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Concise and Efficient Synthesis of Highly Potent and Selective Dipeptidyl Peptidase II Inhibitors

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Abstract: Highly potent and selective DPP II inhibitors N′-(4-Chlorobenzyl)-N′-methyl-4-oxo-4-(1-piperidinyl)-1,3-(*S*)-butane-diamine dihydrochloride **1** and N′-(4-chlorobenzyl)-4-oxo-4-(1-piperidinyl)-1,3-(*S*)-butanediamine dihydrochloride **2** have been efficiently synthesized starting from L-glutamine. A short and high yielding route with simple isolation techniques has been disclosed.

Keywords: DPP II inhibitors, L-glutamine, Hoffmann rearrangement, reductive amination

Dipeptidyl peptidases (DPPs) sequentially release dipeptides from polypeptides. Among these enzymes, DPP II (EC 3.4.14.2) and DPP IV (EC 3.4.14.5) cause the release of N-terminal dipeptides containing proline or alanine at the penultimate position. DPP II and DPP IV are similar with respect to their substrate specificity but differ in other aspects. DPP IV substrates that have recently received special attention are incretins, a class of hormones involved in glucose homeostasis. Inhibition of DPP IV prolongs the in vivo half-life of these incretins (GLP 1 and GIP), and therefore, inhibitors can be valuable in the treatment of type 2 diabetes. Several DPP IV inhibitors are currently under clinical evaluation in this field.[1–3]

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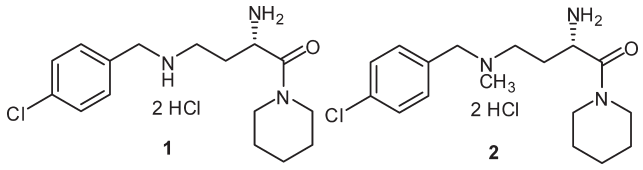


Scheme 1. Most potent and selective DPP-II Inhibitors.

RESULTS AND DISCUSSION

We were not successful in synthesizing sufficient quantities of DPP II inhibitors **1** and **2** known in the literature[4] (Figure 1) for our ongoing research aimed at developing new DPP IV inhibitors. In our hands, the process suffered from low yields and many column purifications. At this point, we felt it necessary to develop some other more practical and general route to synthesize these inhibitors more efficiently. To start with, we selected the much cheaper and abundantly available L-glutamine as our starting material, whereas the original inventors started their synthesis with the much costlier mono-Boc-protected L-2,4-diaminobutyric acid (Boc-L-Dab-OH). Our synthesis started with L-glutamine **3**, which was protected as its Boc derivative **4** by treatment with aq. NaOH and Boc anhydride in quantitative yields. The Hoffmann rearrangement of the amide **4** with both [I,I-bis(triacetoxy)iodo]-benzene (PIDA)[5a] and [I,I-bis(trifluoroacetoxy)iodo]benzene (PIFA)[5c] resulted in low yields of the desired amine **5** and a substantial (∼20–30%) amount of the undesired cyclized product **6** (Scheme 1).

Having failed to enrich the yield of the desired compound **5**, we envisaged formation of amide **7** from carboxylic acid **4** followed by Hoffman rearrangement reaction. Thus, the amide **4** on treatment with dicyclohexylcarbodiimide (DCC) or *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) (both showed similar results), HOBt, and piperidine in acetonitrile resulted in the formation of the amide **7** in 80% yield (Scheme 2). Amide **7** on treatment

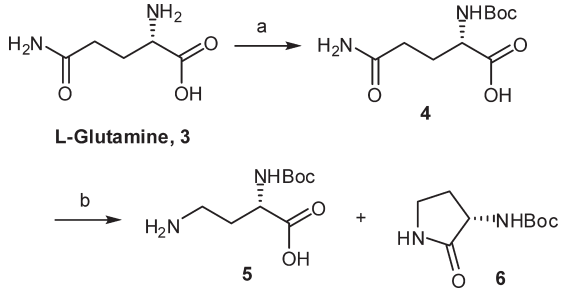
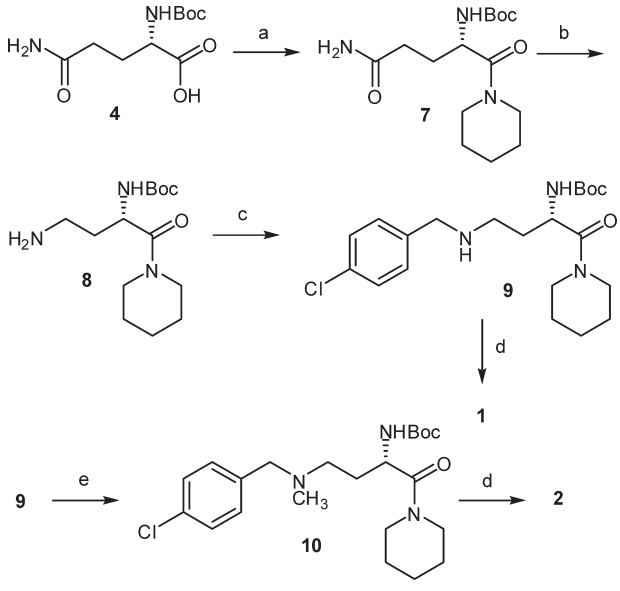


