European Journal of Medicinal Chemistry 44 (2009) 4010–4020

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and antibacterial activity of novel 15-membered macrolide derivatives: 4″-Carbamate, 11,12-cyclic carbonate-4″-carbamate and 11,4″-di-*O*-arylcarbamoyl analogs of azithromycin

Shutao Ma [a,*], Ruixin Ma [b], Zhaopeng Liu [a], Chenchen Ma [a], Xuecui Shen [a]

[a] *Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Shandong University, 44, West Culture Road, Jinan, Shandong 250012, PR China*
[b] *Affiliated Hospital of Medical College, Qingdao University, Qingdao 266003, PR China*

ARTICLE INFO

Article history:
Received 21 February 2009
Received in revised form
16 April 2009
Accepted 20 April 2009
Available online 3 May 2009

Keywords:
Synthesis
Macrolide
15-Membered macrolide analogs
Antibacterial activity

ABSTRACT

4″-Carbamate, 11,12-cyclic carbonate-4″-carbamate and 11,4″-di-*O*-arylcarbamoyl analogs of azithromycin were designed, synthesized and evaluated. The 4″-carbamate analogs retained excellent activity against erythromycin-susceptible *Staphylococcus pneumoniae* and showed improved activity against erythromycin-resistant *Staphylococcus pneumoniae*. Compared with 4″-carbamate analogs, 11,12-cyclic carbonate-4″-carbamate analogs exhibited improved activity against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene or the *erm* and *mef* genes, and 11,4″-di-*O*-arylalkylcarbamoyl analogs showed greatly improved activity (0.25–0.5 μg/mL) against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *erm* gene. Among them, the novel series of 11,4″-di-*O*-arylalkylcarbamoyl analogs **7a**–**k** exhibited potent and balanced activity against susceptible and resistant bacteria. In particular, compounds **7f** and **7k** were the most effective against susceptible bacteria and resistant bacteria encoded by the *erm* gene or the *mef* gene.

1. Introduction

Macrolide antibiotics have been used clinically for more than 50 years. They are used for the treatment of infections of the respiratory tract, skin and soft tissue [1,2]. First-generation macrolides (e.g., erythromycin A) readily lose their antibacterial activity under acidic conditions due to degradation. These degraded products are known to be responsible for undesirable gastrointestinal side effects [3]. Second-generation macrolide antibiotics such as azithromycin (Fig. 1) and clarithromycin have been widely prescribed for infections of the upper and lower respiratory tracts because of their superior antibacterial activity and pharmacokinetic properties compared with first-generation macrolides [4]. The therapeutic utility of these macrolides has led to rapid increase in the resistance rates of bacteria isolated clinically [5]. The molecular mechanisms of macrolide resistance are diverse, but the commonest mechanism of resistance is mediated by *erm*-encoded methylation of 23S rRNA or *mef*-encoded efflux. Expression of an *erm*-resistant determinant in bacteria leads to production of a methyltransferase which modifies the key nucleotide, A2058, in the macrolide–lincosamide–streptogramin B (MLS_B) binding site, thereby conferring resistance to macrolides [6–8].

Emergence of macrolide resistance has prompted further research directed towards the discovery of third-generation macrolides (e.g., ketolides) that can effectively address resistance and other issues associated with current macrolide regimens [9]. Ketolides such as telithromycin and cethromycin may offer alternative therapy for Gram-positive infections attributable to resistant pathogens [10]. Their mechanism of action has been elucidated: the C-11,12 carbamate side chain or the C-6 side chain in the ketolides interacts with nucleotide A752 directly in domain II of the 23S rRNA in addition to the main interaction of the drugs in domain V. This results in tighter binding to ribosomes [11], and imparts some activity against methylated ribosomes in some species [12].

Significant efforts have gone into the discovery of increasingly potent ketolides, but a substantial amount of work has also been carried out on novel macrolide derivatives. These investigations have led to the discovery of 11-*O*-substituted macrolides such as EP-1553 (Fig. 1) and 4″-carbamate macrolides such as CP-544372 (Fig. 1) [13,14]. EP-1553, which has an arylalkyl group tethered to the C-11 position of the erythronolide skeleton, exhibits excellent activity against macrolide-resistant *Staphylococcus aureus*, *Staphylococcus*

* Corresponding author. Tel.: +86 531 88382009; fax: +86 531 88911612.
E-mail address: mashutao@sdu.edu.cn (S. Ma).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.04.030

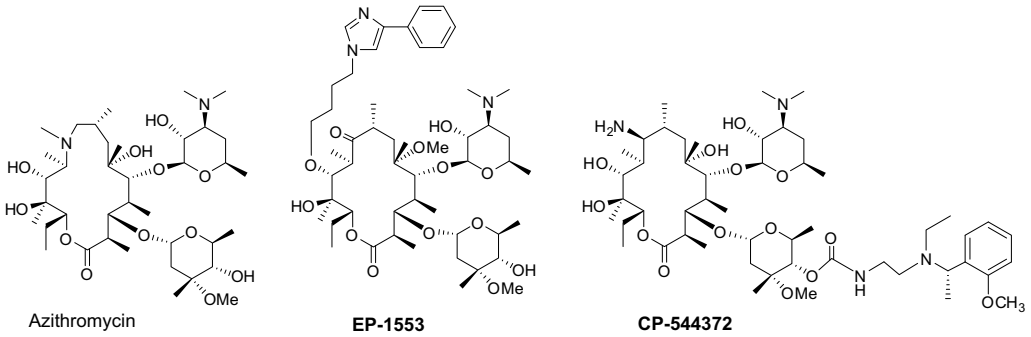


Fig. 1. Structures of azithromycin, EP-1553 and CP-544372.

pneumoniae and *Staphylococcus pyogenes*. CP-544372 contains a long anchor group at the C-4″ position of the cladinose sugar structure. It demonstrates good *in vitro* and *in vivo* activity against macrolide-resistant organisms with competitive binding to chloramphenicol, suggesting that the anchor group reaches the peptidyl transferase center region, the chloramphenicol-binding site [15,16].

Numerous chemical modifications of 14-membered macrolides to overcome bacterial resistance have been investigated over previous decades. Structure–activity relationships (SARs) of these 14-membered macrolide derivatives lead us to believe that the arylalkyl groups attached to the lactone ring or the C-4″ position of the cladinose sugar structure are essential for overcoming MLS_B resistance, whereas the 11,12-cylic carbamate or the 11,12-cylic carbonate linkage is important for overcoming efflux resistance. The structural modification of existing antibiotics therefore remains as one of the most effective approaches for overcoming bacterial resistance.

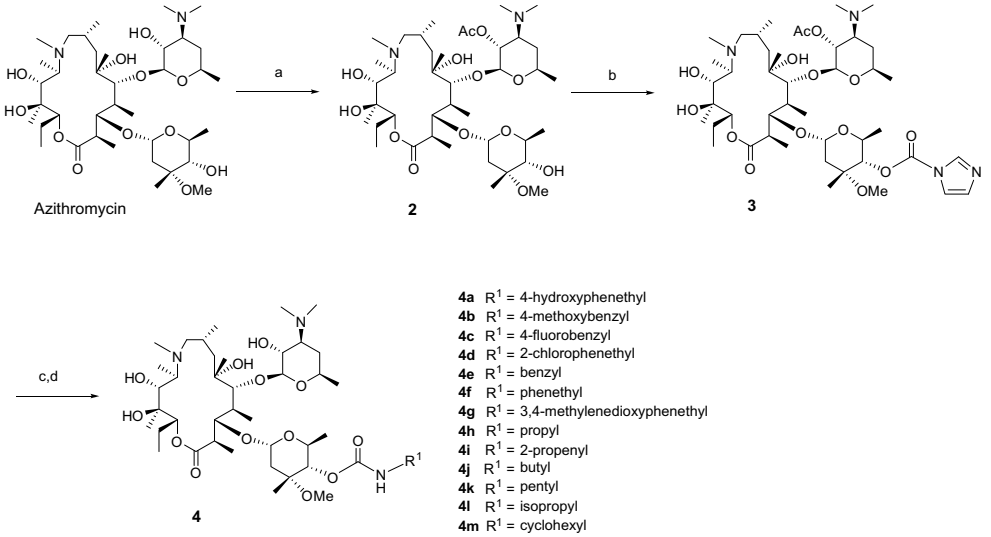
Azithromycin was the first 15-membered macrolide to have nitrogen incorporated into the lactone ring. Azithromycin is superior to erythromycin with regard to having better antibacterial activity as well as excellent pharmacokinetic properties and safety profile. It is one of the most widely prescribed antibiotics, but azithromycin is inactive against resistant bacteria. The azithromycin skeleton is very similar to that of clarithromycin except that the lactone ring is expanded around the 9-position [15,16]. They share a similar mechanism of action: selective binding to the 50S subunit of bacterial ribosome resulting in inhibition of protein synthesis. It seems that azithromycin modifications have not been systemically investigated since it was clinically used [17,18].

On the basis of the considerations detailed above, we designed novel structural 15-membered analogs of macrolides comprising the essential features for addressing macrolide resistance due to efflux and methylation of the ribosome. By introduction of an arylalkyl or an alkyl group into the 4″-position of azithromycin and the 4″-position of 11,12-cyclic carbonate azithromycin, the 4″-carbamate analogs of azithromycin and the 11,12-cyclic carbonate azithromycin were synthesized, respectively. It has been reported [15,16] that introduction of an arylalkyl group into the 4″-position or the 11-position of 14-membered macrolides enhances antibacterial activity (particularly anti-resistant activity). Novel 11,4″-di-*O*-arylcarbamoyl azithromycin analogs were prepared from 11,12-cyclic carbonate azithromycin 4″-carbamates on the basis of report [19] that 11,12-cyclic carbonate azithromycin was treated with corresponding amine in the presence of pyridine hydrochloride or 1-methyl-1*H*-imidazole to provide 11-carbamate of azithromycin.

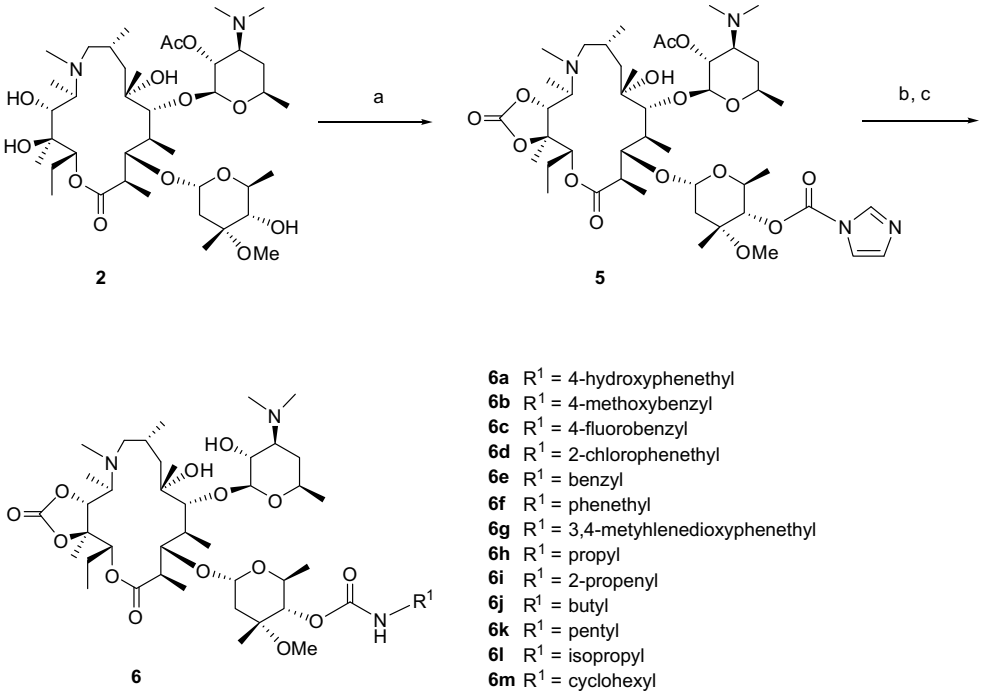
2. Chemistry

2.1. Synthesis of 4″-carbamate azithromycin analogs

The synthetic method of 4″-carbamate azithromycin analogs is shown in Scheme 1. Protection of the 2′-hydroxyl group of azithromycin with acetic anhydride provided 2′-*O*-acetylazithromycin (**2**). The treatment of **2** with 1,1′-carbonyldiimidazole (CDI) in toluene at room temperature afforded 2′-*O*-acetyl-4″-*O*-acylimidazolyl azithromycin (**3**). Finally, 4″-carbamate azithromycin analogs (**4a**–**m**) were prepared by coupling **3** with corresponding



Scheme 1. Reagents and conditions: (a) acetic anhydride, CH_2Cl_2, Et_3N, rt, 24 h; (b) CDI, Et_3N, toluene, rt, 48 h; (c) R^1NH_2, DMF, DBU, rt, 12 h; (d) CH_3OH, 55 °C, 20 h.



