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(54) Title: AN IMPROVED PROCESS FOR PREPARING LINAGLIPTIN AND ITS KEY INTERMEDIATES

(57) Abstract: The present invention relates to a process for the preparation of Linagliptin or a pharmaceutically acceptable slat thereof. Further aspects of the present invention relates to process for the preparation of Linagliptin key intermediate, having purity more than 98.0 %.

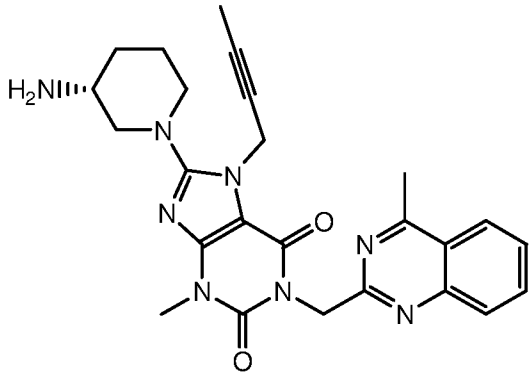
An improved process for preparing Linagliptin and its key Intermediates

Field of Invention

The present invention relates to a process for the preparation of Linagliptin or a pharmaceutically acceptable salt thereof. Further it relates to process for the preparation of Linagliptin key intermediates, 8-bromo xanthine and Boc-Linagliptin having purity more than 98.0 %.

Background of the invention

Linagliptin is chemically known 8-[(3*R*)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1*H*-purine-2,6-dione and is structurally represented by formula (I):



Formula I

Linagliptin is approved for the treatment of Diabetes and is available in the market as Tradjenta® with the strength 5 mg of Tablet for oral administration.

U.S. Patent No. 7,407,955 describes Linagliptin and process for the preparation thereof. Further, Matthias et al., in Journal of Medicinal Chemistry 2007 50(26) Pages 6450-6453, discloses a process for the preparation of Linagliptin from Boc protected Linagliptin.

The process disclosed in the US '955 and Matthias article for Boc protected Linagliptin involves condensation of 8-chloro xanthine compound with -(R)-Boc aminopiperidine in presence potassium carbonate.

The reported process suffers one or the other problems like yield and purity due to the selection of suitable solvent and reaction condition. Hence, there is a need for a simple process for making large scale quantities of Linagliptin or a pharmaceutically acceptable salt thereof.

The inventors of the present invention surprisingly found that the positive improvement, for example, yield and purity, due to the use of organic base than the inorganic base for the condensation reaction to provide Boc protected Linagliptin.

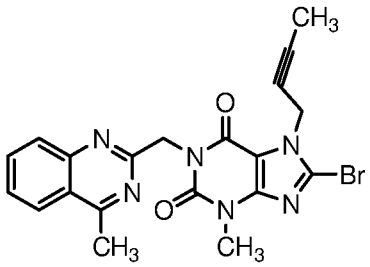
The inventors of the present invention also noticed that Linagliptin in yield and purity could be prepared by using substantially pure intermediates in suitable solvent such as amide and water or mixture thereof. The intermediates 8-bromo-7-(but-2-ynyl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6(3H,7H)-dione (referred to *herein* as "8-bromo xanthine") of Formula-II and (R)-1-(7-(but-2-ynyl)-2,3,6,7-tetrahydro-3-methyl-1-((4-methylquinazolin-2-yl) methyl)-2,6-dioxo-1H-purin-8-yl)piperidin-3-ylcarbamate (referred to *herein* as "Boc-Linagliptin") of Formula-III can be used to prepare highly pure Linagliptin in the subsequent reaction steps.

Summary of the Invention

The present invention provides an improved process for the preparation of Linagliptin or pharmaceutically acceptable salt thereof. Further, the present invention provides the process for the preparation of substantially pure Linagliptin key intermediates, e.g. bromopurine and Boc-Linagliptin, having purity more than 98.0 %.

The present invention provides a process for the preparation of Linagliptin of Formula I or its pharmaceutically acceptable salt, which includes steps of condensation of 2-(chloromethyl)-4-methylquinazoline compound of Formula A or its pharmaceutically acceptable salt with 8-bromo-7-(but-2-ynyl)-3-methyl-1H-purine-2,6(3H,7H)-dione of Formula B or its pharmaceutically acceptable salt, in presence of a suitable base in suitable solvent to obtain 8-bromo xanthine of compound of Formula II or its pharmaceutically acceptable salt. Purification of 8-bromo xanthine of Formula II as obtained in step (a) in the suitable solvent. Condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C or its pharmaceutically acceptable salt, using a suitable base in presence of a suitable solvent to obtain Boc-Linagliptin of Formula III or its pharmaceutically acceptable salt. Deprotection of Boc-Linagliptin using triflouroacetic acid in presence of dichloromethane to obtain crude Linagliptin. Acid and base treatment to crude Linagliptin yields substantially pure Linagliptin.

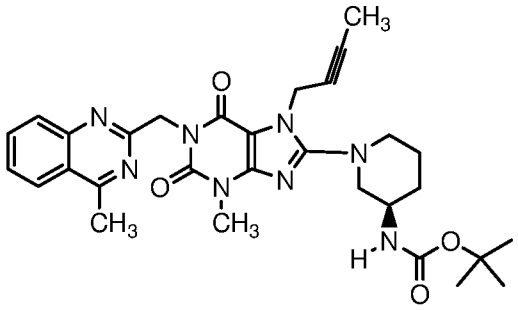
The present invention provides a process for preparing substantially pure 8-bromo xanthine Formula II or pharmaceutically acceptable salt thereof:



Formula II

and its conversion to Linagliptin or pharmaceutically acceptable salt thereof.

