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Original article

Synthesis and antibacterial activity of 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A: A novel class of acylides

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ABSTRACT

A novel series of acylides, 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A, were synthesized and evaluated for their antibacterial activity. These compounds have significant antibacterial activity against Gram-positive pathogens, including erythromycin-resistant but methicillin-susceptible *Staphylococcus aureus*, erythromycin-resistant and methicillin-resistant *S. aureus*, erythromycin-resistant *Streptococcus pneumoniae*, and Gram-negative pathogens, such as *Haemophilus influenzae*. Among the derivatives tested, compounds **4p**, **4r**, **4w**, **4x** and **4z** were found to have potent activity against most susceptible and resistant bacteria. Compound **4p** exhibited excellent antibacterial activity in comparison to the others.

1. 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 medical need for new antibiotics to address the problem of antibiotic resistance. Under these circumstances, a substantial amount work has been carried out on novel macrolides. These investigations have led to the discovery of the 3-acylides. Acylides, the C-3 acylated analogs of erythromycin A, were first reported in 1997 by Asaka et al. [7,8].

The C-3 cladinose group was long considered to be crucial for the antibacterial activity of erythromycin A. However, recent structural studies have revealed that the C3 substituent of macrolides and ketolides contributes little to the binding interaction with the bacterial ribosome, and appears to occupy a region of considerable steric bulk tolerance. In addition, researchers have shown that macrolides in which the cladinose sugar is replaced by a C3-*O*-acyl group are active against many bacterial respiratory pathogens, including erythromycin-resistant strains [9–11]. 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 [12–14]. The C-3 cladinose sugar attached to the 14-membered ring macrolides is believed to be responsible for the inducibility of macrolide resistance. This moiety also appears to be responsible for efflux resistance. Removal of the cladinose can also improve activity against efflux [15]. Both FMA 199 and FMA 481 (Fig. 1) appear to have well-balanced *in vitro* activity against *Streptococcus pneumoniae* [16]. TEA 0777 (Fig. 2) shows significant potent activity against erythromycin-susceptible Gram-positive pathogens and macrolides-lincosamides-streptogramin B (MLS_B) resistant *Staphylococcus aureus* and efflux-resistant *S. pneumoniae* [17]. FMA 0122 (Fig. 2) is active against *Haemophilus influenzae*. However, TEA 0929 (Fig. 2), which shows potent antibacterial activity against almost all of the main causative pathogens of community-acquired pneumonia tested, exhibits excellent *in vivo* efficacy [11]. These results indicate that acylides have potential as next-generation macrolide antibiotics.

The new macrolide derivatives such as FMA 199, FMA 481 (Fig. 1), TEA 0929, CP-544372 (Fig. 2), telithromycin (Fig. 3) [18] and cethromycin (Fig. 3) [19] are carbamate macrolide derivatives modified by introduction of various carbamate groups. The compound CP-544372 also demonstrates good *in vitro* and *in vivo*

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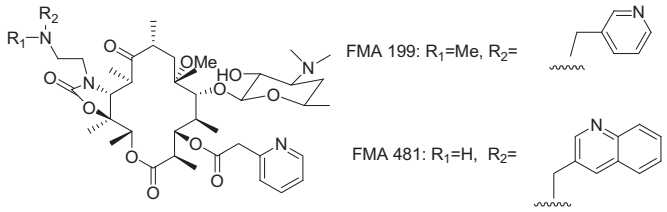


Fig. 1. Structures of FMA 199 and FMA 481.

activity against macrolide-susceptible and -resistant organisms [13–17]. Compounds **CAM-4j** and **CAM-4k** (Fig. 4) appeared potent activity against erythromycin-susceptible *S. aureus*, *Streptococcus pyogenes* and *S. pneumoniae*. Compounds **CAM-4d**, **CAM-4h** and **CAM-4i** (Fig. 4) showed potent activity against erythromycin-resistant *S. pneumoniae* encoded by the *mef* gene and compounds **CAM-4h** and **CAM-4i** displayed greatly improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* gene. Compound **AZM-7c** (Fig. 4) exhibited improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* and *mef* genes [20]. Also, 6,11-di-*O*-methylerythromycin A (Fig. 5) exhibits excellent *in vitro* and *in vivo* antibacterial activity against Gram-positive bacteria and *Mycoplasma pneumoniae* [21]. The structural modification of existing antibiotics, therefore, remains one of the most effective approaches for overcoming bacterial resistance.

On the basis of the above details, we obtained some new derivatives of 6,11-di-*O*-methylerythromycin A by substituting L-cladinose with various carbamate groups. Herein, we describe the synthesis and biological properties of a novel class of acylides, 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A, which showed significant antibacterial activity against Gram-positive pathogens and *H. influenzae*.

2. Chemistry

3-*O*-Carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A were synthesized as follows (Scheme 1). 6,11-di-*O*-methylerythromycin A was treated with diluted acid to accomplish cleavage of cladinose producing compound **1**. Desosamine sugar remains intact under these conditions. In order to perform chemical transformations on the hydroxyl group at position 3, 2′-hydroxyl group, which is the most reactive one, must be suitably protected. Hydroxyl groups at position 12 is much less reactive. Consequently, reaction of macrolides **1** with acetic anhydride in acetone at room temperature selectively gave 2′-acetate **2** as a sole product, which can be later easily deprotected by methanolysis.

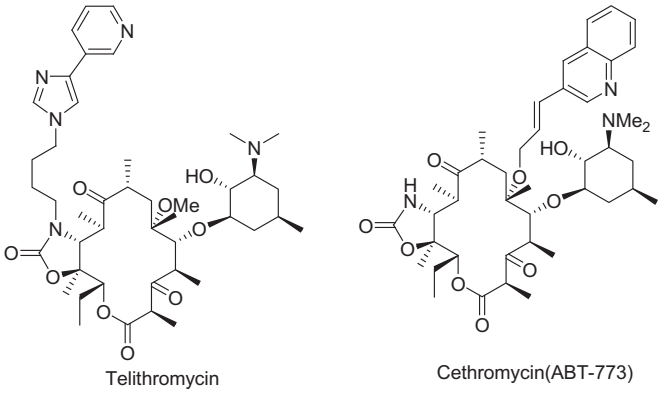


Fig. 3. Structures of Telithromycin and Cethromycin.

By using the method of Baker et al. [18,22,23], **2** was treated with excess 1,1-carbonyldiimidazole (CDI) and sodium hydride in DMF at 0 °C for 1 h, 2′-*O*-acetyl-3-*O*-acylimidazolyl-5-*O*-desosaminyl-6, 11-di-*O*-methylerythronolide A (**3**) was obtained in a yield of 76%. The structure of **3** was confirmed by ^{13}C NMR spectrum in which two carbon peaks of carbonate and carbamate could be found at δ 169.7 and δ 148.6. Compounds **4a-z** were prepared by reacting compound **3** with corresponding amines and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by deprotection of the acetate group with methanol (Scheme 1). The structures of **4a-z** were determined by ^{13}C NMR, ^{1}H NMR, MS and IR spectra.

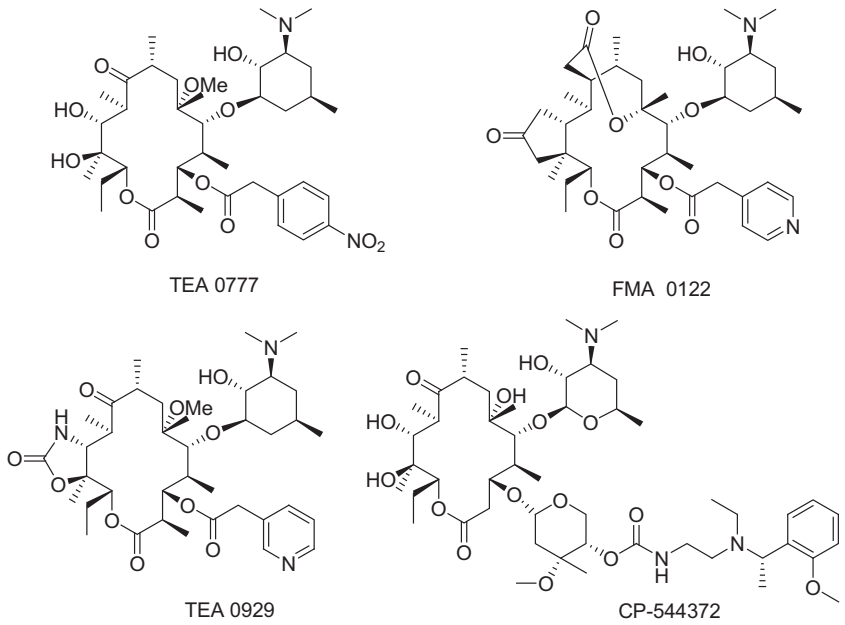
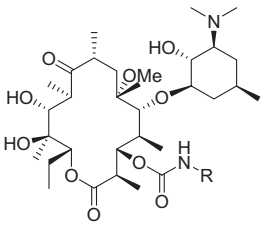
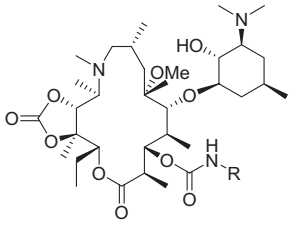


Fig. 2. Structures of TEA 0777, FMA 0122, TEA 0929 and CP-544372.





CAM-4d	R=2-chlorophenethyl
CAM-4h	R=propyl
CAM-4i	R=propenyl
CAM-4j	R=butyl
CAM-4k	R=pentyl

AZM-7c R=2-chlorophenethyl

Fig. 4. Structures of **CAM-4** and **AZM-7**.

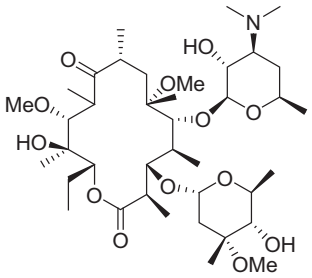


Fig. 5. Structure of 6,11-di-*O*-methylerythromycin A.

