The Journal of Antibiotics (2010) 63, 343–350

www.nature.com/ja

ORIGINAL ARTICLE

Synthesis and antibacterial activity of novel 4″-carbamates of 6,11-di-*O*-methylerythromycin A

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A novel series of 4″-carbamates of 6,11-di-*O*-methylerythromycin A were synthesized and evaluated. These compounds have significant antibacterial activity against Gram-positive pathogens, including erythromycin-resistant but methicillin-susceptible *Staphylococcus aureus*, erythromycin-resistant and methicillin-resistant *Staphylococcus aureus*, erythromycin-resistant *Streptococcus pneumoniae* and Gram-negative pathogens, such as *Haemophilus influenzae* To our surprise, most of the derivatives tested had potent activity against most resistant bacteria. Among these, compounds 10u, 10v, 10w and 10y were found to have potent activity against most susceptible and resistant bacteria. In particular, compound 10y exhibited excellent antibacterial activity in comparison to others.

The Journal of Antibiotics (2010) **63,** 343–350; doi:10.1038/ja.2010.44; published online 7 May 2010

Keywords: antibacterial activity; 4″-carbamates; macrolides; resistance; synthesis; 6,11-di-*O*-methylerythromycin A

INTRODUCTION

The rapid development of antibiotic resistance among the major respiratory pathogens has created a serious problem for the effective management of respiratory tract infections.[1–6] There is a great need for new antibiotics that address the problem of antibiotic resistance. Under these circumstances, a substantial amount study has been carried out on novel macrolides. These investigations have led to the discovery of C-4″-carbamate macrolides. One of the leading C-4″-carbamates, CP-544372 (Figure 1, compound **1**), has demonstrated good *in vitro* antibacterial activity against erythromycin-susceptible and -resistant organisms.[7–9]

The study of high-resolution X-ray co-crystal structures has shown that the 3-position group of macrolides is located near G2505 and C2610, and the cladinose group of erythromycin or clarithromycin is located at and fits with the cavity formed by G2505, C2610 and C2611 in domain V of the erythromycin-binding site.[9–11] The C-3 cladinose sugar attached to the 14-membered ring macrolides is believed to be responsible for the induction of macrolide resistance. This moiety also seems to be responsible for efflux resistance.[12] Fernandes *et al.* have reported that the induction of methylase in macrolide-resistant bacteria could be dissociated from inhibition of the bacteria by using erythromycin analogs with modification at the 4″ position of the cladinose sugar.[13] Some studies have reported that the introduction of certain groups to the 4″ position of the cladinose sugar results in a negligible effect on antibacterial activity. 4″ modification can alter the relative potency of an antibiotic.[9,14] Many new derivatives of macrolides for the effective management of erythromycin resistance have been investigated.[13] A-60565 (Figure 1, compound **2**) has lower MICs than erythromycin does against inducibly and constitutively resistant bacteria.[9,15] Compound **3** (Figure 2) has an MIC against erythromycin-susceptible and -resistant *Streptococcus pneumoniae* of $\leqslant 0.02$ and $\leqslant 2\,\mu g\,ml^{-1}$, respectively.[16] Compound **4** (Figure 2) has potent activity against most resistant bacteria.[9] Compounds **5a** and **5b** (Figure 3) were found to have potent activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* or *mef* gene.[17,18] Compounds **6a** and **6b** (Figure 3) are effective (0.5 and $0.5\,\mu g\,ml^{-1}$) against two strains of erythromycin-resistant *S. pneumoniae*, whose resistance is encoded by the *erm* and *mef* gene, respectively.[19]

6,11-Di-*O*-methylerythromycin A (Figure 4, compound **7**) shows excellent *in vitro* and *in vivo* antibacterial activity against Gram-positive bacteria and *Mycoplasma pneumoniae*.[20] On the basis of the above findings, we designed novel structural 14-membered analogs of macrolide antibiotics that comprised the essential features for addressing macrolide resistance. By introduction of various amino carbonyl chain to the 4″-hydroxyl group of the 6,11-di-*O*-methylerythromycin A, a series of novel 4″-carbamates were obtained.

RESULTS

Chemistry

The synthetic method of 4″-carbamates of 6,11-di-*O*-methylerythromycin A is shown in Scheme 1. Our approach to get 4″-substituted derivatives is to regioselectively protect 2′-OH of 6,11-di-*O*-methylerythromycin A (**7**) and to modify the 4″-OH. 2′-*O*-acetyl 6,11-di-*O*-methylerythromycin A (**8**) provided a convenient starting

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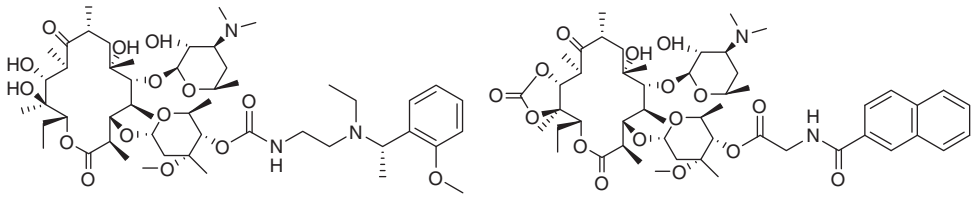
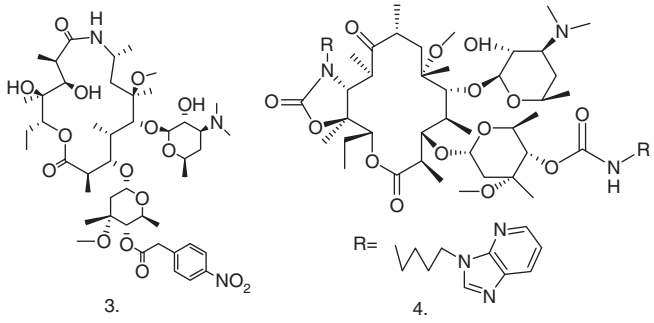
Received 18 February 2010; revised 18 March 2010; accepted 11 April 2010; published online 7 May 2010



1. CP-544372 2. A-60565

Figure 1 Structures of CP-544372 and A-60565.



3. 4.

Figure 2 Structures of compound **3** and compound **4**.

material for the chemical modification leading to the 4″-substituted derivatives.

By using the method of Baker *et al*.,[21–23] **8** was treated with excess 1,1-carbonyldiimidazole and sodium hydride in DMF at 0 °C for 1 h, 6,11-di-*O*-methyl-2′-*O*-acetyl-4″-*O*-acylimidazolyl erythromycin A (**9**) was obtained in a yield of 93%. The structure of **9** was confirmed by ^{13}C NMR spectrum in which two carbon peaks of carbonate and carbamate could be found at δ 170.0 and δ 148.5. Compounds **10a–y** were prepared by reacting compound **9** with corresponding amines and 1,8-diazabicyclo[5.4.0]undec-7-ene, followed by deprotection of the acetyl group with methanol (Scheme 1). The structures of **10a–y** were determined by ^{13}C NMR, ^{1}H NMR, MS and IR spectra.

Antibacterial activity

All of the 4″-carbamates synthesized, as well as erythromycin, clarithromycin and azithromycin as reference compounds, were tested for *in vitro* antibacterial activity against three strains of *Staphylococcus aureus* and two strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*. The activities are reported in Table 1 as MICs, which were determined by the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards.

To evaluate the potential antibacterial activity of each analog to overcome macrolide resistance, various macrolide-resistant strains were included: *S. aureus* ATCC25923: erythromycin-susceptible strain; *S. aureus* A265: erythromycin-resistant but methicillin-susceptible strain; *S. aureus* A333: erythromycin-resistant and methicillin-resistant strain; *S. pneumoniae* ATCC49619: erythromycin-susceptible strain; *S. pneumoniae* 3469: erythromycin-resistant strain; *H. influenzae* ATCC49247: ampicillin-susceptible strain; and *H. influenzae* 3300: ampicillin-resistant strain.

The results in Table 1 show the antibacterial activity of 4″-carbamates and reference compounds (erythromycin, clarithromycin and azithromycin). We presumed that chemical modification that affected the conformation would affect the ability of the antibiotics to bind to bacterial ribosomes. We obtained some new derivatives of 6,11-di-*O*-methylerythromycin A by modifying the 4″ OH group with various carbamate groups such as alkylcarbamoyl, hydroxy-alkylcarbamoyl, alkoxy-alkylcarbamoyl, heterocyclic-carbamoyl, substituted benzylcarbamoyl and substituted phenethylcarbamoyl. To our surprise, most of the derivatives tested had potent activity against most resistant bacteria. Among these, compounds **10u**, **10v**, **10w** and **10y** were found to have potent activity against most susceptible and resistant bacteria. In particular, compound **10y** exhibited excellent antibacterial activity in comparison to others.

DISCUSSION

A simple and efficient method for preparation of 4″-carbamates of macrolides was developed. These carbamates were evaluated for antibacterial activity against macrolide-susceptible and -resistant pathogens. To our surprise, most of the derivatives tested had potent activity against most resistant bacteria. Among these, compounds **10u**, **10v**, **10w** and **10y** were found to have potent activity against most susceptible and resistant bacteria. In particular, compound **10y** showed excellent antibacterial activity in comparison to others. This study may present a major opportunity for the development of new macrolide antibiotics to combat effectively the growing problem of macrolide resistance.

The improved antibacterial activity against resistant bacteria achieved by these derivatives was possibly because the induction of methylase in macrolide-resistant bacteria could be dissociated from inhibition of the bacteria by using erythromycin analogs with modification at the 4″ position of the cladinose sugar. It is worthy of notice that 4″-modified derivatives of 14-membered macrolides are probably the effective management of macrolide resistance, and this study may present a major opportunity for the development of new macrolide antibiotics to combat the growing problem of antibiotic resistance.