Figure 1. (a) $NaOH/(BOC)_2O$, 0°C to rt, 4 h 87%; (b) $PhI(OAc)_2$, EtOAc, CH_3CN, $H_2O/PhI(OCOCF_3)_2$, CH_3CN, H_2O, 5°C to rt, 4 h.



Scheme 2. (a) DCC or EDC, HOBt, Et_3N, DMF, rt, 81% (b) $PhI(OCOCF_3)_2$, H_2O, CH_3CN, rt, 83% (c) 4-Cl-PhCHO, $NaCNBH_3$, AcOH, MeOH, 0°C to rt, 85% (d) 3N HCl/EtOAc, 0°C to rt, 92–95% (e) Paraformaldehyde, $NaCNBH_3$, AcOH, r.t 84%.

with both PIDA and PIFA in a suitable solvent system afforded amine **8** in 77% yield. The cyclization product **6** was not observed in either of these two reactions. The amine, on reductive amination with 4-chlorobenzaldehyde and $NaCNBH_3$ in methanol, yielded compound **9** in 90% yield. Boc removal from compound **9** with 3 N HCl in ethyl acetate at ambient temperature afforded the desired dihydrochloride salt **1** in quantitative yields. Compound **9** on treatment with paraformaldehyde and $NaCNBH_3$ in acetic acid–methanol, afforded compound **10**. The Boc deprotection of compound **10** with 3 N HCl in ethyl acetate afforded dihydrochloride salt **2** in 75% yield (for two steps). The spectral data of compounds **1** and **2** are in excellent agreement with the reported values.

In conclusion, we have demonstrated a more practical, nonchromatographic, high-yielding, and shorter route for the synthesis of DPP II inhibitors starting from the much cheaper and abundantly available L-glutamine.

EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich or Across. Solvents were dried or distilled prior to use.

Characterization of all compounds was done with ^1H NMR and mass spectrometry. ^1H NMR spectra were recorded on a Bruker Avance 300 spectrometer

(300 MHz). Electrospray (ES+) mass spectra were acquired on an ion trap mass spectrometer. Purity was verified using two diverse high performance liquid chromatography (HPLC) systems using mass and ultra violet (UV) detection. Reversed-phase HPLC was run on a Alliance Waters instrument (model 2695) equipped with Inertsil ODS column 3 V, 250 × 4.6 mm, 5 μm, and UV detector [20–80% acetonitrile (ACN) and phosphate buffer (pH = 3), 40 min, 218 nm, 0.5 mL/min]. Elemental analyses were performed on a ThermoFinnigan instrument and were within 0.4% of the theoretical values.

(2*S*)-5-Amino-2-[(*tert*-butoxycarbonyl)amino]-5-oxopentanoic Acid (4)

A solution of di-tert-butyl dicarbonate [$(Boc)_2O$] (14.0 mL, 60 mmol) in dioxane (40 mL) was added to an ice-cold, magnetically stirred solution of L-glutamine **3** (5.84 g, 40 mmol) in 1 N sodium hydroxide (84 mL) by means of an addition funnel. The two-phase mixture was stirred at 5°C for 30 min and then allowed to warm to rt over 4 h, at which time thin-layer chromatography (TLC) analysis showed completion of the reaction. The mixture was concentrated to half its original volume by rotary evaporation at 35°C, cooled in an ice-water bath, acidified to pH 2–3 by the slow addition of 1 N potassium bisulfate (90 mL), and then extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give Boc-L-glutamine **4** (8.6 g) as a colorless solid in 87% yield. Mp 48.0–49.8°C; m/z (M + 1) 247; ^{1}H NMR ($CDCl_3$) 300 MHz δ 6.36 (bs, 1H), 6.20 (bs, 1H), 5.65 (d, $J = 6.0$ Hz, 1H), 4.35–4.20 (m, 1H), 2.60–2.36 (m, 2H), 2.25–2.0 (m, 2H), 1.44 (s, 9H). Elem. anal. for $C_{10}H_{18}N_2O_5$: C, 39.98; H, 7.54; N, 11.32.

