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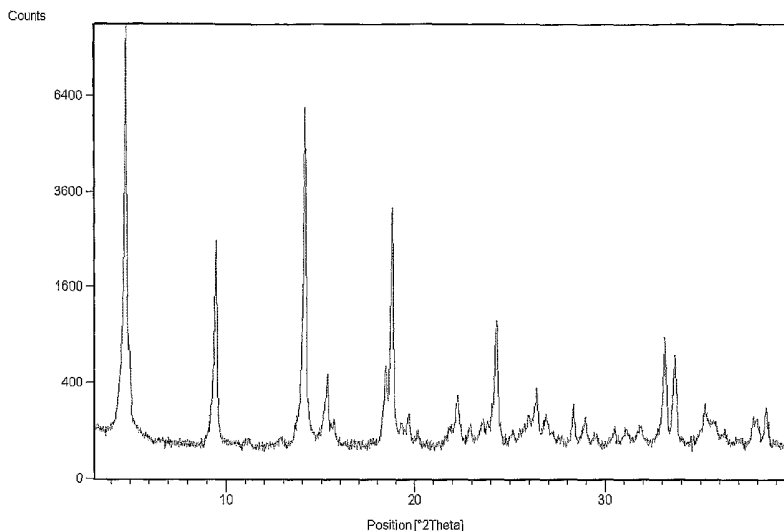
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(54) Title: NOVEL CRYSTALLINE FORMS OF A PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR



(57) Abstract: The present invention relates to crystalline anhydrate polymorphs of the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3- α]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine as well as a process for their preparation, pharmaceutical compositions containing these novel forms, and methods of use of the novel forms and pharmaceutical compositions for the treatment of diabetes, obesity, and high blood pressure. The invention also concerns novel crystalline solvates of the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3- α]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine as well as a crystalline desolvated polymorph and their use for the preparation of the anhydrate polymorphs of the present invention.

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TITLE OF THE INVENTION

NOVEL CRYSTALLINE FORMS OF A PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

5 FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of a dihydrogenphosphate salt of a dipeptidyl peptidase-IV inhibitor. More particularly, the invention relates to novel crystalline solvates and anhydrides of the dihydrogenphosphate salt 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 a potent inhibitor of dipeptidyl peptidase-IV (DPP-IV). These novel crystalline forms of the DPP-IV inhibitor are useful for the preparation of pharmaceutical compositions containing the inhibitor which 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, hyperglycemia, insulin resistance, obesity, and high blood pressure. The invention further concerns pharmaceutical compositions comprising the novel crystalline dihydrogenphosphate salt anhydrate polymorphic forms of the present invention; processes for preparing the dihydrogenphosphate salt solvates and anhydrides and their pharmaceutical compositions; and methods of treating conditions for which a DPP-IV inhibitor is indicated comprising administering a composition of the present invention.

20 BACKGROUND OF THE INVENTION

Inhibition of dipeptidyl peptidase-IV (DPP-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 DPP-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," Exp. 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," Exp. Opin. Investig. Drugs, 12: 87-100 (2003).

WO 03/004498 (published 16 January 2003) and U.S. Patent No. 6,699,871 (issued March 2, 2004), both assigned to Merck & Co., describe a class of beta-amino tetrahydrotriazolo[4,3-*a*]pyrazines, which are potent inhibitors of DPP-IV and therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in WO 03/004498 is (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.

However, there is no disclosure in the above references of the newly discovered crystalline solvates and anhydrides of the dihydrogenphosphate salt 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 of structural formula I below (hereinafter referred to as Compound I).

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SUMMARY OF THE INVENTION

The present invention is concerned with novel crystalline solvates and anhydrides of the dihydrogenphosphate salt of the dipeptidyl peptidase-IV (DPP-IV) inhibitor (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 of structural formula I (Compound I). The crystalline solvates and anhydrides of the present invention have advantages in the preparation of pharmaceutical compositions of the dihydrogenphosphate salt 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, such as ease of processing, handling, and dosing. In particular, they exhibit improved physicochemical properties, such as solubility, stability to stress, and rate of dissolution, rendering them particularly suitable for the manufacture of various pharmaceutical dosage forms. The invention also concerns pharmaceutical compositions containing the novel anhydrate polymorphs; processes for the preparation of these solvates and anhydrides and their pharmaceutical compositions; and methods for using them for the prevention or treatment of Type 2 diabetes, hyperglycemia, insulin resistance, obesity, and high blood pressure.

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BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a characteristic X-ray diffraction pattern of the crystalline anhydrate Form I of Compound I.

FIG. 2 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline anhydrate Form I of Compound I.

FIG. 3 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline anhydrate Form I of Compound I.

FIG. 4 is a typical DSC curve of the crystalline anhydrate Form I of Compound I.

FIG. 5 is a typical thermogravimetric (TG) curve of the crystalline anhydrate Form I of Compound I.

FIG. 6 is a characteristic X-ray diffraction pattern of the crystalline desolvated anhydrate Form II of Compound I.

FIG. 7 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline desolvated anhydrate Form II of Compound I.

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FIG. 8 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline desolvated anhydrate Form II of Compound I.

FIG. 9 is a typical DSC curve of the crystalline desolvated anhydrate Form II of Compound I.

5 FIG. 10 is a typical TG curve of the crystalline desolvated anhydrate Form II of Compound I.

FIG. 11 is a characteristic X-ray diffraction pattern of the crystalline anhydrate Form III of Compound I.

10 FIG. 12 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline anhydrate Form III of Compound I.

FIG. 13 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline anhydrate Form III of Compound I.

FIG. 14 is a typical DSC curve of the crystalline anhydrate Form III of Compound I.

FIG. 15 is a typical TG curve of the crystalline anhydrate Form III of Compound I.

15 FIG. 16 is a characteristic X-ray diffraction pattern of the crystalline ethanol solvate of Compound I.

FIG. 17 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline ethanol solvate of Compound I.

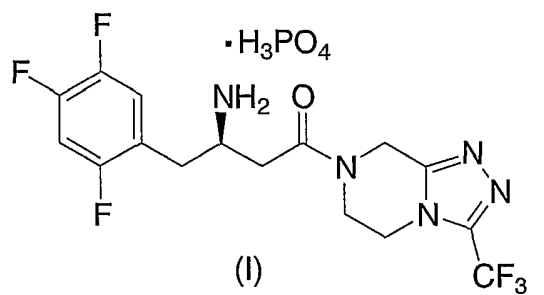
20 FIG. 18 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline ethanol solvate of Compound I.

FIG. 19 is a typical DSC curve of the crystalline ethanol solvate of Compound I.

FIG. 20 is a typical TG curve of the crystalline ethanol solvate of Compound I.

DETAILED DESCRIPTION OF THE INVENTION

25 This invention provides novel crystalline solvates and anhydrides of the dihydrogenphosphate salt 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 of structural formula I (Compound I):



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