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(54) Title: PROCESS FOR THE PREPARATION OF SAXAGLIPTIN AND ITS INTERMEDIATES

(57) Abstract: The present invention provides intermediates of saxagliptin and processes for their preparation. The present invention also provides a process for the preparation of saxagliptin or salts or hydrates thereof by using the intermediates.



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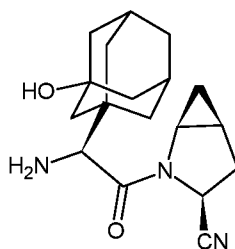
PROCESS FOR THE PREPARATION OF SAXAGLIPTIN AND ITS INTERMEDIATES

Field of the Invention

The present invention provides intermediates of saxagliptin and processes for their preparation. The present invention also provides a process for the preparation of saxagliptin or salts or hydrates thereof by using the intermediates.

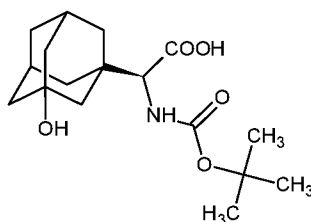
Background of the Invention

Saxagliptin of Formula A, an orally-active inhibitor of the dipeptidyl peptidase IV enzyme, chemically designated as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.



Formula A

U.S. Patent No. 6,395,767 provides a process for the preparation of (2*S*)-[(*tert*-butoxycarbonyl)amino](3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid of Formula I, an intermediate for the preparation of saxagliptin. This patent also provides a process for the preparation of saxagliptin trifluoroacetate.



Formula I

U.S. Patent Nos. 6,995,183 and 8,158,394; PCT Publication No. WO 2011/117393; and Indian Application Nos. 4203/CHE/2011 and 4256/CHE/2012 provide

processes for the preparation of saxagliptin intermediate, (2*S*)-[(*tert*-butoxycarbonyl)amino](3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid of Formula I.

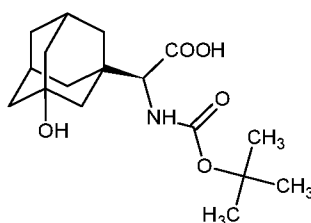
PCT Publication Nos. WO 2004/052850, WO 2005/106011, WO 2012/162507, and WO 2013/111158 provide processes for the preparation of saxagliptin and its intermediates.

Voloboev *et al.*, “Synthesis and Reactivity of Aldehydes of the Adamantane Series,” *Russian Journal of General Chemistry (Zhurnal Obshchei Khimii)*, 71(7):1121-1125 (2001) provides a method for the preparation of 3-chlorotricyclo[3.3.1.1^{3,7}]decane-1-carbonitrile from 3-hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carbonitrile by using stannous chloride and hydrochloric acid in the presence of water, wherein 3-hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carbaldehyde is also obtained as a byproduct.

The present invention provides an alternate process for the preparation of saxagliptin and its intermediate compounds in good yield that can be scaled up to an industrial scale.

Summary of the invention

The present invention provides a process for the preparation of (2*S*)-[(*tert*-butoxycarbonyl)amino](3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid of Formula I, by using novel intermediates.



Formula I

The present invention also provides a process for the preparation of saxagliptin or salts or hydrates thereof by using novel intermediates.

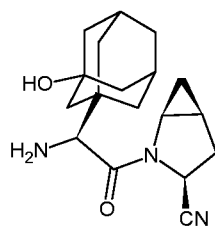
Detailed Description of the Invention

The term “solvent,” as used herein, refers to any solvent or solvent mixtures, including water, alkanols, esters, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, and mixtures thereof. Examples of alkanols include primary, secondary, and tertiary alcohols having from one to six carbon atoms, such as methanol, ethanol, *n*-

propanol, isopropanol, *n*-butanol, *sec*-butanol, isobutanol, and *tert*-butanol. Examples of esters include ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate. Examples of halogenated hydrocarbons include dichloromethane, chloroform, and 1,2-dichloroethane. Examples of ketones include acetone and methyl ethyl ketone. Examples of ethers include diethyl ether and tetrahydrofuran. Examples of polar aprotic solvents include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.

The term “base,” as used herein, refers to hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals; ammonia; alkyl amines; pyridine; hydrazine; and the like. Examples of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals include lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate. Examples of alkyl amines include diethyl amine, triethyl amine, and methyl diethyl amine.

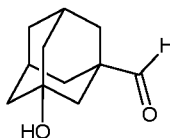
A first aspect of the present invention provides a process for the preparation of saxagliptin of Formula A or salts or hydrates thereof,



Formula A

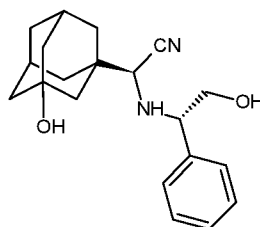
comprising the steps of:

- (a) treating a compound of Formula VI

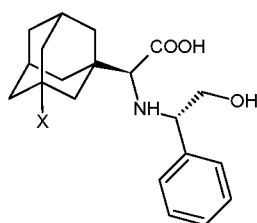


Formula VI

with (*R*)-(-)-2-phenylglycinol and a cyanide source to obtain a compound of Formula V;

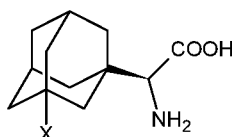
**Formula V**

- (b) treating the compound of Formula V with an acid and a halogen source to obtain a compound of Formula IV or salts thereof,

**Formula IV**

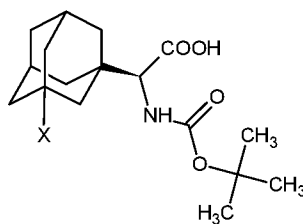
wherein X is selected from chloro, bromo, fluoro, or iodo;

- (c) hydrogenolysing the compound of Formula IV or salts thereof to obtain a compound of Formula III or salts thereof,

**Formula III**

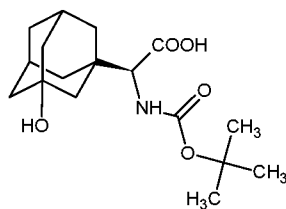
wherein X is selected from chloro, bromo, fluoro, or iodo;

- (d) treating the compound of Formula III or salts thereof with di-*tert*-butyl dicarbonate to obtain a compound of Formula II,

**Formula II**

wherein X is selected from chloro, bromo, fluoro, or iodo;

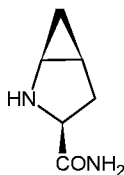
- (e) hydroxylating the compound of Formula II with a hydroxylating agent to obtain a compound of Formula I;



5

Formula I

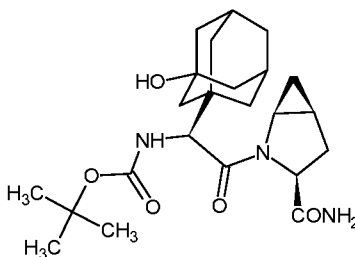
- (f) coupling the compound of Formula I with (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carboxamide of Formula X or salts thereof



Formula X

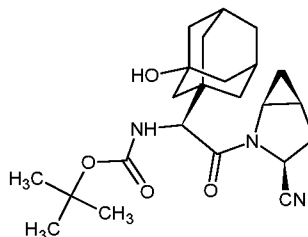
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to provide a compound of Formula XI;



Formula XI

- (g) converting the compound of Formula XI to a compound of Formula XII; and

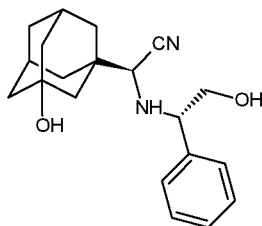


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Formula XII

- (h) deprotecting the compound of Formula XII to obtain saxagliptin of Formula A or salts or hydrates thereof.

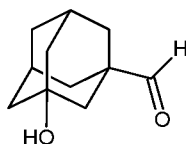
A second aspect of the present invention provides a process for the preparation of a compound of Formula V,



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Formula V

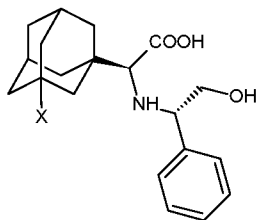
which comprises treating a compound of Formula VI



Formula VI

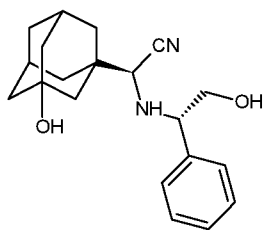
- 10 with (*R*)-(-)-2-phenylglycinol and a cyanide source.

