SUBSTITUTE for PTO/SB/05 (04-04) Utility Patent Application Transmittal
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# UTILITY PATENT APPLICATION TRANSMITTAL

*(Only for new nonprovisional applications under 37 CFR 1.53(b))*

| | |
|---|---|
| *Attorney Docket No.* | 21409Y |
| *First Inventor or Application Identifier* | Alex Minhua Chen, et al. |
| Title | PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE IV INHIBITOR |
| *Express Mail Label No.* | EL989589055US |

## APPLICATION ELEMENTS
*See MPEP chapter 600 concerning utility patent application contents.*

*ADDRESS TO:* **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

1. ☒ Fee Transmittal Form *(Submit an original, and a duplicate for fee processing)*
2. ☒ Specification [ *Total Pages* 25 ]
3. ☒ Drawing(s) *(35 USC 113)* [ *Total Sheets* 5 ]
4. Oath or Declaration
   a. ☒ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 14 completed)*
      i. ☐ DELETION OF INVENTOR(S)
      Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33 (b).
5. ☐ Application Data Sheet. See 37 CFR 1.76
6. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ paper
   c. ☐ Statements verifying identity of above copies

## ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment papers (cover sheet & document(s))
8. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
9. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
10. ☐ Preliminary Amendment
11. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
12. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
13. ☐ Other: _____

14. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. ____/_____

*Prior application information:* *Examiner* _____ *Group/Art Unit:* _____

**For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference.**

## 15. CORRESPONDENCE ADDRESS

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| Name | Philippe L. Durette | *Registration No. (Attorney/Agent)* | 35,125 |
| Signature | Philippe L. Durette | Date | 6/23/2004 |

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**DATE OF DEPOSIT** June 23, 2004

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**MAILED BY** Lori Schepel **DATE** June 23, 2004

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PATENT

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
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Alexandria, VA 22313-1450

Deposit Acct. 13-2755
MERCK & CO., INC.
Our Case Docket No. 21409Y

Sir:

Transmitted herewith for filing under 37 C.F.R. §1.53(b) is the patent application of Inventor(s):
Alex Minhua Chen, Russell R. Ferlita, Karl Hansen, Ivan Lee, Stephen Howard Cypes, Vicky K. Vydra, Robert M Wenslow

For: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

| For | Number Filed | Number Extra | Rate | Basic Fee $770 |
|---|---|---|---|---|
| Total Claims | 35 - 20 = | 15 X | $18 | = $270 |
| Independent Claims | 2 - 3 = | 0 X | $86 | = $0 |
| Multiple Dependent Claims* | | | $290 | = |
| * Add this fee if application contains any multiple dependent claims, regardless of number. | | TOTAL FILING FEE ⟶ | | $1,040 |

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☐ Under the provisions of 37 C.F.R. §1.53, this application is being filed without the declaration of each inventor.

Respectfully,

Philippe L. Durette

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Date: June 23, 2004

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**MAILED BY** Lora Schepisi **DATE** June 23, 2004

**IN DUPLICATE**

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TITLE OF THE INVENTION

PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional application Serial No. 60/482,161, filed June 24, 2003, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to a particular salt of a dipeptidyl peptidase-IV inhibitor. More particularly, the invention relates to a dihydrogenphosphate salt 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, which is a potent inhibitor of dipeptidyl peptidase-IV. This novel salt and crystalline 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 dihydrogenphosphate salt and crystalline hydrates thereof useful to treat Type 2 diabetes, obesity, and high blood pressure as well as processes for preparing the dihydrogenphosphate salt and crystalline hydrates thereof and their pharmaceutical compositions.

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.

However, there is no specific disclosure in the above reference of the newly discovered monobasic dihydrogenphosphate salt 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 of structural formula I below.

## SUMMARY OF THE INVENTION

The present invention is concerned with a novel dihydrogenphosphate salt 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 crystalline hydrates thereof, in particular a crystalline monohydrate. The dihydrogenphosphate salt and crystalline 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 ease of processing, handling, and dosing. In particular, they exhibit improved physical and chemical stability, such as stability to stress, high temperatures and humidity, as well as improved physicochemical properties, such as solubility 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 salt and hydrates 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 characteristic X-ray diffraction pattern of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

FIG. 2 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

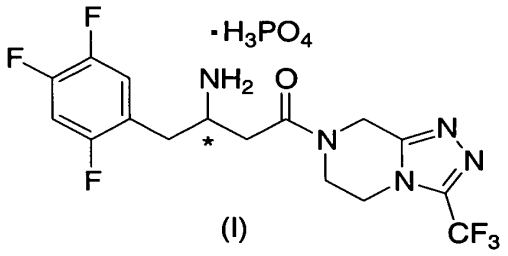
FIG. 3 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

FIG. 4 is a typical thermogravimetric analysis (TGA) curve of the crystalline monohydrate dihydrogenphosphate salt of structural formula II.

FIG. 5 is a typical differential scanning calorimetry (DSC) curve of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a new monobasic dihydrogenphosphate salt 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 of the following structural formula I:

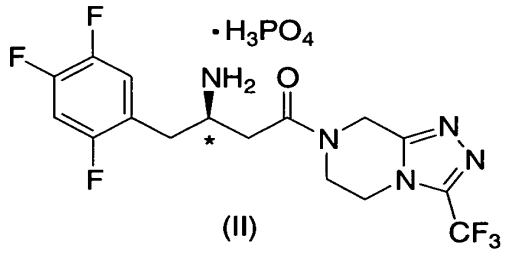



(I)

or a crystalline hydrate thereof. In particular, the instant invention provides a crystalline monohydrate of the dihydrogenphosphate salt of formula I.

The dihydrogenphosphate salt 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.

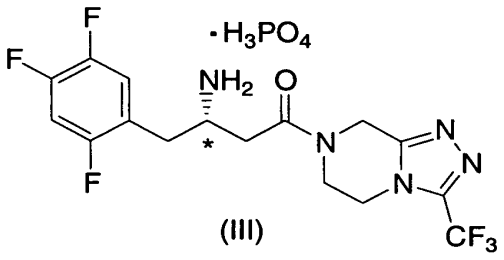
One embodiment of the present invention provides the dihydrogenphosphate salt of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula II:




(II)

or a crystalline hydrate thereof.

A second embodiment of the present invention provides the dihydrogenphosphate salt 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 of structural formula III:




(III)

or a crystalline hydrate thereof.

More specifically, the dihydrogenphosphate salt of the present invention is comprised of one molar equivalent of mono-protonated 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 cation and one molar equivalent of dihydrogenphosphate (biphosphate) anion.

In a further embodiment of the present invention, the dihydrogenphosphate salt of structural formulae I-III is a crystalline hydrate. In one class of this embodiment, the crystalline hydrate is a crystalline monohydrate.

A further embodiment of the present invention provides the dihydrogenphosphate salt drug substance of structural formulae I-III that comprises the crystalline monohydrate present in a detectable amount. By "drug substance" is meant the active pharmaceutical ingredient ("API"). The amount of crystalline monohydrate in the drug substance can be quantified by the use of physical methods such as X-ray powder diffraction, solid-state fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance spectroscopy, solid-state carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance spectroscopy, solid state Fourier-transform infrared spectroscopy, and Raman spectroscopy. In a class of this embodiment, about 5% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a second class of this embodiment, about 10% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a third class of this embodiment, about 25% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a fourth class of this embodiment, about 50% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a fifth class of this embodiment, about 75% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a sixth class of this embodiment, substantially all of the dihydrogenphosphate salt drug substance is the crystalline monohydrate of the present invention, i.e., the dihydrogenphosphate salt drug substance is substantially phase pure monohydrate.

The crystalline dihydrogenphosphate salt of the present invention exhibits pharmaceutic advantages over the free base and the previously disclosed hydrochloride salt (WO 03/004498) in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient. In

particular, the enhanced chemical and physical stability of the crystalline dihydrogenphosphate salt monohydrate constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient.

The dihydrogenphosphate salt of the present invention, which exhibits potent DP-IV inhibitory properties, is particularly useful for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

Another aspect of the present invention provides a method for the prevention or treatment of clinical conditions for which an inhibitor of DP-IV is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate thereof. Such clinical conditions include diabetes, in particular Type 2 diabetes, hyperglycemia, insulin resistance, and obesity.

The present invention also provides the use of the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate, for the manufacture of a medicament for the prevention or treatment of clinical conditions for which an inhibitor of DP-IV is indicated.

The present invention also provides pharmaceutical compositions comprising the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate, in association with one or more pharmaceutically acceptable carriers or excipients. In one embodiment the pharmaceutical composition comprise a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises a detectable amount of the crystalline monohydrate of the present invention. In a second embodiment the pharmaceutical composition comprise a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises about 5% to about 100% by weight of the crystalline monohydrate of the present invention. In a class of this second embodiment, the active pharmaceutical ingredient in such compositions comprises about 10% to about 100% by weight of the crystalline monohydrate. In a second class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 25% to about 100% by weight of the crystalline monohydrate. In a third class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 50% to about 100% by weight of the crystalline monohydrate. In a fourth class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 75% to about 100% by weight of the crystalline monohydrate. In a fifth class of this embodiment, substantially all of the active pharmaceutical ingredient is the crystalline dihydrogenphosphate salt monohydrate of the

present invention, i.e., the active pharmaceutical ingredient is substantially phase pure dihydrogenphosphate salt monohydrate.

The compositions in accordance with the invention are suitably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories. The compositions are intended for oral, parenteral, intranasal, sublingual, or rectal administration, or for administration by inhalation or insufflation. Formulation of the compositions according to the invention can conveniently be effected by methods known from the art, for example, as described in Remington's Pharmaceutical Sciences, 17th ed., 1995.

The dosage regimen is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. An ordinarily skilled physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

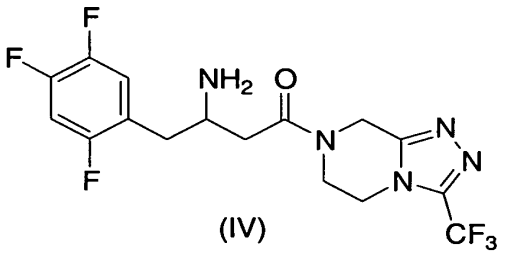
Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 200, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 200 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the crystalline forms of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the crystalline forms of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the dihydrogenphosphate salt and crystalline hydrates herein described in detail can form the active pharmaceutical ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active pharmaceutical ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the active pharmaceutical ingredient can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The dihydrogenphosphate salt of structural formula I and the crystalline monohydrate have been found to possess a high solubility in water, rendering it especially amenable to the preparation of formulations, in particular intranasal and intravenous formulations, which require relatively concentrated aqueous solutions of active ingredient. The solubility of the crystalline dihydrogenphosphate salt monohydrate of formula I in water has been found to be about 72 mg/mL.

According to a further aspect, the present invention provides a process for the preparation of the dihydrogenphosphate salt of formula I, which process comprises reacting 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 IV below:




(IV)

with approximately one equivalent of phosphoric acid in a suitable $C_1$-$C_5$ alkanol, such as methanol, ethanol, isopropyl alcohol (IPA), and isoamyl alcohol (IAA) or aqueous $C_1$-$C_5$ alkanol. The reaction is carried out at a temperature range of about 25 °C to about 80 °C. The phosphoric acid solution can be added to a solution of the amine, or the addition can be performed in the reverse direction. The crystalline dihydrogenphosphate salt monohydrate is obtained by crystallization from an aqueous $C_1$-$C_5$ alkanol solution of the dihydrogenphosphate salt as described below.

GENERAL METHODS FOR CRYSTALLIZING THE MONOHYDRATE OF THE DIHYDROGENPHOSPHATE SALT OF STRUCTURAL FORMULA I:

(a) In ethanol/water system at 25 °C:
(1) crystallization from a mixture of compound I in ethanol and water, such that the water concentration is above 31 weight percent,
(2) recovering the resultant solid phase, and
(3) removing the solvent therefrom.

(b) In isoamyl alcohol (IAA)/water system at 25 °C:
(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 2.9 weight percent;
(2) recovering the resultant solid phase; and
(3) removing the solvent therefrom.

(c) In IAA/water system at 40 °C:
(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 3.6 weight percent;
(2) recovering the resultant solid phase; and
(3) removing the solvent therefrom

(d) In IAA/water system at 60 °C:
(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 4.5 weight percent;
(2) recovering the resultant solid phase; and
(3) removing the solvent therefrom.

(e) In Isopropyl alcohol (IPA)/water system at 25 °C:
(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above 7.0 weight percent;
(2) recovering the resultant solid phase; and
(3) removing the solvent therefrom

(f) In IPA/water system at 40 °C:

(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above 8.1 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(g) In IPA/water system at 75°C:

(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above about 20 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

The starting compound of structural formula IV can be prepared by the procedures detailed in Schemes 1-3 and Example 1 below.

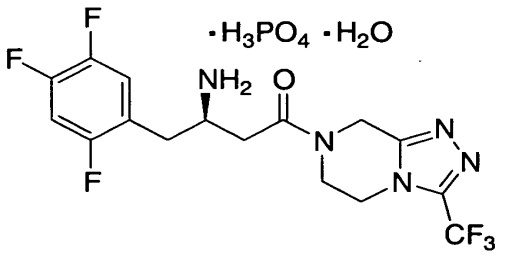
In a still further aspect, the present invention provides a method for the treatment and/or prevention of clinical conditions for which a DP-IV inhibitor is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the salt of Formula I as defined above or a crystalline hydrate thereof.

The following non-limiting Examples are intended to illustrate the present invention and should not be construed as being limitations on the scope or spirit of the instant invention.

Compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I.

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity."

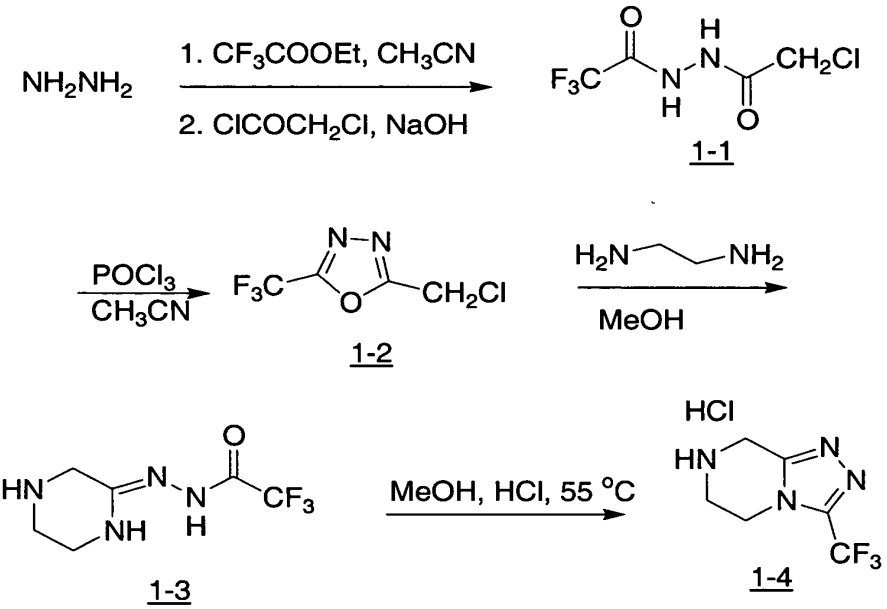
EXAMPLE



(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 dihydrogenphosphate monohydrate

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloride (1-4)

Scheme 1




Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.

$^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole (1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

$^1$H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm.

$^{13}$C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2*Z*)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC).

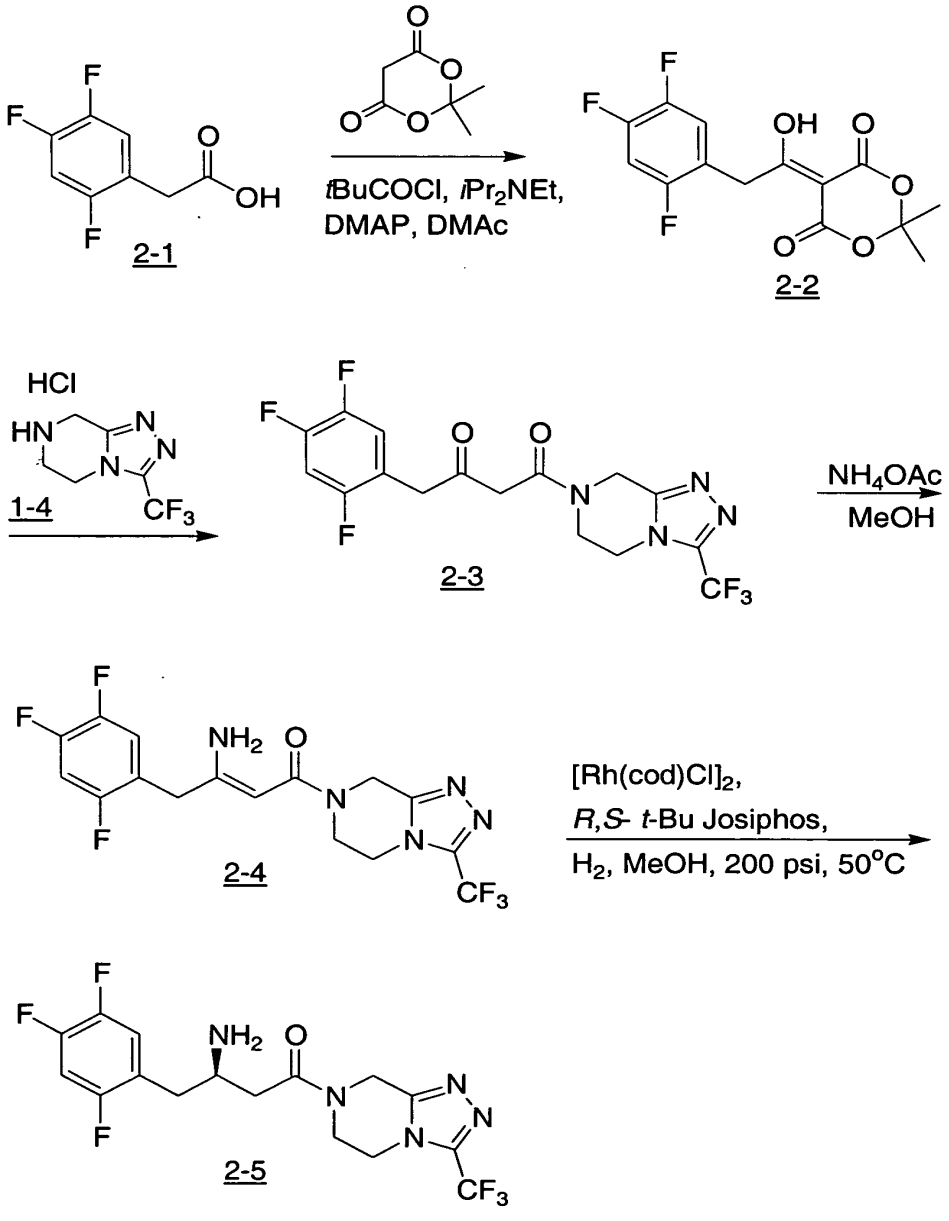
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) ppm.

Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloride (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30

min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC).
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ: 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

Scheme 2



Step A: Preparation 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-one (2-3)

2,4,5-Trifluorophenylacetic acid (2-1) (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino)pyridine (DMAP) (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. *N,N*-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to dissolve the solids. *N,N*-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5 °C. The reaction mixture was aged at 5 °C for 1 h. Triazole hydrochloride 1-4 (180 g, 0.789 mol) was added in one portion at 40-50 °C. The reaction solution was aged at 70 °C for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20 – 45 °C. The batch was seeded and aged at 20 – 30 °C for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0 – 5 °C and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product 2-3 was 89%.

Step B: Preparation of (2*Z*)-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)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30 °C during the addition. Additional methanol (100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5 °C in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid (180 g); m.p. 271.2 °C.

Step C: Preparation 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 (2-5)

Into a 500 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]$_2$}(292 mg, 1.18 mmol) and (*R,S*) *t*-butyl Josiphos (708 mg, 1.3 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (200 mL) and the mixture was stirred at room temperature for 1 h. Into a 4 L hydrogenator was charged the enamine amide 2-4 (118 g, 0.29 mol) along with MeOH (1 L). The slurry was degassed. The catalyst solution was then transferred to the hydrogenator under

nitrogen. After degassing three times, the enamine amide was hydrogenated under 200 psi hydrogen gas at 50 °C for 13 h. Assay yield was determined by HPLC to be 93% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl *t*-butyl ether (MTBE) (45 mL). Into this solution was added aqueous $H_3PO_4$ solution (0.5 M, 95 mL). After separation of the layers, 3*N* NaOH (35 mL) was added to the water layer, which was then extracted with MTBE (180 mL + 100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75 °C). The hot toluene solution was then allowed to cool to 0 °C slowly (5 – 10 h). The crystals were isolated by filtration (13 g, yield 72%, 98 – 99% ee); m.p. 114.1 – 115.7 °C.

$^1$H NMR (300 MHz, $CD_3CN$): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:

$^{13}$C NMR ($CD_3CN$): δ 171.8, 157.4 (ddd , $J_{CF}$ = 242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; $J_{CF}$ = 246.7, 14.2, 12.9 Hz), 147.4 (ddd, $J_{CF}$ = 241.2, 12.3, 3.7 Hz), 144.2 (q, $J_{CF}$ = 38.8 Hz), 124.6 (ddd , $J_{CF}$ = 18.5, 5.9, 4.0 Hz), 120.4 (dd , $J_{CF}$ = 19.1, 6.2 Hz), 119.8 (q, $J_{CF}$ = 268.9 Hz), 106.2 (dd , $J_{CF}$ = 29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

The crystalline free base can also be isolated as follows:

(a) The reaction mixture upon completion of the hydrogenation step is charged with 25 wt% of Ecosorb C-941. The mixture is stirred under nitrogen for one h and then filtered. The cake is washed with 2L/kg of methanol. Recovery of free base is about 95% and optical purity about 95% ee.

(b) The freebase solution in methanol is concentrated to 3.5-4.0 L/kg volume (based on free base charge) and then solvent-switched into isopropanol (IPA) to final volume of 3.0 L/kg IPA.

(c) The slurry is heated to 40 °C and aged 1 h at 40°C and then cooled to 25 °C over 2 h.

(d) Heptane (7L/kg) is charged over 7 h and the slurry stirred for 12 h at 22-25°C. The supernatant concentration before filtering is 10-12 mg/g.

(e) The slurry is filtered and the solid washed with 30% IPA/heptane (2L/kg).

(f) The solid is dried in a vacuum oven at 40 °C.

(g) The optical purity of the free base is about 99% ee.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

Column: Waters Symmetry C18, 250 mm x 4.6 mm

Eluent: Solvent A: 0.1 vol% $HClO_4/H_2O$

Solvent B: acetonitrile
Gradient: 0 min 75% A : 25% B
10 min 25% A : 75% B
12.5 min 25% A : 75% B
15 min 75% A : 25% B
Flow rate: 1 mL/min
Injection Vol.: 10 µL
UV detection: 210 nm
Column temp.: 40 °C
Retention times: compound 2-4: 9.1 min
compound 2-5: 5.4 min
*t*Bu Josiphos: 8.7 min

The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:
Column: Chirapak, AD-H, 250 mm x 4.6 mm
Eluent: Solvent A: 0.2 vol.% diethylamine in heptane
Solvent B: 0.1 vol% diethylamine in ethanol
Isochratic Run Time: 18 min
Flow rate: 0.7 mL/min
Injection Vol.: 7 µL
UV detection: 268 nm
Column temp.: 35 °C
Retention times: (*R*)-amine 2-5: 13.8 min
(*S*)-amine 2-5: 11.2 min

(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 dihydrogenphosphate monohydrate

A 250 mL round bottom flask equipped with an overhead stirrer, heating mantle and thermocouple, was charged with 31.5 mL of isopropanol (IPA), 13.5 mL water, 15.0 g (36.9 mmol) 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 freebase and 4.25 g (36.9 mmol) of 85% aqueous phosphoric acid. The mixture was heated to 75 °C. A thick white precipitate formed at lower temperatures but dissolved upon reaching 75 °C. The solution was cooled to 68 °C and then held at that temperature for 2 h. A slurry bed of solids formed during this age time [the solution can be seeded with 0.5 to 5 wt% of small particle size

(alpine milled) monohydrate]. The slurry was then cooled at a rate of 4 °C/h to 21 °C and then held overnight. 105 mL of IPA was then added to the slurry. After 1 h the slurry was filtered and washed with 45 mL IPA (solids can also be washed with a water/IPA solution to avoid turnover to other crystal forms). The solids were dried on the frit with open to air. 18.6 g of solids were recovered. The solids were found to be greater than 99.8% pure by HPLC area percentage (HPLC conditions same as those given above). The particle size distribution analysis of the isolated solids showed a mean PSD of 80 microns with 95% less than 180 microns. The crystal form of the solids was shown to be monohydrate by X-ray powder diffraction and thermogravimetric analysis.

X-ray powder diffraction studies are widely used to characterize molecular structures, crystallinity, and polymorphism. The X-ray powder diffraction pattern of the crystalline dihydrogenphosphate monohydrate was generated on a Philips Analytical X'Pert PRO X-ray Diffraction System with PW3040/60 console. A PW3373/00 ceramic Cu LEF X-ray tube K-Alpha radiation was used as the source.

FIG. 1 shows the X-ray diffraction pattern for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate exhibited characteristic diffraction peaks corresponding to d-spacings of 7.42, 5.48, and 3.96 angstroms. The monohydrate was further characterized by the d-spacings of 6.30, 4.75, and 4.48 angstroms. The monohydrate was even further characterized by the d-spacings of 5.85, 5.21, and 3.52 angstroms.

.In addition to the X-ray powder diffraction patterns described above, the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II was further characterized by its solid-state carbon-13 and fluorine-19 nuclear magnetic resonance (NMR) spectra. The solid-state carbon-13 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4 mm double resonance CPMAS probe. The carbon-13 NMR spectrum utilized proton/carbon-13 cross-polarization magic-angle spinning with variable-amplitude cross polarization. The sample was spun at 15.0 kHz, and a total of 2048 scans were collected with a recycle delay of 20 seconds. A line broadening of 40 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 p.p.m.) as a secondary reference.

The solid-state fluorine-19 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4mm CRAMPS probe. The NMR spectrum utilized a simple pulse-acquire pulse program. The samples were spun at 15.0 kHz, and a total of 16 scans were collected with a recycle delay of 30 seconds. A vespel endcap was utilized to minimize fluorine background. A line broadening of 100 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported using poly(tetrafluoroethylene) (teflon) as an external secondary reference which was assigned a chemical shift of –122 ppm.

FIG. 2 shows the solid-state carbon-13 CPMAS NMR spectrum for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate form exhibited characteristic signals with chemical shift values of 169.1, 120.8, and 46.5 p.p.m. Further characteristic of the monohydrate form were the signals with chemical shift values of 159.0, and 150.9, and 40.7 ppm.

FIG. 3 shows the solid-state fluorine-19 MAS NMR spectrum for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate form exhibited characteristic signals with chemical shift values of -64.5, -114.7, -136.3, and -146.2 p.p.m. Further characteristic of the monohydrate form were the signals with chemical shift values of -96.5, -104.4, -106.3, and -154.5 ppm.

FIG. 4 shows the characteristic thermogravimetric analysis (TGA) curve for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. A Perkin Elmer model TGA 7 or equivalent instrument was used. Experiments were performed under a flow of nitrogen and using a heating rate of 10 °C/min to a maximum temperature of approximately 250 °C. After automatically taring the balance, 5 to 20 mg of sample was added to the platinum pan, the furnace was raised, and the heating program started. Weight/temperature data were collected automatically by the instrument. Analysis of the results was carried out by selecting the Delta Y function within the instrument software and choosing the temperatures between which the weight loss was to be calculated. Weight losses are reported up to the onset of decomposition/evaporation. TGA indicated a weight loss of about 3.3647 % from ambient temperature to about 250 °C.

FIG. 5 shows the characteristic DSC curve for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. A TA Instruments DSC 2910 or equivalent instrumentation was used. Between 2 and 6 mg sample was weighed into an open pan. This pan was then crimped and placed at the sample position in the calorimeter cell. An empty pan was placed at the reference position. The calorimeter cell was closed and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of 10 °C/min to a temperature of approximately 250 °C. The heating program was started. When the run was completed, the data were analyzed using the DSC analysis program contained in the system software. The melting endotherm was integrated between baseline temperature points that are above and below the temperature range over which the endotherm was observed. The data reported are the onset temperature, peak temperature, and enthalpy.

The crystalline dihydrogenphosphate salt monohydrate of the present invention has a phase purity of at least about 5% of the form with the above X-ray powder diffraction, fluorine-19 MAS NMR, carbon-13 CPMAS NMR, and DSC physical characteristics. In one embodiment the phase purity is at least about 10% of the form with the above solid-state physical characteristics. In a second

embodiment the phase purity is at least about 25% of the form with the above solid-state physical characteristics. In a third embodiment the phase purity is at least about 50% of the form with the above solid-state physical characteristics. In a fourth embodiment the phase purity is at least about 75% of the form with the above solid-state physical characteristics. In a fifth embodiment the phase purity is at least about 90% of the form with the above solid-state physical characteristics. In a sixth embodiment the crystalline dihydrogenphosphate salt monohydrate is the substantially phase pure form with the above solid-state physical characteristics. By the term "phase purity" is meant the solid state purity of the dihydrogenphosphate salt monohydrate with regard to a particular crystalline or amorphous form of the salt as determined by the solid-state physical methods described in the present application.

The crystalline dihydrogenphosphate salt monohydrate was found to be stable under ambient condition. It was found to convert to dehydrated monohydrate if heated to above 40 °C under very dry nitrogen flow. Dehydrated monohydrate converted back to monohydrate under ambient condition.

EXAMPLES OF PHARMACEUTICAL COMPOSITIONS:

1) Direct compression process:

The dihydrogenphosphate salt monohydrate was formulated into a tablet by a direct compression process. A 100 mg potency tablet was composed of 128.4 mg of the active ingredient, 127.8 mg microcrystalline cellulose, 127.8 mg of mannitol (or 127.8 mg of dicalcium phosphate), 8 mg of croscarmellose sodium, 8 mg of magnesium stearate and 16 mg of Opadry white (proprietary coating material made by Colorcon, West Point, PA). The active ingredient, microcrystalline cellulose, mannitol (or dicalcium phosphate), and croscarmellose were first blended, and the mixture was then lubricated with magnesium stearate and pressed into tablets. The tablets were then film coated with Opadry White.

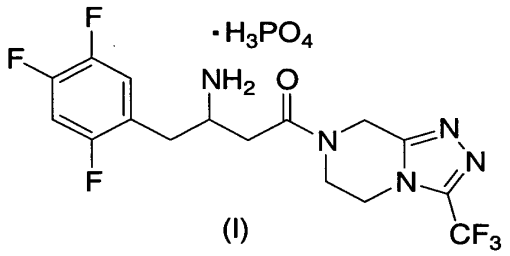
2) Roller compaction process:

The dihydrogenphosphate salt monohydrate was formulated into a tablet by a roller compaction process. A 100 mg potency tablet was composed of 128.4 mg of the active ingredient, 45 mg microcrystalline cellulose, 111.6 mg of dicalcium phosphate, 6 mg of croscarmellose sodium, 9 mg of magnesium stearate and 12 mg of Opadry white (proprietary coating material made by Colorcon, West Point, PA). The active ingredient, microcrystalline cellulose, dicalcium phosphate, and croscarmellose were first blended, and the mixture was then lubricated with one third the total amount of magnesium stearate and roller compacted into ribbons. These ribbons were then milled and then resulting granules were lubricated with the remaining amount of the magnesium stearate and pressed into tablets. The tablets were then film coated with Opadry White.

3) An intravenous (i.v.) aqueous formulation is defined as the monohydrate of dihydrogenphosphate salt of formula I in 10 mM sodium acetate/0.8% saline solution at pH 4.5 ± 0.2. For a formulation with a concentration of 4.0 mg/mL, 800 mg of NaCl is dissolved in 80 mL of water, then 57.5 µL of glacial acetic acid is added, followed by 512 mg of the dihydrogenphosphate salt monohydrate. The pH is adjusted to 4.5 ± 0.2 with 0.1 N NaOH solution. The final volume is adjusted to 100 mL with water. A 2.0 mg/mL solution can be made by dilution of 50.0 mL of the 4.0 mg/mL solution to 100.0 mL with placebo. A 1.0 mg/mL solution can be made by dilution of 25.0 mL of the 4.0 mg/mL solution to 100.0 mL with placebo.

WHAT IS CLAIMED IS:

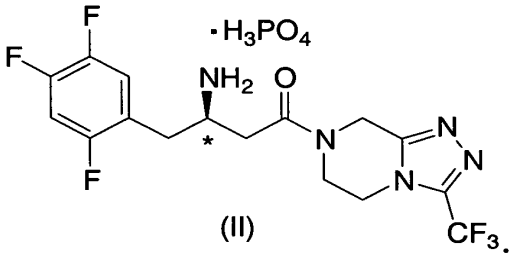
1. A dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I:




(I)

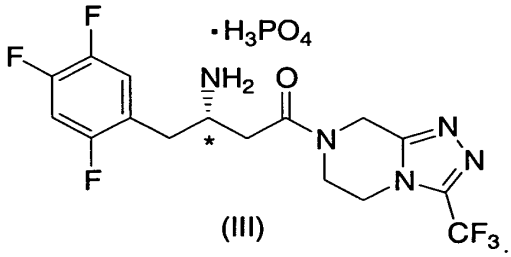
or a pharmaceutically acceptable hydrate thereof.

2. The salt of Claim 1 of structural formula II having the (*R*)-configuration at the chiral center marked with an *




(II)

3. The salt of Claim 1 of structural formula III having the (*S*)-configuration at the chiral center marked with an *




(III)

4. The salt of Claim 2 characterized in being a crystalline monohydrate.

5. The monohydrate of Claim 4 characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 7.42, 5.48, and 3.96 angstroms.

6. The monohydrate of Claim 5 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 6.30, 4.75, and 4.48 angstroms.

7. The monohydrate of Claim 6 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 5.85, 5.21, and 3.52 angstroms.

8. The monohydrate of Claim 7 further characterized by the X-ray powder diffraction pattern of FIG. 1.

9. The monohydrate of Claim 4 characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 169.1, 120.8, and 46.5 ppm.

10. The monohydrate of Claim 9 further characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 159.0, 150.9, and 40.7 ppm.

11. The monohydrate of Claim 10 further characterized by the solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum of FIG. 2.

12. The monohydrate of Claim 4 characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at -64.5, -114.7, -136.3, and -146.2 ppm.

13. The monohydrate of Claim 12 further characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at -96.5, -104.4, -106.3, and -154.5 ppm.

14. The monohydrate of Claim 13 further characterized by the solid-state fluorine-19 MAS nuclear magnetic resonance spectrum of FIG. 3.

15. The monohydrate of Claim 4 characterized by the thermogravimetric analysis curve of FIG. 4.

16. The monohydrate of Claim 4 characterized by the differential scanning calorimetric curve of FIG. 5.

17. The salt of Claim 4 comprising a detectable amount of said crystalline monohydrate.

18. The salt of Claim 4 comprising about 5% to about 100% by weight of said crystalline monohydrate.

19. The salt of Claim 4 comprising about 10% to about 100% by weight of said crystalline monohydrate.

20. The salt of Claim 4 comprising about 25% to about 100% by weight of said crystalline monohydrate.

21. The salt of Claim 4 comprising about 50% to about 100% by weight of said crystalline monohydrate.

22. The salt of Claim 4 comprising about 75% to about 100% by weight of said crystalline monohydrate.

23. The salt of Claim 4 comprising substantially all by weight of said crystalline monohydrate.

24. A salt comprising the ions of monoprotonated 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 cation and dihydrogenphosphate anion.

25. A pharmaceutical composition comprising a prophylactically or therapeutically effective amount of the salt according to Claim 1 or a pharmaceutically acceptable solvate thereof in association with one or more pharmaceutically acceptable carriers.

26. A pharmaceutical composition comprising a prophylactically or therapeutically effective amount of the salt according to Claim 4 or a pharmaceutically acceptable solvate thereof in association with one or more pharmaceutically acceptable carriers.

27. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to Claim 1 or a pharmaceutically acceptable hydrate thereof.

28. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to Claim 4.

29. A process for preparing the salt of Claim 1 comprising the step of contacting one equivalent 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 in an organic solvent or aqueous organic solvent with about a one equivalent of phosphoric acid at a temperature in the range of about 25-100°C.

30. The process of Claim 29 wherein said organic solvent is a $C_1$-$C_5$ linear or branched alkanol.

31. Use of the salt of Claim 1 as active ingredient in the manufacture of a medicament for use in the treatment of type 2 diabetes.

32. Use of the salt of Claim 4 as active ingredient in the manufacture of a medicament for use in the treatment of type 2 diabetes.

33. The pharmaceutical composition of Claim 25 adapted for i.v. administration.

34. The phosphoric acid salt 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 prepared according to the process of Claim 29.

35. A process for preparing the crystalline monohydrate of Claim 4 comprising the steps of:

(a) crystallizing said dihydrogenphosphate salt of Claim 1 at 25 °C from a mixture of isopropanol and water, such that the water concentration is above 6.8 weight percent;

(b) recovering the resultant solid phase; and

(c) removing the solvent therefrom.

ABSTRACT OF THE DISCLOSURE

The dihydrogenphosphate salt 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 is a potent inhibitor of dipeptidyl peptidase-IV and is useful for the prevention and/or treatment of non-insulin dependent diabetes mellitus, also referred to as type 2 diabetes. The invention also relates to a crystalline monohydrate of the dihydrogenphosphate salt as well as a process for its preparation, pharmaceutical compositions containing this novel form and methods of use for the treatment of diabetes, obesity, and high blood pressure.

# DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

| | |
|---|---|
| **Attorney Docket Number** | 21409Y |
| **First Named Inventor** | Cypes, et al. |
| ***COMPLETE IF KNOWN*** | |
| Application Number | |
| Filing Date | |
| Group Art Unit | |
| Examiner Name | |

**As a below named inventor, I hereby declare that:**

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

*(Title of the Invention)*

the specification of which

☒ bears the Attorney Docket Number and Title of the Invention noted above

OR

☐ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) ☐ as United States Application Number or PCT International Application Number ☐ and was amended on (MM/DD/YYYY) ☐ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f) or 365(b) of any foreign application(s) for patent or inventor's certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate(s), or of any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Attorney Docket Number | Priority Claimed? YES | NO |
|---|---|---|---|---|---|
| | | | | ☐ | ☐ |
| | | | | ☐ | ☐ |
| | | | | ☐ | ☐ |
| | | | | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YYYY) | Attorney Docket Number |
|---|---|---|
| 60/482,161 | 06/24/2003 | 21409PV |
| | | |
| | | |
| | | |



Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 09/18/2003

# DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information known to me to be material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| U.S. Parent Application or PCT Parent Application Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (*if applicable*) |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint, respectively and individually, as my attorney(s) or agent(s) with full power of substitution and revocation, the following registered practitioner(s) to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith:

☐ Customer Number
OR
☒ Registered practitioner(s) name/registration number listed below

| Name | Registration Number | Name | Registration Number |
|---|---|---|---|
| Philippe L. Durette | 35,125 | Melvin Winokur | 32,763 |
| | | | |
| | | | |
| | | | |

Direct all correspondence to: ☒ Customer Number 000210

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name** | Philippe L. Durette | | | | | | |
| **Address** | Merck & Co., Inc. - Patent Department | | | | | | |
| **Address** | P.O. Box 2000, RY60-30 | | | | | | |
| **City** | Rahway | | | **State** | NJ | **ZIP** | 07065-0907 |
| **Country** | USA | **Telephone** | (732)594-4568 | | | **Fax** | (732)594-4720 |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**Name of Sole or First Inventor:** ☐ A petition has been filed for this unsigned inventor

| Given Name (first and middle [if any]) | Family Name or Surname |
|---|---|
| Stephen Howard | Cypes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Inventor's Signature** | | | | | | **Date** | |
| **Residence: City** | Santa Clara | **State** | CA | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | | | **State** | NJ | **ZIP** | 07065-0907 |

☒ Additional inventors are being named on the 2 supplemental Additional Inventors(s) sheet(s) PTO/SB/02A attached hereto.

Approved for use through 07/31/2006. OMB 0651-0032
SUBSTITUTE for PTO/SB/02A (08-03), Declaration (Additional Inventors)

| DECLARATION AND POWER OF ATTORNEY | ADDITIONAL INVENTOR(S) Supplemental Sheet |
|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | Family Name or Surname | | | | |
| Alex Minhua | | | Chen | | | | |
| **Inventor's Signature** | Alex Chen | | | | **Date** | 10, May 2004 | |
| **Residence: City** | Metuchen | **State** NJ | **Country** US | | **Citizenship** | CN | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** NJ | **ZIP** 07065-0907 | | | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | Family Name or Surname | | | | |
| Russell R. | | | Ferlita | | | | |
| **Inventor's Signature** | | | | | **Date** | 10 May 2004 | |
| **Residence: City** | Westfield | **State** NJ | **Country** US | | **Citizenship** | US | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** NJ | **ZIP** 07065-0907 | | | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | Family Name or Surname | | | | |
| Karl | | | Hansen | | | | |
| **Inventor's Signature** | | | | | **Date** | 10 May 2004 | |
| **Residence: City** | Atlantic Highlands | **State** NJ | **Country** US | | **Citizenship** | US | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** NJ | **ZIP** 07065-0907 | | | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | Family Name or Surname | | | | |
| Ivan | | | Lee | | | | |
| **Inventor's Signature** | | | | | **Date** | 10, May 2004 | |
| **Residence: City** | Piscataway | **State** NJ | **Country** US | | **Citizenship** | US | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** NJ | **ZIP** 07065-0907 | | | | |



Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 09/18/2003

Approved for use through 07/31/2006. OMB 0651-0032
SUBSTITUTE for PTO/SB/02A (08-03), Declaration (Additional Inventors)

| DECLARATION AND POWER OF ATTORNEY | ADDITIONAL INVENTOR(S) Supplemental Sheet |
|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Vicky K. | | | | Vydra | | | |
| **Inventor's Signature** | Vicky Vydra | | | | **Date** | 10 May 2004 | |
| **Residence: City** | Fair Lawn | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Robert M. | | | | Wenslow Jr. | | | |
| **Inventor's Signature** | | | | | **Date** | 10 May 2004 | |
| **Residence: City** | East Windsor | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |

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|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| **Inventor's Signature** | | | | | **Date** | | |
| **Residence: City** | | **State** | | **Country** | | **Citizenship** | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| **Inventor's Signature** | | | | | **Date** | | |
| **Residence: City** | | **State** | | **Country** | | **Citizenship** | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |



Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 09/18/2003

# DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

| | |
|---|---|
| **Attorney Docket Number** | 21409Y |
| **First Named Inventor** | Cypes, et al. |
| ***COMPLETE IF KNOWN*** | |
| Application Number | |
| Filing Date | |
| Group Art Unit | |
| Examiner Name | |

**As a below named inventor, I hereby declare that:**

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

*(Title of the Invention)*

the specification of which

☒ bears the Attorney Docket Number and Title of the Invention noted above

OR

☐ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) ☐ as United States Application Number or PCT International Application Number ☐ and was amended on (MM/DD/YYYY) ☐ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f) or 365(b) of any foreign application(s) for patent or inventor's certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate(s), or of any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YYYY) | Attorney Docket Number | Priority Claimed? YES | NO |
|---|---|---|---|---|---|
| | | | | ☐ | ☐ |
| | | | | ☐ | ☐ |
| | | | | ☐ | ☐ |
| | | | | ☐ | ☐ |

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YYYY) | Attorney Docket Number |
|---|---|---|
| 60/482,161 | 06/24/2003 | 21409PV |
| | | |
| | | |
| | | |



Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 09/18/2003

# DECLARATION AND POWER OF ATTORNEY for Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information known to me to be material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| U.S. Parent Application or PCT Parent Application Number | Parent Filing Date (MM/DD/YYYY) | Parent Patent Number (*if applicable*) |
|---|---|---|
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| | | |
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☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint, respectively and individually, as my attorney(s) or agent(s) with full power of substitution and revocation, the following registered practitioner(s) to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith:

☐ Customer Number
OR
☒ Registered practitioner(s) name/registration number listed below

| Name | Registration Number | Name | Registration Number |
|---|---|---|---|
| Philippe L. Durette | 35,125 | Melvin Winokur | 32,763 |
| | | | |
| | | | |
| | | | |

Direct all correspondence to: ☒ Customer Number 000210

| | | | | | |
|---|---|---|---|---|---|
| **Name** | Philippe L. Durette | | | | |
| **Address** | Merck & Co., Inc. - Patent Department | | | | |
| **Address** | P.O. Box 2000, RY60-30 | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 |
| **Country** | USA | **Telephone** | (732)594-4568 | **Fax** | (732)594-4720 |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**Name of Sole or First Inventor:** ☐ A petition has been filed for this unsigned inventor

| Given Name (first and middle [if any]) | Family Name or Surname |
|---|---|
| Stephen Howard | Cypes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Inventor's Signature** | | | | | **Date** | 07-MAY-2004 | |
| **Residence: City** | Santa Clara | **State** | CA | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |

☒ Additional inventors are being named on the 2 supplemental Additional Inventors(s) sheet(s) PTO/SB/02A attached hereto.

Approved for use through 07/31/2006. OMB 0651-0032
SUBSTITUTE for PTO/SB/02A (08-03), Declaration (Additional Inventors)

| DECLARATION AND POWER OF ATTORNEY | ADDITIONAL INVENTOR(S) Supplemental Sheet |
|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Alex Minhua | | | | Chen | | | |
| **Inventor's Signature** | | | | **Date** | | | |
| **Residence: City** | Metuchen | **State** | NJ | **Country** | US | **Citizenship** | CN |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Russell R. | | | | Ferlita | | | |
| **Inventor's Signature** | | | | **Date** | | | |
| **Residence: City** | Westfield | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Karl | | | | Hansen | | | |
| **Inventor's Signature** | | | | **Date** | | | |
| **Residence: City** | Atlantic Highlands | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Ivan | | | | Lee | | | |
| **Inventor's Signature** | | | | **Date** | | | |
| **Residence: City** | Piscataway | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |



Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 09/18/2003

Approved for use through 07/31/2006. OMB 0651-0032
SUBSTITUTE for PTO/SB/02A (08-03), Declaration (Additional Inventors)

| DECLARATION AND POWER OF ATTORNEY | ADDITIONAL INVENTOR(S) Supplemental Sheet |
|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Vicky K. | | | | Vydra | | | |
| **Inventor's Signature** | | | | | **Date** | | |
| **Residence: City** | Fair Lawn | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| Robert M. | | | | Wenslow Jr. | | | |
| **Inventor's Signature** | | | | | **Date** | | |
| **Residence: City** | East Windsor | **State** | NJ | **Country** | US | **Citizenship** | US |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| **Inventor's Signature** | | | | | **Date** | | |
| **Residence: City** | | **State** | | **Country** | | **Citizenship** | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |
| **Name of Additional Joint Inventor, if any:** | | ☐ A petition has been filed for this unsigned inventor | | | | | |
| Given Name (first and middle [if any]) | | | | Family Name or Surname | | | |
| | | | | | | | |
| **Inventor's Signature** | | | | | **Date** | | |
| **Residence: City** | | **State** | | **Country** | | **Citizenship** | |
| **Post Office Address** | Merck & Co., Inc., P.O. Box 2000 | | | | | | |
| **City** | Rahway | **State** | NJ | **ZIP** | 07065-0907 | | |



Computer generated form " Declaration Pwr of Atty" (Application Filing Folder), Merck & Co., Inc. 09/18/2003

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

06/28/2004 ANABI1 00000049 132755 10874992

01 FC:1001 770.00 DA
02 FC:1202 270.00 DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/59033

## PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10874992

### CLAIMS AS FILED - PART I

| | (Column 1) | (Column 2) |
|---|---|---|
| TOTAL CLAIMS | 35 | |
| FOR | NUMBER FILED | NUMBER EXTRA |
| TOTAL CHARGEABLE CLAIMS | 35 minus 20= | * 15 |
| INDEPENDENT CLAIMS | 2 minus 3 = | * |
| MULTIPLE DEPENDENT CLAIM PRESENT | | ☐ |

* If the difference in column 1 is less than zero, enter "0" in column 2

| SMALL ENTITY TYPE ☐ | | | OR | OTHER THAN SMALL ENTITY | |
|---|---|---|---|---|---|
| RATE | FEE | | | RATE | FEE |
| BASIC FEE | 385.00 | | OR | BASIC FEE | 770.00 |
| XS 9= | | | OR | X$18= | 970.00 |
| X43= | | | OR | X86= | |
| +145= | | | OR | +290= | |
| TOTAL | | | OR | TOTAL | 1040.00 |

### CLAIMS AS AMENDED - PART II

| AMENDMENT A | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total | * | Minus | ** | = |
| Independent | * | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM | | | | ☐ |

| SMALL ENTITY | | | OR | OTHER THAN SMALL ENTITY | |
|---|---|---|---|---|---|
| RATE | ADDITIONAL FEE | | | RATE | ADDITIONAL FEE |
| X$ 9= | | | OR | X$18= | |
| X43= | | | OR | X86= | |
| +145= | | | OR | +290= | |
| TOTAL ADDIT. FEE | | | OR | TOTAL ADDIT. FEE | |

| AMENDMENT B | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total | * | Minus | ** | = |
| Independent | * | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM | | | | ☐ |

| | | | | | |
|---|---|---|---|---|---|
| RATE | ADDITIONAL FEE | | | RATE | ADDITIONAL FEE |
| X$ 9= | | | OR | X$18= | |
| X43= | | | OR | X86= | |
| +145= | | | OR | +290= | |
| TOTAL ADDIT. FEE | | | OR | TOTAL ADDIT. FEE | |

| AMENDMENT C | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total | * | Minus | ** | = |
| Independent | * | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM | | | | ☐ |

| | | | | | |
|---|---|---|---|---|---|
| RATE | ADDITIONAL FEE | | | RATE | ADDITIONAL FEE |
| X$ 9= | | | OR | X$18= | |
| X43= | | | OR | X86= | |
| +145= | | | OR | +290= | |
| TOTAL ADDIT. FEE | | | OR | TOTAL ADDIT. FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