Scheme 2. Reagents and conditions: (a) CDI, Et_3N, toluene, 75 °C, 24 h; (b) R^1NH_2, DMF, DBU, rt, 12 h; (c) CH_3OH, 55 °C, 20 h.

amines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by methanolysis.

2.2. Synthesis of 11,12-cyclic carbonate azithromycin 4″-carbamate analogs

Scheme 2 describes the synthesis of 11,12-cyclic carbonate azithromycin 4″-carbamate analogs starting from **2**. 11,12-Carbonate 4-*O*-acylimidazolide **5** was prepared in toluene at 75 °C by treatment of **2** with CDI in the presence of triethylamine (Et_3N). 11,12-cyclic carbonate azithromycin 4″-carbamate analogs (**6a**–**m**) were prepared by treatment of **5** with corresponding amines in the presence of DBU. This was followed by deprotection of the acetate protection group with methanol at 55 °C.

2.3. Synthesis of 11,4″-di-O-arylalkylcarbamoyl azithromycin analogs

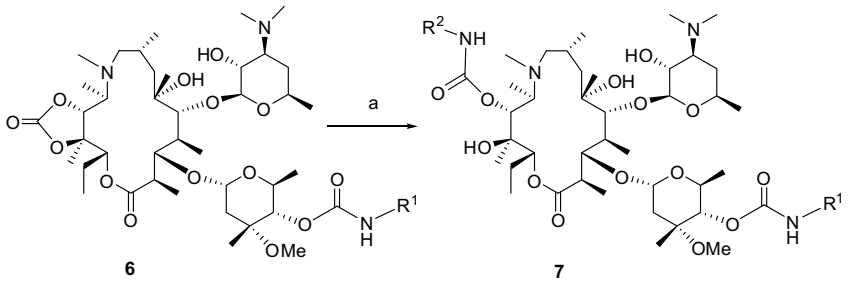
11,4″-Di-*O*-arylalkylcarbamoyl azithromycin analogs were prepared from compounds **6a**–**d** (Scheme 3). Compounds **6a**–**d**, which have an aromatic side chain at the 4″-position of their cladinose sugar structures, were readily converted to 11,4″-di-*O*-arylalkylcarbamoyl azithromycin analogs (**7a**–**k**) by coupling with the corresponding amines in the presence of pyridine hydrochloride or 1-methyl-1*H*-imidazole at room temperature for 2–5 days in yields ranging from 64% to 79%.

3. Antibacterial activity

The antibacterial screening of 4″-carbamate, 11,12-cyclic carbonate-4″-carbamate and 11,4″-di-*O*-arylcarbamoyl analogs of azithromycin prepared above was performed by a standard dilution assay for the determination of minimal inhibitory concentrations (MICs). MIC values for all compounds were determined in comparison with azithromycin (AZM) and clarithromycin (CAM) on a panel of sensitive and resistant Gram-positive bacterial strains. The strains are *Streptococcus pneumoniae* ATCC49619 (erythromycin-susceptible strain), *Staphylococcus pneumoniae* B1 (erythromycin-resistant strain encoded by the *erm* gene), *Staphylococcus pneumoniae* A22072 (erythromycin-resistant strain encoded by the *mef* gene) and *Staphylococcus pneumoniae* AB11 (erythromycin-resistant strain encoded by the *erm* and *mef* genes).

4. Results and discussion

MIC values for 4″-carbamate analogs are presented in Table 1. Most of the 4″-carbamate analogs retained excellent activity against erythromycin-susceptible *Staphylococcus pneumoniae* and



Scheme 3. Reagents and conditions: (a) R^2NH_2, pyridine hydrochloride or 1-methyl-1*H*-imidazole, rt, 2–5 days.

showed improved activity against erythromycin-resistant *Staphylococcus pneumoniae* compared with azithromycin (AZM) and clarithromycin (CAM). In particular, 4″-*O*-arylalkylcarbamoyl analogs possessed greatly improved and balanced activity against erythromycin-resistant *Staphylococcus pneumoniae* compared with 4″-*O*-alkylcarbamoyl analogs. Among 4″-*O*-arylalkylcarbamoyl analogs, compounds **4a**, **4c**, **4e** and **4g** showed potent activity against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene (0.06–0.5 μg/mL), and compound **4e** had the most potent activity (0.06 μg/mL). These results suggested that introduction of the arylalkylcarbamoyl group into the 4″-position of 15-membered macrolides can enhance antibacterial activity against erythromycin-resistant bacteria.

Compared with parent 4″-carbamate analogs, 11,12-cyclic carbonate azithromycin 4″-carbamate analogs showed similar activity against erythromycin-susceptible *Staphylococcus pneumoniae* and erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *erm* gene, and exhibited improved activity against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene or the *erm* and *mef* genes (Table 2). Almost all of the tested compounds with 4″-*O*-arylalkylcarbamoyl groups showed remarkably improved activity against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene or the *erm* and *mef* genes, compared with compounds having 4″-*O*-alkylcarbamoyl groups. Among them, compounds **6c**, **6f** and **6g** possessed the most potent activity against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene (0.06 μg/mL), showing 4-fold, 16-fold and 8-fold better activity than their precursors **4c**, **4f** and **4g**, respectively. These results clearly indicated that introduction of a cyclic carbonate into the 11,12-position of 15-membered macrolide 4″-carbamate analogs, particularly 4″-*O*-arylalkylcarbamoyl analogs, dramatically enhance their antibacterial activity against erythromycin-resistant bacteria encoded by the *mef* gene. This is consistent with reports [20,21] that introduction of a cyclic carbonate or carbamate into the 11,12-position of 14-macrolide derivatives increases their antibacterial activity.

MIC values for 11,4′-di-*O*-arylalkylcarbamoyl analogs are shown in Table 3. All the compounds (**7a**–**k**) showed greatly improved activity (0.25–0.5 μg/mL) against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *erm* gene in comparison with their precursors **6a**–**d** (8 μg/mL) and **4a**–**d** (4–64 μg/mL). This suggested that introduction of an arylalkyl group into the 11-position of 4″-*O*-arylalkylcarbamoyl analogs of 15-membered macrolides greatly enhances their antibacterial activity against erythromycin-resistant bacteria encoded by the *erm* gene. Most of the tested compounds **7a**–**k** (0.06–1 μg/mL) retained similar potent activity to the compounds **6a**–**d** (0.06–1 μg/mL) and showed better activity than compounds **4a**–**d** (0.25–4 μg/mL) against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene. That is, most of the compounds **7a**–**k** exhibited potent and balanced activity against susceptible and resistant bacteria. Among them, compounds **7f** and **7k** were the most effective against susceptible bacteria and resistant bacteria encoded by the *erm* gene or the *mef* gene, and compound **7g** had the most potent activity against susceptible bacteria and resistant bacteria encoded by the *erm* and *mef* genes. These results demonstrate that the arylalkyl side chain at the 11-position can interact with a new binding site of nucleotide in domain II of the 23S rRNA, resulting in tighter binding to ribosomes in macrolide-resistant bacteria.

Table 1
In vitro antibacterial activity of 4″-carbamate azithromycin analogs.

Compound	MICs (μg/mL)			
	S. pneumoniae ATCC49619[a]	*S. pneumoniae* B1[b]	*S. pneumoniae* A22072[c]	*S. pneumoniae* AB11[d]
4a	<0.03	4	0.5	2
4b	0.12	64	4	32
4c	<0.03	4	0.25	16
4d	<0.03	8	1	8
4e	<0.03	16	0.06	64
4f	0.06	8	1	32
4g	<0.03	8	0.5	8
4h	0.12	64	4	64
4i	<0.03	16	1	32
4j	<0.03	8	1	128
4k	<0.03	8	0.5	32
4l	0.12	128	8	256
4m	0.12	32	8	128
AZM	<0.03	128	4	256
CAM	<0.03	64	4	128

[a] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b] *S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm* gene.
[c] *S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef* gene.
[d] *S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm* and *mef* genes.

Table 2
In vitro antibacterial activity of 11,12-cyclic carbonate azithromycin 4″-carbamate analogs.

Compound	MICs (μg/mL)			
	S. pneumoniae ATCC49619[a]	*S. pneumoniae* B1[b]	*S. pneumoniae* A22072[c]	*S. pneumoniae* AB11[d]
6a	<0.03	8	1	4
6b	<0.03	8	0.25	16
6c	0.06	8	0.06	4
6d	0.06	8	0.25	2
6e	<0.03	8	0.12	8
6f	0.06	8	0.06	2
6g	<0.03	4	0.06	2
6h	0.06	16	0.12	16
6i	0.12	64	1	128
6j	0.12	8	1	16
6k	0.06	16	8	16
6l	0.12	16	8	128
6m	0.06	16	2	32
AZM	<0.03	128	4	256
CAM	<0.03	64	4	128

[a] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b] *S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm* gene.
[c] *S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef* gene.
[d] *S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm* and *mef* genes.

5. Conclusion

On the basis of the SARs of 14-membered macrolides, 4″-carbamate, 11,12-cyclic carbonate-4″-carbamate and 11,4″-di-*O*-arylcarbamoyl analogs of azithromycin were designed, synthesized and evaluated. Most of the 4″-carbamate analogs retained excellent activity against erythromycin-susceptible *Staphylococcus pneumoniae* and showed improved activity against erythromycin-resistant *Staphylococcus pneumoniae*. In particular, 4″-*O*-arylalkylcarbamoyl analogs possessed greatly improved activity against erythromycin-resistant *Staphylococcus pneumoniae* compared with 4″-*O*-alkylcarbamoyl analogs. This suggested that introduction of the arylalkylcarbamoyl group into the 4″-position of 15-membered macrolides can enhance antibacterial activity against erythromycin-resistant bacteria. Compared with the parent 4″-carbamate analogs, most of the 11,12-cyclic carbonate-4″-carbamate analogs exhibited improved activity against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *mef* gene or the *erm* and *mef* genes. This clearly indicated that introduction of a cyclic carbonate into the 11,12-position of 15-membered macrolide analogs, particularly 4″-*O*-arylalkylcarbamoyl analogs, dramatically enhances their antibacterial activity against erythromycin-resistant bacteria

Table 3
In vitro antibacterial activity of 11,4″-di-*O*-arylalkylcarbamoyl azithromycin analogs.

Strain/compound	MICs (μg/mL)												
	7a	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**	**7j**	**7k**	**AZM**	**CAM**
S. pneumoniae ATCC49619[a]	<0.03	<0.03	<0.03	0.06	0.06	<0.03	<0.03	<0.03	<0.03	0.06	<0.03	<0.03	<0.03
S. pneumoniae B1[b]	0.25	0.25	0.25	0.5	0.5	0.25	0.25	0.5	0.25	0.25	0.25	128	64
S. pneumoniae A22072[c]	1	0.25	0.12	1	1	0.06	0.12	0.5	0.25	0.25	0.06	4	4
S. pneumoniae AB11[d]	128	16	128	32	128	32	2	16	4	4	16	256	128

[a] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b] *S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm* gene.
[c] *S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef* gene.
[d] *S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm* and *mef* genes.

encoded by the *mef* gene. 11,4″-di-*O*-arylalkylcarbamoyl analogs showed greatly improved activity (0.25–0.5 μg/mL) against erythromycin-resistant *Staphylococcus pneumoniae* encoded by the *erm* gene in comparison with their precursors 11,12-cyclic carbonate-4″-carbamate analogs (8 μg/mL) or 4″-carbamate analogs (4–64 μg/mL). This suggested that introduction of an arylalkyl group into the 11-position of 4″-*O*-arylalkylcarbamoyl analogs of 15-membered macrolides greatly enhanced their antibacterial activity against erythromycin-resistant bacteria encoded by the *erm* gene. Among three series of 15-membered macrolide analogs, the novel series of 11,4″-di-*O*-arylalkylcarbamoyl analogs **7a**–**k** exhibited potent and balanced activity against susceptible and resistant bacteria. In particular, compounds **7f** and **7k** were the most effective against susceptible bacteria and resistant bacteria encoded by the *erm* gene or the *mef* gene.

6. Experimental

All necessary solvents were purified prior to use, unless noted otherwise. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm pre-coated silica gel plates. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm). Infrared spectra were recorded on KBr pellets using Nicolet Nexus 470FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance DRX 600 spectrometer at ambient temperature. Mass spectra were recorded on API 4000 instrument. The C, H, N analyses were carried out on PE-2400 II elemental analyser. Melting points are uncorrected and were determined on an X-6 melting point apparatus.