A third aspect of the present invention provides a process for the preparation of a compound of Formula IV or salts thereof,



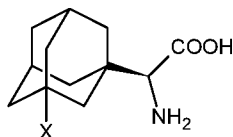
Formula IV

- 15 wherein X is selected from chloro, bromo, fluoro, or iodo, which comprises treating a compound of Formula V

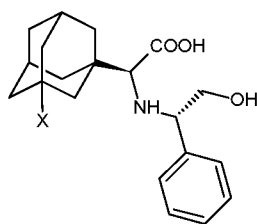
**Formula V**

with an acid and a halogen source.

A fourth aspect of the present invention provides a process for the preparation of a
5 compound of Formula III or salts thereof,

**Formula III**

which comprises hydrogenolysing a compound of Formula IV or salts thereof,

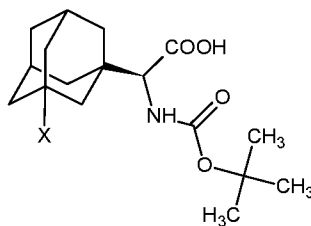


10

Formula IV

wherein X is selected from chloro, bromo, fluoro, or iodo.

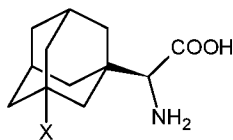
A fifth aspect of the present invention provides a process for the preparation of a
compound of Formula II,



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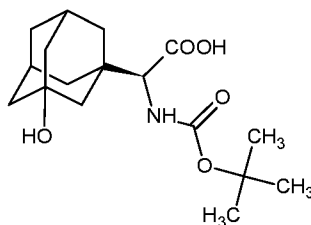
Formula II

which comprises treating a compound of Formula III or salts thereof,

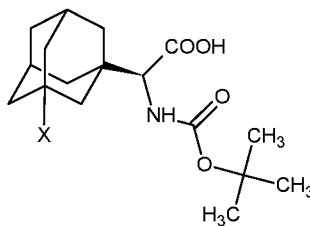
**Formula III**

wherein X is selected from chloro, bromo, fluoro, or iodo, with di-*tert*-butyl dicarbonate.

A sixth aspect of the present invention provides a process for the preparation of a
5 compound of Formula I,

**Formula I**

which comprises hydroxylating a compound of Formula II,



10

Formula II

wherein X is selected from chloro, bromo, fluoro, or iodo, with a hydroxylating agent.

In one embodiment of the present invention, the compound of Formula VI is treated with (*R*)-(-)-2-phenylglycinol and a cyanide source in the presence of a solvent.

The cyanide source may include alkali metal cyanide, for example, potassium
15 cyanide or sodium cyanide. Preferably, the solvent used is methanol, water, or a mixture thereof.

In another embodiment of the present invention, the compound of Formula VI is added to water and sodium bisulphite, cooled to about -5°C to about 5°C, preferably 0°C, followed by the addition of sodium cyanide while stirring. The reaction mixture is added
20 to a solution of (*R*)-(-)-2-phenylglycinol in methanol at a temperature of from about -10°C

to about 5°C, preferably from about -5°C to about 0°C, for about 10 minutes to about 1 hour, preferably about 30 minutes. The reaction mixture is warmed to about 22°C to about 30°C under stirring, for about 1 hour to about 4 hours, preferably about 2 hours, followed by heating from about 60°C to about 90°C, preferably from about 80°C to about 85°C while stirring for about 10 hours to about 15 hours, preferably about 12 hours. The reaction mixture is cooled, preferably to 0°C, followed by the addition of ethyl acetate and a sodium chloride solution. The solution so formed is allowed to settle and the layers are separated. The compound of Formula V is isolated from the organic layer by recovery of a solvent.

10 In one embodiment of the present invention, the treatment of a compound of Formula V with an acid and a halogen source is performed in the presence of a solvent.

The acid is selected from the group comprising hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, and the like. The halogen source is selected from the group comprising alkali metal halides, such as sodium halide, potassium halide, zinc halide, and the like. Preferably, the solvent used is methanol, ethyl acetate, water, or mixtures thereof.

In another embodiment of the present invention, the compound of Formula V is added to concentrated hydrochloric acid, heated to about 60°C to about 90°C, preferably from about 80°C to about 85°C, while stirring for about 30 minutes to about 2 hours, preferably about 1 hour. The reaction mixture is added to zinc chloride while stirring at from about 60°C to about 90°C, preferably from about 80°C to about 85°C for about 10 hours to about 15 hours, preferably about 12 hours. The solvents are recovered under reduced pressure and cooled to about 0°C to about 20°C, preferably about 10°C. The reaction mixture is added to water and ethyl acetate while stirring at about 22°C to about 30°C. The solution so formed is allowed to settle and the layers are separated. The aqueous layer is extracted with ethyl acetate. The organic layers are combined and the solvent is recovered under reduced pressure to obtain a sticky mass. To the sticky mass, aqueous methanol is added while stirring for about 2 hours to about 8 hours, preferably from about 4 hours to about 6 hours at from about 20°C to about 30°C, preferably, from about 23°C to about 26°C. The solid is filtered and dried to obtain a compound of Formula IV.

In one embodiment of the present invention, the hydrogenolysis of a compound of Formula IV or salts thereof is performed with a hydrogen source in the presence of a hydrogenolytic catalyst in a solvent.

The hydrogenolytic catalyst may be selected from transition metal compounds.

- 5 Examples of transition metal compounds include palladium compounds such as palladium/carbon or palladium hydroxide; platinum compounds such as platinum oxide or platinum/carbon; ruthenium compounds such as ruthenium oxide; rhodium compounds such as rhodium/carbon; and nickel compounds such as Raney nickel. Preferably, the hydrogenolytic catalyst used is palladium hydroxide. The hydrogen source may be
10 hydrogen gas. Preferably, the solvent used is methanol, water, or mixtures thereof.

Hydrogenolysing the compound of Formula IV or a salt thereof is performed at normal pressure or at elevated pressure depending on the choice of catalyst. In general, it may be carried out at a hydrogen pressure in the range of from about 2 kg to about 5 kg.

- In another embodiment of the present invention, the compound of Formula IV in a
15 glass par bottle is added to methanol, acetic acid, and palladium hydroxide. The bottle is fixed on a parr hydrogenator, purged, and evacuated with hydrogen gas twice, followed by the application of hydrogen gas with heating at about 40°C to about 60°C, preferably 50°C. The reaction mixture is shaken with hydrogen gas at a hydrogen pressure in the range of from about 2 kg to about 5 kg, preferably from about 3 kg to about 4 kg at from
20 about 40°C to about 60°C, preferably, from about 45°C to about 55°C for about 3 hours to about 8 hours, preferably from about 4 hours to about 6 hours. The precipitated reaction mass is added to methanol while stirring for about 10 minutes to about 40 minutes, preferably about 20 minutes, and filtered. The filtrates are combined. The solvent is recovered under reduced pressure, followed by the addition of water while stirring at
25 ambient temperature, and then distilled to remove water. The reaction mixture is added to ethyl acetate while stirring for about 10 minutes to about 50 minutes, preferably about 30 minutes at from about 20°C to about 30°C, preferably from about 23°C to about 26°C. The solid is filtered and dried to obtain a compound of Formula III.

- In one embodiment of the present invention, a compound of Formula III or salts
30 thereof is treated with di-*tert*-butyl dicarbonate in a solvent in the presence of a base.

Preferably, the solvent used is tetrahydrofuran, water, or a mixture thereof. Preferably, the base used is potassium carbonate.

In another embodiment of the present invention, the compound of Formula III is treated with potassium carbonate in water while stirring, cooled to about 0°C to about 10°C, preferably about 4°C, followed by the addition of tetrahydrofuran at from about 0°C to about 20°C, preferably from about 4°C to about 10°C while stirring. The reaction mixture is treated with di-*tert*-butyl dicarbonate at from about 0°C to about 20°C, preferably from about 4°C to about 10°C while stirring for about 30 minutes to about 2 hours, preferably about 1 hour. The temperature of the reaction mixture is raised to about 15°C to about 25°C, preferably about 18°C to about 22°C, while stirring for about 30 minutes to about 2 hours, preferably about 1 hour. Tetrahydrofuran is recovered under reduced pressure, followed by the addition of hexane to the aqueous layer. The solution so formed is allowed to settle and the layers are separated. The aqueous layer is extracted with ethyl acetate. The organic layers are combined and the solvent is recovered under reduced pressure. The resulting mixture is added to hexane and cooled from about -5°C to about 5°C, preferably 0°C, while stirring. The temperature of the reaction mixture is raised to about 15°C to about 25°C, preferably about 18°C to about 22°C in about 1 hour to about 5 hours, preferably about 3 hours. The solid is filtered and dried to obtain a compound of Formula II.

In one embodiment of the present invention, the hydroxylation of a compound of Formula II with a hydroxylating agent is performed in the presence of a base.

The hydroxylating agent used is water. Preferably, the base used is potassium carbonate.

