



(51) International Patent Classification:
C07D 473/06 (2006.01)

(21) International Application Number:
PCT/IB2014/063132

(22) International Filing Date:
15 July 2014 (15.07.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2193/DEL/2013 23 July 2013 (23.07.2013) IN

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

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: PROCESS FOR THE PREPARATION OF LINAGLIPTIN AND AN INTERMEDIATE THEREOF

(57) Abstract: The present invention provides an improved process for the preparation of linagliptin and an intermediate thereof.



WO 2015/011609 A1

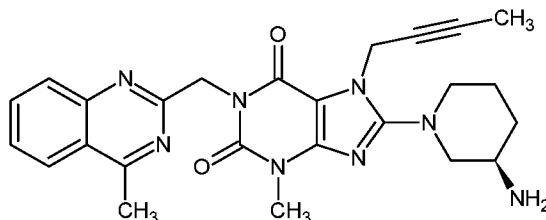
PROCESS FOR THE PREPARATION OF LINAGLIPTIN AND AN INTERMEDIATE THEREOF

Field of the Invention

The present invention provides an improved process for the preparation of
5 linagliptin and an intermediate thereof.

Background of the Invention

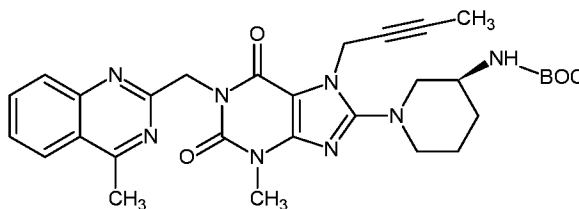
Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4)
enzyme. It is chemically designated as 1H-purine-2,6-dione, 8-[(3R)-3-amino-1-
piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-.
10 Its chemical structure is depicted below in Formula I.



Formula I

Linagliptin is marketed in the United States under the trade name Tradjenta[®], for
the treatment of type 2 diabetes mellitus. It is also marketed in the United States in
15 combination with metformin hydrochloride, under the trade name Jentadueto[®], for the
treatment of type 2 diabetes mellitus.

PCT Publication No. WO 2004/018468 and U.S. Patent No. 7,407,955 disclose a
process for the preparation of linagliptin using a *tert*-butoxycarbonyl protected
intermediate of Formula II.

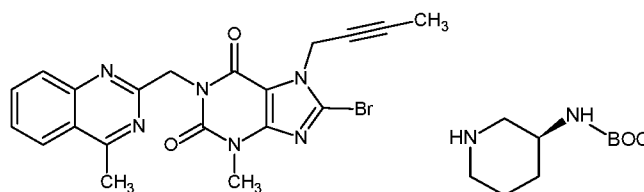


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Formula II

The process disclosed in PCT Publication No. WO 2004/018468 involves the
preparation of the intermediate of Formula II by the reaction of a quinazoline

bromoxanthine intermediate of Formula III with an R-Boc-amino piperidine intermediate of Formula IV in the presence of potassium carbonate in an N,N-dimethylformamide solvent, followed by purification using column chromatography.



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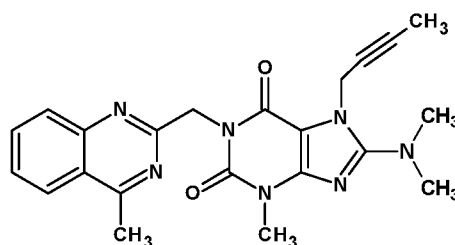
Formula III**Formula IV**

U.S. Patent No. 7,820,815 discloses that the preparation of linagliptin using the *tert*-butoxycarbonyl protected intermediate of Formula II is not suitable for an industrial scale preparation of linagliptin due to the formation of impurities attributable to the protecting group used. It further mentions that these impurities are difficult to remove on an industrial scale, and that the preparation of an enantiomerically pure precursor of Formula II is complicated and expensive.

U.S. Publication No. 2012/0165525 discloses a process for the preparation of a *tert*-butoxycarbonyl protected derivative of Formula II using azide intermediates.

The present inventors have found that the preparation of the *tert*-butoxycarbonyl protected intermediate of Formula II, as per the process disclosed in PCT Publication No. WO 2004/018468, results in the formation of 1.19% of a quinazoline dimethyl aminoxanthine impurity of Formula V appearing at a relative retention time (RRT) of 0.65.