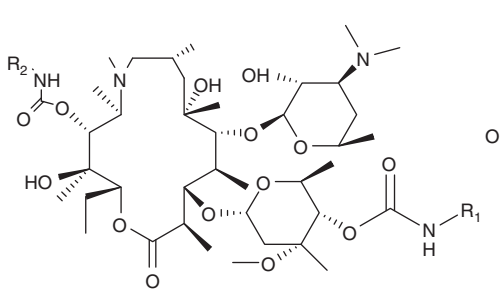
METHODS

General experimental procedures

Reagents were purchased from commercial sources. Solvents and reagents were dried and purified according to the literature methods. Melting points were uncorrected and measured on an XT-4 apparatus. IR spectra were recorded from KBr pellets at a range of 400–4000 cm^{-1} on a Spectrum One (Perkin Elmer, Shelton, CT, USA) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury VX400 apparatus (American Varian Inc., Palo Alto, CA, USA) in $CDCl_3$ with TMS as internal standard. The elemental analysis (C, H, N) data were obtained from a VarioEL III elemental analyzer (German Elementar. Co., Ltd, Hanau, Germany). All the ampicillin- and erythromycin-resistant strains chosen in this test are constitutively resistant strains supplied by the Ministry of Health National Antimicrobial Resistance Investigation Net (China).

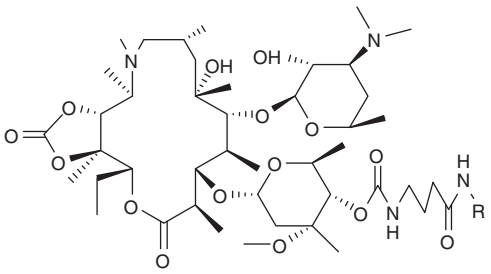
6,11-Di-*O*-methyl-2′-*O*-acetylerythromycin A (8)

To a solution of 6,11-di-*O*-methylerythromycin A (**7**) (3.05 g, 4.0 mmol) in acetone (20 ml) at room temperature were added acetic anhydride (7.5 ml, 8 mmol, 2.0 equiv.) and K_2CO_3 (1.10 g, 8 mmol, 2.0 equiv.). The resulting solution was allowed to stir for 24 h at the same temperature. The reaction was quenched with 5% aqueous $NaHCO_3$ (20 ml) and the aqueous layer was extracted with CH_2Cl_2 (3×20 ml). The combined organic layers



5a. R_1 = 4-fluorobenzyl, R_2 = phenethyl
5b. R_1 = 2-chlorophenethyl, R_2 = 4-hydroxyphenethyl

5.



6a. R= 4-methoxybenzyl
6b. R= 2-chlorophenethyl

6.

Figure 3 Structures of compound **5** and compound **6**.

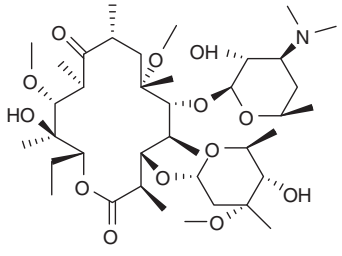


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Figure 4 Structure of 6,11-di-*O*-methylerythromycin A.

were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was crystallized to afford 3.03 g (94%) of **8** as a white solid: m.p. 167–170 °C; IR (KBr): 3474, 2976, 2940, 2875, 1723, 1460, 1374, 1242, 1171, 1106, 1058, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.97–4.94 (m, 2H), 4.83 (m, 1H), 4.66 (m, 1H), 4.00 (m, 1H), 3.73 (d, J=5.9 Hz, 1H), 3.68 (d, J=10.1 Hz, 1H), 3.57 (s, 3H), 3.41 (s, 1H), 3.37 (s, 3H), 3.07 (s, 3H), 3.05–2.93 (m, 3H), 2.71 (m, 1H), 2.37 (s, 6H), 2.17 (m, 1H), 2.07 (s, 3H), 2.03–1.99 (s, 3H), 1.98–1.80 (m, 3H), 1.70–1.61 (m, 2H), 1.47 (m, 1H), 1.37 (s, 3H), 1.34 (m, 1H), 1.30–0.94 (m, 18H), 0.92–0.90 (m, 3H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.0, 174.9, 169.7, 99.4, 95.6, 79.1, 78.4, 77.8, 77.2, 77.0, 75.5, 72.4, 70.7, 67.2, 65.7, 62.2, 60.4, 49.9, 48.8, 45.1, 44.4, 39.4, 37.4, 37.3, 36.7, 34.6, 30.0, 29.8, 21.1, 21.0, 20.8, 20.0, 18.8, 18.2, 17.6, 17.1, 15.6, 12.3, 10.0, 8.7. MS (ESI) m/z calcd. for $C_{41}H_{73}NO_{14}$ 803.5; found ($M+H^+$) 804.1.

6,11-Di-*O*-methyl-2′-*O*-acetyl-4″-*O*-acylimidazolyl erythromycin A (9)

To a solution of **8** (1.61 g, 2 mmol) in DMF (20 ml) were added NaH (0.096 g, 4 mmol, 2.0 equiv.) and carbonyldiimidazole (0.705 g, 4 mmol, 2.0 equiv.). The resulting solution was stirred at 0 °C for 1 h. The reaction was quenched with saturated $NaHCO_3$ (20 ml) and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified to afford 1.67 g (93%) of **9** as a white solid: m.p. 171–174 °C; IR (KBr): 3469, 2975, 2941, 1773, 1753, 1721, 1464, 1392, 1345, 1288, 1239, 1172, 1110, 1059, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.38 (s, 1H), 7.11 (s, 1H), 5.06 (d, J=6.7 Hz, 1H), 4.97 (m, 1H), 4.81–4.76 (m, 3H), 4.48 (m, 1H), 3.73–3.67 (m, 2H), 3.63 (m, 1H), 3.58 (s, 3H), 3.41 (s, 3H), 3.08 (m, 1H), 3.07 (s, 3H), 3.04–2.97 (m, 2H), 2.71 (m, 1H), 2.58 (m, 1H), 2.49 (d, J=15.2 Hz, 1H), 2.30 (s, 6H), 2.17 (m, 1H), 2.06 (s, 3H), 2.03 (m, 1H), 1.94–1.86 (m, 3H), 1.78–1.68 (m, 4H), 1.53 (m, 1H), 1.50 (m, 1H), 1.35 (s, 3H), 1.32 (m, 1H), 1.26–1.23 (m, 9H), 1.16–1.10 (m, 6H), 1.05–0.99 (m, 6H), 0.87–0.84 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.4, 175.2, 170.0, 148.5, 136.8, 130.9, 116.9, 99.9, 96.0, 82.9, 79.5, 78.8, 78.5, 76.0, 72.6, 71.7, 67.9, 67.5, 63.5, 63.1, 60.8, 50.3, 49.4, 45.6, 44.7, 40.7, 37.7, 37.6, 37.0, 35.2, 30.5, 29.6, 25.6, 21.5, 21.3, 21.1, 20.3, 19.3, 18.3, 17.6, 16.1, 12.8, 10.4, 9.2. MS (ESI) m/z calcd. for $C_{45}H_{75}N_3O_{15}$ 897.52; found ($M+H^+$) 898.0.

General methods for 4″-carbamates of 6,11-di-*O*-methylerythromycin A 10(a–y)

To a solution of **9** (1.35 g, 1.50 mmol) in DMF (15 ml) at 0 °C were added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.33 ml, 2.25 mmol, 1.5 equiv.) and corresponding amine (2.25 mmol, 1.5 equiv.). The resulting solution was raised to room temperature and stirred for 24 h at the same temperature. The reaction was quenched with water (30 ml) and the aqueous layer was extracted with ethyl acetate (315 ml). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuum to afford a crude product.

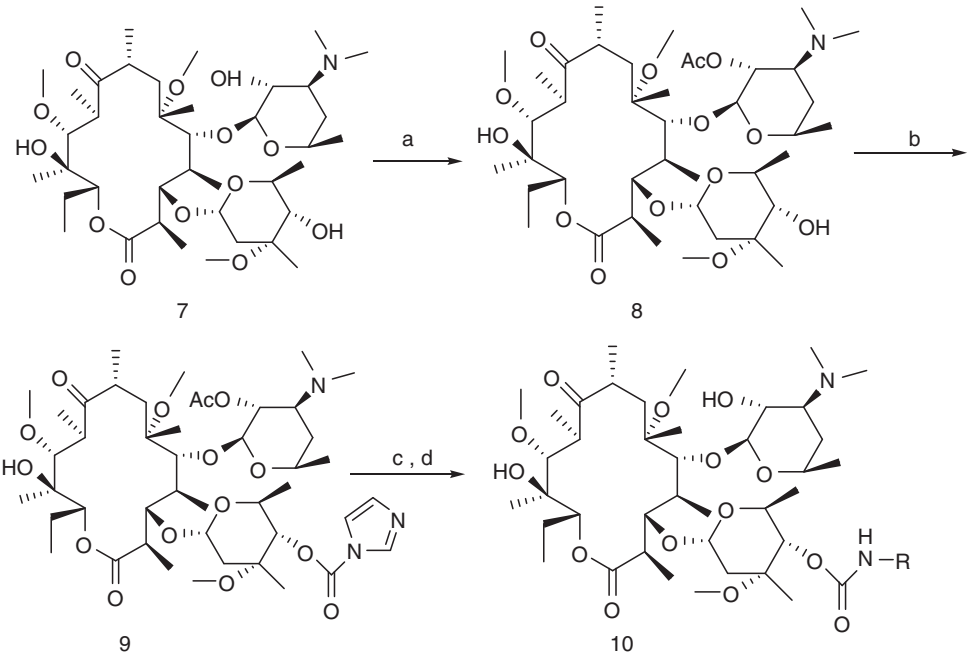
A solution of the above crude product in methanol (15 ml) was heated to 55 °C and stirred for 20 h at the same temperature. After concentrating the reaction solution in vacuum, the residue was purified by chromatography to afford products **10**(**a**–**y**).

