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Synthesis of Main Impurity of Vildagliptin

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A four-step synthesis of the main impurity of vildagliptin has been easily accomplished with high-yielding starting from L-proline. This compound can be used as a reference marker in an analytical method to determine the chemical purity of the vildagliptin.

Keywords: DPP-IV inhibitors, Vildagliptin, L-proline, Impurity.

INTRODUCTION

As the significant prevalence of type 2 diabetes mellitus (T2DM), numerous reports have documented this wide-spread incidence around the world. Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L-cells in response to meal ingestion, which is a novel pharmacological target with multiple antihyperglycemic actions. The active forms of GLP-1, which include glucose-dependent enhancement of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying and reduction of food intake[1]. However, GLP-1 was extremely rapidly inactivated by the dipeptidyl peptidase IV (DPP-IV), so that the peptide is not immediately clinically applicable and as a therapeutic principle[2]. It was found that DPP-IV inhibitors could enhance the survival of the intactness and biological activity[3] of GLP-1. Not only was DPP-IV inhibition was capable of preventing the N-terminal degradation of GLP-1 completely, but was also associated with the enhancement of its insulinotropic effects[4]. Inhibition of DPP-IV prolongs and enhances the activity of the endogenous GLP-1,which serves as the important prandial stimulators of insulin secretion and the regulators of blood glucose control[5]. A wide range of DPP-IV inhibitors have been developed, several of whose structures and characteristics have been in clinical used in a number of countries recently (Fig. 1), such as sitagliptin[6,7], vildagliptin[8-10], saxagliptin[11,12], alogliptin[13,14] and linagliptin[15,16].

The vildagliptin is one of the important drugs available in the market for the treatment of type 2 diabetes. However, The US FDA as well as European authorities for drug control usually requires the content of an individual impurity in the API (Active Pharmaceutical Ingredient) not to exceed the limit of 0.1 %. The purpose is to achieve maximum safety of use of the medicament in the clinical practice. Therefore, there is a necessity to synthesize vildagliptin with high stereochemical purity. Encouragingly, it has been discovered that the compound **1** (Fig. 2) is very useful as a reference marker for the analysis of vildagliptin or the compositions vildagliptin comprising. Unfortunately, a reliable and scalable synthetic procedure of those compounds has not been developed up to now. Despite two methods reported for synthesis of this compound (**Scheme-I**), but so far, all these methods still have serious demerits.

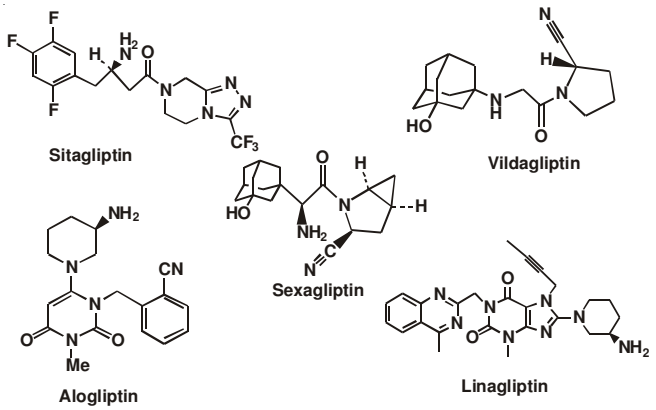

Fig.1. Chemical structures of dipeptidyl peptidase-4 (DPP-4) inhibitors

As mentioned earlier in route 1, Stephen *et al.*[17] developed a strategy for the synthesis of compound **1** using the expensive L-prolinamide (**6**) as a staring material, the overall yield was 47.52 %. However, the purity was not reported and the reaction time was particularly long reach 5 h. As show in the route 2[18], synthesis of this compound involves the use of an expensive starting material L-prolinamide and the reagent TFAA. Moreover, column chromatography has to be used so that the overall yield of isolated product from 6 was extremely

