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Synthesis and antibacterial activity of 4″-*O*-carbamoyl analogs of clarithromycin

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Abstract

A series of novel 4″-*O*-carbamoyl analogs of clarithromycin were synthesized and evaluated for their *in vitro* antibacterial activity. All of the desired compounds showed excellent activity against erythromycin-susceptible *S. pneumoniae*. Particularly, 4-fluorobenzyl carbamate **7a** demonstrated potent activity against erythromycin-resistant *S. pneumoniae* encoded by the *mef* gene, and remarkably improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* gene, and the *erm* and *mef* genes.

Keywords: Clarithromycin analogs; 4″-*O*-carbamate; Synthesis; Antibacterial activity; Resistant bacteria

First generation macrolides as exemplified by erythromycin A (EMA) demonstrated broad-spectrum antimicrobial activity and were primarily prescribed for respiratory, skin and soft tissue infections, but they lose readily their antibacterial activity attributing to degradation under acidic conditions [1,2]. Second generation macrolides such as clarithromycin (CAM) (Fig. 1) and azithromycin (AZM) were developed to overcome the shortcomings of EMA [3]. However, the therapeutic utility of these macrolides has led to rapid increases in the resistance rates of bacteria isolated clinically. Unfortunately, all of the macrolides belonging to the second generation exhibited less improvement in the activity against erythromycin-resistant strains [4].

A significant amount of work has been carried out to discover new macrolides against resistant strains. It has been reported that CP-544372 (Fig. 1) showed potent activity against both susceptible and resistant bacteria [5]. CP-544372 contains a prolonged aromatic side chain attached to the 4″-position of the cladinose sugar, reaching to the binding site of chloramphenicol [6,7]. Otherwise, our studies also confirmed that the 4″-*O*-carbamoyl groups play an important role in overcoming MLS_B (macrolide–lincosamide–streptogramin B) resistance [8,9].

In order to probe the effect of a long 4″-*O*-carbamoyl side chain in the antibacterial activity, five amines **4a–e** were obtained from 6-aminohexanonic acid by protection of $(BOC)_2O$, condensation reaction with corresponding amines catalized by DCC and HOBt, and finally, deprotection of the BOC groups in HCl as shown in Scheme 1.

CAM has been widely used in the treatment of respiratory tract infections owing to its high efficacy, ideal pharmacokinetic property and safety [10,11]. In anticipation of inheriting these beneficial profiles of CAM, a series of novel 4″-*O*-cabamate analogs of CAM **7a–e** were prepared by condensation with the amines synthesized above as

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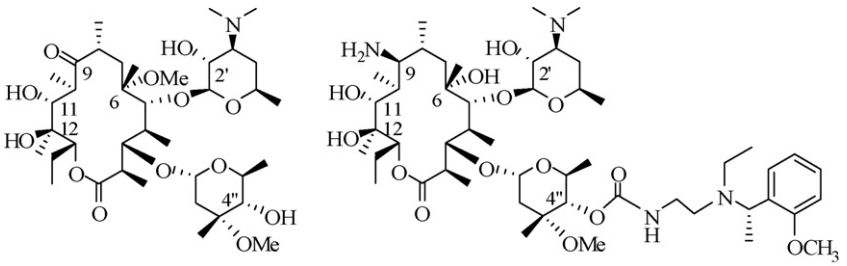
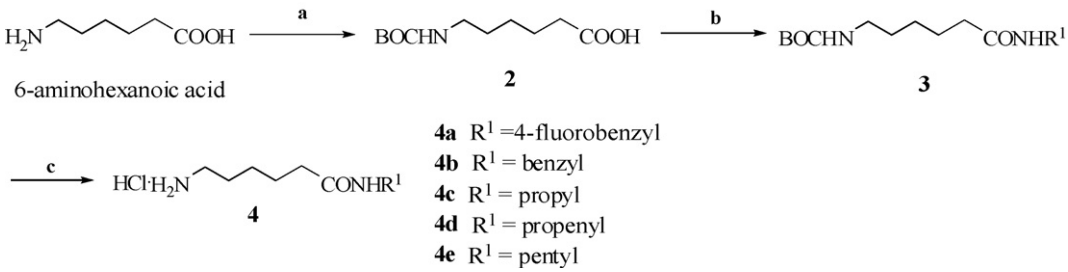