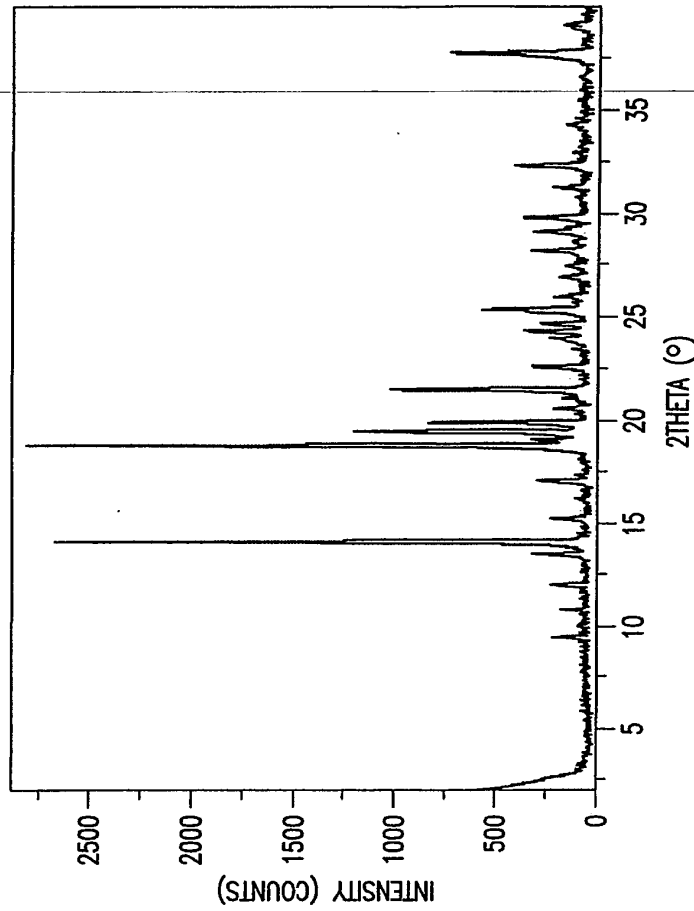



FIG. 1

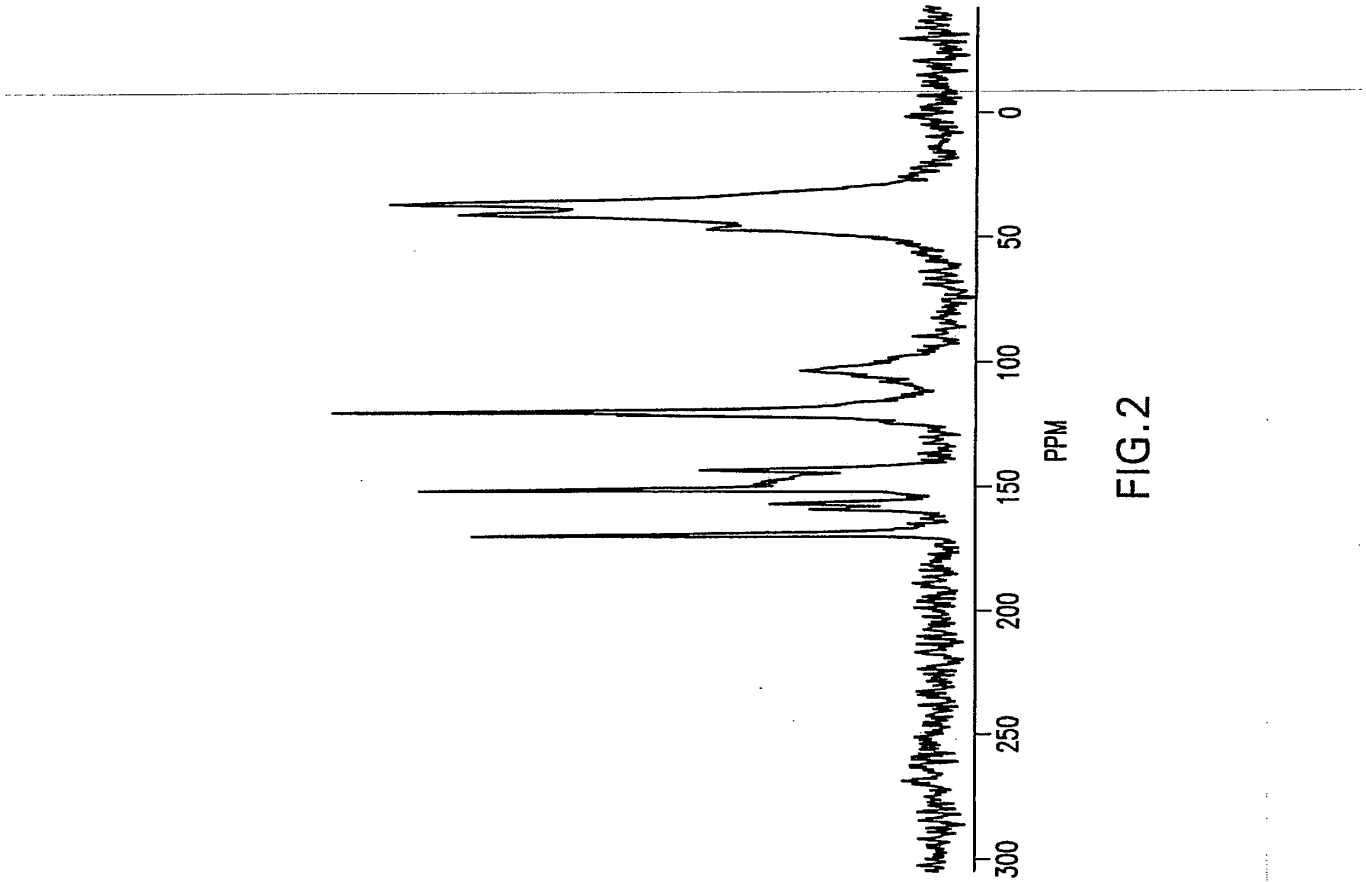



FIG.2

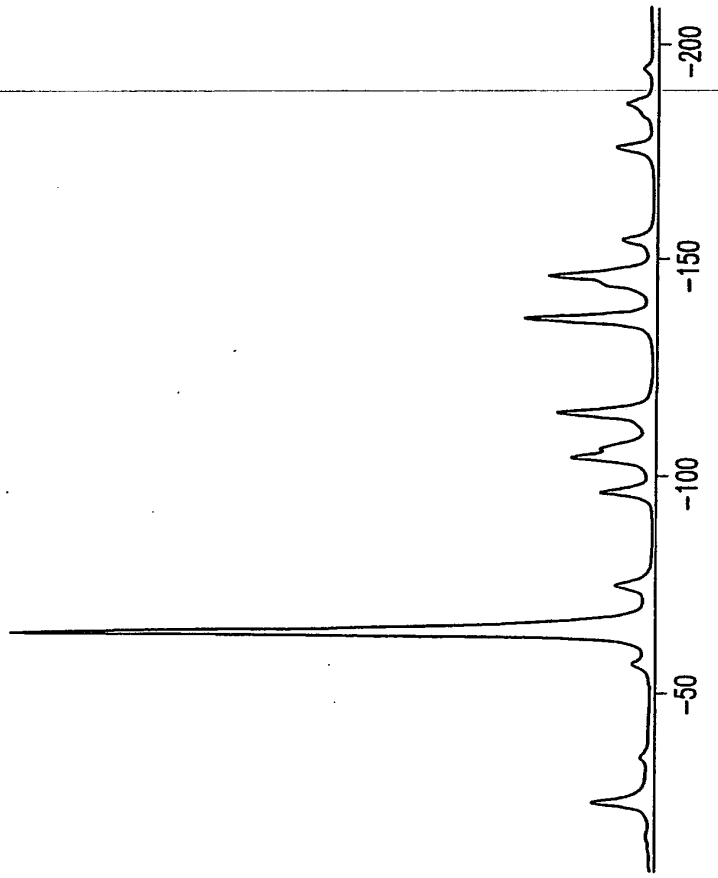



FIG.3

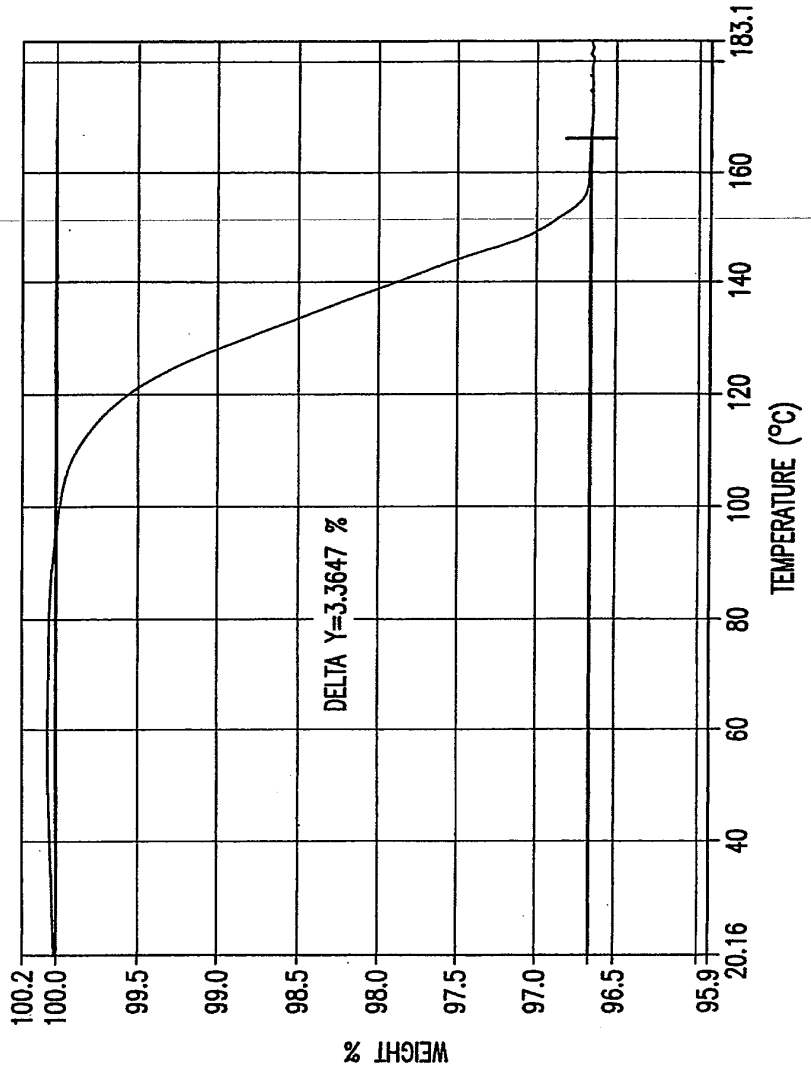
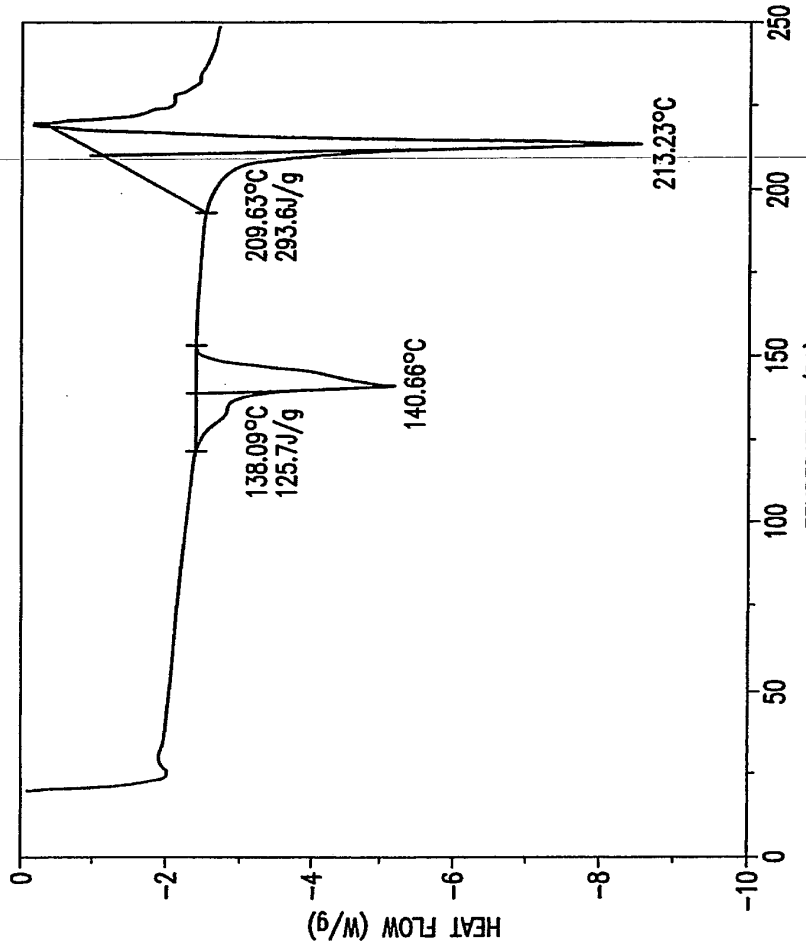



FIG.4


213.23°C
209.63°C
293.6J/g
140.66°C
138.09°C
125.7J/g
HEAT FLOW (W/g)
TEMPERATURE (°C)
0
-2
-4
-6
-8
-10
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50
100
150
200
250

FIG.5

IFW

PATENT Case No. 21409Y

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Chen, et al.

Serial No. 10/874,992

Filed: June 23, 2004

For: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

Art Unit: _____

Examiner: _____

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

Sir:

1. In compliance with 37 C.F.R. 1.97, submitted on the attached form herewith is a list of patents, publications or other information which are requested to be made of record in this application. This Information Disclosure Statement is not an admission that any patent, publication or other information referred to herein is "prior art" for this invention. In accordance with 37 C.F.R. 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. 1.56(b).

2. In accordance with 37 C.F.R. 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made.

3. Applicants respectfully request that the Examiner initial the attached form after reviewing the pertinence of each reference.

4. Pursuant to the waiver by the Office of the requirement under 37 CFR 1.98 (a)(2)(i) dated July 11, 2003, if the filing date of this application is after June 30, 2003, copies of each cited U.S. patent and each U.S. patent application publication are not enclosed herewith.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

**MERCK & CO., INC.**

By Denise K. Brown Date 9-9-2004

PATENT Case No. 21409Y

## INFORMATION DISCLOSURE STATEMENT

5. Pursuant to 37 C.F.R. 1.98(d), copies of references listed on the attached form that were submitted to or cited by the Office in a related application upon which the instant application relies for an earlier filing date under 35 U.S.C. 120 are not enclosed. Related application(s) in which references were submitted to or cited by the Office are as follows:

| | RELATED APPLICATION | |
|---|---|---|
| **U. S. SERIAL NUMBER** | **FILING DATE** | **MERCK CASE** |
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If this is inconvenient, additional copies will be submitted upon request.

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☑ the attached information is filed within three months of the filing date of the captioned case.

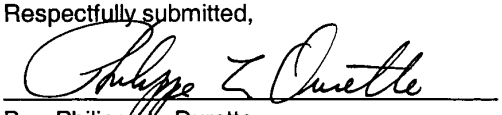
☐ the attached information is filed more than three months after the filing date but prior to the mailing of a first Office Action on the merits.

☐ the attached information is being filed more than three months after the filing date and after the mailing of a first Office Action on the merits, but before the mailing date of a Final Action or Notice of Allowance. The enclosed authorization is therefore given to charge Deposit Account No. 13-2755 for the fee required under 37 C.F.R. 1.17(p).

☐ the undersigned certifies that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Statement.

☐ the undersigned certifies that no item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated under 37 C.F.R. 1.56(c) more than three months prior to the filing of this Statement.

Respectfully submitted,



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(732)594-4568
Date: September 9, 2004

Approved for use through 7/31/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (08-03), Information Disclosure Statement by Applicant
Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

Sheet 1 of 1

| *COMPLETE IF KNOWN* | |
|---|---|
| **Application Number** | 10/874,992 |
| **Filing Date** | June 23, 2004 |
| **First Named Inventor** | Chen, et al. |
| Group Art Unit | |
| Examiner Name | |
| Attorney Docket Number | 21409Y |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. | U.S. Patent Document Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
| | 1 | US 2003/0100563 A1 | | Edmondson, et al. | 05/29/2003 |
| | 2 | US 6,699,871 | | Edmondson, et al. | 03/02/2004 |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No. | Foreign Patent Document Office | Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|---|
| | 3 | PCT | WO 03/004498 | | MERCK & CO., INC. | 01/16/2003 |
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| Examiner Signature | | Date Considered | |
|---|---|---|---|

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 January 2003 (16.01.2003)

PCT

(10) International Publication Number
WO 03/004498 A1

(51) International Patent Classification[7]: C07D 487/04, A61K 31/4985, A61P 3/10

(21) International Application Number: PCT/US02/21349

(22) International Filing Date: 5 July 2002 (05.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/303,474 6 July 2001 (06.07.2001) US

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

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

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*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.*

WO 03/004498 A1

(54) Title: BETA-AMINO TETRAHYDROIMIDAZO (1, 2-A) PYRAZINES AND TETRAHYDROTRIOAZOLO (4, 3-A) PYRAZINES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

(57) Abstract: The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

# BETA-AMINO TETRAHYDROIMIDAZO (1,2-A) PYRAZINES AND TETRAHYDROTRIAZOLO (4,3-A) PYRAZINES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

## BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic

condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β–cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensititization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (e.g. acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DP-IV" or "DPP-IV") enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly type 2 diabetes. See for example WO

97/40832, WO 98/19998, U.S. Patent No. 5,939,560, *Bioorg. Med. Chem. Lett.*, 6(10), 1163-1166 (1996); and *Bioorg. Med. Chem. Lett.*, 6(22), 2745-2748 (1996). The usefulness of DP-IV inhibitors in the treatment of type 2 diabetes is based on the fact that DP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DP-IV leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DP-IV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

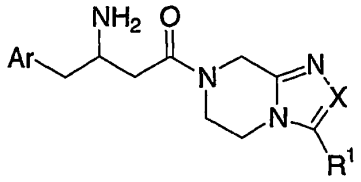
DP-IV inhibitors also have other therapeutic utilities, as discussed herein. DP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

## SUMMARY OF THE INVENTION

The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

wherein:

Ar is phenyl which is unsubstituted or substituted with 1-5 of $R^3$, wherein $R^3$ is independently selected from the group consisting of:

(1) halogen,

(2) $C_{1-6}$alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,

(3) $OC_{1-6}$alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens, and

(4) CN;

X is selected from the group consisting of:

(1) N, and

(2) $CR^2$;

$R^1$ and $R^2$ are independently selected from the group consisting of:

(1) hydrogen,

(2) CN,

(3) $C_{1-10}$alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 halogens or phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, $R^4$, $OR^4$, $NHSO_2R^4$, $SO_2R^4$, $CO_2H$, and $CO_2C_{1-6}$alkyl, wherein the $CO_2C_{1-6}$alkyl is linear or branched,

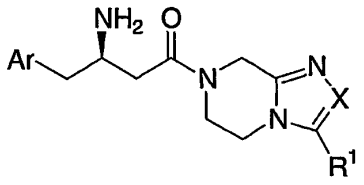
(4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, $R^4$, $OR^4$, $NHSO_2R^4$, $SO_2R^4$, $CO_2H$, and $CO_2C_{1-6}$alkyl, wherein the $CO_2C_{1-6}$alkyl is linear or branched, and

(6) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, OH, halogen, $C_{1-6}$alkyl, and $OC_{1-6}$alkyl, wherein the $C_{1-6}$alkyl and $OC_{1-6}$alkyl are linear or branched and optionally substituted with 1-5 halogens;

$R^4$ is $C_{1-6}$alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 groups independently selected from halogen, $CO_2H$, and $CO_2C_{1-6}$alkyl, wherein the $CO_2C_{1-6}$alkyl is linear or branched;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

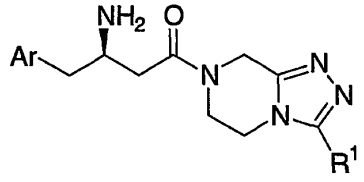
An embodiment of the present invention includes compounds of the formula Ia:



Ia

wherein X, Ar and $R^1$ are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

Another embodiment of the present invention includes compounds of the formula Ib:

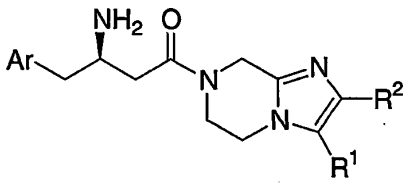


Ib

wherein Ar and $R^1$ are defined herein;

and pharmaceutically acceptable salts and individual diastereomers thereof.

Another embodiment of the present invention includes compounds of the formula Ic:



Ic

wherein Ar, $R^1$ and $R^2$ are defined herein;
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

In the present invention it is preferred that Ar is phenyl which is unsubstituted or substituted with 1-5 substitutents which are independently selected from the group consisting of:

(1) fluoro,
(2) bromo, and
(3) $CF_3$.

In the present invention it is more preferred that Ar is selected from the group consisting of:

(1) phenyl,
(2) 2-fluorophenyl,
(3) 3,4-difluorophenyl,
(4) 2,5-difluorophenyl,
(5) 2,4,5-trifluorophenyl,
(6) 2-fluoro-4-(triflouromethyl)phenyl, and
(7) 4-bromo-2,5-difluorophenyl.

In the present invention it is preferred that $R^1$ is selected from the group consisting of:

(1) hydrogen, and

(2) $C_{1-6}$alkyl, which is linear or branched and which is unsubstituted or substituted with phenyl or 1-5 fluoro.

In the present invention it is more preferred that $R^1$ is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) $CF_3$,
(5) $CH_2CF_3$,
(5) $CF_2CF_3$
(6) phenyl, and
(7) benzyl.

In the present invention it is more preferred that $R^1$ is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) $CF_3$, and
(5) $CH_2CF_3$.

In the present invention it is even more preferred that $R^1$ is hydrogen or $CF_3$.

In the present invention it is preferred that $R^2$ is selected from:

(1) hydrogen,
(2) $C_{1-6}$alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 fluoro,
(3) phenyl, which is unsubstituted or substituted with 1-3 substituents independently selected from fluoro, $OCH_3$, and $OCF_3$.

In the present invention it is more preferred that $R^2$ is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) $CF_3$,
(5) $CH_2CF_3$,
(5) $CF_2CF_3$
(6) phenyl,
(7) (4-methoxy)phenyl,
(8) (4-trifluoromethoxy)phenyl,
(9) 4-fluorophenyl, and
(10) 3,4-difluorophenyl.

In the present invention it is even more preferred that $R^2$ is $CF_3$ or $CF_2F_3$.

In the present invention it is preferred that $R^3$ is F, Br or $CF_3$.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The compounds of the instant invention have one asymmetric center at the beta carbon atom. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers.

The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

Formula I shows the structure of the class of compounds without preferred stereochemistry. Formula Ia shows the preferred sterochemistry at the carbon atom that is attached to the amine group of the beta amino acid from which these compounds are prepared.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines

including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, $C_{1-8}$, as in $C_{1-8}$alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a linear or branched arrangement, such that $C_{1-8}$alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl. Likewise, $C_0$, as in $C_0$alkyl is defined to identify the presence of a direct covalent bond. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein is intended to include 5- or 6-membered ring systems which are within the following listing: benzimidazolyl, benzodioxanyl, benzofuranyl, benzopyrazolyl, benzothiadiazolyl, benzotriazolyl, benzothiophenyl, benzoxadiazolyl, benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl,

dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydroimidazolyl, tetrahydroisoquinolinyl, and tetrahydrothienyl.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of inhibiting the dipeptidyl peptidase-IV enzyme in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as inhibitors of dipeptidyl peptidase-IV enzyme activity.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The present invention is further directed to a method for the manufacture of a medicament for inhibiting dipeptidyl peptidase-IV enzyme activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom inhibition of dipeptidyl peptidase-IV enzyme activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibitors of dipeptidyl peptidase-IV enzyme activity may be demonstrated by methodology known in the art. Inhibition constants are determined as follows. A continuous fluorometric assay is employed with the substrate Gly-Pro-AMC, which is cleaved by DP-IV to release the fluorescent AMC leaving group. The kinetic parameters that describe this reaction are as follows: $K_m = 50\ \mu M$; $k_{cat} = 75\ s^{-1}$; $k_{cat}/K_m = 1.5 \times 10^6\ M^{-1}s^{-1}$. A typical reaction contains approximately 50 pM enzyme, 50 μM Gly-Pro-AMC, and buffer (100 mM HEPES, pH 7.5, 0.1 mg/ml BSA) in a total reaction volume of 100 μl. Liberation of AMC is monitored continuously in a 96-well plate fluorometer using an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Under these conditions, approximately 0.8 μM AMC is produced in 30 minutes at 25 degrees C. The enzyme used in these studies was soluble (transmembrane domain and cytoplasmic extension excluded) human protein produced in a baculovirus expression system (Bac-To-Bac, Gibco BRL). The kinetic constants for hydrolysis of Gly-Pro-AMC and GLP-1 were found to be in accord with literature values for the native enzyme. To measure the dissociation constants for compounds, solutions of inhibitor in DMSO were added to reactions containing enzyme and substrate (final DMSO concentration is 1%). All experiments were

conducted at room temperature using the standard reaction conditions described above. To determine the dissociation constants ($K_i$), reaction rates were fit by non-linear regression to the Michaelis-Menton equation for competitive inhibition. The errors in reproducing the dissociation constants are typically less than two-fold.

In particular, the compounds of the following examples had activity in inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays, generally with an $IC_{50}$ of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as inhibitors the dipeptidyl peptidase-IV enzyme activity.

Dipeptidyl peptidase-IV enzyme (DP-IV) is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes in humans or other species.

Accordingly, the subject compounds are useful in a method for the prevention or treatment of the following diseases, disorders and conditions.

Type II Diabetes and Related Disorders: It is well established that the incretins GLP-1 and GIP are rapidly inactivated *in vivo* by DP-IV. Studies with DP-$IV^{(-/-)}$-deficient mice and preliminary clinical trials indicate that DP-IV inhibition increases the steady state concentrations of GLP-1 and GIP, resulting in improved glucose tolerance. By analogy to GLP-1 and GIP, it is likely that other glucagon family peptides involved in glucose regulation are also inactivated by DP-IV (eg. PACAP, glucagon). Inactivation of these peptides by DP-IV may also play a role in glucose homeostasis.

The DP-IV inhibitors of the present invention therefore have utility in the treatment of type II diabetes and in the treatment and prevention of the numerous conditions that often accompany Type II diabetes, including metabolic syndrome X, reactive hypoglycemia, and diabetic dyslipidemia. Obesity, discussed below, is another condition that is often found with Type II diabetes that may respond to treatment with the compounds of this invention.

The following diseases, disorders and conditions are related to Type 2 diabetes, and therefore may be treated, controlled or in some cases prevented, by

treatment with the compounds of this invention: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component.

Obesity: DP-IV inhibitors may be useful for the treatment of obesity. This is based on the observed inhibitory effects on food intake and gastric emptying of GLP-1 and GLP-2. Exogenous administration of GLP-1 in humans significantly decreases food intake and slows gastric emptying (Am. J. Physiol. 277, R910-R916 (1999)). ICV administration of GLP-1 in rats and mice also has profound effects on food intake (Nature Medicine 2, 1254-1258 (1996)). This inhibition of feeding is not observed in GLP-1R$^{(-/-)}$ mice, indicating that these effects are mediated through brain GLP-1 receptors. By analogy to GLP-1, it is likely that GLP-2 is also regulated by DP-IV. ICV administration of GLP-2 also inhibits food intake, analogous to the effects observed with GLP-1 (Nature Medicine 6, 802-807 (2000)).

Growth Hormone Deficiency: DP-IV inhibition may be useful for the treatment of growth hormone deficiency, based on the hypothesis that growth-hormone releasing factor (GRF), a peptide that stimulates release of growth hormone from the anterior pituitary, is cleaved by the DP-IV enzyme *in vivo* (WO 00/56297). The following data provide evidence that GRF is an endogenous substrate: (1) GRF is efficiently cleaved *in vitro* to generate the inactive product GRF[3-44] (BBA 1122, 147-153 (1992)); (2) GRF is rapidly degraded in plasma to GRF[3-44]; this is prevented by the DP-IV inhibitor diprotin A; and (3) GRF[3-44] is found in the plasma of a human GRF transgenic pig (J. Clin. Invest. 83, 1533-1540 (1989)). Thus DP-IV inhibitors may be useful for the same spectrum of indications which have been considered for growth hormone secretagogues.

Intestinal Injury: The potential for using DP-IV inhibitors for the treatment of intestinal injury is suggested by the results of studies indicating that glucagon-like peptide-2 (GLP-2), a likely endogenous substrate for DP-IV, may exhibit trophic effects on the intestinal epithelium (Regulatory Peptides 90, 27-32 (2000)). Administration of GLP-2 results in increased small bowel mass in rodents and attenuates intestinal injury in rodent models of colitis and enteritis.

Immunosuppression: DP-IV inhibition may be useful for modulation of the immune response, based upon studies implicating the DP-IV enzyme in T cell activation and in chemokine processing, and efficacy of DP-IV inhibitors in *in vivo* models of disease. DP-IV has been shown to be identical to CD26, a cell surface marker for activated immune cells. The expression of CD26 is regulated by the differentiation and activation status of immune cells. It is generally accepted that CD26 functions as a co-stimulatory molecule in *in vitro* models of T cell activation. A number of chemokines contain proline in the penultimate position, presumably to protect them from degradation by non-specific aminopeptidases. Many of these have been shown to be processed *in vitro* by DP-IV. In several cases (RANTES, LD78-beta, MDC, eotaxin, SDF-1alpha), cleavage results in an altered activity in chemotaxis and signaling assays. Receptor selectivity also appears to be modified in some cases (RANTES). Multiple N-terminally truncated forms of a number of chemokines have been identified in *in vitro* cell culture systems, including the predicted products of DP-IV hydrolysis.

DP-IV inhibitors have been shown to be efficacious immunosupressants in animal models of transplantation and arthritis. Prodipine (Pro-Pro-diphenyl-phosphonate), an irreversible inhibitor of DP-IV, was shown to double cardiac allograft survival in rats from day 7 to day 14 (Transplantation 63, 1495-1500 (1997)). DP-IV inhibitors have been tested in collagen and alkyldiamine-induced arthritis in rats and showed a statistically significant attenuation of hind paw swelling in this model (Int. J. Immunopharmacology 19, 15-24 (1997), Immunopharmacology 40, 21-26 (1998)). DP-IV is upregulated in a number of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, Graves' disease, and Hashimoto's thyroiditis (Immunology Today 20, 367-375 (1999)).

HIV Infection: DP-IV inhibition may be useful for the treatment or prevention of HIV infection or AIDS because a number of chemokines which inhibit HIV cell entry are

potential substrates for DP-IV (Immunology Today 20, 367-375 (1999)). In the case of SDF-1alpha, cleavage decreases antiviral activity (PNAS 95, 6331-6 (1998)). Thus, stabilization of SDF-1alpha through inhibition of DP-IV would be expected to decrease HIV infectivity.

Hematopoiesis: DP-IV inhibition may be useful for the treatment or prevention of hematopiesis because DP-IV may be involved in hematopoiesis. A DP-IV inhibitor, Val-Boro-Pro, stimulated hematopoiesis in a mouse model of cyclophosphamide-induced neutropenia (WO 99/56753).

Neuronal Disorders: DP-IV inhibition may be useful for the treatment or prevention of various neuronal or psychiatric disorders because a number of peptides implicated in a variety of neuronal processes are cleaved *in vitro* by DP-IV. A DP-IV inhibitor thus may have a therapeutic benefit in the treatment of neuronal disorders. Endomorphin-2, beta-casomorphin, and substance P have all been shown to be *in vitro* substrates for DP-IV. In all cases, *in vitro* cleavage is highly efficient, with $k_{cat}/K_m \sim 10^6\ M^{-1}s^{-1}$ or greater. In an electric shock jump test model of analgesia in rats, a DP-IV inhibitor showed a significant effect that was independent of the presence of exogenous endomorphin-2 (Brain Research 815, 278-286 (1999)).

Tumor Invasion and Metastasis: DP-IV inhibition may be useful for the treatment or prevention of tumor invasion and metastasis because an increase or decrease in expression of several ectopeptidases including DP-IV has been observed during the transformation of normal cells to a malignant phenotype (J. Exp. Med. 190, 301-305 (1999)). Up- or down-regulation of these proteins appears to be tissue and cell-type specific. For example, increased CD26/DP-IV expression has been observed on T cell lymphoma, T cell acute lymphoblastic leukemia, cell-derived thyroid carcinomas, basal cell carcinomas, and breast carcinomas. Thus, DP-IV inhibitors may have utility in the treatment of such carcinomas.

Benign Prostatic Hypertrophy: DP-IV inhibition may be useful for the treatment of benign prostatic hypertrophy because increased DP-IV activity was noted in prostate tissue from patients with BPH (Eur. J. Clin. Chem. Clin. Biochem 30, 333-338 (1992)).

Sperm motility/male contraception: DP-IV inhibition may be useful for the altering sperm motility and for male contraception because in seminal fluid, prostatosomes, prostate derived organelles important for sperm motility, possess very high levels of DP-IV activity (Eur. J. Clin. Chem. Clin. Biochem 30, 333-338 (1992)).

Gingivitis: DP-IV inhibition may be useful for the treatment of gingivitis because DP-IV activity was found in gingival crevicular fluid and in some studies correlated with periodontal disease severity (Arch. Oral Biol. 37, 167-173 (1992)).

Osteoporosis: DP-IV inhibition may be useful for the treatment or prevention of osteoporosis because GIP receptors are present in osteoblasts.

Tthe compounds of the present invention have utility in treating or preventing one or more of the following conditions or diseases: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type II diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be treated or prevented by inhibition of DP-IV.

The subject compounds are further useful in a method for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a

compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also includes therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

(a) other dipeptidyl peptidase IV (DP-IV) inhibitors;

(b) insulin sensitizers including (i) PPARγ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like) and other PPAR ligands, including PPARα/γ dual agonists, such as KRP-297, and PPARα agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(c) insulin or insulin mimetics;

(d) sulfonylureas and other insulin secretagogues such as tolbutamide and glipizide, meglitinide, and related materials;

(e) α-glucosidase inhibitors (such as acarbose);

(f) glucagon receptor antagonists such as those disclosed in WO 98/04528, WO 99/01423, WO 00/39088, and WO 00/69810;

(g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists such as those disclosed in WO00/42026 and WO00/59887;

(h) GIP and GIP mimetics such as those disclosed in WO00/58360, and GIP receptor agonists;

(i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists such as those disclosed in WO 01/23420;

(j) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, rosuvastatin, and other statins), (ii) sequestrants (cholestyramine,

colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPARα/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe, and (viii) anti-oxidants, such as probucol;

(k) PPARδ agonists, such as those disclosed in WO97/28149;

(l) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y5 inhibitors, and β3 adrenergic receptor agonists;

(m) an ileal bile acid transporter inhibitor; and

(n) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Non-limiting examples include combinations of compounds having Formula I with two or more active compounds selected from biguanides, sulfonylureas, HMG-CoA reductase inhibitors, PPAR agonists, PTP-1B inhibitors, other DP-IV inhibitors, and anti-obesity compounds.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with

another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules,

or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,

for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water,

Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of The present invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require inhibition of dipeptidyl peptidase-IV enzyme activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

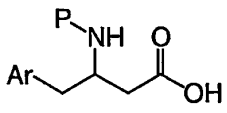
When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single

daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

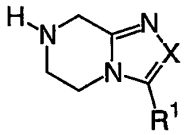
It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

The compounds of the present invention can be prepared from beta amino acid intermediates such as those of formula II and substituted heterocyclic intermediates such as those of formula III, using standard peptide coupling conditions followed by deprotection. The preparation of these intermediates is described in the following schemes.



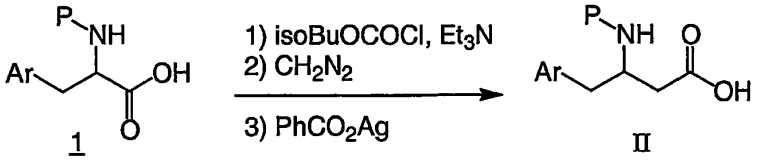

II




III

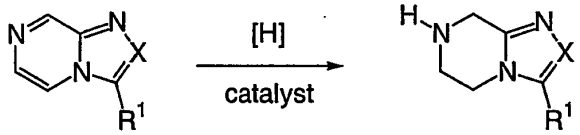
where Ar, X and $R^1$ are as defined above and P is a suitable nitrogen protecting group such as tert-butoxycarbonyl, benzyloxycarbonyl, or 9-fluorenylmethoxycarbonyl.

SCHEME 1



Compounds of formula II are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Acid 1, which may be commercially available or readily prepared from the corresponding amino acid by protection using, for example, di-*tert*-butyl-dicarbonate (for P = Boc), carbobenzyloxy chloride (for P = Cbz), or *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (for P = Fmoc), is treated with isobutyl chloroformate and a base such as triethylamine or diisopropylethylamine, followed by diazomethane. The resultant diazoketone is then treated with silver benzoate in a solvent such as methanol or aqueous dioxane and may be subjected to sonication following the procedure of Sewald et al., *Synthesis*, 837 (1997) in order to provide the beta amino acid II. As will be understood by those skilled in the art, for the preparation of enantiomerically pure beta amino acids II, enantiomerically pure alpha amino acids 1 may be used. Alternate routes to these compounds can be found in the following reviews: E. Juaristi, *Enantioselective Synthesis of β-Amino Acids*, Ed., Wiley-VCH, New York: 1997, Juaristi et al., *Aldrichimica Acta*, 27, 3 (1994), Cole et al., *Tetrahedron*, 32, 9517 (1994).

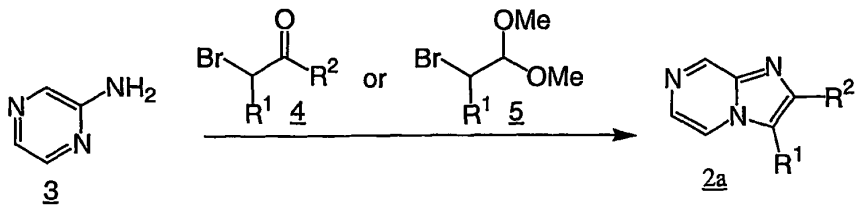
SCHEME 2




2 III

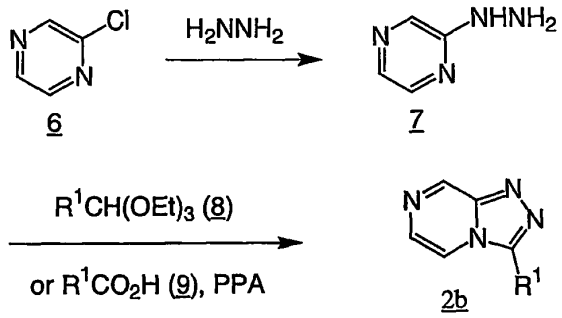
Compounds III are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One convenient method is shown in Scheme 2. Unsaturated derivative 2 is reduced, for example, by treatment with hydrogen gas and a catalyst such as palladium on carbon or platinum oxide in a solvent such as methanol or ethanol to provide Compound III.

SCHEME 3



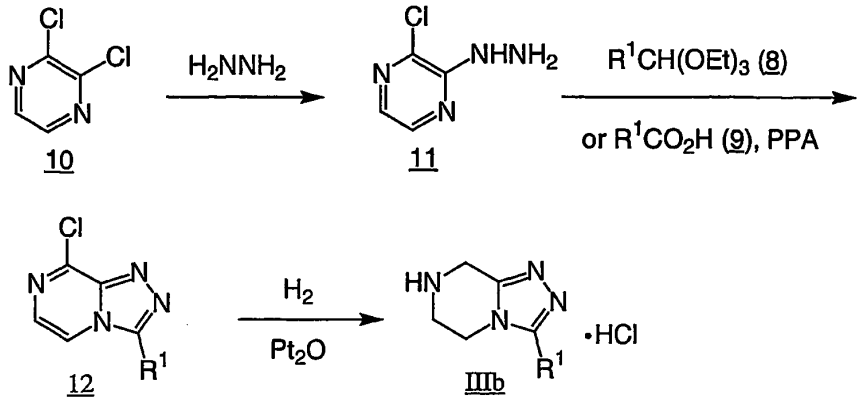

Intermediates 2, from Scheme 2, are themselves commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One such method when X is $CR^2$ is illustrated in Scheme 3. Aminopyrazine 3 is treated with a 2-haloketone such as 2-bromoketone 4 in a solvent such as methanol or ethanol to provide intermediate 2a. Alternatively, for the preparation of intermediate 2a where $R^2$ is H, 2-bromo-dimethylacetal 5 and a catalytic amount of acid such as hydrochloric acid may be employed instead of intermediate 4.

SCHEME 4



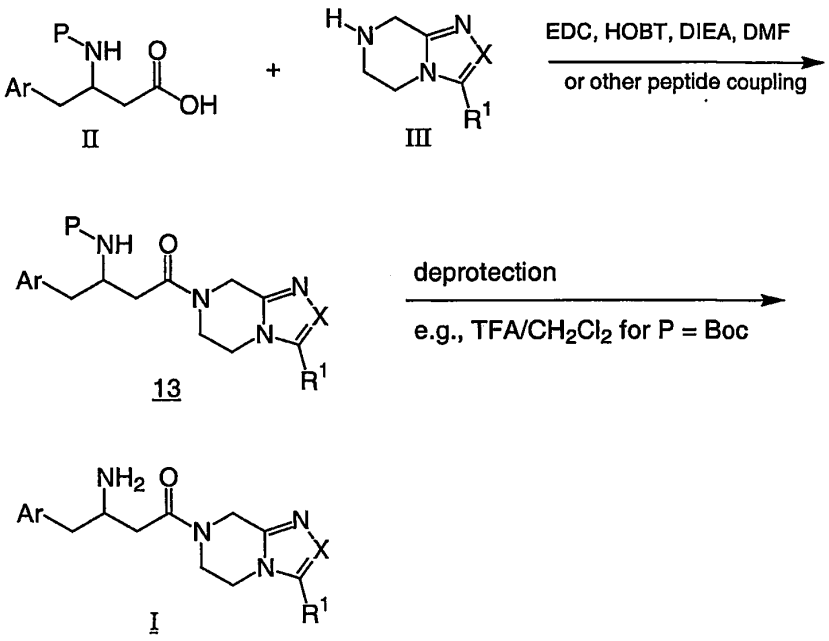

A convenient method for the preparation of intermediate 2b, where X is N, is illustrated in Scheme 4. Chloropyrazine 6 is treated with hydrazine to provide hydrazinopyrazine 7. Compound 7 may be condensed with either an orthoester such as triethyl orthoester 8 to give 2b or with a carboxylic acid 9 in polyphosphoric acid at elevated temperatures to give 2b.

SCHEME 5




An alternate route for the preparation of Compound IIIb wherein X is N is illustrated in Scheme 5. Compound 12 is prepared according to the method outlined above employing dichloropyrazine 10 instead of chloropyrazine 6. Compound 12 is then subjected to catalytic hydrogenation using a catalyst such as platinum oxide to provide Compound IIIb, as its monohydrochloride salt.

SCHEME 6

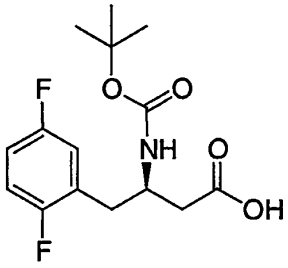



Intermediates II and III are coupled under standard peptide coupling conditions, for example, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 1-hydroxybenzotriazole (HOBT), and a base, generally diisopropylethylamine, in a solvent such as N,N-dimethylformamide (DMF) or dichloromethane for 3 to 48 hours at ambient temperature to provide intermediate 13 as shown in Scheme 6. The protecting group is then removed with, for example, trifluoroacetic acid or methanolic hydrogen chloride in the case of Boc to give the desired amine I. The product is purified from unwanted side products, if necessary, by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still et al, *J. Org. Chem.*, 43, 2923 (1978), or HPLC. Compounds which are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

In some cases the intermediate 13 from the coupling reaction described in Scheme 6 may be further modified before removal of the protecting group, for example, by manipulation of substituents on X or $R^1$. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1




(3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid

Step A. (*R,S*)-*N*-(1,1-Dimethylethoxycarbonyl)-2,5-difluorophenylalanine

To a solution of 0.5 g (2.49 mmol) of 2,5-difluoro-DL-phenylalanine in 5 mL of *tert*-butanol were added sequentially 1.5 mL of 2N aqueous sodium hydroxide solution and 543 mg of di-*tert*-butyl dicarbonate. The reaction was stirred at ambient temperature for 16 h and diluted with ethyl acetate. The organic phase was washed sequentially with 1N hydrochloric acid and brine, dried over magnesium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 97:2:1 dichloromethane:methanol:acetic acid) to afford 671 mg of the title compound. MS 302 (M + 1).

Step B. (*R,S*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-1-diazo-4-(2,5-difluoro-phenyl)butan-2-one

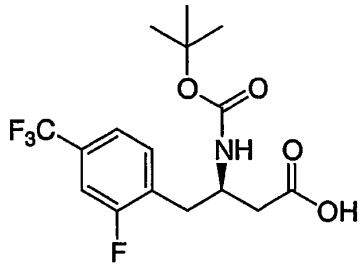
To a solution of 2.23 g (7.4 mmol) of (*R,S*)-*N*-(1,1-dimethylethoxycarbonyl)-2,5-difluorophenylalanine in 100 mL of diethyl ether at 0 °C were added sequentially 1.37 mL (8.1 mmol) of triethylamine and 0.931 mL (7.5 mmol) of isobutyl chloroformate and the reaction was stirred at this temperature for 15 min. A cooled ethereal solution of diazomethane was then added until the yellow color persisted and stirring was continued for a further 16 h. The excess

diazomethane was quenched by dropwise addition of acetic acid, and the reaction was diluted with ethyl acetate and washed sequentially with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (silica gel, 4:1 hexane:ethyl acetate) afforded 1.5 g of diazoketone. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.03-6.95 (m, 1H), 6.95-6.88 (m, 2H), 5.43 (bs, 1H), 5.18 (bs, 1H), 4.45 (bs, 1H), 3.19-3.12 (m, 1H), 2.97-2.80 (m, 1H), 1.38 (s, 9H).

Step C. (3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid

To a solution of 2.14 g (6.58 mmol) of (*R,S*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-1-diazo-4-(2,5-difluorophenyl)butan-2-one dissolved in 100 mL of methanol at –30 °C were added sequentially 3.3 mL (19 mmol) of diisopropylethylamine and 302 mg (1.32 mmol) of silver benzoate. The reaction was stirred for 90 min before diluting with ethyl acetate and washing sequentially with 2N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried over magnesium sulfate, concentrated in vacuo and the enantiomers were separated by preparative chiral HPLC (Chiralpak AD column, 5% ethanol in hexanes) to give 550 mg of the desired (*R*)-enantiomer, which eluted first. This material was dissolved in 50 mL of a mixture of tetrahydrofuran:methanol:1N aqueous lithium hydroxide (3:1:1) and stirred at 50 °C for 4 h. The reaction was cooled, acidified with 5% dilute hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 360 mg of the title compound as a white foamy solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.21 (m, 1H), 6.98 (m, 2H), 6.10 (bs, 1H), 5.05 (m,1H), 4.21 (m, 1H), 2.98 (m, 2H), 2.60 (m, 2H), 1.38 (s, 9H).

INTERMEDIATE 2



(3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-[2-fluoro-4-(trifluoromethyl)phenyl]-butanoic acid

Step A. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(2'-fluoro-4'-(trifluoromethyl)benzyl)-5-isopropylpyrazine

To a solution of 3.32 g (18 mmol) of commercially available (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine in 100 mL of tetrahydrofuran at –70 °C was added 12 mL (19 mmol) of a 1.6M solution of butyllithium in hexanes. After stirring at this temperature for 20 min, 5 g (19.5 mmol) of 2-fluoro-4-trifluoromethylbenzyl bromide in 20 mL of tetrahydrofuran was added and stirring was continued for 3 h before warming the reaction to ambient temperature. The reaction was quenched with water, concentrated in vacuo, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried, and concentrated in vacuo. Purification by flash chromatography (silica gel, 0-5% ethyl acetate in hexanes) afforded 5.5 g of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (m, 3H), 4.35-4.31 (m, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.60 (t, 1H, J = 3.4 Hz), 3.33 (dd, 1H, J = 4.6, 13.5 Hz), 3.03 (dd, 1H, J = 7, 13.5 Hz), 2.25-2.15 (m, 1H), 1.0 (d, 3H, J = 7 Hz), 0.66 (d, 3H, J = 7 Hz).

Step B. (*R*)-*N*-(1,1-Dimethylethoxycarbonyl)-2-fluoro-4-trifluoromethyl)phenyl-alanine methyl ester

To a solution of 5.5 g (15 mmol) of (2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-(2'-fluoro-4'-(trifluoromethyl)benzyl)-5-isopropylpyrazine in 50 mL of a mixture of acetonitrile:dichloromethane (10:1) was added 80 mL of 1N aqueous trifluoroacetic acid. The reaction was stirred for 6 h and the organic solvents were removed in vacuo. Sodium carbonate was added until the solution was basic (>pH 8),

and then the reaction was diluted with 100 mL of tetrahydrofuran and 10 g (46 mmol) of di-*tert*-butyl dicarbonate was added. The resulting slurry was stirred for 16 h, concentrated in vacuo, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% ethyl acetate in hexanes) afforded 5.1 g of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 3H), 5.10 (bd, 1H), 4.65-3.98 (m, 1H), 3.76 (s, 3H), 3.32-3.25 (m, 1H), 3.13-3.05 (m, 1H), 1.40 (s, 9H).

Step C. (*R*)-*N*-(1,1-Dimethylethoxycarbonyl)-2-fluoro-4-trifluoromethyl)phenyl-alanine

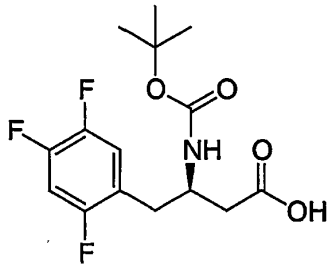
A solution of 5.1 g (14 mmol) of (*R,S*)-*N*-(1,1-dimethylethoxycarbonyl)-2-fluoro-4-trifluoromethyl)phenylalanine methyl ester in 350 mL of a mixture of tetrahydrofuran: methanol:1N lithium hydroxide (3:1:1) was stirred at 50 °C for 4 h. The reaction was cooled, acidified with 5% dilute hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 4.8 g of the title compound. $^1$H NMR (500 MHz, $CD_3OD$) δ 7.45-7.38 (m, 3H), 4.44-4.40 (m, 1H), 3.38-3.33 (m, 1H), 2.98 (dd, 1H, J = 9.6, 13.5 Hz), 1.44 (s, 9H).

Step D. (3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-[2-fluoro-4-(trifluoromethyl)-phenyl]butanoic acid

To a solution of 3.4 g (9.7 mmol) of the product from Step C in 60 mL of tetrahydrofuran at 0 °C were added sequentially 2.3 mL (13 mmol) of diisopropylethylamine and 1.7 mL (13 mmol) of isobutyl chloroformate and the reaction was stirred at this temperature for 30 min. A cooled ethereal solution of diazomethane was then added until the yellow color persisted and stirring was continued for a further 16 h. The excess diazomethane was quenched by dropwise addition of acetic acid, and the reaction was diluted with ethyl acetate and washed sequentially with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (silica gel, 9:1 hexane:ethyl acetate) afforded 0.5 g of diazoketone. To a solution of 0.5 g (1.33 mmol) of the diazoketone dissolved in 100 mL of methanol at 0 °C were added sequentially 0.7 mL (4 mmol) of diisopropylethylamine and 32 mg (0.13 mmol) of silver benzoate. The reaction was

stirred for 2 h before diluting with ethyl acetate and washing sequentially with 2N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried over magnesium sulfate, concentrated in vacuo and dissolved in 50 mL of a mixture of tetrahydrofuran:methanol:1N aqueous lithium hydroxide (3:1:1) and stirred at 50 °C for 3 h. The reaction was cooled, acidified with 5% dilute hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 410 mg of the title compound as a white foamy solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 7.47-7.33 (m, 3H), 4.88 (bs, 1H), 4.26-3.98 (m, 1H), 3.06-3.01 (m, 1H), 2.83-2.77 (m, 1H), 2.58-2.50 (m, 2H), 1.29 (s, 9H).

INTERMEDIATE 3




(3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid

Step A. (2*S*, 5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2',4',5'trifluorobenzyl)-pyrazine

The title compound (3.81 g) was prepared from 3.42 g (18.5 mmol) of (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine using the procedure described for Intermediate 2, Step A. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.01 (m, 1H), 6.85 (m, 1H), 4.22 (m, 1H), 3.78 (m, 3H), 3.64 (m, 3H), 3.61 (m, 1H), 3.20 (m, 1H), 2.98 (m, 1H), 2.20 (m, 1H), 0.99 (d, 3H, J = 8 Hz), 0.62 (d, 3H, J = 8 Hz).

Step B. (*R*)-*N*-(1,1-Dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine methyl ester

To a solution of 3.81 g (11.6 mmol) of (2*S*, 5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(2',4',5'trifluoro-benzyl)pyrazine in 20 mL of acetonitrile was added 20 mL of 2N hydrochloric acid. The reaction was stirred for 72 h and

concentrated in vacuo. The residue was dissolved in 30 mL of dichloromethane and 10 mL (72 mmol) of triethylamine and 9.68 g (44.8 mmol) of di-*tert*-butyldicarbonate were added. The reaction was stirred for 16 h, diluted with ethyl acetate and washed sequentially with 1N hydrochloric acid and brine. The organic phase was dried over sodium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 9:1 hexanes:ethyl acetate) to afford 2.41 g of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) δ 6.99 (m, 1H), 6.94 (m, 1H), 5.08 (m, 1H), 4.58 (m, 1H), 3.78 (m, 3H), 3.19 (m, 1H), 3.01 (m, 1H), 1.41 (s, 9H).

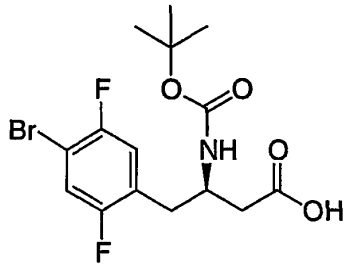
Step C. (*R*)-*N*-(1,1-Dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine

The title compound (2.01 g) was prepared from 2.41 g (7.5 mol) of (*R*)-*N*-(1,1-dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine methyl ester using the procedure described for Intermediate 2, Step C. MS (M + 1)-BOC 220.9.

Step D. (3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)-butanoic acid

To a solution of 0.37 g (1.16 mmol) of (*R*)-*N*-(1,1-dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine in 10 mL of diethyl ether at -20 °C were added sequentially 0.193 mL (1.3 mmol) of triethylamine and 0.18 mL (1.3 mmol) of isobutyl chloroformate, and the reaction was stirred at this temperature for 15 min. A cooled ethereal solution of diazomethane was then added until the yellow color persisted and stirring was continued for a further 1 h. The excess diazomethane was quenched by dropwise addition of acetic acid, and the reaction was diluted with ethyl acetate and washed sequentially with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (silica gel, 3:1 hexane:ethyl acetate) afforded 0.36 g of diazoketone. To a solution of 0.35 g (1.15 mmol) of the diazoketone dissolved in 12 mL of 1,4-dioxane: water (5:1) was added 26 mg (0.113 mmol) of silver benzoate. The resultant solution was sonicated for 2 h before diluting with ethyl acetate and washing sequentially with 1N hydrochloric acid and brine, drying over magnesium sulfate and concentrating in vacuo. Purification by flash chromatography (silica gel, 97:2:1 dichloromethane:methanol:acetic acid) afforded 401 mg of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.06 (m, 1H), 6.95 (m, 1H), 5.06 (bs, 1H), 4.18 (m, 1H), 2.98 (m, 2H), 2.61 (m, 2H), 1.39 (s, 9H).

INTERMEDIATE 4




(3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(4-bromo-2,5-difluorophenyl)-butanoic acid

Step A. 4-Bromo-2,5-difluorobenzyl bromide

To a solution of 2 g (8.44 mmol) of 4-bromo-2,5-difluorobenzoic acid (prepared according to the procedure of Ishikawa et al., *Kogyo Kagaku Zasshi*, pg 972-979, **1970**) in 20 mL of tetrahydrofuran was added 40 mL of a 1M solution of borane-tetrahydrofuran complex. The solution was heated under reflux for 64 h, cooled to ambient temperature and 100 mL of methanol was added. The reaction was then heated for a further 2 h, cooled and concentrated in vacuo. Purification by flash chromatography (silica gel, 9:1 hexane:ethyl acetate) afforded 1.6 g of 4-bromo-2,5-difluorobenzyl alcohol. To a solution of 1.3 g (5.6 mmol) of 4-bromo-2,5-difluorobenzyl alcohol in 20 mL of dichloromethane at 0 °C was added 2.27 g (6.7 mmol) of carbon tetrabromide and 1.8 g (6.7 mmol) of triphenylphosphine. The reaction was stirred for 2 h at this temperature, the solvent was removed in vacuo and the residue stirred with 100 mL of diethyl ether. The solution was filtered, concentrated in vacuo, and purified by flash chromatography (silica gel, 9:1 hexane:ethyl acetate) to afford 1.5 g of the title compound.

Step B. (2*S*, 5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(4'-bromo-2',5'-difluorobenzyl)pyrazine

The title compound (1.61 g) was prepared from 0.865 g (4.7 mmol) of (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and 1.5 g (5.2 mmol) of 4-bromo-2,5-difluorobenzyl bromide using the procedure described for Intermediate 2, Step A. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H), 6.97 (m, 1H), 4.25 (m, 1H),

3.78 (s, 3H), 3.70-3.64 (m, 4H), 3.25-3.18 (m, 1H), 2.96-2.90 (m, 1H), 2.25-2.16 (m, 1H), 1.01 (d, 3H, J = 8 Hz), 0.65 (d, 3H, J = 8 Hz).

Step C. (*R*)-*N*-(1,1-Dimethylethoxycarbonyl)-4-bromo-2,5-difluorophenylalanine methyl ester

To a solution of 1.61 g (4.14 mmol) of (2*S*, 5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4'-bromo-2',5'-difluorobenzyl)pyrazine in 10 mL of acetonitrile was added 10 mL of 2N hydrochloric acid. The reaction was stirred for 16 h and concentrated in vacuo. The residue was dissolved in 30 mL of dichloromethane and 5.6 mL (40 mmol) of triethylamine and 2.2 g (10 mmol) of di-*tert*-butyldicarbonate were added. The reaction was stirred for 16 h, diluted with ethyl acetate and washed sequentially with saturated aqueous sodium bicarbonate solution and brine. The organic phase was dried over magnesium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 9:1 hexanes:ethyl acetate) to afford 1.22 g of the title compound. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27-7.15 (m, 1H), 6.98-6.93 (m, 1H), 5.08 (bs, 1H), 4.61-4.55 (m, 1H), 3.78 (s, 3H), 3.23-3.18 (m, 1H), 3.05-2.95 (m, 1H), 1.41 (s, 9H).

