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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 March 2005 (10.03.2005)

PCT

(10) International Publication Number
WO 2005/020920 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/027983

(22) International Filing Date: 27 August 2004 (27.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/499,629 2 September 2003 (02.09.2003) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WENSLOW, Robert, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ARMSTRONG, Joseph, D., III** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **CHEN, Alex, M.** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **CYPES, Stephen** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **FERLITA, Russell, R.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HANSEN, Karl** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LINDEMANN, Christopher, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SPARTALIS, Evangelia** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

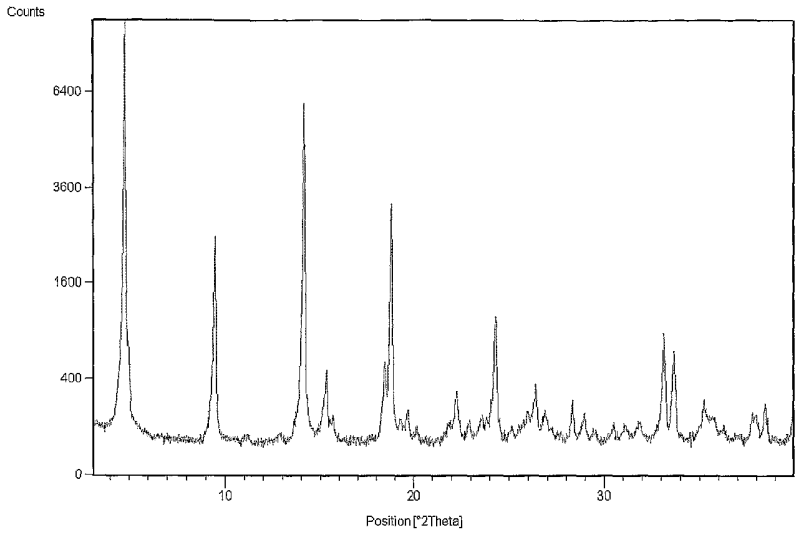
(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(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 (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8*H*)-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 (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8*H*)-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.

WO 2005/020920 A2

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, HU, IE, IT, LU, MC, NL, 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:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE OF THE INVENTION

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

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 anhydrates 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 anhydrates 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.

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 anhydrates 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).

SUMMARY OF THE INVENTION

The present invention is concerned with novel crystalline solvates and anhydrates 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 anhydrates 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 anhydrates 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.

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.

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.

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.

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.

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.

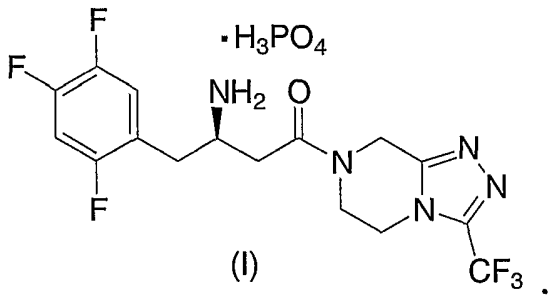
FIG. 18 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline ethanol solvate of Compound I.

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

This invention provides novel crystalline solvates and anhydrates 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):



(I)

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.