6,11-Di-*O*-methyl-4″-*O*-(*N*-propylcarbamoyl)erythromycin A (10a)

White solid, yield 86.1%, m.p. 216–220 °C; IR (KBr): 3350, 2974, 2931, 1732, 1715, 1539, 1457, 1380, 1265, 1164, 1109, 1091, 1039, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.97 (d, J=6.7 Hz, 2H), 4.72 (d, J=8.3 Hz, 1H), 4.54–4.49 (m, 2H), 4.30 (m, 1H), 3.75 (d, J=6.4 Hz, 1H), 3.71–3.65 (m, 2H), 3.57 (s, 3H), 3.50 (m, 1H), 3.43 (s, 1H), 3.32 (s, 3H), 3.20 (m, 1H), 3.09 (s, 3H), 3.07–3.04 (m, 2H), 2.98 (m, 1H), 2.62–2.53 (m, 2H), 2.43 (d, J=15.2 Hz, 1H), 2.30 (s, 6H), 2.06–2.03 (m, 2H), 1.95–1.85 (m, 3H), 1.82–1.59 (m, 6H), 1.51–1.46 (m, 1H), 1.38 (s, 3H), 1.33–1.30 (m, 2H), 1.26–1.08 (m, 23H), 0.84–0.80 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 155.4, 102.1, 96.5, 79.4, 78.9, 78.6, 77.7, 76.0, 72.9, 71.2, 67.8, 65.0, 63.5, 60.8, 50.6, 49.9, 49.6, 45.6, 44.7, 40.2, 38.0, 37.9, 37.7, 35.3, 33.2, 28.8, 25.4, 24.7, 21.8, 21.5, 20.9, 20.3, 19.4, 18.4, 17.4, 16.0, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{43}H_{78}N_2O_{14}$ 846.55; found ($M+H^+$) 847.1; *Anal.* calcd. (%) for $C_{43}H_{78}N_2O_{14}$: C 60.97, H 9.28, N 3.31; found: C 60.95, H 9.25, N 3.34.

6,11-Di-*O*-methyl-4″-*O*-(*N*-butylcarbamoyl)erythromycin A (10b)

White solid, yield 76.3%, m.p. 202–206 °C; IR (KBr): 3470, 2973, 2936, 1729, 1715, 1458, 1376, 1342, 1170, 1092, 1053, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.98 (d, J=8.2 Hz, 2H), 4.79 (m, 1H), 4.56–4.52 (m, 2H), 4.30 (m, 1H), 3.75 (d, J=6.6 Hz, 1H), 3.72–3.70 (m, 2H), 3.59 (s, 3H), 3.44 (s, 1H), 3.32 (s, 3H), 3.27–3.17 (m, 2H), 3.10 (s, 3H), 3.06–3.03 (m, 2H), 2.99 (m, 1H), 2.63–2.57 (m, 2H), 2.43 (d, J=14.4 Hz, 1H), 2.31 (s, 6H), 2.06 (m, 1H), 1.90–1.64 (m, 12H), 1.52–1.39 (m, 1H), 1.37 (s, 3H), 1.35–1.33 (m, 2H), 1.32–1.09 (m, 20H), 0.93–0.88 (m, 3H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.3, 102.1, 96.5, 79.5, 79.0, 78.7, 78.6, 77.7, 76.0, 73.0, 71.2, 67.8, 65.0, 63.5, 60.8, 50.6, 49.5, 45.5, 44.8, 40.8, 38.0, 37.9, 37.7,



Scheme 1 Reagents and conditions: (a) acetic anhydride, acetone, K_2CO_3, $NaHCO_3$, 24 h; (b) CDI, NaH, DMF, 0°C, 1 h; (c) RNH_2, DMF, DBU, rt, 24 h; (d) CH_3OH, 55°C, 20 h.

35.4, 32.0, 29.7, 28.9, 21.7, 21.5, 20.9, 20.3, 19.8, 19.4, 18.3, 17.4, 16.0, 13.7, 12.8, 10.2, 9.3; MS (ESI) *m/z* calcd. for $C_{44}H_{80}N_2O_{14}$ 860.56; found ($M+H^+$) 861.1; *Anal.* calcd. (%) for $C_{44}H_{80}N_2O_{14}$: C 61.37, H 9.36, N 3.25; found: C 61.34, H 9.34, N 3.28.

6,11-Di-*O*-methyl-4″-*O*-(*N*-pentylcarbamoyl)erythromycin A (10c)

White solid, yield 74.5%, m.p. 167–170 °C; IR (KBr): 3464, 2966, 2930, 2849, 2367, 1725, 1460, 1170, 1103, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.98 (d, *J*=8.3 Hz, 2H), 4.75 (m, 1H), 4.56–4.52 (m, 2H), 4.31 (m, 1H), 3.76 (d, *J*=6.6 Hz, 1H), 3.72–3.67 (m, 2H), 3.59 (s, 3H), 3.43 (s, 1H), 3.35 (s, 3H), 3.28–3.15 (m, 2H), 3.10 (s, 3H), 3.06–3.04 (m, 2H), 2.97 (m, 1H), 2.63–2.59 (m, 2H), 2.43 (d, *J*=15.1 Hz, 1H), 2.35 (s, 6H), 2.08–2.05 (m, 2H), 1.95–1.89 (m, 3H), 1.86 (m, 1H), 1.73–1.62 (m, 3H), 1.54–1.44 (m, 5H), 1.39 (s, 3H), 1.36–1.29 (m, 2H), 1.25–1.09 (m, 22H), 0.91–0.88 (m, 3H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.4, 175.6, 156.3, 101.9, 96.5, 79.5, 78.8, 78.9, 78.6, 77.7, 76.0, 72.9, 71.2, 67.7, 65.1, 63.5, 60.8, 50.6, 49.5, 45.6, 44.8, 41.1, 40.3, 38.0, 37.9, 37.7, 35.4, 31.9, 29.7, 29.6, 28.8, 22.7, 22.3, 21.5, 20.9, 20.3, 19.5, 18.3, 17.4, 16.0, 13.9, 12.8, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{45}H_{82}N_2O_{14}$ 874.58; found ($M+H^+$) 875.1; *Anal.* calcd. (%) for $C_{45}H_{82}N_2O_{14}$: C 61.76, H 9.44, N 3.20; found: C 61.73, H 9.41, N 3.23.

6,11-Di-*O*-methyl-4″-*O*-(*N*-cyclohexylcarbamoyl)erythromycin A (10d)

White solid, yield 70.6%, m.p. 198–203 °C; IR (KBr): 3447, 2974, 2936, 2856, 1724, 1653, 1540, 1457, 1378, 1251, 1172, 1053, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.97 (d, *J*=7.7 Hz, 2H), 4.86 (m, 1H), 4.55–4.51 (m, 2H), 4.31 (m, 1H), 3.74 (d, *J*=6.5 Hz, 1H), 3.71–3.68 (m, 2H), 3.58 (s, 3H), 3.43 (s, 1H), 3.32 (s, 3H), 3.33–3.13 (m, 3H), 3.10 (s, 3H), 3.07–2.98 (m, 2H), 2.96 (m, 1H), 2.62–2.54 (m, 2H), 2.43 (d, *J*=15.2 Hz, 1H), 2.30 (s, 6H), 2.07–2.03 (m, 2H), 1.92–1.89 (m, 2H), 1.85–1.82 (m, 1H), 1.68–1.63 (m, 4H), 1.55–1.45 (m, 4H), 1.39 (s, 3H), 1.29–0.93 (m, 25H), 0.91–0.87 (m, 3H), 0.84–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.3, 102.1, 96.5, 79.5, 78.9, 78.7, 78.6, 77.7, 77.3, 76.0, 73.0, 71.2, 67.8, 65.0, 63.5, 60.8, 50.6, 49.5, 45.6, 44.8, 42.8, 40.2, 38.0, 37.9, 37.7, 35.3, 29.7, 28.9, 23.2, 21.7, 21.5, 20.9, 20.3, 19.4, 18.3, 17.4, 16.0, 12.8, 11.1, 10.5; MS (ESI) *m/z* calcd. for $C_{46}H_{82}N_2O_{14}$ 886.58; found ($M+H^+$) 887.1; *Anal.* calcd. (%) for $C_{46}H_{82}N_2O_{14}$: C 62.28, H 9.32, N 3.16; found: C 62.25, H 9.30, N 3.19.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(3-methoxypropyl)carbamoyl) erythromycin A (10e)

