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Synthesis and antibacterial evaluation of novel clarithromycin derivatives with C-4″ elongated arylalkyl groups against macrolide-resistant strains

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ABSTRACT

Novel clarithromycin derivatives with C-4″ elongated arylalkyl groups were designed, synthesized and evaluated to probe the effect of different lengths of their C-4″ side chains on the activity against resistant bacterial strains. These derivatives had excellent activity against erythromycin-susceptible *Streptococcus pneumoniae*, *Streptococcus aureus* or *Streptococcus pyogenes* and some of them exhibited greatly improved activity against erythromycin-resistant strains. Compounds **18** and **16**, which had the C-4″ elongated arylalkyl groups with eight atoms from the 4″-oxygen atom to the terminal benzene ring, were the most effective against *S. pneumoniae* expressing the *erm* gene and the *erm* and *mef* genes. In contrast, the most potent compounds **3**, **5**, **9**, **17** and **18** against *S. pneumoniae* expressing the *mef* gene had C-4″ elongated arylalkyl groups with three to eight atoms between the 4″-oxygen atom and the terminal aromatic ring.

1. Introduction

First generation macrolides such as erythromycin A (EMA) (Fig. 1) were introduced in the 1950s as a safe and effective agents, and have enjoyed widespread clinical use especially in patients with allergic reactions to penicillin [1,2]. However, the major problem associated with erythromycin A is its acid instability [3], leading to the formation of a 6,9-hemiketal and consequential degradation products which are directly responsible for its poor pharmacokinetic profile and gastrointestinal (GI) side effects [4]. To address the problems, second generation macrolides exemplified by clarithromycin (CAM) [5] and azithromycin (AZM) [6] (Fig. 1) were introduced in late 1980s and not only prevent the formation of 6,9-hemiketal degradation products, but also show remarkably improved pharmacokinetics and better GI tolerability than first generation macrolides [7]. In addition to retaining potent activity against erythromycin-susceptible organisms, the second generation macrolides also exhibited increased activity against *Haemophilus influenza*, *Helicobactor pylori*, *Legionella*, *Chlamydia* and *Pasteurella mutocida*. The mechanism of action has been elucidated that they bind reversibly to the nucleotide A2058 in domain V of the 23S rRNA in the ribosomal 50S subunit and block protein synthesis [8].

However, the therapeutic utility of the above macrolides has been severely compromised by the emergence of resistant pathogens isolated clinically [9]. Two distinct mechanisms have accounted for the majority of macrolide resistance [10,11]. The first mechanism involves the methylation of A2058 by a ribosomal methylase encoded by the *erm* gene, which confers a high level of resistance to MLS_B (macrolide–lincosamide–streptogramin B) antibiotics. The second mechanism involves efflux pump encoded by the *mef* gene, which pumps the macrolides out of intracellular space and prevents them from reaching the binding sites. To overcome the bacterial resistance, third generation macrolides known as ketolides such as telithromycin [12] and cethromycin [13] (Fig. 2) were developed in 1990s. They show excellent activity against several types of macrolide-resistant strains and offer alternative therapy for Gram-positive infections attributable to resistant pathogens. The ketolides may interact with a secondary ribosomal binding site A752 directly in domain II of the 23S rRNA by their C-11,12 carbamate or the C-6 side chains in addition to the main interaction of the drugs in domain V, which imparts activity against *erm*-resistant bacteria [14].

While significant efforts have gone into the discovery of increasingly potent ketolides, a substantial amount of work has been done in order to develop new generation macrolides to effectively overcome bacterial resistance. Consequently, these investigations have led to the discovery of C-4″ modified macrolides, anhydrolides [15] and

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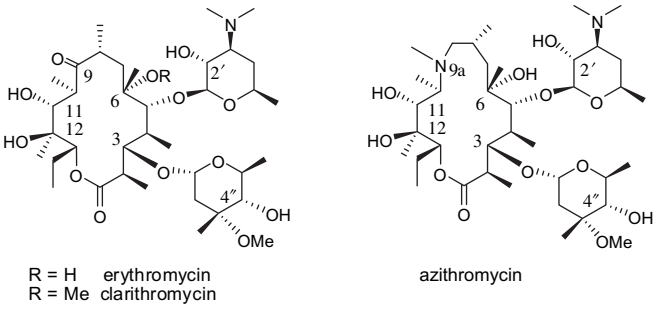


Fig. 1. Structures of erythromycin, clarithromycin and azithromycin.

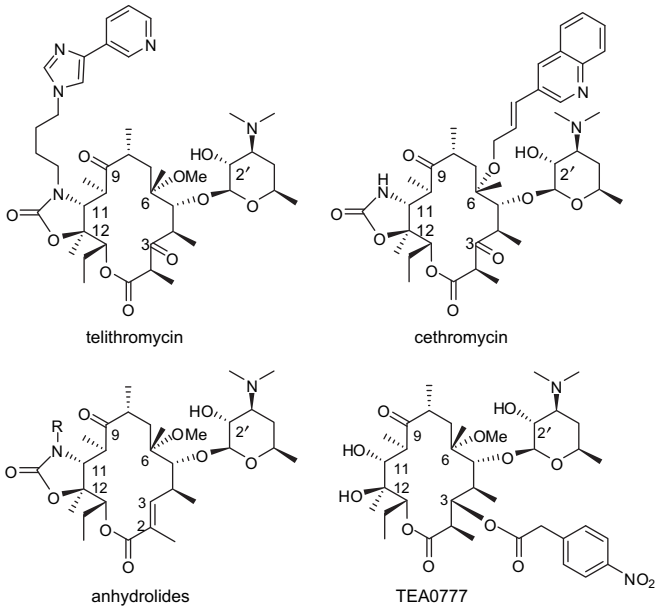


Fig. 2. Structures of telithromycin, cethromycin, anhydrolides and TEA0777.

acylides [16] such as TEA0777 (Fig. 2). In particular, C-4″ modified macrolides display potent activity against Gram-positive pathogens including MLS_B-resistant and efflux-resistant *Streptococcus pneumonia* [17]. C-4″ modified erythromycin A-60565 [18] (Fig. 3) reported by Abbott Laboratories in 1989 showed potent activity against both the inducibly resistant and constitutively resistant strains. The length of the aryl groups attached to the C-4″ position is a distance of four atoms from the 4″-oxygen atom to the terminal aromatic ring. 9 (*S*)-Erythromycylamine C-4″-carbamate CP-544372 [19] (Fig. 3) reported in 1998 exhibited excellent *in vitro* and *in vivo* activity against *erm*-resistant strains with competitive binding to chloramphenicol, suggesting that the anchor group reached the peptidyl transferase center (PTC) region, the chloramphenicol-binding site [20]. It contains a long C-4″ anchor group with six atoms from 4″-oxygen atom to the terminal benzene ring. Macrolide C-4″ malonic monoesters [21] reported in 2006 were capable of binding to 50S ribosomal subunits and inhibited protein synthesis in cell-free system. Their C-4″ malonic groups are five atoms from the 4″-oxygen atom to the terminal benzene ring. C-4″ modified 10,11-anhydroclarithromycins [22] reported in 2008, which possesses a 4″-*O*-heteroarylcarbamoyl group with six atoms between the 4″-oxygen atom and the terminal aromatic ring, showed improved activity against the erythromycin-resistant strains, including *S. pneumonia*, *Streptococcus pyogenes* and *S. pyogenes* expressing the *erm* B gene. In our previous work [23,24], two series of 4"-carbamate and 11,12-cyclic carbonate-4"-carbamate azithromycin derivatives were found to retain excellent activity against erythromycin-susceptible *Streptococcus pneumoniae* and show improved activity against erythromycin-resistant *S. pneumoniae* expressing the *mef* gene or the *erm* and *mef* genes. The length of their C-4″ side chains is a distance of three to four atoms from the 4″-oxygen atom to the terminal aromatic ring. The C-4″ modified macrolides described above display a higher affinity for the ribosome of resistant bacteria due to the additional interaction mediated by the C-4″ arylalkyl groups. The structure–activity relationships of the C-4″ modified derivatives lead us to believe that the arylalkyl groups attached to the C-4″ position of macrolides are essential for overcoming MLS_B resistance, while their lengths are important for conferring potent activity against resistant bacteria.

The studies of the high-resolution X-ray co-crystal structures have revealed that the binding sites of CAM, clindamycin and chloramphenicol differ from each other, but they show some overlapping nucleotides in the domain between the PTC and the macrolide roadblock [25]. The studies have also demonstrated that there are a number of new nucleotide binding sites including G2505, U2504, U2506, U2500, G2061 and C2452 in the domain. Accordingly, a reasonably long arylalkyl group at the C-4″ position will be helpful for the interaction with these nucleotide binding sites in the domain. To probe the effect of different lengths of the C-4″ side chains on antibacterial activity, we designed several novel structural series of clarithromycin derivatives with C-4″ elongated arylalkyl groups which are three, four, eight, nine, ten and eleven atoms from the 4″-oxygen atom to the terminal aromatic ring. The terminal groups of the C-4″ elongated side chains chosen here are aryl, alkyl, alkenyl and cycloalkyl groups, which may be helpful for enhancing affinity for the ribosome of resistant bacteria through hydrogen bonding and π-stacking, and VDW interaction.

2. Chemistry

The synthesis of 4″-*O*-arylalkylcarbamoyl clarithromycin derivatives (**3**–**13**) began with the conversion of CAM as a starting material

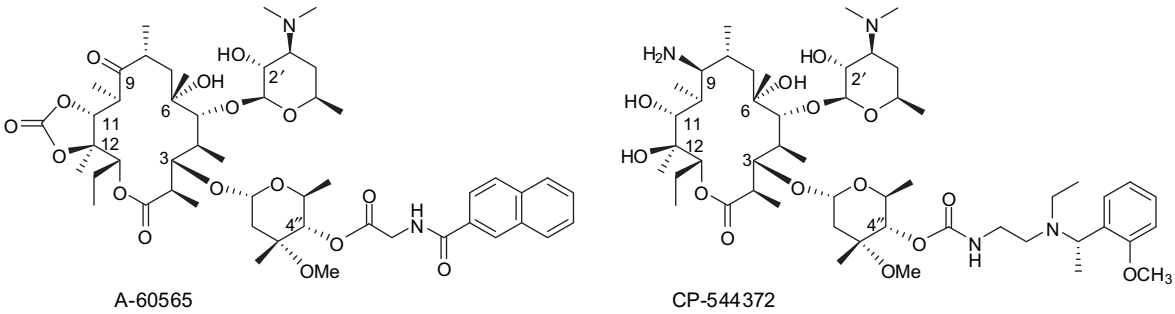
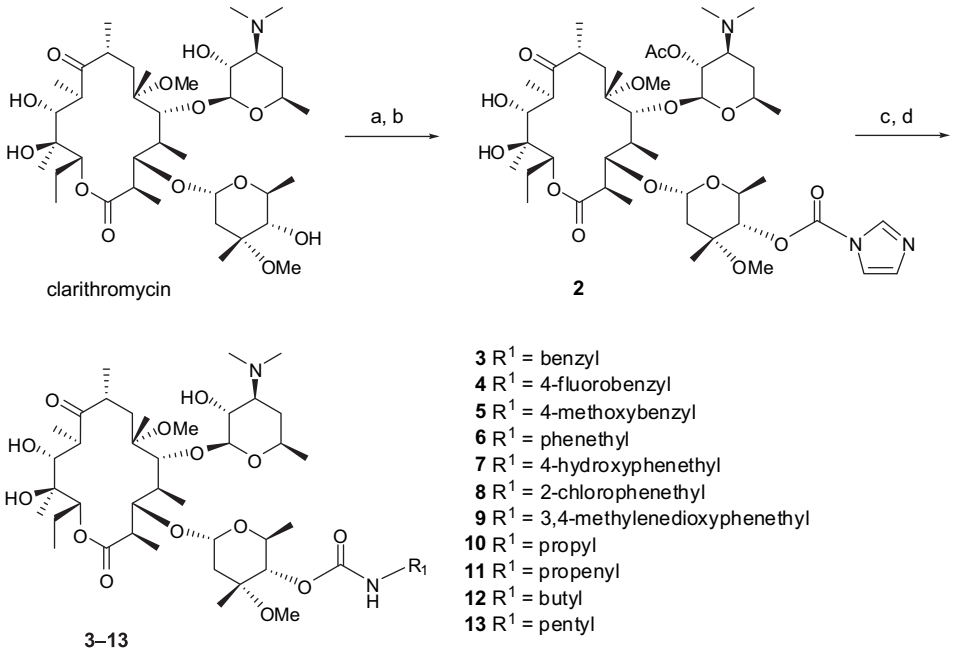


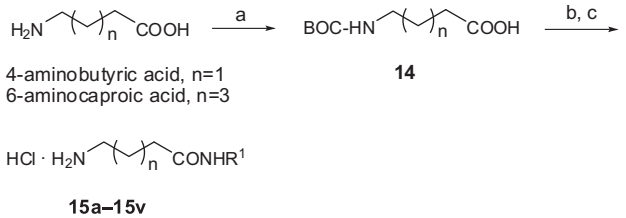
Fig. 3. Structures of A-60565 and CP-544372.



