(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 August 2009 (20.08.2009)

PCT

(10) International Publication Number
WO 2009/102226 A1

(51) **International Patent Classification**:
C07D 417/12 (2006.01) ***A61P 3/10*** (2006.01)
A61K 31/4439 (2006.01)

(21) **International Application Number**:
PCT/PL2009/000015

(22) **International Filing Date**:
11 February 2009 (11.02.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
PL384446 12 February 2008 (12.02.2008) PL

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2009/102226 A1

(54) **Title**: MALONIC ACID SALT OF 5-[[4-[2-(METHYL-2-PYRIDINYLAMINO)ETHOXY]PHENYL]METHYL]- 2,4-THIAZOLIDINEDIONE

(57) **Abstract**: The invention discloses the malonic acid salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, encompassing its isomers, tautomers and/or solvates thereof, and their use for the treatment and/or prevention of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Malonic acid salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione

Field of invention

The present invention relates to new acid addition salt of 5-[[4-[2-(methyl-2-piridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione and to its use in medicine.

Technical background

European patent application EP-A-0 306 228 discloses a group of thiazolidinedione derivatives with hypoglycemic and antidiabetic activity. One of compounds described in EP-A-0 306 228 is 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione also known under international non-proprietary name (INN) rosiglitazone.

EP-A-0 306 228 reveals that rosiglitazone may exist in several tautomeric forms and/or solvated forms. Document also discusses the possibility of formation of pharmaceutically acceptable salts of rosiglitazone with alkali metals *via* thiazolidinedione moiety.

European patent application EP-A-0 658 161 discloses certain acid addition salts of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione formed by association of hydrogen atom of the acid moiety with any possible salt forming rosiglitazone group, particularly with nitrogen atom of pyridine. Particular example of rosiglitazone salt is maleic acid salt which is able to form tautomeric forms and/or solvates, especially hydrates. Moreover, it is known that 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione maleate and the hydrates thereof are able to crystallize in various polymorphic forms depending on conditions (WO 99/31093, WO 99/31094, WO 99/31095, WO 00/64892, WO 00/064893, WO 02/026737, WO 2004/085435, WO 2005/073227).

The ability of active substance to exist in various polymorphic and pseudo-polymorphic forms and their interconversions, e.g. at elevated temperatures or in contact with humidity, may negatively affect homogeneity and reproducibility of the production batches and as a result cause difficulties in manufacturing process as well as unpredictable transformations of the active substance during handling and a shelf-life of the finished solid dosage forms.

Thus, numerous efforts are taken to develop others rosiglitazone salts characterized with similar pharmacological profile of maleate but devoid of its disadvantageous physicochemical properties.

Unexpectedly it has been found that hitherto undisclosed salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione overcomes the inconveniences described above, by being particularly stable and homogenous, and hence is suitable for bulk preparation and handling.

Brief description of the figures

Fig. 1 illustrates rosiglitazone malonate spatial conformation.

Fig. 2 illustrates packing of molecules in crystal lattice of rosiglitazone malonate - along the X axis of unit cell projection.

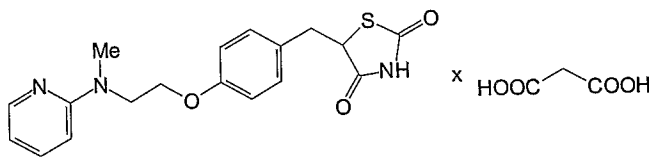
Fig. 3 is the X-ray powder diffraction pattern (XRPD) of the crystalline rosiglitazone malonate.

Fig. 4 shows infrared spectrum (KBr) of the crystalline rosiglitazone malonate.

Detailed description of the invention

The present invention provides malonic acid salt of 5-[[4-[2-(methyl-2-piridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione as a new chemical compound, referred hereinafter as rosiglitazone malonate.

The salt according to the present invention is isolated in stoichiometry wherein the molar ratio of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (rosiglitazone base) to malonic acid is 1:1. Thus, the chemical structure of rosiglitazone malonate may be represented by the general formula (I)



The invention encompasses all possible isomers, tautomers and/or solvates of the compound represented by formula (I).

The invention also provides a process for preparation of rosiglitazone malonate, its isomers, tautomers and/or solvates thereof, which consists in that 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione or the salt thereof, dispersed or dissolved in organic solvent, is reacted with malonic acid or its source.

The starting compound for the preparation process, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (rosiglitazone base), may be obtained according to any procedure known in the art, e.g. by the method disclosed in European Patent application EP-A-0 306 228.

The salt forming reaction is carried out with the use of a molar ratio of malonic acid to rosiglitazone base in a range from 1:1 to 1.2:1.

The suitable reaction solvents are aliphatic ketones, such as acetone; carboxylic acids esters, such as ethyl acetate; ethers, such as tetrahydrofurane, dioxane; nitriles, such as acetonitrile, or mixtures thereof.

