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(54) **Title**: PROCESS FOR THE PREPARATION OF A XANTHINE-BASED COMPOUND

(57) **Abstract**: This invention relates to a method for preparation of a xanthine-based compound, as well as to intermediates useful in such preparation.

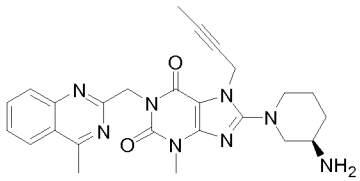
Process for the preparation of a xanthine-based compound

TECHNICAL FIELD

This invention relates to a method for preparation of a xanthine-based pharmaceutically active ingredient, namely Linagliptin, as well as to intermediates useful in such preparation.

BACKGROUND

1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)- xanthine, whose international nonproprietary name is Linagliptin, has the following structure as shown below:



Up to now, several synthetic routes to synthesize the molecule have been described by several references.

For example, a process for the preparation of Linagliptin is disclosed in the references WO 2004/018468 and WO 2006/048427.

The reference WO 2014/059938 describes a further process for preparation of Linagliptin involving a phase transfer catalyst and using protected (R)-piperidine-3-amine derivatives. The process of WO 2014/059938 requires an amine protecting group, such as *tert*-butyloxy carbonyl (Boc) protection and de-protection of the intermediates used in the late stage of the synthesis process.

The reference WO 2013/098775 describes a further process for preparation of Linagliptin: (R)-piperidine-3-amine (or its dihydrochloride) is said to be used directly to react with 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine in the presence of a suitable base (particularly K_2CO_3) in an inert organic solvent (particularly DMF or MIBK) to give Linagliptin. However, the reference WO 2013/098775 only discloses to use the 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine as intermediate.

It is desired to find a further process for the preparation of Linagliptin which is suitable for large scale production, particularly for pharmaceutical purposes.

DESCRIPTION OF THE INVENTION

It has now been found that the process, which is described in greater detail herein, does not require any amine protecting group and provides an efficient, short, robust and scalable method for preparation of Linagliptin and is particularly suitable for the preparation of pure Linagliptin such as for pharmaceutical and medical purposes.

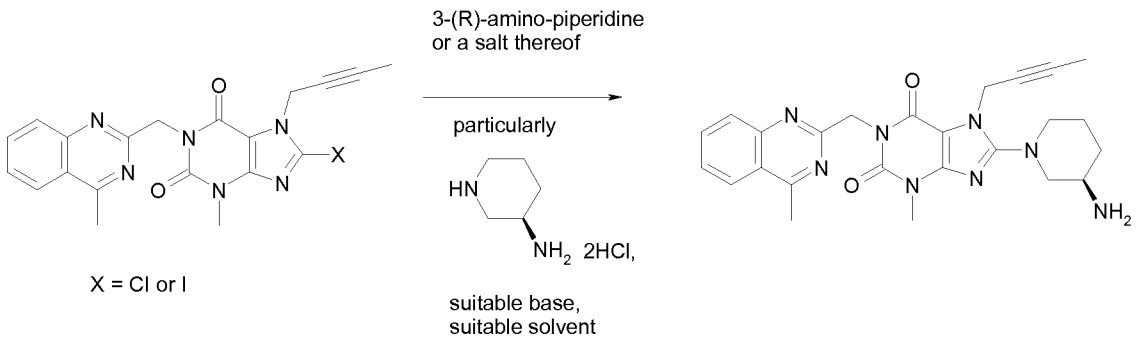
Accordingly, the present invention relates to a process for preparation of Linagliptin, intermediates useful in such process, and use of the process and the intermediates for preparation of Linagliptin for use as medicament.

The invention further relates to a process for preparation of a pharmaceutical composition of Linagliptin, said process comprising i) preparing Linagliptin according to a process as described herein, and ii) combining Linagliptin with one or more pharmaceutically acceptable excipients in order to form the pharmaceutical composition.

Based on our studies, besides Br as a leaving group, Cl or I can serve as the leaving groups in the 8-position of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-xanthine and their corresponding substrates, namely 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-chloro-xanthine and 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-iodo-xanthine, can be directly reacted with piperidine-3-amine [particularly (R)-piperidine-3-amine] or a salt thereof (such as the dihydrochloride salt), preferably (R)-piperidine-3-amine dihydrochloride, in the presence of a suitable base (such as an inorganic or organic base, e.g. Na_2CO_3 (sodium carbonate), K_2CO_3 (potassium carbonate), $NaHCO_3$ (sodium bicarbonate) or $KHCO_3$ (potassium bicarbonate)) in a suitable solvent (such as an organic or aqueous solvent, or mixtures of solvents, particularly an aprotic polar solvent, e.g. NMP (N-methyl-2-pyrrolidone), DMSO (dimethyl sulfoxide), DMAc (N,N-dimethylacetamide) or DMF (N,N-dimethylformamide)) to give Linagliptin with good yield and purity.

A method for preparing Linagliptin is outlined in the following **SCHEME 1** involving the coupling reaction according to the present invention.

