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An overview of recent development towards the synthesis of Linagliptin a DPP-4 inhibitor

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Abstract: Linagliptin is xanthine-based second generation selective dipeptidyl peptidase-4 inhibitor used for the treatment for type -2 diabetes mellitus developed by Boehringer Ingelheim. Due to its potent activity and more selectivity for dipeptidyl peptidase-4 inhibition over dipeptidyl peptidase-8 inhibition, the development of the general methods for the synthesis is an area of interest. In this direction over the past few years, various synthetic strategy for synthesis of Linagliptin were appeared in literature. In this review we have outlined the recent advances towards the synthesis of Linagliptin along with the advantages and limitations of the synthetic strategy used.

1.0 Introduction

Type 2 diabetes mellitus is growing concern all over the world and about 6% of the total population is affected. [1] International Diabetes Federation predicted the number of cases reach to 109 million worldwide by 2035 and after china, India has the highest number of diabetic patients. [2,3,4,5] The Gliptin family (Linagliptin, sitagliptin, teneligliptin, saxagliptin, alogliptin, vildagliptin, etc.) which are dipeptidyl peptidase-4 inhibitors and are being hoped for permanent cure of type 2 diabetes. [6,7,8] Linagliptin (trade name-Tradjenta) is one of the xanthine-based second generation dipeptidyl peptidase-4 inhibitor used for the treatment for type -2 diabetes mellitus and it was developed by Boehringer Ingelheim. The dipeptidyl peptidase-4 is an enzyme that degrades the endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP). [9] Both enzymes are helpful for the insulin biosynthesis and release from pancreatic beta cells. glucagon-like peptide-1 helps to minimize the glucagon secretion from pancreatic alpha cells, that leads to lower production in hepatic glucose output. Thus, Linagliptin stimulates the release of insulin in

a glucose dependent manner and decreases the levels of glucagon in the circulation. [10] The recommendation is that the single 5 mg oral dose with or without food. [11] Moreover, Linagliptin and metformin formulation (Brand name: Jentadueto) also effective for the treatment of type-2 diabetes. [12]

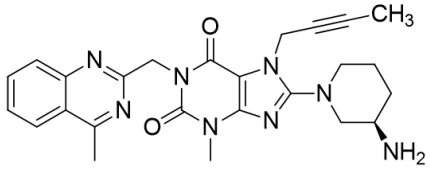
Linagliptin has potent activity and more selectivity for dipeptidyl peptidase-4 inhibition over dipeptidyl peptidase-8 inhibitions, therby its demand is increased, and its number of the new synthetic strategies have been appeared in the literature. [13] In this review we have summarized key routes which have been using for the production of Linagliptin with controlling the inprocess impurities to get the final API as per the required specifications. The goal of this review to showcase the recent advances towards the synthesis of Linagliptin along with the advantages and limitations of the synthetic strategy used, this helps researchers having all synthetic method at one place to explore novel syntheses in the near future.

2. Synthetic Approaches to Linagliptin

Various synthetic approaches have been published in the literature for synthesis of Linagliptin. Herein, we have outlined, the key routes for Linagliptin synthesis, which have been using for the production with controlling the in-process impurities to get the final API as per the required specifications. Mainly the synthesis involve the use of the 3-methyl xanthine as a key starting material.

2.1 Boehringer Ingelheim's synthetic approach for Linagliptin (US7407955)

In the first product patent (US7407955) by Boehringer Ingelheim, the synthesis of the Linagliptin API was achieved in the five steps starting form 3-methylxanthine (**Scheme-1**). In the first step, the bromination of 3-methylxanthine **2** was carried out with bromine in the presence of sodium acetate in acetic acid at 63 °C. The *N*-alkylation of the resulting 8-bromo-3-methylxanthine **3**, was carried out with 2-butynyl bromide in the presence of tributylmethyl ammonium chloride (Bu_3NMeCl) and *N, N* diisopropylethyl amine in *N, N*-dimethylformamide (DMF) at 68 °C to yield 7-butynyl xanthine . Coupling of the 2-(chloromethyl)-4-methylquinazoline with 3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine in the presence of Na_2CO_3 in DMF at 85 °C or *N, N*-dimethylacetamide at 90 °C or tetrabutyl ammonium bromide (Bu_4NBr) in dimethyl sulfoxide (DMSO) at 78 °C provides