tert-Butyl-[(1*S*)-4-amino-4-oxo-1-(piperidin-1-ylcarbonyl)butyl] Carbamate (5)

[I,I-Bis(triacetoxy)iodo]benzene (3.86 g, 12.0 mmol) was added to a stirred mixture of compound **4** (2.46 g, 10.0 mmol), ethyl acetate (10 mL), acetonitrile (10 mL), and water (10 mL) cooled at 10°C and the reaction mixture was gradually warmed to rt and stirred for 4 h. The volatiles were removed with a rotary evaporator. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to obtain a crude reaction mixture, which was purified by column chromatography to obtain compound **5** (0.1 g) as a viscous liquid. m/z (M + 1) 219; ^{1}H NMR ($CDCl_3$) 300 MHz δ 5.58 (bs, 1H), 4.35–4.25 (m, 1H), 3.5 (t, $J = 6.5$ Hz, 1H), 2.50–2.40 (m, 1H), 2.10–2.0 (m, 1H), 1.28 (s, 9H). Compound **5** also was isolated as off-white solid (0.12 g). m/z (M + 1) 201; ^{1}H NMR

($CDCl_3$) 300 MHz δ 5.80 (bs, 1H), 5.09 (bs, 1H), 4.21–4.19 (m, 1H), 3.43–3.30 (m, 2H), 2.53–2.15 (m, 1H), 2.07–1.90 (m, 1H), 1.45 (s, 9H). Elem. anal. for $C_9H_{18}N_2O_4$: C, 49.23; H, 8.36; N, 12.78.

tert-Butyl-[(1*S*)-4-amino-4-oxo-1-(piperidin-1-ylcarbonyl)butyl] Carbamate (7)

Et_3N (3.5 mL, 25 mmol), HOBt (2.4 g, 18 mmol), DCC (4.0 g, 18 mmol), and piperidine (2 mL, 20 mmol) were sequentially added to a stirred solution of Boc-L-glutamine **4** (4.0 g, 16.3 mmol) in DMF (33 mL) cooled at ice-bath temperature. The reaction mixture was gradually warmed to rt and stirred for 16 h. The reaction mixture was diluted with EtOAc and filtered through a small pad of Celite®. The filtrate was washed with water and brine, then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain a residue, which was triturated with ether, and the combined ether fractions were evaporated under reduced pressure to obtain the product, which was passed through a small pad of silica gel (60–120 mesh) using a 1:1 mixture of EtOAc and hexane to obtain compound **7** (5.5 g) in 81% yield as off-white solid. Mp 136.8–139.3°C; m/z (M + 1) 314; ^{1}H NMR ($CDCl_3$) 300 MHz δ 6.57 (bs, 1H), 5.77 (d, J = 8.0 Hz, 1H), 5.36 (bs, 1H), 4.65–4.55 (m, 1H), 3.61–3.48 (m, 4H), 2.43–2.22 (m, 2H), 2.10–2.0 (m, 1H), 1.75–1.40 (m, 7H), 1.44 (s, 9H). Elem. anal. for $C_{15}H_{27}N_3O_4$: C, 57.28; H, 8.91; N, 13.27.

tert-Butyl-[(1*S*)-3-amino-1-(piperidin-1-ylcarbonyl)propyl] Carbamate (8)

Deionized water (8 mL) was added to a stirred solution of [I,I-bis(trifluoroacetoxy)iodo]benzene (3.36 g, 7.8 mmol) covered with aluminum foil in acetonitrile (8 mL). A solution of carboxamide **7** (1.9 g, 6.0 mmol) in acetonitrile (8 mL) was added, and the reaction mixture was stirred for 4 h. The acetonitrile was removed with a rotary evaporator. The aqueous layer was cooled to ice-bath temperature and acidified to pH 2–3 with 10 N HCl and extracted with diethyl ether. The aqueous layer was cooled again to ice-bath temperature, basified to pH 12–13 with 50% aq. NaOH solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to obtain amine **8** (1.4 g) as a viscous liquid in 83% yield. m/z (M + 1) 286; ^{1}H NMR ($CDCl_3$) 300 MHz δ 5.60 (d, J = 8.4 Hz, 1H), 4.80–4.68 (m, 1H), 3.67–3.30 (m, 4H), 2.90–2.70 (m, 2H), 1.90–1.40 (m, 8H), 1.44 (s, 9H). Elem. anal. for $C_{14}H_{27}N_3O_3$: C, 58.67; H, 9.64; N, 14.59.