White solid, yield 74.6%, m.p. 224–227 °C; IR (KBr): 3445, 2973, 2935, 1725, 1461, 1377, 1345, 1170, 1112, 1059, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.17 (m, 1H), 4.99–4.97 (m, 2H), 4.58 (d, *J*=7.2 Hz, 1H), 4.53 (d, *J*=9.8 Hz, 1H), 4.32 (m, 1H), 3.76 (d, *J*=6.6 Hz, 1H), 3.73–3.69 (m, 2H), 3.58 (s, 3H), 3.51–3.43 (m, 3H), 3.33 (s, 3H), 3.32 (s, 3H), 3.20 (m, 1H), 3.10 (s, 3H), 3.08–3.02 (m, 2H), 2.98 (m, 1H), 2.63–2.55 (m, 2H), 2.43 (d, *J*=15.1 Hz, 1H), 2.32 (s, 6H), 2.08–2.03 (m, 2H), 1.95–1.85 (m, 2H), 1.83–1.76 (m, 3H), 1.68–1.63 (m, 4H), 1.52–1.43 (m, 2H), 1.39 (s, 3H), 1.34 (m, 1H), 1.25–1.08 (m, 21H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.3, 101.9, 96.4, 79.4, 78.9, 78.8, 78.4, 77.7, 76.0, 72.9, 71.5, 71.2, 67.7, 65.1, 63.4, 60.8, 58.8, 50.6, 49.4, 45.6, 44.7, 40.2, 39.6, 37.9, 37.8, 37.6, 35.4, 29.7, 29.6, 28.9, 21.7, 21.5, 20.9, 20.2, 19.4, 18.4, 17.4, 16.0, 12.8, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{44}H_{80}N_2O_{15}$ 876.56; found ($M+H^+$) 877.2; *Anal.* calcd. (%) for $C_{44}H_{80}N_2O_{15}$: C 60.25, H 9.19, N 3.19; found: C 60.22, H 9.20, N 3.18.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(3-ethoxypropyl)carbamoyl) erythromycin A (10f)

White solid, yield 76.8%, m.p. 198–202 °C; IR (KBr): 3444, 2975, 2935, 2875, 1727, 1504, 1459, 1378, 1266, 1166, 1111, 1051, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (m, 1H), 4.99–4.96 (m, 2H), 4.57 (d, *J*=7.3 Hz, 1H), 4.53 (d, *J*=9.7 Hz, 1H), 4.31 (m, 1H), 3.76 (d, *J*=6.5 Hz, 1H), 3.75–3.66 (m, 2H), 3.59 (s, 3H), 3.50–3.43 (m, 5H), 3.32 (s, 3H), 3.19 (m, 1H), 3.10 (s, 3H), 2.99–2.97 (m, 2H), 2.93 (m, 1H), 2.63–2.55 (m, 2H), 2.43 (d, *J*=14.4 Hz, 1H), 2.32 (s, 6H), 2.08–2.05 (m, 3H), 1.99–1.89 (m, 3H), 1.86 (m, 1H), 1.80–1.77 (m, 2H), 1.69–1.63 (m, 3H), 1.49 (m, 1H), 1.39 (s, 3H), 1.34 (m, 1H), 1.27–1.12 (m, 21H), 1.11–1.09 (m, 3H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.3, 101.9, 96.4, 79.4, 78.9, 78.5, 77.7, 76.0, 72.9, 71.2, 68.6, 67.7, 66.3, 65.1, 63.5, 60.8, 50.6, 49.4, 45.6, 44.7, 40.2, 39.3, 37.9, 37.8, 37.6, 35.4, 29.8, 29.7, 28.9, 21.7, 21.5, 20.8, 20.3, 19.4, 18.4, 17.4, 16.0, 15.1, 12.8, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{45}H_{82}N_2O_{15}$ 890.57;

Table 1 ***In vitro*** **antibacterial activities of prepared macrolides**

	MIC ($\mu g\ ml^{-1}$)						
	S. aureus			*S. pneumoniae*		*H. influenzae*	
Compound	*ATCC25923*	*A265*	*A333*	*ATCC49619*	*3469*	*ATCC49247*	*3300*
10a	1.000	2.000	32.000	0.125	0.125	>64.000	4.000
10b	2.000	2.000	64.000	0.125	0.125	>64.000	4.000
10c	0.125	0.250	32.000	0.250	2.000	64.000	2.000
10d	4.000	4.000	>64.000	0.125	0.125	>64.000	4.000
10e	0.125	0.250	>64.000	0.500	0.500	>64.000	1.000
10f	1.000	1.000	>64.000	0.125	0.125	>64.000	2.000
10g	0.125	1.000	64.000	0.125	0.125	64.000	1.000
10h	0.125	2.000	>64.000	0.250	0.125	>64.000	4.000
10i	0.125	0.125	>64.000	0.125	32.000	>64.000	0.250
10j	0.125	2.000	64.000	1.000	1.000	>64.000	2.000
10k	0.125	0.500	64.000	0.125	0.125	>64.000	4.000
10l	0.250	0.500	16.000	0.125	0.125	>64.000	2.000
10m	0.125	0.125	32.000	0.125	0.125	>64.000	0.250
10n	0.125	0.125	32.000	0.125	8.000	>64.000	0.125
10o	0.125	0.125	8.000	0.125	16.000	>64.000	0.125
10p	0.125	1.000	64.000	0.500	0.125	>64.000	1.000
10q	0.125	2.000	>64.000	0.250	0.250	32.000	2.000
10r	0.125	0.125	>64.000	0.125	16.000	>64.000	0.125
10s	0.125	0.125	64.000	0.125	0.125	>64.000	2.000
10t	0.125	0.125	64.000	0.125	0.125	16.000	4.000
10u	0.125	0.500	64.000	0.125	0.125	8.000	0.250
10v	0.500	0.250	8.000	0.125	0.125	16.000	0.250
10w	0.125	0.125	16.000	0.125	0.500	8.000	4.000
10x	0.125	0.500	32.000	0.125	0.125	>64.000	0.125
10y	0.125	0.125	8.000	0.125	0.125	4.000	0.125
AZM	0.500	8.000	>64.000	0.125	0.125	4.000	4.000
CAM	0.250	4.000	>64.000	0.125	0.125	8.000	8.000
EMA	0.125	2.000	>64.000	0.125	0.125	16.000	16.000

Abbreviations: AZM, azithromycin; CAM, clarithromycin; EMA, erythromycin; *H. influenzae, Haemophilus influenzae*; MIC, minimal inhibitory concentration; *S. aureus, Staphylococcus aureus; S. pneumoniae, Streptococcus pneumoniae.*
S. aureus ATCC25923: erythromycin-susceptible strain. *S. aureus* A265: erythromycin-resistant and methicillin-susceptible strain. *S. aureus* A333: erythromycin-resistant and methicillin-resistant strain. *S. pneumoniae* ATCC49619: erythromycin-susceptible strain. *S. pneumoniae* 3469: erythromycin-resistant strain. *H. influenzae* ATCC49247: ampicillin-susceptible strain. *H. influenzae* 3300: ampicillin-resistant strain.

found (M+H$^+$) 891.2; *Anal.* calcd. (%) for $C_{45}H_{82}N_2O_{15}$: C 60.65, H 9.27, N 3.14; found: C 60.62, H 9.24, N 3.17.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(3-isopropoxypropyl)carbamoyl) erythromycin A (10g)

White solid, yield 70.8%, m.p. 173–176 °C; IR (KBr): 3438, 2972, 2932, 1728, 1716, 1506, 1378, 1265, 1168, 1129, 1051, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (m, 1H), 4.92–4.90 (m, 2H), 4.50 (d, J=7.2 Hz, 1H), 4.46 (d, J=9.8 Hz, 1H), 4.24 (m, 1H), 3.69 (d, J=6.4 Hz, 1H), 3.62–3.60 (m, 2H), 3.51 (s, 3H), 3.45–3.39 (m, 5H), 3.24 (s, 3H), 3.16–3.12 (m, 2H), 3.03 (s, 3H), 3.00–2.97 (m, 2H), 2.92 (m, 1H), 2.56–2.47 (m, 2H), 2.36 (d, J=15.1 Hz, 1H), 2.26 (s, 6H), 2.01–1.92 (m, 3H), 1.87–1.76 (m, 3H), 1.72–1.68 (m, 2H), 1.61–1.56 (m, 4H), 1.43 (m, 1H), 1.32 (s, 3H), 1.27 (m, 1H), 1.20–1.07 (m, 18H), 1.05–1.02 (m, 6H), 0.85–0.74 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 216.4, 174.5, 155.3, 100.9, 95.4, 78.3, 77.9, 77.8, 77.4, 76.7, 76.3, 75.0, 71.9, 70.6, 70.1, 66.7, 64.1, 62.5, 59.8, 49.6, 48.4, 44.6, 43.7, 39.2, 38.4, 36.9, 36.8, 36.6, 34.4, 29.0, 28.6, 27.9, 21.1, 21.0, 20.7, 20.5, 19.8, 19.2, 18.4, 17.3, 16.4, 15.0, 11.8, 9.5, 8.3; MS (ESI) m/z calcd. for $C_{46}H_{84}N_2O_{15}$ 904.59; found (M+H$^+$) 905.2; *Anal.* calcd. (%) for $C_{46}H_{84}N_2O_{15}$: C 61.04, H 9.35, N 3.09; found: C 61.01, H 9.32, N 3.08.