In the preferred embodiment of the present invention malonate salt of rosiglitazone is prepared in a process comprising:

(i) mixing of 5-[[4-[2-(methyl-2-piridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione and malonic acid in an equimolar ratio, in an organic solvent,

(ii) heating the mixture under reflux until the solid completely dissolves,

(iii) filtration of the solution and cooling down to the crystallization temperature (5°C - 20°C),

(iv) crystallization and isolation of the product, eg. by filtration, and

(v) drying the isolated product.

The most preferred reaction solvent according to the present invention is ethyl acetate.

Rosiglitazone malonate is obtained with a high yield. In case of the process performed in ethyl acetate the yield usually exceeds 93% (calculated on the starting rosiglitazone base).

The salt according to the invention is isolated from the reaction mixture in a crystalline form which is furthe aspect of the invention.

The crystalline salt of rosiglitazone malonate isolated from the reaction mixture is distinguished by very high chemical purity, regardless of the starting rosiglitazone base purity. The purity (according to HPLC) of rosiglitazone malonate prepared in the process of the invention, without any further purification, exceeds 99.5%.

In another embodiment of the present invention rosiglitazone malonate is obtained *in situ*, namely in the same solvent in which rosiglitazone base synthesis is carried out - without isolation from reaction mixture or purification of rosiglitazone base.

Rosiglitazone malonate according to the present invention is chemically stable. Under long-term and stress storage conditions neither the impurities nor water content increase was observed.

Rosiglitazone malonate according to the present invention consists of the moieties of rosiglitazone base and malonic acid in a molar ratio 1:1. The chemical structure of the new salt is confirmed by nuclear magnetic resonance ^{1}H-NMR and ^{13}C-NMR.

The particular structure of crystalline rosiglitazone malonate was elucidated by single-crystal X-ray diffraction analysis. Crystallographic data, in particular the unit cells dimensions, the volume of each cell, calculated density, and the measurement parameters are collected in Table 1.

Table 1. Crystallographic data and measurement parameters

Molecular formula	$C_{21}H_{23}N_3O_7S$
Molecular weight	461.48
Measurement temperature / K	293(2)
Wavelenght / Å	0,71073
Crystalline system space group	Triclinic
Point group/ symmetry class	P -1
Unit cell dimensions	
a/ Å	4.6105(8)
b/ Å	12.0348(15)
c/ Å	20.628(4)
α/ °	104.863(19)
β/ °	95.744(16)
γ/ °	95.557(12)
Volume V /Å^3	1091.8(3)
Z	2
Density (calculated) /mg·m^{-3}	1.404
$[\sin\theta/\lambda]_{max}$	29.7
μ / cm^{-1}	0.197
F(000)	484
range	-4≤h≤4, -11≤k≤11, -19≤l≤19
Collected reflections	2040

The atomic coordinates of unit cells of rosiglitazone malonate are given in Table 2.

Table 2. Final atomic coordinates and equivalent isotropic temperature factors

Atom	x	y	z	U_{izo}
S(1)	7164(4)	3780(1)	4096(1)	82(1)
C(2)	5177(16)	3554(6)	3288(3)	72(2)
O(3)	5629(11)	4162(4)	2917(2)	101(2)
N(4)	3102(12)	2618(4)	3142(3)	63(2)
C(5)	2812(15)	2048(6)	3628(3)	58(2)
O(6)	910(10)	1260(4)	3587(2)	74(1)
C(7)	5205(13)	2488(5)	4214(3)	71(2)
C(8)	4210(14)	2633(6)	4893(3)	90(2)
C(9)	6587(13)	2521(7)	5437(3)	65(2)
C(10)	7469(17)	1456(6)	5430(4)	83(2)
C(11)	9500(16)	1316(5)	5927(4)	80(2)
C(12)	10837(14)	2253(6)	6433(3)	60(2)
C(13)	10010(14)	3330(5)	6435(3)	67(2)
C(14)	7920(15)	3442(6)	5940(4)	73(2)
O(15)	12864(10)	2025(3)	6894(2)	73(1)
C(16)	14085(13)	2931(5)	7465(3)	67(2)
C(17)	16170(14)	2410(5)	7886(3)	72(2)
N(18)	14749(11)	1395(4)	8055(3)	59(1)
C(19)	14931(13)	255(5)	7594(3)	77(2)
C(20)	13130(14)	1490(6)	8563(3)	52(2)
N(21)	11700(12)	514(4)	8659(3)	58(2)
C(22)	10001(16)	526(7)	9164(4)	76(2)
C(23)	9677(16)	1532(8)	9599(3)	88(2)
C(24)	11066(18)	2543(7)	9514(4)	85(2)
C(25)	12758(16)	2553(5)	9015(4)	74(2)
O(1M)	10495(14)	5229(4)	8685(3)	139(2)
O(2M)	13609(15)	3749(4)	9236(3)	117(2)
C(3M)	11500(20)	4262(7)	8755(4)	87(2)
C(4M)	10412(15)	3551(5)	8310(3)	82(2)
C(5M)	11825(17)	2314(5)	8416(4)	70(2)
O(6M)	10851(10)	1778(3)	8012(2)	82(2)
O(7M)	13856(10)	1898(3)	8882(2)	94(2)

The spatial conformation and the packing of molecules in crystal lattice of rosiglitazone malonate are depicted at Fig.1 and Fig.2.

