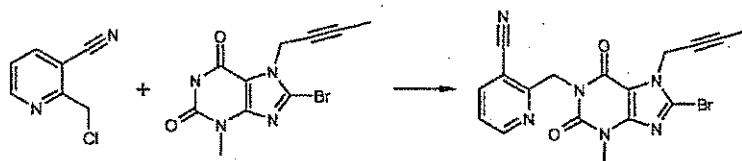
a. 3-cyano-2-(chloromethyl)-pyridine

165.5 g (0.98 mol) 2-hydroxymethyl-3-pyridinecarboxamide are heated together with 270 ml of phosphorus oxychloride for 1 hour at 90-100°C. The reaction mixture is cooled to ambient temperature and then added dropwise to about 800 ml of water at a temperature of 50-60°C. After hydrolysis of the phosphorus oxychloride the mixture is neutralised while being cooled with sodium hydroxide solution, whereupon

the product is precipitated. It is filtered off, washed with 300 ml of water and then dried at 35-40°C.

Yield: 122.6 g (82% of theoretical)

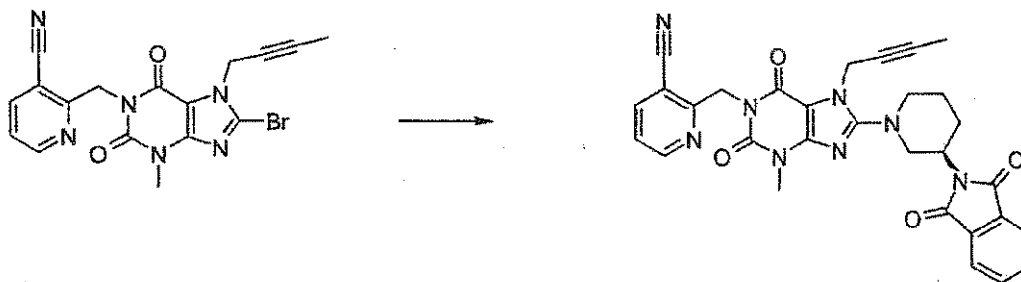
b. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine



202 g (0.68 mol) 3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine, 188.5 g (1.36 mol) anhydrous potassium carbonate and 1.68 litres of N-methyl-2-pyrrolidone are placed in the reactor and heated to 70°C. Then 119 g (0.75 mol) 2-chloromethyl-3-cyanopyridine in 240 ml N-methyl-2-pyrrolidone (NMP) are added dropwise. The contents of the reactor are stirred for 19 hours at 70°C. After the reaction has ended 2.8 litres of water are added to the reaction mixture and it is cooled to 25°C. The product is filtered off, washed with 2 litres of water and dried in the drying cupboard at 70°C while being rendered inert.

Yield: 257.5 g (91% of theoretical)

c. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-phthalimido-piperidin-1-yl)-xanthine

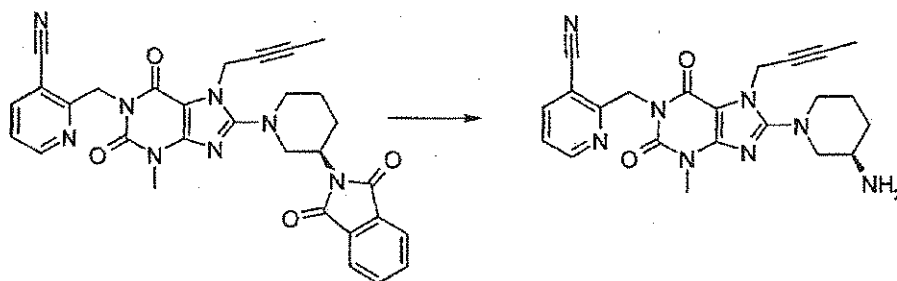


230 g (0.557 mol) 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine, 318 g (0.835 mol) 3-(phthalimido)piperidine D-tartrate and 1.15 litres of N-methyl-2-pyrrolidone are placed in the reactor. The contents of the reactor are heated to 140°C. After reaching this temperature, 478 ml (2.78 mol) diisopropylethylamine are metered in within 20 minutes and the reaction mixture is then stirred for 2 hours at 140°C. Then the reaction mixture is cooled to 75°C and

