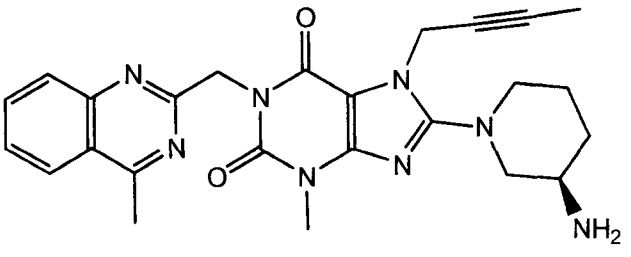
## Field of Invention

The present invention relates to a novel process for the preparation of (*R*)-8-(3-amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (**A**), also known as linagliptin from 1-[(4-methylquinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine (**B**)

## Background of the Invention

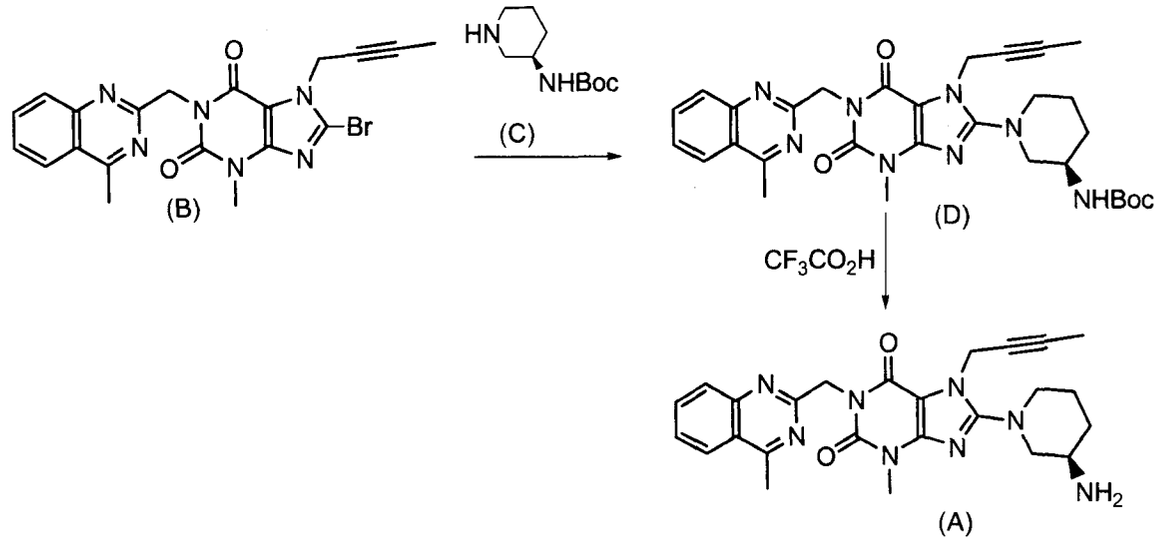
Linagliptin, namely 8-(3*R*)-3-aminopiperidinyl)-7-butyn-2-yl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione of formula (**A**), a dipeptidylpeptidase-IV (DPP-IV) inhibitor with a long term action is an approved drug by US FDA for the treatment of type II diabetes mellitus.



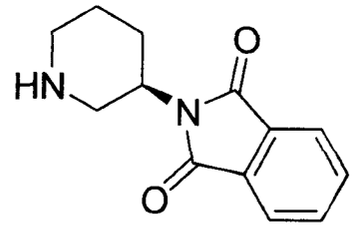

(**A**)

The synthesis of linagliptin is reported in US 7,407,955 as depicted in the Scheme-I below, where 8-bromo xanthine of formula (**B**) is condensed with 3-(*R*)-BOC-aminopiperidine of formula (**C**) to obtain a compound of formula (**D**), which is converted to linagliptin (**A**) by deprotection of the amine function.

**Scheme-I**




However, the preparation of chiral BOC protected (*R*)-(-)-3-aminopiperidine compound (**C**) is both difficult and expensive. In addition to this, the process also suffers from impurities that are difficult to remove on an industrial scale. The process also suffers from acid labile and highly sensitive BOC protection. Therefore, the process was not amenable for industrial scale production of 8-(3*R*)-3-aminopiperidinyl)-7-butyn-2-yl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione. It is also desired that an API is manufactured with high purity. The patent application US 2009/0192314 describes an alternative process for the preparation of linagliptin (**A**) making use of 3-(*R*)-aminopiperidine protected as a phthalimide of formula (**E**).

