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(54) **Title:** NOVEL CRYSTALLINE SALTS OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

(57) **Abstract:** Novel crystalline 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-&agr; amine are potent inhibitors of dipeptidyl peptidase-IV and are useful for the treatment of non-insulin dependent (Type 2) diabetes mellitus. The invention also relates to pharmaceutical compositions containing these novel salts, processes to prepare these salts and their pharmaceutical compositions as well as uses thereof for the treatment of Type 2 diabetes.

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TITLE OF THE INVENTION

NOVEL CRYSTALLINE SALTS OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

FIELD OF THE INVENTION

The present invention relates to novel crystalline salts of a dipeptidyl peptidase-IV inhibitor. More particularly, the invention relates to novel crystalline hydrochloric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, 10-camphorsulfonic acid, and tartaric 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 a potent inhibitor of dipeptidyl peptidase-IV. These novel crystalline salts, and hydrates thereof, 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 novel crystalline salts of the present invention, or hydrates thereof, useful to treat Type 2 diabetes, obesity, and high blood pressure as well as processes for the preparation of such salts and their pharmaceutical compositions.

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," Expert. Opin. Ther. Patents, 13: 499-510 (2003); 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); and M.A. Nauck et al., "Incretins and Their Analogues as New Antidiabetic Drugs," Drug News Perspect., 16: 413-422 (2003).

US Patent No. 6,699,871 (issued March 2, 2004) and WO 03/004498 (published 16 January 2003), 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 US Patent No. 6,699,871 and 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. Pharmaceutically acceptable salts of this compound are generically encompassed within the scope of WO 03/004498 and US Patent No. 6,699,871.

However, there is no specific disclosure in WO 03/004498 and US Patent No. 6,699,871 of the newly discovered crystalline hydrochloric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, 10-camphorsulfonic acid, or tartaric acid 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.

SUMMARY OF THE INVENTION

The present invention is concerned with novel crystalline hydrochloric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, 10-camphorsulfonic acid, and tartaric acid salts 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. Such salts, and hydrates thereof, have advantages in the preparation of pharmaceutical compositions 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 solution, rendering them particularly suitable for the manufacture of various pharmaceutical dosage forms. The invention also concerns pharmaceutical compositions containing the novel salts, or hydrates thereof, as well as methods for using them as DPP-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 characteristic X-ray diffraction pattern of the crystalline hydrochloric acid salt monohydrate of Compound I of the present invention.

FIG. 2 is a typical thermogravimetric analysis (TGA) curve of the crystalline hydrochloric acid salt monohydrate of Compound I of the present invention.

FIG. 3 is a typical differential scanning calorimetry (DSC) curve of the crystalline hydrochloric acid salt monohydrate of Compound I of the present invention.

FIG. 4 is a characteristic X-ray diffraction pattern of the crystalline L-tartaric acid salt hemihydrate of Compound I of the present invention.

FIG. 5 is a typical thermogravimetric analysis (TGA) curve of the crystalline L-tartaric acid salt hemihydrate of Compound I of the present invention.

FIG. 6 is a typical differential scanning calorimetry (DSC) curve of the crystalline L-tartaric acid salt hemihydrate of Compound I of the present invention.

FIG. 7 is a characteristic X-ray diffraction pattern of the crystalline benzenesulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 8 is a typical thermogravimetric analysis (TGA) curve of the crystalline benzenesulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 9 is a typical differential scanning calorimetry (DSC) curve of the crystalline benzenesulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 10 is a characteristic X-ray diffraction pattern of the crystalline *p*-toluenesulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 11 is a typical thermogravimetric analysis (TGA) curve of the crystalline *p*-toluenesulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 12 is a typical differential scanning calorimetry (DSC) curve of the crystalline *p*-toluenesulfonic acid salt anhydrate of Compound I of the present invention.

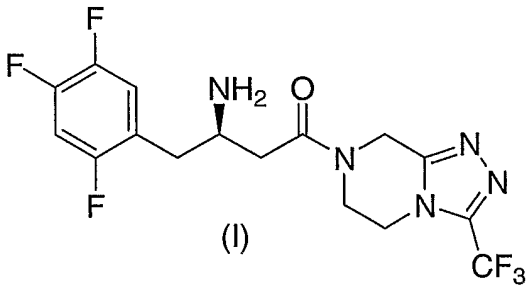
FIG. 13 is a characteristic X-ray diffraction pattern of the crystalline (1*S*)-(+)-10-camphorsulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 14 is a typical thermogravimetric analysis (TGA) curve of the crystalline (1*S*)-(+)-10-camphorsulfonic acid salt anhydrate of Compound I of the present invention.

FIG. 15 is a typical differential scanning calorimetry (DSC) curve of the crystalline (1*S*)-(+)-10-camphorsulfonic salt anhydrate of Compound I of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a crystalline acid 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):



(I)

or a hydrate thereof;

wherein the acid is selected from the group consisting of hydrochloric acid, tartaric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, and 10-camphorsulfonic acid.

One embodiment of the present invention provides a crystalline hydrochloric acid 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 (Compound I).

In a class of this first embodiment the crystalline hydrochloric acid salt of Compound I is in the form of a monohydrate.

A second embodiment of the present invention provides a crystalline tartaric acid 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 (Compound I).

In a class of this second embodiment the crystalline tartaric acid salt is the crystalline L-tartaric acid salt. In a second class of this embodiment the crystalline tartaric acid salt is the crystalline D-tartaric acid salt. In a third class the crystalline tartaric acid salt is the crystalline racemic DL tartaric acid salt. In a subclass of this third class, the crystalline tartaric acid salt of Compound I is in the form of a hemihydrate.

A third embodiment of the present invention provides a crystalline benzenesulfonic acid 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 (Compound I).

In a class of this third embodiment the crystalline benzenesulfonic acid salt of Compound I is in the form of an anhydrate.

A fourth embodiment of the present invention provides a crystalline *p*-toluenesulfonic acid 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 (Compound I).

In a class of this fourth embodiment the crystalline *p*-toluenesulfonic acid salt of Compound I is in the form of an anhydrate.

A fifth embodiment of the present invention provides a crystalline 10-camphorsulfonic acid 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 (Compound I).

In a class of this fifth embodiment the crystalline 10-camphorsulfonic salt is the crystalline (1*R*)-(-)-camphorsulfonic acid salt. In a second class the crystalline 10-camphorsulfonic salt is the crystalline (1*S*)-(+)-camphorsulfonic acid salt. In a third class the crystalline 10-camphorsulfonic acid salt is the crystalline racemic (+/-)-10-camphorsulfonic acid salt. In a subclass of this third class, the crystalline 10-camphorsulfonic acid salt of compound I is in the form of an anhydrate.

A further embodiment of the present invention provides a particular salt drug substance that comprises a crystalline salt of the present invention present in a detectable amount. By "drug substance" is meant the active pharmaceutical ingredient. The amount of

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