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Novel Synthesis of Heterocycle-Containing Adamantane Derivatives

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A novel approach to synthesize the of heterocycle-containing adamantane derivatives 1-{[(3-hydroxy-1-adamantyl)amino]acetyl}-2-cyano-(S)-pyrrolidine and N-{2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl}adamantane-1-carboxamide, which were effective in treatment of diabetes and depression respectively, have been described. The target compounds were synthesized by raw materials of inexpensive L-proline and available 1-(2-pyrimidinyl) piperazine respectively. Compared with traditional synthetic routes, the method provides several advantages such as inexpensive and readily available raw materials, convenient manipulation and high yield.

Key Words: Adamantane, Synthesis, Vildagliptin, Adatanserin.

INTRODUCTION

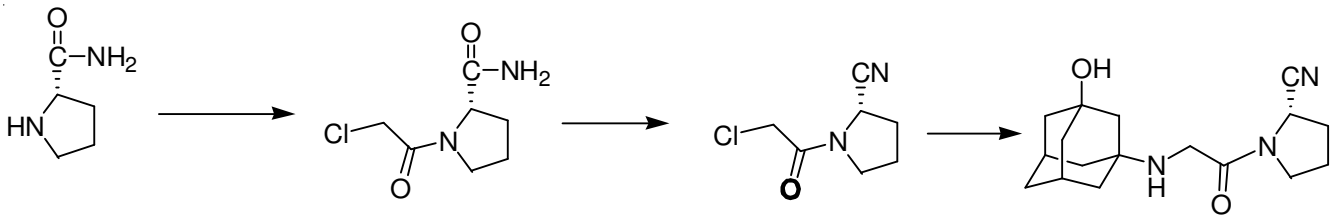
Adamantane is an extremely interesting compound and can entirely affect the ADME (absorption, distribution, metabolism, excretion) properties for the design of drugs based on a lead molecule[1-3]. The antiviral action of l-adamantanamine hydrochloride first detected, served as an impetus to the wide pharmacological study of adamantane derivatives. With the psychopharmacological properties, these kinds of compounds are usually used as antidepressants, antidiabetic and antiparkinsonian medications in clinical practice[4-6].

In recent years, there has been significant interest in the inhibition of dipeptidyl peptidase IV (DPP-IV) which proved to be lower blood glucose levels, increase glucose tolerance and improve insuin response in patients with type 2 diabetes. The vildagliptin **3** containing adamantane was best known example, which is a highly potent, orally available reversible DPP-IV inhibitor as new treatment option for type-II diabetes[7]. The approach to vildagliptin has been described in the literature[7-9] shown in **Scheme-I**, but the need for expensive starting L-prolinamine and the low overall yield (20.8 %) indicate that alternative synthese is still required. In order to develop a more efficient and general route, The vildagliptin was synthesized from inexpensive L-proline and one-pot synthesis would be utilized in the last two conversions shown in **Scheme-II** and the overall yield was raised to 44.2 %.

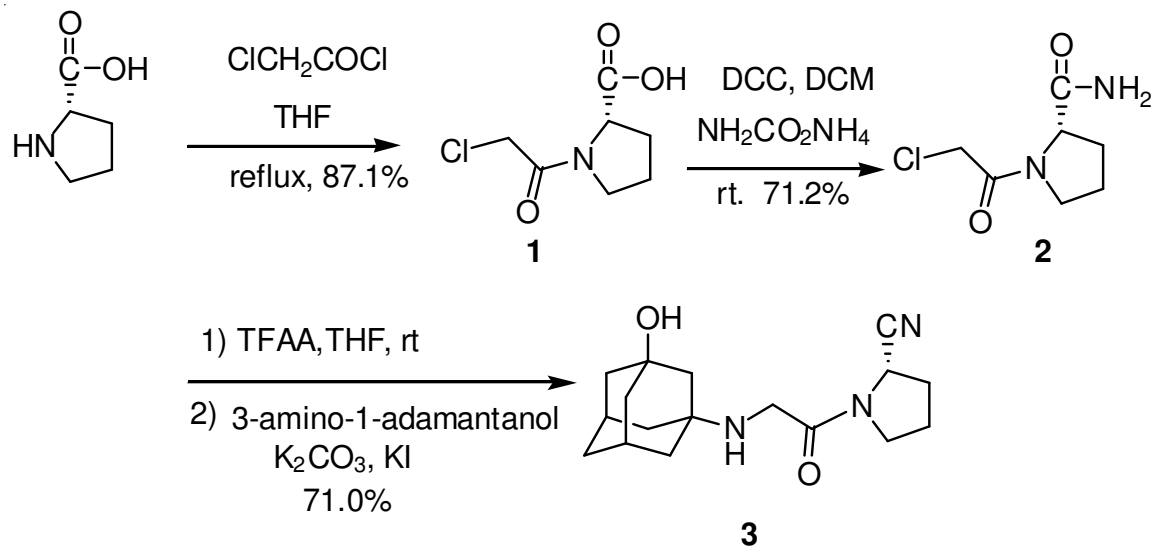
Adatanserin **6**, an adamantane derivative, is the selective 5-HT_{1A} agonist and 5-HT_{2A} antagonist as an efficient antidepressant accompanied by significant anxiolytic activity and also an effective neuroprotectant agent[10]. It was directly prepared by adamantanecarbonyl chloride and 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethylamine in the previous approach[11,12] shown in **Scheme-III**, while the intermediate of 2-[4-(2-pyrimidinyl)-1-piperazinyl]ethylamine is unavailable, we wished to report a practical and convenient method for the synthesis of Adatanserin using available materials of 1-(2-pyrimidinyl)piperazine, through N-alkylation, Gabriel hydrolysis and amidation, which was shown in **Scheme-IV**.

