The present invention relates to a process for the preparation of vildagliptin.
IMPROVED PROCESS FOR PREPARATION OF VILDAGLIPTIN

PRIORITY
This application claims the benefit to Indian Provisional Application No. 3622/MUM/2012, filed on December 26, 2012, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION
The present invention relates to an improved process for the preparation of vildagliptin.

BACKGROUND OF THE INVENTION
Vildagliptin is a dipeptidyl peptidase IV (DPP-IV) inhibitor and chemically known as (S)-1-[2-(3-hydroxyadamantan-1-ylamino) acetyl] pyrrolidine-2-carbonitrile and is represented by compound of Formula I.

![Formula I](image)

(S)-Vildagliptin is currently marketed in the European Union under the trade name GALVUS®, which is indicated for type-2 diabetes mellitus, as tablets in the dosage strengths of 50 mg and 100 mg.

European patent EP 1137635 B1 (‘635 patent) describes process for the preparation of vildagliptin.


In light of the evolving and more rigorous requirements demanded of drug manufacturers and the prevailing disadvantages present with the prior art, there is a need for an improved process for
the preparation of vildagliptin and its intermediates, which circumvents the likely formation of isomeric and other process-related impurities; while ensuring a target vildagliptin product with optimum yield and purity.

Surprisingly, it has been found that use of nitrile solvent in the preparation of compound of formula IV has significant advantages in getting easily filterable compound of formula IV with high purity, which leads to vildagliptin with high purity for pharmaceutical use. There is disadvantage in reported process that if a solvent other than nitrile solvent is used then there is formation of sticky mass of compound of formula IV, which is not easily filterable and hence not a commercially viable process.

The present invention provides a process which is simple, ecofriendly, inexpensive, reproducible, robust and well suited on commercial scale.

SUMMARY OF THE INVENTION

A process for the preparation of vildagliptin, a compound of Formula I,

\[
\begin{align*}
\text{HO} & \quad \text{NH} \quad \text{N} \quad \text{CN} \\
\text{Formula I} \\
\text{HN} & \quad \text{HN} \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{Formula VI}
\end{align*}
\]

comprising: a) reacting a compound of Formula VI

with a compound of formula V,
in the presence of a nitrile solvent to form a compound of formula IV;

Formula IV

b) reacting the compound of formula IV with a dehydrating agent to form a compound of formula III,

Formula III

c) reacting the compound of formula III with a compound of formula II, to form a compound of formula I.
DETAILED DESCRIPTION OF INVENTION

A process for the preparation of vildagliptin, a compound of Formula I,

\[
\text{Formula I}
\]

comprising: a) reacting a compound of Formula VI

\[
\text{Formula VI}
\]

with a compound of formula V,

\[
\text{Formula V}
\]

in the presence of a nitrile solvent to form a compound of formula IV;

\[
\text{Formula IV}
\]

b) reacting the compound of formula IV with a dehydrating agent to form a compound of formula III.
c) reacting the compound of formula III with a compound of formula II,

\[
\begin{align*}
\text{Formula III} & \quad \begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{N} \\
\text{CN}
\end{array} \\
\text{Formula II} & \quad \begin{array}{c}
\text{HO} \\
\text{NH}_2
\end{array}
\end{align*}
\]

to form a compound of formula I.

In step a), the reaction of a compound of formula VI, with a compound of formula V, is carried out in presence of a nitrile solvent. The nitrile solvent may be selected from the group consisting of acetonitrile, propionitrile, butyronitrile, isobutyronitrile, benzonitrile and the like. Preferably, acetonitrile.

In step a), the reaction of a compound of formula VI, with a compound of formula V, may be carried out in presence or absence of a base.

The base may be selected from an inorganic base or organic base.

The inorganic base may be selected from alkali metal or alkaline earth metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, alkali metal or alkaline earth metal hydroxide, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, alkali metal alkoxide such as sodium methoxide, potassium methoxide and the like. Preferably, potassium bicarbonate.

