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ORIGINAL ARTICLE

Synthesis and antibacterial activity of novel 11-[3-[(arylcarbamoyl)oxy]propylamino]-11-deoxy-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate derivatives

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A series of novel 11-[3-[(arylcarbamoyl)oxy]propylamino]-11-deoxy-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate derivatives (6a–h) were designed, synthesized and evaluated for their antibacterial activities *in vitro*. Most of these compounds had significant antibacterial activity against two groups of pathogens of Methicillin-sensitive *Staphylococcus aureus* ($MIC_{50} = 0.031–2\ \mu g\ ml^{-1}$) except 6g and Methicillin-sensitive *S. epidermidis* ($MIC_{50} = 0.031–0.5\ \mu g\ ml^{-1}$). MIC_{90} of 6d against Methicillin-resistant *S. epidermidis* was at least 16-fold better than that of erythromycin (EMA), azithromycin (AZM) and ABT-773. 6d and 6e had more potent antibacterial activity against *S. pneumoniae* than EMA, AZM and ABT-773. In particular, compounds 6d and 6e also showed relatively potent activity against *Haemophilus influenzae* and *Streptococcus hemolyticus*.
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INTRODUCTION

The rapid development of antibiotics-resistant strains such as Methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant *Enterococcus*, Penicillin-resistant *S. pneumoniae*, has created a serious problem for the clinical treatment in recent years.[1] In a research on clinic ophthalmic bacteria, 87% of the Methicillin-resistant *Staphylococcus aureus* isolates were resistant to azithromycin (AZM) and 42% of the Methicillin-resistant *S. epidermidis* (MRSE) strains tested were resistant to AZM, respectively.[2] The clinically relevant coagulase-negative *Staphylococcal* species, *S. epidermidis* are among the leading causes of nosocomial infections in humans, particularly in neonates, immunocompromised patients and patients with indwelling and implanted devices.[3] Farrell *et al.*[4] reported that resistant *S. pneumoniae* possessing both *erm* and *mef* genes markedly increase in only 3 years in the United States. Therefore, there is an urgent need for novel macrolide antibiotics to suppress the resistance. Macrolides antibiotics, which are active against Gram-positive bacteria, especially *S. pneumoniae*, belong to one of the most commonly used families of clinically important antibiotics.

Erythromycin A (EMA), the representative of first-generation macrolides, has been widely used to treat respiratory infections for almost 60 years. However, EMA is prone to degrade under acidic conditions, leading to the undesirable gastrointestinal side effects and low bioavailability. With the purpose of improving the acid stability, second-generation macrolides, including clarithromycin and AZM (Figure 1), have been developed and widely prescribed for upper and lower respiratory tract infections.[5,6] These compounds demonstrated a broader spectrum of antibacterial activity, better pharmacokinetic properties and fewer gastrointestinal side effects as compared with EMA. Unfortunately, the therapeutic utility of these macrolides has resulted in the increasing emergence of resistant pathogens. The two primary mechanisms of macrolide resistance are mediated by erm-encoded methylation of 23S ribosomal RNA and mef-encoded efflux, respectively.[7,8]

To overcome the growing problems of macrolide resistance, the research has focused on the discovery of novel macrolides with greater efficacy and safety. The third-generation macrolides, ketolides such as telithromycin and cethromycin (Figure 1),[9,10] displayed improved activity against some of the resistant strains and may offer alternative therapy for Gram-positive infections attributable to resistant pathogens. Both telithromycin and cethromycin share the same key structure features, including 3-keto group, 11,12-cyclic carbamate and a proper hetero-arylalkyl side chain, which is essential for interacting with the 23S ribosomal RNA of bacteria.[11,12]

Recently, intensive research focusing on the structural modifications of the ketolide core skeleton in search of novel potent ketolides has yielded many ketolides derivatives, such as 6-*O*-alkyl ketolides,[10,13–15] 9-oxime macrolides,[16–18] 11,12-cyclic carbamate ketolides,[19–21] 13-substituents ketolides and 6,11-bridged ketolides.[22–24] Herein, we described the synthesis and *in vitro* biological evaluation of a set of