EXPERIMENTAL

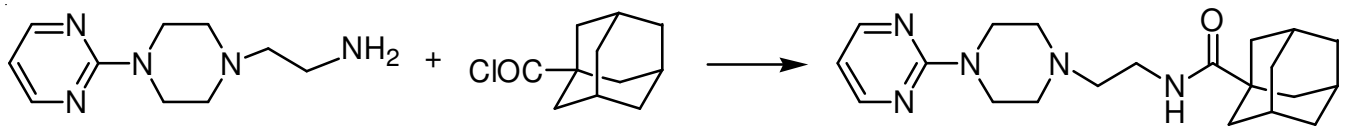
All compounds were characterized by ^{1}H NMR, IR spectra. Melting points were determined with a WRS-1B melting point



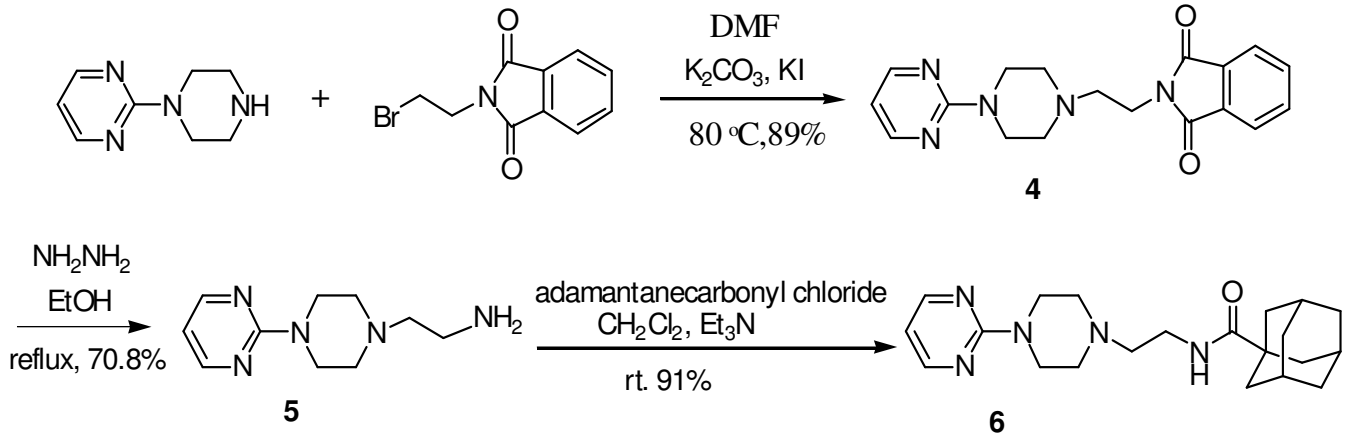
Scheme-I: Previous approach for synthesis of vildagliptin



Scheme-II: Synthesis of vildagliptin



Scheme-III: Previous approach for synthesis of adatanserin



Scheme-IV: Synthesis of adatanserin

apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercucy-Plus 300 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Elemental analyses were performed for C, H and N using an Elementar Vario EL-III element analyzer.