The organic base may be selected from the group consisting of organic amines such as triethylamine, diisopropylethylamine, N,N-dimethylaniline, 4-Bromo-N,N-dimethylaniline, pyridine, 2-bromopyridine, 3-bromopyridine, 4-bromopyridine, 4-dimethylaminopyridine, Di-tert butyl pyridine, 2,6-Di-tert-butyl-4-methylpyridine, Quinoline, tri-n-butylamine, N-
methylmorpholine, 2,6-Lutidine, imidazole, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-
diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like and bases
having pKa value 2.5 to 12.

In step a), the reaction of a compound of formula VI, with a compound of formula V, may be
carried out in presence of an acid scavenger. The acid scavenger is a substance that scavenges
the acid formed in the reaction for example alkali or alkaline earth metal salt of acids such as
sodium acetate, sodium hexanoate and the like.

In step b), the dehydrating agent may be selected from the group consisting of phosphorous
oxychloride (POCl3), Vilsmeier reagent (a mixture of dimethylformamide (DMF) and POCl3),
cyanuric acid halide, trifluoroacetic anhydride, Gold reagent (prepared from cyanuric chloride and
DMF), mixture of DMF and triphosgene, mixture of diethylformamide (DEF) and POCl3,
mixture of DMF and thionyl chloride (SOCI2), mixture of DMF and oxalyl chloride and the like.
Preferably, Vilsmeier reagent.

The reaction of compound of formula IV with a dehydrating agent may be carried out with or
without a solvent.

The solvent may be selected from the group consisting of halogenated hydrocarbon, esters and
ether.

The halogenated hydrocarbon may be selected from the group consisting of ethylene dichloride,
methylene dichloride and the like.

The ester solvent may be selected from the group consisting of ethyl acetate, butyl acetate and
the like.

The ether solvent may be selected from the group consisting of tetrahydrofuran, tetrahydropyran
and the like.

The reaction of compound of formula IV with a dehydrating agent may be carried out in the
temperature of about -5° C to about 40° C, preferably at about 0° C to 20° C more preferably at
about 15° C to 20° C.
In one embodiment the compound of formula IV obtained may be isolated from the reaction mixture by crystallization or slurrying in an organic solvent.

In one embodiment the compound of formula IV is isolated from the reaction mixture by slurrying in presence of nitrile solvent, ester solvent or a mixture of nitrile solvent and ester solvent. For example a mixture of acetonitrile and ethyl acetate may be used for isolating the compound of formula IV.

In one embodiment the compound of formula IV is isolated from the reaction mixture by crystallizing the compound of formula IV from the reaction mixture by removal of solvent the reaction mixture or addition of an anti-solvent to the reaction mixture.

After completion of reaction the pH of the reaction mixture is adjusted in the range of about 6-8 by use of a base.

The base may be selected from alkali metal or alkaline earth metal hydroxide, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, alkali metal alkoxide such as sodium methoxide, potassium methoxide, alkali metal or alkaline earth metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and the like.

The compound of formula III obtained may be isolated from the reaction mixture by crystallization or slurrying in an organic solvent.

In one embodiment the compound of formula III is isolated from the reaction mixture by slurrying in presence of an ether solvent such as methyl tert butyl ether.

In one embodiment the compound of formula III is isolated from the reaction mixture by slurrying in presence of a mixture of an alcoholic solvent and ether solvent. For example a mixture of isopropyl alcohol and methyl tert butyl ether may be used for isolating the compound of formula III.

In one embodiment the compound of formula III is isolated from the reaction mixture by crystallizing the compound of formula III from the reaction mixture by removal of solvent the reaction mixture or addition of an anti-solvent to the reaction mixture.
In step c) the compound of formula III is reacted with compound of formula II.

The reaction of compound of formula III with a compound of formula II may be carried out in presence of a base.

The base may be selected from an inorganic base or organic base.