20

**Formula V**

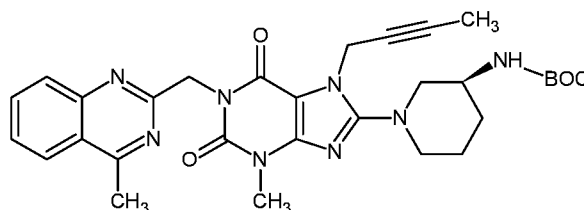
Thus, there exists a need for an industrially advantageous process for the preparation of linagliptin that controls the formation of the quinazoline dimethyl aminoxanthine impurity of Formula V to pharmaceutically acceptable levels.

Summary of the Invention

The present invention provides an improved, economical, and industrially advantageous process for the preparation of the intermediate of Formula II having a controlled amount of the quinazoline dimethyl aminoxanthine impurity of Formula V.

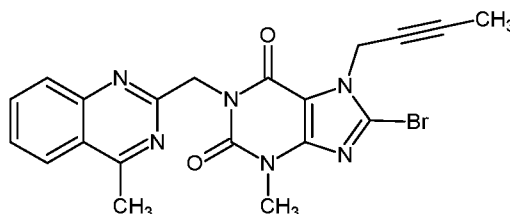
- 5 The process of the present invention involves the preparation of the intermediate of Formula II by the reaction of the intermediate of Formula III with the intermediate of Formula IV in the presence of sodium carbonate in N-methyl-2-pyrrolidone solvent. The process of the present invention avoids the need for purification of the intermediate of Formula II using column chromatography.

- 10 A first aspect of the present invention provides a process for the preparation of the *tert*-butyloxycarbonyl protected intermediate of Formula II



Formula II

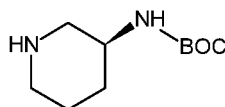
comprising reacting the intermediate of Formula III



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Formula III

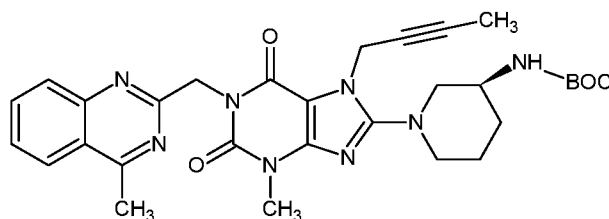
with the intermediate of Formula IV



Formula IV

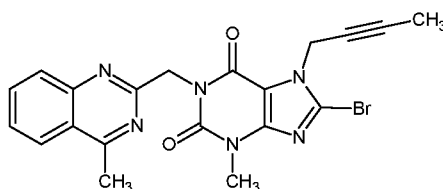
- 20 using sodium carbonate.

A second aspect of the present invention provides a process for the preparation of a *tert*-butoxycarbonyl protected intermediate of Formula II



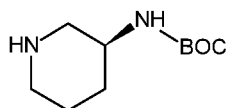
Formula II

5 comprising reacting an intermediate of Formula III



Formula III

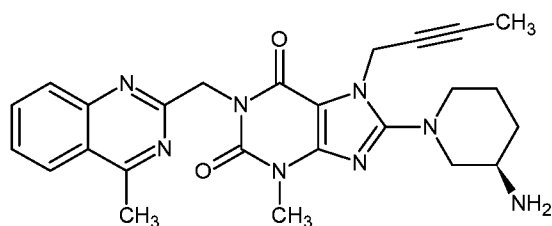
with an intermediate of Formula IV



Formula IV

10 using sodium carbonate in N-methyl-2-pyrrolidone.

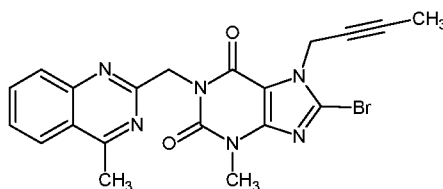
A third aspect of the present invention provides a process for the preparation of linagliptin of Formula I



Formula I

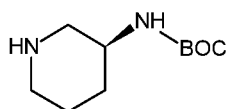
15 comprising the steps of:

a) reacting an intermediate of Formula III



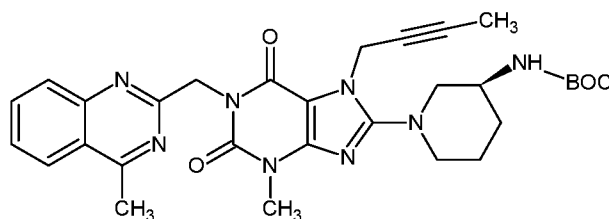
Formula III

with an intermediate of Formula IV



Formula IV

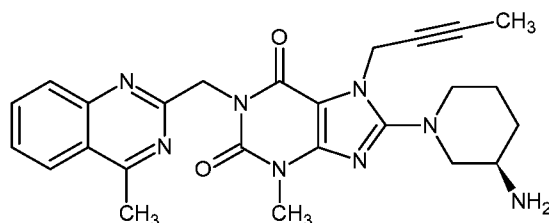
using sodium carbonate to obtain an intermediate of Formula II; and



Formula II

b) converting the intermediate of Formula II into linagliptin of Formula I.