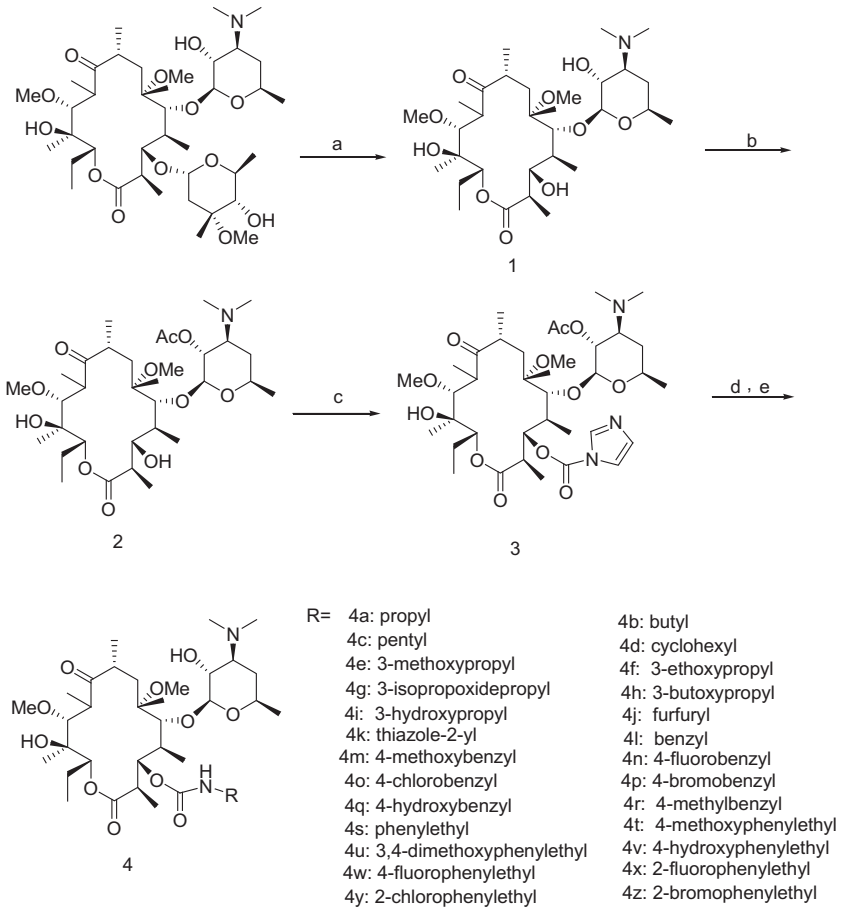
3. Antibacterial activity

All of the 3-*O*-carbamoyl derivatives synthesized, as well as erythromycin, clarithromycin and azithromycin as reference compounds, were tested for *in vitro* antibacterial activity against three strains of *S. aureus* and two strains of each *S. pneumoniae* and *H. influenzae*. The activities are reported in Table 1 as minimum inhibitory concentrations (MICs) determined by the broth micro-dilution method, as recommended by the National Committee for Clinical Laboratory Standards.

To evaluate the potential 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.

4. Results and discussion

The results tabulated in Table 1 show the antibacterial activity of 3-*O*-carbamates with reference compounds (erythromycin,



Scheme 1. Reagents and conditions: (a) H_2O, HCl, pH = 1; (b) acetic anhydride, acetone, K_2CO_3, $NaHCO_3$, 24 h; (c) CDI, NaH, DMF, 0 °C, 1 h; (d) RNH_2, CH_3CN, H_2O, 65 °C, 12 h or RNH_2, DMF, DBU, rt, 24 h; (e) CH_3OH, 55 °C, 20 h.

Table 1
In vitro antibacterial activities of prepared macrolides.

Compound	**MIC** (μg/mL)						
	S. aureus			*S. pneumoniae*		*H. influenzae*	
	ATCC25923	A265	A333	ATCC49619	3469	ATCC49247	3300
4a	2	1	>64	0.125	0.125	>64	64
4b	1	1	>64	0.125	0.125	4	4
4c	2	4	>64	0.125	0.25	4	4
4d	8	2	>64	0.125	0.125	4	4
4e	8	4	>64	0.125	0.125	32	16
4f	8	8	>64	0.125	0.125	8	8
4g	4	4	>64	0.5	8	16	32
4h	4	16	>64	2	>64	32	64
4i	4	16	>64	1	8	32	32
4j	2	1	>64	0.5	16	2	2
4k	32	32	>64	0.125	8	32	32
4l	2	0.125	>64	0.125	0.125	8	4
4m	0.125	0.125	>64	0.5	0.5	1	0.5
4n	4	0.125	>64	0.125	0.125	4	4
4o	4	0.125	>64	0.125	0.5	2	4
4p	0.125	0.125	32	0.125	0.125	2	2
4q	1	0.25	>64	1	32	1	1
4r	0.25	0.125	64	0.125	0.25	4	4
4s	8	8	>64	4	64	4	4
4t	4	8	>64	0.125	0.125	16	16
4u	2	8	>64	0.125	0.25	32	32
4v	4	2	>64	0.25	0.25	8	8
4w	2	2	32	0.125	0.125	8	8
4x	8	16	64	0.125	0.125	16	16
4y	4	1	>64	0.125	0.125	8	16
4z	4	4	64	0.125	8	8	4
AZM	0.5	8	>64	0.5	4	4	4
CAM	0.25	4	>64	0.25	2	8	8
EMA	0.125	2	>64	0.25	1	16	16

AZM: azithromycin; **CAM**: clarithromycin; **EMA**: erythromycin; *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.

clarithromycin and azithromycin). The C-3 cladinose sugar attached to the 14-membered ring macrolides is believed to be responsible for the inducibility of macrolide resistance. Removal of the L-cladinosyl moiety of clarithromycin resulted in a complete loss of antibacterial activity. Simple introduction of an acetyl group at the 3-*O*-position did not completely restore the antibacterial activity, although it did seem to be slightly effective against the erythromycin-susceptible strain. Accordingly, we obtained some new derivatives of 6,11-di-*O*-methylerythromycin A by substituting L-cladinose with various carbamate groups, such as alkylcarbamoyl, hydroxy-alkylcarbamoy, alkoxy-alkylcarbamoyl, heterocyclic-carbamoyl, substituted benzylcarbamoyl, and substituted phenethylcarbamoyl.

Among the tested compounds, some new derivatives of 6,11-di-*O*-methylerythromycin A by substituting L-cladinose with substituted benzylcarbamoyl (**4l**–**4r**) were found to have more potent activity (MIC 0.125–0.25 mg/mL) against the erythromycin-resistant but methicillin-susceptible *S. aureus* A265, which were comparable to the other new 3-*O*-carbamates and reference compounds. In addition, compounds **4p**, **4r**, **4w**, **4x** and **4z** improved the activity (MIC 32–64 mg/mL) against erythromycin-resistant and methicillin-resistant *S. aureus* A333, MIC values for **AZM**, **CAM** and **ERM** are >64 mg/mL. Most of the new compounds displayed excellent activity against erythromycin-resistant and -suscepible *S. pneumoniae* such as *S. pneumoniae* 3469 and *S. pneumoniae* ATCC49619. Moreover, most of the new 3-*O*-carbamates have potent activity against ampicillin-resistant and -suscepible *H. influenzae* such as *H. influenzae* ATCC49247 and *H. influenzae* 3300, among them, **4m**–**4s** were more active than others.

The 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A are 14-membered macrolide derivatives with the 3-*O*-carbamoyl side chain in place of L-cladinose at the 3-*O*-position. This new class of antibiotics exhibited potent activity against some key erythromycin-resistant and -susceptible pathogens. The results suggested that the 3-*O*-carbamoyl side chain in their structures could interact with the binding sites in the cavity formed by G2505, C2610 and C2611 in domain V, resulting in a higher affinity to bacterial ribosomes.

5. Conclusion

A simple and efficient method for preparation of 3-*O*-carbamoyl analogs of 5-*O*-desosaminyl-6, 11-di-*O*-methylerythronolide A was developed. These carbamates were evaluated for antibacterial activity against macrolide-susceptible and macrolide-resistant pathogens. Among the target derivatives, compounds **4p**, **4q**, **4w**, **4x** and **4z** were found to have potent activity against most susceptible and resistant bacteria. In particular, compound **4p** exhibited excellent antibacterial activity in comparison to the others. The results suggested that introduction of the 3-*O*-carbamoyl side chains at the 3-*O*-position shows improved the activity against erythromycin-resistant against the erythromycin-resistant but methicillin-susceptible *S. aureus*, and introduction of the 3-*O*-carbamoyl side chain at the 3-*O*-position may increase the activity against erythromycin-resistant and methicillin-resistant *S. aureus* and ampicillin-resistant and -suscepible *H. influenzae*.

The improved antibacterial activity against resistant bacteria achieved by these derivatives is possibly due to the C-3 cladinose sugar attached to the 14-membered ring macrolides which is believed to be responsible for the inducibility of macrolide resistance. It is worthy of notice that 3-*O*-carbamate derivatives of 14-membered macrolides are probably the effective management of macrolide resistance, and this study possibly presents a major

opportunity for the development of new macrolide antibiotics to combat the growing problem of antibiotic resistance.

6. Experimental

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 Perkin–Elmer (Spectrum One) spectrometer. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury VX400 apparatus in $CDCl_3$ with TMS as internal standard. The elemental analysis (C, H, N) data were obtained from a Vario EL III (German) elemental analyzer. All the ampicillin-resistant and erythromycin-resistant strains chosen in this test are constitutively resistant strains supplied by the Ministry of Health National Antimicrobial Resistance Investigation Net (MOHNARIN, China).

6.1. 3-O-descladinosyl-6,11-di-O-methylerythromycin A (**1**)

6,11-Di-*O*-methylerythromycin A (3.05 g, 4.0 mmol) was suspended in water (20 mL) and the pH was adjusted to 1 using 6 N HCl. The reaction mixture was stirred for 24 h at room temperature, CH_2Cl_2 (10 mL) was added, and pH adjusted to 8. The layers were separated and aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). Combined organic extracts were rinsed with saturated aqueous $NaHCO_3$ solution, brine, and water, and dried over anhydrous Na_2SO_4. The solvent was evaporated to afford **1** (1.89 g, 78%) as a white solid, mp 110–113 °C.