In another embodiment of the present invention, the compound of Formula II is treated with potassium carbonate in water while stirring at from about 30°C to about 60°C, preferably from about 40°C to about 45°C for about 10 hours to about 15 hours, preferably about 12 hours, followed by the addition of ethyl acetate. The solution so formed is allowed to settle and the layers are separated. The aqueous layer is extracted with ethyl acetate. The organic layers are combined and the solvent is recovered under reduced pressure. The solid is filtered and dried to obtain a compound of Formula I.

In one embodiment of the present invention, the coupling the compound of Formula I with (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carboxamide of Formula X or salts thereof is carried out in the presence of a coupling agent, a solvent, and a base.

The compound of Formula X or salts thereof is prepared by any of the methods known in the art, for example, U.S. Patent No. 6,395,767.

The coupling agent may be selected from 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC.HCl)/hydroxybenzotriazole (HOBt), i-
5 BuCOCOCl/triethylamine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop)/N-methylmorpholine (NMM). Preferably, the solvent used is dichloromethane, water, or a mixture thereof. Preferably the base used is triethylamine.

In another embodiment of the present invention, the compound of Formula I is dissolved in dichloromethane and treated with (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-
10 carboxamide hydrochloride of Formula X in the presence of EDAC.HCl/HOBt and triethylamine at about -10°C to about 5°C, preferably about -7°C to about 0°C for about 15 minutes to about 2 hours, preferably about 1 hour. The temperature of the reaction mixture is raised to from about 8°C to about 15°C, preferably about 10°C under stirring for about 10 hours to about 20 hours, preferably about 14 hours to about 16 hours, and
15 cooled to 0°C. The reaction mixture is added to water. The solution so formed is allowed to settle and the layers are separated. The aqueous layer is extracted with dichloromethane and layers are allowed to settle and be separated. The organic layers are combined and the pH is adjusted to 3.96 with hydrochloric acid. The reaction mixture is allowed to settle and the layers are separated. The compound of Formula XI is obtained from the organic
20 layer by the recovery of solvent.

In one embodiment of the present invention, the compound of Formula XI is converted to a compound of Formula XII in the presence a solvent and a base.

Preferably, the solvent used is tetrahydrofuran, methanol, and a mixture thereof. Preferably the base used is pyridine, potassium carbonate, or mixtures thereof.

25 In another embodiment of the present invention, the compound of Formula XI is added to tetrahydrofuran and trifluoroacetic anhydride in the presence of pyridine at a temperature of about -10°C to about 10°C, preferably, about -5°C to about 5°C for about 15 minutes to about 2 hours, preferably about 1 hour. The temperature of the reaction mixture is raised to about 10°C to about 20°C, preferably about 15°C while stirring for
30 about 1 hour to about 8 hours, preferably from about 2 hours to about 5 hours. The solvent is recovered under reduced pressure and the residue is added to methanol. The pH of the reaction mixture is adjusted to between 10 and 10.5 with potassium carbonate

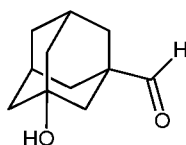
solution while stirring for about 30 hours to about 50 hours, preferably, for about 40 hours to about 45 hours at about 5°C to about 20°C, preferably about 10°C to about 15°C. The solvent in the reaction mixture is recovered under vacuum and the aqueous layer is added to ethyl acetate while stirring. The solution so formed is allowed to settle and the layers
5 are separated. The aqueous layer is extracted with ethyl acetate. The organic layers are combined. The compound of Formula XII is obtained from the organic layer by recovery of the solvent.

In one embodiment of the present invention, deprotecting the compound of Formula XII is performed with an acid in the presence of a solvent.

10 The acid may be selected from hydrochloric acid, acetic acid, trifluoroacetic acid, oxalic acid, and the like. Preferably, the solvent used is dichloromethane, water, or a mixture thereof.

In another embodiment of the present invention, the compound of Formula XII in dichloromethane is treated with trifluoroacetic acid in dichloromethane at about -10°C to
15 about 10°C, preferably about -5°C to about 5°C while stirring for about 2 hours to about 6 hours, preferably about 3 hours to about 5 hours. The solvents are recovered under reduced pressure and the residue is added to crushed ice at about 0°C to about 10°C, preferably about 5°C. The solid is filtered, washed with ethyl acetate, and dried to obtain saxagliptin trifluoroacetate.

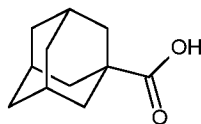
20 A seventh aspect of the present invention provides a process for the preparation of a compound of Formula VI,



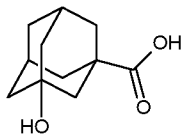
Formula VI

comprising the steps of:

25 (a) hydroxylating a compound of Formula IX

**Formula IX**

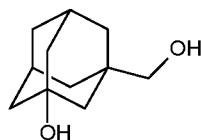
with a hydroxylating agent to provide a compound of Formula VIII;



5

Formula VIII

- (b) reducing the compound of Formula VIII with a reducing agent to provide a compound of Formula VII; and

**Formula VII**

- 10 (c) oxidizing the compound of Formula VII with an oxidizing agent to provide the compound of Formula VI.

Hydroxylating the compound of Formula IX with a hydroxylating agent in step (a) may be performed in the presence of an acid.

The acid may be selected from sulphuric acid, nitric acid, and a mixture thereof.

- 15 The hydroxylating agent used is water.

In one embodiment of the present invention, the compound of Formula IX is treated with a previously cooled, preferably about -10°C to about 5°C, mixture of sulfuric acid and nitric acid at from about -15°C to about 10°C, preferably from about -10°C to about 5°C, while stirring for about 2 hours to about 6 hours, preferably about 4 hours. A
 20 mixture of sulfuric acid and nitric acid is further added to the reaction mixture at from about -10°C to about 10°C, preferably from about -5°C to about 5°C while stirring for about 10 hours to about 15 hours, preferably from about 12 hours to about 13 hours. The reaction mixture is treated with water at 5°C to about 20°C, preferably from about 10°C to

about 12°C for about 2 hours to about 6 hours, preferably about 4 hours. The solid is filtered and dried to obtain a compound of Formula VIII.

Reducing the compound of Formula VIII with a reducing agent in step (b) may be performed in the presence of a solvent.

- 5 The reducing agent may be selected from sodium borohydride/boron trifluoride etherate, borane-tetrahydrofuran complex/boron trifluoride etherate, dimethylsulfide borane (DMSB)/trimethylborate, or lithium aluminum hydride. Preferably, the solvent used is tetrahydrofuran, ethyl acetate, water, or mixtures thereof.

- 10 In one embodiment of the present invention, the compound of Formula VIII in tetrahydrofuran is treated with sodium borohydride at a temperature of about -10°C to about 15°C, preferably about 0°C to about 10°C, stirred at from about 25°C to about 35°C for about 1 hour to about 4 hours, preferably about 2 hours, and cooled, preferably to about 0°C. The reaction mixture is added to boron trifluoride etherate at about -5°C to about 10°C, preferably about 0°C to about 5°C; warmed to about 25°C to about 35°C
15 while stirring for about 10 hours to about 20 hours, preferably about 14 hours; and then cooled, preferably to about 0°C. Ethyl acetate and water are added to the reaction mixture. The pH of the solution is adjusted to 8 by the addition of sodium carbonate, then the mixture is stirred at about 30°C to about 45°C, preferably about 35°C to about 40°C. The solution so formed is allowed to settle and the layers are separated. The compound of
20 Formula VII is obtained from the organic layer by recovery of the solvent.

Oxidizing the compound of Formula VII with an oxidizing agent in step (c) may be performed in a solvent in the presence of a base.

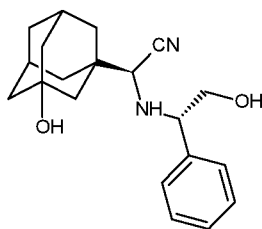
- 25 The oxidizing agent is selected from the group comprising oxalyl chloride/dimethyl sulfoxide, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)/sodium hypochlorite, pyridinium chlorochromate, tetrapropylammonium perruthenate (TPAP) in the presence of excess of *N*-methylmorpholine *N*-oxide (NMO), 2-iodoxybenzoic acid, or collins reagent (chromium(VI) oxide with pyridine in dichloromethane).

Preferably, the solvent used is dichloromethane, water, or a mixture thereof. Preferably the base used is sodium bicarbonate.