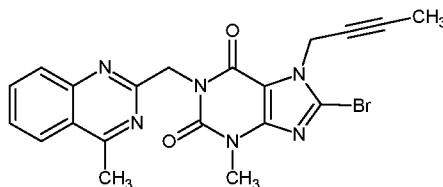
A fourth aspect of the present invention provides a process for the preparation of linagliptin of Formula I



Formula I

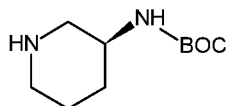
comprising the steps of:

a) reacting an intermediate of Formula III



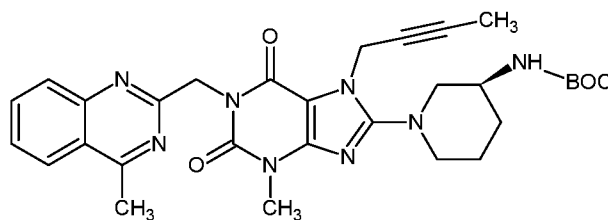
Formula III

with an intermediate of Formula IV



Formula IV

using sodium carbonate in N-methyl-2-pyrrolidone to obtain an intermediate of Formula II; and



Formula II

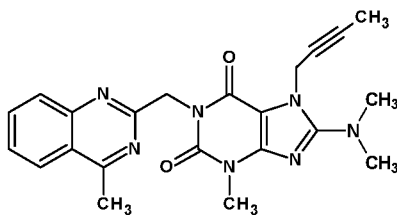
b) converting the intermediate of Formula II into linagliptin of Formula I.

A fifth aspect of the present invention provides the intermediate of Formula II having an HPLC purity greater than 99%.

A sixth aspect of the present invention provides the intermediate of Formula II substantially free of the quinazoline dimethyl aminoxanthine impurity of Formula V.

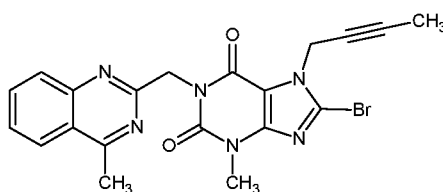
A seventh aspect of the present invention provides linagliptin of Formula I substantially free of the quinazoline dimethyl aminoxanthine impurity of Formula V.

An eighth aspect of the present invention provides a process for the preparation of the quinazoline dimethyl aminoxanthine impurity of Formula V



Formula V

- 5 comprising reacting a quinazoline bromoxanthine of Formula III



Formula III

with dimethyl amine in the presence of sodium carbonate in N,N-dimethylformamide.

Detailed Description of the Invention

- 10 Various aspects and embodiments of the present invention are described hereafter.

The quinazoline dimethyl aminoxanthine impurity of Formula V is chemically 7-(but-2-yn-1-yl)-8-(dimethylamino)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione.

- 15 The term “about”, as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

The term “ambient temperature”, as used herein, refers to a temperature in the range of about 20°C to about 35°C.

- 20 The term “substantially free”, as used herein, refers to the intermediate of Formula II, or linagliptin of Formula I, having less than 1%, preferably less than 0.5%, and most preferably having no detectable amount of the quinazoline dimethyl aminoxanthine impurity of Formula V.

The preparation of the quinazoline bromoxanthine intermediate of Formula III may be carried out by the processes known in the literature, such as by the process disclosed in PCT Publication No. WO 2004/018468, which is incorporated herein by reference.

The R-Boc-aminopiperidine intermediate of Formula IV is available commercially.

- 5 The present inventors have carried out an extensive study for controlling the formation of the quinazoline dimethyl aminoxanthine impurity of Formula V in the intermediate of Formula II. On the basis of various experiments carried out for controlling the formation of the impurity of Formula V, the present inventors have found that the use of sodium carbonate in N-methyl-2-pyrrolidone is advantageous over the use of potassium carbonate in N,N-dimethylformamide, as it controls the formation of the quinazoline dimethyl aminoxanthine impurity of Formula V to pharmaceutically acceptable levels.
- 10 The present inventors further observed that changing the base from potassium carbonate to sodium carbonate while using the same solvent, *i.e.*, N,N-dimethylformamide, controlled the formation of the quinazoline dimethyl aminoxanthine impurity of Formula V.
- 15 However, when both the base and the solvent were changed, in addition to controlling the formation of the quinazoline dimethyl aminoxanthine impurity of Formula V, the reaction also occurred at a lower temperature. Table 1 summarizes the results of the various experiments carried out by the present inventors.