IR (KBr): 3458, 2975, 2931, 2875, 1724, 1458, 1376, 1346, 1169, 1108, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.99 (m, 1H), 4.42 (d, J = 4.4 Hz, 1H), 3.77 (d, J = 1.2 Hz, 1H), 3.67 (m, 1H), 3.57 (s, 3H), 3.55-3.52 (m, 2H), 3.49 (m, 1H), 3.25 (m, 1H), 3.14 (s, 1H), 3.02 (s, 3H), 2.97 (m, 1H), 2.71 (m, 1H), 2.61 (m, 1H), 2.47 (m, 1H), 2.25 (s, 6H), 2.13 (m, 1H), 1.97-1.91 (m, 3H), 1.68-1.65 (m, 3H), 1.52-1.48 (m, 2H), 1.39 (s, 3H), 1.28-1.10 (m, 17H), 0.87-0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.8, 175.3, 106.4, 86.9, 78.8, 78.5, 78.4, 77.7, 76.0, 70.6, 70.1, 65.6, 61.1, 49.4, 45.8, 44.6, 40.2, 37.9, 37.5, 36.2, 28.0, 21.8, 21.3, 19.2, 18.9, 17.4, 15.1, 12.9, 10.4, 8.35; MS (ESI) m/z calcd. for $C_{31}H_{57}NO_{10}$ 603.40; found (M + H^+) 604.2; Anal. calcd. (%) for $C_{31}H_{57}NO_{10}$: C 61.67, H 9.52, N 2.32; Found: C 61.64, H 9.50, N 2.34.

6.2. 2′-O-acetyl-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**2**)

Compound **1** (1.81 g, 3.0 mmol) in acetone (15 mL) at room temperature was added acetic anhydride (5.6 mL, 6 mmol, 2.0 equiv) and K_2CO_3 (0.83 g, 6 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 $NaHCO_3$ (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was crystallized to afford 1.80 g (93%) of **2** as a white solid, mp 129–131 °C.

IR (KBr): 3474, 2970, 2936, 2359, 1749, 1732, 1716, 1456, 1374, 1239, 1167, 1110, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.00 (m, 1H), 4.77(m, 1H), 4.60 (d, J = 7.6 Hz, 1H), 3.80 (d, J = 2.6 Hz, 1H), 3.57 (s, 3H), 3.41-3.51 (m, 2H), 3.12 (s, 1H), 3.03 (m, 1H), 2.99 (s, 1H), 3.02 (s, 3H), 2.75-2.69 (m, 2H), 2.57 (m, 1H), 2.61 (m, 1H), 2.26 (s, 6H), 2.13 (m, 1H), 2.08 (s, 3H), 2.03 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.72 (m, 3H), 1.51 (m, 1H), 1.38 (m, 1H), 1.29 (s, 3H), 1.28-1.09 (m, 13H), 0.97 (d, J = 0.97 Hz, 3H), 0.85-0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.1, 174.9, 170.0, 99.7, 79.8, 78.7, 78.1, 77.6, 77.4, 76.0, 71.4, 68.7, 63.2, 61.1, 49.6, 46.0, 44.1, 40.6, 37.6, 37.2, 36.0, 30.9, 21.8, 21.5, 21.1, 19.6, 19.3, 17.5, 15.2, 13.0, 10.4, 8.2; MS (ESI) m/z calcd. for $C_{33}H_{59}NO_{11}$ 645.41; found (M + H^+) 646.1; Anal. calcd. (%) for $C_{33}H_{59}NO_{11}$: C 61.37, H 9.21, N 2.17; Found: C 61.34, H 9.20, N 2.18.

6.3. 2′-O-acetyl-3-O-acylimidazolyl -3-O-descladinosyl-6,11-di-O-methylerythromycin A (**3**)

To a solution of **2** (1.29 g, 2 mmol) in DMF (20 mL) was added NaH (0.096 g, 4 mmol, 2.0 equiv) and CDI (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 by chromatography to afford 1.12 g (76%) of **3** as a white solid, mp 88–91 °C.

IR (KBr): 3448, 2977, 2928, 1765, 1711, 1463, 1400, 1377, 1343, 1314, 1290, 1240, 1172, 1108, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.52 (s, 1H), 7.18 (s, 1H), 5.16 (d, J = 11.2 Hz, 1H), 5.07 (d, J = 9.2 Hz, 1H), 4.63 (m, 1H), 3.88 (d, J = 7.4 Hz, 1H), 3.80 (d, J = 3.2 Hz, 1H), 3.60 (s, 3H), 3.43 (s, 1H), 3.14 (s, 3H), 3.12 (m, 1H), 3.10-3.03 (m, 2H), 2.56 (m, 1H), 2.41-2.32 (m, 2H), 2.23 (m, 1H), 2.18 (s, 6H), 2.10 (s, 3H), 2.04-1.94 (m, 1H), 1.73 (m, 1H), 1.53 (m, 1H), 1.50 (m, 3H), 1.46-1.36 (m, 2H), 1.28 (s, 3H), 1.26-1.07 (m, 16H), 0.86-0.83 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.6, 173.0, 169.7, 148.6, 131.3, 117.0, 100.1, 82.6, 78.6, 78.4, 78.0, 75.9, 75.8, 71.1, 69.1, 63.0, 61.0, 50.0, 45.9, 42.4, 40.5, 37.6, 36.9, 35.9, 30.1, 21.6, 21.4, 20.9, 19.5, 19.2, 17.6, 14.8, 13.0, 11.1, 10.4, 8.8; MS (ESI) m/z calcd. for $C_{37}H_{61}N_3O_{13}$ 739.89; found (M + Na^+) 762.1; Anal. calcd. (%) for $C_{37}H_{61}N_3O_{12}$: C 60.06, H 8.31, N 5.68; Found: C 60.04, H 8.27, N 5.71.

6.4. General methods for the preparation of 3-O-arylalkylcarbamoyl-3-O-descladinosyl-6,11-di-O-methylerythromycin A derivatives (**4a-z**)

Method I: To a solution of **3** (1.11 g, 1.50 mmol) in CH_3CN (20 mL) and water (2 mL) was added the corresponding alkylamine (7.5 mmol, 1.5 equiv). The resulting solution was stirred for 12 h at 65 °C. The reaction was quenched with 0.5 M NaH_2PO_4 (15 mL) and the aqueous layer was extracted with ethyl acetate (3 × 15 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 12 h at the same temperature. After concentrating the reaction solution in vacuo, the residue was purified by chromatography to afford the desired products **4(a–i)**.

Method II: To a solution of **3** (1.11 g, 1.50 mmol) in DMF (15 mL) at 0 °C was added DBU (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 (3 × 15 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 **4** (**j**–**z**).

6.4.1. 3-O-((Propyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4a**)

White solid, yield 82%, mp 142–146 °C; IR (KBr): 3377, 2971, 2940, 2881, 2360, 1725, 1652, 1541, 1460, 1377, 1344, 1258, 1174, 1109, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.05 (m, 1H), 5.02 (m,

1H), 4.86 (d, J = 11.0 Hz, 1H), 4.08 (d, J = 7.4 Hz, 1H), 3.87 (m, 1H), 3.58 (s, 3H), 3.48 (m, 1H), 3.36 (m, 1H), 3.27 (m, 2H), 3.20 (m, 1H), 3.17 (s, 3H), 3.04 (m, 2H), 2.86 (m, 1H), 2.74 (m, 1H), 2.57 (m, 1H), 2.40 (m, 1H), 2.28 (s, 6H), 2.22 (m, 1H), 1.98-1.83 (m, 4H), 1.65-1.48 (m, 6H), 1.30 (s, 3H), 1.25-1.07 (m, 16H), 0.96-0.92 (m, 3H), 0.84-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.6, 103.0, 79.6, 78.5, 78.0, 77.9, 77.7, 76.0, 70.6, 69.5, 65.9, 61.1, 49.9, 45.9, 43.0, 42.9, 40.3, 37.6, 37.4, 35.7, 28.6, 23.2, 21.7, 21.2, 19.7, 19.4, 17.3, 14.7, 13.0, 12.3, 10.5, 9.2; MS (ESI) m/z calcd. for $C_{35}H_{64}N_2O_{11}$ 688.45; found ($M + H^+$) 689.1; Anal. calcd. (%) for $C_{35}H_{64}N_2O_{11}$: C 61.02, H 9.36, N 4.07; Found: C 60.99, H 9.35, N 4.06.

6.4.2. 3-O-((Butyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4b**)

White solid, yield 77%, mp 135–138 °C; IR (KBr): 3445, 2974, 2954, 2875, 1733, 1532, 1457, 1380, 1345, 1251, 1172, 1109, 1064, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (m, 1H), 5.05 (m, 1H), 4.86 (d, J = 11.0 Hz, 1H), 4.09 (d, J = 7.3 Hz, 1H), 3.87 (d, J = 2.9 Hz, 1H), 3.59 (s, 3H), 3.51 (m, 1H), 3.38 (m, 1H), 3.29 (m, 1H), 3.26-3.14 (m, 2H), 3.10 (s, 3H), 3.06 (m, 1H), 3.03 (m, 1H), 2.87 (m, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 2.29 (s, 6H), 2.22 (m, 1H), 1.98-1.84 (m, 3H), 1.62 (m, 1H), 1.53-1.50 (m, 5H), 1.40-1.34 (m, 3H), 1.31 (s, 3H), 1.23-1.08 (m, 16H), 0.95-0.92 (m, 4H), 0.85-0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.5, 102.9, 79.5, 79.4, 78.5, 78.0, 77.7, 76.0, 70.5, 69.4, 65.9, 61.0, 49.9, 46.0, 43.0, 40.9, 40.3, 37.6, 37.3, 35.7, 32.0, 28.6, 21.7, 21.1, 20.0, 19.9, 19.6, 17.3, 14.6, 13.7, 13.0, 10.4, 9.1; MS (ESI) m/z calcd. for $C_{36}H_{66}N_2O_{11}$ 702.47; found ($M + H^+$) 703.2; Anal. calcd. (%) for $C_{36}H_{66}N_2O_{11}$: C 61.51, H 9.46, N 3.99; Found: C 61.49, H 9.45, N 4.02.