SCHEME 1



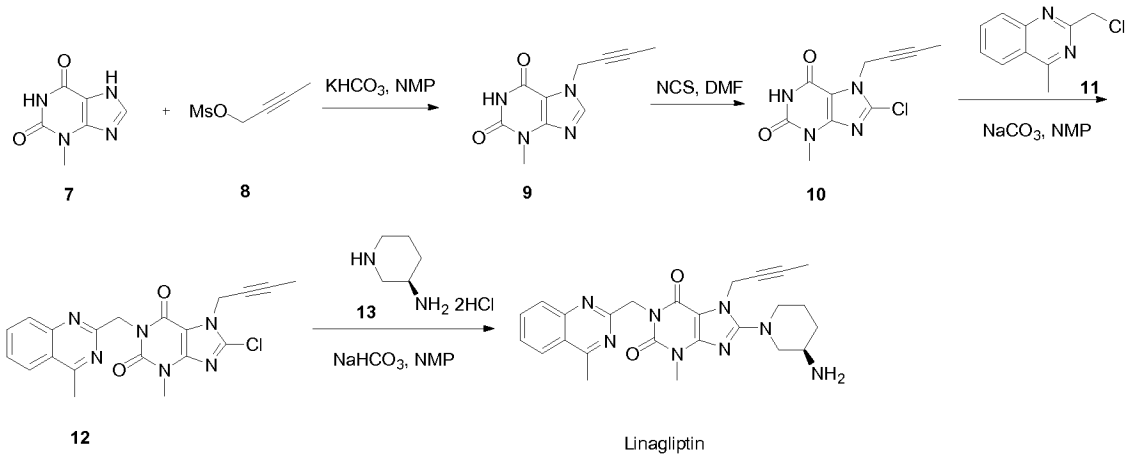
In certain more detailed embodiments of the invention, the present invention relates to the processes, methods and/or the individual process steps and/or the individual reaction conditions substantially as described by way of illustrative example in the following.

A process for preparing Linagliptin is outlined in the following **SCHEME 2**. In one embodiment, the present invention is directed to the multi-step synthetic method for preparing Linagliptin as substantially set forth in **SCHEME 2** below. In other embodiments, the invention is directed to each of the individual steps of **SCHEME 2** and any combination of two or more successive steps of **SCHEME 2**. The invention is also directed to the intermediate compounds, e.g. as set forth in **SCHEME 2**.

In more detailed example, the synthesis (**SCHEME 2**) may start with alkylation of 3-methyl-3,7-dihydro-purine-2,6-dione (7) for example with methanesulfonic acid but-2-ynyl ester (8) in the presence of a suitable base and a suitable solvent, such as in the presence of $KHCO_3$ in NMP to give Compound 9 with around 94% yield. Compound 9 may then be chlorinated for example by NCS such as in DMF to afford Compound 10 with around 83% yield. Alternatively, the chlorination may also be carried out in NMP, which makes one pot reaction from Compound 7 to Compound 10 possible. Then, Compound 10 may be reacted with 2-chloromethyl-4-methyl-quinazoline (11) in the presence of a suitable base and a suitable solvent, such as in the presence of Na_2CO_3 in NMP to give 7-but-2-ynyl-8-chloro-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (12) in 78% yield.

The coupling reaction of Compound 12 with (R)-3-aminopiperidine dihydrochloride (13) to form Linagliptin can be worked with different bases, like Na_2CO_3, $NaHCO_3$, or $KHCO_3$. For this coupling reaction, different kind of aprotic polar solvents can be used, including but not limited to NMP, DMSO, or DMF. The study shows that the combination of using $NaHCO_3$ as base and NMP as solvent offers the best results in terms of conversion and cleanness of reaction profile. Finally, after purification, e.g. by recrystallization such as in toluene, Linagliptin is obtained in 77% yield with 99.2% purity.

SCHEME 2



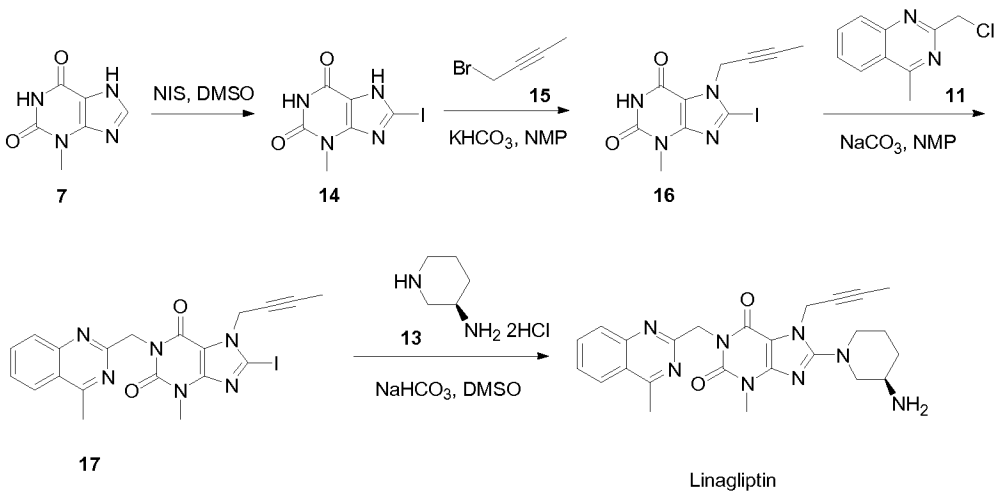
Another process for preparing Linagliptin is outlined in the following **SCHEME 3**. In one embodiment, the present invention is directed to the multi-step synthetic method for preparing Linagliptin as substantially set forth in **SCHEME 3** below. In other embodiments, the invention is directed to each of the individual steps of **SCHEME 3** and any combination of two or more successive steps of **SCHEME 3**. The invention is also directed to the intermediate compounds, e.g. as set forth in **SCHEME 3**.