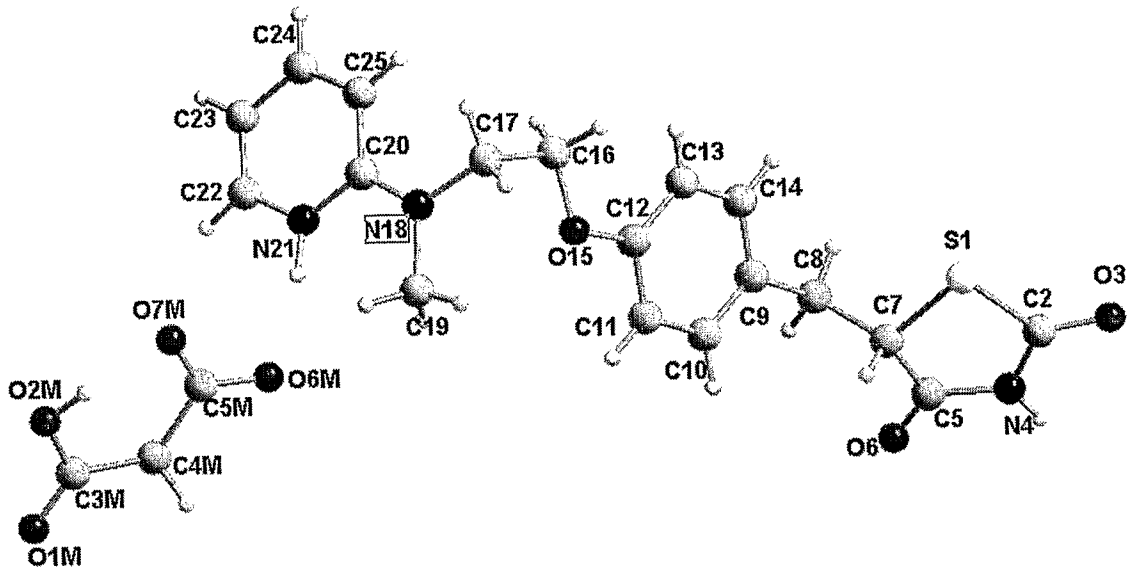


Fig. 1. Spatial structure of rosiglitazone malonate

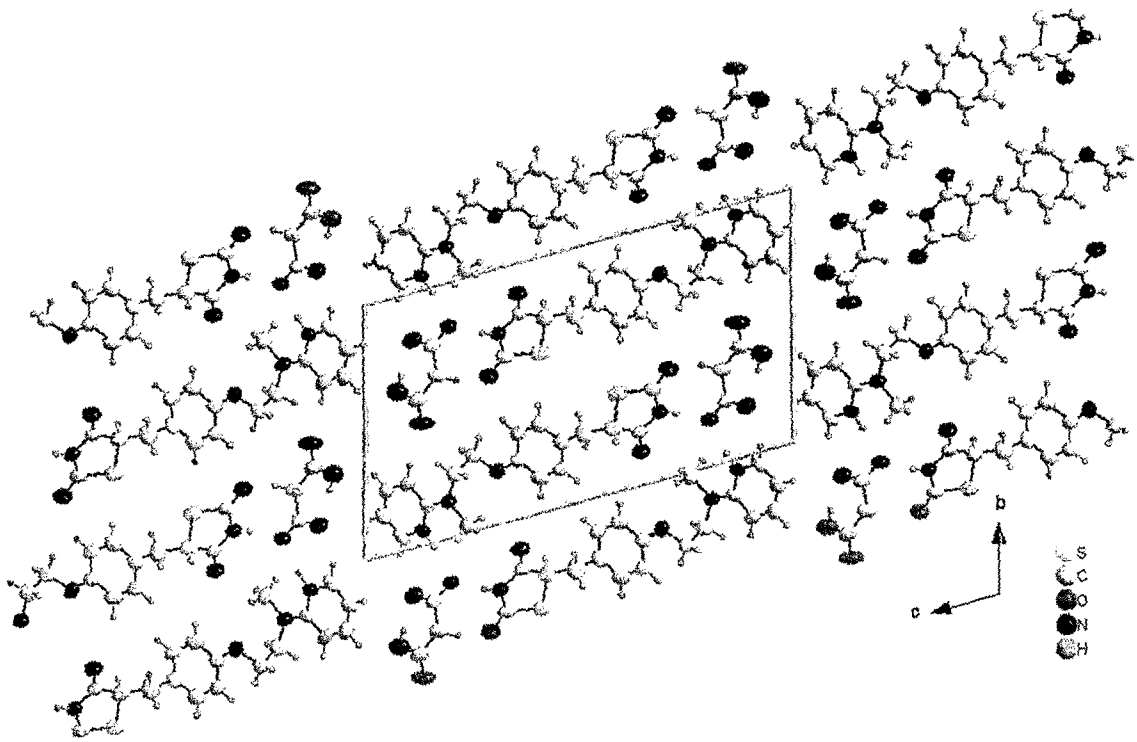


Fig. 2. Packing of molecules in crystal lattice of rosiglitazone malonate - projection along the X axis of unit cell

The crystalline rosiglitazone malonate isolated in the process of the invention is characterized by an X-ray powder diffraction pattern (XRPD) showing characteristic main peaks with relative intensities I/I_0 above 20% at 2θ about 4,47, 15,35, 17,12, 17,93, 20,58, 21,78, 22,53, 23,29, 23,93 ± 0.2 °.