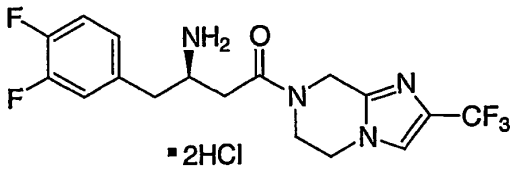
Step D. (*R*)-*N*-(1,1-Dimethylethoxycarbonyl)-4-bromo-2,5-difluorophenylalanine

The title compound (1.34 g) was prepared from 1.4 g (3.5 mmol) of (*R*)-*N*-(1,1-dimethylethoxycarbonyl)-4-bromo-2,5-diifluorophenylalanine methyl ester using the procedure described for Intermediate 2, Step C. MS (M + 1) 380.3 and 382.3.

Step E. (3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(4'-bromo-2',5'-difluorophenyl)butanoic acid

The title compound (0.36 g) was prepared from 0.6 g (1.57 mmol) of (*R*)-*N*-(1,1-dimethylethoxycarbonyl)-4-bromo-2,5-diifluorophenylalanine using the procedure described for Intermediate 3, Step D. MS (M + 1) 394.1 and 396.1.

EXAMPLE 1




7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

Step A. 2-(Trifluoromethyl)imidazo[1,2-*a*]pyrazine

To a solution of 2-aminopyrazine (5.25 g, 55.2 mmol) in ethanol (120 mL) was added 1-bromo-3,3,3-trifluoroacetone (5.73 mL, 55.2 mmol). The reaction was stirred at reflux for 20 h. After evaporation of solvent, the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3x). The combined organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (silica gel, 1:1 ethyl acetate:hexane, then 100% ethyl acetate) to give 2.35 g of the title compound as a solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 2H), 8.13(m, 1H), 9.22 (s, 1H). ESI-MS 188 (M+1).

Step B. 2-(Trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine

To a solution of 2-(trifluoromethyl)imidazo[1,2-*a*]pyrazine (2.0 g, 10.46 mmol, from Step A) in methanol (100 mL) was added 10% palladium on carbon (400 mg). The mixture was stirred under atmospheric hydrogen at ambient temperature for 14 h. The mixture was filtered through Celite and washed with methanol (3X). The filtrate was concentrated and purified by flash chromatography (silica gel, 10% methanol in ethyl acetate, then 15% methanol in chloroform with 1% aqueous ammonium hydroxide) to give 1.33 g of the title compound as a solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.93 (bs, 1H), 3.26 (t, 2H, J=5.5 Hz), 3.99 (t, 2H, J=5.5 Hz), 4.10 (s, 1H), 7.16 (s, 1H). ESI-MS 192 (M+1).

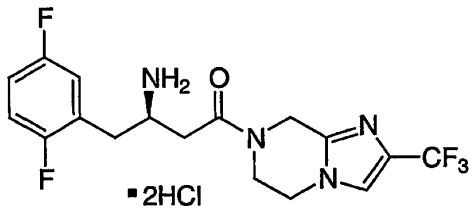
Step C. 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine

To a solution of 2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (64.3 mg, 0.34 mmol, from Step B) and (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoic acid (105.9 mg, 0.34 mmol) in dichloromethane (5 mL) was added HOBT (54.5 mg, 0.42 mmol) at 0 °C . The reaction was stirred at 0 °C for 10 min, then EDC (96.6 mg, 0.50 mmol) was added. After removal of the ice-bath, the reaction was allowed to stir at ambient temperature for 14 h. The mixture was concentrated and purified by HPLC (Gilson; YMC-Pack Pro C18 column, 100 x 20 mm I.D.; solvent gradient from 10% acetonitrile, 90% water, and 0.1 % trifluoroacetic acid to 90% acetonitrile, 10% water, and 0.1 % trifluoroacetic acid) to give 115 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.62 (m, 2H), 2..86 (m, 2H) 3.34 (bs, 1H), 3.86 (m, 1H), 4.05 (m, 4H). 4.85 (m, 1H) 5.30-5.38 (m, 1H) 6.97 (m, 3H), 7.28 (m, 1H). LC/MS 489 (M+1).

Step D. 7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

To 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (110.8 mg, 0.226 mmol, from Step C) was added 2 mL of methanol saturated with hydrogen chloride. The reaction was stirred at ambient temperature for 1 h. Concentration gave 89.5 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 2.97-3.10 (m, 4H), 3.91-4.34 (m, 5H), 4.90-5.04 (m, 2H), 7.16-7.33 (m, 2H), 8.01-8.08 (m, 1H). ESI-MS 389 (M+1).

EXAMPLE 2




7-[(3*R*)-3-Amino-4-(2,5-difluorophenyl)butanoyl]-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

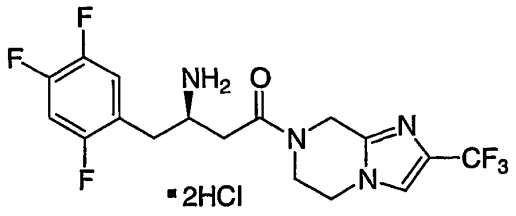
Step A. 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine

The title compound was prepared from 2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (277 mg, 1.45 mmol, from Example 1, Step B), (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid (Intermediate 1, 416 mg, 1.32 mmol), DIPEA (226 mg, 1.58 mol), HOBT (216 mg, 1.98 mol) and HATU (753 mg, 1.98 mol) in DMF (6 mL), using a procedure analogous to that described in Example 1 Step C, except for the purification method. The compound was purified by preparative TLC (silica gel, 20% hexane in ethyl acetate, then 10% methanol in dichloromethane) to give 360 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.62 (m, 2H), 2.88 (m, 2H) 3.88-4.16 (m, 5H), 4.73 (s, 1H), 4.85 (m, 1H) 5.26-5.39 (m, 1H) 6.90 (bs, 1H), 7.06(m, 2H), 7.24(m, 1H). ESI-MS 489 (M+1).

Step B. 7-[(3*R*)-3-Amino-4-(2,5-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

The title compound was prepared from 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-4-(2,5-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (349.8 mg, 0.72 mol, from Step A) in 1.5 mL of methanol saturated with hydrogen chloride, using a procedure analogous to that described in Example 1, Step D. Evaporation of solvent gave 299 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CD_3OD$): δ 3.10-3.17 (m, 2H), 2.89-2.99 (m, 2H), 3.94-4.22 (m, 4H), 4.33 (m, 1H), 4.91-5.48 (m, 2H), 7.07-7.23 (m, 3H), 8.05 (m, 1H). ESI-MS 389(M+1).

EXAMPLE 3




7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

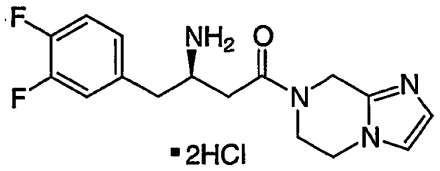
Step A. 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine

The title compound was prepared from 2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (31.7 mg, 0.166 mmol, from Example 1, Step B), (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid (Intermediate 3, 57 mg, 0.166 mmol), HOBT (26.9 mg,0.199 ) mmol, and EDC (47.8 mg, 0.249 mmol) in 4 mL of dichloromethane, using a procedure analogous to that described in Example 1, Step C. Purification by preparative TLC (silica gel, 100% ethyl acetate, then 10% methanol in dichloromethane) gave 40 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.00 (m, 2H), 3.30 (m, 2H), 3.93 (m, 1H) 4.04-4.24 (m, 2H), 4.23 (s, 1H), 4.35 (m, 1H) 4.97-5.48 (m, 2H) 7.22 (m, 1H), 7.44 (m, 1H), 8.04 (m, 1H). ESI-MS 507 (M+1).

Step B. 7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

The title compound was prepared from 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (38 mg, 0.075 mmol, from Step A), in 1.5 mL of methanol saturated with hydrogen chloride, using a procedure analogous to that described in Example 1, Step D. Evaporation of solvent gave 34 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CD_3OD$): δ 2.59-2.66 (m, 2H), 2.92 (m, 2H), 3.89-4.16-4.22 (m, 5H), 4.70-4.84 (m, 2H), 5.42 (m, 1H), 6.86 (m, 1H), 7.06 (m, 1H), 7.24 (m, 1H). ESI-MS 407(M+1).

EXAMPLE 4




7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

Step A. Imidazo[1,2-*a*]pyrazine

To a solution of 2-aminopyrazine (2.0 g, 21.03 mmol) in ethanol (40 mL) was added 2-bromo-1,1-dimethoxyethane (2.5 mL, 21.03 mmol) followed by 5 drops of concentrated hydrochloric acid. After refluxing for 14 hours, the solvent was evaporated. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3x). The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography (100% ethyl acetate, 10% methanol in ethyl acetate, then 10% methanol in dichloromethane) to give 536 mg of the title compound as a solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.70 (bs, 1H), 7.82 (bs, 1H), 7.89 (d, 1H, J=4.4 Hz), 8.10 (d, 1H, J=4.6 Hz), 9.12 (s, 1H).

Step B. 5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrazine

The title compound was prepared from imidazo[1,2-*a*]pyrazine (500 mg, 4.20 mmol, from Step A) and platinum oxide (250 mg) in methanol (50 mL), using a procedure analogous to that described in Example 1, Step B. Concentration gave the title compound (512 mg) as a viscous oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 3.37 (t, 1H, J=5.5 Hz), 4.18 (t, 2H, J=5.6 Hz), 4.88 (s, 1H), 7.27 (d, J=1.6 Hz, 1H), 7.33 (d, 1H).

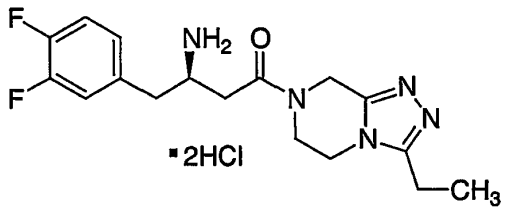
Step C. 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine

The title compound was prepared from 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (31.3 mg, 0.254 mmol, from Step B), (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoic acid (80 mg, mmol), DIPEA (32.8 mg, 0.254 mmol), HOBT (41.2 mg, 0.305 mmol) and EDC (73 mg, 0.381 mmol) in 5 mL of dichloromethane, using a procedure analogous to that described in Example 1, Step C. Purification by HPLC (Gilson; YMC-Pack Pro C18 column, 100 x 20 mm I.D.; solvent gradient system from 10% acetonitrile, 90% water, and 0.1% trifluoroacetic acid to 90% acetonitrile, 10% water, and 0.1% trifluoroacetic acid) gave 75 mg of the title compound as a viscous oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.05 (bs, 1H), 2.62 (m, 2H), 2.89 (m, 2H) 3.81-4.04 (m, 5H), 4.64-4.88 (m, 2H). 5.38 (m, 1H) 6.88 (m, 2H), 7.0 5(m, 3H). ESI-MS 421 (M+1).

Step D. 7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

The title compound was prepared from 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-4-(3,4-difluorophenyl)butanoyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (72 mg, 0.171 mmol, from Step C), in 1.5 mL of methanol saturated with hydrogen chloride, using a procedure analogous to that described in Example 1, Step D. Concentration gave 66 mg of the title compound as a foamy solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 2.96-3.13 (m, 4H), 3.93 (m, 1H), 4.13 (m, 2H), 4.26-4.38 (m, 2H), 4.26-4.38 (m, 2H), 4.90-5.04 (m, 2H), 7.19-7.36 (m, 3H), 7.58 (m, 1H). ESI-MS 321 (M+1).

EXAMPLE 5




7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-3-ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, dihydrochloride

Step A. 8-Chloro-3-ethyl-1,2,4-triazolo[4,3-*a*]pyrazine

To 3-chloro-2-hydrazinopyrazine (3.0 g, 20.75 mmol), prepared from 2,3-dichloropyrazine and hydrazine using a procedure analogous to that described in the literature (Huynh-Dinh et al, *J. Org. Chem.* **1979**, *44*, 1028), was added 8 mL of triethyl orthopropionate. After refluxing for 10 h, the reaction was cooled down to ambient temperature and the precipitate was filtered. The solid was purified by flash chromatography (100% ethyl acetate, then 10% methanol in ethyl acetate) to give 2.73 g of the title compound as a solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.54 (t, 3H, J=7.6 Hz), 3.16 (q, 2H, J=7.8 Hz), 7.70 (d, 1H, J=4.5 Hz), 7.83 (d, 1H, J=4.8 Hz).

Step B. 3-Ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*] pyrazine, hydrochloride

The title compound was prepared from 8-chloro-3-ethyl-1,2,4-triazolo[4,3-*a*]pyrazine (2.70 g, 14.8 mmol, from Step A) and platinum oxide (0.4 g)

in 200 mL of methanol in a paar shaker under hydrogen (50 psi) for 14 hours. Filtration through Celite followed by concentration gave the title compound as a solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.36 (t, 3H, J=6.0 Hz), 2.84 (q, 2H, J=6.0 Hz), 3.70 (t, 2H, J=8.0 Hz), 4.28 (t, 2H, J=8.0 Hz). 4.06(s, 2H). ESI-MS 153 (M+1).

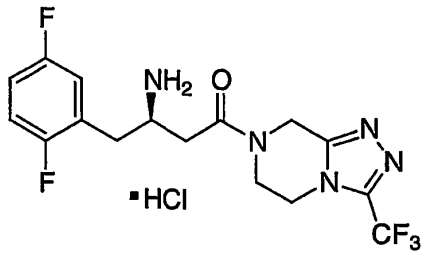
Step C. 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-3-ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine

The title compound was prepared from 3-ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine hydrochloride (400 mg, 2.12 mmol, from Step B), (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoic acid (668 mg, 2.12 mmol), DIPEA (1.1 mL, 4.24 mmol), HOBT (343.8 mg, 2.54 mmol) and EDC (609.6 mg, 3.18 mmol) in 20 mL of dichloromethane, using a procedure analogous to that described in Example 1, Step C. The crude product was purified by HPLC (Gilson; YMC-Pack Pro C18 column, 100 x 20 mm I.D.; solvent gradient from 10% acetonitrile, 90% water, and 0.1% trifluoroacetic acid to 90% acetonitrile, 10% water, and 0. % trifluoroacetic acid) to give 366.3 mg of the title compound as a viscous oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.31-1.34 (m, 12H), 2.67-2.92 (m, 6H), 4.03-4.12 (m, 4H), 5.03-5.31 (m, 3H), 6.93 (s, 1H), 7.05 (m, 2H). ESI-MS 450 (M+1).

Step D. 7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-3-ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*] pyrazine, dihydrochloride

The title compound was prepared from 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-4-(3,4-difluorophenyl)butanoyl]-3-ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine (30 mg, 0.067 mmol from Step C), in 1.5 mL of methanol saturated with hydrogen chloride, using a procedure analogous to that described in Example 1, Step D. Evaporation of solvent afforded 28 mg of the title compound as a viscous oil. $^1$H NMR (500 MHz, $CD_3OD$) δ 1.45 (t, 3H), 2.93-3.07 (m, 6H), 3.90-4.31 (m, 5H), 5.08 (m, 2H), 7.16 (s, 1H), 7.31 (m, 2H). ESI-MS 350 (M+H).

EXAMPLE 6



7-[(3*R*)-3-Amino-4-(2,5-difluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, hydrochloride

Step A. 3-(Trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine

A mixture of 2-hydrazinopyrazine (820 mg, 7.45 mmol), prepared from 2-chloropyrazine and hydrazine using a procedure analogous to that described in the literature (P.J. Nelson and K.T. Potts, *J. Org. Chem.* **1962**, *27*, 3243, except that the crude product was extracted into 10%methanol/dichloromethane and filtered, and the filtrate was concentrated and purified by flash chromatography on silica gel, eluting with 100% ethyl acetate followed by 10% methanol in dichloromethane), TFA (2.55 g, 22.4 mmol), and polyphosphoric acid (10 mL) was heated to 140 °C with stirring for 18 h. The solution was added to ice and neutralized by the addition of ammonium hydroxide. The aqueous solution was extracted with ethyl acetate (3X), washed with brine, and dried over anhydrous magnesium sulfate. Concentration followed by flash chromatography (silica gel, 1:1 hexane:ethyl acetate, then 100% ethyl acetate) afforded the title compound as a solid (861 mg). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.17~8.20 (m, 2H), 9.54 (s, 1H). LC/MS (M+1) 189.

Step B. 3-(Trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine

3-(Trifluoromethyl)-1,2,4-triazolo[4,3-*a*] pyrazine (540 mg, 2.87 mmol, from Step A) was hydrogenated under atmospheric hydrogen with 10% Pd/C (200 mg) as a catalyst in ethanol (10 mL) at ambient temperature for 18 h. Filtration through Celite followed by concentration gave a dark colored oil. Dichloromethane was added to the above oil and the insoluble black precipitate was filtered off. Concentration of the filtrate gave the title compound as an oil (495 mg). $^1$H NMR

(500 MHz, $CDCl_3$) δ 2.21 (br, 1H), 3.29 (t, 2H, J = 5.5 Hz), 4.09 (t, 2H, J = 5.5 Hz), 4.24 (s, 2H). LC/MS (M+1) 193.

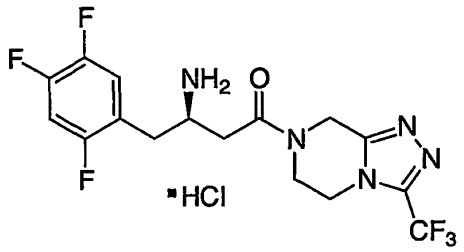
Step C. 7-[(3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine

The title compound was prepared from (3*R*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-4-(2,5-difluorophenyl)butanoic acid (Intermediate 1, 50 mg, 0.16 mmol) and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine (30 mg, 0.16 mmol) using a procedure analogous to that described for Example 1, Step C. The crude product was purified by preparative TLC (silica gel, 100% ethyl acetate, then 10% methanol/dichloromethane (2X)) to afford the title compound (38.1 mg) as a solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.57~3.05 (m, 4H), 3.85~4.30 (m, 5H), 4.90 (s, 1H), 4.95~5.15 (m, 1H), 5.22~5.40 (br, 1H), 6.86~7.24 (m, 3H). LC/MS (M+1-t-Boc) 390.

Step D. 7-[(3*R*)-3-Amino-4-(2,5-difluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*] pyrazine, hydrochloride

The title compound was prepared from 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-4-(2,5-difluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine (19.1 mg, 0.039 mmol, from Step C) using a procedure analogous to that described for Example 1, Step D. Concentration afforded the title compound (16.1 mg) as a solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 2.75~3.16 (m, 4H), 3.86~4.35 (m, 5H), 4.95~5.05 (m, 2H), 7.03~7.20 (m, 3H). LC/MS (M+1) 390.

EXAMPLE 7



7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, hydrochloride

Step A. 7-[(3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)-butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine

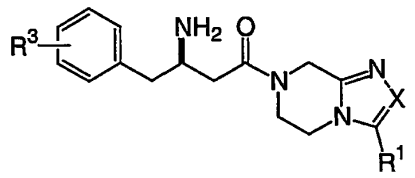
The title compound was prepared from (3*R*)-3-[(1,1-dimethylethoxy-carbonyl)-amino]-4-(2,4,5-trifluorophenyl)butanoic acid (Intermediate 3, 50.1 mg, 0.15 mmol) and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine (39.2 mg, 0.20 mmol) using a procedure analogous to that described for Example 1, Step C. The crude product was purified by preparative TLC (silica gel, 100% ethyl acetate) to afford the title compound (29 mg) as a solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.61~3.00 (m, 4H), 3.92~4.30 (m, 5H), 4.93 (s, 1H), 4.95~5.12 (m, 1H), 5.22~5.35 (br, 1H), 6.83~6.95 (m, 1H), 7.02~7.12 (m, 1H). LC/MS (M+1-t-Bu) 452.

Step B. 7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*] pyrazine, hydrochloride

The title compound was prepared from 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)-amino]-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine (22 mg, 0.039 mmol, from Step A) using a procedure analogous to that described for Example 1, Step D. Concentration afforded the title compound (16.5 mg) as a solid. $^1$H NMR (500 MHz, $CD_3OD$) δ 2.75~3.15 (m, 4H), 3.82~4.35 (m, 5H), 4.90~5.05 (m, 2H), 7.16~7.25 (m, 1H), 7.30~7.42 (m, 1H). LC/MS (M+1) 408.

Essentially following the procedures outlined for Examples 1-7, the compounds listed in Table 1 were prepared.

TABLE 1



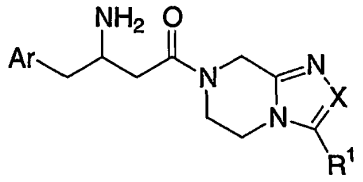
| Example | $R^3$ | X | $R^1$ | MS (M+1) |
|---|---|---|---|---|
| 8 | 2-F | C-Et | H | 331 |
| 9 | 3-F,4-F | C-Et | H | 349 |
| 10 | 2-F | CH | H | 303 |
| 11 | 2-F | C-$CF_3$ | H | 371 |
| 12 | 3-F,4-F | C-(4-F-Ph) | H | 415 |
| 13 | 3-F,4-F | C-Ph | H | 397 |
| 14 | 3-F,4-F | C-(4-OMe-Ph) | H | 427 |
| 15 | 3-F,4-F | C-(3-F,4-F-Ph) | H | 433 |
| 16 | 3-F,4-F | C-(4-$OCF_3$-Ph) | H | 481 |
| 17 | 3-F,4-F | C-$C_2F_5$ | H | 439 |
| 18 | 2-F | N | Et | 352 |
| 19 | 3-F,4-F | N | Et | 336 |
| 20 | 2-F | N | Me | 318 |

| | | | | |
|---|---|---|---|---|
| 21 | 2-F,5-F | N | Et | 350 |
| 22 | 2-F | N | H | 304 |
| 23 | 3-F,4-F | N | H | 322 |
| 24 | 3-F,4-F | N | $CF_3$ | 390 |
| 25 | 2-F,4-$CF_3$ | N | $CF_3$ | 440 |
| 26 | 3-F,4-F | N | $CH_2CF_3$ | 404 |
| 27 | 2-F,5-F | N | $CH_2CF_3$ | 404 |
| 28 | 2-F | CH | $CH_2Ph$ | 393 |
| 29 | 2-F | CH | Ph | 379 |
| 30 | 2-F, 4-$CF_3$ | C-$CF_3$ | H | 439 |
| 31 | 2-F,4-F,5-F | C-$CF_2CF_3$ | H | 379 |
| 32 | 4-Br,2-F,5-F | C-$CF_3$ | H | 467, 469 |
| 33 | 4-Br,2-F,5-F | N | $CF_3$ | 468, 470 |

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. The specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

Ar is phenyl which is unsubstituted or substituted with 1-5 of $R^3$, wherein $R^3$ is independently selected from the group consisting of:

(1) halogen,

(2) $C_{1-6}$alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,

(3) $OC_{1-6}$alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens, and

(4) CN;

X is selected from the group consisting of:

(1) N, and

(2) $CR^2$;

$R^1$ and $R^2$ are independently selected from the group consisting of:

(1) hydrogen,

(2) CN,

(3) $C_{1-10}$alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 halogens or phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, $R^4$, $OR^4$, $NHSO_2R^4$, $SO_2R^4$, $CO_2H$, and $CO_2C_{1-6}$alkyl, wherein the $CO_2C_{1-6}$alkyl is linear or branched,

(4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, $R^4$, $OR^4$, $NHSO_2R^4$,

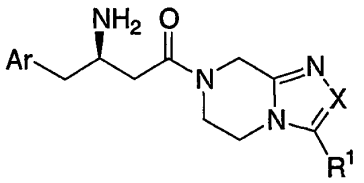
$SO_2R^4$, $CO_2H$, and $CO_2C_{1-6}$alkyl, wherein the $CO_2C_{1-6}$alkyl is linear or branched, and

(6) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, OH, halogen, $C_{1-6}$alkyl, and $OC_{1-6}$alkyl, wherein the $C_{1-6}$alkyl and $OC_{1-6}$alkyl are linear or branched and optionally substituted with 1-5 halogens;

$R^4$ is $C_{1-6}$alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 groups independently selected from halogen, $CO_2H$, and $CO_2C_{1-6}$alkyl, wherein the $CO_2C_{1-6}$alkyl is linear or branched;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

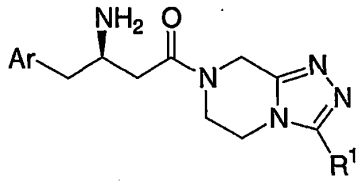
2. The compound of Claim 1 of the formula Ia:




Ia

wherein X, Ar and $R^1$ are defined in Claim 1;
and pharmaceutically acceptable salts and individual diastereomers thereof.

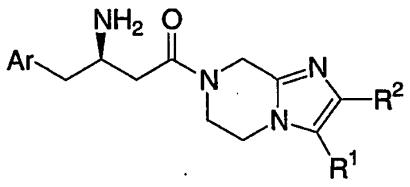
3. The compound of Claim 1 of the formula Ib:




Ib

wherein Ar and $R^1$ are defined in Claim 1;
and pharmaceutically acceptable salts and individual diastereomers thereof.

4. The compound of Claim 1 of the formula Ic:



Ic

wherein Ar , $R^1$ and $R^2$ are defined in Claim 1;
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5. The compound of Claim 1 wherein Ar is phenyl which is unsubstituted or substituted with 1-5 substitutents which are independently selected from the group consisting of:

(1) fluoro,
(2) bromo, and
(3) $CF_3$.

6. The compound of Claim 1 wherein Ar is selected from the group consisting of:

(1) phenyl,
(2) 2-fluorophenyl,
(3) 3,4-difluorophenyl,
(4) 2,5-difluorophenyl,
(5) 2,4,5-trifluorophenyl,
(6) 2-fluoro-4-(triflouromethyl)phenyl, and
(7) 4-bromo-2,5-difluorophenyl.

7. The compound of Claim 1 wherein $R^1$ is selected from the group consisting of:

(1) hydrogen, and

(2) $C_{1-6}$alkyl, which is linear or branched and which is unsubstituted or substituted with phenyl or 1-5 fluoro.

8. The compound of Claim 1 wherein $R^1$ is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) $CF_3$,
(5) $CH_2CF_3$,
(5) $CF_2CF_3$
(6) phenyl, and
(7) benzyl.

9. The compound of Claim 1 wherein $R^1$ is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) $CF_3$, and
(5) $CH_2CF_3$.

10. The compound of Claim 1 wherein $R^1$ is hydrogen or $CF_3$.

11. The compound of Claim 1 wherein $R^2$ is selected from:

(1) hydrogen,
(2) $C_{1-6}$alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 fluoro,
(3) phenyl, which is unsubstituted or substituted with 1-3 substituents independently selected from fluoro, $OCH_3$, and $OCF_3$.

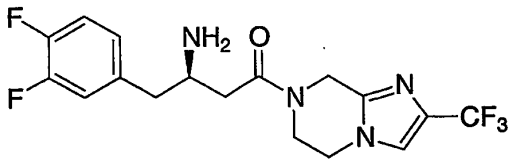
12. The compound of Claim 1 wherein $R^2$ is selected from the group consisting of:

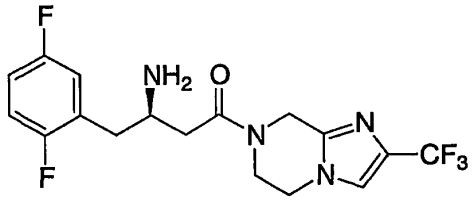
(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) $CF_3$,
(5) $CH_2CF_3$,
(5) $CF_2CF_3$
(6) phenyl,
(7) (4-methoxy)phenyl,
(8) (4-trifluoromethoxy)phenyl,
(9) 4-fluorophenyl, and
(10) 3,4-difluorophenyl.

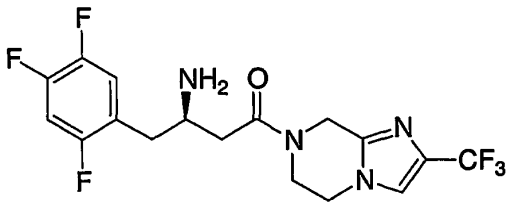
13. The compound of Claim 1 wherein $R^2$ is $CF_3$ or $CF_2F_3$.

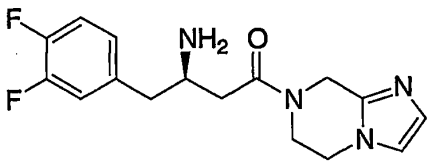
14. The compound of Claim 1 wherein $R^3$ is F, Br or $CF_3$.

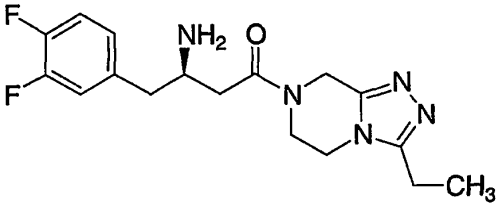
15. A compound which is selected from the group consisting of:

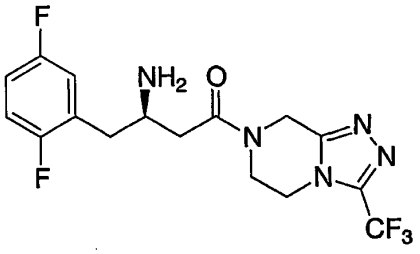


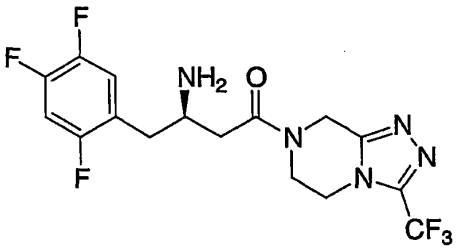













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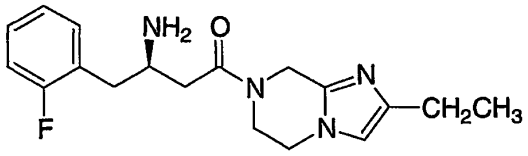

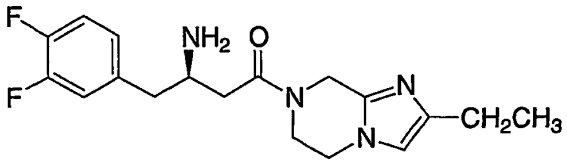

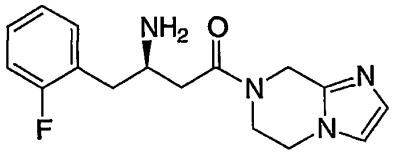

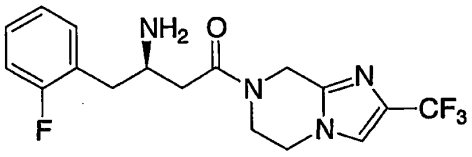

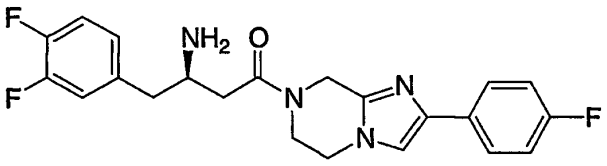

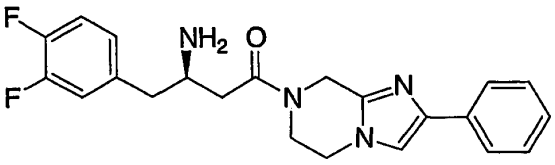

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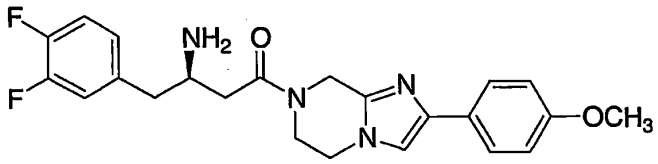

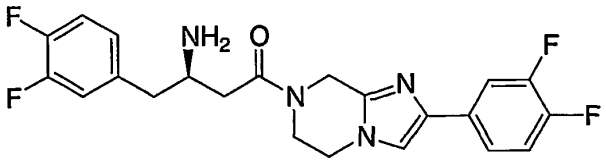

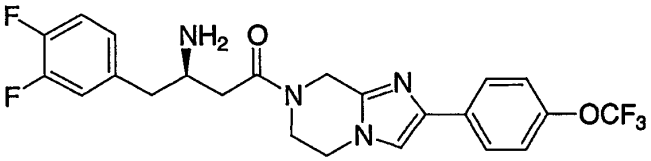

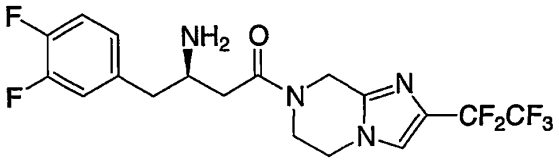

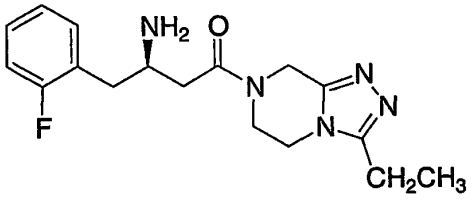

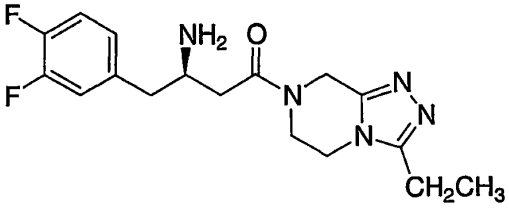

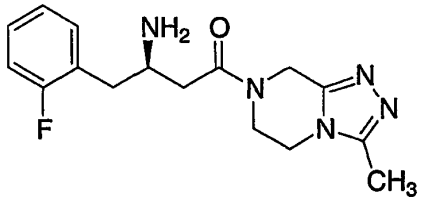

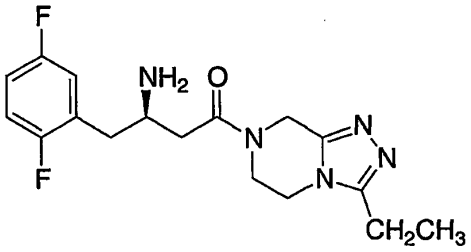

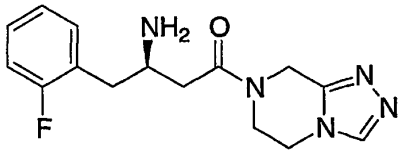

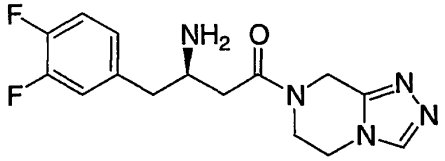

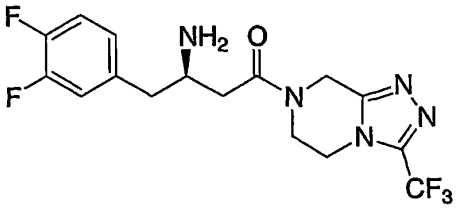

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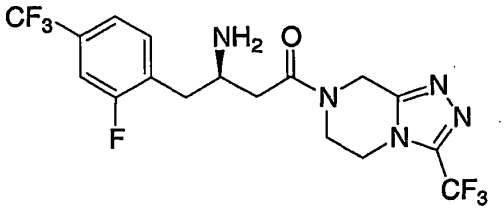

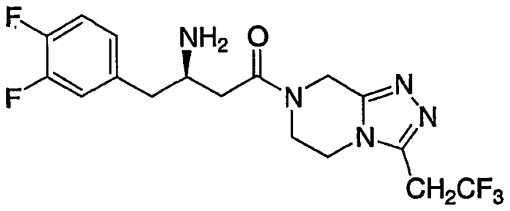

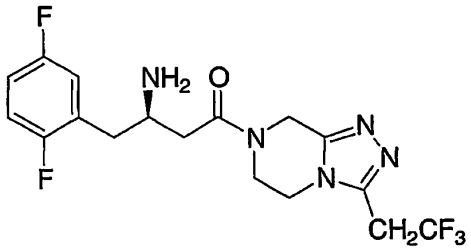

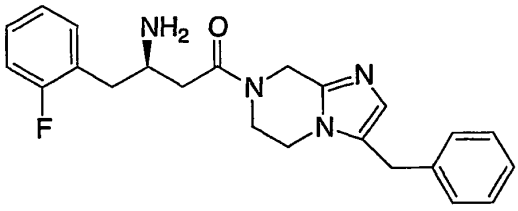

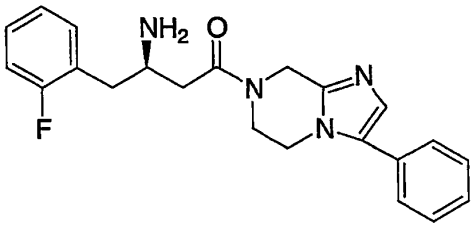

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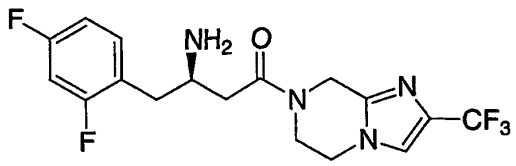

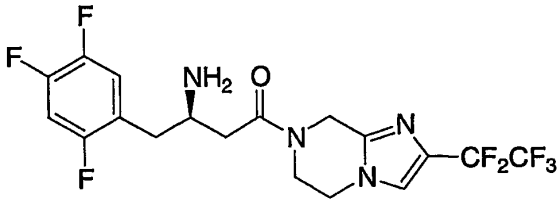

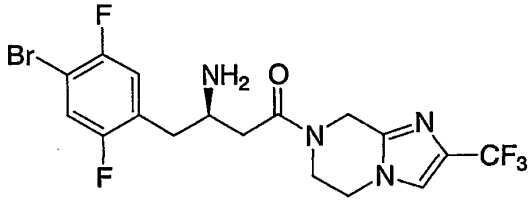

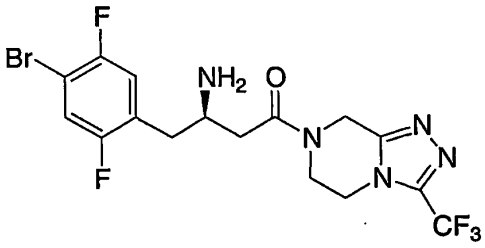

and pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

17. A method for inhibition of dipeptidyl peptidase-IV enzyme activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

18. A method for treating, controlling, or preventing diabetes comprising the administration to a patient of an effective amount of the compound of Claim 1.

19. A method for treating, controlling, or preventing non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

20. A method for treating, controlling or preventing hyperglycemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

21. A method for treating, controlling or preventing obesity in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

22. A method for treating, controlling or preventing insulin resistance in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

23. A method for treating, controlling or preventing one or more lipid disorders selected from the group conisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

24. A method for treating, controlling or preventing atherosclerosis in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

25. A method for treating or controlling growth hormone deficiency in a mammalian patient in need of such treatment which comprises

administering to the patient a therapeutically effective amount of a compound of Claim 1.

26. A method for modulating the immune response in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

27. A method for treating or controlling HIV infection in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

28. A method for treating, controlling or preventing in a mammalian patient in need of treatment one or more disorders selected from the group consisting of neutropenia, neuronal disorders, tumor metastasis, benign prostatic hypertrophy, gingivitis, hypertension and osteoporosis which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

29. A method for reducing sperm motility in a male mammalian patient which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

30. A method for treating, controlling or preventing in a mammalian patient in need of treatment one or more conditions selected from the group consisitng of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, wherein the method comprises the administration to the patient of a therapeutically effective amount of a compound of Claim 1.

31. A method for treating, controlling or preventing in a mammalian patient in need of treatment one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type II diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be treated by inhibition of DP-IV, wherein the treatment comprises the administration to the patient of a therapeutically effective amount of a first compound of Claim 1, or a pharmaceutically acceptable salt thereof, and one or more other compounds selected from the group consisting of:

(a) other dipeptidyl peptidase IV (DP-IV) inhibitors,

(b) insulin sensitizers selected from the group consisting of (i) PPAR agonists, (ii) biguanides, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(c) insulin or insulin mimetics;

(d) sulfonylureas or other insulin secretagogues;

(e) α-glucosidase inhibitors;

(f) glucagon receptor agonists;

(g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;

(h) GIP, GIP mimetics, and GIP receptor agonists;

(i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;

(j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists, (v) PPARα/γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;

(k) PPARδ agonists;

(l) antiobesity compounds;
(m) an ileal bile acid transporter inhibitor; and
(n) anti-inflammatory agents.

32. A method for the treatment, control, or prevention of one or more conditions selected from intestinal injury, inflammatory bowel disease, Crohn's disease, and ulcerative colitis, which method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Claim 1.

33. A method for the treatment, control, or prevention of one or more conditions selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Claim 1 and an HMG-CoA reductase inhibitor.

34. The method of Claim 33, wherein the HMG-CoA reductase inhibitor is a statin.

35. The method of Claim 34, wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

36. A method for the treatment, control, or prevention of atherosclerosis in a mammalian patient in need of such treatment comprising the administration to the patient of an effective amount of a compound of Claim 1 and an effective amount of an HMG-CoA reductase inhibitor.

37. The method as recited in Claim 36, wherein the HMG-CoA reductase inhibitor is a statin.

38. The method as recited in Claim 37, wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

39. A pharmaceutical composition for the treatment, prevention or control of atherosclerosis, comprising: (1) a compound of Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

40. A pharmaceutical composition comprising

(1) a compound of Claim 1,

(2) one or more compounds selected from the group consisting of :

(a) other dipeptidyl peptidase IV (DP-IV) inhibitors;

(b) insulin sensitizers selected from the group consisting of (i) PPARγ agonists, other PPAR ligands, PPARα/γ dual agonists, and PPARα agonists, (ii) biguanides, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(b) insulin or insulin mimetics;

(c) sulfonylureas or other insulin secretagogues;

(d) α-glucosidase inhibitors;

(f) glucagon receptor agonists;

(g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;

(h) GIP, GIP mimetics, and GIP receptor agonists;

(i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;

(j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists, (v) PPARα/γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;

(k) PPARδ agonists;

(l) antiobesity compounds;

(m) an ileal bile acid transporter inhibitor; and

(n) anti-inflammatory agents; and

(3) a pharmaceutically acceptable carrier.

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| APPLICATION NUMBER | FILING OR 371 (c) DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NUMBER |
|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y |

**CONFIRMATION NO. 9276**

000210
MERCK AND CO INC
P O BOX 2000
RAHWAY, NJ 070650907

**FORMALITIES LETTER**

*OC000000013809544*

Date Mailed: 09/15/2004

## NOTICE TO FILE CORRECTED APPLICATION PAPERS

### *Filing Date Granted*

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121 are required. The drawings submitted are not acceptable because:
    - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 1-5.

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PART 3 - OFFICE COPY

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| Applicants: | Stephen H. Cypes, et al. | |
| Serial No.: | 10,874,992 | Case No.: 21409Y |
| Filed: | June 23, 2004 | |
| For: | PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR | |

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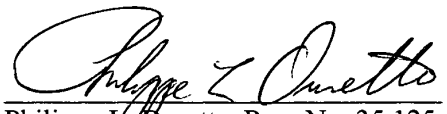
RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Sir:

In response to the Notice to File Corrected Application Papers under 37 CFR 1.84 and 37 CFR 1.121, mailed June 23, 2004, which is attached hereto, enclosed are the replacement drawings.

Respectfully submitted,

By 

Philippe L. Durette, Reg. No. 35,125
Attorney for Applicants

MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065
Tel.: (732) 594-4568

Date: October 20, 2004

UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICATION NUMBER | FILING OR 371 (c) DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NUMBER |
|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y |

**CONFIRMATION NO. 9276**

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MERCK AND CO INC
P O BOX 2000
RAHWAY, NJ 070650907

**FORMALITIES LETTER**

*OC000000013809544*

Date Mailed: 09/15/2004

## NOTICE TO FILE CORRECTED APPLICATION PAPERS

### *Filing Date Granted*

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

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  - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 1-5.

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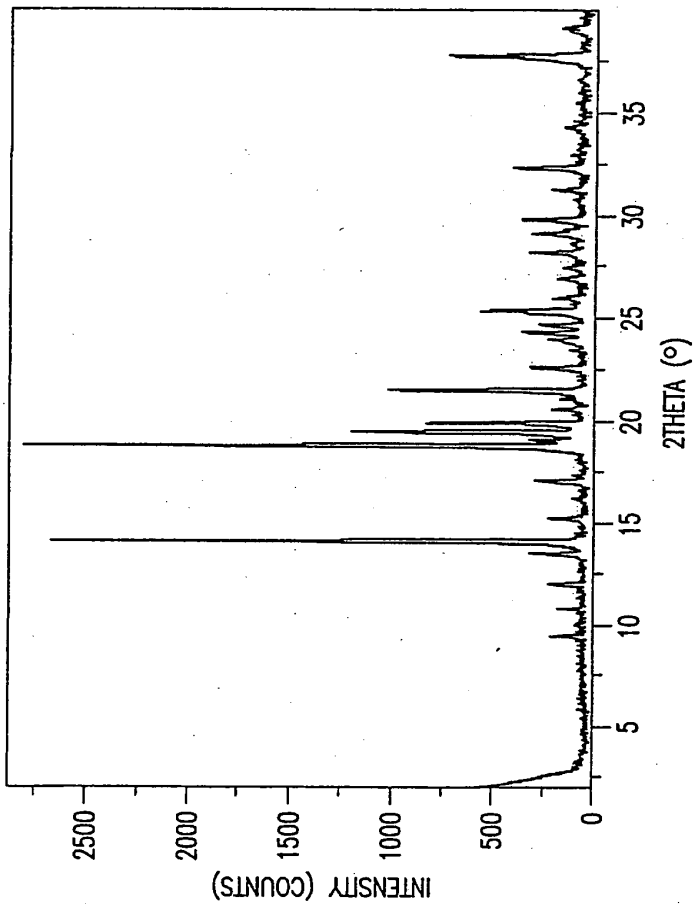


FIG.1

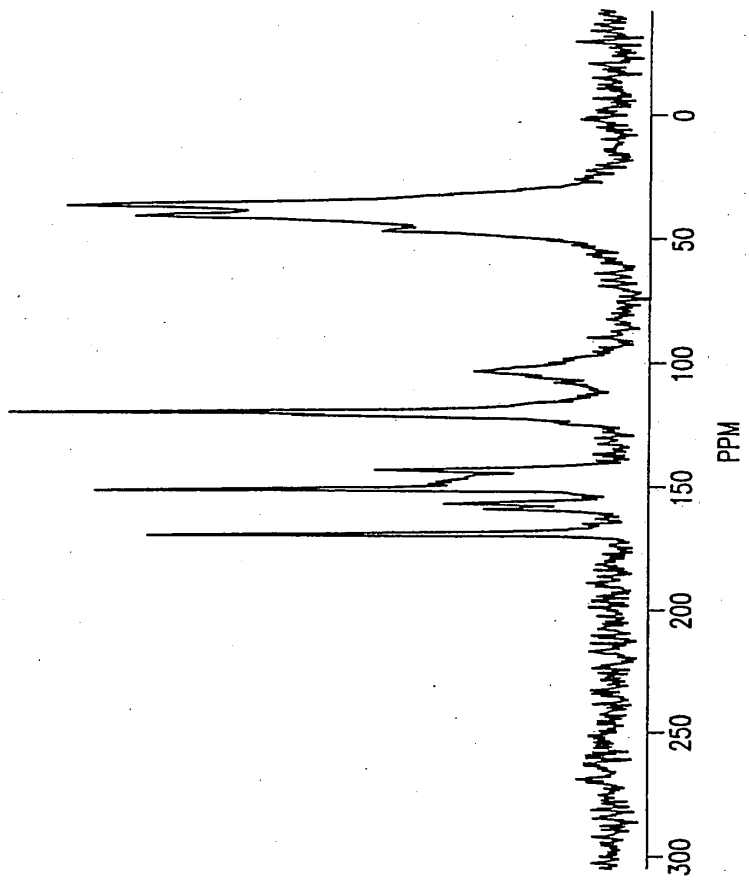


FIG.2

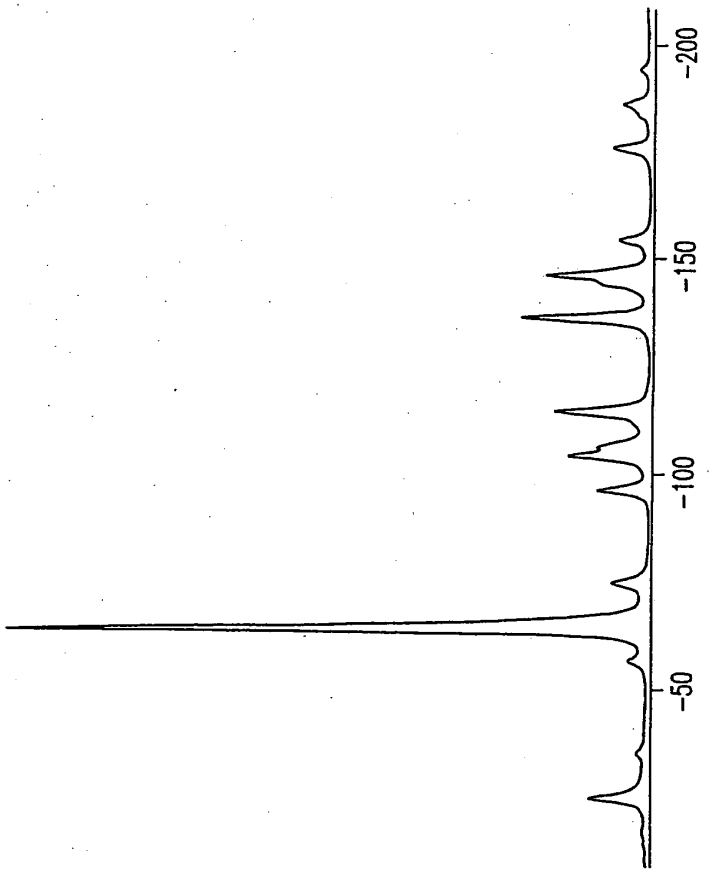


FIG.3

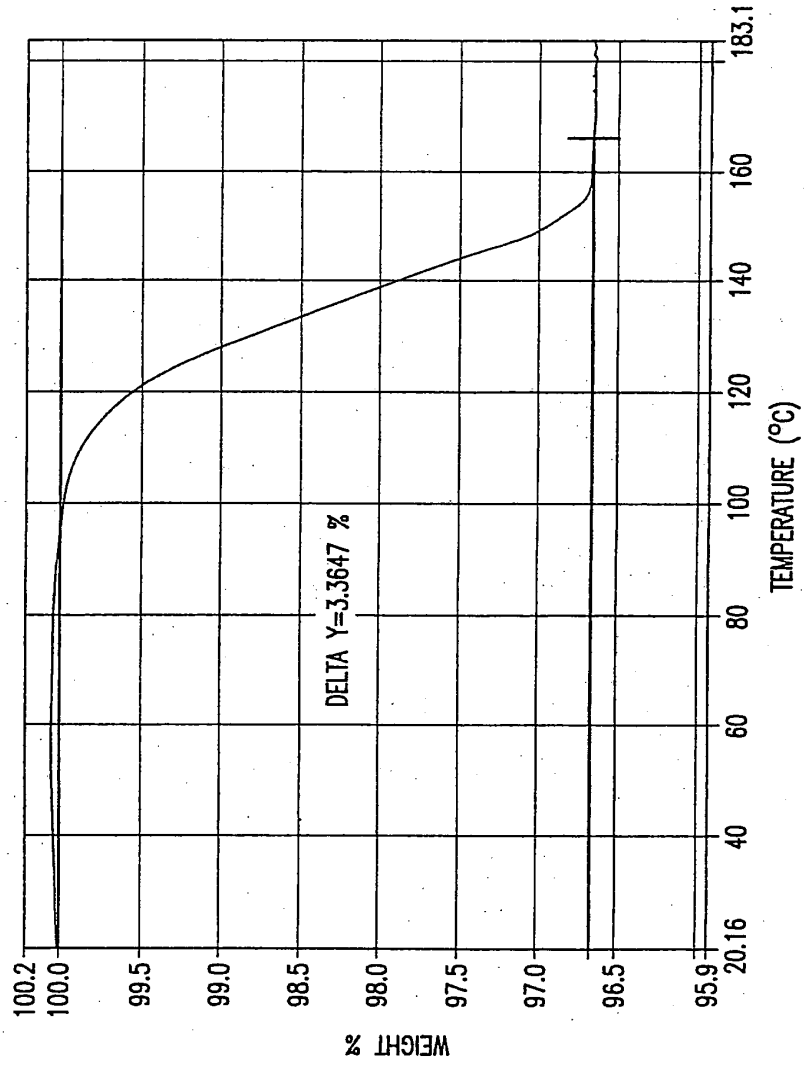


FIG.4

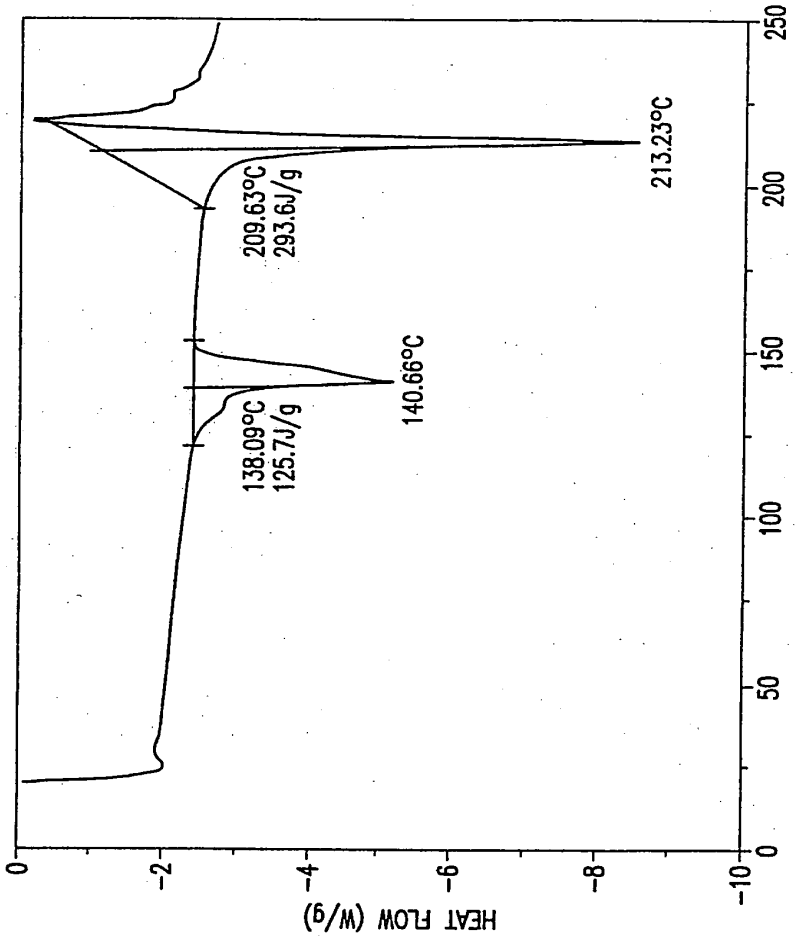


FIG.5

PATENT Case No. 21409Y IFW

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Chen, et al


Serial No. 10/874,992

Filed: June 23, 2004

For: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

Art Unit: 1626

Examiner: Ebenezer Sackey

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

SUPPLEMENTAL
## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

Sir:

1. In compliance with 37 C.F.R. 1.97, submitted on the attached form herewith is a list of patents, publications or other information which are requested to be made of record in this application. This Information Disclosure Statement is not an admission that any patent, publication or other information referred to herein is "prior art" for this invention. In accordance with 37 C.F.R. 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. 1.56(b).