Table 1: Experiments carried out for controlling the impurity of Formula V

Experi- ment	Base	Solvent	Reaction Temperature	HPLC purity	Impurity of Formula V
1	Potassium carbonate	N,N- dimethylformamide	100°C-110°C	95.75%	1.19%
2	Sodium carbonate	N,N- dimethylformamide	130°C-140°C	97.79%	0.63%
3	Sodium carbonate	N-methyl-2- pyrrolidone	85°C-90°C	99.95%	Not detected

- 20 As is evident from Experiment 1, Experiment 2, and Experiment 3 provided in Table 1, preparation of the intermediate of Formula II in the presence of sodium carbonate controlled the formation of the quinazoline dimethyl aminoxanthine impurity of Formula V. Preparation of the intermediate of Formula II in the presence of sodium carbonate in N-methyl-2-pyrrolidone is industrially advantageous as the reaction occurred at a lower
- 25 temperature.

Thus, in the processes of the present invention, the reaction of the intermediate of Formula III with the intermediate of Formula IV to obtain the *tert*-butyloxycarbonyl protected intermediate of Formula II is carried out in the presence of sodium carbonate in N-methyl-2-pyrrolidone.

5 The reaction of the intermediate of Formula III with the intermediate of Formula IV is carried out at a temperature of about 60°C to about 95°C. In a preferred embodiment of the present invention, the reaction of the intermediate of Formula III with the intermediate of Formula IV is carried out at a temperature of about 80°C to 90°C.

10 The intermediate of Formula II may be purified by crystallization in a solvent selected from the group comprising of nitriles, ketones, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, or mixtures thereof. Examples of ketones include acetone, ethyl methyl ketone, methyl *iso*-butyl ketone, or mixtures thereof.

In a preferred embodiment of the present invention, the intermediate of Formula II is purified by crystallization in acetonitrile.

15 In another preferred embodiment of the present invention, the intermediate of Formula II is purified by crystallization in acetone.

The conversion of the intermediate of Formula II into linagliptin of Formula I may be carried out by processes known in the literature, such as the process disclosed in PCT Publication No. WO 2004/018468.

20 In general, the conversion of the intermediate of Formula II into linagliptin of Formula I is carried out by deprotection of the *tert*-butyloxycarbonyl group of the intermediate of Formula II by treatment with trifluoroacetic acid in *iso*-propanol at about 0°C to 80°C.

25 The preparation of the quinazoline dimethyl aminoxanthine impurity of Formula V is carried out by the reaction of the quinazoline bromoxanthine of Formula III with dimethyl amine in the presence of sodium carbonate in N,N-dimethylformamide. The reaction may be carried out at ambient temperature to the reflux temperature of the solvent. In a preferred embodiment of the present invention, the reaction is carried out at ambient temperature to about 80°C.

30 Isolation may be carried out by concentration, precipitation, cooling, filtration, centrifugation, or combinations thereof, followed by drying. Drying may be carried out

using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying. Drying may be carried out at ambient temperature to about 100°C for about 30 minutes to about 20 hours.

In the preferred embodiments of the present invention, the isolation is carried out by concentrating the reaction mixture under reduced pressure followed by drying at a temperature of about 40°C to about 80°C.

The process of the present invention provides the intermediate of Formula II having an HPLC purity greater than 99%.

The process of the present invention provides the intermediate of Formula II substantially free of the quinazoline dimethyl aminoxanthine impurity of Formula V.

The process of the present invention provides linagliptin of Formula I substantially free of the quinazoline dimethyl aminoxanthine impurity of Formula V.

Methods

The NMR spectrum was recorded using a Bruker® Avance III 400 MHz.

The Mass spectrum was recorded using an AB SCIEX® QTRAP® 2000.

The HPLC purity was determined using a Kromasil® C18 (250 × 4.6 mm), 5 µm column with a flow rate of 1.0 mL/minute; Column oven temperature 30°C; Sample tray temperature: 10°C; Detector UV: 225 nm; Injection volume: 10 µL; Run time: 50 minutes.