- 30 In one embodiment of the present invention, the compound of Formula VII is added to dichloromethane, water, potassium bromide, and sodium bicarbonate and cooled

to about -5°C to about 10°C, preferably about 0°C to about 5°C, followed by the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and sodium hypochlorite. The solution obtained is allowed to settle and the layers are separated. The aqueous layer is extracted with dichloromethane. The organic layers are combined and the solvent is recovered to obtain the solid. The solid is dissolved in ethyl acetate, cooled to about 10°C to about 20°C, preferably about 15°C, and extracted with aqueous sodium bisulphite. The aqueous layer is added to ethyl acetate, cooled to about 5°C to about 20°C, preferably to about 10°C to about 15°C. The resultant mixture is adjusted to pH 10 with sodium hydroxide while stirring. The solution so formed is allowed to settle and the layers are separated. The compound of Formula VI is isolated from the organic layer by the recovery of solvent.

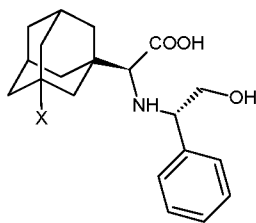
An eighth aspect of the present invention provides a compound of Formula V, or salts thereof.



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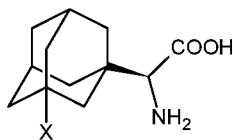
Formula V

A ninth aspect of the present invention provides a compound of Formula IV, or salts thereof,

**Formula IV**

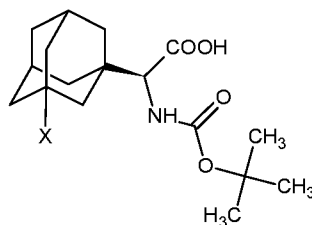
wherein X is selected from chloro, bromo, fluoro, or iodo.

A tenth aspect of the present invention provides a compound of Formula III, or salts thereof,

**Formula III**

wherein X is selected from chloro, bromo, fluoro, or iodo.

An eleventh aspect of the present invention provides a compound of Formula II, or
 5 salts thereof,

**Formula II**

wherein X is selected from chloro, bromo, fluoro, or iodo.

A twelfth aspect of the present invention provides use of compounds of Formula II,
 10 Formula III, Formula IV, and Formula V as intermediates for the preparation of
 saxagliptin or salts or hydrates thereof.

In one embodiment of the first aspect of the present invention, saxagliptin or salts
 or hydrates thereof obtained are free from the compounds of Formula II, Formula III,
 Formula IV, and Formula V.

15 In another embodiment of the first aspect of the present invention, saxagliptin or
 salts or hydrates thereof obtained are having less than 0.5% of the compound of Formula
 II.

In another embodiment of the first aspect of the present invention, saxagliptin or
 salts or hydrates thereof obtained are having less than 0.5% of the compound of Formula
 20 III.

In another embodiment of the first aspect of the present invention, saxagliptin or
 salts or hydrates thereof obtained are having less than 0.5% of the compound of Formula
 IV.

In another embodiment of the first aspect of the present invention, saxagliptin or salts or hydrates thereof obtained are having less than 0.5% of the compound of Formula V.

5 A thirteenth aspect of the present invention provides use of saxagliptin or salts or hydrates thereof free from the compounds of Formula II, Formula III, Formula IV, and Formula V for the manufacturing of a medicament used for the treatment of type 2 diabetes mellitus.

A fourteenth aspect of the present invention provides use of saxagliptin or salts or hydrates thereof having less than 0.5% of the compound of Formula II for the
10 manufacturing of a medicament used for the treatment of type 2 diabetes mellitus.

A fifteenth aspect of the present invention provides use of saxagliptin or salts or hydrates thereof having less than 0.5% of the compound of Formula III for the manufacturing of a medicament used for the treatment of type 2 diabetes mellitus.

A sixteenth aspect of the present invention provides use of saxagliptin or salts or
15 hydrates thereof having less than 0.5% of the compound of Formula IV for the manufacturing of a medicament used for the treatment of type 2 diabetes mellitus.

A seventeenth aspect of the present invention provides use of saxagliptin or salts or hydrates thereof having less than 0.5% of the compound of Formula V for the manufacturing of a medicament used for the treatment of type 2 diabetes mellitus.

20 An eighteenth aspect of the present invention provides use of saxagliptin or salts or hydrates thereof free from the compounds of Formula II, Formula III, Formula IV, and Formula V for the preparation of a pharmaceutical composition.

EXAMPLES

Example 1: Preparation of 3-Hydroxytricyclo[3.3.1.^{3,7}]decane-1-carboxylic acid
25 (Formula VIII)

Concentrated sulphuric acid (400 mL) was charged to a round bottom flask at 25°C and cooled to -10°C. Nitric acid (50 mL; 50% w/w aqueous solution) was added at -10°C to 0°C over 1 hour, followed by the addition of tricyclo[3.3.1.^{3,7}]decane-1-carboxylic

acid (Formula IX; 100 g) in portions at -5°C to 0°C over 1 hour, then further stirred for 4 hours at -1°C to 1°C. A mixture of concentrated sulfuric acid and 50% w/w aqueous solution of nitric acid in a 1:1 ratio (25 mL each) was added to the reaction mixture over 30 minutes, stirred for 12 hours to 13 hours at -1°C to 1°C, followed by the addition of
5 water (2500 mL) at 0°C to 10°C, and further stirred for 4 hours at 10°C to 12°C to obtain a solid. The obtained solid was filtered, washed with chilled water (500 mL), dried under suction for 2 hours, and then air dried in an oven for 10 hours at 40°C to 45°C to obtain the title compound.

Yield: 97.4 g

10 Example 2: Preparation of 3-(Hydroxymethyl)tricyclo[3.3.1.1^{3,7}]decan-1-ol (Formula VII)

3-Hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid obtained by Example 1 (Formula VIII; 25 g) was added to tetrahydrofuran (250 mL) at 31°C, cooled to 0°C, then sodium borohydride (6.3 g) was added at 0°C to 10°C over 30 minutes, the mixture was stirred for 2 hours at 28°C to 31°C, then cooled to 0°C. Boron trifluoride etherate (20.5
15 mL) was added to the reaction mixture over 30 minutes at 0°C to 2°C, the mixture was warmed to 30°C while stirring for 14 hours, then cooled to 0°C. Water (250 mL) was added for 1 hour at 0°C to 10°C, followed by the addition of ethyl acetate (200 mL) at 10°C. The pH of the reaction mixture was adjusted to 8 by using 25% w/v aqueous sodium carbonate (40 mL), then the mixture was stirred for 15 minutes at 35°C to 38°C.
20 The organic layer was stored and the aqueous layer was extracted twice with ethyl acetate (50 mL) at 35°C to 38°C. The organic layers were combined, washed with saturated brine solution (25 mL), and the solvents were recovered under reduced pressure at 45°C to 47°C to obtain the title compound.

Yield: 29.5 g

25 Example 3: Preparation of 3-Hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carbaldehyde (Formula VI)

3-(Hydroxymethyl)tricyclo[3.3.1.1^{3,7}]decan-1-ol as obtained by Example 2 (Formula VII; *in-situ*), was added to dichloromethane (250 mL), water (100 mL), potassium bromide (10 g), and sodium bicarbonate (11 g) at 30°C. The obtained mixture
30 was cooled to 0°C, followed by the addition of TEMPO (0.02 g) and 10% w/v of sodium hypochlorite (230 mL) in portions at 0°C to 5°C. After completion of the reaction, the organic layer was stored and the aqueous layer was extracted with dichloromethane (50

mL). The organic layers were combined and washed with 10% w/v aqueous sodium thiosulphate (100 mL) and saturated brine solution (25 mL). The solvents were recovered under reduced pressure at 35°C to 37°C to obtain a yellowish solid (14 g). The obtained solid was dissolved in ethyl acetate (75 mL) and cooled to 15°C. The organic layer was
5 extracted with 10% w/v aqueous sodium bisulphite (100 mL). The aqueous layer was separated, added to ethyl acetate (75 mL), and cooled to 10°C. The pH of the reaction mixture was adjusted to 10 by using a 25% w/v aqueous sodium hydroxide solution (30 mL) at 10°C to 15°C. The resulting mixture was stirred at 30°C for 10 minutes. The organic layer was separated while the aqueous layer was extracted twice with ethyl acetate
10 (25 mL). The organic layers were combined and solvents were recovered under reduced pressure at 45°C to 47°C to obtain the title compound.

Yield: 11.5 g

Example 4: Preparation of (2S)-[[(1S)-2-Hydroxy-1-phenylethyl] amino]-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanenitrile (Formula V)

15 3-Hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carbaldehyde obtained by Example 3 (Formula VI; 20 g) was added to water (200 mL) at 22°C, and then cooled to 0°C. Sodium bisulphite (11.55 g) was added at 0°C, the mixture was stirred for 10 minutes at 0°C to 2°C, followed by the addition of sodium cyanide (5.45 g), and further stirring for 10 minutes at 0°C to 2°C. The reaction mixture was added to a solution containing *R*-(-)-
20 2-phenylglycinol (15.3 g) in methanol (80 mL) at -4°C to 0°C for 30 minutes, then the mixture was warmed to 22°C and stirred for 2 hours at 22°C to 25°C. The temperature of the reaction mixture was raised to 80°C while stirring for 12 hours, and then cooled to 0°C. The aqueous layer was decanted to obtain a sticky mass. The sticky mass was dissolved in ethyl acetate (100 mL) and 10% w/v aqueous sodium chloride solution (10
25 mL) at 22°C. The organic layer was separated and solvents were recovered under reduced pressure at 45°C to 47°C to obtain the title compound.