(S)-1-(2-Chloroacetyl)pyrrolidine-2-carboxylic acid (1): To a flask containing L-proline (25.0 g, 0.217 mol) and dry THF (250 mL) was added chloroacetyl chloride (32.7 mL, 0.434 mol) at room temperature. The mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into water (15 mL) and filtered for 0.5 h. Saturated brine (20 mL) and ethyl acetate (100 mL) were added and the aqueous layer was extracted with ethyl acetate (40 mL × 2). The combined organic extracts were dried and concentrated *in vacuo*.The residue was stirred in diisopropyl ether (80 mL) for 0.5 h at room temperature and the mixture was then cooled to 0 ºC. The precipitated white solid was filtered and washed with diisopropyl ether to afford white solid (36.2 g, 87.1%), m.p. 106-108 ºC, $[\alpha]^{20}$-0.884 (c 1.00 g/100 mL, anhydrous ethanol), ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.90-2.45 (m, 4H), 3.52-3.71 (m, 2H), 4.01-4.10 (m, 2H, CH_2Cl), 4.61-4.62 (m, 1H, CHCOOH), 7.49 (brs, 1H, COOH); IR (KBr, ν_{max}, cm^{-1}): 3422, 2968, 2836, 1756, 1645, 1438, 1399; Anal. calcd. for $C_7H_{10}NO_3Cl$: C 43.88, H 5.26, N 7.31. Found: C 43.21, H 5.24, N 7.29.

(S)-1-(2-Chloroacetyl)pyrrolidine-2-carboxamide (2): To a solution of compound **1** (20 g, 0.104 mol) in dichloromethane (200 mL) was slowly added a solution of dicyclohexylcarbodiimide (21.7 g, 0.104 mol) in dichloromethane (40 mL) in ice bath and the mixture was stirred at room temperature for 5 h. Then, ammonium carbamate (41 g, 0.525 mol) was added and the mixture was stirred for 6 h at room temperature.

After completion of the reaction, the mixture was filtered and the residue was washed with dichloromethane. The filtrates were collected, combined and concentrated under vacuum. The residue was dissolved in acetone (30 mL) and cooled to 0 ºC and the mixture was filtered and concentrated *in vacuo*. The crude product was recrystallized from mixture solution of diisopropyl ether and THF to afford white solid (14.2, 71.2 %), m.p.133-135 ºC (Lit[9] m.p. 132-137 ºC), $[\alpha]^{20}$-0.736 (c 1.00 g/100 mL, anhydrous ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.94-2.34 (m, 4H), 3.56-3.73 (m, 2H), 4.00-4.10 (m, 2H, CH_2Cl), 4.53-4.57 (m, 1H, $CHCONH_2$); IR (KBr, ν_{max}, cm^{-1}): 3383, 3164, 2980, 1683, 1653, 1418; Anal. calcd. for $C_7H_{11}N_2O_2Cl$: C 44.10, H 5.82, N 14.70. Found: C 44.91, H 5.84, N 14.76.

(2S)-1-{[(3-Hydroxy-1-adamantanyl)amino]acetyl}-2-pyrrolidinecarbonitrile (3): To a solution of compound **2** (10 g, 0.052 mol) in dry THF (100 mL) was slowly added trifluoroacetic anhydride (10.9 g, 0.052 mol) in ice bath and the mixture was stirred at room temperature for 2 h to afford yellow solution. A mixture of 3-amino-1-adamantanol (8.0 g, 0.052 mol) in THF (100 mL), potassium iodide (0.8 g, 0.005 mol) and potassium carbonate (36.1 g, 0.260 mol) was slowly added the yellow solution of above step at 40 ºC during 1.5 h, then stirred for 2 h, refluxed for 5 h and filtered. After addition of saturated brine, the aqueous layer extracted with ethyl acetate. The combined organic extracts were dried and concentrated under vacuum. The crude product was recrystallized from mixture solution of butanone and ethyl acetate to give white solid (11.3 g, 71.0 %), m.p. 140-142 ºC (Lit[7] m.p. 138-140 ºC), $[\alpha]^{20}$ 0.812 (c 1.00 g/100 mL, anhydrous ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.53-1.66 (m, 12H), 1.81 (m, 2H), 2.15-2.20 (m, 2H), 2.27-2.30 (m, 4H), 3.41-3.50 (m, 3H), 3.56-3.63 (m, 1H), 4.85-4.87 (m, 1H); IR (KBr, ν_{max}, cm^{-1}): 3408, 3293, 2914, 2849, 2237, 1657, 1405; Anal. calcd. for $C_{17}H_{25}N_3O_2$: C 67.30, H 8.31, N 13.85. Found: C 67.13, H 8.29, N 13.89.