The inorganic base may be selected from alkali metal or alkaline earth metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, alkali metal or alkaline earth metal hydroxide, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, alkali metal alkoxide such as sodium methoxide, potassium methoxide and the like. Preferably, potassium carbonate.

The organic base may be selected from the group consisting of organic amines such as triethylamine, diisopropylethylamine, N,N-dimethylaniline, 4-Bromo-N,N-dimethylaniline, pyridine, 2-bromopyridine, 3-bromopyridine, 4-bromopyridine, 4-dimethylaminopyridine, Diter-butyl pyridine, 2,6-Di-tert-butyl-4-methylpyridine, Quinoline, tri-n-butylamine, N-methylmorpholine, 2,6-Lutidine, imidazole, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like and bases having pKa value 2.5 to 12.

The reaction of compound of formula III with a compound of formula II may be carried out in presence of a solvent.

The solvent may be selected from the group consisting of nitrile, ester and alcohols. Preferably nitriles such as acetonitrile.

The reaction of compound of formula III with a compound of formula II may be carried out in the temperature range of about 30°C to about 100°C, preferably about 40°C to 80°C, more preferably about 70°C to 75°C.

In one embodiment the present invention provides a process for preparation of vildagliptin, compound of formula I, by reaction of compound of formula III with a compound of formula II, wherein compound of formula III was added in lot wise, preferably in four lots at about 40°C to 80°C, preferably at about 70°C to 75°C to control impurity D.
In one embodiment the present invention provides a process for preparation of vildagliptin, compound of formula I, wherein compound of formula III and compound of formula IV may be used in-situ.

In one embodiment the present invention provides a process for preparation of vildagliptin, compound of formula I, comprising:

a) reacting a compound of formula VI with a compound of formula V in the presence of a nitrile solvent to form a compound of formula IV;

b) purifying the compound of formula IV with nitrile solvent, ester solvent or mixture thereof;

c) reacting the compound of formula IV with a dehydrating agent to form a compound of formula III;

d) purifying the compound of formula III with alcohol solvent, ether solvent or mixture thereof; and

e) reacting the compound of formula III with a compound of formula II to form a compound of formula I.

The nitrile solvent, ester solvent, ether solvent and alcohol solvent are as discussed supra.

In one embodiment the present invention provides a process for preparation of vildagliptin, compound of formula I, having impurity G and/or impurity H less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC, obtained by process as described above.

The compound of formula I obtained may be isolated from the reaction mixture in a solvent selected from the group consisting of esters, ketones, alcohols or mixtures thereof by slurrying or recrystallization.

The esters may be selected from the group consisting of ethyl acetate, propyl acetate, butyl acetate and the like.

The ketones may be selected from the group consisting of acetone, methyl ethyl ketone and the like.
The alcohols may be selected from the group consisting of methanol, ethanol, propanol, isopropanol and the like.

In one embodiment the compound of formula I is isolated from the reaction mixture by slurrying in ethyl acetate.

5 In one embodiment the compound of formula I is isolated from the reaction mixture by slurrying in methyl ethyl ketone.

In one embodiment the compound of formula I is isolated from the reaction mixture by recrystallization in methyl ethyl ketone.

In one embodiment the present invention provides a process for purification of vildagliptin, compound of formula I by a process comprising recrystallizing in an alcoholic solvent system.

In one embodiment the present invention provides a process for purification of vildagliptin, compound of formula I by a process comprising recrystallizing in isopropyl alcohol.

In one embodiment, the present invention provides vildagliptin obtained by the processes herein described, having purity more than about 99.6% as measured by High Performance Liquid Chromatography (HPLC).

In one embodiment, the present invention provides vildagliptin having compound of formula IV less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.

In one embodiment, the present invention provides vildagliptin having compound of formula III less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.

20 In one embodiment, the present invention provides vildagliptin having compound of formula II less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.