Yield: 34.4 g

Example 5: Preparation of (2S)-[3-Chlorotricyclo(3.3.1.1^{3,7})dec-1-yl]-[[(1S)-2-hydroxy-1-phenylethyl]amino]ethanoic acid hydrochloride (Formula IV)

30 (2S)-[[(1S)-2-hydroxy-1-phenylethyl] amino]-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanenitrile obtained by Example 4 (Formula V; 10 g), was added to concentrated hydrochloric acid (50 mL) at 24°C, then heated to 80°C while stirring for 1 hour. Zinc

chloride (5 g) was added at 80°C and the mixture was stirred for 12 hours at 80°C to 82°C. The solvent was recovered under reduced pressure at 48°C to 50°C, cooled to 10°C, followed by the addition of water (50 mL) at 10°C and ethyl acetate (50 mL) while stirring. The reaction mixture was warmed to 24°C while stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL). The organic layers were combined and the solvent was recovered under reduced pressure at 45°C to 47°C to obtain a sticky mass (12 g). The sticky mass was treated with 5% v/v of aqueous methanol (100 mL) at 24°C and stirred for 5 hours at 24°C to 25°C to obtain a solid. The obtained solid was filtered, washed with 5% v/v of aqueous methanol (20 mL), dried under suction for 1 hour, and then air dried in a vacuum oven for 8 hours at 48°C to 50°C to obtain the title compound.

Yield: 7.8 g

Example 6: Preparation of (2S)-Amino(3-chlorotricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid hydrochloride (Formula III)

A mixture of (2S)-[3-chlorotricyclo(3.3.1.1^{3,7})dec-1-yl]-[[(1S)-2-hydroxy-1-phenylethyl]amino]ethanoic acid hydrochloride obtained by Example 5 (Formula IV; 1.2 g), methanol (24 mL), acetic acid (2.4 mL), and 20% w/w palladium hydroxide (0.24 g) was charged in a glass parr bottle at 22°C. The bottle was fixed on a parr hydrogenator, purged, and evacuated with hydrogen gas (1 Kg/cm²) twice, followed by the application of hydrogen gas (4 Kg/cm²), and then heated to 50°C. The reaction mixture was shaken for 5 hours at 3.5 Kg/cm² to 4.0 Kg/cm² of hydrogen gas at 48°C to 52°C. To the precipitated solid from the reaction mixture, methanol (24 mL) was added and the mixture was stirred for 20 minutes at 54°C to 55°C. The reaction mixture was filtered and washed with methanol (10 mL). The filtrate and washings were combined and the solvents were distilled off under reduced pressure at 50°C. The resultant mixture was added to water (24 mL), stirred for 5 minutes at 30°C to 35°C, and water was distilled off under reduced pressure at 50°C. Ethyl acetate (24 mL) was added at 24°C to 25°C and the mixture was stirred for 30 minutes to obtain a solid. The obtained solid was filtered, washed with ethyl acetate (10 mL), dried under suction for 10 minutes, and then air dried in a vacuum oven for 18 hours at 23°C to 27°C to obtain the title compound.

Yield: 0.63 g

Example 7: Preparation of (2S)-[(*tert*-Butoxycarbonyl)amino](3-chlorotricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid (Formula II)

(2S)-Amino(3-chlorotricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid hydrochloride obtained by Example 6 (Formula III; 2 g) was added to a previously cooled potassium carbonate solution (potassium carbonate (2.95 g) in water (40 mL) at 4°C) and tetrahydrofuran (20 mL) under stirring for 5 minutes at 8°C to 10°C. The obtained mixture was cooled to 4°C under stirring. Di-*tert*-butyl dicarbonate (2.33 g) was added drop-wise at 4°C to 5°C and the mixture was stirred for 1 hour at 5°C to 10°C. The temperature of the reaction mixture was raised to 18°C to 22°C over 15 minutes and the mixture was stirred for 1 hour at the same temperature. Tetrahydrofuran was recovered under reduced pressure at 26°C, while the aqueous layer was extracted with hexane (10 mL) twice under stirring for 10 minutes at 25°C to 26°C. The aqueous layer was separated, stirred, and cooled to 3°C, followed by the addition of ethyl acetate (20 mL), and then the mixture was stirred for 5 minutes at 3°C. The pH of the reaction mixture was adjusted to 2.7 by adding 1N hydrochloric acid solution (24 mL) at 3°C to 5°C, and the mixture was stirred for 10 minutes. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL) at 3°C to 5°C. The organic layers were combined and washed with a 5% w/v solution of sodium chloride (20 mL), followed by the separation of the organic layer at 5°C to 10°C, and dried over sodium sulphate. The solvents were recovered under reduced pressure at 27°C, hexane (40 mL) was added, then stirred and cooled to 0°C over 15 minutes. The temperature was raised to 20°C while stirring for 1 hour, then the mixture was stirred for an additional 2 hours at the same temperature to obtain a solid. The obtained solid was filtered, washed with hexane (10 mL), and dried under suction for 45 minutes to obtain the title compound.

Yield: 2.33 g

Example 8: Preparation of (2S)-[(*tert*-Butoxycarbonyl)amino](3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid (Formula I)

A mixture of potassium carbonate (2.5 g), water (17 mL), and tetrahydrofuran (8.5 mL) was stirred for 5 minutes at 26°C, then cooled to 3°C over 15 minutes. (2S)-Amino(3-chlorotricyclo[3.3.1.1^{3,7}]dec-1-yl)ethanoic acid hydrochloride obtained by Example 6 (Formula III; 1.7 g) was added at 3°C to 5°C, the mixture was warmed to 8°C to 10°C under stirring for 10 minutes, and then cooled to 3°C. The obtained mixture was

added to di-*tert*-butyl dicarbonate (1.35 g) at 3°C to 5°C over 5 minutes. The temperature was raised to 26°C over 30 minutes and the mixture was stirred for 2 hours while maintaining the temperature between 25°C to 26°C. Tetrahydrofuran was recovered under reduced pressure at 29°C to 30°C. The aqueous layer was added to hexane (10 mL) at 5 26°C while stirring, followed by the separation of the aqueous layer, then washed again with hexane (10 mL) at 25°C to 26°C. The aqueous layer was separated, heated to 40°C while stirring for 12 hours, then cooled to 25°C. The reaction mixture was added to ethyl acetate (10 mL) and stirred for 10 minutes at 25°C. The aqueous layer was separated and cooled to 3°C. The pH was adjusted to 3.0 by adding 1N hydrochloric acid (18.5 mL) at 10 3°C to 5°C. The mixture was then warmed to 25°C and stirred for 15 minutes at 25°C. The reaction mixture was allowed to settle, and the organic layer was stored while the aqueous layer was extracted with ethyl acetate (10 mL). The organic layers were combined and washed with water (5 mL). The organic layer was separated and the solvents were recovered under reduced pressure at 45°C to 46°C to obtain the title 15 compound.

Yield: 1.16 g

Example 9: Preparation of *tert*-butyl [(1*S*)-2-[(1*S*,3*S*,5*S*)-3-carbamoyl-2-azabicyclo[3.1.0]hex-2-yl]-1-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-oxoethyl]carbamate (Formula XI)

20 (2*S*)-[(*tert*-Butoxycarbonyl)amino](3-hydroxytricyclo [3.3.1.1^{3,7}]dec-1-yl)ethanoic acid obtained by Example 8 (Formula I; 50 g) was added to dichloromethane (500 mL), then cooled to -5°C while stirring for 15 minutes, followed by the addition of HOBt (31.14 g) at -5°C to 0°C, and the mixture was stirred for 5 minutes. EDAC, HCl and (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (Formula X; 23.74 g) were 25 added under stirring at -5°C to 0°C. The reaction mixture was added to triethyl amine (117.8 mL) at -6°C to 0°C over 15 minutes and then stirred for 20 minutes at -7°C to -6°C. The temperature was raised to 10°C over 1 hour, and then the mixture was stirred for 14 hours at the same temperature. The reaction mixture was cooled to 0°C over 15 minutes, then water (150 mL) was added and the mixture was stirred for 20 minutes at 6°C to 8°C. 30 The layers were allowed to settle for 20 minutes, the organic layer was stored while the aqueous layer was extracted with dichloromethane (100 mL) at 6°C. The organic layers were combined and cooled to 2°C while stirring. The pH of the reaction mixture was

adjusted to 3.96 by adding 2N aqueous hydrochloric acid (210 mL) at 2°C to 8°C over 25 minutes, and then the mixture was stirred for 20 minutes at 6°C to 8°C. The layers were allowed to settle for 40 minutes at 10°C to 16°C. The organic layer was separated and extracted with 8% aqueous sodium bicarbonate (100 mL) at 10°C to 13°C. The organic
5 layer was separated and extracted with water (100 mL) at 10°C to 12°C. The organic layer was separated again and solvent was distilled off under reduced pressure at 25°C to 28°C, followed by the addition of hexane (250 mL) at 25°C. The resultant mixture was stirred at 25°C to 26°C for 30 minutes to obtain a solid, which was filtered, washed with hexane (100 mL), and dried under vacuum at 25°C to 30°C for 6 hours to obtain the title
10 compound.

