ABSTRACT

The invention relates to an improved process for preparation of sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I) by using O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) of Formula (A) as coupling agent.

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FIG.1

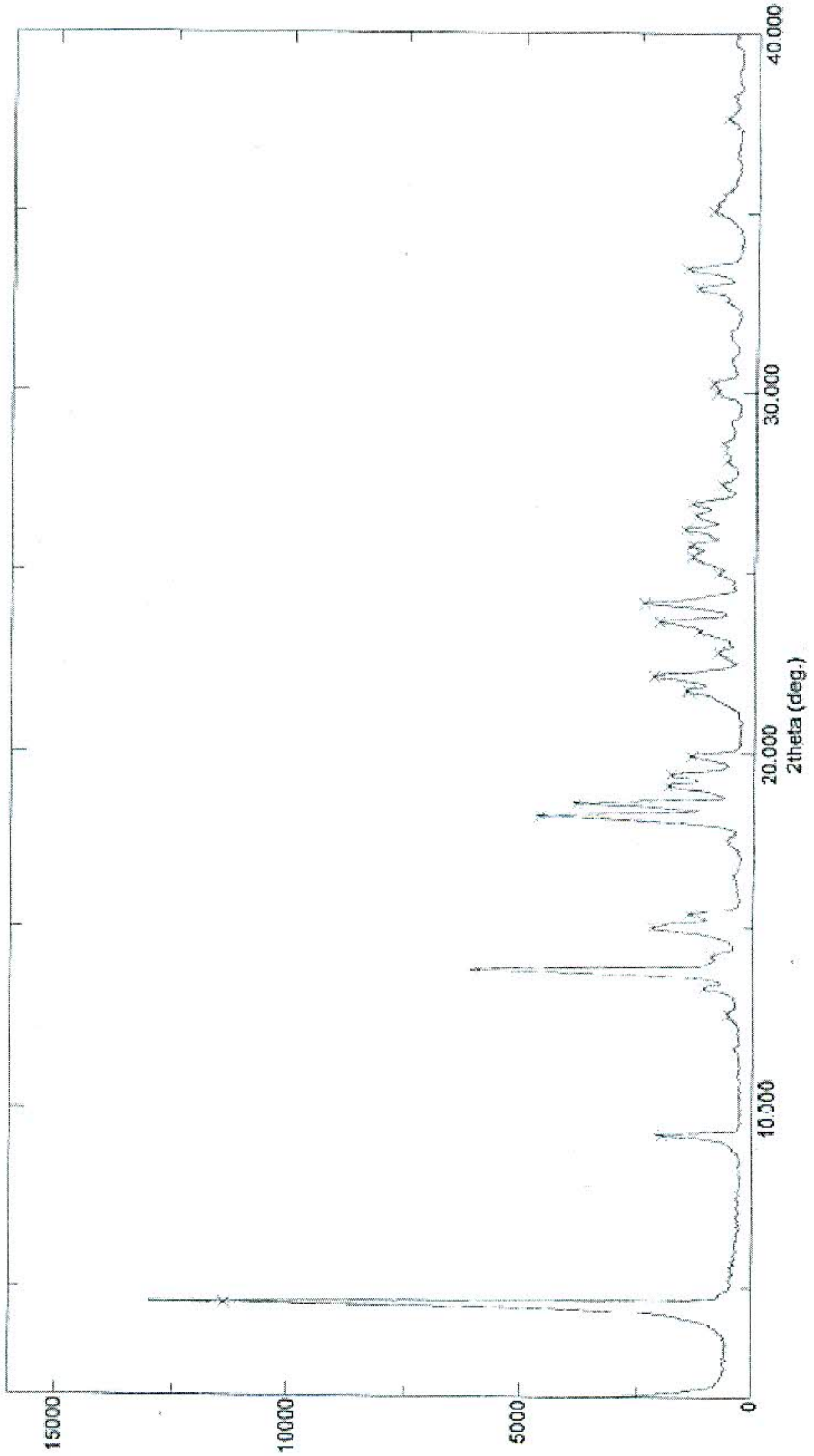

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FIG. 2

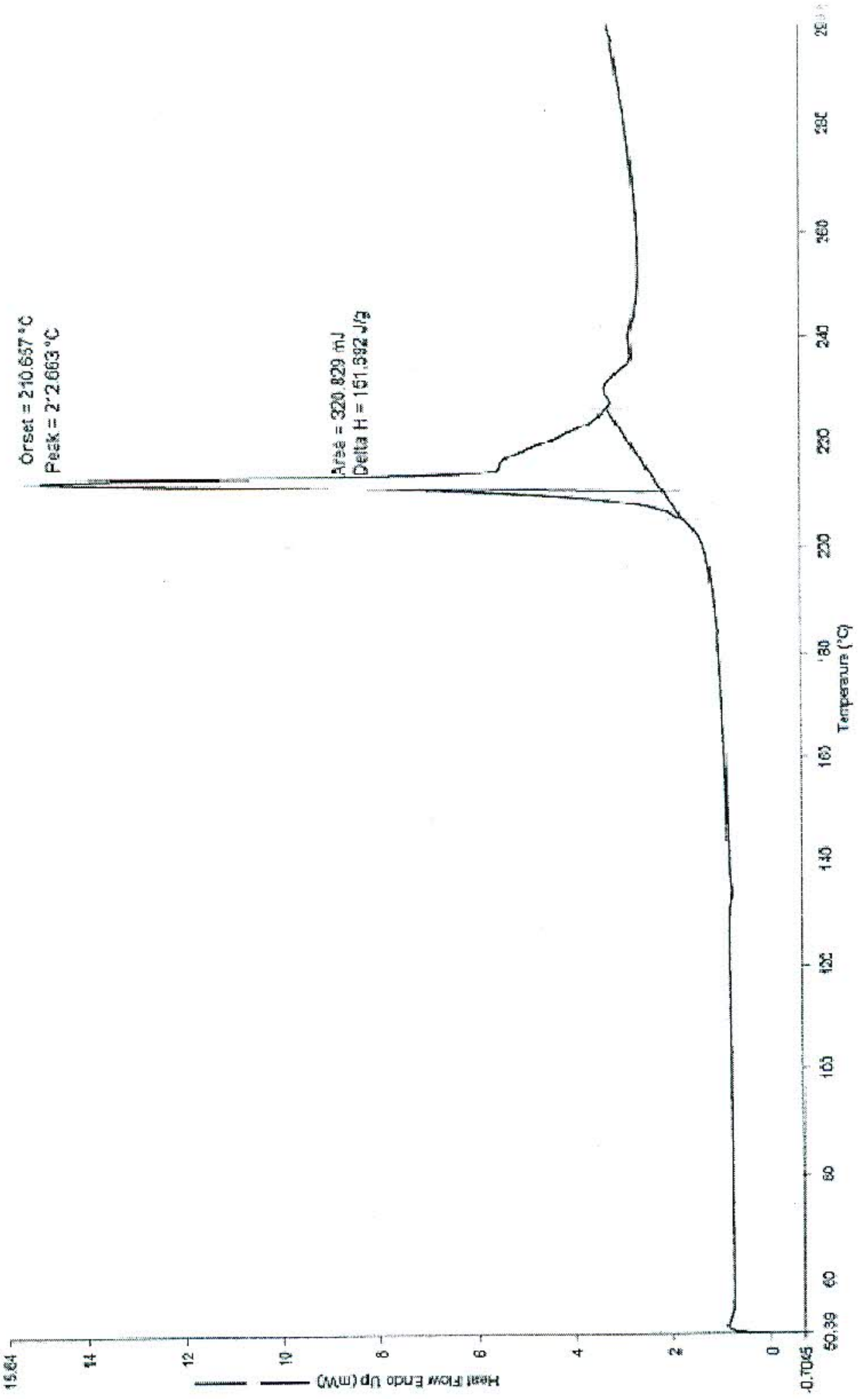

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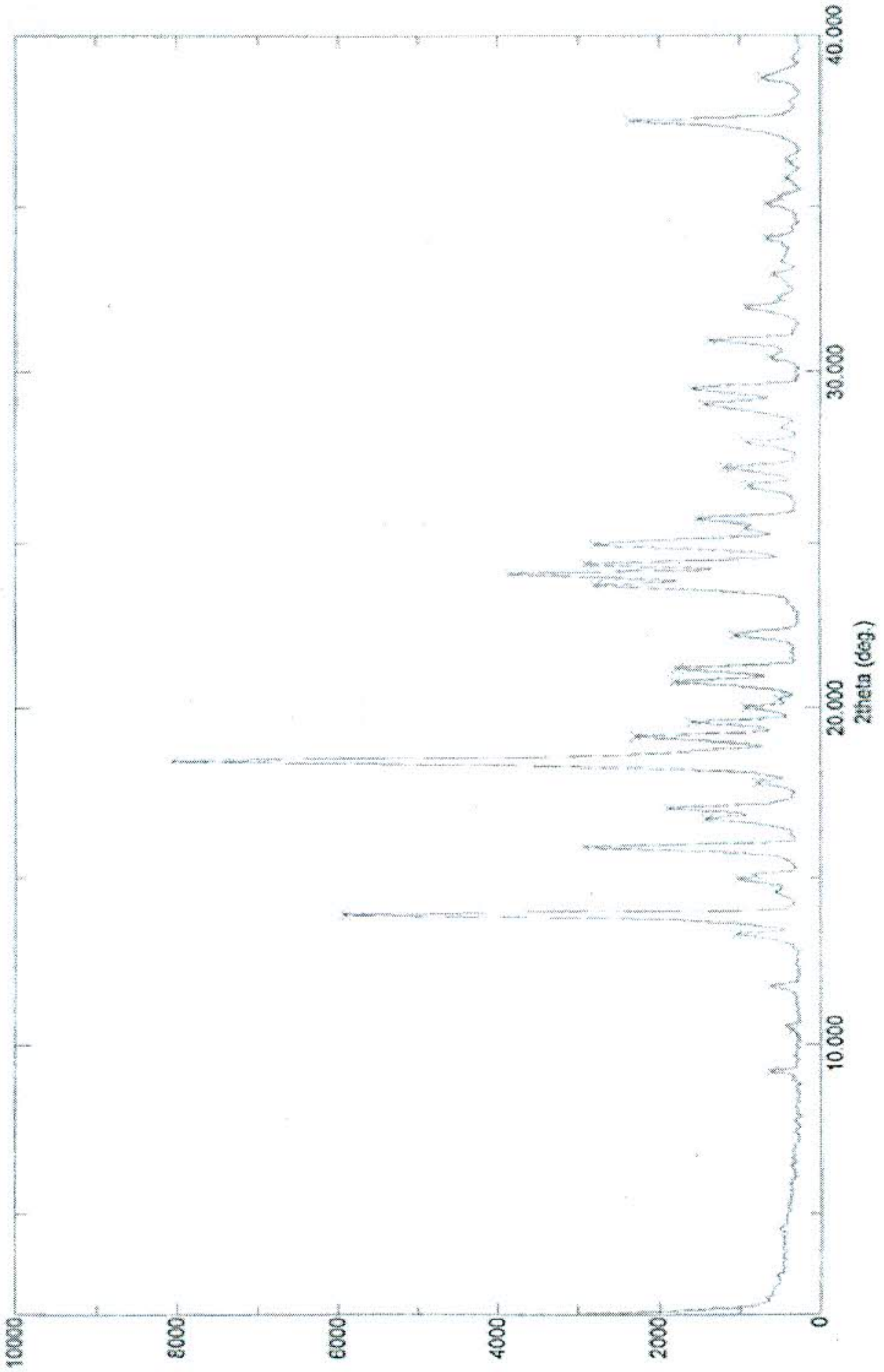
FIG. 3