In one embodiment, the present invention provides vildagliptin having impurity D less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.
In one embodiment, the present invention provides vildagliptin having impurity E or its isomer or its salt less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.

In one embodiment, the present invention provides vildagliptin having impurity F or its isomer or its salt less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.

In one embodiment, the present invention provides S-vildagliptin having R-vildagliptin impurity is present less than 0.15% w/w relative to the amount of S-vildagliptin as determined by chiral HPLC.
In one embodiment, the present invention provides compound of formula III and/or vildagliptin free of impurity G or its isomer or its salt as determined by HPLC.

In one embodiment, the present invention provides compound of formula IV, compound of formula III, and/or vildagliptin free of impurity H or its isomer or its salt as determined by HPLC.

In one embodiment, the present invention provides vildagliptin, where is one or more of compounds of formula II, III, IV, impurity D, impurity E or impurity F are present less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC and R-vildagliptin is present less than 0.15% w/w relative to the amount of vildagliptin as determined by chiral-HPLC.
In one embodiment, the present invention provides vildagliptin, having compound of formula III (genotoxic impurity) below detection limit, preferably below 15 parts per million (ppm).

In one embodiment, the present invention provides vildagliptin, having compound of formula IV (genotoxic impurity) below detection limit, preferably below 15 parts per million (ppm).

In one embodiment the present invention provides vildagliptin, compound of formula I having bulk density of 0.54 g/cc.

In yet another embodiment, the present invention provides pharmaceutical compositions comprising vildagliptin obtained by the processes herein described, having a \(D_{50}\) particle size of about 375 microns, \(D_{50}\) particle size of about 207 microns and \(D_{10}\) particle size of about 37 microns.

In yet another embodiment, the present invention provides pharmaceutical compositions comprising micronized vildagliptin obtained by the processes herein described, having a \(D_{90}\) particle size of about 78 microns, \(D_{50}\) particle size of about 17 microns and \(D_{10}\) particle size of about 4 microns.

In one embodiment the present invention provides a process for the preparation of a compound of Formula IV,

\[
\begin{align*}
\text{Formula IV} \\
\end{align*}
\]

comprising: a) reacting a compound of Formula VI

\[
\begin{align*}
\text{Formula VI} \\
\end{align*}
\]
with a compound of formula V,

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Cl}
\end{array}
\]

Formula V

in the presence of an ester, halogenated hydrocarbons, ether solvent to form a compound of Formula IV;

The ester solvent may be selected from the group consisting of methyl acetate, ethyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like and mixtures thereof.

The halogenated hydrocarbons solvent may be selected from methylene chloride (MDC), ethylene chloride (EDC) and like. Ether solvent may be selected from tetrahydrofuran, tetrahydropyran and the like.

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.
EXAMPLES

Example 1: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carboxamide, compound of Formula IV.

In a clean round bottom flask, 100gm L-prolinamide, 1800ml acetonitrile and 290.16gm K₂C₀₃ were charged. The reaction mass was stirred, cooled to about 10-20°C and 108.8gm of chloroacetyl chloride was added. Temperature of reaction mass was raised to about RT, stirred for about one hour, filtered, washed with acetonitrile and concentrated under vacuum. 300ml ethyl acetate was added to reaction mass, stirred at about 50-55 °C, cooled to about 0-5 °C and stirred for about 1-2 hour. The reaction mass was filtered, washed with ethyl acetate and dried under vacuum and product isolated as a solid 130-140gm. (Yield: 77-85%; HPLC purity >97%). Impurity H is less than 0.2% w/w relative to the amount of compound of formula IV as determined by HPLC.

Example 2: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carboxamide, compound of Formula IV.