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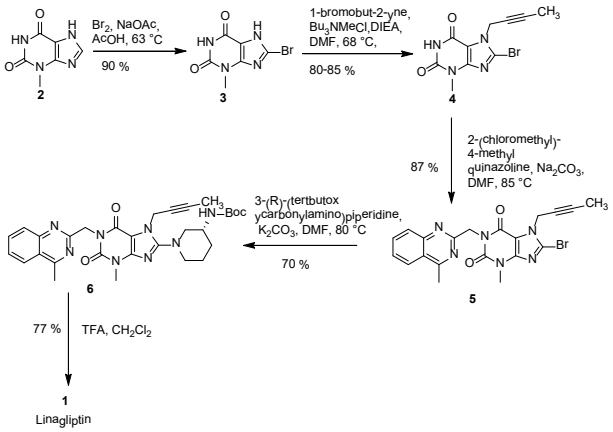
Generic name: Linagliptin
Brand name: Tradjenta
IUPAC Name: 1*H*-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]
Dosage form and Route: Tablet (5 mg); Oral
Polymorph: Mixture of Form A and Form B
Molecular formula: $C_{25}H_{28}N_8O_2$
Molecular weight: 472.54
CAS No.: 668270-12-0
Innovator: Boehringer Ingelheim
Product patent status: US 7407955 (Aug 12, 2023-OB Expiry)
Description: White to yellowish powder
Melting range: 198-202 °C

Figure1. Molecular structure of Linagliptin and its details.

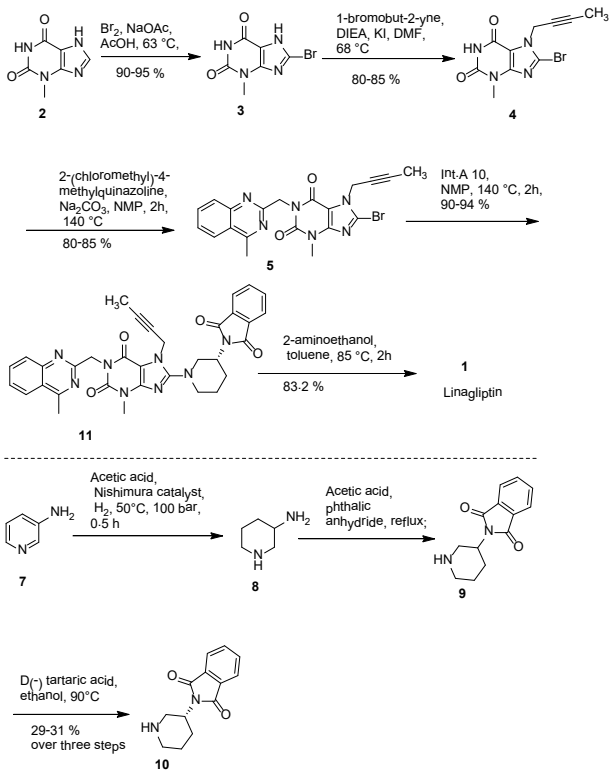
1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine **5**. Then coupling of bromoxanthine intermediate **5** with 3-(R) (tertbutoxycarbonylamino)piperidine in presence of potassium carbonate (K_2CO_3) in *N, N*- dimethylformamide (DMF) at 80 °C to give the *N*-protected piperidine derivative **6**. For this coupling reaction the alternative reaction solvents such as Tetrahydrofuran (THF), *N, N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,4 dioxane, butanol or ethylene glycol and bases such as potassium carbonate, sodium carbonare, potassium hydroxide, organic bases can be triethyl amine (TEA), *N, N* diisopropylethyl amine can be used. Alternatively, organic base as solvent as well used, and the rate of reaction accelerate using additives such as metal halides like KI. Moreover, the reaction can be accomplished without use of the solvent when used the excess of the 3-aminopiperidine. In the next step, Boc deprotection was performed using trifluoroacetic acid (TFA) in dichloromethane (DCM) or toluene to yield **1**. The main disadvantage of this route is that, it involves the use of (R)-*N*-Boc piperidine is very expensive intermediate and purification by column chromatography. [14]



Scheme 1. Boehringer Ingelheim approach for Linagliptin syntheis (US7407955)

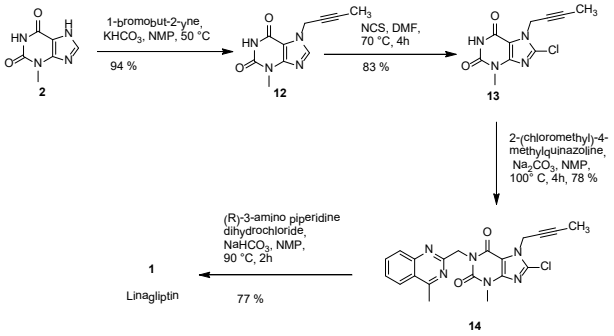
2.2 The second Boehringer Ingelheim's approach towards Linagliptin synthesis (WO20060142310 A1)