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

EXAMPLES

Comparative Examples

Comparative Example 1: Preparation of *tert*-butyloxycarbonyl protected intermediate (Formula II) in the presence of potassium carbonate in N,N-dimethylformamide

N,N-dimethylformamide (10 mL), quinazoline bromoxanthine (Formula III; 1 g), potassium carbonate (0.47 g), and R-Boc-aminopiperidine (Formula IV; 0.47 g) were added into a reaction vessel at ambient temperature. The reaction mixture was heated to 100°C to 110°C and stirred for 18 hours. On completion, the reaction mixture was cooled to ambient temperature and deionized water (40 mL) was added. The reaction mixture

was stirred for 2 hours, filtered, washed with deionized water (10 mL), and dried under reduced pressure at 45°C to 48°C for 2 hours and 30 minutes to obtain the intermediate of Formula II.

Yield: 91.2%

5 HPLC Purity: 95.75%

Impurity of Formula V: 1.19%

Comparative Example 2: Preparation of *tert*-butyloxycarbonyl protected intermediate (Formula II) in the presence of sodium carbonate in N,N-dimethylformamide

N, N-dimethylformamide (562.5 mL), quinazoline bromoxanthine (Formula III; 75 g), sodium carbonate (35 g), and R-Boc-aminopiperidine (Formula IV; 36.4 g) were added into a reaction vessel at ambient temperature. The reaction mixture was heated to 130°C to 140°C and stirred for 4 hours. On completion, the reaction mixture was cooled to ambient temperature and water (1700 mL) was added at 10°C to 20°C. The reaction mixture was stirred at ambient temperature for 30 minutes, filtered, washed with water (1500 mL), and dried under reduced pressure at 45°C to 50°C to obtain a solid. The solid was dissolved in dichloromethane (1125 mL), and the organic and aqueous layers were separated. Activated carbon (7.5 g) was added to the organic layer. The contents were stirred at ambient temperature for 30 minutes, and then filtered through a Hyflo[®] bed. The solvent was removed by distillation under reduced pressure to obtain the intermediate of Formula II.

Yield: 89%

HPLC Purity: 97.79%

Impurity of Formula V: 0.63%

25 **Working Examples**

Working Example 1: Preparation of *tert*-butyloxycarbonyl protected intermediate (Formula II) in the presence of sodium carbonate in N-methyl-2-pyrrolidone

Quinazoline bromoxanthine (Formula III; 140 g), R-Boc-aminopiperidine (Formula IV; 68 g), and sodium carbonate (66 g) were added into a reaction vessel containing N-methyl-2-pyrrolidone (560 mL) at ambient temperature. The reaction

5 mixture was heated to 85°C to 90°C and stirred for 8 hours. Progress of the reaction was monitored by HPLC. The reaction mixture was cooled to 26°C and water (1120 mL) was added at 26°C to 40°C. The reaction mixture was stirred at 30°C to 35°C for 30 minutes. The solid obtained was filtered and washed with water (700 mL) to obtain a wet solid (910 g).

The wet solid (388g) was added into a reaction vessel containing water (87 mL) and acetonitrile (400 mL). The reaction mixture was heated to 70°C to 75°C for 30 minutes, and then cooled to 40°C to 50°C. The reaction mixture was stirred for 1 hour, further cooled to 25°C to 30°C, and stirred for 1 hour. The solid obtained was filtered, washed with a mixture of acetonitrile (50 mL) and water (50 mL), and then dried at 50°C to 55°C under reduced pressure to obtain the pure intermediate of Formula II.

Yield: 86%

HPLC Purity: 99.95%

Impurity of Formula V: Not detected

15 Working Example 2: Preparation of *tert*-butyloxycarbonyl protected intermediate (Formula II) in the presence of sodium carbonate in N-methyl-2-pyrrolidone

Quinazoline bromoxanthine (Formula III; 10 g), R-Boc-aminopiperidine (Formula IV; 4.86 g), and sodium carbonate (4.68 g) were added into a reaction vessel containing N-methyl-2-pyrrolidone (40 mL) at ambient temperature. The reaction mixture was heated to 85°C to 90°C and stirred for 12 hours. Progress of the reaction was monitored by HPLC. The reaction mixture was cooled to 40°C and deionized water (120 mL) was added at 40°C to 45°C. The reaction mixture was stirred for 1 hour. The solid obtained was filtered and washed with water (150 mL) to obtain a wet solid (Impurity of Formula V: 0.04%).

25 The wet solid (46 g) was added into another reaction vessel containing water (36.6 mL) and acetone (140 mL). The reaction mixture was heated to 60°C to 65°C for 30 minutes, and then cooled to 25°C to 30°C. The reaction mixture was stirred for 2 hours. The solid obtained was filtered, washed with a mixture of acetone (20 mL) and deionized water (20 mL), and then dried at 50°C to 60°C under reduced pressure for 12 hours to obtain the pure intermediate of Formula II.

