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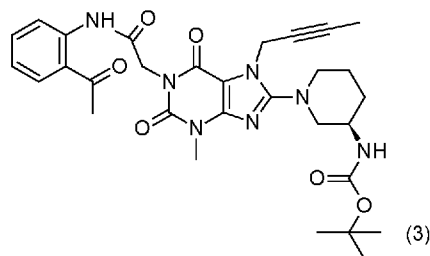
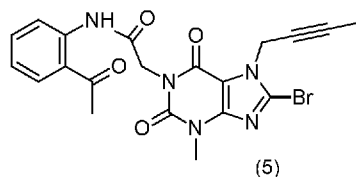
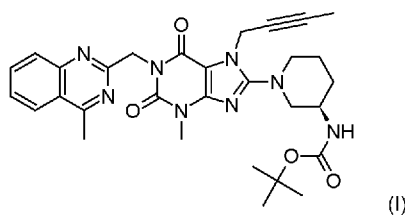
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(54) Title: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF BOC-LINAGLIPTIN



(57) Abstract: This invention relates to novel processes for the synthesis of Linagliptin, the pharmaceutically active ingredient, and the key intermediate thereof, BOC-Linagliptin. (I) The processes are performed via new intermediate compounds of Formula (5) and Formula (3).



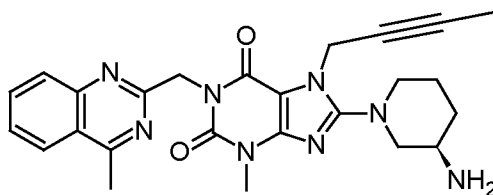
PROCESS AND INTERMEDIATES FOR THE PREPARATION OF BOC-LINAGLIPTIN

FIELD OF THE INVENTION

The present invention relates to novel processes for the synthesis of a xanthine-based
5 pharmaceutically active ingredient, i.e., Linagliptin, and intermediates thereof.

BACKGROUND OF THE INVENTION

Linagliptin is a compound of Formula 1 chemically known as 8-[(3R)-3-amino-1-piperidiny]-
7-(2-butyn-1-yl)-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-3,7-dihydro-1H-purine-2,6-
10 dione.

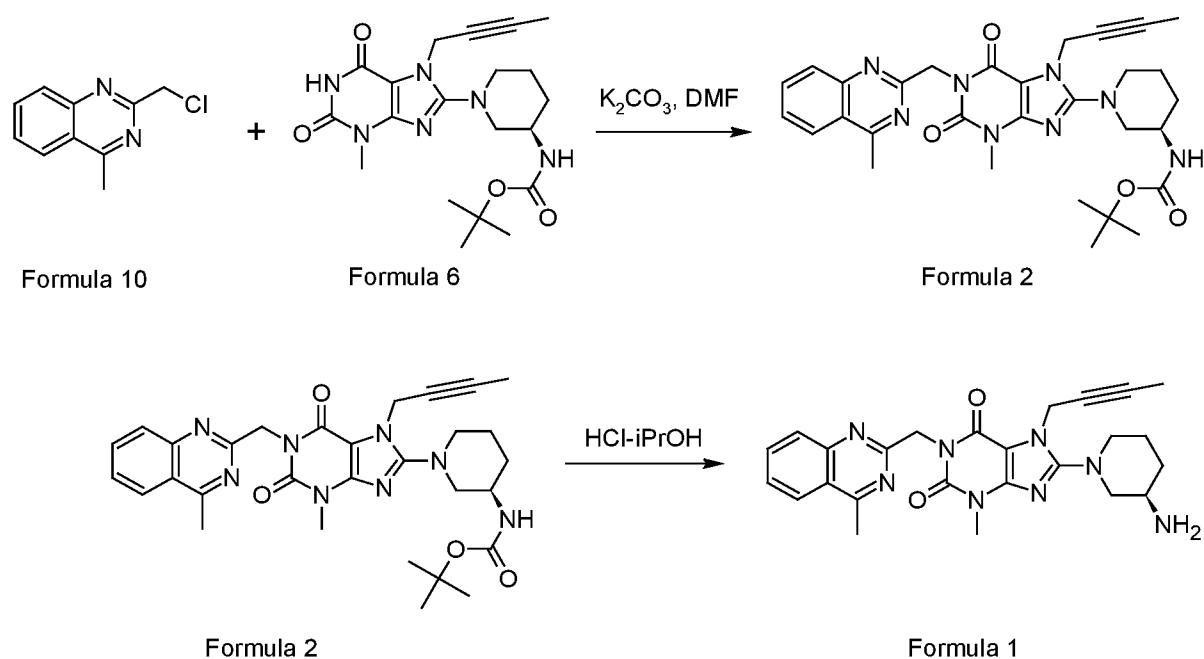


Formula 1

Linagliptin is used for the treatment of type-II diabetes mellitus and marketed in the United
States under the trade name Trajenta and in combination with metformin hydrochloride under
15 the trade name Jentadueto.