2. In accordance with 37 C.F.R. 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made.

3. Applicants respectfully request that the Examiner initial the attached form after reviewing the pertinence of each reference.

4. Pursuant to 37 C.F.R. 1.98 (a)(2)(ii), copies of each cited U.S. patent and each U.S. patent application publication are not enclosed herewith.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

**MERCK & CO., INC.**

By Pamela Spalding Date 7-25-06

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PATENT Case No. 21409Y

## INFORMATION DISCLOSURE STATEMENT

5. Pursuant to 37 C.F.R. 1.98(d), copies of references listed on the attached form that were submitted to or cited by the Office in a related application upon which the instant application relies for an earlier filing date under 35 U.S.C. 120 are not enclosed. Related application(s) in which references were submitted to or cited by the Office are as follows:

| | RELATED APPLICATION | |
|---|---|---|
| U. S. SERIAL NUMBER | FILING DATE | MERCK CASE |
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If this is inconvenient, additional copies will be submitted upon request.

6. In accordance with 37 C.F.R. 1.97, (check one)

☐ the attached information is filed within three months of the filing date of the captioned case.

☑ the attached information is filed more than three months after the filing date but prior to the mailing of a first Office Action on the merits.

☐ the attached information is filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

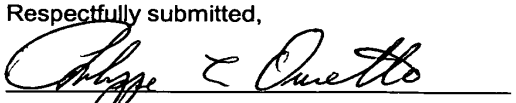
☐ the attached information is being filed more than three months after the filing date and after the mailing of a first Office Action on the merits, but before the mailing date of a Final Action, Notice of Allowance, or an action that otherwise closes prosecution in the application. The enclosed authorization is therefore given to charge Deposit Account No. 13-2755 for the fee required under 37 C.F.R. 1.17(p).

☐ each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Statement.

☐ each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart application *and this communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of the information disclosure statement.*

☐ no item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated under 37 C.F.R. 1.56(c) more than three months prior to the filing of this Statement.

Respectfully submitted,



By: Philippe L. Durette
Attorney For Applicant(s)
Reg. No. 35,125
MERCK & CO., INC.
Patent Dept., RY60-30
P.O. Box 2000
Rahway, N.J. 07065-0907
(732)594-4568
Date: July 25, 2006

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Approved for use through 7/31/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (07-05), Information Disclosure Statement by Applicant
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Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*



Sheet 1 of 2

| *COMPLETE IF KNOWN* | |
|---|---|
| **Application Number** | 10/874,992 |
| **Filing Date** | June 23, 2004 |
| **First Named Inventor** | Chen, et al |
| Group Art Unit | 1626 |
| Examiner Name | Ebenezer Sackey |
| Attorney Docket Number | 21409Y |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. | U.S. Patent Document Number | Kind Code *(if known)* | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No. | Foreign Patent Document Office | Number | Kind Code *(if known)* | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
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| Examiner Signature | | Date Considered | |
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*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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SUBSTITUTE for PTO/SB/08A (07-05), Information Disclosure Statement by Applicant
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

Sheet 2 of 2

| *COMPLETE IF KNOWN* | |
|---|---|
| **Application Number** | 10/874,992 |
| **Filing Date** | June 23, 2004 |
| **First Named Inventor** | Chen, et al |
| Group Art Unit | 1626 |
| Examiner Name | Ebenezer Sackey |
| Attorney Docket Number | 21409Y |

## NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. | Include name of the author, title, date, page(s), volume-issue number(s) and place of publication. |
|---|---|---|
| | 1 | Edmondson, S.D., Drug Data Report, Vol. 25, No. 3, Pages 245-246 (2003) |
| | 2 | Database Prous DDR Online -- Database Accession No: 2003: 3561 |
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| Examiner Signature | | Date Considered | |
|---|---|---|---|

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

SEND TO: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450. Computer generated form " IDS Form" (IDS Folder), Merck & Co., Inc., -7/12/2005

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=>
=> s l1 sss full
FULL SEARCH INITIATED 09:25:07 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      434 TO ITERATE

100.0% PROCESSED      434 ITERATIONS                              62 ANSWERS
SEARCH TIME: 00.00.01

L3            62 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     185.15     185.36

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FILE COVERS 1907 - 29 May 2007  VOL 146 ISS 23
FILE LAST UPDATED: 28 May 2007  (20070528/ED)

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http://www.cas.org/infopolicy.html

=> s l3
L4            93 L3

=> s l4 and diabetes
         125334 DIABETES
L5            73 L4 AND DIABETES

=> s l5 and obesity and high blood pressure
           42852 OBESITY
         4050662 HIGH
         1307090 BLOOD
         1247826 PRESSURE
            2402 HIGH BLOOD PRESSURE
                   (HIGH(W)BLOOD(W)PRESSURE)
L6             4 L5 AND OBESITY AND HIGH BLOOD PRESSURE

=> d l6 ibib abs hitstr 1-4
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L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:298857 CAPLUS
DOCUMENT NUMBER: 144:338150
TITLE: Amorphous form of a phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor
INVENTOR(S): Ferlita, Russell R.; Wenslow, Robert M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2006033848 | A1 | 20060330 | WO 2005-US32079 | 20050909 |

W: 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, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-610019P P 20040915

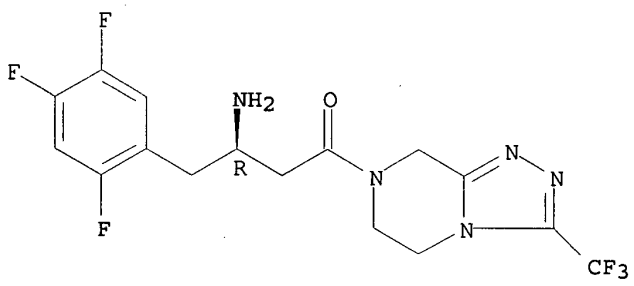
AB The present invention relates to a novel amorphous form of the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine as well as a process for its preparation, pharmaceutical compns. containing this novel form, and methods of use of the novel form and pharmaceutical compns. for the treatment of diabetes, obesity, and high blood pressure.

IT 654671-78-0P
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amorphous form of a phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor)
RN 654671-78-0 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)-, phosphate (1:1) (CA INDEX NAME)

CM 1

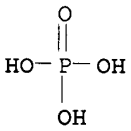
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



CM 2

CRN 7664-38-2
CMF H3 O4 P



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:300188 CAPLUS
DOCUMENT NUMBER: 142:360851
TITLE: Novel crystalline form of a phosphate salt of a dipeptidyl peptidase-IV inhibitor
INVENTOR(S): Chen, Alex M.; Wenslow, Robert M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005030127 | A2 | 20050407 | WO 2004-US30434 | 20040917 |
| WO 2005030127 | A3 | 20050526 | | |
| W: 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 | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1667524 | A2 | 20060614 | EP 2004-784324 | 20040917 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK | | | | |
| US 2007021430 | A1 | 20070125 | US 2006-570409 | 20060303 |
| PRIORITY APPLN. INFO.: | | | US 2003-505118P P | 20030923 |
| | | | WO 2004-US30434 W | 20040917 |

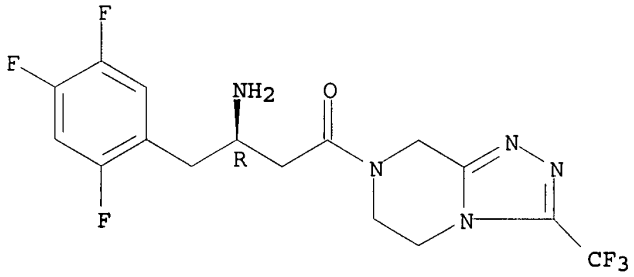
AB The present invention relates to a novel crystalline anhydrate polymorph of the dihydrogen phosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine as well as a process for their preparation, pharmaceutical compns. containing this form, and methods of use of the form for the treatment of diabetes, obesity, and high blood pressure.

IT 654671-77-9P 654671-78-0P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(crystalline form of phosphate salt of dipeptidyl peptidase-IV inhibitor)
RN 654671-77-9 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)-, phosphate, hydrate (1:1:1) (CA INDEX NAME)

CM 1

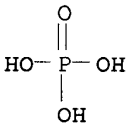
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



CM 2

CRN 7664-38-2
CMF H3 O4 P

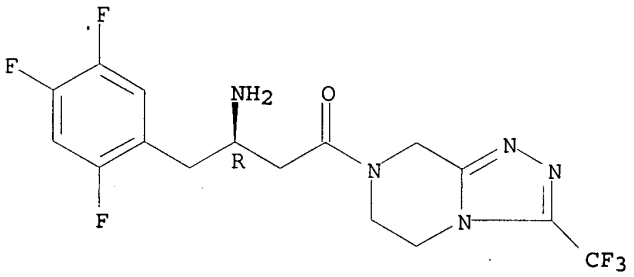


RN 654671-78-0 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)-, phosphate (1:1) (CA INDEX NAME)

CM 1

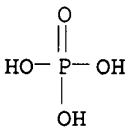
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



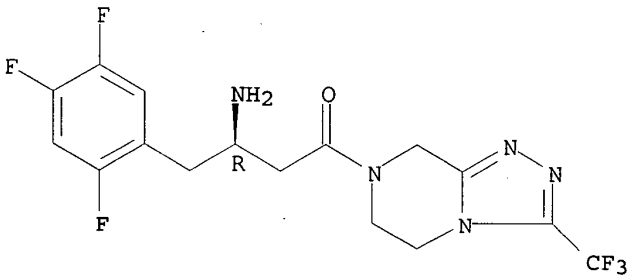
CM 2

CRN 7664-38-2
CMF H3 O4 P



IT 486460-32-6P
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(crystalline form of phosphate salt of dipeptidyl peptidase-IV inhibitor)
RN 486460-32-6 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)- (CA INDEX NAME)

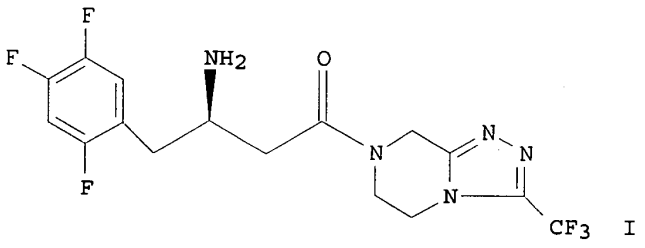
Absolute stereochemistry.



L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:216618 CAPLUS
DOCUMENT NUMBER: 142:303604
TITLE: Novel crystal forms of a dihydrogen phosphate salt of a trizolopyrazine dipeptidyl peptidase IV inhibitor
INVENTOR(S): Wenslow, Robert M.; Armstrong, Joseph D., III; Chen, Alex M.; Cypes, Stephen; Ferlita, Russell R.; Hansen, Karl; Lindemann, Christopher M.; Spartalis, Evangelia
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2005020920 | A2 | 20050310 | WO 2004-US27983 | | 20040827 |
| WO 2005020920 | A3 | 20050428 | | | |
| W: 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 | | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| AU 2004268024 | A1 | 20050310 | AU 2004-268024 | | 20040827 |
| CA 2536251 | A1 | 20050310 | CA 2004-2536251 | | 20040827 |
| EP 1662876 | A2 | 20060607 | EP 2004-782460 | | 20040827 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK | | | | | |
| CN 1845674 | A | 20061011 | CN 2004-80025043 | | 20040827 |
| JP 2007504230 | T | 20070301 | JP 2006-525371 | | 20040827 |
| US 2006287528 | A1 | 20061221 | US 2006-569566 | | 20060227 |
| PRIORITY APPLN. INFO.: | | | US 2003-499629P | P | 20030902 |
| | | | WO 2004-US27983 | W | 20040827 |

OTHER SOURCE(S): CASREACT 142:303604
GI




I

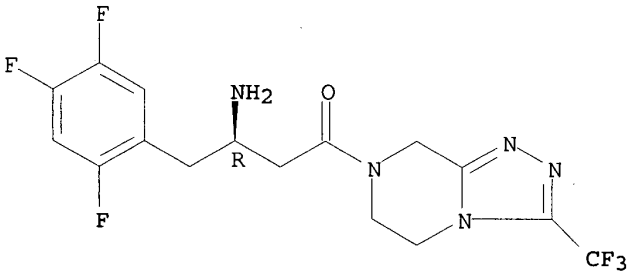
AB The present invention relates to crystalline anhydrate polymorphs of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine dihydrogen phosphate salt (I) as well as a process for their preparation,

pharmaceutical compns. containing these novel forms, and methods of use of the novel forms and pharmaceutical compns. for the treatment of diabetes, obesity, and high blood pressure.

IT 486460-32-6P 654671-78-0P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(crystal forms of a trizolopyrazine dihydrogen phosphate salt dipeptidyl peptidase IV inhibitor)

RN 486460-32-6 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)- (CA INDEX NAME)

Absolute stereochemistry.

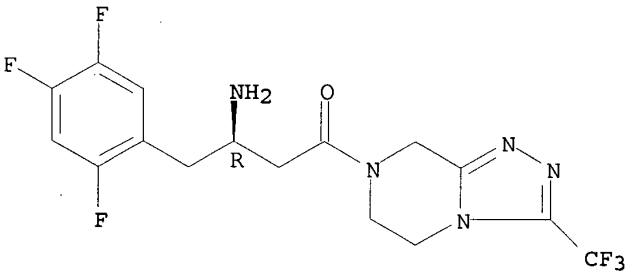


RN 654671-78-0 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)-, phosphate (1:1) (CA INDEX NAME)

CM 1

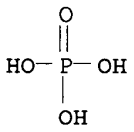
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



CM 2

CRN 7664-38-2
CMF H3 O4 P

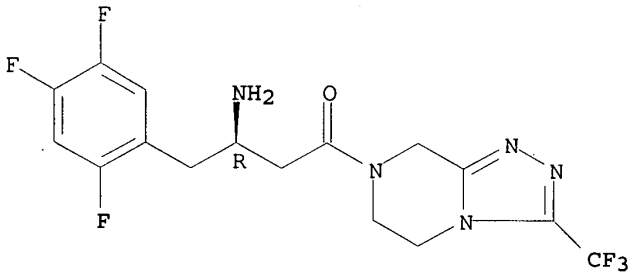


IT 847445-75-4 847445-76-5 847445-77-6
847445-78-7 847445-79-8 847445-80-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal forms of a trizolopyrazine dihydrogen phosphate salt dipeptidyl peptidase IV inhibitor)
RN 847445-75-4 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate, compd. with 2-propanone (1:1:?) (9CI) (CA INDEX NAME)

CM 1

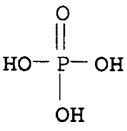
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



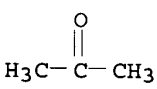
CM 2

CRN 7664-38-2
CMF H3 O4 P



CM 3

CRN 67-64-1
CMF C3 H6 O

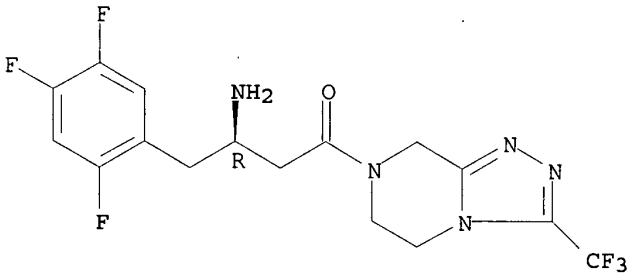


RN 847445-76-5 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate, compd. with acetonitrile (1:1:?) (9CI) (CA INDEX NAME)

CM 1

CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



CM 2

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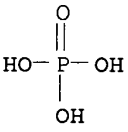
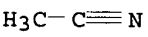
CMF H3 O4 P



CM 3

CRN 75-05-8
CMF C2 H3 N

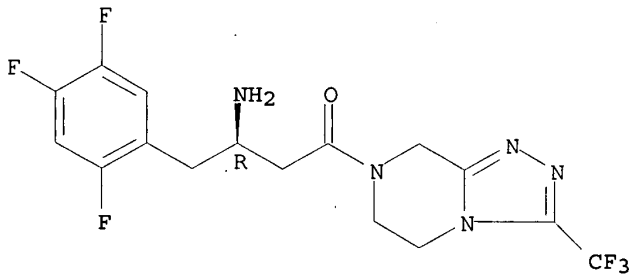


RN 847445-77-6 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate, compd. with methanol (1:1:?) (9CI) (CA INDEX NAME)

CM 1

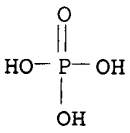
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



CM 2

CRN 7664-38-2
CMF H3 O4 P



CM 3

CRN 67-56-1
CMF C H4 O

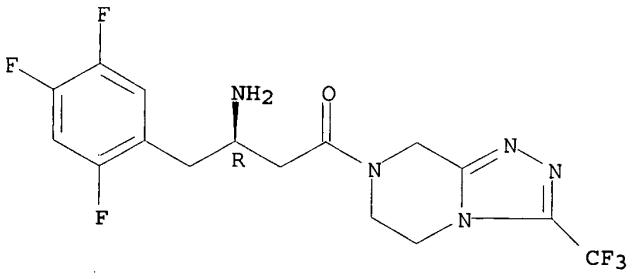
$H_3C-OH$

RN 847445-78-7 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate, compd. with ethanol (1:1:?) (9CI) (CA INDEX NAME)

CM 1

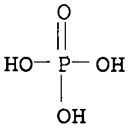
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



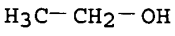
CM 2

CRN 7664-38-2
CMF H3 O4 P



CM 3

CRN 64-17-5
CMF C2 H6 O

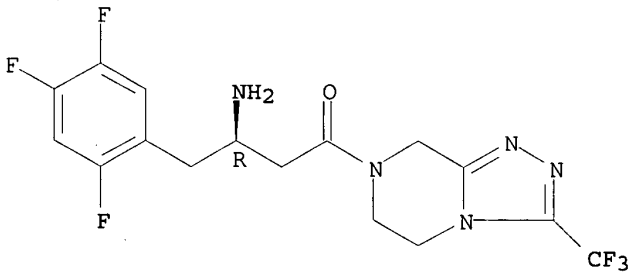


RN 847445-79-8 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate, compd. with 1-propanol (1:1:?) (9CI) (CA INDEX NAME)

CM 1

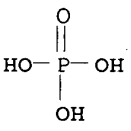
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



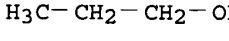
CM 2

CRN 7664-38-2
CMF H3 O4 P



CM 3

CRN 71-23-8
CMF C3 H8 O

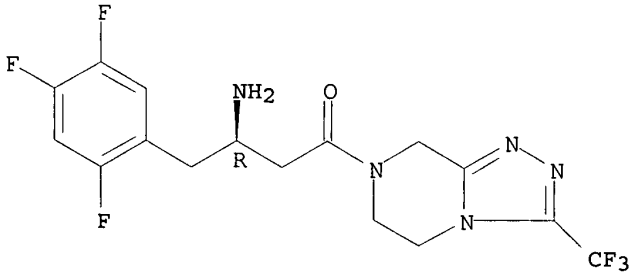


RN 847445-80-1 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate, compd. with 2-propanol (1:1:?) (9CI) (CA INDEX NAME)

CM 1

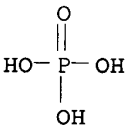
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



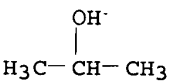
CM 2

CRN 7664-38-2
CMF H3 O4 P



CM 3

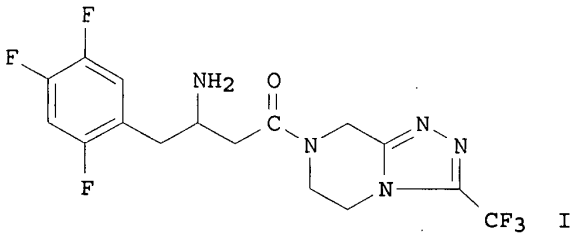
CRN 67-63-0
CMF C3 H8 O



L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:29336 CAPLUS
DOCUMENT NUMBER: 142:114455
TITLE: Preparation of phosphoric acid salt of a β-amino acid amide dipeptidyl peptidase-IV inhibitor and its monohydrate
INVENTOR(S): Cypes, Stephen Howard; Chen, Alex Minhua; Ferlita, Russell R.; Hansen, Karl; Lee, Ivan; Vydra, Vicky K.; Wenslow, Robert M., Jr.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2005003135 | A1 | 20050113 | WO 2004-US19683 | | 20040618 |
| W: 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 | | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| AU 2004253889 | A1 | 20050113 | AU 2004-253889 | | 20040618 |
| CA 2529400 | A1 | 20050113 | CA 2004-2529400 | | 20040618 |
| EP 1654263 | A1 | 20060510 | EP 2004-755691 | | 20040618 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | | | |
| JP 2006516268 | T | 20060629 | JP 2005-518292 | | 20040618 |
| BR 2004011726 | A | 20060808 | BR 2004-11726 | | 20040618 |
| CN 1832949 | A | 20060913 | CN 2004-80017544 | | 20040618 |
| US 2005032804 | A1 | 20050210 | US 2004-874992 | | 20040623 |
| NO 2006000362 | A | 20060323 | NO 2006-362 | | 20060123 |
| PRIORITY APPLN. INFO.: | | | US 2003-482161P | P | 20030624 |
| | | | WO 2004-US19683 | W | 20040618 |

GI



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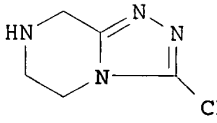

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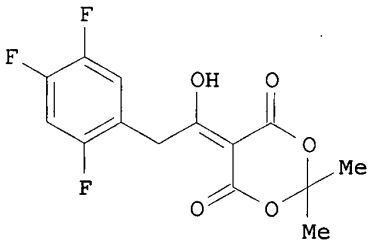


III

AB The invention is related to the preparation of dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5- trifluorophenyl)butan-2-amine (I•H3PO4) which is a potent inhibitor of dipeptidyl peptidase-IV and therefore useful for the prevention and/or treatment of type 2 diabetes. The invention also relates to the preparation of hydrates, in particular a crystalline monohydrate of the dihydrogenphosphate salt I, its pharmaceutical compns., and methods of use for the treatment of diabetes, obesity, and high blood pressure. Thus, treating II•HCl (preparation given) with III (preparation given), followed by reaction with NH4OAc in MeOH, and hydrogenation gave amine (R)-I. Reaction of amine (R)-I with 85% aqueous H3PO4 and recrystn. from isopropanol/water gave (R)-I•H3PO4•H2O.

IT 654671-77-9P, (2R)-4-Oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine dihydrogen phosphate monohydrate
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(DPPIV inhibitor; preparation of triazolopyrazine beta amino amide dihydrogenphosphates and their monohydrates as peptidase-iv inhibitor)

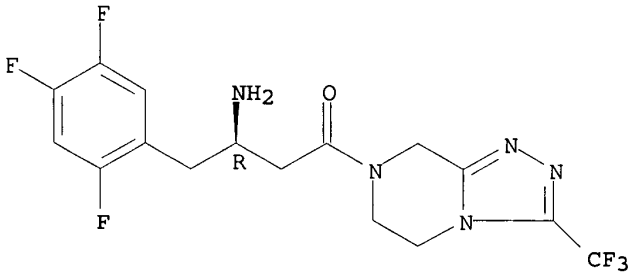
RN 654671-77-9 CAPLUS

CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)-, phosphate, hydrate (1:1:1) (CA INDEX NAME)

CM 1

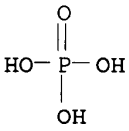
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



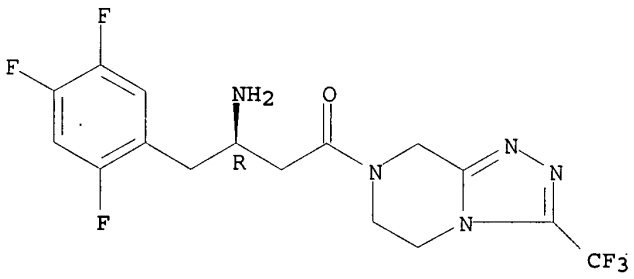
CM 2

CRN 7664-38-2
CMF H3 O4 P



IT 486460-32-6P, (2R)-4-Oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of triazolopyrazine beta amino amide dihydrogenphosphates and their monohydrates as peptidase-iv inhibitor)
RN 486460-32-6 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)- (CA INDEX NAME)

Absolute stereochemistry.



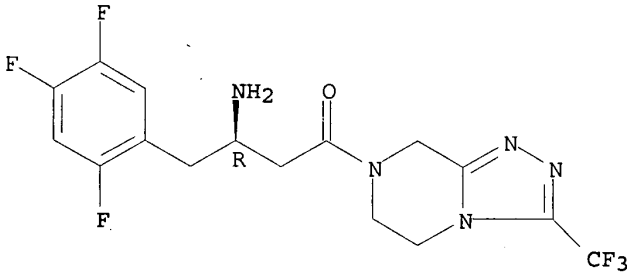
IT 654671-78-0P 823817-57-8P 823817-58-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of triazolopyrazine beta amino amide dihydrogenphosphates and their monohydrates as peptidase-iv inhibitor)
RN 654671-78-0 CAPLUS
CN 1-Butanone, 3-amino-1-[5,6-dihydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)-, (3R)-, phosphate (1:1)

(CA INDEX NAME)

CM 1

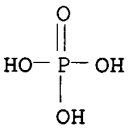
CRN 486460-32-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



CM 2

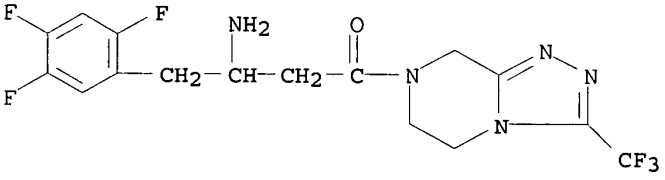
CRN 7664-38-2
CMF H3 O4 P



RN 823817-57-8 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate (1:1) (9CI) (CA INDEX NAME)

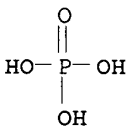
CM 1

CRN 823817-56-7
CMF C16 H15 F6 N5 O



CM 2

CRN 7664-38-2
CMF H3 O4 P

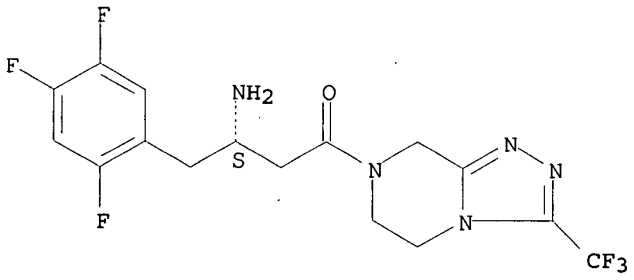


RN 823817-58-9 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3S)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 823817-55-6
CMF C16 H15 F6 N5 O

Absolute stereochemistry.



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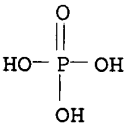
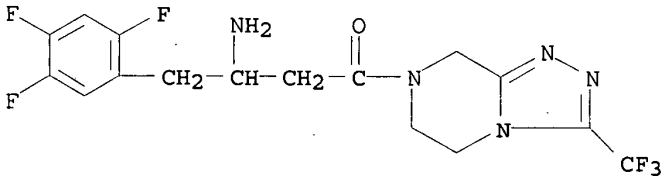
CRN 7664-38-2
CMF H3 O4 P

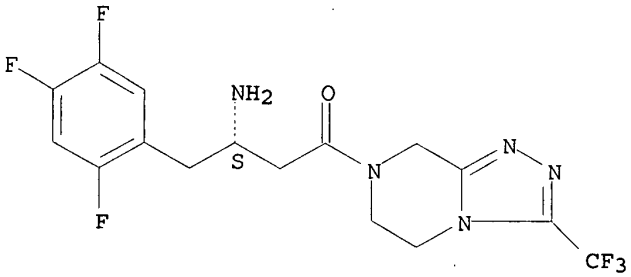


IT 823817-56-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of triazolopyrazine beta amino amide dihydrogenphosphates and their monohydrates as peptidase-iv inhibitor)
RN 823817-56-7 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)



IT 823817-55-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of triazolopyrazine beta amino amide dihydrogenphosphates and their monohydrates as peptidase-iv inhibitor)
RN 823817-55-6 CAPLUS
CN 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3S)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/874992

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=>  d his

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L2            6 S L1
L3           62 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 09:25:21 ON 29 MAY 2007
L4           93 S L3
L5           73 S L4 AND DIABETES
L6            4 S L5 AND OBESITY AND HIGH BLOOD PRESSURE

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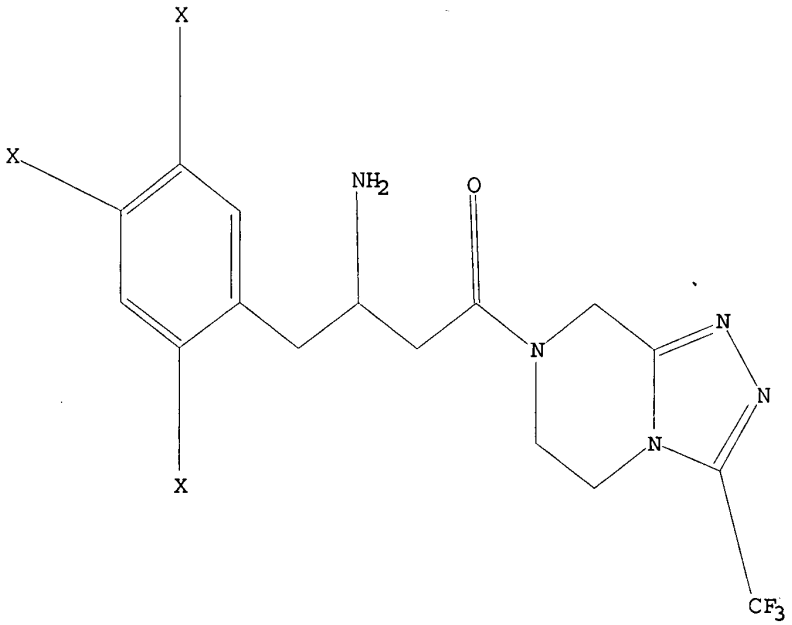


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Structure attributes must be viewed using STN Express query preparation.

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Executing the logoff script...

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COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
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FULL ESTIMATED COST                           33.95      219.31
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10/874992

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -3.12 | -3.12 |

STN INTERNATIONAL LOGOFF AT 09:29:06 ON 29 MAY 2007

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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y | 9276 |

210 7590 06/11/2007
MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

| EXAMINER | |
|---|---|
| SACKEY, EBENEZER O | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/11/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/874,992 | CYPES ET AL. | |
| | Examiner | Art Unit | |
| | EBENEZER SACKEY | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29, 30 and 35* is/are allowed.

6)☒ Claim(s) *1-28 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/13/04, 07/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### Status of the Claims

Claims 1-35 are pending.

### *Specification*

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

### *Information Disclosure Statement*

Receipt of the Information Disclosure Statement filed on 09/13/04 and 07/28/06 respectively is acknowledged and has been entered into the file. Signed copies of the 1449 are attached herewith.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 31-32 provides for the use of a compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 31-32 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds on pages 9-15, does not reasonably provide enablement for solvate of those compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims recite specific compounds of structural formula (I) and solvates of said compounds. However, the specification fails to teach the preparation of solvates. Therefore, the specification is not adequately enabled for solvates.

Identifying a solvate requires knowledge of properties of the solvents and solutes of the instant compounds and nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist thus, such a scope as literally claimed herein is non-enabled.

The examples presented all fail to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.,* 28 USPQ .2d 1190 "the specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However, .... there is no evidence that such compounds exist..... the examples of the '881' patent do not produce the postulated compounds.....there is ....no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compositions actually exist; if they did, they would have been formed. Hence, applicants must now show that solvates can be made, or limit the claims accordingly.

It is not the norm that one can predict with any accuracy a particular solvate form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo*. The specification provides no guidance as to what type(s) are suitable for instant compounds.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art.

See below:

1) Nature of the invention.

The nature of the invention is the preparation of compounds and compositions under the genus of structural formula (I). As stated, however, solvates are also intended.

2) State of the prior art .

The state of the prior art is that solvates are known in the pharmaceutical industry.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue. For example, identifying a solvate requires knowledge of the properties of the solvents and solutes and their

reactions and/or transformation, nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist and thus, such a scope as literally claimed herein is non-enabled.

4) Level of predictability in the art.

The art pertaining to the preparation and use of solvates are high as solvates are compound specific.

5) Amount of direction and guidance provided by the inventor.

There is no guidance provided as all the examples in the specification are drawn to the preparation of compounds and not solvates. Additionally, the specification provides no guidance as to what type(s) solvates are suitable for the instant compounds.

6) Existence of working examples.

No examples of solvates have been provided in the specification.

7) Breadth of claims.

The breath of the recited compounds and the solvates render the claims overly broad.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high due to the unpredictability in the chemical art.

Hence, the specification fails to provide sufficient support for solvates as claimed herein. As a result, necessitating one of ordinary skill in the art to perform an exhaustive search to determine which of the claimed solvates can be employed to practice the claimed invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of "comprises" in defining a compound claim is not permitted since the use of the term is inclusive and fails to exclude unrecited elements. Comprising leaves the claim open for inclusion of unspecified elements. *Ex parte Davis et al.*,80 USPQ 448 (PTO Bd. App. 1948). Claims, especially compound claims should be defined as --- consisting of----.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-28 and 33-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 23-33 and 46-50 of copending Application No. 10/569,566. Although the conflicting claims are not identical, they are not patentably distinct from each other because there are structural similarities between the instant salts and salts of '566' for treating type-2 diabetes. The instant compounds differ from '566' in the form of the compounds, i.e., '566' being in crystalline anhydrate form, and instant compounds in crystalline monohydrate form. The motivation to prepare the instant compounds derives from the fact that structurally similar compounds would possess virtually the same or similar properties. Thus, one of ordinary skill in the art would have been motivated to prepare the instant salts with a reasonable expectation that the resulting salts would be useful for treating type-2 diabetes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-28 and 33-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, and 12-15 of copending Application No. 10/570,409. Although the conflicting claims are not identical, they are not patentably distinct from each other because there are structural similarities between the instant salts and salts of '409' for treating type-2 diabetes. The instant compounds differ from '409' in the form of the compounds, i.e., '409' being in crystalline anhydrate form, and instant compounds in crystalline monohydrate form. The motivation to prepare the instant compounds derives from the fact that structurally similar compounds would possess virtually the same or similar properties. Thus, one of ordinary skill in the art would have been motivated to prepare the instant salts with a reasonable expectation that the resulting salts would be useful for treating type-2 diabetes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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Any inquiry concerning this communication or earlier communications from the

examiner should be directed to E. Sackey whose telephone number is (571) 272-0704. The examiner can normally be reached on Monday-Friday from 7:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached on (571) 272-0661. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

EOS
June 7, 2007

James O. Wilson
Supervisory Patent Examiner
Art Unit 1624, Group 1600
Technology Center 1

GOLAM M. M. SHAMEEM, PH.D
PRIMARY EXAMINER

Approved for use through 7/31/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (08-03), Information Disclosure Statement by Applicant
Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

Sheet 1 of 1

| COMPLETE IF KNOWN | |
|---|---|
| Application Number | 10/874,992 |
| Filing Date | June 23, 2004 |
| First Named Inventor | Chen, et al. |
| Group Art Unit | 1624 |
| Examiner Name | E. Sackey |
| Attorney Docket Number | 21409Y |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. | U.S. Patent Document Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
| ES | 1 | US 2003/0100563 A1 | | Edmondson, et al. | 05/29/2003 |
| ES | 2 | US 6,699,871 | | Edmondson, et al. | 03/02/2004 |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No. | Foreign Patent Document Office | Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|---|
| | 3 | PCT | WO 03/004498 | | MERCK & CO., INC. | 01/16/2003 |

| Examiner Signature | | Date Considered | 5/29/07 |
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*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

SEND TO: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450. Computer generated form "IDS Form" (IDS Folder), Merck & Co., Inc., 09/05/2003

Approved for use through 7/31/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (07-05), Information Disclosure Statement by Applicant
Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*



Sheet 1 of 2

| COMPLETE IF KNOWN | |
|---|---|
| Application Number | 10/874,992 |
| Filing Date | June 23, 2004 |
| First Named Inventor | Chen, et al |
| Group Art Unit | 1626 |
| Examiner Name | Ebenezer Sackey |
| Attorney Docket Number | 21409Y |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. | U.S. Patent Document Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
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| Examiner Signature | Ebenezer Sackey | Date Considered | 5/29/07 |
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*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Approved for use through 7/31/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (07-05), Information Disclosure Statement by Applicant
Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

Substitute for form 1449B/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

Sheet 2 of 2

| COMPLETE IF KNOWN | |
|---|---|
| Application Number | 10/874,992 |
| Filing Date | June 23, 2004 |
| First Named Inventor | Chen, et al |
| Group Art Unit | 1626 |
| Examiner Name | Ebenezer Sackey |
| Attorney Docket Number | 21409Y |

## NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. | Include name of the author, title, date, page(s), volume-issue number(s) and place of publication. |
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| ES | 1 | Edmondson, S.D., Drug Data Report, Vol. 25, No. 3, Pages 245-246 (2003) |
| ES | 2 | Database Prous DDR Online -- Database Accession No: 2003: 3561 |
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| Notice of References Cited | Application/Control No. 10/874,992 | Applicant(s)/Patent Under Reexamination CYPES ET AL. | |
|---|---|---|---|
| | Examiner EBENEZER SACKEY | Art Unit 1624 | Page 1 of 1 |

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| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
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| * | B | US-2007/0021430 | 01-2007 | Chen et al. | 514/249 |
| * | C | US-6,479,692 | 11-2002 | Ekwuribe et al. | 558/413 |
| | D | US- | | | |
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**FOREIGN PATENT DOCUMENTS**

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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UNITED STATES PATENT AND TRADEMARK OFFICE

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Bib Data Sheet

**CONFIRMATION NO. 9276**

| SERIAL NUMBER | FILING OR 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004<br>RULE | 514 | 1626 | 21409Y |

**APPLICANTS**

Stephen Howard Cypes, Santa Clara, CA;
Alex Minhua Chen, Metuchen, NJ;
Russell R. Ferlita, Westfield, NJ;
Karl Hansen, Atlantic Highlands, NJ;
Ivan Lee, Piscataway, NJ;
Vicky K. Vydra, Fair Lawn, NJ;
Robert M. Wenslow JR., East Windsor, NJ;

** CONTINUING DATA **********

This appln claims benefit of 60/482,161 06/24/2003

** FOREIGN APPLICATIONS **********

**IF REQUIRED, FOREIGN FILING LICENSE GRANTED**
** 09/15/2004

| Foreign Priority claimed | STATE OR COUNTRY | SHEETS DRAWING | TOTAL CLAIMS | INDEPENDENT CLAIMS |
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| ☐ yes ☒ no | CA | 5 | 35 | 2 |

35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance

Verified and Acknowledged Examiner's Signature Initials

**ADDRESS**
210

**TITLE**

Phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor

| FILING FEE RECEIVED | |
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☐ All Fees
☐ 1.16 Fees ( Filing )
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☐ 1.18 Fees ( Issue )
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☐ Credit

| Search Notes | Application/Control No. | Applicant(s)/Patent under Reexamination | |
|---|---|---|---|
| | 10/874,992 | CYPES ET AL. | |
| | Examiner | Art Unit | |
| | EBENEZER SACKEY | 1624 | |

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| 514 | 249 | 5/29/2007 | ES |
| 544 | 350 | 5/29/2007 | ES |
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| SEARCH NOTES (INCLUDING SEARCH STRATEGY) | | |
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## Index of Claims

| Application/Control No. | Applicant(s)/Patent under Reexamination |
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| 10/874,992 | CYPES ET AL. |
| **Examiner** | **Art Unit** |
| EBENEZER SACKEY | 1624 |

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PATENT Case No. 21409Y

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Stephen Howard Cypes, et al.

Serial No. 10/874,992

Filed: June 23, 2004

For: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

Art Unit: 1624

Examiner: Ebenezer Sackey

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

Sir:

1. In compliance with 37 C.F.R. 1.97, submitted on the attached form herewith is a list of patents, publications or other information which are requested to be made of record in this application. This Information Disclosure Statement is not an admission that any patent, publication or other information referred to herein is "prior art" for this invention. In accordance with 37 C.F.R. 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. 1.56(b).

2. In accordance with 37 C.F.R. 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made.

3. Applicants respectfully request that the Examiner initial the attached form after reviewing the pertinence of each reference.

4. Pursuant to 37 C.F.R. 1.98 (a)(2)(ii), copies of each cited U.S. patent and each U.S. patent application publication are not enclosed herewith.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

**MERCK & CO., INC.**

By Pamela Spalding Date 6-25-07

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## INFORMATION DISCLOSURE STATEMENT

5. Pursuant to 37 C.F.R. 1.98(d), copies of references listed on the attached form that were submitted to or cited by the Office in a related application upon which the instant application relies for an earlier filing date under 35 U.S.C. 120 are not enclosed. Related application(s) in which references were submitted to or cited by the Office are as follows:

| | RELATED APPLICATION | |
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| U. S. SERIAL NUMBER | FILING DATE | MERCK CASE |
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If this is inconvenient, additional copies will be submitted upon request.

6. In accordance with 37 C.F.R. 1.97, (check one)

☐ the attached information is filed within three months of the filing date of the captioned case.

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Respectfully submitted,

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Date: June 25, 2007

Approved for use through 09/30/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (07-06), Information Disclosure Statement by Applicant
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*



Sheet 1 of 1

| *COMPLETE IF KNOWN* | |
|---|---|
| **Application Number** | 10/874,992 |
| **Filing Date** | June 23, 2004 |
| **First Named Inventor** | Stephen Howard Cypes, et al. |
| Group Art Unit | 1624 |
| Examiner Name | Ebenezer Sackey |
| Attorney Docket Number | 21409Y |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. | U.S. Patent Document Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No. | Foreign Patent Document Office | Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|---|
| | 1 | PCT | WO 2005/072530 A1 | | Merck & Co., Inc. | 08/11/2005 |
| | 2 | PCT | WO 2006/033848 A1 | | Merck & Co., Inc. | 03/30/2006 |
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SEND TO: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450. Computer generated form " IDS Form" (IDS Folder), Merck & Co., Inc., 8/24/2006

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2005 (11.08.2005)

PCT

(10) International Publication Number
WO 2005/072530 A1

(51) International Patent Classification[7]: A01N 43/58, 43/60, A61K 31/495, 31/50, C07D 487/00, 491/00, 495/00, 497/00

(21) International Application Number: PCT/US2005/000951

(22) International Filing Date: 12 January 2005 (12.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/537,073 16 January 2004 (16.01.2004) US

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(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, 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, IS, IT, LT, 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:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*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.*

WO 2005/072530 A1

(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.

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.

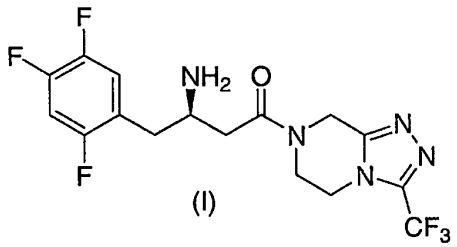
FIG. 13 is a characteristic X-ray diffraction pattern of the crystalline (1*S*)-(+)-10-camphorsulfonic acid salt anhydrate of Compound I of the present invention.

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

crystalline salt in the drug substance can be quantified by the use of physical methods such as X-ray powder diffraction, solid-state fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance spectroscopy, solid-state carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance spectroscopy, solid state Fourier-transform infrared spectroscopy, and Raman spectroscopy. In a class of this embodiment, about 5% to about 100% by weight of the crystalline salt of the present invention is present in the drug substance. In a second class of this embodiment, about 10% to about 100% by weight of the crystalline salt is present in the drug substance. In a third class of this embodiment, about 25% to about 100% by weight of the crystalline salt is present in the drug substance. In a fourth class of this embodiment, about 50% to about 100% by weight of the crystalline salt is present in the drug substance. In a fifth class of this embodiment, about 75% to about 100% by weight of the crystalline salt is present in the drug substance. In a sixth class of this embodiment, substantially all of the salt drug substance is the crystalline salt of the present invention, i.e., the salt drug substance is substantially phase pure crystalline salt.

The crystalline salts of the present invention exhibit pharmaceutic advantages over the free base and the previously disclosed amorphous hydrochloric acid salt (WO 03/004498) in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient. In particular, the enhanced chemical and physical stability of the crystalline salts constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient.

The crystalline salts of the present invention, which exhibit potent DPP-IV inhibitory properties, are particularly useful for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

Another aspect of the present invention provides a method for the prevention or treatment of clinical conditions for which an inhibitor of DPP-IV is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of a crystalline salt of the present invention, or a hydrate thereof. Such clinical conditions include diabetes, in particular Type 2 diabetes, hyperglycemia, insulin resistance, and obesity.

The present invention also provides for the use of a crystalline salt of Compound I of the present invention, or a hydrate thereof, for the prevention or treatment in a mammal of clinical conditions for which an inhibitor of DPP-IV is indicated, in particular Type 2 diabetes, hyperglycemia, insulin resistance, and obesity.

The present invention also provides for the use of a crystalline salt of Compound I of the present invention, or a hydrate thereof, for the manufacture of a medicament for the

prevention or treatment in a mammal of clinical conditions for which an inhibitor of DPP-IV is indicated, in particular Type 2 diabetes, hyperglycemia, insulin resistance, and obesity.

The present invention also provides pharmaceutical compositions comprising a crystalline salt of the present invention, or a hydrate thereof, in association with one or more pharmaceutically acceptable carriers or excipients. In one embodiment the pharmaceutical composition comprises a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises a detectable amount of a crystalline salt of the present invention. In a second embodiment the pharmaceutical composition comprises a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises about 5% to about 100% by weight of a crystalline salt of the present invention. In a class of this second embodiment, the active pharmaceutical ingredient in such compositions comprises about 10% to about 100% by weight of the crystalline salt. In a second class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 25% to about 100% by weight of the crystalline salt. In a third class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 50% to about 100% by weight of the crystalline salt. In a fourth class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 75% to about 100% by weight of the crystalline salt. In a fifth class of this embodiment, substantially all of the active pharmaceutical ingredient is the crystalline salt of the present invention, i.e., the active pharmaceutical ingredient is substantially phase pure crystalline salt.

The compositions in accordance with the invention are suitably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories. The compositions are intended for oral, parenteral, intranasal, sublingual, or rectal administration, or for administration by inhalation or insufflation. Formulation of the compositions according to the invention can conveniently be effected by methods known from the art, for example, as described in Remington's Pharmaceutical Sciences, 17th ed., 1995.

The dosage regimen is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. An ordinarily skilled physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100

mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 200 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the crystalline salts of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the crystalline salts of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the crystalline salts and their hydrates herein described in detail can form the active pharmaceutical ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug component can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The crystalline salts of Compound I of the present invention have been found to possess a high solubility in water, rendering them especially amenable to the preparation of

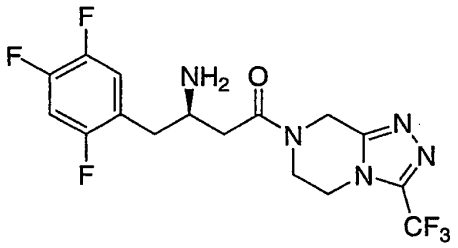
formulations, in particular intranasal and intravenous formulations, which require relatively concentrated aqueous solutions of active pharmaceutical ingredient.

In a still further aspect, the present invention provides a method for the treatment and/or prevention of clinical conditions for which a DPP-IV inhibitor is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of a crystalline salt of Compound I as defined above or a hydrate thereof in combination with another agent useful for the treatment of Type 2 diabetes, obesity, and high blood pressure.

Compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I.

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity."

According to a further aspect, the present invention provides a process for the preparation of the crystalline salts of Compound I of the present invention, which process comprises treating a solution of free base (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):

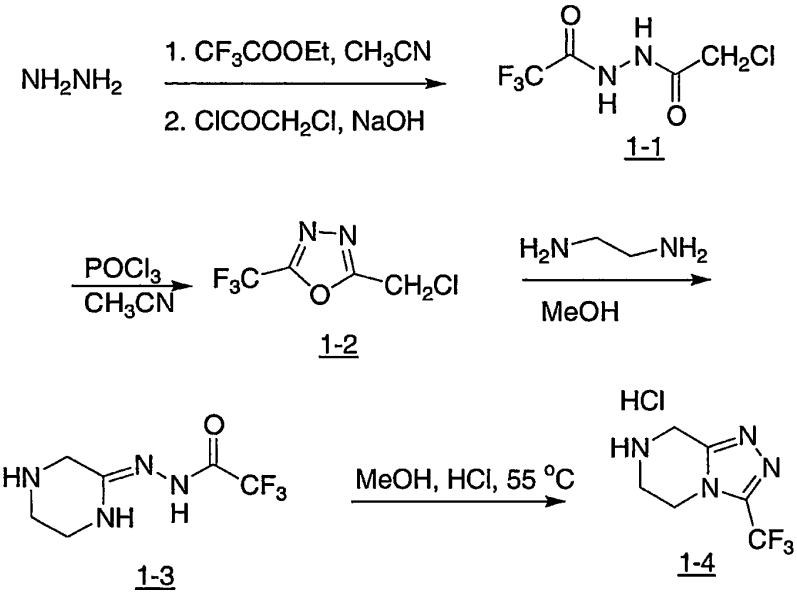



in a suitable organic solvent with a solution of the appropriate acid in a suitable organic solvent or water or mixture thereof. The process is carried out generally at about 0°C to about 100°C, and preferably at about 20°C to about 60°C. Generally, the organic solvent is a linear or branched $C_{1-4}$ alkanol, such as methanol, ethanol, or isopropanol (IPA), a linear or branched $C_{1-4}$ alkyl acetate, such as ethyl acetate or isopropyl acetate, diethyl ether, tetrahydrofuran, toluene, acetone, or acetonitrile. A mixture of water and the organic solvent may also be employed. Crystallization is then effected by cooling the mixture and optional seeding with crystals of the authentic acid salt, but the latter is not essential. The acid salts are then isolated by filtration and drying.

Compound I can be prepared by the procedures detailed in Schemes 1 and 2 below.

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloric acid (1-4)

Scheme 1




Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

$^1$H-NMR (400 MHz, DMSO-d6): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.

$^{13}$C-NMR (100 MHz, DMSO-d6): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole (1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

$^{1}$H-NMR (400 MHz, CDCl3): δ 4.8 (s, 2H) ppm.

$^{13}$C-NMR (100 MHz, CDCl3): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC).

$^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm.

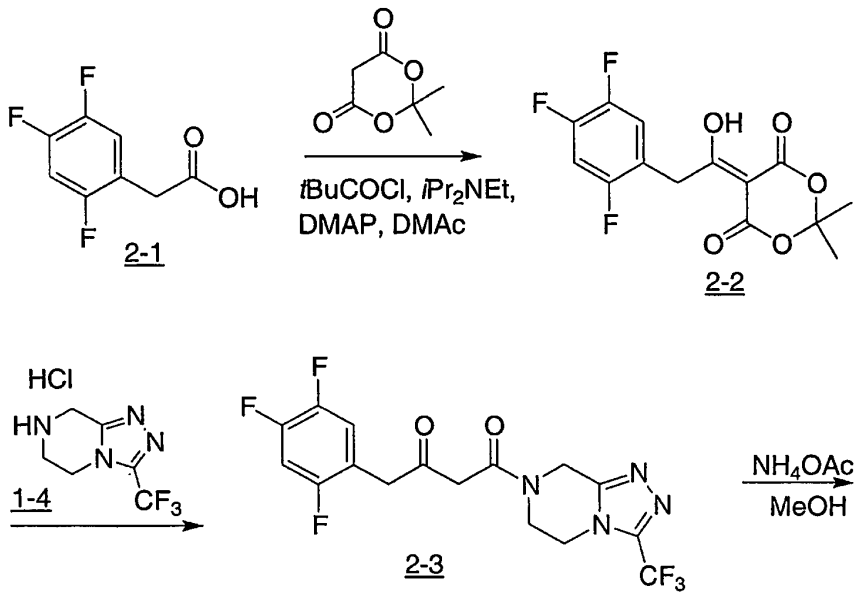
$^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) ppm.