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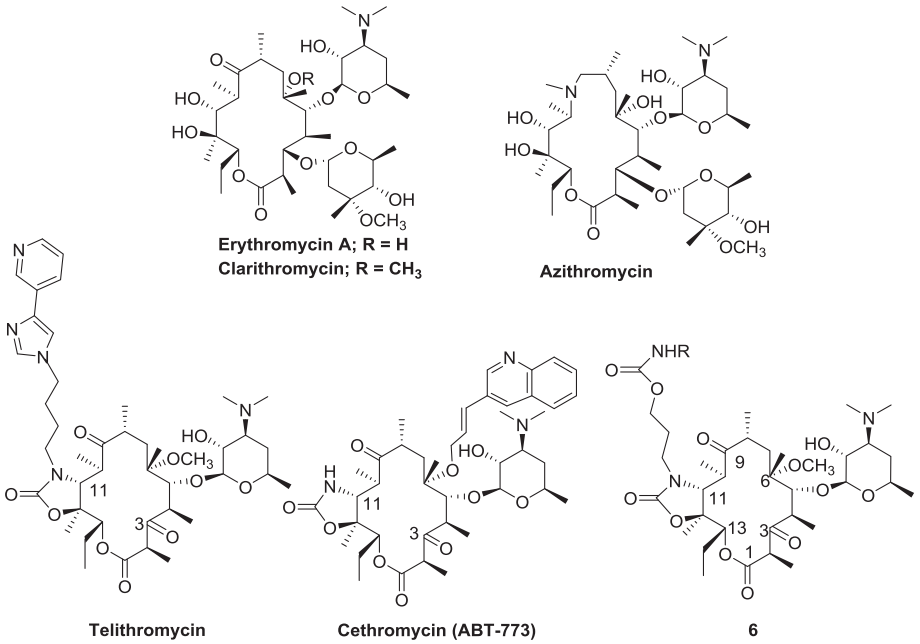


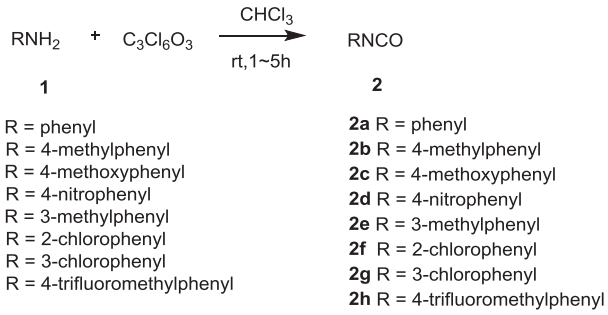
Figure 1 Structures of erythromycin, clarithromycin, azithromycin, telithromycin and cethromycin (ABT-773).

novel 14-membered macrolide analogs that comprised the essential features for addressing macrolide resistance especially by erm-encoded methylation of 23S ribosomal RNA. By introducing various substituted-phenyl carbamate propyl chain to the 11-*N* of the 11-amino-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*, 12-*O* cyclic carbamate, a series of novel 11-*N*,12-*O*-cyclic carbamate ketolides were obtained.

RESULTS AND DISCUSSION

A simple and efficient method for preparation of novel 14-membered macrolide analogs was developed. The objective compounds were evaluated for antibacterial activity against macolide-susceptible and -resistant pathogens. Most of the compounds tested showed potent activity against most resistant bacteria, indicating that the introduction of phenyl substituents to the 11-*N* position can markedly enhance the antibacterial activity. Accounding to the structure–activity relationship studies it is demonstrated that 11,12-cyclic carbamate would increase the stability of the conformation of the ketolides, and meanwhile might be beneficial for the activitiy against macrolide-susceptible and -resistant bacteria. Accordingly, we hoped that introducing a carbamate group to the 11-*N*-alkyl position might remarkbly increase the antibacterial activity. However, almost all of the compounds did not possess better antibacterial activities than those of compounds with alkyl substituents at the 11-*N* position.

