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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 December 2012 (06.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/166420 A1

(51) International Patent Classification:
A61K 31/4985 (2006.01) *A61P 3/10* (2006.01)

(21) International Application Number:
PCT/US2012/038917

(22) International Filing Date:
22 May 2012 (22.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/490,819 27 May 2011 (27.05.2011) US

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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, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

(54) **Title**: PHOSPHORIC ACID SALTS OF SITAGLIPTIN

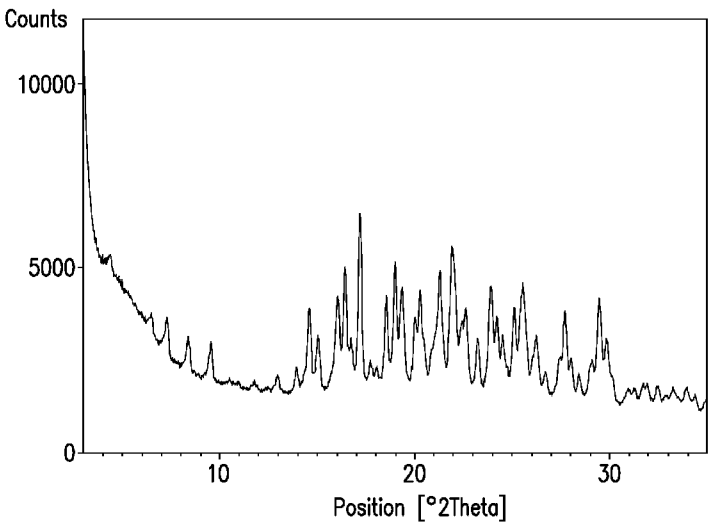

FIG.1

(57) **Abstract**: The present invention relates to novel phosphoric acid salts of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, and polymorphs, hydrates and solvates thereof, which are potent inhibitors of dipeptidyl peptidase-IV useful for the prevention and/or treatment of non-insulin dependent diabetes mellitus, also referred to as type 2 diabetes. The present invention also relates to the process for preparing the novel phosphoric acid salts of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, as well as pharmaceutical compositions containing the novel phosphoric acid salts, and methods of use thereof for the treatment of diabetes, obesity, and high blood pressure.

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TITLE OF THE INVENTION
PHOSPHORIC ACID SALTS OF SITAGLIPTIN

FIELD OF THE INVENTION

The present invention relates to novel phosphoric acid salts of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]-triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, also known as sitagliptin, which is a potent inhibitor of dipeptidyl peptidase-IV. More particularly, the invention relates to the bis(sitagliptin) phosphoric acid salt, the sitagliptin ammonia phosphoric acid salt, and the sitagliptin bis(phosphoric acid) salt, and polymorphs, hydrates and solvates thereof. These novel phosphoric acid salts, and their polymorphs, hydrates and solvates, are useful for the treatment and prevention of diseases and conditions for which an inhibitor of dipeptidyl peptidase-IV is indicated, in particular Type 2 diabetes, obesity, and high blood pressure. The invention further concerns pharmaceutical compositions comprising the bis(sitagliptin) phosphoric acid salt, the sitagliptin ammonia phosphoric acid salt, and the sitagliptin bis(phosphoric acid) salt, and polymorphs, hydrates and solvates thereof, and methods of using these novel phosphoric acid salts, and their polymorphs, hydrates and solvates, to treat Type 2 diabetes, obesity, and high blood pressure. The invention further concerns processes for preparing the novel phosphoric acid salts of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]-triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, and polymorphs, hydrates and solvates thereof.

BACKGROUND OF THE INVENTION

Inhibition of dipeptidyl peptidase-IV (DP-IV), an enzyme that inactivates both glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), represents a novel approach to the treatment and prevention of Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM). The therapeutic potential of DP-IV inhibitors for the treatment of Type 2 diabetes has been reviewed: C. F. Deacon and J.J. Holst, "Dipeptidyl peptidase IV inhibition as an approach to the treatment and prevention of Type 2 diabetes: a historical perspective," Biochem. Biophys. Res. Commun., 294: 1-4 (2000); K. Augustyns, et al., "Dipeptidyl peptidase IV inhibitors as new therapeutic agents for the treatment of Type 2 diabetes," Expert. Opin. Ther. Patents, 13: 499-510 (2003); and D.J. Drucker, "Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of Type 2 diabetes," Expert Opin. Investig. Drugs, 12: 87-100 (2003).

WO 03/004498 (published 16 January 2003), assigned to Merck & Co., describes a class of beta-amino tetrahydrotriazolo[4,3-*a*]pyrazines, which are potent inhibitors of DP-IV and

therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in WO 03/004498 is 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine. Pharmaceutically acceptable salts of this compound are generically encompassed within the scope of WO 03/004498. WO 05/003135, assigned to Merck & Co., describes other phosphoric acid salts of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine.

SUMMARY OF THE INVENTION

The present invention is concerned with novel phosphoric acid salts of the dipeptidyl peptidase-IV (DP-IV) inhibitor 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine and polymorphs, hydrates and solvates thereof, in particular the bis(sitagliptin) phosphoric acid monohydrate salt, the bis(sitagliptin) monohydrogen phosphate trihydrate salt, the sitagliptin ammonia phosphoric acid 2.5 hydrate salt, and the sitagliptin bis(phosphoric acid) salt. The novel phosphoric acid salts, polymorphs and hydrates of the present invention have advantages in the preparation of pharmaceutical compositions of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]-triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, such as physical stability and the resulting ease of processing, handling, and dosing. The invention also concerns pharmaceutical compositions containing the novel phosphoric acid salts, polymorphs, hydrates and solvates thereof, as well as methods for using them as DP-IV inhibitors, in particular for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a X-ray diffraction pattern of the crystalline trihydrate of the bis(sitagliptin) phosphoric acid salt of structural formula III-a.