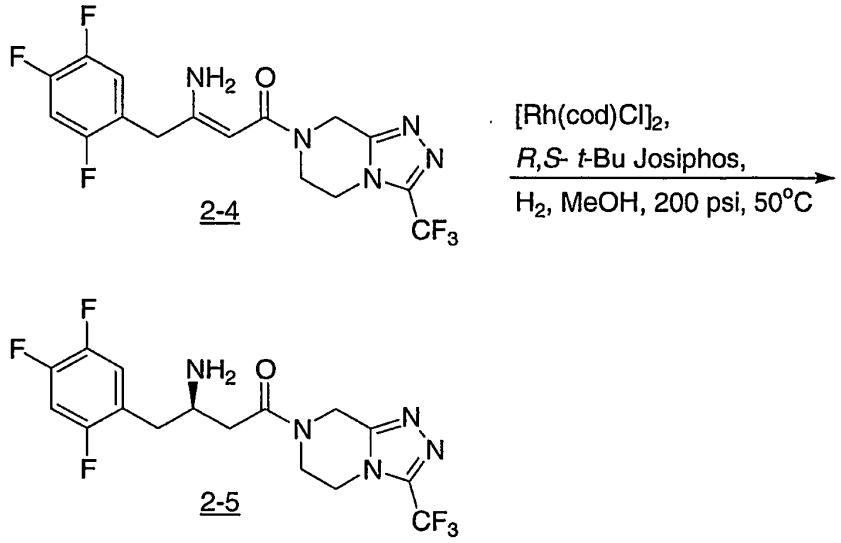
Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloric acid (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

Scheme 2






2-4




2-5

Step A: Preparation 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-one (2-3)

2,4,5-Trifluorophenylacetic acid (2-1) (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino)pyridine (DMAP) (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. *N,N*-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to dissolve the solids. *N,N*-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5 °C. The reaction mixture was aged at 5 °C for 1 h. Triazole hydrochloric acid 1-4 (180 g, 0.789 mol) was added in one portion at 40-50 °C. The reaction solution was aged at 70 °C for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20 – 45 °C. The batch was seeded and aged at 20 – 30 °C for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0 – 5 °C and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product 2-3 was 89%.

Step B: Preparation of (2*Z*)-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)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30 °C during the addition. Additional methanol (100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5 °C in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid (180 g); m.p. 271.2 °C.

Step C: Preparation 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 (2-5)

Into a 500 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]$_2$}(292 mg, 1.18 mmol) and (*R*,*S*) *t*-butyl Josiphos (708 mg, 1.3 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (200 mL) and the mixture was stirred at room temperature for 1 h. Into a 4 L hydrogenator was charged the enamine amide 2-4 (118 g, 0.29 mol) along with MeOH (1 L). The slurry was degassed. The catalyst solution was then transferred to the hydrogenator under nitrogen. After degassing three times, the enamine amide was hydrogenated under 200 psi hydrogen gas at 50 °C for 13 h. Assay yield was determined by HPLC to be 93% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl *t*-butyl ether (MTBE) (45 mL). Into this solution was added aqueous $H_3PO_4$ solution (0.5 M, 95 mL). After separation of the layers, 3*N* NaOH (35 mL) was added to the water layer, which was then extracted with MTBE (180 mL + 100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75 °C). The hot toluene solution was then allowed to cool to 0 °C slowly (5 – 10 h). The crystals were isolated by filtration (13 g, yield 72%, 98 – 99% ee); m.p. 114.1 – 115.7 °C.

$^1$H NMR (300 MHz, $CD_3CN$): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:

$^{13}C$ NMR ($CD_3CN$): δ 171.8, 157.4 (ddd , $J_{CF}$ = 242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; $J_{CF}$ = 246.7, 14.2, 12.9 Hz), 147.4 (ddd, $J_{CF}$ = 241.2, 12.3, 3.7 Hz), 144.2 (q, $J_{CF}$ = 38.8 Hz), 124.6 (ddd , $J_{CF}$ = 18.5, 5.9, 4.0 Hz), 120.4 (dd , $J_{CF}$ = 19.1, 6.2 Hz), 119.8 (q, $J_{CF}$ = 268.9 Hz), 106.2 (dd , $J_{CF}$ = 29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

The crystalline free base can also be isolated as follows:

(a) The reaction mixture upon completion of the hydrogenation step is charged with 25 wt% of Ecosorb C-941. The mixture is stirred under nitrogen for one h and then filtered. The cake is washed with 2L/kg of methanol. Recovery of free base is about 95% and optical purity about 95% ee.

(b) The freebase solution in methanol is concentrated to 3.5-4.0 L/kg volume (based on free base charge) and then solvent-switched into isopropanol (IPA) to final volume of 3.0 L/kg IPA.

(c) The slurry is heated to 40 °C and aged 1 h at 40°C and then cooled to 25 °C over 2 h.

(d) Heptane (7L/kg) is charged over 7 h and the slurry stirred for 12 h at 22-25°C. The supernatant concentration before filtering is 10-12 mg/g.

(e) The slurry is filtered and the solid washed with 30% IPA/heptane (2L/kg).

(f) The solid is dried in a vacuum oven at 40 °C.

(g) The optical purity of the free base is about 99% ee.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

Column: Waters Symmetry C18, 250 mm x 4.6 mm
Eluent: Solvent A: 0.1 vol% $HClO_4/H_2O$
Solvent B: acetonitrile
Gradient: 0 min 75% A : 25% B
10 min 25% A : 75% B
12.5 min 25% A : 75% B
15 min 75% A : 25% B
Flow rate: 1 mL/min
Injection Vol.: 10 µL
UV detection: 210 nm
Column temp.: 40 °C
Retention times: compound 2-4: 9.1 min
compound 2-5: 5.4 min
*t*Bu Josiphos: 8.7 min

The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:

Column: Chirapak, AD-H, 250 mm x 4.6 mm
Eluent: Solvent A: 0.2 vol.% diethylamine in heptane
Solvent B: 0.1 vol% diethylamine in ethanol
Isochratic Run Time: 18 min
Flow rate: 0.7 mL/min
Injection Vol.: 7 μL
UV detection: 268 nm
Column temp.: 35 °C
Retention times: (*R*)-amine 2-5: 13.8 min
(*S*)-amine 2-5: 11.2 min

The following non-limiting Examples are intended to illustrate the present invention and should not be construed as being limitations on the scope or spirit of the instant invention.

EXAMPLE 1

(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 hydrochloric acid salt monohydrate

Compound I freebase (20 mg) was dissolved in 0.25 ml of 90% isopropanol/methanol (v/v). A solution of HCl in diethyl ether (0.025 ml, 2 M solution) was added. A thick slurry of crystals formed. The mixture was heated to 55°C and then slowly cooled to room temperature. The solid was filtered and washed with IPA. The crystal form of the solids was shown to be a monohydrate by the physical methods below.

EXAMPLE 2

(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 L-tartaric acid salt hemihydrate

Compound I free base (1.80 g) was dissolved in 90 mL of IPA and heated to 50°C. A solution of L-tartaric acid in water (0.675 g in 9 mL water) was added. A thick slurry formed which was heated to 60°C and aged overnight (about 18 h). The solution was filtered and washed with IPA and then dried in a vacuum oven at 40°C with a nitrogen sweep. The crystal form of the solids was shown to be a hemihydrate by the physical methods below.

EXAMPLE 3

(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 benzenesulfonic acid salt anhydrate

Compound I free base (10.40 g) was dissolved in 520 mL of isopropyl acetate (IPAc). The solution was heated to 50°C and a solution of benzenesulfonic acid (4.10 g) in 50 mL IPAc was added to the solution over one h. After 20% of the addition, the solution was seeded with 0.1% benzenesulfonic acid salt and the addition was resumed. Upon complete addition, the slurry was cooled to room temperature and then filtered and washed with 25 mL of IPA and 50 mL of hexanes. The solids were dried on the filter frit with a nitrogen sweep. The crystal form of the solids was shown to be an anhydrate by the physical methods below.

EXAMPLE 4

(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 *p*-toluenesulfonic acid salt anhydrate

1.15 g of *p*-Toluenesulfonic acid in methanol (5 mL) was added to 5.25 g of a 47 wt% solution of Compound I free base in methanol. A slurry formed and the mixture was charged with 15 mL methyl-*tert*-butyl ether (MTBE). The slurry was filtered and then washed with 5 mL of MTBE. The solids were dried on the frit. The crystal form of the solids was shown to be an anhydrate by the physical methods below.

EXAMPLE 5

(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 (1*S*)-(+)-camphorsulfonic acid salt anhydrate

A solution of Compound I free base in 3L/kg of methanol was charged with 1.0 equivalent of (1*S*)-(+)-camphorsulfonic acid. The solution was aged and a slurry developed. 7L/kg of MTBE was added to the slurry and the mixture was aged at room temperature. The slurry was filtered and then washed with MTBE. The solids were dried at 40°C in a vacuum oven under a nitrogen gas sweep. The crystal form of the solids was shown to be an anhydrate by the physical methods below.

X-ray powder diffraction studies are widely used to characterize crystalline structures, crystallinity, and polymorphism. The X-ray powder diffraction patterns of the various crystalline salts of the present invention were generated on a Philips Analytical X'Pert PRO X-

ray Diffraction System with PW3040/60 console. A PW3373/00 ceramic Cu LEF X-ray tube K-Alpha radiation was used as the source.

FIG. 1 shows the X-ray diffraction pattern for the crystalline hydrochloric acid salt monohydrate of Compound I of the present invention. The hydrochloric acid salt exhibited characteristic diffraction peaks corresponding to d-spacings of 3.0, 3.3, 3.5, 6.5, and 11.0 angstroms.

FIG. 4 shows the X-ray diffraction pattern for the crystalline L-tartaric acid salt hemihydrate of Compound I of the present invention. The L-tartaric acid salt exhibited characteristic diffraction peaks corresponding to d-spacings of 3.2, 3.4, 3.8, 4.1, 4.3, 4.9, and 5.8 angstroms.

FIG. 7 shows the X-ray diffraction pattern for the crystalline benzenesulfonic acid salt anhydrate of Compound I of the present invention. The benzenesulfonic acid salt exhibited characteristic diffraction peaks corresponding to d-spacings of 3.4, 3.7, 4.0, 4.6, 4.8, 5.2, and 12.7 angstroms.

FIG. 10 shows the X-ray diffraction pattern for the crystalline *p*-toluenesulfonic acid salt anhydrate of Compound I of the present invention. The *p*-toluenesulfonic acid salt exhibited characteristic diffraction peaks corresponding to d-spacings of 3.9, 4.3, 4.5, 5.1, 5.7, 5.9, 7.6, and 15.0 angstroms.

FIG. 13 shows the X-ray diffraction pattern for the crystalline (1*S*)-(+)-10-camphorsulfonic acid salt anhydrate of Compound I of the present invention. The 10-camphorsulfonic acid salt exhibited characteristic diffraction peaks corresponding to d-spacings of 3.4, 3.5, 4.0, 5.1, 5.3, 6.3, and 13.5 angstroms.

In addition to the X-ray powder diffraction patterns described above, the crystalline salts of Compound I of the present invention were further characterized by means of their differential scanning calorimetry (DSC) curves and their thermogravimetric analysis (TGA) curves.

A TA Instruments DSC 2910 or equivalent instrumentation was used to obtain the DSC curves. Between 2 and 6 mg sample was weighed into an open pan. This pan was then crimped and placed at the sample position in the calorimeter cell. An empty pan was placed at the reference position. The calorimeter cell was closed and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of 10 °C/min to a temperature of approximately 250 °C. The heating program was started. When the run was completed, the data were analyzed using the DSC analysis program contained in the system software. The melting endotherm was integrated between baseline temperature points that are

above and below the temperature range over which the endotherm was observed. The data reported are the onset temperature, peak temperature, and enthalpy.

FIG. 3 shows a characteristic DSC curve for the crystalline hydrochloric acid salt monohydrate of Compound I. The hydrochloric acid salt exhibited a broad endotherm at about 74 °C, attributed to evolution of water, with an onset temperature of about 60 °C and an enthalpy of about 54 J/g and a melting endotherm with an onset temperature of about 165 °C, a peak temperature of about 170 °C, and an enthalpy of about 41 J/g.

FIG. 6 shows a characteristic DSC curve for the crystalline L-tartaric acid salt hemihydrate of Compound I. The L-tartaric acid salt exhibited a broad endotherm at about 54 °C, attributed to evolution of water, with an onset temperature of about 34 °C and an enthalpy of about 11 J/g and a melting and decomposition endotherm with a peak temperature of about 204 °C.

FIG. 9 shows a characteristic DSC curve for the crystalline benzenesulfonic acid salt anhydrate of Compound I. The benzenesulfonic acid salt exhibited a sharp melting endotherm with an onset temperature of about 176 °C, a peak temperature of about 179 °C, and an enthalpy of about 55 J/g.

FIG. 12 shows a characteristic DSC curve for the crystalline *p*-toluenesulfonic acid salt anhydrate of Compound I. The *p*-toluenesulfonic acid salt exhibited a sharp melting endotherm with an onset temperature of about 219 °C, a peak temperature of about 222 °C, and an enthalpy of about 74 J/g.

FIG. 15 shows a characteristic DSC curve for the crystalline (1*S*)-(+)-10-camphorsulfonic acid salt anhydrate of Compound I. The camphorsulfonic acid salt anhydrate exhibited a sharp melting endotherm with an onset temperature of about 186 °C, a peak temperature of about 190 °C, and an enthalpy of about 93 J/g.

A Perkin Elmer model TGA 7 or equivalent instrument was used to obtain the TGA curves. Experiments were performed under a flow of nitrogen and using a heating rate of 10 °C/min to a maximum temperature of approximately 250 °C. After automatically taring the balance, 5 to 20 mg of sample was added to the platinum pan, the furnace was raised, and the heating program started. Weight/temperature data were collected automatically by the instrument. Analysis of the results was carried out by selecting the Delta Y function within the instrument software and choosing the temperatures between which the weight loss was to be calculated. Weight losses are reported up to the onset of decomposition/evaporation.

FIG. 2 shows a characteristic thermogravimetric analysis (TGA) curve for the crystalline hydrochloric acid salt monohydrate of Compound I. TGA indicated a weight loss of about 3.1% from ambient temperature to about 83 °C.

FIG. 5 shows a characteristic thermogravimetric analysis (TGA) curve for the crystalline L-tartaric acid salt hemihydrate of Compound I. TGA indicated a weight loss of about 1.4% from ambient temperature to about 198 °C.

FIG. 8 shows a characteristic thermogravimetric analysis (TGA) curve for the crystalline benzenesulfonic acid salt anhydrate of Compound I. TGA indicated a weight loss of about 0.1% from about 63 °C to about 203 °C.

FIG. 11 shows a characteristic thermogravimetric analysis (TGA) curve for the crystalline *p*-toluenesulfonic acid salt anhydrate of Compound I. TGA indicated a weight loss of about 0.1% from ambient temperature to about 225 °C.

FIG. 14 shows a characteristic thermogravimetric analysis (TGA) curve for the crystalline (1*S*)-(+)-10-camphorsulfonic acid salt anhydrate of Compound I. TGA indicated a weight loss of about 0.0% from ambient temperature to about 190 °C.

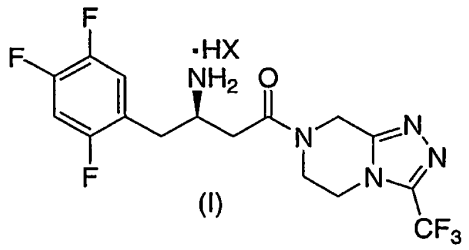
The crystalline salts of the present invention have a phase purity of at least about 5% of the form with the above X-ray powder diffraction and DSC physical characteristics. In one embodiment the phase purity is at least about 10% of the form with the above solid-state physical characteristics. In a second embodiment the phase purity is at least about 25% of the form with the above solid-state physical characteristics. In a third embodiment the phase purity is at least about 50% of the form with the above solid-state physical characteristics. In a fourth embodiment the phase purity is at least about 75% of the form with the above solid-state physical characteristics. In a fifth embodiment the phase purity is at least about 90% of the form with the above solid-state physical characteristics. In a sixth embodiment the crystalline salts of the present invention are the substantially phase pure forms with the above solid-state physical characteristics. By the term "phase purity" is meant the solid state purity of the particular salt with regard to a particular crystalline form of the salt as determined by the solid-state physical methods described in the present application.

EXAMPLES OF PHARMACEUTICAL COMPOSITIONS:

The crystalline salts of the present invention can be formulated into a tablet by a direct compression process. A 100 mg potency tablet is composed of 100 mg of the active ingredient, 276 mg mannitol, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active ingredient, microcrystalline cellulose, and croscarmellose are first blended, and the mixture is then lubricated with magnesium stearate and pressed into tablets.

WHAT IS CLAIMED IS:

1. A crystalline 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:




(I)

or a hydrate thereof;
wherein HX is an acid selected from the group consisting of hydrochloric acid, tartaric acid, benzenesulfonic acid, *p*-toluenesulfonic acid, and 10-camphorsulfonic acid.

2. The crystalline salt of Claim 1 wherein said acid is hydrochloric acid.

3. The crystalline salt of Claim 1 wherein said acid is benzenesulfonic acid.

4. The crystalline salt of Claim 1 wherein said acid is *p*-toluenesulfonic acid.

5. The crystalline salt of Claim 1 wherein said acid is tartaric acid.

6. The crystalline salt of Claim 1 wherein said acid is 10-camphorsulfonic acid.

7. The crystalline salt of Claim 5 wherein said tartaric acid is L-tartaric acid.

8. The crystalline salt of Claim 5 wherein said tartaric acid is D-tartaric acid.

9. The crystalline salt of Claim 6 wherein said 10-camphorsulfonic acid is (1*S*)-(+)-10-camphorsulfonic acid.

10. The crystalline salt of Claim 6 wherein said 10-camphorsulfonic acid is (1*R*)-(-)-10-camphorsulfonic acid.

11. The crystalline hydrochloric acid salt of Claim 2 characterized as being a monohydrate.

12. The crystalline hydrochloric acid salt of Claim 11 characterized by characteristic reflections obtained from the X-ray powder diffraction pattern at spectral d-spacings of 3.0, 3.3, 3.5, 6.5, and 11.0 angstroms.

13. The crystalline hydrochloric acid salt of Claim 12 further characterized by the X-ray powder diffraction pattern of FIG. 1.

14. The crystalline hydrochloric acid salt of Claim 11 further characterized by the differential scanning calorimetric (DSC) curve of FIG. 3.

15. The crystalline hydrochloric acid salt of Claim 11 further characterized by the thermogravimetric analysis (TGA) curve of FIG. 2.

16. The crystalline L-tartaric acid salt of Claim 7 characterized as being a hemihydrate.

17. The crystalline L-tartaric acid salt of Claim 16 characterized by characteristic reflections obtained from the X-ray powder diffraction pattern at spectral d-spacings of 3.2, 3.4, 3.8, 4.1, 4.3, 4.9, and 5.8 angstroms.

18. The crystalline L-tartaric acid salt of Claim 17 further characterized by the X-ray powder diffraction pattern of FIG. 4.

19. The crystalline L-tartaric acid salt of Claim 16 further characterized by the differential scanning calorimetric (DSC) curve of FIG. 6.

20. The crystalline L-tartaric acid salt of Claim 16 further characterized by the thermogravimetric analysis (TGA) curve of FIG. 5.

21. The crystalline benzenesulfonic acid of Claim 3 characterized as being an anhydrate.

22. The crystalline benzenesulfonic acid salt of Claim 21 characterized by characteristic reflections obtained from the X-ray powder diffraction pattern at spectral d-spacings of 3.4, 3.7, 4.0, 4.6, 4.8, 5.2, and 12.7 angstroms.

23. The crystalline benzenesulfonic acid salt of Claim 22 further characterized by the X-ray powder diffraction pattern of FIG. 7.

24. The crystalline benzenesulfonic acid salt of Claim 21 further characterized by the differential scanning calorimetric (DSC) curve of FIG. 9.

25. The crystalline benzenesulfonic acid salt of Claim 21 further characterized by the thermogravimetric analysis (TGA) curve of FIG. 8.

26. The crystalline *p*-toluenesulfonic salt of Claim 4 characterized as being an anhydrate.

27. The crystalline *p*-toluenesulfonic acid salt of Claim 26 characterized by characteristic reflections obtained from the X-ray powder diffraction pattern at spectral d-spacings of 3.9, 4.3, 4.5, 5.1, 5.7, 5.9, 7.6, and 15.0 angstroms.

28. The crystalline *p*-toluenesulfonic acid salt of Claim 27 further characterized by the X-ray powder diffraction pattern of FIG. 10.

29. The crystalline *p*-toluenesulfonic acid salt of Claim 26 further characterized by the differential scanning calorimetric (DSC) curve of FIG. 12.

30. The crystalline *p*-toluenesulfonic acid salt of Claim 26 further characterized by the thermogravimetric analysis (TGA) curve of FIG. 11.

31. The crystalline (1*S*)-(+)-10-camphorsulfonic acid salt of Claim 9 characterized in being an anhydrate.

32. The crystalline (1*S*)-(+)-10-camphorsulfonic acid salt of Claim 31 characterized by characteristic reflections obtained from the X-ray powder diffraction pattern at spectral d-spacings of 3.4, 3.5, 4.0, 5.1, 5.3, 6.3, and 13.5 angstroms.

33. The crystalline (1*S*)-(+)-10-camphorsulfonic acid salt of Claim 32 further characterized by the X-ray powder diffraction pattern of FIG. 13.

34. The crystalline (1*S*)-(+)-10-camphorsulfonic acid salt of Claim 31 further characterized by the differential scanning calorimetric (DSC) curve of FIG. 15.

35. The crystalline (1*S*)-(+)-10-camphorsulfonic acid salt of Claim 31 further characterized by the thermogravimetric analysis (TGA) curve of FIG. 14.

36. A pharmaceutical composition comprising a therapeutically effective amount of a salt according to Claim 1 in association with one or more pharmaceutically acceptable carriers or excipients.

37. A method of treating Type 2 diabetes comprising administering to a mammal in need of such treatment a therapeutically effective amount of a salt according to Claim 1.

38. Use a salt according to Claim 1 as active ingredient in the manufacture of a medicament for use in the treatment of Type 2 diabetes in a mammal.

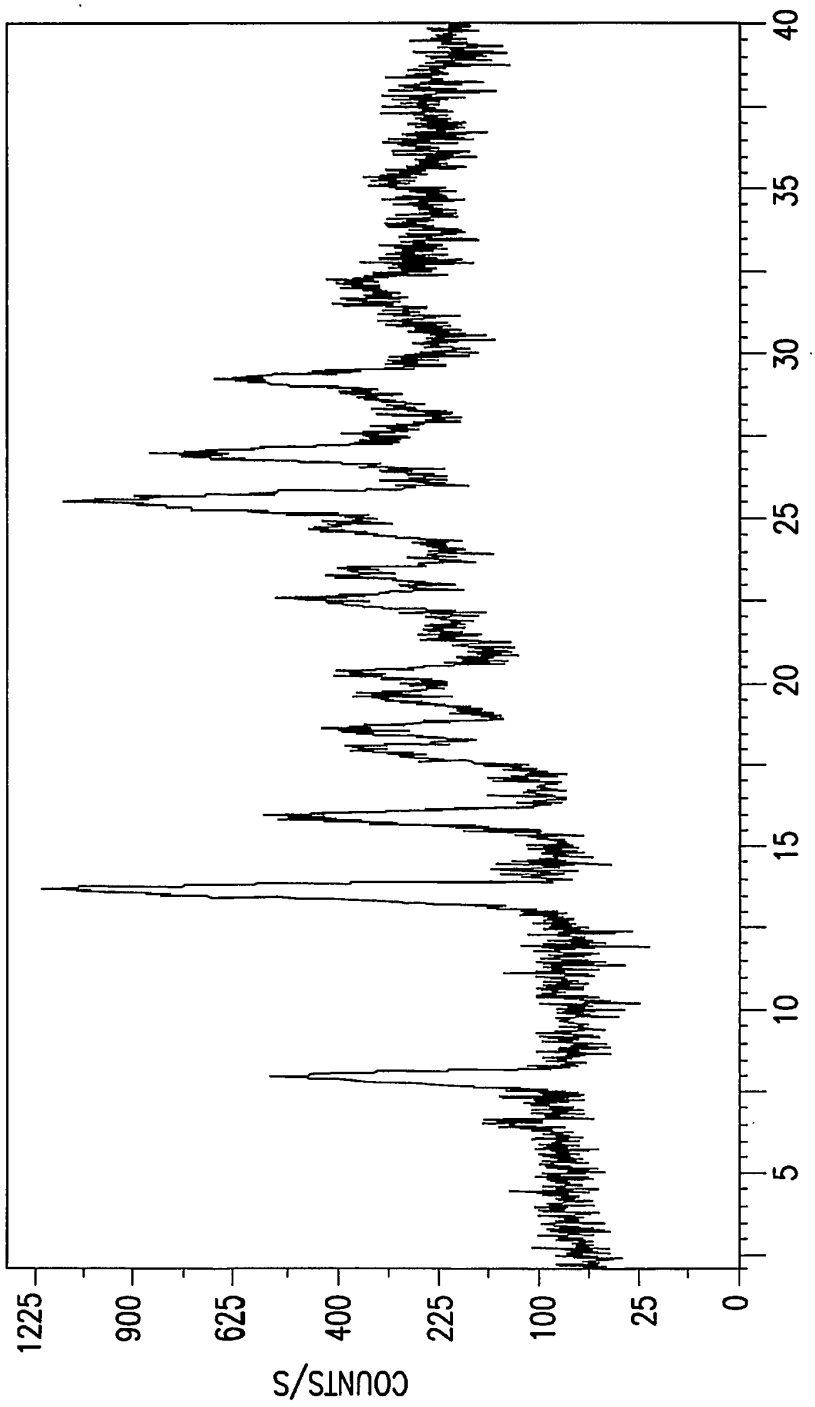

COUNTS/S
1225
900
625
400
225
100
25
0
5
10
15
20
25
30
35
40
°2 THETA

FIG. 1

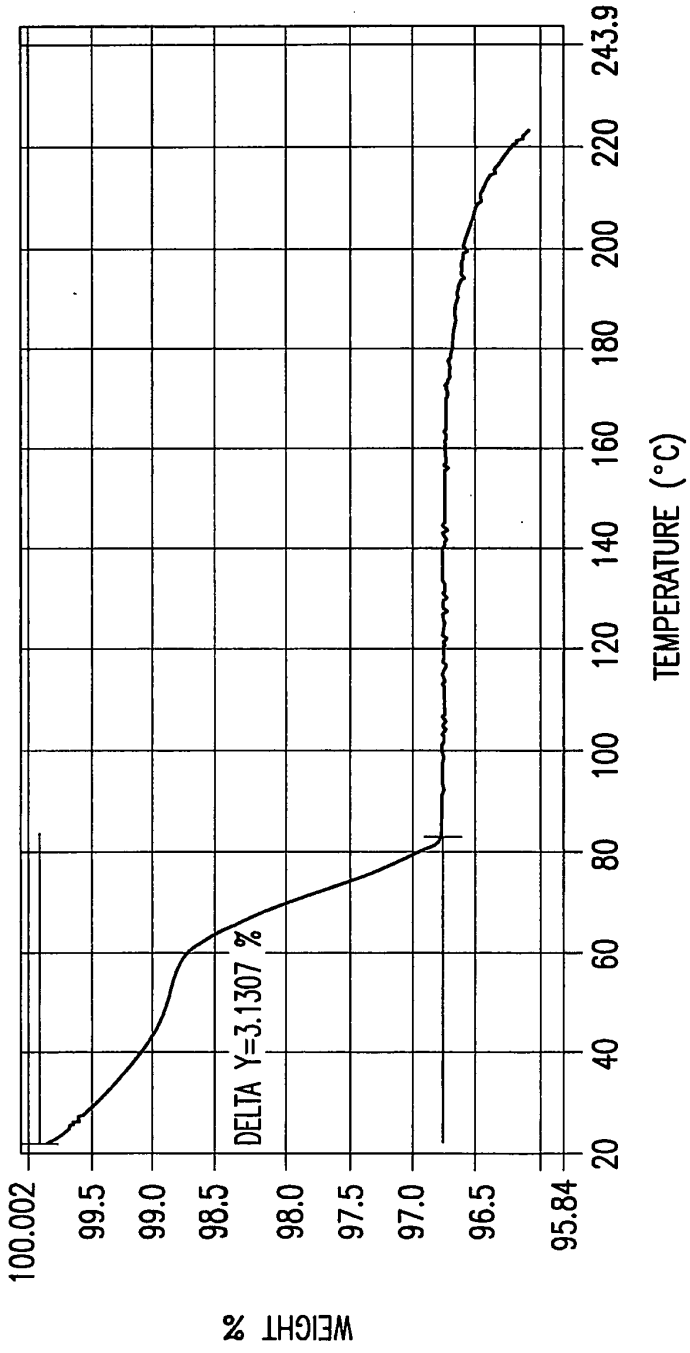

100.002
99.5
99.0
98.5
98.0
97.5
97.0
96.5
95.84
WEIGHT %
DELTA Y=3.1307 %
20
40
60
80
100
120
140
160
180
200
220
243.9
TEMPERATURE (°C)

FIG.2

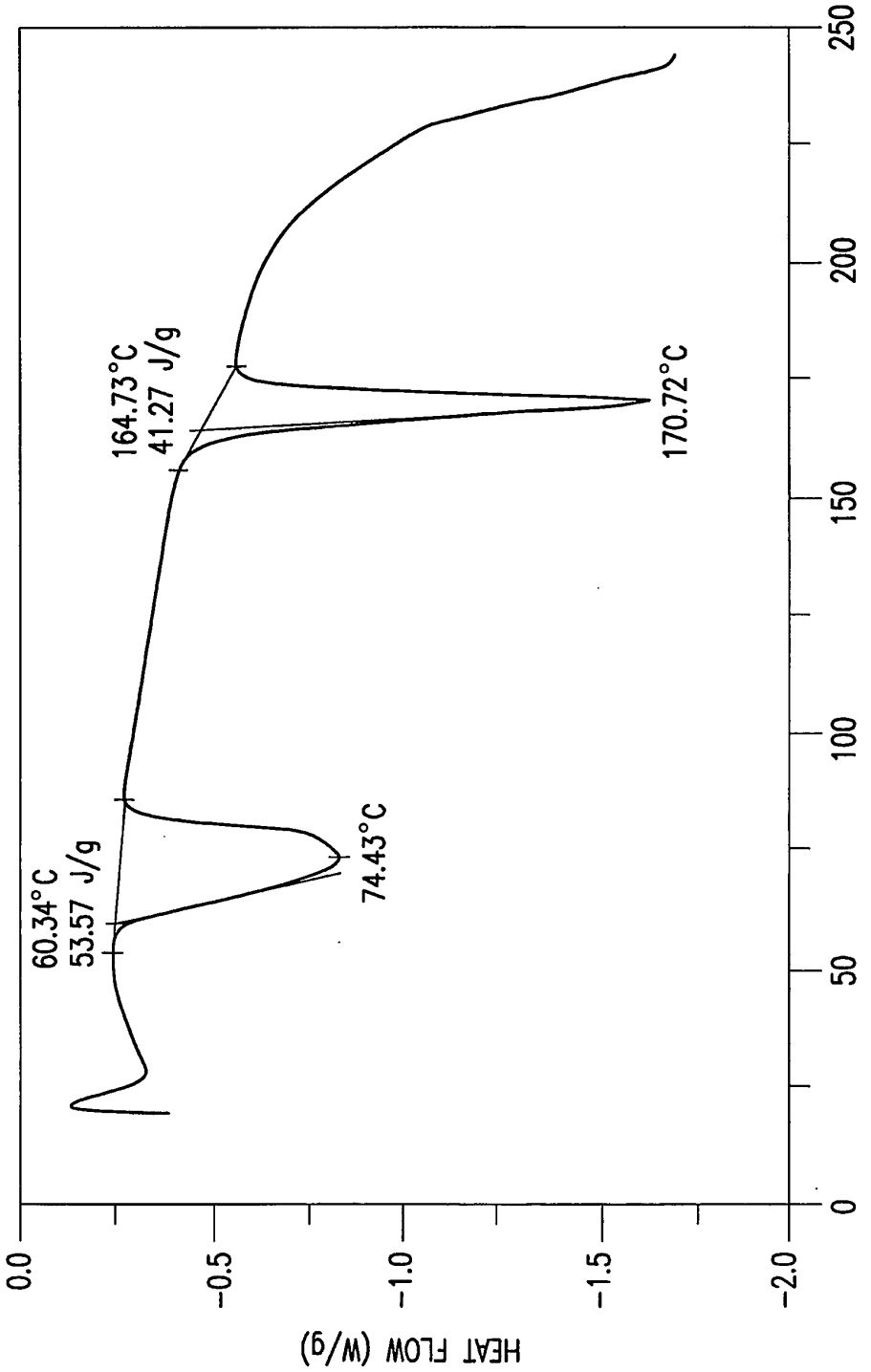

HEAT FLOW (W/g)
0.0
-0.5
-1.0
-1.5
-2.0
TEMPERATURE (°C)
0
50
100
150
200
250
60.34°C
53.57 J/g
74.43°C
164.73°C
41.27 J/g
170.72°C

FIG.3

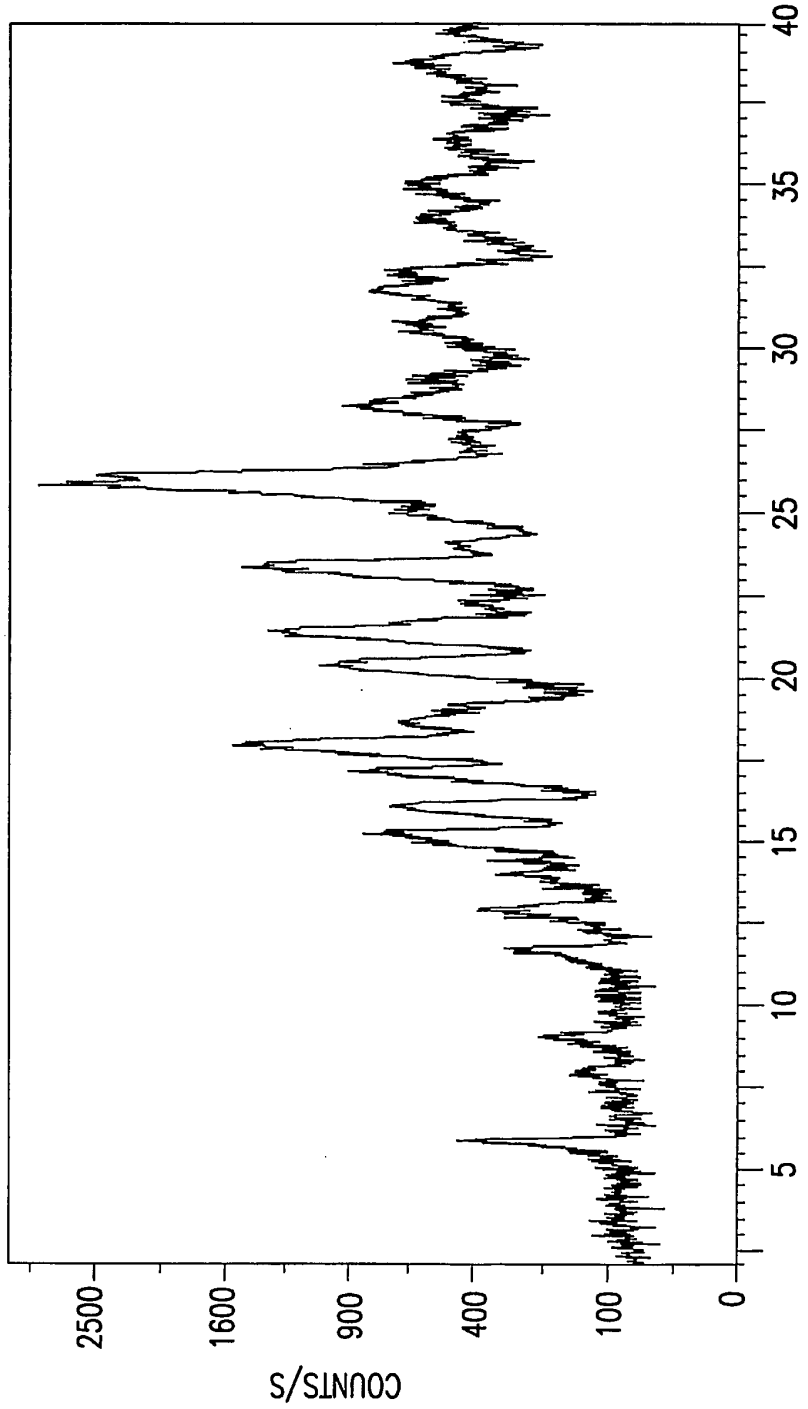



FIG.4

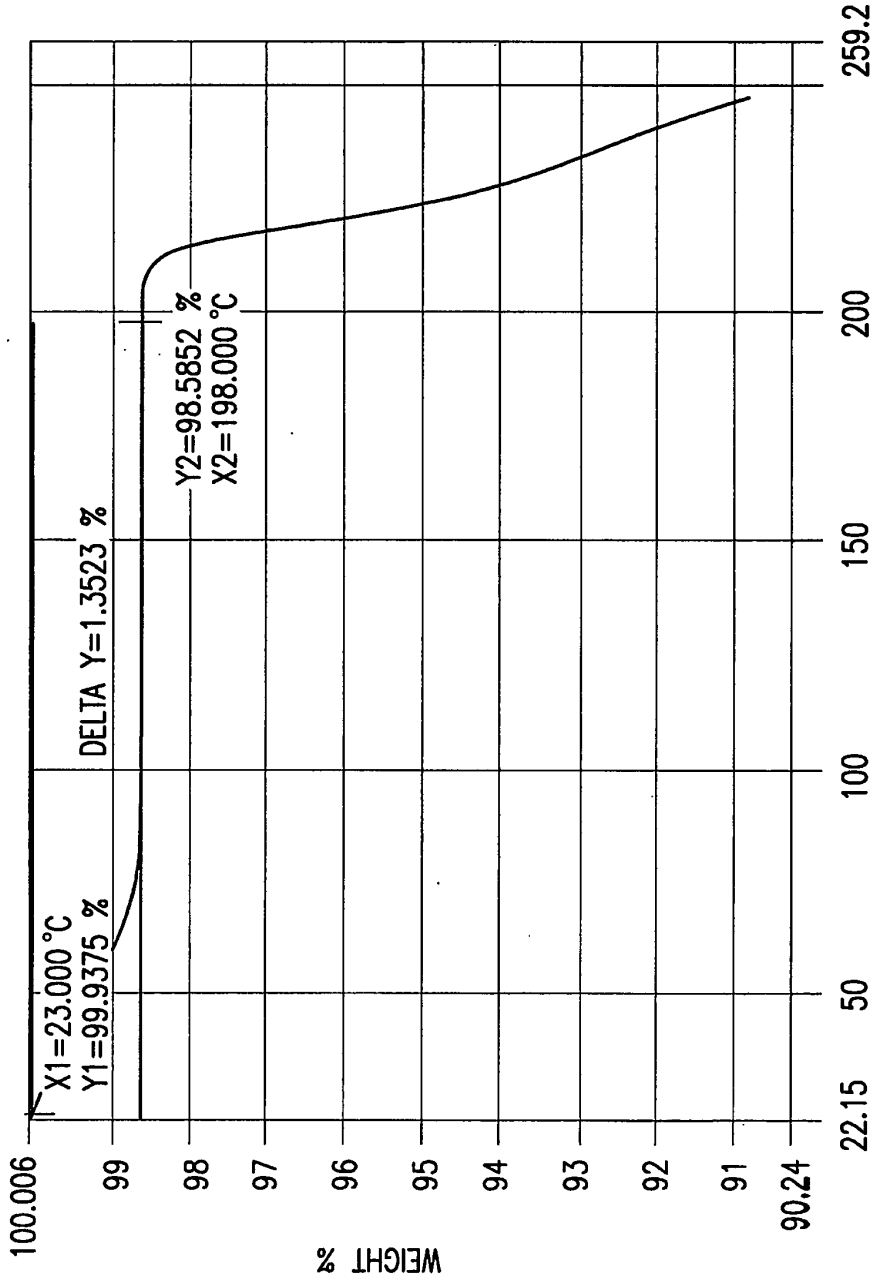

100.006
99
98
97
96
95
94
93
92
91
90.24
WEIGHT %
22.15
50
100
150
200
259.2
TEMPERATURE (°C)
X1=23.000 °C
Y1=99.9375 %
DELTA Y=1.3523 %
Y2=98.5852 %
X2=198.000 °C

FIG.5

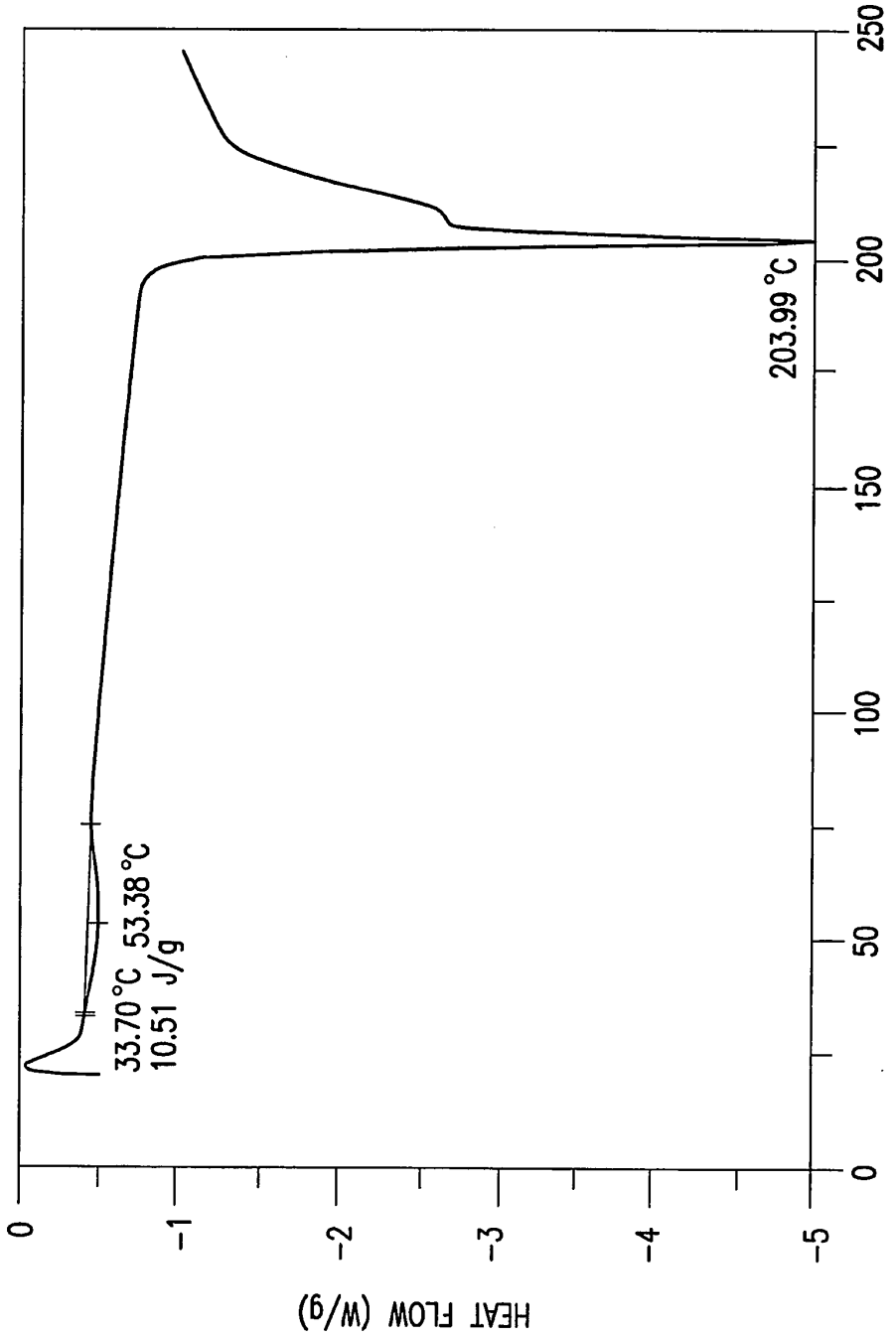

HEAT FLOW (W/g)
0
-1
-2
-3
-4
-5
TEMPERATURE (°C)
0
50
100
150
200
250
203.99 °C
33.70 °C 53.38 °C
10.51 J/g

FIG.6

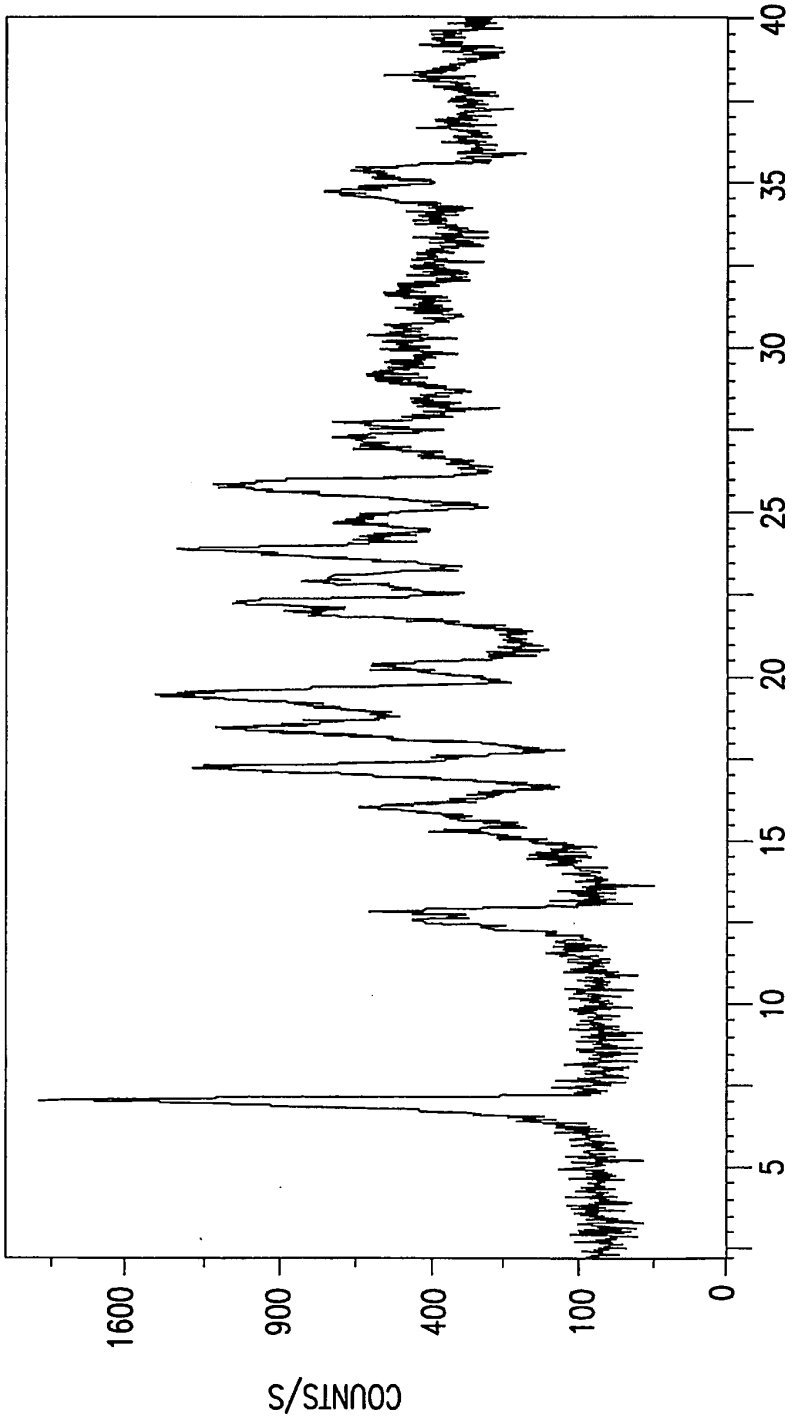



FIG. 7

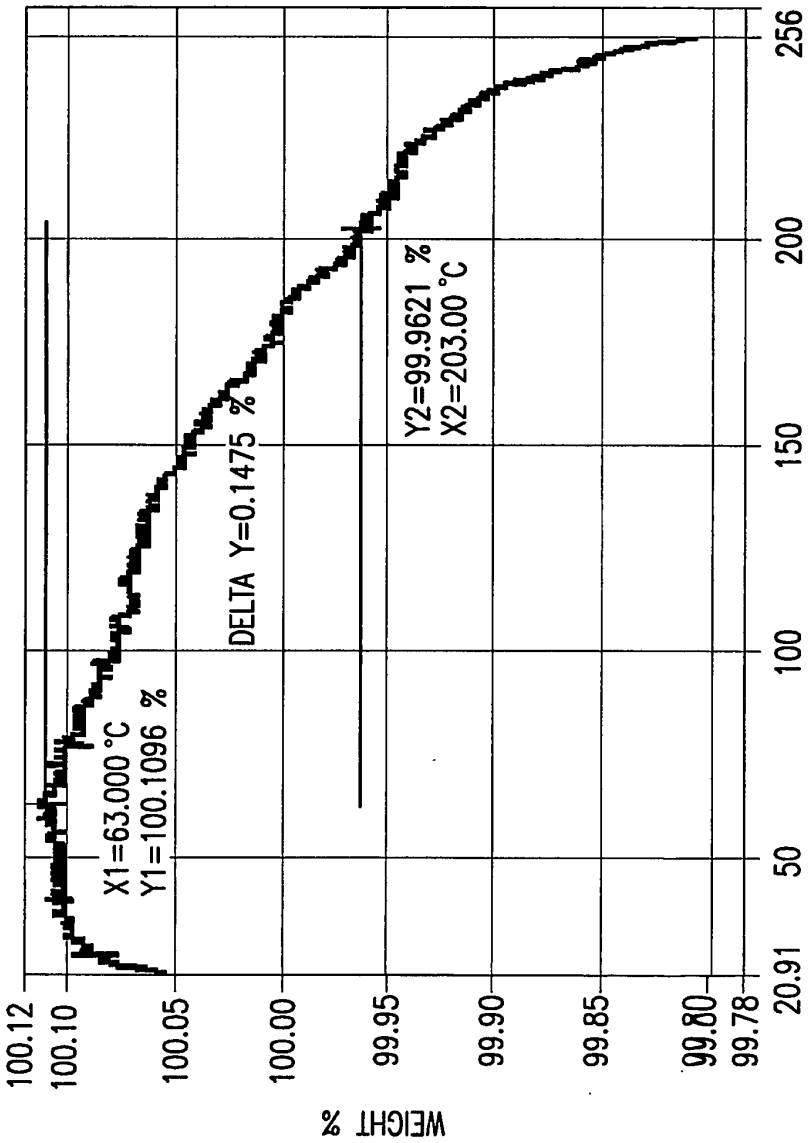

WEIGHT %
100.12
100.10
100.05
100.00
99.95
99.90
99.85
99.80
99.78
X1=63.000 °C
Y1=100.1096 %
DELTA Y=0.1475 %
Y2=99.9621 %
X2=203.00 °C
20.91
50
100
150
200
256
TEMPERATURE (°C)

FIG.8

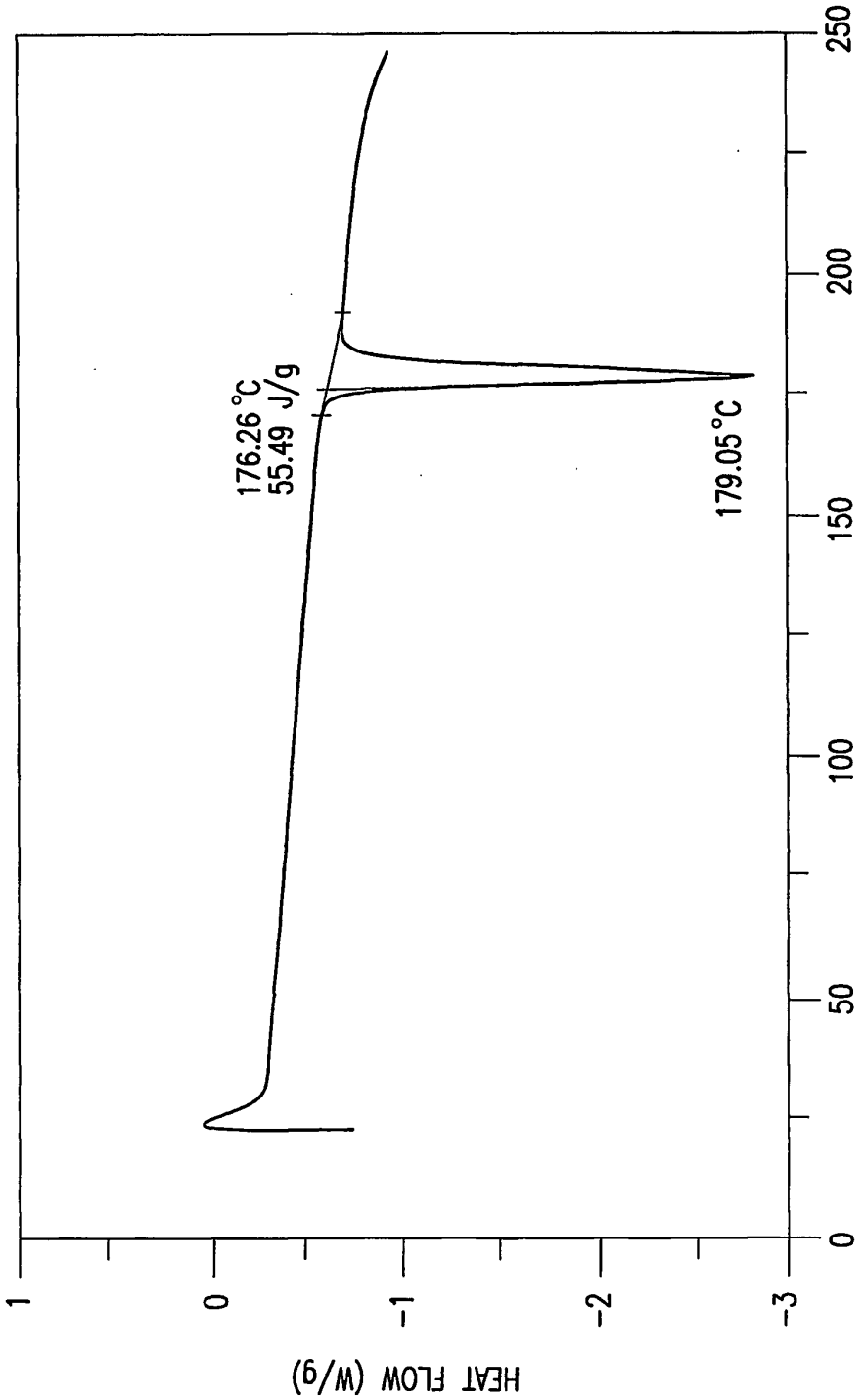
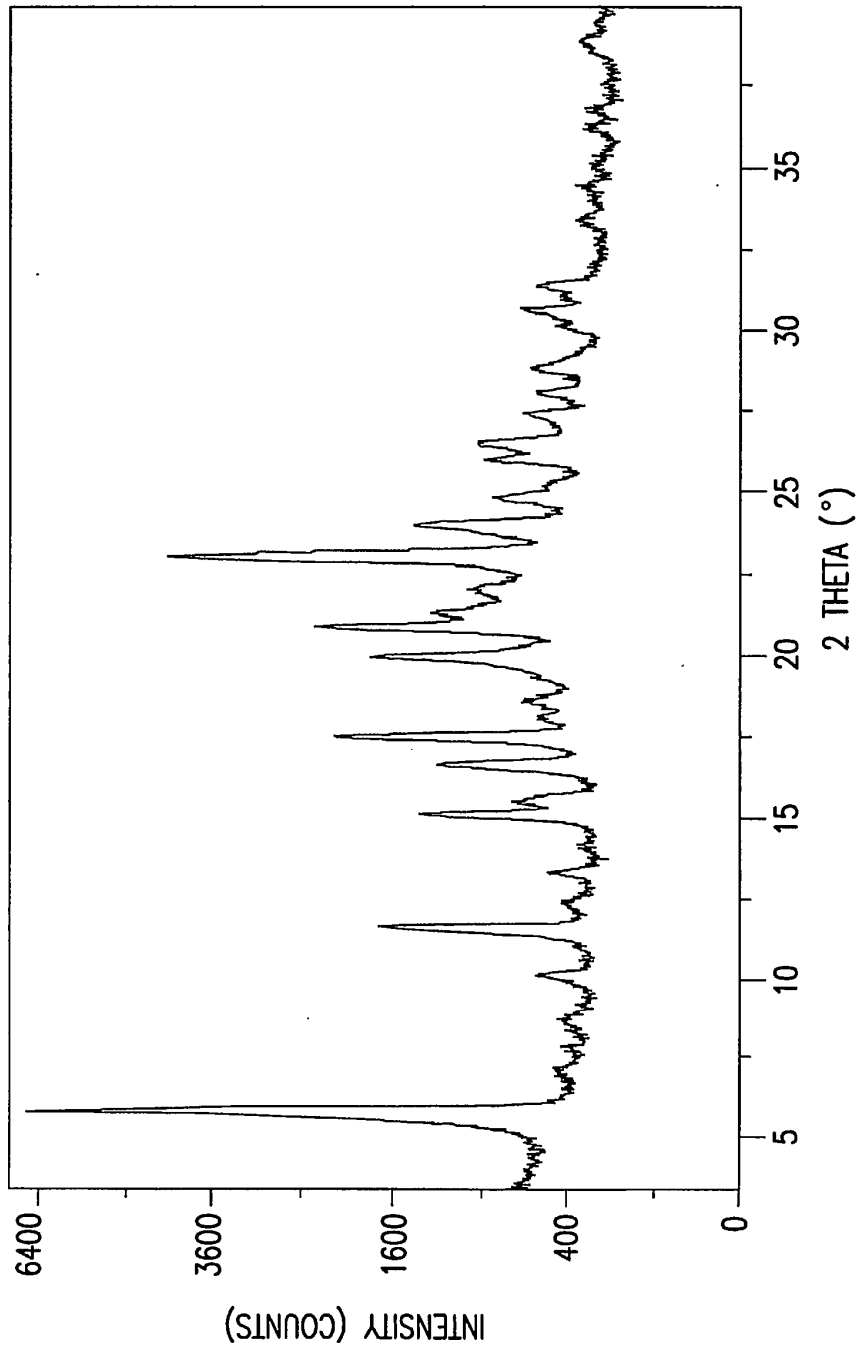