6.1. 2′-O-*Acetylazithromycin* (**2**)

To a solution of azithromycin (2.0 g, 2.67 mmol) in dichloromethane (20 mL) at room temperature was added acetic anhydride (0.5 mL, 5.34 mmol, 2.0 equiv) and Et_3N (1.48 mL, 10.68 mmol, 4.0 equiv). The resulting solution was allowed to stir for 24 h at the same temperature. The reaction was quenched with 5% aqueous $NaHCO_3$ (20 mL) and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was crystallized from acetone–water (2:1) to afford 1.84 g (92%) of **2** as a white solid: mp 167–170 °C; $R_f = 0.52$ (dichloromethane/methanol, 10:1); MS (ESI) *m*/*z* calcd. for $C_{40}H_{74}N_2O_{13}$ 791.0; found ($M + H^+$) 792.3.

6.2. 2′-O-*Acetyl*-4″-O-*acylimidazolyl azithromycin* (**3**)

To a solution of **2** (1.5 g, 1.90 mmol) in toluene (20 mL) was added Et_3N (0.68 mL, 4.33 mmol, 2.3 equiv) and CDI (0.67 g, 3.80 mmol, 2.0 equiv). The resulting solution was stirred at room temperature for 48 h. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and the aqueous layer was extracted with toluene (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol, 20:1) to afford 1.60 g (95%) of **3** as a white solid: mp 147–150 °C; $R_f = 0.59$ (dichloromethane/methanol, 10:1); MS (ESI) *m*/*z* calcd. for $C_{44}H_{76}N_4O_{14}$ 884.5; found ($M + H^+$) 885.2.

6.3. *General methods for 4″-O-arylalkylcarbamoyl azithromycin analogs* (***4a***–***m***)

To a solution of **3** (1.33 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 12 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 vacuo 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 vacuo, the residue was purified by flash chromatography (dichloromethane/methanol, 5:1) to afford products **4a**–**m**.

6.3.1. 4″-O-*(4-Hydroxyphenethyl-carbamoyl)azithromycin* (***4a***)

White solid, yield 73.5%, mp 159–162 °C, $[\alpha]_D^{20} = -32.4$ (*c* 0.5, EtOH), TLC $R_f = 0.31$ (dichloromethane/methanol, 5:1); IR (KBr): 3435, 2973, 2937, 2878, 1724, 1615, 1516, 1456, 1379, 1356, 1255, 1170, 1108, 1072, 1035, 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.02 (d, $J = 8.3$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 2H), 5.14 (d, $J = 4.7$ Hz, 1H), 4.71 (d, $J = 9.9$ Hz, 1H), 4.54 (d, $J = 7.3$ Hz, 1H), 4.48 (d, $J = 9.8$ Hz, 1H), 4.38 (m, 1H), 4.27 (m, 2H), 4.23 (m, 1H), 3.68 (s, 1H), 3.62–3.59 (m, 2H), 3.55 (m, 2H), 3.35 (s, 3H), 2.80–2.70 (m, 3H), 2.55 (d, $J = 10.5$ Hz, 1H), 2.46 (s, 6H), 2.39 (d, $J = 15.2$ Hz, 1H), 2.32 (s, 3H), 2.10 (m, 1H), 2.01 (m, 2H), 1.90 (m, 2H), 1.73 (d, $J = 14.6$ Hz, 1H), 1.65 (m, 1H), 1.47 (m, 2H), 1.28 (s, 3H), 1.25 (m, 2H), 1.24–1.20 (m, 6H), 1.16 (d, $J = 8.6$ Hz, 3H), 1.11–1.09 (m, 6H), 1.03 (d, $J = 7.5$ Hz, 3H), 0.97 (d, $J = 7.2$ Hz, 3H), 0.92–0.89 (m, 6H); MS (ESI) *m*/*z* calcd. for $C_{47}H_{81}N_3O_{14}$ 912.2; found ($M + H^+$) 913.1; Anal. calcd (%) for $C_{47}H_{81}N_3O_{14}$: C 61.89, H 8.95, N 4.61. Found: C 61.77, H 8.94, N 4.56.

6.3.2. 4″-O-*(4-Methoxybenzyl-carbamoyl)azithromycin* (***4b***)

White solid, yield 71.0%, mp 140–143 °C, $[\alpha]_D^{20} = -41.2$ (*c* 0.5, EtOH), TLC $R_f = 0.32$ (dichloromethane/methanol, 5:1); IR (KBr): 3457, 2972, 2936, 2833, 1727, 1613, 1514, 1457, 1424, 1379, 1249, 1173, 1108, 1094, 1073, 1034, 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.2$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.13 (d, $J = 4.6$ Hz, 1H), 4.72 (d, $J = 9.0$ Hz, 1H), 4.60–4.56 (m, 2H), 4.38–4.31 (m, 3H), 4.27 (m, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.70 (s, 1H), 3.66 (d, $J = 6.8$ Hz, 1H), 3.31(s, 3H), 2.87–2.72 (m, 3H), 2.55 (d, $J = 10.6$ Hz, 1H), 2.48 (s, 6H), 2.41 (d, $J = 7.1$ Hz, 1H), 2.32 (s, 3H),

2.10 (m, 1H), 2.02 (m, 2H), 1.90 (m, 2H), 1.75 (d, $J = 14.6$ Hz, 1H), 1.67 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.48 (m, 1H), 1.31(s, 3H), 1.29 (m, 1H), 1.27 (m, 2H), 1.24 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 7.4$ Hz, 3H), 1.19 (s, 3H), 1.16–1.12 (m, 6H), 1.09 (s, 3H), 1.05 (d, $J = 7.5$ Hz, 3H), 0.94–0.90 (m, 6H); MS (ESI) *m/z* calcd. for $C_{47}H_{81}N_3O_{14}$ 912.1; found $(M + H^+)$ 913.1; Anal. calcd (%) for $C_{47}H_{81}N_3O_{14}$: C 61.89, H 8.95, N 4.61. Found: C 61.98, H 8.99, N 4.66.

*6.3.3. 4″-O-(4-Fluorobenzyl-carbamoyl)azithromycin (**4c**)*

White solid, yield 68.4%, mp 140–143 °C, $[\alpha]_D^{20} = -38.4$ (*c* 0.6, EtOH), TLC $R_f = 0.31$ (dichloromethane/methanol, 5:1); IR (KBr): 3457, 2972, 2937, 2830, 1727, 1605, 1511, 1456, 1380, 1338, 1256, 1223, 1170, 1110, 1094, 1073, 1046, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.27–7.25 (m, 2H), 7.03–7.01 (m, 2H), 5.13 (d, $J = 4.5$ Hz, 1H), 4.72 (d, $J = 9.1$ Hz, 1H), 4.60–4.55 (m, 2H), 4.41–4.45 (m, 3H), 4.28 (m, 1H), 3.72 (m, 1H), 3.69 (s, 1H), 3.64 (d, $J = 6.6$ Hz, 1H), 3.30 (s, 3H), 2.85–2.72 (m, 3H), 2.54 (d, $J = 10.8$ Hz, 1H), 2.45 (s, 6H), 2.41 (d, $J = 15.1$ Hz, 1H), 2.35 (s, 3H), 2.09 (m, 1H), 2.07 (m, 2H), 1.90 (m, 2H), 1.76 (d, $J = 14.6$ Hz, 1H), 1.67 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.48 (m, 1H), 1.31 (s, 3H), 1.29 (m, 1H), 1.24–1.21 (m, 8H), 1.18 (s, 3H), 1.14 (d, $J = 6.0$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H), 1.09 (s, 3H), 1.05 (d, $J = 7.4$ Hz, 3H), 0.93–0.90 (m, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 178.5, 163.0, 156.4, 134.4, 129.1, 115.6, 102.1, 95.0, 79.4, 78.2, 77.2, 77.0, 76.8, 74.3, 73.5, 73.2, 71.1, 70.0, 67.7, 65.4, 63.5, 62.4, 49.4, 45.1, 44.5, 42.4, 41.4, 36.4, 35.2, 26.7, 22.0, 21.4, 21.2, 21.1, 17.9, 16.2, 15.0, 11.2, 9.4, 7.6; MS (ESI) *m/z* calcd. for $C_{46}H_{78}FN_3O_{13}$ 900.1; found $(M + H^+)$ 901.2; Anal. calcd (%) for $C_{46}H_{78}FN_3O_{13}$: C 61.38, H 8.73, F 2.11, N 4.67. Found: C 61.47, H 8.78, F 2.14, N 4.59.

*6.3.4. 4″-O-(2-Chlorophenethyl-carbamoyl)azithromycin (**4d**)*

White solid, yield 69.0%, mp 135–137 °C, $[\alpha]_D^{20} = -41.0$ (*c* 0.5, EtOH), TLC $R_f = 0.31$ (dichloromethane/methanol, 5:1); IR (KBr): 3475, 2972, 2937, 2877, 2830, 2788, 1727, 1632, 1507, 1457, 1378, 1344, 1255, 1170, 1109, 1094, 1073, 1050, 1036, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36 (m, 1H), 7.23–7.18 (m, 3H), 5.15 (d, $J = 4.7$ Hz, 1H), 4.71 (d, $J = 9.8$ Hz, 1H), 4.59 (m, 1H), 4.54–4.90 (m, 2H), 4.51 (m, 2H), 4.27 (m, 1H), 3.70–3.64 (m, 3H), 3.59–3.46 (m 2H), 3.31 (s, 3H), 2.87 (m, 1H), 2.79 (m, 1H), 2.71 (m, 1H), 2.54 (d, $J = 10.8$ Hz, 1H), 2.40 (m, 3H), 2.33 (s, 6H), 2.18 (s, 1H), 2.07 (m, 1H), 2.00 (m, 2H), 1.90 (m, 2H), 1.79 (d, $J = 14.6$ Hz, 1H), 1.66 (d, $J = 5.1$ Hz, 1H), 1.63 (d, $J = 5.0$ Hz, 1H), 1.48 (m, 1H), 1.31 (s, 3H), 1.28 (m, 1H), 1.21 (m, 2H), 1.20–1.19 (m, 6H), 1.15 (s, 3H), 1.11–1.09 (m, 9H), 1.06 (d, $J = 7.5$ Hz, 3H), 0.92–0.89 (m, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 178.7, 156.3, 136.2, 134.1, 131.1, 129.6, 128.1, 126.9, 102.4, 95.0, 83.1, 79.3, 77.2, 77.0, 76.8, 74.3, 74.0, 73.5, 73.1, 71.0, 68.7, 65.4, 63.2, 49.4, 45.0, 42.4, 41.6, 40.6, 36.4, 35.1, 33.8, 27.4, 26.8, 21.9, 21.6, 21.2, 21.1, 17.8, 16.2, 14.9, 11.3, 9.3, 7.5; MS (ESI) *m/z* calcd. for $C_{47}H_{80}ClN_3O_{13}$ 930.6; found $(M + H^+)$ 931.1; Anal. calcd (%) for $C_{47}H_{80}ClN_3O_{13}$: C 60.66, H 8.66, Cl 3.81, N 4.52. Found: C 60.54, H 8.60, Cl 3.77, N 4.54.

*6.3.5. 4″-O-(Benzyl-carbamoyl)azithromycin (**4e**)*

White solid, yield 73.8%, mp 136–139 °C, $[\alpha]_D^{20} = -45.0$ (*c* 0.6, EtOH), TLC $R_f = 0.31$ (dichloromethane/methanol, 5:1); IR (KBr): 3427, 2972, 2936, 2877, 1721, 1642, 1506, 1455, 1380, 1344, 1256, 1170, 1109, 1075, 1046, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34–7.31 (m, 2H), 7.28–7.25 (m, 3H), 5.11 (d, $J = 4.6$ Hz, 1H), 4.70 (d, $J = 9.6$ Hz, 1H), 4.59 (d, $J = 9.7$ Hz, 1H), 4.54 (d, $J = 6.6$ Hz, 1H), 4.43–4.36 (m, 3H), 4.27 (m, 1H), 3.73 (m, 1H), 3.69 (s, 1H), 3.65 (d, $J = 6.6$ Hz, 1H), 3.30 (s, 3H), 2.80–2.70 (m, 3H), 2.52 (d, $J = 10.2$ Hz, 1H), 2.42 (s, 6H), 2.37 (d, $J = 7.9$ Hz, 1H), 2.31 (s, 3H), 2.10 (m, 1H), 2.00 (m, 2H), 1.89 (m, 2H), 1.74 (d, $J = 14.4$ Hz, 1H), 1.65 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.46 (m, 1H), 1.30 (s, 3H), 1.28 (m, 1H), 1.25 (m, 2H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.21 (d, $J = 7.4$ Hz, 3H), 1.18 (s, 3H), 1.13 (d, $J = 6.0$ Hz, 3H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.07 (s, 3H), 1.04 (d, $J = 7.5$ Hz, 3H), 0.93–0.88 (m, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 178.4, 156.5, 138.5, 128.3, 127.4, 102.2, 95.1, 79.4, 78.3, 77.2, 77.0, 76.8, 74.3, 73.5, 73.2, 71.1, 70.0, 67.7, 65.4, 63.5, 62.4, 49.4, 45.2, 42.4, 41.4, 36.5, 35.3, 27.2, 26.7, 22.0, 21.4, 21.2, 21.1, 17.9, 16.2, 15.0, 11.2, 9.4, 7.6; MS (ESI) *m/z* calcd. for $C_{46}H_{79}N_3O_{13}$ 882.1; found $(M + H^+)$ 883.0; Anal. calcd (%) for $C_{46}H_{79}N_3O_{13}$: C 62.63, H 9.03, N 4.76. Found: C 62.68, H 9.09, N 4.70.