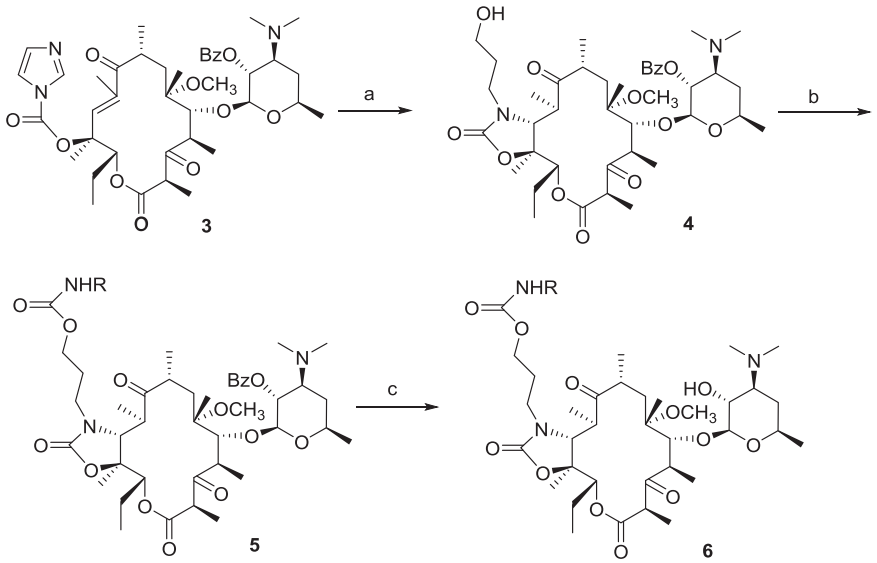
In general, the derivative **6a** without substituents on the phenyl ring was less active than those containing substituents except **6g**. The position and properties of substituents on the benzene ring had great influence on the *in vitro* antibacterial activity. In the 4-substitution, a comparison among **6b**, **6c**, **6d** and **6h** indicated that electrical property had little effect on the activity. MIC_{90} of **6d** with 4-nitro substituent against MRSE was better than other derivatives with the 4-substitution group. **6h** had the least activity against *S. pneumoniae* among the four compounds. In contrast, the derivatives **6e** and **6g** with substitution at the 3-position of the phenyl ring displayed a great difference on antibacterial activity. **6e** with a methyl group was much powerful than **6g** containing a chloro group. This result suggested that the 3-substituent was very important for the activity. In addition, **6f** with a chloro group substitution in the 2-position showed more potent activity than **6g**. These results indicated the importance of the presence and location of the functional groups for activity. Further research on the structure–activity relationship is necessary especially on 3-postion substitution, which maybe is useful for designing new ketolides with broader antibacterial spectrum. On the whole, **6d** and **6e** showed potent activity against MSSA-EAR, MRSE and *Haemophilus influenzae*, whereas **6g** was the least active compound.



Scheme 1 Synthesis of a set of isocyanate (**2a**–**h**).

Chemistry

The synthetic method of aryl isocyanates (**2**) is shown in Scheme 1. Condensation of **1** with bis(trichloromethyl) carbonate gave the desired aryl isocyanates (**2a**–**h**). Scheme 2 describes the synthesis of 11-[3-[(arylcarbamoyl)oxy]propylamino]-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (**6**) starting from 2′-*O*-benzoyl-10,11-dehydro-3-des(hexopyranosyloxy)-12-*O*-imidazolylcarbonyl-6-*O*-methyl-3-oxoerythromycin A (**3**). Treatment of **3** with 1-amino propanol in N,N-Dimethylformamide (DMF) at room temperature afforded compound **4**. Compounds (**6a**–**h**) were prepared by reacting compound **4** with corresponding aryl



Scheme 2 Reagents and conditions: (**a**) $NH_2CH_2CH_2CH_2OH$, N,N-Dimethylformamide (DMF), room temperature (rt), 62 h, 85%; (**b**) dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), RNCO is R-N = C = O, DMAP, CH_2Cl_2, rt, 20 h, 75–90%; (**c**) CH_3OH, reflux, 20 h, 90 ~ 98%.

Table 1 ***In vitro*** **antibacterial activity (MIC (μg ml^{-1})) of prepared macrolides against** ***S. aureus*** **and** ***S. epidermidis***