Scheme 1. Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h, 86.2%; (b) CDI, Et_3N, CH_2Cl_2, rt, 24 h, 93%; (c) arylalkylamines, DBU, DMF, 60 °C, 7 h; (d) CH_3OH, 45 °C, 12 h, 61%–68% for 2 steps.

to 4″-*O*-acylimidazolide intermediate (**2**) as a common intermediate to introduce various functional groups at the C-4″ position as shown in Scheme 1. This was carried out by acetylation of the 2′-hydroxyl group of CAM with acetic anhydride (Ac_2O) followed by transformation of the 4″-hydroxyl group to the acyl imidazole utilizing 1,1′-carbonyldiimidazole (CDI) and triethylamine (Et_3N). These reactions proceeded very smoothly at room temperature in 80% yield. Subsequent condensation of intermediate **2** with the corresponding arylalkylamine in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) at 60 °C was followed by selective removal of the 2′-*O*-acetyl group by heating with methanol to give the target derivatives **3**–**13** in yields ranging from 61% to 68%.

In order to obtain C-4″ modified clarithromycins with elongated C-4″ side chains, a series of primary amines hydrochloride (**15a**–**15v**) were synthesized from 4-aminobutyric acid or 6-aminocaproic acid as a starting material as shown in Scheme 2.



15a–15v

15a	n=1, R^1 = benzyl	**15l**	n=3, R^1 = benzyl
15b	n=1, R^1 = 4-fluorobenzyl	**15m**	n=3, R^1 = 4-fluorobenzyl
15c	n=1, R^1 = 4-methoxybenzyl	**15n**	n=3, R^1 = 4-methoxybenzyl
15d	n=1, R^1 = 4-hydroxyphenethyl	**15o**	n=3, R^1 = 4-hydroxyphenethyl
15e	n=1, R^1 = 2-chlorophenethyl	**15p**	n=3, R^1 = 2-chlorophenethyl
15f	n=1, R^1 = cyclohexyl	**15q**	n=3, R^1 = cyclohexyl
15g	n=1, R^1 = isopropyl	**15r**	n=3, R^1 = isopropyl
15h	n=1, R^1 = propyl	**15s**	n=3, R^1 = propyl
15i	n=1, R^1 = propenyl	**15t**	n=3, R^1 = propenyl
15j	n=1, R^1 = butyl	**15u**	n=3, R^1 = butyl
15k	n=1, R^1 = pentyl	**15v**	n=3, R^1 = pentyl

Scheme 2. Reagents and conditions: (a) BOC_2O, 1 M NaOH, THF, rt, 24 h; (b) HOBt, DCC, THF, 0 °C, 8 h, arylalkylamines, rt, 2 h; (c) HCl, AcOEt, rt, 2 h.

Protection of the amino group of corresponding amino acid with di-tert-butyl dicarbonate (BOC_2O) provided BOC-amino acid (**14**). Condensation of **14** with corresponding arylalkylamines catalyzed by dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) was followed by subsequent removal of the BOC moiety using saturated hydrochloric acid (HCl) in ethyl acetate to give the desired primary amines **15a**–**15v**.

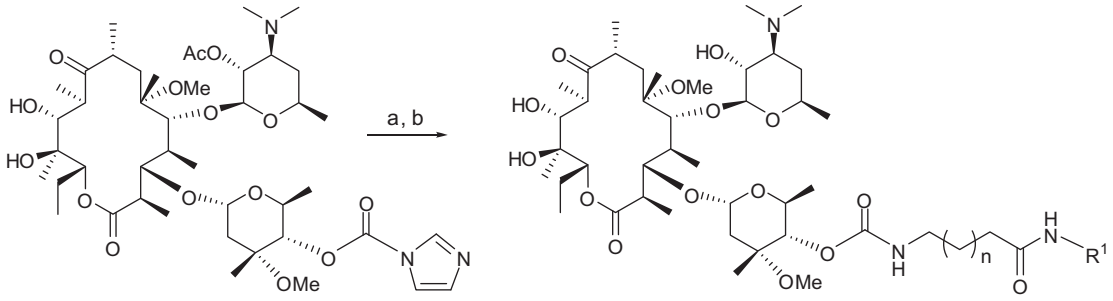
Scheme 3 describes the synthesis of 4″-*O*-((arylalkylamino)-4-oxo-butyl)carbamoyl and 4″-*O*-((arylalkylamino)-6-oxo-hexyl)carbamoyl clarithromycin derivatives (**16**–**26** and **27**–**37**) starting from the intermediate **2**. Coupling of the intermediate **2** with the corresponding primary amine hydrochloride prepared above in the presence of DBU at room temperature and subsequent deprotection of the acetyl group with methanol 55 °C afforded the target derivatives **16**–**37** in yields ranging from 69% to 79%.

3. Antibacterial activity

Three series of the C-4″ modified clarithromycin derivatives **3**–**13**, **16**–**26** and **27**–**37** prepared above, as well as EMA, CAM and AZM as references, were tested for *in vitro* antibacterial activity against eight phenotypes of Gram-positive strains. Their activities are reported as minimum inhibitory concentrations (MICs) determined using the broth microdilution method recommended by the National Committee for Clinical Laboratory Standards. *S. pneumonia* ATCC49619 is an erythromycin-susceptible strain, and *S. pneumoniae* B1, *S. pneumonia*e A22072 and *S. pneumoniae* AB11 are three erythromycin-resistant strains whose resistance is encoded by the *erm* gene, the *mef* gene, and the *erm* and *mef* genes, respectively. *Streptococcus aureus* ATCC25923 and *S. pyogenes* S2 are two erythromycin-susceptible strains. *S. aureus* P1 is a penicillin-susceptible strain isolated clinically and *S. pyogenes* R2 is an erythromycin-resistant strain isolated clinically.

4. Results and discussion

MIC values for 4″-*O*-arylalkylcarbamoyl clarithromycin derivatives (**3**–**13**) are presented in Table 1. All of the 4″-*O*-arylalkyl



16 n=1, R^1 = benzyl
17 n=1, R^1 = 4-fluorobenzyl
18 n=1, R^1 = 4-methoxybenzyl
19 n=1, R^1 = 4-hydroxyphenethyl
20 n=1, R^1 = 2-chlorophenethyl
21 n=1, R^1 = cyclohexyl
22 n=1, R^1 = isopropyl
23 n=1, R^1 = propyl
24 n=1, R^1 = propenyl
25 n=1, R^1 = butyl
26 n=1, R^1 = pentyl
27 n=3, R^1 = benzyl
28 n=3, R^1 = 4-fluorobenzyl
29 n=3, R^1 = 4-methoxybenzyl
30 n=3, R^1 = 4-hydroxyphenethyl
31 n=3, R^1 = 2-chlorophenethyl
32 n=3, R^1 = cyclohexyl
33 n=3, R^1 = isopropyl
34 n=3, R^1 = propyl
35 n=3, R^1 = propenyl
36 n=3, R^1 = butyl
37 n=3, R^1 = pentyl

Scheme 3. Reagents and conditions: (a) corresponding primary amines hydrochloride, DBU, DMF, rt, 24 h; (b) CH_3OH, 55 °C, 24 h, 69%–79% for 2 steps.

derivatives showed excellent activity against the tested erythromycin-susceptible strains. Among them, compounds **5** and **6** were found to have the most potent activity (0.03 μg/mL) against *S. pneumoniae* ATCC49619 comparable to EMA, CAM and AZM. Compounds **4**–**6** and **8** showed the same activity (0.12 μg/mL) against *S. aureus* ATCC25923 as CAM, which were better than EMA and AZM. Compounds **4**–**8**, **11** and **13** were the most active (0.03 μg/mL) against *S. pyogenes* S2 similar to EMA, CAM and AZM. In particular, compounds **5** and **6** with terminal 4-methoxybenzyl and phenethyl groups displayed the most potent activity against all of the three erythromycin-susceptible strains tested above. On the other hand, most of the 4″-*O*-arylalkyl derivatives exhibited improved activity against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene, the *mef* gene or the *erm* and *mef* genes, and erythromycin-resistant *S. pyogenes* R2 in comparison with the references. Among them, compounds **3** and **4** had greatly improved activity against *S. pneumoniae* B1 and *S. pneumoniae* AB11, showing 16-fold and 16-fold higher activity than the parent CAM, respectively. Compounds **3**, **5**, **9** and **13** presented the most potent activity (0.25 μg/mL) against *S. pneumoniae* A22072 expressing the *mef* gene. Compounds **5** and **13** were the most effective against erythromycin-resistant *S. pyogenes* R2. The results suggest that the introduction of the C-4″ arylalkyl groups with 3–4 atoms from the 4″-oxygen atom to the terminal benzene ring into the C-4″ position of CAM, on the whole, retains the activity against erythromycin-susceptible strains, and shows improved activity against erythromycin-resistant strains.

The activities are reported in Table 2 for 4″-*O*-((arylalkylamino)-4-oxo-butyl)carbamoyl clarithromycin derivatives (**16**–**26**). Almost all of the 4″-*O*-arylalkylamino-4-oxo-butyl derivatives showed potent activity against the tested erythromycin-susceptible strains similar to the series of 4″-*O*-arylalkyl derivatives. Among them, MIC values of the most active compounds against *S. pneumoniae* ATCC49619, *S. aureus* ATCC25923 and *S. pyogenes* S2 were 0.03, 0.12 and 0.03 μg/mL, respectively. Those indicate that the introduction of the C-4″ elongated arylalkyl groups with 8–9 atoms from the

Table 1
In vitro antibacterial activity of 4″-*O*-arylalkylcarbamoyl clarithromycin derivatives.