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No. 916/MUM/2013

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FIG. 4

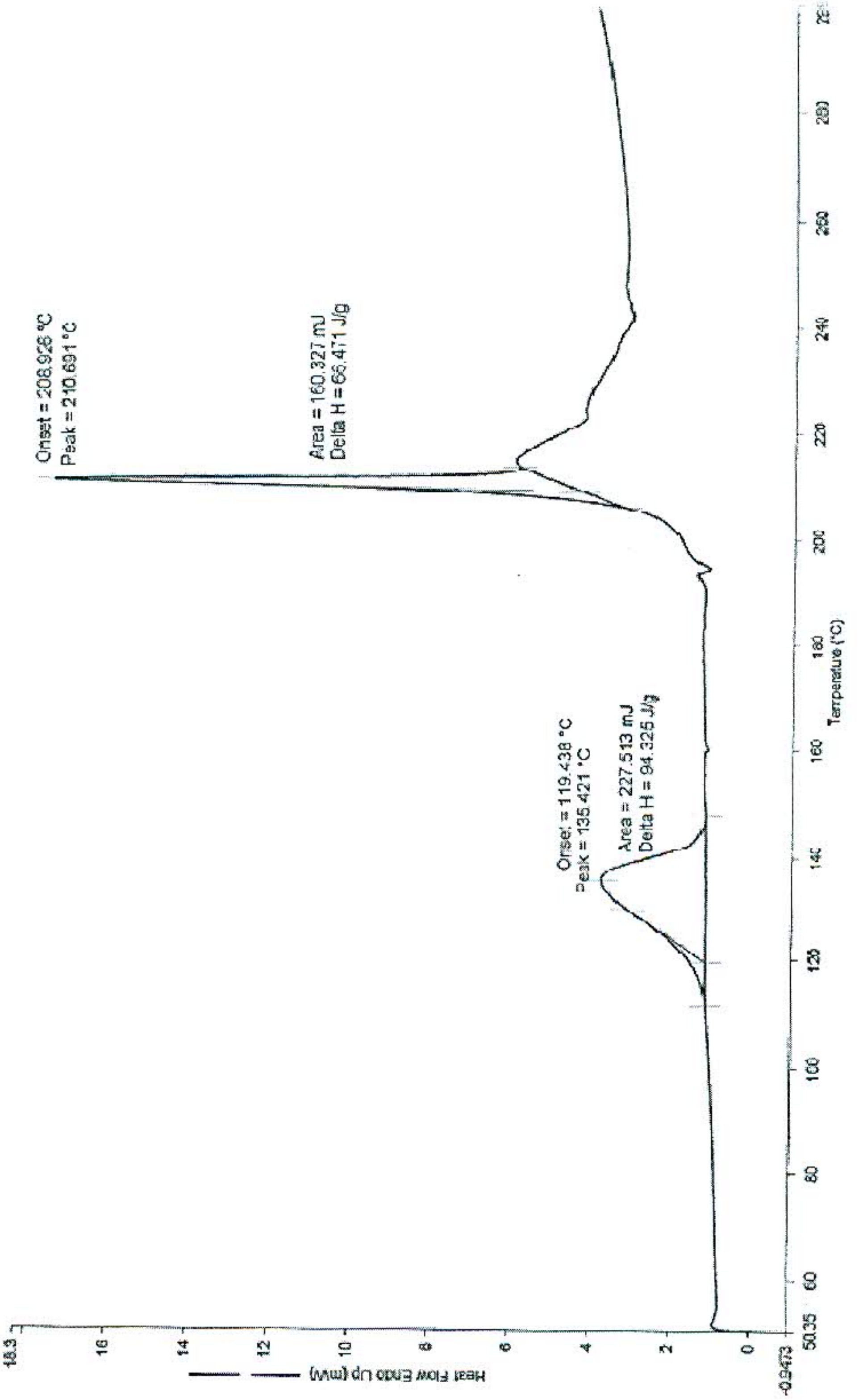

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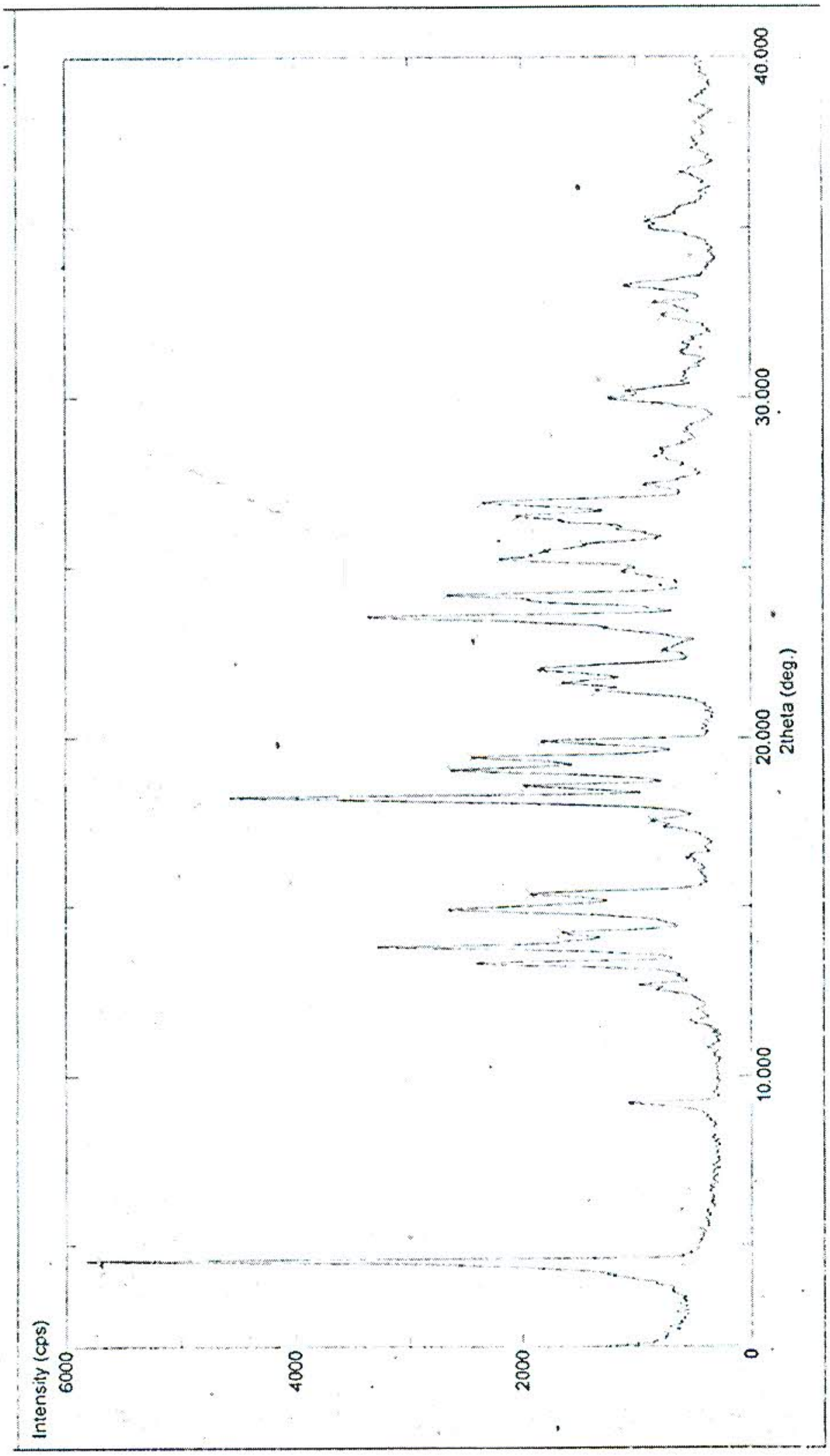
FIG. 5