	MSSA-EAS[a]		*MSSA-EAR*[b]		*MRSA*[c]		*MRSE*[d]		*MSSE*[e]	
Compound/strain	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
6a	1	2	2	2	256	256	2	16	0.5	2
6b	0.062	0.125	0.125	0.125	128	256	0.062	256	0.062	0.062
6c	0.031	0.125	0.125	0.25	256	>256	16	32	0.031	0.062
6d	0.25	0.25	0.5	0.5	>256	>256	1	8	0.25	0.25
6e	0.125	0.125	0.25	0.25	128	256	1	128	0.031	0.031
6f	0.062	0.125	0.125	0.25	128	256	0.5	32	0.25	0.25
6g	0.25	0.5	>256	>256	>256	>256	>256	>256	0.25	0.25
6h	0.062	0.25	0.062	2	256	>256	2	256	0.125	0.5
4	0.5	0.5	0.5	1	>256	>256	2	>256	0.25	0.25
ABT-773	<0.016	<0.016	<0.016	<0.016	256	>256	<0.016	128	<0.016	<0.016
EMA	0.125	0.25	>256	>256	>256	>256	>256	>256	0.125	0.125
AZM	0.031	0.125	>256	>256	>256	>256	>256	>256	<0.016	0.031

Abbreviations: ABT-773, cethromycin; AZM, azithromycin; EMA, erythromycin; MRSA, methicillin resistant *Staphylococcus aureus*; MRSE, methicillin resistant *Staphylococcus epidermidis*; MSSA-EAS, methicillin susceptible *Staphylococcus aureus* and erythromycin susceptible; MSSA-EAR, methicillin susceptible *Staphylococcus aureus* and erythromycin resistant; MSSE, methicillin susceptible *Staphylococcus epidermidis*.
[a]10 strains for MSSA-EAS.
[b]10 strains for MSSA-EAR.
[c]10 strains for MRSA.
[d]10 strains for MRSE.
[e]10 strains for MSSE.

isocyanates (**2a–h**) in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at room temperature,[25] followed by deprotection of the benzoyl group with methanol.

Antibacterial activity

The 11-[3-[(arylcarbamoyl)oxy]propylamino]-11-deoxy-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate derivatives, as well as cethromycin (ABT-773), EMA, azithromycin as references, were tested for *in vitro* antibacterial activity against three groups of *S. aureus*, two groups of *S. epidermis*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Streptococcus hemolyticus*. The activities are reported in Tables 1 and 2 MICs determined using the broth microdilution method.

The results in Tables 1 and 2 show the antibacterial activity of 11-[3-[(arylcarbamoyl)oxy]propylamino]-11-deoxy-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate derivatives and reference compounds (ABT-773, EMA and AZM). MIC_{50} (the concentration in which growth of 50% of strains were inhibited) and MIC_{90} (the concentration in which 90% of strains were inhibited) were tested. All of the tested compounds except **6g** proved to have good antibacterial activity against MSSA (MIC_{50} = 0.031–2 μg ml^{-1}), MSSE (MIC_{50} = 0.031–0.5 μg ml^{-1}), *Streptococcus pneumoniae* (MIC_{50} = 0.062–16 μg ml^{-1}). The MIC_{90} of **6d** for MRSE were 2–16 times better than EMA, AZM and ABT-773. Compounds **6d** and **6e** had more potent antibacterial activity against *Streptococcus pneumoniae* than the reference compounds EMA, AZM and ABT-773. Specifically,

Table 2 ***In vitro*** **antibacterial activity (MIC (μg mL^{-1})) of prepared macrolides against other strains**

Compound/ strain	*Enterococcus faecalis*[a]		*Streptococcus pneumoniae*[b]		*Haemophilus influenzae*[c]		*Streptococcus hemolyticus*[d]	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
6a	>256	>256	16	32	32	32	4	32
6b	>256	>256	0.5	2	16	64	1	2
6c	>256	>256	0.25	2	16	32	2	16
6d	>256	>256	0.125	0.25	4	8	2	2
6e	>256	>256	0.062	0.125	4	8	1	2
6f	>256	>256	2	8	64	128	8	8
6h	>256	>256	4	32	32	64	2	4
4	>256	>256	4	8	16	16	2	8
ABT-773	32	32	0.5	1	1	2	1	2
EMA	>256	>256	2	4	4	8	2	4
AZM	>256	>256	1	2	2	8	16	16

[a]10 strains for *E. faecalis*.
[b]10 strains for *S. pneumoniae*.
[c]10 strains for *H. influenzae*.
[d]10 strains for *S. hemolyticus*.

compounds **6d** and **6e** showed more potent activity against *S. hemolyticus* than EMA and AZM, which was similar with ABT-773.