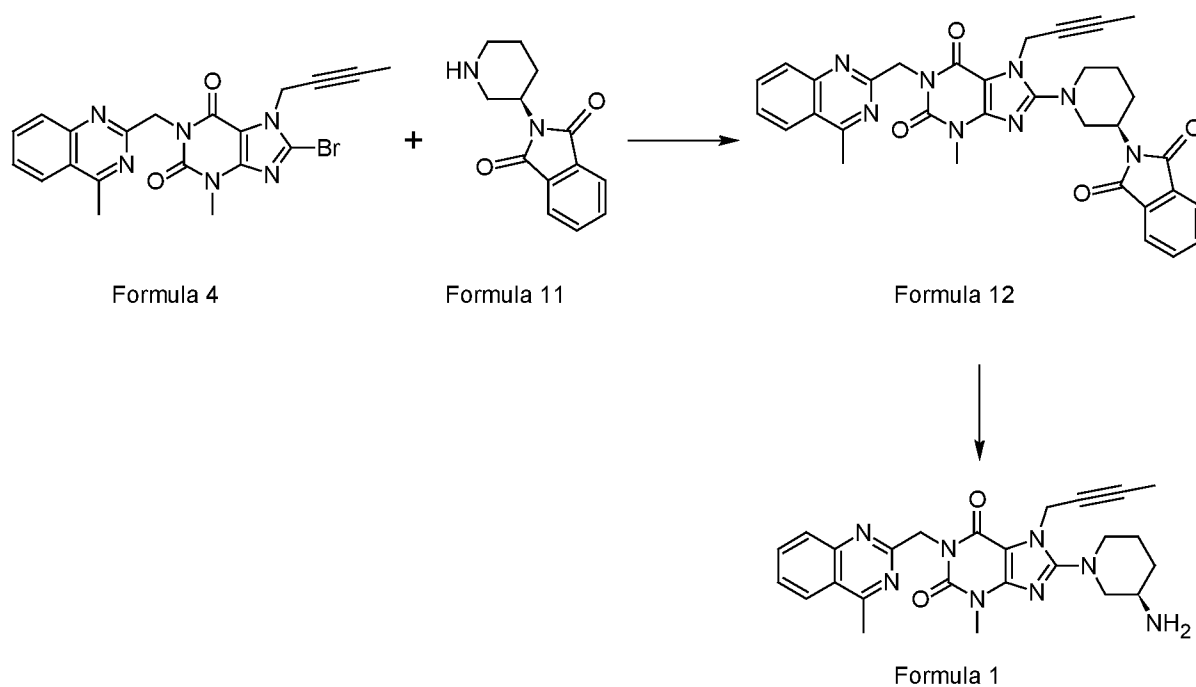
There are several methods describing the synthesis of Linagliptin known in literature.

WO 2004/018468 and US 7,407,955 disclose the following process for the preparation of
Linagliptin:

**Scheme 1**

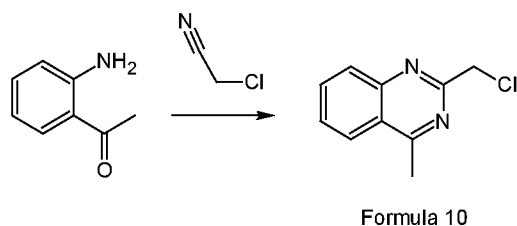
Impurities forming in this process are difficult to remove, especially on industrial scale and are attributed to the protecting group used.

- 5 WO 2006/048427 and US 7,820,815 describe the following process for the synthesis of Linagliptin:



Scheme 2

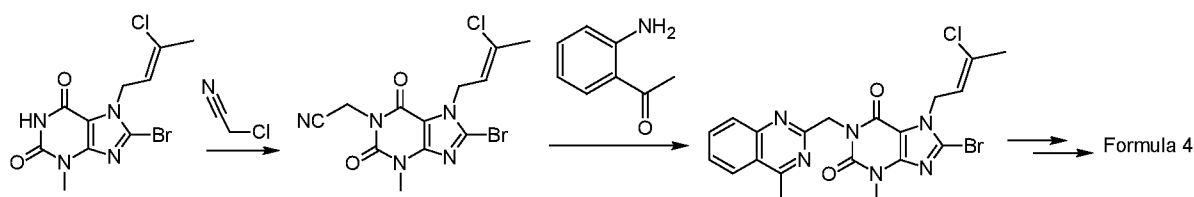
US 7,820,815 also discloses the preparation of 2-chloromethyl-4-methylquinazoline in the following way:



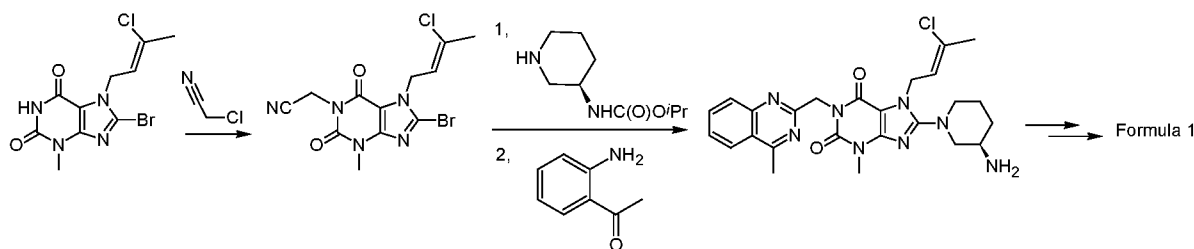
5

Scheme 3

The reference WO 2015/067539 describes a method for the synthesis of quinazolinyl-xanthine (Formula 4):