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FIELD OF THE INVENTION

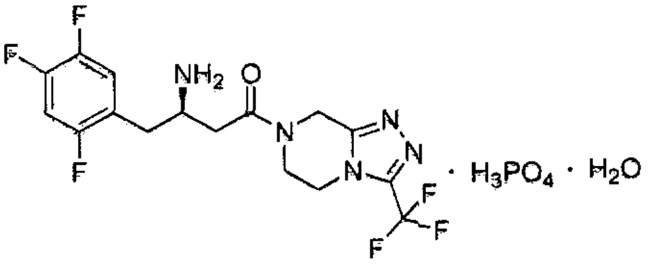
The field of present invention relates to an improved process for the preparation of sitagliptin phosphate. In particular, the invention relates to the process for the preparation of substantially pure sitagliptin phosphate. More particularly, the invention relates to an improved process for preparation of Sitagliptin Phosphate.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Sitagliptin (CAS 486460-32-6) is an oral antihyperglycemic (antidiabetic drug) of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. It was developed, and is marketed, by Merck & Co under the trade name of JANUVIA. The tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. This enzyme-inhibiting drug is used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidinedione) for treatment of diabetes mellitus type 2.

Sitagliptin phosphate monohydrate is chemically named as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate and has the following structural Formula (I).



(I)

U.S. Patent No. 6,699,871 B2 (the US'871 Patent) and *J. Med. Chem.* 2005, Vol. 48(1), 141-151 discloses process for preparation of sitagliptin by coupling (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid of Formula (V) with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine of Formula (IV) or salt thereof under standard peptide coupling conditions by using 1-ethyl-3-(3-dimethylaminopropyl)carbodimide (EDC), 1-hydroxy-benzotriazole (HOBT) and a base diisopropylethylamine in solvents like N,N-dimethylformamide (DMF) or methylene dichloride (MDC).

U.S. Patent No. 7,326,708 B2 (the US'708 Patent) discloses preparation of sitagliptin dihydrogenphosphate salt and crystalline hydrates thereof, in particular a crystalline monohydrate and their pharmaceutical compositions.

U.S. Patent No. 7,495,123 B2 (the US'123 Patent) discloses process for preparation of enantiomerically enriched beta amino acid derivatives i.e. sitagliptin wherein the amino group is unprotected by asymmetric hydrogenation of a prochiral beta amino acrylic acid or derivative thereof, wherein the enamine amino group is unprotected, in the presence of a rhodium metal precursor complexed with a chiral mono- or bisphosphine ligand.

U.S. Patent Application Publication No. 2009/0123983 A1 discloses the enzymatic reduction processes for the preparation of (S) or (R) methyl 4-(2,4,5-trifluorophenyl)-3-hydroxybutanoate, an intermediate in the synthesis of sitagliptin by combining methyl 4-(2,4,5-trifluorophenyl)-3-hydroxybutanoate with an enzyme that stereoselectively reduces a ketone to form an alcohol, and co-factor.

U.S. Patent Application Publication No. 2009/0192326 A1 (the US '326 A1) discloses a process for preparation of 3-amino-4-(2,4,5-trifluorophenyl)butanoic acid alkyl ester, an intermediate of sitagliptin and process for preparation of sitagliptin. The US '326 A1 discloses reacting 3-tert-butoxycarbonylamino-4-(2,4,5-trifluorophenyl)butanoic acid with 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine hydrochloride in presence of dicyclohexylcarbodiimide as coupling agent and 4-dimethylaminopyridine (DMAP) as catalyst to obtain 4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)-4-oxobutan-2-yl-carbamate in N,N-dimethylformamide (DMF), and then removing the amino protected group in 4-(3-

(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)-4-oxobutan-2-yl-carbamate to obtain sitagliptin.

International (PCT) Publication WO 2010/122578 A2 discloses process for preparation of sitagliptin by coupling (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid of Formula (V) with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine hydrochloride of Formula (IV) under standard peptide coupling conditions using suitable condensing agent N,N'-Dicyclohexyl carbodiimide (DCC) in presence of hydroxybenzotriazole (HOBT) or 4-dimethylaminopyridine (DMAP).

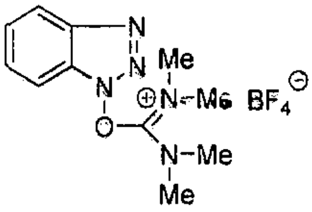
International (PCT) Publication WO 2012/150328 A2 discloses alternative processes for the preparation of sitagliptin wherein N,N'-Dicyclohexyl carbodiimide (DCC) or 1-ethyl-3-(3-dimethyl-aminopropyl)carbodimide (EDC) is used as coupling agent in presence of hydroxybenzotriazole (HOBT).

International (PCT) Publication WO 2013/013833 A1 discloses the process for preparation of sitagliptin comprises reaction carried out under standard peptide coupling conditions, using 1-ethyl-3-(3-dimethylaminopropyl)carbodimide (EDC), 1-hydroxybenzotriazole (HOBT) and a base usually diisopropylethylamine, in a solvent such as N,N-Dimethylformamide (DMF) or methylene dichloride (MDC). The protecting group is then removed with trifluoroacetic acid or methanolic hydrogen chloride in the case of tert-butoxycarbonyl as protecting group.

Therefore, one of the objectives of the present invention is to provide an alternative approach for the preparation of sitagliptin which avoids use of standard coupling agents and which provides atleast an useful alternative approach over the one disclosed in the art. In view of the above cited prior art, it is therefore, desirable to provide an efficient process for the preparation of sitagliptin.