EXPERIMENTAL PROCEDURE

All necessary solvents were purified before use, unless noted otherwise. Reactions were monitored by TLC using 0.20-mm pre-coated silica gel plates Merck DC-alurolle Kieselgel 60GF254. Column chromatography was performed with the indicated solvents using silica gel H (Qingdao Marine chemical plant, Shandong, China). IR spectra were recorded on KBr pellets using a Shimadzu IR-435 spectrometer. ^{1}H NMR spectra were recorded on a WYS-300 or VarianX1-400 or Inova-500 spectrometer at ambient temperature (TMS as internal standard of chemical shifts). Mass spectra were obtained on a ZAB-2F or Autospect-Ultima ETOF mass spactrometer for FAB-MS or ESI-MS. Melting points are uncorrected and were determined on an X-6 or RY-1 melting point apparatus. The starting material, 2′-*O*-benzoyl-10,11-dehydro-3-des(hexopyranosyloxy)-12-*O*-imidazolylcarbonyl-6-*O*-methyl-3-oxoerythromycin A (**3**), was prepared according to the published procedure.[26]

General methods for aryl isocyanate (2a–h)

To a solution of bis(trichloromethyl) carbonate in $CHCl_3$ was added dropwise aromatic amines in $CHCl_3$ in an ice bath. When the addition was finished, the reaction mixture was stirred at room temperature for 1–8 h and then heated at reflux until the reaction solution clarified. After the solvent was evaporated under atmospheric pressure, the residual liquid could be evaporated under reduced pressure.

Phenyl isocyanate (2a)

To a solution of bis(trichloromethyl) carbonate (16.3 g, 0.55 mol) in $CHCl_3$ (60 ml) was added dropwise **1a** (9.3 g, 0.1 mol) in $CHCl_3$ (40 ml) in an ice bath. When the addition was finished, the reaction mixture was stirred at room temperature for 1 h and then heated at reflux until the reaction solution clarified. After the solvent was evaporated under atmospheric pressure, the residual liquid was evaporated under reduced pressure to give 10.1 g (85%) of **2a** as colorless liquid: boiling point (bp) 65–68 °C per 30 mm Hg.

4-Methylphenyl isocyanate (2b)

1b (10.8 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to give 14.04 g (90%) of **2b** as colorless liquid: bp 69–70 °C per 30 mm Hg.

4-Methoxyphenyl isocyanate (2c)

1c (12.4 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated to give 12.75 g (85%) of **2c** as colorless liquid: bp 75–77 °C per 30 mm Hg.

4-Nitrophenyl isocyanate (2d)

1d (13.8 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated to give 13.27 g (81%) of **2d** as yellow solid: bp 85–86 °C per 30 mm Hg.

3-Methylphenyl isocyanate (2e)

1e (10.8 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated to give 11.13 g (70%) of **2e** as colorless liquid: bp 69–70 °C per 30 mm Hg.

2-Chlorophenyl isocyanate (2f)

1f (12.85 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated to give 11.87 g (77%) of **2f** as colorless liquid: bp 64–66 °C per 20 mm Hg.

3-Chlorophenyl isocyanate (2g)

1g (12.86 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 3.5 h. The solvent was evaporated to give 11.29 g (73%) of **2g** as colorless liquid: bp 66–68 °C per 20 mm Hg.

4-Trifluoromethylphenyl isocyanate (2h)

1h (16.1 g, 0.1 mol) in $CHCl_3$ was added dropwise according to the method for phenyl isocyanate. When the addition was finished, the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated to give 15.01 g (80%) of **2h** as colorless liquid: bp 71–73 °C per 30 mm Hg.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-11-(3-hydroxyprolylamino)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (4)

2′-*O*-Benzoyl-10,11-dehydro-3-des(hexopyranosyloxy)-12-*O*-imidazolylcarbonyl-6-*O*-methyl-3-oxoerythromycin A (**3**) (10.7 g, 13.9 mmol) and 1-amino propanol (11 ml, 14.3 mmol) were dissolved in DMF (80 ml) and the mixture was stirred for 62 h at room temperature. Water (150 ml) was added to the resulting solution and the aqueous layer was extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with water (150 ml), brine (100 ml), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (acetone:hexane, 3:6) to give 10.7 g (85%) of **4** as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05(d, J=7.6 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.63(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.49(t, J=7.6 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, 1H, J=10.8 Hz, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.26(s, 6H, $N(CH_3)_2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.80(t, J=7.2 Hz, 3H, *15-H*). ESI-MS (*m/z*):775(M+H)$^+$.