Further, the crystalline rosiglitazone malonate according to invention is characterized by the X-ray powder diffraction pattern (XRPD) substantially as depicted in Fig.3.

At the X-ray diffraction pattern the characteristic peaks are observed presented as the relation of reflection angles 2θ (°), interplanar spacings d (Å), and relative intensities in attitude to the most intensive diffraction peak, I/I_0 (%), as depicted in Table 3:

Table 3. X-ray powder diffraction of rosiglitazone malonate

No. of reflection	2θ (°)	d (Å)	I/I_0 (%)
1.	4.466	19.7695	21.8
2.	7.759	11.3848	18.2

3.	8.939	9.8848	11.6
4.	9.853	8.9701	3.2
5.	10.091	8.7589	6.8
6.	13.425	6.5898	2.7
7.	15.348	5.7685	98.2
8.	17.117	5.1762	56.6
9.	17.933	4.9424	55.8
10.	20.576	4.3131	38.2
11.	21.780	4.0772	23.1
12.	22.531	3.9431	31.7
13.	23.291	3.8161	26.4
14.	23.927	3.7160	100.0
15.	24.800	3.5873	15.4
16.	26.463	3.3654	15.9
17.	26.692	3.3370	8.4
18.	27.970	3.1874	4.4
19.	30.632	2.9162	11.0
20.	31.361	2.8500	5.2
21.	33.127	2.7021	10.4
22.	34.073	2.6291	5.5
23.	34.768	2.5782	3.1
24.	35.686	2.5140	5.1
25.	36.854	2.4369	5.8

The new rosiglitazone salt with malonic acid is well tolerated and pharmaceutically accepted (see, Handbook of Pharmaceutical Salts, ed. P.H. Stahl. C.G. Wermuth, Verlag Helvetica Chimica Acta, 2002). Due to its advantageous physicochemical and toxicological properties, it may be used in the therapy and prophylaxis in humans. Pharmacological properties of malonate salt are expected to be the same as of rosiglitazone maleate.

The present invention accordingly provides rosiglitazone malonate, its isomers, tautomers and/or solvates thereof for use as an active therapeutic substance.

In particular, the present invention provides the use of rosiglitazone malonate, its isomers, tautomers and/or solvates thereof as the insulin sensitizer increasing glycaemic control, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the therapeutic applications the active substance rosiglitazone malonate may be administered to the patient *per se,* or as a pharmaceutical composition comprising therapeutically effective amount of the active substance together with at least one pharmaceutically acceptable carrier and/or excipient.

Accordingly, the present invention also provides a pharmaceutical composition which may be administered to a patient in a need for treatment in an appropriate pharmaceutical dosage form, dependent on the mode of administration. The orally or parenterally administrable pharmaceutical dosage forms are preferred.

The active substance dose selection and the treatment regimes depend on the disease progression, age, body weight and condition of the patient, and may be determined by a skilled person basing on the known treatment and prophylaxis regimes appropriate for this kind of diseases.

The appropriate daily dose of rosiglitazone malonate may range from 1 to 16 mg per day, more preferably from 2 to 8 mg per day (calculated on rosiglitazone base). Rosiglitazone malonate may be administered to the patient either as a single daily dose or in 2 or more divided doses, as monotherapy or in combination with other therapeuticals, such as sulfonylureas, biguanides and/or alpha-glucosidase inhibitors. The components of such combinations may be administered to the patient in the form of one combined fixed-dosage pharmaceutical formulation or in separate formulations one after the other in order and time intervals established by a skilled person.

The pharmaceutical composition according to the present invention may be administered in the pharmaceutical form well-known to those skilled in the art. See: e .g. Remington's Pharmaceutical Sciences, 18th ed., red. A.R.Gennaro, Mack Publ. Co., 1990, Easton, Pensylwania.

The pharmaceutical compositions may be adopted for oral administration, although compositions for administration by other routs, such as parenteral, are also envisaged.

The pharmaceutical oral dosage forms comprise solid dosage forms, such as tablets, coated tablets, powders, granules, pellets or capsules; and liquid dosage forms, such as suspensions, elixirs, solutions and syrups. In addition to the active substance they contain pharmaceutically acceptable fillers and/or excipients. The pharmaceutically acceptable fillers and/or excipients are the substances or mixtures thereof generally known in the art as not exerting their own pharmacological effect.

The suitable fillers for use in the solid dosage forms for the conventional release of the active substance include starch, lactose, microcrystalline cellulose, saccharose, sorbitol, talc, mannitol, mono- or dibasic calcium phosphate, pregelatinized starch, glycine and others.