*6.3.6. 4″-O-(Phenethyl-carbamoyl)azithromycin (**4f**)*

White solid, yield 70.1%, mp 134–136 °C, $[\alpha]_D^{20} = -52.5$ (*c* 0.6, EtOH), TLC $R_f = 0.32$ (dichloromethane/methanol, 5:1); IR (KBr): 3446, 2972, 2936, 2877, 1728, 1506, 1455, 1378, 1345, 1255, 1170, 1109, 1050, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 7.25–7.19 (m, 3H), 5.13 (d, $J = 4.7$ Hz, 1H), 4.70 (d, $J = 9.5$ Hz, 1H), 4.55–4.49 (m, 2H), 4.43–4.32 (m, 3H), 4.29 (m, 1H), 3.70–3.60 (m, 3H), 3.57–3.43 (m, 2H), 3.31(s, 3H), 2.85–2.79 (m, 3H), 2.53 (d, $J = 10.8$ Hz, 1H), 2.40 (d, $J = 15.2$ Hz, 1H), 2.34 (s, 3H), 2.33 (s, 6H), 2.13 (m, 1H), 2.01 (m, 2H), 1.91 (m, 2H), 1.79 (d, $J = 14.7$ Hz, 1H), 1.65 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.48 (m, 1H), 1.31 (s, 3H), 1.28 (m, 1H), 1.25 (m, 2H), 1.22–1.19 (m, 6H), 1.15 (s, 3H), 1.11–1.09 (m, 9H), 1.06 (d, $J = 5.8$ Hz, 3H), 0.92–0.90 (m, 6H); MS (ESI) *m/z* calcd. for $C_{47}H_{81}N_3O_{13}$ 896.2; found $(M + H^+)$ 897.2; Anal. calcd (%) for $C_{47}H_{81}N_3O_{13}$: C 62.99, H 9.11, N 4.69. Found: C 62.90, H 9.07, N 4.64.

*6.3.7. 4″-O-(3,4-Methylenedioxyphenethyl-carbamoyl) azithromycin (**4g**)*

White solid, yield 74.0%, mp 161–163 °C, $[\alpha]_D^{20} = -40.7$ (*c* 0.7, EtOH), TLC $R_f = 0.32$ (dichloromethane/methanol, 5:1); IR (KBr): 3443, 2972, 2937, 2878, 1727, 1616, 1504, 1491, 1456, 1378, 1248, 1170, 1109, 1038, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.75 (d, $J = 7.9$ Hz, 1H), 6.68 (s, 1H), 6.64 (d, $J = 7.9$ Hz, 1H), 5.94 (m, 2H), 5.11 (d, $J = 4.6$ Hz, 1H), 4.70 (d, $J = 8.8$ Hz, 1H), 4.55–4.52 (m, 2H), 4.35–4.29 (m, 4H), 3.70 (m, 1H), 3.66–3.65 (m, 2H), 3.53–3.37 (m, 2H), 3.33 (s, 3H), 2.79–2.71 (m, 3H), 2.52 (d, $J = 10.3$ Hz, 1H), 2.32 (s, 3H), 2.24–2.28 (m, 6H), 2.05 (m, 1H), 2.02 (m, 3H), 1.90 (m, 1H), 1.76 (m, 1H), 1.66 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.49 (m, 1H), 1.31–1.27 (s, 6H), 1.22–1.19 (m, 6H), 1.16 (s, 3H), 1.11–1.06 (m, 12H), 0.93–0.90 (m, 6H); MS (ESI) *m/z* calcd. for $C_{48}H_{81}N_3O_{15}$ 940.2; found $(M + H^+)$ 941.3; Anal. calcd (%) for $C_{48}H_{81}N_3O_{15}$: C 61.32, H 8.68, N 4.47. Found: C 61.22, H 8.689, N 4.44.

*6.3.8. 4″-O-(Propyl-carbamoyl)azithromycin (**4h**)*

White solid, yield 70.4%, mp 138–140 °C, $[\alpha]_D^{20} = -39.1$ (*c* 0.7, EtOH), TLC $R_f = 0.34$ (dichloromethane/methanol, 5:1); IR (KBr): 3427, 2969, 2935, 2875, 1727, 1509, 1459, 1378, 1259, 1170, 1109, 1074, 1050, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.13 (d, $J = 4.6$ Hz, 1H), 4.78 (m, 1H), 4.71 (m, $J = 8.0$ Hz, 1H), 4.54 (m, 2H), 4.34 (m, 1H), 4.26 (m, 1H), 4.09 (d, $J = 6.7$ Hz, 1H), 3.76 (m, 1H), 3.69 (s, 1H), 3.65 (d, $J = 6.7$ Hz, 1H), 3.33 (s, 3H), 3.19 (m, 1H), 3.14 (m, 1H), 2.76 (m, 2H), 2.71 (d, $J = 6.7$ Hz, 1H), 2.52 (d, $J = 10.8$ Hz, 1H), 2.45 (s, 6H), 2.38 (d, $J = 15.2$ Hz, 2H), 2.33 (s, 3H), 2.02 (m, 4H), 1.89 (m, 2H), 1.75 (d, $J = 14.5$ Hz, 1H), 1.64 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.51 (m, 2H), 1.46 (m, 1H), 1.30–1.28 (m, 4H), 1.25 (m, 2H), 1.21–1.19 (m, 9H), 1.16 (s, 3H), 1.11 (m, 3H), 1.08 (s, 3H), 1.04 (d, $J = 7.6$ Hz, 3H), 0.99 (d, $J = 6.7$ Hz, 3H), 0.93–0.88 (m, 9H); MS (ESI) *m/z* calcd. for $C_{42}H_{79}N_3O_{13}$ 834.1; found $(M + H^+)$ 835.3; Anal. calcd (%) for $C_{42}H_{79}N_3O_{13}$: C 60.48, H 9.55, N 5.04. Found: C 60.59, H 9.51, N 5.11.

*6.3.9. 4″-O-(Propenyl-carbamoyl)azithromycin (**4i**)*

White solid, yield 72.7%, mp 142–145 °C, $[\alpha]_D^{20} = -41.5$ (*c* 0.7, EtOH), TLC $R_f = 0.32$ (dichloromethane/methanol, 5:1); IR (KBr): 3458, 3083, 2972, 2937, 2877, 2830, 1728, 1644, 1505, 1456, 1423, 1379, 1335, 1256, 1170, 1108, 1094, 1073, 047, 1015 cm^{-1}; ^1H NMR

(600 MHz, $CDCl_3$): δ 5.87 (m, 1H), 5.21–5.14 (m, 3H), 4.78 (m, 1H), 4.71 (d, $J = 8.9$ Hz, 1H), 4.55 (m, 2H), 4.47 (m, 1H), 4.39 (m, 1H), 4.29 (m, 1H), 3.85 (m, 1H), 3.70 (m, 2H), 3.70 (s, 1H), 3.66 (d, $J = 6.8$ Hz, 1H), 3.33 (s, 3H), 3.28 (m, 1H), 3.27 (m, 1H), 2.73 (m, 1H), 2.52 (d, $J = 10.9$ Hz, 1H), 2.41–2.39 (m, 2H), 2.35–2.34 (m, 9H), 2.08–2.00 (m, 4H), 1.91 (m, 2H), 1.79 (d, $J = 14.7$ Hz, 1H), 1.66 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.49 (m, 1H), 1.32–1.28 (m, 4H), 1.25 (m, 2H), 1.23–1.21 (m, 9H), 1.18 (s, 3H), 1.11 (m, 3H), 1.09 (s, 3H), 1.07 (d, $J = 7.5$ Hz, 3H), 0.93–0.89 (m, 6H); MS (ESI) *m/z* calcd. for $C_{42}H_{77}N_3O_{13}$ 832.1; found $(M + H^+)$ 833.8; Anal. calcd (%) for $C_{42}H_{77}N_3O_{13}$: C 60.63, H 9.33, N 5.05. Found: C 60.53, H 9.38, N 5.06.

*6.3.10. 4″-O-(Butyl-carbamoyl)azithromycin (**4j**)*

White solid, yield 76.5%, mp 145–148 °C, $[\alpha]_D^{20} = -39.5$ (*c* 0.6, EtOH), TLC $R_f = 0.33$ (dichloromethane/methanol, 5:1); IR (KBr): 3457, 2970, 2936, 2874, 1727, 1632, 1509, 1459, 1378, 1255, 1170, 1108, 1094, 1073, 1052, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.12 (d, $J = 6.7$ Hz, 1H), 4.71–4.70 (m, 2H), 4.54 (m, 2H), 4.40 (m, 1H), 4.29 (m, 1H), 3.75 (m, 1H), 3.70 (m, 1H), 3.67 (s, 1H), 3.66 (d, $J = 6.8$ Hz, 1H), 3.33 (s, 3H), 3.25 (m, 1H), 3.18 (m, 1H), 2.81 (m, 2H), 2.72 (d, $J = 4.9$ Hz, 1H), 2.54 (d, $J = 10.2$ Hz, 2H), 2.49–2.38 (m, 8H), 2.09 (s, 3H), 1.91 (m, 2H), 1.76 (d, $J = 14.4$ Hz, 1H), 1.64 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.52–1.48 (m, 4H), 1.37 (m, 1H), 1.30–1.28 (m, 4H), 1.25 (m, 2H), 1.24–1.21 (m, 9H), 1.18 (s, 3H), 1.12 (m, 3H), 1.09 (s, 3H), 1.06 (d, $J = 7.5$ Hz, 3H), 0.95–0.90 (m, 9H); MS (ESI) *m/z* calcd. for $C_{43}H_{81}N_3O_{13}$ 848.1; found $(M + H^+)$ 849.1; Anal. calcd (%) for $C_{43}H_{81}N_3O_{13}$: C 60.90, H 9.63, N 4.95. Found: C 60.83, H 9.60, N 4.99.

*6.3.11. 4″-O-(Pentyl-carbamoyl)azithromycin (**4k**)*

White solid, yield 77.8%, mp 144–146 °C, $[\alpha]_D^{20} = -41.2$ (*c* 0.6, EtOH), TLC $R_f = 0.33$ (dichloromethane/methanol, 5:1); IR (KBr): 3438, 2970, 2935, 2873, 2830, 1726, 1638, 1509, 1458, 1378, 1346, 1277, 1255, 1170, 1108, 1046, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.11 (d, $J = 4.6$ Hz, 1H), 4.70 (d, $J = 8.8$ Hz, 1H), 4.36 (m, 1H), 4.30 (m, 2H), 4.17 (m, 2H), 3.73–3.68 (m, 4H), 3.34 (s, 3H), 3.22 (m, 1H), 3.19 (m, 1H), 2.82 (m, 2H), 2.71 (m, 1H), 2.52 (d, $J = 10.3$ Hz, 1H), 2.41–2.28 (m, 11H), 1.90 (m, 2H), 1.79 (d, $J = 14.0$ Hz, 1H), 1.66 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.53–1.48 (m, 3H), 1.36–1.28 (m, 10H), 1.23–1.21 (m, 9H), 1.18 (s, 3H), 1.11–1.07 (m, 9H), 0.93–0.89 (m, 9H); MS (ESI) *m/z* calcd. for $C_{44}H_{83}N_3O_{13}$ 862.1; found $(M + H^+)$ 863.3; Anal. calcd (%) for $C_{44}H_{83}N_3O_{13}$: C 61.30, H 9.70, N 4.87. Found: C 61.38, H 9.66, N 4.82.