6,11-Di-*O* -methyl-4″-*O*-(*N*-(3-butoxypropyl)carbamoyl) erythromycin A (10h)

White solid, yield 75.1%, m.p. 148–152 °C; IR (KBr): 3459, 2962, 2929, 2863, 1725, 1461, 1382, 1348, 1268, 1171, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (m, 1H), 4.92–4.90 (m, 2H), 4.51 (d, J=7.1 Hz, 1H), 4.46 (d, J=9.7 Hz, 1H), 4.15 (m, 1H), 3.69 (d, J=6.2 Hz, 1H), 3.64–3.60 (m, 2H), 3.51 (s, 3H), 3.40–3.32 (m, 5H), 3.24 (s, 3H), 3.18 (m, 1H), 3.03 (s, 3H), 3.01–2.96 (m, 2H), 2.92 (m, 1H), 2.56–2.51 (m, 2H), 2.36 (d, J=15.3 Hz, 1H), 2.27 (s, 6H), 2.01–1.97 (m, 2H), 1.90–1.76 (m, 2H), 1.73–1.69 (m, 2H), 1.67–1.55 (m, 5H), 1.51–1.44 (m, 2H), 1.40–1.34 (m, 4H), 1.32 (s, 3H), 1.28 (m, 1H), 1.20–1.07 (m, 18H), 0.93–0.81 (m, 6H), 0.78–0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.4, 175.5, 156.3, 101.9, 96.4, 79.3, 78.9, 78.8, 78.5, 77.7, 76.0, 72.9, 71.2, 70.9, 68.8, 67.7, 65.1, 63.5, 60.8, 50.6, 49.5, 45.6, 44.7, 40.2, 38.7, 37.9, 37.6, 35.4, 31.7, 30.5, 29.7, 28.9, 23.7, 23.0, 21.7, 20.8, 20.3, 19.2, 18.4, 17.4, 16.0, 13.9, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{47}H_{86}N_2O_{15}$ 918.60; found (M+H$^+$) 919.2; *Anal.* calcd. (%) for $C_{47}H_{86}N_2O_{15}$: C 61.41, H 9.43, N 3.05; found: C 61.38, H 9.41, N 3.07.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(3-hydroxypropyl)carbamoyl) erythromycin A (10i)

White solid, yield 66.3%, m.p. 67–72 °C; IR (KBr): 3473, 2962, 2925, 2855, 1722, 1461, 1374, 1257, 1169, 1090, 1052, 938 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99–4.97 (m, 2H), 4.78 (m, 1H), 4.64 (d, J=11.2 Hz, 1H), 4.03 (m, 1H), 3.73 (d, J=6.0 Hz, 1H), 3.65–3.57 (m, 2H), 3.59 (s, 3H), 3.58–3.48 (m, 3H), 3.43 (s, 1H), 3.39 (s, 3H), 3.10 (m, 1H), 3.09 (s, 3H), 3.07–3.03 (m, 2H), 2.99 (m, 1H), 2.69–2.58 (m, 2H), 2.38 (d, J=15.0 Hz, 1H), 2.27 (s, 6H), 2.23 (m, 1H), 2.10–1.99 (m, 4H), 1.97–1.92 (m, 2H), 1.76–1.72 (m, 3H), 1.69–1.62 (m, 2H), 1.55–1.42 (m, 2H), 1.39 (s, 3H), 1.32–1.24 (m, 11H), 1.16–1.11 (m, 6H), 0.89–0.82 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.4, 175.4, 170.0, 100.2, 96.1, 81.2, 79.5, 78.9, 78.3, 77.8, 77.5, 76.0, 72.8, 71.8, 68.1, 66.0, 63.5, 60.8, 50.4, 49.3, 45.8, 45.6, 44.9, 40.7, 37.9, 37.8, 37.2, 35.0, 31.9, 29.7, 29.4, 22.7, 21.6, 21.5, 21.3, 20.4, 18.7, 17.6, 16.1, 12.8, 10.4, 9.1; MS (ESI) m/z calcd. for $C_{43}H_{78}N_2O_{15}$ 862.54; found (M+H$^+$) 862.9; *Anal.* calcd. (%) for $C_{43}H_{78}N_2O_{15}$: C 59.84, H 9.11, N 3.25; found: C 59.82, H 9.09, N 3.27.

611-Di-*O*-methyl-4″-*O*-(*N*-furfurylcarbamoyl)erythromycin A (10j)

White solid, yield 63.7%, m.p. 240–243 °C; IR (KBr): 3481, 3333, 2976, 2942, 2360, 1733, 1684, 1507, 1457, 1381, 1246, 1126, 1107, 1052, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J=3.1 Hz, 2H), 6.34 (m, 1H), 6.25 (d, J=3.2 Hz, 1H), 5.13 (m, 1H), 5.01–4.98 (m, 2H), 4.58–4.56 (m, 2H), 4.41–4.40 (m, 2H), 4.34 (m, 1H), 3.76 (d, J=6.8 Hz, 1H), 3.73–3.71 (m, 2H), 3.51 (s, 3H), 3.45 (m, 1H), 3.36 (s, 3H), 3.21 (m, 1H), 3.12 (s, 3H), 3.08–3.06 (m, 2H), 3.01 (m, 1H), 2.62–2.55 (m, 2H), 2.45 (d, J=14.8 Hz, 2H), 2.32 (s, 6H), 2.24 (m, 1H), 2.07 (m, 1H), 1.91 (m, 1H), 1.84 (m, 1H), 1.82–1.58 (m, 6H), 1.37 (s, 3H), 1.33 (m, 1H), 1.32–1.26 (m, 18H), 0.87–0.83 (m, H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.5, 156.1, 142.2, 110.4, 107.1, 102.0, 96.4, 79.4, 79.2, 78.9, 78.6, 77.7, 76.0, 72.9, 71.2, 67.8, 65.0, 63.4, 60.8, 50.5, 49.5, 45.6, 44.7, 40.2, 38.0, 37.9, 37.6, 35.3, 29.7, 28.8, 21.6, 21.5, 20.8, 20.2, 19.4, 18.3, 17.4, 16.0, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{45}H_{80}N_2O_{15}$ 888.56; found (M+H$^+$) 889.1; *Anal.* calcd. (%) for $C_{47}H_{86}N_2O_{15}$:C 60.79, H 9.07, N 3.15; found: C 60.78, H 9.04, N 3.13.

6,11-Di-*O*-methyl-4″-*O*-(*N*-benzylcarbamoyl)erythromycin A (10k)

White solid, yield 73.6%, m.p. 234–238 °C; IR (KBr): 3357, 2976, 2939, 1723, 1460, 1383, 1346, 1257, 1168, 1103, 1071, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.32 (m, 2H), 7.30–7.27 (m, 3H), 5.22 (m, 1H), 4.99–4.97 (m, 2H), 4.59–4.53 (m, 2H), 4.42–4.41 (m, 2H), 4.33 (m, 1H), 3.75 (d, J=6.4 Hz, 1H), 3.71 (d, J=10.0 Hz, 1H), 3.65 (m, 1H), 3.59 (s, 3H), 3.46–3.34 (m, 2H), 3.32 (s, 3H), 3.19 (m, 1H), 3.11 (s, 3H), 3.08–3.00 (m, 3H), 2.61 (m, 1H), 2.52 (m, 1H), 2.44 (d, J=15.1 Hz, 1H), 2.27 (s, 6H), 2.16–1.95 (m, 3H), 1.93–1.86 (m, 3H), 1.70–1.59 (m, 3H), 1.49 (m, 1H), 1.40 (s, 3H), 1.30 (m, 1H), 1.26–1.09 (m, 21H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.2, 175.6, 156.4, 138.4, 128.7, 127.6, 127.3, 102.1, 96.4, 79.5, 79.1, 78.9, 78.6, 77.7, 76.1, 72.9, 71.2, 67.8, 65.0, 63.4, 60.8, 50.6, 49.5, 45.6, 45.2, 44.8, 40.2, 38.0, 37.9, 37.7, 35.4, 29.7, 28.8, 21.7, 21.5, 20.9, 20.3, 19.4, 18.4, 17.4, 16.0, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{47}H_{78}N_2O_{14}$ 894.55; found (M+H$^+$) 895.1;

Anal. calcd. (%) for $C_{47}H_{78}N_2O_{14}$: C 63.06, H 8.78, N 3.13; found: C 63.03, H 8.76, N 3.16.

6,11-Di-*O*-methyl-4″-*O* -(*N*-(4-methoxybenzyl)carbamoyl) erythromycin A (10l)

White solid, yield 69.2%, m.p. 193–196 °C; IR (KBr): 3402, 2972, 2935, 2360, 1722, 1620, 1461, 1379, 1242, 1172, 1103, 1078, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J=8.3 Hz, 2H), 6.85 (d, J=8.4 Hz, 2H), 5.11 (m, 1H), 4.96 (m, 2H), 4.57–4.52 (m, 2H), 4.33–4.32 (m, 3H), 3.78 (s, 3H), 3.74 (d, J=6.5 Hz, 1H), 3.69 (d, J=6.1 Hz, 1H), 3.57 (m, 1H), 3.42 (s, 3H), 3.39–3.34 (m, 2H), 3.29 (s, 3H), 3.22 (m, 1H), 3.09 (s, 3H), 3.07–2.99 (m, 3H), 2.71–2.60 (m, 2H), 2.42 (d, J=15.2 Hz, 1H), 2.26 (s, 6H), 2.16–1.95 (m, 3H), 1.90–1.84 (m, 2H), 1.68–1.62 (m, 4H), 1.58–1.42 (m, 2H), 1.38 (s, 3H), 1.31 (m, 1H), 1.27–0.94 (m, 18H), 0.90–0.86 (m, 3H), 0.84–0.80 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.5, 159.0, 156.3, 130.5, 128.6, 114.0, 102.0, 96.4, 79.3, 79.0, 78.9, 78.5, 77.7, 77.5, 76.0, 72.8, 71.1, 67.7, 64.9, 63.4, 60.7, 59.0, 55.2, 50.6, 49.4, 45.8, 44.7, 44.6, 40.2, 37.9, 37.8, 37.6, 35.3, 29.6, 28.7, 21.6, 21.5, 20.8, 20.2, 19.4, 18.4, 17.4, 16.0, 12.8, 10.4, 9.2; MS (ESI) *m/z* calcd. for $C_{48}H_{80}N_2O_{15}$ 924.56; found ($M+H^+$) 925.1; *Anal.* calcd. (%) for $C_{48}H_{80}N_2O_{15}$: C 62.32, H 8.72, N 2.88; found: C 62.30, H 8.69, N 2.90.