176.26 °C
55.49 J/g
179.05 °C
HEAT FLOW (W/g)
TEMPERATURE (°C)
1
0
-1
-2
-3
0
50
100
150
200
250

FIG.9


INTENSITY (COUNTS)
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3600
1600
400
0
5
10
15
20
25
30
35
2 THETA (°)

FIG.1O

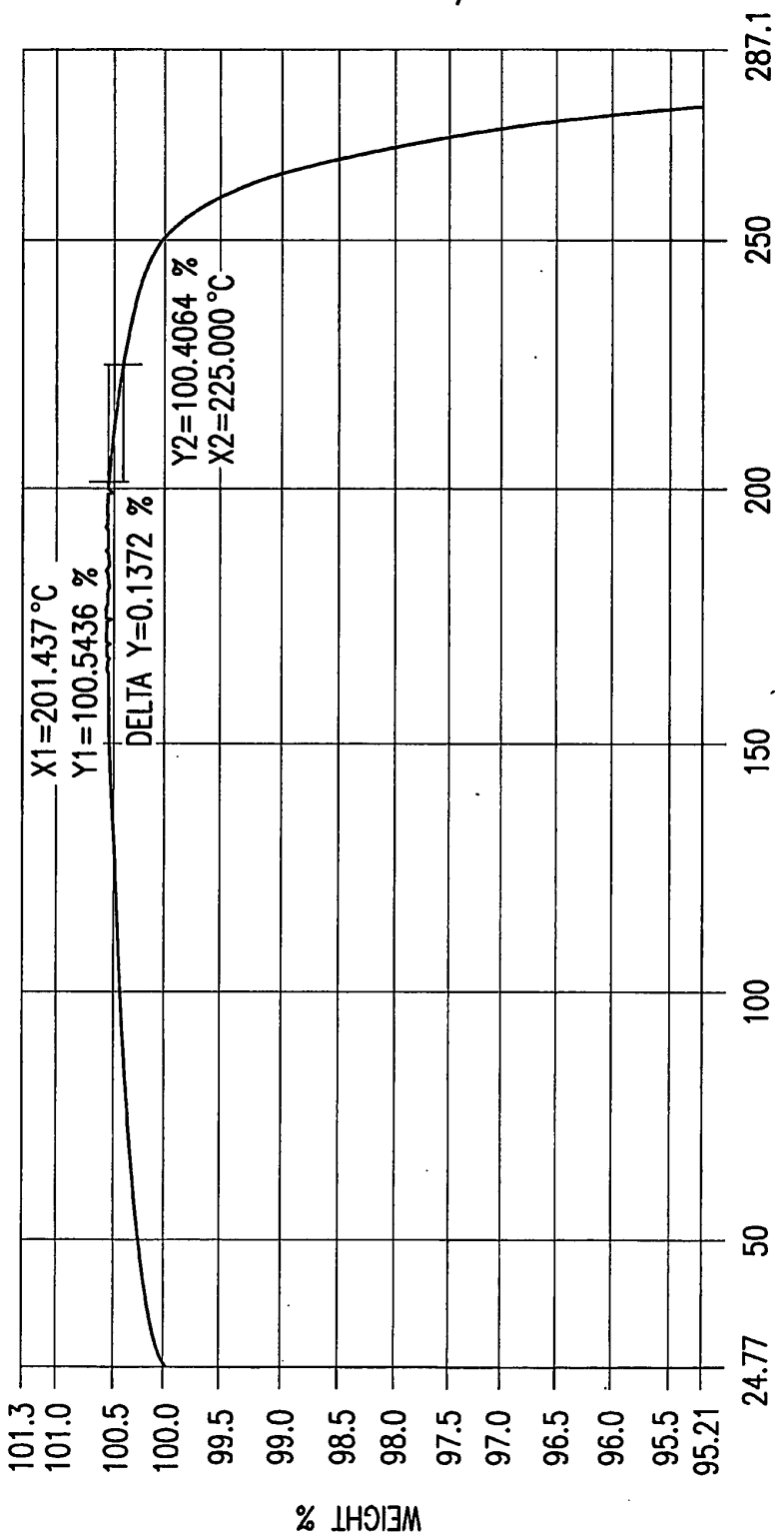
X1=201.437 °C
Y1=100.5436 %
DELTA Y=0.1372 %
Y2=100.4064 %
X2=225.000 °C
WEIGHT %
101.3
101.0
100.5
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.21
24.77
50
100
150
200
250
287.1
TEMPERATURE (°C)

FIG. 11

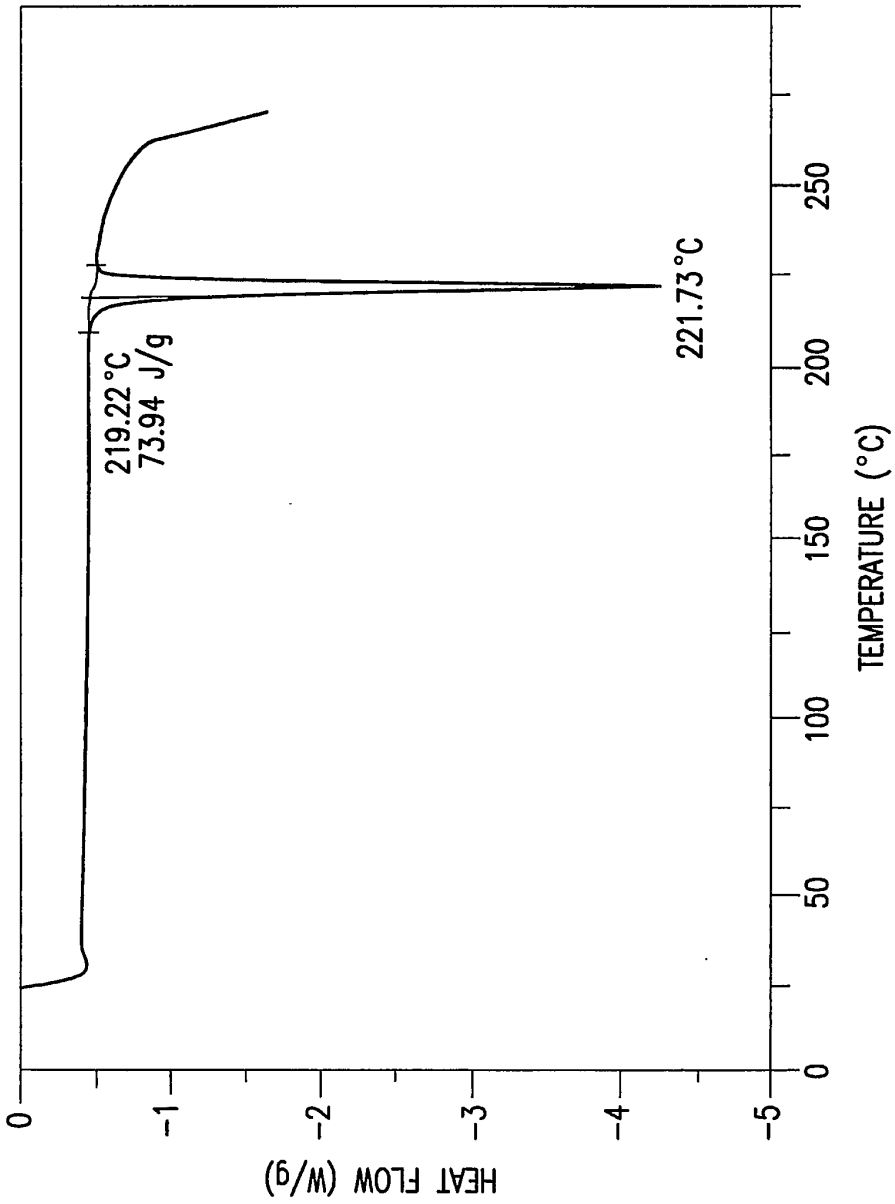


FIG.12

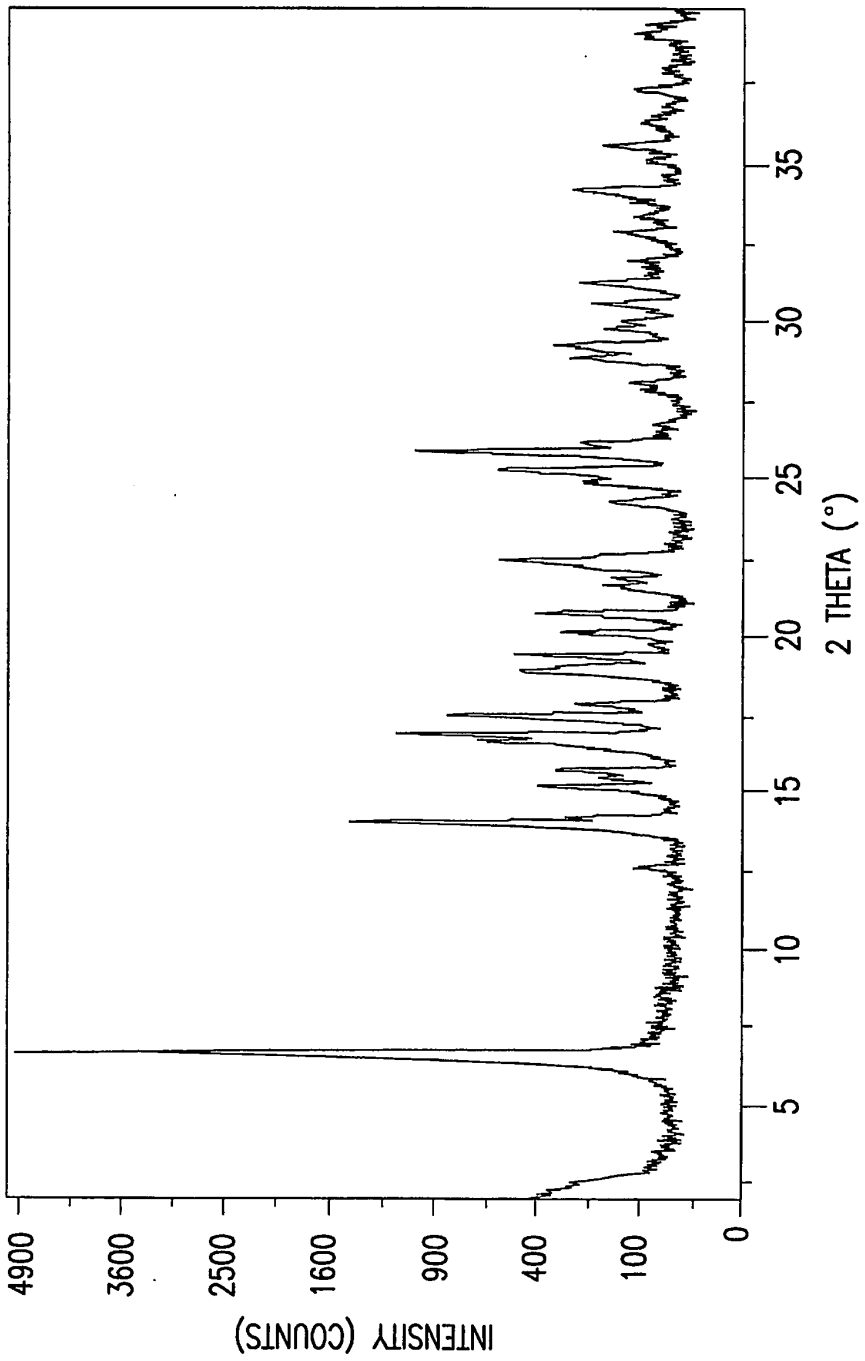
INTENSITY (COUNTS)
4900
3600
2500
1600
900
400
100
0
5
10
15
20
25
30
35
2 THETA (°)

FIG.13

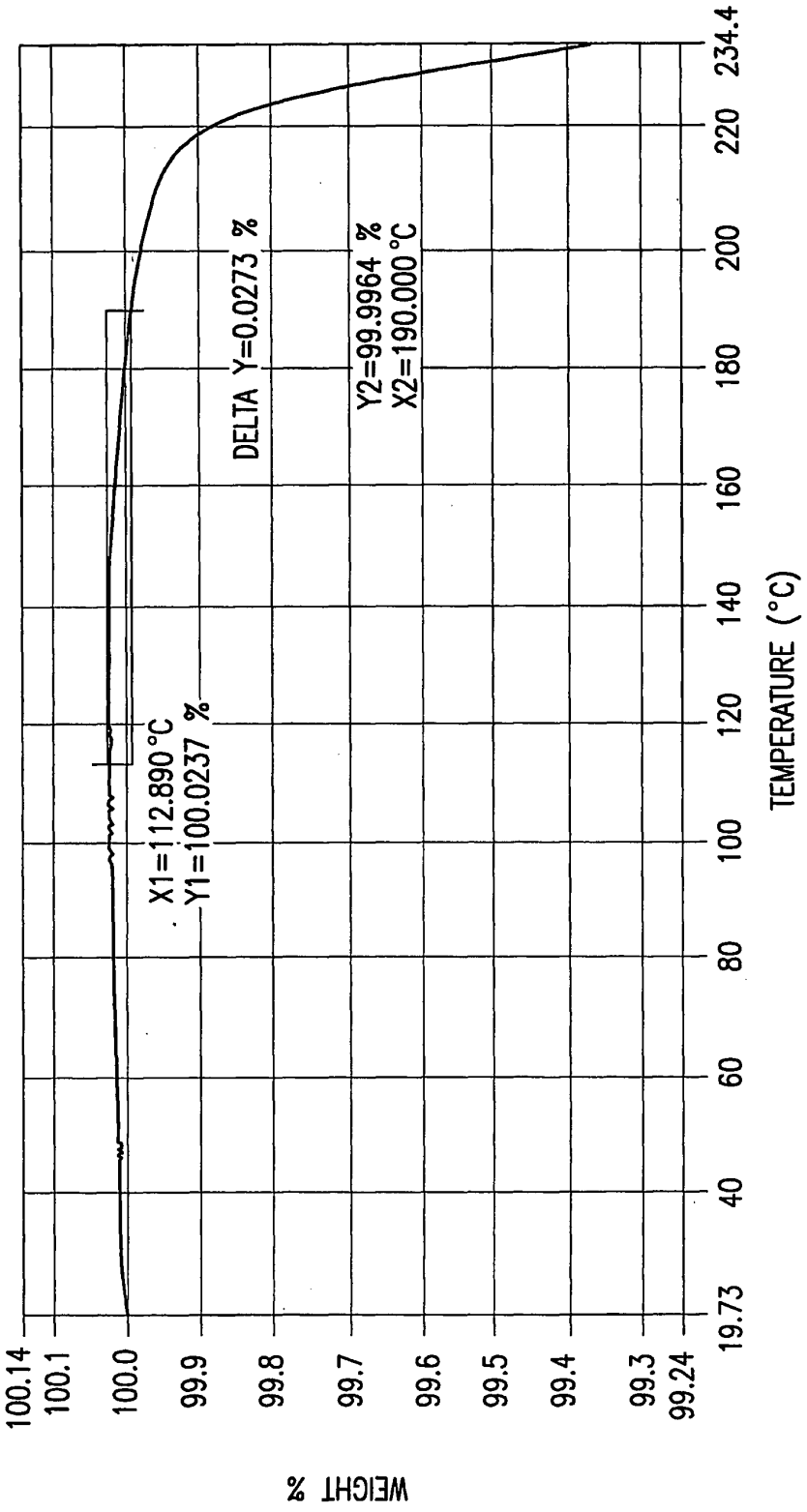
DELTA Y=0.0273 %
Y2=99.9964 %
X2=190.000 °C
X1=112.890 °C
Y1=100.0237 %
WEIGHT %
100.14
100.1
100.0
99.9
99.8
99.7
99.6
99.5
99.4
99.3
99.24
19.73
40
60
80
100
120
140
160
180
200
220
234.4
TEMPERATURE (°C)

FIG. 14

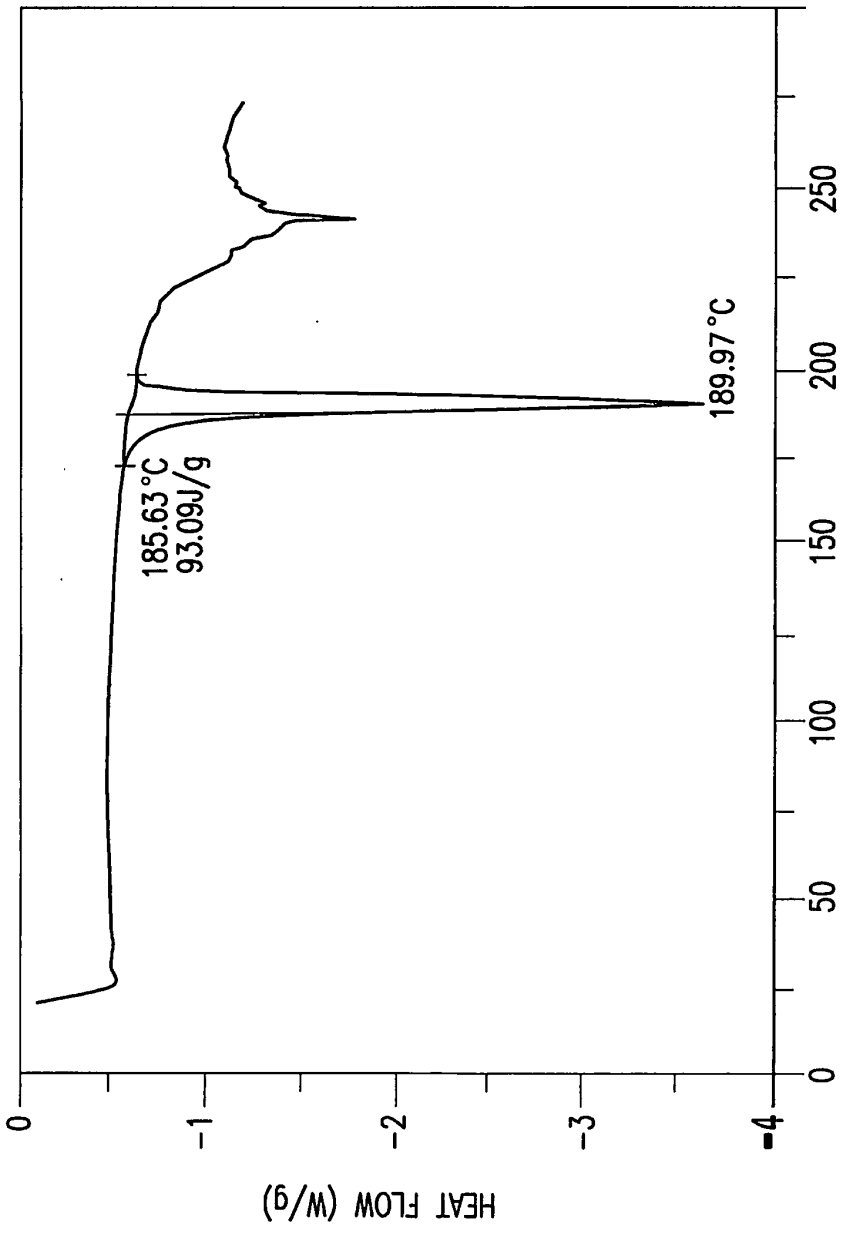
189.97°C
185.63°C
93.09J/g
HEAT FLOW (W/g)
TEMPERATURE (°C)
0
-1
-2
-3
-4
0
50
100
150
200
250

FIG. 15

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/00951

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A01N 43/58, 43/60; A61K 31/495, 31/50; C07D 487/00, 491/00, 495/00, 497/00
US CL : 514/249; 544/350
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)
U.S. : 514/249; 544/350

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 practicable, search terms used)
STN: structure search in file REGISTRY, answer set cross-referenced in filed CAPLUS.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 03/004498 (EDMONDSON et al) 16 January 2003 (16.1.2003), example 7 and pages 9-10. | 1-10 and 21-38 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
24 May 2005 (24.05.2005)

Date of mailing of the international search report
09 JUN 2005

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/033848 A1

(51) International Patent Classification:
*A61K 31/4985* (2006.01) *C07D 487/04* (2006.01)

(21) International Application Number:
PCT/US2005/032079

(22) International Filing Date:
9 September 2005 (09.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/610,019 15 September 2004 (15.09.2004) US

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FERLITA, Russell, R.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **WENSLOW, Robert, M.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 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, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, 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, 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, IS, IT, LT, LU, LV, 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:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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(54) Title: AMORPHOUS FORM OF A PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

(57) Abstract: The present invention relates to a novel amorphous form 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-a mine as well as a process for its preparation, pharmaceutical compositions containing this novel form, and methods of use of the novel form and pharmaceutical compositions for the treatment of diabetes, obesity, and high blood pressure.

WO 2006/033848 A1

TITLE OF THE INVENTION

AMORPHOUS FORM OF A PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

FIELD OF THE INVENTION

The present invention relates to a novel amorphous form of a dihydrogenphosphate salt of a dipeptidyl peptidase-IV (DPP-IV) inhibitor. More particularly, the invention relates to a novel amorphous form 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 DPP-IV. This novel amorphous form of the DPP-IV inhibitor is 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 DPP-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 amorphous dihydrogenphosphate salt of the present invention; processes for preparing the amorphous dihydrogenphosphate salt and its 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); 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); and C.F. Deacon, et al., "Inhibitors of dipeptidyl peptidase IV: a novel approach for the prevention and treatment of Type 2 diabetes,"Exp. Opin. Investig. Drugs, 13: 1091-1102 (2004).

U.S. Patent No. 6,699,871 (issued March 2, 2004), the contents of which are incorporated by reference herein in their entirety, describes a class of beta-amino tetrahydrotriazolo[4,3-*a*]pyrazines, which are potent inhibitors of DPP-IV useful for the treatment of Type 2 diabetes. Specifically disclosed in this U.S. patent 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 of the newly discovered amorphous form 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 a novel amorphous form of the dihydrogenphosphate salt of the 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 amorphous form of the present invention displays distinct dissolution characteristics relative to crystalline forms 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 may have advantages in the preparation of certain pharmaceutical compositions of Compound I. Amorphous forms of Compound I may also exhibit distinct bioavailability and other pharmacokinetic characteristics compared to crystalline forms rendering them preferred forms for certain clinical applications. The present invention also concerns pharmaceutical compositions containing the novel amorphous form; processes for the preparation of this amorphous form and its 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 DRAWINGS

FIG. 1 is a characteristic X-ray diffraction pattern of the amorphous Compound I of the present invention.

FIG. 2 is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the amorphous Compound I of the present invention.

FIG. 3 is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the amorphous Compound I of the present invention.

FIG. 4 is a typical DSC curve of the amorphous Compound I of the present invention.

FIG. 5 is a typical TG curve of the amorphous Compound I of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

Text The present invention provides (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 an amorphous form.

X-ray powder diffraction studies are widely used to characterize molecular structures, crystallinity, and polymorphism. The X-ray powder diffraction pattern of the amorphous Compound I was generated on a Philips Analytical X'Pert PRO X-ray Diffraction System with PW3040/60 console. A PW3373/00 ceramic Cu LEF X-ray tube K-Alpha radiation was used as the source.

FIG. 1 shows the X-ray diffraction pattern for amorphous Compound I. The pattern for the amorphous Compound I is characterized by broad diffuse halos having very low counts with no distinctive absorption bands in contrast to sharp peaks typically observed with crystalline materials.

In addition to the X-ray powder diffraction patterns described above, the amorphous form of Compound I was further characterized by its solid-state carbon-13 and fluorine-19 nuclear magnetic resonance (NMR) spectra. The solid-state carbon-13 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4 mm double resonance CPMAS probe. The carbon-13 NMR spectrum utilized proton/carbon-13 cross-polarization magic-angle spinning with variable-amplitude cross polarization. The sample was spun at 15.0 kHz, and a total of 1024 scans were collected with a recycle delay of 5 seconds. A line broadening of 40 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 p.p.m.) as a secondary reference.

The solid-state fluorine-19 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4mm CRAMPS probe. The NMR spectrum utilized a simple pulse-acquire pulse program. The samples were spun at 15.0 kHz, and a total of 128 scans were collected with a recycle delay of 5 seconds. A vespel endcap was utilized to minimize fluorine background. A line broadening of 100 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported using poly(tetrafluoroethylene) (teflon) as an external secondary reference which was assigned a chemical shift of –122 p.p.m.

DSC data were acquired using TA Instruments DSC 2910 or equivalent instrumentation is used. Between 2 and 6 mg sample is weighed into an open pan. This pan is then crimped and placed at the sample position in the calorimeter cell. An empty pan is placed at the reference position. The calorimeter cell is closed and a flow of nitrogen is passed through the cell. The heating program is set to heat the sample at a heating rate of 10 °C/min to a temperature of approximately 250 °C. The heating program is started. When the run is completed, the data are analyzed using the DSC analysis program contained in the system software. The melting endotherm is integrated between baseline temperature points that are above and below the temperature range over which the endotherm is observed. The data reported are the onset temperature, peak temperature and enthalpy.

TG data were acquired using a Perkin Elmer model TGA 7. Experiments were performed under a flow of nitrogen and using a heating rate of 10 °C/min to a maximum temperature of approximately 250 °C. After automatically taring the balance, 5 to 20 mg of sample was added to the platinum pan, the furnace was raised, and the heating program started. Weight/temperature data were collected automatically by the instrument. Analysis of the results was carried out by selecting the Delta Y function within the instrument software and choosing the temperatures between which the weight loss was to be calculated. Weight losses are reported up to the onset of decomposition/evaporation.

FIG. 2 shows the solid-state carbon-13 CPMAS NMR spectrum for amorphous Compound I. Amorphous Compound I exhibited characteristic signals with chemical shift values of 169.6, 150.6, 120.1, and 41.9 p.p.m.

FIG. 3 shows the solid-state fluorine-19 MAS NMR spectrum for amorphous Compound I. Amorphous Compound I exhibited characteristic signals with chemical shift values of -63.7, -118.5, -136.6, and -143.3 p.p.m.

FIG. 4 shows a characteristic DSC curve for amorphous Compound I. The broad endotherm up to approximately 90 °C is the loss of the adsorbed water. The step transition at approximately 105 °C is due to the glass transition of the material. The exotherm at approximately 140 °C is the crystallization of the material to anhydrous Form I. The endotherm at approximately 190 °C is the melt of Form I.

FIG.5 shows a characteristic thermogravimetric analysis (TGA) curve for amorphous Compound I. The initial weight loss on the TGA is due to adsorbed water on the amorphous material.

Another aspect of the present invention provides the Compound I drug substance that comprises the amorphous form in a detectable amount. By "drug substance" is meant the active pharmaceutical ingredient (API). The amount of the amorphous form in the drug substance can be quantified by the use of physical methods such as X-ray powder diffraction, solid-state fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance spectroscopy, solid-state carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance spectroscopy, solid state Fourier-transform infrared spectroscopy, and Raman spectroscopy. A detectable amount is an amount that can be detected by such physical methods. The limits of detection of such methods is anticipated to improve with technological advances. The remainder of the drug substance may additionally comprise various crystalline forms of Compound I and polymorphs and pseudopolymorphs thereof. In a class of this embodiment, about 5% to about 100% by weight of the amorphous form is present in the drug substance. In a second class of this embodiment, about 10% to about 100% by weight of the amorphous form is present in the drug substance. In a third class of this embodiment, about 25% to about 100% by weight of the amorphous form is present in the drug substance. In a fourth class of this embodiment, about 50% to about 100% by weight of the amorphous form is present in the drug substance. In a fifth class of this embodiment, about 75% to about 100% by weight of the amorphous form is present in the drug substance. In a sixth class of this embodiment, substantially all of the Compound I drug substance is the amorphous form, i.e., the Compound I drug substance is substantially phase pure amorphous form.

Another aspect of the present invention provides a method for the prevention or treatment of clinical conditions for which an inhibitor of DPP-IV is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the amorphous form of Compound I. Such clinical conditions include diabetes, in particular Type 2 diabetes, hyperglycemia, insulin resistance, obesity, and high blood pressure.

The present invention also provides for the use of the amorphous Compound I of the present invention in the manufacture of a medicament for the prevention or treatment of clinical conditions for which an inhibitor of DPP-IV is indicated, in particular, Type 2 diabetes, hyperglycemia, insulin resistance, obesity, and high blood pressure. In one embodiment the clinical condition is Type 2 diabetes.

Another aspect of the present invention provides the amorphous Compound I for use in the treatment of clinical conditions for which an inhibitor of DPP-IV is indicated, in particular, Type 2 diabetes, hyperglycemia, insulin resistance, obesity, and high blood pressure. In one embodiment of this aspect the clinical condition is Type 2 diabetes.

The present invention also provides pharmaceutical compositions comprising the amorphous Compound I, in association with one or more pharmaceutically acceptable carriers or excipients. In one embodiment the pharmaceutical composition comprises a prophylactically or therapeutically effective amount of the active pharmaceutical ingredient (API) in admixture with pharmaceutically acceptable excipients wherein the API comprises a detectable amount of the amorphous form of the present invention. In a second embodiment the pharmaceutical composition comprises a prophylactically or therapeutically effective amount of the API in admixture with pharmaceutically acceptable excipients wherein the API comprises about 5% to about 100% by weight of amorphous Compound I of the present invention. In a class of this second embodiment, the API in such compositions comprises about 10% to about 100% by weight of amorphous Compound I. In a second class of this embodiment, the API in such compositions comprises about 25% to about 100% by weight of amorphous Compound I. In a third class of this embodiment, the API in such compositions comprises about 50% to about 100% by weight of amorphous Compound I. In a fourth class of this embodiment, the API in such compositions comprises about 75% to about 100% by weight of amorphous Compound I. In a fifth class of this embodiment, substantially all of the API is amorphous Compound I, i.e., the API is substantially phase pure amorphous Compound I. When not comprising substantially phase pure amorphous Compound I, such compositions may additionally comprise various crystalline forms of Compound I and polymorphs and pseudopolymorphs thereof.

The compositions in accordance with the invention are suitably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories. The compositions are intended for oral, parenteral, intranasal, sublingual, or rectal administration, or for administration by inhalation or insufflation. Formulation of the compositions according to the invention can conveniently be effected by methods known from the art, for example, as described in Remington's Pharmaceutical Sciences, 17th ed., 1995.

The dosage regimen is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. An ordinarily skilled

physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the API for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the API, preferably, from about 1 mg to about 200 mg of API. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the amorphous Compound I of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the amorphous form of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the amorphous Compound I herein described in detail can form the API, and is typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active pharmaceutical ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral API can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The amorphous form of Compound I has been found to possess a high solubility in water, rendering it especially amenable to the preparation of formulations, in particular intranasal and intravenous formulations, which require relatively concentrated aqueous solutions of the API.

The pharmaceutical compositions of the present invention may include one or more additional agents useful for the treatment of Type 2 diabetes, such as metformin; a sulfonylurea, such as glipizide, glyburide, and glimepiride; a PPARγ agonist, such as pioglitazone and rosiglitazone; and a PPARα/γ dual agonist, such as muraglitazar.

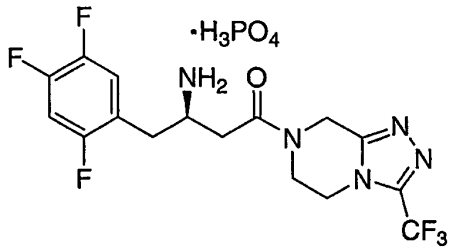
In a still further aspect, the present invention provides a method for the treatment and/or prevention of clinical conditions for which a DPP-IV inhibitor is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of amorphous Compound I of the present invention or a pharmaceutical composition containing a prophylactically or therapeutically effective amount of amorphous Compound I.

The following non-limiting Examples are intended to illustrate the present invention and should not be construed as being limitations on the scope or spirit of the instant invention.

Compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I.

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity.

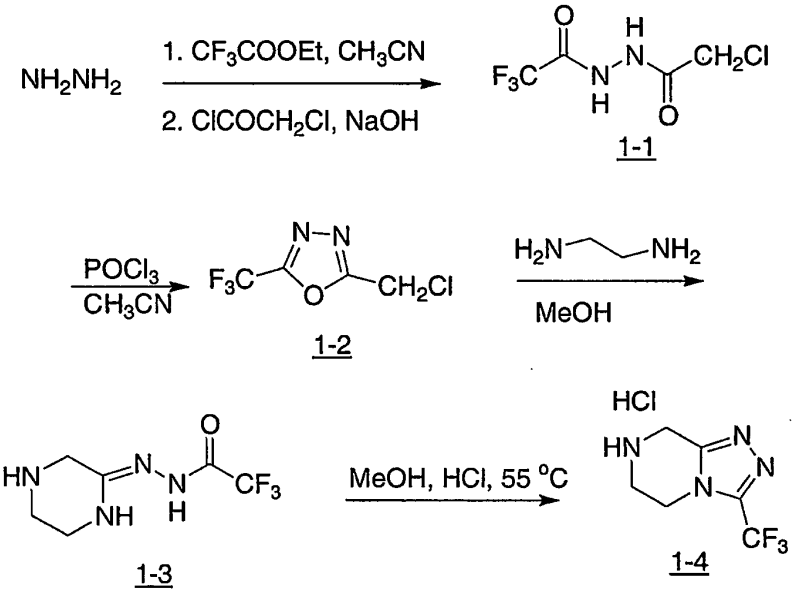
EXAMPLE



Preparation of amorphous form 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 dihydrogenphosphate

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloride (1-4)

Scheme 1



Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26

~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) p.p.m..

$^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 p.p.m..

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole(1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

$^1$H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) p.p.m..

$^{13}$C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 p.p.m..

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide(1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) p.p.m.. $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) p.p.m..

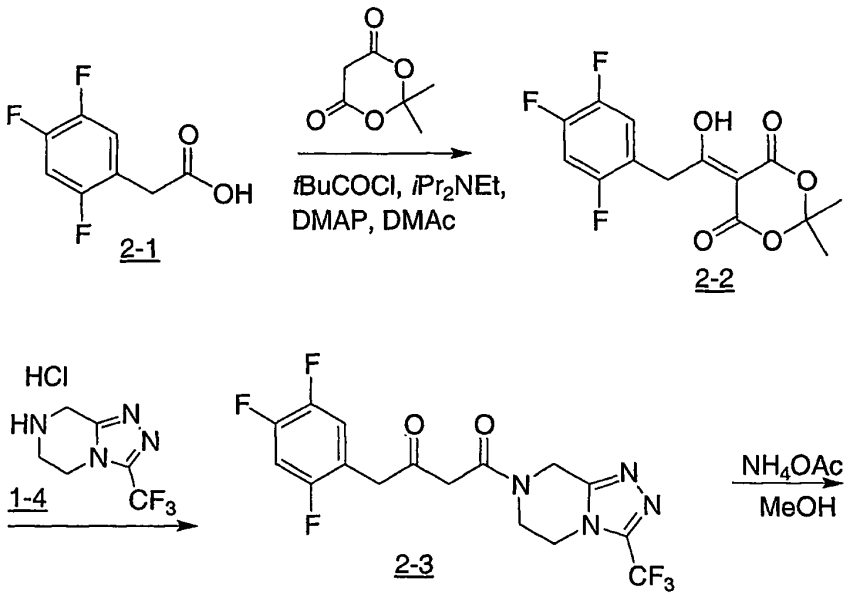
Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloride (1-4)

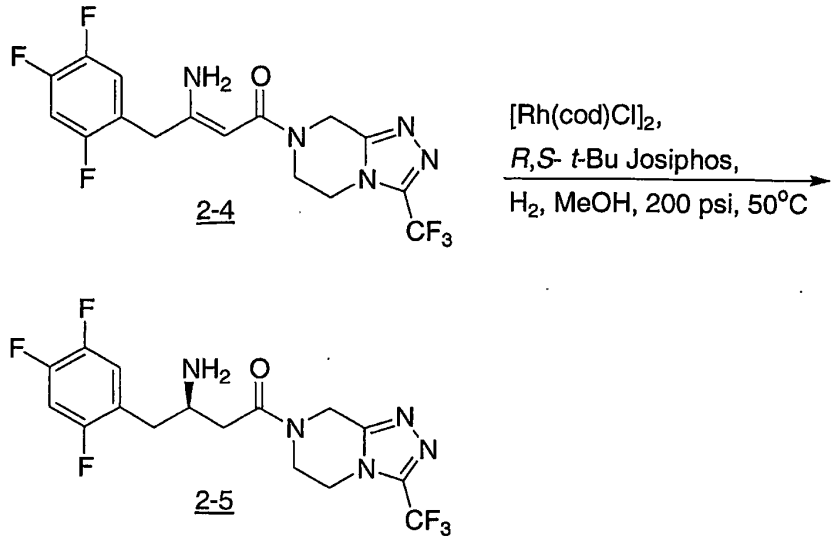
A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The

solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) p.p.m.; $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ: 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 p.p.m..

Scheme 2






Step A: Preparation 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-one (2-3)

2,4,5-Trifluorophenylacetic acid (2-1) (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino)pyridine (DMAP) (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. *N,N*-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to dissolve the solids. *N,N*-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5 °C. The reaction mixture was aged at 5 °C for 1 h. Triazole hydrochloride 1-4 (180 g, 0.789 mol) was added in one portion at 40-50 °C. The reaction solution was aged at 70 °C for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20 – 45 °C. The batch was seeded and aged at 20 – 30 °C for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0 – 5 °C and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product 2-3 was 89%.

Step B: Preparation of (2Z)-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)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30 °C during the addition. Additional methanol

(100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5 °C in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid (180 g); m.p. 271.2 °C.

Step C: Preparation 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 (2-5)

Into a 500 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]$_2$}(292 mg, 1.18 mmol) and (*R*,*S*) *t*-butyl Josiphos (708 mg, 1.3 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (200 mL) and the mixture was stirred at room temperature for 1 h. Into a 4 L hydrogenator was charged the enamine amide 2-4 (118 g, 0.29 mol) along with MeOH (1 L). The slurry was degassed. The catalyst solution was then transferred to the hydrogenator under nitrogen. After degassing three times, the enamine amide was hydrogenated under 200 psi hydrogen gas at 50 °C for 13 h. Assay yield was determined by HPLC to be 93% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl *t*-butyl ether (MTBE) (45 mL). Into this solution was added aqueous $H_3PO_4$ solution (0.5 M, 95 mL). After separation of the layers, 3*N* NaOH (35 mL) was added to the water layer, which was then extracted with MTBE (180 mL + 100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75 °C). The hot toluene solution was then allowed to cool to 0 °C slowly (5 – 10 h). The crystals were isolated by filtration (13 g, yield 72%, 98 – 99% ee); m.p. 114.1 – 115.7 °C.
$^1$H NMR (300 MHz, $CD_3CN$): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).
Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:
$^{13}$C NMR ($CD_3CN$): δ 171.8, 157.4 (ddd , $J_{CF}$ = 242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; $J_{CF}$ = 246.7, 14.2, 12.9 Hz), 147.4 (ddd, $J_{CF}$ = 241.2, 12.3, 3.7 Hz), 144.2 (q, $J_{CF}$ = 38.8 Hz), 124.6 (ddd , $J_{CF}$ = 18.5, 5.9, 4.0 Hz), 120.4 (dd , $J_{CF}$ = 19.1, 6.2 Hz), 119.8 (q, $J_{CF}$ = 268.9 Hz), 106.2 (dd , $J_{CF}$ = 29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

The crystalline free base 2-5 can also be isolated as follows:

(a) The reaction mixture upon completion of the hydrogenation step is charged with 25 wt% of Ecosorb C-941. The mixture is stirred under nitrogen for one h and then filtered. The cake is washed with 2L/kg of methanol. Recovery of free base is about 95% and optical purity about 95% ee.

(b) The freebase solution in methanol is concentrated to 3.5-4.0 L/kg volume (based on free base charge) and then solvent-switched into isopropanol (IPA) to final volume of 3.0 L/kg IPA.

(c) The slurry is heated to 40 °C and aged 1 h at 40°C and then cooled to 25 °C over 2 h.

(d) Heptane (7L/kg) is charged over 7 h and the slurry stirred for 12 h at 22-25°C. The supernatant concentration before filtering is 10-12 mg/g.

(e) The slurry is filtered and the solid washed with 30% IPA/heptane (2L/kg).

(f) The solid is dried in a vacuum oven at 40 °C.

(g) The optical purity of the free base is about 99% ee.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

| | |
|---|---|
| Column: | Waters Symmetry C18, 250 mm x 4.6 mm |
| Eluent: | Solvent A: 0.1 vol% $HClO_4/H_2O$ |
| | Solvent B: acetonitrile |
| Gradient: | 0 min 75% A : 25% B |
| | 10 min 25% A : 75% B |
| | 12.5 min 25% A : 75% B |
| | 15 min 75% A : 25% B |
| Flow rate: | 1 mL/min |
| Injection Vol.: | 10 µL |
| UV detection: | 210 nm |
| Column temp.: | 40 °C |
| Retention times: | compound 2-4: 9.1 min |
| | compound 2-5: 5.4 min |
| | *t*Bu Josiphos: 8.7 min |

The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:

| | |
|---|---|
| Column: | Chirapak, AD-H, 250 mm x 4.6 mm |
| Eluent: | Solvent A: 0.2 vol.% diethylamine in heptane |
| | Solvent B: 0.1 vol% diethylamine in ethanol |
| Isochratic Run Time: | 18 min |
| Flow rate: | 0.7 mL/min |
| Injection Vol.: | 7 µL |
| UV detection: | 268 nm |
| Column temp.: | 35 °C |
| Retention times: | (*R*)-amine 2-5: 13.8 min |
| | (*S*)-amine 2-5: 11.2 min |

Preparation of crystalline (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 dihydrogenphosphate monohydrate:

A 250 mL round bottom flask equipped with an overhead stirrer, heating mantle and thermocouple, was charged with 31.5 mL of isopropanol (IPA), 13.5 mL water, 15.0 g (36.9 mmol) 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 freebase and 4.25 g (36.9 mmol) of 85% aqueous phosphoric acid. The mixture was heated to 75 °C. A thick white precipitate formed at lower temperatures but dissolved upon reaching 75 °C. The solution was cooled to 68 °C and then held at that temperature for 2 h. A slurry bed of solids formed during this age time [the solution can be seeded with 0.5 to 5 wt% of small particle size (alpine milled) monohydrate]. The slurry was then cooled at a rate of 4 °C/h to 21 °C and then held overnight. 105 mL of IPA was then added to the slurry. After 1 h the slurry was filtered and washed with 45 mL IPA. The solids were dried on the frit with open to air. The solids were found to greater than 99.8% pure by HPLC area percentage (HPLC conditions same as those given above).

Preparation of amorphous (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 dihydrogenphosphate:

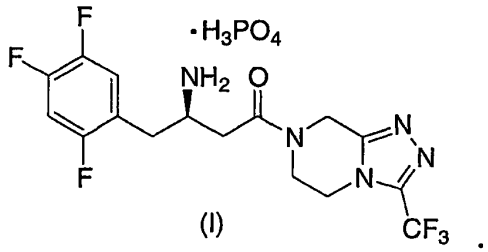
The above crystalline monohydrate was dissolved in water at a concentration of approximately 50 mg/mL. The mixture was agitated until no solid material was apparent, and the solution was filtered through a 0.2 $\mu$m filter into a clean container. The solution was then frozen using a dry ice/methanol bath. The sample was pulled under vacuum to remove the solvent and leave a fluffy, white amorphous solid. The solid displays no reflections when analyzed be X-ray powder diffraction.

EXAMPLE OF A PHARMACEUTICAL COMPOSITION:

Amorphous Compound I (API) is formulated into a tablet by a direct compression process. A 100 mg potency tablet is composed of 124 mg of the API, 130 mg microcrystalline cellulose, 130 mg of mannitol (or 130 mg of dicalcium phosphate), 8 mg of croscarmellose sodium, 8 mg of magnesium stearate and 16 mg of Opadry white (proprietary coating material made by Colorcon, West Point, PA). The API, microcrystalline cellulose, mannitol (or dicalcium phosphate), and croscarmellose sodium are first blended, and the mixture is then lubricated with magnesium stearate and pressed into tablets. The tablets are then film coated with Opadry White.

WHAT IS CLAIMED IS:

1. An amorphous form 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:




(I)

2. The amorphous form of Claim 1 characterized by the X-ray powder diffraction pattern of FIG. 1.

3. The amorphous form of Claim 1 characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at -63.7, -118.5, -136.6, and -143.3 p.p.m.

4. The amorphous form of Claim 3 further characterized by the solid-state fluorine-19 MAS nuclear magnetic resonance spectrum of FIG. 3.

5. The amorphous form of Claim 1 characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 169.6, 150.6, 120.1, and 41.9 p.p.m.

6. The amorphous form of Claim 5 further characterized by the solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum of FIG. 2.

7. The amorphous form of Claim 1 characterized by the thermogravimetric analysis curve of FIG. 5.

8. The amorphous form of Claim 1 characterized by the differential scanning calorimetric (DSC) curve of FIG. 4.

9. A drug substance comprising a detectable amount of the amorphous form of Claim 1.

10. The drug substance of Claim 9 comprising about 5% to about 100% by weight of said amorphous form.

11. The drug substance of Claim 9 comprising about 10% to about 100% by weight of said amorphous form.

12. The drug substance of Claim 9 comprising about 25% to about 100% by weight of said amorphous form.

13. The drug substance of Claim 9 comprising about 50% to about 100% by weight of said amorphous form.

14. The drug substance of Claim 9 comprising about 75% to about 100% by weight of said amorphous form.

15. The drug substance of Claim 9 comprising substantially all by weight of said amorphous form.

16. A pharmaceutical composition comprising a prophylactically or therapeutically effective amount of the amorphous form of Claim 1 in association with one or more pharmaceutically acceptable carriers or excipients.

17. A method of treating Type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the amorphous form according to Claim 1.

18. The amorphous form of Claim 1 for use in the treatment of Type 2 diabetes.

19. Use of the amorphous form of Claim 1 as active ingredient in the manufacture of a medicament for use in the treatment of Type 2 diabetes.

