(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 August 2023 (24.08.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/156675 A1

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

(21) International Application Number:
PCT/EP2023/054282

(22) International Filing Date:
21 February 2023 (21.02.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P-202200021 21 February 2022 (21.02.2022) SI

(71) Applicant: **KRKA, D.D., NOVO MESTO** [SI/SI]; Šmarješka cesta 6, 8501 NOVO MESTO (SI).

(72) Inventors: **GOSAK, Kaja**; c/o Krka, d.d., Novo mesto;, Šmarješka cesta 6, 8501 NOVO MESTO (SI). **KIDEMET, Davor**; c/o Krka, d.d., Novo mesto;, Šmarješka cesta 6, 8501 NOVO MESTO (SI). **KRAŠOVEC, Tone**; c/o Krka, d.d., Novo mesto;, Šmarješka cesta 6, 8501 NOVO MESTO (SI). **JOŽICA, Ulcnik**; c/o Krka, d.d., Novo mesto;, Šmarješka cesta 6, 8501 NOVO MESTO (SI).

(74) Agent: **HOEFER & PARTNER PATENTANWÄLTE MBB**; Pilgersheimer Str. 20, 81543 München (DE).

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

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

Published:
— *with international search report (Art. 21(3))*

WO 2023/156675 A1

(54) Title: PROCESS FOR PURIFICATION OF LINAGLIPTIN

(57) Abstract: The present invention relates to a process for purification of linagliptin. Furthermore, the present application pertains to linagliptin purified by this process, as well as to a novel compound and its use.

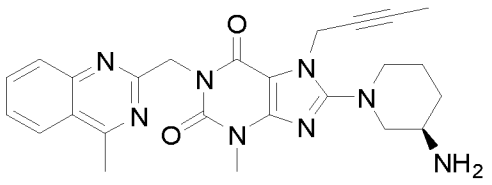
PROCESS FOR PURIFICATION OF LINAGLIPTIN

FIELD OF THE INVENTION

The present invention relates to a process for purification of linagliptin.

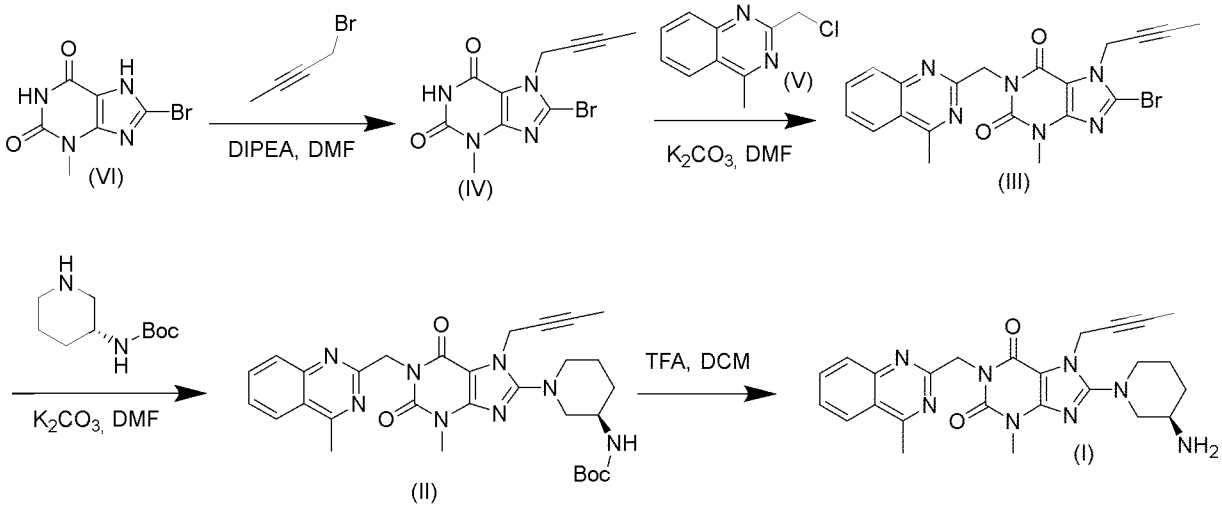
BACKGROUND OF THE INVENTION

Linagliptin is a dipeptidyl peptidase-IV (DPP-IV) inhibitor used to treat diabetes mellitus type 2. The structural formula (I) of linagliptin is



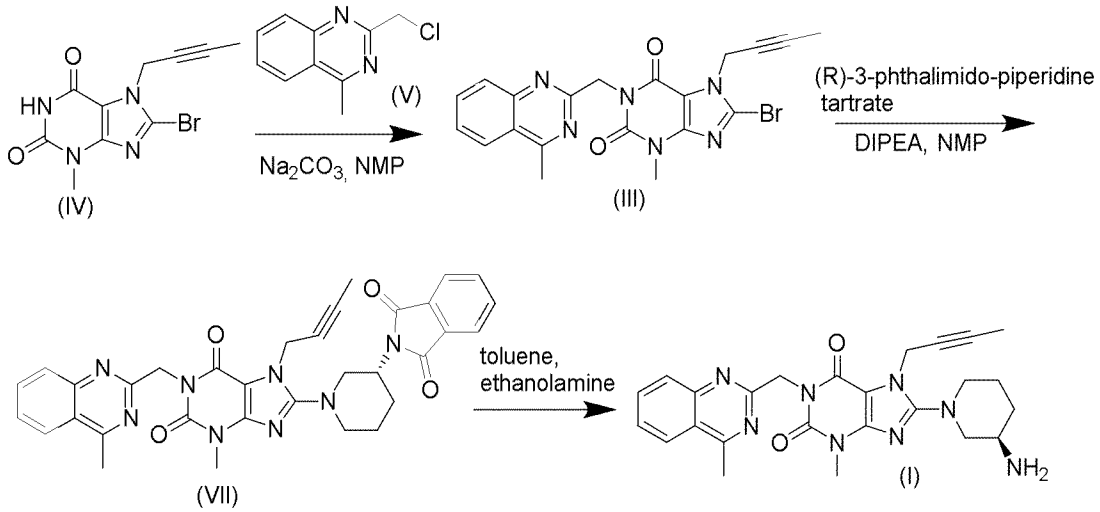
(I).

Linagliptin has been disclosed in the patent application WO2004018468 which describes a process for the preparation of linagliptin involving deprotection of tert-butyloxycarbonyl (Boc) protected linagliptin followed by purification using chromatography. The process is represented in Scheme 1.