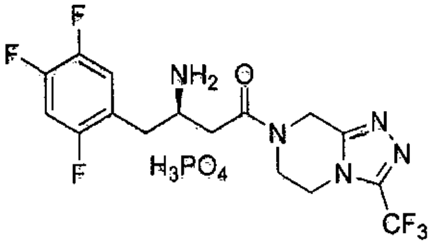
SUMMARY OF THE INVENTION

In one general aspect, there is provided use of O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) of Formula (A) as coupling agent for the preparation of sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I).

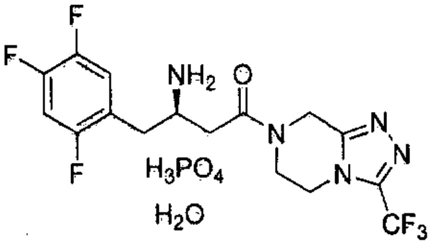


(A)

In another general aspect, there is an improved process for the preparation of sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I),



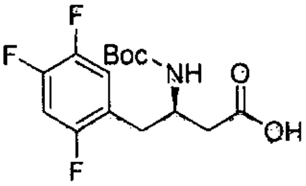
(II)



(I)

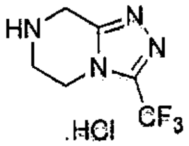
the process comprising:

(a) coupling (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid of Formula (V),



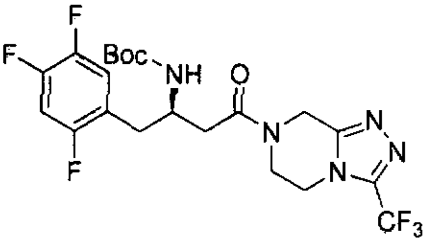
(V)

with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine or its hydrochloride of Formula (IV),



(IV)

in presence of coupling agent TBTU and a base in suitable organic solvent to obtain (*R*)-tert-butyl 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-ylcarbamate of Formula (III);

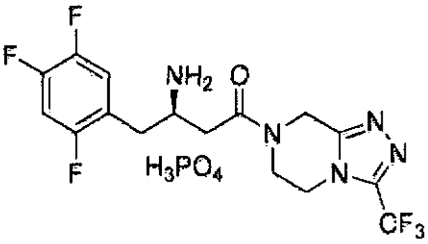


(III)

(b) deprotecting the compound of Formula (III) with suitable acid in first organic solvent to obtain sitagliptin base by removal of first organic solvent;

(c) treating sitagliptin free base *in-situ* with a base in second organic solvent followed by removal of second organic solvent to obtain residue;

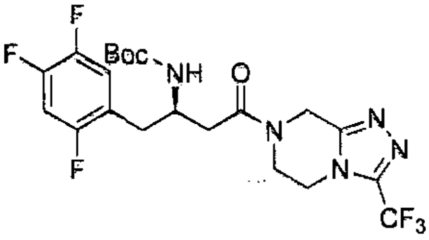
(d) treating the residue with phosphoric acid in first organic solvent or optionally mixture thereof with water to obtain sitagliptin phosphate of Formula (II) by removal of solvent; and



(II)

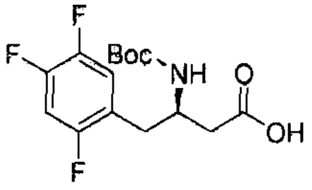
(e) optionally, converting sitagliptin phosphate of Formula (II) to its monohydrate of Formula (I) by *reaction with water.*

In another general aspect, there is provided an improved process for the preparation of (*R*)-tert-butyl 4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluoro phenyl)butan-2-ylcarbamate of Formula (III), an intermediate for sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I),

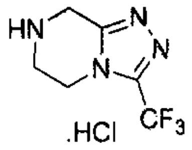


(III)

the process comprising coupling (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl) butanoic acid of Formula (V) with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine or its hydrochloride of Formula (IV),



(V)



(IV)

in presence of coupling agent TBTU and a base in suitable organic solvent to obtain reaction mixture and obtaining compound (III) by addition of water in the reaction mixture.

In another general aspect, there is provided sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I) prepared by the process of present invention and having purity greater than 99.90%, or greater than 99.95% when measured by area percentage of HPLC.

In another general aspect, there is provides sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I) substantially free from impurities, prepared by the process of present invention.

In another general aspect, there is provided a pharmaceutical composition comprising therapeutically effective amount of sitagliptin phosphate of Formula (II) and one or more of pharmaceutically acceptable carriers, diluents or excipients.

In another general aspect, there is provided a pharmaceutical composition comprising therapeutically effective amount of sitagliptin phosphate monohydrate of Formula (I) and one or more of pharmaceutically acceptable carriers, diluents or excipients.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

FIG 1. Shows the X-ray diffractogram (XRD) of sitagliptin phosphate as per example-2.
FIG 2. Shows the differential scanning calorimetry (DSC) of sitagliptin phosphate as per example-2.
FIG 3. Shows the X-ray diffractogram (XRD) of sitagliptin phosphate as per example-3.
FIG 4. Shows the differential scanning calorimetry (DSC) of sitagliptin phosphate as per example-3.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have discovered that use of use of O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) of Formula (A) as a coupling agent provides high purity intermediates, which in turn provides substantially pure sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I).

All ranges recited herein include the endpoints, including those that recite a range "between" two values. Terms such as "about", "general", "substantially" and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those skill in the art. This includes, at the very least, a degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

When a molecule or other material is identified herein as "substantially pure", it generally means, unless specified otherwise, that the material is about 99% pure or more. In general, this refers to purity with regard to unwanted residual solvents, reaction byproducts, impurities and unreacted starting materials.

As used here in the term "obtaining" may include filtration, filtration under vacuum, centrifugation, and decantation to isolate product. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a hot air oven, tray drier, dried under vacuum and/or in a Fluid Bed Drier.

"Suitable solvent" means a single or a combination of two or more solvents.

The terms used throughout the description is defined herein below.

"HOBT" refers to hydroxybenzotriazole.
"EDC" refers to 1-ethyl-3-(3-dimethyl- aminopropyl)carbodimide.
"DCC" refers to N,N'-Dicyclohexyl carbodiimide.
"TBTU" refers to O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

"DMAP" refers to 4-dimethylaminopyridine.

"DMF" refers to N,N-dimethylforamide.

"DMAc" refers to N,N-dimethylacetamide.

"MDC" refers to methylene dichloride.