**Scheme 4**

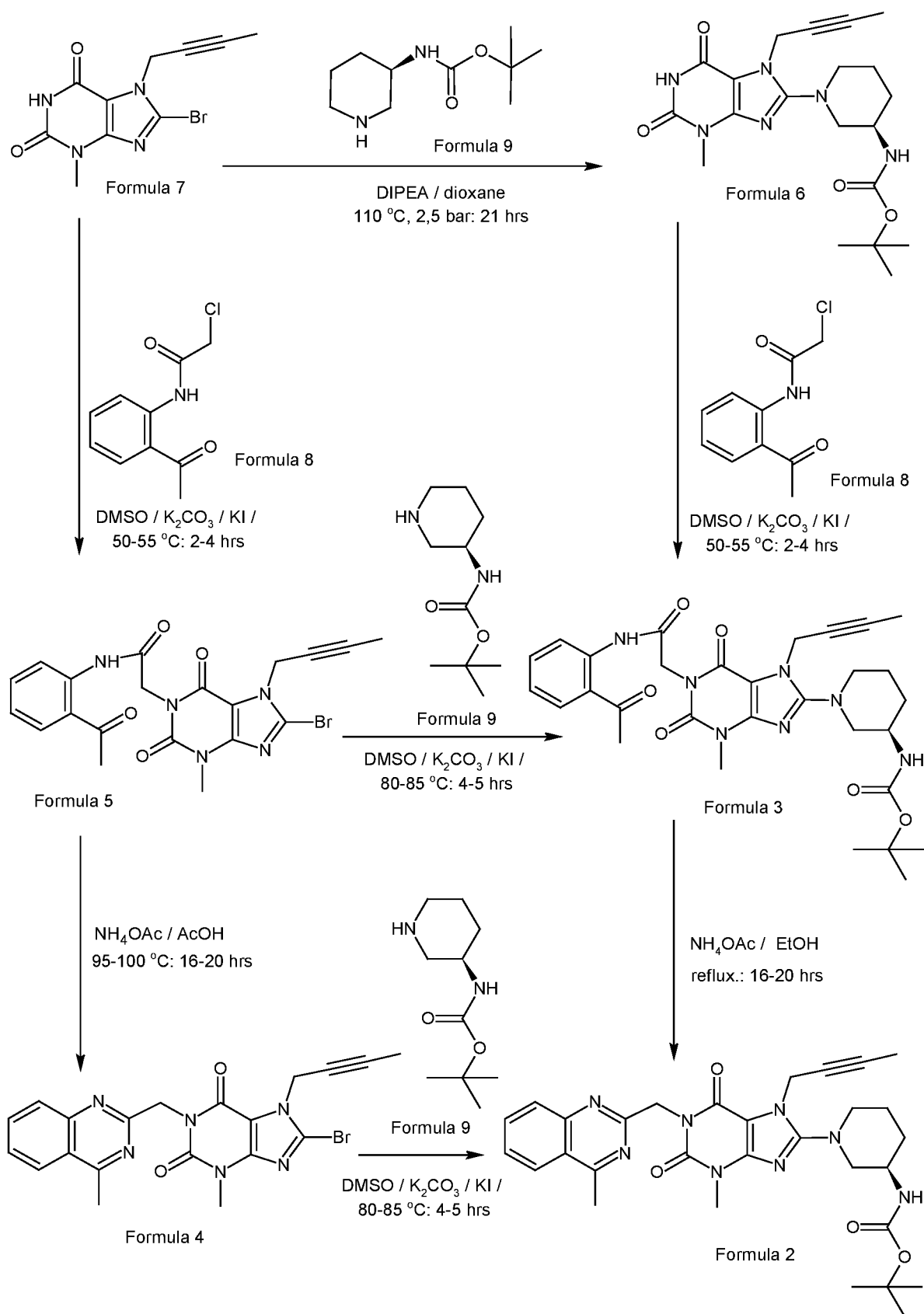
10 and that of Linagliptin (Formula 1):

**Scheme 5****SUMMARY OF THE INVENTION**

15 Our invention is summarized in **Scheme 6**.

This invention is a new, industrially applicable process for the preparation of BOC-Linagliptin of Formula 2, in new synthetic routes via chemically new intermediates (Formula

5 and Formula 3). These new intermediates enable the formation of the quinazoline part of Linagliptin on the xanthine scaffold in a ring-closing reaction.



Scheme 6

DETAILED DESCRIPTION OF THE INVENTION

According to Scheme 6, there are three different routes available for preparation of BOC-Linagliptin that are different embodiments of this invention.

In one possible route reacting Butynyl-Br-Me-xanthine of Formula 7 with Acetylphenyl-chloroacetamide of Formula 8, a new compound, Acetylphenylamino-But-Br-Me-xanthine of Formula 5 is formed (**Example 2**). The alkylation of Butynyl-Br-Me-xanthine can be carried out in dipolar aprotic solvents such as dimethylformamide (DMF), dimethylacetamide (DMAA), *N*-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO) using inorganic bases like sodium, potassium, cesium carbonate or hydrogen carbonate. Sodium or potassium iodide in catalytic amount accelerate the reaction. The reaction advantageously takes place in DMSO solution in the presence of potassium iodide and potassium carbonate. The temperature of this reaction is in the range of 40-90 °C, advantageously in 50-55 °C. The formed new intermediate is transformed into Quinazolinyl-xanthine of Formula 4 at temperature between 60 and 120 °C in a ring-closing reaction (**Example 3**). Ammonia, ammonium acetate, ammonium formate, ammonium chloride and the like can be used as nitrogen- source for ring-closure. The solvent was selected from among alcohols (like methanol, ethanol or 2-propanol), acetic acid, toluene and the like. To accomplish this reaction, the mixture is stirred at 95-100 °C for 16-20 hrs, preferably in acetic acid. Quinazolinyl-xanthine of Formula 4 is reacted with Boc-aminopiperidine of Formula 9 resulting the formation of Boc-Linagliptin of Formula 2 (**Example 7**). The reaction can be carried out in different polar aprotic solvents (e.g. DMF, DMAA, NMP, DMSO) in the presence of base (e.g. sodium, potassium, cesium carbonate or bicarbonate) and sodium or potassium iodide as catalyst. This *N*-arylation requires higher temperature (60-120 °C) than alkylation of Butynyl-Br-Me-xanthine. The reaction preferably takes place in DMSO in the presence of potassium carbonate and potassium iodide at 80-85 °C.