In more detailed example, the iodide analogue (17) may be used for the direct coupling with (R)-3-aminopiperidine dihydrochloride (13) to prepare Linagliptin (**SCHEME 3**).

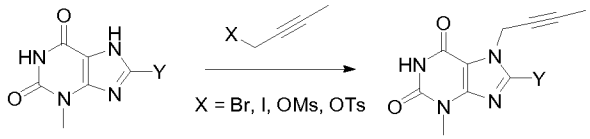
The synthesis may start with iodination of 3-methyl-3,7-dihydro-purine-2,6-dione (7) for example with NIS to give Compound 14 with around 91% yield, which may be followed by alkylation for example with 1-bromo-2-butyne (15) in the presence of a suitable base and a suitable solvent, such as in NMP in the presence of Na_2CO_3 to give Compound 16 in 97% yield. Then, Compound 16 may be reacted with 2-chloromethyl-4-methyl-quinazoline (11) in the presence of a suitable base and a suitable solvent, such as in the presence of Na_2CO_3 in NMP to give Compound 17 in 65% yield.

The coupling reaction of Compound 17 with (R)-3-aminopiperidine dihydrochloride (13) to form Linagliptin can be worked in different kind of high polar solvents, like NMP, DMSO, DMAc, or DMF. Also, different kinds of bases can be used for this reaction, including but not limited to K_2CO_3, Na_2CO_3, $NaHCO_3$, or $KHCO_3$. Our study shows that the combination of DMSO as solvent and $NaHCO_3$ as base offers the best results in terms of the reaction conversion and cleanness of reaction profile. Finally, after purification, e.g. by column chromatography, Linagliptin is obtained in 54% yield with 99.0% purity.

SCHEME 3



The alkylation reaction of Compound 7 or Compound 14 to prepare Compound 9 or Compound 16, respectively, can be represented as below. Based on our studies, the leaving group X used can be either of Br, I, OMs, or OTs in this reaction.



Compound **7**: Y = H
Compound **14**: Y = I

Compound **9**: Y = H
Compound **16**: Y = I

In certain embodiments, the present invention relates to an indicated intermediate or final compound in isolated form, such as e.g. in solid, amorphous, lyophilized or crystalline form.

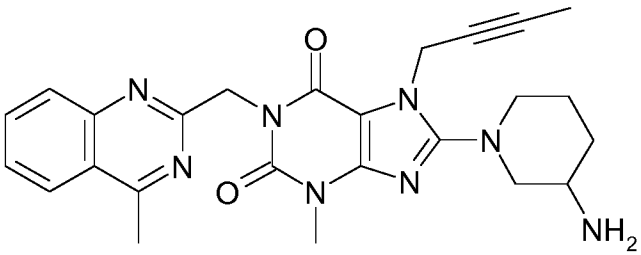
In certain embodiments, the present invention relates to an indicated intermediate or final compound in solution form (such as e.g. present in a reaction solvent).

Further, the present invention relates to an indicated intermediate or final compound obtainable or obtained by a process or method according to the present invention.

In an embodiment, the present invention relates to Linagliptin isolated (such as e.g. crystallized) from the (reaction) solvents mentioned herein, such as e.g. toluene.

Accordingly, the invention further relates to the following particular Embodiments 1-10:

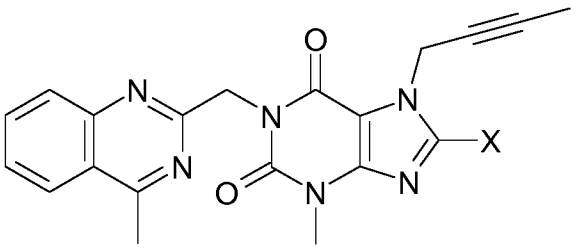
1. A method of preparing a compound of formula (I),



(I)

said method comprising

reacting a compound of formula (II)

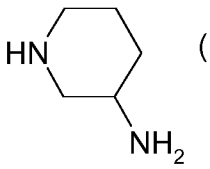


(II)

in which X is iodine or chlorine,

with

3-aminopipderidine of formula (III), or an enantiomer thereof,


(III)

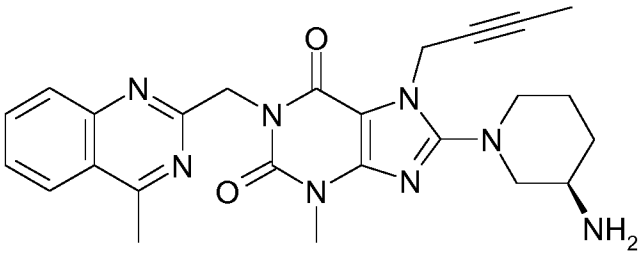
or a salt thereof,

optionally in the presence of a suitable base,

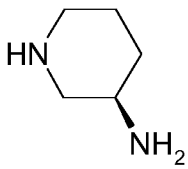
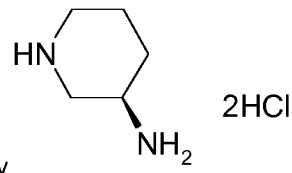
optionally in the presence of a suitable solvent,

to form the compound of formula (I).