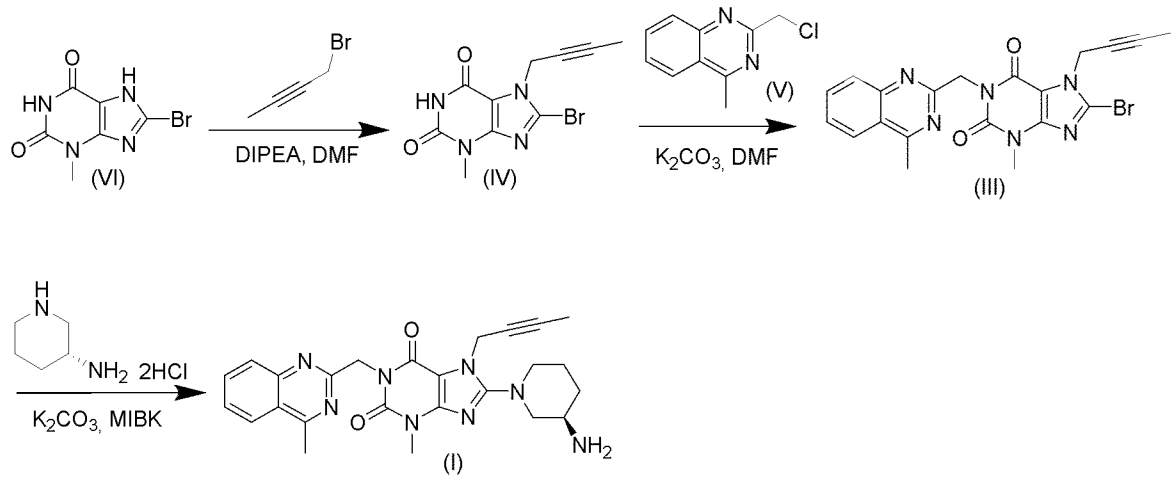
Scheme 1

Alternative process for preparation of linagliptin involving deprotection of phthalimide protected linagliptin is disclosed in WO2006048427. The process is represented in Scheme 2.



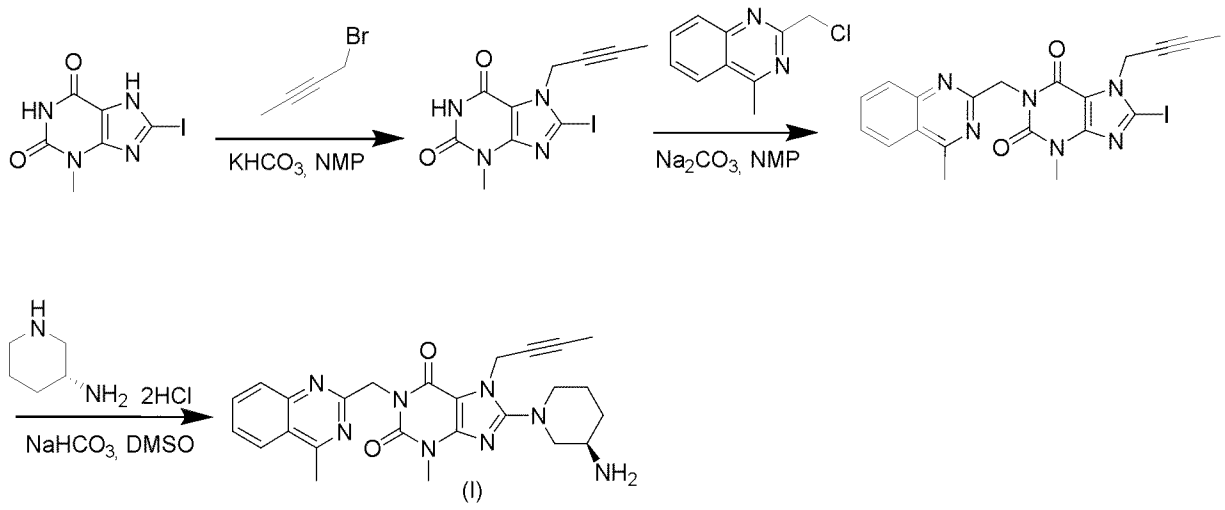
Scheme 2

WO2013098775 describes a process that does not involve the deprotection step and wherein linagliptin is directly obtained from a compound of formula (III). The process is represented in Scheme 3.



Scheme 3

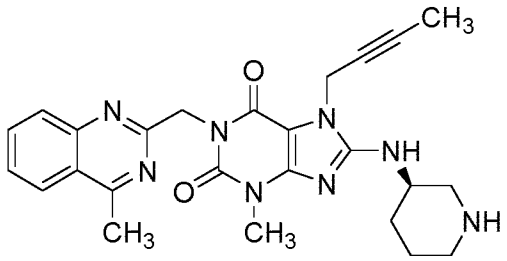
WO2016207364 also describes a process that does not involve a protection and deprotection of 3-aminopiperidine moiety. The process uses iodine or chlorine instead of bromine as the leaving group and is represented in Scheme 4.



Scheme 4

DETAILED DESCRIPTION OF THE INVENTION

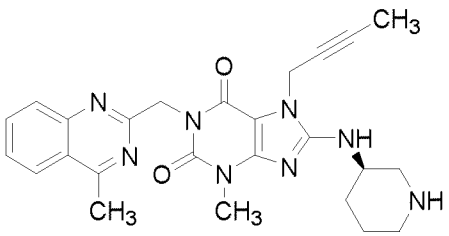
The synthetic routes for linagliptin that do not require protection of 3-aminopiperidine moiety are shorter but generate increased amount of impurity A, which is difficult to remove by conventional processes.



(impurity A)

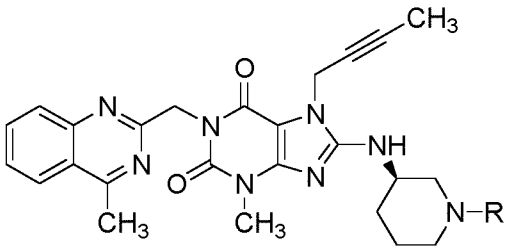
The inventors of the present invention have found a simple process for removal of impurity A present in linagliptin. The invention is based on the finding that impurity A reacts faster with acyl halides, organic acid anhydrides and sulfonyl halides than linagliptin, which enables derivatization of impurity A and its removal from linagliptin by extraction.

The object of the present invention is a process for purification of linagliptin comprising subjecting linagliptin, comprising impurity A



(impurity A),

to a derivatization agent to produce a compound of formula (B)


(B),

wherein R is acyl, SO_2R^1 or CO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group; and

removing the compound of formula (B) from linagliptin. Acyl can be e.g. $C(O)R^1$; R^1 being unsubstituted or substituted hydrocarbon group.

R^1 can be unsubstituted or substituted alkyl, cycloalkyl, aryl or arylalkyl hydrocarbon group. R^1 can for example comprise from 1 to 12 carbon atoms, in particular from 2 to 8 carbon atoms.