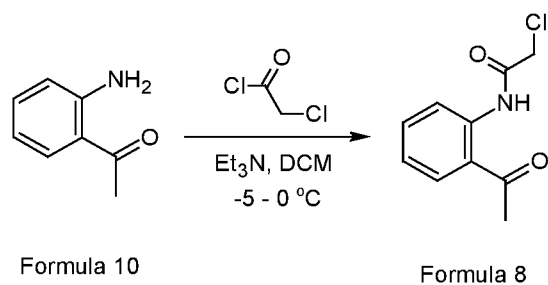
In the next possible route, Butynyl-Br-Me-xanthine of Formula 7 can be reacted with Acetylphenyl-chloroacetamide of Formula 8 while a new compound, Acetylphenylamino-But-Br-Me-xanthine of Formula 5 is formed (for the reaction conditions see **Example 2**). This new intermediate can be reacted with Boc-aminopiperidine of Formula 9 to prepare Acetylphenylamino-piperidinyl-xanthine of Formula 3 (**Example 5**). The applied conditions could be the same as in the reaction of Quinazolinyl-xanthine of Formula 4 with Boc-aminopiperidine of Formula 9. The reaction advantageously can be carried out in DMSO at 80-

85 °C using potassium carbonate as base and potassium iodide as catalyst. This latter new compound can be converted into the aimed Boc-linagliptin of Formula 2 (*Example 6*) in a ring-closing reaction. Ammonia, ammonium acetate, ammonium formate, ammonium chloride and the like can be used as nitrogen- source for ring-closure. The solvent was selected from among
5 alcohols (like methanol, ethanol or 2-propanol) or toluene at temperature between 60 and 120 °C. Acetic acid is not recommended because of the acid-sensitive Boc protecting group.

According to Scheme 6, in a third route, Butynyl-Br-Me-xanthine of Formula 7 can be reacted with Boc-aminopiperidine of Formula 9 to get Piperidinyl-xanthine of Formula 6. The reaction can be accomplished in solvents such as DMSO, DMAA, NMP, acetonitrile, 1,4-dioxane in the
10 presence of inorganic (e.g. sodium, potassium, cesium carbonate or bicarbonate) or organic base (e.g. triethylamine or *N,N*-diisopropylethylamine) at temperature of 60 to 140 °C. The reaction advantageously takes place in Dioxane in the presence of *N,N*-Diisopropylethylamine (DIPEA) at 110 °C. Reacting Piperidinyl-xanthine of Formula 6 with Acetylphenyl-chloroacetamide of Formula 8, the new compound of Formula 3 (*Example 4*) is prepared. This latter new compound
15 can be converted into the aimed Boc-Linagliptin of Formula 2 in a ring-closing reaction (*Example 6*) (for the reaction conditions see *Example 3*).

EXAMPLES

Example 1: Synthesis of Acetylphenyl-chloroacetamide (Formula 8)

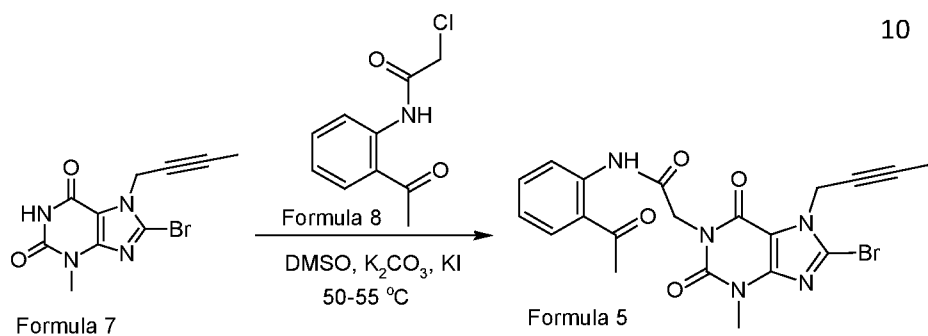


Scheme 7

To a solution of 2'-aminoacetophenone (9.0 mL, 10.0 g, 74 mmol; 1 eq) in dry dichloromethane (80 mL) was added triethylamine (15.5 mL, 11.23 g, 111 mmol; 1.5 eq) under nitrogen
25 atmosphere. To the reaction mixture the solution of chloroacetyl chloride (8.2 mL, 11.7 g, 104

mmol; 1.4 eq) in DCM (20 mL) was slowly added at -5-0 °C, then the reaction mixture was stirred under such conditions for 2 hrs. The reaction was monitored by TLC (silica, hexane:ethyl-acetate=7:3). The reaction mixture was diluted with DCM (150 mL) and washed with aq. NaHCO₃ (5%, 1x60 mL), hydrochloric acid (10%, 2x40 mL) and brine (1x40 mL),
 5 respectively. The organic phase was dried and evaporated under reduced pressure at 30-35 °C. The residue was recrystallized from 2-propanol and dried under vacuum at 50 °C to get acetylphenyl-chloroacetamide as a beige powder (12.7 g, HPLC: 96.7%).