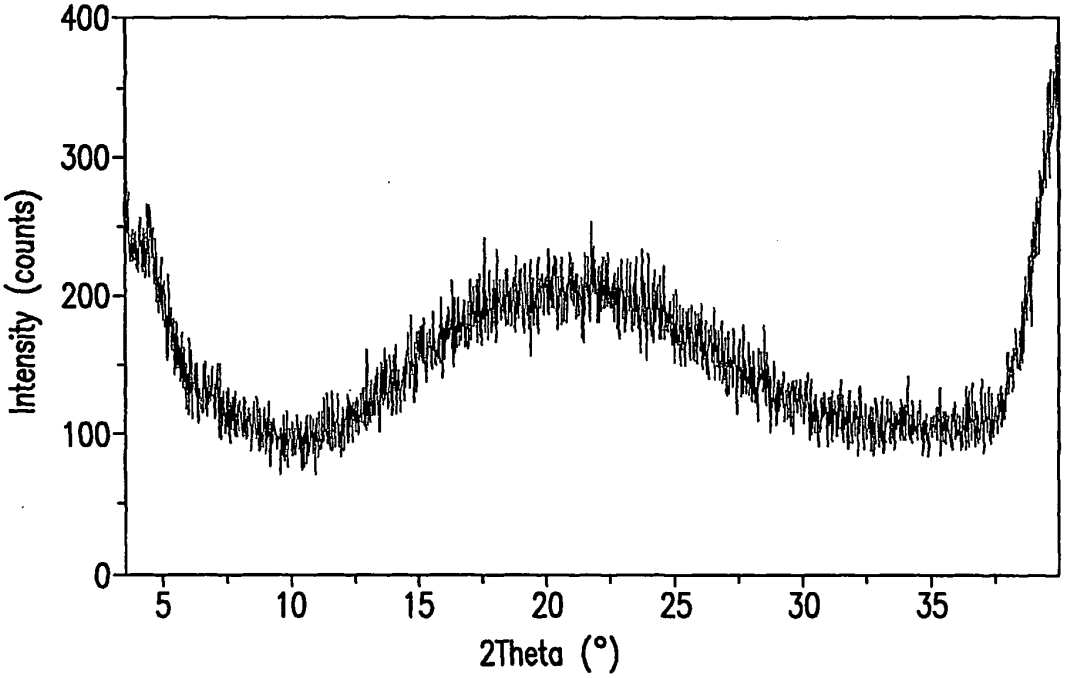



FIG.1

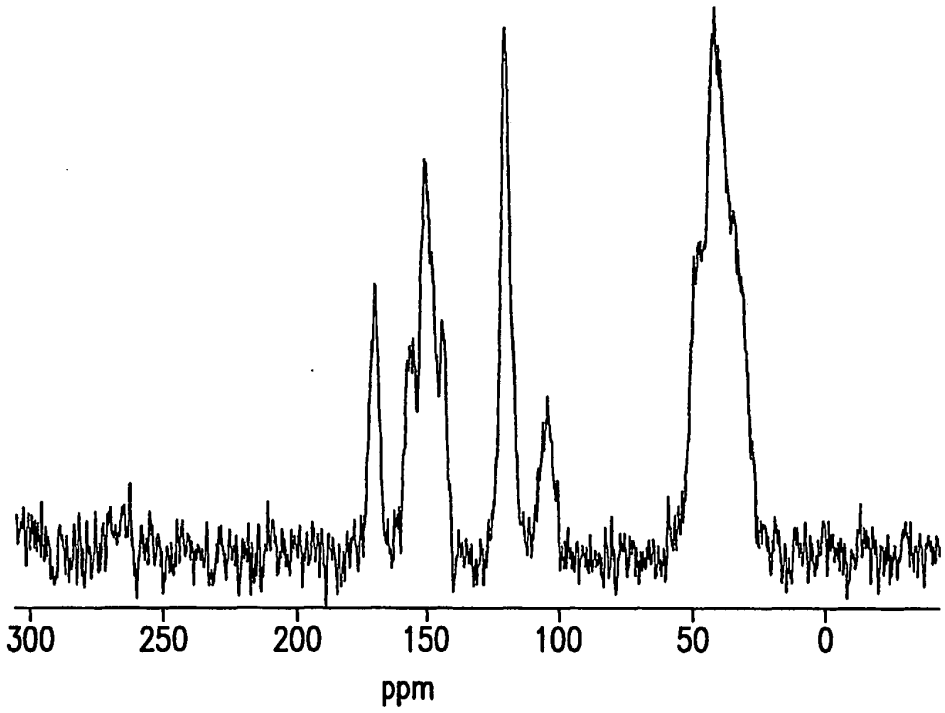



FIG.2

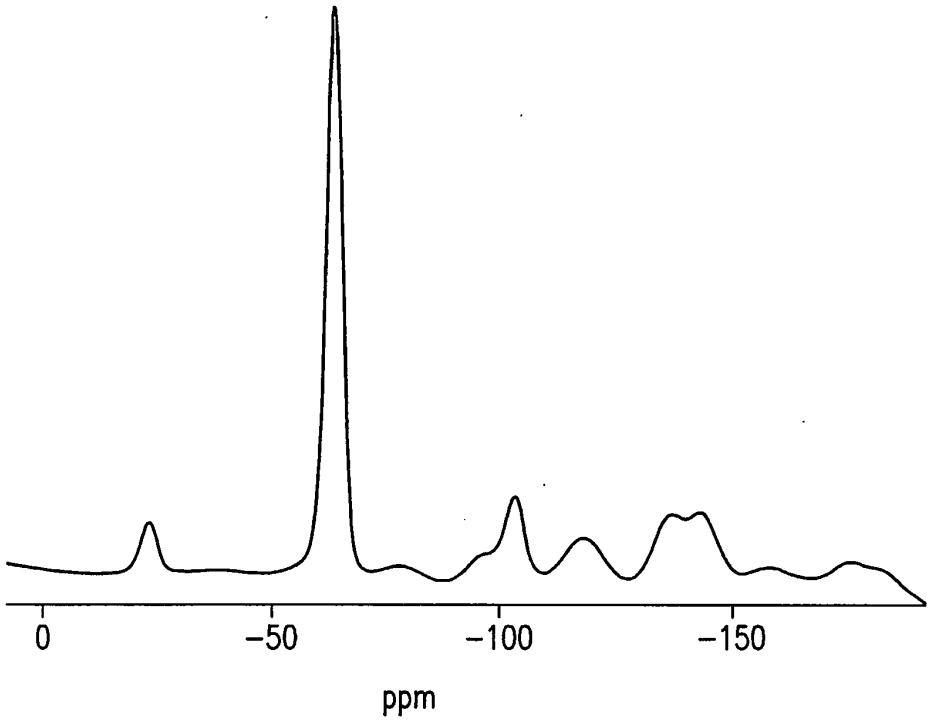



FIG.3

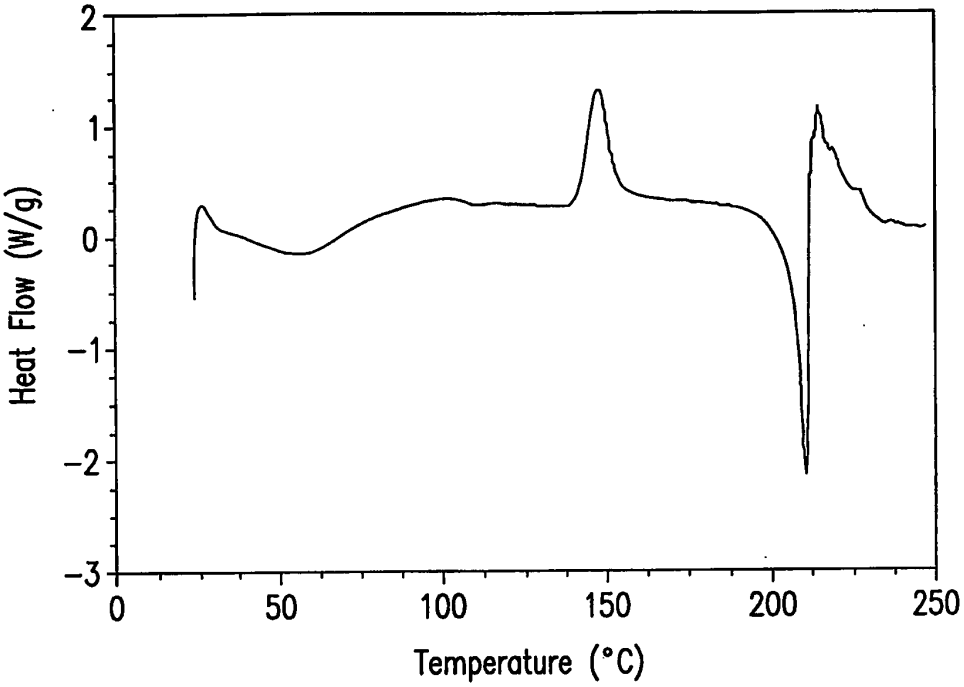
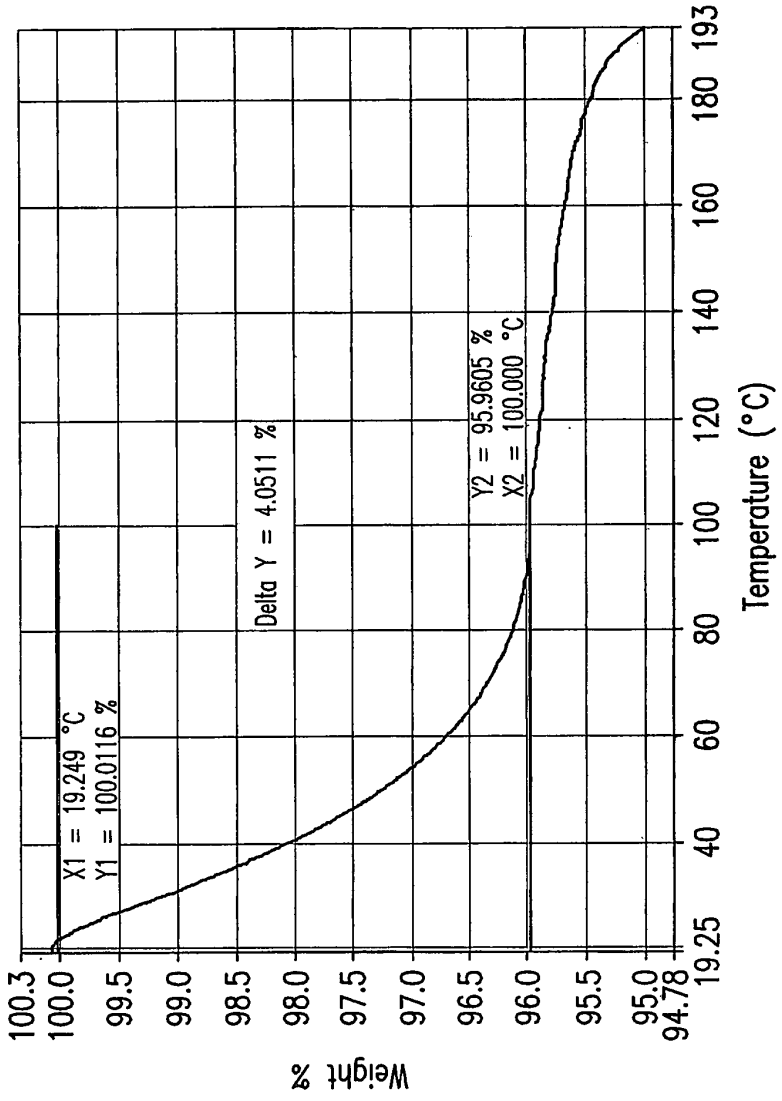



FIG.4


Weight %
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100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
94.78
19.25
40
60
80
100
120
140
160
180
193
Temperature (°C)
X1 = 19.249 °C
Y1 = 100.0116 %
Delta Y = 4.0511 %
Y2 = 95.9605 %
X2 = 100.000 °C

FIG.5

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/32079

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) : A61K 31/4985; C07D 487/04
US CL : 514/249; 544/350
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)
U.S. : 514/249; 544/350

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 practicable, search terms used)
STN: structure searched in file REGISTRY, answer set was then cross-referenced into the CAPLUS file.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 6,699,871 (EDMONDSON et al) 2 March 2004 (02.03.2004), paragraph bridging columns 6 and 7, and col. 15, lines 37-67 - col. 16, the entire column. | 1 and 9-19 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

" A" document defining the general state of the art which is not considered to be of particular relevance

" E" earlier application or patent published on or after the international filing date

" L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

" O" document referring to an oral disclosure, use, exhibition or other means

" P" document published prior to the international filing date but later than the priority date claimed

" T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

" X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

" Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

" &" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 January 2006 (24.01.2006) | 02 FEB 2006 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (571) 273-3201 | Authorized officer<br>Zachary C. Tucker<br>Telephone No. (571) 272-1600 |

Form PCT/ISA/210 (second sheet) (April 2005)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y | 9276 |

210 7590 07/31/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

| EXAMINER | |
|---|---|
| SACKEY, EBENEZER O | |
| **ART UNIT** | **PAPER NUMBER** |
| 1624 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 07/31/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

| Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/874,992 | CYPES ET AL. | |
| | Examiner | Art Unit | |
| | EBENEZER SACKEY | 1624 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *EBENEZER SACKEY*. (3)*PHILIPPE L. DURETTE*.

(2) *GOLAM SHAMEEM*. (4)_____.

Date of Interview: *24 July 2007*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *all pending claims, in addition to 10/569,566 and 10/570,409*.

Identification of prior art discussed: *None*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *applicants attorney, will present arguments to rebut the rejections of record in each of the cited applications. Additionally, diffractograms will be recited in pertinent claims to obviate the rejection of record*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

## Summary of Record of Interview Requirements

**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

**Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews**
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

---

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

**Examiner to Check for Accuracy**

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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MERCK

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065

Patent Department

# Facsimile Cover Sheet

**TODAY'S DATE:** August 6, 2007

***PLEASE DELIVER THE FOLLOWING MESSAGE TO:***

Examiners Name: Ebenezer O. Sackey

Examiner's fax number: 571-273-8300

Examiner's phone number: 571-272-0704

Group number: 1624

***THIS MESSAGE IS FROM:***

Name: Philippe L. Durette

Phone No.: (732) 594-4568 Mail Location: RY60-30

Fax No.: (732) 594-4720

***RE:*** Applicants: S. H. Cypes, et al
Case No.: 21409Y
Serial No.: 10/874,992
Filed: June 23, 2004
Title: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

NUMBER OF PAGES BEING TRANSMITTED (INCLUDING COVER): 11

**IF YOU DO NOT RECEIVE ALL OF THE PAGES, PLEASE CALL (732) 594-4744**

***CERTIFICATION OF FACSIMILE TRANSMISSION***

**I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below**

Pamela Spalding
*Type or print name of person signing certification*

Pamela Spalding
*Signature*

August 6, 2007
*Date*

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| Applicants: | S.H. Cypes, et al. |
| Serial No.: | 10/874,992 (Case No. 21409Y) |
| Filed: | June 23, 2004 |
| For: | PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR |

Art Unit: 1624

Examiner: E.O. Sackey

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**AMENDMENT UNDER 37 C.F.R. 1.111**

Sir:

In response to the Official Action dated June 11, 2007, for which a response is due by September 11, 2007, please amend this application as follows and consider the accompanying remarks which are deemed to place it in condition for allowance.

Please amend this application as follows:

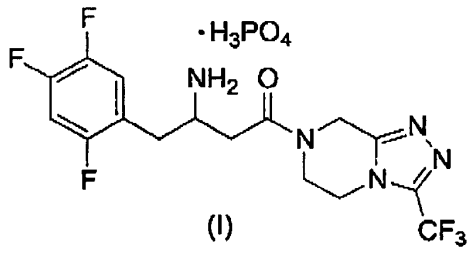
**Amendments to the Claims** are reflected on page 2 of this response. **Remarks** begin on page 7 of this response.

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:**

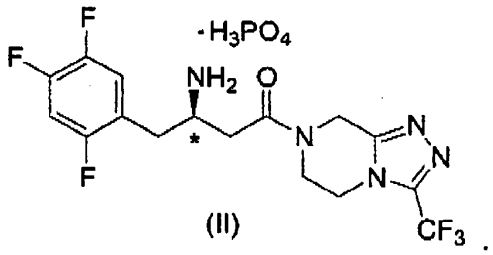
Claim 1 (currently amended): A dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I:




(I)

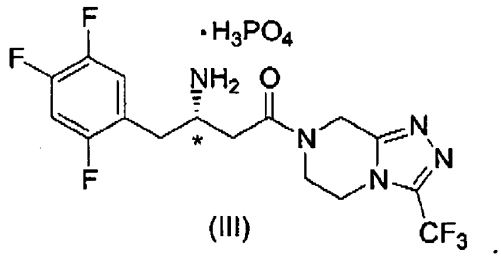
or a ~~pharmaceutically acceptable~~ hydrate thereof.

Claim 2 (original): The salt of Claim 1 of structural formula II having the (*R*)-configuration at the chiral center marked with an *




(II)

Claim 3 (original): The salt of Claim 1 of structural formula III having the (*S*)-configuration at the chiral center marked with an *




(III)

Claim 4 (original): The salt of Claim 2 characterized in being a crystalline monohydrate.

Claim 5 (currently amended): The salt ~~monohydrate~~ of Claim 4 characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 7.42, 5.48, and 3.96 angstroms.

Claim 6 (currently amended): The salt ~~monohydrate~~ of Claim 5 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 6.30, 4.75, and 4.48 angstroms.

Claim 7 (currently amended): The salt ~~monohydrate~~ of Claim 6 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 5.85, 5.21, and 3.52 angstroms.

Claim 8 (currently amended): The salt ~~monohydrate~~ of Claim 7 further characterized by the X-ray powder diffraction pattern of FIG. 1.

Claim 9 (currently amended): The salt ~~monohydrate~~ of Claim 4 characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 169.1, 120.8, and 46.5 ppm.

Claim 10 (currently amended): The salt ~~monohydrate~~ of Claim 9 further characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 159.0, 150.9, and 40.7 ppm.

Claim 11 (currently amended): The salt ~~monohydrate~~ of Claim 10 further characterized by the solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum of FIG. 2.

Claim 12 (currently amended): The salt ~~monohydrate~~ of Claim 4 characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at -64.5, -114.7, -136.3, and -146.2 ppm.

Claim 13 (currently amended): The salt ~~monohydrate~~ of Claim 12 further characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at -96.5, -104.4, -106.3, and -154.5 ppm.

Claim 14 (currently amended): The salt ~~monohydrate~~ of Claim 13 further characterized by the solid-state fluorine-19 MAS nuclear magnetic resonance spectrum of FIG. 3.

Claim 15 (currently amended): The salt ~~monohydrate~~ of Claim 4 characterized by the thermogravimetric analysis curve of FIG. 4.

Claim 16 (currently amended): The salt ~~monohydrate~~ of Claim 4 characterized by the differential scanning calorimetric curve of FIG. 5.

Claim 17 (currently amended): A drug substance ~~The salt of Claim 4~~ comprising a detectable amount of the ~~said~~ crystalline monohydrate of Claim 4.

Claim 18 (currently amended): The drug substance ~~salt~~ of Claim ~~4~~ 17 comprising about 5% to about 100% by weight of said crystalline monohydrate.

Claim 19 (currently amended): The drug substance ~~salt~~ of Claim ~~4~~ 17 comprising about 10% to about 100% by weight of said crystalline monohydrate.

Claim 20 (currently amended): The drug substance ~~salt~~ of Claim 4 17 comprising about 25% to about 100% by weight of said crystalline monohydrate.

Claim 21 (currently amended): The drug substance ~~salt~~ of Claim 4 17 comprising about 50% to about 100% by weight of said crystalline monohydrate.

Claim 22 (currently amended): The drug substance ~~salt~~ of Claim 4 17 comprising about 75% to about 100% by weight of said crystalline monohydrate.

Claim 23 (currently amended): The drug substance ~~salt~~ of Claim 4 17 comprising substantially all by weight of said crystalline monohydrate.

Claim 24 (cancelled)

Claim 25 (currently amended): A pharmaceutical composition comprising a ~~prophylactically or~~ therapeutically effective amount of the salt according to Claim 2 ~~1 or a pharmaceutically acceptable solvate thereof~~ in association with one or more pharmaceutically acceptable carriers.

Claim 26 (currently amended): A pharmaceutical composition comprising a ~~prophylactically or~~ therapeutically effective amount of the salt according to Claim 4 ~~or a pharmaceutically acceptable solvate thereof~~ in association with one or more pharmaceutically acceptable carriers.

Claim 27 (currently amended): A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to Claim 2 ~~1~~ or a ~~pharmaceutically acceptable~~ hydrate thereof.

Claim 28 (original): A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to Claim 4.

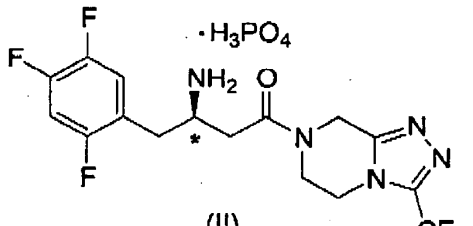
Claim 29 (currently amended): A process for preparing the salt of Claim 2 ~~1~~ comprising the step of contacting one equivalent of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine in an organic solvent or aqueous organic solvent with about a one equivalent of phosphoric acid at a temperature in the range of about 25-100°C.

Claim 30 (original): The process of Claim 29 wherein said organic solvent is a $C_1$-$C_5$ linear or branched alkanol.

Claims 31-33 (cancelled)

Claim 34 (currently amended): The phosphoric 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 prepared according to the process of Claim 29.

Claim 35 (currently amended): A process for preparing the crystalline monohydrate of Claim 4 comprising the steps of:
(a) crystallizing ~~said~~ the dihydrogenphosphate salt of ~~Claim 1~~ structural formula (II):




(II)

at 25 °C from a mixture of isopropanol and water, such that the water concentration is above 6.8 weight percent;
(b) recovering the resultant solid phase; and
(c) removing the solvent therefrom.

## REMARKS

The Office Action dated June 11, 2007, has been carefully considered. The Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks.

Claims 1-35 were pending in the application. Claims 29, 30, and 35 have been allowed. Claims 1-28 and 31-34 have been rejected. Claims 24 and 31-33 have been cancelled without prejudice. Claims 1, 5-23, 25-27, 29, 34, and 35 have been amended. Claims 1-23, 25-30, 34, and 35 remain pending following the above amendments. All amendments to the claims are fully supported by Applicants' description and therefore do not introduce new matter.

*Interview Summary*

A face-to-face interview at the request of Applicants' attorney Philippe L. Durette was held on July 24, 2007, at the U.S. Patent and Trademark Office in Alexandria, VA, with Examiners Ebenezer Sackey and Golam Shameem. Towards overcoming objections cited in the Office Action dated June 11, 2007, amendments to all pending claims proposed by Applicants' attorney were discussed in addition to proposed amendments to all pending claims in copending Applications Serial No. 10/569,566 and 10/570,409. No agreement was reached with respect to the claims. However, it was agreed that Applicants' attorney would present arguments to rebut the rejections of record in each of the cited applications. Additionally, it was agreed that diffractograms would be recited in pertinent claims to obviate the double patenting rejection of record.

*Claims 31 and 32 stand rejected under 35 U.S.C. § 101, as not being proper process claims.*

Claims 31 and 32 have been cancelled without prejudice. In light of this amendment, the Applicants respectfully request withdrawal of the section 101 rejection.

*Claims 25 and 26 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.*

Claims 25 and 26 have been amended to remove the objected-to "solvate" term and the term "prophylactically" from the claims. In light of this amendment, the Applicants respectfully request withdrawal of the section 112, first paragraph, rejection.

*Claims 17-24 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.*

Claim 24 has been cancelled. Claims 17-23 have been amended to recite "a drug substance" and not the objected-to "compound". Support for this amendment can be found on page 4, lines 10-26, of Applicants' description. In light of this amendment, the Applicants respectfully request withdrawal of the section 112, second paragraph, rejection.

*Claims 1-28 and 33-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 23-33, and 46-50 of copending Application No. 10/569,566.*

Claims 24 and 33 of the present application have been cancelled without prejudice. Claims 23-33 and 46-48 of copending Application No. 10/569,566 have been withdrawn subject to a restriction requirement in a separate reply to an Office Action for SN 10/569,566, dated July 11, 2007, being filed simultaneously with the US Patent Office with the present amendment by way of facsimile transmission to Examiner Ebenezer Sackey of Art Unit 1624. Claim 1 and dependent claims 49 and 50 of copending Application No. 10/569,566 have been amended to recite diffractograms to obviate the double patenting rejection of record. The Applicants maintain that dihydrogenphosphate salt and the crystalline monohydrate form of the present application do not suggest the crystalline anhydrate pseudopolymorph of copending Application No. 10/569,566.

Therefore, the Applicants maintain that the monohydrate form of the present application is patentably distinct from the anhydrate form of amended Claims 1, 49, and 50

of copending Application No. 10/569,566, and they respectfully request withdrawal of the double patenting rejection.

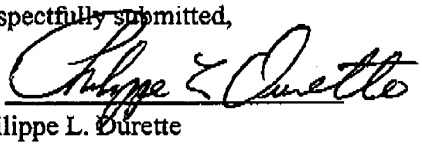
*Claims 1-28 and 33-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 and 12-15 of copending Application No. 10/570,409.*

Claims 24 and 33 of the present application have been cancelled without prejudice. Claims 12 and 13 of copending Application No. 10/570,409 have been cancelled without prejudice in a separate reply to an Office Action for SN 10/570,409, dated June 21, 2007, being filed simultaneously with the US Patent Office with the present amendment by way of facsimile transmission with Examiner Ebenezer Sackey of Art Unit 1624. Claim 1 and dependent claims 14 and 15 of copending Application No. 10/570,409 have been amended to recite diffractograms to obviate the double patenting rejection of record. The Applicants maintain that dihydrogenphosphate salt and its crystalline monohydrate form of the present application do not suggest the crystalline anhydrate pseudopolymorph of copending Application No. 10/570,409. Therefore, the Applicants maintain that the monohydrate form of the present application is patentably distinct from the anhydrate form of amended Claims 1, 14, and 15 of copending Application No. 10/570,409, and they respectfully request withdrawal of the double patenting rejection.

Serial No.: 10/874,992
Case No.: 21409Y
Page No.: 10

The Applicants believe that all of the objections have been overcome by amendment, and they therefore earnestly solicit an early Notice of Allowance.

Respectfully submitted,

By 

Philippe L. Durette
Reg. No. 35,125
Attorney for Applicants
Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-4568

Date: August 6, 2007

PTO/SB/06 (06-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 10/874,992

## CLAIMS AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE | SMALL ENTITY FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY FEE |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a)) | | | | | OR | | 770 |
| TOTAL CLAIMS (37 CFR 1.16(c)) | 35 minus 20 = | * 15 | X $ = | | OR | X $ 18 = | 270 |
| INDEPENDENT CLAIMS (37 CFR 1.16(b)) | 2 minus 3 = | * 0 | X $ = | | OR | X $ = | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(d)) | | | + $ = | | OR | + $ = | |
| | | | TOTAL | | OR | TOTAL | 1040 |

* If the difference in column 1 is less than zero, enter "0" in column 2.

## CLAIMS AS AMENDED – PART II

AMENDMENT A — 8/6/7

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total (37 CFR 1.16(c)) | 37 | Minus | ** 35 | = 2 |
| Independent (37 CFR 1.16(b)) | 1 | Minus | *** 3 | = 0 |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | |

| SMALL ENTITY RATE | SMALL ENTITY ADDITIONAL FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY ADDITIONAL FEE |
|---|---|---|---|---|
| X $ = | | OR | X $ = | |
| X $ = | | OR | X $ = | |
| + $ = | | OR | + $ = | |
| TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

AMENDMENT B

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total (37 CFR 1.16(c)) | | Minus | ** | = |
| Independent (37 CFR 1.16(b)) | | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | |

| RATE | ADDITIONAL FEE | OR | RATE | ADDITIONAL FEE |
|---|---|---|---|---|
| X $ = | | OR | X $ = | |
| X $ = | | OR | X $ = | |
| + $ = | | OR | + $ = | |
| TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

AMENDMENT C

| | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA |
|---|---|---|---|---|
| Total (37 CFR 1.16(c)) | | Minus | ** | = |
| Independent (37 CFR 1.16(b)) | | Minus | *** | = |
| FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d)) | | | | |

| RATE | ADDITIONAL FEE | OR | RATE | ADDITIONAL FEE |
|---|---|---|---|---|
| X $ = | | OR | X $ = | |
| X $ = | | OR | X $ = | |
| + $ = | | OR | + $ = | |
| TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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# NOTICE OF ALLOWANCE AND FEE(S) DUE

210 7590 11/05/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

| EXAMINER | |
|---|---|
| SACKEY, EBENEZER O | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

DATE MAILED: 11/05/2007

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y | 9276 |

TITLE OF INVENTION: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1440 | $300 | $0 | $1740 | 02/05/2008 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**



PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

## PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**
**or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

210 7590 11/05/2007

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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y | 9276 |

TITLE OF INVENTION: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1440 | $300 | $0 | $1740 | 02/05/2008 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| SACKEY, EBENEZER O | 1624 | 514-249000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y | 9276 |

210 7590 11/05/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

| EXAMINER | |
|---|---|
| SACKEY, EBENEZER O | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

DATE MAILED: 11/05/2007

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 657 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 657 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.



PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/874,992 | CYPES ET AL. | |
| | Examiner | Art Unit | |
| | EBENEZER SACKEY | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *amendment filed on 08/06/07*.

2. ☒ The allowed claim(s) is/are *claims 1-16, 25-30 and 34-25 now claims 1-24 respectively*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 06/27/07
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

**EXAMINER'S AMENDMENT**

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Philippe Durette on 10/18/07.

The application has been amended as follows:

**IN THE CLAIMS:**

Claims 17-23 have been cancelled. Applicants reserve the right to file one or more divisional applications drawn to the cancelled subject matter.

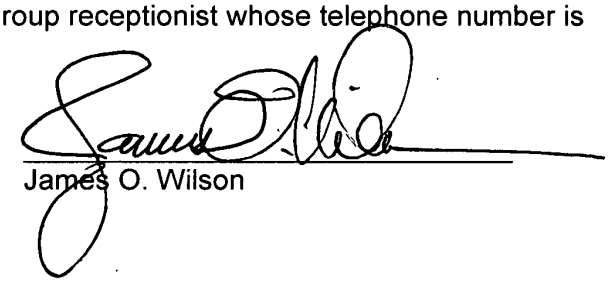
---

Any inquiry concerning this communication or earlier communications from the examiner should be directed to E. Sackey whose telephone number is (571) 272-0704. The examiner can normally be reached on Monday-Friday from 7:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached on (571) 272-0661. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

EOS
October 24, 2007



James O. Wilson

Supervisory Patent Examiner
Art Unit 1624, Group 1600
Technology Center 1

Approved for use through 09/30/2006. OMB 0651-0031
SUBSTITUTE for PTO/SB/08A (07-06). Information Disclosure Statement by Applicant
Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)



Sheet 1 of 1

| COMPLETE IF KNOWN | |
|---|---|
| Application Number | 10/874,992 |
| Filing Date | June 23, 2004 |
| First Named Inventor | Stephen Howard Cypes, et al. |
| Group Art Unit | 1624 |
| Examiner Name | Ebenezer Sackey |
| Attorney Docket Number | 21409Y |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. | U.S. Patent Document Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No. | Foreign Patent Document Office | Number | Kind Code (if known) | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|---|
| ES | 1 | PCT | WO 2005/072530 A1 | | Merck & Co., Inc. | 08/11/2005 |
| ES | 2 | PCT | WO 2006/033848 A1 | | Merck & Co., Inc. | 03/30/2006 |
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| | | | | | | |

| Examiner Signature | Monah Sackey | Date Considered | 10/24/07 |
|---|---|---|---|

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

SEND TO: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450. Computer generated form "IDS Form" (IDS Folder), Merck & Co., Inc., 8/24/2006

| Issue Classification | Application/Control No. | Applicant(s)/Patent under Reexamination | |
|---|---|---|---|
| | 10/874,992 | CYPES ET AL. | |
| | Examiner | Art Unit | |
| | EBENEZER SACKEY | 1624 | |

# ISSUE CLASSIFICATION

| ORIGINAL | | | | | CROSS REFERENCE(S) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CLASS | | | | SUBCLASS | CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | | |
| 514 | | | | 249 | 544 | 350 | | | | | |
| INTERNATIONAL CLASSIFICATION | | | | | | | | | | | |
| A | 6 | 1 | K | 31/495 | | | | | | | |
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EBENEZER SACKEY 10/24/07
(Assistant Examiner) (Date)

10/31/07
(Legal Instruments Examiner) (Date)

JAMES O. WILSON
(Primary Examiner) (Date)

**Total Claims Allowed: 24**

| O.G. Print Claim(s) | O.G. Print Fig. |
|---|---|
| 1 | NONE |

☐ **Claims renumbered in the same order as presented by applicant** ☐ CPA ☐ T.D. ☐ R.1.47

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
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| 1 | 1 | | 31 | | 61 | | 91 | | 121 | | 151 | | 181 |
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| 7 | 7 | | 37 | | 67 | | 97 | | 127 | | 157 | | 187 |
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| 21 | 29 | | 59 | | 89 | | 119 | | 149 | | 179 | | 209 |
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www.uspto.gov

Bib Data Sheet

**CONFIRMATION NO. 9276**

| SERIAL NUMBER | FILING OR 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004<br>RULE | 514 | 1626 | 21409Y |

**APPLICANTS**

Stephen Howard Cypes, Santa Clara, CA;
Alex Minhua Chen, Metuchen, NJ;
Russell R. Ferlita, Westfield, NJ;
Karl Hansen, Atlantic Highlands, NJ;
Ivan Lee, Piscataway, NJ;
Vicky K. Vydra, Fair Lawn, NJ;
Robert M. Wenslow JR., East Windsor, NJ;

** CONTINUING DATA **********

This appln claims benefit of 60/482,161 06/24/2003

** FOREIGN APPLICATIONS **********

**IF REQUIRED, FOREIGN FILING LICENSE GRANTED**
** 09/15/2004

| Foreign Priority claimed | STATE OR COUNTRY | SHEETS DRAWING | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|
| ☐ yes ☒ no<br>35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance<br>Verified and Acknowledged Examiner's Signature Initials | CA | 5 | 35 | 2 |

**ADDRESS**
210

**TITLE**

Phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor

| FILING FEE RECEIVED | |
|---|---|
| 1040 | FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following: |

☐ All Fees
☐ 1.16 Fees ( Filing )
☐ 1.17 Fees ( Processing Ext. of time )
☐ 1.18 Fees ( Issue )
☐ Other _____
☐ Credit

## Index of Claims

| Application/Control No. | Applicant(s)/Patent under Reexamination |
|---|---|
| 10/874,992 | CYPES ET AL. |
| **Examiner** | **Art Unit** |
| EBENEZER SACKEY | 1624 |

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| Search Notes | Application/Control No. | Applicant(s)/Patent under Reexamination |
|---|---|---|
| | 10/874,992 | CYPES ET AL. |
| | Examiner | Art Unit |
| | EBENEZER SACKEY | 1624 |

| SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 514 | 249 | 5/29/2007 | ES |
| 544 | 350 | 5/29/2007 | ES |
| updated | | 10/24/07 | ES |
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| SEARCH NOTES (INCLUDING SEARCH STRATEGY) | | |
|---|---|---|
| | DATE | EXMR |
| Cas online search for structural formula (I), Inventors name searched | 5/29/2007 | ES |
| updated | 10/24/07 | ES |
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U.S. Patent and Trademark Office

Part of Paper No. 20070529

| Search Notes | Application/Control No. | Applicant(s)/Patent under Reexamination |
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| | 10/874,992 | CYPES ET AL. |
| | Examiner | Art Unit |
| | EBENEZER SACKEY | 1624 |

| SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 514 | 249 | 5/29/2007 | ES |
| 544 | 350 | 5/29/2007 | ES |
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| SEARCH NOTES (INCLUDING SEARCH STRATEGY) | | |
|---|---|---|
| | DATE | EXMR |
| Cas online search for structural formula (I), Inventors name searched | 5/29/2007 | ES |
| updated | 10/24/07 | ES |
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## PART B - FEE(S) TRANSMITTAL



**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**
**or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

210 7590 11/05/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

12/14/2007 TNGUYEN3 00000001 132755 10874992

01 FC:1501 1440.00 DA
02 FC:1504 300.00 DA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| | |
|---|---|
| Pamela Spalding | (Depositor's name) |
| Pamela Spalding | (Signature) |
| December 11, 2007 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 06/23/2004 | Stephen Howard Cypes | 21409Y | 9276 |

TITLE OF INVENTION: PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1440 | $300 | $0 | $1740 | 02/05/2008 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| SACKEY, EBENEZER O | 1624 | 514-249000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Philippe L. Durette
2 Catherine D. Fitch
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Merck & Co., Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Rahway, New Jersey USA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☐ Issue Fee
☑ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 13-2755 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Philippe L. Durette Date December 11, 2007

Typed or printed name Philippe L. Durette Registration No. 35,125

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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www.uspto.gov

| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/874,992 | 02/05/2008 | 7326708 | 21409Y | 9276 |

210 7590 01/16/2008

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 657 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Stephen Howard Cypes, Santa Clara, CA;
Alex Minhua Chen, Metuchen, NJ;
Russell R. Ferlita, Westfield, NJ;
Karl Hansen, Atlantic Highlands, NJ;
Ivan Lee, Piscataway, NJ;
Vicky K. Vydra, Fair Lawn, NJ;
Robert M. Wenslow JR., East Windsor, NJ;

IR103 (Rev. 11/05)

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

| | |
|---|---|
| MERCK SHARP & DOHME CORP.<br>126 East Lincoln Avenue<br>Rahway, New Jersey 07065<br><br>Plaintiff,<br>v.<br><br>HON. DAVID KAPPOS<br>Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office<br>Office of General Counsel<br>United States Patent and Trademark Office<br>P.O. Box 15667, Arlington, VA 22215<br>Madison Building East, Rm. 10B20<br>600 Dulaney Street, Alexandria, VA 22314<br><br>Defendant. | Civil Action No._____<br><br>Case: 1:10-cv-01110<br>Assigned To : Friedman, Paul L.<br>Assign. Date : 6/30/2010<br>Description: General Civil |

## COMPLAINT

Plaintiff Merck Sharp & Dohme Corp. ("Merck") for its complaint against the Honorable David Kappos, states as follows:

## NATURE OF THE ACTION

1. This is an action by the assignee of United States Patent No. 7,326,708 ("the '708 Patent," attached as the Exhibit) seeking judgment, pursuant to 35 U.S.C. § 154(b)(4)(A), that the patent term adjustment for the '708 patent be changed from 657 days to 883 days in view of this Court's decision in *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008) as set forth below.

2. This action arises under 35 U.S.C. § 154 and the Administrative Procedures Act, 5 U.S.C. §§ 701-706.

## JURISDICTION AND VENUE

3. This Court has jurisdiction to hear this action and is authorized to issue the relief sought pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1361, 35 U.S.C. § 154(b) and 5 U.S.C. §§ 701-706.

4. Venue is proper in this district by virtue of 35 U.S.C. § 154(b)(4)(A).

5. This Complaint is timely filed in accordance with 28 U.S.C. § 2401 and 35 U.S.C. § 154(b)(4)(A) by application of the doctrine of equitable tolling.

## THE PARTIES

6. Plaintiff Merck Sharp & Dohme Corp. is a corporation organized under the laws of New Jersey, having a principal place of business at 126 East Lincoln Avenue, Rahway, New Jersey, NJ 07065.

7. Defendant David Kappos is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office ("PTO" or "Agency"), acting in his official capacity. The Director is the head of the Agency, charged by statute with providing management supervision for the PTO and for the issuance of patents. The Director is the official responsible for determining the period of patent term adjustment under 35 U.S.C. § 154.

## BACKGROUND

8. Stephen Howard Cypes, Alex Minhua Chen, Russell R. Ferlita, Karl Hansen, Ivan Lee, Vicky K. Vydra, and Robert M. Wenslow, Jr. are the co-inventors of the invention claimed in U.S. patent application number 10/874,992 ("the '992 application") entitled

"Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor," which issued as the '708 patent on February 5, 2008. The '708 patent is directed to the dihydrogenphosphate salt of a specified amine - or a hydrate thereof - which is a potent inhibitor of dipeptidyl peptidase -IV. As such, the invention is an important tool in the medical treatment or prevention of Type 2 diabetes, obesity, and high blood pressure.

9. Plaintiff Merck Sharp & Dohme Corp. is the assignee of the '708 Patent, as evidenced by the assignment document recorded at Reel 023861, Frame 0910 in the PTO.

10. Section 154 of title 35 of the United States Code requires that the Director of the PTO grant a patent term adjustment in accordance with the provisions of Section 154(b). Specifically, 35 U.S.C. § 154(b)(3)(D) states that "[t]he Director shall proceed to grant the patent after completion of the Director's determination of a patent term adjustment under the procedures established under this subsection, notwithstanding any appeal taken by the applicant of such determination."

11. In determining patent term adjustment, the Director is required to extend the term of a patent for a period equal to the total number of days attributable to delay by the PTO under 35 U.S.C. § 154(b)(1), as limited by any overlapping periods of delay by the PTO as specified under 35 U.S.C. § 154(b)(2)(A), any disclaimer of patent term by the applicant under 35 U.S.C. § 154(b)(2)(B), and any delay attributable to the applicant under 35 U.S.C. § 154(b)(2)(C).

12. The Director made a determination of patent term adjustment pursuant to 35 U.S.C. § 154(b)(3) and issued the '708 patent reflecting that determination.

13. 35 U.S.C. § 154(b)(4)(A) provides that "[a]n applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after grant of the patent. Chapter 7 of title 5 shall apply to such an action."

## CLAIM FOR RELIEF

### Count I

14. The allegations of paragraphs 1-13 are incorporated in this claim for relief as if fully set forth.

15. The patent term adjustment for the '708 Patent, as determined by the Director under 35 U.S.C. § 154(b) and indicated on the face of the '708 Patent, is 657 days. (*See* Ex. at 1). The determination of this 657 day patent term adjustment is in error because the PTO failed to properly account for the delays that occurred after the date that was three years after the actual filing date of the '992 application, pursuant to 35 U.S.C. § 154(b)(1)(B). The correct patent term adjustment for the '708 Patent is 883 days.

16. The '992 Patent application was filed June 23, 2004, and claims the benefit of priority of U.S. provisional application number 60/482,161, filed June 24, 2003. The '992 application issued as the '708 Patent on February 5, 2008.

17. Under 35 U.S.C. § 154(b)(1)(A), the total number of days attributable to PTO examination delay ("A Delay") is 657 days. The PTO was due to issue a first action on the merits on or before August 24, 2005, the date that is fourteen months after the date on which the '992 application was filed (June 23, 2004). However, the PTO did not mail the first action on the merits pursuant to 35 U.S.C. § 132 until June 11, 2007. Accordingly, 657 days of term credit

are due to compensate for the PTO's failure to issue an Office Action no later than 14 months after the filing date of the '708 Patent. Thus, **657 days** of term adjustment are required to compensate for the **A Delay** attributable to PTO examination inaction. The PTO granted this A Delay term adjustment, as indicated on the face of the '708 Patent.

18. Under 35 U.S.C. § 154(b)(1)(B), the number of days attributable to PTO's failure to issue the '708 Patent within three (3) years of application pendency ("B Delay") is 226 days. This figure is calculated as the number of days between the date that was three years after the date on which the '992 application was filed (*i.e.*, June 23, 2004) and the date that the '708 Patent was issued (*i.e.*, February 5, 2008). The period beginning on June 24, 2007 (the day after the date that is three years after June 23, 2004) and ending on February 5, 2008, totals **226 days** of **B Delay**.

19. Under 35 U.S.C. § 154(b)(2)(C), the number of days of patent term adjustment is limited by the number of days that an Applicant failed to engaged in reasonable efforts to conclude prosecution on the merits. Here, the Applicant was diligent during the prosecution of the '992 application, and therefore there are no days of **Applicant Delay**.

20. 35 U.S.C. § 154(b)(2)(A) provides that "to the extent that periods of delay attributable to grounds specified in paragraph [b](1) overlap, the period of any adjustment ... shall not exceed the actual number of days the issuance of the patent was delayed." The A Delay accumulated as follows:

August 24, 2005 to June 11, 2007: 657 days

The B Delay accumulated as follows:

June 24, 2007 to February 5, 2008: 226 days

As evidenced above, the period of A Delay and the period of B Delay do not **overlap** (*i.e.* occur on the same calendar day). Thus, the **overlap** calculus is **0 days**.

21. The '708 patent is not subject to a disclaimer of term.

22. Accordingly, the correct patent term adjustment under 35 U.S.C. § 154(b)(1) and § 154(b)(2) is the sum of the A Delay and B Delay (883 days) reduced by the number of days of overlap (0 days), further reduced by the period of Applicant Delay (0 days), for a net patent term adjustment of **883 days**.

23. The Director erred in the determination of patent term adjustment by treating the entire period of PTO examination delay — instead of ***only*** any period of PTO examination delay that occurred after the date that was three years after the actual filing date of the '992 application — as the period of overlap between the A Delay and the B Delay. Thus, the Director erroneously determined that the net patent term adjustment should be limited under 35 U.S.C. § 154(b)(2)(A) by 226 days, rather than correctly determining that there were no concurrent calendar days of overlap under 35 U.S.C. § 154(b)(2)(A), and arrived at an incorrect net patent term adjustment of 657 days.

24. In *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008), this Court explained the proper construction of the provisions of 35 U.S.C. § 154(b) for determining patent term adjustment. The *Wyeth* Court held that the Director has incorrectly applied the statute by 1) treating the period of B Delay, for the purposes of overlap calculations, as commencing upon the filing date, as opposed to calculating the B Delay only after the PTO has failed to issue a patent

within three years of filing, and 2) only allowing patentees the longer of an A Delay or a B Delay, but not both. This construction by the District Court was recently upheld on appeal by the United States Court of Appeals for the Federal Circuit ("Federal Circuit"). *Wyeth v. Kappos*, No. 2009-1120 (Fed. Cir. Jan. 7, 2010). In accordance with *Wyeth*, the patent term adjustment for the '708 Patent is properly determined to be 883 days, as explained above.

25. On information and belief, prior to the issuance of the Federal Circuit's decision in *Wyeth*, the Director declined to calculate the patent term adjustment figure in the manner set forth *supra*. Over a period of years, the PTO steadfastly adhered to its interpretation that Applicants were only entitled under the statute to the longer of either an A Delay or a B Delay period. Merck was induced by the PTO's conduct and pronouncements into believing that the law did not permit it to obtain additional patent term for both an A Delay and a B Delay, and relied to its detriment on the PTO's representations that any attempt at further recalculation would be futile. The Federal Circuit's contrary determination in *Wyeth* - and the PTO's election not to appeal this decision to the United States Supreme Court - resulted in a recent change of law governing the adjustment of patent term under 35 U.S.C. § 154. This change of law constitutes an extraordinary circumstance triggering the application of the doctrine of equitable tolling to the filing of this Complaint.

**Count II**

26. Merck realleges paragraphs 1-25 as if fully set forth herein.

27. As explained in Count I, the PTO erred in its determination of the patent term adjustment due the '708 Patent when it failed to include in its calculus the period of time lost during the Agency's delay in issuing the '708 Patent, *i.e.*, the B Delay. *See* ¶ 18, *supra*. The B

Delay constitutes the period that elapsed as of the day after the date that is three years after the filing date of the '708 Patent and running to the patent's issue date. *Id.* Because the B Delay captures time up to issuance, the Notice of Allowance mailed for the '992 application did not - and could not - recite the patent term adjustment due in view of the B Delay period.

28. The procedures for patent term adjustment determination are set forth in 35 U.S.C. § 154(b)(3)(B). The statute requires the PTO to identify to the Applicant any period of patent term adjustment at the time the Notice of Allowance is mailed, and affords Applicant one opportunity to request reconsideration by the PTO of the period of any patent term adjustment so identified. The statute also provides that "[a]n Applicant dissatisfied with a determination made by the Director under paragraph (3) shall have a remedy at civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after the grant of the patent." 35 U.S.C. § 154(b)(4)(A). Paragraph (3) of the statute speaks to delays identifiable at the time the Notice of Allowance is mailed.

29. On information and belief, Merck pleads that in the absence of equitable tolling, this Complaint is timely filed because at issue is the omission of a B Delay from the Director's patent term adjustment determination, which is not subject to the 180 day post-grant filing limitation of 35 U.S.C. § 154(b)(4)(A).

30. The Director's determination that the '708 Patent is entitled to only 657 days of patent term adjustment is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law by, *inter alia,* violating the Administrative Procedures Act, or is in excess of statutory jurisdiction, authority, or limitation. No public harm arises from the timing of the filing of this Complaint. Merck, acting with clean hands, timely acted after monitoring the

progress of the *Wyeth* case through the PTO's decision not to seek further review by the United States Supreme Court and the Federal Circuit's mandating of the case. Furthermore, the filing of this Complaint results in no immediate prejudice to third parties, as the additional period sought will not take effect until the end of the existing term of the '708 Patent - which is currently over 15 years.

## PRAYER FOR RELIEF

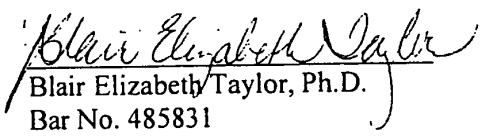
Wherefore, Merck demands judgment against Defendant and respectfully requests that this Court enter Orders:

A. Changing the period of patent term adjustment for the '708 Patent term from 657 days to 883 days and requiring the Director to extend the term of the '708 Patent to reflect the 883 day patent term adjustment.

B. Granting such other and future relief as the nature of the case may admit or require and as may be just and equitable.

Dated: June 30, 2010

Respectfully submitted,



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# EXHIBIT

US007326708B2

(12) **United States Patent**
**Cypes et al.**

(10) **Patent No.: US 7,326,708 B2**
(45) **Date of Patent: Feb. 5, 2008**

(54) **PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR**

(75) Inventors: **Stephen Howard Cypes**, Santa Clara, CA (US); **Alex Minhua Chen**, Metuchen, NJ (US); **Russell R. Ferlita**, Westfield, NJ (US); **Karl Hansen**, Atlantic Highlands, NJ (US); **Ivan Lee**, Piscataway, NJ (US); **Vicky K. Vydra**, Fair Lawn, NJ (US); **Robert M. Wenslow, Jr.**, East Windsor, NJ (US)

(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 657 days.

(21) Appl. No.: **10/874,992**

(22) Filed: **Jun. 23, 2004**

(65) **Prior Publication Data**

US 2005/0032804 A1 Feb. 10, 2005

**Related U.S. Application Data**

(60) Provisional application No. 60/482,161, filed on Jun. 24, 2003.

(51) **Int. Cl.**
*A61K 31/495* (2006.01)
*C07D 471/04* (2006.01)

(52) **U.S. Cl.** ..... 514/249; 544/350

(58) **Field of Classification Search** ..... 514/249; 544/350

See application file for complete search history.

(56) **References Cited**

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Database Prous DDR Online—Database Accession No. 2003: 3561.

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*Primary Examiner*—James O. Wilson
*Assistant Examiner*—Ebenezer Sackey
(74) *Attorney, Agent, or Firm*—Philippe L. Durette; Catherine D. Fitch

(57) **ABSTRACT**

The dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine is a potent inhibitor of dipeptidyl peptidase-IV and is useful for the prevention and/or treatment of non-insulin dependent diabetes mellitus, also referred to as type 2 diabetes. The invention also relates to a crystalline monohydrate of the dihydrogenphosphate salt as well as a process for its preparation, pharmaceutical compositions containing this novel form and methods of use for the treatment of diabetes, obesity, and high blood pressure.

**24 Claims, 5 Drawing Sheets**

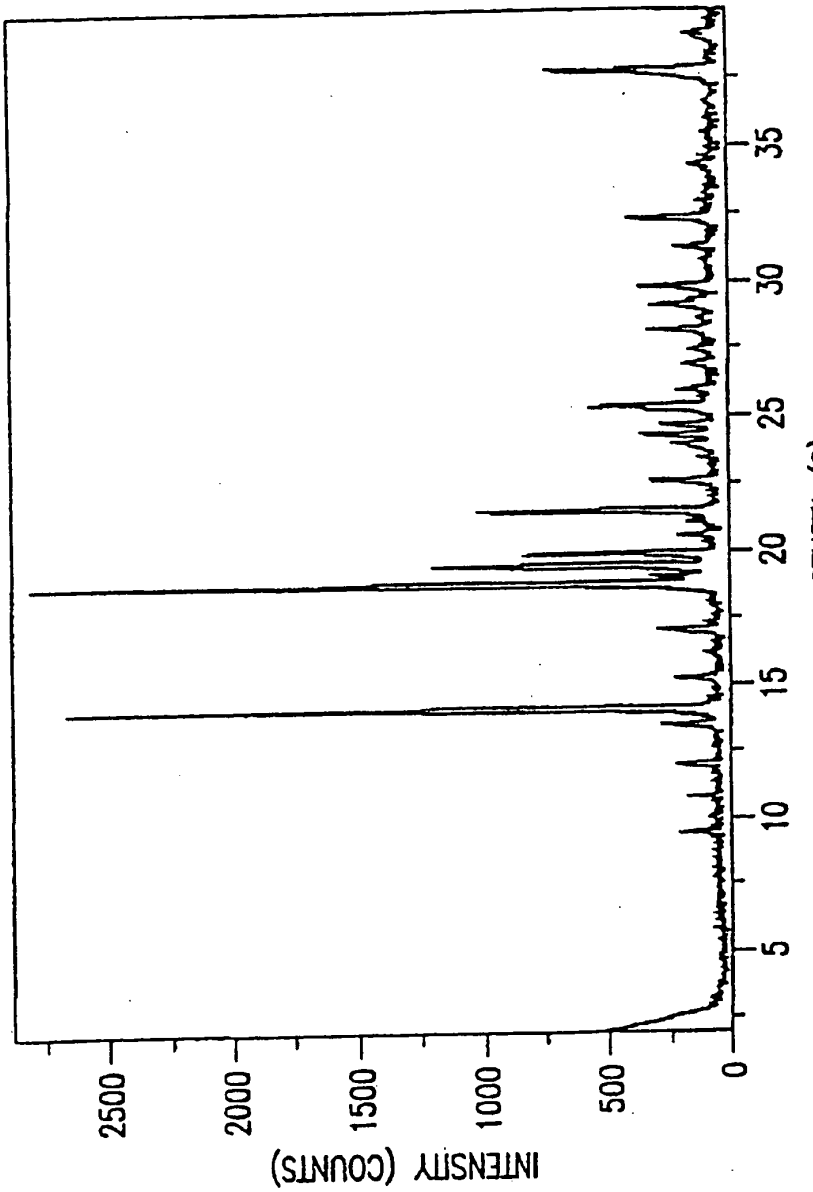



FIG. 1

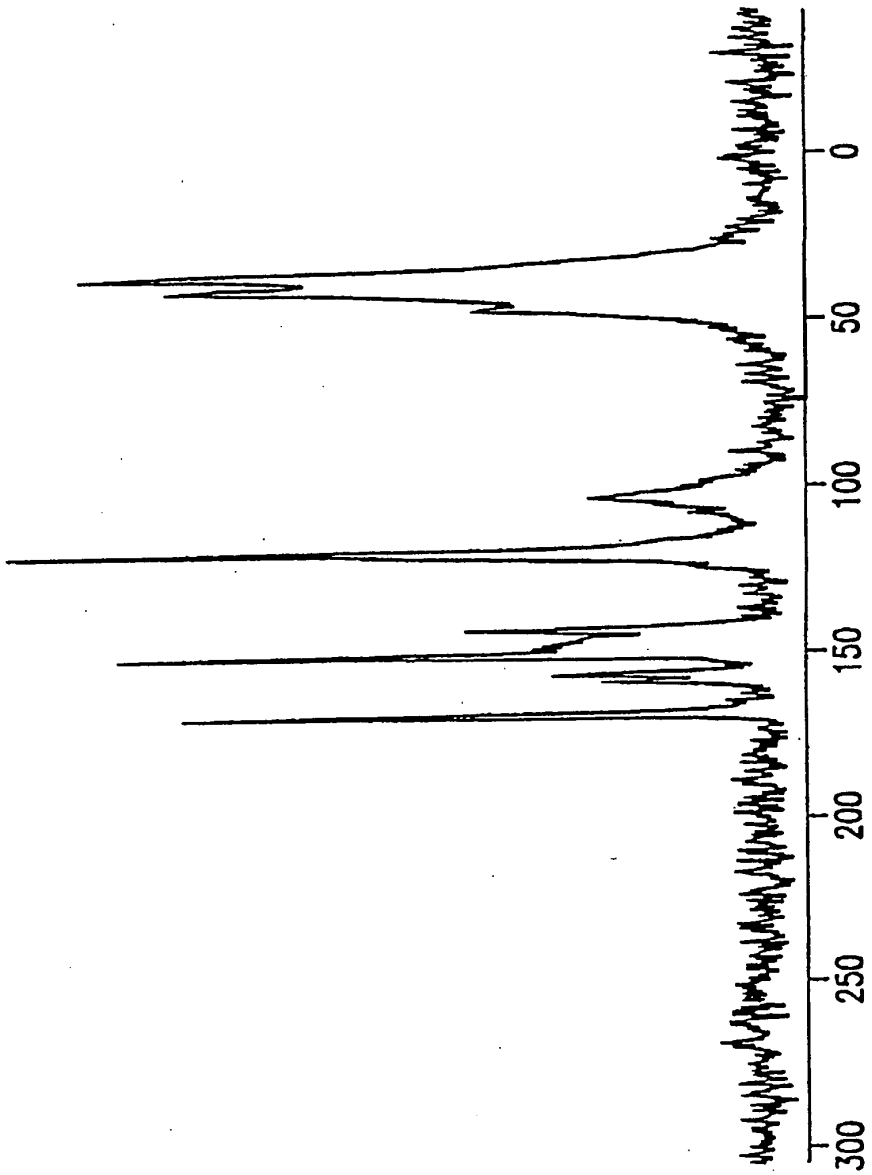



FIG.2

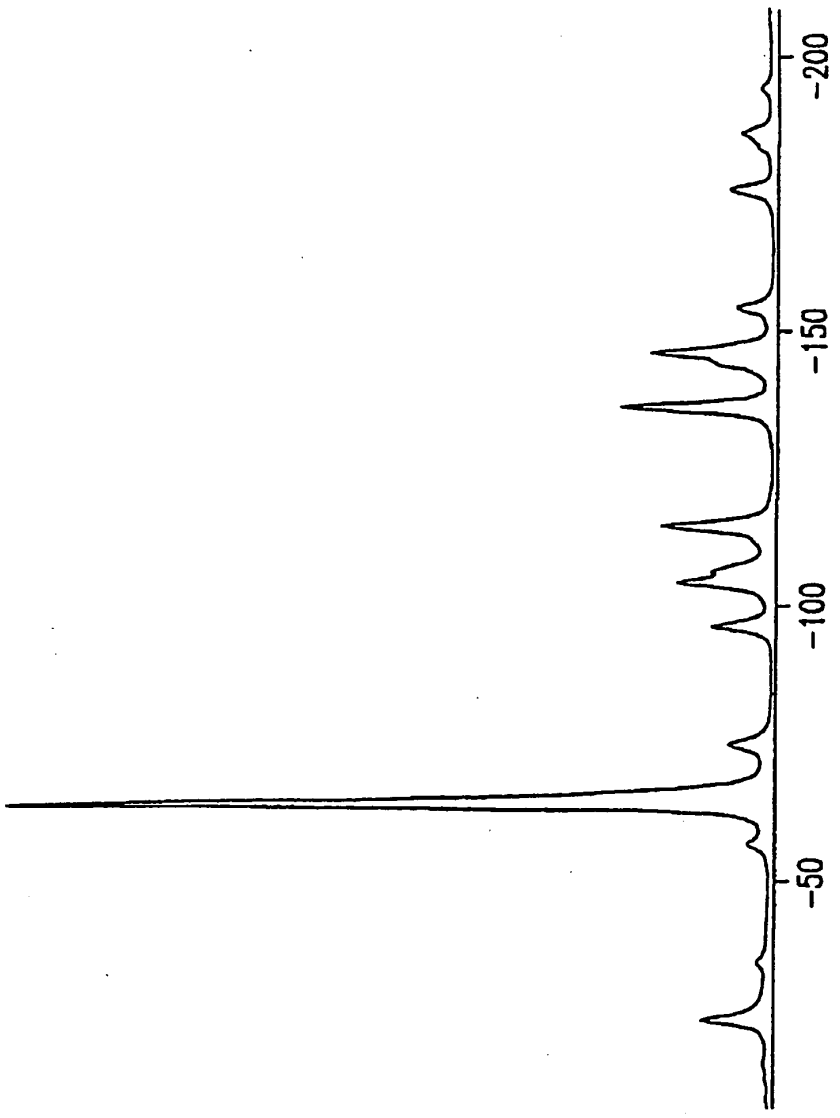



FIG.3

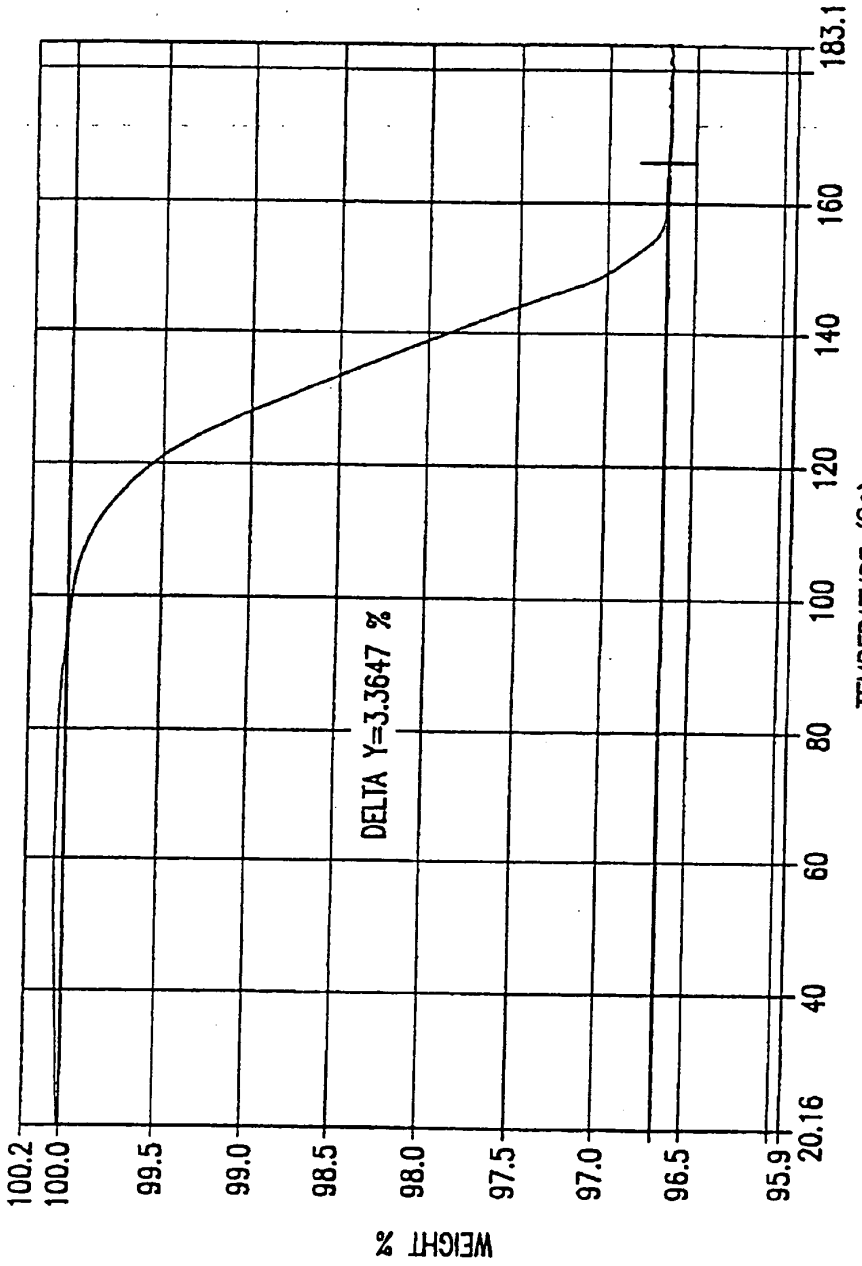



FIG. 4

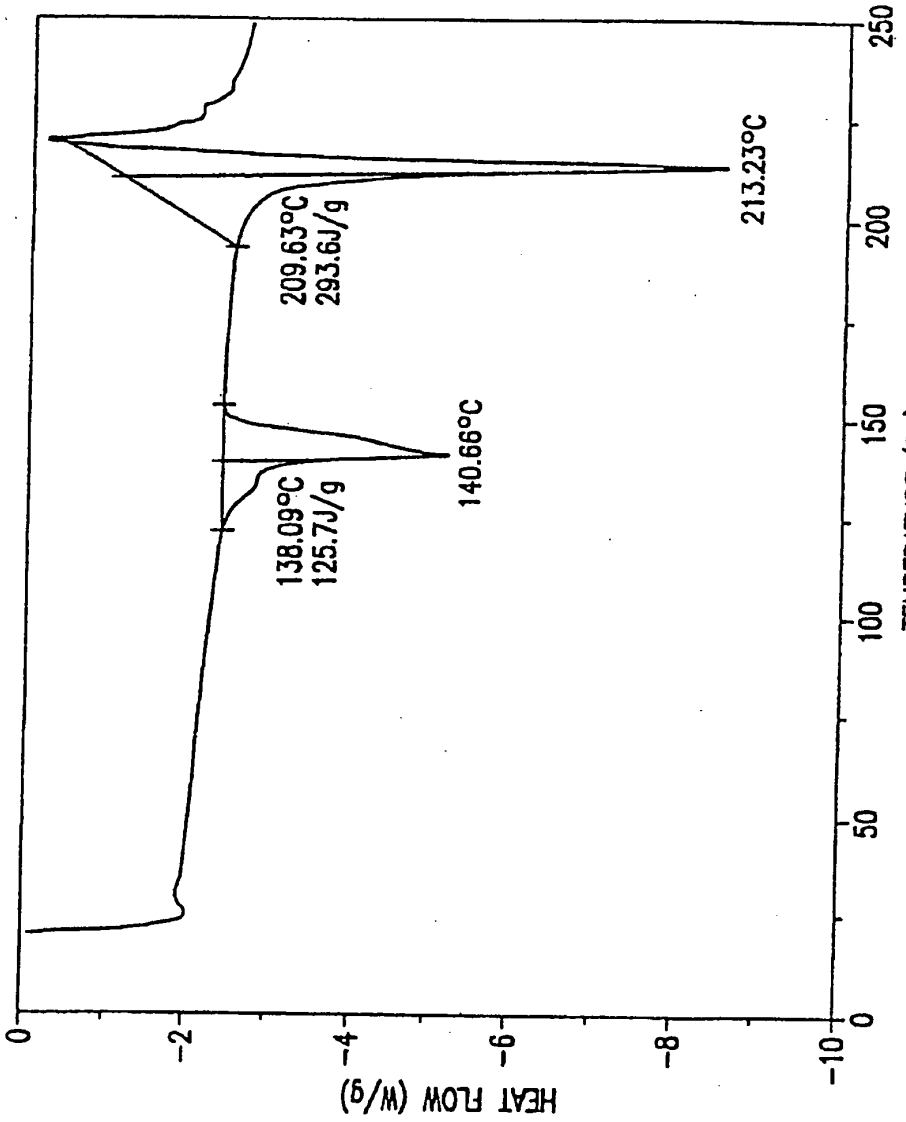



FIG.5

# PHOSPHORIC ACID SALT OF A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

## CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional application Ser. No. 60/482,161, filed Jun. 24, 2003, the contents of which are hereby incorporated by reference.