Preferably, the process comprises the following steps:

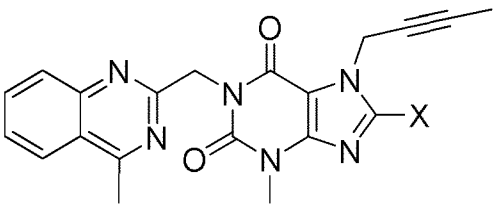
a) dissolving linagliptin, (said linagliptin) comprising impurity A, in the first organic solvent to form linagliptin organic solution; or
preparing linagliptin reaction mixture by reacting 8-halo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione with 3-aminopiperidine in the first organic solvent;
b) adding a derivatization agent to the linagliptin organic solution or linagliptin reaction mixture and mixing the obtained mixture;
c) adding an acidic aqueous solution to the mixture and mixing the mixture;
d) separating the liquid phases and removing the organic phase;
e) adding the second organic solvent and a base to the aqueous phase and mixing the obtained mixture;
f) separating the liquid phases and removing the aqueous phase; and
g) isolating linagliptin from the organic phase.

Linagliptin organic solution (e.g. formed in step a)) can be in particular a solution comprising or consisting of linagliptin, impurity A, and the first organic solvent.

Step d) can be in particular separating the liquid phases (e.g. organic liquid phase and aqueous liquid phase) from the mixture prepared in step c), and subsequently removing the organic phase. Especially, step d) can be allowing separation of the liquid phases from the mixture prepared in step c), and subsequently removing the organic phase.

Step f) can be in particular separating the liquid phases (e.g. organic liquid phase and aqueous liquid phase) from the mixture comprising the second organic solvent (e.g. prepared in step e)) and removing the aqueous phase. Especially, step f) can be allowing separation of the liquid phases from the mixture comprising the second organic solvent (e.g. prepared in step e)) and removing the aqueous phase.

The formula of 8-halo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione is



, wherein X is a halogen.

The amount of impurity A present in linagliptin can be determined by a chromatographic method such as gas chromatography (GC) or high-performance liquid chromatography (HPLC). Preferably, the chromatographic method is HPLC. The amount of impurity A and other impurities in the examples of the present invention were determined via high performance liquid chromatography (HPLC), by using a Titan C18 column (100 x 2.1 mm i.d., 1.9 µm particles). Any other equivalent column with the reverse phase

C18 as stationary phase may also be applied. Gradient elution using mobile phase A (0.15 % trifluoroacetic acid in water) and mobile phase B (acetonitrile) was applied. Before use, both mobile phases were degassed and filtered over a 0.45 µm filter.

Gradient elution

t/min	%A	%B
0	99	1
3	92	8
10	50	50
17	2	98
18	99	1

Flow rate: approximately 0.25 mL/min

Detection: UV 225 nm

Injection volume: 0.5 µL

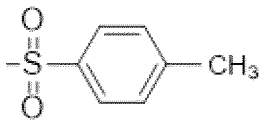
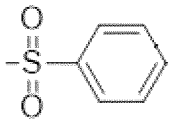
Temperature: 25°C

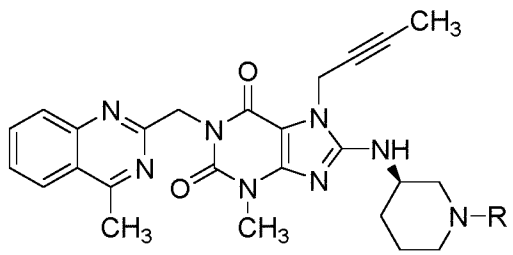
HPLC results are expressed in terms of peak area %.

The amount of impurity A present in linagliptin is usually not higher than 1 % (w/w). The derivatization agent which reacts with impurity A is preferably added in stoichiometric excess with respect to impurity A. The derivatization agent can be added directly to the reaction mixture comprising linagliptin without prior isolation of linagliptin. The derivatization agent can be added in an amount of 1-20 mol %, preferably 3-15 mol % and most preferably 5-12 mol % with respect to linagliptin (in particular with respect to the molar amount of linagliptin). The temperature at which the derivatization takes place

is not limited but is preferably a room temperature. Room temperature can be for example 18°C to 25°C, optionally 20°C to 23°C, especially 22°C.

The derivatization agent can be selected from the group comprising acyl halides, organic acid anhydrides and/or sulfonyl halides. Preferably, the derivatization agent is selected from acyl chlorides, carboxylic anhydrides and/or sulfonyl chlorides. More preferably, the derivatization agent is selected from sulfonyl chlorides and/or di-tert-butyl dicarbonate (Boc anhydride). Even more preferably, the derivatization agent is a sulfonyl chloride. Still even more preferably, the derivatization agent is p-toluenesulfonyl chloride and/or benzenesulfonyl chloride. Most preferably, the derivatization agent is p-toluenesulfonyl chloride.

In an embodiment, when using p-toluenesulfonyl chloride as derivatization agent, compound (B) wherein R- is  can be obtained. When using benzenesulfonyl chloride as derivatization agent, compound (B) wherein R- is  can be obtained.

In an embodiment, when using an acyl halide R-Hal (R being acyl, and Hal can be selected from F, Cl, Br, I, especially can be Cl) as derivatization agent, a compound (B)  (B), wherein R is acyl can be obtained.

In an embodiment, when using an organic acid anhydride R^1-O-C(O)-O-C(O)-O-R^1, R^1 being unsubstituted or substituted hydrocarbon group), as derivatization agent, a compound (B), wherein R is CO_2R^1 can be obtained.

In an embodiment, when using a sulfonyl halide Hal-SO_2R^1 as derivatization agent (Hal can be selected from F, Cl, Br, I, especially can be Cl), a compound (B), wherein R is SO_2R^1 can be obtained.

The first organic solvent should not react with the derivatization agent and should be immiscible or partially miscible in water and can be selected from the group consisting of a C4-C10 ketone, such as methyl isobutyl ketone (MIBK), 2-butanone (MEK), diisobutyl ketone; a hydrocarbon, such as benzene, toluene, hexane, xylene, ethylbenzene; an ether, such as diethyl ether; and/or halogenated hydrocarbon such as dichloromethane. Preferably, the first organic solvent is a C4-C10 ketone. A C4-C10 ketone can be selected from C4 ketone, C5 ketone, C6 ketone, C7 ketone, C8 ketone, C9 ketone, C10 ketone, and mixtures thereof. More preferably, the first organic solvent is 2-butanone, methyl isobutyl ketone, and/or diisobutyl ketone. Most preferably, the first organic solvent is methyl isobutyl ketone.
In an embodiment, the first organic solvent does not react with the derivatization agent (especially at the temperature at which the derivatization takes place). In an embodiment, the first organic solvent is immiscible with water or partially miscible in water. In an embodiment, the first organic solvent does not react with the derivatization agent (especially at the temperature at which the derivatization takes place) and is immiscible with water or partially miscible in water.