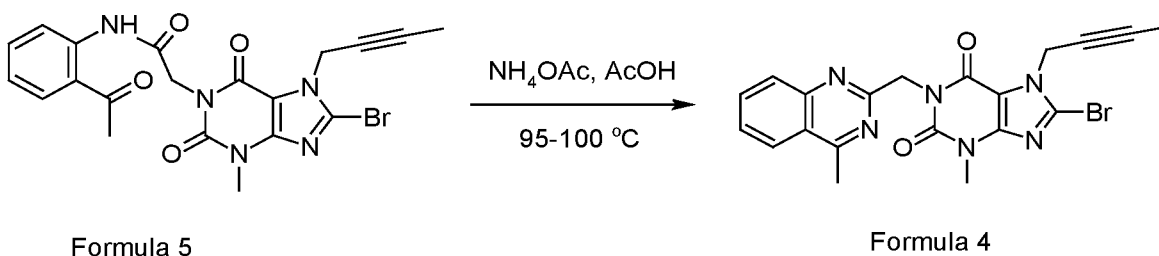
Example 2: Synthesis of Acetylphenylamino-But-Br-Me-xanthine (Formula 5)



Scheme 8

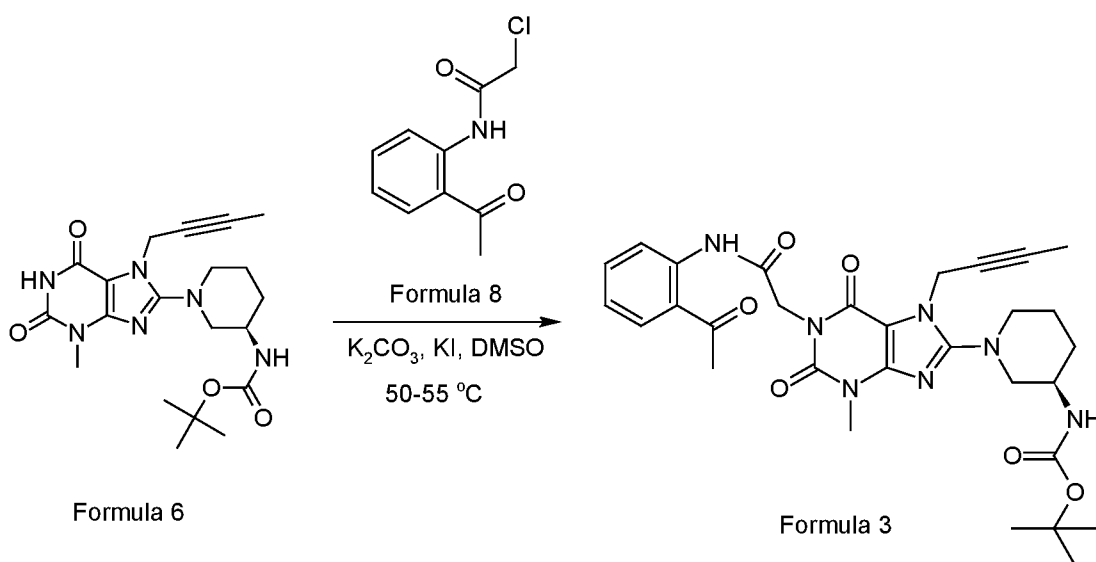
To a solution of butynyl-Br-Me-xanthine [Formula 7] (5.0 g, 16.9 mmol, 1 eq) in DMSO (65 mL) acetylphenyl-chloroacetamide [Formula 8] (3.55 g, 16.9 mmol, 1 eq), potassium iodide
 15 (0.28 g, 1.69 mmol, 0.1 eq) and powdered potassium carbonate (2.55 g, 18.6 mmol, 1.1 eq) were added under nitrogen atmosphere. The reaction mixture was heated to 50-55 °C and stirred for 2-4 hrs. (The reaction was monitored by TLC (silica; DCM:MeOH=95:5).) The reaction mixture was cooled down to room temperature and water was added dropwise. The suspension was stirred for 1 hr, then the precipitate was filtered, washed with water and dried in vacuum at
 20 50 °C to get the product as a pale yellow powder (7.4 g, HPLC: 97.4%).

Example 3: Synthesis of Quinazolinyl-xanthine (Formula 4)

**Scheme 9**

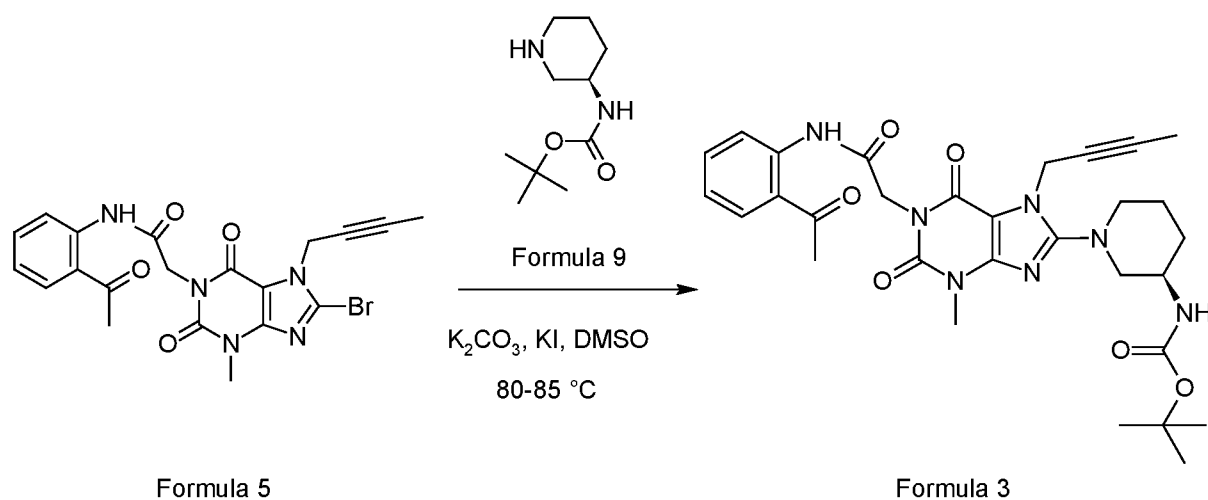
To a suspension of acetylphenylamino-But-Br-Me-xanthine [Formula 5] (5.0 g, 10.6 mmol, 1 eq) in acetic acid (50 mL) ammonium acetate (8.0 g, 106 mmol, 10 eq) was added under nitrogen atmosphere and the reaction mixture was stirred at 95-100 °C for 16-20 hrs. The reaction was monitored by TLC (silica; hexane:ethyl acetate = 6:4). The reaction mixture was cooled down to room temperature and water (150 mL) was added dropwise during vigorous stirring (the temperature was kept below 25 °C). The reaction mixture was stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (2x20 mL) and dried at 50 °C in vacuum to obtain the product as a yellow powder (4.4 g, HPLC: 95.2%), which was purified by suspending in 2-propanol (off-white powder, yield: 95%, HPLC: 97%).