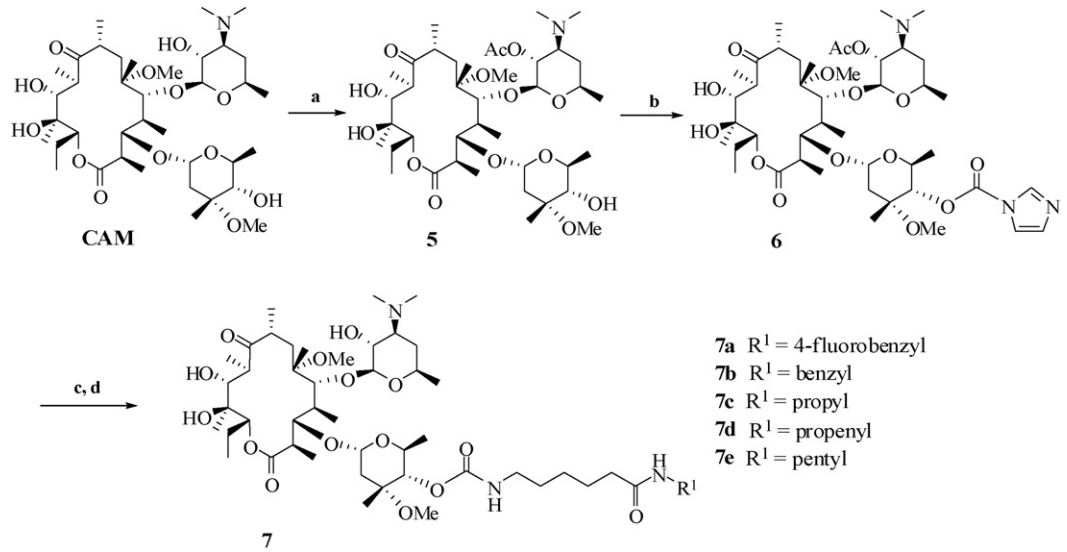
Fig. 1. Structures of clarithromycin and CP-544372.

outlined in Scheme 2. CAM was subjected to acetylation reaction with acetic anhydride to give 2′-*O*-acetate **5**. The 2′-*O*-acetate **6** was obtained by reaction of **5** with CDI (*N*,*N*-carbonyldiimidazole) in toluene in the presence of Et_3N (triethylamine) in good yield. Reaction of **6** with the corresponding amines **4** in DMF in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) followed by methanolysis at 55 °C gave the desired compounds **7a–e** (Table 1). Their structures were confirmed by MS, IR, ^{1}H NMR and elemental analysis [12].

The activity of **7a–e** against four phenotypes of Gram-positive strains was evaluated using broth microdilution method as shown in Table 2. All of the compounds tested retained excellent activity against erythromycin-susceptible



Scheme 1. Reagents and conditions: (a) $(BOC)_2O$, 1 mol/L NaOH, THF, rt, 24 h, 76.0%; (b) DCC, HOBt, THF, 0 °C, 8 h, R^1NH_2, rt, 2 h; (c) HCl, AcOEt, rt, 2 h 78.1–85.4% for 2 steps.



Scheme 2. Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h, 85.4%; (b) CDI, toluene, rt, 48 h, 92.9%; (c) R^1NH_2·HCl, DBU, DMF, rt, 24 h; (d) CH_3OH, 55 °C, 24 h, 73.2–77.7% for 2 steps.

Table 1
Data of the target compounds **7a–e**.

Compounds	R^1	Molecular formula	Molecular weight	Mp (°C)	Overall yield (%)
7a	4-Fluorobenzyl-	$C_{52}H_{86}FN_3O_{15}$	1011.6	110–112	59.7
7b	Benzyl-	$C_{52}H_{87}N_3O_{15}$	994.3	115–118	58.0
7c	Propyl-	$C_{48}H_{87}N_3O_{15}$	946.2	112–115	61.6
7d	Propenyl-	$C_{48}H_{85}N_3O_{15}$	944.2	119–122	58.8
7e	Pentyl-	$C_{50}H_{91}N_3O_{15}$	974.3	104–107	58.9

Table 2
In vitro antibacterial activity of the target compounds **7a–e**.

Compounds	Strain/MIC (μg/mL)			
	S. pneumoniae ATCC49619	*S. pneumoniae* B1 (*erm*B)	*S. pneumoniae* A22072 (*mef*A)	*S. pneumoniae* AB11 (*erm*B + *mef*A)
EAM	0.03	128	8	256
CAM	0.03	64	4	128
AZM	0.03	128	4	256
7a	0.03	2	0.5	4
7b	0.03	64	2	64
7c	0.03	128	4	128
7d	0.03	128	2	128
7e	0.03	128	4	128