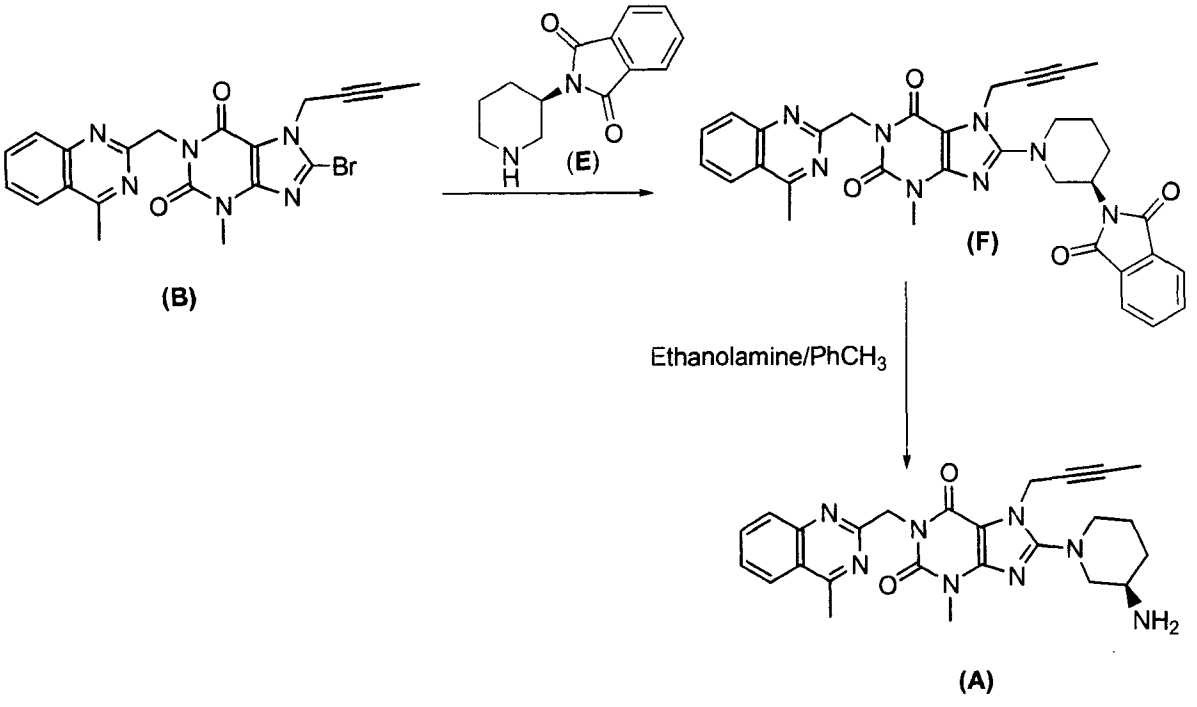



(**E**)

The phthalimide protected 3-(*R*)-aminopiperidine (**E**) was prepared by hydrogenating 3-aminopyridine at a high pressure (100 kg) using Nishimura catalyst (a commercially available rhodium/platinum catalyst) followed by reaction with phthalic anhydride. This was followed by a resolution process through diastereoisomeric salts using D-tartaric acid and final cleavage of the tartrate salt to afford the required target intermediate (**E**).

The preparation of intermediate (**E**) is also cumbersome and expensive. Furthermore, the substitution reaction of intermediate (**E**) and the bromoxanthine derivative of formula (**B**) to afford the compound of the molecular formula (**F**), is not an environmentally benign process, due to the drastic reaction conditions such as heating at 140°C in N-methylpyrrolidone (Scheme-II).