6.4.3. 3-O-((Pentyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4c**)

White solid, yield 76%, mp 131–133 °C; IR (KBr): 3340, 2962, 2932, 2872, 1727, 1528, 1460, 1377, 1344, 1246, 1175, 1109, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (m, 1H), 4.94 (m, 1H), 4.79 (d, J = 11.0 Hz, 1H), 4.01 (d, J = 7.3 Hz, 1H), 3.81 (d, J = 3.0 Hz, 1H), 3.52 (s, 3H), 3.41 (d, J = 3.6 Hz, 1H), 3.32-3.18 (m, 2H), 3.13 (m, 1H), 3.03 (s, 3H), 2.98 (m, 3H), 2.81 (m, 1H), 2.52 (m, 1H), 2.38 (m, 1H), 2.22 (s, 6H), 2.16 (m, 1H), 2.10 (m, 1H), 1.92-1.77 (m, 3H), 1.59 (m, 1H), 1.47-1.36 (m, 5H), 1.26-1.25 (m, 3H), 1.24 (s, 3H), 1.19-1.00 (m, 18H), 0.85-0.81 (m, 3H), 0.78-0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.0, 156.6, 102.7, 79.3, 78.4, 77.9, 77.5, 75.9, 70.5, 69.2, 65.8, 60.9, 50.2, 49.8, 45.8, 42.9, 41.1, 40.2, 37.5, 37.3, 35.6, 29.6, 29.5, 28.9, 28.6, 22.2, 21.6, 21.1, 19.6, 19.2, 17.3, 14.6, 13.9, 12.9, 10.3, 9.1; MS (ESI) m/z calcd. for $C_{37}H_{68}N_2O_{11}$ 716.48; found ($M + H^+$) 717.2; Anal. calcd. (%) for $C_{37}H_{68}N_2O_{11}$: C 61.98, H 9.56, N 3.91; Found: C 61.96, H 9.55, N 3.89.

6.4.4. 3-O-((Cyclohexyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4d**)

White solid, yield 70%, mp 113–117 °C; IR (KBr): 3453, 2974, 2935, 2857, 2784, 1727, 1533, 1458, 1376, 1345, 1273, 1240, 1174, 1108, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02 (m, 1H), 4.91 (d, J = 8.2 Hz, 1H), 4.85 (d, J = 10.9 Hz, 1H), 4.09 (d, J = 3.3 Hz, 1H), 3.85 (d, J = 3.1 Hz, 1H), 3.59 (s, 3H), 3.48 (m, 1H), 3.40 (m, 1H), 3.20 (m, 1H), 3.10 (s, 3H), 3.02 (m, 1H), 2.87 (m, 1H), 2.58 (m, 1H), 2.48 (m, 1H), 2.30 (s, 6H), 2.27 (m, 1H), 2.17-1.81 (m, 5H), 1.72-1.62 (m, 5H), 1.54-1.51 (m, 3H), 1.36 (m, 1H), 1.31 (s, 3H), 1.25-1.07 (m, 23H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.9, 174.1, 155.8, 103.1, 80.0, 78.5, 78.0, 77.7, 77.6, 76.0, 70.5, 69.3, 65.9, 61.1, 50.4, 50.2, 49.9, 45.9, 43.1, 40.2, 37.6, 37.4, 35.7, 33.4, 30.9, 25.5, 25.0, 24.6, 21.7, 21.2, 19.7, 19.3, 17.3, 14.7, 13.0, 10.4, 9.2; MS (ESI) m/z calcd. for $C_{38}H_{68}N_2O_{11}$ 728.48; found ($M + H^+$) 729.2; Anal. calcd. (%) for $C_{38}H_{68}N_2O_{11}$: C 62.61, H 9.40, N 3.84; Found: C 62.58, H 9.37, N 3.81.

6.4.5. 3-O-((3-methoxypropyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4e**)

White solid, yield 74%, mp 240–243 °C; IR (KBr): 3419, 2957, 2928, 2857, 1728, 1459, 1380, 1256, 1173, 1111, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (m, 1H), 5.03 (m, 1H), 4.86 (d, J = 11.1 Hz, 1H), 4.13 (d, J = 7.2 Hz, 1H), 3.87 (d, J = 3.1 Hz, 1H), 3.59 (s, 3H), 3.48-3.40 (m, 5H), 3.45 (s, 3H), 3.30-3.18 (m,3H), 3.10 (s, 3H), 3.04 (m, 1H), 2.88 (m, 1H), 2.67 (m, 1H), 2.60 (m, 1H), 2.39 (s, 6H), 2.31-2.17 (m, 1H), 1.97-1.86 (m, 1H), 1.83-1.78 (m, 2H), 1.76-1.65 (m, 4H), 1.51-1.40 (m, 3H), 1.30 (s, 3H), 1.25-1.08 (m, 16H), 0.96(m, 1H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.2, 156.6, 102.5, 79.4, 78.5, 78.0, 77.7, 76.0, 71.0, 70.5, 69.1, 65.8, 65.6, 61.6, 58.8, 49.9, 45.9, 43.0, 40.2, 39.2, 37.6, 35.7, 34.4, 30.5, 29.7, 21.1, 19.7, 19.1, 17.3, 14.7, 13.7, 13.0, 10.5, 9.2; MS (ESI) m/z calcd. for $C_{36}H_{66}N_2O_{12}$ 718.46; found ($M + H^+$) 719.0; Anal. calcd. (%) for $C_{36}H_{66}N_2O_{12}$: C 60.14, H 9.25, N 3.90; Found: C 60.11, H 9.23, N 3.87.

6.4.6. 3-O-((3-ethoxypropyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4f**)

White solid, yield 76%, mp 99–103 °C; IR (KBr): 3450, 2974, 2938, 2875, 1729, 1527, 1460, 1378, 1345, 1253, 1174, 1111, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (m, 1H), 5.01 (m, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.86 (m, 1H), 3.55 (s, 3H), 3.49-3.42 (m, 5H), 3.40-3.32 (m, 2H), 3.19-3.13 (m, 3H), 3.07 (s, 3H), 2.99 (m, 1H), 2.85 (m, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 2.25 (s, 6H), 2.22 (m, 1H), 1.93-1.84 (m, 2H), 1.80-1.66 (m, 2H), 1.62 (m, 1H), 1.49-1.34 (m, 4H), 1.27 (s, 3H), 1.22-1.04 (m, 20H), 0.93 (m, 1H), 0.81-0.77 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.5, 102.7, 79.0, 78.5, 78.0, 77.5, 76.0, 70.5, 69.3, 68.8, 66.3, 65.8, 61.0, 52.7, 49.9, 45.9, 42.9, 42.0, 40.2, 37.6, 37.3, 35.7, 29.6, 28.6, 21.6, 21.1, 19.6, 19.3, 17.3, 15.1, 14.6, 12.9, 10.3, 9.1; MS (ESI) m/z calcd. for $C_{37}H_{68}N_2O_{12}$ 732.48; found ($M + H^+$) 733.2; Anal. calcd. (%) for $C_{37}H_{68}N_2O_{12}$: C 60.63, H 9.35, N 3.82; Found: C 60.61, H 9.32, N 3.84.

6.4.7. 3-O-((3-isopropoxidepropyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4g**)

White solid, yield 73%, mp 98–102 °C; IR (KBr): 3451, 2974, 2936, 2879, 1729, 1639, 1529, 1460, 1376, 1343, 1255, 1174, 1109, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (m, 1H), 5.02 (m, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.11 (d, J = 7.2 Hz, 1H), 3.89 (d, J = 3.1 Hz, 1H), 3.62 (m, 1H), 3.59 (s, 3H), 3.55 (m, 1H), 3.53-3.50 (m, 2H), 3.48 (m, 1H), 3.43-3.36 (m, 2H), 3.24-3.18 (m, 2H), 3.10 (s, 3H), 3.03 (m, 1H), 2.90 (m, 1H), 2.59 (m, 1H), 2.47 (m, 1H), 2.30 (s, 6H), 2.22 (m, 1H), 1.83-2.05 (m, 4H), 1.80-1.71 (m, 2H), 1.63 (m, 1H), 1.52-1.45 (m, 3H), 1.30 (s, 3H), 1.25-1.08 (m, 23H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.5, 102.7, 79.1, 78.5, 78.0, 77.6, 76.0, 71.7, 70.5, 69.4, 66.5, 65.8, 61.1, 52.9, 49.9, 45.9, 42.9, 40.3, 39.7, 37.6, 37.4, 35.7, 29.8, 28.7, 22.1, 21.7, 21.2, 19.7, 19.4, 17.3, 14.7, 13.0, 10.4, 9.1; MS (ESI) m/z calcd. for $C_{38}H_{70}N_2O_{12}$ 746.49; found ($M + H^+$) 747.1; Anal. calcd. (%) for $C_{38}H_{70}N_2O_{12}$: C 61.10, H 9.45, N 3.75; Found: C 61.07, H 9.42, N 3.72.