Example 4: Synthesis of Acetylphenylamino-piperidinyl-xanthine (Formula 3)

**Scheme 10**

To a suspension of piperidinyl-xanthine [Formula 6] (5.0 g, 12.0 mmol, 1 eq) in DMSO (75 mL) acetylphenyl-chloroacetamide [Formula 8] (2.54 g, 12 mmol, 1 eq), powdered K_2CO_3 (1.82 g, 13.2 mmol, 1.1 eq) and KI (0.2 g, 10 mol%) were added under nitrogen atmosphere and the reaction mixture was stirred at 50-55 °C for 4-6 hrs. The reaction was monitored by
 5 TLC (silica; DCM:MeOH=95:5). The reaction mixture was cooled down to room temperature and water (300 mL) was added dropwise. The resulted suspension was stirred for one hour. The precipitate was filtered, washed with water (2x25 mL) and dried under vacuum at 50 °C to get the product as a beige powder (6,98 g, HPLC: 88,6%).

10 **Example 5: Synthesis of Acetylphenylamino-piperidinyl-xanthine (Formula 3)**

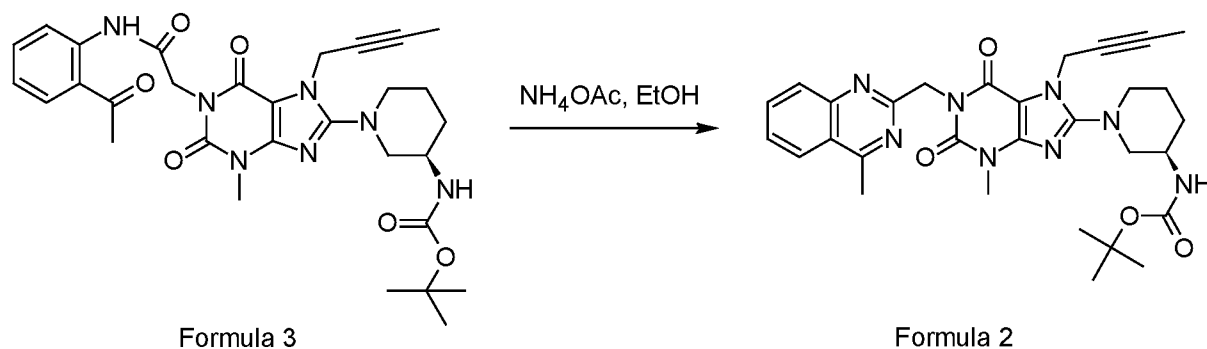


Scheme 11

15 To a suspension of acetylphenylamino-But-Br-Me-xanthine [Formula 5] (1.0 g, 2.12 mmol, 1 eq) in DMSO (10 mL) Boc-aminopiperidine [Formula 9] (0.51 g, 2.54 mmol, 1.2 eq), potassium carbonate (0.44 g, 3.18 mmol, 1.5 eq) and potassium iodide (50 mg, 10 w/w%) were added in inert atmosphere. The temperature was raised to 80-85 °C and the reaction mixture was stirred at this temperature for 4-5 hrs. The reaction was followed by TLC (silica; DCM:MeOH = 95:5).
 20 After completion of the reaction reaction mixture was cooled to room temperature, water (40 mL) was added dropwise and the reaction mixture was stirred at 20-25 °C for half hour. The

precipitate was filtered, washed with water and dried at 50 °C in vacuum to get titled compound as a pale brown powder. (1.1 g, HPLC: 92.3%)

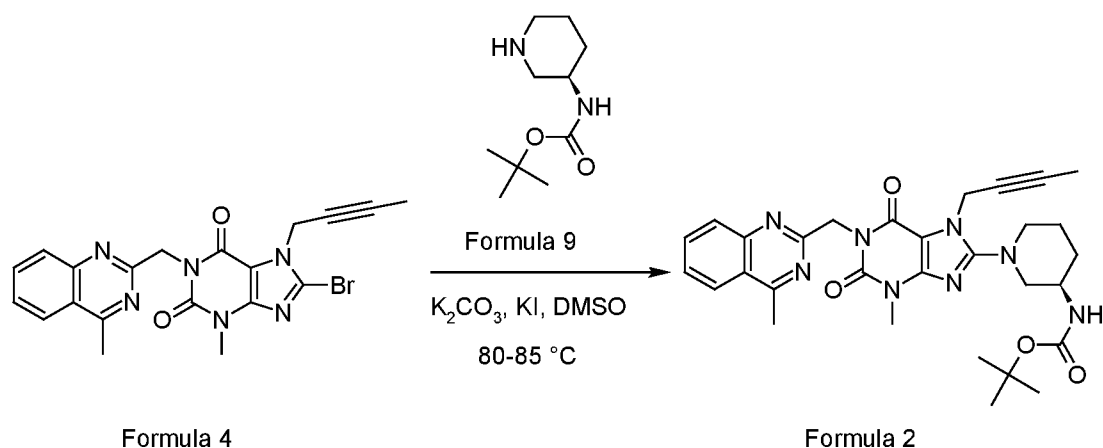
Example 6: Synthesis of BOC-Linagliptin (Formula 2)