In a clean round bottom flask, 100gm L-prolinamide, 1000ml MDC and 290.16gm K₂C₀₃ were charged. The reaction mass was stirred, cooled to about 10-20°C and 108.8gm of chloroacetyl chloride was added. Temperature of reaction mass was raised to about RT, stirred for about one hour, filtered, washed with MDC and concentrated under vacuum. 300ml ethyl acetate was added to reaction mass, stirred at about 50-55 °C, cooled to about 0-5 °C. The reaction mass was filtered, washed with ethyl acetate and dried under vacuum and product isolated as a solid 100gm. (HPLC purity >97%)

Example 3: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carboxamide, compound of Formula IV.

In a clean round bottom flask, 100gm L-prolinamide, 1500ml acetonitrile and 93.39gm sodium acetate were charged. The reaction mass was stirred, cooled to about 10-15°C and 108.8gm of chloroacetyl chloride was added. Temperature of reaction mass was raised to about RT, stirred for about one hour, filtered, washed with acetonitrile and concentrated under vacuum. Ethyl acetate was added to reaction mass, stirred and cooled to about 0-5 °C. The reaction mass was
filtered, washed with ethyl acetate and dried under vacuum and product isolated as a solid 100gm. (HPLC purity >97%)

Example 4: Preparation of (S)-l-(2-chloroacetyl) pyrroUidine-2-carboxamide, compound of Formula IV.

In a clean round bottom flask, 100gm L-prolinamide, 1000ml THF and 166gm sodium 2-ethyl hexanoate were charged. The reaction mass was stirred, cooled to about 10-15°C and 108.8gm of chloroacetyl chloride was added. Temperature of reaction mass was raised to about RT, stirred for about one hour and cooled to about 0-5 °C. The reaction mass was filtered, washed with THF and dried under vacuum and product isolated as a solid 135gm. (HPLC purity >97%)

Example 5: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, 100gm compound IV, 3000ml ethyl acetate and phosphorous oxychloride were charged and temperature of reaction mass was raised to about 80-85°C. The reaction mass was cooled to about 5-10°C and water was added. Aqueous layer was extracted with ethyl acetate and pH was adjusted to about 7-8 by NaOH solution. Ethyl acetate layer was concentrated under vacuum to get residue and IPA and methyl tert butyl ether was added to residue. The precipitated solid was stirred for about 2 hours at about 0-5°C, filtered, washed with cold methyl tert butyl ether and dried under vacuum and product isolated as a solid 58-62gm (Yield 65-68%; HPLC purity > 99%).

Example 6: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, 100gm compound IV, 1200ml ethyl acetate and 76.6gm DMF were charged and reaction mass was cooled to about 15°C. Phosphorous oxychloride was added to the reaction mass, stirred for about 90 minutes, cooled to about 5-10°C and water was added. Aqueous layer was extracted with ethyl acetate and pH was adjusted to about 7-8 by K₂CＯ₃ solution. Ethyl acetate layer was concentrated under vacuum to get residue and methyl tert butyl ether was added to residue. The precipitated solid was stirred at about 0-5°C for about 2 hours, filtered, washed with cold methyl tert-butyl ether and dried under vacuum and product isolated...
as a solid 58-62gm. (Yield 65-68%; HPLC purity > 98% and other isomer less than 0.15%). Impurity G is less than 0.2% w/w relative to the amount of compound of formula III as determined by HPLC.

Example 7: Preparation of (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, 100gm compound IV, 500ml diethylformamide (DEF) were charged. The reaction mass was cooled to 15°C. Phosphorus oxychloride was added through addition funnel at 15-20°C and the reaction mass was stirred for 90 min. The reaction mass was cooled to 5-10°C. The reaction mass was quenched by adding water. The aqueous layer was separated and extracted with ethyl acetate. The pH of ethyl acetate layer was adjusted the pH to -7-8 by using potassium carbonate solution. The aqueous layer was separated. The ethyl acetate layer was concentrated under vacuum (40-45°C). The residue was degassed. Methyl tert butyl ether was charged to the residue. The precipitated solid was stirred at 0-5°C for 120 min. The solid was filtered and washed with cold methyl tert butyl ether and suck dried. The solid was dried under vacuum at 30-35°C. 58-62gm of solid was obtained (Yield 65-68%, HPLC purity > 98% and other isomer less than 0.15%).