diluted with 720 ml of methanol. 2.7 litres of water are then added at 68-60°C and the mixture is cooled to 25°C. The product is filtered off and washed with 2 litres of water. It is dried in the drying cupboard at 70°C while being rendered inert. The crude product thus obtained is then stirred into 1 litre of methanol at boiling temperature, filtered hot, washed with 200 ml of methanol and then dried at 70°C while being rendered inert.

Yield: 275 g (88 % of theoretical)

d. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine



412.5 g (0.733 mol) of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-(3-(*R*)-phthalimido-piperidin-1-yl)-xanthine are heated to 80°C in 4125 ml of toluene. Then at 75-80°C 445 ml of ethanolamine (7.33 mol) are added to the suspension. To complete the reaction the mixture is stirred for another 2 hours at 80-85°C, during which time the solids go into solution. Then the phases are separated. The ethanolamine phase is extracted twice with warm toluene (1 litre in each case). The combined toluene phases are washed twice with 2 litres of 75-80°C warm water on each occasion. The toluene phases are dried with sodium sulphate, filtered and then reduced to a volume of about 430 ml by distillation in vacuo. Then at 50-55°C 1 litre of tert.-butylmethylether is metered in and the mixture is then cooled to 0-5°C. The product is isolated by filtration, washed with tert.-butylmethylether and dried at 60°C in the drying cupboard.

Yield: 273.25 g (86.2% of theoretical)

melting point: 188 ± 3 °C (anhydrous form)

The anhydrous form of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine is stable at relative humidities up to about 50%, above 50 % r.h. This form takes up about 4 % water and changes into a monohydrate, as can clearly be seen from the absorption diagram in Figure 4 . If the relative humidity is subsequently brought back to 50 % or less, the anhydrous form is formed again, i.e. The conversion into the monohydrate is totally reversible.

Table 1: X-ray reflections with intensities (standardised) for the anhydrous form of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine

2 Θ [°]	d_{hkl} [Å]	Intensity I/I ₀ [%]
8.17	10.81	22
8.37	10.56	19
10.29	8.59	100
11.40	7.76	14
11.70	7.56	6
12.48	7.09	9
14.86	5.96	1
15.49	5.72	2
16.26	5.45	7
16.75	5.29	18
18.38	4.82	11
18.60	4.77	7
18.92	4.69	3
19.35	4.58	3
19.55	4.54	2
20.73	4.28	24
21.34	4.16	1
21.77	4.08	4

2θ [°]	d_{hkl} [Å]	intensity I/I ₀ [%]
22.10	4.02	7
22.60	3.93	4
22.86	3.89	5
23.09	3.85	5
23.47	3.79	11
24.30	3.66	12
24.66	3.61	5
25.58	3.48	2
26.02	3.42	2
26.52	3.36	13
27.15	3.28	3
27.60	3.23	2
28.22	3.16	4
28.60	3.12	2
28.84	3.09	3
29.80	3.00	5
30.02	2.97	8

Table 2: X-ray reflections with intensities (standardised) for the monohydrate of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine

2θ [°]	d_{hkl} [Å]	intensity I/I ₀ [%]
8.00	11.05	12
8.45	10.46	26
9.27	9.54	5
10.43	8.48	100

2θ [°]	d_{hkl} [Å]	intensity I/I ₀ [%]
11.45	7.72	23
11.74	7.53	4
12.53	7.06	6
15.91	5.57	8
16.01	5.53	7
16.73	5.30	29
16.94	5.23	17
17.99	4.93	11
18.43	4.81	15
18.95	4.68	7
19.31	4.59	2
20.54	4.32	36
20.85	4.26	30
21.86	4.06	19
22.13	4.01	8
22.70	3.91	7
22.96	3.87	15
23.43	3.79	8
24.56	3.62	18
25.45	3.50	2
25.84	3.44	14
25.99	3.43	14
26.58	3.35	6
26.88	3.31	4
28.06	3.18	3
29.04	3.07	4
29.29	3.05	9
30.22	2.96	6