S. pneumoniae comparable to the references (MIC 0.03 μg/mL), and some of them showed improved activity against erythromycin-resistant *S. pneumoniae*. Among them, 4-fluorobenzyl carbamate **7a** showed greatly improved activity against both *S. pneumoniae* B1 strain encoded by the *erm* B gene and *pneumonia* AB11 strain encoded by the *erm* B and *mef* A genes, exhibiting 64-fold, 32-fold and 64-fold better activity than EMA, CAM and AZM, respectively. Similarly, 4-fluorobenzyl carbamate **7a** also had potent activity against *S. pneumoniae* A22072 encoded by the *mef* A gene, demonstrating 16-fold, 8-fold and 8-fold greater than EMA, CAM and AZM, respectively. In contrast, alkylcarbamates **7c–e** possessed slightly improved activity against erythromycin-resistant strains compared with the references. These results suggested that the prolonged arylalkylcarbamoyl group may enhance activity against erythromycin-resistant strains. Besides, 4-fluorobenzyl carbamate **7a** was 32-fold, 4-fold and 16-fold more potent activity against erythromycin-resistant strains tested than benzyl carbamate **7b**, indicating that the electron-withdrawing group may further increase activity against erythromycin-resistant strains.

In conclusion, a series of novel 4″-*O*-carbamate analogs of CAM were synthesized and evaluated. All of these analogs tested, without exception, exhibited excellent activity against erythromycin-susceptible *S. pneumoniae*, and some of them showed improved activity against erythromycin-resistant *S. pneumoniae*. Particularly, 4-fluorobenzyl carbamate **7a** demonstrated potent activity against erythromycin-resistant *S. pneumoniae* encoded by the *mef* gene, and remarkably improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* gene, and the *erm* and *mef* genes.