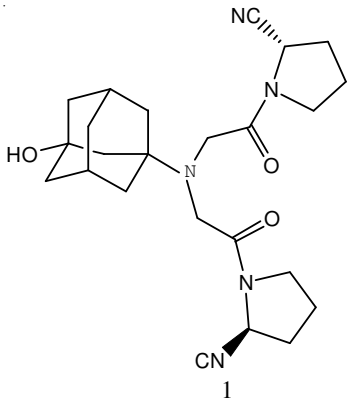

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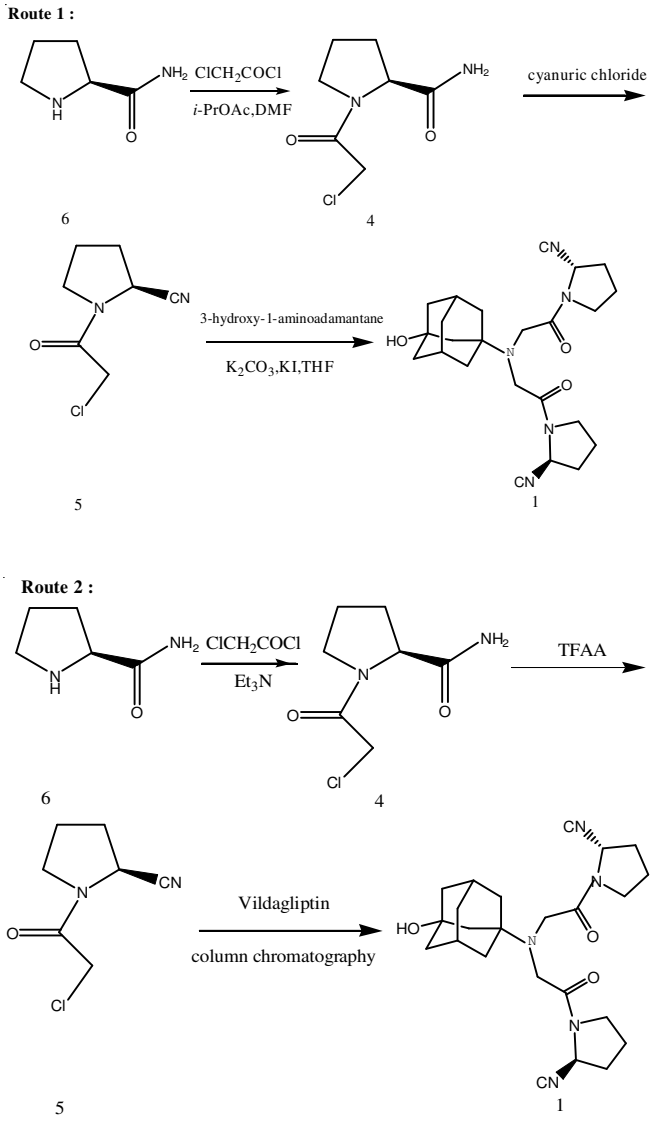
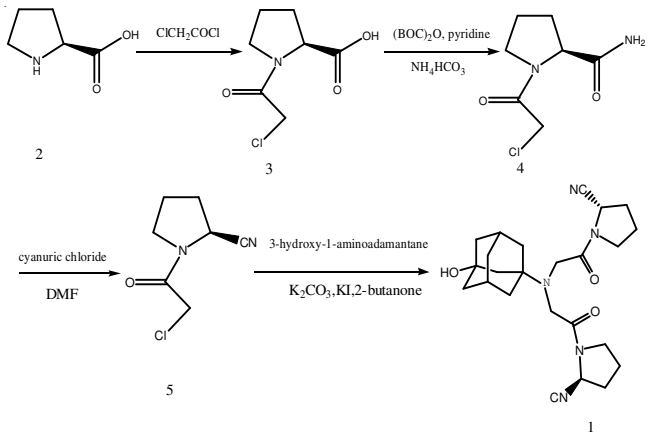
Fig. 2. Major impurity of vildagliptin (**1**)



Scheme-I: Reported methods for the synthesis of compound **1**

low only about 16.2 % and the purity of product was only 95.8 %. Because of the compound **1** can be used as a reference marker in an analytical method to determine the chemical purity of the vildagliptin and compound 5 has become a widely used key intermediate for the synthesis of many DPP-4 inhibitors including vildagliptin. So, a practical, convenient and high-yielding process for the compound **1** is required.