Example 3

1 -[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine monohydrochloride _____

5.00 g of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine base are dissolved in 50 ml of methanol. Then 3.0 ml of a 3.9 molar solution of hydrogen chloride in isopropanol are added. The solvent is distilled off and the residue is suspended in 40 ml ethyl acetate and refluxed, during which time a precipitate is formed. It is cooled to ambient temperature, the precipitate is filtered off and washed with a little ethyl acetate and dried.

The product is then recrystallised from absolute ethanol.

Yield: 2.7 g (50 % of theory)

melting point: 265 ± 5 °C (with decomposition)

The monohydrochloride exhibits less marked hygroscopic characteristics; there is no reversible change into a hydrate phase as is observed with the free base between 50 and 60 % r.h. (see the absorption characteristics of the monohydrochloride in Figure 7). Also, the monohydrochloride only absorbs water at very high relative humidities (> 80 % r.h.). Humidity-dependent X-ray powder images show that there is no phase change above 80% r.h. for the monohydrochloride.

Table 3: X-ray reflections with intensities (standardised) for the anhydrous form of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine monohydrochloride

d_{hkl} [Å]	2θ [°]	Intensity I/I_0 [%]
17.95	4.92	5
10.38	8.51	100
8.99	9.83	22
6.80	13.01	26
5.97	14.82	1
5.19	17.07	12

4.99	17.78	5
4.74	18.72	8
4.44	20.00	10
4.31	20.60	13
3.98	22.33	10
3.93	22.61	11
3.80	23.38	4
3.57	24.91	11
3.50	25.43	11
3.32	26.87	4
3.15	28.35	2
2.96	30.20	1
2.89	30.97	2
2.80	31.92	5
2.74	32.63	2
2.57	34.89	2

Example 4

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

1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine base (1.00 g; 2.31 mmol) are dissolved in 9.5 ml abs. ethanol and 0.5 ml methyl-tert.-butylether at boiling temperature. Then 1.2 ml of a 3.9 molar solution of hydrogen chloride in isopropanol is added. A precipitate is formed. After cooling to ambient temperature the mixture is filtered, washed with a little MTBE and dried.

Yield: 1.04 g (89.0% of theory)

Melting point: 205 ± 5 °C (with decomposition); above about 150°C gaseous HCl is given off.

The dihydrochloride also exhibits unremarkable hygroscopic behaviour; there is no reversible change into a hydrate phase as observed with the free base between 50 and 60 % r.h. (see the absorption characteristics of the dihydrochloride in Figure 10). The dihydrochloride takes up a certain amount of water continuously over the whole range of relative humidities. Humidity-dependent X-ray powder images show that there is no phase change in the humidity range from 10 – 90 r.h.

Table 4: X-ray reflections with intensities (standardised) for the anhydrous form of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine-dihydrochloride

2θ [°]	d_{hkl} [Å]	intensity I/I_0 [%]
7.20	12.26	3
7.86	11.24	27
9.34	9.46	3
10.04	8.81	54
11.53	7.67	100
11.87	7.45	5
12.20	7.25	19
13.25	6.68	2
13.97	6.33	5
14.47	6.12	15
15.77	5.61	18
16.65	5.32	4
17.15	5.17	2
18.05	4.91	11
18.50	4.79	37
18.80	4.72	14
20.16	4.40	15
20.46	4.34	2
21.03	4.22	3
21.36	4.16	10
21.64	4.10	18
22.54	3.94	9
23.17	3.84	13
23.90	3.72	15
24.57	3.62	7

2 θ [°]	d_{hkl} [Å]	intensity I/I_0 [%]
24.86	3.58	9
25.06	3.55	11
25.39	3.50	13
25.95	3.43	6
26.14	3.41	13
26.52	3.36	12
26.79	3.32	43
27.24	3.27	4
27.66	3.22	3
28.15	3.17	6
29.22	3.05	3
29.48	3.03	23
30.16	2.96	18

The melting points were determined by DSC, using an apparatus supplied by Mettler-Toledo (type: DSC 821). The melting temperature used was the temperature of onset of the corresponding melt peak in the DSC diagram. Heating rates of 10 K/min were used and the experiments were carried out under a nitrogen atmosphere.