Example 8: Preparation of (S)-1-(2-chloroacetyl) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, 100gm compound IV, 1200 ml of ethyl acetate and 76.6g diethylformamide (DEF) were charged. The reaction mass was cooled to 15°C. Phosphorus oxychloride was added through addition funnel at 15-20°C and the reaction mass was stirred for 90 min. The reaction mass was cooled to 5-10°C. The reaction mass was cooled to 5-10°C. The reaction mass was quenched by adding water. The aqueous layer was separated and extracted with ethyl acetate. The ethyl acetate layers were combined and adjusted the pH to -7-8 by using potassium carbonate solution. The aqueous layer was separated. The ethyl acetate layer was concentrated under vacuum (40-45°C). The residue was degassed. Methyl tert butyl ether was charged to the residue. The precipitated solid was stirred at 0-5°C for 120 min. The solid was filtered and washed with cold methyl tert butyl ether and suck dried. The solid was dried under
vacuum at 30-35°C. 58-62gm of solid was obtained (Yield 65-68%, HPLC purity > 98% and other isomer less than 0.15%).

Example 9: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, 100gm compound IV and 1200 ml of MDC were charged. DMF (76.6gm) was charged in the flask. The reaction mass was cooled to 15°C. Phosphorus oxychloride was added through addition funnel at 15-20°C and the reaction mass was stirred for 90 min. Cool the reaction mass to 5-10°C. The reaction mass was cooled to 5-10°C. The reaction mass was cooled to 5-10°C. The reaction mass was quenched by adding water. The aqueous layer was separated and extracted with MDC. The MDC layers were combined and the pH adjusted to 7-8 by using potassium carbonate solution. The aqueous layer was separated. The MDC layer was concentrated under vacuum (40-45°C). The residue was degassed. Methyl tert butyl ether was charged to the residue. The precipitated solid was stirred at 0-5°C for 120 min. The solid was filtered and washed with cold methyl tert butyl ether and suck dried. The solid was dried under vacuum at 30-35°C. 58-62gm of solid was obtained (Yield 65-68%, HPLC purity > 98% and other isomer less than 0.15%).

Example 10: Preparation of (S)-l-(2-chloroacetyl) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, 100gm compound IV and 500ml of DMF were charged. The reaction mass was cooled to 15°C. A solution of cyanuric chloride (142.8g) in THF was added through addition funnel at 5-10°C. After complete addition, the temperature was raised to 10-15°C and stirred for 90 minutes. The reaction mass was quenched in to cold water and pH was adjusted to 6-7 using potassium carbonate. The reaction mass was extracted with MDC. The MDC layer was washed with water. The MDC layer was concentrated under vacuum (40-45°C). The residue was degassed. The residue was degassed. Methyl tert butyl ether was charged to the residue. The precipitated solid was stirred at 0-5°C for 120 min. The solid was filtered and washed with cold methyl tert butyl ether and suck dried. The solid was dried under vacuum at 30-35°C. 22-35gm of solid was obtained (Yield 25-38%, HPLC purity > 99% and other isomer less than 0.15%).
Example 11: Preparation of \((S)-1-(2\text{-chlooroacetyl})\) pyrrolidine-2-carbonitrile, compound of Formula III.

In a clean round bottom flask, thiposgene (100gm) and 100ml of MDC were charged. The reaction mass was cooled to 5-10°C. A solution of DMF (75gm) in MDC (100ml) was added. After complete addition, the temperature was raised to 15-20°C. The reaction mass was stirred for 30 minutes. The reaction mass was cooled to 5-10°C. The compound of IV was added in one lot. The reaction mass was quenched by adding water. The MDC layer was separated and pH was adjusted to 6-7 by using potassium carbonate. The MDC layer was concentrated under vacuum (40-45°C). The residue was degassed. The residue was degassed. Methyl tert butyl ether was charged to the residue. The precipitated solid was stirred at 0-5°C for 120 min. The solid was filtered and washed with cold methyl tert-butyl ether and suck dried. The solid was dried under vacuum at 30-35°C. 45-50gm of solid was obtained (Yield 50-55%, HPLC purity > 97%).