Strain	MICs (μg/mL)													
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	EMA	CAM	AZM
S. pneumoniae ATCC49619[a]	0.25	0.06	0.03	0.03	0.12	0.06	0.06	0.25	0.25	0.25	0.06	0.03	0.03	0.03
S. pneumoniae B1[b]	4	4	16	16	128	16	32	64	32	64	32	128	64	128
S. pneumoniae A22072[c]	0.25	0.5	0.25	1	4	0.5	0.25	2	0.5	1	0.25	8	4	4
S. pneumoniae AB11[d]	8	8	32	64	128	32	64	32	128	64	128	256	128	256
S. aureus ATCC25923[e]	0.25	0.12	0.12	0.12	0.25	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.12	0.25
S. aureus P1[f]	1	2	8	0.06	16	0.25	0.5	16	32	8	16	0.25	0.03	0.12
S. pyogenes S2[g]	0.12	0.03	0.03	0.03	0.03	0.03	0.5	0.5	0.03	0.25	0.03	0.03	0.03	0.03
S. pyogenes R2[h]	16	0.5	0.12	0.25	0.25	0.5	0.5	1	1	4	0.12	4	4	8

[a] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b] *S. pneumoniae* B1: erythromycin-resistant strain expressing the *erm* gene.
[c] *S. pneumoniae* A22072: erythromycin-resistant strain expressing the *mef* gene.
[d] *S. pneumoniae* AB11: erythromycin-resistant strain expressing the *erm* and *mef* genes.
[e] *S. aureus* ATCC25923: erythromycin-susceptible strain.
[f] *S. aureus* P1: penicillin-susceptible strain isolated clinically.
[g] *S. pyogenes* S2: erythromycin-susceptible strain isolated clinically.
[h] *S. pyogenes* R2: erythromycin-resistant strain isolated clinically.

Table 2
In vitro antibacterial activity of 4″-*O*-((arylalkylamino)-4-oxo-butyl)carbamoyl clarithromycin derivatives.

Strain	MICs (μg/mL)													
	16	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	EMA	CAM	AZM
S. pneumoniae ATCC49619[a]	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
S. pneumoniae B1[b]	2	1	0.06	0.25	32	32	128	128	128	128	8	128	64	128
S. pneumoniae A22072[c]	0.5	0.25	0.25	0.5	1	2	8	4	4	8	2	8	4	4
S. pneumoniae AB11[d]	0.25	2	1	1	32	64	128	128	128	128	32	256	128	256
S. aureus ATCC25923[e]	0.12	0.12	0.12	0. 5	0.25	0.5	0.25	0.25	0.25	0.25	0.5	0.25	0.12	0.25
S. aureus[f]	4	1	8	9	32	8	8	32	8	8	16	0.25	0.03	0.12
S. pyogenes S2[g]	0.25	0.25	0.03	0.5	0.03	0.25	0.5	1	0.03	0.5	0.5	0.03	0.03	0.03
S. pyogenes R2[h]	64	16	0.5	8	1	8	16	32	64	16	16	4	4	8

[a] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b] *S. pneumoniae* B1: erythromycin-resistant strain expressing the *erm* gene.
[c] *S. pneumoniae* A22072: erythromycin-resistant strain expressing the *mef* gene.
[d] *S. pneumoniae* AB11: erythromycin-resistant strain expressing the *erm* and *mef* genes.
[e] *S. aureus* ATCC25923: erythromycin-susceptible strain.
[f] *S. aureus* P1: penicillin-susceptible strain isolated clinically.
[g] *S. pyogenes* S2: erythromycin-susceptible strain isolated clinically.
[h] *S. pyogenes* R2: erythromycin-resistant strain isolated clinically.

4″-oxygen atom to the terminal benzene ring still retain the activity against erythromycin-susceptible strains. As for the activity against the erythromycin-resistant *S. pneumonia*, some of 4″-*O*-arylalkylamino-4-oxo-butyl derivatives showed improved activity in comparison with corresponding 4″-*O*-arylalkyl derivatives. Particularly, compound **18** was found to be the most effective (0.06 μg/mL) against *S. pneumoniae* B1, showing 267-fold and 1067-fold higher activity than corresponding compound **5** and parent CAM, respectively, and compound **16** displayed the most potent activity (0.25 μg/mL) against *S. pneumoniae* AB11, exhibiting 32-fold and 512-fold better activity than corresponding **3** and parent CAM, respectively. The C-4″ elongated side chains of compounds **16** and **18** contained 5 more atoms from the 4″-oxygen atom to the terminal benzene ring than those of corresponding compounds **3** and **5**.

MIC values for the 4″-*O*-((arylalkylamino)-6-oxo-hexyl)carbamoyl clarithromycin derivatives (**27**–**37**) are shown in Table 3. All of the 4″-*O*-arylalkylamino-6-oxo-hexyl derivatives showed potent activity against the tested erythromycin-susceptible strains similar to 4″-*O*-arylalkylamino-4-oxo-butyl derivatives, indicating that the introduction of the C-4″ elongated arylalkyl groups with 10–11 atoms from the 4″-oxygen atom to the terminal benzene ring retains the activity against the erythromycin-susceptible strains as well. In contrast, only a few of the 4″-*O*-arylalkylamino-6-oxo-hexyl derivatives had improved activity against all tested erythromycin-resistant strains in comparison with parent CAM. Particularly, compounds **28** and **29** showed the highest activity (0.5 and 0.5 μg/mL) against *S. pneumoniae* A22072, but less activity than corresponding compounds **17** (0.25 μg/mL) and **18** (0.25 μg/mL). These results suggest that the introduction of the C-4″ elongated side chains with 10–11 atoms from the 4″-oxygen atom to the terminal benzene ring reduces or eliminates their activity against the resistant *S. pneumoniae* strains.

On the whole, although they had the different lengths of C-4″ arylalkyl groups, the novel structural series described above showed excellent activity against erythromycin-susceptible strains. The results demonstrate that the C-4″ arylalkyl groups with three to eleven atoms from the 4″-oxygen atom to the terminal benzene ring do not obviously affect the affinity for the ribosomes of the susceptible bacteria. The lengths and sizes of the C-4″ arylalkyl groups potentially fit the domain between the PTC and the macrolide roadblock in 50S ribosomal subunits. As for the erythromycin-resistant strains, only some compounds in the novel structural series exhibited improved activity against resistant strains. In particular, compounds **18** and **19**, which belong to the series of 4″-*O*-((arylalkylamino)-4-oxo-butyl)carbamoyl derivatives, displayed significantly potent activity against *S. pneumoniae* expressing the *erm* gene. The most active compound **18** (0.06 μg/mL) had the C-4″ elongated arylalkyl group with eight atoms from the 4″-oxygen atom to the terminal 4-methoxyphenyl group. Similarly, the most effective compound **16** (0.25 μg/mL) against *S. pneumoniae*

Table 3
In vitro antibacterial activity of 4″-*O*-((arylalkylamino)-6-oxo-hexyl)carbamoyl clarithromycin derivatives.

Strain	MICs (μg/mL)													
	27	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	EMA	CAM	AZM
S. pneumoniae ATCC49619[a]	0.03	0.03	0.03	0.06	0.03	0.03	0.06	0.03	0.03	0.06	0.03	0.03	0.03	0.03
S. pneumoniae B1[b]	64	2	64	64	64	128	128	128	128	128	128	128	64	128
S. pneumoniae A22072[c]	2	0.5	0.5	8	1	1	8	4	2	1	4	8	4	4
S. pneumoniae AB11[d]	64	4	64	64	32	128	128	128	128	128	128	256	128	256
S. aureus ATCC25923[e]	0.5	0.25	0.12	0.25	0.25	0.25	0.25	0.5	0.25	0.25	0.5	0.25	0.12	0.25
S. aureus[f]	8	32	1	1	0.5	1	1	2	16	8	8	0.25	0.03	0.12
S. pyogenes S2[g]	0.12	0.03	0.12	0.5	0.06	0.12	0.12	0.03	0.5	0.25	0.25	0.03	0.03	0.03
S. pyogenes R2[h]	0.25	0.25	32	64	64	32	32	16	4	8	16	4	4	8

[a] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b] *S. pneumoniae* B1: erythromycin-resistant strain expressing the *erm* gene.
[c] *S. pneumoniae* A22072: erythromycin-resistant strain expressing the *mef* gene.
[d] *S. pneumoniae* AB11: erythromycin-resistant strain expressing the *erm* and *mef* genes.
[e] *S. aureus* ATCC25923: erythromycin-susceptible strain.
[f] *S. aureus* P1: penicillin-susceptible strain isolated clinically.
[g] *S. pyogenes* S2: erythromycin-susceptible strain isolated clinically.
[h] *S. pyogenes* R2: erythromycin-resistant strain isolated clinically.

expressing the *erm* and *mef* genes possessed the C-4″ elongated arylalkyl group with eight atoms from the 4″-oxygen atom to the terminal phenyl group as well. This led us to presume that the C-4″ elongated arylalkyl group with eight atoms between the 4″-oxygen atom and the terminal aromatic ring might be a suitable length, and the terminal 4-methoxyphenyl group might easily interact with the new binding sites of nucleotides between PTC and the macrolide roadblock through hydrogen bonding, π-stacking etc. resulting in a higher affinity for the ribosome of resistant bacteria. In contrast, the most active compounds **3**, **5**, **9**, **13**, **17** and **18** (0.25 μg mL^{-1}) against *S. pneumoniae* expressing the *mef* gene had the C-4″ elongated arylalkyl groups with three to eight atoms between the 4″-oxygen atom and the terminal aromatic ring.

5. Conclusions

The novel structural series of 4″-*O*-arylalkylcarbamoyl, 4″-*O*-((arylalkylamino)-4-oxo-butyl)carbamoyl and 4″-*O*-((arylalkylamino)-6-oxo-hexyl)carbamoyl clarithromycin derivatives were designed, synthesized and evaluated for their *in vitro* antibacterial activities. The novel structural series had excellent activity against erythromycin-susceptible *S. pneumoniae* ATCC49619, *S. aureus* ATCC25923 or *S. pyogenes* S2, and the most active compounds were comparable to CAM and better than EMA and AZM. In marked contrast, only some derivatives in the novel structural series exhibited greatly improved activity against erythromycin-resistant *S. pneumoniae* B1, *S. pneumoniae* A22072, *S. pneumoniae* AB11 or *S. pyogenes* R2. Among them, compound **18** with terminal 4-methoxyphenyl group and compound **16** with terminal phenyl group were the most effective against *S. pneumoniae* expressing the *erm* gene and the *erm* and *mef* genes, respectively. It is noteworthy that the length of their C-4″ elongated arylalkyl side chains is a distance of eight atoms from the 4″-oxygen atom to the terminal benzene ring. Besides, the most active compounds **3**, **5**, **9**, **17** and **18** had C-4″ elongated arylalkyl groups with three to eight atoms against *S. pneumoniae* expressing 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 (Qingdong Yumingyuan silica gel reagent factory, Shandong, China, YUYUAN). Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm, Qingdong Yumingyuan silica gel reagent factory, Shandong, China, YUYUAN). Infrared spectra were recorded on KBr pellets using Nicolet Nexus 470FT-IR spectrometer (Wisconsin, USA). ^{1}H NMR spectra were recorded on Bruker Avance DRX 600 spectrometer (Bruker, Switzerlands) at ambient temperature (TMS as internal standard of chemical shifts). Mass spectra were recorded on API 4000 instrument (Applied Biosystems, Connecticut, USA). The C, H, N analyses were carried out on PE-2400 II elemental analyser (Perkin–Elmer, Massachusetts, USA). Melting points are uncorrected and were determined on an X-6 melting point apparatus (Beijing Tianchengwode Biotech Co. Ltd, Beijing, China). EMA was used as starting material from Nexchem Pharmaceutical Co., Ltd.

6.1. General procedure for the preparation of 4″-*O*-arylalkylcarbamoyl clarithromycin derivatives (**3**–**13**)

To a solution of **2** (1.50 g, 1.70 mmol) in DMF (15 mL) was added DBU (0.33 mL, 2.25 mmol) and corresponding arylalkylamine (4.50 mmol). The resulting solution was stirred for 7 h at 60 °C. The reaction was quenched with water (15 mL) and the aqueous layer was extracted with ethyl acetate (2 × 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 crude product in methanol (15 mL) was heated to 45 °C and stirred for 12 h at the same temperature. After concentrating the reaction solution in vacuo, the residue was purified by flash chromatography (dichloromethane/methanol 25:1) to give compounds **3**–**13** in yields ranging from 60.8% to 68.4%.