The second organic solvent should be immiscible or partially miscible in water and can be selected from the group consisting of a C4-C10 ketone, such as

methyl isobutyl ketone (MIBK), 2-butanone (MEK), diisobutyl ketone; a hydrocarbon, such as benzene, toluene, hexane, xylene, ethylbenzene; an ether, such as diethyl ether; a C4-C10 alcohol, such as 2-butanol; and/or halogenated hydrocarbon, such as dichloromethane. A C4-C10 ketone can be selected from C4 ketone, C5 ketone, C6 ketone, C7 ketone, C8 ketone, C9 ketone, C10 ketone, and mixtures thereof. A C4-C10 alcohol can be selected from C4 alcohol, C5 alcohol, C6 alcohol, C7 alcohol, C8 alcohol, C9 alcohol, C10 alcohol, and mixtures thereof. Preferably, the second organic solvent is a C4-C10 alcohol and/or a hydrocarbon. More preferably, the second organic solvent is 2-butanol and/or toluene. Most preferably, the second organic solvent is toluene. In an embodiment, the second organic solvent is immiscible with water or partially miscible in water. Both the first organic solvent and the second organic solvent can be immiscible with water or partially miscible in water.

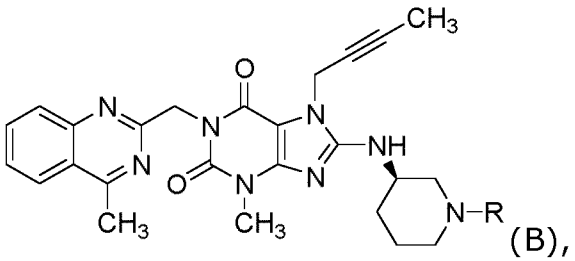
The acidic aqueous solution comprises water and an acid. The acid can be selected from inorganic acids and/or organic acids. For example, the acid can be selected from hydrochloric acid, sulfuric acid, acetic acid, citric acid, tartaric acid, oxalic acid and/or formic acid. Preferably, the acid is acetic acid, citric acid and/or tartaric acid, and most preferably, the acid is citric acid. The pH of the aqueous phase after addition of the acid in step c) is preferably below 4.

The base can be inorganic or organic. Preferably, the base is inorganic and can be selected from alkali metal or alkaline earth metal carbonates, bicarbonates, hydroxides, alkoxides, hydrides, ammonia and the like or mixture thereof. More preferably, the base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, lithium hydroxide, sodium alkoxide, potassium alkoxide, sodium carbonate, potassium carbonate, calcium carbonate, magnesium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, magnesium

bicarbonate and the like. Most preferably, the base is sodium hydroxide. The base is preferably added as an aqueous solution. The pH of the aqueous phase after addition of the base in step e) is preferably above 10.

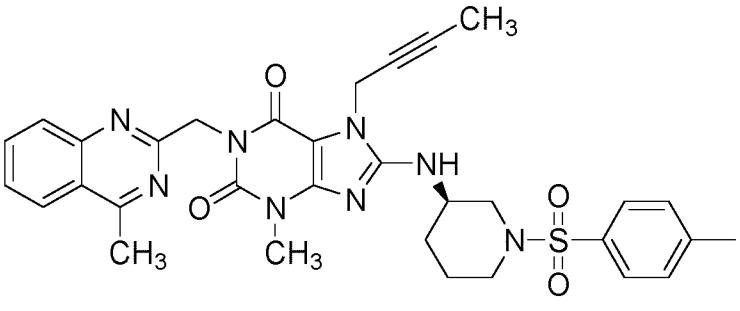
Preferable aspect of the present invention is a process wherein the derivatization agent is a sulfonyl chloride and the first organic solvent is a C4-C10 ketone. More preferable aspect of the present invention is a process wherein the derivatization agent is a sulfonyl chloride and the first organic solvent is methyl isobutyl ketone. The most preferable aspect of the present invention is a process wherein the derivatization agent is p-toluenesulfonyl chloride and the first organic solvent is methyl isobutyl ketone.

Another object of the present invention is a compound of formula (B)



(B),

wherein R is acyl, SO_2R^1 or CO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group. Preferably, R is *tert*-butoxycarbonyl or SO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group. More preferably, R is SO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group. Even more preferably, R is p-toluenesulfonyl or benzenesulfonyl. Most preferably, R is p-toluenesulfonyl, which is depicted as formula (C)


(C).

Still another aspect of the present invention is use of the compound of formula (B) in the process for purification of linagliptin. Preferred aspect of the present invention is a compound of formula (C) and its use in the process for purification of linagliptin, especially for the removal of impurity A.

Yet another aspect of the present invention is linagliptin purified by the process of the present invention.

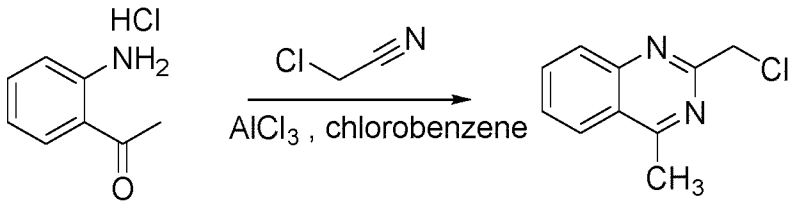
According to yet another aspect, there is provided the use of derivatization agent selected from acyl halides, organic acid anhydrides, sulfonyl halides, and mixtures thereof for reducing the content of impurity A in a solution comprising linagliptin, solvent (preferably organic solvent, more preferably first organic solvent as defined herein supra), and impurity A.

According to yet another aspect, there is provided the use of derivatization agent selected from acyl halides, organic acid anhydrides, sulfonyl halides, and mixtures thereof for (partially or completely) removing impurity A from a solution comprising linagliptin, solvent (preferably organic solvent, more preferably first organic solvent as defined herein supra), and impurity A.

The invention is illustrated in more detail on the basis of the following non-limiting examples.

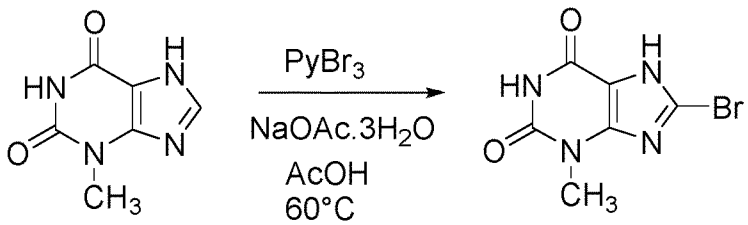
EXAMPLES

Example 1: Synthesis of 2-(chloromethyl)-4-methylquinazoline



10 g of 1-(2-aminophenyl)ethan-1-one hydrochloride is suspended in 100 mL of chlorobenzene. Subsequently 7.76 g of $AlCl_3$ and 11.06 mL of 2-chloroacetonitrile are added and reaction mixture is heated to 80 °C. Reaction is monitored with HPLC. When completed, the reaction mixture is cooled to room temperature and poured into 140 mL of water. After phases are separated, the aqueous phase is extracted with chlorobenzene. Combined organic phases are washed with saturated $NaHCO_3$ and the solvent is evaporated to obtain 10.31 g of 2-(chloromethyl)-4-methylquinazoline with 99.5 % HPLC purity.