*6.3.12. 4″-O-(Isopropyl-carbamoyl)azithromycin (**4l**)*

White solid, yield 62.1%, mp 144–146 °C, $[\alpha]_D^{20} = -49.6$ (*c* 0.6, EtOH), TLC $R_f = 0.34$ (dichloromethane/methanol, 5:1); IR (KBr): 3450, 2972, 2937, 2877, 2830, 1727, 1632, 1500, 1457, 1379, 1343, 1257, 1170, 1108, 1076, 1050, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.17 (d, $J = 4.5$ Hz, 1H), 4.70 (d, $J = 9.8$ Hz, 1H), 4.58–4.52 (m, 3H), 4.34 (m, 1H), 4.28 (s, 1H), 3.85 (m, 1H), 3.74 (m, 1H), 3.64 (d, $J = 6.8$ Hz, 1H), 3.30 (s, 3H), 3.27 (m, 1H), 2.93 (s, 1H), 2.54 (d, $J = 10.4$ Hz, 1H), 2.41–2.38 (m, 2H), 2.27 (s, 6H), 1.99 (m, 3H), 1.78 (m, 1H), 1.75 (m, 1H), 1.63 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 2H), 1.45 (m, 2H), 1.30 (s, 6H), 1.23–1.21 (m, 8H), 1.18–1.14 (m, 9H), 1.10–1.09 (m, 6H), 1.05 (d, $J = 7.6$ Hz, 3H), 0.91–0.88 (m, 6H); MS (ESI) *m/z* calcd. for $C_{42}H_{79}N_3O_{13}$ 834.1; found $(M + H^+)$ 835.2; Anal. calcd (%) for $C_{42}H_{79}N_3O_{13}$: C 60.48, H 9.55, N 5.04. Found: C 60.59, H 9.50, N 5.07.

*6.3.13. 4″-O-(Cyclohexyl-carbamoyl)azithromycin (**4m**)*

White solid, yield 59.9%, mp 135–137 °C, $[\alpha]_D^{20} = -45.9$ (*c* 0.7, EtOH), TLC $R_f = 0.34$ (dichloromethane/methanol, 5:1); IR (KBr): 3449, 2972, 2935, 2877, 2832, 1727, 1654, 1631, 1499, 1455, 1379, 1336, 1266, 1170, 1108, 1073, 1048, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.10 (m, 1H), 4.70 (m, 1H), 4.69–4.63 (m, 2H), 4.59–4.55 (m, 1H), 4.53 (d, $J = 9.8$ Hz, 1H), 4.29–4.26 (m, 2H), 3.80 (s, 1H), 3.6 (m, 1H), 3.64 (m, 1H) 3.31 (s, 3H), 2.96 (s, 1H), 2.89 (s, 1H), 2.84 (m, 1H), 2.77 (m, 1H), 2.72 (m, 1H), 2.54 (m, 3H), 2.40 (s, 1H), 2.37 (s, 1H), 2.32 (s, 6H), 2.03–2.00 (m, 3H), 1.91–1.89 (m, 2H), 1.71–1.62 (m, 3H), 1.47 (m, 1H), 1.35–1.29 (m, 5H), 1.26–1.21 (m, 9H), 1.13 (s, 3H), 1.11 (m, 3H), 1.08 (s, 3H), 1.03 (m, 3H), 0.93–0.89 (m, 6H); MS (ESI) *m/z* calcd. for $C_{45}H_{83}N_3O_{13}$ 874.2; found $(M + H^+)$ 875.2; Anal. calcd (%) for $C_{45}H_{83}N_3O_{13}$: C 61.83, H 9.57, N 4.81. Found: C 61.74, H 9.54, N 4.78.

*6.4. 2′-O-Acetyl-4″-O-acylimidazolyl azithromycin 11,12-cyclic carbonate (**5**)*

To a solution of **2** (1.5 g, 1.90 mmol) in toluene (20 mL) was added Et_3N (0.68 mL, 4.33 mmol, 2.3 equiv) and CDI (1.23 g, 7.60 mmol, 4.0 equiv.). The resulting solution was heated to 75 °C and stirred at the same temperature for 24 h. The reaction was quenched with saturated $NaHCO_3$ (40 mL) and the aqueous layer was extracted with toluene (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol, 20:1) to afford 1.61 g (93%) of **5** as a white solid: mp 117–120 °C; $R_f = 0.61$ (dichloromethane/methanol, 10:1); MS (ESI) *m/z* calcd. for $C_{45}H_{74}N_4O_{15}$ 911.1; found $(M + H^+)$ 912.4.

*6.5. General methods for 4″-O-arylalkylcarbamoyl azithromycin 11,12 -cyclic carbonates (**6a**–**m**)*

To a solution of **5** (1.5 g, 1.65 mmol) in DMF (15 mL) at 0 °C was added DBU (0.33 mL, 2.25 mmol, 1.4 equiv) and corresponding amine (2.25 mmol, 1.4 equiv). The resulting solution was raised to room temperature and stirred for 12 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 vacuo 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 vacuo, the residue was purified by flash chromatography (dichloromethane/methanol, 5:1) to afford products **6a**–**m**.

*6.5.1. 4″-O-(4-Hydroxyphenethyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6a**)*

White solid, yield 73%, mp 152–155 °C, $[\alpha]_D^{20} = -42.4$ (*c* 0.6, EtOH), TLC $R_f = 0.60$ (dichloromethane/methanol, 5:1); IR (KBr): 3427, 2972, 2936, 2880, 1812, 1727, 1615, 1516, 1456, 1380, 1353, 1238, 1168, 1109, 1074, 1046, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.10 (m, 2H), 6.99 (m, 2H), 5.05 (m, 1H), 4.87 (m, 1H), 4.56–4.55 (m, 2H), 4.42 (s, 1H), 4.35 (m, 2H), 4.19 (m, 1H), 3.60 (d, $J = 6.7$ Hz, 1H), 3.56–3.50 (m, 2H), 3.45–3.43 (m, 2H), 3.33 (s, 3H), 2.85 (m, 2H), 2.79 (m, 6H), 2.47 (m, 1H), 2.34 (m, 1H) 2.22 (s, 3H), 2.02 (m, 2H), 1.92 (m, 2H), 1.85 (m, 2H), 1.68–1.60 (m, 4H), 1.45 (s, 3H), 1.27–1.21 (m, 6H), 1.18 (s, 3H), 1.16 (m, 6H), 1.09 (m, 6H), 0.95–0.88 (m, 6H); MS (ESI) *m/z* calcd. for $C_{48}H_{79}N_3O_{15}$ 938.2; found $(M + H^+)$ 939.1; Anal. calcd (%) for $C_{48}H_{79}N_3O_{15}$: C 61.45, H 8.49, N 4.48. Found: C 61.38, H 8.41, N 4.53.

*6.5.2. 4″-O-(4-Methoxybenzyl-carbamoyl)azithromycin 11, 12-cyclic carbonate (**6b**)*

White solid, yield 78%, mp 138–142 °C, $[\alpha]_D^{20} = -33.7$ (*c* 0.5, EtOH), TLC $R_f = 0.66$ (dichloromethane/methanol, 5:1); IR (KBr): 3434, 2973, 2937, 2880, 2834, 2788, 1814, 1727, 1613, 1586, 1513, 1457, 1380, 1352, 1337, 1302, 1240, 1169, 1109, 1073, 1045,

1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.20 (m, $J = 8.5$ Hz, 2H), 6.84 (m, $J = 8.6$ Hz, 2H), 5.07 (m, 1H), 4.89 (dd, $J = 9.3$ Hz, $J = 3.2$ Hz, 1H), 4.60 (d, $J = 9.8$ Hz, 1H), 4.44 (m, 1H), 4.39–4.36 (m, 3H), 4.30 (m, 1H), 3.80 (s, 3H), 3.63–3.60 (m, 3H), 3.30 (s, 3H), 2.84 (m, 3H), 2.41 (d, $J = 10.4$ Hz, 2H), 2.30 (s, 6H), 2.19 (s, 3H), 2.06–2.00 (m, 4H), 1.90 (m, 1H), 1.82 (m, 1H), 1.65 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.58 (m, 1H), 1.44 (s, 3H), 1.28 (s, 3H), 1.26–1.20 (m, 6H), 1.18–1.16 (m, 6H), 1.07–1.05 (m, 9H), 0.93–0.91 (m, 6H); MS (ESI) m/z calcd. for $C_{48}H_{79}N_3O_{15}$ 938.1; found $(M + H^+)$ 939.1; Anal. calcd (%) for $C_{48}H_{79}N_3O_{15}$: C 61.45, H 8.49, N 4.48. Found: C 61.56, H 8.47, N 4.43.

6.5.3. 4″-O-(4-Fluorobenzyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6c**)

White solid, yield 76%, mp 140–142 °C, $[\alpha]_D^{20} = -36.6$ (c 0.7, EtOH), TLC $R_f = 0.62$ (dichloromethane/methanol, 5:1); IR (KBr): 3427, 2973, 2937, 2880, 2830, 1813, 1727, 1605, 1510, 1456, 1381, 1353, 1337, 1223, 1111, 1093, 1073, 1046, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.25 (m, 2H), 7.02 (m, 2H), 5.20 (d, 1H), 5.09 (d, $J = 4.4$ Hz, 1H), 4.90 (dd, $J = 9.3$ Hz, $J = 3.2$ Hz, 1H), 4.61 (d, $J = 9.7$ Hz, 1H), 4.47 (m, 1H), 4.43–4.33 (m, 6H), 3.64 (m, 1H), 3.61 (d, $J = 5.6$ Hz, 1H), 3.32 (s, 3H), 2.86 (m, 2H), 2.41 (m, 6H), 2.36 (d, 1H), 2.21 (s, 3H), 2.18 (m, 1H), 2.05 (m, 2H), 1.95 (m, 1H), 1.93 (m, 1H), 1.83 (m, 2H), 1.64 (m, 2H), 1.60 (m, 2H), 1.45 (s, 3H), 1.29 (s, 3H), 1.22 (m, 6H), 1.18 (m, 6H), 1.07 (m, 6H), 0.93 (m, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 176.8, 163.0, 156.4, 153.3, 134.3, 129.5, 115.6, 102.9, 95.6, 79.4, 78.2, 77.2, 77.0, 76.8, 76.3, 73.3, 70.7, 68.3, 67.4, 65.2, 63.4, 61.1, 49.6, 45.3, 44.5, 43.9, 41.7, 35.4, 34.3, 26.7, 26.2, 22.1, 21.9, 21.2, 21.0, 17.7, 15.0, 14.4, 11.2, 10.4; MS (ESI) m/z calcd. for $C_{47}H_{76}FN_3O_{14}$ 926.1; found $(M + H^+)$ 927.1; Anal. calcd (%) for $C_{47}H_{76}FN_3O_{14}$: C 60.95, H 8.27, F 2.05, N 4.54. Found: C 60.86, H 8.23, F 2.09, N 4.48.

6.5.4. 4″-O-(2-Chlorobenethyl-carbamoyl)azithromycin 11, 12-cyclic carbonate (**6d**)

White solid, yield 80%, mp 130–133 °C, $[\alpha]_D^{20} = -34.1$ (c 0.7, EtOH), TLC $R_f = 0.64$ (dichloromethane/methanol, 5:1); IR (KBr): 3443, 2973, 2938, 2883, 2830, 1815, 1728, 1634, 1058, 1457, 1379, 1534, 1237, 1167, 1110, 1073, 1047, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36 (m, 1H), 7.23–7.16 (m, 3H), 5.09 (d, $J = 4.5$ Hz, 1H), 4.89 (dd, $J = 9.3$ Hz, $J = 3.2$ Hz, 1H), 4.83 (m, 1H), 4.56 (d, $J = 9.8$ Hz, 1H), 4.43–4.33 (m, 5H), 3.61–3.60 (m, 2H), 3.59–3.49 (m, 2H), 3.31 (s, 3H), 2.98 (m, 2H), 2.87 (m, 2H), 2.44 (d, $J = 10.7$ Hz, 1H), 2.34 (m, 6H), 2.22 (s, 3H), 2.18 (m, 1H), 2.09–1.98 (m, 2H), 1.93 (m, 1H), 1.84 (m, 1H), 1.65 (m, 2H), 1.63–1.57 (m, 2H), 1.50 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H), 1.20 (m, 6H), 1.16 (m, 6H), 1.07 (m, 6H), 0.93 (m, 6H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 176.9, 156.3, 153.4, 136.3, 134.2, 131.1, 129.6, 128.0, 126.9, 103.3, 95.6, 85.3, 79.3, 77.2, 77.0, 76.8, 76.1, 73.5, 73.4, 70.7, 68.5, 65.2, 63.3, 61.0, 49.6, 45.0, 42.4, 41.7, 40.6, 35.5, 34.2, 33.8, 26.7, 26.3, 22.0, 21.9, 21.4, 21.0, 17.7, 14.9, 14.4, 11.4, 10.4, 5.8; MS (ESI) m/z calcd. for $C_{48}H_{78}ClN_3O_{14}$ 956.6; found $(M + H^+)$ 957.1; Anal. calcd (%) for $C_{48}H_{78}ClN_3O_{14}$: C 60.27, H 8.22, Cl 3.71, N 4.39. Found: C 60.29, H 8.18, Cl 3.74, N 4.33.