6.1.1. 4″-*O*-(Benzyl)carbamoylclarithromycin (**3**)

White crystals, yield 64.6%, mp 228–231 °C, TLC R_f = 0.35 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3450, 2974, 2938, 2883, 2832, 2786, 1732, 1639, 1498, 1456, 1378, 1339, 1279, 1266, 1242, 1171, 1110, 1073, 1052, 1033, 1012 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33–7.29 (m, 2H), 7.28–7.26 (m, 2H), 5.07–4.97(d, *J* = 1.5 Hz, 1H), 4.97–4.96 (d, *J* = 4.9 Hz, 1H), 4.60–4.58 (d, *J* = 4.1 Hz, 1H), 4.42–4.41 (m, 2H), 4.30 (m, 1H), 3.99–3.98 (m, 1H), 3.78–3.75 (m, 2H), 3.67–3.65 (d, *J* = 7.2 Hz, 1H), 3.49 (m, 1H), 3.36 (s, 1H), 3.30 (s, 3H), 3.18–3.04 (m, 2H), 3.04 (s, 3H), 2.99–2.95 (m, 1H), 2.90 (m, 1H), 2.57 (m, 1H), 2.43–2.41 (m, 1H), 2.28 (s, 3H), 2.19–2.18 (m, 4H), 1.94–1.90 (m, 3H), 1.68–1.61 (m, 4H), 1.48–1.39 (m, 1H), 1.38 (s, 3H), 1.23–1.16 (m, 12H), 1.13–1.09 (m, 15H), 0.84 (t, 3H); MS (ESI) *m*/*z* calcd. for $C_{46}H_{76}N_2O_{14}$ 880.5; found $[M + H]^+$ 882.0; Analysis calculated for $C_{46}H_{76}N_2O_{14}$: C 62.70, H 8.69, N 3.18. Found: C 62.79, H 8.66, N 3.20.

6.1.2. 4″-*O*-(4-Fluorobenzyl)carbamoylclarithromycin (**4**)

White crystals, yield 65.6%, mp 205–208 °C, TLC R_f = 0.40 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3658, 3447, 2976, 2938, 2876, 2834, 2788, 1732, 1687, 1607, 1547, 1511, 1458, 1378, 1349, 1332, 1268, 1228, 1171, 1128, 1110, 1082, 1051, 1033, 1011 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26–7.25 (s, 1H), 7.03–7.00 (t, 2H), 5.07–5.06 (m, 2H), 4.98–4.96 (m, 1H), 4.58–4.57 (d, *J* = 9.7 Hz, 1H), 4.50–4.49 (d, *J* = 7.0 Hz, 1H), 4.39–4.34 (m, 2H), 4.31–4.29 (m, 1H), 4.00–3.99 (m, 1H), 3.77–3.75 (m, 3H), 3.66–3.65 (d, *J* = 7.2 Hz, 1H), 3.42–3.40 (m, 1H), 3.30 (m, 3H), 3.20–3.19 (m, 2H), 3.04 (s, 3H), 2.99–2.98 (m, 2H), 2.31 (s, 6H), 1.94–1.90 (m, 3H), 1.70–1.62 (m, 4H), 1.48–1.47 (m, 1H), 1.39 (s, 3H), 1.20–1.17 (m, 12H), 1.13–1.09 (m, 15H), 0.84–0.83 (t, 3H); MS (ESI) *m*/*z* calcd. for $C_{46}H_{75}FN_2O_{14}$ 898.5; found $[M + H]^+$ 900.1; Analysis calculated for $C_{46}H_{75}FN_2O_{14}$: C 61.45, H 8.41, N 3.12. Found: C 61.37, H 8.44, N 3.10.

6.1.3. 4″-*O*-(4-Methoxybenzyl)carbamoylclarithromycin (**5**)

White crystals, yield 66.7%, mp 145–148 °C, TLC R_f = 0.40 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3454, 2973, 2938, 2884, 2833, 2786, 1731, 1613, 1586, 1514, 1458, 1378, 1340, 1247, 1172, 1109, 1071, 1033, 1012 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20–7.19 (d, *J* = 8.4 Hz, 2H), 6.87–6.85 (d, *J* = 8.6 Hz, 2H), 5.07 (dd, *J* = 10.9 Hz, *J* = 1.5 Hz, 1H), 4.97–4.96 (m, 1H), 4.58–4.56 (d, *J* = 9.7 Hz, 1H), 4.51–4.50 (d, *J* = 6.8 Hz, 1H), 4.34–4.33 (d, *J* = 6.1 Hz, 2H), 4.30–4.29 (m, 1H), 3.98 (s,,1H), 3.80 (s, 3H), 3.77–3.75 (m, 2H), 3.67–3.65 (m, 1H), 3.63–3.62 (m, 1H), 3.30 (s, 3H), 3.18 (m, 2H), 3.04 (s, 3H), 3.00–2.99 (m, 1H), 2.89–2.88 (m, 1H), 2.43–2.40 (m, 2H), 2.32 (s, 5H), 1.94–1.82 (m, 2H), 1.69–1.66 (m, 3H), 1.65–1.63 (m, 2H), 1.38 (s, 3H), 1.20–1.18 (m, 12H), 1.17–1.09 (m, 15H) 0.84–0.83 (t, 3H); MS (ESI) *m*/*z* calcd. for $C_{47}H_{78}N_2O_{15}$ 910.5; found $[M + H]^+$ 912.1; Analysis calculated for $C_{47}H_{78}N_2O_{15}$: C 61.96, H 8.63, N 3.07. Found: C 62.05, H 8.60, N 3.09.

6.1.4. 4″-*O*-(4-Hydroxyphenethyl)carbamoylclarithromycin (**6**)

White crystals, yield 63.9%, mp 146–148 °C, TLC R_f = 0.31 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3438, 2974, 2938, 2884, 2832, 2787, 1732, 1615, 1595, 1516, 1458, 1378, 1344, 1245, 1171, 1110, 1070, 1054, 1033, 1012 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.01–6.99 (m, 2H), 6.88–6.76 (m, 2H), 5.07–5.05 (d, *J* = 11.0 Hz, 1H), 4.96–4.95 (d, *J* = 4.0 Hz, 1H), 4.53–4.52 (d, *J* = 6.6 Hz, 1H),

4.47–4.45 (d, J = 9.7 Hz, 1H), 4.43–4.41 (m, 1H), 4.13–4.11 (m, 1H), 3.96 (s, 1H), 3.80–3.76 (m, 1H), 3.75–3.73 (m, 1H), 3.64–3.63 (m, 1H), 3.50–3.48 (m, 2H), 3.39–3.37 (m, 3H), 3.30 (s, 3H), 3.18–3.02 (m, 1H), 3.02 (s, 3H), 2.99–2.97 (m, 1H), 2.87–2.84 (m, 2H), 2.77–2.73 (m, 3H), 2.71 (s, 4H), 2.59–2.56 (m, 1H), 2.42–2.37 (m, 2H), 2.08–2.06 (m, 1H), 1.94–1.88 (m, 3H), 1.63–1.61 (m, 2H), 1.65–1.57 (m, 2H), 1.33 (s, 3H), 1.29–1.27 (m, 3H), 1.21 (d, J = 6.9 Hz, 3H), 1.18–1.16 (m, 2H), 1.12–1.11 (m, 11H), 1.08–1.06 (m, 3H), 0.92–0.90 (m, 3H), 0.84 (t, 3H); MS (ESI) m/z calcd. for $C_{47}H_{78}N_2O_{15}$ 910.5; found $[M + H]^+$ 912.1; Analysis calculated for $C_{47}H_{78}N_2O_{15}$: C 61.96, H 8.63, N 3.07. Found: C 62.07, H 8.61, N 3.10.

*6.1.5. 4″-O-(2-Chlorophenethyl)carbamoylclarithromycin (**7**)*

White crystals, yield 62.2%, mp 180–185 °C, TLC R_f = 0.37 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3450, 2973, 2937, 2884, 2832, 2785, 1732, 1057, 1458, 1378, 1342, 1267, 1245, 1171, 1110, 1071, 1051, 1034, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.35 (m, 1H), 7.20 (m, 3H), 5.07 (dd, J = 11.1 Hz, J = 1.9 Hz, 1H), 4.96–4.95 (d, J = 5.0 Hz, 1H), 4.83 (m, 1H), 4.55–4.53 (d, J = 2.0 Hz, 2H), 4.25 (m, 1H), 3.98 (s, 1H), 3.75–3.65 (m, 2H), 3.64–3.62 (d, J = 7.1 Hz, 1H), 3.62–3.60 (m, 1H), 3.57–3.55 (m, 1H), 3.55–3.50 (m, 1H), 3.29 (s, 2H), 3.18 (m, 1H), 3.04–3.00 (s, 2H), 2.99–2.96 (m, 3H), 2.89–2.87 (m, 1H), 2.59–2.57 (m, 2H), 2.41 (s, 4H), 2.05 (m, 1H), 1.94–1.90 (m, 2H), 1.83–1.81 (m, 2H), 1.68–1.62 (m, 3H), 1.48–1.47 (m, 2H), 1.38 (s, 3H), 1.27–1.24 (m, 2H), 1.20–1.19 (m, 3H), 1.19–1.09 (m, 24H) 0.84–0.83 (t, 3H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 221.0, 175.7, 156.2, 136.3, 134.2, 131.1, 129.6, 128.1, 126.9, 96.2, 80.5, 79.0, 78.3, 77.2, 77.0, 76.8, 76.6, 74.3, 73.0, 71.1, 69.0, 65.1, 63.3, 50.7, 49.5, 45.3, 44.9, 40.5, 39.3, 37.2, 35.3, 33.7, 21.6, 21.0, 20.9, 19.7, 18.3, 18.1, 16.0, 15.9, 12.4, 10.6, 9.2; MS (ESI) m/z calcd. for $C_{47}H_{77}ClN_2O_{14}$ 928.5; found $[M + H]^+$ 930.2; Analysis calculated for $C_{47}H_{77}ClN_2O_{14}$: C 60.73, H 8.35, N 3.01. Found: C 60.65, H 8.32, N 2.99.

*6.1.6. 4″-O-(Phenethyl)carbamoylclarithromycin (**8**)*

White crystals, yield 60.8%, mp 136–139 °C, TLC R_f = 0.38 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3450, 2974, 2938, 2884, 2831, 2785, 1731, 1634, 1498, 1456, 1378, 1342, 1267, 1245, 1171, 1110, 1071, 1052, 1033, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.30–7.28 (m, 2H), 7.20 (m, 1H), 7.19–7.17 (m, 2H), 5.06 (d, J = 1.5 Hz, 1H), 4.96–4.95 (d, J = 4.9 Hz, 1H), 4.79 (m, 1H), 4.53–4.49 (m, 2H), 4.23–4.21 (m, 1H), 3.98 (s, 1H), 3.76–3.74 (m, 2H), 3.64–3.63 (d, J = 7.3 Hz, 1H), 3.57–3.53 (m, 2H), 3.45–3.44 (m, 1H), 3.29 (s, 3H), 3.22–3.18 (m, 2H), 3.04 (s, 3H), 2.99–2.97 (m, 1H), 2.86–2.82 (m, 3H), 2.58–2.56 (m, 2H), 2.39 (m, 6H), 1.94–1.90 (m, 3H), 1.86–1.76 (m, 2H), 1.65–1.62 (m, 3H), 1.48–1.45 (m, 1H), 1.38 (s, 3H), 1.25–1.19 (m, 4H), 1.18–1.16 (m, 6H), 1.13–1.11 (m, 9H), 1.09–1.07 (d, 3H), 1.05–1.03 (d, 3H), 0.85–0.82 (m, 3H); MS (ESI) m/z calcd. for $C_{47}H_{78}N_2O_{14}$ 894.6; found $[M + H]^+$ 896.1; Analysis calculated for $C_{47}H_{78}N_2O_{14}$: C 63.09, H 8.78, N 3.13. Found: C 63.01, H 8.81, N 3.11.