611-Di-*O*-methyl-4″-*O*-(*N*-(4-fluorobenzyl)carbamoyl) erythromycin A (10m)

White solid, yield 68.5%, m.p. 129–133 °C; IR (KBr): 3399, 2968, 2937, 1723, 1616, 1517, 1462, 1379, 1344, 1256, 1172, 1102, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22–7.19 (m, 2H), 6.88–6.86 (m, 2H), 5.11 (m, 1H), 5.00 (m, 2H), 4.59–4.54 (m, 2H), 4.35–4.34 (m, 3H), 3.75 (d, J=6.3 Hz, 1H), 3.71 (d, J=10.0 Hz, 1H), 3.66 (m, 1H), 3.59 (s, 3H), 3.44 (s, 1H), 3.31 (s, 3H), 3.20 (m, 2H), 3.11 (s, 3H), 3.08–3.03 (m, 2H), 3.01 (m, 1H), 2.61–2.53 (m, 2H), 2.44 (d, J=15.4 Hz, 1H), 2.30 (s, 6H), 2.17 (s, 1H), 2.08–2.05 (m, 2H), 1.95–1.89 (m, 2H), 1.83 (m, 1H), 1.70–1.63 (m, 3H), 1.50 (m, 1H), 1.40 (s, 3H), 1.32 (m, 1H), 1.26–1.09 (m, 21H), 0.86–0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.5, 159.0, 156.3, 130.5, 128.7, 114.0, 101.9, 96.4, 79.4, 79.0, 78.9, 78.5, 76.0, 72.9, 71.1, 67.7, 65.0, 63.4, 60.8, 55.2, 50.6, 49.4, 45.5, 44.7, 44.6, 40.2, 37.9, 37.8, 37.6, 35.3, 29.6, 28.9, 21.6, 21.5, 20.8, 20.2, 19.4, 18.4, 17.4, 16.0, 12.8, 10.4, 9.3; MS (ESI) *m/z* calcd. for $C_{47}H_{77}FN_2O_{14}$ 912.54; found ($M+H^+$) 913.1; *Anal.* calcd. (%) for $C_{47}H_{77}FN_2O_{14}$: C 61.82, H 8.50, F 2.08, N 3.07; found: C 61.78, H 8.48, F 2.07, N 3.09.

611-Di-*O*-methyl-4″-*O*-(*N*-(4-chlorobenzyl)carbamoyl) erythromycin A (10n)

White solid, yield 73.3%, m.p. 123–127 °C; IR (KBr): 3454, 2958, 2925, 2856, 1723, 1638, 1460, 1342, 1260, 1174, 1103, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J=8.7 Hz, 2H), 6.92 (d, J=9.1 Hz, 2H), 5.28 (m, 1H), 4.91–4.87 (m, 2H), 4.44 (d, J=7.2 Hz, 1H), 4.19–4.15 (m, 2H), 3.98 (m, 1H), 3.70 (d, J=6.7 Hz, 1H), 3.64–3.60 (m, 2H), 3.52 (s, 3H), 3.49–3.42 (m, 2H), 3.37 (s, 1H), 3.27 (s, 3H), 3.17 (m, 1H), 3.03 (s, 3H), 2.99–2.96 (m, 2H), 2.93 (m, 1H), 2.55–2.53 (m, 3H), 2.32 (s, 6H), 2.28–2.11 (m, 2H), 2.00–1.90 (m, 3H), 1.88–1.67 (m, 2H), 1.61–1.50 (m, 2H), 1.38 (m, 1H), 1.34 (s, 3H), 1.31 (m, 1H), 1.29–1.10 (m, 12H), 1.09–0.95 (m, 6H), 0.85–0.75 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.4, 175.6, 157.0, 139.9, 131.9, 130.0, 128.8, 102.4, 96.4, 79.9, 78.9, 78.7, 77.8, 77.5, 76.0, 72.1, 71.0, 68.4, 66.0, 65.6, 60.8, 50.5, 49.4, 45.4, 44.9, 41.2, 40.3, 38.2, 38.0, 37.7, 35.3, 29.7, 29.4, 22.7, 21.4, 20.4, 19.4, 18.7, 17.4, 16.0, 14.1, 12.8, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{47}H_{77}ClN_2O_{14}$ 928.51; found ($M+H^+$) 929.2; *Anal.* calcd. (%) for $C_{47}H_{77}ClN_2O_{14}$: C 60.73, H 8.35, Cl 3.81, N 3.01; found: C 60.70, H 8.32, Cl 3.79, N 3.03.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(4-bromobenzyl)carbamoyl) erythromycin (10o)

White solid, yield 74.6%, m.p. 113–117 °C; IR (KBr): 3446, 3280, 2956, 2924, 2852, 1729, 1646, 1557, 1458, 1382, 1260, 1176, 1091, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.4 Hz, 2H), 7.16(d, J=8.3 Hz, 2H), 4.98 (m, 1H), 4.95–4.94 (m, 2H), 4.50 (d, J=7.2 Hz, 1H), 4.39–4.38 (m, 2H), 4.05 (m, 1H), 3.77 (d, J=6.7 Hz, 1H), 3.71 (m, 1H), 3.59 (s, 3H), 3.55 (m, 2H), 3.49 (s, 1H), 3.44 (s, 1H), 3.34 (s, 3H), 3.26 (m, 1H), 3.10 (s, 3H), 3.07–3.02 (m, 2H), 3.00 (m, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 2.39 (m, 1H), 2.36 (s, 6H), 2.23 (m, 1H), 1.97–1.84 (m, 2H), 1.82–1.72 (m, 3H), 1.66–1.62 (m, 2H), 1.60–1.59 (m, 1H), 1.46 (m, 1H), 1.41 (s, 3H), 1.38 (m, 1H), 1.31–1.21 (m, 12H), 1.15–1.09 (m, 9H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 155.1, 137.4, 131.7, 129.5, 121.3, 102.4, 96.3, 79.8, 79.0, 77.4, 77.1, 76.0, 72.8, 71.0, 68.2, 66.0, 65.6, 60.8, 50.6, 49.5, 45.5, 44.9, 43.0, 40.3, 38.2, 38.0, 37.6, 35.0, 29.7, 23.2, 22.7, 21.7, 21.5, 20.4, 19.4, 18.7, 16.1, 14.1, 12.8, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{47}H_{77}BrN_2O_{14}$ 972.46; found ($M+H^+$) 973.1; *Anal.* calcd. (%) for $C_{47}H_{77}BrN_2O_{14}$: C 57.96, H 7.97, Br 8.20, N 2.88; found: C 57.93, H 7.94, Br 8.18, N 2.89.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(4-hydroxybenzyl)carbamoyl) erythromycin A (10p)

White solid, yield 65.8%, m.p. 135–139 °C; IR (KBr): 3446, 2975, 2935, 2359, 1732, 1558, 1457, 1383, 1260, 1171, 1108, 1073, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J=8.3 Hz, 2H), 6.78 (d, J=8.2 Hz, 2H), 5.30 (m, 1H), 5.21 (m, 1H), 4.99–4.97 (m, 2H), 4.63–4.50 (m, 2H), 4.35–4.21 (m, 3H), 3.74 (d, J=6.6 Hz, 1H), 3.70 (d, J=9.9 Hz, 1H), 3.66 (m, 1H), 3.59 (s, 3H), 3.44 (m, 1H), 3.11 (s, 3H), 3.25–3.16 (m, 2H), 3.10 (s, 3H), 3.06–3.00 (m, 3H), 2.72–2.53 (m, 2H), 2.43 (d, J=14.8 Hz, 1H), 2.31 (s, 6H), 2.18–1.97 (m, 3H), 1.91–1.82 (m, 2H), 1.67–1.59 (m, 4H), 1.49 (m, 1H), 1.39 (s, 3H), 1.34–1.30 (m, 2H), 1.29–1.04 (m, 18H), 0.91–0.82 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.8, 175.6, 156.7, 156.3, 129.0, 128.8, 115.7, 102.0, 96.4, 79.5, 78.9, 78.6, 77.7, 76.1, 73.0, 71.2, 67.7, 64.8, 63.5, 60.8, 53.5, 50.6, 49.5, 44.8, 44.7, 40.2, 38.0, 37.9, 37.7, 35.3, 29.7, 28.5, 21.6, 21.5, 20.9, 20.3, 19.4, 18.4, 17.4, 16.1, 12.8, 10.5, 9.4; MS (ESI) *m/z* calcd. for $C_{47}H_{78}N_2O_{15}$ 910.54; found ($M+H^+$) 910.0; *Anal.* calcd. (%) for $C_{47}H_{78}N_2O_{15}$: C 61.96, H 8.63, N 3.07; found: C 61.94, H 8.60, N 3.09.