2. The method according to Embodiment 1, wherein the compound of formula (I) has the following formula (I*):


(I*)

3. The method according to Embodiment 1 or 2, wherein the 3-aminopipderidine of formula (III) used in the reaction is


, or a salt thereof, preferably 
.

4. The method according to Embodiment 1, 2 or 3, wherein the suitable base is Na_2CO_3, K_2CO_3, $NaHCO_3$ or $KHCO_3$.

5. The method according to Embodiment 1, 2, 3 or 4, wherein the suitable solvent comprises NMP, DMSO, DMAc or DMF.

6. The method according to Embodiment 1, 2, 3, 4 or 5, wherein X is Cl.

7. The method according to Embodiment 1, 2, 3, 4 or 5, wherein X is Cl, the suitable base is $NaHCO_3$ and the suitable solvent is NMP.

8. The method according to Embodiment 1, 2, 3, 4 or 5, wherein X is I.

9. The method according to Embodiment 1, 2, 3, 4 or 5, wherein X is I, the suitable base is $NaHCO_3$ and the suitable solvent is DMSO.

10. The method according to any one of Embodiments 1 to 9, wherein the reaction is conducted at elevated reaction temperature, such as from 20°C to 120°C, preferably 40°C to 110°C.

11. The method according to any one of Embodiments 1 to 10, further comprising (re-)-crystallizing the compound of formula (I) from a suitable solvent (e.g. toluene) or mixture of solvents.

The intermediates and final compounds of the invention may be obtained using methods of synthesis known in principle, or analogously or similarly to known procedures. Preferably, the intermediates involved and the final compounds may be obtained by the following methods according to the invention which are described in more detailed example herein after.

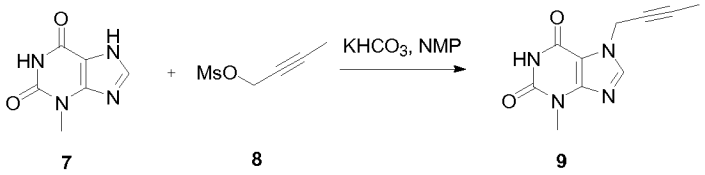
The process steps may be performed substantially as described herein by way of example. A process or method of this invention may comprise one or more steps of converting and/or reacting the mentioned intermediates with the appropriate reaction partners, suitably under conditions as disclosed herein (e.g. by using the indicated reagents and/or solvents and/or temperatures, etc.).

Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by gas chromatography (GC), High Pressure Liquid Chromatography (HPLC) or Thin Layer Chromatography, if desired.

SYNTHETIC EXAMPLES

In order that this invention would be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred (independent or dependent) embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

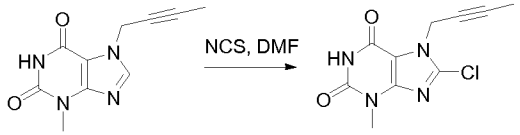
Example 1: Preparation of 7-but-2-ynyl-3-methyl-3,7-dihydro-purine-2,6-dione (**9**)



7 8 9

To a suspension of 20.0 g of 3-methyl-3,7-dihydro-purine-2,6-dione (**7**) and 13.2 g of $KHCO_3$ in 140 mL of NMP at 50 °C, was charged a solution of 20.5 g of methanesulfonic acid but-2-ynyl ester (**8**) in 60 mL of NMP in 15 min. The reaction mixture was stirred at 50 °C for 7.5 h. Then, a total of 400 mL of water was added dropwise. The reaction mixture was cooled down to room temperature and stirred for 1 h. The product was collected by filtration and washed with 200 mL of water, then dried under vacuum. A total of 24.76 g (yield 94%) of Compound **9** was obtained as white solid with 97.6% HPLC purity. ^{1}H NMR (500 MHz, D_2O): δ 7.46 (s, 1H), 4.61 (d, 3H, *J* = 2.0 Hz), 3.03 (s, 3H), 1.57 (t, 3H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, D_2O): δ 164.87, 159.51, 149.98, 139.86, 108.56, 84.33, 71.44, 36.52, 29.22, 2.52; Mass (m/z): 219.1 $(M+H)^+$, 241.1 $(M+Na)^+$.

