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Synthesis of the major metabolites of Tolvaptan

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Abstract

Tolvaptan is a nonpeptide arginine vasopressin (AVP) V_2-receptor antagonist and used in the treatment of heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone secretion or other high-volume capacity of hyponatremia. The metabolites of tolvaptan are mainly produced by CYP_3A_4, including two major compounds named DM-4103 and DM-4107. Herein, the chemical synthesis of those two metabolites is described in this article for further study.

Keywords: Tolvaptan; Metabolites; Synthesis

Tolvaptan (*N*-[±-4-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-3-methylphenyl]-2-methyl-benzamide) was researched and developed by Otsuka Pharmaceutical Company of Japan (Otsuka Pharm) [1]. As the only oral selective V_2 receptor antagonist, Tolvaptan made great progress in the treatment of heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone secretion and other high-volume capacity of hyponatremia [2–4].

Tolvaptan is metabolized by the CYP_3A_4 in the liver. However, till date the pharmacokinetic data for its metabolites in human is still limited. Meanwhile, many side effects such as polyuria and pollakiuria were reported [5,6]. Therefore, it is essential to investigate the pathway and the metabolites of tolvaptan in human. We are particularly interested in two main metabolites of tolvaptan *in vivo* named DM-4103 and DM-4107 (Fig. 1) [7]. To the best of our knowledge, there is no report on the synthesis of those two important compounds yet.

Retrosynthetic analysis (Fig. 2) led us to compound **i** as the key intermediate. It has been reported that *N*-acetyl-*p*-toluidine cannot be acetylated [8]. Here, we found that *N*-(4-chlorophenyl)acetamide still cannot be acetylated under any F–C conditions. Thus, we tried another way to synthesis **i** involved using 4-chloroaniline as the starting material, which was coupled with succinic anhydride to form amide **2** as shown in Scheme 1. Jarikote et al. have reported that compound **2** can be cycled to get **3** by heating in PPA/AcOH [9]. However, the ^{1}H NMR spectra indicated a product with a highly symmetrical structure. Combined with the MS, the final product proved to be **4** actually.

As shown in Scheme 2, after aldol condensation and nitration reaction, we successfully synthesized compound **3a** in 57.6% yield, the next step requires reducing **3a** to get **i**. A number of reducing conditions were investigated, including reduction catalyzed by PtO_2, Pt, and Raney Ni/N_2H_4·H_2O. However, all attempts leaded to complicate

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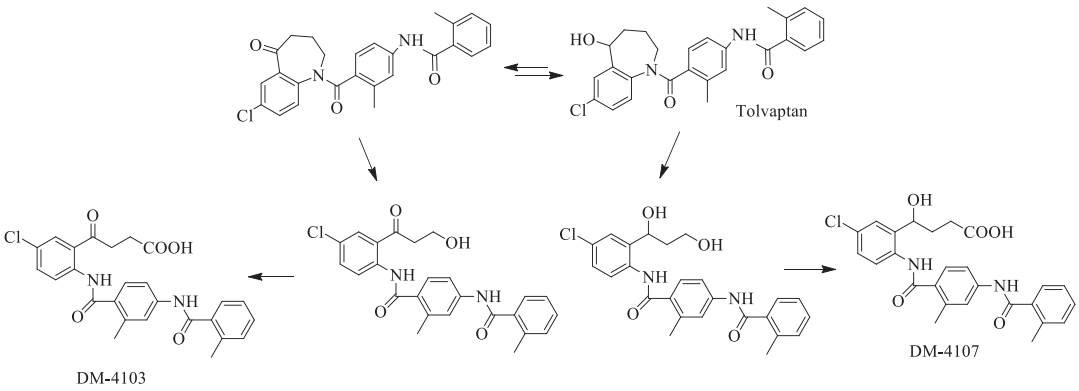


Fig. 1. Proposed metabolic pathway of tolvaptan in humans.