6.5.5. 4″-O-(Benzyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6e**)

White solid, yield 78.5%, mp 155–158 °C, $[\alpha]_D^{20} = -39.4$ (c 0.7, EtOH), TLC $R_f = 0.63$ (dichloromethane/methanol, 5:1); IR (KBr): 3435, 2973, 2936, 2880, 2830, 2788, 1818, 1731, 1634, 1506, 1455, 1380, 1352, 1337, 1300, 1236, 1166, 1110, 1075, 1046, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.28 (m, 3H), 5.15 (m, 1H), 5.09 (m, 1H), 4.90 (m, 1H), 4.61 (d, $J = 9.8$ Hz, 1H), 4.48–4.35 (m, 6H), 3.61–3.60 (m, 2H), 3.32 (s, 3H), 2.88 (m, 2H), 2.44–2.33 (m, 7H), 2.20 (s, 3H), 2.18 (m, 1H), 2.02 (m, 2H), 1.92 (m, 2H), 1.83 (m, 2H), 1.67 (m, 2H), 1.62 (m, 2H), 1.45 (s, 3H), 1.32 (s, 3H), 1.24 (m, 6H), 1.18 (m, 6H), 1.08 (m, 6H), 0.93 (m, 6H); MS (ESI) m/z calcd. for $C_{47}H_{77}N_3O_{14}$ 908.1; found $(M + H^+)$ 909.1; Anal. calcd (%) for $C_{47}H_{77}N_3O_{14}$: C 62.16, H 8.55, N 4.63. Found: C 62.10, H 8.52, N 4.68.

6.5.6. 4″-O-(Phenethyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6f**)

White solid, yield 76.5%, mp 138–141 °C, $[\alpha]_D^{20} = -48.4$ (c 0.6, EtOH), TLC $R_f = 0.65$ (dichloromethane/methanol, 5:1); IR (KBr): 3442, 2973, 2938, 2881, 2830, 1815, 1728, 1634, 1506, 1455, 1380, 1353, 1336, 1238, 1167, 1111, 1046, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 7.27–7.19 (m, 3H), 5.06 (m, 1H), 4.90 (d, $J = 8.9$ Hz, 1H), 4.57–4.56 (m, 2H), 4.39–4.32 (m, 3H), 4.29 (m, 1H), 3.61–3.54 (m, 3H), 3.46 (m, 2H) 3.30 (s, 3H), 2.87–2.84 (m, 4H), 2.45 (d, $J = 10.2$ Hz, 1H), 2.38 (m, 1H), 2.20 (s, 3H), 2.05–2.02 (m, 2H), 1.92 (m, 1H), 1.91 (m, 1H), 1.67 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 1.64 (m, 1H), 1.61 (s, 7H), 1.27 (s, 3H), 1.26 (m, 1H), 1.25 (m, 2H), 1.23 (m, 3H), 1.16 (s, 3H), 1.09 (m, 6H), 1.09 (d, $J = 6.6$ Hz, 3H), 1.06 (m, 3H), 0.95–0.92 (m, 6H); MS (ESI) m/z calcd. for $C_{48}H_{79}N_3O_{14}$ 922.1; found $(M + H^+)$ 923.1; Anal. calcd (%) for $C_{48}H_{79}N_3O_{14}$: C 62.52, H 8.63, N 4.56. Found: C 62.43, H 8.61, N 4.49.

6.5.7. 4″-O-(3,4-Methylenedioxyphenethyl-carbamoyl) azithromycin 11,12-cyclic carbonate (**6g**)

White solid, yield 78.6%, mp 153–156 °C, $[\alpha]_D^{20} = -37.6$ (c 0.5, EtOH), TLC $R_f = 0.62$ (dichloromethane/methanol, 5:1); IR (KBr): 3434, 2972, 2936, 2881, 1813, 1727, 1632, 1504, 1491, 1456, 1379, 1353, 1247, 1167, 1110, 1074, 1044, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.73 (d, $J = 7.8$ Hz, 1H), 6.67 (s, 1H), 6.63 (d, $J = 7.8$ Hz, 1H), 5.07 (m, 1H), 4.88 (dd, $J = 9.2$ Hz, $J = 3.2$ Hz, 1H), 4.57 (d, $J = 9.8$ Hz, 2H), 4.44–4.33 (m, 4H), 3.61 (m, 1H), 3.51–3.48 (m, 2H), 3.39 (m, 2H), 3.31(s, 3H), 2.87 (m, 1H), 2.75 (m, 2H), 2.44 (m, 1H), 2.38–2.32 (m, 3H), 2.20 (s, 3H), 2.05–1.83 (m, 6H), 1.80 (m, 1H), 1.63 (m, 7H), 1.46 (s, 3H), 1.29 (s, 3H), 1.19 (m, 6H), 1.17–1.13 (m, 6H), 1.09–1.05 (m, 6H), 0.94–0.89 (m, 6H); MS (ESI) m/z calcd. for $C_{49}H_{79}N_3O_{16}$ 966.2; found $(M + H^+)$ 967.2; Anal. calcd (%) for $C_{49}H_{79}N_3O_{16}$: C 60.91, H 8.24, N 4.35. Found: C 60.98, H 8.20, N 4.31.

6.5.8. 4″-O-(Propyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6h**)

White solid, yield 77.6%, mp 202–205 °C, $[\alpha]_D^{20} = -37.6$ (c 0.7, EtOH), TLC $R_f = 0.64$ (dichloromethane/methanol, 5:1); IR (KBr): 3435, 2971, 2935, 2875, 2830, 1815, 1730, 1631, 1508, 1458, 1379, 1354, 1260, 1166, 1110, 1047, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.05 (s, 1H), 4.88 (d, $J = 6.6$ Hz, 1H), 4.83 (m, 1H), 4.56 (m, 2H), 4.45 (m, 1H), 4.38 (m, 2H), 3.65 (m, 1H), 3.62 (d, $J = 4.5$ Hz, 1H), 3.32 (s, 3H), 3.16 (m, 3H), 2.80 (m, 2H), 2.44 (d, $J = 10.0$ Hz, 1H), 2.38 (d, $J = 15.1$ Hz, 1H), 2.19 (s, 6H), 2.05–2.02 (m, 2H), 1.82 (s, 3H), 1.66 (m, 2H), 1.60 (m, 1H), 1.57 (m, 1H), 1.28–1.25 (m, 7H), 1.22–1.20 (m, 8H), 1.17 (s, 6H), 1.07–1.06 (m, 6H), 0.93–0.84 (m, 12H); MS (ESI) m/z calcd. for $C_{43}H_{77}N_3O_{14}$ 860.1; found $(M + H^+)$ 861.1; Anal. calcd (%) for $C_{43}H_{77}N_3O_{14}$: C 60.05, H 9.02, N 4.89. Found: C 60.13, H 9.07, N 4.85.

6.5.9. 4″-O-(Propenyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6i**)

White solid, yield 77.6%, mp 151–154 °C, TLC $R_f = 0.63$ (dichloromethane/methanol, 5:1); IR (KBr): 3431, 3084, 2973, 2936, 2879, 2830, 2788, 1814, 1728, 1643, 1507, 1457, 1425, 1380, 1353, 1335, 1237, 1167, 1110, 1074, 1046, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.85 (m, 1H), 5.22–5.12 (m, 2H), 5.07 (m, 1H), 4.89 (m, 1H), 4.88 (m, 1H), 4.58 (m, 2H), 4.45 (m, 1H), 4.39 (m, 1H), 3.82 (m, 3H), 3.65 (s, 1H), 3.61 (d, $J = 5.2$ Hz, 1H), 3.31 (s, 3H), 2.95 (m, 1H), 2.85 (m, 2H), 2.43 (d, $J = 10.7$ Hz, 1H), 2.38–2.35 (m, 2H), 2.30 (m, 6H), 2.19 (s, 6H), 2.07–2.00 (m, 2H), 1.91 (m, 1H), 1.82 (m, 1H), 1.71–1.52 (m, 7H), 1.43 (s, 3H), 1.28 (s, 3H), 1.25 (m, 3H), 1.21 (m, 6H), 1.17 (s, 3H), 1.06 (d, $J = 6.5$ Hz, 3H), 0.92–0.86 (m, 6H); MS (ESI) m/z calcd. for $C_{43}H_{75}N_3O_{14}$ 858.1; found $(M + H^+)$ 859.0; Anal.

calcd (%) for $C_{43}H_{75}N_3O_{14}$: C 60.19, H 8.81, N 4.90. Found: C 60.11, H 8.88, N 4.85.

6.5.10. 4″-O-(Butyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6j**)

White solid, yield 76.9%, mp 99–102 °C, $[\alpha]_D^{20} = -39.3$ (*c* 0.7, EtOH), TLC $R_f = 0.64$ (dichloromethane/methanol, 5:1); IR (KBr): 3427, 2970, 2938, 2873, 2830, 1815, 1724, 1511, 1458, 1379, 1357, 1244, 1167, 1110, 1047, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.09 (m, 1H), 4.91 (d, $J = 9.0$ Hz, 1H), 4.81 (m, 1H), 4.71 (d, $J = 9.7$ Hz, 1H), 4.57 (m, 1H), 4.45–4.36 (m, 4H), 3.67 (m, 1H), 3.62 (d, $J = 5.5$ Hz, 1H), 3.30 (s, 3H), 2.87 (m, 2H), 2.44–2.34 (m, 7H), 2.20 (s, 3H), 2.07 (m, 1H), 2.02 (m, 2H), 1.92 (m, 1H), 1.84 (m, 1H), 1.70 (m, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.46 (s, 3H), 1.28 (s, 3H), 1.22 (m, 6H), 1.17 (s, 6H), 1.08 (m, 6H), 0.93 (m, 6H); MS (ESI) *m*/*z* calcd. for $C_{44}H_{79}N_3O_{14}$ 874.1; found ($M + H^+$) 875.1; Anal. calcd (%) for $C_{44}H_{79}N_3O_{14}$: C 60.46, H 9.11, N 4.81. Found: C 60.53, H 9.07, N 4.84.

6.5.11. 4″-O-(Pentyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6k**)

White solid, yield 74.9%, mp 105–110 °C, $[\alpha]_D^{20} = -33.3$ (*c* 0.7, EtOH), TLC $R_f = 0.64$ (dichloromethane/methanol, 5:1); IR (KBr): 3419, 2969, 2935, 2872, 2830, 1815, 1724, 1670, 1510, 1457, 1379, 1353, 1336, 1256, 1238, 1167, 1109, 1093, 1073, 1045, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07 (m, 1H), 4.89 (d, $J = 9.1$ Hz, 1H), 4.69 (m, 1H), 4.55 (m, 2H), 4.36 (m, 2H), 3.69–3.60 (m, 4H), 3.30 (s, 3H), 3.21 (m, 1H), 3.16 (m, 1H), 2.86 (m, 2H), 2.58 (m, 1H), 2.43 (m, 1H), 2.35–2.29 (m, 3H), 2.19 (m, 2H), 1.90 (s, 6H), 1.64 (m, 2H), 1.63 (m, 1H), 1.50–1.47 (m, 4H), 1.44 (s, 3H), 1.33–1.29 (m, 7H), 1.26 (s, 3H), 1.23–1.21 (m, 9H), 1.17 (s, 3H), 1.09–1.06 (m, 6H), 0.93–0.88 (m, 9H); MS (ESI) *m*/*z* calcd. for $C_{45}H_{81}N_3O_{14}$ 888.1; found ($M + H^+$) 889.3; Anal. calcd (%) for $C_{45}H_{81}N_3O_{14}$: C 60.86, H 9.19, N 4.73. Found: C 60.80, H 9.14, N 4.78.

6.5.12. 4″-O-(Isopropyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6l**)

White solid, yield 65.1%, mp 140–143 °C, TLC $R_f = 0.64$ (dichloromethane/methanol, 5:1); IR (KBr): 3442, 2920, 2850, 1814, 1741, 1644, 1499, 1462, 1378, 1354, 1336, 1296, 1238, 1168, 1112, 1075, 1045, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07 (d, $J = 4.5$ Hz, 1H), 4.89 (d, $J = 9.1$ Hz, 1H), 4.68 (m, 1H), 4.50–4.45 (m, 2H), 4.42–4.36 (m, 2H), 3.80 (m, 2H), 3.71 (m, 1H), 3.61 (d, $J = 7.4$ Hz, 1H), 3.30 (s, 3H), 2.85 (m, 3H), 2.44 (m, 8H), 2.19 (s, 3H), 2.07–2.02 (m, 2H), 1.65–1.64 (m, 2H), 1.62–1.58 (m, 2H), 1.58 (s, 5H), 1.28 (s, 6H), 1.25–1.23 (m, 6H), 1.20–1.19 (m, 6H), 1.10–1.04 (m, 6H), 0.93–0.86 (m, 9H); MS (ESI) *m*/*z* calcd. for $C_{43}H_{77}N_3O_{14}$ 860.1; found ($M + H^+$) 861.1; Anal. calcd (%) for $C_{43}H_{77}N_3O_{14}$: C 60.05, H 9.02, N 4.89. Found: C 60.07, H 9.07, N 4.83.