Yield: 69.15 g

Example 10: Preparation of *tert*-butyl [(1*S*)-2-[(1*S*,3*S*,5*S*)-3-cyano-2-azabicyclo[3.1.0]hex-2-yl]-1-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-oxoethyl]carbamate (Formula XII)

15 Tetrahydrofuran (325 mL) was added to *tert*-butyl [(1*S*)-2-[(1*S*,3*S*,5*S*)-3-carbamoyl-2-azabicyclo[3.1.0]hex-2-yl]-1-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-oxoethyl]carbamate obtained by Example 9 (Formula XI; 65 g) and cooled to -3°C under stirring over 15 minutes. Pyridine (31.14 g) was added at -3°C to 0°C, stirred at -2°C to 0°C for 5 minutes, and then trifluoro acetic anhydride (52.1 mL) was added at -3°C to 2°C
20 over 35 minutes. The temperature of the reaction mixture was raised to 15°C over 105 minutes and the mixture was stirred for 4 hours at 12°C to 15°C. The solvent was recovered under reduced pressure at 15°C to 20°C, followed by the addition of chilled methanol (975 mL) to dissolve the residues at 5°C to 15°C, then cooled to 0°C to 5°C under stirring. The pH of the reaction mixture was adjusted to 10 to 10.5 by the addition
25 of 10% w/v potassium carbonate solution (560 mL) at 7°C to 10°C, the mixture was warmed to 15°C, then stirred for 40 hours to 45 hours at the same temperature. The solvents were removed by distillation under vacuum at 20°C. The aqueous layer was added to ethyl acetate (650 mL), stirred for 20 minutes at 20°C to 22°C, followed by the addition of sodium chloride (130 g) and stirred for 20 minutes. The reaction mixture was
30 allowed to settle for 20 minutes. The aqueous layer was separated and extracted with ethyl acetate (135 mL) at 20°C to 22°C, followed by the separation of the organic layer. The organic layers were combined, cooled to 5°C under stirring in 15 minutes, washed

with 2N aqueous hydrochloric acid (325 mL) at 5°C to 13°C in 10 minutes, and then stirred for 20 minutes at 15°C to 16°C. The layers were allowed to settle for 20 minutes, the organic layer was separated, then cooled to 8°C while stirring, followed by the addition of saturated sodium bicarbonate (500 mL) at 8°C to 15°C in 10 minutes and stirred for 20 minutes. The layers were allowed to settle for 20 minutes. The organic layer was separated, washed with water (135 mL) at 16°C for 20 minutes, then dried over sodium sulphate. The reaction mixture was filtered and the solvent was removed by distillation under reduced pressure at 20°C for 30 minutes to obtain an oily mass. Ethyl acetate (65 mL) was added to the oily mass at 5°C to 6°C over 45 minutes, filtered, slurry washed with ethyl acetate (30 mL), and dried under vacuum for 12 hours at 25°C to 30°C to obtain the title compound.

Yield: 40.92 g

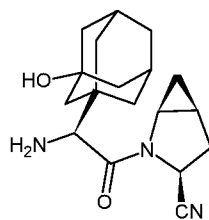
Example 11: Preparation of saxagliptin trifluoro acetate

A mixture of trifluoro acetic acid (60 mL) and dichloromethane (10 mL) was cooled to -5°C while stirring. The (*tert*-butyl)[(1*S*)-2-[(1*S*,3*S*,5*S*)-3-cyano-2-azabicyclo[3.1.0]hex-2-yl]-1-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-oxoethyl]carbamate obtained by Example 10 (Formula XII; 20 g) was dissolved in dichloromethane (50 mL) at 5°C in 15 minutes and added to the above mixture drop-wise at -5°C to -3°C over 35 minutes. The obtained mixture was stirred for 3 hours to 5 hours at -2°C to 2°C. The solvent was recovered under reduced pressure at 5°C to 10°C and charged with crushed ice (60 g) at 5°C. The solvent was again recovered under reduced pressure at 15°C and added to methanol (60 mL). The solvent was further recovered under reduced pressure at 15°C and added to ethyl acetate (30 mL). The solvent was recovered under reduced pressure to obtain a white gel solid. The obtained solid was added to ethyl acetate (200 mL) and stirred for 20 minutes to 25 minutes at 13°C to 17°C to obtain a solid. The solid was filtered, washed with chilled ethyl acetate (50 mL), kept under suction for 10 minutes to 20 minutes, and dried under vacuum at 20°C to 25°C for 14 hours to 16 hours to obtain the title compound.

Yield: 17.05 g.

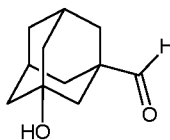
We claim:

- 1 1. A process for the preparation of saxagliptin of Formula A or salts or hydrates
2 thereof,

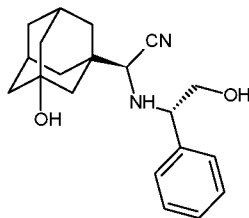
**Formula A**

3
4
5 comprising the steps of:

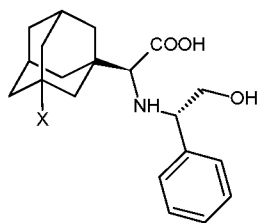
- 6 (a) treating a compound of Formula VI

**Formula VI**

7
8
9 with (*R*)-(-)-2-phenylglycinol and a cyanide source to obtain a compound of
10 Formula V;

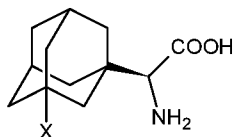
**Formula V**

- 11
12
13 (b) treating the compound of Formula V with an acid and a halogen source to
14 obtain a compound of Formula IV or salts thereof,

**Formula IV**

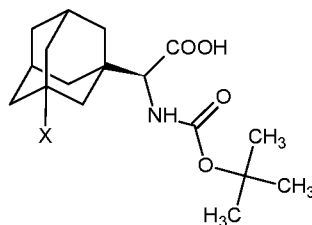
wherein X is selected from chloro, bromo, fluoro, or iodo;

- (c) hydrogenolysing the compound of Formula IV or salts thereof to obtain a compound of Formula III or salts thereof,

**Formula III**

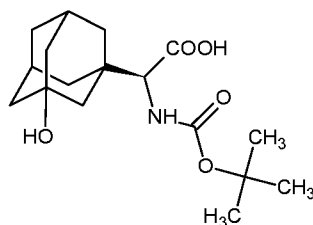
wherein X is selected from chloro, bromo, fluoro, or iodo;

- (d) treating the compound of Formula III or salts thereof with di-*tert*-butyl dicarbonate to obtain a compound of Formula II,

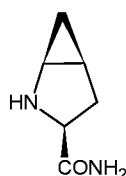
**Formula II**

wherein X is selected from chloro, bromo, fluoro, or iodo;

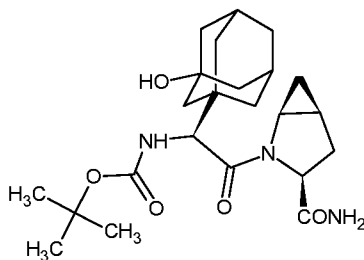
- (e) hydroxylating the compound of Formula II with a hydroxylating agent to obtain a compound of Formula I;

**Formula I**

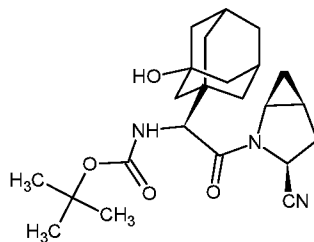
- (f) coupling the compound of Formula I with (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carboxamide of Formula X or salts thereof

**Formula X**

to provide a compound of Formula XI;

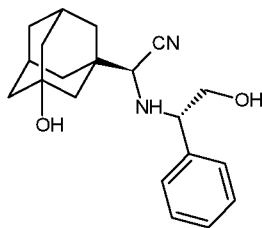
**Formula XI**

- (g) converting the compound of Formula XI to a compound of Formula XII; and

**Formula XII**

- (h) deprotecting the compound of Formula XII to obtain saxagliptin of Formula A or salts or hydrates thereof.