6.4.8. 3-O-((3-butoxypropyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4h**)

White solid, yield 72%, mp 107–110 °C; IR (KBr): 3335, 2970, 2938, 2875, 2788, 1732, 1458, 1377, 1342, 1252, 1173, 1109, 1076, 1051 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ 5.43 (s, 1H), 4.97 (m, 1H), 4.78 (d, J = 11.0 Hz, 1H), 4.03 (d, J = 7.3 Hz, 1H), 3.82 (d, J = 3.0 Hz, 1H), 3.52 (s, 3H), 3.47-3.41 (m, 4H), 3.37-3.34 (m, 3H), 3.31-3.29 (m, 2H), 3.14 (m, 3H), 3.03 (s, 3H), 2.97 (m, 1H), 2.81 (m, 1H), 2.52 (m, 1H), 2.41 (m, 1H), 2.22 (s, 6H), 2.15 (m, 1H), 1.86 (m, 1H), 1.79-1.57 (m, 2H), 1.53-1.39 (m, 3H), 1.37-1.27 (m, 2H), 1.23 (s, 3H), 1.18-1.00 (m, 21H), 0.88-0.85 (m, 3H), 0.78-0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.9, 174.1, 156.5, 102.7, 79.0, 78.5, 77.9, 77.6, 76.0, 70.9, 70.5, 69.6, 69.5, 69.4, 65.8, 61.0, 49.9, 45.9, 42.9, 40.2, 39.8, 37.6,

37.3, 35.7, 31.7, 29.6, 28.6, 21.7, 21.2, 19.7, 19.4, 19.3, 17.3, 14.7, 13.9, 13.0, 10.4, 9.0; MS (ESI) *m/z* calcd. for $C_{39}H_{72}N_2O_{12}$ 760.51; found ($M + H^+$) 761.2; Anal. calcd. (%) for $C_{39}H_{72}N_2O_{12}$: C 61.55, H 9.54, N 3.68; Found: C 61.52, H 9.52, N 3.70.

*6.4.9. 3-O-((3-hydroxypropyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4i**)*

White solid, yield 67%, mp 181–186 °C; IR (KBr): 3367, 2974, 2944, 2883, 1719, 1654, 1459, 1377, 1346, 1252, 1175, 1108, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.50 (s, 1H), 5.04 (m, 1H), 4.88 (d, $J = 11.0$ Hz, 1H), 4.10 (d, $J = 7.6$ Hz, 1H), 3.85 (d, $J = 3.0$ Hz, 1H), 3.75-3.70 (m, 2H), 3.60 (s, 3H), 3.51-3.48 (m, 2H), 3.37 (m, 1H), 3.26-3.20 (m, 2H), 3.11 (s, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.59 (m, 1H), 2.50 (m, 1H), 2.31 (s, 6H), 2.29-2.20 (m, 3H), 1.98-1.90 (m, 2H), 1.86 (m, 1H), 1.78 (m, 1H), 1.73-1.66 (m, 2H), 1.55-1.48 (m, 3H), 1.32 (s, 3H), 1.28-1.14 (m, 15H), 1.11-1.09 (m, 3H), 0.86-0.82 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.1, 174.1, 157.3, 103.1, 80.0, 78.5, 78.0, 77.7, 76.0, 70.7, 69.4, 65.7, 61.1, 59.8, 49.9, 45.9, 43.0, 40.3, 38.2, 37.6, 37.4, 35.7, 32.4, 29.4, 28.6, 21.7, 21.2, 19.7, 19.3, 17.3, 14.7, 13.0, 10.5, 9.2; MS (ESI) *m/z* calcd for $C_{35}H_{64}N_2O_{12}$ 704.45; found ($M + H^+$) 705.1; Anal. calcd (%) for $C_{35}H_{64}N_2O_{12}$: C 59.64, H 9.15, N 3.97; Found: C 59.62, H 9.12, N 3.96.

*6.4.10. 3-O-(Furfurylcarbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4j**)*

White solid, yield 61%, mp 190–193 °C; IR (KBr): 3446, 2962, 2927, 2357, 1732, 1653, 1457, 1378, 1344, 1260, 1170, 1109, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, $J = 3.0$ Hz, 1H), 7.63 (m, 1H), 7.47 (d, $J = 3.1$ Hz, 1H), 4.94 (m, 1H), 4.79 (d, $J = 10.6$ Hz, 1H), 4.37-4.32 (m, 2H), 4.30 (d, $J = 7.3$ Hz, 1H), 3.86 (d, $J = 3.2$ Hz, 1H), 3.70 (m, 1H), 3.51 (s, 3H), 3.41 (m, 1H), 3.26-3.09 (m, 3H), 3.01 (s, 3H), 2.81 (m, 1H), 2.64 (m, 1H), 2.47 (m, 1H), 2.21 (s, 6H), 2.05 (m, 1H), 1.96-1.74 (m, 4H), 1.58-1.66 (m, 2H), 1.44-1.38 (m, 3H), 1.30 (s, 3H), 1.25-0.99 (m, 17H), 0.77-0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.1, 174.1, 156.7, 137.4, 133.2, 130.9, 106.4, 103.1, 87.0, 78.5, 78.0, 77.7, 76.0, 70.7, 70.1, 65.7, 61.1, 58.7, 49.9, 45.9, 43.2, 40.3, 37.6, 36.3, 35.7, 34.4, 29.7, 21.3, 21.1, 19.7, 19.3, 17.3, 14.8, 12.9, 10.4, 9.3; MS (ESI) *m/z* calcd. for $C_{37}H_{62}N_2O_{12}$ 726.43; found ($M + H^+$) 727.1; Anal. calcd. (%) for $C_{37}H_{62}N_2O_{12}$: C 61.14, H 8.60, N 3.85; Found: C 61.11, H 8.58, N 3.84.

*6.4.11. 3-O-((Thiazole-2-yl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4k**)*

White solid, yield 59%, mp 148–151 °C; IR (KBr): 3446, 2975, 2936, 2788, 2359, 1733, 1564, 1458, 1376, 1333, 1235, 1173, 1108, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, $J = 3.6$ Hz, 1H), 7.00 (d, $J = 3.6$ Hz, 1H), 5.08 (m, 1H), 5.05 (m, 1H), 4.10 (d, $J = 6.9$ Hz, 1H), 3.95 (d, $J = 2.8$ Hz, 1H), 3.63 (s, 3H), 3.52 (m, 1H), 3.16 (s, 3H), 3.11-2.99 (m, 4H), 2.61 (m, 1H), 2.34 (m, 1H), 2.19 (s, 1H), 2.14 (s, 6H), 2.01-1.86 (m, 3H), 1.58-1.51 (m, 2H), 1.42 (m, 1H), 1.35 (s, 3H), 1.33-1.27 (m, 5H), 1.22-1.07 (m, 13H), 1.07-1.05 (m, 3H), 0.87-0.84 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.7, 173.6, 161.3, 154.0, 137.2, 112.7, 103.4, 81.1, 80.4, 78.6, 78.1, 76.0, 70.3, 69.5, 65.7, 61.1, 50.0, 45.9, 42.9, 40.3, 37.7, 37.4, 36.0, 29.7, 28.3, 21.7, 21.0, 19.8, 19.3, 17.4, 14.9, 13.0, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{35}H_{59}N_3O_{11}S$ 729.39; found ($M + H^+$) 730.1; Anal. calcd. (%) for $C_{35}H_{59}N_3O_{11}S$: C 57.59, H 8.15, N 5.76, S 4.39; Found: C 57.56, H 8.12, N 5.74, S 4.38.

*6.4.12. 3-O-((Benzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4l**)*

White solid, yield 76%, mp 156–160 °C; IR (KBr): 3515, 3347, 2973, 2938, 2877, 2788, 1736, 1456, 1380, 1343, 1256, 1170, 1142, 1108, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 5.63 (m, 1H), 5.04 (m, 1H), 4.89 (d, $J = 11.0$ Hz, 1H), 4.46 (m, 1H), 4.41 (m, 1H), 4.34 (m, 1H), 4.01 (d, $J = 3.2$ Hz, 1H), 3.84 (d, $J = 2.9$ Hz, 1H), 3.58 (s, 3H), 3.48 (m, 1H), 3.45 (m, 1H), 3.14 (m, 1H), 3.09 (s, 3H), 3.05 (m, 1H), 3.01 (m, 1H), 2.88 (m, 1H), 2.57 (m, 1H), 2.25 (m, 1H), 2.23 (s, 6H), 2.21 (m, 1H), 2.19-1.93 (m, 2H), 1.86-1.83 (m, 2H), 1.52-1.44 (m, 3H), 1.29 (s, 3H), 1.28-1.06 (m, 17H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.6, 138.4, 128.8, 127.8, 127.7, 103.0, 80.0, 78.5, 78.4, 78.0, 77.7, 76.0, 70.5, 69.2, 65.6, 61.1, 49.9, 45.9, 45.2, 43.1, 40.2, 37.6, 37.4, 35.7, 28.5, 21.7, 21.2, 19.7, 19.3, 17.3, 14.9, 13.0, 10.4, 9.2; MS (ESI) *m/z* calcd. for $C_{39}H_{64}N_2O_{11}$ 736.45; found ($M + H^+$) 737.1; Anal. calcd. (%) for $C_{39}H_{64}N_2O_{11}$: C 63.56, H 8.75, N 3.80; Found: C 63.54, H 8.73, N 3.82.

*6.4.13. 3-O-((4-methoxybenzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4m**)*

White solid, yield 74%, mp 230–234 °C; IR (KBr): 3450, 2962, 2934, 1728, 1637, 1536, 1457, 1342, 1244, 1173, 1112, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25-7.21 (d, $J = 8.5$ Hz, 2H), 6.86-6.84 (d, $J = 8.6$ Hz, 2H), 5.47 (m, 1H), 5.04 (m, 1H), 4.88 (d, $J = 11.0$ Hz, 1H), 4.34-4.29 (m, 2H), 3.98 (d, $J = 7.3$ Hz, 1H), 3.82 (m, 1H), 3.79 (m, 1H), 3.59 (s, 3H), 3.57 (s, 1H), 3.48 (s, 1H), 3.15 (m, 1H), 3.13 (s, 3H), 3.01 (m, 2H), 2.87 (m, 1H), 2.60-2.56 (m, 1H), 2.26-2.22 (m, 2H), 2.24 (s, 6H), 2.20 (m, 1H), 1.95-1.85 (m, 2H), 1.54-1.39 (m, 3H), 1.30 (s, 3H), 1.26-1.07 (m, 21H), 0.88-0.83 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 159.1, 156.5, 130.5, 129.2, 114.1, 103.1, 80.2, 78.5, 78.4, 78.0, 77.7, 76.0, 70.5, 69.2, 65.7, 61.1, 55.3, 49.9, 45.9, 44.7, 43.1, 40.2, 37.6, 37.4, 35.7, 28.4, 21.7, 21.2, 19.7, 19.3, 17.3, 14.9, 13.0, 10.5, 9.2; MS (ESI) *m/z* calcd. for $C_{40}H_{66}N_2O_{12}$ 766.46; found ($M + H^+$) 767.2; Anal. calcd. (%) for $C_{40}H_{66}N_2O_{12}$: C 62.64, H 8.67, N 3.65; Found: C 62.61, H 8.65, N 3.62.