*6.1.7. 4″-O-(3,4-Methylenedioxyphenethyl) carbamoylclarithromycin (**9**)*

White crystals, yield 67.1%, mp 235–237 °C, TLC R_f = 0.31 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3447, 2974, 2938, 2884, 2832, 2784, 1731, 1631, 1054, 1491, 1457, 1378, 1339, 1247, 1171, 1109, 1071, 1035, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.74–6.73 (d, J = 7.7 Hz, 1H), 6.67 (s, 1H), 6.63–6.62 (d, J = 7.7 Hz, 1H), 5.94–5.92 (d, J = 3.5 Hz, 2H), 5.07–5.05 (d, J = 11.0 Hz, 1H), 4.98–4.96 (m, 1H), 4.58–4.51 (d, J = 4.7 Hz, 2H), 4.21–4.20 (m, 1H), 3.98 (s, 1H), 3.76–3.74 (m, 2H), 3.66 (m, 2H), 3.50–3.48 (m, 1H), 3.41–3.38 (m, 1H), 3.28 (s, 4H), 3.18 (m, 1H), 3.03 (s, 3H), 3.00–2.98 (m, 1H), 2.89–2.86 (m, 1H), 2.76–2.74 (m, 2H), 2.60–2.56 (m, 2H), 2.38–2.35 (m, 2H), 2.17 (s, 1H), 1.94–1.91 (m, 2H), 1.63–1.58 (m, 10H), 1.48–1.46 (m, 1H), 1.37 (s, 3H), 1.25–1.21 (m, 4H), 1.20 (m, 6H), 1.17–1.09 (m, 9H), 1.08–1.04 (m, 6H), 0.86–0.82 (t, 3H); MS (ESI) m/z calcd. for $C_{48}H_{78}N_2O_{16}$ 938.5; found $[M + H]^+$ 940.1; Analysis calculated for $C_{48}H_{78}N_2O_{16}$: C 61.39, H 8.37, N 2.98. Found: C 61.30, H 8.40, N 3.01.

*6.1.8. 4″-O-(Propyl)carbamoylclarithromycin (**10**)*

White crystals, yield 68.4%, mp 220–223 °C, TLC R_f = 0.45 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3458, 2972, 2938, 2878, 2832, 2785, 1732, 1638, 1508, 1459, 1378, 1340, 1265, 1245, 1171, 1110, 1083, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07–5.04 (d, J = 10.1 Hz, 1H), 4.99–4.95 (m, 1H), 4.78–4.77 (m, 1H), 4.55–4.53 (m, 2H), 4.27–4.26 (m, 1H), 3.98 (s, 1H), 3.77–3.75 (m, 2H), 3.68–3.66 (m, 2H), 3.32 (s, 3H), 3.20–3.13 (m, 4H), 3.04 (s, 3H), 3.01–2.95 (m, 1H), 2.89–2.86 (m, 1H), 2.42–2.40 (m, 3H), 1.94–1.91 (m, 2H), 1.69–1.61(m, 9H), 1.56–1.49 (m, 3H), 1.39 (s, 3H), 1.25–1.21 (m, 3H), 1.20–1.18 (m, 12H), 1.15–1.09 (m, 12H), 0.92 (t, 3H), 0.84 (t, 3H); MS (ESI) m/z calcd. for $C_{42}H_{76}N_2O_{14}$ 832.5; found $[M + H]^+$ 834.1; Analysis calculated for $C_{42}H_{76}N_2O_{14}$: C 60.55, H 9.20, N 3.36. Found: C 60.48, H 9.24, N 3.38.

*6.1.9. 4″-O-(Propenyl)carbamoylclarithromycin (**11**)*

White crystals, yield 65.3%, mp 225–227 °C, TLC R_f = 0.41 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3459, 3340, 2973, 2941, 2885, 2831, 2781, 1735, 1742, 1692, 1641, 1537, 1505, 1457, 1404, 1377, 1336, 1278, 1266, 1247, 1164, 1109, 1082, 1053, 1032, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.85–5.82 (m, 1H), 5.20–5.13 (m, 2H), 5.08–5.06 (dd, J = 9.6 Hz, J = 1.9 Hz, 1H), 4.98–4.97 (d, J = 4.9 Hz, 2H), 4.56–4.55 (m, 1H), 4.28 (m, 1H), 3.97 (s, 1H), 3.85–3.82 (m, 2H), 3.77–3.74 (m, 3H), 3.67–3.66 (d, J = 6.6 Hz, 1H), 3.30 (s, 4H), 3.18 (m, 1H), 3.00 (s, 3H), 2.99–2.97 (m, 1H), 2.89–2.87 (m, 2H), 2.60–2.59 (m, 3H), 2.42–2.39 (m, 2H), 1.85–2.01 (m, 3H), 1.80–1.78 (m, 2H), 1.67–1.62 (m, 6H), 1.48–1.46 (m, 2H), 1.37 (s, 3H), 1.22–1.18 (m, 12H), 1.14–1.12 (m, 9H), 1.07–1.05 (m, 3H), 0.85–0.83 (t, 3H); MS (ESI) m/z calcd. for $C_{42}H_{74}N_2O_{14}$ 830.5; found $[M + H]^+$ 832.1; Analysis calculated for $C_{42}H_{74}N_2O_{14}$: C 60.70, H 8.98, N 3.37. Found: C 60.62, H 8.95, N 3.39.

*6.1.10. 4″-O-(Butyl)carbamoylclarithromycin (**12**)*

White crystals, yield 61.8%, mp 229–232 °C, TLC R_f = 0.45 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3459, 2973, 2938, 2877, 2832, 2785, 1733, 1638, 1507, 1459, 1378, 1342, 1266, 1245, 1209, 1171, 1110, 1093, 1071, 1053, 1033, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07–5.04 (d, J = 8.7 Hz, 1H), 4.96 (s, 1H), 4.73–4.72 (m, 1H), 4.54–4.51 (m, 2H), 4.29–4.27 (m, 1H), 3.99–3.98 (d, J = 4.4 Hz, 1H), 3.78–3.76 (m, 2H), 3.67–3.65 (m, 2H), 3.42 (m, 1H), 3.32–3.31 (m, 3H), 3.26–3.20 (m, 4H), 3.04–3.00 (m, 3H), 3.00–2.99 (m, 1H), 2.89–2.80 (m, 1H), 2.33 (s, 5H), 1.93–1.83 (m, 3H), 1.69–1.67 (m, 2H), 1.66–1.63 (m, 4H), 1.48–1.47 (m, 4H), 1.39–1.38 (m, 3H), 1.20–1.17 (m, 15H), 1.13–1.11 (m, 12H), 0.93 (t, 3H), 0.84 (t, 3H); MS (ESI) m/z calcd. for $C_{43}H_{78}N_2O_{14}$ 846.6; found $[M + H]^+$ 848.2; Analysis calculated for $C_{43}H_{78}N_2O_{14}$: C 60.97, H 9.28, N 3.31. Found: C 61.06, H 9.25, N 3.29.

*6.1.11. 4″-O-(Pentyl)carbamoylclarithromycin (**13**)*

White crystals, yield 63.8%, mp 135–137 °C, TLC R_f = 0.46 (methanol/dichlormethane, 1:5, v/v); IR (KBr): 3459, 2972, 2937, 2877, 2832, 2785, 1732, 1507, 1458, 1378, 1342, 1279, 1247, 1171, 1109, 1093, 1071, 1050, 1034, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07–5.06 (d, J = 9.9 Hz, 1H), 4.97–4.96 (d, J = 4.8 Hz, 1H), 4.55–4.53(d, J = 9.8 Hz, 1H), 3.98 (s, 1H), 3.78–3.74 (m, 2H), 3.69–3.66 (m, 1H), 3.31 (s, 3H), 3.25–3.16 (m, 4H), 3.04 (s, 3H), 3.00–2.97 (m, 1H), 2.89–2.87 (m, 1H), 2.17 (s, 1H), 1.93–1.91 (m, 2H), 1.67–1.63 (dd, J = 15.1 Hz, J = 5.1 Hz, 2H), 1.57 (s, 15H), 1.50–1.48 (m, 3H), 1.38 (s, 3H), 1.34–1.27 (m, 5H), 1.21–1.18 (m, 12H), 1.13–1.08 (m, 12H), 0.90–0.85 (t, 3H), 0.85–0.83 (t, 3H); MS (ESI) m/z calcd. for $C_{44}H_{80}N_2O_{14}$ 860.6; found $[M + H]^+$ 862.5;

Analysis calculated for $C_{44}H_{80}N_2O_{14}$: C 61.37, H 9.36, N 3.25. Found: C 61.44, H 9.32, N 3.24.

6.2. General procedure for the preparation of arylalkylcarbamoyl alkylamines hydrochloride (**15a**–**15v**)

To a solution of aminoalkyl acid (15.27 mmol) in 1 mol/L sodium hydroxide (15.30 mL) was added dropwise BOC_2O (3.70 g, 16.97 mmol) in THF (5 mL). The resulting solution was allowed to stir for 24 h at the room temperature. The reaction was concentrated in vacuo to remove THF. And then the reaction was neutralized to pH 2–3 with 1 mol/L citric acid and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and dried in vacuum to afford BOC-aminoalkyl acid (**14**) as a white solid.

To a solution of **14** (7.35 mmol) and HOBt (1.13 g, 8.09 mmol) in THF (10 mL) was dropwised dicyclohexylcarbodiimide (DCC) (1.67 g, 8.09 mmol) in THF (5 mL). The resulting solution was allowed to stir for 8 h at 0 °C. After the corresponding arylalkylamine (7.35 mmol) was added, the solution was stirred for another 2 h. The reaction was concentrated in vacuo to get the white solid. And then the solid was dissolved in ethyl acetate (20 mL). After filtration, the filtrate was washed with 1 mol/L citric acid (25 mL). The resulting solution was allowed to stir for 0.5 h in water bath (50 °C). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo to afford a crude product as a white solid. A solution of the crude product in ethyl acetate with saturated hydrochloride acid (10 mL) was stirred for 24 h at the room temperature. The resulting preciptitate was collected to afford the desired products **15a**–**15v**.

6.3. General procedure for the preparation of 4″-O-((arylalkylamino)-4-oxo-butyl)carbamoyl clarithromycin derivatives (**16**–**26**)

To a solution of **2** (1.50 g, 1.70 mmol) in DMF (15 mL) was added DBU (0.50 mL, 3.41 mmol),Et_3N (1.50 mL, 10.90 mmol) and corresponding arylalkylcarbamoyl alkylamines hydrochloride (**15**a–**15**k) (6.67 mmol). The resulting solution was stirred for 24 h at the room temperature. The reaction was quenched with water (30 mL) and the aqueous layer was extracted with ethyl acetate (2 × 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 crude product in methanol (15 mL) was heated to 55 °C and stirred for 24 h at the same temperature. After concentrating the reaction solution in vacuo, the residue was purified by flash chromatography (dichloromethane/methanol 40:1) to afford products **16**–**26** in yields ranging from 69% to 77%.