"DMSO" refers to N,N-dimethylsulfoxide.

"NMP" refers to N-methylpyrrolidone.

"THF" refers to tetrahydrofuran.

"IPA" refers to isopropanol.

"TEA" refers to triethylamine.

"TBA" refers to tert-butyl amine.

"DIPA" refers to diisopropyl amine.

"DIPEA" refers to diisopropyl ethylamine.

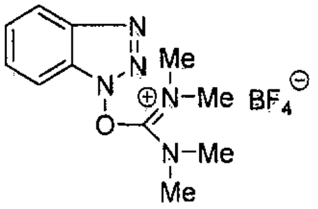
"DBU" refers to 1,8-diazabicyclo[5.4.0]undec-7-ene.

"DABCO" refers to 1,4-diazabicyclo[2.2.2]octane.

"DBN" refers to 1,5-Diazabicyclo[4.3.0]non-5-ene

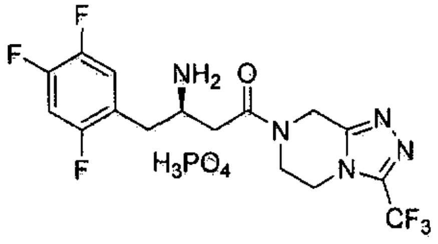
"HPLC" refers to high performance liquid chromatography.

In one general aspect, there is provided use of O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) of Formula (A) as coupling agent for the preparation of sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I).

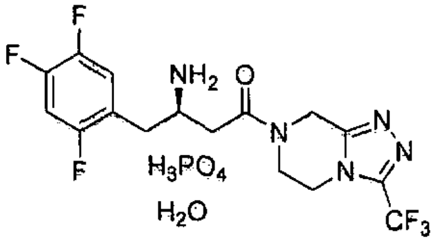


(A)

In another general aspect, there is an improved process for the preparation of sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I),



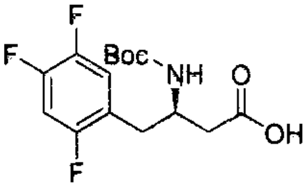
(II)



(I)

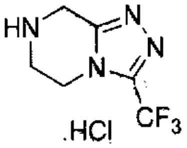
the process comprising:

(a) coupling (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid of Formula (V),



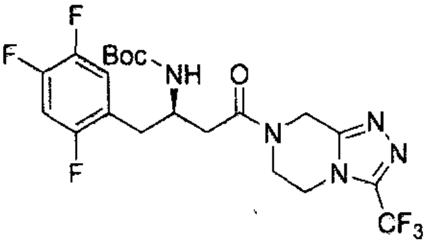
(V)

with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine or its hydrochloride of Formula (IV),



(IV)

in presence of coupling agent TBTU and a base in suitable organic solvent to obtain (*R*)-tert-butyl 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-ylcarbamate of Formula (III);

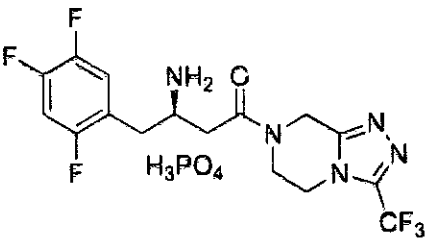


(III)

(b) deprotecting the compound of Formula (III) with suitable acid in first organic solvent to obtain sitagliptin base by removal of first organic solvent;

(c) treating sitagliptin free base *in-situ* with a base in second organic solvent followed by removal of second organic solvent to obtain residue;

(d) treating the residue with phosphoric acid in first organic solvent or optionally mixture thereof with water to obtain sitagliptin phosphate of Formula (II) by removal of solvent; and



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(II)

(e) optionally, converting sitagliptin phosphate of Formula (II) to its monohydrate of Formula (I) by reaction with water.

In general, the base comprises alkali metal hydroxides like sodium hydroxide, potassium hydroxide, lithium hydroxide; alkali metal carbonates like sodium carbonate, potassium carbonate and alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or its aqueous solution or organic bases like methyl amine, ethyl amine, TEA, TBA, DIPA, DIPEA, pyridine, piperidine, morpholine, DBU, DABCO or DBN and the like. In particular, DIPEA may be used.

In general, the suitable organic solvent comprises one or more of water, methanol, ethanol, isopropanol, ethyl acetate, isopropyl acetate, n-butyl acetate, acetone, methyl ethyl ketone, methyl isobutyl ketone, DMF, DMAc, DMSO, NMP, MDC, THF, 1,4-dioxane and the like. In particular, DMF or MDC may be used.

In general, the suitable acid comprises hydrochloric acid, triflouroacetic acid, sulfuric acid, pivalic acid, acetic acid, formic acid and the like. In particular hydrochloric acid or triflouroacetic acid may be used. The embodiments of the process comprises use of hydrochloric acid in form of its isopropanolic solution, hydrochloric acid gas or its solution in suitable solvent like acetone, ethyl acetate etc. More particularly, the isopropanolic hydrochloride solution may be used.

The first organic solvent comprises one or more of alcohols like methanol, ethanol, n-propanol, isopropanol, n-butanol; ketones like acetone, methyl ethyl ketone, methyl isobutyl ketone; chloro solvents like MDC, chloroform, ethylene dichloride and chlorobenzene; hydrocarbons like toluene, xylene, ethylbenzene; esters like ethyl acetate, isopropyl acetate, n-butyl acetate; ethers like tetrahydrofuran, diethyl ether, diisopropyl ether, methyl tert-butyl ether and polar solvents like water, DMF, DMAc, DMSO, NMP and the like. In particular, isopropanol may be used.

The first organic solvent may be removed by the known techniques in the art but not limited to distillation, distillation under vacuum, filtration, decantation, evaporation or evaporation under reduced pressure, centrifugation and the like. The removal of first organic solvent provides sitagliptin base which is not isolated.

The sitagliptin free base may be *in-situ* treated with a base. The suitable base comprises alkali metal hydroxides like sodium hydroxide, potassium hydroxide, lithium hydroxide; alkali metal carbonates like sodium carbonate, potassium carbonate and alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or its aqueous solution. In particular, 40% sodium hydroxide solution may be used.