*6.4.14. 3-O-((4-fluorobenzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4n**)*

White solid, yield 70%, mp 94–98 °C; IR (KBr): 3453, 2975, 2939, 2878, 1729, 1606, 1511, 1458, 1343, 1254, 1172, 1109, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 2H), 7.02-6.98 (m, 2H), 5.63 (s, 1H), 5.02 (d, $J = 10.6$ Hz, 1H), 4.86 (d, $J = 3.0$ Hz, 1H), 4.43-4.24 (m, 2H), 3.97 (d, $J = 3.1$ Hz, 1H), 3.82 (m, 1H), 3.57 (s, 3H), 3.55 (m, 1H), 3.45 (m, 1H), 3.11-3.15 (m, 2H), 3.08 (s, 3H), 3.02-3.00 (m, 2H), 2.87 (m, 1H), 2.56 (m, 1H), 2.23 (s, 6H), 2.21-2.17 (m, 3H), 1.92-1.80 (m, 2H), 1.49-1.37 (m, 3H), 1.29 (s, 3H), 1.24-1.05 (m, 18H), 0.83-0.80 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.1, 174.0, 165.8, 156.7, 134.6, 129.5, 115.5, 102.8, 79.7, 78.5, 78.3, 78.0, 77.6, 75.9, 70.4, 69.1, 65.6, 61.0, 49.8, 45.8, 44.3, 43.0, 40.2, 37.6, 37.3, 35.6, 29.7, 21.6, 21.1, 19.6, 19.2, 17.2, 14.7, 13.0, 10.4, 9.1; MS (ESI) *m/z* calcd. for $C_{39}H_{63}FN_2O_{11}$ 754.44; found ($M + H^+$) 755.1; Anal. calcd. (%) for $C_{39}H_{63}FN_2O_{11}$: C 62.05, H 8.41, F 2.52, N 3.71; Found: C 62.01, H 8.39, F 2.51, N 3.68.

*6.4.15. 3-O-((4-chlorobenzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4o**)*

White solid, yield 77%, mp 86–91 °C; IR (KBr): 3453, 2974, 2939, 2877, 2784, 1732, 1531, 1458, 1344, 1250, 1171, 1109, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, $J = 8.4$ Hz, 2H), 7.55 (d, $J = 8.5$ Hz, 2H), 5.80 (s, 1H), 5.04 (m, 1H), 4.88 (d, $J = 10.7$ Hz, 1H), 4.36 (m, 1H), 4.24 (m, 1H), 3.98 (d, $J = 7.2$ Hz, 1H), 3.79 (d, $J = 2.5$ Hz, 1H), 3.61 (s, 3H), 3.58 (m, 1H), 3.50 (m, 1H), 3.19-3.16 (m, 2H), 3.11(s, 3H), 3.04 (m, 1H), 2.91 (m, 1H), 2.61 (m, 1H), 2.34 (s, 6H), 2.31-2.19 (m, 2H), 1.99-1.87 (m, 2H), 1.76-1.70 (m, 3H), 1.45-1.31 (m, 3H), 1.27 (s, 3H), 1.19-0.93 (m, 17H), 0.87-0.83 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.7, 173.9, 168.0, 156.5, 138.8, 130.9, 128.8, 102.9, 80.6, 78.6, 78.5, 78.0, 77.8, 76.0, 70.5, 68.2, 65.6, 61.1, 49.9, 45.9, 44.4, 43.2, 40.1, 38.7, 37.6, 35.7, 29.7, 23.7, 22.7, 19.7, 19.2, 17.3, 13.7, 13.0, 10.5, 9.3; MS (ESI) *m/z* calcd. for $C_{39}H_{63}ClN_2O_{11}$ 770.41; found ($M + H^+$) 771.0; Anal. calcd. (%) for $C_{39}H_{63}ClN_2O_{11}$: C 60.72, H 8.23, Cl 4.60, N 3.63; Found: C 60.68, H 8.21, Cl 4.58, N 3.61.

*6.4.16. 3-O-((4-bromobenzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4p**)*

White solid, yield 75%, mp 85–88 °C; IR (KBr): 3444, 3285, 2970, 2933, 2358, 1727, 1652, 1536, 1458, 1379, 1172, 1108, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 5.73 (m, 1H), 5.02 (m, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.34-4.31 (m, 2H), 3.94 (d, J = 6.0 Hz, 1H), 3.80 (d, J = 2.7 Hz, 1H), 3.59 (s, 3H), 3.53 (m, 1H), 3.41 (m, 1H), 3.11-3.15 (m, 2H), 3.09 (s, 3H), 3.02 (m, 1H), 2.93-2.86 (m, 2H), 2.58 (m, 1H), 2.23 (s, 6H), 2.22-2.14 (m, 2H), 1.97-1.82 (m, 4H), 1.54-1.39 (m, 3H), 1.32 (m, 1H), 1.29 (s, 3H), 1.21-1.11 (m, 13H), 1.08-1.06 (m, 3H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.1, 174.0, 161.2, 156.6, 136.8, 131.8, 129.7, 103.1, 80.2, 78.5, 78.0, 77.7, 76.0, 70.5, 69.2, 65.6, 61.1, 49.9, 45.9, 44.5, 42.9, 41.4, 40.2, 37.6, 37.4, 35.7, 29.7, 21.7, 21.2, 19.7, 19.3, 17.3, 14.9, 13.0, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{39}H_{63}BrN_2O_{11}$ 814.36; found ($M + H^+$) 815.0; Anal. calcd. (%) for $C_{39}H_{63}BrN_2O_{11}$: C 57.42, H 7.78, Br 9.79, N 3.43; Found: C 57.38, H 7.75, Br 9.77, N 3.41.

*6.4.17. 3-O-((4-hydroxybenzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4q**)*

White solid, yield 68%, mp 147–151 °C; IR (KBr): 3408, 2976, 2936, 2875, 1729, 1621, 1518, 1458, 1376, 1346, 1252, 1173, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.1 Hz, 2H), 6.81 (d, J = 8.2 Hz, 2H), 5.47 (m, 1H), 5.31 (s, 1H), 5.03 (m, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.34-4.21 (m, 2H), 3.97 (d, J = 7.2 Hz, 1H), 3.84 (d, J = 2.5 Hz, 1H), 3.59 (s, 3H), 3.49 (m, 1H), 3.29 (m, 1H), 3.19-3.15 (m, 2H), 3.09 (s, 3H), 3.05-3.02 (m, 2H), 2.87 (m, 1H), 2.58 (m, 1H), 2.27 (s, 6H), 2.24 (m, 1H), 1.99-1.92 (m, 3H), 1.88-1.81 (m, 2H), 1.67 (m, 1H), 1.50 (m, 3H), 1.29 (s, 3H), 1.26-1.07 (m, 16H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.4, 174.1, 157.3, 156.3, 138.8, 128.8, 115.7, 102.3, 80.2, 78.5, 78.3, 78.0, 77.7, 76.0, 70.7, 69.2, 65.4, 61.2, 49.9, 45.9, 44.8, 43.1, 40.3, 37.7, 37.4, 35.7, 29.7, 21.7, 21.1, 19.7, 19.3, 17.3, 14.7, 13.0, 10.5, 9.3; MS (ESI) m/z calcd. for $C_{39}H_{64}N_2O_{12}$ 752.46; found ($M + H^+$) 753.1; Anal. calcd. (%) for $C_{39}H_{64}N_2O_{12}$: C 62.21, H 8.57, N 3.72; Found: C 62.18, H 8.55, N 3.73.

*6.4.18. 3-O-((4-methylbenzyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4r**)*

White solid, yield 69%, mp 65–68 °C; IR (KBr): 3444, 2966, 2934, 2875, 1728, 1668, 1548, 1458, 1379, 1345, 1252, 1172, 1110, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23-7.15 (m, 4H), 5.36 (m, 1H), 5.05 (m, 1H), 4.91 (d, J = 11.0 Hz, 1H), 4.49-4.29 (m, 3H), 4.00 (d, J = 7.4 Hz, 1H), 3.86 (d, J = 3.0 Hz, 1H), 3.61 (s, 3H), 3.51 (s, 1H), 3.16 (m, 1H), 3.12 (s, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.60 (m, 1H), 2.36 (m, 1H), 2.35 (s, 3H), 2.31-2.28 (m, 2H), 2.25 (s, 6H), 2.19 (m, 1H), 2.05-1.84 (m, 4H), 1.80-1.63 (m, 3H), 1.53-1.44 (m, 1H), 1.32 (s, 3H), 1.27-1.09 (m, 16H), 0.87-0.84 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.8, 174.1, 156.5, 137.4, 137.3, 129.4, 127.8, 103.1, 80.0, 78.6, 78.5, 78.1, 77.7, 76.0, 70.5, 69.2, 66.0, 61.1, 49.9, 46.0, 44.6, 42.0, 40.2, 37.7, 37.5, 35.8, 28.5, 21.8, 21.2, 21.1, 19.8, 19.4, 17.3, 14.9, 13.0, 10.5, 9.2; MS (ESI) m/z calcd. for $C_{40}H_{66}N_2O_{11}$ 750.47; found ($M + H^+$) 751.2; Anal. calcd. (%) for $C_{40}H_{66}N_2O_{11}$: C 63.98, H 8.86, N 3.73; Found: C 63.96, H 8.85, N 3.70.