30 Yield: 83%

HPLC Purity: 99.94%

Impurity of Formula V: Not detected

Working Example 3: Preparation of Linagliptin (Formula I)

tert-Butyloxycarbonyl protected intermediate (Formula II; 35 g; prepared according to the process of Working Example 2 and dichloromethane (525 mL) were added into a reaction vessel at ambient temperature. The moisture content was adjusted to less than 0.1% by azeotropically distilling dichloromethane from the reaction mixture. The reaction mixture was cooled to 1°C, and trifluoroacetic acid (139.6 g) was added slowly into the reaction mixture at 1°C to 4°C. The reaction mixture was stirred at 10°C to 15°C for 20 hours. Progress of the reaction was monitored by HPLC. The reaction mixture was cooled to 2°C, and aqueous sodium hydroxide solution (56 g in 560 mL water) was slowly added at 2°C to 13°C. The reaction mixture was stirred at 26°C to 28°C for 4 hours followed by layer separation. The organic layer was washed with water (2 x 175 mL). Activated carbon (3.5g) was added to the organic layer, and the contents were stirred for 30 minutes at 27°C to 28°C. The contents were filtered through a Hyflo[®] bed and washed with dichloromethane (2 x 35 mL). The organic layer was concentrated at 30°C under reduced pressure. Iso-propanol (105 mL) was added, and the contents were stirred at about 28°C for 2 hours and 30 minutes. The contents were filtered, washed with iso-propanol (35 mL), and dried under reduced pressure at 60°C to 65°C for 14 hours to obtain linagliptin.

Yield: 79%

HPLC Purity: 99.83%

Working Example 4: Preparation of quinazoline dimethyl aminoxanthine impurity (Formula V)

Quinazoline bromoxanthine (Formula III; 1g), N,N-dimethylformamide (7.6 mL), and sodium carbonate (0.5 g) were added into a reaction vessel at 25°C to 30°C under a nitrogen atmosphere. Dimethyl amine (7.5 mL) was added into the reaction vessel at 25°C to 30°C under a nitrogen atmosphere. The temperature of the reaction mixture was raised to 50°C to 55°C, and the reaction mixture was stirred for 24 hours. The progress of the reaction was monitored by HPLC. Water (80 mL) was added to the reaction mixture at ambient temperature, and the reaction mixture was stirred for 30 minutes. The reaction

mixture was filtered to obtain a solid. The solid was washed with water (20 mL), and then dried in a hot air oven at 35°C to 40°C for 3 hours to obtain quinazoline dimethyl aminoxanthine.

Yield: 71.66%

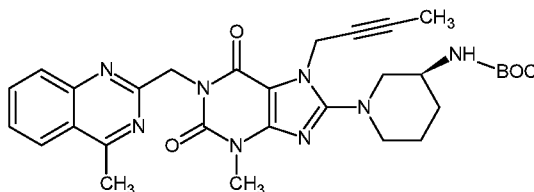
- 5 ^1H NMR (400 MHz, DMSO), δ (in ppm): 1.78 (t, 3H), 2.89 (s, 3H), 3.11 (t, 6H), 3.40 (s, 3H), 4.99 (s, 2H), 5.31 (s, 2H), 7.66-8.26 (m, 4H).

Mass: 418.2 $[\text{M} + \text{H}]^+$; MS/MS: 418.2, 365.2, 350.1, 336.1, 208.1, 167.0, 158.0, 139.1.

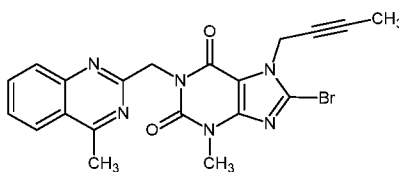
IR in KBr, (in cm^{-1}): 2222 (HCECH stretching), 1695 (-C=N stretching), 1662 (-C=O stretchings), 735, 760 (aryl C-H bendings).

We claim:

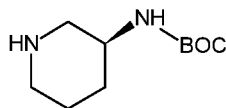
- 1 1. A process for the preparation of the *tert*-butyloxycarbonyl protected intermediate
- 2 of Formula II

**Formula II**

- 5 comprising reacting the intermediate of Formula III

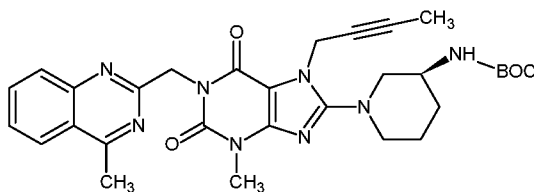
**Formula III**

- 8 with the intermediate of Formula IV

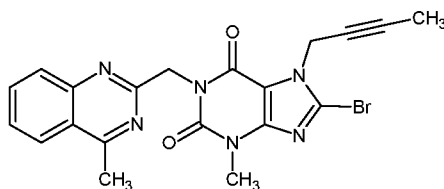
**Formula IV**

- 11 using sodium carbonate.