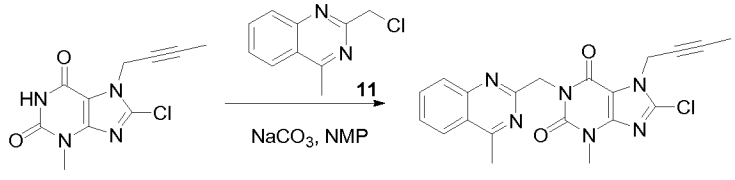
Example 2: Preparation of 7-but-2-ynyl-8-chloro-3-methyl-3,7-dihydro-purine-2,6-dione (**10**)



9 10

To a solution of 24.5 g of 7-but-2-ynyl-3-methyl-3,7-dihydro-purine-2,6-dione (**9**) in 245 mL of DMF, was charged a total of 20.6 g of NCS (*N*-chlorosuccinimide). The reaction mixture was stirred at 70 °C (internal temperature) for 4 h and then cooled down to 50 °C. A total of 368 mL of water was added dropwise to the reaction mixture. The resulting suspension was cooled down to room temperature and stirred for 30 min. The product was collected by filtration and washed with 100 mL of water, then dried under vacuum. A total of 23.4 g (yield 83%) of Compound **10** was obtained as light brown solid with 97.0% HPLC purity. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.46 (s, 1H), 4.61 (d, 3H, *J* = 2.0 Hz), 3.03 (s, 3H), 1.57 (t, 3H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.96, 150.42, 148.13, 137.56, 107.07, 81.88, 72.15, 35.37, 28.53, 2.97; Mass (m/z): 253.1 $(M+H)^+$, 275.0 $(M+Na)^+$.

Example 3: Preparation of 7-but-2-ynyl-8-chloro-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (**12**)

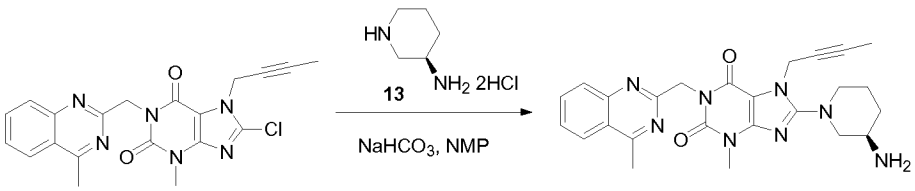


10 12

A total of 23.4 g of 7-but-2-ynyl-8-chloro-3-methyl-3,7-dihydro-purine-2,6-dione (**10**), 18.2 g of 2-chloromethyl-4-methyl-quinazoline (**11**), 10.8 g of Na_2CO_3 and 70 mL of NMP was added into a 250 mL

three-necked round-bottomed flask. The resulting reaction mixture was heated to 100 °C and stirred for 4 h, then cooled down to 60 °C. A total of 140 mL of EtOH and 140 mL of H_2O was mixed together and added to the reaction mixture slowly in 20 min, followed by addition of 11.2 g of acetic acid. The resulting suspension was stirred at 60 °C for 30 min, then cooled down to 25 °C and stirred for another 30 min. The product was collected by filtration, washed with a mixture of 45 mL of water and 45 mL of EtOH, dried under vacuum. A total of 29.3 g (yield 78%) of Compound **12** was obtained as white solid with 91.2% HPLC purity. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.25 (d, 1H, *J* = 8.5 Hz), 7.92 (t, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 8.5 Hz), 7.68 (t, 1H, *J* = 7.5 Hz), 5.35 (s, 2H), 5.14 (d, 2H, *J* = 2.0 Hz), 3.43 (s, 3H), 2.89 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.50, 160.87, 153.94, 151.06, 149.49, 147.49, 138.73, 134.66, 128.33, 127.74, 126.24, 123.00, 107.19, 82.51, 72.62, 46.28, 36.05, 30.10, 22.06, 3.46; Mass (m/z): 409.1 $(M+H)^+$.

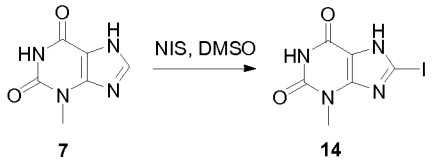
Example 4: Preparation of Linagliptin



12 Linagliptin

A total of 10.0 g of 7-but-2-ynyl-8-chloro-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (**12**), 5.1 g of (R)-3-aminopiperidine dihydrochloride (**13**), 30 mL of NMP and 7.2 g of sodium bicarbonate was added into a 250 mL three-necked round-bottomed flask. The reaction mixture was heated to 90 °C and stirred for 2 h, then cooled down to 40 °C. Then, a total of 90 mL of dichloromethane (DCM) and 90 mL of water were charged, and the reaction mixture was stirred for 25 min. The organic phase was collected and the aqueous phase was extracted with another 30 mL of DCM. The combined organic phase was washed with 90 mL of H_2O for 3 times (each washing takes no less than 20 min) and then stirred with 122.9 g of acetic acid solution (2.4 wt% in water) for 30 min. To the collected aqueous phase was charged with 120 mL of DCM and 49 mL of 1 N aq. NaOH solution. The resulting mixture was stirred for 30 min. The organic phase was collected and concentrated to dryness. The resulting yellow crude product was suspended in 30 mL of toluene and heated to reflux and stirred for 1 h. Then it was cooled down to 70 °C and stirred for 1 h. Next, it was cooled down to 50 °C slowly and stirred for 1 h. Finally, it was cooled down to 25 °C slowly and stirred for 2 h. The product was collected by filtration and dried under vacuum. A total of 8.9 g (yield 77%) of Linagliptin was obtained as pale yellow solid with 99.2% HPLC purity. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (d, 1H, *J* = 8.0 Hz), 7.89 (m, 1H), 7.80 (d, 1H, *J* = 8.5 Hz), 7.68 (m, 1H), 5.32 (s, 2H), 4.90 (s, 2H), 3.59-3.67 (m, 2H), 3.00 (m, 1H), 2.88 (s, 3H), 2.81-2.85 (m, 1H), 2.74-2.78 (m, 1H), 1.78-1.88 (m, 5H), 1.59-1.66 (m, 3H), 1.20-1.27 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.78, 160.97, 156.11, 153.20, 150.90, 149.01, 147.71, 134.01, 127.83, 127.08, 125.67, 122.45, 103.17, 81.10, 73.74, 57.61, 49.54, 47.27, 45.53, 35.47, 33.23, 29.39, 23.28, 21.53, 3.05; Mass (m/z): 473.2 $(M+H)^+$.