*6.4.19. 3-O-((Phenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4s**)*

White solid, yield 78%, mp 179–184 °C; IR (KBr): 3371, 2976, 2941, 2878, 1735, 1532, 1457, 1378, 1343, 1247, 1171, 1142, 1108, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 2H), 7.28-7.20 (m, 3H), 5.05 (m, 1H), 4.96 (m, 1H), 4.88 (d, J = 11.2 Hz, 1H), 4.05 (d, J = 7.3 Hz, 1H), 3.90 (d, J = 3.3 Hz, 1H), 3.68 (m, 1H), 3.61 (s, 3H), 3.51 (m, 1H), 3.32-3.26 (m, 3H), 3.18 (m, 1H), 3.13 (s, 3H), 3.05 (m, 1H), 2.89-2.83 (m, 3H), 2.59 (m, 1H), 2.36 (m, 1H), 2.28 (s, 6H), 2.19 (m, 1H), 1.96-1.84 (m, 2H), 1.81-1.67 (m, 3H), 1.62-1.49 (m, 2H), 1.32 (s, 3H), 1.22-1.09 (m, 18H), 0.87-0.85 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.9, 174.1, 156.5, 138.4, 128.7, 126.7, 102.7, 81.2, 79.1, 78.5, 78.0, 77.7, 76.0, 70.6, 69.5, 65.9, 61.1, 50.0, 45.9, 42.9, 42.3, 40.3, 37.7, 37.4, 36.1, 35.4, 28.6, 21.7, 21.2, 19.7, 19.4, 17.3, 14.7, 13.0, 10.4, 9.1; MS (ESI) m/z calcd. for $C_{40}H_{66}N_2O_{11}$ 750.47; found ($M + H^+$) 751.2; Anal. calcd. (%) for $C_{40}H_{66}N_2O_{11}$: C 63.98, H 8.86, N 3.73; Found: C 63.96, H 8.83, N 3.70.

*6.4.20. 3-O-((4-methoxyphenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4t**)*

White solid, yield 66%, mp 48–51 °C; IR (KBr): 3442, 2965, 2927, 1727, 1642, 1558, 1457, 1255, 1172, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.3 Hz, 2H), 4.96 (m, 1H), 4.79 (d, J = 11.2 Hz, 1H), 4.24 (m, 1H), 4.15 (m, 1H), 3.98 (d, J = 7.2 Hz, 1H), 3.80 (d, J = 2.9 Hz, 1H), 3.72 (s, 3H), 3.57 (m, 1H), 3.51 (s, 3H), 3.41 (m, 1H), 3.31-3.20 (m, 2H), 3.12 (m, 1H), 3.04 (s, 3H), 2.95 (m, 1H), 2.78 (m, 1H), 2.73-2.69 (m, 2H), 2.50 (m, 1H), 2.31 (m, 1H), 2.21 (s, 6H), 2.19 (s, 1H), 1.92-1.75 (m, 3H), 1.65-1.52 (m, 3H), 1.44-1.25 (m, 2H), 1.23 (s, 3H), 1.18-1.00 (m, 17H), 0.78-0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.0, 173.1, 157.3, 155.6, 131.2, 128.6, 113.1, 101.6, 77.9, 77.8, 77.5, 77.0, 75.0, 69.5, 68.3, 67.1, 60.0, 57.5, 54.2, 48.9, 44.9, 41.9, 41.5, 39.2, 37.6, 36.7, 34.7, 34.2, 28.6, 20.7, 20.2, 18.7, 18.1, 16.3, 13.7, 12.0, 9.4, 8.1; MS (ESI) m/z calcd. for $C_{41}H_{68}N_2O_{12}$ 780.48; found ($M + H^+$) 781.1; Anal. calcd. (%) for $C_{41}H_{68}N_2O_{12}$: C 63.05, H 8.78, N 3.59; Found: C 63.02, H 8.75, N 3.62.

*6.4.21. 3-O-((3,4-dimethoxy-phenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4u**)*

White solid, yield 79%, mp 49–54 °C; IR (KBr): 3444, 2962, 2926, 2855, 1726, 1643, 1561, 1460, 1211, 1170, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, J = 7.9 Hz, 1H), 6.68 (m, 1H), 6.64 (d, J = 7.9 Hz, 1H), 5.06 (m, 1H), 5.01-4.95 (m, 2H), 4.79 (d, J = 11.2 Hz, 1H), 3.99 (d, J = 7.3 Hz, 1H), 3.81 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.59 (m, 1H), 3.52 (s, 3H), 3.40 (m, 1H), 3.30-3.18 (m, 3H), 3.12 (m, 1H), 3.06 (s, 3H), 2.95 (m, 1H), 2.73-2.68 (m, 3H), 2.49 (m, 1H), 2.33 (m, 1H), 2.22 (s, 6H), 2.18 (m, 1H), 1.96-1.75 (m, 4H), 1.53 (m, 1H), 1.48-1.45(m, 2H), 1.28 (s, 3H), 1.25-1.00 (m, 17H), 0.78-0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.0, 173.1, 155.5, 148.0, 146.7, 130.0, 119.6, 110.9, 110.8, 101.7, 78.2, 77.5, 77.0, 76.8, 76.6, 75.0, 69.5, 68.3, 64.8, 60.1, 57.7, 54.9, 48.9, 44.9, 41.9, 41.4, 39.2, 36.6, 36.3, 34.8, 34.1, 28.6, 20.7, 20.2, 18.7, 18.3, 16.3, 13.7, 12.0, 9.4, 8.1; MS (ESI) m/z calcd. for $C_{42}H_{70}N_2O_{13}$ 810.49; found ($M + H^+$) 811.1; Anal. calcd. (%) for $C_{42}H_{70}N_2O_{13}$: C 62.20, H 8.70, N 3.45; Found: C 62.18, H 8.67, N 3.42.

*6.4.22. 3-O-((4-hydroxyphenethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methyl erythromycin A (**4v**)*

White solid, yield 68%, mp 76–80 °C; IR (KBr): 3443, 2967, 2870, 2345, 1728, 1651, 1554, 1416, 1259, 1173, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.73 (s, 1H), 5.06 (m, 1H), 5.00 (m, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.01 (d, J = 7.2 Hz, 1H), 3.87 (d, J = 3.3 Hz, 1H), 3.65 (m, 1H), 3.60 (s, 3H), 3.57-3.52 (m, 2H), 3.42-3.48 (m, 2H), 3.32 (m, 1H), 3.25-3.20 (m, 2H), 3.11 (s, 3H), 3.05-3.03 (m, 2H), 2.86 (m, 1H), 2.82-2.73 (m, 2H), 2.60 (m, 1H), 2.40 (m, 1H), 2.36 (s, 6H), 2.25 (m, 1H), 2.20 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.65 (m, 1H), 1.52-1.46 (m, 2H), 1.30 (s, 3H), 1.28 (s, 3H), 1.21-1.09 (m, 13H), 0.88-0.85(m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.4, 174.2, 161.8, 155.3, 133.8, 129.7, 115.8, 102.2, 78.7, 78.5, 78.0, 77.8, 77.7, 76.1, 70.8, 69.3, 65.3, 60.9, 50.2, 45.9, 42.9, 42.6, 40.4, 39.7, 37.7, 37.4, 34.5, 29.2, 21.7, 21.1, 19.7, 19.4, 17.4, 14.7, 13.0, 10.5, 9.2; MS (ESI) m/z calcd. for $C_{40}H_{66}N_2O_{11}$ 766.46; found ($M + H^+$) 767.2; Anal. calcd. (%) for $C_{40}H_{66}N_2O_{11}$: C 62.64, H 8.67, N 3.65; Found: C 62.61, H 8.64, N 3.62.

*6.4.23. 3-O-((4-fluorophenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4w**)*

White solid, yield 70%, mp 116–119 °C; IR (KBr): 3444, 2970, 2930, 1714, 1639, 1540, 1459, 1249, 1170, 1108, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.10-7.07 (m, 2H), 6.95-6.93 (m, 2H), 5.04 (m, 1H), 4.96 (m, 1H), 4.78 (d, J = 11.0 Hz, 1H), 3.98 (d, J = 7.2 Hz, 1H), 3.80 (d, J = 2.9 Hz, 1H), 3.58 (m, 1H), 3.52 (s, 3H), 3.40 (m, 1H), 3.27-3.16 (m, 3H), 3.14-3.08 (m, 2H), 3.03 (s, 3H), 2.95 (m, 1H), 2.80-2.70 (m, 3H), 2.50 (m, 1H), 2.33 (m, 1H), 2.21 (s, 6H), 2.17 (m, 1H), 1.94-1.75 (m, 3H), 1.54-1.51 (m, 2H), 1.44-1.39 (m, 3H), 1.23 (s, 3H), 1.18-1.00 (m, 16H), 0.78-0.75 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 160.4, 156.5, 134.2, 130.1, 115.4, 102.7, 79.0, 78.5, 78.0, 77.8, 77.6, 76.0, 70.5, 69.3, 65.8, 61.0, 49.9, 45.9, 42.9, 42.3, 40.2, 37.6, 37.3, 35.7, 35.3, 29.6, 21.7, 21.2, 19.7, 19.3, 17.3, 14.7, 13.0, 10.4, 9.1; MS (ESI) m/z calcd. for $C_{40}H_{65}FN_2O_{11}$ 768.46; found ($M + H^+$) 769.1; Anal. calcd. (%) for $C_{40}H_{65}FN_2O_{11}$: C 62.48, H 8.52, F 2.47, N 3.64; Found: C 62.45, H 8.49, F 2.45, N 3.67.