General methods for 11-[3-[(arylcarbamoyl)oxy]propylamino]-2′-*O*-benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamates (5a-h)

To a solution of 2′-*O*-benzoyl-11-deoxy-3-des(hexopyranosyloxy)-11-(3-hydroxyprolylamino)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (**4**) (0.4 g, 0.516 mmol), DCC (0.11 g, 0.516 mmol) and DMAP (0.063 g, 0.516 mmol) in CH_2Cl_2 (20 ml) was added dropwise corresponding aryl isocyanate (2.58 mmol) in CH_2Cl_2 (10 ml) in an ice bath. The reaction mixture was allowed to slowly warm to room temperature and was stirred for 20 h under nitrogen. The reaction was quenched with methanol (3 ml), filtered and concentrated in vacuum. The residue was purified by flash chromatography (cyclohexane-ethyl acetate, 5:1 ~ 2:1) to afford products **5a-h** as a white solid.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-11-[3-[(phenylcarbamoyl)oxy]propylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate (5a)

White solid, yield 82%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.38(d, J=8.0 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.28(d, J=8.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.05(t, J=7.6 Hz, 1H, phenyl-*H4*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, 1H, J=10.8 Hz, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.26(s, 6H, $N(CH_3)_2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17 (d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 894(M+H)$^+$.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(4-methylphenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (5b)

White solid, yield 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.37(d, J=8.0 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.06(d, J=8.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.92(dd, J=2.1, 8.7 Hz, *1H*, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, 1H, J=10.8 Hz, *5-H*), 3.83 (q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05 (ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.27(s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Hb*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 908(M+H)$^+$.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(4-methoxyphenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (5c)

White solid, yield 83%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.47(d, J=8.0 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 6.89(d, J=8.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, 1H, J=10.8 Hz, *5-H*), 3.83 (q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.60(s, 3H, phenyl-OCH_3), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41 (m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.27 (s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m,1H, *14-Ha*), 1.73(m,1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m,1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24 (m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 924(M+H)$^+$.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(4-nitrophenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (5d)

White solid, yield 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 8.05(d, J=8.2 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.68 (t, J=6.9 Hz, 1H, phenyl-*H4*), 7.63(d, J=8.2 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, J=10.8 Hz, 1H, *5-H*), 3.83 (q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.60(s, 3H, phenyl-OCH_3), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41 (m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.27 (s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*,), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 939(M+H)$^+$.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(3-methylphenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (5e)

White solid, yield 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.50(s, 1H, phenyl-*H2*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.45(d, J=7.7 Hz, 1H, phenyl-*H6*), 7.04(d, J=7.7 Hz, 1H, phenyl-*H5*), 6.82(d, J=7.7 Hz, 1H, phenyl-*H4*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, 1H, J=10.8 Hz, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50 (m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05 (ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.27(s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha)*, 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 908(M+H)$^+$.

2′-*O*-Benzoyl-11-[3-[(2-chlorophenylcarbamoyl)oxy]propylamino]-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (5f)

White solid, yield 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10(t, J=6.9 Hz, 1H, phenyl-*H6*), 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.85(s, 1H, phenyl-*H2*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.15(t, J=7.7 Hz, phenyl-*H3*), 7.00(t, J=8.0 Hz, 1H, phenyl-*H5*), 6.92(t, J=8.0 Hz, 1H, phenyl-*H4*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, J=10.8 Hz, 1H, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.27(s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 928(M+H)$^+$.

2′-*O*-Benzoyl-11-[3-[(3-chlorophenylcarbamoyl)oxy]propylamino]-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (5g)

White solid, yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.85(s, 1H, phenyl-*H2*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.55(d, J=7.7 Hz, 1H, phenyl-*H6*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.21(d, J=7.7 Hz, 1H, phenyl-*H5*), 7.03 (d, J=7.7 Hz, 1H, phenyl-*H4*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, J=10.8 Hz, 1H, *5-H*), 3.83 (q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*), 2.27(s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.78(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 928(M+H)$^+$.