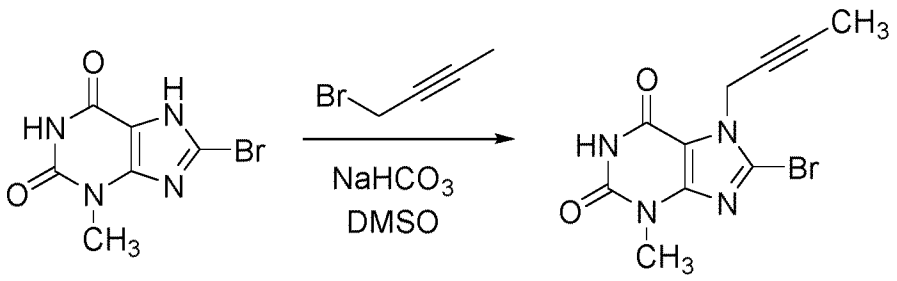
Example 2: Synthesis of 8-bromo-3-methyl-3,7-dihydro-1H-purine-2,6-dione



In a flask 25 g of 3-methyl-3,7-dihydro-1H-purine-2,6-dione, 22.52 g of sodium acetate trihydrate and 52.94 g of pyridinium tribromide is combined and 100 mL of acetic acid is added. Reaction mixture is heated to 60°C and

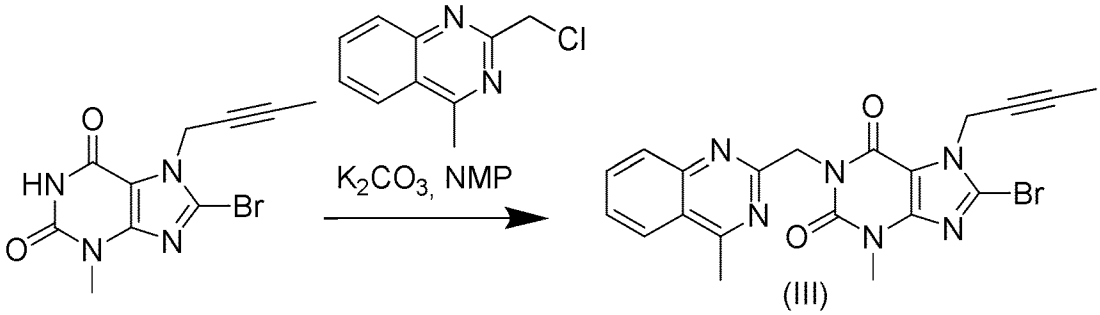
monitored with HPLC. When the reaction is completed the mixture is cooled to room temperature and 200 mL of water is added and mixed at room temperature for 2h. Suspension is filtered off and crude product is suspended in methanol and mixed at 60°C for 1h, then it is cooled to 40°C and mixed for 1h. Finally, the suspension is filtered and washed with methanol and vacuum dried at 40 °C to collect 32.28 g of 8-bromo-3-methyl-3,7-dihydro-1H-purine-2,6-dione with 99.5 % HPLC purity.

Example 3: Synthesis of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione



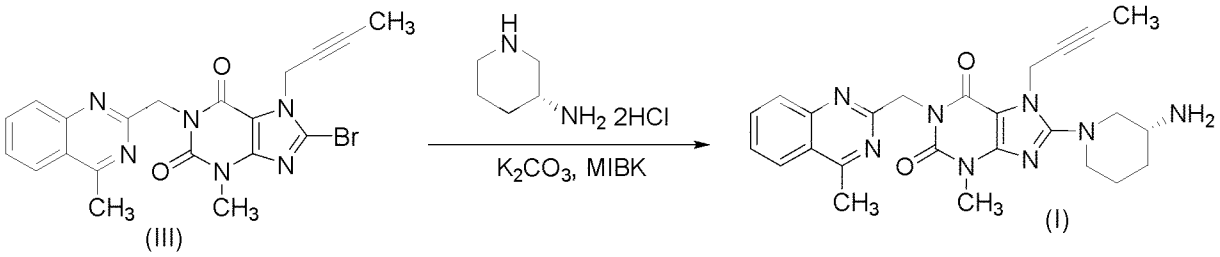
In a flask 3 g of 8-bromo-3-methyl-3,7-dihydro-1H-purine-2,6-dione is suspended in 30 mL of DMSO, subsequently 1.54g of sodium hydrogen carbonate is added and 1.28 mL of 1-bromo-2-butine is added dropwise. Reaction mixture is heated to 30°C until reaction completion. 50 mL of water is added and is mixed for 2 h at room temperature. The product is filtered, washed with water and dried in vacuum drier at 40 °C to obtain 3.23 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione.

Example 4: Synthesis of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione



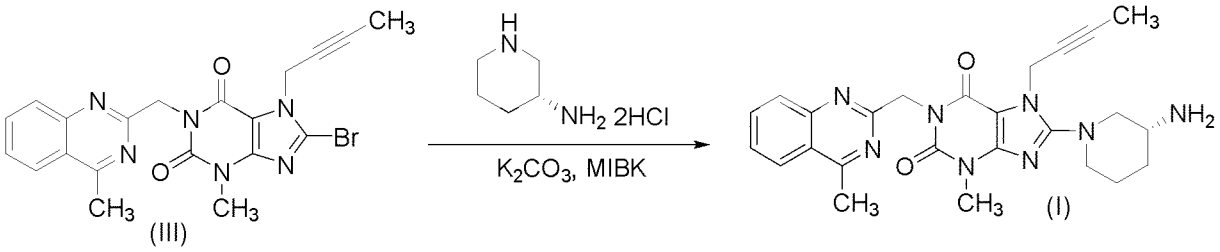
In reaction vessel 75 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione and 51.06 g of 2-(chloromethyl)-4-methylquinazoline and 375 mL of N-methyl-2-pyrrolidone is added. Suspension is heated to 90 °C and 45.35 g of potassium carbonate is added. Reaction mixture is heated at 90 °C for 3 h, then it is slowly cooled to 60 °C and mixture of 450 mL of ethanol and 412 mL of water is added dropwise. To the vessel a mixture of 30 mL of acetic acid and 37.5 mL of water is added dropwise at 60 °C. After completion, reaction mixture is heated at 60 °C for 1 h and afterwards it is cooled to room temperature and mixed for 3 h. Precipitate is filtered and washed with mixture of 150 mL of ethanol and 150 mL of water, and then with mixture of 300 ml of ethanol and 300 mL of water. Product is collected and dried in vacuum drier at 40 °C to obtain 104.9 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione with 99.3 % HPLC purity.