*6.4.24. 3-O-((2-fluorophenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4x**)*

White solid, yield 72%, mp 110–114 °C; IR (KBr): 3452, 2976, 2940, 1729, 1535, 1499, 1458, 1378, 1345, 1242, 1173, 1109, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.20 (m, 2H), 7.12-7.03 (m, 2H), 5.06 (m, 1H), 5.03 (m, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.89 (d, J = 3.2 Hz, 1H), 3.65 (m, 1H), 3.60 (s, 3H), 3.57 (m, 1H), 3.50 (m, 1H), 3.33-3.28 (m, 2H), 3.19 (m, 1H), 3.12 (s, 3H), 3.04 (m, 1H), 2.93-2.85 (m, 3H), 2.60 (m, 1H), 2.39 (m, 1H), 2.29 (s, 6H), 2.25 (m, 1H), 1.98-1.84 (m, 4H), 1.60-1.50 (m, 3H), 1.31 (s, 3H), 1.29-1.09 (m, 18H), 0.88-0.85 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 216.9, 174.1, 161.3, 156.5, 131.2, 131.1, 128.4, 124.3, 115.5, 102.7, 79.0, 78.5, 78.0, 77.9, 77.6, 76.0, 70.5, 69.5, 65.8, 61.1, 49.9, 45.9, 42.9, 42.3, 40.3, 38.1, 37.6, 37.4, 35.7, 28.6, 21.7, 21.2, 19.7, 19.4, 17.3, 14.7, 13.0, 10.4, 9.1; MS (ESI) m/z calcd. for $C_{40}H_{65}FN_2O_{11}$ 768.46; found ($M + H^+$) 769.1; Anal. calcd. (%) for $C_{40}H_{65}FN_2O_{11}$: C 62.48, H 8.52, F 2.47, N 3.64; Found: C 62.46, H 8.49, F 2.46, N 3.67.

*6.4.25. 3-O-((2-chlorophenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4y**)*

White solid, yield 74%, mp 110–114 °C; IR (KBr): 3445, 2975, 2939, 1729, 1524, 1461, 1376, 1342, 1248, 1172, 1109, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 1H), 7.24-7.21 (m, 3H), 5.19 (m, 1H), 5.03 (m, 1H), 4.86 (d, J = 11.0 Hz, 1H), 4.05 (d, J = 7.3 Hz, 1H), 3.87 (d, J = 3.0 Hz, 1H), 3.61 (s, 3H), 3.58 (m, 1H), 3.51-3.47 (m, 3H), 3.38-3.29 (m, 2H), 3.17 (m, 1H), 3.10 (s, 3H), 3.04-2.95 (m, 3H), 2.86 (m, 1H), 2.57 (m, 1H), 2.39 (m, 1H), 2.27 (s, 6H), 2.24 (m, 1H), 1.95-1.85 (m, 3H), 1.62-1.58 (m, 2H), 1.51-1.48 (m, 3H), 1.30 (s, 3H), 1.28-1.07 (m, 16H), 0.85-0.81 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.5, 136.1, 134.0, 131.0, 129.7, 128.3, 127.1, 102.8, 79.3, 78.5, 78.0, 77.7, 76.0, 70.6, 69.5, 65.8, 61.1, 49.9, 45.9, 42.9, 40.6, 40.3, 37.8, 37.6, 37.4, 35.7, 33.8, 28.6, 21.7, 21.2, 19.7, 19.4, 17.3, 14.8, 13.0, 10.5, 9.2; MS (ESI) m/z calcd. for $C_{40}H_{65}ClN_2O_{11}$ 784.43; found ($M + H^+$) 785.1; Anal. calcd. (%) for $C_{40}H_{65}ClN_2O_{11}$: C 61.17, H 8.34, Cl 4.51, N 3.57; Found: C 61.15, H 8.31, Cl 4.48, N 3.59.

*6.4.26. 3-O-((2-bromophenylethyl)carbamoyl)-3-O-descladinosyl-6,11-di-O-methylerythromycin A (**4z**)*

White solid, yield 73%, mp 96–99 °C; IR (KBr): 3354, 2974, 2939, 1729, 1524, 1461, 1376, 1342, 1248, 1172, 1109, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (m, 1H), 7.21-7.16 (m, 2H), 7.03 (m, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.79 (d, J = 11.0 Hz, 1H), 3.98 (d, J = 7.2 Hz, 1H), 3.81 (d, J = 2.6 Hz, 1H), 3.56 (m, 1H), 3.51 (s, 3H), 3.47-3.33 (m, 2H), 3.31-3.21 (m, 2H), 3.08 (m, 1H), 3.03 (s, 3H), 2.98-2.89 (m, 3H), 2.80 (m, 1H), 2.50 (m, 1H), 2.34 (m, 1H), 2.20 (s, 6H), 2.18 (m, 1H), 1.88-1.75 (m, 2H), 1.54 (m, 1H), 1.47-1.39 (m, 2H), 1.23 (s, 3H), 1.18-1.00 (m, 20H), 0.78-0.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): 217.0, 174.1, 156.5, 137.8, 133.0, 131.0, 128.4, 127.6, 124.5, 102.8, 79.2, 78.5, 78.0, 77.6, 76.0, 70.5, 69.5, 65.9, 61.1, 50.0, 45.9, 42.9, 40.7, 40.3, 37.6, 37.4, 36.7, 36.3, 35.7, 28.6, 21.7, 21.2, 19.7, 19.4, 17.3, 14.8, 13.0, 10.5, 9.1; MS (ESI) m/z calcd. for $C_{40}H_{65}BrN_2O_{11}$ 828.38; found ($M + H^+$) 829.0; Anal. calcd. (%) for $C_{40}H_{65}BrN_2O_{11}$: C 57.89, H 7.89, Br 9.63, N 3.38; Found: C 57.87, H 7.86, Br 9.60, N 3.40.

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References

[1] M.R. Jacobs, S. Bajaksouzian, A. Zilles, G. Lin, G.A. Pankuch, P. C Appelbaum, Antimicrob. Agents Chemother 43 (1999) 1901–1908.
[2] C. Thornsberry, P.T. Ogilvie, H.P. Holley, D.F. Sahm, Antimicrob. Agents Chemother 43 (1999) 2612–2623.
[3] G.V. Doern, A.B. Brueggemann, H. Huynh, E. Wingert, P. Rhomberg, Emerg. Infect. Dis. 5 (1999) 757–765.
[4] G.V. Doern, K.P. Heilmmann, H.K. Huynh, P.R. Rhomberg, S.L. Coffman, A. B. Burueggemann, Antimicrob. Agents Chemother 45 (2001) 1721–1729.
[5] L. Katz, D.T.W. Chu, J.J. Plattner, J. Med. Chem. 39 (1996) 3853–3874.
[6] R.P. Bax, R. Anderson, J. Crew, P. Fletcher, T. Johnson, E. Kaplan, B. Knaus, K. Kristinsson, M. Malek, L. Strandberg, Nat. Med 4 (1998) 545–546.
[7] T. Asaka, M. Kashimura, K. Tanikawa, T. Ishii, A. Matsuura, K. Matsumoto, K. Suzuki, K. Numata, T. Akashi, S. Morimoto, 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Abstr. No. F-262.
[8] T. Asaka, M. Kashimura, A. Matsuura, T. Sugimoto, T. Tanikawa, WO 9921869.
[9] B. Zhu, B.A. Marinelli, D. Abbanat, B.D. Foleno, T.C. Henninger, K. Bush, M. J. Macielag, Bioorg. Med. Chem. Lett. 16 (2006) 1054–1059.
[10] T. Asaka, M. Kashimura, A. Manaka, T. Tanikawa, T. Ishii, T. Sugimoto, K. Suzuki, H. Sugiyama, T. Akashi, H. Saito, T. Adachi, S. Morimoto, In 39th ICAAC, San Francisco, USA; 1999 Abstract 2159.
[11] T. Tanikawa, T. Asaka, M. Kashimura, K. Suzuki, H. Sugiyama, M. Sato, K. Kameo, S. Morimoto, A. Nishida, J. Med. Chem. 46 (2003) 2706–2715.
[12] H. Takashima, Curr. Top. Med. Chem. 3 (2003) 991–999.
[13] P. Xu, L. Liu, Z. Jin, G. Wang, J. Liu, Y. Li, P. Lei, Bioorg. Med. Chem. Lett. 18 (2008) 5507–5511.
[14] F. Schlünzen, R. Zarivach, J. Harms, A. Bashan, A. Tocilj, R. Albrecht, A. Yonath, F. Franceschi, Nature 413 (2001) 814–821.
[15] Z. Ma, Peter A. Nemoto, Curr. Med. Chem. – Anti-Infect. Agents 1 (2002) 15–34.
[16] Y.J. Wu, W.G. Su, Curr. Med. Chem. 8 (2001) 1727–1758.
[17] T. Tanikawa, T. Asaka, M. Kashimura, Y. Misawa, K. Suzuki, M. Sato, K. Kameo, S. Morimoto, A. Nishida, J. Med. Chem. 44 (2001) 4027–4030.
[18] C. Agouridas, A. Denis, J.-M. Augar, Y. Benedetti, A. Bonnefoy, F. Bretin, J.-F. Chantot, A. Dussarat, C. Fromentin, S.G. D'Ambrieres, S. Lachaud, P. Laurin, O. Le Martret, V. Loyau, N. Tessot, J. Med. Chem. 41 (1998) 4080–4100.
[19] Z. Ma, R.F. Clark, A. Brazzale, S. Wang, M.J. Rupp, L. Li, G. Griesgraber, S. Zhang, H. Yong, L.T. Phan, P.A. Nemoto, D.T.W. Chu, J.J. Plattner, X. Zhang, P. Zhong, Z. Cao, A.M. Nilius, V.D. Shortridge, R. Flamm, M. Mitten, J. Meulbroek, P. Ewing, J. Alder, Y.S. Or, J. Med. Chem. 44 (2001) 4137–4156.
[20] L. Zhang, L. Song, Z. Liu, H. Lu, Z. Li, S. Ma, Eur. J. Med. Chem. 44 (2009) 4010–4020.
[21] S. Morimoto, Y. Misawa, T. Adachi, T. Nagate, Y. Watanabe, S. Omura, J. Antibiot. 43 (1990) 286–294.
[22] W.R. Baker, J.D. Clark, R.L. Stephens, K.H. Kim, J. Org. Chem. 53 (1988) 2340–2345.
[23] A. Denis, C. Agouridas, J.M. Auger, Y. Benedetti, A. Bonefoy, F. Breti, J.-F. Chantot, Y. Dussaratti, C. Fromentin, S.G.D. Ambrieres, S. Lachaud, P. Laurin, O. Le Martret, V. Loyau, N. Tessot, J.M. Pejac, S. Perron, Bioorg. Med. Chem. Lett. 9 (1999) 3075–3080.