Inventor Boehringer Ingelheim, has claimed another method for the preparation of enantiomerically pure Linagliptin. In this strategy, the phthalimide protected enantiomerically pure, 3-amino piperidine **10** was used as a source of amino piperidine for the synthesis of intermediate **11**. For the preparation of rac-3 amino piperidine **8** is depicted in scheme **2**, 3-amino pyridine **7** was reduced using technical grade Nishimura catalyst (rhodium and platinum mixture supported on activated charcoal) in acetic acid at 100 bar H_2 pressure at 50 °C. The resulting rac-amino piperidine **8** on refluxing with the phthalic anhydride in acetic acid yields racemic phtalimide **9** in acetic acid, the 30% of the acetic acid was distilled out and used for next stage of optical resolution without any purification to get enatiomerically pure (R)-2-(piperidin-3-yl) isoindoline-1,3-dione **10**. The previously reported (US7407955) reaction procedure were followed for the synthesis of the intermediate 5, the condensation of 1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine **5** with 3(R) (phthalimido)piperidine ditartarate **10** was achieved by heating at 140 °C in *N*-methyl-2-pyrrolidone. To give **11**, which on heating with 2-aminoethanol in toluene at 85 °C produces Linagliptin. [15] The main advantage of this route over previous report is, while preparation of Boc protected piperidine the controlling the generation of impurities were difficult. However, in case of the phthalimide protection, the enantiomeric pure expensive 3-amino piperidine was synthesized easily in required purity. The limitation of this route is the overall low atom economy and use of expensive Nishimura catalyst for the synthesis of (R)-3-(phthalimido)piperidine ditartrate chiral intermediate.



Scheme 2. Boehringer Ingelheim 2nd approach for the synthesis of Linagliptin (WO20060142310 A1)

14. Condensation of intermediate **14** with (R)-3-amino piperidine dihydrochloride in presence of sodium bicarbonate in *N*-methyl-2-pyrrolidinone (NMP) at 90 °C for 2 h to provide Linagliptin. [16] The advantage of this route is the four step operation form commercially available starting materials however the main disadvantage of this route is use of chiral (R)-3-amino piperidine dihydrochloride without any protecting group led to formation of the byproduct.



Scheme 3. Boehringer Ingelheim 3rd approach for the synthesis of Linagliptin (WO 2013/098775)

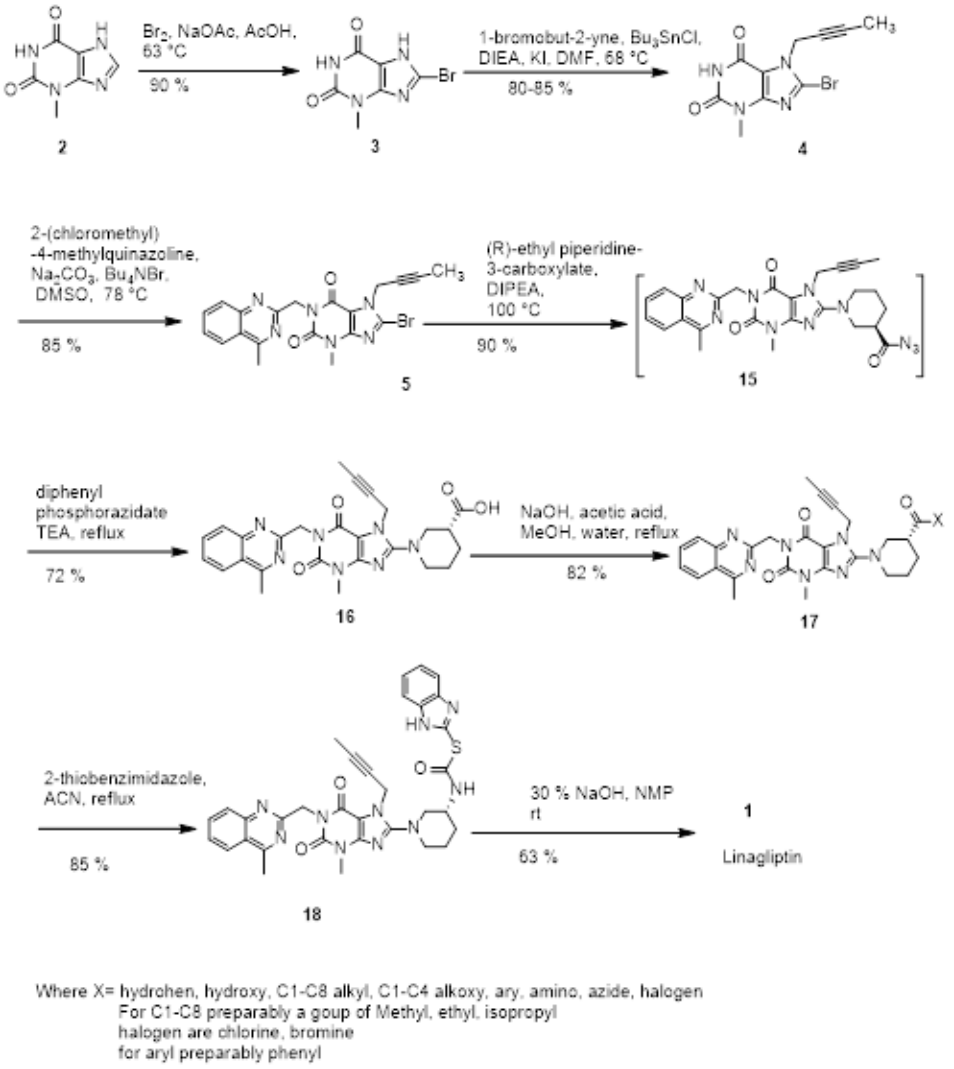
2.3 Boehringer Ingelheim's approach for the synthesis of Linagliptin (WO 2013/098775)