The X-ray powder diagrams, with one exception, were recorded using an STOE Stadi P X-ray powder diffractometer. This diffractometer operates with $\text{CuK}_{\alpha 1}$ radiation ($\lambda = 1.5406 \text{ Å}$) and a location-sensitive detector. The X-ray generator was operated at 40 mA and 40 kV.

The X-ray powder diagram of the monohydrate of the free base was recorded with a Bruker D8 Advance X-ray powder diffractometer on which a special air humidity cell made by MRI had been placed. The diagram was recorded at about 72 % r.h.. The Bruker D8 Advance operates with CuK_{α} radiation ($\lambda = 1.5418 \text{ Å}$) and also a location-sensitive detector. The X-ray generator was operated at 30 mA and 40 kV.

Example 5Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	<u>1.5 mg</u>
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinyl pyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks about 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 6Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	<u>2.0 mg</u>
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, faceted on both sides and notched on one side.

Example 7Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	<u>1.0 mg</u>
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm.

The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 8Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		150.0 mg
corn starch (dried)	approx.	180.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		<u>3.0 mg</u>
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule

Example 9Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	<u>840.0 mg</u>
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

continued

Example 10Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. Water	ad 100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 11Ampoules containing 10 mg active substanceComposition:

active substance		10.0 mg
0.01 N hydrochloric acid	q.s.	
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 12Ampoules containing 50 mg of active substanceComposition:

active substance		50.0 mg
0.01 N hydrochloric acid	q.s.	
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A hydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine.
2. A monohydrochloride or dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine.
3. A monohydrochloride or dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine in a crystalline non-hydrate form.
4. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine monohydrochloride.
5. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine dihydrochloride.
6. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine monohydrochloride having a melting point of $265 \pm 5^{\circ}\text{C}$.
7. 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine dihydrochloride having a melting point of $205 \pm 5^{\circ}\text{C}$.
8. The monohydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine, wherein an x-ray powder diagram of said monohydrochloride comprises characteristic d values at about 10.38 Å, 8.99 Å, 6.80 Å, 5.19 Å, 4.44 Å, 4.31 Å, 3.98 Å, 3.93 Å, 3.57 Å, 3.50 Å.

9. The dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine, wherein an x-ray powder diagram of said dihydrochloride comprises characteristic d values at about 11.24 Å, 8.81 Å, 7.67 Å, 7.25 Å, 5.61 Å, 4.79 Å, 4.10 Å, 3.32 Å, 3.03 Å, 2.96 Å.
10. Use of a compound according to any one of claims 1 to 9 for preparing a pharmaceutical composition which is suitable for the treatment of type I or type II diabetes mellitus, arthritis, obesity, allograft transplantation or osteoporosis caused by calcitonin.
11. Use of a compound according to any one of claims 1 to 9 for preparing a pharmaceutical composition which is suitable for the treatment of type II diabetes mellitus or obesity.
12. Pharmaceutical composition, containing a salt according to any one of claims 1 to 9 optionally together with one or more inert carriers and/or diluents.
13. Pharmaceutical composition, containing the monohydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine optionally together with one or more inert carriers and/or diluents.
14. Pharmaceutical composition, containing the dihydrochloride salt of 1-[(3-cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine optionally together with one or more inert carriers and/or diluents.

15. A process for preparing a pharmaceutical composition according to claim 12 comprising incorporating a salt according to any one of claims 1 to 9 in one or more inert carriers and/or diluents.

16. Pharmaceutical composition, containing or made from a monohydrochloride salt according to any one of claims 4, 6 and 8 and, optionally, one or more inert carriers and/or diluents.