Example 5: Synthesis of linagliptin



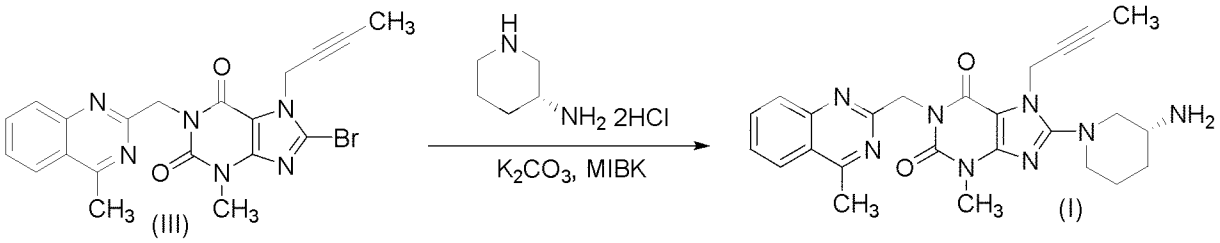
In a vessel 10 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione, 4.01 g of 3-aminopiperidine dihydrochloride and 10.65 g of potassium carbonate is charged. 100 mL of methyl isobutyl ketone is added and mixture is heated to 90 – 100 °C. Reaction is monitored with TLC and when completed, hot reaction mixture is filtered off and salts on the filter are washed with methyl isobutyl ketone. The solution is cooled to room temperature, 100 mL of 6% citric acid is added, mixed, and phases are separated. Aqueous phase is washed with mixture of 30 mL of toluene and 10 mL of 2-butanol, then 100 mL of 2-butanol is added. With 10% $NaOH_{(aq)}$ pH is corrected above 10, then phases are separated and water phase is discarded. Two times half of solvent in the mixture is evaporated and replaced with the same volume of fresh 2-butanol until water content in the mixture is below 2 %. The mixture is mixed at room temperature few hours, filtered and the residue is washed with 2-butanol. The product is dried in a vacuum drier at 40 °C to obtain 6.32g of linagliptin with 99.07 % HPLC purity and with 0.71 % of impurity A.

Example 6: Synthesis of linagliptin and purification with p-toluenesulfonyl chloride



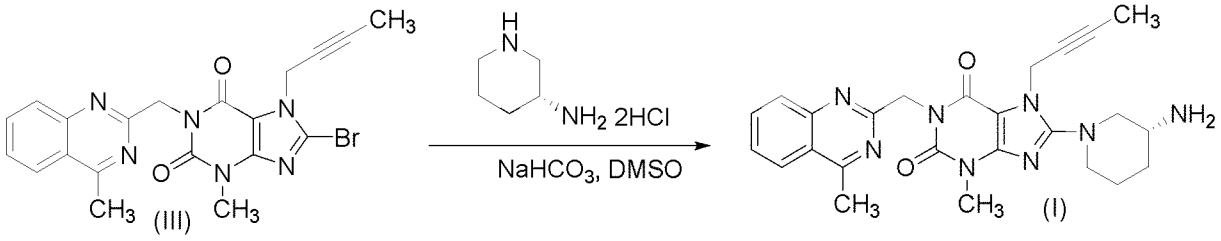
In a vessel 19 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione, 7.62 g of 3-aminopiperidine dihydrochloride and 20.27 g of potassium carbonate is charged. 190 mL of methyl isobutyl ketone is added and mixture is heated to 90 – 100 °C. Reaction is monitored with TLC and when completed, hot reaction mixture is filtered and salts on the filter are washed with methyl isobutyl ketone. The obtained solution is cooled to room temperature and 900 mg of p-toluenesulfonyl chloride is added to the solution. The mixture is mixed for 30 minutes, then 200 mL 5 % aqueous solution of citric acid is added, mixed and phases are separated. Aqueous phase is washed with mixture of 60 mL of toluene and 30 mL of 2-butanol, then 300 mL of toluene is added. With 20 % $NaOH_{(aq)}$ pH is corrected above 10, then phases are separated. Organic phase is washed with 50 mL of 5 % aqueous solution of NaCl. Then 0.5 g of active charcoal is added and mixed for 15 min at 40 – 50 °C. The suspension is filtered and approximately 200 mL of toluene is distilled from the filtrate and cooled to 0 °C. Linagliptin starts to precipitate, suspension is filtered and washed with toluene. The product is dried in a vacuum drier at 40 °C to obtain 14.28 g of linagliptin. HPLC purity: 99.69 %, impurity A: 0.07 %.

Example 7: Synthesis of linagliptin and purification with benzenesulfonyl chloride



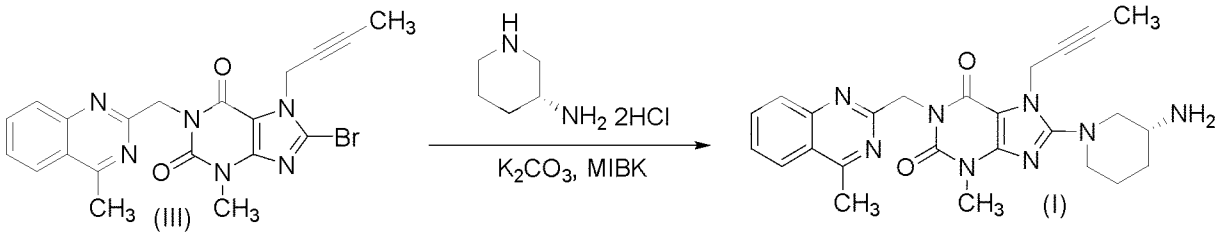
In a vessel 20 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione, 8.02 g of 3-aminopiperidine dihydrochloride and 21.4 g of potassium carbonate is charged. 200 mL of methyl isobutyl ketone is added and mixture is heated to 90 – 100 °C. Reaction is monitored with TLC and when completed, hot reaction mixture is filtered and salts on the filter are washed with methyl isobutyl ketone. The obtained solution is cooled to room temperature and 582 µL of benzenesulfonyl chloride is added to the solution. The mixture is mixed for 30 minutes, then 200 mL 5% aqueous solution of citric acid is added, mixed and phases are separated. Aqueous phase is washed with mixture of 80 mL of toluene and 20 mL of 2-butanol, then 200 mL of toluene is added. With 20 % $NaOH_{(aq)}$ pH is corrected above 10, then phases are separated. Organic phase is washed with 50 mL of 5% aqueous solution of NaCl after 0.5 g of active charcoal is added and mixed for 15 min at 40 – 50 °C. Then, suspension is filtered and approximately 140 mL of toluene is distilled from the filtrate and cooled to 0 °C. Linagliptin starts to precipitate, suspension is filtered and wash with toluene. The product is dried in a vacuum drier at 40 °C to obtain 16.0 g of linagliptin with 99.60 % HPLC purity and with 0.05 % of impurity A.