In the patent WO 2013/098775, the team B. I. has disclosed the new synthesis of 1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine intermediate **14.** The 3-methylxanthine **2** was *N*-alkylated with but-2-ynyl ester in presence of potassium bicarbonate ($KHCO_3$) in *N*-methyl-2-pyrrolidone (NMP) at 50 °C to get intermediate **12** which on treatment with *N*-chlorosuccinimide (NCS) in *N,N* dimethylformamide at 70 °C provides intermediate **13**. Coupling of 2-(chloromethyl)-4-methylquinazoline with 3-methyl-7-(2-butyn-1-yl)-8-chloroxanthine **13** in the presence of sodium carbonate (Na_2CO_3) in *N*-methyl-2-pyrrolidinone (NMP) at 100° C for 4 h gave 1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-chloroxanthine

2.4 Dipharma's approach towards Linagliptin (EP 2468749 A1)

EP 2468749 A1, has invented and claimed that the process the preparation single enantiomer or mixture of Linagliptin without the use of an expensive (R)-tert-butyl piperidin-3-ylcarbamate/ (R)-2-(piperidin-3-yl) isoindoline-1,3-dione. For the synthesis of intermediate **5** reactions are performed as per the US 7407955. If the compound having X= azide group was converted by doing Curtius reaction to isocyanate, which on hydrolysis yields Linagliptin. In case of X = hydroxy it is converted to azide intermediate using diphenylphosphorylazide (DPPA) followed by Curtius rearrangement and subsequent hydrolysis to Linagliptin. The Curtius reaction can be performed in various solvents such as *N, N*-dimethylformamide (DMF),

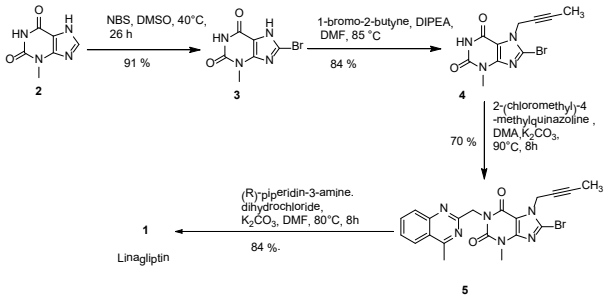
dimethylsulfoxide (DMSO), acetonitrile, dimethylacetamide, tetrahydrofuran (THF), dioxane , Methyl-tert-butyl ether (MTBE), acetone, dichloromethane (DCM), toluene, ethyl acetate or isopropyl acetate but more preferably acetonitrile. Condensation of 8-bromoxanthine intermediate **5** with ethyl piperidine-3-(R)-carboxylate- L-tartrate salt in the presence of DIEA in refluxing NMP furnishes 8-(1-piperidinyl) xanthine intermediate **15**, which upon ester hydrolysis with sodium hydroxide in refluxing water/ methanol yields the corresponding carboxylic acid **16**. Reaction of carboxylic acid **16** with DPPA in the presence of triethylamine (Et_3N) in refluxing acetonitrile, followed by Curtius rearrangement of the obtained azide **17** with 2-thiobenzimidazole or dodecyl thiocarbamate at 60 °C affords thiocarbamate **18**, which upon hydrolysis with sodium hydroxide in *N*-methyl-2-pyrrolidinone (NMP) to get Linagliptin.[17] The limitations of this route is, the use protection, deprotection increases manufacturing cycle time, effluent load and involves the use of the smelling thiol derivatives. Moreover, the DPPA (diphenoxyphosphoryl azide) is very toxic and a potential explosive like most other azide compounds.