Scheme-II: New methods for the synthesis of compound **1**

EXPERIMENTAL

The compounds synthesized were characterized by NMR, IR, HPLC and LC/MS. ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz). IR spectra were recorded on a Perkin Elmer UK Spectrum one with KBr tablet. LC/MS spectra were recorded on a Agilent 6120 single quadrupole LC/MS (model G6120B) equipped with a Agilent C18 column, 50 × 2.1 mm, 1.8 µm and a ESI (+) scan mode detector. HPLC purity was determined with an Agilent (model 1200) equipped with a Lichrospher C18 column, 250 × 4.6 mm, 5 µm [mobile phase, water:methanol (30:70), 4.38 min, 210 nm, 1.0 mL/min].

Preparation of (S) 1-(2-chloroacetyl)pyrrolidine-2-carboxylic acid (3): L-proline (10 g, 0.087 mol)was added to a round-bottomed flask with THF (100 mL). Then chloroacetyl chloride (10.0 mL, 0.132 mol) was added slowly at 0°C under an argon atmosphere. The mixture was refluxed under stirring for 2.5 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with water (20 mL) and stirred for 20 min. Then saturated brine (20 mL) and ethyl acetate (200 mL) were added and the organic layer was collected. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (100 mL × 2), the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was crystallized by the isopropyl ether to afford compound **3** (15.0 g, 90 %). m.p. 106-108 °C (lit.[21] 108-110.9 °C).

Preparation of (S) 1-(2-chloroacetyl)pyrrolidine-2-carboxamide (4): A mixture of compound **3** (4 g, 0.021 mol), di-*tert*-butyl dicarbonate (5.6 mL, 0.026 mol) and ammonium bicarbonate (9.12 g, 0.12 mol) was added in the MeCN (40 mL) under an argon atmosphere. Pyridine (0.96 mL, 0.012 mol) was added in one portion and the mixture was stirred for 1.5 h at room temperature, The reaction was monitored by TLC (10 % MeOH-CH_2Cl_2). After completing consumption of the starting material, filtered. Evaporation of the solvent gave a residue, which was crystallized by the THF to afford compound **4** (3.3 g, 84.0 %). m.p. 134-136 °C (lit.[21] 133-137 °C).

Preparation of (S) 1-(2-chloroacetyl)pyrrolidine-2-carbonitrile (5): To a stirred solution of the compound **4** (4 g, 0.021 mol) in dry DMF (40 mL), cyanuric chloride (2 g, 0.011 mol) was added at 0 °C and the resulting mixture was stirred

for 4.5 h at room temperature. The reaction was treated with water (100mL) and extracted with ethyl acetate (100 mL).The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (50 mL × 2), The combined organic layers was washed with 5 % sodium bicarbonate and saturated brine solution, dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was crystallized by the isopropyl ether to afford compound **5** (3.33 g, 87 %). HPLC Purity 98 %. m.p. 62-63 °C (lit.[20] 53-57 °C). IR (KBr, ν_{max}, cm^{-1}) : 2952, 2887, 2241, 1655. ^{1}H NMR (300 MHz, $CDCl_3$): 2.15-2.40 (m, 4H), 3.55-3.65 (m, 1H), 3.70-3.80 (m, 1H), 4.07-4.12 (s, 2H), 4.72-4.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 24.5, 25.7, 30.1, 32.5, 41.9, 46.7, 46.7, 46.9, 47.5, 117.4, 164.9, 165.3; MS (ESI$^+$) 173.1(M^++1).