Example 8: Synthesis of linagliptin in DMSO



In a vessel 10 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione, 4.23 g of 3-aminopiperidine dihydrochloride and 6.12 g of sodium hydrogen carbonate is charged. 50 mL of dimethyl sulfoxide is added and mixture is heated to 90 – 100 °C. Reaction is monitored with TLC and when completed, hot reaction mixture is filtered and salts on the filter are washed with methyl isobutyl ketone. The solution is cooled to room temperature, 100 mL of 6% acetic acid is added, mixed, and phases are separated. Aqueous phase is washed with mixture of 30 mL of toluene and 10 mL of 2-butanol, then 100 mL of 2-butanol is added. With 10 % NaOH pH is corrected above 10, then phases are separated. Two times half of solvent in the mixture is evaporated and is replaced with the same volume of fresh 2-butanol, until water content in the mixture is below 2%. The mixture is mixed at room temperature few hours, filtered and washed with 2-butanol. The product is dried in a vacuum drier at 40 °C to obtain 6.36 g of linagliptin with 98.51 % HPLC purity and with 0.56 % of impurity A.

Example 9: Synthesis of linagliptin and purification with di-*tert*-butyl dicarbonate



In a vessel 10 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione, 4.58 g of 3-aminopiperidine dihydrochloride and 7.61 g of potassium carbonate is charged. 100 mL of methyl isobutyl ketone (MIBK) is added and mixture is heated to reflux. Reaction is monitored with TLC and when completed, hot reaction mixture is filtered and salts on the filter are washed with MIBK. The solution is cooled to room temperature and 0.92 g of di-*tert*-butyl dicarbonate is added to the solution. The mixture is mixed for 30 minutes, then 100 mL of 6% aqueous solution of acetic acid is added, mixed and phases are separated. Aqueous phase is washed with 40 mL of toluene, then 100 mL of 2-butanol is added. With 10% NaOH pH is corrected above 10, then phases are separated. Two times half of solvent in the organic phase is evaporated and is replaced with the same volume of fresh 2-butanol, until water content in the mixture is below 2%. The mixture is mixed at room temperature few hours, filtered and washed with 2-butanol. The product is dried in a vacuum drier at 40°C to obtain 8.00 g of linagliptin with 99.79% HPLC purity and with impurity A below detecting threshold.

Example 10: Purification of linagliptin with benzenesulfonyl chloride

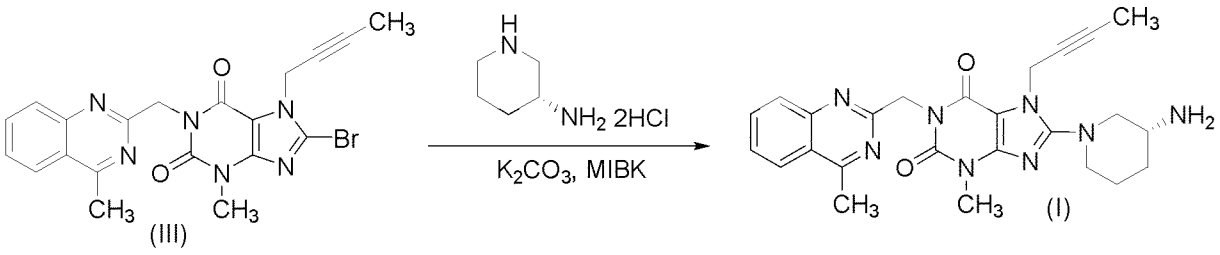
To 2 g of linagliptin (with 0.56 % of impurity A) 20 mL of MIBK is added. Suspension is heated to reflux until clear solution is obtained. After the solution is cooled to room temperature 54 µL of benzenesulfonyl chloride is charged. The reaction mixture is mixed for 30 min. Then, 20 mL of 6% aqueous solution of acetic acid is added, phases are separated and aqueous phase is washed with 5 mL of toluene. 20 mL of 2-butanol is added to the aqueous phase and pH is corrected above 10 with 10% solution of $NaOH_{(aq)}$ and phases are separated. Two times half of solvent in the organic phase is evaporated and is replaced with the same volume of fresh 2-butanol, until water content in the mixture is below 2 %. The mixture is mixed at room temperature few hours, filtered and washed with 2-butanol. The product is dried in a vacuum drier at 40 °C to obtain 1.28g of linagliptin with impurity A below detecting threshold.

Example 11: Purification of linagliptin with di-tert-butyl dicarbonate

To 5 g of linagliptin (with 0.56 % of impurity A) 75 mL of MIBK is added. Suspension is heated to reflux until clear solution is obtained. After the solution is cooled to room temperature, 115 mg of di-tert-butyl dicarbonate is charged. The reaction mixture is mixed for 30 min. Then, 50 mL of 6 % aqueous solution of acetic acid is added and phases are separated. The aqueous phase is washed with 20 mL of toluene. 50 mL of 2-butanol is added to the aqueous phase and pH is corrected above 10 with 10% solution of $NaOH_{(aq)}$ and phases are separated. Two times half of solvent in the organic phase is evaporated and is replaced with the same volume of fresh 2-butanol, until water content in the mixture is below 2 %. The mixture is mixed at room temperature for several hours, filtered and washed with 2-butanol. The product is dried in a vacuum

drier at 40 °C to obtain 3.18g of linagliptin with impurity A below detecting threshold.

