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NOVEL AND PRACTICAL SYNTHESIS OF CANDESARTAN CILEXETIL

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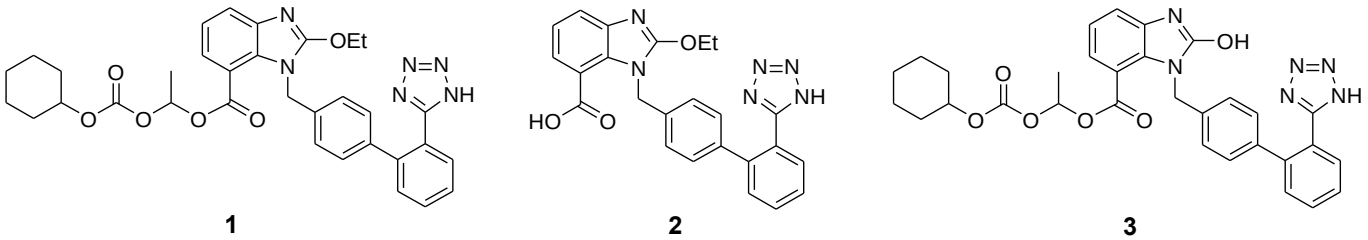
Abstract – A novel and convergent synthetic route of candesartan cilexetil (API of Atacand), an effective angiotensin II receptor blocker, is described. Cleavage of the *N*-Boc and *N*-trityl protective group are implemented simultaneously and formation of the benzimidazole ring is conducted at the last step of this route, which gives candesartan cilexetil in 55% yield over six steps with 99.1% purity (HPLC).

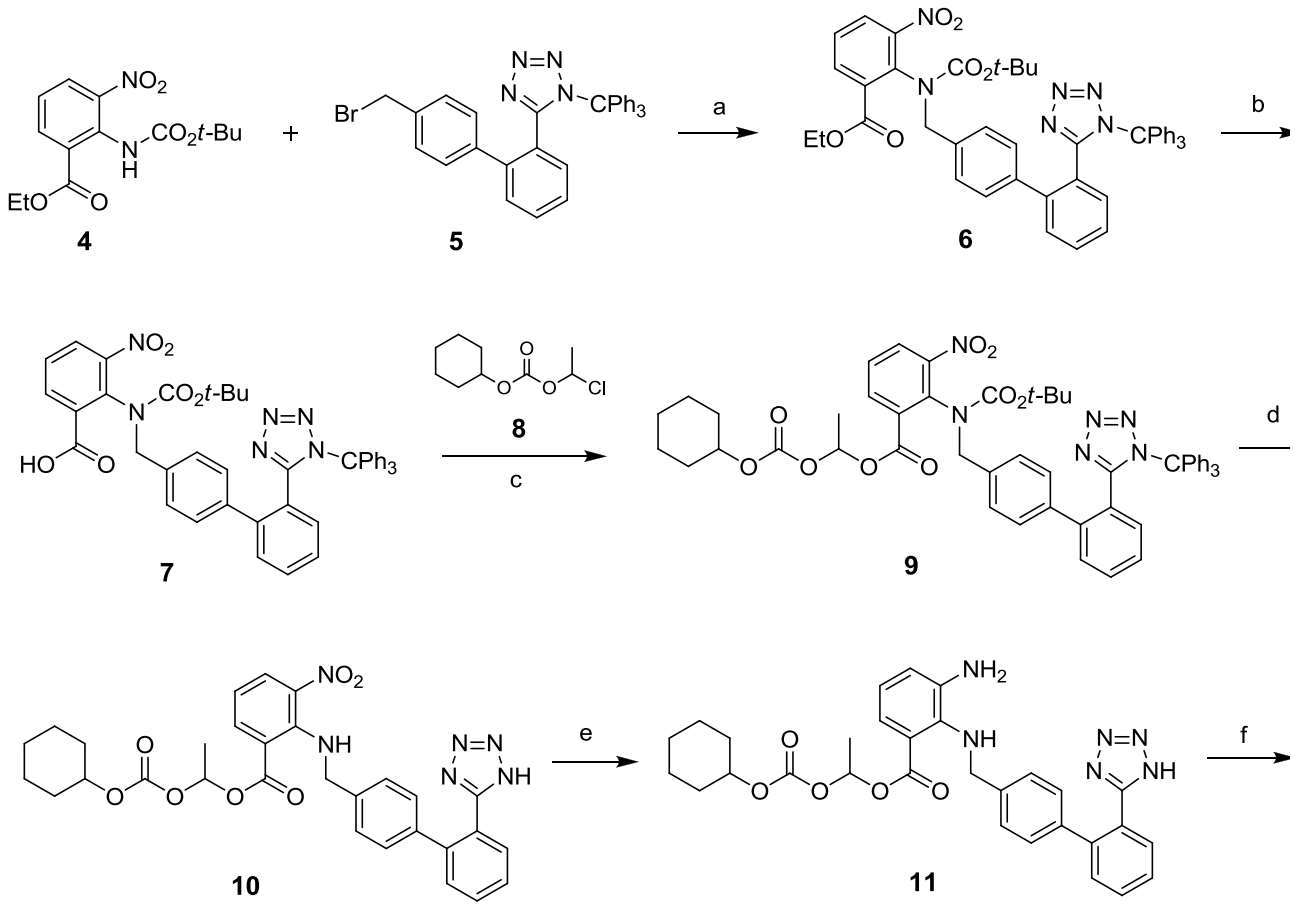
Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are known in treating hypertension and heart failure effectively. Candesartan cilexetil (**1**, Atacand, Figure 1) is a potent angiotensin II receptor antagonist that exhibits selective and antagonistic activity to the AT_1 subtype for treatment of hypertension. It is clinically used as the prodrug form of cyclohexyl 1-hydroxyethyl carbonate ester, which is metabolised completely to the active moiety candesartan (**2**) by esterases on the intestinal wall during absorption.[1]