The solid oral dosage forms may further contain excipients facilitating the manufacturing process and imparting required physicomechanical properties to the finished dosage form. Further excipients may be selected from disintegrants, such as starch and starch derivates, crosscarmellose sodium, microcrystalline cellulose, crosslinked polyvinylpyrrolidone, starch sodium glycolate or other products based on crosslinked polymer; binders, such as polyvinylpyrrolidone, gelatin, natural and synthetic gums, cellulose derivative, *e.g.* hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose; lubricants, such as sodium lauryl sulphate; glidants, such as colloidal silicon dioxide, stearic acid, magnesium stearate, talc, fumaric acid and others.

The tablets optionally may be coated as described for example in Pharmaceutical Dosage Forms and Drug Delivery Systems, H.C.Ansel, L.V.Allen, N.G.Popovich, VIIth ed. (1999), Lippincott Williams & Wilkins. The coating formulations preferably contain film coating substance selected to provide the dissolution or fragmentation of the coating in the desired gastrointestinal tract section, together with the pharmaceutical excipients, such as plasticizers, fillers, opacifiers, colourants and polishing agents. The film coating substances are preferably polymers such as cellulose derivatives, acrylic polymers and copolymers, high molecular weight polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol and others. Suitable plasticizers can be polyols, such as glycerol; organic esters such as phtalates, sebacates or citrates, and others.

Administration of the pharmaceutical compositions comprising rosiglitazone malonate in the parenteral dosage form, e.g. for intravenous, subcutaneous or intramuscular administration, may also be considered. The parenteral compositions comprise sterile water, water-organic and non-water solutions and suspensions; lyophylisates and tablets suitable for reconstitution *ex tempore*. For liquid formulations suspending agents providing uniform active substance distribution in the liquid phase, such as polysorbates, lecithin, polyoxyethylene and polyoxypropylene copolymers; peptizers, such as phosphates, polyphosphates and citrates, water-soluble polymers, such as carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone, hydrogenated oils, gums or gelatin, may be applied.

The parenteral formulations may further contain pharmaceutically acceptable additives, such as solubilizers, preservatives, pH adjusting agents, buffers and tonicity agents.

The present invention provides crystalline rosiglitazone malonate salt distinguished by high stability and polymorphic homogeneity. The invention further provides efficient, reproducible manufacturing process of high chromatographic purity salt of rosiglitazone malonate.

The present invention is further illustrated by the following, non-limiting, examples.

Examples

Analytical methods

The infrared absorption spectra were obtained from KBr pellets on SPECTRUM BX FT-IR system Perkin-Elmer spectrophotometer with Fourier transform.

The magnetic nuclear resonance spectra were recorded using GEMINI-200 Varian spectrophotometer.

The melting point was measured using differential scanning calorimetry on Mettler Toledo DSC 822 apparatus in alumina crucibles in temperature range of 40-200°C starting with the isothermic segment (40°C, 3 minutes) followed by dynamic segment at heating rate 10°C/min. The melting point was determined in two methods: (i) as "extrapolated peak", ie., the intersection of tangent to the peak, and (ii) as "onset", ie., the intersection of tangents to the base line and to the rising peak line.

The X-ray powder diffraction (XRPD) patterns were recorded on a *MiniFlex* (Rigaku) powder diffractometer with copper radiation (CuKα, λ= 1,54056Å), with the following measurement parameters:

2Θ scanning range: 3° - 40°

Scanning rate Δω: 0.5°/min

Stepsize Δ2θ: 0.03°

Measurement temperature: room temperature

Detector: scintillation counter

Obtained diffraction patterns were analyzed and handled using DHN_PDS program.

Crystal structure was analyzed using mono-crystalline diffractometer KUMA CCD with copper radiation $MoCuK_{\alpha}$, at generator tension: 50KV and generator current: 25mA.

Example 1

In round bottom flask rosiglitazone (10,4 g, 29,1 mmol) and ethyl acetate (250 mL) were heated to boiling temperature while mixing. Then malonic acid was added (3,1 g, 29,8 mmol) and the reaction mixture was kept under reflux for 5 minutes. Then, the mixture was stirred at room temperature for 60 minutes and directly afterwards reaction mixture was left in fridge (0°C) for 4 h. Solid was filtered off, washed with cold ethyl acetate (50 mL), then dried in vacuum-dryer (50°C, 50 mbar,16 h). Rosiglitazone malonate was obtained with 96% yield (12.9 g)

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.99 i 3.07 (1H, dd), 3.06 (3H,s), 3,22 (2H,s), 3.24 i 3.31 (1H, dd), 3.88 (2H,t), 4.09 (2H,t), 4.84 (1H, m), 6.60 (2H, m), 6.85 (2H,d), 7.12 (2H,d), 7.49 (1H, m), 8.06 (1H,m)

^{13}C-NMR (DMSO-d_6), δ (ppm): 36.304, 37.131, 41.914, 48.603, 53.090, 65.344, 106.001, 111.588, 114.337, 128.701, 130.448, 137.569, 147.257, 157.529, 157.886, 168.614, 171.772, 175.773.