Example 12: Synthesis of linagliptin and purification with p-toluenesulfonyl chloride

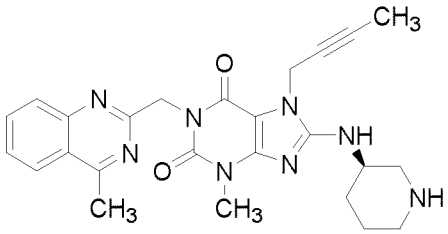


In a vessel 150 g of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-dihydro-1H-purine-2,6-dione, 60.14 g of 3-aminopiperidine dihydrochloride and 160.06 g of potassium carbonate are charged. 1500 mL of methyl isobutyl ketone and 3 mL of water are added and mixture is heated to 90 – 100 °C. Reaction is monitored with TLC and when completed, hot reaction mixture is filtered and salts on the filter are washed with methyl isobutyl ketone. The obtained solution is cooled to room temperature and 5.4 g of p-toluenesulfonyl chloride are added to the solution. The mixture is mixed for 30 minutes, then 1500 mL 5 % aqueous solution of citric acid is added, mixed and phases are separated. Aqueous phase is washed with mixture of 450 mL of toluene and 150 mL of 2-butanol, then 2250 mL of toluene is added. With 10 % $NaOH_{(aq)}$ pH is corrected above 10 (430 ml of solution used), then phases are separated. The organic phase is filtered and concentrated by distillation to approximately 600 ml. 1800 ml of methanol is added and the mixture is concentrated to approximately 600 ml, this step being repeated once again. The mixture is then cooled to 25 °C in 1 h. Seeding crystals are added (0.75 g). Linagliptin starts to precipitate. The mixture is stirred at 25 °C for 1 h, then cooled to 3 °C in 3 h. After stirring for another 6

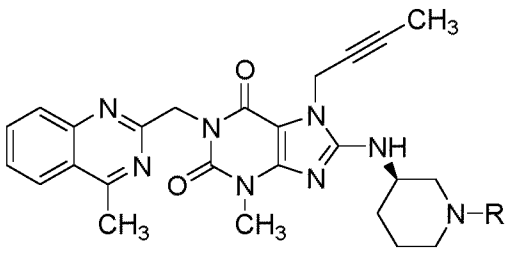
h at 3 °C the suspension is filtered and washed with 50 ml of methanol. The product is dried in a vacuum dryer at 40 °C to yield 118 g of linagliptin. HPLC purity: 99.82 %, impurity A: 0.02 %.

CLAIMS

1. A process for purification of linagliptin comprising subjecting linagliptin, comprising impurity A


(impurity A),

to a derivatization agent to produce a compound of formula (B)


(B) ,

wherein R is acyl, SO_2R^1 or CO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group; and
removing the compound of formula (B) from linagliptin.

2. A process according to claim 1, comprising the following steps:

a) dissolving linagliptin, comprising impurity A, in the first organic solvent to form linagliptin organic solution; or
preparing linagliptin reaction mixture by reacting 8-halo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-3,7-

dihydro-1H-purine-2,6-dione with 3-aminopiperidine in the first organic solvent;

b) adding a derivatization agent to the linagliptin organic solution or linagliptin reaction mixture and mixing the obtained mixture;

c) adding an acidic aqueous solution to the mixture and mixing the mixture;

d) separating the liquid phases and removing the organic phase;

e) adding the second organic solvent and a base to the aqueous phase and mixing the obtained mixture;

f) separating the liquid phases and removing the aqueous phase; and

g) isolating linagliptin from the organic phase.

3. The process according to claim 1, wherein the derivatization agent is selected from acyl halides, organic acid anhydrides and/or sulfonyl halides.

4. The process according to claim 3, wherein the derivatization agent is selected from acyl chlorides, carboxylic anhydrides and/or sulfonyl chlorides.

5. The process according to claim 4, wherein the derivatization agent is selected from sulfonyl chlorides and/or di-tert-butyl dicarbonate.

6. The process according to claim 5, wherein the derivatization agent is a sulfonyl chloride.

7. The process according to claim 6, wherein the derivatization agent is p-toluenesulfonyl chloride.

8. The process according to claim 2, wherein the first organic solvent is selected from the group consisting of a C4-C10 ketone, a hydrocarbon, an ether, and/or halogenated hydrocarbon.

9. The process according to claim 8, wherein the first organic solvent is a C4-C10 ketone.

10. The process according to claim 9, wherein the first organic solvent is 2-butanone, methyl isobutyl ketone, and/or diisobutyl ketone.

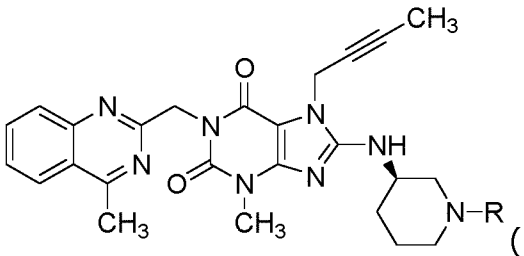
11. The process according to claim 10, wherein the first organic solvent is methyl isobutyl ketone.

12. The process according to claim 2, wherein the second organic solvent is selected from the group consisting of a C4-C10 ketone, a hydrocarbon, an ether, a C4-C10 alcohol and/or halogenated hydrocarbon.

13. The process according to claim 12, wherein the second organic solvent is a C4-C10 alcohol and/or a hydrocarbon.

14. The process according to claim 1, wherein the derivatization agent is added in an amount of 1-20 mol % with respect to linagliptin.

15. A compound of formula (B)


(B), wherein R is acyl, SO_2R^1 or CO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group.

16. The compound according to claim 15, wherein R is *tert*-butoxycarbonyl or SO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group.

17. The compound according to claim 16, wherein R is SO_2R^1; R^1 is unsubstituted or substituted hydrocarbon group.

18. The compound according to claim 17, wherein R is p-toluenesulfonyl or benzenesulfonyl.

19. The compound according to claim 18, wherein R is p-toluenesulfonyl.

20. Use of the compound of formula (B) of claim 15 in the process for purification of linagliptin.

21. Linagliptin purified by the process of claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/054282

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, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 105 712 995 B (ZHEJIANG JINGXIN PHARMACEUTICAL CO LTD ET AL.) 3 November 2017 (2017-11-03)	21
A	the whole document	1-20
X	WO 2019/219620 A1 (CAMBREX PROFARMACO MILANO S R L [IT]) 21 November 2019 (2019-11-21)	21
A	the whole document in particular, pages 1-6, examples 9, 10, 12 and 17 and claim 4	1-20
X	WO 2013/098775 A1 (REDDYS LAB LTD DR [IN]) 4 July 2013 (2013-07-04) cited in the application	21
A	the whole document in particular, pages 3-8, examples 10, 12 and 16 and claim 32	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 2023	30/05/2023

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/054282

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 105712995 B	03-11-2017	NONE	
WO 2019219620 A1	21-11-2019	CA 3097628 A1	21-11-2019
		EP 3794001 A1	24-03-2021
		ES 2912409 T3	25-05-2022
		HR P20220627 T1	24-06-2022
		JP 2021523187 A	02-09-2021
		KR 20210010487 A	27-01-2021
		PL 3794001 T3	08-08-2022
		SI 3794001 T1	29-07-2022
		US 2021238178 A1	05-08-2021
		WO 2019219620 A1	21-11-2019
WO 2013098775 A1	04-07-2013	US 2014357863 A1	04-12-2014
		WO 2013098775 A1	04-07-2013