Preparation of (2S)-1-{[{2[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}[(3-hydroxytricyclo[3.3.1.1(3,7)]dec-1-yl)-amino]]acetyl}-pyrrolidine-2-carbonitrile (1): The compound **5** (2.2 g, 0.0127 mol) and 3-hydroxy-1-aminoadamantane (1 g, 6 mmol) were dissolved in 2-butanone (15 mL), then K_2CO_3 (3.3 g, 24 mmol) and KI (50 mg, 0.3 mmol) were added. The resulting reaction mixture was stirred in refluxing for 4 h. After completing consumption of the starting material, filtered. Evaporation of the solvent gave a residue, which was recrystallized by ethyl acetate and methanol (1:1) to afford compound **1** (2 g, 77 %). HPLC Purity 98.17 %. m.p. 182-184 °C (lit[17] 181-183 °C). IR (KBr, ν_{max}, cm^{-1}): 3419, 2920, 2906, 2880, 2851, 2239, 1649, 1450, 1424, 1404, 1311, 1003. ^{1}H NMR (300 MHz, DMSO-d_6) : 1.30-1.68 (m,12H), 1.75-2.38 (m, 10H), 3.10-3.30(m,1H), 3.35-3.87 (m, 6.7H), 4.40-4.50 (m, 1H), 4.57-4.73, (m, 1H);^{13}C NMR (75 MHz, DMSO-d_6): δ 24.4, 28.9, 29.8, 34.4, 37.7, 43.9, 45.7, 45.9, 46.5, 49.9, 57.8, 67.5, 118.5, 170.0; MS (ESI$^+$) 440.3 (M^++1).

RESULTS AND DISCUSSION

In this study (**Scheme-I**), we planned to use L-proline in place of L-prolinamide on account of its easy availability. Furthermore, the chloroacetyl group was used to play the role of a protecting group and it could also avoid being removed. As previously reported in the literature[19], L-proline (**2**) was N-acylated with chloroacetyl chloride in refluxing THF to afford compound **3** and this process should avoid any aqueous media. Finally, we found that an appropriate extension of time to 2.5 h can improve its yield up to about 90 %.

We attempted to convert the carboxylic acid moiety of compound **3** to the amide, but unfortunately, most of these methods had restrictions on the utility and applicability due to the extreme toxicity, cumbersome operation and high costs in the availability of the reagents[20-21]. However, after several attempts, a method was successfully applied to carboxylic acid just simply by using the di-*tert*-butyl dicarbonate-pyridine system[22]. While optimizing the reaction condition, we noted that the solvent and the temperature have significant effects on this process. The compound **3** was treated with di-*tert*-butyl dicarbonate and pyridine (13:6) at room temperature in MeCN followed by ammonium bicarbonate. Thus, the compound **4** was prepared in 84 % yield.

Taking into account our interest for the nitrile synthesis,we investigated the possibility of synthesizing compound **5** with some low cost reagent, such as cyanuric chloride, as dehydration agent of amide[23]. The compound **6** in dry DMF was treated with cyanuric chloride at room temperature, and after the accomplishment of the reaction, the side product was quenched with water and the objective product **6** was isolated from the ethyl acetate extract with saturated aqueous sodium bicarbonate solution. Therefore, the compound **6** was prepared in 87 % yield.

To prepare the ultimate target compound **1**, we started from compound **5** with 3-hydroxy-1-aminoadamantane as the route 1, and we changed the solvent was 2-butanone refluxing under potassium carbonate and potassium iodide condition. According to this method, we avoided the use of expensive vildagliptin as a reaction material and the column chromatography was also avoided been used to isolate the product, meanwhile, the reaction time has been shortened to only 4h and the purity of the product also was improved. Finally, the crude product was purified by recrystallization from ethyl acetate and methanol (1:1) to obtain colorless crystals in 77 % yield.

Thus the method becomes very convenient and gives the desired products in excellent overall yields of 50.64 % and the purity of 98.17 %.

Conclusion

In conclusion, a new practical, convenient and high-yielding method of improving the compound **1** has been developed, which provides material with high quality. This progress almost avoids all the drawbacks, as it does not involve the use of expensive L-prolinamide, TFFA and other non-commercially available reagents. It also delivers the products **5** into a higher yield than previously reported syntheses. This known method will be used in large-scale preparations.

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