The present invention also provides a process for preparing substantially pure Boc-Linagliptin of Formula III or pharmaceutically acceptable salt thereof:



Formula III

and its conversion to Linagliptin or pharmaceutically acceptable salt thereof.

In another aspect, the present invention specifically provides the process for the preparation of intermediate of Linagliptin of Formula III or its pharmaceutically acceptable salt, which includes condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C or its pharmaceutically acceptable salt using an organic base in the presence of a solvent.

In another aspect, the present invention provides Linagliptin or a pharmaceutically acceptable salt thereof having purity greater than or equal to 99%.

In another aspect, the present invention provides highly pure Linagliptin or a pharmaceutically acceptable salt thereof substantially free of impurities, e.g. N-(1-(7-(but-2-ynyl)-2,3,6,7-tetrahydro-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-1H-purin-8-yl)piperidin-3-yl)-2,2,2-trifluoroacetamide (referred to *herein* as “TFA-impurity”)

In another aspect, there is provided a composition comprises Linagliptin or a pharmaceutically acceptable salt thereof of the present invention and at least one pharmaceutically acceptable carrier or excipient.

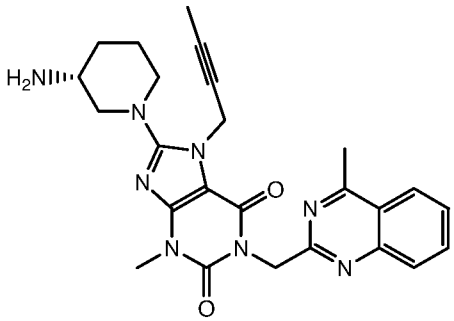
Description of the Invention

For purposes of the present invention, the following terms are defined below.

The term "substantially pure" as used herein, unless otherwise defined, the compound that has purity of greater than about 97 % or greater than about 98%.

The intermediates and starting materials of the present invention may be used as free bases or its salts.

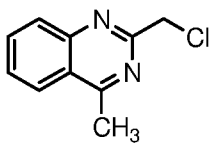
In an aspect, the present invention provides a process for the preparation of Linagliptin of Formula I



Formula I

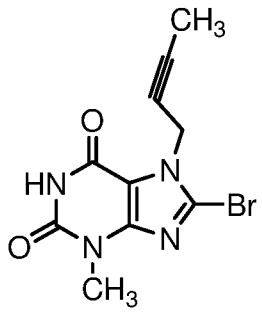
or its pharmaceutically acceptable salt, which includes steps of

a) condensation of 2-(chloromethyl)-4-methylquinazoline compound of Formula A



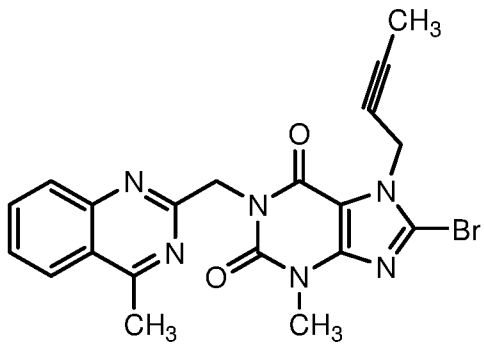
Formula A

or its pharmaceutically acceptable salt with 8-bromo-7-(but-2-ynyl)-3-methyl-1H-purine-2,6(3H,7H)-dione of Formula B



Formula B

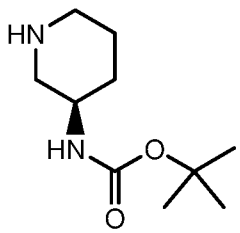
or its pharmaceutically acceptable salt, in presence of base in a suitable solvent to obtain 8-bromo xanthine of compound of Formula II or its pharmaceutically acceptable salt



Formula II

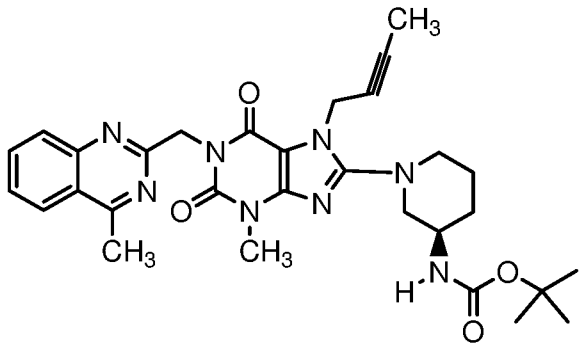
b) purification of 8-bromo xanthine of Formula II as obtained in step (a) in the suitable solvent.

c) condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C



Formula C

or its pharmaceutically acceptable salt, in presence of a suitable base in a suitable solvent to obtain Boc-Linagliptin of Formula III



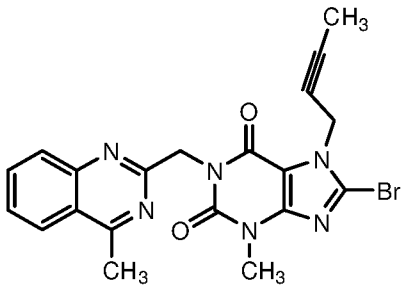
Formula III

or its pharmaceutically acceptable salt

d) deprotection of Boc-Linagliptin of step c) using triflouroacetic acid in presence of dichloromethane to obtain crude Linagliptin.

e) treatment with suitable acid base to crude Linagliptin obtained in step (d) to obtain substantially pure Linagliptin.