6,11-Di-*O*-methyl-4″-*O* -(*N*-(phenylethyl)carbamoyl) erythromycin A (10q)

White solid, yield 78.6%, m.p. 204–207 °C; IR (KBr): 3528, 3460, 3282, 2975, 2936, 1719, 1459, 1398, 1344, 1255, 1173, 1056, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.30 (m, 2H), 7.26–7.19 (m, 3H), 4.99–4.98 (m, 2H), 4.80 (m, 1H), 4.53 (d, J=8.8 Hz, 1H), 3.74 (d, J=6.3 Hz, 1H), 3.71 (d, J=10.4 Hz, 1H), 3.59 (s, 3H), 3.56–3.54 (m, 2H), 3.49–3.44 (m, 2H), 3.30 (s, 3H), 3.19 (m, 1H), 3.11 (s, 3H), 3.06 (m, 1H), 2.99 (m, 1H), 2.89–2.85 (m, 2H), 2.60 (m, 1H), 2.54 (m, 1H), 2.43 (d, J=15.2 Hz, 1H), 2.31 (s, 6H), 2.17 (m, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.67–1.63 (m, 2H), 1.58 (m, 1H), 1.48 (m, 1H), 1.39 (s, 3H), 1.34 (m, 1H), 1.26 (s, 3H), 1.23–1.04 (m, 21H), 0.86–0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.2, 138.6, 128.8, 128.6, 126.6, 102.0, 96.4, 79.4, 78.9, 77.7, 77.4, 77.3, 77.1, 76.7, 76.0, 72.9, 71.2, 67.7, 65.0, 63.4, 60.8, 50.6, 49.5, 45.6, 44.8, 42.1, 40.2, 38.0, 37.9, 37.7, 35.9, 35.4, 29.7, 28.8, 21.6, 21.5, 20.9, 20.3, 19.5, 18.3, 17.4, 16.1, 12.8, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{48}H_{80}N_2O_{14}$ 908.56; found ($M+H^+$) 909.2; *Anal.* calcd. (%) for $C_{47}H_{78}N_2O_{15}$: C 63.41, H 8.87, N 3.08; found: C 63.38, H 8.85, N 3.06.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(4-methoxyphenylethyl)carbamoyl) erythromycin A (10r)

White solid, yield 64.8%, m.p.146–149 °C; IR (KBr): 3453, 2960, 2925, 2857, 1730, 1460, 1377, 1262, 1171, 1080, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67–7.63 (m, 2H), 7.47–7.45 (m, 2H), 4.91–4.87 (m, 2H), 4.42 (d, J=7.2 Hz, 1H), 4.19–4.10 (m, 2H), 3.96 (m, 1H), 3.74 (m, 1H), 3.69 (d, J=6.7 Hz, 1H), 3.63 (d, J=9.7 Hz, 1H), 3.52 (s, 3H), 3.47–3.37 (m, 3H), 3.26 (s, 3H), 3.14 (m, 1H), 3.03 (s, 3H), 2.99–2.89 (m, 2H), 2.86 (m, 1H), 2.71 (m, 1H), 2.54 (m, 1H), 2.40 (m, 1H), 2.30 (d, J=15.3 Hz, 1H), 2.25 (s, 6H), 2.13 (m, 1H), 1.98 (m, 1H), 1.87–1.76 (m, 2H), 1.68–1.51 (m, 3H), 1.44–1.38 (m, 2H), 1.34 (s, 3H), 1.30 (m, 1H), 1.32–1.02 (m, 12H), 0.98–0.80 (m, 6H), 0.78–0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 216.3, 174.5, 166.7, 160.1, 131.4, 129.9, 127.8, 101.4, 95.3, 80.5, 78.9, 78.0, 76.9, 75.0, 71.7, 70.0, 67.5, 67.1, 64.9, 64.5, 59.8, 54.3, 49.5, 48.5, 44.5, 43.9, 41.8, 39.2, 38.3, 37.7, 37.2, 36.9, 36.7, 29.3, 27.9, 22.7, 22.0, 21.7, 20.4, 19.3, 18.4, 18.2, 17.7, 13.0, 9.9, 9.5; MS (ESI) *m/z* calcd. for $C_{49}H_{82}N_2O_{15}$ 938.57; found ($M+H^+$) 939.2; *Anal.* calcd. (%) for $C_{49}H_{82}N_2O_{15}$: C 62.66, H 8.80, N 2.98; found: C 62.63, H 8.78, N 2.96.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(3,4-dimethoxyphenylethyl)carbamoyl) erythromycin A (10s)

White solid, yield 74.9%, m.p. 217–220 °C; IR (KBr): 3446, 2974, 2937, 1730, 1652, 1558, 1516, 1457, 1378, 1237, 1171, 1109, 1074, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (m, 1H), 6.72 (m, 2H), 4.97 (d, J=7.2 Hz, 2H), 4.85 (m, 1H), 4.52 (d, J=9.0 Hz, 2H), 4.28 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.73 (d, J=6.4 Hz, 1H), 3.69 (d, J=10.2 Hz, 1H), 3.58 (s, 3H), 3.53–3.36 (m, 3H), 3.32 (m, 1H), 3.30 (s, 3H), 3.19 (m, 1H), 3.10 (s, 3H), 3.07–3.04 (m, 2H), 2.99 (m, 1H), 2.79 (m, 2H), 2.64–2.54 (m, 2H), 2.42 (d, J=15.1 Hz, 1H), 2.31 (s, 6H), 2.16 (m, 1H), 2.06 (m, 1H), 1.97–1.82 (m, 2H), 1.65–1.57 (m, 3H), 1.49–1.43 (m, 2H), 1.38 (s, 3H), 1.32 (m, 1H), 1.31–1.04 (m, 21H), 0.85–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.5, 156.2, 149.0, 147.7, 130.9, 120.7, 111.8, 111.2, 101.9, 96.4, 79.4, 78.9, 78.5, 77.7, 76.0, 72.9, 71.1, 67.7, 64.9, 63.4, 60.8, 58.8, 55.9, 55.8, 50.6, 49.4, 45.5, 44.7, 42.2, 40.2, 37.9, 37.8, 37.6, 35.5, 35.3, 29.7, 28.8, 21.6, 21.5, 20.8, 20.3, 19.4, 18.3, 17.4, 16.0, 12.8, 10.5, 9.3, 8.3; MS (ESI) m/z calcd. for $C_{50}H_{84}N_2O_{16}$ 968.58; found ($M+H^+$) 969.3; *Anal.* calcd. (%) for $C_{50}H_{84}N_2O_{16}$: C 61.96, H 8.74, N 2.89; found: C 61.94, H 8.71, N 2.86.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(4-hydroxyphenylethyl)carbamoyl) erythromycin A (10t)

White solid, yield 74.3%, m.p. 78–81 °C; IR (KBr): 3371, 2976, 2937, 1721, 1657, 1554, 1461, 1379, 1257, 1171, 1078, 939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, J=7.9 Hz, 2H), 6.73 (d, J=8.3 Hz, 2H), 5.30–5.21 (m, 3H), 4.87–4.85 (m, 2H), 4.46 (m, 1H), 3.58 (d, J=7.1 Hz,1H), 3.56–3.54 (m, 2H), 3.46 (s, 3H), 3.45–3.41 (m, 3H), 3.26 (s, 3H), 3.23 (m, 1H), 3.13 (s, 3H), 3.10–3.08 (m, 2H), 2.98 (m, 1H), 2.95–2.88 (m, 2H), 2.61–2.49 (m, 5H), 2.32 (s,6H), 2.16 (m, 1H), 2.02–1.97 (m, 2H), 1.80 (m, 1H), 1.69–1.62 (m, 3H), 1.55–1.52 (m, 2H), 1.31 (s, 3H), 1.26 (m, 1H), 1.22–0.98 (m, 21H), 0.73–0.70 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.7, 175.4, 156.2, 156.0, 132.2, 130.9, 129.6, 115.7, 115.6, 101.6, 96.3, 79.4, 78.8, 78.5, 78.3, 77.7, 76.0, 72.9, 71.0, 67.2, 64.9, 63.4, 60.2, 50.5, 49.4, 44.7, 42.3, 40.1, 39.6, 38.1, 37.5, 34.8, 34.4, 30.5, 29.6, 23.1, 21.5, 21.3, 20.8, 20.3, 19.3, 18.3, 17.4, 16.0, 12.8, 10.4, 9.4; MS (ESI) m/z calcd. for $C_{48}H_{80}N_2O_{15}$ 924.56; found ($M+H^+$) 925.2; *Anal.* calcd. (%) for $C_{48}H_{80}N_2O_{15}$: C 62.32, H 8.72, N 3.03; found: C 62.29, H 8.70, N 3.05.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(4-fluorophenylethyl)carbamoyl) erythromycin A (10u)

White solid, yield 69.5%, m.p. 71–75 °C; IR (KBr): 3435, 2962, 2929, 1722, 1658, 1514, 1460, 1249, 1169, 1111, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.13 (m, 2H), 7.00–6.96 (m, 2H), 4.96–4.93 (m, 3H), 4.54 (d, J=7.2 Hz, 1H), 4.51 (d, J=9.8 Hz, 1H), 4.26 (m, 1H), 3.73 (d, J=6.5 Hz, 1H), 3.70 (d, J=10.0 Hz, 1H), 3.60 (m, 1H), 3.58 (s, 3H), 3.51–3.39 (m, 3H), 3.30 (s, 3H), 3.22 (m, 1H), 3.10 (s, 3H), 3.07–3.02 (m, 2H), 2.98 (m, 1H), 2.83–2.80 (m, 2H), 2.71–2.53 (m, 5H), 2.40 (s, 6H), 2.20 (m, 1H), 2.08–2.00 (m, 2H), 1.91 (m, 1H), 1.69–1.60 (m, 3H), 1.57–1.43 (m, 2H), 1.42 (s, 3H), 1.34 (m, 1H), 1.25–1.05 (m, 18H), 0.93–0.88 (m, 3H), 0.84–0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.3, 175.8, 163.0, 156.4, 134.3, 130.2, 130.1, 115.4, 115.2, 101.8, 96.4, 79.5, 78.9, 78.7, 78.5, 77.7, 76.0, 72.9, 71.1, 67.5, 64.8, 63.4, 60.8, 50.5, 49.4, 45.4, 44.7, 42.1, 40.1, 38.0, 37.6, 35.3, 35.1, 34.4, 31.9, 29.6, 22.6, 21.4, 20.8, 20.3, 19.4, 18.3, 17.4, 16.0, 12.8, 10.4, 9.3; MS (ESI) m/z calcd. for $C_{48}H_{79}FN_2O_{14}$ 926.55; found ($M+H^+$) 927.2; *Anal.* calcd. (%) for $C_{48}H_{79}FN_2O_{14}$: C 62.18, H 8.59, F 2.05, N 3.02; found: C 62.16, H 8.57, F 2.02, N 3.04.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(2-fluorophenylethyl)carbamoyl) erythromycin A (10v)