tert-Butyl-(*S*)-4-(4-chlorobenzylamino)-1-oxo-1-(piperidine-1-yl) butan-2-yl Carbamate (9)

Acetic acid (1.0 mL, 17.5 mmol), 4-chlorobenzaldehyde (0.49 g, 3.5 mmol), and $NaCNBH_3$ (0.22 g, 3.5 mmol) were added to a stirred solution of **8** (1.0 g, 3.5 mmol) in methanol (14 mL) cooled at 0°C. The reaction mixture was gradually warmed to rt and stirred for 16 h. The volatiles were removed under reduced pressure; the residue was diluted with 2 N HCl (10 mL) and extracted with diethyl ether. The aqueous layer was cooled to ice-bath temperature, basified to pH 12–13 with aq. 50% sodium hydroxide solution, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain compound **9** (1.2 g) as a viscous liquid in 85% yield. m/z (M + 1) 410; ^{1}H NMR ($CDCl_3$) 300 MHz δ 7.32–7.18 (m, 4H), 5.63 (d, $J = 8.2$ Hz, 1H), 4.75–4.65 (m, 1H), 3.74 (d, $J = 6.2$ Hz, 2H), 3.60–3.35 (m, 4H), 2.85–2.68 (m, 2H), 2.15–2.05 (m, 1H), 1.90–1.80 (m, 1H), 1.75–1.50 (m, 6H), 1.43 (s, 9H). Elem. anal. for $C_{21}H_{32}ClN_3O_3$: C, 61.62; H, 7.93; N, 10.36.

(3*S*)-*N*1-(4-Chlorobenzyl)-4-oxo-4-piperidin-1-ylbutane-1,3-diamine (1)

3 N HCl (5 mL) was added to compound **9** (0.35 g, 0.86 mmol) placed at ice-bath temperature, and the resultant mixture was stirred at rt for 2 h. The volatiles were removed under reduced pressure, and the product was triturated several times with diethyl ether to obtain compound **1** (0.31 g) in 95% yield. m/z (M + 1) 310; ^{1}H NMR (DMSO-d_6) 300 MHz δ 9.85 (bs, 1H), 9.62 (bs, 1H), 8.40 (bs, 3H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 2H), 4.65–4.53 (m, 1H), 4.14 (bs, 2H), 3.60–3.34 (m, 4H), 3.17–3.03 (m, 1H), 3.03–2.90 (m, 1H), 2.30–2.05 (m, 2H), 1.68–1.40 (m, 6H). Elem. anal. for $C_{16}H_{24}ClN_3O$: C, 62.17; H, 7.97; N, 13.45.

tert-Butyl-(*S*)-4-(*N*-chlorobenzyl)-*N*-methylamino)-1-oxo-1-(piperidine-1-yl)butan-2-yl Carbamate (10)

Paraformaldehyde (0.15 g) and $NaCNBH_3$ (70 mg, 1.1 mmol) were added to a stirred solution of compound **9** (0.15 g, 0.37 mmol) in methanol (1.5 mL) and acetic acid (0.11 mL) cooled at 10–15°C. The reaction mixture was stirred for 16 h, and the volatiles were removed under reduced pressure. The residue was diluted with 2 N HCl (4 mL) and extracted with diethyl ether. The aqueous layer was cooled to ice-bath temperature, basified to pH 12–13 with aq. 50% NaOH solution, and extracted with EtOAc. The combined organic

layer were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to obtain compound **10** (0.13 g) in 84% yield as a viscous liquid. This compound was used for the deprotection of the Boc group without further purification and characterization.

(3*S*)-*N*1-(4-chlorobenzyl)-*N*1-methyl-4-oxo-4-piperidin-1-ylbutane-1,3-diamine (2)

3 N HCl (1 mL) was added to compound **10** (0.1 g, 0.24 mmol) placed in a ice bath, and the resultant mixture was stirred at rt for 2 h. The volatiles were removed under reduced pressure, and the product was triturated several times with diethyl ether to obtain compound **2** (0.11 g) in 92% yield. The spectral data of this compound is in excellent agreement with the reported compound.[4]

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