Scheme 12

To a suspension of acetylphenylamino-piperidiny-xanthine [Formula 3] (1.0 g, 1.69 mmol, 1 eq) in abs. ethanol (20 mL) ammonium acetate (1.3 g, 16.9 mmol, 10 eq) was added under nitrogen atmosphere and the reaction mixture was stirred at reflux temperature for 16-20 hrs. The reaction was monitored by TLC (silica; DCM:MeOH = 95:5). The reaction mixture was cooled down to room temperature and water (60 mL) was added dropwise during vigorous stirring (the temperature was kept below 25 °C). The reaction mixture was stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (2x5 mL) and dried at 50 °C in vacuum to obtain the product as a yellowish brown powder (~100%, HPLC: 90.2%).

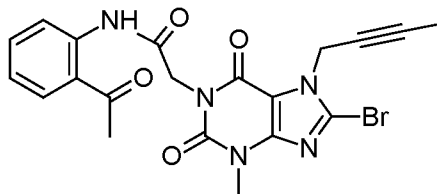
Example 7: Synthesis of Boc-Linagliptin (Formula 2)

**Scheme 13**

To a suspension of quinazolinyl xanthine [Formula 4] (1.0 g, 2.21 mmol, 1 eq) in DMSO (10 mL) BOC-aminopiperidine [Formula 9] (0.53 g, 2.65 mmol, 1.2 eq), potassium carbonate (0.46 g, 3.32 mmol, 1.5 eq) and potassium iodide (50 mg, 10 w/w%) were added under nitrogen atmosphere. The reaction mixture was heated to 80-85 °C and stirred for 4-5 hrs. The reaction was followed by TLC (silica; DCM:MeOH = 95:5). The reaction mixture was cooled down to room temperature, water (40 mL) was added dropwise and the reaction mixture was stirred at 20-25 °C for half hour. The precipitate was filtered, washed with water and dried under vacuum at 50 °C to get title compound [Formula 2] as a pale yellow powder (1.2 g, HPLC: 96.7%).

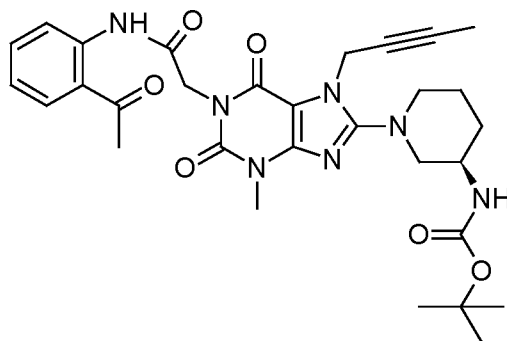
CLAIMS:

1. The intermediate compound Acetylphenylamino-But-Br-Me-xanthine (*N*-(2-acetylphenyl)-2-[8-bromo-7-(but-2-yn-1-yl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl]acetamide) of **Formula 5**.



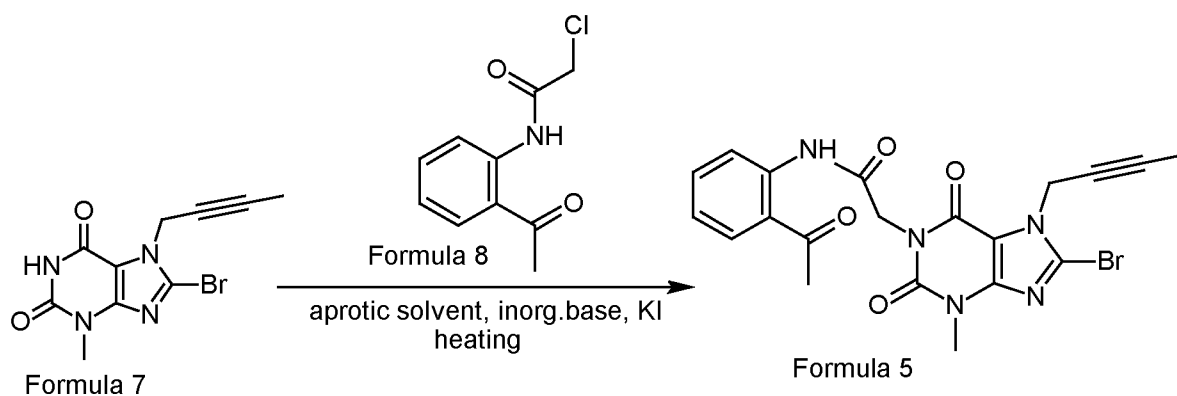
Formula 5

2. The intermediate compound Acetylphenylamino-piperidinyl-xanthine (*tert*-butyl {(3*R*)-1-[1-{2-[(2-acetylphenyl)amino]-2-oxoethyl}-7-(but-2-yn-1-yl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl]piperidin-3-yl} carbamate) of **Formula 3**.