- 1 2. A process for the preparation of a *tert*-butyloxycarbonyl protected intermediate of
- 2 Formula II

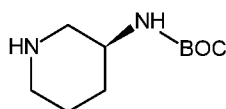
**Formula II**

- 5 comprising reacting an intermediate of Formula III



Formula III

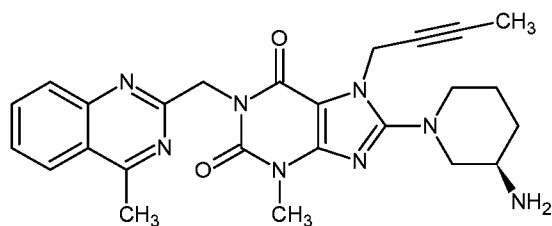
with an intermediate of Formula IV



Formula IV

using sodium carbonate in N-methyl-2-pyrrolidone.

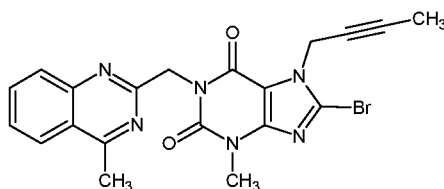
3. A process for the preparation of linagliptin of Formula I



Formula I

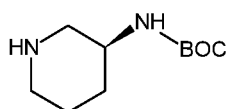
comprising the steps of:

a) reacting an intermediate of Formula III



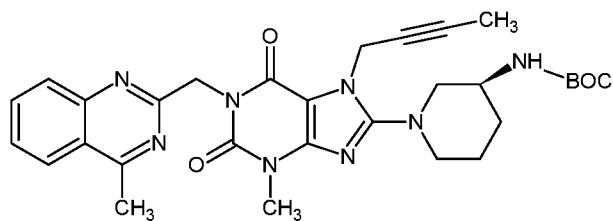
Formula III

with an intermediate of Formula IV



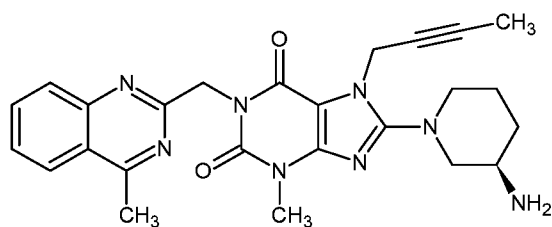
Formula IV

using sodium carbonate to obtain an intermediate of Formula II; and

**Formula II**

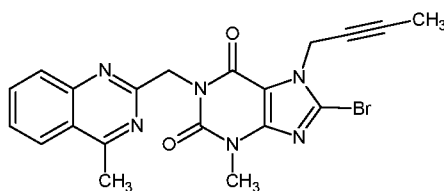
b) converting the intermediate of Formula II into linagliptin of Formula I.

4. A process for the preparation of linagliptin of Formula I

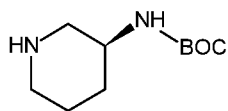
**Formula I**

comprising the steps of:

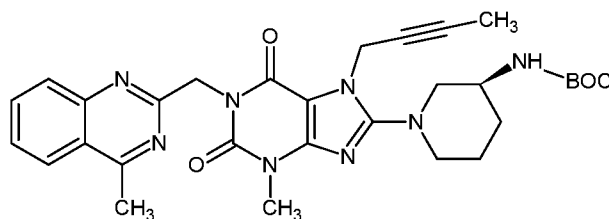
a) reacting an intermediate of Formula III

**Formula III**

with an intermediate of Formula IV

**Formula IV**

using sodium carbonate in N-methyl-2-pyrrolidone to obtain an intermediate of Formula II; and



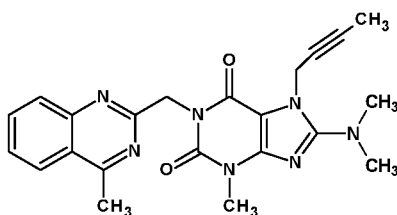
Formula II

b) converting the intermediate of Formula II into linagliptin of Formula I.

5. The process according to any of claims 1-4, wherein the reaction of the intermediate of Formula III with the intermediate of Formula IV is carried out at a temperature of about 60°C to about 95°C.