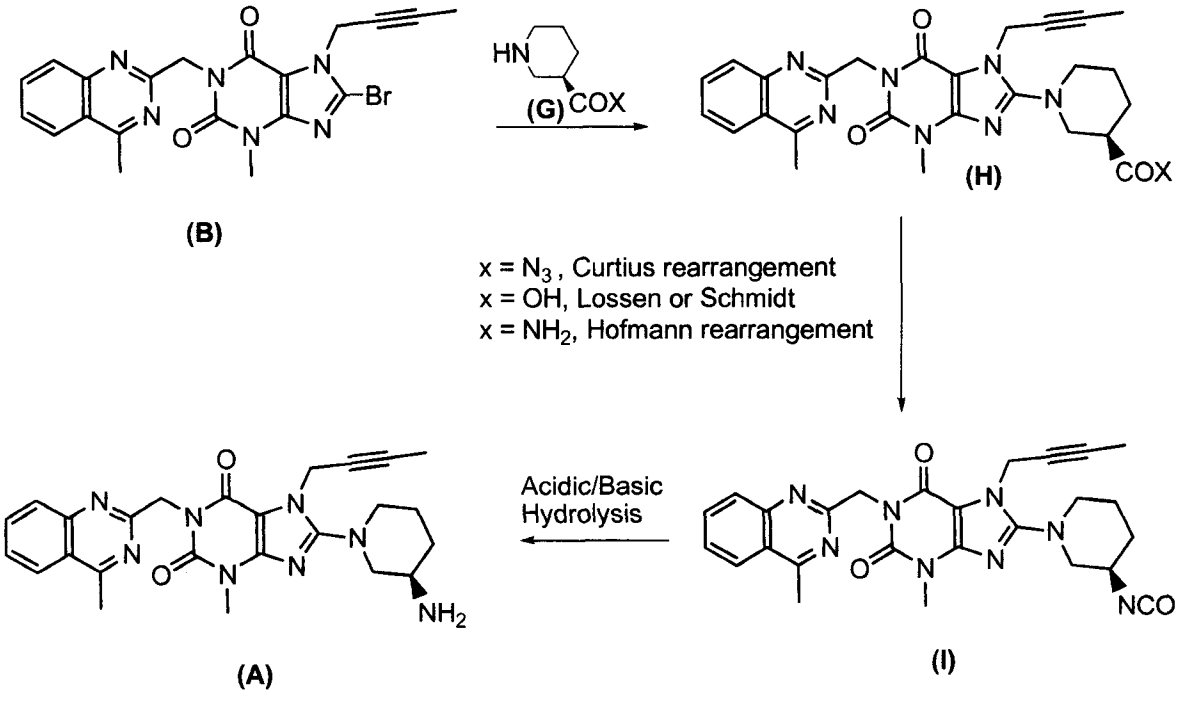
**Scheme-II**



In the patent application US2012165525A1, another process for the synthesis of linagliptin (**A**) is reported to overcome the difficulties associated with existing processes.

The following Scheme-III depicts the process, which consists of reacting intermediate (**B**) with a piperidine derivative of formula (**G**) to obtain intermediate of formula (**H**).

**Scheme-III**




The intermediate of the compound of formula (**H**) is converted into isocyanate or carbamate of formula (**I**) by making use of one of the named reactions depending on the nature of 'X' as follows:

i) by Curtius rearrangement;

ii) if X is hydroxyl, it is subjected to Lossen or Schmidt rearrangement;

iii) if X is $NH_2$, it is subjected to Hofmann degradation reaction.

Further, the isocyanate or carbamate intermediate (**I**) is converted into the compound (**A**) either by acid or base hydrolysis.

The main drawbacks of this invention are lower product yields and harsh reaction conditions, which are not desirable on an industrial scale. The synthesis of intermediate (**G**) involves a sequence of multistage reactions with unsatisfactory yields.

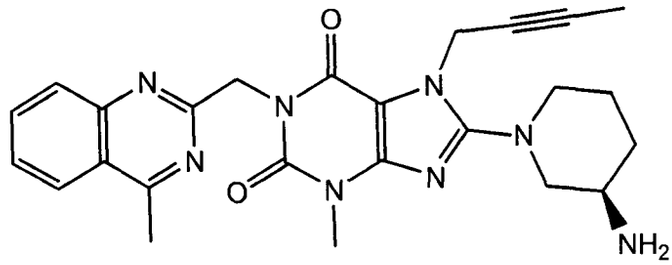
Thus there is a need for an alternative synthetic approach to afford linagliptin (**A**) with high enantiomeric and chemical purity in an industrially feasible and economic pathway.

In the light of above described disadvantages of the known preparation processes, it is an object of the present invention to provide a process which allows the preparation of chemically and enantiomerically pure 8-(3*R*)-3-aminopiperidinyl)-7-butyn-2-yl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione, linagliptin (**A**) using readily available starting materials.