1 **2** **3**

Figure 1

Several synthetic methods were developed for the preparation of **1** and most of these routes were linear.[2] In general, candesartan (**2**) was prepared through 5–8 steps in medium overall yield. Protection of the tetrazole of **2** with trityl group and alkylation with 1-chloroethyl cyclohexyl carbonate were the usual methods. The detritylation reaction of the last step was carried out in strong acidic condition, which was always accompanied with the formation of the 2-hydroxy-benzimidazole **3** (Figure 1) as a major impurity in the final product. The impurity **3** has similar properties to **1** so that it is difficult to purify the final product with satisfying recovery yield. Herein we will describe a novel and practical synthetic route of **1** with good yield and purity.[3]



Reagents and conditions: (a) K_2CO_3, MeCN, 92%; (b) NaOH, THF, H_2O, 94%; (c) K_2CO_3, MeCN; (d) AcCl

Scheme 1

The new synthetic route of **1** is outlined in Scheme 1. Commercially available benzyl bromide **5** can be prepared from 4'-methyl-(1,1'-diphenyl)-2-carbonitrile through three steps according to the established method.[4] Commercially available aniline **4** is *N*-alkylated by treating with **5** in K_2CO_3-MeCN system to give the intermediate **6** in 92% isolated yield. Hydrolysis of the ethyl ester group in **6** is carried out with NaOH in THF-H_2O solution to afford the corresponding acid **7** in high yield.[5] By the similar conditions

applied for preparing **6**, the acid **7** is converted into the ester **9** by treating with 1-chloroethyl cyclohexyl carbonate (**8**) in satisfying yield. Further, cleavage of the *N*-Boc and the *N*-trityl group of **9** are carried out concurrently in HCl-EtOH solution at room temperature to give the nitrobenzote **10** without hydrolysis of the cilexetil ester chain. The nitro group in **10** is reduced with stannous chloride to the corresponding amino intermediate **11**. Ring closure of **11** is performed with tetraethyl orthocarbonate and acetic acid to afford the final product **1**. In 2008, we reported a facile one-pot reductive cyclization of benzimidazole from 2-nitroanilines.[6] Here, however, product **1** can not be prepared from 2-nitroaniline **10** in satisfying results using the similar one-pot process.

In summary, we have developed a novel, convergent and practical synthetic route of candesartan cilexetil. The overall yield of **1** obtained in this route is around 55% (from **5**, six steps) with 99.1% purity (HPLC) which makes it a potential convenient preparative method of **1**.

EXPERIMENTAL

All commercially available materials and solvents were used as received products without further purification. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer and ^{13}C NMR spectra were obtained from a Bruker AMX 400/600 at 400 MHz using TMS as an internal standard. Infrared spectra were recorded using a Thermo-Nicolet MAGNA-IR 750. The mass spectra were obtained from a Finnigan MAT-95/711 spectrometer.