1 2. A process for the preparation of a compound of Formula V,

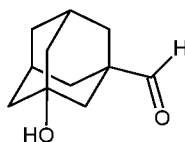


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Formula V

4 which comprises treating a compound of Formula VI



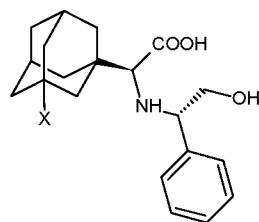
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Formula VI

7 with (*R*)-(-)-2-phenylglycinol and a cyanide source.

1 3. A process for the preparation of a compound of Formula IV or salts thereof,

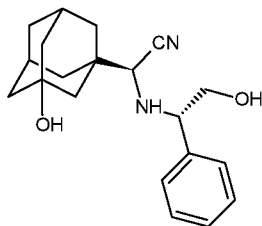


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Formula IV

4 wherein X is selected from chloro, bromo, fluoro, or iodo, which comprises treating a
5 compound of Formula V



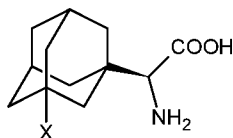
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7

Formula V

8 with an acid and a halogen source.

- 1 4. A process for the preparation of a compound of Formula III or salts thereof,

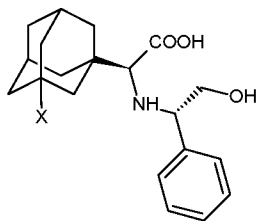


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Formula III

- 4 which comprises hydrogenolysing a compound of Formula IV or salts thereof,



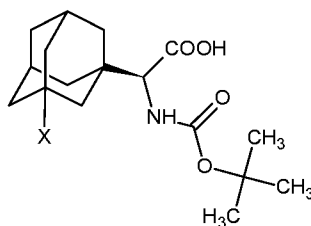
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6

Formula IV

- 7 wherein X is selected from chloro, bromo, fluoro, or iodo.

- 1 5. A process for the preparation of a compound of Formula II,

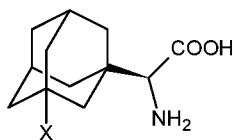


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Formula II

- 4 which comprises treating a compound of Formula III or salts thereof,



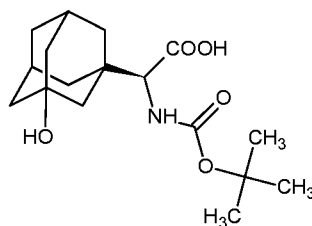
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Formula III

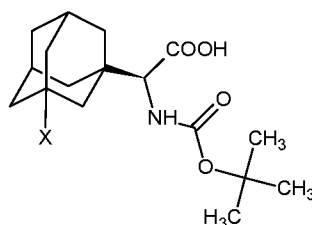
- 7 wherein X is selected from chloro, bromo, fluoro, or iodo, with di-*tert*-butyl dicarbonate.

- 1 6. A process for the preparation of a compound of Formula I,



2
3 **Formula I**

- 4 which comprises hydroxylating a compound of Formula II,



5
6 **Formula II**

- 7 wherein X is selected from chloro, bromo, fluoro, or iodo, with a hydroxylating agent.

- 1 7. The process according to claim 1 or claim 2, wherein treating the compound of
2 Formula VI with (*R*)-(-)-2-phenylglycinol and a cyanide source is performed in the
3 presence of a solvent.

- 1 8. The process according to claim 1 or claim 2, wherein the cyanide source is selected
2 from potassium cyanide and sodium cyanide.

- 1 9. The process according to claim 1 or claim 2, wherein treating the compound of
2 Formula VI with (*R*)-(-)-2-phenylglycinol and a cyanide source is performed at a
3 temperature of -10°C to 90°C.

- 1 10. The process according to claim 7, wherein the solvent is selected from water,
2 alkanols, esters, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, and
3 mixtures thereof.

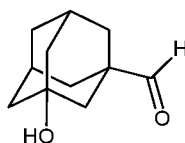
- 1 11. The process according to claim 10, wherein the alkanol is selected from methanol,
2 ethanol, *n*-propanol, isopropanol, *n*-butanol, *sec*-butanol, isobutanol, and *tert*-butanol.

- 1 12. The process according to claim 10, wherein the ester is selected from ethyl acetate,
2 *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate.

- 1 13. The process according to claim 10, wherein the halogenated hydrocarbon is
2 selected from dichloromethane, chloroform, and 1,2-dichloroethane.
- 1 14. The process according to claim 10, wherein the ketone is selected from acetone
2 and methyl ethyl ketone.
- 1 15. The process according to claim 10, wherein the ether is selected from diethyl ether
2 and tetrahydrofuran.
- 1 16. The process according to claim 10, wherein the polar aprotic solvent is selected
2 from *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile,
3 and *N*-methylpyrrolidone.
- 1 17. The process according to claim 1 or claim 3, wherein treating the compound of
2 Formula V with an acid and a halogen source is performed in the presence of a solvent.
- 1 18. The process according to claim 1 or claim 3, wherein the acid is selected from
2 hydrochloric acid, sulphuric acid, nitric acid, and phosphoric acid.
- 1 19. The process according to claim 1 or claim 3, wherein the halogen source is selected
2 from sodium halide, potassium halide, and zinc halide.
- 1 20. The process according to claim 1 or claim 3, wherein treating the compound of
2 Formula V with an acid and a halogen source is performed at 60°C to 90°C.
- 1 21. The process according to claim 17, wherein the solvent is selected from methanol,
2 ethyl acetate, water, or mixtures thereof.
- 1 22. The process according to claim 1 or claim 4, wherein hydrogenolysing the
2 compound of Formula IV or salts thereof is performed with a hydrogen source in the
3 presence of a hydrogenolytic catalyst in a solvent.
- 1 23. The process according to claim 22, wherein the hydrogen source is hydrogen gas.
- 1 24. The process according to claim 22, wherein the hydrogenolytic catalyst is selected
2 from palladium compounds, platinum compounds, ruthenium compounds, rhodium
3 compounds, and nickel compounds.
- 1 25. The process according to claim 1 or claim 4, wherein hydrogenolysing the
2 compound of Formula IV or salts thereof is performed at a hydrogen pressure in the range
3 of from about 2 kg to 5 kg.

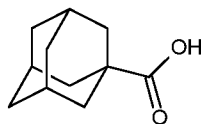
- 1 26. The process according to claim 1 or claim 4, wherein hydrogenolysing the
2 compound of Formula IV or salts thereof is performed at 40°C to 60°C.
- 1 27. The process according to claim 22, wherein the solvent is selected from methanol,
2 water, or mixtures thereof.
- 1 28. The process according to claim 1 or claim 5, wherein treating the compound of
2 Formula III or salts thereof with di-*tert*-butyl dicarbonate is performed in a solvent in the
3 presence of a base.
- 1 29. The process according to claim 28, wherein the base is selected from hydroxides,
2 carbonates, and bicarbonates of alkali and alkaline earth metals; ammonia; alkyl amines;
3 pyridine; and hydrazine.
- 1 30. The process according to claim 28, wherein the base is potassium carbonate.
- 1 31. The process according to claim 1 or claim 5, wherein treating the compound of
2 Formula III or salts thereof with di-*tert*-butyl dicarbonate is performed at 0°C to 25°C.
- 1 32. The process according to claim 28, wherein the solvent is selected from
2 tetrahydrofuran, water, and mixtures thereof.
- 1 33. The process according to claim 1 or claim 6, wherein hydroxylating the compound
2 of Formula II with a hydroxylating agent is performed in the presence of a base.
- 1 34. The process according to claim 1 or claim 6, wherein the hydroxylating agent is
2 water.
- 1 35. The process according to claim 33, wherein the base is potassium carbonate.
- 1 36. The process according to claim 1 or claim 6, wherein hydroxylating the compound
2 of Formula II with a hydroxylating agent is performed at a temperature of 30°C to 60°C.
- 1 37. The process according to claim 1, wherein coupling the compound of Formula I
2 with (1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3-carboxamide of Formula X or salts thereof
3 is carried out in the presence of a coupling agent, a solvent, and a base.
- 1 38. The process according to claim 37, wherein the coupling agent is selected from 1-
2 ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
3 (EDAC.HCl)/hydroxybenzotriazole (HOBt), *i*-BuCOCOCl/triethylamine, and
4 (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop)/N-methyl
5 morpholine (NMM).