**Summary of the Invention**

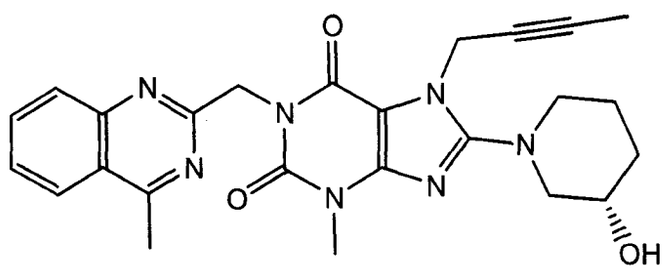
The present invention provides an operationally simple route of synthesis for the production of linagliptin in high yield and purity via novel intermediates of formula-**J**, **K** and **L**. The process of the invention has both economic as well as environmental advantages compared to those reported in the prior art.

The inventive steps for the preparation 8-(3*R*)-3-aminopiperidinyl)-7-butyn-2-yl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione (**A**) consists of:



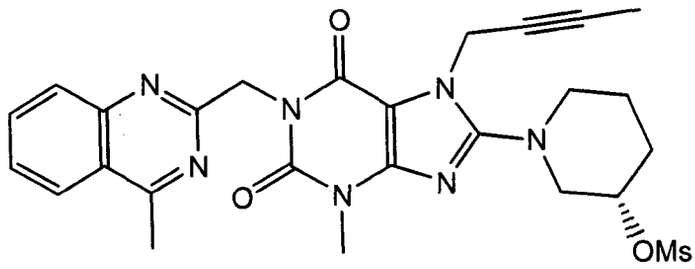
**(A)**

a) providing a compound (*S*)-7-(but-2-ynyl)-8-(3-hydroxypiperidin-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6-(3H,7H)-dione (**J**) obtained from compound 8-bromo-7-(but-2-ynyl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6-(3H,7H)-dione (**B**) by N-alkylation with compound (3*S*)-3-hydroxypiperidin-1-ium(2*S*,3*S*)-3-[(4-chlorophenyl)carbamoyl]-2,3-dihydroxypropanoate (**M**) in presence of $K_2CO_3$ and



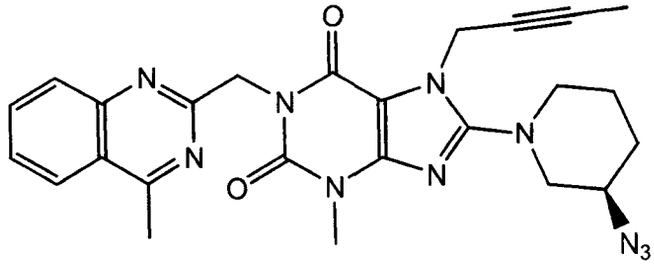
**(J)**

b) mesylating the compound of formula (**J**) using methane sulfonylchloride in presence of a base to give the novel compound (3*S*)-1-(7-(but-2-ynyl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)piperidin-3-yl methanesulfonate (**K**) and




**(K)**

c) reacting the compound of formula (**K**) with sodium azide in an $SN^2$ manner to afford a novel compound (3*R*)-8-(3-azidopiperidin-1-yl)-7-(but-2-ynyl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6(3H,7H)-dione (**L**) with inversion in configuration and finally