N-{2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl}phthalimide (4): 1-(2-Pyrimidinyl)piperazine (4.6 g, 0.028 mol) and DMF (75 mL) were placed in a three-necked. Potassium iodide (1.0 g, 0.006 mol), potassium carbonate (7.8 g, 0.056 mol) and N-(2-bromoethyl)phthalimide (7.1 g, 0.028 mol) were added to the mixture and stirred for 15 h at 80 ºC. The hot mixture was filtered and concentrated under vacuum. After addition of saturated brine and dichloromethane to residue, the layers were separated, the organic layer was collected and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried and concentrated under vacuum. The crude product was recrystallized from isopropyl alcohol to afford white solid (10.75 g, 89 %), m.p. 125-126 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.46 (t, *J* = 5.2 Hz, 4H), 2.56 (t, *J* = 6.1 Hz, 2H), 3.62 (t, *J* = 4.8 Hz, 4H, CH_2N-Ar), 3.72 (t, *J* = 6.3 Hz, 2H, CH_2N-imide), 6.57 (t, *J* = 4.7 Hz, 1H), 7.79-7.89 (m, 4H, Ph-H), 8.30 (d, *J* = 4.7 Hz, 2H). IR (KBr, ν_{max}, cm^{-1}): 1709, 1588, 1396, 716; Anal. calcd. for $C_{18}H_{19}N_5O_2$: C 64.08, H 5.68, N 20.76. Found: C 63.89, H 5.66, N 20.70.

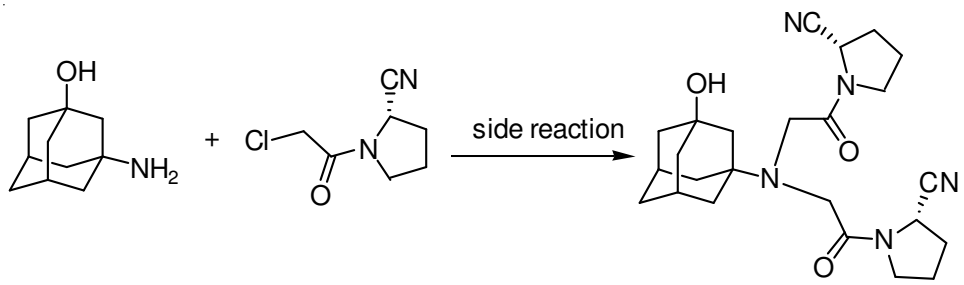
2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethylamine (5): A mixture of compound **4** (2.0 g, 0.006 mol) in ethanol and 99 % hydrazine hydrate (1.5 mL, 0.030 mol) was reflux for 12 h, cooled to room temperature, filtered and concentrated under vacuum. Water and chloroform was added to the residue adjusting to alkaline with 2 mol/L sodium hydroxide. The mixture was extracted with chloroform (3 × 30 mL) and organic extracts were dried. Then the mixture was added a few drops of concentrated hydrochloric acid, concentrated and dried under vacuum to give a little yellow monohydrochloride salt solid (1.0 g, 70.8 %), m.p. 204-207 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.00 (t, *J* = 4.3 Hz, 4H), 3.09 (t, *J* = 7.6 Hz, 2H), 3.25 (t, *J* = 7.3 Hz, 2H, CH_2-NH_2), 3.78 (t, *J* = 4.1 Hz, 4H), 6.65 (t, *J* = 4.7 Hz, 1H, Ar-H), 8.30 (d, *J* = 4.7 Hz, 2H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 2979, 2856, 1589, 1519, 1360; Anal. calcd. for $C_{10}H_{18}N_5Cl$: C 49.28, H 7.44, N 28.73. Found: C 49.45, H 7.42, N 28.68.

N-{2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl}adamantane-1-carboxamide (6): Triethylamine (2.6 mL, 0.018 mol) was added to compound **5** (1.8 g, 0.009 mol) in dichloromethane (40 mL) under an nitrogen atmosphere. The stirring solution was placed in an ice bath and adamantinecarbonyl chloride (2 g, 0.010 mol) in dichloromethane (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was washed with water and concentrated under vacuum to give yellow solid which was recrystallized from the mixed solvent of ethanol and water to afford yellow solid (3.0 g, 91 %). m.p. 162-163 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.67-1.86 (m, 12H), 2.03-2.05 (m, 3H), 2.50-2.56 (m, 6H), 3.33 (t, *J* = 6.1 Hz, 2H), 3.81 (t, *J* = 5.0 Hz, 4H), 6.27 (brs, 1H), 6.48 (t, *J* = 4.7 Hz, 1H, Ar-H), 8.28 (d, *J* = 4.7 Hz, 2H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3395, 2902, 2849, 1645, 1583, 1545, 1479; Anal. calcd. for $C_{21}H_{31}N_5O$: C 68.26, H 8.46, N 18.95. Found: C 68.31, H 8.43, N 18.60.