2′-*O*-Benzoyl-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-11-[3-[(4-trifluoromethylphenylcarbamoyl)oxy]propylamino] erythromycin A 11-*N*,12-*O*-cyclic carbamate (5h)

White solid, yield 92%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.85(d, J=7.2 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.49(t, J=6.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.44(d, J=7.2 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 4.92(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.57(dd, J=8.0, 10.1 Hz, 1H, *2′-H*), 4.12(d, 1H, J=10.8 Hz, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.72(m, 2H, $CH_2CH_2CH_2OH$), 3.60(s, 3H, phenyl-OCH_3), 3.55(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.41(m, 1H, *4-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 3.05(ql, J=6.9 Hz, 1H, *10-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.78(s, 3H, 6-O-CH_3), 2.7(m, 1H, *3′-H*),2.27(s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.52(s, 3H, 6-CH_3), 1.38(m, 1H, *7-Ha*), 1.32(m, 1H, *7-Hb*), 1.26(s, 3H, 12-CH_3), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.79(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 962(M+H)$^+$.

General methods for 11-[3-[(arylcarbamoyl)oxy]propylamino]-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamates (6a-h)

11-[3-[(Arylcarbamoyl)oxy]propylamino]-2′-*O*-benzoyl-11-deoxy-3-des (hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (**5**) (0.5 mmol) was dissolved in methanol (20 ml) and the solution was refluxed for 20 h under nitrogen. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by flash chromatography (cyclohexane-ethyl acetate, 5:2) to afford product **6** as a white solid.

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-11-[3-[(phenylcarbamoyl)oxy]propylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate (6a)

White solid, yield 95%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01(s, 1H, OCON*H*-phenyl), 7.39(d, J=7.8 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.29(d, J=8.1 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.03(t, J=7.8 Hz, 1H, phenyl-*H4*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27(d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, 1H, J=8.0 Hz, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.59 (d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10(m, 2H, *10-H*, *4-H*), 3.20 (dd, J=7.5, 8.8 Hz, *1H*, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, N $(CH_3)_2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2OH$), 1.63(m, 1H, *14-Hb*), 1.47(s, 3H, 12-CH_3), 1.38(m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17 (d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.85(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 790(M+H)$^+$.

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(4-methylphenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (6b)

White solid, yield 96%. ^{1}H NMR($CDCl_3$, 400 MHz) δ 8.9(s, 1H, OCON*H*phenyl), 7.37(d, J=8.0 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.06 (d, J=8.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27(d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, J=8.0 Hz, 1H, *5-H*), 3.83 (q, J=7.0 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.59 (d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10(m, 2H, 10-H, *4-H*), 3.20 (dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, $N(CH_3)_2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47(s, 3H, 12-CH_3), 1.38 (m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12 (d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.85 (t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 804(M+H)$^+$.

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(4-methoxyphenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*,12-*O*-cyclic carbamate (6c)

White solid, yield 93%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78(s, 1H, OCON*H*phenyl), 7.47(d, J=8.0 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 6.89 (d, J=8.0 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27(d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, J=8.0 Hz, 1H, *5-H*), 3.83 (q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.60(s, 3H, phenyl-OCH_3), 3.59(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10 (m, 2H, 10-H, *4-H*), 3.20(dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, $N(CH_3)_2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65 (m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47(s, 3H, 12-CH_3), 1.38 (m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12 (d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.84 (t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 820(M+H)$^+$.

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(4-nitrophenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*, 12-*O*-cyclic carbamate (6d)

White solid, yield 86%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.08(s, 1H, OCON*H*phenyl), 8.05(d, J=8.2 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 7.63 (d, J=8.2 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27(d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, J=8.0 Hz,1H, *5-H*), 3.83 (q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.59 (d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10(m, 2H, 10-H, *4-H*), 3.20 (dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2O$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, N $(CH_3)_2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47(s, 3H, 12-CH_3), 1.38(m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17 (d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.84(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 835(M+H)$^+$.

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[3-[(3-methylphenylcarbamoyl)oxy]propylamino]-3-oxoerythromycin A 11-*N*, 12-*O*-cyclic carbamate (6e)

White solid, yield 96%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.61(s, 1H, OCON*H*phenyl), 7.50(s, 1H, phenyl-*H2*), 7.45(d, J=7.7 Hz, 1H, phenyl-*H6*), 7.04(d, J=7.7 Hz, 1H, phenyl-*H5*), 6.82(d, J=7.7 Hz, 1H, phenyl-*H4*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27(d, J=7.5 Hz, 1H, *1′-H*), 4.23 (d, 1H, J=8.0 Hz, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H,