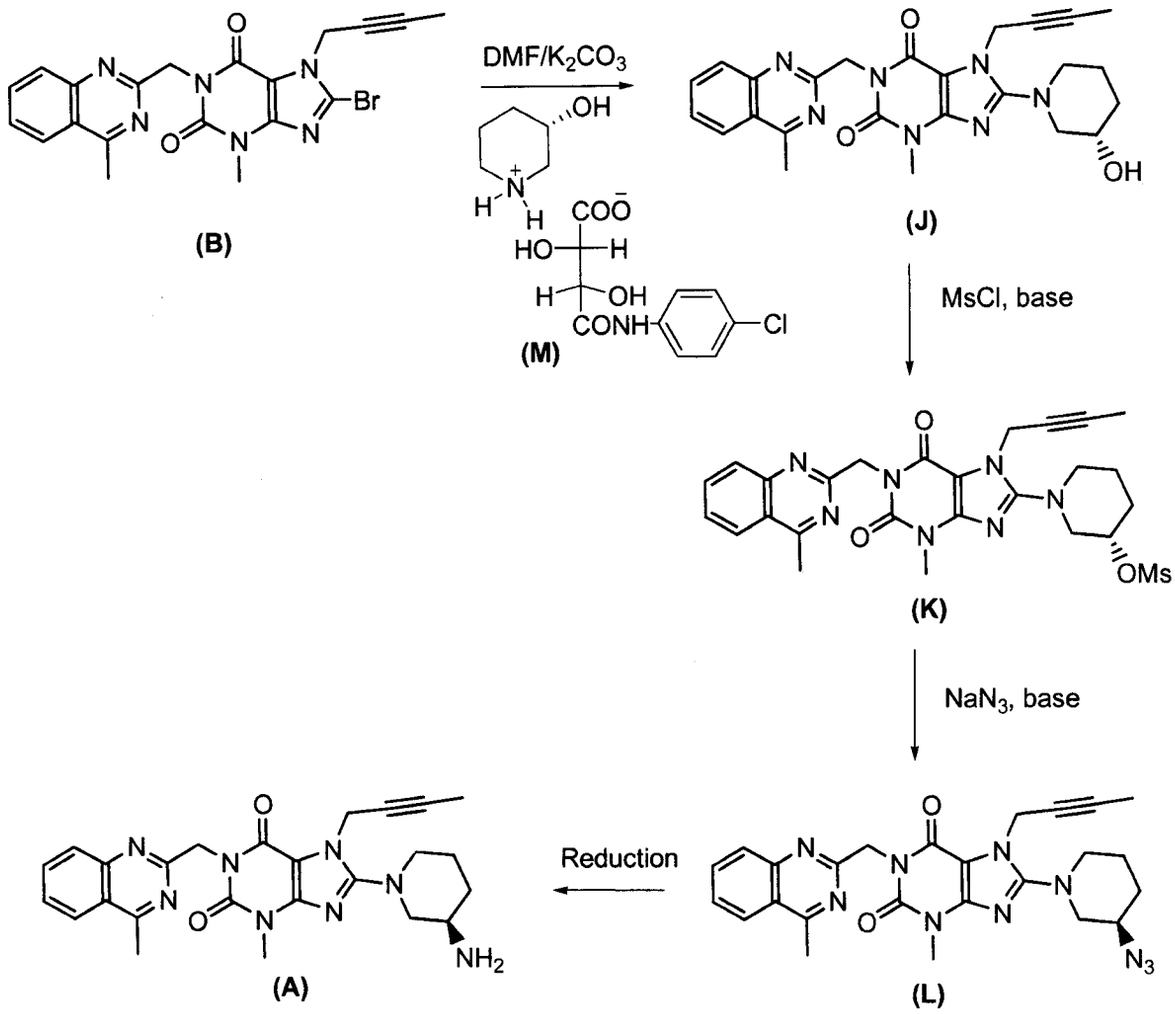

**(L)**

d) reducing the compound of formula (**L**) to obtain the compound of formula (**A**) using a suitable source of hydrogen.

**Detailed disclosure of the Invention**

The present invention relates to the direct synthesis of linagliptin of the formula (**A**) as per the scheme depicted below.

**Scheme-IV**




One embodiment of the present invention refers to the process for preparing a compound of formula (**J**) by reacting the compound of formula (**B**) with the 4-chloro-(l)-tartranilic acid salt of optically pure form of 3-hydroxypiperdine. The compound of formula (**M**) has preferably absolute configuration (*S*).

The reaction of a compound of formula (**M**) with the compound of formula (**B**) can be carried out in a suitable solvent, selected from the group comprising of dipolar aprotic

solvents, typically dimethylformamide, dimethylacetamide, N-methylpyrrolidone, acetonitrile or dimethylsulfoxide. Preferably, the reaction is carried out in N,N-dimethylformamide in the presence of an inorganic base such as sodium carbonate, lithium carbonate, potassium carbonate, preferably potassium carbonate.

According to a preferred aspect of the invention, a compound of formula (**J**) with single enantiomer can be converted to a mesylated compound of formula (**K**), by reacting with methane sulfonyl chloride in presence of a base with complete retention configuration. The reaction can be carried out in chlorinated solvents such as ethylene dichloride or dichloromethane, preferably in dichloromethane in presence of an organic base such as N,N-diisopropylethylamine (Hunig's base), diisopropylamine, tri-n-butylamine, triethylamine, tertiarybutylamine, pyridine, preferably triethylamine, in presence of a catalytic amount of 4-(N,N-dimethylamino)pyridine. In order to effect the above transformation towards the desired product, a temperature range of -10 to 10°C, preferably 0-5° C is to be employed.