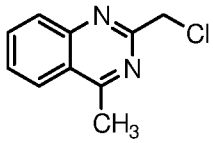
In an another aspect, the present invention provides a process for the preparation of substantially pure 8-bromo xanthine of Formula II or its pharmaceutically acceptable salt,



Formula II

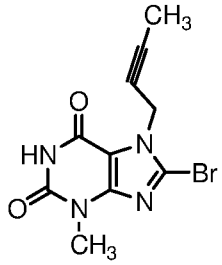
which includes step of

a) condensation of 2-(chloromethyl)-4-methylquinazoline compound of Formula A



Formula A

or its pharmaceutically acceptable salt with 8-bromo-7-(but-2-ynyl)-3-methyl-1H-purine-2,6(3H,7H)-dione of Formula B

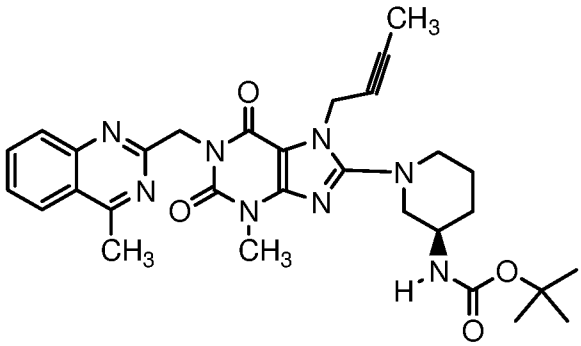


Formula B

or its pharmaceutically acceptable salt, in presence of base in a suitable solvent.

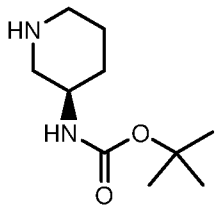
b) purification of 8-bromo xanthine of Formula II obtained in step (a) in the suitable solvent.

In an another aspect, the present invention provides a process for the preparation of substantially pure Boc-Linagliptin of Formula III



Formula III

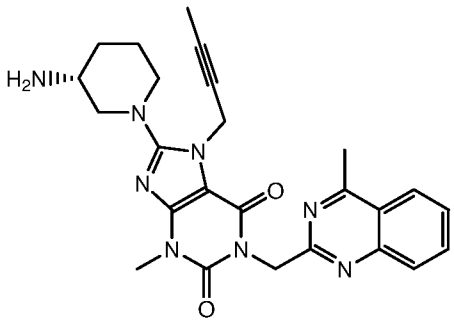
or its pharmaceutically acceptable salt, which includes condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C



Formula C

or its pharmaceutically acceptable salt in presence of a suitable base in a suitable solvent.

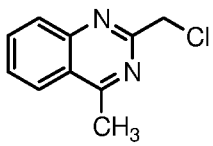
In another aspect, the present invention provides a process for the preparation of Linagliptin of Formula I



Formula I

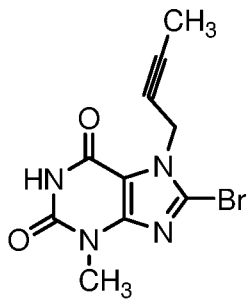
or its pharmaceutically acceptable salt, which includes steps of

a) condensation of 2-(chloromethyl)-4-methylquinazoline compound of Formula A



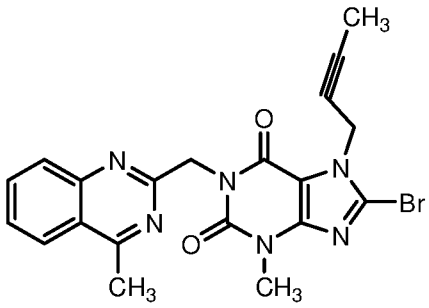
Formula A

or its pharmaceutically acceptable salt with 8-bromo-7-(but-2-ynyl)-3-methyl-1H-purine-2,6(3H,7H)-dione of Formula B



Formula B

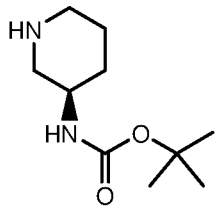
or its pharmaceutically acceptable salt, in presence of potassium carbonate base in dimethylacetamide solvent to obtain 8-bromo xanthine of compound of Formula II or its pharmaceutically acceptable salt.



Formula II

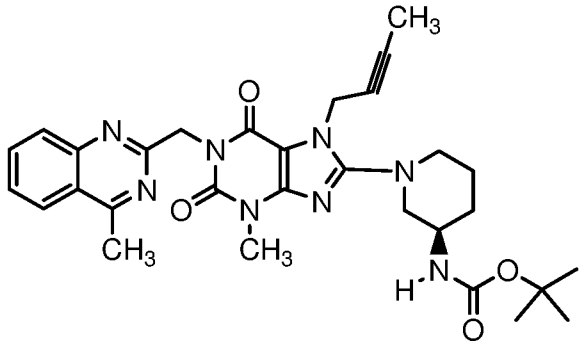
b) purification of 8-bromo xanthine of Formula II as obtained in step (a) in dimethylformamide.

c) condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C



Formula C

or its pharmaceutically acceptable salt, in presence of potassium carbonate base in dimethylacetamide solvent to obtain Boc-Linagliptin of Formula III



Formula III

or its pharmaceutically acceptable salt

d) deprotection of Boc-Linagliptin of step c) using triflouroacetic acid in presence of dichloromethane to obtain crude Linagliptin.

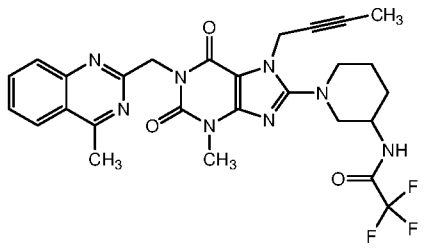
e) treatment with suitable acid base to crude Linagliptin obtained in step (d) to obtain substantially pure Linagliptin.