Example 12: Preparation of vildagliptin, compound of Formula I.

In a clean round bottom flask, (100gm) of l-amino-3-adamantol in 1000ml of acetonitrile were charged. 239.8gm of potassium carbonate was charged to the above flask. The reaction mass was heated to 82-85°C. The compound of formula III (4x25gm), was charged after 60-90 min intervals. After completion of reaction, the reaction mass was cooled to 65-70°C. The reaction mass was filtered and the solid was washed with 500ml acetonitrile and suck dried. The acetonitrile was distilled out from filtrate under vacuum at 50-55°C. Ethyl acetate was charged to the residue and the slurry stirred at 50-55°C for 30-45 minutes. The slurry was cooled to 20-30°C and stirred for 60-90 minutes. The solid was filtered and washed with ethyl acetate and suck dried. The wet cake was suspended in IPA and heated to 80-85°C to get a clear solution. The clear solution was charcoalised and filtered through hyflo. The filtrate was distilled out under vacuum to get final volume to 5Volume. The reaction mass was cooled to -5 to 5°C and stirred for 60-90 minutes. The solid was filtered and washed with IPA and suck dried. The solid was dried under vacuum at 50-55°C. 105 to 120gm of solid was obtained (yield 59-68%, HPLC purity >98%)
Example 13: Preparation of vildagliptin, compound of Formula I.

In a clean round bottom flask, (100gm) of L-amino-3-adamantol in 1000ml of acetonitrile were charged. 239.8gm of potassium carbonate was charged to the above flask. The reaction mass was heated to 82-85°C. The compound of formula III (4x25gm), was charged after 60-90 minutes intervals. After completion of reaction, the reaction mass was cooled to 65-70°C. The reaction mass was filtered and the solid was washed with 500ml acetonitrile and suck dried. The acetonitrile was distilled out from filtrate under vacuum at 50-55°C. Methyl ethyl ketone was charged to the residue and the slurry stirred at 50-55°C for 30-45 minutes. The slurry was cooled to 20-30°C and stirred for 60-90 minutes. The solid was filtered and washed with methyl ethyl ketone and suck dried. The wet cake was suspended in IPA and heated to 80-85°C to get a clear solution. The clear solution was charcoalled and filtered through hyflo. The filtrate was distilled out under vacuum to get final volume to 5Volume. The reaction mass was cooled to -5 to 5°C and stirred for 60-90 minutes. The solid was filtered and washed with IPA and suck dried. The solid was dried under vacuum at 50-55°C. 105 to 120gm of solid was obtained (yield 59-68%, HPLC purity >98%)

Example 14: Purification of Vildagliptin, compound of Formula I.

In a clean round bottom flask 100gm of vildagliptin and 450ml IPA were charged. The reaction mass was heated to 80-85°C to get clear solution. The clear solution was stirred for 30-45 min. The reaction mass was cooled to 70-75°C. The clear solution was filtered through micron filter; and the micron filter was washed with IPA (50ml). IPA was distilled under vacuum to get final volume 350ml. The reaction mass was cooled to -5 to 5°C and stirred for 60-90 minutes. The solid obtained was filtered and washed with IPA (50ml) and suck dried. The solid was dried under vacuum at 50-55°C. 88-92gm of solid was obtained (Yield 88-92%, HPLC purity >99.6%). R-vildagliptin is less than 0.01%, impurity D is less than 0.03%, impurity E is less than 0.01%, compound of formula III (genotoxic impurity) is below detection limit, compound of formula IV (genotoxic impurity) is below detection limit, bulk density of 0.54 g/cc, Particle size distribution: d10 about 34 microns, d50 about 177 microns and d90 about 318 microns.
We claim:

1) A process for the preparation of vildagliptin, a compound of formula I,

\[
\text{Formula I}
\]

comprising:

a) reacting a compound of formula VI

\[
\text{Formula VI}
\]

with a compound of formula V,

\[
\text{Formula V}
\]

in the presence of a nitrile solvent to form a compound of formula IV;

\[
\text{Formula IV}
\]

b) reacting the compound of formula IV with a dehydrating agent to form a compound of

formula III,
c) reacting the compound of formula III with a compound of formula II,

5 to form a compound of formula I.

2) The process as claimed in claim 1, wherein in step a) the nitrile solvent is acetonitrile.

3) The process as claimed in claim 1, wherein the step a) is carried out in presence of a base.

4) The process as claimed in claim 3, wherein the base is potassium carbonate.

5) The process as claimed in claim 1, wherein the step b) is carried out in presence of a dehydrating agent selected from group consisting of POCl$_3$, Vilsmeier reagent, Gold reagent, mixture of DMF and triphosgene, mixture of DMF and SOCl$_2$, mixture of DMF and oxalyl chloride.

6) The process as claimed in claim 1, wherein in step b) reaction of compound of formula IV with a dehydrating agent is carried out at 0°C to about 20°C.

7) The process as claimed in claim 1, wherein the compound of formula III and/or compound of formula IV is isolated from the reaction mixture.

8) The process as claimed in claim 7, wherein the compound of formula III and/or compound of formula IV is isolated by slurrying the reaction mixture with an organic solvent.
9) The process as claimed in claim 8, wherein the organic solvent is ether solvent, alcohol solvent or mixtures of ether solvent and alcohol solvent.

10) The process as claimed in claim 1, wherein in step c) reaction of compound of formula III with compound of formula II is carried out at about 40°C to about 80°C.

11) The process as claimed in claim 1, wherein vildagliptin a compound of formula I, obtained has impurity G and impurity H less than 0.15% w/w relative to the amount of vildagliptin as determined by HPLC.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2013/000787

A. CLASSIFICATION OF SUBJECT MATTER
C07D 207/16(2006.01)

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)
C07D 207/-

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)
CNPAT, CNKI, WPI, EPODOC, ISI Web of Knowledge, CASREACT(STN): glenmark, vildagliptin?, dipeptidyl w peptidase?, diabetes?, searching the reaction

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>WO 2011012322A2 (KRKA, D.D., NOVO MESTO ET AL.) 03 February 2011 (2011-02-03)</td>
<td>1-1 1</td>
</tr>
<tr>
<td></td>
<td>example 2A, 3, page 13, lines 1-8</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>JP 2012197291A (MITSUBISHI TANABE PHARMA CORPORATION) 18 October 2012 (2012-10-18)</td>
<td>1-1 1</td>
</tr>
<tr>
<td></td>
<td>reference example 1</td>
<td></td>
</tr>
</tbody>
</table>

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 but 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
- R: 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
- Z: document member of the same patent family

Date of the actual completion of the international search 16 April 2014
Date of mailing of the international search report 08 May 2014

Name and mailing address of the ISA/STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN)
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China
100088 China

Authorized officer CHEN Xi

Facsimile No. (86-10)62019451 Telephone No. (86-10)82246724

Form PCT/ISA/210 (second sheet) (July 2009)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date (day/month/year)</th>
<th>Patent family member(s)</th>
<th>Publication date (day/month/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2011012322A2</td>
<td>03 February 2011</td>
<td>WO 2011012322A9</td>
<td>11 August 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wo 2011012322A3</td>
<td>30 June 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2459531A2</td>
<td>06 June 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EA 201290032A1</td>
<td>29 June 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2008066083A1</td>
<td>05 June 2008</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (July 2009)