In general the second organic solvent comprises one or more of alcohols like methanol, ethanol, n-propanol, isopropanol, n-butanol; ketones like acetone, methyl ethyl ketone, methyl isobutyl ketone; chloro solvents like MDC, chloroform, ethylene dichloride and chlorobenzene; hydrocarbons like toluene, xylene, ethylbenzene; esters like ethyl acetate, isopropyl acetate, n-butyl acetate; ethers like tetrahydrofuran, diethyl ether, diisopropyl ether, methyl tert-butyl ether and polar solvents like water, DMF, DMAc, DMSO, NMP and the like. In particular, MDC may be used,

The second organic solvent may be removed by the known techniques in the art but not limited to distillation, distillation under vacuum, filtration, decantation, evaporation or evaporation under reduced pressure, centrifugation and the like. The removal of second organic solvent provides sitagliptin base as residue which is not isolated.

The embodiments of the process include treating the residue with phosphoric acid in first organic solvent or mixture thereof with water. In particular, the residue may be treated with 85% phosphoric acid in mixture of isopropanol and water to obtain sitagliptin phosphate of Formula (II).

The sitagliptin phosphate of Formula (II) may be obtained by removal of solvent by the known techniques in the art but not limited to distillation, distillation under vacuum, filtration, decantation, evaporation or evaporation under reduced pressure, centrifugation and the like. In particular, sitagliptin phosphate of Formula (II) may be obtained by filtration of obtained precipitates and drying. The sitagliptin phosphate thus obtained was anhydrous having moisture content less than 0.5% wt/wt.

The anhydrous sitagliptin phosphate is crystalline in nature and may be characterized by X-ray powder diffraction pattern substantially as depicted in FIG.1 and differential scanning calorimetry substantially as depicted in FIG.2.

The anhydrous sitagliptin phosphate may be characterized by X-ray powder diffraction pattern having characteristic peaks at about 4.5°, 9.2°, 13.9°, 15.0°, 18.2°, 22.0°, 32.9° and 33.4°±0.2° 2θ.

The anhydrous sitagliptin phosphate may be characterized by differential scanning calorimetery having endothermic peak at about 212.6°C.

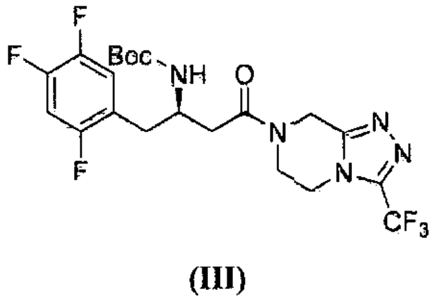
The anhydrous sitagliptin phosphate thus obtained may be optionally converted to its monohydrate of Formula (I) by reaction with water. In particular, the sitagliptin phosphate may be treated with water in isopropanol at about 75°C to 80°C optionally in presence of seed crystals of sitagliptin phosphate monohydrate.

The sitagliptin phosphate monohydrate of Formula (I) thus obtained is crystalline in nature and may be characterized by X-ray powder diffraction pattern substantially as depicted in FIG.3 and differential scanning calorimetry substantially as depicted in FIG.4.

The sitagliptin phosphate monohydrate may be characterized by X-ray powder diffraction pattern having characteristic peaks at about 13.2°, 13.8°, 15.9°, 18.4°, 19.1°, 21.2°, 24.0°, 25.0°, 25.7°, 29.5°, and 30.9°±0.2° 2θ.

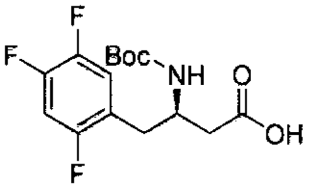
The sitagliptin phosphate monohydrate may be characterized by differential scanning calorimetery having endothermic peaks at about 135.4°C and 210.6°C.

In another general aspect, there is provided an improved process for the preparation of (*R*)-tert-butyl 4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluoro phenyl)butan-2-ylcarbamate of Formula (III), an intermediate for sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I),

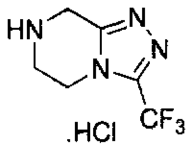


(III)

the process comprising coupling (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl) butanoic acid of Formula (V) with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine or its hydrochloride of Formula (IV),



(V)



(IV)

in presence of coupling agent TBTU and a base in suitable organic solvent to obtain reaction mixture and obtaining compound (III) by addition of water in the reaction mixture.

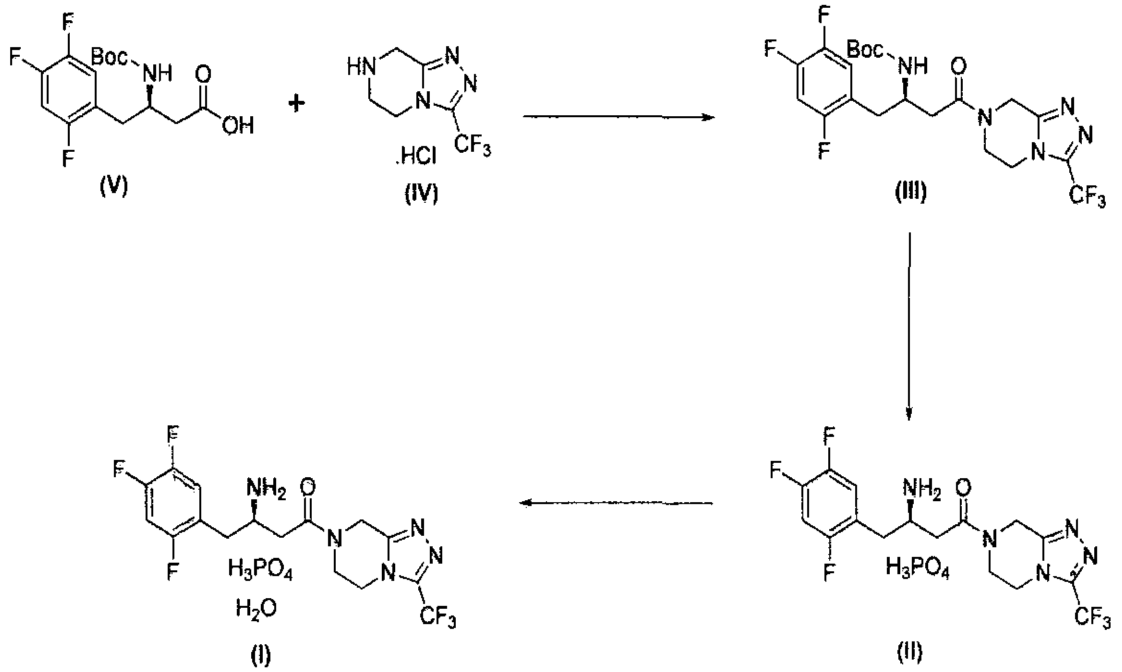
In another general aspect, there is provided sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I) prepared by the process of present invention and having purity greater than 99.90%, or greater than 99.95% when measured by area percentage of HPLC.