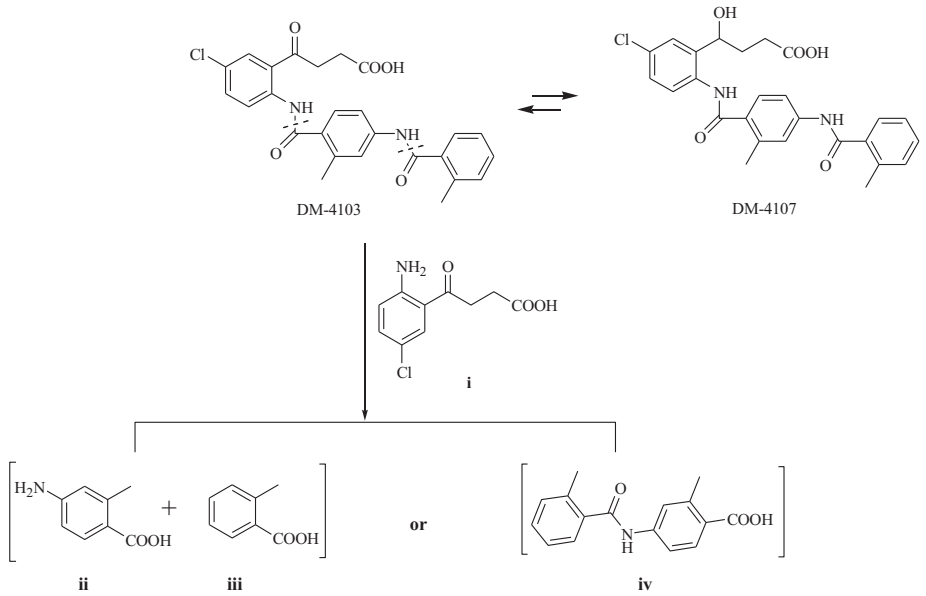
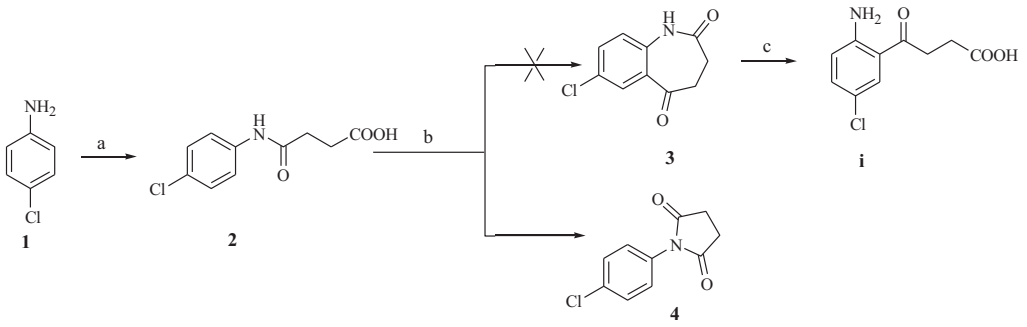


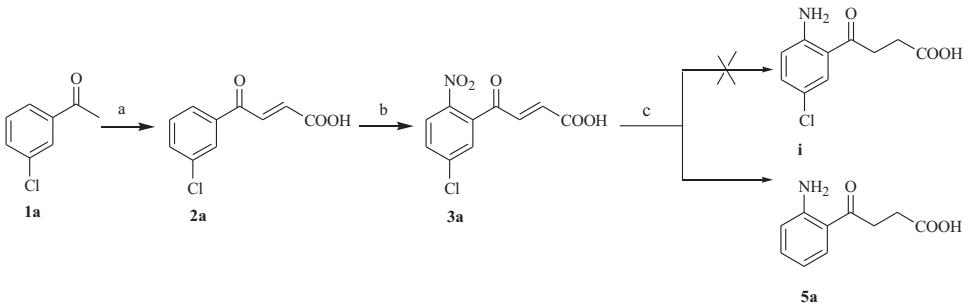
Fig. 2. Retrosynthetic analysis of the metabolites.

results. When using Pd/C as the catalyst, the main product is compound **5a**. In this case it is necessary to separate the reduction into two single steps.

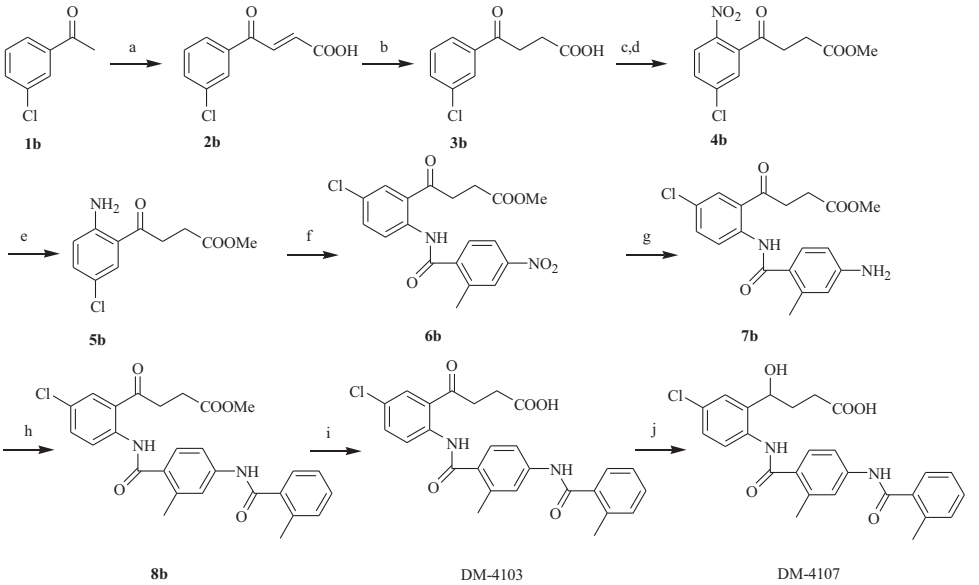
Then we went though a lot of effort to find a convenient and efficient route to synthesis DM-4103 and DM-4107 (Scheme 3). First, condensation of 1-(3-chlorophenyl)ethanone with the 2-oxoacetic acid gave compound **2**. Compound **2**



Scheme 1. Reagents and conditions: (a) succinic anhydride, acetone, rt, 95%; (b) PPA, AcOH, reflux, 2 h; (c) aqueous HCl.