In another aspect, the present invention provides a process for the preparation of Linagliptin or pharmaceutically acceptable salt thereof, which includes:

a) condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C or its pharmaceutically acceptable salt using an organic base such as N,N-Diisopropylethylamine in the presence of dimethyl acetamide to provide Boc protected Linagliptin; and
b) deprotection of Boc-Linagliptin of step a) using triflouroacetic acid in presence of dichloromethane to provide Linagliptin.

In another aspect, the present invention provides Linagliptin or a pharmaceutically acceptable salt thereof having purity greater than or equal to 99%.

In another aspect, the present invention provides highly pure Linagliptin or a pharmaceutically acceptable salt thereof substantially free of impurities, such as N-(1-(7-(but-2-ynyl)-2,3,6,7-tetrahydro-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-1H-purin-8-yl)piperidin-3-yl)-2,2,2-trifluoroacetamide (referred to *herein* as “impurity-A”)



Impurity-A

The suitable base may be selected from inorganic base or organic base. The inorganic base includes but are not limited to sodium hydroxide, sodium

carbonate, sodium bicarbonate, potassium carbonate, potassium hydroxide, potassium bicarbonate and the like; the organic base may be selected from triethyl amine, diisopropyl amine, methyl amine, pyridine, N-methyl pyrrolidine and the like.

The suitable solvent selected from the group comprising amides, water and their combination. The amides solvents are, such as dimethyl acetamide and dimethyl formamide and the like.

The condensation reaction may be conducted at elevated temperature of about 45 °C to about 110°C temperature. The reaction may be maintained till to the completion of starting materials at elevated temperature, for about 2 hours or more.

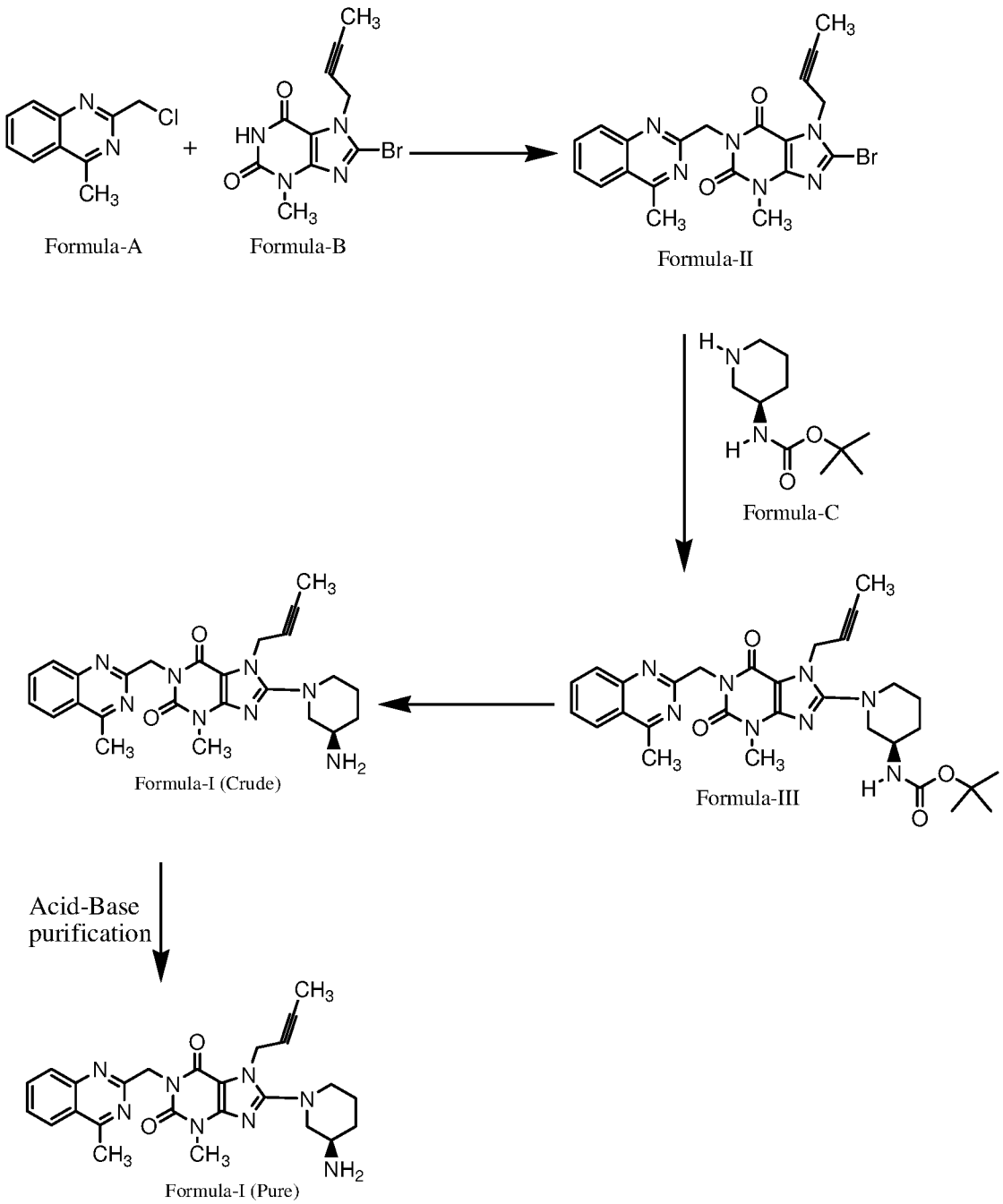
After completion of the reaction, the reaction mixture may be quenched with water or acid and solid isolation by using suitable techniques, such as addition of organic solvent, antisolvent, concentrate, pH adjustment and cooling of reaction mixture or mass.