6.3.1. 4″-O-(((Benzyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**16**)

White crystals, yield 73.2%, mp 133–142 °C, TLC R_f = 0.33 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3449, 2973, 2938, 1731, 1662, 1513, 1456, 1378, 1337, 1266, 1171, 1110, 1073, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.27 (m, 5H), 5.79 (m, 1H), 5.63 (m, 1H), 5.14 (m, 1H), 5.08–5.06 (m, 1H), 4.98–4.97 (m, 1H), 4.53 (m, 2H), 4.35 (m, 1H), 3.99 (s, 1H), 3.79–3.74 (m, 3H), 3.68–3.67 (m, 2H), 3.39–3.36 (m, 1H), 3.34–3.30 (m, 3H), 3.28–3.25 (m, 2H), 3.25–2.90 (m, 6H), 2.62–2.52 (m, 2H), 2.44–2.41 (m, 1H), 2.31 (m, 4H), 2.25–2.23 (m, 1H), 2.21–2.19 (m, 2H), 1.99–1.89 (m, 4H), 1.88–1.78 (m, 3H), 1.73–1.67 (m, 4H), 1.66–1.64 (m, 1H), 1.61 (m, 4H), 1.52–1.34 (m, 5H), 1.26–1.20 (m, 6H), 1.20–1.15 (m, 4H), 1.14–1.12 (m, 8H), 0.85 (m, 2H); MS (ESI) m/z calcd. for $C_{50}H_{83}N_3O_{15}$ 965.6; found $[M + H]^+$ 967.0; Analysis calculated for $C_{50}H_{83}N_3O_{15}$: C 62.15, H 8.66, N 4.35. Found: C 62.08, H 8.69, N 4.32.

6.3.2. 4″-O-(((4-Fluorobenzyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**17**)

White crystals, yield 74.7%, mp 127–132 °C, TLC R_f = 0.35 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3449, 2974, 2939, 1731, 1662, 1514, 1459, 1378, 1346, 1248, 1173, 1110, 1072, 1050, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.01–7.27 (m, 4H), 5.07 (dd, J = 11.4 Hz, J = 1.8 Hz, 2H), 4.98 (d, J = 5.4 Hz, 1H), 4.54–4.51 (m, 2H), 4.42–4.41 (m, 2H), 4.30 (m, 1H), 3.99 (s, 1H), 3.79–3.77 (m, 2H), 3.68–3.66 (m, 1H), 3.32–3.18 (m, 6H), 3.05–2.97 (m, 3H), 2.91–2.89 (m, 2H), 2.64–2.52 (m, 1H), 2.44–2.41 (m, 1H), 2.32–2.26 (m, 9H), 1.94–1.90 (m, 2H), 1.90–1.86 (m, 1H), 1.71–1.63 (m, 3H), 1.49 (m, 1H), 1.39 (s, 2H), 1.23–1.17 (m, 15H), 1.14–1.11 (m, 12H), 0.87–0.84 (t, 3H); MS (ESI) m/z calcd. for $C_{50}H_{82}FN_3O_{15}$ 983.6; found $[M + H]^+$ 984.8; Analysis calculated for $C_{50}H_{82}FN_3O_{15}$: C 61.02, H 8.40, N 4.27. Found: C 61.11, H 8.37, N 4.30.

6.3.3. 4″-O-(((4-Methoxybenzyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**18**)

White crystals, yield 75.7%, mp 127–132 °C, TLC R_f = 0.35 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3391, 2972, 2937, 1732, 1656, 1537, 1459, 1379, 1340, 1267, 1172, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, J = 8.4 Hz, 2H), 6.88–6.87 (d, J = 9.0 Hz, 2H), 5.06 (dd, J = 10.8 Hz, J = 1.8 Hz, 1H), 4.97 (d, J = 4.8 Hz, 1H), 4.53–4.51 (m, 2H), 4.38–4.37 (m, 2H), 4.32–4.28 (m, 1H), 3.80 (s, 3H), 3.78–3.77 (m, 2H), 3.69–3.66 (m, 2H), 3.37–3.36 (m, 2H), 3.32 (s, 3H), 3.29–3.25 (m, 2H), 3.22–3.18 (m, 2H), 3.05 (s, 2H), 3.02–3.00 (m, 1H), 2.93–2.88 (m, 1H), 2.61–2.53 (m, 2H), 2.43–2.41 (m, 1H), 2.30 (s, 6H), 2.28–2.24 (m, 1H), 1.94–1.90 (m, 2H), 1.73–1.63 (m, 3H), 1.51–1.47 (m, 1H), 1.39 (s, 3H), 1.24–1.19 (m, 18H), 1.19–1.10 (m, 9H), 0.85 (t, 3H); MS (ESI) m/z calcd. for $C_{51}H_{85}N_3O_{16}$ 995.6; found $[M + H]^+$ 997.1; Analysis calculated for $C_{51}H_{85}N_3O_{16}$: C 61.49, H 8.60, N 4.22. Found: C 61.40, H 8.57, N 4.25.

6.3.4. 4″-O-(((4-Hydroxyphenethyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**19**)

White crystals, yield 69.2%, mp 135–137 °C, TLC R_f = 0.35 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3411, 2972, 1730, 1664, 1626, 1517, 1459, 1378, 1351, 1261, 1168, 1125, 1078, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.12 (d, J = 9.6 Hz, 2H), 6.72 (d, J = 9.6 Hz, 2H), 5.08–5.06 (d, J = 8.4 Hz, 1H), 4.39–4.38 (m, 2H), 4.31–4.28 (m, 1H), 4.01 (m, 1H), 3.82–3.81 (m, 3H), 3.79–3.77 (m, 2H), 3.69–3.67 (m, 2H), 3.33–3.32 (m, 3H), 3.29–3.30 (m, 3H), 3.06–2.93 (m, 3H), 2.92–2.89 (m, 2H), 2.61–2.58 (m, 2H), 2.44–2.42 (m, 1H), 2.34–2.31 (m, 6H), 2.22–2.21 (m, 2H), 1.95–1.85 (m, 1H), 1.73–1.63 (m, 6H), 1.55–1.48 (m, 4H), 1.43–1.35 (m, 5H), 1.29–1.20 (m, 15H), 1.19–1.12 (m, 12H), 0.84 (t, 3H); MS (ESI) m/z calcd. for $C_{51}H_{85}N_3O_{16}$ 995.6; found $[M + H]^+$ 997.1; Analysis calculated for $C_{51}H_{85}N_3O_{16}$: C 61.49, H 8.60, N 4.22. Found: C 61.56, H 8.56, N 4.26.

6.3.5. 4″-O-(((2-Chlorophenethyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**20**)

White crystals, yield 73.1%, mp 117–122 °C, TLC R_f = 0.32 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3442, 2974, 2938, 1731, 1660, 1515, 1457, 1378, 1338, 1266, 1172, 1110, 1072, 1052, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.35 (m, 2H), 7.27–7.09 (m, 2H), 5.08 (d, J = 9.6 Hz, 1H), 4.99–4.98 (m, 1H), 4.53–4.50 (m, 1H), 4.24 (m, 2H), 3.97 (m, 1H), 3.78–3.76 (m, 2H),

3.70–3.67 (m, 1H), 3.59–3.52 (m, 3H), 3.31–3.30 (m, 3H), 3.25–3.18 (m, 3H), 3.04 (m, 3H), 3.00–2.96 (m, 2H), 2.92–2.87 (m, 2H), 2.64–2.58 (m, 3H), 2.42–2.40 (m, 3H), 2.22–2.18 (m, 3H), 1.97–1.90 (m, 3H), 1.85–1.79 (m, 3H), 1.67–1.63 (m, 4H), 1.51–1.46 (m, 1H), 1.40–1.38 (m, 3H), 1.26 (m, 3H), 1.23–1.19 (m, 9H), 1.14–1.13 (m, 6H), 1.09–1.08 (m, 6H), 0.89–0.84 (m, 3H); MS (ESI) *m/z* calcd. for $C_{51}H_{84}ClN_3O_{15}$ 1013.6; found $[M + H]^+$ 1014.6; Analysis calculated for $C_{51}H_{84}ClN_3O_{15}$: C 60.37, H 8.34, N 4.14. Found: C 60.44, H 8.37, N 4.11.

6.3.6. 4″-O-(((Cyclohexyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**21**)

White crystals, yield 75.3%, mp 122–126 °C, TLC R_f = 0.30 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3415, 2973, 2935, 1732, 1650, 1540, 1454, 1379, 1348, 1257, 1171, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.18 (m, 1H), 5.06 (d, J = 9.6 Hz, 1H), 4.97 (m, 1H), 4.53–4.50 (m, 2H), 4.45(d, J = 6.0 Hz, 1H), 4.28 (m, 2H), 3.97 (s, 1H), 3.77–3.72 (m, 3H), 3.69–3.65 (m, 2H), 3.38–3.36 (m, 2H), 3.35–3.29 (m, 3H), 3.28–3.24 (m, 4H), 3.17 (m, 2H), 3.04 (m, 3H), 3.00–2.99 (m, 3H), 2.60 (m, 2H), 2.42–2.18 (m, 8H), 1.94–1.84 (m, 6H), 1.72 (m, 6H), 1.66 (m, 2H), 1.38 (m, 4H), 1.25–1.16 (m, 10H), 1.16–1.10 (m, 10H), 0.84 (t, 3H); MS (ESI) *m/z* calcd. for $C_{49}H_{87}N_3O_{15}$ 957.6; found $[M + H]^+$ 958.8; Analysis calculated for $C_{49}H_{87}N_3O_{15}$: C 61.42, H 9.15, N 4.39. Found: C 61.35, H 9.18, N 4.42.

6.3.7. 4″-O-(((Isopropyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**22**)

White crystals, yield 75.1%, mp 118–121 °C, TLC R_f = 0.30 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3450, 2973, 2938, 1732, 1654, 1515, 1458, 1378, 1338, 1267, 1172, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.14 (m, 1H), 5.07 (dd, J = 10.8 Hz, J = 1.8 Hz, 1H), 4.98–4.97 (m, 1H), 4.54–4.52 (m, 2H), 4.32–4.30 (m, 1H), 3.99 (m, 1H), 3.82–3.78 (m, 2H), 3.70–3.67 (m, 2H), 3.34–3.32 (m, 3H), 3.28–3.25 (m, 2H), 3.21–3.18 (m, 2H), 3.05 (m, 3H), 3.03–2.99 (m, 1H), 2.92–2.89 (m, 1H), 2.60–2.56 (m, 2H), 2.43–2.41 (m, 2H), 2.36–2.27 (m, 5H), 2.21–2.17 (m, 2H), 1.95–1.89 (m, 2H), 1.88–1.82 (m, 3H), 1.72–1.63 (m, 5H), 1.50–1.47 (m, 2H), 1.42–1.40 (m, 3H), 1.32–1.24 (m, 3H), 1.23–1.22 (m, 7H), 1.20–1.15 (m, 7H), 1.14–1.10 (m, 9H), 0.89–0.84 (m, 3H); MS (ESI) *m/z* calcd. for $C_{46}H_{83}N_3O_{15}$ 917.6; found $[M + H]^+$ 919.0; Analysis calculated for $C_{46}H_{83}N_3O_{15}$: C 60.17, H 9.11, N 4.58. Found: C 60.11, H 9.14, N 4.60.