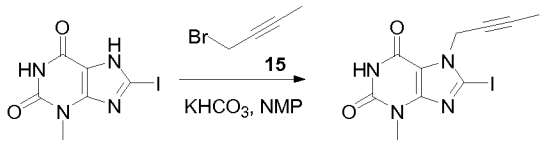
Example 5: Preparation of 8-iodo-3-methyl-3,7-dihydro-purine-2,6-dione (**14**)



7 14

A total of 10.0 g of 3-methyl-3,7-dihydro-purine-2,6-dione(**7**), 17.9 g of NIS (*N*-iodosuccinimide) and 40 mL of DMSO was charged into the reactor. The resulting solution was stirred for 26 h at 40 °C. A total of 60 mL of water was added dropwise. The resulting mixture was stirred at 40 °C for 30 min. The product was collected by filtration, washed with 40 mL of 1:1 DMSO + water and 40 mL of water respectively. It was then dried under vacuum. A total of 16.3 g (yield 91%) of Compound **14** was obtained as yellow solid with 94% HPLC purity. ^{1}H NMR (500 MHz, D_2O): δ 2.69 (s, 3H); ^{13}C NMR (125 MHz, D_2O): δ 164.05, 156.11, 150.53, 118.40, 100.61, 27.40; Mass (m/z): 292.9 $(M+H)^+$.

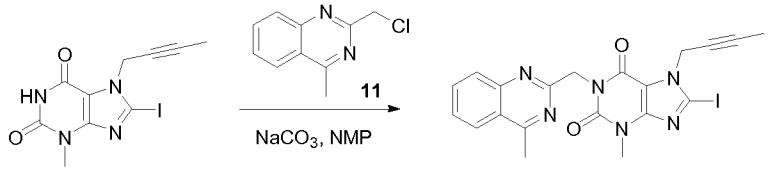
Example 6: Preparation of 7-but-2-ynyl-8-iodo-3-methyl-3,7-dihydro-purine-2,6-dione (**16**)



14 16

A total of 7.2 g of 8-iodo-3-methyl-3,7-dihydro-purine-2,6-dione (**14**), 3.0 g of $KHCO_3$ and 60 mL of NMP was charged to a 250 mL round-bottomed flask. The reaction mixture was heated to 55 °C. A solution of 3.93 g of 1-bromo-2-butyne (**15**) in 10 mL of NMP was added dropwise. The reaction mixture was stirred at 55 °C for 2 h. A total of 70 mL of water was charged into the reaction mixture. The reaction mixture was stirred at 60 °C for 20 min. The product was collected by filtration and dried under vacuum. A total of 8.3 g (yield 97%) of Compound **16** was obtained as white solid with 98.0% HPLC purity. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.26 (s, 1H), 5.00 (d, 1H, *J* = 2.5 Hz), 3.31 (s, 3H), 1.80 (t, 3H, *J* = 2.5Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.55, 150.69, 109.08, 104.50, 81.90, 72.62, 28.51, 2.90; Mass (m/z): 345.0 $(M+H)^+$, 366.9 $(M+Na)^+$.

Example 7: Preparation of 7-but-2-ynyl-8-iodo-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (**17**)

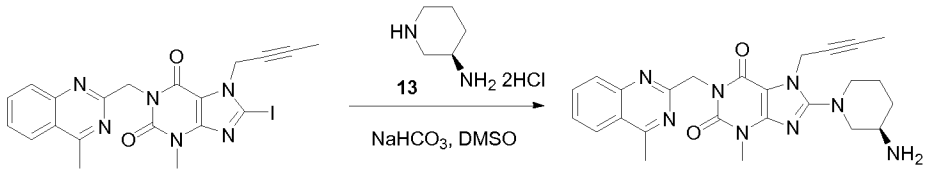


16 17

A total of 6.88 g of 7-but-2-ynyl-8-iodo-3-methyl-3,7-dihydro-purine-2,6-dione (**16**), 2.33 g of Na_2CO_3, 3.85 g of 2-chloromethyl-4-methyl-quinazoline (**11**) and 20 mL of NMP was charged into a 250 mL three-necked round-bottomed flask. The reaction mixture was heated to 90 °C and stirred for 11 h. A total of 40 mL of EtOH was added, followed by addition of 40 mL of water and 2.4 g of acetic acid. The resulting suspension was cooled down to 60 °C and stirred for 0.5 h. It was then cooled down to 25 °C. The product was collected by filtration and dried under vacuum. A total of 6.52 g (yield 65%) of Compound **17** was obtained as pale