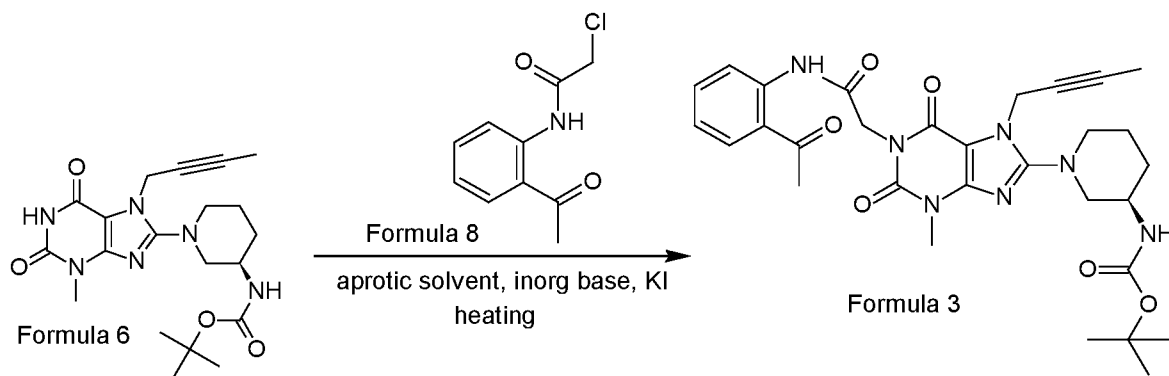
Formula 3

3. The process for the preparation of Acetylphenylamino-But-Br-Me-xanthine of **Formula 5** comprising reacting Butynyl-Br-Me-xanthine of **Formula 7** in a dipolar aprotic solvent, in the presence of an inorganic base with Acetylphenyl-chloroacetamide of **Formula 8** according to **Scheme 8**.



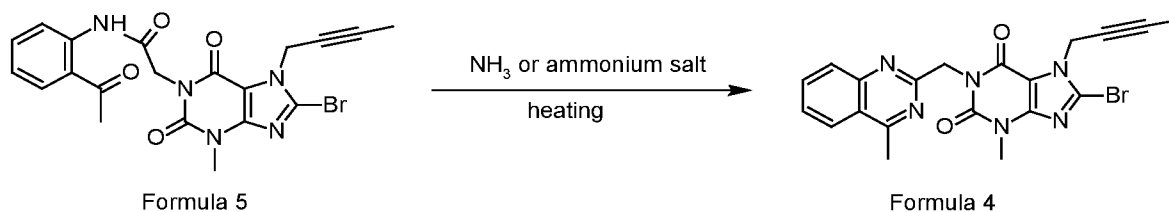
Scheme 8

4. The process for the preparation of Acetylphenylamino-piperidinyl-xanthine of **Formula 3** comprising reacting the compound of Piperidinyl-xanthine of **Formula 6** in a dipolar aprotic solvent, in the presence of an inorganic base with Acetylphenyl-chloroacetamide of **Formula 8** according to Scheme 10.



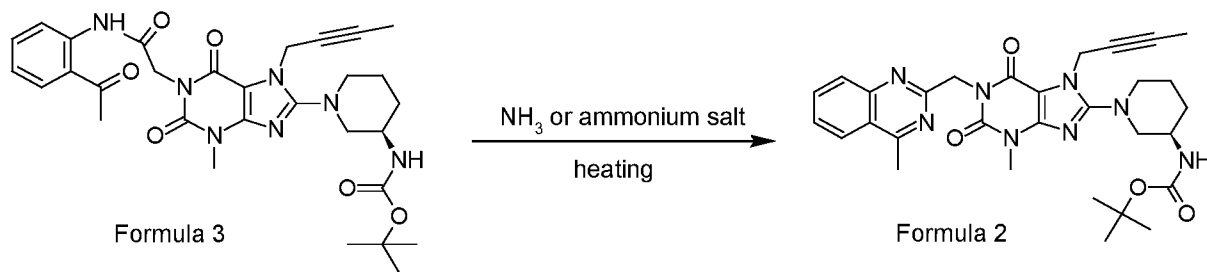
Scheme 10

5. The process for the preparation of Quinazolinyl-xanthine of **Formula 4** comprising reacting the compound of Acetylphenylamino-But-Br-Me-xanthine of **Formula 5** in an alcohol or in an aromatic hydrocarbon solvent using ammonia or an ammonium salt as N-source according to Scheme 9.



Scheme 9

6. The process for the preparation of BOC-Linagliptin of **Formula 2** comprising reacting the compound of Acetylphenylamino-piperidinyl-xanthine of **Formula 3** in an alcohol or in an aromatic hydrocarbon solvent using ammonia or an ammonium salt as N-source according to Scheme 12.



Scheme 12

7. The process according to Claim 3 wherein as a dipolar aprotic solvent dimethyl sulfoxide, as an inorganic base potassium carbonate are used and the reaction temperature is in the range of 50-55 °C.
8. The process according to Claim 4 wherein as a dipolar aprotic solvent dimethyl sulfoxide, as an inorganic base potassium carbonate are used and the reaction temperature is in the range of 50-55 °C.
9. The process according to Claim 5 and 6 wherein as solvent ethanol and as N-source ammonium acetate are used and the reaction is carried out at the reflux temperature.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2019/056592

A. 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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anon: "Preparation of (R)-8-(3-amino-piperidin-1-yl)-7-(but-2-ynyl)-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione", ip.com, 13 August 2014 (2014-08-13), XP055633967, Retrieved from the Internet: URL:https://ip.com/IPCOM/000238270 [retrieved on 2019-10-21]	1,2
Y	page 3, paragraph 1 -----	3,4,7,8
Y	US 2004/138215 A1 (ECKHARDT MATTHIAS [DE] ET AL) 15 July 2004 (2004-07-15) paragraph [0272] - paragraph [0287] -----	3,4,7,8
E	CN 110 240 599 A (QILU PHARM CO LTD) 17 September 2019 (2019-09-17) paragraph [0033] - paragraph [0036] -----	1-3



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Date of the actual completion of the international search

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Date of mailing of the international search report

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Fax: (+31-70) 340-3016

Authorized officer

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2019/056592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			JP 2006508969 A 16-03-2006
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