Organic solvent selected from group methanol, ethanol, isopropyl alcohol, n-butanol and the like. Antisolvent is selected from ethyl acetate, isopropyl acetate and the like. The term antisolvent is defined as the solvent for crystallization in which the solubility of the product to be crystallized is less and it is used for the complete crystallization of the product.

In another aspect, the present invention provides Linagliptin or a pharmaceutically acceptable salt thereof having purity greater than or equal to 99%.

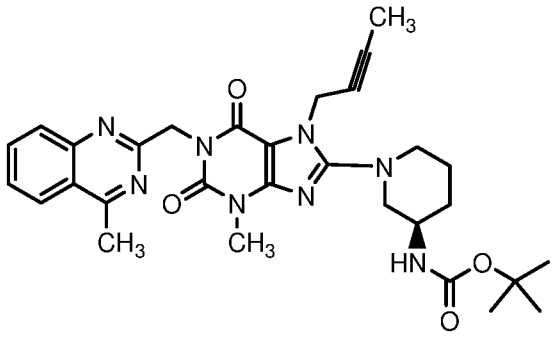
The salt or pharmaceutically acceptable salt compounds of the present invention may include but are not limited to hydrochloride, hydrobromide, methane sulfonate, p-toluene sulfonate, trifluoroacetate, tartrate salt and the like.

The process of the present invention is depicted in the following Scheme A:



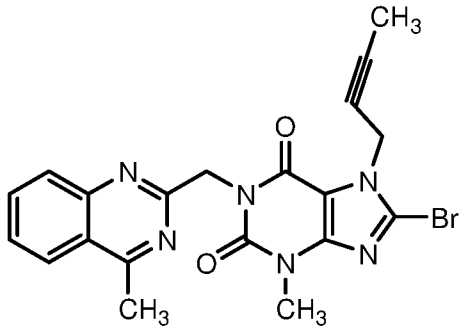
The resultant 8-bromo xanthine or its salt obtained from the present invention has purity greater than about 99% determined by HPLC method. The resultant Boc-Linagliptin or its salt obtained from the present invention has purity greater than about 98% determined by HPLC method. The yield of the 8-bromo xanthine or its salt may be greater than about 90%. The yield of the Boc-Linagliptin or its salt may be greater than about 90%.

In another aspect, the present invention provides the process for the preparation of intermediate of Linagliptin of Formula III:



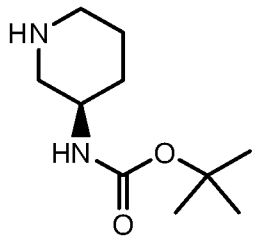
Formula III

or its pharmaceutically acceptable salt, which includes condensation of 8-bromo xanthine compound of Formula II



Formula II

or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C



Formula C

or its pharmaceutically acceptable salt using in presence of organic base in a suitable solvent.

The suitable organic base used for the condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C or its pharmaceutically acceptable salt is selected from Triethyl amine (Et_3N), trimethyl amine (Me_3N), pyridine, tributylamine, diisopropyl ethyl amine (DIPEA) in presence of a suitable solvent.

The suitable solvent for the condensation reaction of the present invention includes but are not limited to dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide and the like. Other solvents may include alcohol such as methanol, ethanol, isopropanol and n-butanol; hydrocarbon such as n-hexane, n-heptane, cyclohexane and toluene; and their combination with dimethyl acetamide.

The starting material, 3-(R)-Boc aminopiperidine or its salt may be used 1 to 1.5 molar equivalents for the equivalent of 8-bromo xanthine compound of Formula II or its salt for preparing Boc-Linagliptin.

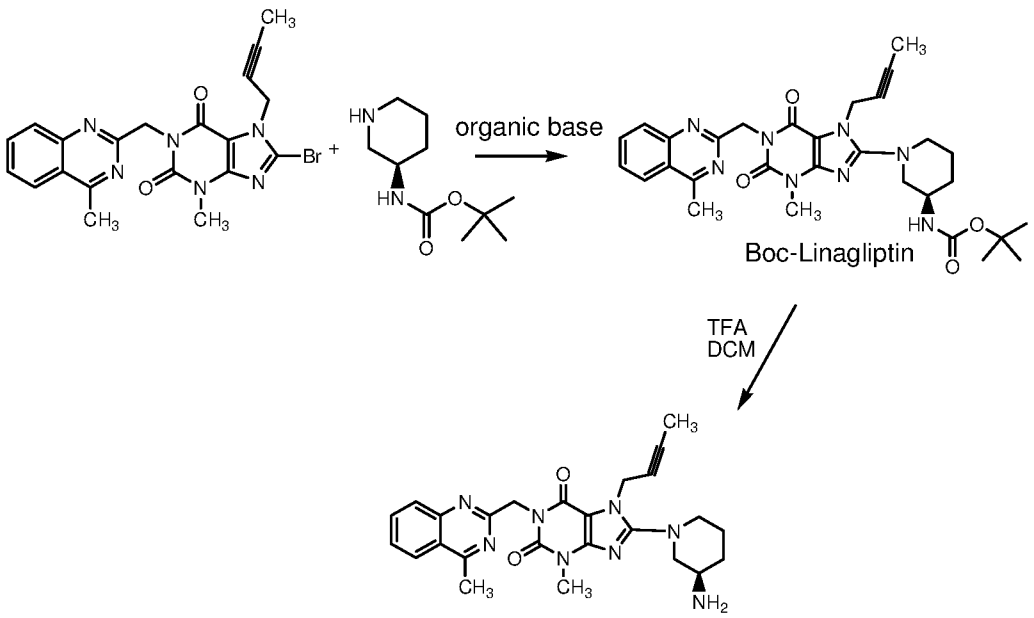
The base used for the condensation reaction may be 1 to 4 molar equivalents per the equivalent of the compound of Formula II or its salt.