6.5.13. 4″-O-(Cyclohexyl-carbamoyl)azithromycin 11,12-cyclic carbonate (**6m**)

White solid, yield 66.7%, mp 140–142 °C, $[\alpha]_D^{20} = -32.6$ (*c* 0.6, EtOH), TLC $R_f = 0.65$ (dichloromethane/methanol, 5:1); IR (KBr): 3387, 2973, 2936, 2879, 1814, 1742, 1719, 1456, 1380, 1353, 1330, 1269, 1236, 1167, 1110, 1087, 1061, 1046, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.08 (m, 1H), 4.89 (d, $J = 9.0$ Hz, 1H), 4.74 (m, 2H), 4.54 (m, 1H), 4.42–4.35 (m, 3H), 3.80 (s, 1H), 3.62 (m, 1H), 3.50 (m, 1H) 3.32 (s, 3H), 3.30 (s, 1H), 2.96 (s, 1H), 2.87 (m, 1H), 2.85 (m, 2H), 2.41 (s, 3H), 2.32 (s, 6H), 2.21 (s, 1H), 2.19 (s, 1H), 2.04–2.02 (m, 3H), 1.93 (m, 2H), 1.71–1.68 (m, 3H), 1.60 (m, 1H), 1.44 (d, 5H), 1.36 (m, 3H), 1.29 (s, 3H), 1.26–1.21 (m, 12H), 1.16 (s, 3H), 1.08 (m, 6H), 0.93–0.91 (m, 6H); MS (ESI) *m*/*z* calcd. for $C_{46}H_{81}N_3O_{14}$ 900.1; found ($M + H^+$) 901.3; Anal. calcd (%) for $C_{46}H_{81}N_3O_{14}$: C 61.38, H 9.07, N 4.67. Found: C 61.44, H 9.05, N 4.64.

6.6. General methods for 11,4″-di-O-arylalkylcarbamoyl derivatives of azithromycin (**7a**–**k**)

Method 1 To a solution of **6** (1.50 mmol) in corresponding amine (5 mL) at room temperature was added pyridine hydrochloride (0.34 g, 3.00 mmol). The resulting solution was allowed to stir for 2–5 days at the same temperature. The reaction was quenched with water (30 mL) and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane–methanol, 10:1) to afford products **7**.

Method 2 To a solution of **6** (1.50 mmol) in 1-methyl-1*H*-imidazole (15 mL) at room temperature was added corresponding amine (3.00 mmol). The resulting solution was allowed to stir for 2–5 days at the same temperature. The reaction was quenched with water (30 mL) and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane–methanol, 10:1) to afford products **7**.

6.6.1. 11-O-(Butyl-carbamoyl)-4″-O-(4-hydroxyphenethyl-carbamoyl) azithromycin (**7a**)

White solid, yield 79.1%, mp 104–107 °C, $[\alpha]_D^{20} = -34.8$ (*c* 0.7, EtOH), TLC $R_f = 0.44$ (dichloromethane/methanol, 5:1); IR (KBr): 3419, 2974, 2934, 2874, 1724, 1615, 1516, 1459, 1382, 1301, 1251, 1170, 1118, 1072, 1049, 016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.02–7.01(m, 4H), 5.05 (m, 1H), 4.98 (d, $J = 9.8$ Hz, 1H), 4.50–4.46 (m, 3H), 4.36 (m, 1H), 4.26 (m, 2H), 3.57–3.50 (m, 3H), 3.48 (m, 2H), 3.32 (m, 2H), 3.29 (s, 3H), 3.15–3.13 (m, 3H), 2.97 (m, 1H), 2.74 (m, 7H), 2.22 (s, 3H), 2.10 (m, 1H), 2.01 (m, 2H), 1.90 (m, 1H), 1.74 (m, 2H), 1.65 (m, 1H), 1.36 (m, 6H), 1.26 (s, 3H), 1.22 (m, 2H), 1.20–1.17 (m, 6H), 1.14 (d, $J = 6.1$ Hz, 3H), 0.99–0.95 (m, 12H), 0.92–0.89 (m, 9H); MS (ESI) *m*/*z* calcd. for $C_{52}H_{90}N_4O_{15}$ 1011.3; found ($M + H^+$) 1012.0; Anal. calcd (%) for $C_{52}H_{90}N_4O_{15}$: C 61.76, H 8.97, N 5.54. Found: C 61.70, H 8.94, N 5.59.

6.6.2. 11-O-(2-Chlorobenethyl-carbamoyl)-4″-O-(4-hydroxyphenethyl-carbamoyl)azithromycin (**7b**)

White solid, yield 76.3%, mp 110–113 °C, $[\alpha]_D^{20} = -36.9$ (*c* 0.7, EtOH), TLC $R_f = 0.45$ (dichloromethane/methanol, 5:1); IR (KBr): 3426, 2974, 2937, 2877, 2830, 1708, 1614, 1516, 1457, 1382, 1344, 1253, 1170, 1111, 1093, 1073, 1046, 1037, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.37 (m, 1H), 7.20–7.02 (m, 3H), 7.01 (m, 4H), 5.05 (m, 1H), 4.99 (d, $J = 9.0$ Hz, 1H), 4.50–4.44 (m, 3H), 4.42 (m, 1H), 4.29–4.26 (m, 3H), 3.59–3.56 (m, 4H), 3.55 (m, 4H), 3.30 (s, 3H), 3.00 (m, 3H), 2.74 (m, 6H), 2.65 (m, 1H), 2.22–2.20 (m, 4H), 2.10 (m, 5H), 1.74–1.71 (m, 2H), 1.65–1.59 (m, 3H), 1.26 (s, 3H), 1.20 (m, 2H), 1.18–1.17 (m, 6H), 1.11 (d, $J = 6.1$ Hz, 3H), 1.04–1.01 (m, 9H), 0.97–0.88 (m, 9H); MS (ESI) *m*/*z* calcd. for $C_{56}H_{89}ClN_4O_{15}$ 1093.7; found ($M + H^+$) 1094.0; Anal. calcd (%) for $C_{56}H_{89}ClN_4O_{15}$: C 61.49, H 8.20, Cl 3.24, N 5.12. Found: C 61.58, H 8.21, Cl 3.21, N 5.15.

6.6.3. 11-O-(Benzyl-carbamoyl)-4″-O-(4-hydroxyphenethyl-carbamoyl) azithromycin (**7c**)

White solid, yield 78.6%, mp 118–120 °C, $[\alpha]_D^{20} = -38.2$ (*c* 0.7, EtOH), TLC $R_f = 0.41$ (dichloromethane/methanol, 5:1); IR (KBr): 3423, 2975, 2937, 2874, 1728, 1615, 1516, 1456, 1379, 1301, 1253, 1170, 1111, 1073, 1047, 1034, 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 2H), 7.30 (m, 3H), 7.21 (m, 3H), 7.03 (m, $J = 8.3$ Hz, 2H), 5.00 (d, $J = 9.8$ Hz, 1H), 4.98 (m, 1H), 4.46–4.36 (m, 4H), 4.26 (m, 2H), 3.62 (m, 1H), 3.57 (m, 2H), 3.50 (m, 2H), 3.45 (m, 1H), 3.27 (s, 3H), 3.00 (m, 2H), 2.62 (m, 2H), 2.50 (m, 6H), 2.32 (m, 2H), 2.25

(s, 3H), 2.10 (m, 1H), 2.02 (m, 2H), 1.90 (m, 2H), 1.74 (m, 3H), 1.45 (m, 2H), 1.26–1.24 (m, 9H), 1.23–1.21 (m, 3H), 1.13 (m, 9H), 1.07 (m, 6H), 1.01 (d, $J = 6.5$ Hz, 3H), 0.89–0.88 (m, 3H); MS (ESI) m/z calcd. for $C_{55}H_{88}N_4O_{15}$ 1045.3; found ($M + H^+$) 1045.9; Anal. calcd (%) for $C_{55}H_{88}N_4O_{15}$: C 63.20, H 8.49, N 5.36. Found: C 63.21, H 8.42, N 5.33.

*6.6.4. 11-O-(Pentyl-carbamoyl)-4″-O-(4-methoxybenzyl-carbamoyl)azithromycin (**7d**)*

White solid, yield 69.4%, mp 115–117 °C, $[\alpha]_D^{20} = -41.1$ (c 0.6, EtOH), TLC $R_f = 0.50$ (dichloromethane/methanol, 5:1); IR (KBr): 3427, 2974, 2934, 2873, 1728, 1613, 1514, 1489, 1379, 248, 1173, 1109, 1093, 1072, 1049, 1034, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.21 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.05 (m, 1H), 5.00 (d, $J = 9.9$ Hz, 1H), 4.61 (m, 2H), 4.44 (m, 1H), 4.34 (m, 2H), 3.85 (m, 1H), 3.81 (s, 3H), 3.63–3.60 (m, 3H), 3.33 (s, 3H), 3.17 (m, 2H), 2.68 (m, 2H), 2.42–2.39 (m, 3H), 2.30 (s, 6H), 2.23 (s, 3H), 2.10–2.01 (m, 3H), 1.90 (m, 2H), 1.65 (m, 2H), 1.51 (m, 4H), 1.37 (m, 6H), 1.26 (s, 3H), 1.25–1.23 (m, 6H), 1.19 (m, 6H), 0.99–0.96 (m, 9H), 0.92–0.89 (m, 9H); MS (ESI) m/z calcd. for $C_{53}H_{92}N_4O_{15}$ 1025.3; found ($M + H^+$) 1026.1; Anal. calcd (%) for $C_{53}H_{92}N_4O_{15}$: C 62.09, H 9.04, N 5.46. Found: C 62.00, H 9.04, N 5.49.

*6.6.5. 11-O-(Butyl-carbamoyl)-4″-O-(4-methoxybenzyl-carbamoyl)azithromycin (**7e**)*

White solid, yield 64%, mp 106–109 °C, $[\alpha]_D^{20} = -47.3$ (c 0.6, EtOH), TLC $R_f = 0.50$ (dichloromethane/methanol, 5:1); IR (KBr): 3419, 2974, 2935, 2854, 1726, 1610, 1513, 1460, 1379, 1301, 1248, 1173, 1109, 1092, 1073, 1049, 1033, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.20 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.04 (m, 1H), 4.97 (d, $J = 9.9$ Hz, 1H), 4.61 (m, 2H), 4.44 (m, 1H), 4.34 (m, 2H), 3.85 (m, 1H), 3.81 (s, 3H), 3.63–3.60 (m, 3H), 3.33 (s, 3H), 3.17 (m, 2H), 2.68 (m, 2H), 2.42–2.39 (m, 3H), 2.30 (s, 6H), 2.23 (s, 3H), 2.10–2.01 (m, 3H), 1.90 (m, 2H), 1.65 (m, 2H), 1.37 (m, 6H), 1.26 (s, 3H), 1.22 (m, 2H), 1.25–1.23 (m, 6H), 1.19 (m, 6H), 0.99–0.96 (m, 9H), 0.95–0.89 (m, 9H); MS (ESI) m/z calcd. for $C_{52}H_{90}N_4O_{15}$ 1011.2; found ($M + H^+$) 1012.0; Anal. calcd (%) for $C_{52}H_{90}N_4O_{15}$: C 61.76, H 8.97, N 5.54. Found: C 61.65, H 8.89, N 5.58.

*6.6.6. 11-O-(Phenethyl-carbamoyl)-4″-O-(4-fluorobenzyl-carbamoyl)azithromycin (**7f**)*

White solid, yield 65%, mp 105–108 °C, $[\alpha]_D^{20} = -28.2$ (c 0.5, EtOH), TLC $R_f = 0.50$ (dichloromethane/methanol, 5:1); IR (KBr): 3435, 2974, 2935, 2854, 1727, 1604, 1511, 1455, 1379, 1339, 1254, 1169, 1112, 1093, 1073, 1047 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.31 (m, 2H), 7.24 (m, 5H), 7.02 (m, 2H), 5.01 (m, 2H), 4.70 (m, 1H), 4.58 (m, 1H), 4.47 (m, 2H), 4.40 (m, 2H), 4.25–4.20 (m, 3H), 3.54 (m, 1H), 3.45 (m, 2H), 3.32 (s, 3H), 3.19 (m, 1H), 2.86 (m, 2H), 2.63 (m, 2H), 2 .37 (m, 1H), 2.32 (m, 6H), 2.23 (s, 3H), 2.20 (m, 1H), 2.05(m, 2H), 1.95(m, 2H), 1.81 (m, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.26 (s, 3H), 1.25–1.21 (m, 15H), 1.10 (d, $J = 6.5$ Hz, 3H), 1.03 (d, $J = 6.4$ Hz, 3H), 0.98 (d, $J = 6.4$ Hz, 3H), 0.88 (m, 3H); MS (ESI) m/z calcd. for $C_{55}H_{87}FN_4O_{14}$ 1047.3; found ($M + H^+$) 1048.0; Anal. calcd (%) for $C_{55}H_{87}FN_4O_{14}$: C 63.08, H 8.37, F 1.81, N 5.35. Found: C 63.01, H 8.39, F 1.84, N 5.39.