yellow solid with 97% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, 1H, *J* = 7.5 Hz), 7.91 (m, 1H), 7.81 (d, 1H, *J* = 8.0 Hz), 7.68 (m, 1H), 5.34 (s, 2H), 5.06 (s, 2H), 3.43 (s, 3H), 2.88 (s, 3H), 1.79 (t, 3H, J = 2.4Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.50, 160.95, 153.54, 151.12, 150.02, 149.46, 134.64, 128.34, 127.73, 126.26, 122.99, 109.10, 106.06, 82.38, 73.23, 46.24, 39.02, 30.03, 22.07, 3.50; Mass (m/z): 501.0 $(M+H)^+$.

Example 8: Preparation of Linagliptin

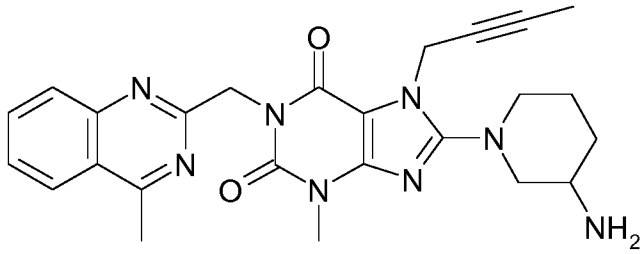


17 Linagliptin

A total of 5.0 g of 7-but-2-ynyl-8-iodo-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (**17**), 1.9 g of (R)-3-aminopiperidine dihydrochloride (**13**), 15 mL of DMSO and 2.77 g of $NaHCO_3$ was charged into a three-necked roud-bottomed flask. The mixture was heated to 110 °C and stirred for 4 h, then cooled down to 40 °C. A total of 45 mL of water was added, followed by addition of 45 mL of dichloromethane. The mixture was stirred for 15 min. The organic phase was collected and the aqueous phase was extracted with 30 mL of dichloromethane. The combined organic phases was washed with 20 mL of water, then concentrated to dryness. The crude product was purified by column chromatography. A total of 2.53 g (yield 54%) of Linagliptin was obtained as pale yellow solid with 99.0% purity. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (d, 1H, *J* = 8.0 Hz), 7.89 (m, 1H), 7.80 (d, 1H, *J* = 8.5 Hz), 7.68 (m, 1H), 5.32 (s, 2H), 4.90 (s, 2H), 3.59-3.67 (m, 2H), 3.00 (m, 1H), 2.88 (s,3H), 2.81-2.85 (m, 1H), 2.74-2.78 (m, 1H), 1.78-1.88 (m, 5H), 1.59-1.66 (m, 3H), 1.20-1.27 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.78, 160.97, 156.11, 153.20, 150.90, 149.01, 147.71, 134.01, 127.83, 127.08, 125.67, 122.45, 103.17, 81.10, 73.74, 57.61, 49.54, 47.27, 45.53, 35.47, 33.23, 29.39, 23.28, 21.53, 3.05; Mass (m/z): 473.2 $(M+H)^+$.

Claims

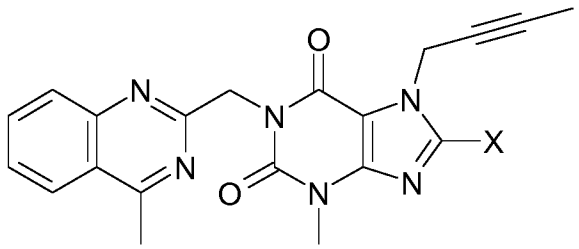
1. A method of preparing a compound of formula (I),



(I)

said method comprising

reacting a compound of formula (II)

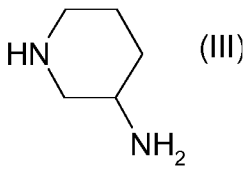


(II)

in which X is iodine or chlorine,

with

3-aminopipderidine of formula (III), or an enantiomer thereof,



(III)

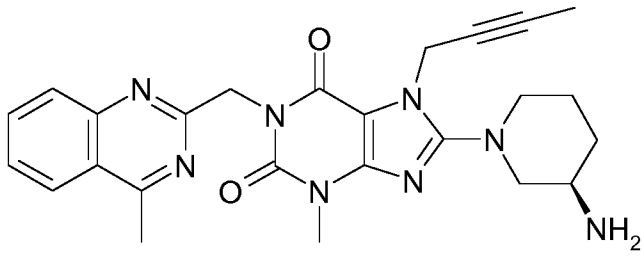
or a salt thereof,

optionally in the presence of a suitable base,

optionally in the presence of a suitable solvent,

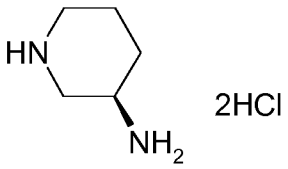
to form the compound of formula (I).