Scheme 4. Dipharma Francis SRL approach for the synthesis of Linagliptin (EP 2468749 A1)

2.5 Dr. Reddy's approach for Linagliptin (WO 2013/098775 A1)

The patent WO 2013/098775 A1, claimed that preparation of enantiomerically pure synthesis of Linagliptin by using (R)-piperidin-3-amine as a free base or salt of hydrochloride or sulphate or dibenzoyl tartarate from 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl) methyl)-1H-purine-2,6(3H,7H)-dione **5**. The brominating of 3-methylxanthine **2** was performed by treatment with NBS in dimethylsulfoxide at 40°C for 26 h. The resulting 3-methyl-8-bromoxanthine **3**, on treatment with 1-bromo-2-butyne in the presence of *N, N* diisopropylethyl amine (DIEA) in N,N-dimethylformamide at 85 °C yields the N-alkylated intermediate 3-methyl-7-(2-butynyl)-8-bromoxanthine **4**. Further, the xanthine intermediate **4** on reaction with 2-(chloromethyl)-4-methylquinazoline in the presence of sodium carbonate in dimethylacetamide (DMA) at 90 °C furnishes bromo adduct **5**, which on condensation with 3(R)-aminopiperidine hydrochloride in presence of potassium carbonate in dimethylformamide at 80°C yields Linagliptin. This condensation can be performed using potassium carbonate in methyl isobutyl ketone at 95°C or free base of (R)-piperidin-3-amine using potassium carbonate in methyl isobutyl ketone at 95 °C or dibenzoyl-D-tartarate salt of (R)-piperidin-3-amine using potassium carbonate (K_2CO_3) in methyl isobutyl ketone at 100 °C. The resulting crude Linagliptin with chemical purity 99.44 %, having regio impurity-0.29 to 0.46 %, bromo impurity-0.02 %, was purified recrystallization from methanol/ methyl-tert-butyl ether to get pure Linagliptin, having chemical purity-99.67 %, Chiral purity- 99.85%, with regio impurity-0.09 %, bromo impurity-0.07 %.[18]
Advantages of this process over the process described in US7407955 patent[14] is use of IPA. HCl for the deprotection of Boc group instead of TFA also it is advantages in comparison with the procedure described in patent US 2004/0097510A1 of (R)-tert-butyl (1-(7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8 yl)piperidin-3-yl)carbamate **6** using IPA/ HCl that generate (R,Z)-8-(3-aminopiperidin-1-yl)-7-(3-chlorobut-2-en-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6(3*H*,7*H*)-dione (chloro impurity) difficult to remove in process. Whereas another advantage over the deprotection of Pthalimide intermediate **11** (Phthalimide protected Linagliptin) which is disclosed in US7820815 patent using ethanolamine which involves the protection and deprotection strategy that causes less yield.

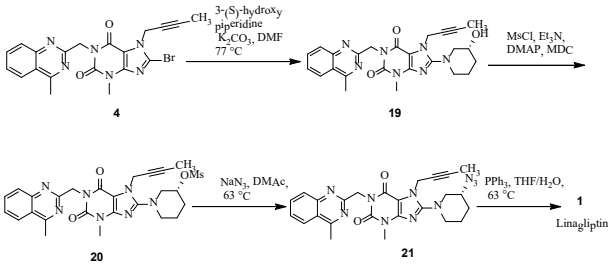


Scheme 5. Dr. Reddy Laboratories for the synthesis of Linagliptin (WO 2013/098775 A1)

2.6 Divis's approach towards Linagliptin (IN 201302189)

Divis Laboratories Limited in patent IN 201302189 has claimed the (S)-hydroxypiperidine as a source of (R)-piperidin-3-amine. The synthesis of **5** reactions was achieved as per the previously reported procedure in the US 7407955 patent. The coupling of 8-bromoxanthine intermediate **5** with 3-(S)-hydroxypiperidine was achieved in the presence of potassium carbonate in *N,N*-dimethylformamide at 77 °C to get piperidinyl xanthine intermediate **19**. The hydroxyl is converted to amine via the formation of good leaving mesyl group followed by nucleophic displacement with azide and reduction of azide group. The mesylation of hydroxyl