$CH_2CH_2CH_2OCON$), 3.59(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10 (m, 2H, 10-H, *4-H*), 3.20(dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2OH$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, $N(CH_3)2$), 2.24(s, 3H, phenyl-CH_3), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47 (s, 3H, 12-CH_3), 1.38(m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.84(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 804(M+H)

11-[3-[(2-Chlorophenylcarbamoyl)oxy]propylamino]-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*, 12-*O*-cyclic carbamate (6f)

White solid, yield 91%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10(t, J=6.9 Hz, 1H, phenyl-*H6*), 7.85(s, 1H, phenyl-*H2*), 7.78(s, 1H, OCON*H*phenyl), 7.15 (t, J=7.7 Hz, 1H, phenyl-*H3*), 7.00(t, J=8.0 Hz, 1H, phenyl-*H5*), 6.92(t, J=8.0 Hz, 1H, phenyl-*H4*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27 (d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, J=8.0 Hz, 1H, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.59(d, J=2.5 Hz, 1H, *11-H*), 3.50 (m, 1H, *5′-H*), 3.10(m, 2H, *10-H*, *4-H*), 3.20(dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2O$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, $N(CH_3)2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47 (s, 3H, 12-CH_3), 1.38(m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.84(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 824(M+H)$^+$.

11-[3-[(3-Chlorophenylcarbamoyl)oxy]propylamino]-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*N*, 12-*O*-cyclic carbamate (6g)

White solid, yield 90%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.61(s, 1H, OCON*H*phenyl), 7.85(s, 1H, phenyl-*H2*), 7.55(d, J=7.7 Hz, 1H, phenyl-*H6*), 7.21(d, J=7.7 Hz, 1H, phenyl-*H5*), 7.03(d, J=7.7 Hz, 1H, phenyl-*H4*), 4.97 (dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27(d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, J=8.0 Hz, 1H, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.59(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10(m, 2H, 10-H, *4-H*), 3.20 (dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2O$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, N (CH_3)2), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47(s, 3H, 12-CH_3), 1.38(m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12 (d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.85 (t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 824(M+H)$^+$.

11-Deoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-11-[3-[(4-trifluoromethylphenylcarbamoyl)oxy]propylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate (6h)

White solid, yield 93%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85(d, J=7.2 Hz, 2H, phenyl-*H3*, phenyl-*H5*), 7.68(t, J=6.9 Hz, 1H, phenyl-*H4*), 7.44(d, J=7.2 Hz, 2H, phenyl-*H2*, phenyl-*H6*), 4.97(dd, J=2.1, 8.7 Hz, 1H, *13-H*), 4.27 (d, J=7.5 Hz, 1H, *1′-H*), 4.23(d, J=8.0 Hz, 1H, *5-H*), 3.83(q, J=7.8 Hz, 1H, *2-H*), 3.70(m, 2H, $CH_2CH_2CH_2OCON$), 3.59(d, J=2.5 Hz, 1H, *11-H*), 3.50(m, 1H, *5′-H*), 3.10(m, 2H, *10-H*, *4-H*), 3.20(dd, J=7.5, 8.8 Hz, 1H, *2′-H*), 3.10(q, J=7.0 Hz, 1H, *8-H*), 2.86(m, 2H, $NCH_2CH_2CH_2O$), 2.61(s, 3H, 6-O-CH_3), 2.48(m, 1H, *3′-H*), 2.29(s, 6H, $N(CH_3)_2$), 1.93(m, 1H, *14-Ha*), 1.73(m, 1H, *4′-Ha*), 1.65(m, 2H, $NCH_2CH_2CH_2O$), 1.63(m, 1H, *14-Hb*), 1.47 (s, 3H, 12-CH_3), 1.38(m, 1H, *7-Ha*), 1.34(s, 3H, 6-CH_3), 1.32(m, 1H, *7-Hb*), 1.24(m, 1H, *4′-Hb*), 1.17(d, J=7.0 Hz, 3H, 8-CH_3), 1.13(d, J=7.8 Hz, 3H, 2-CH_3), 1.12(d, J=6.9 Hz, 3H, 10-CH_3), 1.10(d, J=7.4 Hz, 3H, 4-CH_3), 0.85(t, J=7.2 Hz, 3H, *15-H*). ESI-MS(*m/z*): 858(M+H)$^+$.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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