2. The method according to Claim 1, wherein the compound of formula (I) has the following formula (I*):



(I*)

3. The method according to Claim 1 or 2, wherein the 3-aminopipderidine of formula (III) used in the reaction is



.

4. The method according to Claim 1, 2 or 3, wherein the suitable base is Na_2CO_3, K_2CO_3, $NaHCO_3$ or $KHCO_3$.

5. The method according to Claim 1, 2, 3 or 4, wherein the suitable solvent comprises NMP, DMSO, DMAc or DMF.

6. The method according to Claim 1, 2, 3, 4 or 5, wherein X is Cl.

7. The method according to Claim 1, 2, 3, 4 or 5, wherein X is Cl, the suitable base is $NaHCO_3$ and the suitable solvent is NMP.

8. The method according to Claim 1, 2, 3, 4 or 5, wherein X is I.

9. The method according to Claim 1, 2, 3, 4 or 5, wherein X is I, the suitable base is $NaHCO_3$ and the suitable solvent is DMSO.

10. The method according to any one of Claims 1 to 9, wherein the reaction is conducted at elevated reaction temperature, such as from 20°C to 120°C, preferably 40°C to 110°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/064692

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/064692

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/04
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, EMBASE, 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	WO 2013/098775 A1 (REDDYS LAB LTD DR [IN]) 4 July 2013 (2013-07-04) cited in the application claim 1; examples 1-8	1-10
X	WO 2014/009970 A2 (HETERO RESEARCH FOUNDATION [IN]; PARTHASARADHI REDDY BANDI [IN]; RATHN) 16 January 2014 (2014-01-16) example 1	1-10

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[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
25 July 2016	02/08/2016

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	Moriggi, J

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	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] figures 1, 2; compound 1	1-10
A	CN 103 450 201 A (BRIGHTGENE BIO MEDICAL TECHNOOGY CO LTD) 18 December 2013 (2013-12-18) paragraph [0008]; claim 1; example 9	1-10
A	DE 10 2004 054054 A1 (BOEHRINGER INGELHEIM PHARMA [DE]) 11 May 2006 (2006-05-11) paragraph [0009]; claim 1; example 2	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/064692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013098775 A1	04-07-2013	US 2014357863 A1	04-12-2014
		WO 2013098775 A1	04-07-2013
WO 2014009970 A2	16-01-2014	NONE	
CN 103450201 A	18-12-2013	NONE	
DE 102004054054 A1	11-05-2006	AR 051947 A1	21-02-2007
		AU 2005300559 A1	11-05-2006
		BR PI0517093 A	30-09-2008
		CA 2586938 A1	11-05-2006
		CN 101048409 A	03-10-2007
		CN 102127080 A	20-07-2011
		CN 102391267 A	28-03-2012
		CN 102432593 A	02-05-2012
		CN 103351388 A	16-10-2013
		DE 102004054054 A1	11-05-2006
		DK 2287164 T3	10-03-2014
		EA 200700974 A1	26-10-2007
		EA 200900536 A1	30-04-2010
		EA 201200491 A1	30-08-2012
		EP 1812438 A1	01-08-2007
		EP 2287164 A1	23-02-2011
		EP 3029040 A1	08-06-2016
		ES 2458106 T3	29-04-2014
		HK 1109405 A1	12-09-2014
		HR P20140373 T1	23-05-2014
		IL 182923 A	30-09-2013
		JP 5063356 B2	31-10-2012
		JP 5766661 B2	19-08-2015
		JP 5947492 B2	06-07-2016
		JP 2008519005 A	05-06-2008
		JP 2011201908 A	13-10-2011
		JP 2012211174 A	01-11-2012
		KR 20070085744 A	27-08-2007
		KR 20130016414 A	14-02-2013
		KR 20140068267 A	05-06-2014
		MY 145604 A	15-03-2012
		NZ 555324 A	24-12-2010
		NZ 589450 A	29-06-2012
		PE 02322010 A1	29-03-2010
		PE 09212006 A1	30-10-2006
		PT 2287164 E	17-03-2014
		RS 53166 B	30-06-2014
		SG 157371 A1	29-12-2009
		SG 185967 A1	28-12-2012
		SG 189768 A1	31-05-2013
		SI 2287164 T1	30-04-2014
		TW I374885 B	21-10-2012
		TW 201305166 A	01-02-2013
		US 2006142310 A1	29-06-2006
		US 2009192314 A1	30-07-2009
		US 2013178485 A1	11-07-2013
		US 2015025089 A1	22-01-2015
		UY 29190 A1	30-06-2006
		WO 2006048427 A1	11-05-2006
		ZA 200701996 B	27-08-2008

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-10

A method for preparing a compound of formula (I)

1.1. claims: 8, 9(completely); 1-5, 10(partially)

A method for preparing a compound of formula (I) by reacting a compound of formula (III) with a compound of formula (II) in which X is iodine

1.2. claims: 6, 7(completely); 1-5, 10(partially)

A method for preparing a compound of formula (I) by reacting a compound of formula (III) with a compound of formula (II) in which X is chlorine

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