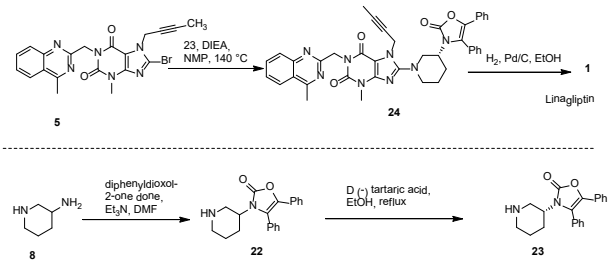
group is achieved using the Mesyl chloride in the presence of triethyl amine and catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane to get the corresponding mesylate intermediate **20**, which on reaction with sodium azide in DMF at 63 °C yields azide intermediate **21.** The azide was reduced under staudinger reaction condition to give Linagliptin. The limitation of this process is effluent load will be high due to the use of triphenylphosphine for reduction of azide.[19]



Scheme 6. Divis Laboratories approach for the synthesis of Linagliptin (IN 201302189)

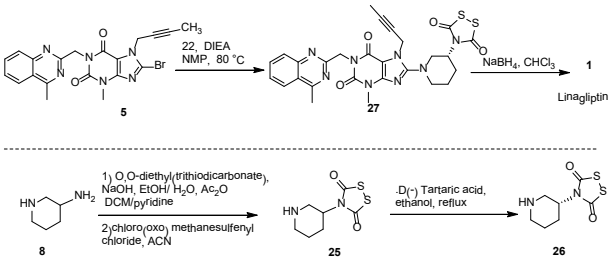
2.7 Brightgene's approaches for the synthesis of Linagliptin (CN 103450201)

Brightgene in his patent claimed the four strategy for the synthesis of Linagliptin. For the synthesis of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione **5** reactions performed as per US patent US 7407955. In the first route, has used (R)-4,5-diphenyl-3-(piperidin-3-yl)oxazol-2(3*H*)-one **23** instead of Boc-protected amino piperidine. Synthesis was performed as per the sequence depicted in scheme **7**. The reaction of 3-aminopiperidine **8** with 4,5-diphenyldioxol-2-one performed in the presence of triethylamine (Et_3N) in *N,N*-dimethylformamide to get 5-diphenyl-3-piperidin3yloxazol-2-one **22.** It was purified preparation of the salt using (-) tartaric acid on refluxing in ethanol (EtOH) to get entiomerically pure (R) 3-amino piperidine **23**. Further coupling of (R)-4,5-diphenyl-3-(piperidin-3-yl)oxazol-2(3H)-one with bromoxanthine derivative **5** in the presence of *N,N*-diisopropylethylamine (DIEA) in *N*-methyl-2-pyrrolidinone at 140 °C gave **24**. Which in presence of palladium on carbon (Pd/C) in ethanol (EtOH) under hydrogen atmosphere provide the access to Linagliptin (scheme-7). [20]



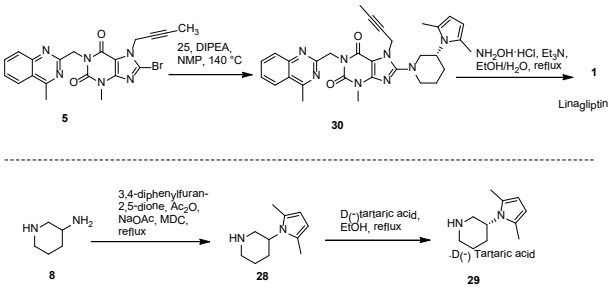
Scheme 7. Brightgene first approach for the synthesis of Linagliptin (CN 103450201)

In the second approach, team Brightgene used (R)-4-(piperidin-3-yl)-1,2,4-dithiazolidine-3,5-dione **26** instead of (R) Boc-amino piperidine. The condensation of 3-aminopiperidine **8** with *O,O*-diethyl(trithiodicarbonate) in the presence of sodium hydroxide in EtOH/H_2O and subsequent reaction with acetic anhydride (Ac_2O) in dichloromethane/pyridine, followed by cyclization with chloro(oxo) methanesulfenyl chloride in acetonitrile furnishes 4-piperidin-3-yl-1,2,4-dithiazolidine-3,5-dione **25.** The resolution of the intermediate **25** was performed by making the salt with D (-) tartaric acid in refluxing ethanol affords the (R) isomer of 3-amino piperidine **26** in required chiral purity. Coupling of piperidine derivative **26** with bromoxanthine intermediate **5** in the presence of *N, N*-diisopropylethylamine in *N*-methyl-2-pyrrolidinone at 80 °C gave **27**, which upon reduction with sodium borohydride ($NaBH_4$) in chloroform provides the access to Linagliptin (scheme-8).[20]