- 1 39. The process according to claim 37, wherein the base is triethylamine.
- 1 40. The process according to claim 1, wherein coupling the compound of Formula I
2 with (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carboxamide of Formula X or salts thereof is
3 performed at -10°C to 15°C.
- 1 41. The process according to claim 37, wherein the solvent is selected from
2 dichloromethane, water, and mixtures thereof.
- 1 42. The process according to claim 1, wherein converting the compound of Formula
2 XI to the compound of Formula XII is performed in a solvent in the presence of a base.
- 1 43. The process according to claim 42, wherein the base is selected from the group
2 consisting of pyridine, potassium carbonate, and mixtures thereof.
- 1 44. The process according to claim 1, wherein converting the compound of Formula
2 XI to the compound of Formula XII is performed at -10°C to 20°C.
- 1 45. The process according to claim 42, wherein the solvent is selected from
2 tetrahydrofuran, methanol, and a mixture thereof.
- 1 46. The process according to claim 1, wherein deprotecting the compound of Formula
2 XII is performed with an acid in the presence of a solvent.
- 1 47. The process according to claim 46, wherein the acid is selected from hydrochloric
2 acid, acetic acid, trifluoroacetic acid, and oxalic acid.
- 1 48. The process according to claim 1, wherein deprotecting the compound of Formula
2 XII is performed at a temperature of -10°C to 10°C.
- 1 49. The process according to claim 46, wherein the solvent is selected from
2 dichloromethane, water, and mixtures thereof.
- 1 50. A process for the preparation of a compound of Formula VI,

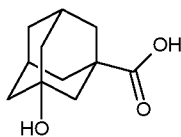


Formula VI

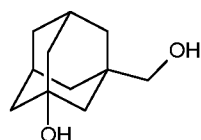
- 4 comprising the steps of:
- 5 (a) hydroxylating a compound of Formula IX

**Formula IX**

with a hydroxylating agent to provide a compound of Formula VIII;

**Formula VIII**

(b) reducing the compound of Formula VIII with a reducing agent to provide a compound of Formula VII; and

**Formula VII**

(c) oxidizing the compound of Formula VII with an oxidizing agent to provide a compound of Formula VI.

51. The process according to claim 50, wherein hydroxylating the compound of Formula IX with a hydroxylating agent is performed in the presence of an acid.

52. The process according to claim 50, wherein the hydroxylating agent is water.

53. The process according to claim 51, wherein the acid is selected from sulphuric acid, nitric acid, and mixtures thereof.

54. The process according to claim 50, wherein hydroxylating the compound of Formula IX with a hydroxylating agent is performed at -15°C to 10°C.

55. The process according to claim 50, wherein reducing the compound of Formula VIII with a reducing agent in step (b) is performed in the presence of a solvent.

56. The process according to claim 50, wherein the reducing agent is selected from the group consisting of sodium borohydride/boron trifluoride etherate, borane-tetrahydrofuran

3 complex/boron trifluoride etherate, dimethylsulfide borane (DMSB)/trimethylborate, and
4 lithium aluminum hydride.

1 57. The process according to claim 50, wherein reduction of the compound of Formula
2 VIII with a reducing agent is performed at -10°C to 35°C.

1 58. The process according to claim 55, wherein the solvent is selected from
2 tetrahydrofuran, ethyl acetate, water, and mixtures thereof.

1 59. The process according to claim 50, wherein the oxidation of the compound of
2 Formula VII with an oxidizing agent is performed in a solvent in the presence of a base.

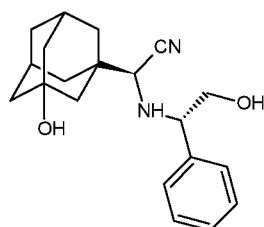
1 60. The process according to claim 50, wherein the oxidizing agent is selected from
2 oxalyl chloride/dimethyl sulfoxide, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl
3 (TEMPO)/sodium hypochlorite, pyridinium chlorochromate, tetrapropylammonium
4 perruthenate (TPAP) in the presence of excess of *N*-Methylmorpholine *N*-oxide (NMO),
5 2-iodoxybenzoic acid, and Collins reagent (chromium(VI) oxide with pyridine in
6 dichloromethane).

1 61. The process according to claim 59, wherein the base is sodium bicarbonate.

1 62. The process according to claim 50, wherein oxidizing the compound of Formula
2 VII with an oxidizing agent is performed at -5°C to 20°C.

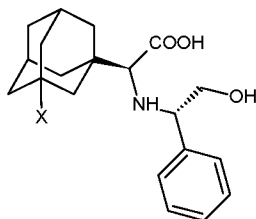
1 63. The process according to claim 59, wherein the solvent is selected from
2 dichloromethane, water, and mixtures thereof.

1 64. A compound of Formula V, or salts thereof.



2
3 **Formula V**

- 1 65. A compound of Formula IV, or salts thereof,



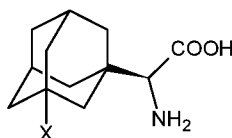
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Formula IV

- 4 wherein X is selected from chloro, bromo, fluoro, or iodo.

- 1 66. A compound of Formula III, or salts thereof,



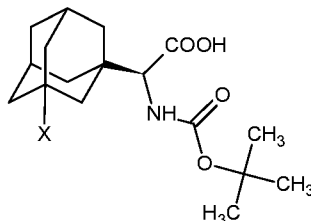
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Formula III

- 4 wherein X is selected from chloro, bromo, fluoro, or iodo.

- 1 67. A compound of Formula II, or salts thereof,



2

3

Formula II

- 4 wherein X is selected from chloro, bromo, fluoro, or iodo

- 1 68. Use of compounds of Formula II, Formula III, Formula IV, and Formula V as
2 intermediates for the preparation of saxagliptin or salts or hydrates thereof.

- 1 69. The process according to claim 1, wherein saxagliptin or salts or hydrates obtained
2 are free from the compounds of Formula II, Formula III, Formula IV, and Formula V.

- 1 70. The process according to claim 1, wherein saxagliptin or salts or hydrates obtained
2 are having less than 0.5% of the compound of Formula II.

1 71. The process according to claim 1, wherein saxagliptin or salts or hydrates obtained
2 are having less than 0.5% of the compound of Formula III.

1 72. The process according to claim 1, wherein saxagliptin or salts or hydrates obtained
2 are having less than 0.5% of the compound of Formula IV.

1 73. The process according to claim 1, wherein saxagliptin or salts or hydrates obtained
2 are having less than 0.5% of the compound of Formula V.

1 74. Use of saxagliptin or salts or hydrates thereof free from the compounds of Formula
2 II, Formula III, Formula IV, and Formula V for the manufacturing of a medicament used
3 for the treatment of type 2 diabetes mellitus.

1 75. Use of saxagliptin or salts or hydrates thereof having less than 0.5% of the
2 compound of Formula II for the manufacturing of a medicament used for the treatment of
3 type 2 diabetes mellitus.

1 76. Use of saxagliptin or salts or hydrates thereof having less than 0.5% of the
2 compound of Formula III for the manufacturing of a medicament used for the treatment of
3 type 2 diabetes mellitus.

1 77. Use of saxagliptin or salts or hydrates thereof having less than 0.5% of the
2 compound of Formula IV for the manufacturing of a medicament used for the treatment of
3 type 2 diabetes mellitus.

1 78. Use of saxagliptin or salts or hydrates thereof having less than 0.5% of the
2 compound of Formula V for the manufacturing of a medicament used for the treatment of
3 type 2 diabetes mellitus.

1 79. Use of saxagliptin or salts or hydrates thereof free from the compounds of Formula
2 II, Formula III, Formula IV, and Formula V for the preparation of a pharmaceutical
3 composition.

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/066769

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/52 C07C255/31 C07C53/138 A61K31/403 A61P3/10
ADD.

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 C07C

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)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P. COLE ET AL: "Saxagliptin", DRUGS OF THE FUTURE, vol. 33, no. 7, 1 January 2008 (2008-01-01), page 577, XP55082506, ISSN: 0377-8282, DOI: 10.1358/dof.2008.033.07.1229229	74-79
Y	see Scheme 1 and 2	1-73
X	US 6 395 767 B2 (ROBL JEFFREY A [US] ET AL) 28 May 2002 (2002-05-28) cited in the application	74-79
Y	columns 1,57-63	1-73
	----- -/-	



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

"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

23 January 2015

Date of mailing of the international search report

10/02/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Lauro, Paola

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/066769

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	S. N. VOLOBOEV ET AL: RUSSIAN JOURNAL OF GENERAL CHEMISTRY, vol. 71, no. 7, 1 January 2001 (2001-01-01), pages 1121-1125, XP055164283, ISSN: 1070-3632, DOI: 10.1023/A:1013178326353 compound XI -----	50

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/066769

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