Ethyl 2-[(*N*-*t*-butoxycarbonyl)-[[2'-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-amino]-3-nitrobenzote (6). Ethyl 2-[(*N*-*t*-butoxycarbonyl)amino]-3-nitrobenzote (**4**) (31 g, 0.1 mol), 5-[4'-(bromomethyl)biphenyl-2-yl]-1-(triphenylmethyl)-1*H*-tetrazole (**5**) (56 g, 0.1 mol), and K_2CO_3 (28 g, 0.2 mol) were suspended in MeCN (500 mL). The reaction mixture was stirred and heated at reflux for 5 h. The resulting solution was then cooled to rt and filtered. The filtrate was concentrated and the residue was partitioned between EtOAc and water. The organic layer was dried and concentrated to give a pale yellow oil. *i*-PrOH (150 mL) was added and the mixture was stirred at rt for 30 min. The resulting solid was filtered, washed with *i*-PrOH and dried to afford **6** as a pale yellow solid (72 g, 92%). IR (KBr): 3433, 3060, 2978, 2931, 1711, 1603, 1535, 1448, 1367, 1290, 1163, 1128, 1022, 760, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.20 (t, 3H, J = 7.2 Hz), 1.26–1.44 (2s, 9H), 4.09 (q, 2H, J = 7.2 Hz), 4.39–4.60 (2d, 2H), 6.80–8.10 (m, 26H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.74, 27.52, 27.88, 53.02, 61.66, 80.12, 82.25, 125.64, 126.61, 127.49, 127.79, 128.01, 128.25, 128.60, 128.73, 128.96, 129.13, 129.58, 130.29, 130.47, 131.77, 133.58, 134.50, 134.84, 139.41, 140.78, 141.20, 148.15, 153.07, 163.54, 164.19; ESI-MS *m*/*z* 809.1 (M+23). Anal. Calcd for $C_{47}H_{42}N_6O_6$: C, 71.74; H, 5.38; N, 10.68. Found: C, 72.06; H, 5.58; N, 10.32.

2-[(*N*-*t*-Butoxycarbonyl)-[[2'-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-3-nitrobenzoic acid (7). The benzoate **6** (70 g, 0.089 mol) was added to a solution of NaOH (4.3 g, 0.107 mol) in H_2O (50 mL) and THF (500 mL). The reaction mixture was stirred and heated at reflux for 12 h. The solvent was recovered and the residue was treated with water (500 mL), then acidified to pH~7 with 2 M HCl. The resulting solid was collected via suction filtration, dried to provide **7** as a pale yellow solid (63 g, 94%). IR (KBr): 3448, 3060, 2978, 1686, 1608, 1533, 1448, 1367, 1161, 1014, 760, 698, 640 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.25–1.32 (2s, 9H), 4.31–5.15 (2d, 2H), 6.80–7.80 (m, 26H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 27.67, 28.02, 52.87, 79.41, 82.27, 123.91, 125.72, 126.68, 127.24, 127.58, 127.82, 127.87, 128.33, 129.01, 129.61, 130.38, 130.49, 130.59, 132.18, 134.15, 135.72, 138.83, 140.81, 141.47, 147.82, 147.98, 153.55, 163.69, 168.26; ESI-MS *m*/*z* 757.0 (M–1). Anal. Calcd for $C_{45}H_{38}N_6O_6$: C, 71.23; H, 5.05; N, 11.08. Found: C, 71.58; H, 5.28; N, 10.76.

(±)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-[(*N*-*t*-butoxycarbonyl)-[[2'-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-3-nitrobenzote (9). The benzoic acid **7** (61 g, 0.08 mol), K_2CO_3 (23 g, 0.16 mol) and (±)-1-chloroethyl cyclohexyl carbonate (**8**) (25 g, 0.12 mol) were suspended in MeCN (500 mL), and the reaction mixture was stirred and heated at reflux for 6 h. The resulting solution was then cooled to rt and filtered. The filtrate was concentrated and the residue was partitioned between EtOAc and water. The organic layer was dried and concentrated to afford crude **9** as a pale yellow oil (~ 80 g) which was used directly in the next step. A small reference sample was obtained by chromatography on silica gel. IR (KBr): 3433, 2937, 2862, 1755, 1714, 1537, 1450, 1379, 1288, 1255, 1163, 1074, 1007, 762, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.20–1.85 (m, 22H), 4.20–4.80 (2d, 2H), 4.55 (m, 1H), 6.80–8.10 (m, 27H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.24, 22.89, 24.57, 27.53, 27.91, 30.75, 76.76, 80.31, 82.25, 92.14, 125.66, 127.84, 128.29, 128.69, 129.15, 129.61, 129.93, 130.14, 130.32, 130.49, 133.96, 134.05, 134.18, 135.29, 139.50, 139.60, 140.79, 141.20, 148.37, 151.94, 152.91, 162.12, 162.47, 163.56; ESI-MS *m*/*z* 951.3 (M+23). Anal. Calcd for $C_{54}H_{52}N_6O_9$: C, 69.81; H, 5.64; N, 9.05. Found: C, 69.47; H, 5.72; N, 8.99.