In another embodiment, the present invention refers to the conversion of the mesylated compound of formula (**K**) by reacting with sodium azide to obtain an azido compound of formula (**L**) with an inversion at the reacting steric centre.

The transformation can be effected in solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, preferably in dimethylsulfoxide, more preferably in N,N-dimethylformamide and most preferably in N,N-dimethylacetamide. The azidinating agent may be such as tosyl azide, diphenylphosphoryl azide or sodium azide, preferably sodium azide. To obtain the desired product, the preferred temperature range is 50°C to 130°C, particularly at 90°C to 110°C for a period of 8-16 h, preferably for a period of 10-12 h.

In another embodiment, the present invention refers to the process for the preparation of optically pure linagliptin of formula (**A**) by reducing the compound of formula (**L**) by using a suitable hydrogen source. The reaction can be carried out in alcoholic solvents such as ethanol, methanol, isopropyl alcohol, tertiary butanol or ethereal solvents such as tetrahydrofuran, 1,2-dimethoxy ethane, 1,4-dioxane, preferably in ethanol. The hydrogen source may be from a reaction of a metal in the presence of $NH_4Cl$ or dilute HCl or using triphenylphosphine in presence of water. The preferred temperature to afford the desired product is within the range of 60-100°C, preferably at 60-70°C for a period of 7-20 h, and in particular 10-12 h. The intermediate (**M**) has been prepared by following the literature method (*Tetrahedron*, **1995**, *51*, 5935-5950).

The following examples illustrate the present invention without limiting the scope. Persons skilled in the art can vary the conditions and reagents without affecting the invention.

**Examples**

**Example 1: Preparation of (*S*)-7-(but-2-ynyl)-8-(3-hydroxypiperidin-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6-(3H,7H)-dione (J)**

To a suspension of 1-[(4-methylquinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine (**B**) 50.0 g (0.11 mol) and potassium carbonate 45.73 g (0.33 mol) in dimethylformamide (300 ml), was added (*S*)-3-hydroxypiperidine (-)-4-chlorotartranilate (**M**) 43.47 g (0.121 mol). The reaction mixture was subsequently stirred at 75-80°C for 6h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, diluted with 600 ml of demineralised (DM) water. The solid formed was filtered and washed subsequently with DM water 2 x 100 ml. The solid was dried at 50°C for 6 h to afford the title compound of formula (**J**) as pale yellow solid. Yield: 49.04-50.08 g (94-96%).

Mp:175-179°C; Purity by HPLC: 99.5%; $^1$HNMR ($CDCl_3$, 300 M Hz): 1.58-1.67 (1H, m), 1.80 (3H, s),1.79-1.85 (2H, m), 1.95-2.01 (1H, m), 2.88 (3H, s), 3.30-3.39 (1H, m), 3.49-3.53 (3H, m), 3.54 (3H, s), 3.75-3.85 (1H, m), 3.95-4.05 (1H, m), 4.78-5.00 (2H, m), 5.56 (2H, s), 7.49-7.54 (1H, m), 7.73-7.78 (1H, m), 7.87 (1H, d, $J$ = 8.41 Hz),8.01 (1H, *d*, $J$ =8.41 Hz); $(M+H)^+$: 474.

**Example 2: Preparation of (3*S*)-1-(7-(but-2-ynyl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)piperidin-3-yl methanesulfonate (K)**

Methanesulfonyl chloride 36.3 g (0.317 mol) was added to a solution of 1-[(4-methylquinazolin- 2-yl)methyl]- 3-methyl- 7-( 2-butyn- 1-yl)- 8-((*S*)- 3-hydroxypiperidinyl)xanthine (J) 50.0 g (0.105 mol), triethylamine 37.43 gm (0.369 mol) and 4-DMAP 0.64 g (0.0052 mol) in dichloromethane (300 ml) dropwise at 0-5°C during 1 h. The reaction mixture subsequently stirred at the same temperature for 3h. After completion of the reaction, 300 ml of DM water was added and the organic layer separated. The organic layer was washed with DM water (2 x 100 ml) followed by 5% sodium bicarbonate solution (2 x 200 ml and brine solution (200 ml) and dried over anhydrous sodium sulfate. The solvent was then evaporated, 200 ml diisopropylether added and stirred for 2h at ambient temperature. The resulting precipitate was filtered and washed with 100 ml diisopropylether to afford the title compound (**K**) as pale yellow solid 54.75g (94%). Mp: 135-138°C Purity by HPLC: 99.4%;