RESULTS AND DISCUSSION

The influences of catalysts, mole ratio of the reactants and reaction times of the reaction on the yield of compound **1** (S)-1-(2-chloroacetyl)pyrrolidine -2-carboxylic acid were investigated. The results were shown in Table-1. In this amidation reaction, the catalyst was added to increase the reaction rate, the reaction time was shortened, but also caused an increase in side reactions. Table-1 shows that without catalysts in the case of slightly extended time, it will cause the reaction to proceed sufficiently, in order to avoid the generation of side products, the catalyst was not added as the best choice. When L-proline was converted into the compound **1** N-acylated with chloroacetyl chloride, we found the quantity of chloroacetyl chloride had great influence on the yield. When the amount of chloroacetyl chloride increased to 1.8 equivalent, L-proline was completely dissolved in solution and the yield of compound **1** increased to 87.4 %. Because the amine and carboxyl group of L-proline could react with acyl chloride, in this step adding more than 1 equivalent of acyl chloride could make the amidation complete. Then we hydrolyzed the anhydride by adding water and stirring for 0.5 h to achieve the compound **1**.

While preparation of compound **2** had reported earlier[9], the carboxylic acid was converted to the amide **2** with DCC and amination reagents in anhydrous solvent in our approach. By using different amination reagents such an ammonium



Scheme-V: Side reaction of twice N-alkylation

TABLE-1
INFLUENCE OF REACTION CONDITION ON YIELD OF COMPOUND **1**

No.	Catalysts	Time (h)	Ratio (mol/mol)	Yield (%)
1	/	3	1:1	52.3
2	Triethylamine	1	1:2	50.4
3	Triethylamine and DMAP	0.5	1:3	52.2
4	/	3	1:1.2	52.9
5	/	3	1:1.4	59.3
6	/	3	1:1.6	68.7
7	/	3	1:1.8	87.4
8	/	3	1:2	85.6

Ratio = L-proline (mol)/chloroacetyl chloride (mol)

bicarbonate, ammonium carbonate, ammonium carbamate, we found ammonium carbamate gave highest yield of 71.2 %, as ammonium carbamate was the most instable and easily released ammonia gas. The last step contained two conversion procedures of amide dehydration and N-alkylation.

One-pot synthesis was adopted to prepare target compound **3** with the solvent THF, which reduced the tedious separation and purification and avoided the loss of intermediate product in the last step. The difficulty for final procedure of N-alkylation was that side product of twice N-alkylation was generated and increase complicated workup for purification. The process of control side product was further investigated through reaction time and temperature in two phase to obtain target compound, the result were showed in Table-2. It showed that the reaction had a high yields of 71.0 % at a constant temperature of 35 ºC for 2 h, refluxed for 5 h. The side reaction was shown in **Scheme-V**.

TABLE-2
INFLUENCE OF REACTION TIME ON YIELD OF COMPOUND **3**

No.	Reaction time (h)	Reflux process time (h)	Yield (%)
1	1	3	57.4
2	1	5	65.6
3	1	7	61.3
4	2	5	71. 0
5	3	5	68.2
6	4	5	67.3

As to the synthesis of adatanserin **6**, the preparation of adatanserin from compound **5** was reported[11]. Because compound **5** was unavailable, our task here is to find a convenient and high yield method to prepare it. In order to figure out it, we designed that the group of ethylamino would be connected with N atom of piperazine ring to form C-N bone using Gabriel reaction. The synthesis method was started with 1-(2-pyrimidinyl)piperazine and N-(2-bromoethyl) phthalimide at 80 ºC for 15 h to afford the new intermediate **4** in a good yield (89%). Then compound **4** was hydrolyzed by hydrazine hydrate under refluxed for 12 h in ethanol and compound **5** was easily obtained. In the last step, compound **5** was treated with adamantanecarbonyl chloride following the literature with slight modification in excellent yield of 91 %. The compound **6** was recrystallized with mixed solvent of ethanol and water instead of silica column.

Conclusion

We have developed alternative and effective routes of two adamantane derivatives. Vildagliptin was prepared with inexpensive material L-proline instead of the expensive L-prolinamine, by three steps in total yield of 44.2 % compared to the 20.8 % of existing method. In addition, we synthesized Adatanserin starting from readily available 1-(2-pyrimidinyl) piperazine in total yield of 47.2 % and Gabriel reaction was introduced to prepare key intermediate amine **5** under mild condition.

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