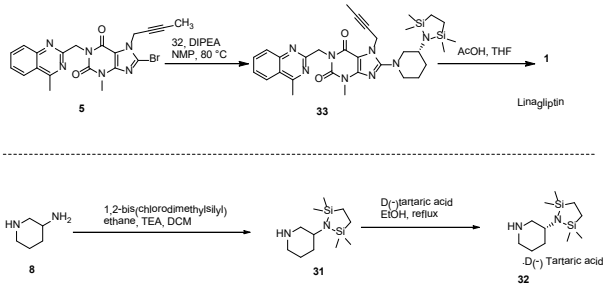
Scheme 8. Brightgene second approach for the synthesis of Linagliptin (CN 103450201)

The third approach disclosed in this patent involves the condensation of 3-aminopiperidine **8** with 3,4-diphenylfuran-2,5-dione on refluxing in the presence of acetic anhydride and sodium acetate in dichloromethane furnishes 3,4-diphenyl-1-piperidin-3-ylpyrrole-2,5-dione **28.** The resolution was carried out using D (-) tartaric acid in ethanol to affords the desired (R) isomer **29**. Coupling of piperidine derivative **29** with bromoxanthine derivatives **5** in the presence of *N, N*-diisopropylethylamine in *N*-methyl-2-pyrrolidinone at 140 °C gave **30**. The deprotection of the **30** using $NH_2OH{\cdot}HCl$ in the presence of triethylamine in mixture of ethanol and water at reflux provides Linagliptin (scheme-9). [20]



Scheme 9. Brightgene third approach for the synthesis of Linagliptin (CN 103450201)

In the fourth strategy disclosed in the patent involves, the condensation of 3-aminopiperidine **8** with [2(chlorodimethylsilyl)ethyl]dimethylsilyl chloride in the presence of triethylamine in dichloromethane to get 3-(2,2,5,5-tetramethyl-1,2,5-azadisilolidin-1-yl) piperidine **31**. The resolution of **31** was performed using D (-) tartaric acid to affords the desired (R)isomer of piperidine **32**. Coupling of piperidine derivative **32** with bromoxanthine **5** in the presence of *N, N*-diisoprpylethylamine in *N*-methyl-2-pyrrolidinone at 80 °C gave **33**, which on deprotection on treatment with acetic acid in tetrahydrofuran provides the Linagliptin. [20] This patent gave four approaches to Linagliptin, however, the protection and deprotection increases the number of steps which increases manufacturing cycle time (Scheme-10).

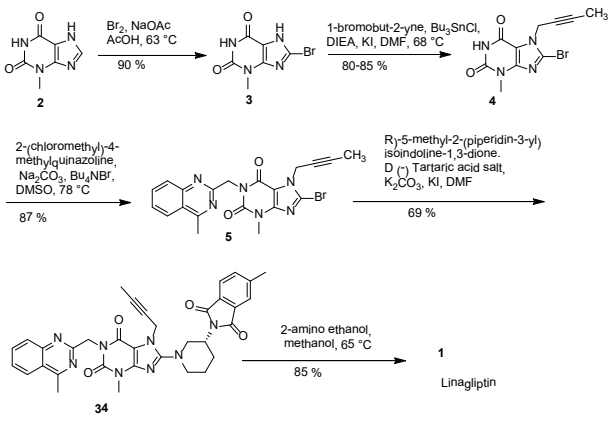


Scheme 10. Brightgene fourth approach for the synthesis of Linagliptin (CN 103450201)

2.8 Glenmark approach towards Linagliptin (WO2014033746)

Glenmark's has disclosed that the synthesis of Linagliptin in patent applications WO2014033746, it involves the use of methyl phthalimide protected amino piperidine as a source of amino piperidine. The synthesis of Intermediate **5** was performed as per the procedure reported in patent US7407955. The bromination of 3-methylxanthine was performed by treatment with Br_2 in the presence of sodium acetate in acetic acid at 63 °C to get 8-bromo-3-methylxanthine **3**. Which on reaction with 2-butynyl bromide in the presence of Bu_3NMeCl or tributyltin chloride (Bu_3SnCl), triethylamine or N, N-diisopropylethylamine in presence or absence of potassium iodide in N, N-dimethylformamide at 68 °C produces the 7-butynyl xanthine **4**. The reaction of