(±)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-[[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-3-nitrobenzote (10). Acetyl chloride (30 mL) was added slowly to EtOH (220 mL) in an ice-water bath, then the crude ester **9** (80 g, 0.08 mol) was added and the reaction mixture was stirred for 12 h. The reaction solution was then diluted with EtOAc (600 mL) and ice-water, basified to pH~7 with 2 M NaOH. The organic layer was separated, dried and concentrated to give crude **10**, which was chromatographed on silica gel using 20% EtOAc in PE to afford pure **10** as a white solid (39 g, 83%). IR (KBr): 3323, 2935, 2858, 1753, 1701, 1604, 1581, 1529, 1502, 1450, 1356, 1244, 1072, 1007, 762 cm^{-1}; ^1H NMR (DMSO-d_6,

300 MHz): δ 1.57 (d, 3H, J = 4.8 Hz), 1.20–1.90 (m, 10H), 4.16 (d, 2H, J = 5.1 Hz), 4.55 (m, 1H), 6.70–6.80 (m, 2H), 7.07 (d, 2H, J = 7.8 Hz), 7.25 (d, 2H, J = 7.8 Hz), 7.50–7.70 (m, 4H), 8.03 (dd, 1H, J = 8.1 Hz, 1.8 Hz), 8.13 (dd, 1H, J = 8.1 Hz, 1.8 Hz), 8.45 (t, 1H, J = 6.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.25, 22.94, 24.63, 30.79, 49.67, 76.84, 91.97, 115.62, 116.00, 127.73, 127.89, 129.16, 130.69, 131.21, 131.97, 137.05, 137.18, 140.99, 144.56, 151.99, 164.82; ESI-MS m/z 587.4 (M+1), 609.2 (M+23). Anal. Calcd for $C_{30}H_{30}N_6O_7$: C, 61.43; H, 5.15; N, 14.33. Found: C, 61.19; H, 5.28; N, 14.20.

(±)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 3-amino-2-[[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-amino]benzote (11). The nitrobenzote **10** (30 g, 0.051 mol) and stannous chloride dihydrate (32 g, 0.14 mol) were suspended in EtOAc (200 mL). The reaction mixture was stirred at 60 ºC for 1 h. The reaction solution was then diluted with EtOAc (300 mL) and ice-water, basified to pH~7 with 2 M NaOH, and filtered. The organic layer of the filtrate was separated, washed with water, dried and concentrated to provide **11** as a pale yellow solid (27 g, 95%). IR (KBr): 3431, 3348, 2939, 2860, 1753, 1701, 1604, 1471, 1286, 1063, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.49 (d, 3H, J = 6.0 Hz), 1.20–1.90 (m, 10H), 4.11 (s, 2H), 4.55 (m, 1H), 6.75–6.82 (m, 2H), 6.93 (dd, 1H, J = 7.7 Hz, 1.5 Hz), 7.02–7.08 (m, 4H), 7.24 (s, 1H), 7.27 (s, 1H), 7.52–7.70 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.28, 22.89, 24.57, 30.75, 48.55, 76.60, 91.39, 118.71, 118.95, 119.70, 121.62, 123.36, 127.69, 128.68, 130.58, 130.62, 131.04, 137.78, 138.13, 139.28, 141.24, 142.45, 151.93, 166.04; ESI-MS m/z 579.2 (M+23), 555.0 (M–1). Anal. Calcd for $C_{30}H_{32}N_6O_5$: C, 64.73; H, 5.79; N, 15.10. Found: C, 64.46; H, 5.88; N, 14.91.

(±)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-l-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (1). A mixture of the aminobenzote **11** (22 g, 0.04 mol), acetic acid (2.3 mL, 0.04 mol) and tetraethyl orthocarbonate (9.2 mL, 0.044 mol) in toluene (100 mL) was stirred at 60 ºC for 2 h. The reaction mixture was then diluted with PE (~ 100 mL) and cooled to rt. The resulting solid was filtered and dried to provide crude **1** as a pale solid (23 g). Recrystallization from EtOAc-PE afforded product **1** (20 g, 81%), purity at 99.1% (HPLC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.41 (t, 3H, J = 7.5 Hz), 1.42 (d, 3H, J = 5.4 Hz), 1.20–1.85 (m, 10H), 4.56 (m, 1H), 4.62 (q, 2H, J = 7.5 Hz), 5.52 (s, 2H), 6.80 (q, 1H, J = 5.4 Hz), 6.90 (d, 2H, J = 8.1 Hz), 7.01 (d, 2H, J = 8.1 Hz), 7.22 (t, 1H, J = 7.8 Hz), 7.45–7.75 (m, 5H); ESI-MS m/z 633.2 (M+23), 609.1 (M–1). HPLC Conditions: Waters XTerra MS C18 4.6 mm × 150 mm × 5 μm; Detection: 210 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 5 μL; Concentration: 0.5 mg/mL; Run time: 20 min; Mobile phase A: buffer (water / o-phosphoric acid, 85% = 100 mL / 0.1 mL); Mobile phase B: MeCN; Gradient program: time (min): 0 15 20; % of mobile phase A: 45, 10, 0; % of mobile phase B: 55, 90, 100; Retention time of **1**: 6.381 min.

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