Scheme 2. Reagents and conditions: (a) glyoxylic acid monohydrate, concd. H_2SO_4, 1,4-dioxane, reflux, 80%; (b) HNO_3, concd H_2SO_4, −20 °C, 72%; (c) H_2, 5% Pd/C, EtOH, rt, 62%.



Scheme 3. Reagents and conditions: (a) glyoxylic acid monohydrate, concd. H_2SO_4, 1,4-dioxane, reflux, 80%; (b) Zn, CH_3COOH/H_2O = 27:1, rt, 91%; (c) HNO_3, concd. H_2SO_4, −20 °C, 72%; (d) MeOH, H_2SO_4, reflux, 95%; (e) H_2, 1% Pt/C, EtOH, 85%; (f) 2-methyl-4-nitrobenzoyl chloride, pyridine, DCM, 87%; (g) H_2, 1% Pt/C, EtOH, rt, 88%; (h) 2-methylbenzoyl chloride, Et_3N, DCM, rt, 89%; (i) 10% NaOH, MeOH, rt, 95%; (j) $NaBH_4$, MeOH, rt, 96%.

was then reduced to give **3**, which was converted to compound **4** *via* nitration reaction in concentrated sulfuric acid and nitric acid. Finally, we obtained the key intermediate **5** from **4** through hydrogenation catalyzed by 1% Pt.

The condensation of intermediate **5** with 2-methyl-4-nitrobenzoic acid was catalyzed by pyridine to afford **6**. After reducing the nitro into the free amino **7**, the intermediate was then condensated with 2-methylbenzoic acid to give **8**. The following hydrolysis of **8** in methanol solution of sodium hydroxide got the target compound DM-4103, which can easily be reduced into DM-4107 by sodium borohydride in excellent yield. Both of those two target compounds were confirmed by elemental analyses, IR, NMR and MS data analysis [10].

In summary, we herein reported the synthesis of tolvaptan main metabolites, 4-(5-chloro-2-(2-methyl-4-(2-methylbenzamido)benzamido)phenyl)-4-oxobutanoic acid DM-4103 and 4-(5-chloro-2-(2-methyl-4-(2-methylbenzamido)benzamido)phenyl)-4-hydroxybutanoic acid DM-4107, which are crucial for our future *in vivo* studies on the metabolism of tolvaptan.

Acknowledgment

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[10] Physical and spectral data of the target compounds. DM-4103: Mp: 230–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (br, 1H), 11.41 (s, 1H), 10.50 (s, 1H), 8.41 (d, 1H, J = 8.8 Hz), 8.09 (d, 1H, J = 2.4 Hz), 7.70–7.72 (m, 3H), 7.56 (d, 1H, J = 7.6 Hz), 7.48 (d, 1H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.2), 7.31 (t, 2H, J = 7.6), 3.31–3.35 (m, 4H), 2.57 (t, 2 H, J = 6.4 Hz), 2.43 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 19.557, 20.393, 28.345, 35.152, 39.073, 117.097, 121.969, 123.037, 125.925, 126.824, 127.213, 127.423, 127.518, 128.236, 130.066, 130.741, 130.827, 133.734, 135.556, 137.162, 137.655, 137.872, 141.500, 167.410, 168.404, 174.009; HRMS calcd. for $C_{26}H_{23}ClN_2O_5$ m/z: 478.1295. Found: 501.1120 $[M+Na]^+$. Anal. Calcd. for $C_{26}H_{23}ClN_2O_5$: C, 65.20; H, 4.84; Cl, 7.40; N, 5.85. Found: C, 65.14; H, 4.58; Cl, 7.45; N, 5.90. DM-4107: Mp: 144–146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.44 (s, 1H), 9.99 (s, 1H), 7.77 (d, 1H, J = 8.4 Hz), 7.67–7.69 (m, 2H), 7.53 (d, 1H, J = 7.6 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.30–7.43 (m, 5H), 4.84 (d, 1H, J = 4.4 Hz), 2.43 (s, 3H), 2.39 (s, 3H), 2.24-2.31 (m, 2H), 1.89 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 19.651, 20.362, 30.908, 33.010, 69.408, 116.971, 121.795, 126.015, 126.837, 127.133, 127.277, 127.559, 128.255, 129.448, 130.113, 130.908, 131.623, 134.574, 135.583, 137.265, 137.341, 140.445, 140.976, 167.760, 168.433, 174.851; HRMS calcd. for $C_{26}H_{23}ClN_2O_5$ m/z: 480.1452. Found: 503.1355 $[M+Na]^+$; Anal. Calcd. for $C_{26}H_{25}ClN_2O_5$: C, 64.93; H, 5.24; Cl, 7.37; N, 5.82. Found: C, 64.66; H, 5.35; Cl, 7.54; N, 5.62.