2-(chloromethyl)-4-methylquinazoline with 3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine **4** in the presence of sodium carbonate or potassium carbonate and optionally potassium iodide, tetrabutyl ammonium hydroxide (Bu_4NOH) in *N*-methyl-2-pyrrolidinone at 128 °C or N, N-dimethylformamide at 85 °C or dimethylacetamide at 90 °C or tetrabutylammonium bromide (Bu_4NBr) in dimethyl sulfoxide at 78 °C provides 1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine **5**. Condensation of 1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine **5** with 3(R) (4-methylphthalimido) piperidine ditartrate gave Int. **34**, which is deprotected by refluxing with 2-aminoethanol in toluene at 85 °C or in methanol/ ethanol/ isopropanol/ acetonitrile at 65 °C or hydrazine hydrate in alcoholic solvent to get Linagliptin.[21] Pthalimide group with one or more substituents like halo, alkyl, nitro or amino group. In this patent, they have claimed the preparation of Linagliptin free base using Linagliptin dibenzoyl-D-tartaric acid with the chiral HPLC purity 99.95 %. The main disadvantages are protection and deprotection method increases manufacturing cycle time and high effluent load.



Scheme 11. Glenmark approach towards the Synthesis of Linagliptin (WO2014033746)

Conclusion

In summary, we have highlighted the key synthetic approaches for the Linagliptin synthesis using 3-methyl xanthine as key starting material. In all the synthetic routes, the (R)-piperidin-3-amine is major cost contributor intermediate, since the chemist are persistent in searching a new route for the synthesis of (R)-piperidin-3-amine, it will reduce the production cost up to great extent and helpful for the further development of Linagliptin.

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References

1. S. Melmed, K. Polonsky, P. R. Larsen, H. Kroneberg, *Williams textbook of endocrinology* (12th ed.), 2011, 1371–1435.
2. International Diabetes Federation Diabetes Atlas, sixth ed., The Global Burden, 2013, 29-50. http://www.idf.org/diabetesatlas/download-book.
3. American Diabetes Association, Diagnosis and classification of diabetes mellitus, *Diabetes Care,* 2010, 33, S62-S69.
4. (a) T. Scully, Diabetes in numbers, *Nat. Outlook: Diabetes,* 2012, 485, S2-S3; (b) P. Shetty, India's diabetes time bomb, *Nat. Outlook: Diabetes,* 2012, 485, S14-S16.
5. R. Kushwaha, W. Haq and S. B. Katti**,** Chemistry and biology interface, 2014, 4,137-162.
6. B. Patel, M. Ghate, *Eur. J. Med. Chem.,* 2014, 74, 574-605.
7. S. Gwaltney IInd, *Curr. Top. Med. Chem.,* 2008, 8, 17, 1545-1552.
8. Y. Liu, Y. Hu, T. Liu, *Curr. Med. Chem.,* 2012, 19, 23, 3982-3999.
9. A. Barnett, International Journal of Clinical Practice, 2006, 60, 11, 1454–70.
10. J. Neumiller, S. Setter, *Clinical Therapeutics.* 2012, 34, 5.
11. G. Gomes, R. Desouza, S. Camila, P. Mariana, A. Baldoni, Linagliptin safety profile: A systematic review, Prim Care Diabetes. 2018, 12, 6, 477-490.
12. Jentadueto-linagliptin and metformin hydrochloride tablet,

film coated, *DailyMed*, 2019.
13. C. McIntosh, H. Demuth, J. Pospisilik, R. Pederson, *Regulatory Peptides*. 2005, 128, 2, 159–165.
14. E. Matthias, H. Sbach, L. Elke, R. Lotzralf, M. Roland, M. Michael, T Mohammad, US7407955B2, 2008.
15. W. Pfrengle, T. Pachur, S. Nichola, A. Duran, US20060142310A1, 2006.
16. W. Dong, Y. Huang, S. Shengmi, Y. Sun, P. Zhang. WO2016207364A1, 2016.
17. P. Allegrini, M. Artico, E. Attolino, EP2468749A1, 2012.
18. P. Haldar, V. Muvva, A. Prataprao, V. Karri, P. Tadaru, N. Birudraju, WO2013098775A1, 2013.
19. Divis Laboratories Limited, IN201302189, 2013.
20. Y. Jiadong, CN103450201 A, 2013.
21. S. Singh, S. Srivastava, S. Bhirud, WO2014 033746, 2014.