FIG. 2 is a thermogravimetric analysis (TGA) curve of the crystalline trihydrate of the bis(sitagliptin) phosphoric acid salt of structural formula III-a.

FIG. 3 is a differential scanning calorimetry (DSC) curve of the crystalline trihydrate of the bis(sitagliptin) phosphoric acid salt of structural formula III-a.

FIG. 4 is a X-ray diffraction pattern of the crystalline monohydrate of the bis(sitagliptin) phosphoric acid salt of structural formula IV-a.

FIG. 5 is a thermogravimetric analysis (TGA) curve of the crystalline monohydrate of the bis(sitagliptin) phosphoric acid salt of structural formula IV-a.

FIG. 6 is a differential scanning calorimetry (DSC) curve of the crystalline monohydrate of the bis(sitagliptin) phosphoric acid salt of structural formula IV-a.

FIG. 7 is a X-ray diffraction pattern of the crystalline 2.5 hydrate of the sitagliptin ammonia phosphoric acid salt of structural formula VI-a.

FIG. 8 is a thermogravimetric analysis (TGA) curve of the crystalline 2.5 hydrate of the sitagliptin ammonia phosphoric acid salt of structural formula VI-a.

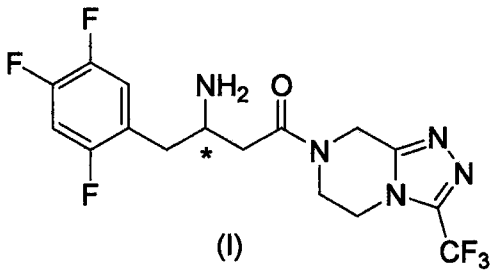
FIG. 9 is a differential scanning calorimetry (DSC) curve of the crystalline 2.5 hydrate of the sitagliptin ammonia phosphoric acid salt of structural formula VI-a.

FIG. 10 is a X-ray diffraction pattern of the amorphous sitagliptin bis(phosphoric acid) salt of structural formula VII-a.

FIG. 11 is a thermogravimetric analysis (TGA) curve of the amorphous sitagliptin bis(phosphoric acid) salt of structural formula VII-a.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides novel phosphoric acid salts of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (sitagliptin), which is the compound of structural formula I:



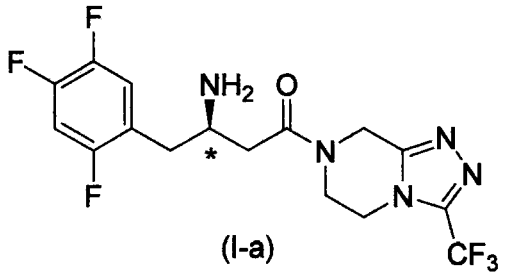
(I)

and polymorphs, hydrates and solvates thereof. In a class of this embodiment, the present invention provides a bis-[4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine] phosphoric acid trihydrate salt, a bis-[4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine] phosphoric acid monohydrate salt, a 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)-butan-2-amine ammonia phosphoric acid 2.5 hydrate salt, and a 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)-butan-2-amine bis(phosphoric acid) salt, and polymorphs, and solvates thereof.

The phosphoric acid salts of the present invention has a center of asymmetry at the stereogenic carbon atom indicated with an * and can thus occur as a racemate, racemic mixture, and single enantiomers, with all isomeric forms being included in the present invention. The

separate enantiomers, substantially free of the other, are included within the scope of the invention, as well as mixtures of the two enantiomers.

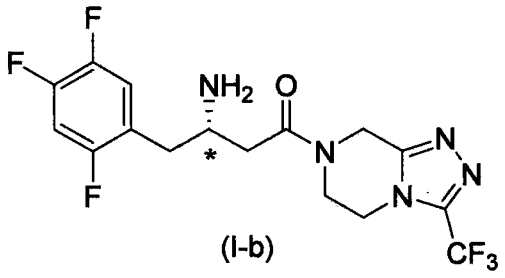
One embodiment of the present invention provides novel phosphoric acid salts of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, which is the compound of structural formula I-a (also known as sitagliptin free base):



(I-a)

and polymorphs, hydrates and solvates thereof. In a class of this embodiment, the present invention provides a bis(sitagliptin) phosphoric acid trihydrate salt, a bis(sitagliptin) phosphoric acid monohydrate salt, a sitagliptin ammonia phosphoric acid 2.5 hydrate salt, and a sitagliptin bis(phosphoric acid) salt, and polymorphs, hydrates and solvates thereof.

Another embodiment of the present invention provides novel phosphoric acid salts of (2*S*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, which is the compound of structural formula I-b:



(I-b)

and polymorphs, hydrates and solvates thereof. In a class of this embodiment, the present invention provides a bis-[(2*S*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine] phosphoric acid trihydrate salt, a bis-[(2*S*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine] phosphoric acid monohydrate salt, a (2*S*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine ammonia phosphoric acid 2.5 hydrate salt, and a (2*S*)-4-oxo-4-[3-

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