6. The *tert*-butoxycarbonyl protected intermediate of Formula II having an HPLC purity greater than 99%.

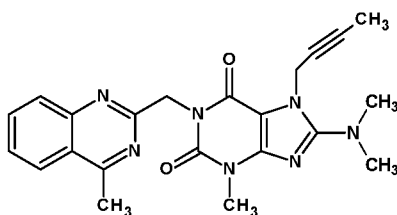
7. The *tert*-butoxycarbonyl protected intermediate of Formula II substantially free of the quinazoline dimethyl aminoxanthine impurity of Formula V



Formula V.

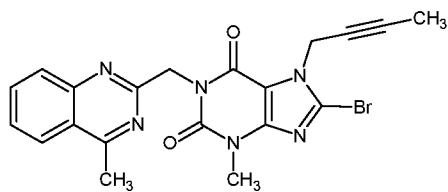
8. Linagliptin of Formula I substantially free of the quinazoline dimethyl aminoxanthine impurity of Formula V.

9. A process for the preparation of the quinazoline dimethyl aminoxanthine impurity of Formula V



Formula V

comprising reacting a quinazoline bromoxanthine of Formula III

**Formula III**

- 6
- 7
- 8 with dimethyl amine in the presence of sodium carbonate in N,N-dimethylformamide.
- 1 10. The process according to claim 10, wherein the reaction is carried out at ambient
- 2 temperature to about 80°C.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/063132A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/06
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

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, WPI Data, EMBASE, 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	WO 2004/018468 A2 (BOEHRINGER INGELHEIM PHARMA [DE]; HIMMELSBACH FRANK [DE]; LANGKOPF ELK) 4 March 2004 (2004-03-04) cited in the application pages 28-31, 47, 60, 73; claims 17, 22 ----- -/--	1-10



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

12 September 2014

Date of mailing of the international search report

22/09/2014

Name and mailing address of the ISA/

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

Authorized officer

Moriggi, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/063132

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ECKHARDT MATTHIAS ET AL: "8-(3-(R)-aminopiperidin-1-yl)-7-but-2-yny 1-3-methyl-1-(4-methyl-quina zolin-2-ylmethyl)-3,7-dihydropurine-2,6-di one (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 50, no. 26, 1 December 2007 (2007-12-01), pages 6450-6453, XP002495244, ISSN: 0022-2623, DOI: 10.1021/JM701280Z [retrieved on 2007-12-01] scheme 2; compound 9bk; the synthetic intermediate of Step I, page S6 of the Supporting Information; compound I & Matthias Eckhardt ET AL: "Supporting Information 8-(3-(R)-Amino-piperidin-1-yl)-7-but-2-yny 1-3-methyl-1-(4-methyl-quinazolin-2-ylmeth yl)-3,7- dihydro-purine-2,6-dione (BI 1356): A Highly Potent, Selective, Long-Acting, and Orally Bioavailable DPP-4 Inhibitor for the Treatment of Type 2 Diabetes", Journal of Medicinal Chemistry, 1 January 2007 (2007-01-01), pages S1-S18, XP055139755, Retrieved from the Internet: URL: http://pubs.acs.org/doi/suppl/10.1021/ jm701280z/suppl_file/jm701280z-file001.pdf [retrieved on 2014-09-11] page S6	6-8
X	8-(3-(R)-Amino-piperidin-1-yl)-7-but-2-yny 1-3-methyl-1-(4-methyl-quinazolin-2-ylmeth yl)-3,7- dihydro-purine-2,6-dione (BI 1356): A Highly Potent, Selective, Long-Acting, and Orally Bioavailable DPP-4 Inhibitor for the Treatment of Type 2 Diabetes", Journal of Medicinal Chemistry, 1 January 2007 (2007-01-01), pages S1-S18, XP055139755, Retrieved from the Internet: URL: http://pubs.acs.org/doi/suppl/10.1021/ jm701280z/suppl_file/jm701280z-file001.pdf [retrieved on 2014-09-11] page S6	6-8
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X,P	----- WO 2014/097314 A1 (MYLAN LAB LTD [IN]; CHAVHAN BHAUSAHEB [IN]; RATHINAPANDIAN JEBARAJ [IN]) 26 June 2014 (2014-06-26) examples 4-7	1-4,6-8
X,P	----- WO 2014/059938 A1 (2Y CHEM LTD [CN]) 24 April 2014 (2014-04-24) examples 6, 8, 10, 11 -----	6-8

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Information on patent family members

International application No

PCT/IB2014/063132

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/063132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2014059938	A1	24-04-2014	CN 103319483 A 25-09-2013
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