The condensation reaction may be conducted at elevated temperature of about 45°C to about reflux temperature. The reaction may be maintained till completion of the reaction, for example, to about 2 hours or more.

After completion of the reaction, the reaction mixture may be quenched with quenching agent, for example, water or acid, and then subjected for solid isolation by using suitable techniques, for example, slurry for a certain period of time, cooling, recrystallization and the like.

In another aspect, the present invention provides a process for the preparation of intermediate of Linagliptin of Formula III or its pharmaceutically acceptable salt, which includes condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C or its pharmaceutically acceptable salt using an organic base such as N,N-Diisopropylethylamine.

The process of the present invention is depicted in the following Scheme B:



The salt or pharmaceutically acceptable salt compounds of the present invention may include but are not limited to hydrochloride, hydrobromide, methane sulfonate, p-toluene sulfonate, trifluoroacetate, tartrate salt and the like.

The obtained Boc-Linagliptin or its salt is used for the conversion to Linagliptin by the treatment of acid, for example, triflouroacetic acid, in presence of chlorinated solvent, for example, dichloromethane.

The resultant Boc-Linagliptin or its salt obtained from the present invention has purity greater than about 95% determined by HPLC method. The yield of the Boc-Linagliptin or its salt may be greater than about 92%

The present invention is further illustrated by the following example, which does not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present application.

EXAMPLES:

Example-1: Preparation of Bromopurine

To the stirring mixture of purine (200g) in dimethylacetamide (1400 ml) were added quinazoline (147g), potassium carbonate powder (140 g) at 25-30 °C. The reaction mixture was heated to 80-85°C for 10 hr. To the reaction mixture, water was charged (5600 ml). After addition of water, reaction mixture was cooled to 25-30°C and maintained for 30 min. Filtered reaction mixture to give bromopurine (282 g) which is further purified from dimethyl formamide to give pure bromopurine (253 g).

HPLC Purity: 99.47%

Example-2: Preparation of Boc-Linagliptin

Method A:

To the stirring mixture of Boc-Amino piperidine (14 g) in dimethylacetamide (175ml) were added potassium carbonate powder (31 g) and bromopurine (18 g) at 25-30 °C. The reaction mixture was heated to 80-85°C for 12 hr. To the reaction mixture, water was added (525 ml). After addition of water, reaction mass cooled to 35-40°C and maintained for 30 min. Filtered reaction mixture to get Boc-Linagliptin (35 g).

HPLC Purity: 98.03%

Method B:

Bromo xanthine (5 gm) and Boc-Amino piperidine (3.4 gm) were added into dimethyl acetamide (50 mL) at room temperature. Diisopropylethyl amine (5.6 gm) was added to the reaction mixture and then heated to 100-110 °C and maintain for 12 hours. After completion of reaction, reaction mixture was quenched with water (50 mL) and stirred at RT for 30 minutes. The precipitated material was filtered, washed with water (20 mL) and dried under vacuum at 65-

70 °C to get Boc-Linagliptin (5.75 gm, 92% yield) with HPLC purity > 96.76 % (0.19 % of bromopurine (starting material) observed).

Example-3: Preparation of Linagliptin-Crude

To the stirring solution of Boc-Linagliptin (35 gm) in dichloromethane (350 ml) at 15 °C was added trifluoroacetic acid (140g) slowly. After addition of trifluoro acetic acid, reaction mixture was heated to 25-30 °C and maintained for 3 hour. Reaction mixture was cooled to 5°C and water was added (200 ml) and adjust ed the pH of the reaction mixture 9-10 using ammonia solution (110 g). Dichloromethane layer Separated and concentrated. The reaction mass is treated with Isopropyl Acetate (490 ml) and its partial removal by distillation and cooling to 10-15°C yields crude Linagliptin (23 g).

HPLC Purity: 98.43%

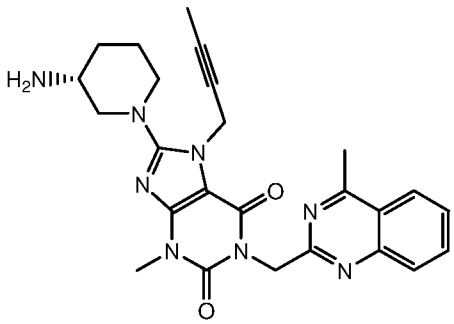
Example-4: Preparation of Linagliptin

To the stirring mixture of crude Linagliptin (20 g) water (200 ml) was added concentrated hydrochloric acid (5 ml) at temperate 5-15°C. The reaction mixture was washed with dichloromethane and subsequently by ethyl acetate. The aqueous layer was treated with dichloromethane and the pH is adjusted to 10-11 using potassium carbonate solution at temperate below 15°C. Separated dichloromethane layer was washed with 25% sodium chloride solution. Further dichloromethane was distilled out and reaction mass was treated with Methanol (80 ml) partial removal of methanol and addition isopropyl acetate yields the Linagliptin which is filtered and dried. Yield 13 g.