$^1$HNMR ($CDCl_3$, 300 M Hz): 1.80 ( t, $J$ = 1.98 Hz, 3H) superimposed on 1.79-2.15 (m, 4H), 2.89 (s, 3H), 3.08 (s, 3H), 3.29-3.35 (m, 1H), 3.45-3.51 (m, 2H), 3.55 (s, 3H), 3.73-3.78 (m, 1H), 4.90-4.91 ( q, $J$ = 1.8 Hz, 2H), 4.95-5.05 (m, 1H), 5.56 (s, 2H), 7.49-7.55 (m, 1H) 7.73- 7.79 (m, 1H), 7.88 (d, $J$ =8.2 Hz, 1H), 8.05 (d, $J$ =8.2 Hz, 1H). $(M+H)^+$: 553

**Example 3: Preparation of (3*R*)-8-(3-azidopiperidin-1-yl)-7-(but-2-ynyl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6-(3H,7H)-dione (L)**

To a suspension of 1-[(4-methylquinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*S*)-3-O-methanesulfonyl piperidinyl)xanthine (**K**) 50.0 g (0.907 mol) in 300 ml dimethylacetamide, sodium azide (17.69 g, 0.272 mol) was added at ambient temperature and subsequently stirred at 60-65°C for 24h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, diluted with 600 ml DM water. The solid formed was filtered and washed with another 200 ml of DM water. It was dried at 50°C for 6 h to afford the title compound (**L**) as pale yellow solid. Yield: 38.86 g (86%). Mp: 181-185°C. $^1$HNMR ($CDCl_3$, 300 M Hz): 1.65-1.85 (m, 2H) superimposed on 1.80 (t, 4H), 1.90-2.12 (m, 2H), 2.88 (s, 3H), 3.18-3.29 (m, 2H), 3.45-3.51 (m, 1H), 3.56 (s, 3H), 3.70-3.80 (m, 2H), 4.90 (s, 2H), 5.56 (s, 2H), 7.49-7.55 (m, 1H), 7.73- 7.79 (m, 1H), 7.88 (d, $J$ =8.3 Hz, 1H), 8.05 (d, $J$ =8.3 Hz, 1H). $(M+H)^+$: 499

**Example 4: Preparation of linagliptin (A)**

To a suspension of 1-[(4-methylquinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*S*)-3-azidopiperidinyl)xanthine (**L**) 20.0 g (0.040 mol) in 80 ml of a solvent mixture of tetrahydrofuran and water (9:1), triphenylphosphine (21.0 g, 0.080 mol) was added at ambient temperature and subsequently stirred at 60-65°C for 12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature and subsequently the solvent evaporated. Acetic acid (150 ml, 10%) was added to the reaction mixture and stirred for 1 h at the same temperature. The residue formed was filtered, the filtrate collected (150 ml) and subsequently washed with dichloromethane (3x 20 ml). The pH of the reaction mixture was adjusted to 8.0 with aqueous ammonia solution (~ 6-8 ml). The product was extracted with dichloromethane (3 x 30 ml). The dichloromethane layer was washed with brine

solution (50 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford pale yellow solid. Further recrystallization from a mixture of solvents (dichloromethane and MTBE) afforded the title compound as white solid.

Yield: 38.86 g (75%). Mp: 201-202°C. $^1$HNMR (DMSO-d6, 300 MHz): 1.19-1.30 (m, 1H) 1.60-1.69 (m, 1H), 1.77 (s, 3H), 1.84-1.88 (m, 1H), 2.73-2.83 (m, 2H), 2.88 (s, 3H), 2.96-3.05 (m, 1H), 3.40 (s, 3H), 3.59-3.68 (m, 1H), 4.89-4.90 (m, 2H), 5.30 (s, 2H), 7.64-7.70 (m, 1H), 7.79- 7.81 (d, $J$ =8.3 Hz, 1H ), 7.88-7.94 (m, 1H), 8.24 (d, $J$ =8.3 Hz, 1H). $(M+H)^+$: 473