Example 2

In 10L capacity reactor equipped with mechanical stirrer and reflux condenser rosiglitazone (300,0 g, 0,84 mol) and ethyl acetate (5.5 L) were heated to reflux when stirring. Malonic acid (90,0 g, 0,87 mol) mixture in ethyl acetate (1.5 L) was added to the boiling rosiglitazone solution. Malonic acid mixture containing vessel has been washed with 400 mL of ethyl acetate and the washings were added to the reaction mixture. Reaction mixture was kept under reflux for 15 minutes, then heating was removed and stirring was applied for 18h. The obtained solid was filtered off using Büchner funnel and then washed with cold ethyl acetate (-15°C) (1.5 L). Product was dried in vacuum-dryer (40°C, 50 mbar, 48 h). Rosiglitazone malonate was obtained with 93% yield (362.1 g).

Example 3

In round- bottom flask rosiglitazone (1,16 g, 3,25 mmol) and malonic acid (0,34 g, 3,27 mmol) in 15 mL of acetone were heated on water bath to reflux during stirring for 0.5 h. Obtained clear solution has been cooled to 20°C and stirred at 1000 rpm for additional 0.5 h. The formed solid was filtered off, washed with cold acetone (5 mL) and dried in vacuum-dryer (50°C, 50 mbar, 16 h). Rosiglitazone malonate was obtained with 74% yield (1.1 g).

Example 4

In round- bottom flask rosiglitazone (1,34 g, 3,75 mmol) and malonic acid (0,39 g, 3,75 mmol) in 75 mL of acetonitrile were heated on water bath at 60°C while stirring for 0.5 h. Obtained clear solution has been concentrated to about 45 mL and allowed to crystallize at 5°C for 1 h. The formed solid was filtered off, washed with acetonitrile (5 mL) and dried in vacuum-dryer (50°C, 50 mbar, 16 h). Rosiglitazone malonate was obtained with 79% yield (1.37 g)

Example 5

In round- bottom flask rosiglitazone (1,64 g, 4.59 mmol) and malonic acid (0,48 g, 4.61 mmol) in 35 mL of THF were heated on water bath to reflux while stirring for 0.5 h. Obtained clear solution has been concentrated to about 17 mL and allowed to crystallize at 5°C for 16 h. The formed solid was filtered off, washed with cold THF (5 mL) and dried in vacuum-dryer (50°C, 50 mbar, 16 h). Rosiglitazone malonate was obtained with 68% yield (1.45 g).

Example 6

In 1 L capacity round-bottom flask equipped with stirrer and reflux condenser rosiglitazone malonate (8.0 g, 2.17 mmol) in 620 mL of ethyl acetate was heated to reflux with stirring for 5 minutes. Then water-bath has been removed and reaction mixture was stirred for 5 h at room temperature. The formed solid was filtered off using Büchner funnel, washed with cold ethyl acetate (-15°C, 50 mL) and dried in vacuum-dryer (40°C, 50 mbar, 16 h). Rosiglitazone malonate was obtained (5.4 g). Crystallization yield 68%.

Example 7

Rosiglitazone malonate stability studies

Stability studies were performed under both stress and long-term storage conditions:

- **temperature: 40°C ± 2°C; relative humidity: 75% ± 5% RH**
- **temperature: 25°C ± 2°C; relative humidity: 60% ± 5% RH**

Table 4A. Stability under stress conditions (storage period: 3 months) temp. 40°C ± 2°C; RH 75% ± 5%

Type of examination	**Requirement**	**Storage period / results**		
		Start	After 1 month	After 3 months
Appearance	White or whitish crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder
Identity • IR • XRPD	Identical with standard IR spectrum and XRPD pattern	• Salt structure confirmed by IR • Polymorphic form determined by XRPD	No changes were observed	No changes were observed
HPLC purity • Impurities capacity	< 0,1 %	Imine (RRT 0,7) - 0,05% RRT 1,4 - 0,04%	Imine (RRT 0,7) - 0,05% RRT 1,4 - 0,04%	Imine (RRT 0,7) - 0,04% RRT 1,4 -0,04%
• Impurities total	< 0,5 %	0,15%	0,14%	0,12%
Water content	< 0,5 %	0,15%	-	0,16 %

Table 4B. Stability under long-term conditions (storage period: 6 months) temp. 25°C ± 2°C; RH 60% ± 5%

Type of examination	**Requirement**	**Storage period / results**		
		Start	After 1 month	After 6 months
Appearance	White or whitish crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder
Identity • IR • XRPD	Identical with standard IR spectrum and XRPD pattern	• Salt structure confirmed by IR • Polymorphic form determined by XRPD	No changes were observed	No changes were observed
HPLC purity • Impurities capacity	< 0,1 %	Imine (RRT 0,7) - 0,05% RRT 1,4 - 0,04%	Imine (RRT 0,7) - 0,05% RRT 1,4 - 0,04%	Imine (RRT 0,7) - 0,04% RRT 1,4 - 0,04%
• Impurities total	< 0,5 %	0,15%	0,14%	0,12%
Water content	< 0,5 %	0,15%	-	0,15%

Rosiglitazone malonate samples under stress and long-term storage conditions revealed neither impurities level nor water content increase tendency.