HPLC Purity: 99.59%

We Claim:

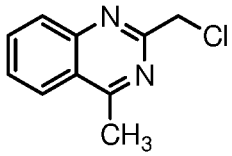
1. A process for the preparation of Linagliptin of Formula I



Formula I

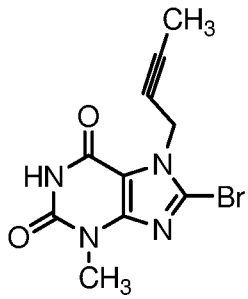
or its pharmaceutically acceptable salt, which comprises steps of

a) condensation of 2-(chloromethyl)-4-methylquinazoline compound of Formula A



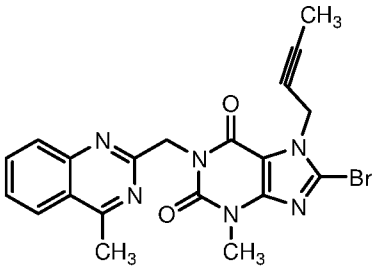
Formula A

or its pharmaceutically acceptable salt with 8-bromo-7-(but-2-ynyl)-3-methyl-1H-purine-2,6(3H,7H)-dione of Formula B



Formula B

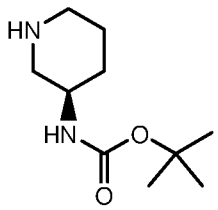
or its pharmaceutically acceptable salt, in presence of a suitable base in a suitable solvent to obtain 8-bromo xanthine of compound of Formula II or its pharmaceutically acceptable salt.



Formula II

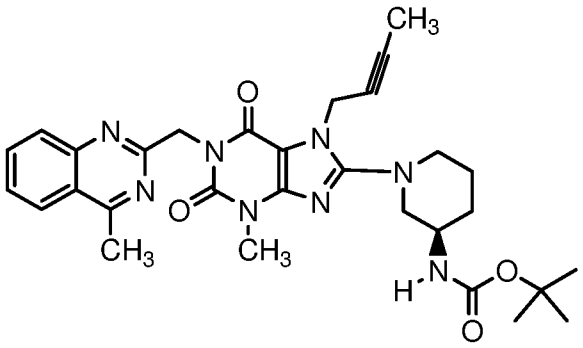
b) purification of 8-bromo xanthine of Formula II as obtained in step (a) in a suitable solvent.

c) condensation of 8-bromo xanthine compound of Formula II or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C



Formula C

or its pharmaceutically acceptable salt, in presence of a suitable base in a suitable solvent to obtain Boc-Linagliptin of Formula III



Formula III

or its pharmaceutically acceptable salt

d) deprotection of Boc-Linagliptin of step c) using triflouroacetic acid in presence of dichloromethane to obtain crude Linagliptin.

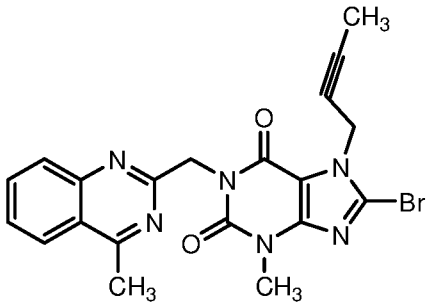
e) treatment with suitable acid base to crude Linagliptin obtained in step (d) to obtain substantially pure Linagliptin.

2. The process of claim 1, wherein the suitable solvent is selected from the group comprising amides and water and their combination.

3. The process of claim 2, wherein the amide solvent is selected from the group comprising dimethyl acetamide, dimethyl formamide and dimethyl sulfoxide.

4. The process of claim 2, wherein the solvent is dimethyl acetamide and water.

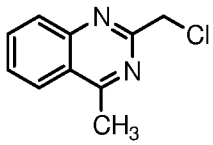
5. A process for the preparation of substantially pure 8-bromo xanthine of Formula II



Formula II

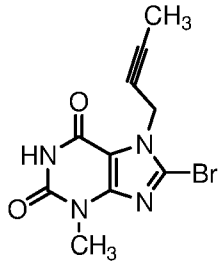
or its pharmaceutically acceptable salt, which comprises steps of

a) condensation of 2-(chloromethyl)-4-methylquinazoline compound of Formula A



Formula A

or its pharmaceutically acceptable salt with 8-bromo-7-(but-2-ynyl)-3-methyl-1H-purine-2,6(3H,7H)-dione of Formula B



Formula B

or its pharmaceutically acceptable salt in presence of a suitable base in a suitable solvent.

b) purification of 8-bromo xanthine of Formula II obtained in step (a) in the suitable solvent.

6. The process of claim 5, wherein the substantially pure 8-bromo xanthine has the purity more than 99% by HPLC.

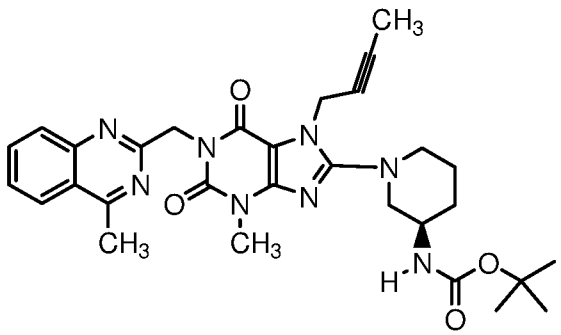
7. The process of claim 5, wherein the suitable solvent is selected from the group comprising amides and water and their combination.

8. The process of claim 7, wherein the amide solvent is selected from the group comprising dimethyl acetamide, dimethyl formamide and dimethyl sulfoxide.

9. The process of claim 8, wherein the suitable solvent is dimethyl acetamide and water.

10. The process according to claim 5, wherein compound of formula-II subsequently converted to Linagliptin or a pharmaceutically acceptable slat thereof.

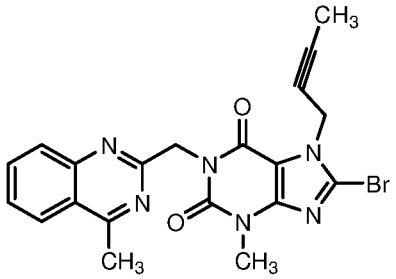
11. A process for the preparation of substantially pure Boc-Linagliptin of Formula III



Formula III

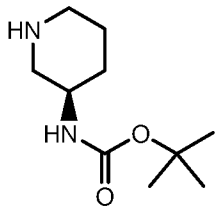
or its pharmaceutically acceptable salt, which comprises steps

a) condensation of 8-bromo xanthine compound of Formula II



Formula II

or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C



Formula C

or its pharmaceutically acceptable salt using a suitable base in presence of a suitable solvent.