In another general aspect, there is provides sitagliptin phosphate of Formula (II) or its monohydrate of Formula (I) substantially free from impurities, prepared by the process of present invention.

In another general aspect, there is provided a pharmaceutical composition comprising therapeutically effective amount of sitagliptin phosphate of Formula (II) and one or more of pharmaceutically acceptable carriers, diluents or excipients.

In another general aspect, there is provided a pharmaceutical composition comprising therapeutically effective amount of sitagliptin phosphate monohydrate of Formula (I) and one or more of pharmaceutically acceptable carriers, diluents or excipients.

In another general aspect, sitagliptin phosphate may be prepared by the reaction scheme-1 as shown below, which is also the scope of the present invention.

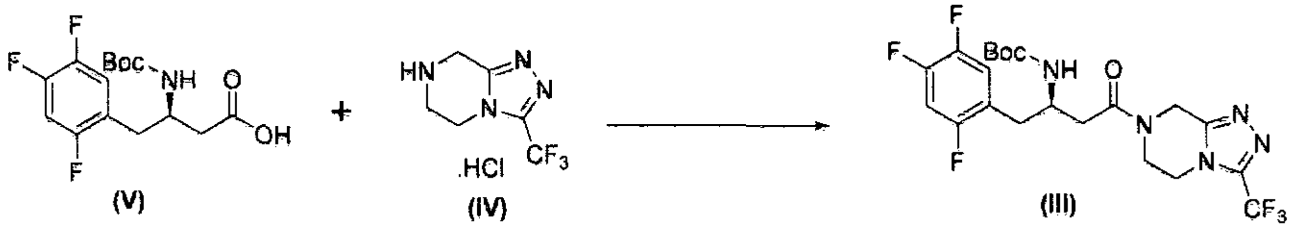


Scheme-1

The present invention is further illustrated by the following example which is provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Examples

Example-1: Preparation of (R)-tert-butyl 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-ylcarbamate of Formula (III)

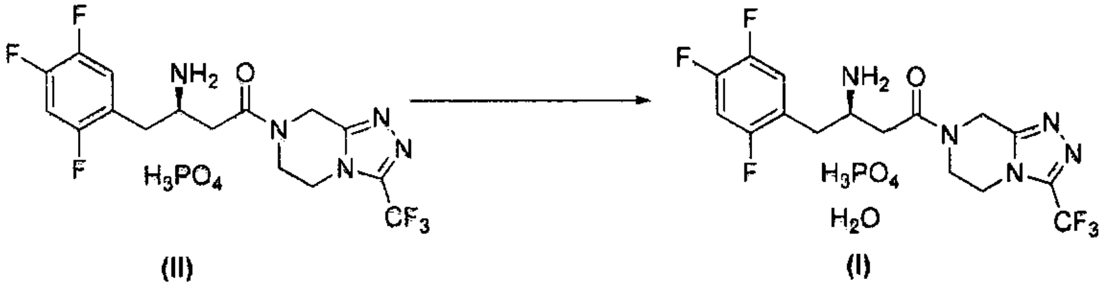


In 250 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, were added 40 mL DMF, 10 gm (3*R*)-N-(tert-butoxycarbonyl)-3-amino-4-(2,4,5-trifluorophenyl) butanoic acid of Formula (V) and 7.2 gm 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyrazine hydrochloride of Formula (IV). The reaction mixture was cooled to 0 to 5°C and 10.6 gm TBTU was added. 11.63 g DIPEA was added to the reaction mixture and stirred for 1 hour. *After the completion of reaction, 100 mL water and 60 mL 1%* $NaHCO_3$ *was added.* The reaction mixture was stirred for 1 hour at 25°C to 35°C. The precipitates were filtered and washed with water. The product was dried under vacuum at 60°C for 4 hours to obtain 15 g of title compound.

Example-2: Preparation of Sitagliptin Phosphate of Formula (II)

In 250 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, was added 26.7 mL IPA.HCl 16% solution. The reaction mass was heated to 50°C *and stir for 5 hours. After the completion of reaction, IPA was distilled completely to get a semisolid* mass under vacuum at about 60°C followed by addition of 56 mL MDC and 56 mL water. The reaction mixture was treated with 40% sodium hydroxide solution to adjust the pH of 12 to 13. The separated aqueous layer was extracted with 28 mL MDC. The MDC layer was washed with 28 mL water, charcoalized and filtered. The filtrate was distilled completely to remove MDC at about 50°C. 7 mL IPA was added and distilled to remove traces of MDC. 14 mL water and 28 mL IPA were added and 3.52 gm, 85% phosphoric acid was added at 25 to 35°C. The reaction mixture was stirred for 1 hour at 25°C and heated to 75 to 80°C for 1 hour. 70 mL IPA was added and stirred for 1 hour. The reaction mixture was cooled to 0 to 5°C and stirred for 1 hour. The precipitates were filtered and washed with IPA. The product was dried under vacuum at 50°C for 4 hours to obtain 11 g sitagliptin phosphate. M/C = 0.31% (XRD: FIG.1) and (DSC: FIG.2).

Example-3: Preparation of Sitagliptin Phosphate Monohydrate (I)



In 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, was added 52.5 mL IPA, 10.5 gm sitagliptin phosphate as obtained in example 2 and

15.8 mL water. The reaction mixture was heated to 75 to 80°C and stirred for 30 min. The seed crystals of sitagliptin phosphate monohydrate were added at temperature of 58 to 60°C and cooled to 0 to 5°C. The reaction mixture was stirred for 1 hour at 0 to 5°C and filtered. The solid was washed with 10.5 mL IPA and dried under vacuum at 50°C for 4 hours to obtain 10.5 g of title compound. M/C: 3.82% (XRD: FIG.3) and (DSC: FIG.4).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Dated this 13th day of March, 2013

Signature:

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GENERAL MANAGER -IPR
CADILA HEALTHCARE LIMITED