Example 8

Coated tablets à 8 mg

Component	Quantity (% w.) / 1000 tablets
Core:	
Rosiglitazone malonate	10,328 g (3,44%)
Lactose monohydrate	172,672 g (57,56%)
Starch sodium glycolate	9,00 g (3%)
Microcrystalline cellulose	190,00 g (30%)
Hydroxypropylmethylcellulose	215,00 g (5%)
Magnesium stearate	3,00 g (1%)
Coating:	
Opadry II	3% (calculated on a core weight)

The components of the core were pressed to round, biconvex tablet cores, 300.00 mg ± 2% each. Cores were coated with Opadry® II coating. Coated tablets with approximated total mass of 309 mg and 10,328 mg of rosiglitazone malonate content (8 mg calculated on the rosiglitazone free base) were obtained.

Claims

1. A salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione with malonic acid, its isomers, tautomers and/or solvates thereof.

2. The salt according to claim 1 having chromatographic purity above 99.5%, determined by HPLC.

3. The salt according to claim 1 in the crystalline form.

4. The salt according to claim 3 characterized by the X-ray powder diffraction pattern showing the characteristic main peaks with relative intensities I/I_0 above 20% at 2θ degree about 4,47, 15,35, 17,12, 17,93, 20,58, 21,78, 22,53, 23,29, 23,93 ± 0.2 °.

5. The salt according to claim 3 characterized by the X-ray powder diffraction pattern (XRPD) showing the following diffraction peaks presented as the relation of reflection angles 2θ (°), interplanar spacings d (Å), and relative intensities in attitude to the most intensive diffraction peak, I/I_0 (%):

2θ (°)	d (Å)	I/I_0 (%)
4.466	19.7695	21.8
7.759	11.3848	18.2
8.939	9.8848	11.6
9.853	8.9701	3.2
10.091	8.7589	6.8
13.425	6.5898	2.7
15.348	5.7685	98.2
17.117	5.1762	56.6
17.933	4.9424	55.8
20.576	4.3131	38.2
21.780	4.0772	23.1
22.531	3.9431	31.7
23.291	3.8161	26.4
23.927	3.7160	100.0
24.800	3.5873	15.4

26.463	3.3654	15.9
26.692	3.3370	8.4
27.970	3.1874	4.4
30.632	2.9162	11.0
31.361	2.8500	5.2
33.127	2.7021	10.4
34.073	2.6291	5.5
34.768	2.5782	3.1

6. The salt according to claim 3, characterized by an X-ray diffractogram substantially as depicted in Fig.3.

7. The salt according to claim 3, characterized by T_{extr} = 131,3°C, determined by differential scanning calorimetry as extrapolated peak.

8. The salt according to claim 3, characterized by at least one of features selected from the group consisting of:
a/ X-ray powder diffraction pattern (CuKα, λ= 1,54056Å) showing the peaks with relative intensities I/I_0 above 20% at 2θ degree about 4,47, 15,35, 17,12, 17,93, 20,58, 21,78, 22,53, 23,29, 23,93 ± 0.2 °, substantially as depicted in Fig.3,
b/ infrared spectrum (KBr) with characteristic peaks at λ: 3424, 2949, 2712, 1744, 1703, 1642, 1616, 1579, 1514, 1482, 1333, 1248, 1180, 1161, 1063, 903, 822, 767, 717, 650, 615, 604, 527, 505 cm^{-1},
c/ T_{extr} = 131,3°C and T_{onset} = 129,1°C, determined by Differential Scanning Calorimetry.

9. A process for the preparation of the salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione with malonic acid, its isomers, tautomers and/or solvates thereof, wherein a 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione as a free base or salt form, suspended or dissolved in organic solvent is reacted with malonic acid or its malonic acid source.

10. The process according to claim 9, wherein malonic acid to rosiglitazone free base molar ratio is in a range from 1:1 to 1.2:1.

11. The process according to claim 9, wherein the solvent is selected from a group comprising aliphatic ketons, carboxylic acids esters, nitriles, or mixtures thereof.