*6.6.7. 11-O-(2-Chlorophenethyl-carbamoyl)-4″-O-(4-fluorobenzyl-carbamoyl)azithromycin (**7g**)*

White solid, yield 67%, mp 104–106 °C, $[\alpha]_D^{20} = -40.3$ (c 0.6, EtOH), TLC $R_f = 0.50$ (dichloromethane/methanol, 5:1); IR (KBr): 3428, 2974, 2928, 2854, 1727, 1605, 1511, 1456, 1380, 1344, 1254, 1169, 1111, 1093, 1073, 1049, 1036, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 1H), 7.25 (m, 2H), 7.24 (m, 3H), 7.02 (m, 2H), 5.01 (m, 2H), 4.70 (m, 1H), 4.59 (m, 1H), 4.41–4.40 (m, 2H), 4.38 (m, 2H), 4.30–4.27 (m, 2H), 4.19 (m, 1H), 3.55 (m, 1H), 3.48 (m, 2H), 3.32 (s, 3H), 2.99 (m, 3H), 2.70 (m, 2H), 2 .38 (m, 1H), 2.33 (m, 6H), 2.23 (s, 3H), 2.20 (m, 1H), 2.05 (m, 2H), 1.95 (m, 2H), 1.81 (m, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.26 (s, 3H), 1.26–1.22 (m, 12H), 1.20–1.10 (m, 6H), 1.03 (d, $J = 6.5$ Hz, 3H), 0.90–0.88 (m, 6H); MS (ESI) m/z calcd. for $C_{55}H_{86}ClFN_4O_{14}$ 1081.7; found ($M + H^+$) 1082.0; Anal. calcd (%) for $C_{55}H_{86}ClFN_4O_{14}$: C 61.78, H 7.84, Cl 3.28, F 1.76, N 5.19. Found: C 61.72, H 7.81, Cl 3.31, F 1.77, N 5.24.

*6.6.8. 11-O-(Pentyl-carbamoyl)-4″-O-(2-chlorophenethyl-carbamoyl)azithromycin (**7h**)*

White solid, yield 67%, mp 98–101 °C, $[\alpha]_D^{20} = -37.8$ (c 0.7, EtOH), TLC $R_f = 0.53$ (dichloromethane/methanol, 5:1); IR (KBr): 3435, 2974, 2935, 2872, 1727, 1515, 1457, 1379, 1344, 1254, 1169, 1110, 1092, 1073, 1046, 1036, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 1H), 7.26–7.18 (m, 3H), 5.03 (m, 2H), 4.53 (d, $J = 9.8$ Hz, 1H), 4.41 (t, 1H), 4.29 (m, 2H), 3.63–3.50 (m, 5H), 3.32 (m, 2H), 3.31 (s, 3H), 3.15 (m, 2H), 2.98 (m, 2H), 2.68 (m, 2H), 2.44 (m, 1H), 2.38 (m, 6H), 2.24 (s, 3H), 2.18 (m, 1H), 2.09–1.98 (m, 2H), 1.89 (m, 2H), 1.61 (m, 1H), 1.50–1.47 (m, 4H), 1.44 (s, 3H), 1.33–1.29 (m, 7H), 1.25–1.19 (m, 12H), 1.15 (s, 3H), 1.10 (s, 3H), 1.08 (d, $J = 6.4$ Hz, 3H), 1.06 (d, $J = 6.5$ Hz, 3H), 0.91 (m, 9H); MS (ESI) m/z calcd. for $C_{53}H_{91}ClN_4O_{14}$ 1043.7; found ($M + H^+$) 1043.9; Anal. calcd (%) for $C_{53}H_{91}ClN_4O_{14}$: C 60.99, H 8.79, Cl 3.40, N 5.37. Found: C 60.87, H 8.74, Cl 3.43, N 5.33.

*6.6.9. 11-O-(Benzyl-carbamoyl)-4″-O-(2-Chlorophenethyl-carbamoyl)azithromycin (**7i**)*

White solid, yield 66%, mp 115–117 °C, $[\alpha]_D^{20} = -43.7$ (c 0.7, EtOH), TLC $R_f = 0.48$ (dichloromethane/methanol, 5:1); IR (KBr): 3439, 2974, 2936, 2877, 1728, 1634, 1510, 1455, 1379, 1344, 1253, 1170, 1111, 1093, 1073, 1046, 1037, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.38 (m, 1H), 7.35 (m, 2H), 7.33 (m, 3H), 7.20 (m, 3H), 5.02 (d, $J = 9.1$ Hz, 1H), 4.95 (m, 1H), 4.46–4.41 (m, 4H), 4.33–4.31 (m, 2H), 3.62 (m, 1H), 3.56 (m, 2H), 3.51 (m, 2H), 3.49 (m, 1H), 3.28 (s, 3H), 2.99 (m, 2H), 2.62 (m, 2H), 2.36 (m, 6H), 2.29 (m, 2H), 2.26 (s, 3H), 2.10 (m, 1H), 2.02 (m, 2H), 1.90 (m, 2H), 1.74 (m, 3H), 1.45 (m, 2H), 1.26–1.24 (m, 8H), 1.18 (d, $J = 5.7$ Hz, 3H), 1.13 (m, 9H), 1.07 (m, 6H), 1.02 (d, $J = 6.5$ Hz, 3H), 0.90–0.89 (m, 3H); MS (ESI) m/z calcd. for $C_{55}H_{87}ClN_4O_{14}$ 1063.7; found ($M + H^+$) 1064.1; Anal. calcd (%) for $C_{55}H_{87}ClN_4O_{14}$: C 62.10, H 8.24, Cl 3.33, N 5.27. Found: C 62.13, H 8.29, Cl 3.30, N 5.21.

*6.6.10. 11-O-(4-Fluorobenzyl-carbamoyl)-4″-O-(2-chlorophene thyl-carbamoyl)azithromycin (**7j**)*

White solid, yield 79%, mp 119–121 °C, $[\alpha]_D^{20} = -42.8$ (c 0.8, EtOH), TLC $R_f = 0.43$ (dichloromethane/methanol, 5:1); IR (KBr): 3445, 2975, 2938, 2854, 1727, 1605, 1511, 1456, 1380, 1344, 1254, 1169, 1111, 1093, 1073, 1049, 1037, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 1H), 7.35 (m, 2H), 7.21 (m, 3H), 7.02 (m, 2H), 4.96 (d, 1H), 4.95 (d, 1H), 4.46–4.41 (m, 4H), 4.33–4.31 (m, 2H), 3.62 (m, 1H), 3.56 (m, 2H), 3.51 (m, 2H), 3.49 (m, 1H), 3.27 (s, 3H), 2.99 (m, 2H), 2.62 (m, 2H), 2.36 (m, 6H), 2.29 (m, 2H), 2.25 (s, 3H), 2.10 (m, 1H), 2.02 (m, 2H), 1.91 (m, 2H), 1.60–1.59 (m, 3H), 1.48 (m, 2H), 1.26–1.24 (m, 8H), 1.18 (d, $J = 5.8$ Hz, 3H), 1.13 (m, 9H), 1.07 (m, 6H), 1.01 (d, $J = 6.5$ Hz, 3H), 0.91–0.89 (m, 3H); MS (ESI) m/z calcd. for $C_{55}H_{86}ClFN_4O_{14}$ 1081.7; found ($M + H^+$) 1082.0; Anal. calcd (%) for $C_{55}H_{86}ClFN_4O_{14}$: C 61.07, H 8.01, Cl 3.28, F 1.76, N 5.18. Found: C 61.01, H 8.07, Cl 3.25, F 1.77, N 5.12.

*6.6.11. 11-O-(4-Hydroxyphenethyl-carbamoyl)-4″-O-(2-chlorophenethyl-carbamoyl)azithromycin (**7k**)*

White solid, yield 65%, mp 121–124 °C, $[\alpha]_D^{20} = -42.6$ (c 0.6, EtOH), TLC $R_f = 0.49$ (dichloromethane/methanol, 5:1); IR (KBr): 3429, 2974, 2935, 2854, 1728, 1614, 1594, 1515, 1457, 1376, 1344, 1245, 1170, 1111, 1093, 1073, 1050, 1036, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.28 (m, 1H), 7.21 (m, 3H), 7.09 (m, 2H), 6.84 (m, 2H), 5.00–4.95 (m, 2H), 4.56 (m, 2H), 4.40 (m, 1H), 4.42 (m,

1H), 4.29–4.26 (m, 3H), 3.59–3.56 (m, 4H), 3.55 (m, 4H), 3.30 (s, 3H), 3.00 (m, 3H), 2.74 (m, 6H), 2.60 (m, 1H), 2.37 (d, $J = 14.8$ Hz, 1H), 2.23 (s, 3H), 2.10 (m, 1H), 2.01 (m, 2H), 1.90 (m, 2H), 1.70–1.62 (m, 1H), 1.47 (m, 2H), 1.26 (s, 3H), 1.20 (m, 2H), 1.25–1.13 (m, 18H), 1.02 (m, 6H), 0.89 (m, 3H); MS (ESI) *m/z* calcd. for $C_{56}H_{89}ClN_4O_{15}$ 1093.7; found $(M + H^+)$ 1094.0; Anal. calcd (%) for $C_{56}H_{89}ClN_4O_{15}$: C 61.49, H 8.20, Cl 3.24, N 5.12. Found: C 61.58, H 8.22, Cl 3.21, N 5.16.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (20872081), Natural Science Foundation of Shandong (Y2006C31) and Shandong Science and Technology Promotion Project (2005GG3202098).

References

[1] S. Omura (Ed.), Macrolide Antibiotics: Chemistry, Biology, and Practice, second ed. Academic Press, London, 2002.
[2] W. Schoenfeld, H.A. Kirst (Eds.), Macrolide Antibiotics, Birkhaeuser, Basel, 2002.
[3] Z. Itoh, K. Nakaya, H. Suzuki, H. Aria, K. Wakabayashi, Am. J. Physiol. 247 (1984) G688–G694.
[4] G.G. Zhanel, M. Dueck, D.J. Hoban, L.M. Vercaigne, J.M. Embil, A.S. Gin, J.A. Karlowsky, Drugs 61 (2001) 443–498.
[5] L. Katz, D.T.W. Chu, J.J. Plattner, J. Med. Chem. 39 (1996) 3853–3874.
[6] C.J. Lai, B. Weisblum, Proc. Natl. Acad. Sci. U.S.A. 68 (1971) 856–860.
[7] B. Weisblum, Antimicrob. Agents Chemother. 39 (1995) 577–585.
[8] G.G. Zhanel, M. Walters, A. Noreddin, L.M. Vercaigne, A. Wierzbowski, J.M. Embil, A.S. Gin, S. Douthwaite, D.J. Hobanl, Drugs 62 (2002) 1771–1804.
[9] 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.
[10] A. Bryskier, Clin. Infect. Dis. 27 (1998) 865–883.
[11] L.H. Hansen, P. Mauvais, S. Douthwaite, Mol. Microbiol. 31 (1999) 623–631.
[12] W.S. Champney, C.L. Tober, Curr. Microbiol. 42 (2001) 203–210.
[13] Y.J. Wu, W.G. Su, Curr. Med. Chem. 8 (2001) 1727–1758.
[14] P. Xu, L. Liu, Z. Jin, G. Wang, J. Liu, Y. Li, P. Lei, Bioorg. Med. Chem. Lett. 18 (2008) 5507–5511.
[15] H. Takashima, Curr. Top. Med. Chem. 3 (2003) 991–999.
[16] S. Pal, Tetrahedron 62 (2006) 3171–3200.
[17] Z.M. Istuk, S. Mutak, N. Kujundzic, G. Kragol, Bioorg. Med. Chem. 15 (2007) 4498–4510.
[18] T. Miura, K. Kanemoto, S. Natsume, K. Atsumi, H. Fushimi, T. Yoshida, K. Ajito, Bioorg. Med. Chem. 16 (2008) 10129–10156.
[19] H. Cheng, M.A. Letavic, C.B. Ziegler, J.K. Dutra, P. Bertinato, B.S. Bronk, U.S. Patent 6,043,227, 2000.
[20] P.B. Fernandes, W.R. Baker, L.A. Freiberg, D.J. Hardy, E. McDonald, J. Antimicrob. Agents Chemother. 33 (1989) 78–81.
[21] W.S. Champney, C.L. Tober, Curr. Microbiol. 38 (1999) 342–348.