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[12] Spectral data of the compounds **7a–e**: **7a**: White solid, yield 83.6%, mp 110–112 °C, TLC R_f = 0.36 (dichloromethane/methanol, 10:1); IR (KBr): 3381, 2974, 2938, 1730, 1658, 1605, 1511, 1459, 1378, 1345, 1266, 1171, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$):δ (7.26–7.24 (m, 2H), 7.04–7.01 (m, 2H), 5.07 (dd, 1H, J = 11.4 Hz, J = 1.8 Hz), 4.98 (m, 1H), 4.41–4.40 (m, 2H), 4.30–4.26 (m, 2H), 4.10–1.09 (m, 1H), 3.82–3.76 (m, 2H), 3.69–3.59 (m, 2H), 3.23–3.17 (m, 8H), 3.05–3.03 (m, 1H), 2.94–2.87 (m, 2H), 2.65–2.55 (m, 2H), 2.43–2.41 (m, 2H), 2.33 (m, 6H), 2.22–2.20 (m, 3H), 1.94–1.92 (m, 1H), 1.72–1.63 (m, 3H), 1.55–1.48 (m, 8H), 1.38–1.35 (m, 9H), 1.26–1.15 (m, 9H), 1.14–1.12 (m, 9H), 0.84 (t, 3H); MS (ESI) m/z calcd. for $C_{52}H_{86}FN_3O_{15}$ 1011.6; found $(M+H)^+$ 1012.8; Anal. Calcd. for $C_{52}H_{86}FN_3O_{15}$ (1012.25) (%): C 61.70, H 8.56, F 1.88, N 4.15, Found (%): C 61.66, H 8.54, F 1.86, N 4.17. **7b**: White solid, yield 81.3%, mp 115–118 °C, TLC R_f = 0.35 (dichloromethane/methanol, 10:1); IR (KBr): 3454, 2974, 2938, 1731, 1514, 1456, 1378, 1346, 1247, 1171, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 5.06 (d, 1H, J = 10.8 Hz), 4.58–4.50 (m, 2H), 4.44–4.43 (m, 2H), 4.30–4.27 (m, 2H), 3.98 (m, 1H), 3.81–3.76 (m, 2H), 3.67–3.63 (m, 2H), 3.35–3.27 (m, 3H), 3.21–3.17 (m, 4H), 3.00–2.98 (m, 2H), 2.90–2.89 (m, 2H), 2.58–2.56 (m, 2H), 2.30–2.29 (m, 7H), 2.22 (t, 2H), 1.94–1.84 (m, 1H), 1.72–1.62 (m, 2H), 1.54–1.46 (m, 8H), 1.39–1.35 (m, 11H), 1.25–1.23 (m, 9H), 1.12–1.10 (m, 9H), 0.84 (t, 3H), MS (ESI) m/z, calcd. for $C_{52}H_{87}N_3O_{15}$ 993.6; found $(M+H)^+$ 995.1; Anal. Calcd. for $C_{52}H_{87}N_3O_{15}$ (994.3) (%): C 62.82, H 8.82, N 4.23, Found (%): C 62.78, H 8.84, N 4.24. **7c**: White solid, yield 86.3%, mp 112–115 °C, TLC R_f = 0.36 (dichloromethane/methanol, 10:1); IR (KBr): 3452, 2972, 2937, 1731, 1655, 1537, 1459, 1378, 1337, 1266, 1171, 1110, 1072, 1050, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07 (d, 1H, J = 10.2 Hz), 4.97–4.96 (m, 1H), 4.57–4.50 (m, 2H), 3.99 (s, 1H), 3.82–3.76 (m, 2H), 3.68–3.59 (m, 2H), 3.36–3.31 (m, 2H), 3.23–3.18 (m, 6H), 3.15–3.09 (m, 1H), 3.05–3.00 (m, 2H), 2.89 (m, 2H), 2.59–2.57 (m, 2H), 2.44–2.41 (m, 1H), 2.31–2.29 (m, 6H), 2.16 (t, 2H), 1.94–1.87 (m, 1H), 1.73–1.63 (m, 3H), 1.54–1.48 (m, 3H), 1.40–1.34 (m, 4H), 1.27–1.24 (m, 2H), 1.24–1.18 (m, 14H), 1.17–1.11 (m, 16H), 0.93 (t, 3H), 0.85 (t, 3H); MS (ESI) m/z calcd. for $C_{48}H_{87}N_3O_{15}$ 945.6; found $(M+H)^+$ 947.1; Anal. Calcd. for $C_{48}H_{87}N_3O_{15}$ (946.2) (%): C 60.93, H 9.27, N 4.44, Found (%): C 60.89, H 9.30, N 4.41. **7d**: White solid, yield 82.3%, mp 119–122 °C, TLC R_f = 0.38 (dichloromethane/methanol, 10:1); IR (KBr): 3454, 2974, 2939, 1731, 1664, 1514, 1458, 1378, 1339, 1266, 1171, 1110, 1072, 1051, 1013, 986, 934 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.87–5.82 (m, 1H), 5.20–5.13 (m, 2H), 5.08–5.07 (m, 1H), 4.98–4.97 (m, 1H), 4.56–4.52 (m, 2H), 4.27 (m, 1H), 3.98 (s, 2H), 3.89 (t, 2H), 3.68–3.67 (m, 2H), 3.32 (m, 3H), 3.23–3.18 (m, 3H), 3.05 (m, 1H), 3.01 (m, 2H), 2.89 (m, 2H), 2.59 (m, 2H), 2.43–2.41 (m, 7H), 2.22–2.19 (m, 2H), 1.96–1.85 (m, 2H), 1.70–1.63 (m, 4H), 1.55–1.49 (m, 6H), 1.39–1.35 (m, 9H), 1.27–1.24 (m, 2H), 1.22–1.14 (m, 9H), 1.13–1.10 (m, 9H), 0.85 (t, 3H,); MS (ESI) m/z, calcd. for $C_{48}H_{85}N_3O_{15}$ 943.6; found $(M+H)^+$ 945.0; Anal. Calcd. for $C_{48}H_{85}N_3O_{15}$ (944.2) (%): C 61.06, H 9.07, N 4.45, Found (%): C 61.10, H 9.04, N 4.48. **7e**: White solid, yield 82.5%, mp 104–107 °C, TLC R_f = 0.34 (dichloromethane/methanol, 10:1); IR (KBr): 3391, 2936, 1731, 1656, 1536, 1459, 1378, 1343, 1247, 1171, 1111, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.08–5.06 (m, 1H), 4.98–4.96 (m, 1H), 4.74 (m, 1H), 4.54–4.51 (m, 2H), 4.31–4.28 (m, 2H), 4.10–4.09 (m, 1H), 3.99–3.97 (m, 2H), 3.79–3.74 (m, 1H), 3.69–3.64 (m, 2H), 3.33–3.31 (m, 2H), 3.26–3.17 (m, 6H), 3.05–2.97 (m, 3H), 2.92–2.88 (m, 2H), 2.60–2.57 (m, 2H), 2.44–2.41 (m, 1H), 2.31–2.92 (m, 6H), 2.17–2.14 (m, 2H), 1.73–1.63 (m, 7H), 1.54–1.47 (m, 6H), 1.40–1.26 (m, 10H), 1.24–1.16 (m, 9H), 1.15–1.12 (m, 9H), 1.11–0.90 (t, 3H), 0.85 (t, 3H); MS (ESI) m/z calcd. for $C_{50}H_{91}N_3O_{15}$ 973.7; found $(M+H)^+$ 975.0; Anal. Calcd. for $C_{50}H_{91}N_3O_{15}$ (974.3) (%): C 61.64, H 9.41, N 4.31, Found (%): C 61.60, H 9.44, N 4.29.