White solid, yield 77.0%, m.p. 134–138 °C; IR (KBr): 3534, 2964, 2934, 2360, 1722, 1652, 1495, 1383, 1231, 1172, 1107, 1053, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17–7.10 (m, 2H), 7.02–6.93 (m, 2H), 4.91–4.89 (m, 2H), 4.74 (m, 1H), 4.47–4.42 (m, 2H), 4.14 (m, 1H), 3.67 (d, J=6.7 Hz, 1H), 3.63 (d, J=9.95 Hz, 1H), 3.51 (s, 3H), 3.48–3.36 (m, 3H), 3.22 (s, 3H), 3.14 (m, 1H), 3.03 (s, 3H), 3.01–2.97 (m, 2H), 2.92 (m, 1H), 2.83–2.80 (m, 2H), 2.53 (m, 1H), 2.45 (m, 1H), 2.35 (d, J=15.1 Hz, 1H), 2.23 (s, 6H), 2.13 (m, 1H), 1.98 (m, 1H), 1.90–1.76 (m, 2H), 1.67–1.53 (m, 3H), 1.44–1.34 (m, 2H), 1.32 (s, 3H), 1.25 (m, 1H), 1.18–0.87 (m, 18H), 0.84–0.74 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 168.0, 156.2, 132.6, 130.9, 128.8, 124.2, 115.4, 101.9, 96.3, 79.4, 78.9, 78.6, 77.7, 76.0, 72.9, 71.2, 67.8, 65.6, 65.0, 63.4, 60.8, 50.6, 49.5, 45.7, 44.8, 41.1, 40.2, 37.9, 37.7, 35.4, 30.7, 29.7, 28.9, 21.7, 20.8, 20.3, 19.3, 18.3, 17.4, 16.1, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{48}H_{79}FN_2O_{14}$ 926.55; found ($M+H^+$) 927.2; *Anal.* calcd. (%) for $C_{48}H_{79}FN_2O_{14}$: C 62.18, H 8.59, F 2.05, N 3.02; found: C 62.15, H 8.57, F 2.02, N 3.05.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(2-chlorophenylethyl)carbamoyl) erythromycin A (10w)

White solid, yield 75.4%, m.p. 180–184 °C; IR (KBr): 3371, 2976, 2937, 1721, 1657, 1554, 1461, 1379, 1257, 1171, 1078, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 1H), 7.29–7.19 (m, 3H), 4.98–4.96 (m, 2H), 4.83 (m, 1H), 4.53–4.52 (m, 2H), 4.29 (m, 1H), 3.74 (d, J=6.2 Hz, 1H), 3.69 (d, J=9.5 Hz, 1H), 3.58 (s, 3H), 3.53–3.43 (m, 3H), 3.29 (s, 3H), 3.20 (m, 1H), 3.10 (s, 3H), 3.07–2.99 (m, 5H), 2.79 (m, 2H), 2.60–2.51 (m, 2H), 2.42 (d, J=15.1 Hz, 1H), 2.29 (s, 6H), 2.17 (m, 1H), 2.05 (m, 1H), 2.04–1.86 (m, 2H), 1.67–1.60 (m, 3H), 1.49–1.47 (m, 2H), 1.39 (s, 3H), 1.34 (m, 1H), 1.32–1.09 (m, 21H), 0.85–0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.2, 136.2, 134.2, 131.0, 129.6, 128.1, 126.9, 102.0, 96.4, 79.4, 78.9, 78.6, 77.7, 76.0, 72.9, 71.2, 67.8, 65.0, 63.4, 60.8, 50.6, 49.5, 45.6, 44.7, 40.6, 40.2, 38.0, 37.9, 37.7, 35.4, 33.7, 29.7, 28.7, 21.7, 21.5, 20.9, 20.3, 19.5, 18.3, 17.4, 16.1, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{48}H_{79}ClN_2O_{14}$ 942.52; found ($M+H^+$) 943.1; *Anal.* calcd. (%) for $C_{48}H_{79}ClN_2O_{14}$: C 61.10, H 8.44, Cl 3.76, N 2.97; found: C 61.07, H 8.41, Cl 3.73, N 3.00.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(2-bromophenylethyl)carbamoyl) erythromycin A (10x)

White solid, yield 71.5%, m.p. 157–160 °C; IR (KBr): 3461, 2970, 2928, 2360, 2341, 1712, 1461, 1378, 1344, 1246, 1172, 1108, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (m, 1H), 7.26–7.23 (m, 2H), 7.12 (m, 1H), 5.01–4.99 (m, 2H), 4.85 (m, 1H), 4.57–4.53 (m, 2H), 4.32 (m, 1H), 3.76 (d, J=7.0 Hz, 1H), 3.72 (d, J=9.7 Hz, 1H), 3.61 (s, 3H), 3.57–3.48 (m, 2H), 3.45 (s, 1H), 3.31 (s, 3H), 3.22 (m, 1H), 3.12 (s, 3H), 3.10–3.05 (m, 2H), 3.04–2.98 (m, 3H), 2.65–2.60 (m, 2H), 2.44 (d, J=15.2 Hz, 1H), 2.33 (s, 6H), 2.21 (m, 1H), 2.09–2.03 (m, 2H), 1.90 (m, 1H), 1.87 (m, 1H), 1.83–1.64 (m, 3H), 1.57–1.45 (m, 2H), 1.41 (s, 3H), 1.35–1.11 (m, 18H), 0.90–0.83 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.5, 175.6, 156.3, 138.0, 133.0, 131.0, 128.4, 127.6, 124.6, 102.0, 96.5, 81.2, 79.5, 78.6, 77.7, 76.1, 73.0, 71.2, 67.8, 65.0, 63.4, 60.8, 50.7, 49.5, 45.6, 44.8, 40.7, 40.3, 38.0, 37.9, 37.7, 36.1, 35.4, 29.7, 28.9, 21.7, 21.5, 20.9, 20.3, 19.5, 18.4, 17.4, 16.1, 12.8, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{48}H_{79}BrN_2O_{14}$ 986.47; found ($M+H^+$) 987.1; *Anal.* calcd. (%) for $C_{48}H_{79}BrN_2O_{14}$: C 58.35, H 8.06, Br 8.09, N 2.84; found: C 58.32, H 8.04, Br 8.07, N 2.86.

6,11-Di-*O*-methyl-4″-*O*-(*N*-(3,4-methylenedioxyphenethyl)carbamoyl) erythromycin A (10y)

White solid, yield 62.8%, m.p. 123–126 °C; IR (KBr): 3514, 2974, 2933, 1722, 1504, 1461, 1378, 1249, 1171, 1109, 1071, 1036, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (d, J=8.3 Hz, 1H), 6.60 (s, 1H), 6.56 (d, J=7.8 Hz, 1H), 5.86 (m, 2H), 4.96–4.89 (m, 2H), 4.78 (m, 1H), 4.47–4.43 (m, 2H), 4.20 (m, 1H), 3.67 (d, J=6.6 Hz, 1H), 3.63 (d, J=9.9 Hz, 1H), 3.51 (s, 3H), 3.43–3.25 (m, 3H), 3.23 (s, 3H), 3.13 (m, 1H), 3.03 (s, 3H), 3.00–2.97 (m, 2H), 2.92 (m, 1H), 2.70–2.66 (m, 2H), 2.56–2.46 (m, 2H), 2.35 (d, J=15.1 Hz, 1H), 2.25 (s, 6H), 2.09 (m, 1H), 2.01–1.90 (m, 2H), 1.87–1.75 (m, 2H), 1.61–1.53 (m, 3H), 1.42 (m, 1H), 1.31 (s, 3H), 1.25 (m, 1H), 1.10–0.99 (m, 21H), 0.77–0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.6, 175.8, 156.2, 147.9, 146.1, 132.3, 121.6, 109.0, 108.3, 101.9, 100.9, 96.4, 79.4, 78.9, 78.8, 78.6, 76.0, 72.9, 71.1, 67.7, 64.9, 63.4, 60.8, 50.6, 49.4, 45.6, 44.7, 42.3, 40.2, 37.9, 37.6, 35.6, 35.3, 29.6, 29.4, 29.1, 21.5, 20.8, 20.3, 19.4, 18.3, 17.4, 16.0, 14.1, 12.8, 10.4, 9.3; MS (ESI) m/z calcd. for $C_{49}H_{80}N_2O_{15}$ 952.55; found ($M+H^+$) 952.9; *Anal.* calcd. (%) for $C_{49}H_{80}N_2O_{15}$: C 61.74, H 8.46, N 2.94; found: C 61.71, H 8.44, N 2.96.

ACKNOWLEDGEMENTS

This research was supported by the Important National Science & Technology Specific Projects (No. 2009ZX09301-14).

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