6.3.8. 4″-O-(((Propyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**23**)

White crystals, yield 75.7%, mp 120–126 °C, TLC R_f = 0.32 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3450, 2973, 2938, 1732, 1654, 1515, 1458, 1378, 1338, 1267, 1172, 1110, 1072, 1051, 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.14 (t, 1H), 5.07 (dd, J = 10.8 Hz, J = 2.4 Hz, 1H), 4.98–4.97 (m, 1H), 4.53–4.52 (m, 2H), 4.32–4.30 (m, 1H), 3.99 (m, 1H), 3.79–3.77 (m, 2H), 3.69–3.67 (m, 2H), 3.32 (m, 2H), 3.29–3.25 (m, 2H), 3.24–3.22 (m, 2H), 3.21–3.18 (m, 2H), 3.05 (m, 3H), 3.03–2.99 (m, 1H), 2.92–2.89 (m, 1H), 2.60–2.53 (m, 2H), 2.44–2.41 (m, 2H), 2.30–2.29 (m, 5H), 2.23–2,21 (m, 2H), 1.95–1.92 (m, 2H), 1.91–1.82 (m, 3H), 1.73–1.63 (m, 5H), 1.55–1.48 (m, 2H), 1.40 (s, 3H), 1.26–1.15 (m, 12H), 1.14–1.11 (m, 10H), 0.93 (t, 3H), 0.85 (t, 3H); MS (ESI) *m/z* calcd. for $C_{46}H_{83}N_3O_{15}$ 917.6; found $[M + H]^+$ 919.0; Analysis calculated for $C_{46}H_{83}N_3O_{15}$: C 60.17, H 9.11, N 4.58. Found: C 60.24, H 9.08, N 4.55.

6.3.9. 4″-O-(((Propenyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**24**)

White crystals, yield 74.2%, mp 135–140 °C, TLC R_f = 0.34 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3436, 2974, 2938, 1731, 1660, 1529, 1458, 1382, 1339, 1266, 1247, 1171, 1110, 1072, 1051, 1013, 986, 933 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) :δ 5.85–5.83 (m, 1H), 5.22–5.19 (m, 1H), 5.16–1.15 (m, 1H), 5.08–5.06 (m, 2H), 4.98–4.97 (m, 1H), 4.54–4.52 (m, 2H), 4.31 (m, 2H), 3.99 (s, 2H), 3.90–3.89 (m, 2H), 3.79–3.77 (m, 2H), 3.68–3.67 (m, 2H), 3.3–3.28 (m, 6H), 3.20–3.18 (m, 2H), 3.05–3.00 (m, 3H), 2.91 (m, 2H), 2.44–2.41 (m, 2H), 2.28–2.24 (m, 6H), 1.94–1.85 (m, 6H), 1.73–1.63 (m, 7H), 1.40 (m, 4H), 1.27–1.19 (m, 9H), 1.17–1.13(m, 8H), 0.85 (t, 3H); MS (ESI) *m/z*, calcd. for $C_{46}H_{81}N_3O_{15}$ 915.6; found $[M + H]^+$ 917.0; Analysis calculated for $C_{46}H_{81}N_3O_{15}$: C 60.31, H 8.91, N 4.59. Found: C 60.25, H 8.94, N 4.57.

6.3.10. 4″-O-(((Butyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**25**)

White crystals, yield 77.2%, mp 127–130 °C, TLC R_f = 0.33 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3435, 2972, 2936, 1730, 1648, 1525, 1459, 1378, 1349, 1261, 1170, 1126, 1080, 1047, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.11 (m, 1H), 5.09 (m, 1H), 4.68 (m, 1H), 4.55–4.51 (m, 1H), 3.99–3.98 (m, 1H), 3.79–3.76 (m, 2H), 3.69–3.67 (m, 2H), 3.31 (m, 6H), 3.05 (m, 3H), 3.02–2.99 (m, 2H), 2.94–2.91 (m, 2H), 2.82–2.57 (m, 8H), 2.43–2.41 (m, 1H), 2.25–2.03 (m, 2H), 2.03 (m, 1H), 1.94–1.89 (m, 2H), 1.88–1.80 (m, 3H), 1.53–1.46 (m, 5H), 1.39–1.35 (m, 9H), 1.28–1.18 (m, 12H), 1.16–1.14 (m, 6H), 1.09–1.08 (m, 3H), 0.96–0.92 (m, 3H), 0.87–0.85 (m, 3H); MS (ESI) *m/z* calcd. for $C_{47}H_{85}N_3O_{15}$ 931.6; found $[M + H]^+$ 932.9; Analysis calculated for $C_{47}H_{85}N_3O_{15}$: C 60.56, H 9.19, N 4.15. Found: C 60.62, H 9.15, N 4.12.

6.3.11. 4″-O-(((Pentyl)amino)-4-oxo-butyl) carbamoylclarithromycin (**26**)

White crystals, yield 71.3%, mp 132–136 °C, TLC R_f = 0.35 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3450, 2973, 2938, 1732, 1654, 1515, 1458, 1378, 1338, 1267, 1172, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.06 (d, J = 9.6 Hz, 1H), 4.97–2.92 (m, 1H), 4.53–4.51 (m, 3H), 3.99 (s, 1H), 3.81–3.76 (m, 2H), 3.69–3.66 (m, 2H), 3.35–3.30 (m, 3H), 3.28–3.18 (m, 6H), 3.10–3.02 (m, 3H), 3.01–2.92 (m, 1H), 2.91–2.87 (m, 1H), 2.59–2.56 (m, 2H), 2.43–2.38 (m, 1H), 2.32–2.24 (m, 6H), 2.22–2.19 (m, 2H), 2.04–1.90 (m, 2H), 1.88–1.81 (m, 2H), 1.75–1.63 (m, 4H), 1.53–1.45 (m, 3H), 1.41–1.39 (m, 3H), 1.35–1.25 (m, 6H), 1.23–1.19 (m, 9H), 1.16 (m, 3H), 1.17–1.11 (m, 10H), 0.89 (t, 3H), 0.84 (t, 3H); MS (ESI) *m/z* calcd. for $C_{48}H_{87}N_3O_{15}$ 945.6; found $[M + H]^+$ 947.1; Analysis calculated for $C_{48}H_{87}N_3O_{15}$: C 60.93, H 9.27, N 4.44. Found: C 60.85, H 9.31, N 4.41.

6.4. General procedure for the preparation of 4″-O-((arylalkylamino)-6-oxo-hexyl)carbamoyl clarithromycin derivatives (**27**–**37**)

To a solution of **2** (1.50 g, 1.70 mmol) in DMF (15 mL) was added DBU (0.50 mL, 3.41 mmol),Et_3N (1.50 mL, 10.90 mmol) and corresponding arylalkylcarbamoyl alkylamines hydrochloride (**15l**–**15v**) (6.67 mmol). The resulting solution was stirred for 24 h at the room temperature. The following procedures were carried out according to 6.3. General procedure for the preparation of 4″-O-((arylalkylamino)-4-oxo-butyl)carbamoyl clarithromycin derivatives. The crudes were purified by flash chromatography (dichloromethane/methanol 40:1) to afford products **27**–**37** in yields ranging from 70% to 79%.

6.4.1. 4″-O-(((Benzyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**27**)

White crystals, yield 73.3%, mp 115–118 °C, TLC R_f = 0.35 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3454, 2974, 2938, 1731, 1514, 1456, 1378, 1346, 1247, 1171, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 5.06 (d, J = 10.8 Hz, 1H), 4.58–4.50 (m, 2H), 4.44–4.43 (m, 2H), 4.30–4.27 (m, 2H), 3.98

(m, 1H), 3.81–3.76 (m, 2H), 3.67–3.63 (m, 2H), 3.35–3.27 (m, 3H), 3.21–3.17 (m, 4H), 3.00–2.98 (m, 2H), 2.90–2.89 (m, 2H), 2.58–2.56 (m, 2H), 2.30–2.29 (m, 7H), 2.22 (t, 2H), 1.94–1.84 (m, 1H), 1.72–1.62 (m, 2H), 1.54–1.46 (m, 8H), 1.39–1.35 (m, 11H), 1.25–1.23 (m, 9H), 1.12–1.10 (m, 9H), 0.84 (t, 3H), MS (ESI) *m/z*, calcd. for $C_{52}H_{87}N_3O_{15}$ 993.6; found $[M + H]^+$ 995.1; Analysis calculated for $C_{52}H_{87}N_3O_{155}$: C 62.82, H 8.82, N 4.23, Found: C 62.71, H 8.78, N 4.25.

*6.4.2. 4″-O-(((4-Fluorobenzyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**28**)*

White crystals, yield 73.6%, mp 110–112 °C, TLC R_f = 0.36 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3381, 2974, 2938, 1730, 1658, 1605, 1511, 1459, 1378, 1345, 1266, 1171, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.26–7.24 (m, 2H), 7.04–7.01 (m, 2H), 5.07 (dd, J = 11.4 Hz, J = 1.8 Hz, 1H), 4.98 (m, 1H), 4.41–4.40 (m, 2H), 4.30–4.26 (m, 2H), 4.10–4.09 (m, 1H), 3.82–3.76 (m, 2H), 3.69–3.59 (m, 2H), 3.23–3.17 (m, 8H), 3.05–3.03 (m, 1H), 2.94–2.87 (m, 2H), 2.65–2.55 (m, 2H), 2.43–2.41 (m, 2H), 2.33 (m, 6H), 2.22–2.20 (m, 3H), 1.94–1.92 (m, 1H), 1.72–1.63 (m, 3H), 1.55–1.48 (m, 8H), 1.38–1.35 (m, 9H), 1.26–1.15 (m, 9H), 1.14–1.12 (m, 9H), 0.84 (t, 3H); MS (ESI) *m/z* calcd. for $C_{52}H_{86}FN_3O_{15}$ 1011.6; found $[M + H]^+$ 1012.8; Analysis calculated for $C_{52}H_{86}FN_3O_{15}$: C 61.70, H 8.56, N 4.15, Found (%): C 61.66, H 8.54, N 4.17.

*6.4.3. 4″-O-(((4-Methoxybenzyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**29**)*

White crystals, yield 70.1%, mp 120–124 °C, TLC R_f = 0.28 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3369, 2973, 2937, 1730, 1654, 1514, 1458, 1378, 1335, 1249, 1172, 1110, 1083, 1048, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.07 (d, J = 8.4 Hz, 1H), 4.39–4.38 (m, 2H), 4.31–4.28 (m, 1H), 4.01 (m, 1H), 3.82–3.81 (m, 3H), 3.79–3.77 (m, 2H), 3.69–3.67 (m, 2H), 3.33–3.32 (m, 3H), 3.29–3.30 (m, 3H), 3.06–2.93 (m, 3H), 2.92–2.89 (m, 2H), 2.61–2.58 (m, 2H), 2.44–2.42 (m, 1H), 2.34–2.31 (m, 6H), 2.22–2.21 (m, 2H), 1.95–1.85 (m, 1H), 1.73–1.63 (m, 6H), 1.55–1.48 (m, 4H), 1.43–1.35 (m, 5H), 1.29–1.20 (m, 15H), 1.19–1.12 (m, 12H), 0.84 (t, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{89}N_3O_{16}$ 1023.6; found $[M + H]^+$ 1025.2; Analysis calculated for $C_{53}H_{89}N_3O_{16}$: C 63.13, H 8.90, N 4.17, Found: C 63.19, H 8.86, N 4.19.

*6.4.4. 4″-O-(((4-Hydroxyphenethyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**30**)*

White crystals, yield 70.2%, mp 129–133 °C, TLC R_f = 0.33 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3409, 2974, 2939, 1731, 1655, 1516, 1457, 1378, 1347, 1247, 1171, 1110, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.05 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 5.07 (d, J = 11.4 Hz, 1H), 4.99 (m, 1H), 4.74 (d, J = 6.6 Hz, 1H), 4.50 (d, J = 9.6 Hz, 1H), 4.20–4.17 (m, 1H), 3.96 (m, 1H), 3.88–3.87 (m, 1H), 3.76–3.73 (m, 2H), 3.66–3.65 (m, 2H), 3.56–3.55 (m, 2H), 3.37–3.28 (m, 6H), 3.21–3.19 (m, 3H), 3.09–3.03 (m, 3H), 3.00–2.92 (m, 2H), 2.90–2.84 (m, 6H), 2.59–2.56 (m, 4H), 2.40 (m, 2H), 1.97–1.91 (m, 1H), 1.78–1.73 (m, 3H), 1.67–1.56 (m, 3H), 1.51–1.42 (m, 2H), 1.41–1.36 (m, 3H), 1.18–1.13 (m, 18H), 1.05–1.03 (m, 4H), 0.89–0.83 (m, 6H); MS (ESI) *m/z* calcd. for $C_{53}H_{89}N_3O_{16}$ 1023.6; found $[M + H]^+$ 1025.2; Analysis calculated for $C_{53}H_{89}N_3O_{16}$: C 63.13, H 8.90, N 4.17, Found: C 63.08, H 8.93, N 4.15.