12. The process of claim 11, wherein the substantially pure Boc-Linagliptin has the purity more than 98% by HPLC.

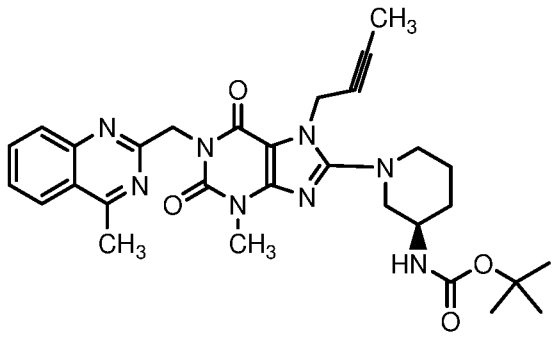
13. The process of claim 11, wherein the suitable solvent is selected from the group comprising amides and water and their combination.

14. The process of claim 13, wherein the amide solvent is selected from the group comprising dimethyl acetamide, dimethyl formamide and dimethyl sulfoxide.

15. The process of claim 14, wherein the suitable solvent is dimethyl acetamide and water.

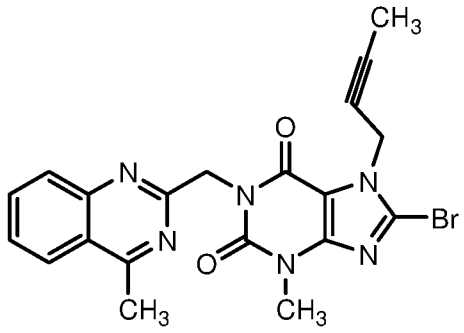
16. The process according to claim 11, wherein compound of formula-III subsequently converted to Linagliptin or a pharmaceutically acceptable slat thereof.

17. A process for the preparation of intermediate of Linagliptin of Formula III:



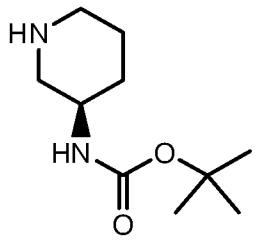
Formula III

or its pharmaceutically acceptable salt, which comprises condensation of 8-bromo xanthine compound of Formula II



Formula II

or its pharmaceutically acceptable salt with 3-(R)-Boc aminopiperidine of Formula C:



Formula C

or its pharmaceutically acceptable salt using an organic base in the presence of a solvent.

18. The process of claim 17, wherein the 3-(R)-Boc aminopiperidine or its salt is 1 to 1.5 molar equivalents for the equivalent of 8-bromo xanthine of Formula II or its salt.

19. The process of claim 17, wherein the base is 1 to 4 molar equivalents per the equivalent of the compound of Formula II or its salt.

20. The process of claim 17, wherein the organic base is selected from he group of Triethyl amine (Et_3N), trimethyl amine (Me_3N), pyridine, tributylamine and diisopropyl ethyl amine (DIPEA).

21. The process of claim 17, wherein the solvent is dimethyl acetamide, dimethyl formamide or dimethyl sulfoxide.

22. The process of claim 17, wherein the condensation reaction is performed at elevated temperature, for example, at 100 °C.

23. The process of claim 17, wherein the Boc-Linagliptin or its salt is used as key intermediate to prepare Linagliptin or its pharmaceutically acceptable salt.

24. The process of claim 17, wherein the Boc-Linagliptin or its salt has the purity of about 95% by HPLC.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/062943

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
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, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG Y ET AL: "BI-1356. Dipeptidyl-peptidase IV inhibitor, antidiabetic agent", DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 33, no. 6, 1 June 2008 (2008-06-01), pages 473-477, XP009110227, ISSN: 0377-8282, DOI: 10.1358/DOF.2008.033.06.1215244 Synthesis; page 473 Scheme 1; page 474	1-24

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
29 October 2014	06/11/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofia

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/062943

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-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydropurine-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, 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] cited in the application Supporting Information	1-24
X	& Matthias Eckhardt ET AL: "Supporting Information 8-(3-(R)-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-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] pages S4, S6	1-24

X	WO 2013/098775 A1 (REDDYS LAB LTD DR [IN]) 4 July 2013 (2013-07-04) abstract; claims 1-8,12-18; examples 15,16 page 4, last paragraph - page 6, paragraph 2nd	1-24

X	WO 2006/048427 A1 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; PFREN) 11 May 2006 (2006-05-11) abstract; example 2	1-24

X,P	WO 2014/097314 A1 (MYLAN LAB LTD [IN]; CHAVHAN BHAUSAHEB [IN]; RATHINAPANDIAN JEBARAJ [IN]) 26 June 2014 (2014-06-26) the whole document in particular examples 1-7	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/062943

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-24

   Process for the preparation of Linagliptin of Formula I and intermediates thereof.

1.1. claims: 1-4

   Process for the preparation of Linagliptin of Formula I.

1.2. claims: 5-10

   Process for the preparation of the 8-bromo xanthine intermediate of Formula II.

1.3. claims: 11-16

   Process for the preparation of the Boc-Linagliptin of Formula III using a suitable base.

1.4. claims: 17-24

   Process for the preparation of the Boc-Linagliptin of Formula III using an organic base.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/062943

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013098775 A1	04-07-2013	NONE	
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