12. The process according to claim 11, wherein the solvent is ethyl acetate.

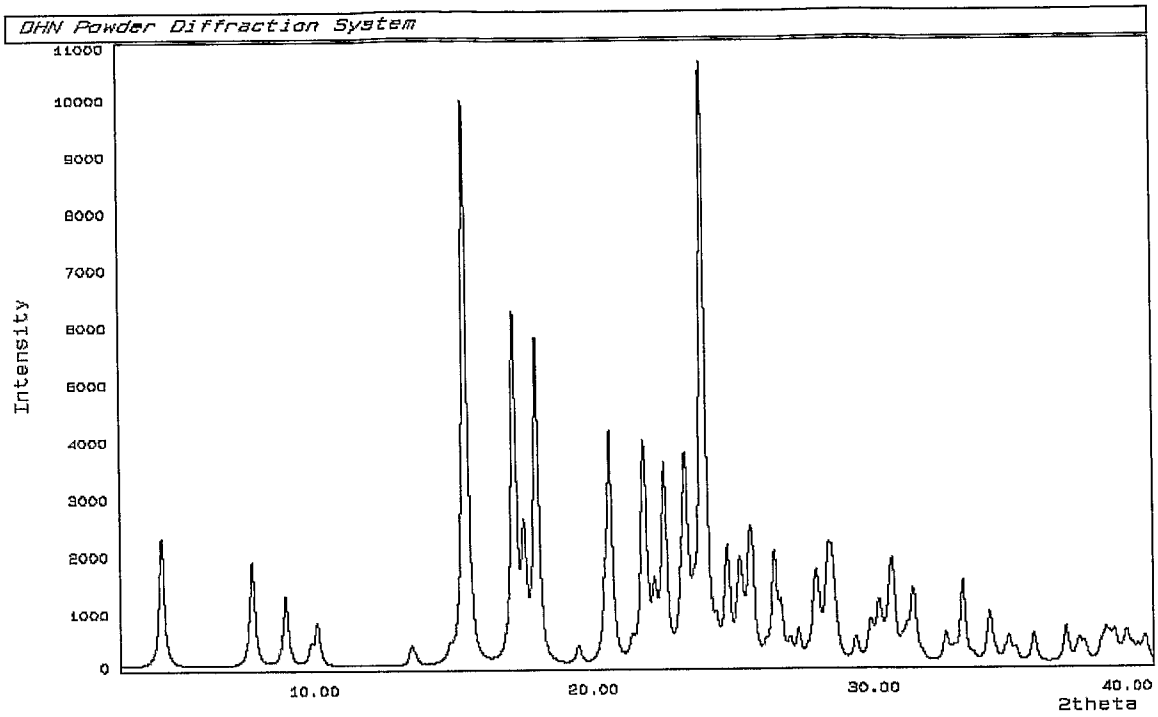
13. A process according to claim 9, comprising the steps of:
(i) mixing of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione and malonic acid in an equimolar ratio, in an organic solvent,
(ii) heating the mixture under reflux until the solid completely dissolves,
(iii) filtration of the solution and cooling down to the crystallization temperature (5°C - 20°C),
(iv) crystallization and isolation of the product, eg. by filtration,
(v) drying the isolated product.

14. The process according to claim 9, wherein the salt is obtained *in situ* without isolation of the free rosiglitazone base from the reaction mixture.

15. A pharmaceutical composition comprising malonate salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, its isomers, tautomer and/or solvate thereof as active ingredient, together with pharmaceutically acceptable carriers and/or excipients.

16. A malonate salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, its isomers, tautomers and/or solvates thereof for use as pharmacologically active substance.

17. A malonate salt of 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, its isomers, tautomers and/or solvates thereof for treatment and/or prevention of diabetes mellitus, dysfunctions associated with diabetes mellitus and certain complications thereof.


DHN Powder Diffraction System
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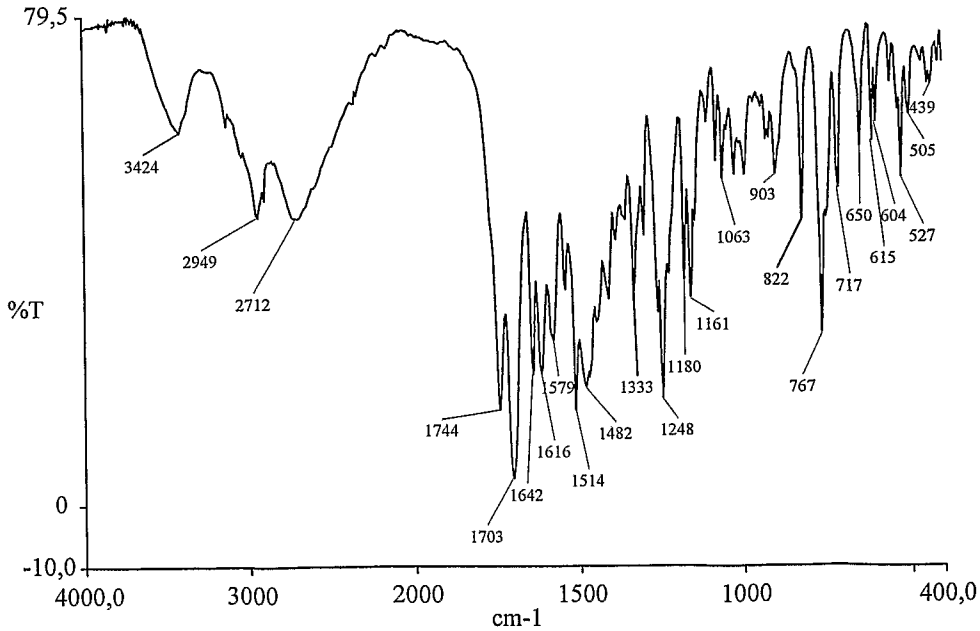
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10.00
20.00
30.00
40.00
2theta

Fig. 3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3424
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1333
1248
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903
822
767
717
650
615
604
527
505
439

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2009/000015

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 306 228 A (BEECHAM GROUP PLC [GB]) 8 March 1989 (1989-03-08) cited in the application the whole document, in particular page 2, lines 8-12; claims 12-16; example 30	1-17
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2009	15/07/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No
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A	WO 03/053962 A (SMITHKLINE BEECHAM PLC [GB]; MILLAN MICHAEL JOHN [GB]) 3 July 2003 (2003-07-03) the whole document, in particular the claims	1-17

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