## FIELD OF THE INVENTION

The present invention relates to a particular salt of a dipeptidyl peptidase-IV inhibitor. More particularly, the invention relates to a dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a] pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, which is a potent inhibitor of dipeptidyl peptidase-IV. This novel salt and crystalline 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 dihydrogenphosphate salt and crystalline hydrates thereof useful to treat Type 2 diabetes, obesity, and high blood pressure as well as processes for preparing the dihydrogenphosphate salt and crystalline hydrates thereof and their pharmaceutical compositions.

## 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 Jan. 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(8H)-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.

However, there is no specific disclosure in the above reference of the newly discovered monobasic dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I below.

## SUMMARY OF THE INVENTION

The present invention is concerned with a novel dihydrogenphosphate salt 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(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine and crystalline hydrates thereof, in particular a crystalline monohydrate. The dihydrogenphosphate salt and crystalline 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(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, such as ease of processing, handling, and dosing. In particular, they exhibit improved physical and chemical stability, such as stability to stress, high temperatures and humidity, as well as improved physicochemical properties, such as solubility 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 salt and hydrates 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 characteristic X-ray diffraction pattern of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

FIG. **2** is a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

FIG. **3** is a fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectrum of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

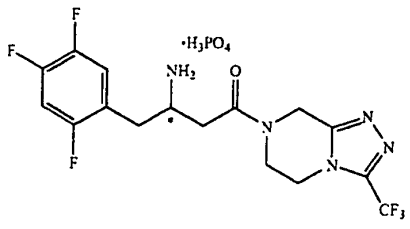
FIG. **4** is a typical thermogravimetric analysis (TGA) curve of the crystalline monohydrate dihydrogenphosphate salt of structural formula II.

FIG. **5** is a typical differential scanning calorimetry (DSC) curve of the crystalline monohydrate of the dihydrogenphosphate salt of structural formula II.

## DETAILED DESCRIPTION OF THE INVENTION

This invention provides a new monobasic dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1 ,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine of the following structural formula I:

(I)



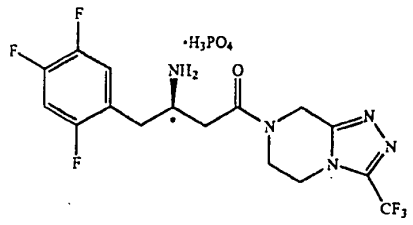

or a crystalline hydrate thereof. In particular, the instant invention provides a crystalline monohydrate of the dihydrogenphosphate salt of formula I.

The dihydrogenphosphate salt 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 the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-triflorophenyl) butan-2-amine of structural formula II:

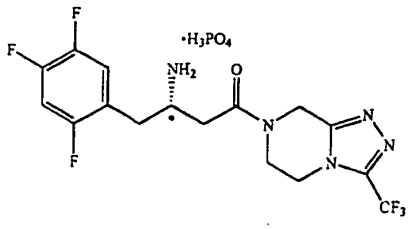
(II)



or a crystalline hydrate thereof.

A second embodiment of the present invention provides the dihydrogenphosphate salt of (2S)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine of structural formula III:

(III)



or a crystalline hydrate thereof.

More specifically, the dihydrogenphosphate salt of the present invention is comprised of one molar equivalent of mono-protonated 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine cation and one molar equivalent of dihydrogenphosphate (biphosphate) anion.

In a further embodiment of the present invention, the dihydrogenphosphate salt of structural formulae I-III is a crystalline hydrate. In one class of this embodiment, the crystalline hydrate is a crystalline monohydrate.

A further embodiment of the present invention provides the dihydrogenphosphate salt drug substance of structural formulae I-III that comprises the crystalline monohydrate present in a detectable amount. By "drug substance" is meant the active pharmaceutical ingredient ("API"). The amount of crystalline monohydrate in the drug substance can be quantified by the use of physical methods such as X-ray powder diffraction, solid-state fluorine-19 magic-angle spinning (MAS) nuclear magnetic resonance spectroscopy, solid-state carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance spectroscopy, solid state Fourier-transform infrared spectroscopy, and Raman spectroscopy. In a class of this embodiment, about 5% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a second class of this embodiment, about 10% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a third class of this embodiment, about 25% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a fourth class of this embodiment, about 50% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a fifth class of this embodiment, about 75% to about 100% by weight of the crystalline monohydrate is present in the drug substance. In a sixth class of this embodiment, substantially all of the dihydrogenphosphate salt drug substance is the crystalline monohydrate of the present invention, i.e., the dihydrogenphosphate salt drug substance is substantially phase pure monohydrate.

The crystalline dihydrogenphosphate salt of the present invention exhibits pharmaceutic advantages over the free base and the previously disclosed hydrochloride salt (WO 03/004498) in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient. In particular, the enhanced chemical and physical stability of the crystalline dihydrogenphosphate salt monohydrate constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient.

The dihydrogenphosphate salt of the present invention, which exhibits potent DP-IV inhibitory properties, is particularly useful for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

Another aspect of the present invention provides a method for the prevention or treatment of clinical conditions for which an inhibitor of DP-IV is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate thereof. Such clinical conditions include diabetes, in particular Type 2 diabetes, hyperglycemia, insulin resistance, and obesity.

The present invention also provides the use of the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate, for the manufacture of a medicament for the prevention or treatment of clinical conditions for which an inhibitor of DP-IV is indicated.

The present invention also provides pharmaceutical compositions comprising the dihydrogenphosphate salt of structural formula I or a hydrate thereof, in particular the crystalline monohydrate, in association with one or more pharmaceutically acceptable carriers or excipients. In one embodiment the pharmaceutical composition comprise a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises a detectable amount of the crystalline monohydrate of the present invention. In a second embodiment the pharmaceutical composition comprise a therapeutically effective amount of the active pharmaceutical ingredient in admixture with pharmaceutically acceptable excipients wherein the active pharmaceutical ingredient comprises about 5% to about 100% by weight of the crystalline monohydrate of the present invention. In a class of this second embodiment, the active pharmaceutical ingredient in such compositions comprises about 10% to about 100% by

weight of the crystalline monohydrate. In a second class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 25% to about 100% by weight of the crystalline monohydrate. In a third class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 50% to about 100% by weight of the crystalline monohydrate. In a fourth class of this embodiment, the active pharmaceutical ingredient in such compositions comprises about 75% to about 100% by weight of the crystalline monohydrate. In a fifth class of this embodiment, substantially all of the active pharmaceutical ingredient is the crystalline dihydrogenphosphate salt monohydrate of the present invention, i.e., the active pharmaceutical ingredient is substantially phase pure dihydrogenphosphate salt monohydrate.

The compositions in accordance with the invention are suitably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories. The compositions are intended for oral, parenteral, intranasal, sublingual, or rectal administration, or for administration by inhalation or insufflation. Formulation of the compositions according to the invention can conveniently be effected by methods known from the art, for example, as described in *Remington's Pharmaceutical Sciences*, 17th ed., 1995.

The dosage regimen is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient. An ordinarily skilled physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 200, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 200 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the crystalline forms of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the crystalline forms of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

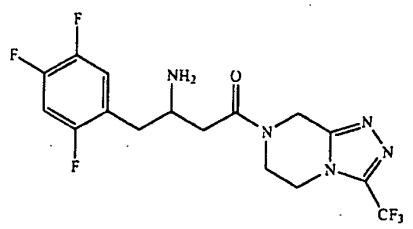
In the methods of the present invention, the dihydrogenphosphate salt and crystalline hydrates herein described in detail can form the active pharmaceutical ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active pharmaceutical ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the active pharmaceutical ingredient can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The dihydrogenphosphate salt of structural formula I and the crystalline monohydrate have been found to possess a high solubility in water, rendering it especially amenable to the preparation of formulations, in particular intranasal and intravenous formulations, which require relatively concentrated aqueous solutions of active ingredient. The solubility of the crystalline dihydrogenphosphate salt monohydrate of formula I in water has been found to be about 72 mg/mL.

According to a further aspect, the present invention provides a process for the preparation of the dihydrogenphosphate salt of formula I, which process comprises reacting 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluoromethyl)butan-2-amine of structural formula IV below:

(IV)




with approximately one equivalent of phosphoric acid in a suitable $C_1$-$C_5$ alkanol, such as methanol, ethanol, isopropyl alcohol (IPA), and isoamyl alcohol (IAA) or aqueous $C_1$-$C_5$ alkanol. The reaction is carried out at a temperature range of about 25 ° C. to about 80 ° C. The phosphoric acid solution can be added to a solution of the amine, or the addition can be performed in the reverse direction. The crystalline dihydrogenphosphate salt monohydrate is obtained by crystallization from an aqueous $C_1$-$C_5$ alkanol solution of the dihydrogenphosphate salt as described below.

General Methods for Crystallizing the Monohydrate of the Dihydrogenphosphate Salt of Structural Formula I

(a) In Ethanol/Water System at 25° C.:

(1) crystallization from a mixture of compound I in ethanol and water, such that the water concentration is above 31 weight percent,

(2) recovering the resultant solid phase, and

(3) removing the solvent therefrom.

(b) In Isoamyl Alcohol (IAA)/Water System at 25° C.:

(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 2.9 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(c) In IAA/Water System at 40° C.:

(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 3.6 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom

(d) In IAA/Water System at 60° C.:

(1) crystallization from a mixture of compound I in IAA and water, such that the water concentration is above 4.5 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(e) In Isopropyl Alcohol (IPA)/Water System at 25° C.:

(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above 7.0 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom

(f) In IPA/Water System at 40° C.:

(1) crystallization from a mixture of compound I in EPA and water, such that the water concentration is above 8.1 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

(g) In IPA/Water System at 75° C.:

(1) crystallization from a mixture of compound I in IPA and water, such that the water concentration is above about 20 weight percent;

(2) recovering the resultant solid phase; and

(3) removing the solvent therefrom.

The starting compound of structural formula IV can be prepared by the procedures detailed in Schemes 1-3 and Example 1 below.

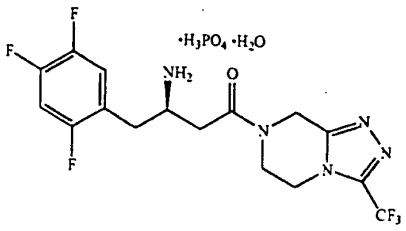
In a still further aspect, the present invention provides a method for the treatment and/or prevention of clinical conditions for which a DP-IV inhibitor is indicated, which method comprises administering to a patient in need of such prevention or treatment a prophylactically or therapeutically effective amount of the salt of Formula I as defined above or a crystalline hydrate thereof.

The following non-limiting Examples are intended to illustrate the present invention and should not be construed as being limitations on the scope or spirit of the instant invention.

Compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I.

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity."

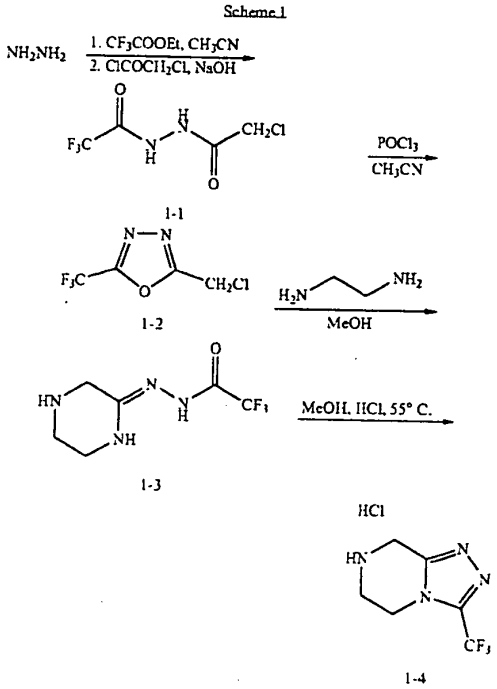
## EXAMPLE




(2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine dihydrogenphosphate monohydrate

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (1-4)

Scheme 1




Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25° C. from 14° C. The resulting solution was aged at 22-25° C. for 60 min. The was cooled to 7° C. 17.9 g of 50 wt % aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16° C. When the reaction was complete, the mixture was vacuum distilled to

remove water and ethanol at 27–30° C. and under 26 –27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area % pure by HPLC assay).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm. $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 41.0, 116.1 (q, J=362 Hz), 155.8 (q, J=50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1.3.4-oxadiazole (1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5° C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10° C. The mixture was heated to 80° C. and aged at this temperature for 24 h until HPLC showed less than 2 area % of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0° C. The reaction slurry was charged to the quench keeping the internal temperature below 10° C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt % aqueous sodium bicarbonate and finally 215 mL of 20 wt % aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55° C. to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

$^1$H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm. $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J–337 Hz), 156.2 (q, J=50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20° C. was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20° C. After the addition was complete, the resulting slurry was aged at –20° C. for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5° C. After 60 min at –5° C., the slurry was filtered and washed with ethanol (60 mL) at –5° C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt % pure by HPLC).

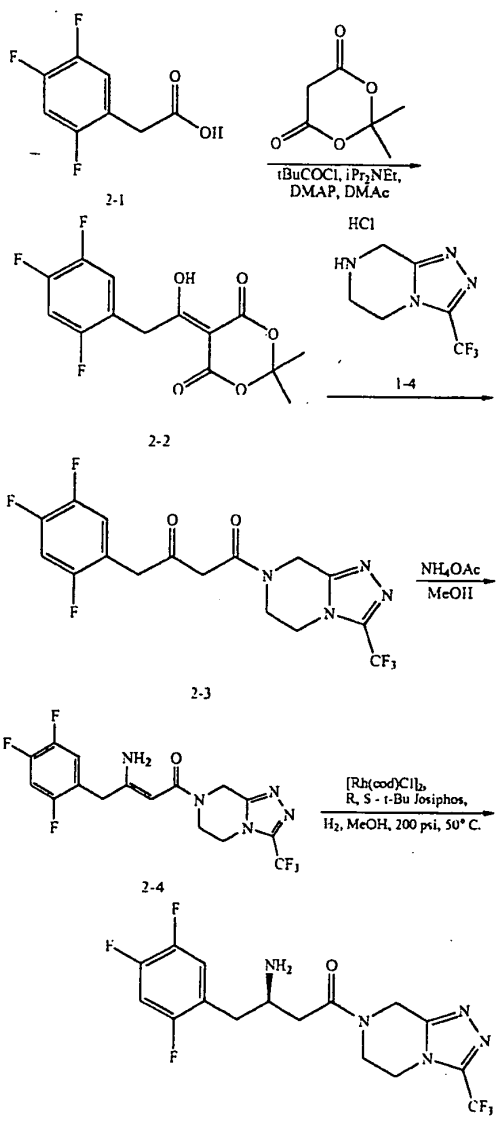
$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 2.9 (t. 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ 40.8, 42.0,43.3, 119.3 (q, J=350 Hz), 154.2, and 156.2 (q, J=38 Hz) ppm.

Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1.2.4]triazolo[4.3-a]pyrazine hydrochloride (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55° C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20° C. and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20° C. over 1 h. The resulting slurry was cooled to 2° C., aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45° C. Yield of triazole 1-4 was 26.7 g (99.5 area wt % pure by HPLC).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; $^{13}$C-NMR (100 MHz, DMSO-$d_6$): δ: 39.4, 39.6, 41.0, 118.6 (q, J=325 Hz), 142.9 (q, J=50 Hz), and 148.8 ppm.

Scheme 2




2-1 2-2 2-3 2-4 2-5

Step A: Preparation of 4-oxo-4-[3-(trifluoromethyl)-5.6-dihydro[1,2,4]triazolo[4.3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-one (2-3)

2,4,5-Trifluorophenylacetic acid (2-1 (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino) pyridine (DMAP) (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. N,N-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to

dissolve the solids. N,N-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40° C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5° C. The reaction mixture was aged at 5° C. for 1 h. Triazole hydrochloride 14 (180 g, 0.789 mol) was added in one portion at 40-50° C. The reaction solution was aged at 70° C. for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20-45° C. The batch was seeded and aged at 20-30° C. for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0-5° C. and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product 2-3 was 89%.

Step B: Preparation of (2Z)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl-]-1-(2,4,5-trifluorophenyl)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30° C. during the addition. Additional methanol (100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5° C. in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid (180 g); m.p. 271.2° C.

Step C: Preparation of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1 2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Into a 500 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]$_2$}(292 mg, 1.18 mmol) and (R,S) t-butyl Josiphos (708 mg, 1.3 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (200 mL) and the mixture was stirred at room temperature for 1 h. Into a 4 L hydrogenator was charged the enamine amide 2-4 (118 g, 0.29 mol) along with MeOH (1 L). The slurry was degassed. The catalyst solution was then transferred to the hydrogenator under nitrogen. After degassing three times, the enamine amide was hydrogenated under 200 psi hydrogen gas at 50° C. for 13 h. Assay yield was determined by HPLC to be 93% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl t-butyl ether (MTBE) (45 mL). Into this solution was added aqueous $H_3PO_4$ solution (0.5 M, 95 mL). After separation of the layers, 3N NaOH (35 mL) was added to the water layer, which was then extracted with MTBE (180 mL+100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75° C.). The hot toluene solution was then allowed to cool to 0° C. slowly (5-10 h). The crystals were isolated by filtration (13 g, yield 72%, 98-99% ee); m.p. 114.1-115.7° C.

$^1$H NMR (300 MHz, $CD_3CN$): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:

$^{13}$C NMR ($CD_3CN$): δ 171.8, 157.4 (ddd, $J_{CF}$=242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; $J_{CF}$=246.7, 14.2, 12.9 Hz), 147.4 (ddd, $J_{CF}$=241.2, 12.3, 3.7 Hz), 144.2 (q, $J_{CF}$=38.8 Hz), 124.6 (ddd, $J_{CF}$=18.5, 5.9, 4.0 Hz), 120.4 (dd, $J_{CF}$=19.1, 6.2 Hz), 119.8 (q, $J_{CF}$=268.9 Hz), 106.2(dd, $J_{CF}$=29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

The crystalline free base can also be isolated as follows:

(a) The reaction mixture upon completion of the hydrogenation step is charged with 25 wt % of Ecosorb C-941. The mixture is stirred under nitrogen for one h and then filtered. The cake is washed with 2 L/kg of methanol. Recovery of free base is about 95% and optical purity about 95% ee.

(b) The freebase solution in methanol is concentrated to 3.5-4.0 L/kg volume (based on free base charge) and then solvent-switched into isopropanol (IPA) to final volume of 3.0 L/kg IPA.

(c) The slurry is heated to 40° C. and aged 1 h at 40° C. and then cooled to 25° C. over 2 h.

(d) Heptane (7 L/kg) is charged over 7 h and the slurry stirred for 12 h at 22-25° C. The supernatant concentration before filtering is 10-12 mg/g.

(e) The slurry is filtered and the solid washed with 30% IPA/heptane (2 L/kg).

(f) The solid is dried in a vacuum oven at 40° C.

(g) The optical purity of the free base is about 99% ee.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

Column: Waters Symmetry C18, 250 mm×4.6 mm
Eluent: Solvent A: 0.1 vol % $HClO_4/H_2O$
Solvent B: acetonitrile
Gradient: 0 min 75% A: 25% B
10 min 25% A: 75% B
12.5 min 25% A: 75% B
15 min 75% A: 25% B
Flow rate: 1 mL/min
Injection Vol.: 10 μL
UV detection: 210 nm
Column temp.: 40° C.
Retention times: compound 2-4: 9.1 min
compound 2-5: 5.4 min
tBu Josiphos: 8.7 min

The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:

Column: Chirapak, AD-H, 250 mm×4.6 mm
Eluent: Solvent A: 0.2 vol. % diethylamine in heptane
Solvent B: 0.1 vol % diethylamine in ethanol
Isochratic Run Time: 18 min
Flow rate: 0.7 mL/min
Injection Vol.: 7 μL
UV detection: 268 nm
Column temp.: 35° C.
Retention times: (R)-amine 2-5: 13.8 min
(S)-amine 2-5: 11.2 min

(2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,24]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine dihydrogenphosphate monohydrate

A 250 mL round bottom flask equipped with an overhead stirrer, heating mantle and thermocouple, was charged with 31.5 mL of isopropanol (IPA), 13.5 mL water, 15.0 g (36.9 mmol) of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,

2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine freebase and 4.25 g (36.9 mmol) of 85% aqueous phosphoric acid. The mixture was heated to 75° C. A thick white precipitate formed at lower temperatures but dissolved upon reaching 75° C. The solution was cooled to 68° C. and then held at that temperature for 2 h. A slurry bed of solids formed during this age time [the solution can be seeded with 0.5 to 5 wt % of small particle size (alpine milled) monohydrate]. The slurry was then cooled at a rate of 4° C./h to 21° C. and then held overnight. 105 mL of EPA was then added to the slurry. After 1 h the slurry was filtered and washed with 45 mL IPA (solids can also be washed with a water/IPA solution to avoid turnover to other crystal forms). The solids were dried on the frit with open to air. 18.6 g of solids were recovered. The solids were found to be greater than 99.8% pure by HPLC area percentage (HPLC conditions same as those given above). The particle size distribution analysis of the isolated solids showed a mean PSD of 80 microns with 95% less than 180 microns. The crystal form of the solids was shown to be monohydrate by X-ray powder diffraction and thermogravimetric analysis.

X-ray powder diffraction studies are widely used to characterize molecular structures, crystallinity, and polymorphism. The X-ray powder diffraction pattern of the crystalline dihydrogenphosphate monohydrate was generated on a Philips Analytical X'Pert PRO X-ray Diffraction System with PW3040/60 console. A PW3373/00 ceramic Cu LEF X-ray tube K-Alpha radiation was used as the source.

FIG. 1 shows the X-ray diffraction pattern for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate exhibited characteristic diffraction peaks corresponding to d-spacings of 7.42, 5.48, and 3.96 angstroms. The monohydrate was further characterized by the d-spacings of 6.30, 4.75, and 4.48 angstroms. The monohydrate was even further characterized by the d-spacings of 5.85, 5.21, and 3.52 angstroms.

In addition to the X-ray powder diffraction patterns described above, the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II was further characterized by its solid-state carbon-13 and fluorine-19 nuclear magnetic resonance (NMR) spectra. The solid-state carbon-13 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4 mm double resonance CPMAS probe. The carbon-13 NMR spectrum utilized proton/carbon-13 cross-polarization magic-angle spinning with variable-amplitude cross polarization. The sample was spun at 15.0 kHz, and a total of 2048 scans were collected with a recycle delay of 20 seconds. A line broadening of 40 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.03 p.p.m.) as a secondary reference.

The solid-state fluorine-19 NMR spectrum was obtained on a Bruker DSX 400WB NMR system using a Bruker 4 mm CRAMPS probe. The NMR spectrum utilized a simple pulse-acquire pulse program. The samples were spun at 15.0 kHz, and a total of 16 scans were collected with a recycle delay of 30 seconds. A vespel endcap was utilized to minimize fluorine background. A line broadening of 100 Hz was applied to the spectrum before FT was performed. Chemical shifts are reported using poly(tetrafluoroethylene) (teflon) as an external secondary reference which was assigned a chemical shift of −122 ppm.

FIG. 2 shows the solid-state carbon-13 CPMAS NMR spectrum for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate form exhibited characteristic signals with chemical shift values of 169.1, 120.8, and 46.5 p.p.m. Further characteristic of the monohydrate form were the signals with chemical shift values of 159.0, and 150.9, and 40.7 ppm.

FIG. 3 shows the solid-state fluorine-19 MAS NM spectrum for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. The monohydrate form exhibited characteristic signals with chemical shift values of −64.5, −114.7, −136.3, and −146.2 p.p.m. Further characteristic of the monohydrate form were the signals with chemical shift values of −96.5, −104.4, −106.3, and −154.5 ppm.

FIG. 4 shows the characteristic thermogravimetric analysis (TGA) curve for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. A Perkin Elmer model TGA 7 or equivalent instrument was used. Experiments were performed under a flow of nitrogen and using a heating rate of 10° C./min to a maximum temperature of approximately 250° C. After automatically taring the balance, 5 to 20 mg of sample was added to the platinum pan, the furnace was raised, and the heating program started. Weight/temperature data were collected automatically by the instrument. Analysis of the results was carried out by selecting the Delta Y function within the instrument software and choosing the temperatures between which the weight loss was to be calculated. Weight losses are reported up to the onset of decomposition/evaporation. TGA indicated a weight loss of about 3.3647 % from ambient temperature to about 250° C.

FIG. 5 shows the characteristic DSC curve for the crystalline monohydrate form of the dihydrogenphosphate salt of structural formula II. A TA Instruments DSC 2910 or equivalent instrumentation was used. Between 2 and 6 mg sample was weighed into an open pan. This pan was then crimped and placed at the sample position in the calorimeter cell. An empty pan was placed at the reference position. The calorimeter cell was closed and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of 10° C./min to a temperature of approximately 250° C. The heating program was started. When the run was completed, the data were analyzed using the DSC analysis program contained in the system software. The melting endotherm was integrated between baseline temperature points that are above and below the temperature range over which the endotherm was observed. The data reported are the onset temperature, peak temperature, and enthalpy.

The crystalline dihydrogenphosphate salt monohydrate of the present invention has a phase purity of at least about 5% of the form with the above X-ray powder diffraction, fluorine-19 MAS NMR, carbon-13 CPMAS NMR, and DSC physical characteristics. In one embodiment the phase purity is at least about 10% of the form with the above solid-state physical characteristics. In a second embodiment the phase purity is at least about 25% of the form with the above solid-state physical characteristics. In a third embodiment the phase purity is at least about 50% of the form with the above solid-state physical characteristics. In a fourth embodiment the phase purity is at least about 75% of the form with the above solid-state physical characteristics. In a fifth embodiment the phase purity is at least about 90% of the form with the above solid-state physical characteristics. In a sixth embodiment the crystalline dihydrogenphosphate salt monohydrate is the substantially phase pure form with the above solid-state physical characteristics. By the term "phase purity" is meant the solid state purity of the dihydrogenphosphate salt monohydrate with regard to a particu-

lar crystalline or amorphous form of the salt as determined by the solid-state physical methods described in the present application.

The crystalline dihydrogenphosphate salt monohydrate was found to be stable under ambient condition. It was found to convert to dehydrated monohydrate if heated to above 40° C. under very dry nitrogen flow. Dehydrated monohydrate converted back to monohydrate under ambient condition.

## EXAMPLES OF PHARMACEUTICAL COMPOSITIONS

1) Direct Compression Process:

The dihydrogenphosphate salt monohydrate was formulated into a tablet by a direct compression process. A 100 mg potency tablet was composed of 128.4 mg of the active ingredient, 127.8 mg microcrystalline cellulose, 127.8 mg of mannitol (or 127.8 mg of dicalcium phosphate), 8 mg of croscarmellose sodium, 8 mg of magnesium stearate and 16 mg of Opadry white (proprietary coating material made by Colorcon, West Point, Pa.). The active ingredient, microcrystalline cellulose, mannitol (or dicalcium phosphate), and croscarmellose were first blended, and the mixture was then lubricated with magnesium stearate and pressed into tablets. The tablets were then film coated with Opadry White.

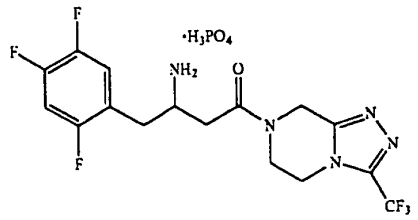
2) Roller Compaction Process:

The dihydrogenphosphate salt monohydrate was formulated into a tablet by a roller compaction process. A 100 mg potency tablet was composed of 128.4 mg of the active ingredient, 45 mg microcrystalline cellulose, 111.6 mg of dicalcium phosphate, 6 mg of croscarmellose sodium, 9 mg of magnesium stearate and 12 mg of Opadry white (proprietary coating material made by Colorcon, West Point, Pa.). The active ingredient, microcrystalline cellulose, dicalcium phosphate, and croscarmellose were first blended, and the mixture was then lubricated with one third the total amount of magnesium stearate and roller compacted into ribbons. These ribbons were then milled and then resulting granules were lubricated with the remaining amount of the magnesium stearate and pressed into tablets. The tablets were then film coated with Opadry White. 3) An intravenous (i.v.) aqueous formulation is defined as the monohydrate of dihydrogenphosphate salt of formula I in 10 mM sodium acetate/0.8% saline solution at pH 4.5±0.2. For a formulation with a concentration of 4.0 mg/mL, 800 mg of NaCl is dissolved in 80 mL of water, then 57.5 μL of glacial acetic acid is added. followed by 512 mg of the dihydrogenphosphate salt monohydrate. The pH is adjusted to 4.5±0.2 with 0.1 N NaOH solution. The final volume is adjusted to 100 mL with water. A 2.0 mg/mL solution can be made by dilution of 50.0 mL of the 4.0 mg/mL solution to 100.0 mL with placebo. A 1.0 mg/mL solution can be made by dilution of 25.0 mL of the 4.0 mg/mL solution to 100.0 mL with placebo.

What is claimed is:

1. A dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I:

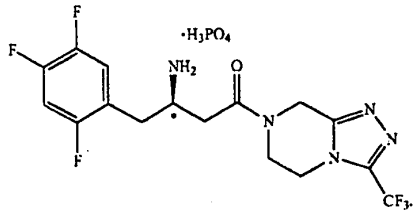
(I)



or a hydrate thereof.

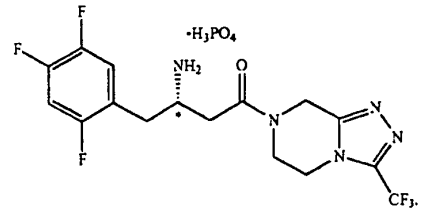
2. The salt of claim 1 of structural formula II having the (R)-configuration at the chiral center marked with an *

(II)



3. The salt of claim 1 of structural formula III having the (S)-configuration at the chiral center marked with an *

(III)



4. The salt of claim 2 characterized in being a crystalline monohydrate.

5. The salt of claim 4 characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 7.42, 5.48, and 3.96 angstroms.

6. The salt of claim 5 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 6.30, 4.75, and 4.48 angstroms.

7. The salt of claim 6 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 5.85, 5.21, and 3.52 angstroms.

8. The salt of claim 7 further characterized by the X-ray powder diffraction pattern of FIG. 1.

9. The salt of claim 4 characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 169.1, 120.8, and 46.5 ppm.

10. The salt of claim 9 further characterized by a solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum showing signals at 159.0, 150.9, and 40.7 ppm.

11. The salt of claim 10 further characterized by the solid-state carbon-13 CPMAS nuclear magnetic resonance spectrum of FIG. 2.

12. The salt of claim 4 characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at −64.5, −114.7, −136.3, and −146.2 ppm.

13. The salt of claim 12 further characterized by a solid-state fluorine-19 MAS nuclear magnetic resonance spectrum showing signals at −96.5, −104.4, −106.3, and −154.5 ppm.

14. The salt of claim 13 further characterized by the solid-state fluorine-19 MAS nuclear magnetic resonance spectrum of FIG. 3.

15. The salt of claim 4 characterized by the thermogravimetric analysis curve of FIG. 4.

16. The salt of claim 4 characterized by the differential scanning calorimetric curve of FIG. 5.

17. A pharmaceutical composition comprising a therapeutically effective amount of the salt according to claim 2 in association with one or more pharmaceutically acceptable carriers.

18. A pharmaceutical composition comprising a therapeutically effective amount of the salt according to claim 4 in association with one or more pharmaceutically acceptable carriers.

19. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof.

20. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 4.

21. A process for preparing the salt of claim 2 comprising the step of contacting one equivalent of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine in an organic solvent or aqueous organic solvent with about a one equivalent of phosphoric acid at a temperature in the range of about 25-100° C.

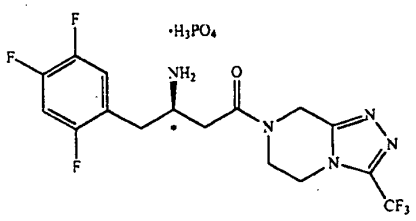
22. The process of claim 21 wherein said organic solvent is a $C_1$-$C_5$ linear or branched alkanol.

23. The phosphoric acid salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine prepared according to the process of claim 21.

24. A process for preparing the crystalline monohydrate of claim 4 comprising the steps of:

(a) crystallizing the dihydrogenphosphate salt of structural formula (II):

(II)




at 25° C. from a mixture of isopropanol and water, such that the water concentration is above 6.8 weight percent;

(b) recovering the resultant solid phase; and

(c) removing the solvent therefrom.

* * * * *

AO 120 (Rev. 3/04)

| TO: | REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK |
|---|---|
| Mail Stop 8<br>Director of the U.S. Patent and Trademark Office<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | |

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Columbia on the following ☑ Patents or ☐ Trademarks:

| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| 10cv1110 | 6/30/2010 | for the District of Columbia |

| PLAINTIFF | DEFENDANT |
|---|---|
| MERCK SHARP & DOHME CORP.<br>126 East Lincoln Avenue<br>Rahway. NJ 07065 | DAVID J. KAPPOS<br>P.O. Box 15667<br>Arlington, VA 22215 |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | 7,326,708 | 2/5/2008 | MERCK SHARP & DOHME CORP. |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

| DATE INCLUDED | INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading | |
|---|---|---|
| PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
| 1 | | |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |

In the above—entitled case, the following decision has been rendered or judgement issued:

| DECISION/JUDGEMENT |
|---|
| 11/06/2014 ORDER granting the plaintiff's 18 Motion for Summary Judgment and denying the defendant's 19 Cross-Motion for Summary Judgment and Opposition to Plaintiff's Motion for Summary Judgment. See Order for further details. The Clerk is directed to close the case. Signed by Judge Beryl A. Howell on November 6, 2014. (lcbah2) (Entered: 11/06/2014) |

| CLERK | (BY) DEPUTY CLERK | DATE |
|---|---|---|
| Angela D. Caesar | /s/ Nicole Wilkens | 11/7/2014 |

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

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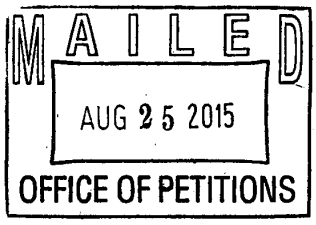
Covington & Burling LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20005




In re Patent No. 7,326,708 :
Cypes et al. : DECISION UPON REMAND AND
Issue Date: February 5, 2008 : RECONSIDERATION OF
Application No. 10/874,992 : PATENT TERM ADJUSTMENT
Filed: June 23, 2004 : and
Atty Docket No. 21409Y : NOTICE OF INTENT TO ISSUE
Title: Phosphoric Acid Salt of Dipeptidyl Peptidase-IV inhibitor : CERTIFICATE OF CORRECTION

This is a decision following request for consideration remand from the United States District Court for the District of Columbia ("District Court") in *Merck Sharp & Dohme Corp. v. Michelle Lee,* Civ. Action No. 1:10-cv-01110, regarding the patent term adjustment (hereinafter referred to as "PTA") indicated on the above-identified patent.

**Relevant Procedural History**

On February 5, 2008, the above-referenced patent issued with 657 days of PTA. On June 30, 2010 patentee filed a civil action pursuant to 35 U.S.C. § 154(b)(4)(A) requesting that patentee be granted not less than 883 days of Patent Term Adjustment. Patentee's civil action was not filed within one hundred and eighty (180) days of the patent issuance date nor do patent file a petition under 37 CFR 1.705(d).

On November 6, 2014, the District Court remanded the case and ordered the U.S. Patent and Trademark Office ("USPTO" or "Office") to recalculate the patent term adjustment of the patent-at-issue, finding against the USPTO as a factual matter on the scope of an alleged concession at issue in that case, and noting that but for the alleged concession, the case against the plaintiff "would be easily resolved on the factual issue of equitable tolling." *See Merck Sharp & Dohme Corp. v. Michelle Lee,* No. 1:10cv-01110, 2014 WL 5775749, at *9 (D.D.C. Nov. 6, 2014). The Office does not concede that the facts here support an equitable tolling claim. This decision is limited to the facts and circumstances of this case. The Office maintains that the *Novartis* and *Daiichi* decisions support the Office's position that equitable tolling does not arise

when an applicant fails to avail himself/herself of the remedies provided under 37 CFR 1.705 and 35 U.S.C.154(b)(4)(A) within the requisite time limits nor does this case give rise to a claim of equitable tolling.

**Decision**

Upon review, the USPTO finds that patentee is entitled to eight hundred eighty-four (884) days of PTA. Reconsideration of "B" delay under 35 U.S.C. 154(b)(1)(B) necessitates review in light of the overlapping periods under 35 U.S.C. § 154(b)(2)(A) *See Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010). Reconsideration of the "B" delay also necessitates reconsideration of the overlapping delay under 35 U.S.C. § 154(b)(2)(A).

**"A" Delay**

The Office finds there are 657 days of "A" delay. The period of "A" delay is:

> 657 days under 37 CFR 1.703(a)(1) beginning on August 24, 2005 (the day after the date that is four months after the day the patentee replied to the restriction requirement) and ending on June 11, 2007 (the mail date of the non-final rejection.);

**"B" Delay**

The *Novartis* decision includes "instructions" for calculating the period of "B" delay. Specifically, the decision states,

> The better reading of the language is that the patent term adjustment time [for "B" delay] should be calculated by determining the length of the time between application and patent issuance, then subtracting any continued examination time (and other time identified in (i), (ii), and (iii) of (b)(1)(B)) and determining the extent to which the result exceeds three years.[1]

The length of time between filing date and issuance is 1323 days, which is the number of days beginning on the filing date of the application (June 23, 2004) and ending on the date the patent issued (February 5, 2008).

The time consumed by continued examination is 43 days.

The number of days beginning on the commencement date of application (November 27, 2000) and ending on the date three years after the filing date of the application (November 27, 2003) is 1,096 days.

[1] *Novartis*, 740 F.3d 593 (Fed. Cir. 2014).

The result of subtracting the time consumed by continued examination (0)days from the length of time between the application filing date and issuance (1323 days) is 1323 days, which exceeds three years (1096 days) by 227 days. Therefore, the period of "B" delay is 227 days.

Patentee asserted that the "B" delay period is 226 days in the complaint but the Office believes that the proper amount of "B" delay is 227.

**"C" Delay**

The amount of "C" delay under 37 CFR 1.703(a)(1) is 0 days.

**Overlap**

The Office finds that the number of overlapping days of Office delay is (0) days. In *Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010), the Court of Appeals for the Federal Circuit determined that overlap occurs when the calendar days overlap between the "A" and "B" delays and the "A" and "C" delays.

**Reduction under 35 U.S.C. § 154(b)(2)(C)(iii) & 37 CFR 1.704 [Applicant Delay]**

The amount of PTA delay by applicants is zero (0) days.

**Overall PTA Calculation**

**Formula:**

"A" delay + "B" delay + "C" delay - Overlap - Applicant delay = X days of PTA

**USPTO's Calculation:**

657 + 227 + 0 – 0 – 0 = 884 days

**PATENTEE's Calculation**

657 + 226 + 0 – 0 – 0 = 883 days

**Conclusion**

Patentee is entitled to PTA of eight hundred and eighty-four (884) days. Using the formula "A" delay + "B" delay + "C" delay - Overlap - Applicant delay = X, the amount of PTA is calculated as follows: 657 + 227 + 0 – 0 – 0 = 884 days.

If patentee seeks a review of this decision, patentee must request reconsideration within TWO (2) months from the mail date of this decision. If applicant does not reply, then the Office will *sua sponte* issue a certificate of correction in the amount of 884 days.

Telephone inquiries specific to this matter should be directed to Attorney Advisor, Kery Fries at (571) 272-7757.

Kery A. Fries
Senior Legal Advisor
Office of Patent Legal Administration
Office of Deputy Commissioner
For Patent Examination Policy

Enclosure: Adjusted PTA calculation
Draft Certificate of Correction


PTA/PTE Information | Patent Term Adjustment | Patent Term Extension | Calculation Explanation

Application Number*: 10874992 Open Explanation of PTA Calculation Explanation of PTE Calculation

Print

PTA Calculations for Application: 10874992

| | | | |
|---|---|---|---|
| Application Filing Date | 06/23/2004 | OverLapping Days Between (A and B) or (A and C) | 0 |
| Issue Date of Patent | 02/05/2008 | Non-Overlapping USPTO Delays: | 657 |
| A Delays | 657 | PTO Manual Adjustment | 227 |
| B Delays | 0 | Applicant Delay (APPL) | 0 |
| C Delays | 0 | Total PTA (days) | 884 |

* - Sorted Column

File Contents History

| Action Number | Action Recorded Date | Action Due Date | Action Code | Action Description | Duration PTO | Duration APPL | Parent Action Number |
|---|---|---|---|---|---|---|---|
| 50 | 08/24/2015 | | P028 | Adjustment of PTA Calculation by PTO | 227 | | 0 |
| 46 | 02/05/2008 | | PTAC | Patent Issue Date Used In PTA Calculation | | | 0 |
| 46.5 | 01/16/2008 | 06/23/2007 | PTA36M | PTA 36 Months | 0 | | 0 |
| 45 | 01/08/2008 | | EFDC | Export to Final Data Capture | | | 0 |
| 44 | 01/03/2008 | | D1935 | Dispatch to FDC | | | 0 |
| 42 | 12/29/2007 | | PILS | Application Is Considered Ready for Issue | | | 0 |
| 43 | 12/27/2007 | | FIDC | Finished Initial Data Capture | | | 0 |
| 41 | 12/13/2007 | | N084 | Issue Fee Payment Verified | | | 0 |
| 40 | 12/13/2007 | | IFEE | Issue Fee Payment Received | | | 0 |
| 39 | 11/09/2007 | | EIDC | Export to Initial Data Capture | | | 0 |
| 38 | 11/05/2007 | | MN/=. | Mail Notice of Allowance | | | 0 |
| 37 | 11/05/2007 | | MEX.A | Mail Examiner's Amendment | | | 0 |
| 36 | 10/31/2007 | | IREV | Issue Revision Completed | | | 0 |
| 35 | 10/31/2007 | | ACRE | Allowed Case Returned to the Examiner for Clerical Processing | | | 0 |
| 34 | 10/31/2007 | | DVER | Document Verification | | | 0 |
| 33 | 10/31/2007 | | EX.A | Examiner's Amendment Communication | | | 0 |
| 32 | 10/31/2007 | | N/=. | Notice of Allowance Data Verification Completed | | | 0 |
| 31 | 10/31/2007 | | CNTA | Allowability Notice | | | 0 |
| 29 | 08/09/2007 | | FWDX | Date Forwarded to Examiner | | | 0 |
| 28 | 08/06/2007 | | A... | Response after Non-Final Action | | | 0 |
| 27 | 07/31/2007 | | MEXIN | Mail Examiner Interview Summary (PTOL - 413) | | | 0 |
| 30 | 06/27/2007 | | IDSC | Information Disclosure Statement considered | | | 0 |
| 25 | 06/27/2007 | | WIDS | Information Disclosure Statement (IDS) Filed | | | 0 |
| 24 | 06/27/2007 | | M844 | Information Disclosure Statement (IDS) Filed | | | 0 |
| 23 | 06/11/2007 | 08/23/2005 | MCTNF | Mail Non-Final Rejection | 657 | | -1 |
| 22 | 06/07/2007 | | CTNF | Non-Final Rejection | | | 0 |
| 21 | 06/07/2007 | | DOCK | Case Docketed to Examiner in GAU | | | 0 |
| 26 | 03/08/2007 | | EXIN | Examiner Interview Summary Record (PTOL - 413) | | | 0 |
| 19 | 07/28/2006 | | IDSC | Information Disclosure Statement considered | | | 0 |
| 18.7 | 07/28/2006 | | M844 | Information Disclosure Statement (IDS) Filed | | | 0 |
| 18 | 07/28/2006 | | WIDS | Information Disclosure Statement (IDS) Filed | | | 0 |
| 17 | 09/15/2005 | | DOCK | Case Docketed to Examiner in GAU | | | 0 |
| 16 | 02/04/2005 | | TSSCOMP | IFW TSS Processing by Tech Center Complete | | | 0 |
| 15 | 02/04/2005 | | DOCK | Case Docketed to Examiner in GAU | | | 0 |
| 12 | 11/03/2004 | | WROIPE | Application Return from OIPE | | | 0 |
| 11 | 11/03/2004 | | ROIPE | Application Return TO OIPE | | | 0 |
| 10 | 11/03/2004 | | OIPE | Application Dispatched from OIPE | | | 0 |
| 9 | 11/03/2004 | | COMP | Application Is Now Complete | | | 0 |

| Action Number | Action Recorded Date | Action Due Date | Action Code | Action Description | Duration PTO | Duration APPL | Parent Action Number |
|---|---|---|---|---|---|---|---|
| 8 | 10/22/2004 | | ADDFLFEE | Additional Application Filing Fees | | | 0 |
| 7 | 10/22/2004 | | CORRDRW | Applicant has submitted new drawings to correct Corrected Papers problems | | | 0 |
| 6 | 09/15/2004 | | CPAP | Corrected Paper | | | 0 |
| 20 | 09/13/2004 | | IDSC | Information Disclosure Statement considered | | | 0 |
| 14 | 09/13/2004 | | RCAP | Reference capture on IDS | | | 0 |
| 13.7 | 09/13/2004 | | M844 | Information Disclosure Statement (IDS) Filed | | | 0 |
| 13 | 09/13/2004 | | WIDS | Information Disclosure Statement (IDS) Filed | | | 0 |
| 5 | 08/12/2004 | | L128 | Cleared by L&R (LARS) | | | 0 |
| 4 | 08/02/2004 | | L198 | Referred to Level 2 (LARS) by OIPE CSR | | | 0 |
| 3 | 08/02/2004 | | CLSS | CASE CLASSIFIED BY OIPE | | | 0 |
| 2 | 07/16/2004 | | SCAN | IFW Scan & PACR Auto Security Review | | | 0 |
| 1 | 06/23/2004 | | IEXX | Initial Exam Team nn | | | 0 |

Export to: Excel

UNITED STATES PATENT AND TRADEMARK OFFICE (Draft)

# CERTIFICATE OF CORRECTION

| | | |
|---|---|---|
| PATENT | : | 7,326,708 |
| DATED | : | February 8, 2008 |
| INVENTOR(S) | : | Cypes et al. |

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by (657) days

Delete the phrase "by 657 days" and insert – by 884 days--

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 7,326,708 B2
APPLICATION NO. : 10/874992
DATED : February 5, 2008
INVENTOR(S) : Cypes et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 884 days.

Signed and Sealed this
Ninth Day of February, 2016

Michelle K. Lee

Michelle K. Lee
*Director of the United States Patent and Trademark Office*