*6.4.5. 4″-O-(((2-Chlorophenethyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**31**)*

White crystals, yield 70.1%, mp 127–131 °C, TLC R_f = 0.31 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3446, 2973, 2934, 1730, 1651, 1534, 1459, 1378, 1348, 1264, 1170, 1110, 1082, 1053, 1011 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.37 (m, 1H), 7.29–7.19 (m, 3H), 5.09 (d, J = 11.4 Hz, 1H), 4.99–4.98 (m, 1H), 4.63–4.62 (m, 1H), 4.55–4.53 (m, 1H), 4.24–4.22 (m, 1H), 3.99 (m, 1H), 3.79–3.76 (m, 4H), 3.69–3.68 (m, 2H), 3.35–3.32 (m, 2H), 3.24–3.21 (m, 2H), 3.11–3.05 (m, 3H), 3.02–2.97 (m, 2H), 2.94–2.87 (m, 2H), 2.65–2.54 (m, 2H), 2.43–2.36 (m, 2H), 2.21–2.16 (m, 2H), 2.05–1.92 (m, 1H), 1.84–1.80 (m, 1H), 1.72–1.64 (m, 3H), 1.55–1.48 (m, 4H), 1.42–1.36 (m, 4H), 1.36–1.33 (m, 4H), 1.27–1.25 (m, 8H), 1.25–1.20 (m, 15H), 1.19–1.14 (m, 8H), 0.91–0.86 (m, 3H); MS (ESI) *m/z* calcd. for $C_{53}H_{88}ClN_3O_{15}$ 1041.6; found $[M + H]^+$ 1043.0; Analysis calculated for $C_{53}H_{88}ClN_3O_{15}$: C 61.05, H 8.51, N 4.03, Found: C 61.12, H 8.48, N 4.06.

*6.4.6. 4″-O-(((Cyclohexyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**32**)*

White crystals, yield 79.3%, mp 100–103 °C, TLC R_f = 0.34 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3435, 2972, 1730, 1648, 1525, 1459, 1378, 1349, 1261, 1170, 1126, 1080, 1047, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.08–5.06 (m, 1H), 4.98–4.96 (m, 1H), 4.74 (m, 1H), 4.54–4.51 (m, 2H), 4.31–4.28 (m, 2H), 4.10–4.09 (m, 1H), 3.99–3.97 (m, 2H), 3.79–3.74 (m, 1H), 3.69–3.64 (m, 2H), 3.33–3.31 (m, 2H), 3.26–3.17 (m, 6H), 3.05–2.97 (m, 3H), 2.92–2.88 (m, 2H), 2.60–2.57 (m, 2H), 2.44–2.41 (m, 1H), 2.31–2.92 (m, 6H), 2.17–2.14 (m, 2H), 1.73–1.63 (m, 7H), 1.54–1.47 (m, 6H), 1.40–1.26 (m, 10H), 1.24–1.16 (m, 9H), 1.15–1.12 (m, 9H), 1.11–0.90 (t, 3H), 0.85 (t, 3H); MS (ESI) *m/z* calcd. for $C_{51}H_{91}N_3O_{15}$ 985.7; found $[M + H]^+$ 987.1; Analysis calculated for $C_{51}H_{91}N_3O_{15}$: C 62.11, H 9.30, N 4.26, Found: C 62.04, H 9.33, N 4.24.

*6.4.7. 4″-O-(((Isopropyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**33**)*

White crystals, yield 69.8%, mp 123–127 °C, TLC R_f = 0.29 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3377, 2973, 2933, 1730, 1643, 1544, 1460, 1382, 1349, 1266, 1170, 1127, 1082, 1046, 1011 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.10 (d, J = 11.4 Hz, 1H), 5.01–5.00 (m, 1H), 4.74–4.73 (d, J = 7.2 Hz, 1H), 4.59–4.53 (m, 1H), 4.12–4.06 (m, 1H), 3.84–3.82 (m, 1H), 3.79–3.73 (m, 2H), 3.69–3.68 (m, 1H), 3.56–3.53 (m, 1H), 3.38–3.28 (m, 6H), 3.27–3.19 (m, 3H), 3.05 (m, 2H), 3.01–2.98 (m, 2H), 2.92–2.81 (m, 2H), 2.63–2.56 (m, 3H), 2.42–2.40 (m, 1H), 2.22–2.16 (m, 3H), 1.95–1.89 (m, 1H), 1.88–1.75 (m, 3H), 1.75–1.65 (m, 5H), 1.50–1.47 (m, 2H), 1.32–1.24 (m, 3H), 1.25–1.19 (m, 15H), 1.19–1.15 (m, 9H), 1.14–1.10 (m, 6H), 0.90–0.85 (m, 6H); MS (ESI) *m/z* calcd. for $C_{48}H_{87}N_3O_{15}$ 945.61; found $[M + H]^+$ 947.2; Analysis calculated for $C_{48}H_{87}N_3O_{15}$: C 60.93, H 9.27, N 4.44, Found: C 688, H 9.30, N 4.42.

*6.4.8. 4″-O-(((Propyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**34**)*

White crystals, yield 76.3%, mp 112–115 °C, TLC R_f = 0.36 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3452, 2972, 2937, 1731, 1655, 1537, 1459, 1378, 1337, 1266, 1171, 1110, 1072, 1050, 1012 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.07 (d, J = 10.2 Hz, 1H), 4.97–4.96 (m, 1H), 4.57–4.50 (m, 2H), 3.99 (s, 1H), 3.82–3.76 (m, 2H), 3.68–3.59 (m, 2H), 3.36–3.31 (m, 2H), 3.23–3.18 (m, 6H), 3.15–3.09 (m, 1H), 3.05–3.00 (m, 2H), 2.89 (m, 2H), 2.59–2.57 (m, 2H), 2.44–2.41 (m, 1H), 2.31–2.29 (m, 6H), 2.16 (t, 2H), 1.94–1.87 (m, 1H), 1.73–1.63 (m, 3H), 1.54–1.48 (m, 3H), 1.40–1.34 (m, 4H), 1.27–1.24 (m, 2H), 1.24–1.18 (m, 14H), 1.17–1.11 (m, 16H), 0.93 (t, 3H), 0.85 (t, 3H); MS (ESI) *m/z* calcd. for $C_{48}H_{87}N_3O_{15}$ 945.6; found $[M + H]^+$ 947.1; Analysis calculated for $C_{48}H_{87}N_3O_{15}$: C 60.93, H 9.27, N 4.44, Found: C 60.89, H 9.30, N 4.41.

*6.4.9. 4″-O-(((Propenyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**35**)*

White crystals, yield 72.3%, mp 119–122 °C, TLC R_f = 0.38 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3454, 2974, 2939, 1731, 1664, 1514, 1458, 1378, 1339, 1266, 1171, 1110, 1072, 1051, 1013, 986, 934 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.87–5.82 (m,1H),

5.20–5.13 (m, 2H), 5.08–5.07 (m, 1H), 4.98–4.97 (m, 1H), 4.56–4.52 (m, 2H), 4.27 (m, 1H), 3.98 (s, 2H), 3.89 (t, 2H), 3.68–3.67 (m, 2H), 3.32 (m, 3H), 3.23–3.18 (m, 3H), 3.05 (m, 1H), 3.01 (m, 2H), 2.89 (m, 2H), 2.59 (m, 2H), 2.43–2.41 (m, 7H), 2.22–2.19 (m, 2H), 1.96–1.85 (m, 2H), 1.70–1.63 (m, 4H), 1.55–1.49 (m, 6H), 1.39–1.35 (m, 9H), 1.27–1.24 (m, 2H), 1.22–1.14 (m, 9H), 1.13–1.10 (m, 9H), 0.85 (t, 3H,); MS (ESI) *m/z*, calcd. for $C_{48}H_{85}N_3O_{15}$ 943.6; found $[M + H]^+$ 945.0; Analysis calculated for $C_{48}H_{85}N_3O_{15}$: C 61.06, H 9.07, N 4.45, Found: C 61.10, H 9.04, N 4.48.

*6.4.10. 4″-O-(((Butyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**36**)*

White crystals, yield 72.0%, mp 102–106 °C, TLC R_f = 0.33 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3431, 2933, 1749, 1734, 1647, 1547, 1457, 1378, 1267, 1172, 1110, 1069, 1011 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.08–5.07 (m, 1H), 5.00–4.97 (m, 1H), 4.56–4.53 (m, 1H), 4.53–4.47 (m, 1H), 3.83–3.77 (m, 1H), 3.74–3.66 (m, 2H), 3.35–3.20 (m, 6H), 3.05–2.98 (m, 4H), 2.45–2.37 (m, 7H), 2.32–2.17 (m, 1H), 2.16–1.73 (m, 3H), 1.72–1.67 (m, 5H), 1.54–1.43 (m, 4H), 1.43–1.34 (m, 6H), 1.33–1.26 (m, 8H), 1.23–1.18 (m, 12H), 1.15–1.12 (m, 12H), 0.95–0.91 (m, 3H), 0.89–0.85 (m, 6H); MS (ESI) *m/z* calcd. for $C_{49}H_{89}N_3O_{15}$ 959.6; found $[M + H]^+$ 961.0; Analysis calculated for $C_{49}H_{89}N_3O_{15}$: C 61.29, H 9.34, N 4.38, Found: C 61.35, H 9.31, N 4.41.

*6.4.11. 4″-O-(((Pentyl)amino)-6-oxo-hexyl) carbamoylclarithromycin (**37**)*

White crystals, yield 72.5%, mp 104–107 °C, TLC R_f = 0.34 (methanol/dichlormethane, 1:10, v/v); IR (KBr): 3391, 2936, 1731, 1656, 1536, 1459, 1378, 1343, 1247, 1171, 1111, 1072, 1051, 1013 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.08–5.06 (m, 1H), 4.98–4.96 (m, 1H), 4.74 (m, 1H), 4.54–4.51 (m, 2H), 4.31–4.28 (m, 2H), 4.10–4.09 (m, 1H), 3.99–3.97 (m, 2H), 3.79–3.74 (m, 1H), 3.69–3.64 (m, 2H), 3.33–3.31 (m, 2H), 3.26–3.17 (m, 6H), 3.05–2.97 (m, 3H), 2.92–2.88 (m, 2H), 2.60–2.57 (m, 2H), 2.44–2.41 (m, 1H), 2.31–2.92 (m, 6H), 2.17–2.14 (m, 2H), 1.73–1.63 (m, 7H), 1.54–1.47 (m, 6H), 1.40–1.26 (m, 10H), 1.24–1.16 (m, 9H), 1.15–1.12 (m, 9H), 1.11–0.90 (t, 3H), 0.85 (t, 3H); MS (ESI) *m/z* calcd. for $C_{50}H_{91}N_3O_{15}$ 973.7; found $[M + H]^+$ 975.0; A Analysis calculated for $C_{50}H_{91}N_3O_{15}$: C 61.64, H 9.41, N 4.31, Found: C 61.60, H 9.44, N 4.29.

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Appendix. Supporting information

Supporting information associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2010.11.035.

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